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REVIEW ARTICLE

What tuberculosis infection control measures are effective in resource-constrained primary healthcare facilities? A systematic review of the literature

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ABSTRACT:

Introduction: Tuberculosis (TB) remains a major global health challenge, killing millions of people, despite the availability of preventive TB medication. The majority of these infections and deaths occur in low-income countries. Therefore, practical public health strategies are required to reduce the global TB burden in these countries effectively. The purpose of this review was to examine the current evidence of tuberculosis infection control (TBIC) measures in reducing TB transmission and explore the barriers and enablers of TBIC measures in resource-constrained primary healthcare settings.

Methods: The PRISMA framework was adopted to identify studies that report on the evidence and barriers and facilitators of administrative, environmental and respiratory control measures at healthcare settings in low- and middle-income countries (LMICs). ProQuest, Scopus, ScienceDirect, Embase and PubMed were searched for English language peer-reviewed studies published since the introduction of TBIC guidelines. Studies not relevant to the topic, were not on TBIC measures or were reviews or commentary-style papers were excluded. Included articles were evaluated based on their aim, study design, geography and health settings interventions (TBIC measures), economic setting (ie LMICs) and main findings.

Results: Our review of the 15 included studies identified a cough officer screening system, isolation of TB patients, modification of consultation rooms, and opening windows and doors as effective TB prevention measures. Lack of patient education, unsupportive workplace culture, inadequate supply of particulate respirators, insufficient isolation facilities and poor physical infrastructures were identified as barriers to TBIC practices. Triaging TB patients, maintenance of health infrastructure, appropriate use of personal protective equipment (PPE) and healthcare workers (HCWs) training on the correct use of PPE were reported as facilitators of TBIC in primary healthcare facilities.

Conclusion: Our review provides consistent evidence of TBIC measures in reducing TB transmission in resource-constrained primary healthcare settings. This review has demonstrated that TB transmission can be successfully controlled using multiple and simple low-cost TBIC measures including administrative, environmental and respiratory controls. Effective implementation of triaging patients with suspected TB alongside maintenance of health infrastructure, appropriate use of PPE and robust HCWs training on TBIC could improve implementation of TBIC measures in primary healthcare settings. Healthcare management should address these areas particularly in rural and remote locations to improve the implementation of TBIC measures in primary healthcare facilities in LMICs.

Keywords:

infection control, low- and middle-income countries, resource-constrained primary health care settings, systematic review, tuberculosis, World Health Organization.

FULL ARTICLE:

Introduction

Every year, despite the availability of preventive medication, tuberculosis (TB) kills millions of people, particularly in low- and middle-income countries (LMICs). In 2019, 10 million people contracted TB globally, of which 1.4 million people died[1]. It is well established that the reduction of active TB cases depends on effective prevention and management. As more than 80% of TB deaths and infections worldwide occur in LMICs, it is critical that prompt diagnosis and treatment in these countries are managed effectively if a significant reduction in active cases is to be achieved. Although the TB mortality rate has declined by 42% in recent decades, it stubbornly remains a leading global public health threat[2]. More effort is required to drive strategies toward accomplishing the global milestone of eradicating TB.

Anyone in TB-endemic countries is at risk of contracting TB, but certain populations have an increased risk of TB infection and advancing to TB disease[3]. These vulnerable populations include people living with HIV/AIDS, health professionals and those living in poverty. According to 2019 global data, about 208 000 people with HIV died from TB, a reduction from 678 000 in 2000[1]. Among all those that were infected with active TB, 8.2% were individuals with positive HIV[1]. Further, the magnitude of TB among healthcare workers (HCWs) in healthcare settings remains higher than in the general population. The pooled incidence of active TB among HCWs was 97 per 100 000 people per year compared with the general population[4]. In 2019, a total of 22 314 HCWs were reported to have TB in 76 countries, with India contributing the most, accounting for 47% of the total cases, followed by China with 18%[5]. The WHO highlighted the positioning of healthcare facilities as key transmission sites in resource-constrained healthcare settings[2]. Besides this, poverty has been demonstrated to be a major determinant of TB, increasing transmission through (i) influence on living standards, such as individuals residing in poorly ventilated and overcrowded homes; (ii) delay in diagnosis and treatment; and (iii) increased susceptibility because of malnutrition[6]. Despite some inconsistencies, the majority of the studies have affirmed this positive relationship between individual poverty and TB in countries like South Africa, Brazil, Vietnam, Zambia and India[6]

In 2015, the WHO introduced the End TB Strategy to combat the global TB epidemic. Its stated aim is to decrease the TB incidence rate by 90% and reduction of TB deaths by 95% by 2035[7]. The strategy stresses the need for prevention across all approaches, including infection prevention and control in healthcare services. These recommendations emerged because of the recurrence of TB associated with diverse factors including the upsurge in HIV infections, disruptions of access to healthcare services in LMICs due to poor healthcare systems, the emergence of drug-resistant TB and increasing incidence of non-communicable diseases (NCDs)[8]. According to Magee et al[9], the rapid increase of the NCDs epidemic has threatened TB control in LMICs, with poor TB prevention and treatment outcomes. The scale-up of interventions to decrease the TB problem will be complicated by the complex relationship between TB and NCDs and the competition for resources between TB and NCDs in resource-limited settings[9].

TB infection and prevention control strategies that were introduced by WHO and the US Centers for Disease Control and Prevention (CDC) in 1999 are widely adopted by healthcare centers to control TB transmission, including administrative, environmental and respiratory controls[10]. The specific strategies for each category reported to effectively reduce TB transmission in countries with high TB burden include administrative controls (triaging people with TB signs and symptoms, respiratory separation or isolation of people with assumed infectious TB, active screening, starting early effective TB treatment for people with TB disease, respiratory hygiene and cough officer), environmental controls (ventilation systems including natural, monitoring windows and hospital doors, mixed-mode ventilation (both natural and mechanical), mechanical ventilation (wall fan)) and respiratory controls (face mask, particulate respirator)[10].

Although the implementation of TBIC measures has proven to reduce the risk of mycobacterium TB transmission, implementation is often limited in resource-constrained primary healthcare settings[10]. This systematic review of the literature aims to review the current evidence on TBIC strategies and identify the barriers and facilitators of TBIC implementation in resource-constrained primary healthcare settings.

Methods

The study protocol was registered with PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42020203468). The Preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA) guidelines were used to develop the method for this systematic literature review (Appendix I)[11].

Search strategy

Peer-reviewed articles were sourced through five online databases: ProQuest Central, ScienceDirect, Scopus, PubMed and Embase. A systematic search was conducted using keywords with Boolean operators and terms specific to the database vocabulary including tuberculosis OR TB AND infection control OR disinfect* OR quarantine* OR infection prevention OR prevent* infection AND resource-poor countr* OR developing countr* OR low-income countr* OR lower middle-income countr* AND effectiveness OR effect OR impact AND health care cent* OR health facilities OR health settings OR hospitals. Since TB infection control guidelines were first introduced in 1999, articles published after 2000 were retrieved for analysis. Although there are some potential publications before 1999, an article published after 1999 was considered appropriate as the cut-off point for examples of contemporary research relating to TB infection prevention and control measures. It has been over two decades since the publication of the WHO guideline in 1999, so this was considered sufficient to capture the most relevant work. The search was conducted from November 2020 until July 2021.

Eligibility criteria and study inclusion

The purpose of this review is to evaluate the evidence of TBIC strategies at reducing TB transmission and factors affecting its implementation at resource-poor healthcare institutions. The term 'resource-poor health institution' refers to 'a locale where the capability to provide care for life-threatening illness is limited to basic critical care resources, including oxygen and trained staff. It may be stratified by categories: No resources, limited resources, and limited resources with possible referral to higher care capability'[12]. Health settings in LMICs are commonly characterized by limited staffing, poor infrastructures, shortages of medical supplies and drugs, and underfunding[13]. Therefore, 'resource-poor settings' in this review refers to settings in LMICs based on the World Bank data[14]. The terms 'LMICs' and/or 'resource-constrained health settings' or 'resource-poor healthcare settings' or 'resource-limited healthcare settings' are used interchangeably throughout this review. Furthermore, we have not included any resource-constrained setting that might exist in high-income countries. Our search strategy was limited to LMICs. This review includes peer-reviewed research published in English, conducted in resource-poor healthcare settings, and reported data on TBIC measures. For this review, peer-reviewed articles that assessed the effectiveness of some form of TBIC at primary health facilities in LMICs were selected. Table 1 provides a summary of the Population, Intervention, Comparison, Outcome, Study Design and Setting (PICOS) framework[15] used to determine the eligibility criteria and screening protocol.

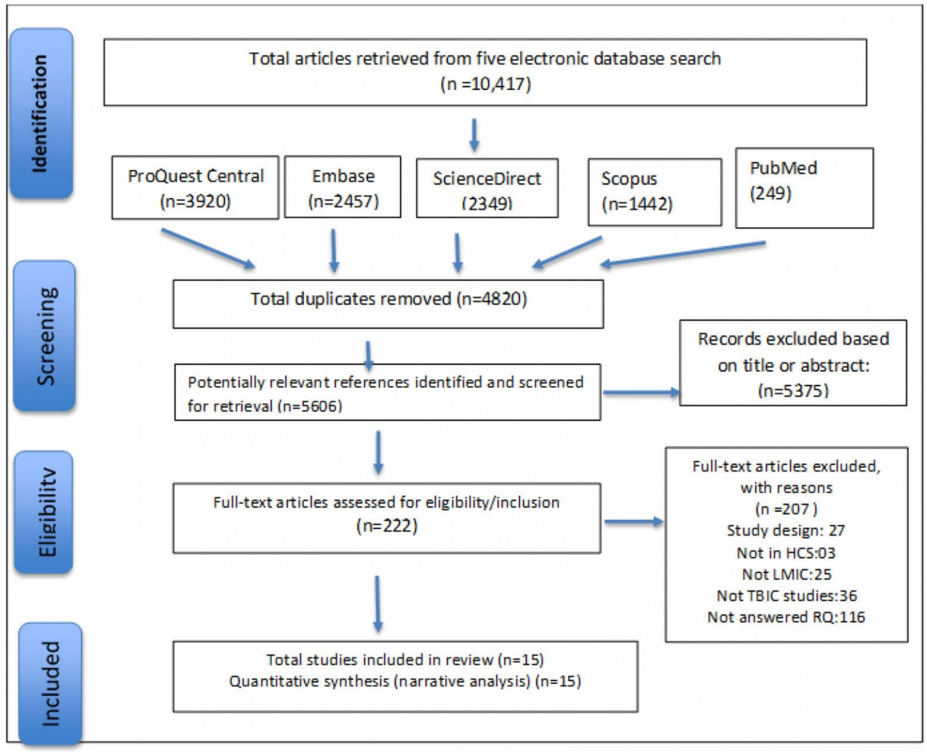
Table 1: Study inclusion and exclusion criteria using the Population, Intervention, Comparison, Outcome, Study Design and Setting approach

Element of PICOS framework	Inclusion criteria	Exclusion criteria
Population	HCWs and families of patients exposed to TB at healthcare settings	HCWs and patients in non-healthcare settings
Intervention	Papers that study TBIC measures including administrative, environmental, or respiratory control	Papers that do not study TBIC measures, vaccinations
Comparison	Papers that compare the impact or effectiveness of TBIC in reducing TB	Papers that do not compare the impact of TBIC measures in reducing TB transmission
Outcome	Quantified reduction/change in risk of TB transmission	No quantified impact
Study design	All quantitative studies: pre–post study design, randomized controlled trials, quantitative analysis, cohort studies, cross-sectional studies	Qualitative analysis, case studies, reports, conference abstracts, poster presentations, modeling studies
Setting	Healthcare settings in resource-poor countries/locations	Healthcare settings in resource-rich/developed countries

HCW, healthcare worker. PICOS, Population, Intervention, Comparison, Outcome, Study Design and Setting. TB, tuberculosis. TBIC, tuberculosis infection control.

Study selection

Figure 1 presents the study selection process following the PRISMA approach of four stages[16]: identification, screening, eligibility and inclusion. After eliminating duplicates, the first author (GM) screened papers by reviewing the titles and abstracts against the review topic and eligibility criteria. To determine eligibility, the first author (GM) undertook a full paper review with two reviewers (SR and NH) confirming selections. The consensus was reached for the final included list of 15 papers through group deliberation.



HCS, healthcare system. LMIC, low- or middle-income country. RQ, research question. TBIC, tuberculosis infection control.

Figure 1: PRISMA flow diagram of the search strategy

Data extraction and analysis

Thematic synthesis was used for data analysis. The first author (GM) independently extracted data from the selected papers that matched the study objective using a predetermined data extraction form sourced from The Cochrane Collaboration[17], which was checked by two reviewers (SR and NH). The key data extracted include year, author, type of health facility, LMICs, interventions (such as administrative control, environmental control, respiratory controls), study design and main outcomes. This information is summarized in Table 2.

Table 2: Summary of included studies

Author, year, health facility, country	Intervention	Study design	Main findings
Administrative controls			
Javed et al (2012) [ref. 19] Civil hospital Pakistan	Routine precautionary measures were taken against TB Administrative measures Personal measures employed against TB	Cross-sectional study, 6 months study (Jan 2011 – Jun 2011), pre-tested questionnaire – closed and open-ended Descriptive study rather than an intervention study	27% had screening tests for TB at the time of their employment 16% had regular screening tests 47% ensured proper workplace ventilation
Lin et al (2010) [ref. 29] Teaching hospital Taiwan	Cough officer screening (an active screening system)	Observational study in two stages: I 2004–2006, II 2006–2008, inpatients admitted: 2004–2008 were enrolled	Stage I: 184 of 7998 patients (2.3%) had TB Among these 184 patients, 142 (77.2%) were examined for TB before cough officer screening alarm and 42 were diagnosed after cough officer screening alarm Stage II: The median time from cough officer screening alarm to clinical action was significantly less (p=0.041) for Stage I (1 day; range: 0–16 days) than for Stage II (2 days; range: 0–10 days). Prompt identification and treatment
Albuquerque et al (2009) [ref. 22] Teaching hospital Brazil	Isolation of TB suspects Isolation of confirmed TB patients Quick turnaround for acid-fast bacilli sputum tests HCW education in the use of a protective respirator	Intervention study: 3-year study, 1336 HCWs tested	TST conversions per 1000 person-months was reduced from 5.8/1000 to 3.7/1000 person-months (p<0.006) Most significant reductions were observed in intensive care unit (from 20.2 to 4.5, p<0.001) and clinical wards (from 10.3 to 6.0, p<0.001). Physicians and nurses had the highest reductions (from 7.6 to 0, p<0.001; from 9.9 to 5.8, p<0.001, respectively)
Ticona et al (2016) [ref. 28] Public referral hospital Peru, Latin America	Construction of respiratory isolation ward with mechanical ventilation Triage segregation of patients Relocation of waiting room to outdoors Rapid sputum smear microscopy	Retrospective study recorded TB data at adult HIV/TB facility	MDR TB rates declined to 20% of TB cases by 2004 (p=0.01). Infection control measures were estimated to have cost US$91,031 while preventing 97 MDR TB cases, potentially saving US$1,430,026
Yanai et al (2013) [ref. 27] Provincial referral hospital Thailand	Annual TST screening and active TB surveillance Preventive interventions were implemented targeting HCWs, hospitalized patients and the hospital environment	Prospective study Skin test and TB surveillance, a total of 1325 HCW participated in the TST screening study. Of these, 1202 (90.7%) completed the first TST, which included all 911 participants from the 1995–1996 cross-sectional study	Number of pulmonary TB cases diagnosed increased steadily from 102 in 1990 to 356 in 1999: After 9 years TST conversion rate was 9.3 (95%CI 3.3–15) per 100 person-years in 1995–1997 but declined steadily to 2.2 (95%CI 0.0–5.1) in 1999 HCWs first screened within 12 months of employment had higher TST conversion rates (adjusted relative risk 9.5, 95%CI 1.8–49.5) compared to those employed for longer than 12 months
Roth et al (2015) [ref. 25] General hospital Brazil	TST TBIC measures	A longitudinal study in two phases – introduced baseline skin test (phase 1), skin test evaluation (phase 2), 7735 eligible HCWs, 4868 (62.8%) consented to participate in the study	Initial TST positivity rate was 63.1%; the follow-up TST conversion rate was 10.7 per 1000 person-months Hospitals without TBIC measures had higher conversion rates than those with control measures (16.0 v 7.8/1000 person-months, p<0.001)
Escombe et al (2010) [ref. 23] Hospitals Lima, Peru, South America	Quantify TB infection risk among HCWs in the emergency department	8773 patients and 70 staff were recruited – ED of the hospital, low-income district setting, sputum smears and cultures performed, blood sample tested (QuantiFERON–TB Gold In-Tube (QFT-G))	Baseline: 56% of 70 staff recruited were QFT-G-positive 27 of 31 baseline negatives followed up after 1 year, 8 (30%, all clinical staff) tested positive TBIC measures were suboptimal: no patient screening, no isolation, inadequate ventilation and sporadic respirator use
Environmental controls			
Escombe et al (2007) [ref. 26] Hospitals Lima, Peru, South America	Natural ventilation Mechanical ventilation	Experimental study, 8 hospitals, 70 natural ventilated clinical rooms	Opening windows and doors provided median ventilation of 28 air changes per hour, more than double that of mechanical ventilation at 12 air changes per hour recommended for high-risk areas and 18 times that with windows and doors closed (p<0.001). Buildings with large windows and high ceilings had greater ventilation (40 versus 17 air changes per hour; p<0.001).
Escombe et al (2019) [ref. 24] Hospitals Lima, Peru, South America	Introduced several environmental control interventions: • UV lights and mixing fans were turned on in the ward, a third animal enclosure alone received ward air • All guinea pigs underwent autopsy to test for TB disease • Ionizers introduced • Time-to-event analysis • An alternative analysis using an airborne infection model	Controlled observational study	35% (106/304) of guinea pigs in the control group developed TB infection. Reduced to 14% (43/303) by ionizers and to 9.5% (29/307) by UV lights (both p<0.0001 compared with the control group) 8.6% (26/304) of control group animals developed TB. Reduced to 4.3% (13/303) by ionizers and to 3.6% (11/307) by UV lights (both p, 0.03 compared with the control group Time-to-event analysis results: both ionizers and UV lights prevented TB Ionizers prevented TB (log-rank 27; p<0.0001) and by UV lights (log-rank 46; p<0.0001) TB disease was prevented by ionizers (log-rank 3.7; p< 0.055) and by UV lights (log-rank 5.4; p< 0.02) An alternative analysis using an airborne infection model: ionizers prevented 60% of TB infection and 51% of TB disease, and UV lights prevented 70% of TB infection and 54% of TB disease
Escombe et al (2019) [ref. 24] Hospital outpatients Lima, Peru, South America	Room ventilation was measured pre-and post-modification using a carbon dioxide tracer-gas technique in four waiting rooms and two consulting rooms Modifications included: • additional windows for cross-ventilation • removing glass from unopenable windows	Intervention study	Room ventilation in 4 waiting rooms increased from 5.5 to 15; 11 to 16; 10 to 17; and 9 to 66 air changes per hour, respectively 2 consulting rooms from mean 3.6 to 17, and 2.7 to 12 air changes per hour, respectively There was a median 72% reduction (interquartile range 51–82%) calculated TB transmission risk for HCWs or waiting patients Modifications cost <US$75 in four rooms and US$1000 and US$7000 in the remaining two rooms

	• unopenable windows • creation of an open skylight • re-building a waiting room in the open air		US$7000 in the remaining two rooms Significant reduction in modeled TB transmission risk at little cost
Ticona et al (2016) [ref. 28] Hospitals Lima, Peru, South America	• Built a respiratory isolation ward with mechanical ventilation • Triaged segregation of patients • Relocation of the outpatient waiting area from within to outside the building • Rapid sputum smear microscopy • Cultured with integrated drug-susceptibility testing with the Microscopic Observation Drug Susceptibility assay	7-year cross-sectional retrospective study, examined facility data, an average of 310 948 outpatient visits and 360 hospitalizations of people	44% (52/117) HIV–TB co-infected patients were diagnosed with MDR TB This percentage increased to peak at 56% (45/80 patients) in 2000, the year before the infection measures took effect, and subsequently decreased to reach 20% (18/91 patients) in 2004 3 years after the infection control measures (2002–2004) when the MDR TB rate fell to 27% (65/244) After the intervention, MDR TB rates declined to 20% of TB cases by the year 2004 (p=0.01) Infection control measures cost US$91,031 while preventing 97 MDR TB cases, potentially saving US$1,430,026
Respiratory controls			
MacIntyre et al (2015) [ref. 36] Tertiary hospital Hanoi, Vietnam	Hospital wards were randomized to medical masks, cloth masks or a control group (usual practice, which included mask-wearing). Participants used the mask on every shift for 4 consecutive weeks	Cluster-randomized trial of medical and cloth mask use for HCWs was conducted in 14 hospitals in Hanoi, Vietnam	Laboratory tests showed the penetration of particles through the cloth masks to be very high (97%) compared with medical masks (44%) (used in trial) and 3M 9320 N95 (<0.01%), 3M Vflex 9105 N95 (0.1%)
Dharmadhikari et al (2012) [ref. 34] Hospital South Africa	Introduced surgical face mask Ward air	Intervention study, wore surgical face mask (intervention group), without a face mask (control group)	69 of 90 control guinea pigs (76.6%; 95%CI 68–85%) became infected 36 of 90 intervention guinea pigs (40%; 95%CI 31–51%), representing a 56% (95%CI 33–70.5%) decreased risk of TB transmission when patients used masks
Multiple TBIC measures			
O'Hara et al (2017) [ref. 20] Hospital South Africa	Analysis of TBIC policies, practices and infrastructure using a comprehensive, 83-item infection control audit and observation tool On-site visits and review of TB registries Workplace assessment	Cross-sectional and mixed method, analysis of TBIC policies, practices and infrastructure using a comprehensive, 83-item infection control audit and observation tool, 39 key informants were purposively selected	Quantitative finding: As administrative score increased, the probability of an HCW with TB at that hospital decreased (OR 0.94, 95%CI 0.87–1.02) HCW risk of TB at that hospital decreased when the environmental (OR 0.88, 95%CI 0.80–0.96), PPE (OR 0.86, 95%CI 0.78 to 0.95) and miscellaneous scores (OR 0.86, 95%CI 0.73–0.99) increased Qualitative finding: As TBIC scores increased, the probability of having an HCW with TB at that hospital decreased, when controlling for the number of TB patients in each hospital
Tiemersma et al (2016) [ref. 21] Public TB health facilities Vietnam	PPE to HCW working in the microbiology department and MDR TB wards Appointment of TBIC focal person	Cross-sectional survey study (2009–2013), 4-year study, questionnaire	5-year TB notification rates decreased with the provision of N95 respirators (354/100 000 HCW-years, 95%CI 277–445) than in those without (448/100 000 HCW-years, 95%CI 180–921 Notification rates were lower in facilities with no TBIC focal person compared to facilities with a TBIC focal person (Kruskal-Wallis rank–sum test, p=0.08 for 2009–2011 and p=0.04 for 2012–2013) Facilities with an appointed IC focal person were 7.6 times more likely to report any TB cases than facilities that had no focal person A weak association was found between IC measures (especially environmental measures) and TB disease incidence, but it was not found in the multivariable analysis The presence of a TBIC focal person was associated with a higher probability of reporting any TB cases (adjusted OR=7.6, 95%CI 1.2–47.7) The presence of a TBIC plan was associated with finding one or more TB cases among staff members

CI, confidence interval. HCW, healthcare worker. MDR, multi-drug resistant. OR, odds ratio. PPE, personal protective equipment. TB, tuberculosis. TBIC, tuberculosis infection control. TST, tuberculin skin test.

Quality assessment (risk of bias)

The authors conducted a quality assessment during the data extraction process. Each study underwent quality assessment using the National Institute of Health (NIH) study assessment tool[18]. The NIH represents a tool that assesses scientific rigor and is frequently used by researchers to assess studies in public health interventions. The tool includes 10 criteria that evaluate the relevance to practice and the scientific validity of each study. Employing this tool, three independent reviewers assessed the quality of the studies and rated each article as good, fair or poor. All 15 studies in the final list were deemed eligible for the comprehensive review and subject to data extraction.

Ethics approval

Ethics approval was not required for this systematic review, as it uses publicly accessible documents as evidence and does not collect personal, sensitive, or confidential information from participants.

Results

A total of 10 417 studies were retrieved from the five online databases. Of those studies, 222 studies were selected for full-text review, 15 of which met the eligibility criteria and were included for data extraction. More than half (5375) of the studies were excluded because they were either not relevant to the topic, were not focused on TBIC measures, or were not original research papers.

Summary of included studies

A summary of the characteristics of the included studies is presented in Table 2. The selected studies were conducted in both private and state-owned hospitals and TB primary healthcare settings across four WHO regional groupings including the Regions of the Americas, South African Region, South-East Asia Region and Regions of the Mediterranean. None of the studies were conducted in rural health services. Most were conducted in the Regions of the Americas. The 15 studies comprised four cross-sectional studies[19-21], four intervention studies[22-25], one experimental study[26], one prospective study[27], two retrospective studies[25,28], two observational studies[29,30] and one randomized controlled trial study[31]. These studies have demonstrated consistent although not extensive evidence of TBIC measures in reducing TB transmission. The major themes have been organized according to WHO guidelines for TBIC in healthcare settings including administrative control, environmental control and respiratory control.

Administrative controls

Administrative controls consist of practices to reduce exposure and thus minimize direct transmission of active *Mycobacterium* TB{2}. Of the 15 included studies, five studies assessed the effectiveness of administrative controls in protecting healthcare workers (HCWs) and patients against active TB[19,22,25,27,29].

Of the five studies, four identified a statistically significant relationship between administrative controls and a gradual reduction in TB transmission. The specific administrative measures identified in these studies include a cough officer screening system, patient isolation, triage, a rapid turnaround for sputum test result (usually test results are available within 24 hours), HCW education on the proper use of protective respirators, effective tuberculin skin testing (TST), active TB screening and surveillance to detect active TB early to initiate prompt treatment and rapid diagnosis, and effective treatment[22,25,27,29].

The four studies indicated that the implementation of these measures provides a protective effect for HCWs. A longitudinal study from Brazil has shown that TST, rapid diagnosis and treatment, and patient isolation lead to lower conversion rates among HCWs[25]. Brazilian hospitals without the implementation of administrative TBIC strategies have a higher conversion rate compared with hospitals with infection control measures (16.0 v 7.8/1000 person-months, $p<0.001$). Furthermore, a retrospective study found that multi-drug resistant TB (MDR TB) rates declined by 20% ($p=0.001$) after introducing isolation wards and patient triage[28]. In this setting, these preventive measures were estimated to have cost US$91,031 (~A$130,700) while preventing 97 MDR TB cases, potentially saving US$1,430,026 (~A$2,054,000)[28].

The fifth study on administrative control measures is a 3-year intervention study that focused on the effect of TST infection control measures on TB reduction[22]. This study found utilizing monthly TB skin tests, isolation of TB suspects and confirmed TB patients, quick turnaround for acid-fast bacilli sputum tests and health worker education in the use of protective respirators for 1000 health workers employed in the intensive care unit and clinical wards has resulted in a significant reduction in TB cases from 20.2 to 4.5 ($p<0.001$) and from 10.3 to 6.0 ($p<0.001$), respectively[22]. The study authors stressed that the infection control interventions cannot be sustained without support from local and national health managers. Thus, strong leadership in the health system is crucial for successful implementation of TBIC measures[22].

This review demonstrates that a combination of multiple administrative control measures like patient isolation, the rapid turnaround for sputum tests and HCW education are more successful than a single method[22]. Our results suggest that simple administrative control measures, which are inexpensive and easy to implement in resource-constrained primary healthcare settings, can be efficient in reducing TB.

Environmental controls

Of the 15 included studies, four studies evaluated the effectiveness of environmental control in reducing TB in healthcare facilities[24,26,30,32]. The environmental controls represent specific measures to reduce the high concentration of infectious bacteria in the air, thereby reducing the danger of TB transmission[2]. This preventive measure is accomplished through the introduction of a ventilation system to improve air circulation to disinfect the air[2].

Of the four studies, three studies utilized natural ventilation systems by opening windows and doors in healthcare facilities[24,26,30,32]. The other study measured implementation of minimal low-cost modifications to existing hospital waiting and consultation rooms and air circulation systems[26]. All four studies found that, after the direct interventions, there was a significant improvement in air circulation. One study found that, after modification of windows and construction of an outdoor waiting room in four separate rooms at the outpatient waiting rooms, air circulation dramatically increased, from 6 to 70 air changes per hour[26]. The other study that measured the effect of direct alteration to current hospital waiting and consultation rooms found similar air changes per hour, preventing the spread of TB among HCWs and waiting patients[24]. Consequently, there was a median 72% reduction in possible TB transmission risk for health workers and waiting patients[24]. The modifications to the existing hospital infrastructure cost US$8000 (~A$11,500). Thus, minor changes to existing physical infrastructure in the hospital have considerably increased natural ventilation and therefore significantly reduced possible TB transmission at little cost[24].

Respiratory protection

Two of the 15 papers included in the review assessed the effectiveness of respiratory protection[33]. Respiratory protection controls aim to reduce the risk of potential exposure to active TB and other respiratory diseases for local health workers employed in risky health care environments[2].

The two studies both assessed the efficacy of respiratory face masks on TB prevention in hospitals[33,34]. Both studies found a positive relationship between wearing respiratory face masks and TB prevention. The first study was a randomized control trial from Hanoi, Vietnam, which examined the efficacy of medical and cloth masks and found that cloth masks resulted in significantly higher rates of infection than medical masks[35]. Laboratory examinations showed higher penetration of particles through the cloth masks (97%) compared with the medical masks (44%). Further, the efficacy of medical masks in this study translates to 92% protection against respiratory infections, suggesting a reduced risk of infection with medical masks. Consequently, cloth masks are not recommended for health workers, particularly in high-risk settings[35]. A recent randomization trial showed that cloth masks were inferior to medical masks and really exposed the wearer to the risk of nosocomial infection[36].

The second study measured the efficacy of surgical face masks when worn by patients with MDR TB[33]. Over 3 months, 17 patients with pulmonary MDR TB occupied an MDR TB ward in South Africa wore face masks on alternate days. Ward air was exhausted to two identical chambers, each accommodating 90 pathogen-free guinea pigs that breathed ward air either when patients wore surgical masks (intervention group) or when patients did not wear masks (control group). The results showed that 90 controlled guinea pigs contracted TB, compared with 36 of 90 intervention guinea pigs, demonstrating a 56% reduced risk of TB transmission when patients used masks[33]. This study demonstrates that the use of face masks on infectious TB patients can significantly reduce TB transmission and offer protective measures against TB infection.

Combined TB infection control measures

Two of the 15 papers in this review reported on the implementation of a combination of administrative, environmental and respiratory control measures[20,21]. The two papers from South Africa and Vietnam conducted in public hospitals reported on the implementation of strategies from all three categories and found that personal protective equipment (PPE), N95 respirators and employment of a TBIC focal person were highly effective in reducing TB transmission. The study that examined the effect of N95 respirators used for health personnel employed in a microbiology department and MDR TB ward found a significant reduction in TB notifications[21]. For instance, 5-year TB notification rates decrease with the provision of N95 respirators (354/100 000 HCW-years, 95% confidence interval (CI) 277–445) compared with those without N95 respirators (448/100 000 HCW-years, 95%CI 180–921)[20]. Additionally, the appointment of a TB focal person was associated with adequate reporting of active TB cases among HCWs. TB notification rates were lower in health facilities with no TBIC focal person compared with facilities with a TBIC focal person (Kruskal-Wallis rank–sum test p-values of p=0.08 for 2009–2011 and p=0.04 for 2012–2013)[20]. Furthermore, health facilities with an infection control officer were 7.6 times more likely to report any TB cases than facilities that had no infection control person[20]. This suggests that the probability of being infected with TB decreases as infection control measures increase.

Barriers and facilitators associated with implementation of TB infection control measures

This review found several barriers that impeded and/or facilitators that mediated the effectiveness of infection control measures at resource-limited healthcare settings. Administrative controls allow prompt identification, social isolation and diagnosis, which decreases the infection of air due to TB[2]. The lack of patient education and unsupportive workplace culture have negatively affected the implementation of these administrative control measures[20]. Further, the availability and appropriate use of PPE protect HCWs from contracting TB. However, inadequate supply of particulate respirators has affected the effective implementation of respiratory control measures[20], while insufficient isolation facilities and physical infrastructure limitations have obstructed the effective implementation of environmental control practices at health facilities[20,27,29]. The finding that these barriers may impinge on the implementation of TBIC measures is supported by earlier studies conducted in China[37] and Uganda[38].

Facilitators that were reported to strengthen the implementation of TBIC measures pointed towards the establishment of a strong healthcare system for the successful implementation of health policies. Triaging patients with suspected TB, maintenance and refurbishment of health infrastructure were identified as facilitators to administrative control[20]. Additionally, appropriate use of PPE, training HCWs on the correct use of PPE, positive influence of infection control champions (eg cough officers) at the healthcare settings and continuous HCW educational training on prevention strategies were reported as facilitators to implementation of TBIC measures at healthcare facilities[22,27,29]. Generally, strengthening the capacity of the healthcare system at the grassroots level through health workers' knowledge and education in the provision of healthcare services is also reported by Alotaibi and colleagues[39] in Saudi Arabia.

Discussion

The conclusions were drawn from the diverse study designs found in this research. Our review found consistent evidence of the benefits of implementing WHO-supported strategies on TBIC measures over the decades in reducing TB transmission among HCWs, patients and the community in LMICs. This discussion is structured around the three recognized categories of intervention for TBIC (administrative, environmental and respiratory controls) and highlights the strategies that have been evidenced as most effective for TBIC in healthcare facilities in LMICs.

Administrative controls are regarded by WHO as the first and most important level of the TBIC hierarchy[2]. These are management strategies that are meant to decrease the threat of exposure to people with infectious TB[40]. This systematic review identified cough officer screening systems, rapid diagnosis and treatment, isolation and triaging of cough patients, tuberculin skin testing and active screening as effective administrative control measures. Collectively, these control measures are found to effectively reduce TB transmission among HCWs and patients. However, of particular note was the reported success of cough officer interventions introduced in a hospital[29]. This intervention represents a relatively low-cost initiative that mobilizes a designated health worker(s) within the organization to take action[29]. By designating a nursing staff member from the general ward as a cough officer, the individual takes responsibility to prioritize action when necessary. All cough officers undergo training on infectious disease control, questioning technique, recording cough conditions and entering data into the computerized cough officer screening system. This positioning has also been effectively used to assist in the control of drug-susceptible and drug-resistant TB in KwaZulu-Natal Province, South Africa[41]. At a conceptual level, the cough officer intervention aligns with the strategy of active case finding[42]. This involves the early detection of active TB among individuals who present to healthcare services with symptoms indicative of TB. Early diagnosis and effective treatment of TB cases are crucial to not only reduce diseases and deaths but also decrease TB transmission within the community[42,43]. Hence, the cough officer screening system was introduced within a hospital to identify patients with pulmonary TB early and to reduce its transmission within the hospital to enhance passive case finding[29]. This measure is cost effective and can be easily applied in resource-constrained healthcare institutions in LMICs.

Triaging (prioritization of patients who have a cough for more than 2 weeks) and separation of presumptive TB patients from other patients in health settings were identified as important administrative control measures. While agreeing that these measures are based on scientifically proven strategies, the concern is being able to translate such strategies into practice in low-income, high TB burden countries where health facilities are often small and overcrowded with inadequate space for triage and isolation[44]. Future TBIC guidelines could consider an alternative control measure to prevent TB transmission in resource-poor settings to address implementation gaps. To address this implementation gap, a recent study suggests that health facilities should consider the verandas and corridors as isolation space[36]. A similar arrangement was formalized in Malawi by arranging isolation areas outdoors when indoor waiting areas were overcrowded[45]. If the healthcare facilities use verandas and corridors as isolation space to manage overcrowding, then patients remain at the health facility and are given proper TB treatment. Therefore, TB transmission among the HCWs and community is prevented.

Environmental control measures decrease the concentration of airborne infectious bacteria in the air[46]. Among environmental controls, the introduction of ventilation systems remains a priority because ventilation decreases the number of infectious bacteria in the air[46]. This review found keeping doors and windows open and making minor changes to existing waiting and consultation rooms in hospital settings have significantly improved ventilation systems[26,30]. An experimental study in Peru showed that natural ventilation generated more than 17–40 air circulations per hour, while well-established mechanical ventilation in isolation rooms generated 12 air circulations per hour[26,46] Further, buildings with large windows and higher ceilings had higher ventilation compared to small windows and low ceilings[26]. This arrangement does not require increased resources and can be easily implemented in resource-constrained healthcare facilities. While natural ventilation is cost-effective its acceptance depends on the local climate and may not be appropriate due to cold climate, mosquitoes and security reasons[46]. However, when used alone, increasing ventilation is not enough to protect individuals from exposure to the pathogens that cause TB. WHO stressed that natural ventilation should be used along with other recommended practices such as physical distancing, and avoidance of crowded indoor spaces, as well as wearing masks and hand-washing[40].

Another intervention study from Lima, Peru measured the impact of minor modifications in waiting and consultation rooms and air circulation in a hospital[24]. The minor modifications included repair and construction of new windows in the sidewall and construction of a separate outdoor waiting room, particularly for respiratory outpatients in waiting and consultation rooms[24]. After the interventions, there was a significant improvement in room ventilation in the four waiting rooms, thus preventing TB transmission. As a medium to long-term strategy, new or renovated facilities should make appropriate ventilation a high priority[47].

Respiratory protection control, the third level of the hierarchy, is the use of respiratory protection design to reduce the risk of exposure to active TB for health personnel in high-risk settings[29]. An experimental study showed that patients who had face masks were protected from contracting TB compared with patients who had no face mask[33]. This study highlighted the importance of using face masks, particularly when meeting infectious patients. A meta-analysis conducted in Canada affirms results presented in this review regarding the usefulness of wearing face masks[48]. Despite its significance, face masks were not always applied despite availability at the health facility[36]. A recent study shows that although adequate masks were provided at the health facility, they were not worn by HCWs in some healthcare settings despite increasing exposure to infectious patients in Nigeria[49]. This trend may increase opportunities for TB transmission and other respiratory infections in healthcare settings, suggesting that the adoption of TBIC measures is required in healthcare facilities delivering TB healthcare services in LMICs. Of concern, cloth masks are commonly used in LMICs to prevent the spread of TB from patients. However, a recent randomized controlled trial showed that cloth masks are inferior to medical masks and are not recommended for use, particularly in high-risk settings[36]. While there are limited studies, cloth masks should be discouraged to protect the wearers from new infections.

Strengths and limitations

The major strength of this systematic review is that it synthesized the current evidence on the implementation of TB control strategies at the health facility level in low-income, high TB burden countries. Despite this key strength, there are several limitations of this research. The primary limitation represents the apparent lack of high-quality published papers using randomized control trials that measured the effectiveness of effective TBIC interventions to help support best infection control practices in LMICs. Another limitation of the review may be in the language bias, as only publications in English were included, which excluded pertinent studies in other local languages. Despite our collaborative efforts to retrieve all relevant articles, it is likely that not all relevant studies are included in this review. Some valuable information could be missing, especially conference papers and poster presentations. Due to the limited number of studies in this review, generalizability is problematic. Finally, there may be some resource-poor health facilities in high-income countries, but these were beyond the scope of our study.

Implications for policy and practice in resource-limited primary healthcare settings

The high burden of active TB identified in LMICs emphasizes the need for an effective public health strategy to improve this complex situation. The WHO recommends that TBIC measures identified in this review can reduce TB transmission in high TB burden locations[2]. One outstanding example would be the implementation of the cough officer screening system in hospitals[29]. This strategy maintains an active screening system in hospital inpatients to improve TB detection rate among the inpatients. This system has improved the detection of TB by reducing the delay from infection to diagnosis, therefore preventing TB transmission among other patients[29]. A critical aspect of effective implementation of the cough officer screening system would be the need to continue training for nurses on TB diagnosis and infection control guidelines.

Another example of TBIC measures is the use of natural ventilation systems like opening doors and windows in TB wards in healthcare facilities[24]. This approach can supplement the administrative control measures to reduce exposure to TB transmission by improving air circulation as demonstrated in several studies[24,26,32]. An important aspect of the implementation of this strategy is training for health workers on good ventilation practices. Maintenance and refurbishment of health infrastructures such as the patient consultation rooms and inpatient wards would be equally crucial, particularly in the context of overcrowded settings in health centers, although these actions would be more costly and need more medium-term strategies and planning.

The use of respiratory masks has the additional benefit of contributing to TB reduction. In particular, this strategy reduces the risk of exposure to *Mycobacterium* TB for health workers in specific areas and circumstances[2]. An essential component of the use of respiratory masks would be the need for health worker training on the proper use of PPE and a steady supply of respirators. It is therefore equally important to consider whether masks are economically and logistically feasible interventions in settings with a high burden of TB.

As a short-term strategy, effective implementation of TBIC measures in resource-poor healthcare settings would require the improvement of the current health facilities, particularly the TB wards, outpatients waiting and consultation rooms. In the long term, investment in healthcare systems such as infrastructure designed for infection control, medical supplies, health financing, healthcare workforce, and governance and leadership will be important for the effective implementation of TBIC measures.

Conclusion

This review demonstrated that the implementation of TBIC measures including administrative, environmental and respiratory control measures have prevented TB transmission in resource-limited settings. Simple and low-cost interventions such as a cough officer screening system, patient isolation and triaging, minor modifications to infrastructure, opening windows and doors and HCWs' utilization of respiratory masks are effective. Collectively, these measures are highly effective in reducing TB transmission and can be easily adopted in health facilities with limited resources accompanied by the right supportive mechanisms such as patient education, supportive workplace culture, availability of PPE, adequate supply of respirators and adequate isolation facilities. Health institutions in locations where TB remains high in communities must invest in improved implementation of these measures to protect their HCWs and to reduce the community burden of TB disease. While TBIC strategies have the potential to reduce active TB transmission, if they are not correctly implemented in resource-constrained settings it will be difficult to achieve the global aim of the WHO End TB Strategy.

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APPENDIX I:

Appendix I: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE: **What tuberculosis infection control measures are effective in resource-constrained primary health care facilities? A systematic review of the literature**			
Title	1	Narrative systemic review	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. Tuberculosis (TB) remains a major public health challenge, killing millions of people, despite the availability of preventive TB medications. The purpose of this review was to examine the current evidence of tuberculosis infection control (TBIC) measures in reducing TB transmission and explore barriers and enablers of TBIC measures in resource-constrained primary healthcare settings. The PRISMA framework was adopted to identify studies that report on the evidence and barriers and facilitators of administrative, environmental, and respiratory control measures in healthcare settings in low-and-middle-income countries. Five databases, including ProQuest, Scopus, ScienceDirect, Embase, and PubMed, were searched to extract relevant data sources published in English. Studies that were not relevant to the topic were excluded. Fifteen studies were identified that demonstrated that TBIC measures can effectively reduce TB transmission if applied correctly. Our review provides low to moderate evidence of TBIC measures in reducing TB transmission in resource-constrained primary healthcare settings. Healthcare management should address the areas of concern, particularly in rural health settings, to improve the implementation of TBIC measures in primary healthcare facilities in LMICs. The study protocol was registered with PROSPERO International Prospective Register of Systematic Reviews: Registration number: CRD42020203468. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines was used to develop the method for this systematic literature review.	3-4
INTRODUCTION			
Rationale	3	**Describe the rationale for the review in the context of what is already known.** TB is a serious public health problem worldwide. The disease is associated with high morbidity and mortality. In 2020, 10.6 million new TB cases were reported and generated 4.6 million deaths each year. More than 80% of these infections and deaths occur in low- and middle-income countries. If the TB pandemic is to be eradicated, more efforts need to be given to these countries with the high burden of TB. Although many TB cases are reported outside of the health facility, infections in healthcare institutions present a considerable challenge to the global TB eradication effort. Thus, TB infection prevention and control measures have emerged as potential preventive public health interventions to prevent TB transmission in healthcare settings among health workers, patients, and those seeking healthcare at health facilities. The World Health Organization (WHO) recommended three TBIC measures, including administrative, environmental, and respiratory control measures, to be implemented in all healthcare institutions that manage TB cases. It is well known that these measures have been effective at reducing and preventing TB transmission in healthcare settings and spreading into the community. This review was conducted to inform healthcare managers, policymakers, and policy implementers of the current evidence of TBIC interventions in reducing TB incidence in healthcare settings. The results may be useful for TB policy development, TB program planning, and management and inform healthcare practitioners at the facility level who are responsible for the implementation of TBIC guidelines.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). This review aims to assess what TB infection control measures are effective in resource-constrain healthcare institutions. The specific objectives are: 1. To examine the current evidence of tuberculosis infection control (TBIC) measures in reducing TB transmission and 2. To explore the barriers and enablers of TBIC measures in resource-constrained primary healthcare settings.	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information, including registration number. The study protocol was registered with PROSPERO International Prospective Register of Systematic Reviews: Registration number: CRD42020203468. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines was used to develop the method for this systematic literature review.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. The purpose of this review is to evaluate the evidence of TBIC strategies for reducing TB transmission and factors affecting its implementation at resource-poor healthcare institutions. The term "resource-poor health institution" refers to "a locale where the capability to provide care for life-threatening illness is limited to basic critical care resources, including oxygen and trained staff. It may be stratified by categories: No resources, limited resources, and limited resources with possible referral to higher care capability. Health settings in low- and middle-income countries are commonly characterized by limited staffing, poor infrastructures, shortages of medical supplies and drugs, and underfunding. Therefore, resource-poor settings in this review refer to settings in low and middle-income countries based on the World Bank data. The terms low-and middle-income countries and or resource-constrain health settings or resource-poor healthcare settings, or resource-limited healthcare settings are used interchangeably throughout this review. Furthermore, we have not included any resource-constrain setting that might exist in high-income countries. Our search strategy was limited to low-and middle-income countries. This review includes peer-reviewed research published in English, conducted in resource-poor healthcare settings, and reported data on TBIC measures. For this review, peer-reviewed articles that assessed the effectiveness of some form of TBIC at primary health facilities in LMICs were selected. The population, intervention, comparison, outcome, study design, and setting (PICOS) framework was used to determine the eligibility criteria and screening protocol.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. This review used peer-reviewed sources through five online databases, including ProQuest Central, ScienceDirect, Scopus, PubMed, and Embase. The search was conducted from November 2020 to July 2021.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. A systematic search was conducted using keywords with Boolean operators and terms specific to the database vocabulary, including tuberculosis OR TB AND infection control OR disinfect* OR quarantine* OR infection prevention OR prevent* infection AND resource-poor countr* OR developing countr* OR low-income countr* OR lower middle-income countr* AND effectiveness OR effect OR impact AND health care cent* OR health facilities OR health settings OR hospitals. Since TB infection control guidelines were first introduced in 1999, articles published after 2000 were retrieved for analysis. Although there might be some potential publications before 1999, an article published after 1999 was considered appropriate as the cut-off point for examples of contemporary publications on TB infection prevention and control measures. It has been over two decades since the publication of the WHO guideline in 1999, so we justify that there is ample time to capture potentially relevant work.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used for the study selection process. PRISMA framework includes four stages: identification, screening, eligibility, and inclusion. After eliminating duplicates, the first author (GM) screened papers by reviewing the titles and abstracts against the review topic and eligibility criteria. To determine	7-8

		eligibility, the first author (GM) undertook a full paper review with two reviewers (SR and NH) confirming selections. The consensus was reached for the final included list of 15 papers through group deliberation.	
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. The first author (GM) independently extracted data from the selected papers that matched the study objective using a predetermined data extraction form sourced from The Cochrane Collaboration that was checked by two reviewers (SR & NH). The key data extracted include year, author, type of health facility, low and middle-income countries, interventions (such as administrative control, environmental control, respiratory controls), study design, and main outcomes.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **Population**: health workers and families exposed to TB in healthcare settings **Interventions**: Papers that study TBIC measures in healthcare settings, including administrative, environmental, and respiratory control measures **Comparison:** papers that compare the impact or effectiveness of TBIC in reducing TB **Outcome**: quantified reduction/change in risk of TB transmission **Settings**: healthcare settings in resource-poor countries/locations	8
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. The authors conducted a quality assessment during the data extraction process. Each study underwent quality assessment using the National Institute of Health (NIH) study assessment tool. The NIH represents a tool that assesses scientific rigor and is frequently used by researchers to assess studies in public health interventions. The tool includes ten criteria that evaluate the relevance to practice and the scientific validity of each study. Employing this tool, three independent reviewers assessed the quality of the studies and rated each article as good, fair, or poor. All 15 studies in the final list were deemed eligible for the comprehensive review and subject to data extraction.	10
RESULTS			
Study selection	13	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. A total of 10,417 studies were retrieved from the five online databases. Of those studies, 222 studies were selected for full-text review, 15 of which met the eligibility criteria and were included for data extraction. More than half (5375) of the studies were excluded because they were either not relevant to the topic, were not focused on TBIC measures, or were not original research papers.	17
Study characteristics	14	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. The selected studies were conducted in both private and state-owned hospitals and TB primary healthcare settings across four WHO regional groupings including the Regions of the Americas, South African Region, South-East Asia Region, and Regions of the Mediterranean. None of the studies were conducted in rural health services. Most were conducted in the Regions of the Americas. The 15 studies comprised four cross-sectional studies (16–18), four intervention studies (19–22), one experimental study (23), one prospective study (24), two retrospective studies(22,25), two observational studies(26,27), and one randomised control trial study(28). These studies have demonstrated consistent but low to moderate evidence of TBIC measures in reducing TB transmission. The major themes have been organized according to WHO guidelines for TBIC in healthcare settings including (i) administrative control; (ii) environmental control; and (iii) respiratory control.	17
DISCUSSION			
Summary of evidence	15	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). The current study found consistent but low to moderate evidence of the WHO-supported strategies on TBIC measures over the decades in reducing TB transmission among HCWs, patients, and the community in LMICs. This discussion is structured around the three recognized categories of intervention for TBIC: administrative, environmental, and respiratory controls and highlights the strategies that have been evidenced as most effective for TBIC in healthcare facilities in LMICs. The findings provide useful evidence that can be useful for policymakers, healthcare managers, TB program managers, and clinicians in resource-constraint primary healthcare settings.	22
Limitation	16	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). The primary limitation represents the apparent lack of high-quality published papers using randomized control trials (RCT) that measured the effectiveness of effective TBIC interventions to help support best IC practices in LMICs. Another limitation of the review may be in the language bias, as only publications in English were included, that excluded pertinent studies in other local languages. Despite our collaborative efforts to retrieve all relevant articles, there is a likely possibility that not all relevant studies are included in this review. Some valuable information could be missing, especially conference papers and poster presentations. Finally, there may be some resource-poor health facilities in high-income countries. However, we have not included any resource-constraint setting that might exist in high-income countries. Thus, our search strategy was limited to low-and middle-income countries. Some potential information may be missing from these settings.	25
Conclusions	17	Provide a general interpretation of the results in the context of other evidence, and implications for future research. This review demonstrated that the implementation of TBIC measures including administrative, environmental, and respiratory control measures have prevented TB transmission in resource-limited settings. Simple and low-cost interventions such as cough officer screening system, patient isolation and triaging, minor modifications to infrastructure, opening windows and doors, and HCWs' utilization of respiratory masks are effective. Collectively, these measures are highly effective in reducing TB transmission and can be easily adopted in health facilities with limited resources accompanied by the right supportive mechanisms such as patient education, supportive workplace culture, availability of PPE, adequate supply of respirators, and adequate isolation facilities. Health institutions in locations where TB remains high in communities must invest in improved implementation of these measures to protect their HCWs and to reduce the community burden of TB disease. While TBIC strategies have the potential to reduce active TB transmission, if they are not correctly implemented in resource-constrained settings, it will be difficult to achieve the global aim of the WHO End TB Strategy	26-27
FUNDING			
Funding	18	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. The principal/corresponding author, Gigil Marme acknowledge the Griffith University, Graduate Research School for the PhD scholarship.	1