Clinical Infectious Diseases
MAJOR ARTICLE

The Effectiveness of Individual and Environmental Infection Control Measures in Reducing the Transmission of *Mycobacterium tuberculosis*: A Systematic Review

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(See the Editorial Commentary by Griffith and Cegielski on pages 27–9 and the Review Article by Karat et al on pages 155–72.)

Background. Transmission of *Mycobacterium tuberculosis* in healthcare settings is a preventable driver of the global tuberculosis epidemic. We aimed to assess the evidence for infection control interventions, including cough etiquette, engineering and personal respiratory protection measures, to prevent transmission of *M. tuberculosis* in healthcare settings.

Methods. Three independent systematic reviews were performed using 6 databases and clinical trials websites. Randomized trials, cohort studies, before-after studies, and case-control studies were included. Searches were performed for controlled studies evaluating respiratory hygiene, engineering, and personal respiratory protection measures. Outcome measures included the incidence of tuberculosis infection and disease. Studies involving transmission to either humans or animals were included.

Results. Evaluation of respiratory hygiene and cough etiquette interventions identified 4 human studies, with 22 855 participants, and 1 guinea pig study. Studies in humans evaluated the effects of multiple concurrent interventions. Patient use of surgical masks reduced infection by 14.8%, and tuberculosis disease was reduced by between 0.5% and 28.9%. Engineering and environmental interventions were evaluated in 10 studies of humans, including 31 776 human participants, and 2 guinea pig studies. Mechanical ventilation was associated with between 2.9% and 14% less infection. Nine studies of personal respiratory protection were included, including 33 913 participants. Infection was reduced by between 0% and 14.8% in studies where particulate respirators were used. The quality of included studies was assessed as low.

Conclusions. Respiratory hygiene, engineering, and environmental infection controls and personal respiratory protection interventions were associated with reduced transmission of *M. tuberculosis* and reduced tuberculosis disease in healthcare settings.

Keyword. Tuberculosis.

Transmission of *Mycobacterium tuberculosis* in healthcare settings is an important driver of the global tuberculosis epidemic, including the dissemination of drug-resistant disease [1, 2]. People attending hospitals and other congregate settings face an elevated risk of infection [3], due to occupational exposure to airborne droplets produced by patients with undiagnosed or partially treated pulmonary tuberculosis [4]. Institutional strategies to protect people attending these facilities from becoming infected remain a top priority for tuberculosis control programs in both high- and low-prevalence settings [5]. The standard framework for global infection prevention and control (IPC) policies in institutions comprises 3 complementary categories of interventions: administrative measures, environmental controls, and the use of personal protective equipment [6]. These strategies seek to detect and isolate cases promptly, while minimizing the probability that uninfected individuals will be exposed and infected.

Limited evidence has been available to inform national and international guidelines. Existing global recommendations predominantly rely upon expert opinion and observational studies, most of which have methodological limitations [6]. This systematic review was performed to inform revised World Health Organization (WHO) guidelines on tuberculosis infection prevention and control [7]. We aimed to evaluate the evidence for the effectiveness of (*a*) policies to promote cough etiquette and respiratory hygiene; (*b*) environmental and engineering controls; and (*c*) the use of personal protective equipment (such as respirators), in reducing transmission of tuberculosis in healthcare and other congregate settings. This review complements a companion review of administrative control measures to reduce tuberculosis transmission [8].

METHODS

We performed 3 separate systematic reviews of the evidence for cough etiquette and respiratory hygiene, environmental measures, personal respiratory equipment, in accordance with

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PRISMA guidelines [9]. A review protocol was developed and approved by the WHO secretariat.

Search Strategy and Selection Criteria

Studies were eligible for inclusion if they measured the incidence of tuberculosis infection or disease among healthcare workers and other persons attending healthcare, or people attending nonhealthcare congregate settings (such as prisons or nursing homes). We included studies where animals were exposed to exhaust air containing airborne droplets from patients with tuberculosis.

Definitions

Respiratory hygiene and cough etiquette interventions were defined as the practice of covering the mouth and nose during breathing, coughing, or sneezing. Such interventions included wearing a surgical mask, cloth mask, covering the mouth with tissues, a sleeve, flexed elbow, or hand (followed by hand hygiene). Environmental control interventions were defined as the introduction of methods of ventilation (including natural, mechanical, mixed-mode, and/or recirculated air filtration), upper room ultraviolet germicidal irradiation (UVGI), or room air cleaner appliances. Personal respiratory protection devices included the use of particulate respirators (N95 respirators or equivalent, introduced with or without a "fit test") or implementation of a respiratory protection program. Comparator groups were populations in which these interventions were not implemented.

Outcome Measures

Outcomes included the incidence or prevalence of latent tuberculosis infection (LTBI) or tuberculosis disease. Detailed definitions of interventions and outcomes are included in the "WHO guidelines on tuberculosis infection prevention and control, 2019 update" [7].

Eligibility of Included Studies

Included study designs were randomized controlled trials, prospective cohort studies, retrospective cohort studies (including before-and-after studies), or case-control studies. Studies were excluded if they did not report the outcomes of interest, lacked a suitable control or comparator group, if outcomes were measured in <10 subjects, or if the study reported modeling without any primary clinical data.

Search Strategy

Data sources included electronic health care databases and evidence-based reviews. Six healthcare databases were searched, including Medline, EMBASE, Web of Science, PubMed, CENTRAL, LILACS, and clinical trials registries. We also searched the Cochrane Database of Systematic Reviews and hand searched the conference abstracts for the annual conference of the International Union of Tuberculosis and Lung Disease and OpenSIGLE. Search strategies were developed in consultation with a librarian with experience in conducting systematic reviews. Detailed search terms are presented in the Supplementary Web Appendix (Tables S1, S2 and S3). To identify studies in which outcomes were measured in animals, additional search terms were added to the overall search at the stage of title/abstract review ("mice," "rats," "pigs, guinea," "animals," "nonhuman species," or "rabbits"). No publication date restrictions or language restrictions were applied. Searches were conducted on 6 March 2018 (cough etiquette), 6 October 2017 (environmental controls), and 1 October 2017 (personal respiratory equipment).

In the first stage of study selection, titles and abstracts were screened independently by 2 reviewers (2 of L. R., V. C., and J. H.), for suitability for subsequent full text review. In the second stage of study selection, full-text papers identified from the first stage were reviewed independently by 2 reviewers (2 of L. R., V. C., and J. H.). An additional search of reference lists of included articles was also conducted to identify further eligible articles.

Data Extraction and Analysis

Two reviewers extracted data from included papers into a standardized data extraction form. Discrepancies in study selection or data extraction between reviewers were resolved by consensus.

Variables extracted from included studies included country, setting, participant characteristics, intervention details, comparator details and methods of measuring outcomes, and the number of participants with each outcome.

Outcomes in intervention and control groups were presented as proportions, with the effects of interventions presented as both absolute risk differences and relative risk difference. Results from animal and human studies were presented separately.

Outcomes were stratified by high or low-prevalence setting for tuberculosis [10]. We intended to stratify results according to human immunodeficiency virus (HIV) status, inpatient versus outpatient healthcare setting, and multidrug resistant tuberculosis (MDR-TB) exposure. Meta-analyses were to be performed if 2 or more studies reported similar interventions and outcomes.

To facilitate comparisons between studies in animals and humans, where outcomes were measured in animals, we applied the relative risk of the interventions to a typical control group of healthcare workers with an average risk of infection. This group was assigned an incidence equal to the mean incidence in 9 human studies included in the 3 systematic reviews performed for this study [11–19]. This approach was adopted because exposure in animal studies is calibrated by researchers, resulting in a higher absolute incidence of infection in the control group than is expected in human studies.

An assessment of the risk of bias of included was conducted according to the Cochrane Collaboration Tool for prospective cohort studies in humans and animals [5], and the Downs and Black tool for retrospective cohort studies [20].

Role of Funding Source

The systematic reviews were supported by WHO. The WHO secretariat developed the research questions and provided input into the study protocol. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Respiratory Hygiene and Cough Etiquette Interventions

The review of respiratory hygiene and cough etiquette interventions yielded 3293 unique papers, of which 5 were selected for inclusion (Figure 1). Table 1 shows the characteristics of studies in all 3 reviews, stratified by World Bank income classification and study design. The outcomes of studies evaluating the effect of respiratory hygiene and cough etiquette are summarized in Table 2. We identified 4 human studies, conducted among 22 855 participants in healthcare settings. Use of masks by patients resulted in an absolute reduction in tuberculin skin test (TST) conversion of between 4.1 and 12.4 conversions per 1000 person-months in Brazilian hospitals [15]; a reduction in TB disease by 0.5% in Malawian hospitals [21]; a reduction in TST conversion by 14.8% and a reduction in TB disease of 0.29 cases per 100 person-years in a Thai hospital [14], and a reduction in TB disease by 28.9% in a ward that treated people living with HIV in Italy [22]. No studies were identified that had been performed in other congregate settings.

One study measured outcomes in animals, with 180 guinea pigs (90 per group) exposed to exhaled air from patients with MDR-TB that had been randomized either to surgical mask use or no mask use. The relative risk of TST conversion among guinea pigs in the intervention group was 0.52, compared to the control group (ie, a 48% reduction in relative risk). Extrapolating this to an average population of healthcare workers, as described above, we would expect the absolute incidence of infection to reduce from 6.5% to 3.4% (an absolute risk difference of −3.1%) [23].

Environmental Control Interventions in Humans

The search for environmental control interventions identified 5615 papers for title and abstract screening, of which 76 papers were eligible for full text review (Figure 2). Ten studies,

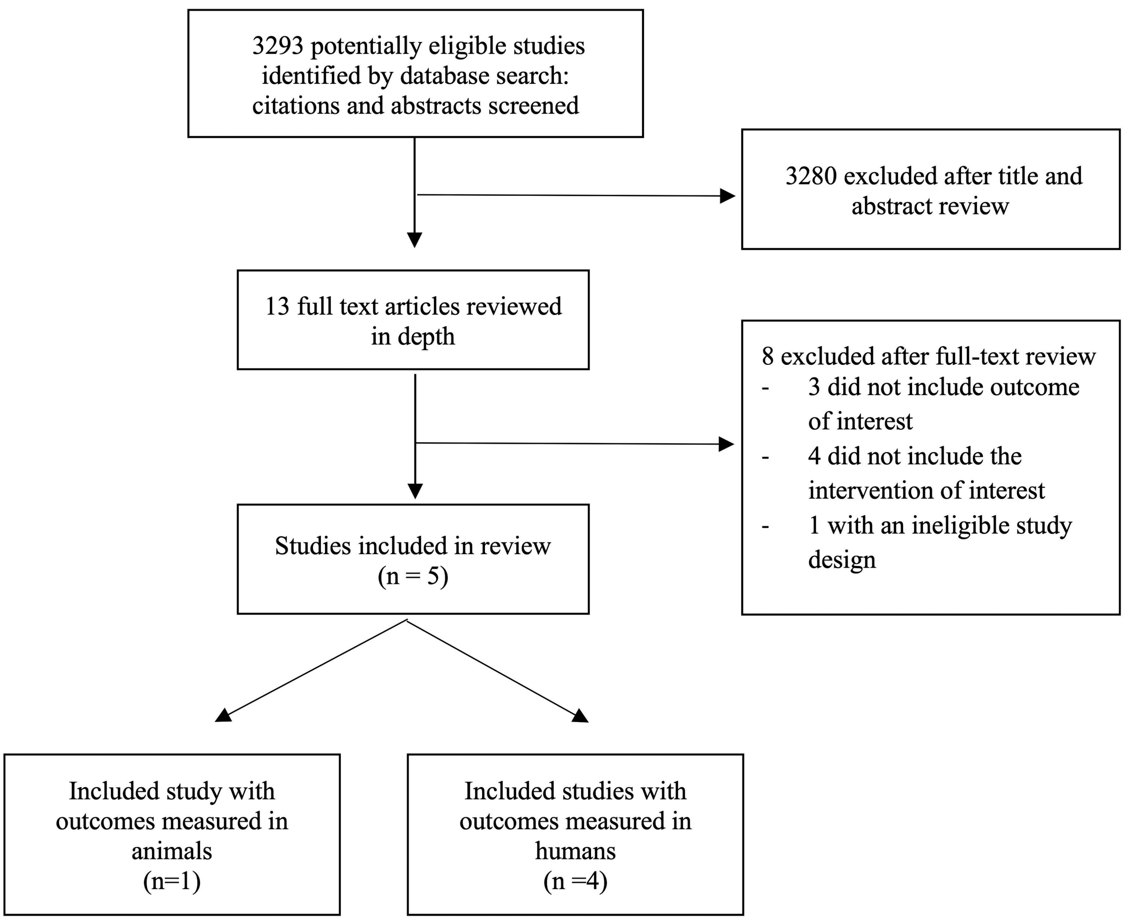

Figure 1. Study selection for respiratory hygiene and cough etiquette interventions to reduce the transmission of *Mycobacterium tuberculosis*.

Table 1. Summary of Characteristics of Included Studies

Characteristic	Number of Studies Conducted		
	Overall Studies n, (Total Participants)	In Low Prevalence Countries, n (%)	In High Prevalence Countries, n (%)
Respiratory hygiene and cough etiquette			
Study design			
Cross-sectional	0	0 (0)	0 (0)
Before/after	3	1 (33%)	2 (67)
Cohort	1	0 (0)	1 (100)
Animal study	1	0 (0)	1 (100)
Population studied			
HCWs	4	1 (25)	3 (75)
Animals	1	0 (0)	1 (100)
Interventions implemented			
Cough etiquette	1	0 (0)	1 (100)
TB patient mask use	5	1 (20)	4 (80)
Outcomes measured			
LTBI incidence	3	0 (0)	3 (100)
TB disease incidence	3	1 (33)	2 (67)
Environmental and engineering controls			
Study design			
Case-control	1	1 (100)	0 (0)
Cross-sectional	1	1 (100%)	0 (0)
Cohort	1	0 (0)	1 (100)
Before/after	7	6 (86)	1 (14)
Animal study	2	0 (0)	2 (100)
Population studied			
HCW	10	8 (80)	2 (20)
Animals	2	0 (0)	2 (100)
Interventions implemented			
Natural ventilation	1	0 (0)	1 (100)
Mechanical ventilation	8	7 (88)	1 (13)
Mixed-mode ventilation	2	1 (50)	1 (50)
UVGI	3	1 (33)	2 (33)
Outcomes measured			
LTBI incidence	12	8 (75)	4 (25)
TB disease incidence	2	0 (0)	2 (100)
Personal respiratory protection			
Study design			
Cohort	1	0 (0)	1 (100)
Before/after	8	6 (75)	2 (25)
Population studied			
HCW	9	6 (67)	3 (33)
Interventions implemented			
Particulate respirators	8	5 (63)	3 (38)
Moulded mask	1	1 (100)	0 (0)
Outcomes measured			
LTBI incidence	9	6 (67)	3 (33)
TB disease incidence	1	0 (0)	1 (100)

Abbreviations: HCW, healthcare worker; LTBI, latent tuberculosis infection; TB, tuberculosis; UVGI, ultraviolet germicidal irradiation.

including 31 776 participants, met the inclusion criteria (Table 3). Mechanical ventilation in combination with other interventions was associated with an increase in TST conversions in 2 before-and-after studies [15], and a decrease in TST conversions by between 2.9% and 14.8% in 7 before-and-after studies [11, 12, 14, 16, 18, 24, 25]. TST conversion was associated with a higher ventilation rate in a case-control study from Canadian tuberculosis laboratories [26].

Environmental Control Interventions in Animals

An additional 2 studies measured outcomes in a total of 791 guinea pigs exposed to exhaust air that had been treated with UVGI, taken from wards where patients had TB [28, 29]. Included studies of environmental control interventions are summarized in Table 2. UVGI treatment of ventilated air from patients with TB in a South African animal facility resulted in a relative risk of 0.28 (ie, a relative reduction in infection of 72%). When extrapolated to an average population of healthcare workers, this corresponds to a reduction in absolute risk from 6.5% to 1.8% (an absolute difference of –4.7%) [29]. The relative risk of infection following UGVI of exhaust air taken from an inpatient tuberculosis ward in Peru was 0.27 (ie, a relative reduction in infection of 73%), corresponding to an absolute reduction in infection among an average population of healthcare workers from 6.5% to 1.8% (an absolute difference of –4.7%) [28].

Personal Respiratory Protection Interventions

The review of personal respiratory protection interventions identified 8186 unique studies for title and abstract review (Figure 3). Among these, 9 studies were identified, including 33 913 participants. All studies were before-and-after studies. Most studies of personal respiratory equipment were performed in the United States, whereas others were performed in Thailand and Brazil [13–15]. These cohort studies evaluated composite infection control measures, comprising a combination of administrative interventions, respiratory protection, and environmental interventions. The characteristics of included studies of personal respiratory protection are shown in Table 4. The use of respirators was associated with an absolute reduction in TST conversion of between 0.4% and 11.5% [11–16, 18, 19]. No difference in infection was observed among staff using respirators in 1 before-and-after study performed in a hospital in the United States [17].

Meta-analyses could not be performed for any of the 3 reviews, given the heterogeneity of the interventions.

Assessment of Study Quality

An evaluation of study quality for each class of interventions is shown in the Supplementary Web Appendix: respiratory hygiene and cough etiquette (Supplementary Tables S4 and S5, for human and animal studies), engineering and environmental control

Table 2. Characteristics of Studies Evaluating the Effectiveness of Respiratory Hygiene and Cough Etiquette (n = 5)

First Author, Year Published	Setting	Study Type	Population	Intervention(s)		Comparator	No Intervention	Respiratory Hygiene Intervention	Outcome(s)
				Respiratory Hygiene	Other				
High burden settings									
Roth, 2005 [15]	Four hospitals in Brazil	Cohort study	HCWs	Surgical mask use by patients	Engineering controls (UVGI) in 1 hospital, administrative controls in 1 hospital. Respirators for HCWs	Hospitals without surgical mask use by patients	Hospital A: Conversions 7.4 / 1000-person months (n = 2349) Hospital B: Conversions 8.1 / 1000-person months (n = 3238)	Hospital C: Conversions 19.8 / 1000-person months (n = 1282) Hospital D: Conversions 12.2 / 1000-person months (n = 866)	Absolute reduction of TST conversions of 4.1 and 12.4 conversions per 1000-person months
Harries, 2002 [21]	40 district and mission hospitals in Malawi	Before and after	HCWs	Surgical masks warn by patients with TB	Introduction of hospital infection control guidelines, comprising 13 interventions	Hospitals before the introduction of guidelines	100/2697 (3.7%) developed TB	96/2979 (3.2%) developed TB	Absolute reduction in TB by 0.5%
Yanai 2003 [14]	One TB hospital in Thailand	Before and after	HCWs	Patients use surgical masks, training in cough etiquette	Administrative, personal respiratory protection	Prior to introduction of guidelines	13/77 (16.9%) TST conversions 30/4357 TB cases (0.7/100-person years)	2/96 TST conversions (2.1%) 19/4780 (0.4 TB cases /100-person years)	Absolute reduction in TST conversions by 14.8%; Absolute reduction in TB cases by 0.29 cases per 100 person-years
Low burden settings									
Moro, 2000 [22]	HIV ward in Italy	Before and after	Patients with HIV hospitalised in health facility	Surgical masks worn by patients with MDR-TB	Isolation of patients with respiratory disease or fever	Hospitals before infection control policies	26/90 (2455 patient-days) (28.9%) developed TB	0/44 (654 patient-days) developed MDR-TB	Absolute reduction in TB disease by 28.9%
Animal studies[a]									
Dharmadhikari, 2012 [23]	Airborne Infection Research Facility, South Africa	Cohort study	Guinea pigs exposed to 17 newly admitted patients with MDR-TB	Ear loop surgical masks worn by MDR-TB patients	None	No masks worn by patients	69/90 (76.6%; 95% CI 68–85%) guinea pigs TST positive	36/90 (40%; 95% CI 31–51%) guinea pigs TST positive	Extrapolated reduction of infection from 6.5% to 3.4% (an absolute reduction of 3.1%, corresponding to a relative risk of 0.52)[b]

Abbreviations: A, administrative controls; CE, cough etiquette and surgical masks; CI, confidence interval; E, engineering controls; HCW, health-care workers; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; MDR-TB, multidrug resistant tuberculosis; PRP, personal respiratory protection; TB, tuberculosis; TST, tuberculin skin test; UVGI, ultraviolet germicidal irradiation.

[a]Studies where outcomes were measured in animals exposed to ventilated air from wards where patients with MDR-TB were housed. Masks worn between 7am and 7pm excluding meals for 3 months on alternate days. Exhaust air expelled into intervention animal chamber on mask days and control chamber on nonmask days.

[b]Based upon applying the effect of the intervention to the incidence of infection in an average control population.

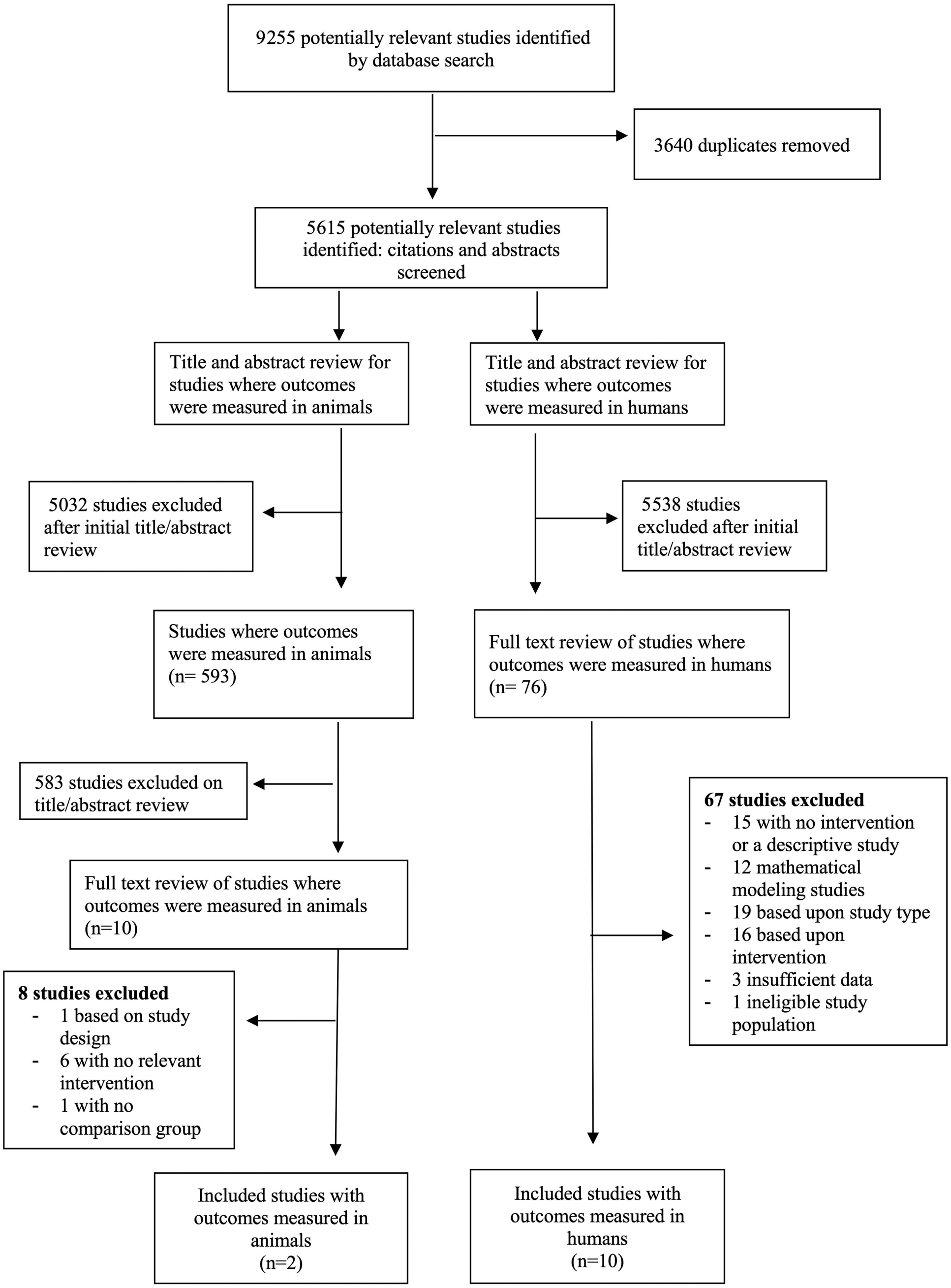

Figure 2. Study selection for environmental control interventions to reduce the transmission of *Mycobacterium tuberculosis*.

(Supplementary Tables S6 and S7, for human and animal studies), and personal respiratory protection (Supplementary Table S8). The PRISMA checklist is included in Supplementary Table S9.

DISCUSSION

We undertook 3 systematic reviews of respiratory hygiene and cough etiquette measures, environmental controls, and personal respiratory equipment interventions to reduce transmission of *M. tuberculosis* in healthcare settings. Most included studies demonstrated a reduction in infection and disease among healthcare workers. These findings were supported by studies in animals, with surgical mask use by patients and the introduction of UVGI resulting in resulted in a reduction in transmission. Together, these studies indicate that infection control measures in healthcare settings are likely to reduce transmission. Most included studies evaluated the effect of multiple concurrent interventions.

Our findings provide support for the expansion of existing infection control measures to reduce transmission of tuberculosis in healthcare settings [5, 6]. In most studies, the absolute reduction in risk of infection was modest, given the relatively

Table 3. Characteristics of Included Studies Evaluating the Effectiveness of Environmental Controls (n = 11)

				Intervention/s			Primary Findings			
First Author, Year Published	Setting	Study Design	Population/s	Environmental Controls	Other	Comparator	No Intervention	Respiratory Hygiene Intervention	Absolute Risk Difference	Other Details
High burden settings										
Roth, 2005 [15]	Four hospitals, Brazil	Cohort study	HCWs	Mechanical ventilation: negative pressure in patient rooms	Use of surgical masks by patients, respirators used by HCWs	Hospital where mechanical ventilation was not used	7.4 conversions / 1000person-years	8.1 per 1000person-years	0.7 / 1000person-years higher in intervention hospital	Comparison between hospital A (control) and hospital B (engineering intervention)
Yanai, 2003 [14]	TB hospital, Thailand	Before and after	HCWs	Mixed mode ventilation in isolation rooms, with local exhaust ventilation and maximum natural ventilation. UVGI installation on high-risk wards	One isolation room established in each ward. Safety cabinet introduced in tuberculosis laboratory	Prior to introduction of guidelines	13/77 (16.9%) TST conversions 30/4357 TB cases (0.7/100 person years)	2/96 TST conversions (2.1%) 19/4780 (0.4 TB cases /100 person years)	Reduction in TST conversions by 14.8%; Absolute reduction in TB cases by 0.29 cases per100 person yrs	
Low burden settings										
Blumberg, 1995 [16]	Tertiary hospital, USA	Before and after	HCWs	Mechanical ventilation: Negative pressure rooms introduced for patients	Administrative (patient isolation, infection control coordinator appointed), respiratory hygiene and HCW education, staff use of masks	Standard practice prior to intervention	118/3579 (3.3%) conversions	23/5153 (0.4%) conversions	Reduced TST conversions by 2.9% in intervention	
Wenger, 1995 [24]	HIV ward of urban hospital, USA	Before and after	HCWs	Mechanical ventilation: Negative pressure introduced to isolation rooms	Patient isolation, stricter isolation procedures, staff use of surgical masks and others	Standard practice prior to intervention	7/25 (28%) conversions	3/17 (18%) conversions	Reduction of 10% TST conversions after intervention	
Maloney, 1995 [12]	MDR-TB wards, USA	Before and after	HCWs	Mechanical ventilation: exhaust fans in isolation rooms	Improved isolation, routine smear testing to guide isolation, moulded surgical masks for health workers	Standard practice prior to intervention	15/90 (16.7%) conversions over 18 months	4/78 (5.1%) conversions over 18 months in intervention period	Reduced TST conversion by 11.5% after intervention	
Fella, 1995 [11]	Urban AIDS center and prison hospital, USA	Before and after	HCW	Mechanical ventilation: negative pressure UVGI installed	Administrative (early isolation), respirators for staff (initially particulate respirators, then mist fume respirators)	Fewer negative pressure rooms. Prior to UVGI installation	41/303 (13.5%) conversions	21/446 tests (4.7%) conversions	Reduced TST conversion by 8.8% after intervention	
Behrman, 1998 [25]	Emergency ward, USA	Before and after	HCWs	Mechanical ventilation: mixed mode ventilation	Ventilation in trauma area, laminar flow from registrars to patients	Standard practice prior to intervention	6/50 (12%)	0/64 (0%)	Reduced TST conversion by 12%	No change in TST conversion infection in other wards where the intervention was not introduced during the same period

Table 3. Continued

First Author, Year Published	Setting	Study Design	Population/s	Intervention/s: Environmental Controls	Intervention/s: Other	Comparator	Primary Findings: No Intervention	Primary Findings: Respiratory Hygiene Intervention	Primary Findings: Absolute Risk Difference	Primary Findings: Other Details
Menzies 2003 [26]	Laboratories, Canada	Case-control	HCWs in laboratories	Mechanical ventilation in laboratories		No ventilation in laboratories	N/A	N/A	N/A	Among conversions, mean ventilation was 16.7 (SD 2.4) ACH. Among non-conversions, mean ventilation was 32.5 (SD 22.7) ACH. $P < .001$
Muecke, 2006 [27]	University, Canada	Cross-sectional	Students	Mechanical ventilation in classrooms		Rooms without mechanical ventilation	75/297 (25%)	73/189 (39%)	Incidence of TST conversions increased by 14% in rooms with mechanical ventilation	
Welbel, 2009 [18]	Urban hospital, USA	Before and after	HCWs	Mechanical ventilation: Conversion of 36 isolation rooms to negative pressure rooms	Use of HEPA filters in the emergency department	Prior to introduction of mechanical ventilation	98/2221, (4.4%) conversions	6/2108 (0.28%) conversions	Reduced TST conversions by 4.1% in the intervention group	
Animal studies[a]										
Escombe, 2009 [28]	TB-HIV ward, Peru	Cohort study	Guinea pigs exposed to exhaust ward air	Ultraviolet germicidal irradiation of exhaust air from patient room; OR Negative air ionization turned-on in-patient room	Two interventions compared with the same control population	UVGI turned off / negative air ionization turned off	106/304 (35%) TST conversions 26/304 (8.6%) TST conversions	(a) UVGI intervention 29/307 (9.5%) TST conversion. 11/307 (3.6%) cases of TB (b) Air ionization intervention 43/303 (14%) TST conversions 13/303 (4.3%) with TB disease	(a) UVGI intervention TST conversion reduced by 25.5% TB reduced by 5%. (b) Air ionisation: TST conversion reduced by 20.7% TB disease reduced by 4.3%	When extrapolated to a human population, the intervention would be expected to reduce infection from 6.5% to 1.8% (an absolute reduction of 4.7%, relative risk of 0.27)
Mphaphlele, 2015 [29]	HIV ward, South Africa	Cohort study	Guinea pigs exposed to exhaust ward air	Ultraviolet germicidal irradiation of exhaust air from patient room		UVGI turned off	58/90 (64.4%) TST conversions	16/90 (18%) TST conversions overall	Reduction in infection by 46.7% (combined over 2 periods) Period 1: 0/90 (0%) (Reduction of 10%) Period 2: 16/90 (17.7%) (Reduction of 36.8%)	When extrapolated to a human population, the intervention would be expected to reduce infection from 6.5% to 1.8% (an absolute reduction of 4.7%, corresponding to a relative risk of 0.28)

Abbreviations: ACH, air changes per hour; HCW, health-care worker; HEPA, high efficiency particulate air; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; MDR-TB, multidrug resistant tuberculosis; SD, standard deviation; TB, tuberculosis; TST, tuberculin skin test; UVGI, ultraviolet germicidal irradiation.

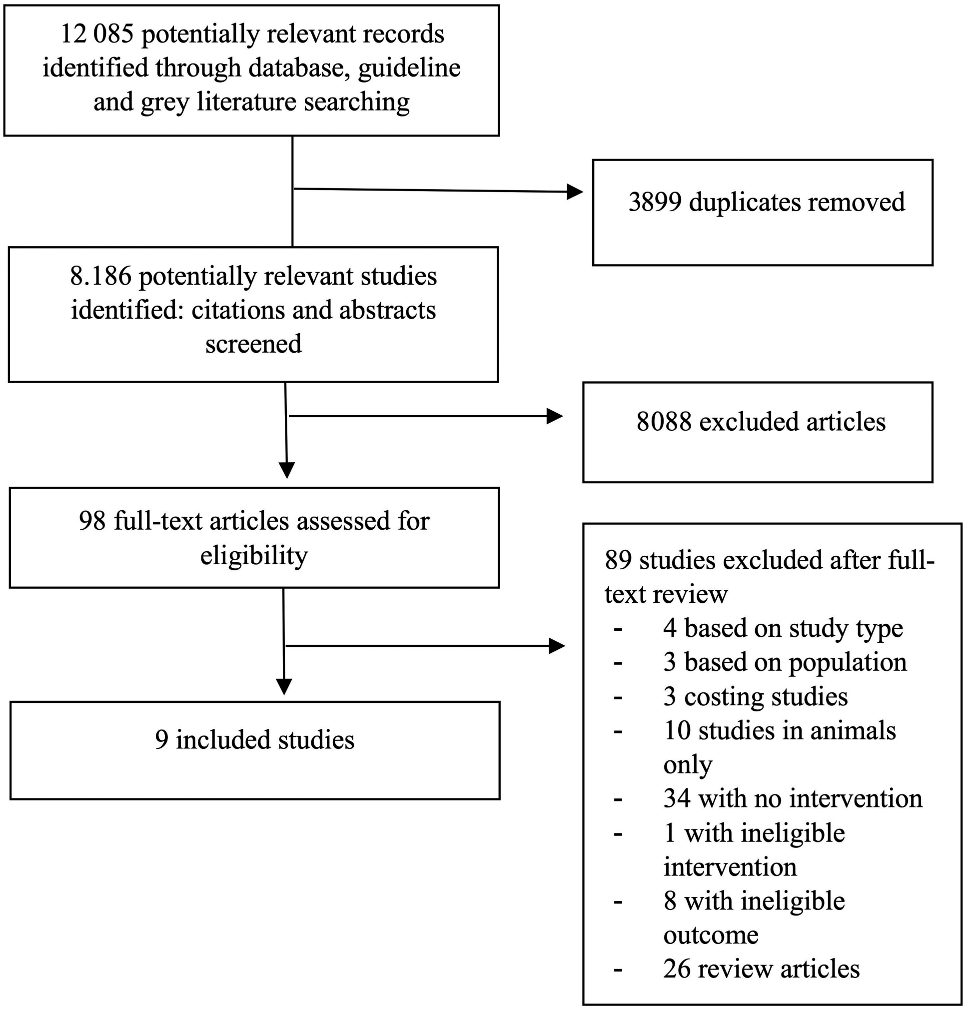

Figure 3. Study selection for personal respiratory protection interventions to reduce the transmission of *Mycobacterium tuberculosis*.

low annual risk of infection. However, over time, the cumulative benefits of sustained infection control measures for staff and patients is likely to be substantial. Such measures are likely to be particularly important for staff in regular contact with patients with undiagnosed, or recently diagnosed, tuberculosis. Prevention of disease in healthcare workers is an important part of workforce health and safety, staff retention, and infection control for other patients. Unrecognized disease among healthcare workers can also result in a substantial risk to the other patients that they treat, many of whom may be highly susceptible on account of comorbidities [30].

Many of the interventions that were evaluated can be delivered at low cost in resource-limited settings. Natural ventilation is a simple means of air disinfection, allowing contaminated exhaled particles to be removed from the healthcare setting, although this approach is less feasible where temperature extremes occur frequently [31]. Similarly, prompt use of surgical masks by patients with presumptive or confirmed active disease can reduce transmission at a relative low cost. In contrast, prevention of transmission can have considerable benefits to patients and health systems, where the treatment costs can be considerable. Further studies are required to evaluate the cost-effectiveness of infection control measures, in order to inform decision making by health system managers about locally appropriate measures.

This systematic review has a number of limitations. We did not identify studies evaluating infection prevention and control measures in other congregate settings outside of the healthcare systems. Further research is required to demonstrate the effect of infection control practices in such settings, including prisons and educational facilities. A second limitation is the absence of randomized trials. Most included studies were retrospective cohort studies, with a before-and-after design. As a result, temporal factors unrelated to the intervention may have contributed to the observed reduction in incidence of infection. Studies of tuberculosis transmission are also prone to secular trends. Changes in the community prevalence of disease and other unrelated improvements in tuberculosis control can result

Table 4. Characteristics of Included Studies Evaluating the Effectiveness of Personal Respiratory Protection (n = 9)

				Intervention/s			Primary Findings		
First Author, Year Published	Setting	Study Design	Population/s	Personal Respiratory Protection	Other	Comparator	No Intervention	Respiratory Hygiene Intervention	Absolute Risk Difference
High burden settings									
Roth, 2005 [15]	Four hospitals, Brazil	Cohort	HCWs	N95 respirators worn by HCWs	Administrative controls used in Hospital A. Engineering controls (mechanical ventilation) also used in Hospital B	Hospitals where respirators were not worn routinely	19.8 per 1000 person-years (hospital C). 12.2 per 1000 person-years (hospital D)	7.4 per 1000 person years (hospital A). 8.1 per 1000 person-years (hospital B)	Reduction of between 4.1 and 12.4 conversions per 1000 person-years, depending upon comparison
Yanai, 2003 [14]	TB hospital, Thailand	Before and after	HCWs	N95 respirator use encouraged, with fit testing, for HCWs	Administrative (an isolation room established in each ward, safety cabinet in TB laboratory), Engineering (local ventilation), Personal cough etiquette training	Prior to introduction of guidelines	13/77 (16.9%) TST conversions 30/4357 TB cases (0.7/100 person years)	2/96 TST conversions (2.1%) 19/4780 (0.4 TB cases /100 person years)	Reduction in TST conversions by 14.8%; Reduction in TB cases by 0.29 cases per 100 person-years
Da Costa, 2009 [19]	General hospital, Brazil	Before and after	HCWs	HCW training to use N95 respirators	Administrative (rapid separation and diagnosis)	Prior to implementation	25 cases / 4307 person months (5.8 / 1000 person-months)	599 people re-tested. 15 cases / 3858 months (3.9 / 1000 person-months)	Reduction in conversions of 1.9 / 1000 person-months
Low burden settings									
Bangsberg, 1997 [17]	Urban hospital, USA	Before and after	HCWs	Particulate respirators with fit testing for medical staff	Administrative (isolation of high-risk patients, patient education) Engineering (negative pressure isolation rooms)	Prior to introduction of the policy	Period 1: 9/109 (10%) conversion Period 2: 2/101 (2%) conversion Period 3: 0/100 (0%) conversion	Period 4: 1/107 (1%) Period 5: 0/106 (0%)	No difference identified; conversion rate had already decreased prior to intervention
Baussano, 2007 [13]	Urban health facilities, Italy	Before and after	HCWs	Particulate respirators during cough-inducing procedures	Administrative (risk evaluation and prompt isolation, appointment of TB control officials); Engineering (laboratory containment)	Prior to the introduction of the policy	2182 participants: 106 infections in 4034 person-years (26.3/1000 person years)	42 infections in 4463 person years (9.4/1000 person-years)	Reduction by 16.9 conversions per 1000 person-years
Blumberg, 1995 [16]	Tertiary hospital, USA	Before and after	HCWs	Particulate respirator use	Administrative (patient isolation, infection control coordinator appointed), Respiratory hygiene. HCW education	Standard practice prior to intervention	118/3579 (3.3%) conversions	23/5153 (0.4%) conversions	Reduced TST conversion by 2.9% in intervention
Maloney, 1995 [12]	MDR-TB wards, USA	Before and after	HCWs	Staff use of moulded masks (3M 1800 Aseptex)	Administrative (Improved isolation, routine smear testing to guide isolation), Engineering (exhaust fans in isolation rooms, portable chambers for cough-inducing procedures)	Standard practice prior to intervention	15/90 (16.7%) conversions over 18 months	4/78 (5.1%) conversions over 18 months in intervention period	Reduced TST conversion by 11.5% after intervention
Fella, 1995 [11]	Urban AIDS center and prison hospital, USA	Before and after	HCW	Particulate respirators then dust mist fume respirators	Administrative (early isolation), Engineering (negative pressure rooms, and UVGI)	Staff use of technol shields / Staff use of particulate respirators	41/303 (13.5%) conversions	21/446 tests (4.7%) conversions	Reduction of 8.8%
Welbel, 2009 [18]	Urban hospital, USA	Before and after	HCWs	Particulate respirators with a fit test	Use of HEPA filters in the Emergency Department, with daily checks for negative pressure in isolation rooms	No respirators, prior to the intervention	98/2221, (4.4%) conversions	6/2108 (0.28%) conversions	Reduced TST by 4.1% in the intervention group

Abbreviations: HCW, health-care workers; HEPA, high efficiency particulate air; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; MDR-TB, multidrug resistant tuberculosis; TB, tuberculosis; TST, tuberculin skin test; UVGI, ultraviolet germicidal irradiation.

in confounding, leading to an under- or overestimation of an intervention's effectiveness. Third, most included studies evaluated the effect of composite interventions, where with multiple interventions introduced concurrently. This is typical of health system approaches to infection control, which endeavor to produce an optimal effect by implementing complementary measures (such as administrative, engineering, and personal respiratory protection controls). However, this approach means that we were unable to compare the effect of alternative infection control strategies nor to assess the interaction between them.

The included animal studies also require careful interpretation. Although animal studies allow the evaluation of individual components of infection control, such as patient mask use or engineering controls, their generalizability to humans is unclear. Guinea pig models are calibrated to measure the relative risk of an intervention, with the duration and intensity exposure titrated to produce a high incidence of infection. As these animals are highly susceptible to infection, they provide a useful model in transmission studies, allowing the relative effect of an intervention to be evaluated. However, this susceptible state means that the absolute rate of infection would be higher in guinea pigs than a similarly exposed human [32]. It is for this reason that the GRADE guidelines recommend downgrading the quality of evidence for studies including animals [33]. In this systematic review, we addressed this concern, by applying the relative risk observed with interventions to an absolute infection risk that is typical among healthcare workers. This approach allowed us to estimate an absolute risk difference that would be observed in humans, when the intervention was applied. Nevertheless, the use of animal models should be regarded as providing only indirect evidence of effectiveness of interventions and should be interpreted in the context evidence from human studies.

Our study findings have several important policy implications. Current evidence demonstrates that introducing a combination of administrative, engineering, and personal respiratory protection measures reduces transmission of *M. tuberculosis* and tuberculosis disease in healthcare settings. This supports WHO recommendations to adopt a comprehensive approach to tuberculosis infection control in healthcare settings. These findings are also consistent with the F-A-S-T approach to tuberculosis control [34], which proposes a combination of measures that aim to detect cases early and promptly separate and treat based upon drug susceptibility test results. However, current studies in humans have not compared the effect of different elements of infection control. Nevertheless, based on this evidence, health system interventions are likely to have a significant benefit for healthcare workers and other visitors to healthcare settings. Importantly, not all infection control measures will be affordable in resource-limited settings, where lower cost measures such as administrative controls and PPE may be prioritized.

This review also demonstrates the value of serial surveillance for infection among staff as a programmatic indicator of transmission in high-prevalence settings. Monitoring infection rates among staff in high-transmission settings can identify whether infection control needs to be strengthened and enables health facilities to prevent disease among staff and improve confidence in infection control practices, contributing to workforce retention.

This review demonstrates the need for further high-quality research to compare the effectiveness of different individual components of infection control within health systems, and other settings. Evaluation of low-cost approaches, such as natural ventilation, is particularly important for resource-limited settings. Studies evaluating a single intervention, rather than concurrent introduction of multiple interventions, will be most informative. A cluster randomized trial design would overcome biases that may be present in before-after studies. Adequately controlled studies in congregate settings such as prisons will also guide infection control policies outside of hospitals.

CONCLUSION

Infection control policies to enhance respiratory hygiene, environmental controls, and personal respiratory protection were associated with a reduction in transmission of *M. tuberculosis* to healthcare workers in low- and high-prevalence settings. A combination of measures is likely to be most effective in healthcare settings. Further research is required to determine which interventions are effective and cost-effective in other congregate settings. The expansion of evidence-based infection control practices will play an important role in reducing transmission of *M. tuberculosis* and is a key strategy for combating the global tuberculosis epidemic.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. G. J. F. was involved in conceptualization, data curation and analysis, funding acquisition and writing the original draft. L. R., V. C., and J. H. were involved in protocol development, title and abstract review, data extraction, and contributed to the final manuscript.

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