WHO guidelines on tuberculosis infection prevention and control

2019 update

Online annexes

THE END TB STRATEGY

World Health Organization

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ONLINE ANNEXES

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PICO 1 - Administrative controls: Triage of people with TB signs, symptom, or with TB disease, to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
Date: 27-29 March 2018
Question: Can triage of people with TB signs, symptoms or with confirmed TB disease, reduce TB transmission to health care workers (HCW) (including community HCWs) when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Triage	No triage	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence in all settings[a]												
6 [1,2,3,4,5,6,b,c,d,e,f]	observational studies[g]	serious[h]	not serious	very serious[i]	serious[j]	none	1966/24852 (7.9%)	1350/9647 (14.0%)	**RR 0.57** (-- to --)	**60 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in low TB burden settings[k]												
5 [2,3,4,5,6,b,c,f,l]	observational studies[g]	serious[h]	not serious	very serious[i]	serious[m]	none	206/22035 (0.9%)	322/8045 (4.0%)	**RR 0.23** (-- to --)	**31 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in high TB burden settings[n]												
1 [1,d]	observational studies	serious[o]	not serious [p]	serious[q]	not serious	none	1760/2817 (62.5%)	1028/1602 (64.2%)	**RR 0.97** (-- to --)	**19 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in secondary/tertiary care[r]												
6 [1,2,3,4,5,6,b,c,d,e,f]	observational studies[g]	serious[h]	not serious	very serious[i]	serious[j]	none	1966/24852 (7.9%)	1350/9647 (14.0%)	**RR 0.57** (-- to --)	**60 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in all settings[s]												
2 [7,8,t,u,v]	observational studies	serious[w]	not serious	very serious[x]	serious[y]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings												
1 [9]	observational studies	not serious	not serious [p]	not serious	serious[z]	none			**RR 0.32** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings[aa]												
2 [7,8,u,v]	observational studies	serious[w]	not serious	very serious[x]	serious[y]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care[bb]												
2 [7,8,t,u,v]	observational studies	serious[w]	not serious	very serious[x]	serious[y]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Please note: The total number of studies measuring the effect of triage on the incidence of LTBI in all settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
b. Study reporting outcome, but not included in summary assessments. Baussano, 2007: incidence rate of TST conversions of 106/4034 person-years before TBIC interventions were implemented, vs. 42 TST conversions per 4463 person-years after implementation (crude rate ratio 0.36 after vs. before).
c. Study reporting outcome, but not included in summary assessments. Blumberg, 1998 (some overlap with 1995 paper): TST conversion rate of 5.98/100 person-years in 1992 (pre-intervention) to 1.09/100 person-years from 1993–1997 (after the intervention was implemented; crude incidence rate ratio 0.18, after vs. before [derived from data presented]; authors report a p-value comparing the two time periods: <0.001).
d. Study reporting outcome, but not included in summary assessments. Yanai, 2003: TST conversions from 9.3 per 100 person-years (95% CI 3.3–15.3) before the implementation of TBIC measures (in 1995–1997) to 6.4 per 100 person-years (95% CI 1.5–11.4) and 2.2 per 100 person-years (95% CI 0–5.1), after implementation, in 1998 and 1999, respectively. Unadjusted rate ratio 0.9 (95% CI 0.4–2.2) for 1998 vs. 1995–1997 and 0.03 (95% CI 0.01–0.2) for 1999 vs. 1995–1997; adjusted rate ratio 0.4 (95% CI 0.1–1.6) and 0.01 (95% CI 0–0.04) for 1998 and 1999 vs. 1995–1997, respectively).
e. Definitions of triage varied widely between the six studies: Bangsberg - "all patients known HIV+, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at the emergency room"; Blumberg 1995 - "expanded respiratory isolation policy"; Holzman - not defined; Roth - "rapid diagnosis and treatment"; Welbel - "revised policy (based on CDC guidelines) for isolation [CDC 1994: "in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room"]; and Wenger - "higher index of suspicion for TB and stricter application of isolation criteria"
f. Study reporting outcome, but not included in summary assessments. Louther, 1997: 7.2 TST conversions per 100 person-years before the implementation of infection control measures, compared with 3.3 per 100 person-years after the implementation (crude rate ratio 0.46 [derived from data presented]; authors report p-value comparing the two groups: 0.001).
g. A mix of before/after, during/after, and prospective and retrospective cohort studies.
h. All studies are observational. Several studies have high risk of bias, with loss to follow-up, or incomplete ascertainment and/or reporting of outcomes of interest
i. Indirectness exists in the wide variation in types of triage and the descriptions of their implementation, as well as the implementation of a large number of infection control measures at one time. Please see assessment of directness for details.
j. Low number of events (<300) in almost all studies and two studies (Bangsberg and Wenger) have fewer than 20 events. The exception is the study by Roth et al., which has a total 2,878 events.
k. Please note: The total number of studies estimating the effect of triage on the incidence of LTBI in low TB burden settings was eight. Three studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; and 3) Louther, 1997. Please see separate footnotes that summarise the results of these studies.
l. Definitions of triage varied widely between the five studies: Bangsberg - "all patients known HIV+, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at the emergency room"; Blumberg 1995 - "expanded respiratory isolation policy"; Holzman - not defined; Welbel - "revised policy (based on CDC guidelines) for isolation [CDC 1994: "in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room"]; and Wenger - "higher index of suspicion for TB and stricter application of isolation criteria"
m. All studies have small numbers of events (<300; two had <20 events) and moderate overall sample sizes (except for Blumberg et al.)
n. Please note: The total number of studies estimating the effect of triage on the incidence of LTBI in high TB burden settings was two. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) Yanai, 2003. Please see the separate footnote that summarises the results of this study.
o. High loss to follow-up.
p. Cannot comment on inconsistency as data from only one study included.
q. Very different definitions of triage used, population not well described, differences in background risk, and triage implemented along with other infection control measures. Please see assessment of directness for details.
r. Please note: The total number of studies measuring the effect of triage on the incidence of LTBI in secondary/tertiary care settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
s. Please note: The total number of studies measuring the effect of triage on the incidence of TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.
t. Study reporting outcome, but not included in summary assessments. Jacobson, 1957: incidence rate of 78 episodes of TB disease among healthcare workers in 38,331 person-years in the control group (1942–51, before the intervention was implemented) to 12 episodes in 18,229 person-years after the implementation of triage (1952–55; crude incidence rate ratio 0.32, after vs. before).
u. Definitions of triage differed between the two studies: Harries - "priority to patients with chronic cough; rapid collection of sputum specimens" and Yanai - "triage/isolation and expedited diagnosis training for health care workers"
v. Study reporting outcome, but not included in summary assessments. O'Hara, 2017: Unadjusted odds ratio (OR) for TB disease in HCW at facilities with a higher administrative score was 0.94 (95% CI 0.87–1.02; p = 0.12). Adjusted OR (adjusted for environmental score, PPE score, miscellaneous score, and number of TB patients) 0.97 (95% CI 0.90–1.04; p = 0.36).
w. Under-ascertainment of outcomes in at least one study; poor reporting of loss to follow-up.
x. Very serious indirectness exists in terms of the population studied and the nature and implementation of the intervention. Please see assessment of directness for details.
y. Small numbers of events in both studies.
z. Small number of outcomes in before (n = 78) and after (n = 12) periods.
aa. Please note: The total number of studies measuring the effect of triage on the incidence of TB disease in high TB burden settings was three. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) O'Hara, 2017. Please see the separate footnote that summarises the results of this study.
bb. Please note: The total number of studies measuring the effect of triage on the incidence of TB disease in secondary/tertiary care settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

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PICO 1 - Administrative controls: Triage of people with TB signs, symptoms, or with TB disease, to reduce transmission of *M. tuberculosis* among other persons attending healthcare settings

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
Date: 27-29 March 2018
Question: Can triage of people with TB signs, symptoms or with confirmed TB disease, reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Triage	No triage	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence in all settings (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in all settings (n = 2 studies)												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings (n = 2 studies)												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in primary care (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care (n = 2 studies)												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in HIV-negative individuals (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in HIV-positive individuals (n = 2 studies)												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.
b. Serious risk of bias, probable to alter the results: exposure is different for each study between before and after groups; and not a clear differentiation of intervention vs. no intervention.
c. Multiple interventions were introduced at the same time. In addition, 'triage' was poorly defined in both studies, as targeting people with "respiratory disease and fever'" but with no mention of expedited diagnosis, or as an "increased index of suspicion for TB" without description of how this was implemented. Please see also assessment of directness.
d. Both studies had small sample sizes. The total at-risk population was 543; a total 50 events were included.

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PICO 1 - Administrative controls: Respiratory isolation/ separation to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
Date: 27-29 March 2018
Question: Can respiratory isolation/separation of people with presumed or demonstrated infectious TB reduce TB transmission to HCWs (including community HCWs) when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory isolation	No respiratory isolation	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence in all settings[a]												
12 [1,2,3,4,5,6,7,8,9,10,11,12,b,c,d,e,f,g,h]	observational studies	very serious[i]	not serious	very serious[j]	serious[k]	none	2413/91397 (2.6%)	1914/40097 (4.8%)	**RR 0.55** (-- to --)	**21 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in low TB burden settings[l]												
11 [1,2,4,5,6,7,8,9,10,11,12,b,c,d,f,h]	observational studies	very serious[m]	not serious	very serious[j]	serious[k]	none	653/88580 (0.7%)	886/38495 (2.3%)	**RR 0.32** (-- to --)	**16 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in high TB burden settings[n]												
1 [3,e,g]	observational studies	serious[o]	not serious[p]	serious[j]	not serious	none	1760/2817 (62.5%)	1028/1602 (64.2%)	**RR 0.97** (-- to --)	**19 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in secondary/tertiary care[q]												
12 [1,2,3,4,5,6,7,8,9,10,11,12,b,c,d,e,f,g,h]	observational studies	very serious[i]	not serious	very serious[j]	serious[k]	none	2413/91397 (2.6%)	1914/40097 (4.8%)	**RR 0.55** (-- to --)	**21 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in all settings[r]												
2 [13,14,s,t]	observational studies	serious[u]	not serious	very serious[v]	serious[w]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reductions in active TB incidence/prevalence in low TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reductions in active TB incidence/prevalence in high TB burden settings[x]												
2 [13,14,s,t]	observational studies	serious[u]	not serious	very serious[v]	serious[w]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reductions in active TB incidence/prevalence in primary care												
1 [15,y]	observational studies	very serious[z]	not serious[p]	very serious[aa]	serious[bb]	none			**OR 1.09** (0.99 to 1.19)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Reductions in active TB incidence/prevalence in secondary/tertiary care[cc]												
2 [13,14,t]	observational studies	serious[u]	not serious	very serious[v]	serious[w]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in all settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Sinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

b. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Baussano, 2007: incidence rate of TST conversions of 106/4034 person-years before TBIC interventions were implemented, vs. 42 TST conversions per 4463 person-years after implementation (crude rate ratio 0.36 after vs. before).

c. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Blumberg, 1998; some overlap with 1995 paper): TST conversion rate of 5.98/100 person-years in 1992 (pre-intervention) to 1.09/100 person-years from 1993-1997 (after the intervention was implemented; crude incidence rate ratio 0.18, after vs. before [derived from data presented]; authors report a p-value comparing the two time periods: <0.001).

d. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Bryan, 1983: TST conversion of 4.5% of HCWs in 1976, before the implementation of TBIC measures, vs. 5.1%, 1.5%, 0.85%, and 0.59% in the four years after implementation (crude risk ratio 1.13, 0.33, 0.19, and 0.13 for 1977–1981, respectively).

e. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. da Costa, 2009: TST conversions incidence rate from 5.8 per 1,000 person-months (95% CI 4.9–6.7), to 3.7 per 1,000 person-months (95% CI 2.8–4.6); rate ratio 0.46 (95% CI 0.23–0.89) after vs. before, p = 0.006; adjusted rate ratio (adjusted for exposure and occupation) 0.24 (95% CI 0.10–0.54).

f. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Sinkowitz, 1996: TST conversion in 0%, 8.0%, and 5.1% of bronchoscopists in hospitals without IC measures and zero TB patients, 1–5 TB patients, and ≥6 TB patients, vs. 3.3%, 8.3%, and 5.7% in hospitals with the same numbers of TB patients but which had implemented four IC measures (crude risk ratio 1.04 and 1.12 [IC vs. no IC] for hospitals with 1–5 TB patients and ≥6 TB patients, respectively). In other HCW, TST conversion in 0.49%, 0.64%, and 0.76% in hospitals without IC measures and zero TB patients, 1–5 TB patients, and 6 TB patients, vs. 0.53%, 0.69% and 0.90% in hospitals with the same numbers of TB patients but which had implemented four IC measures (crude risk ratio 1.08, 1.08, and 1.18 [IC vs. no IC] for hospitals with zero, 1–5 and ≥6 TB patients, respectively).

g. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Yanai, 2003: TST conversions from 9.3 per 100 person-years (95% CI 3.3–15.3) before the implementation of TBIC measures (in 1995–1997) to 6.4 per 100 person-years (95% CI 1.5–11.4) and 2.2 per 100 person-years (95% CI 0–5.1), after implementation, in 1998 and 1999, respectively. Unadjusted rate ratio 0.9 (95% CI 0.4–2.2) for 1998 vs. 1995–1997 and 0.03 (95% CI 0.01–0.2) for 1999 vs. 1995–1997; adjusted rate ratio 0.4 (95% CI 0.1–1.6) and 0.01 (95% CI 0–0.04) for 1998 and 1999 vs. 1995–1997, respectively).

h. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Louther, 1997: 7.2 TST conversions per 100 person-years before the implementation of infection control measures, compared with 3.3 per 100 person-years after the implementation (crude rate ratio 0.46 [derived from data presented]; authors report p-value comparing the two groups: 0.001).

i. Most studies included here have a high or unclear risk of bias. All are observational studies, some with high rates of loss to follow-up (e.g., Roth), low or unclear levels of participation, or incomplete reporting of outcomes (e.g., Blumberg). Two studies do not report results correctly or have missing results.

j. Indirectness was primarily through the implementation of multiple infection control measures together with isolation. Please see assessment of directness for details.

k. Imprecision exists: all except two studies (Fridkin and Roth) have fewer than 300 outcomes and three studies (Bangsberg, Behrman, and Wenger) have fewer than 20 outcomes.

l. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in low TB burden settings was 16. Five studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) Louther, 1997; and 5) Sinkowitz, 1996. Please see separate footnotes that summarise the results of these studies.

m. Most studies included here have a high or unclear risk of bias. All are observational studies, some have incomplete reporting of outcomes (e.g., Blumberg), and two studies do not report results correctly or have missing results.

n. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in high TB burden settings was three. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) da Costa, 2009 and 2) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

o. High proportions were lost to follow-up; those lost to follow-up may have been at higher risk of disease (more likely to be physicians).

p. Cannot comment on inconsistency as data from only one study are included.

q. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in secondary/tertiary care settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Sinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

r. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

s. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Claassens, 2013: Unadjusted odds ratio for smear-positive TB among health care workers in facilities where administrative controls were implemented vs.facilities without (or with fewer) administrative controls 1.09 (95% CI 0.99–1.19), p = 0.07.

t. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. O'Hara, 2017: Unadjusted odds ratio (OR) for TB disease in HCW at facilities with a higher administrative score was 0.94 (95% CI 0.87–1.02; p = 0.12). Adjusted OR (adjusted for environmental score, PPE score, miscellaneous score, and number of TB patients) 0.97 (95% CI 0.90–1.04; p = 0.36).

u. Under-ascertainment of outcome in at least one study. All studies implemented isolation/spatial separation in addition to a number of other TBIC interventions; the effect of isolation/separation on the outcome of interest cannot be determined. Poor reporting of loss to follow-up.

v. Very serious indirectness exists, for populations studied and in the nature of and fidelity to the intervention. Please see assessment of directness for details.

w. Both studies had fewer than 200 events; one had fewer than 100 events.

x. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in high TB burden settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

y. Please note that the odds ratio quoted for this study is for the development of smear-positive TB among healthcare workers at facilities classified by their implementation of infection control measures (i.e., the authors reported slightly increased odds of developing smear-positive TB in healthcare workers in facilities where administrative controls were implemented compared with facilities without or with fewer administrative controls).

z. High likelihood of under-ascertainment of outcome (smear-positive disease in HCW), as only routine records used, without verification or any additional efforts to estimate numbers of cases. In addition, high variability in implementation intervention across different facilities, with isolation only implemented in ~50% of facilities. Most importantly, the study used the facilities as the base unit for assessing risk of TB disease (so reduced TB incidence to a binary of 'any' vs. 'no' HCW developing TB at a particular facility) - individual HCW data not analysed.

aa. aa. Indirectness is severe. Please see assessment of directness for details.

bb. ab. Small effect seen, and in the opposite direction to expected. Confidence interval is narrow, but crosses 1.

cc. ac. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in secondary/tertiary care settings was three. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) O'Hara, 2017. Please see the separate footnote that summarises the results of this study.

References

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2. Jarvis, WR. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. Am J Infect Control; 1995.
3. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
4. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet; 1995.
5. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.

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12. Holzman, RS. A comprehensive control program reduces transmission of tuberculosis to hospital staff. Clin Infect Dis; 1995.
13. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
14. Harries AD, Hargreaves NJ,Gausi F,Kwanjana JH,Salaniponi FM. Preventing tuberculosis among health workers in Malawi. Bull WHO; 2002.
15. Claassens M, van Schalkwyk C,du Toit E,Roest E,Lombard CJ,Enarson DA,Beyers N,Borgdorff MW. Tuberculosis in Healthcare Workers and Infection Control Measures at Primary Healthcare Facilities in South Africa. PLoS One; 2013.

PICO 1 - Administrative controls: Respiratory isolation / separation to reduce transmission of *M. tuberculosis* among other persons attending healthcare settings

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
Date: 27-29 March 2018
Question: Can respiratory isolation / separation of people with presumed or demonstrated infectious TB reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory isolation	No respiratory isolation	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence in all settings (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in all settings (n = 2 studies; n = 543 individuals at risk)												
2 [1,2,a]	observational studies	serious[b]	not serious	very serious[c]	serious[d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings (n = 2 studies; n = 543 individuals at risk)												
2 [1,2,a]	observational studies	serious[b]	not serious	very serious[c]	serious[d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings (n = 0 studies; n = 0 individuals at risk) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in primary care (n = 0 studies; n = 0 individuals at risk) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care (n = 2 studies; n = 543 individuals at risk)												
2 [1,2,a]	observational studies	serious[b]	not serious	very serious[c]	serious[d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in HIV-negative individuals (n = 0 studies; n = 0 individuals at risk) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in HIV-positive individuals (n = 2 studies; n = 543 individuals at risk)												
2 [1,2,a]	observational studies	serious[b]	not serious	very serious[c]	serious[d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.143 (-- to --)**	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.
b. Serious risk of bias, probable to alter the results: exposure is different for each study between before and after groups; also isolation measures were in effect before and then more so after. Not a clear differentiation of intervention vs. no intervention.
c. Multiple interventions were introduced at the same time.
d. Both studies had small sample sizes. The total at-risk population was 543; a total 50 events were included.

References

1. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.
2. Stroud LA, Tokars JI Grieco MH Crawford JT Culver DH Edlin BR Sordillo EM Woodley CL Gilligan ME Schnieder N Williams J Jarvis WR. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York city hospital. Infect Control Hosp Epidemiol; 1995.

PICO 1 - Administrative controls: Prompt initiation of effective treatment of TB patients to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
Date: 27-29 March 2018
Question: Can effective treatment of patients with TB disease reduce TB transmission to HCWs (including community HCWs) when compared to transmission to the same populations in settings where treatment is not yet administered?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effective treatment	Treatment – [delayed or] not DST-based	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence in all settings												
4 [1,2,3,4,a,b]	observational studies	very serious [c]	serious [d]	very serious [e]	very serious [f]	none	42/3081 (1.4%)	155/3260 (4.8%)	**RR 0.29** (-- to --)	**34 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in low TB burden settings												
4 [1,2,3,4,a,b]	observational studies	very serious [c]	serious [d]	very serious [e]	very serious [f]	none	42/3081 (1.4%)	155/3260 (4.8%)	**RR 0.29** (-- to --)	**34 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in high TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in secondary/tertiary care												
4 [1,2,3,4,a,b]	observational studies	very serious [c]	serious [d]	very serious [e]	very serious [f]	none	42/3081 (1.4%)	155/3260 (4.8%)	**RR 0.29** (-- to --)	**34 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in all settings - not measured												
-	-	-	-	-	-	-					-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Please note that the study included by Welbel et al. does not describe, specifically, the implementation of treatment based on drug susceptibility, but only describes the introduction of drug susceptibility testing. We have assumed that the results of testing were then used to inform treatment.
b. Please note that meta-analysis was *not* conducted - pooled estimates and measures of effect are crude estimates.
c. There are design specific issues to these studies. Mainly, it is not possible to ascertain the effect of the intervention in question as the intervention is grouped with other interventions, which presents a serious risk of bias. There is also a serious design issue with the study by Wenger et al., as the intervention only differs slightly between before and after (3 agents vs. 4 agents). Though studies were not designed specifically to answer our question, the way they are designed does not give us confidence in the results of interest.
d. Some inconsistency exists. In the study by Jarvis, in particular, certain results are reported as unavailable, but the site of origin of these results is not specified, so this cannot be accounted for in analysis. In addition, in the study by Welbel et al., overall denominators for at-risk individuals are provided, but not the time period for which these individuals were at risk, reducing confidence in the estimates of risk.
e. Indirectness is severe and from many sources: population, intervention, and comparators (please see assessment of directness for details).
f. Serious imprecision exists. For a dichotomous outcome all studies have fewer than 110 cases (range 10–104). Samples sizes are also low in three studies (range 65–650; the exception is Welbel et al, with a sample size of 4,329).

References

1. Jarvis, WR. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. Am J Infect Control; 1995.
2. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet; 1995.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
4. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF,Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.

PICO 1 - Administrative controls: Prompt initiation of effective treatment of TB patients to reduce transmission of *M. tuberculosis* among other persons attending healthcare settings

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
Date: 27-29 March 2018
Question: Can effective treatment of patients with TB disease reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings where treatment is not yet administered?
Setting: International

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effective treatment	Treatment – [delayed or] not DST-based	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence in all settings (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in all settings (n = 1 study)												
1 [1,a]	observational studies	serious[b]	not serious[c]	very serious[d]	serious[e]	none	5/193 (2.6%)	19/216 (8.8%)	RR 0.295 (-- to --)	62 fewer per 1,000 (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings (n = 1 study)												
1 [1,a]	observational studies	serious[b]	not serious[c]	very serious[d]	serious[e]	none	5/193 (2.6%)	19/216 (8.8%)	RR 0.295 (-- to --)	62 fewer per 1,000 (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in primary care (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care (n = 1 study)												
1 [1,a]	observational studies	serious[b]	not serious[c]	very serious[d]	serious[e]	none	5/193 (2.6%)	19/216 (8.8%)	RR 0.295 (-- to --)	62 fewer per 1,000 (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in HIV-negative individuals (n = 0 studies) - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in HIV-positive individuals (n = 1 study)												
1 [1,a]	observational studies	serious[b]	not serious[c]	very serious[d]	serious[e]	none	5/193 (2.6%)	19/216 (8.8%)	RR 0.295 (-- to --)	62 fewer per 1,000 (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.
b. No significant difference in the treatment in the before and after groups (1.5 vs. 2.0 drugs given before vs. after; range 0-4 in both periods; p = 0.2). Exposure is also different for between before and after groups.
c. As there is only one study included we cannot comment on heterogeneity of results between studies.
d. Authors describe "expanded use of antituberculous drugs" in 'after' period, but no description of time to treatment; therefore unable to assess for difference compared with delayed treatment administration.
e. Small numbers of cases in both arms. Overall number of exposed individuals = 409 (n = 216 before; n = 193 after)

References

1. Stroud LA, Tokars JI Grieco MH Crawford JT Culver DH Edlin BR Sordillo EM Woodley CL Gilligan ME Schnieder N Williams J Jarvis WR. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York city hospital. Infect Control Hosp Epidemiol; 1995.

PICO 2 - Administrative controls: Respiratory hygiene of TB patients to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can respiratory hygiene (or cough etiquette) in people with presumed or confirmed TB reduce TB transmission to healthcare workers in healthcare or other congregate settings to reduce TB transmission when compared to settings where these interventions are not implemented?
Setting: International

Certainty assessment							Impact	Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence - all settings (n=2)									
2 [1,2]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies were included. Heterogeneity in the interventions precluded meta-analysis. The two studies both found a reduction in TST conversions in the intervention compared to control group. In Roth (n=7735), a composite intervention including surgical mask use by patients (comparing two hospitals in the intervention arm to two in the control arm) reduced TST conversions by between 4.1 and 12.4 conversions per 1,000 person months. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. [1,2,c]	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=2)									
2 [2,3]	observational studies	serious[a]	not serious	serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies were included. Heterogeneity in the interventions precluded meta-analysis. In these two studies, surgical mask use by patients was a part of a composite intervention. They both found a reduction in TB in the intervention compared to control group. In Harries 2002, the use of surgical masks by patients as a part of a composite intervention of 13 components reduced the TB notification rate from 100/2697 (3.7%) to 96/2979 (3.2%). In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years. Therefore, both studies were associated with a decrease in TB cases. [2,3,c]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The one included study had a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The intervention is a composite intervention including engineering, respiratory protection and administrative controls, of which cough hygiene is one component (downgraded by one level).
c. No single effect estimate/meta-analysis was possible due to heterogeneity of outcomes.

References

1. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
2. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
3. Harries AD, Hargreaves NJ,Gausi F,Kwanjana JH,Salaniponi FM. Preventing tuberculosis among health workers in Malawi. Bull WHO; 2002.

PICO 2 - Administrative controls: Respiratory hygiene of TB patients to reduce transmission of *M. tuberculosis* among other persons attending healthcare settings

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can respiratory hygiene (or cough etiquette) in people with presumed or confirmed TB reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory hygiene	No respiratory hygiene	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n=1) (Animal study, surgical mask use by patient with TB)												
1 [1,a]	observational studies	not serious[b]	not serious	serious[c]	not serious	strong association	36/90 (40.0%)	69/90 (76.7%)	not pooled	see comment	⊕⊕◯◯ LOW	CRITICAL
Reduction in TB incidence/prevalence (n=1)												
1 [2,d]	observational studies	serious[e]	not serious	serious[f]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not pooled	see comment	⊕⊕◯◯ LOW	CRITICAL
Reduction in TB incidence/prevalence in people living with HIV (n=1)												
1 [2,d]	observational studies	serious[e]	not serious	serious[f]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not estimable		⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Dharmadhikari 2012 measured the effect of surgical mask use by MDR-TB patients upon TST conversion in guinea pigs. The mask use was associated with a substantial reduction in infection 69/90 (76.6%) to 36/90 (40.0%), a reduction by 36.6% in guinea pigs. The reviewers assessed that indirectness was an important concern, given differences between humans and guinea pigs. This led to downgrading the quality of evidence by one point. A steady rise in infection risk over the study period, indicating a dose-response relationship with the duration of exposure. This led to upgrading the quality assessment by one. Therefore, this was rated as low quality evidence.
b. The blinding of the individuals reporting the outcomes was not stated.
c. The biology of latent TB infection in guinea pigs is different than that in humans. Therefore there is a serious concern of indirectness (Downgraded by one level).
d. Moro 2000 (n= 134) study evaluated the effect of surgical mask use for prevention of transmission of MDR-TB, with the outcome of MDR-TB. In this study, surgical mask use by patients was a part of a composite intervention. There was a reduction of 29% in the incidence of TB between the intervention group (0/44 (0%)) and the control group (26/90 (29%)).
e. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
f. The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

References

1. Dharmadhikari, . Surgical Face Masks Worn by Patients with Multidrug-Resistant Tuberculosis. Am J Respir Crit Care Med; 2012.
2. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.

PICO 3 - Environmental controls: Upper room ultraviolet germicidal irradiation to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can upper room GUV reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact				Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Reduction in LTBI incidence/prevalence (n=3)												
3 [1,2,3]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Three studies in humans evaluated this outcome. In Fella, a composite outcome including UVGI was associated with a reduction in TST conversion from 41/303 (13.5%) in the intervention group to 21/446 (4.7%) in the control group – a reduction of 8.8%. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Therefore, both studies demonstrated a reduction in TST conversions. Welbel 1995 showed that mechanical ventilation, in combination with other engineering measures, was associated with a reduction in TST conversions from 98/2,221 (4.4%) to 6/2108 (0.28%), a reduction of 4.1%. Heterogeneity in the interventions precluded meta-analysis.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n= 1)							**Upper room UVGI**	**No upper room UVGI**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [2,c]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. Only one study evaluated this outcome In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control; 1995.
2. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.

PICO 3 - Environmental controls: Upper room ultraviolet germicidal irradiation to reduce transmission of *M. tuberculosis* among other persons attending healthcare settings

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can upper room GUV reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0) in humans									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0) in humans									
0								-	CRITICAL
Reduction in LTBI incidence/prevalence (animal studies) (n=2)									
2 [1,2]	randomised trials	not serious	not serious[1,a]	serious[b]	not serious	none	Two animal studies were included, measuring infection in guinea pigs arising from exhausted air from patient wards. Both studies showed a reduction in infection with use of UVGI. The measured absolute reductions were 25.5% (Escombe), 46.7% (Mphaphlele).	⨁⨁⨁◯ MODERATE	CRITICAL
Reduction in TB incidence/prevalence (animal studies) (n=1)									
1 [2]	randomised trials	not serious	not serious[c]	serious[d]	not serious	none	One animal studies was included. This was conducted in guinea pigs, exposed to air from patients with TB. In this study, UVGI was associated with a reduction in TB on autopsy of 5%.	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval

Explanations

a. The direction and magnitude of the effect was consistent across the studies. One study (Mphaphlele) involved two study periods, where the rate of infectiousness differed based upon the location of the exhaust outlet in the room. The data were pooled in the final analysis. The direction of the effect was the same in both time periods.
b. These three studies evaluated tuberculin skin test conversion among guinea pigs exposed to air removed from tuberculosis wards. Differences in the nature of transmission to guinea pigs, compared to humans, are likely to be significant (Downgraded one level).
c. The direction and magnitude of the effect was consistent across the studies.
d. These studies were conducted among guinea pigs (3 studies) and rabbits (1 study). Tuberculosis was diagnosed by autopy. Differences in the nature of transmission to animals and the measurement of the outcome (autopsy diagnosed disease) compared to humans are likely to be significant (Downgraded one level).

References

1. Mphaphlele M, Dharmadhikari AS,Jensen PA,Rudnick SN,van Reenen TH,Pagano MA,Leuschner W,Sears TA,Milonova SP,van der Walt M,Stoltz AC,Weyer K,Nardell EA. Institutional Tuberculosis Transmission Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines. Am J Respir Crit Care Med; 2015.
2. Escombe AR, Moore DAJ,Gilman RH,Navicopa M,Ticona E,Mitchell B,Noakes C,Martinez C,Sheen P,Ramirez R,Quino W,Gonzalez A,Friedland JS,Evans CA. Upper-Room Ultraviolet Light and Negative Air Ionization to Prevent Tuberculosis Transmission. Plos Medicine; 2009.

PICO 3 - Environmental controls: Mechanical ventilation systems to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can mechanical ventilation reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact				Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Reduction in LTBI incidence/prevalence (n= 7)												
7 [1,2,3,4,5,6,7]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Seven studies evaluated the effect of mechanical ventilation upon TST conversion, each as a part of a composite intervention. Heterogeneity in the interventions precludes meta-analysis. Blumberg 1995 showed that the composite intervention, including 90 negative pressure rooms with fans, was associated with a reduction in TST conversions from 118/3579 (3.3%) to 23/5,153 (0.4%) – a reduction of 2.9%. Welbel 1995 showed that mechanical ventilation, in combination with other engineering measures, was associated with a reduction in TST conversions from 98/2,221 (4.4%) to 6/2108 (0.28%), a reduction of 4.1%. Wenger 1995 found that mechanical ventilation, including installation of 23 isolation rooms, was associated with a reduction in TST conversion from 7/25 (28%) to 3/17 (18%), a reduction of 10%. Maloney 1995 found that mechanical ventilation, in combination with other measures, was associated with a reduction in TST conversions from 15/90 (16.7%) to 4/78 (5.1%), a reduction by 11.5%. Roth 1995 showed that mechanical ventilation was associated with a similar TST conversion rate (7.4 / 1,000 person years without the measures, and 8.1 per 1,000 person years with the measures). Menzies 2002 was conducted among HCWs in microbiology and pathology laboratories. Ventilation was lower among those with TST conversion than among those without TST conversion (p<0.001). The adjusted odds ratio for those with half of the recommended ventilation versus the recommended ventilation was 1.3 (95% CI 0.9-1.9). Finally, in Fella 1995, a composite outcome including UVGI was associated with a reduction in TST conversion from 41/303 (13.5%) in the intervention group to 21/446 (4.7%) in the control group – a reduction of 8.8%. In summary, six of the seven studies showed a reduction in the incidence of TST over the study period.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=0)												
0									not pooled	see comment	-	CRITICAL
Reduction in LTBI incidence/prevalence in TB laboratory workers (n=1)							**Use of ventilation systems (mechanical)**	**No use of ventilation systems (mechanical)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [7,c]	observational studies	serious[a]	not serious	serious[d]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	14	97	-	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions are largely comprised of multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. This study conducted among HCWs in microbiology and pathology laboratories in 17 Canadian hospitals. The study measured mechanical ventilation within the laboratory facilities, and assesed the number of health workers with TST conversions during the study period. The study found that among 14 HCWs with TST conversions, the mean mechanical ventilation was 16.7 (SD 2.4) air changes per hour (ACH) . Among 97 staff without TST conversions, the mean mechanical ventilation was 32.5 (SD 22.7) ACH. Therefore, ventilation was lower among those with TST conversion than among those without TST conversion ($p<0.001$). The adjusted odds ratio for those with half of the recommended ventilation versus the recommended ventilation was 1.3 (95% CI 0.9-1.9).
d. Differences in intervention (applicability). The comparator and intervention is poorly described. The intervention comprises multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

References

1. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control; 1995.
2. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet; 1995.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
4. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF,Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.
5. Blumberg HM, Watkins DL,Berschling JD,Antle A,Moore P,White N,Hunter M,Green B,Ray SM,McGowan Jr. J E. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med; 1995.
6. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
7. Menzies D, Fanning A,Yuan L,FitzGerald JM. Factors associated with tuberculin conversion in Canadian microbiology and pathology workers. Am J Respir Crit Care Med; 2003.

PICO 3 - Environmental controls: Mechanical ventilation systems to reduce transmission of *M. tuberculosis* among others in high TB transmission risk settings

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can mechanical ventilation reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Use of ventilation systems (mechanical)	No use of ventilation systems (mechanical)	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n= 1)												
1 [1,a]	observational studies	serious[b]	not serious	very serious[c]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	73/189 (38.6%)	75/297 (25.3%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=0)												
0											-	CRITICAL

CI: Confidence interval

Explanations

a. Muecke 2006 found rooms with mechanical ventilation were associated with an increase in TST conversions from 75/297 (25%) to 73/189 (39%). Risk difference was +14% with ventilation in rooms compared to no ventilation. Confounding factors are likely, with temporal factors likely playing an important role.
b. Temporal factors may have explained difference, shown by the increased infectivity in the second semester. The opening of windows in ventilated and non-ventilated rooms was not reported.
c. Transmission in rooms with mechanical ventilation was compared to transmission in rooms without mechanical ventilation. The duration of exposure varied between rooms, and seasonal variation means that other forms of ventilation (e.g. open windows) cannot be excluded.

References

1. Muecke C, Isler M,Menzies D,Allard R,Tannenbaum TN,Brassard R. The use of environmental factors as adjuncts to traditional tuberculosis contact investigation. Int J Tuberc Lung Dis; 2006.

PICO 3 - Environmental controls: Ventilation systems (mixed-mode) to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can mixed mode ventilation reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact				Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Reduction in LTBI incidence/prevalence (n= 2)												
2 [1,2]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies addressed this question. Heterogeneity in the interventions precludes meta-analysis. In Yanai 2003, a composite intervention including mixed mode ventilation was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Behrman 1998 evaluated mixed mode ventilation, and other interventions including respiratory protection. TST conversions decreased from 6/50 (12%) to 0/64 (0%) over the study period. Therefore, both studies showed a reduction in TST conversions. Heterogeneity in the interventions precluded meta-analysis.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n= 1)							**Use of ventilation systems (mixed)**	**No use of ventilation systems (mixed)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1,c]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and intervention is poorly described. The intervention comprises multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. The one included study, Yanai 2003, demonstrated that the composite intervention, including mixed mode ventilation, was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction of 0.29 cases/100 person years.

References

1. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
2. Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med; 1998.

PICO 4 - Respiratory protection: Use of particulate respirators to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can the use of particulate respirators reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact				Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Reduction in LTBI incidence/prevalence (n=9)												
9 [1,2,3,4,5,6,7,8,9]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Nine studies examined the effect of particulate respirators upon TST conversion. These studies produced effects in the same direction (reducing infection), however the magnitude of the effect varied considerably between settings. Concerns around confounding due to multiple interventions, and heterogeneity of the interventions, means that the findings were not meta-analyzed. Bangsberg 1997 compared the effect of respiratory masks and fit testing for staff against usual care, prior to the introduction of a new infection control policy. Comparing six months before (0/100, 0% in Jun 1993) to six months after (1/107 1% in Dec 1993) there was a 1% increase in conversion. Comparing the same control period (0% in Jun 1993) to the period 6-12 months after (0% in Jun 1993) there was no difference. Given the low event numbers, these findings were not of significance. Second, Baussano found that staff respiratory protection was associated in a reduction in TST conversion from 26.3/1000 person years to 9.4 / 1000 person years – a reduction of 16.9 / 1000 person years. Third, Blumberg 1995 showed a composite intervention with a particulate respiratory was associated in a reduction of TST conversions from 18/3579 (3.3%) to 25/5153 (0.4%), a 2.9% reduction. Fella 1995 showed that particulate respirators were associated with a reduction in TST conversion from 41/303 (13.5%) to 21/446 (4.7%), a reduction of 8.8%. Dust fume respirators had no effect. Maloney 1995 showed a composite intervention including molded surgical masks was associated with a reduction in TST conversion from 15/90 (16.7%) to 4/78 (5.1%), a reduction by 11.5%. In Yanai 2003, a composite intervention including mixed mode ventilation was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Roth 1995 showed a composite intervention including respirators for health workers was associated with a reduction of infection of between 4.1 and 12.4 conversions per 1,000 persons. Welbel 2009 saw a 4.1% reduction in TST conversions, as a part of a composite intervention. Da costa 2009 showed a reduction of 1.9 TST conversions per month, as a part of a composite intervention.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=1)							**Use of particulate respirators**	**No use**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [4,c]	observational studies	serious[a]	not serious	very serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. Only one study evaluated this outcome. In Yanai 2003, a composite intervention including use of staff particulate respirators was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.
2. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control; 1995.
3. Baussano I, Bugiani M,Carosso A,Mairano D,Barocelli AP,Tagna M,Cascio V,Piccioni P,Arossa W. Risk of tuberculin conversion among healthcare workers and the adoption of preventive measures. Occup Environ Med; 2007.
4. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
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6. Blumberg HM, Sotir M,Erwin M,Bachman R,Shulman JA. Risk of house staff tuberculin skin test conversion in an area with a high incidence of tuberculosis. Clin Infect Dis; 1998.
7. Bangsberg DR, Crowley K,Moss A,Dobkin JF,McGregor C,Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol; 1997.
8. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
9. da Costa P, Trajman A ,Mello FC,Goudinho S,Silva MA,Garret D,Ruffino-Netto A,Kritski AL. Administrative measures for preventing Mycobacterium tuberculosis infection among healthcare workers in a teaching hospital in Rio de Janeiro, Brazil. J Hosp Infect; 2009.

PICO 4 - Respiratory protection: Use of particulate respirators to reduce transmission of *M. tuberculosis* in persons in TB care or in high TB transmission risk settings

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can the use of particulate respirators reduce TB transmission in persons in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Use of particulate respirators	No use	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n=0)												
0											-	CRITICAL
Reduction in TB incidence/prevalence (n=1)												
1 [1,a]	observational studies	serious[b]	not serious	very serious[c]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence in people living with HIV (n=1)												
1 [1,a]	observational studies	serious[b]	not serious	very serious[c]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Moro 2000 evaluated the effect of mask use by people entering isolation rooms (including visitors). Surgical masks were used. At the same time, high-risk pentamidine use (a risk for increased cough and transmission) was also ceased. The effect of this intervention reflects a combination of multiple components. Incident MDR-TB reduced from 26/90 (29%) to 0/44 (0%) during the period after the intervention began. The reduction in MDR-TB incidence was 10.6 / 1,000 patient days. Confounding factors are likely, and the effect cannot only be attributed to the respiratory protection program.
b. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
c. The intervention comprises multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

References

1. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.

PICO 4 - Respiratory protection: Implementation of respiratory protection programmes to reduce transmission of *M. tuberculosis* among healthcare workers

Author(s): University of Sydney
Date: 27-29 March 2018
Question: Can the implementation of respiratory protection programs reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							N° of patients	Effect			Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact					
Reduction in LTBI incidence/prevalence (n= 4)												
4 [1,2,3,4]	observational studies	serious[a]	not serious	serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Four studies reported on the evaluation of fit testing of particulate respirators, as a part of complex composite interventions. In Yanai 2003, a composite intervention including fit testing of HCWs was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Bangsberg 1997 compared the effect of particulate respirators and fit testing for staff against usual care, prior to the introduction of a new infection control policy. Comparing six months before (0/100, 0% in Jun 1993) to six months after (1/107, 1% in Dec 1993) there was a 1% increase in conversion. Comparing the same control period (0% in Jun 1993) to the period 6-12 months after (0% in Jun 1993) there was no difference. Given the low event numbers, these findings were not of significance. Therefore, the two studies show a stable or reduced proportion of HCWs developing LTBI. Welbel found a 4.3% reduction in TST conversions following introduction of particulate respirators and fit testing. Heterogeneity in the interventions precludes meta-analysis. Da Costa 2009 was a before-after study evaluating the effect of a composite administrative, engineering and respiratory protection intervention upon TST conversion among health workers. The respiratory protection component comprised education of health workers to use particulate respirators (N95 masks), including instructions for their use, maintenance and re-use. TST conversion was assessed at the start of the implementation of the intervention, and after it was implemented. The study found TST conversion decreased from 25/4307 person months (5.8 per 1,000 person months) in 1999-2001 to 15/3858 person months (3.9 per 1,000 person months) – a reduction of 1.9 conversions / person-months.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n= 1)							**Respiratory protection programmes**	**No implementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1,c]	observational studies	serious[a]	not serious	serious[b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. One study evaluated this outcome. In Yanai 2003, a composite intervention including fit testing for HCW masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
2. Bangsberg DR, Crowley K,Moss A,Dobkin JF,McGregor C,Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol; 1997.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
4. da Costa P, Trajman A ,Mello FC,Goudinho S,Silva MA,Garret D,Ruffino-Netto A,Kritski AL. Administrative measures for preventing Mycobacterium tuberculosis infection among healthcare workers in a teaching hospital in Rio de Janeiro, Brazil. J Hosp Infect; 2009.

Annex 5 – GRADE evidence-to-decision tables

PICO 1 - Administrative controls: Evidence-to-decision framework for the implementation of triage

<table>
<tr><td colspan="2">CAN TRIAGE OF PEOPLE WITH TB SIGNS, SYMPTOMS OR WITH CONFIRMED TB DISEASE, REDUCE TB TRANSMISSION TO HEALTH WORKERS (INCLUDING COMMUNITY HEALTH WORKERS) AND OTHER PERSONS ATTENDING HEALTH CARE FACILITIES WHEN COMPARED TO TRANSMISSION IN SETTINGS WITH NO INTERVENTION OR DIFFERENT INTERVENTIONS?</td><td rowspan="7">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world's leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>POPULATION:</td><td>Health care settings to reduce TB transmission to health workers (including community health workers) when compared to transmission to health workers (including community health workers) in settings with no triage or different interventions</td></tr>
<tr><td>INTERVENTION:</td><td>Triage of people with TB signs, symptoms</td></tr>
<tr><td>COMPARISON:</td><td>No triage</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Studies varied greatly in their definitions of triage. Among the studies that implemented triage and reported a change in LTBI incidence, estimates of effect ranged from an absolute reduction of 2.3% to 20.5%. Among the studies that implemented triage and estimated the incidence of TB disease, three (in high TB burden settings) showed slight or no reduction in TB incidence among healthcare workers and one (in low TB burden settings) showed a moderate reduction in TB incidence.</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group is being convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
• Yes
○ Varies
○ Don't know</td><td>Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with Mycobacterium tuberculosis while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic (1).

Reference
1. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.</td><td>The Guideline Development Group prioritized this PICO question for review.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
• Moderate
○ Large
○ Varies
○ Don't know</td><td rowspan="2">Estimates of effect are crude summaries - meta-analysis was not conducted. Please note that data from only 5/8 and 2/3 studies, respectively, contributed to the summary estimates presented for reductions in LTBI and active TB incidence/prevalence. Please see detailed footnotes in the evidence tables for more information.

<table><tr><th rowspan="2">Outcomes</th><th colspan="2">Effect</th></tr><tr><th>Relative</th><th>Absolute</th></tr><tr><td>Reduction in LTBI incidence / prevalence in all settings (n=6)</td><td>RR 0.57</td><td>6 fewer per 1000</td></tr><tr><td>Reduction in active TB incidence / prevalence in all settings (n=2)</td><td>RR 0.98</td><td>0 fewer per 1000</td></tr></table>
See GRADE evidence summary table above.</td><td>One Guideline Development Group member noted that studies on a single intervention may be challenged to detect a reduction in transmission of 9.5%. The Guideline Development Group notes that most of the studies included used multiple interventions, challenging the interpretation of individual interventions.

The Guideline Development Group could not agree by consensus, therefore voting was conducted: 2 members voted in favour of ‘small’, 7 members voted in favour of ‘moderate’, 6 members voted in favour of ‘large’, 1 member voted in favour of ‘varies’, there was 1 abstention, and 2 members of the panel were absent during the voting process.</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
• Trivial
○ Varies
○ Don't know</td><td>No research evidence on undesirable outcomes was identified. The Guideline Development Group agreed by consensus that the undesirable anticipated effects would be trivial.</td></tr>
</table>

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>CERTAINTY OF EVIDENCE</td>
<td>What is the overall certainty of the evidence of effects?
• Very low
○ Low
○ Moderate
○ High
○ No included studies</td>
<td>
<table>
<tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>Reduction in LTBI incidence/prevalence in all settings[a]</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW [b,c,d]</td></tr>
<tr><td>Reduction in active TB incidence/prevalence in all settings [e]</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW [f,g,h]</td></tr>
</table>
a. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of LTBI in all settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
b. Indirectness exists in the wide variation in types of triage and the descriptions of their implementation, as well as the implementation of a large number of infection control measures at one time. Please see assessment of directness for details.
c. Low number of events (<300) in almost all studies and two studies (Bangsberg and Wenger) have fewer than 20 events. The exception is the study by Roth et al., which has a total 2,878 events.
d. All studies are observational. Several studies have high risk of bias, with loss to follow-up, or incomplete ascertainment and/or reporting of outcomes of interest
e. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.
f. Very serious indirectness exists in terms of the population studied and the nature and implementation of the intervention. Please see assessment of directness for details.
g. Small numbers of events in both studies.
h. Under-ascertainment of outcomes in at least one study; poor reporting of loss to follow-up.
</td>
<td></td>
</tr>
<tr>
<td>VALUES</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
• No important uncertainty or variability</td>
<td>No research evidence was identified.</td>
<td>The Guideline Development Group noted that stigma is an important consideration for patients presenting to healthcare settings with TB. Patients may feel negatively if they are triaged and sent to another part of the healthcare setting.

The Guideline Development Group also noted that there may be variability depending on the individual's knowledge of TB.

The Guideline Development Group judged that from the perspective of a health workers, there would be no important uncertainty or variability.</td>
</tr>
<tr>
<td>BALANCE OF EFFECTS</td>
<td>Does the balance between desirable and undesirable effects favor the intervention or the comparison?
○ Favors the comparison
○ Probably favors the comparison
○ Does not favor either the intervention or the comparison
○ Probably favors the intervention
• Favors the intervention
○ Varies
○ Don't know</td>
<td>No research evidence was identified.</td>
<td>The Guideline Development Group agreed by consensus that the balance favours the intervention.</td>
</tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies • **Don't know**	No research evidence was identified.	The Guideline Development Group agreed by consensus that they don't know the resource requirements.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • **No included studies**	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies • **No included studies**	No research evidence was identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact • **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that the identification of patients with symptoms may not be conducted as well as other settings depending on training on TB symptom detection and resources available to dedicate to triage. The Guideline Development Group noted that equity may also differ based on HIV prevalence, in certain settings triage of TB symptoms is linked to HIV programming. The Guideline Development Group also noted that the triage of children may be less likely to identify TB due to differences in their symptoms on presentation. Health equity for children may therefore be reduced. The Guideline Development Group judged that implementation of triage would probably increase health equity if uniformly adopted.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Patients and their families: may feel stigma is a serious issue that may be worsened by triage and may therefore be less acceptable. Health workers: may find the intervention acceptable if it reduces their incidence of TB. Policy-Makers/Hospital Administrators: possible challenges with acceptability, may not be acceptable if more health workers or space are required for the implementation. The Guideline Development Group noted that administrators for large hospitals that see many TB patients may be more willing to accept triage. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 13 members voted in favour of 'probably yes'; 1 member voted in favour of 'yes'; 2 member voted in favour of 'varies', there was 1 abstention, and 2 members of the panel were absent during the voting process.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes • **Varies** ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that there are challenges to the implementation of triage of people with TB signs and symptoms depending on the setting and resources available for this intervention. The Guideline Development Group noted that one factor impacting the feasibility was whether there is a trained dedicated staff to conduct triage. The Guideline Development Group therefore agreed by consensus that the feasibility varies.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the implementation of triage

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	Triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce TB transmission to health workers (including community health workers), persons attending health care facilities or other persons in high TB transmission risk settings (Conditional recommendation based on very low certainty in the evidence about the effects).				
JUSTIFICATION	*Desirable Effects*: the Guideline Development Group agreed desirable effects of triage were moderate in reducing TB transmission to health workers. *Undesirable Effects*: the Guideline Development Group judged that the undesirable anticipated effects would be trivial. *Values*: the Guideline Development Group agreed that there would be no important uncertainty or variability in how much healthcare workers value the main outcomes. *Feasibility*: the Guideline Development Group judged that the feasibility varied depending on the setting and resources available for this intervention.				
SUBGROUP CONSIDERATIONS	As per current WHO recommendations, people living with HIV should be systematically screened for active TB disease at each visit to a health care facility. Systematic screening for active tuberculosis: principles and recommendations [WHO/HTM/TB/2013.04]. Available from: http://apps.who.int/iris/bitstream/handle/10665/84971/9789241548601_eng.pdf?sequence=1. World Health Organization: Geneva. 2013. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings [WHO/HTM/TB/2011.11]. Available from: http://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf?sequence=1. World Health Organization: Geneva. 2011.				
IMPLEMENTATION CONSIDERATIONS	1. Implementation of this recommendation needs to include consultation and input from affected patients. 2. The Guideline Development Group noted that one factor impacting the implementation was whether there is a trained dedicated staff to conduct triage. 3. Implementation of this recommendation needs to include consultation and input from affected patients and health workers, in particular health workers conducting triage.				
MONITORING AND EVALUATION	1. The Guideline Development Group judged that for administrative controls, such as triage, clear definitions and process indicators and outcome indicators are needed for monitoring and evaluation. 2. The Guideline Development Group also notes that further assessment and evaluation of the quality of the triage is an important consideration due to variability based on training and implementation of triage. 3. The Guideline Development Group notes that current WHO Key TB Indicators include rates of TB incidence in healthcare workers, further uptake of this existing indicator is suggested.				
RESEARCH PRIORITIES	1. Further research should assess the cost-effectiveness of triage to reduce TB transmission. 2. Evaluation of individual interventions to reduce TB transmission, notably among healthcare workers. 3. Modelling studies may be helpful to improve the knowledge of effect estimates and cost-effectiveness. The Guideline Development Group notes that further evaluation of existing modelling studies may provide additional information. 4. The Guideline Development Group suggests further high quality research studies are needed with a low risk of bias. 5. Research regarding effective TB guideline implementation at the country-level is suggested. 6. The Guideline Development Group suggests further research on the unique triage needs of comorbid HIV and TB.				

PICO 1 - Administrative controls: Evidence-to-decision framework for the implementation of respiratory isolation

<table>
<tr><th colspan="3">CAN RESPIRATORY ISOLATION/SEPARATION / SEPARATION OF PEOPLE WITH PRESUMED OR DEMONSTRATED INFECTIOUS TB REDUCE TB TRANSMISSION TO HEALTH WORKERS (INCLUDING COMMUNITY HEALTH WORKERS) AND OTHER PERSONS ATTENDING HEALTH CARE FACILITIES WHEN COMPARED TO TRANSMISSION IN SETTINGS WITH NO INTERVENTION OR DIFFERENT INTERVENTIONS?</th></tr>
<tr><td>POPULATION:</td><td>Health care settings to reduce TB transmission to health workers (including community health workers) and other persons attending healthcare facilities when compared to transmission to health workers (including community health workers) and other persons attending healthcare facilities in settings with no intervention or different interventions</td><td rowspan="6">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world's leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>INTERVENTION:</td><td>Respiratory isolation (spatial separation) of presumed or demonstrated infectious TB cases</td></tr>
<tr><td>COMPARISON:</td><td>No respiratory isolation</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Among the 12 studies that reported differences in LTBI incidence, effects ranged from an increase of 1% to a reduction of 21%. The two largest studies (more than 300 outcomes) both showed reductions in incidence (of 1% [low TB burden] and 2% [high TB burden]; crude estimates). Six studies reported the incidence of TB disease; estimates of effect ranged from almost no difference between intervention and control groups in three studies (all in high TB burden settings) to a reduction of 29% in one study (low TB burden setting).</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group is being convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
• Yes
○ Varies
○ Don't know</td><td>Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with Mycobacterium tuberculosis while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic (1).

Reference
1. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.</td><td>The Guideline Development Group prioritized this PICO question for review.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
• Moderate
○ Large
○ Varies
○ Don't know</td><td>Estimates of effect are crude summaries - meta-analysis was not conducted. Please note that data from only 12/19 3/4 studies contributed to the summary estimates presented for reductions in LTBI and active TB incidence/prevalence, respectively. Please see detailed footnotes in the evidence tables for more information.</td><td>The Guideline Development Group could not agree by consensus, therefore voting was conducted: 7 members voted in favour of ‘small’; 8 members voted in favour of ‘moderate’; 1 member voted in favour of ‘large’, there was 1 abstention, and 2 members of the panel were absent during the voting process..</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
• Small
○ Trivial
○ Varies
○ Don't know</td><td>
<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="3">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Without isolation</th><th>With isolation</th><th>Difference</th></tr>
<tr><td>Reduction in LTBI incidence/prevalence in all settings. № of participants: 131494 (12 observational studies)[a]</td><td>RR 0.55 (-- to --)</td><td>4.8%</td><td>2.6% (0.0 to 0.0)</td><td>2.1% fewer</td></tr>
<tr><td>Reduction in active TB incidence/prevalence in all settings. № of participants: 13377 (2 observational studies)[b]</td><td>RR 0.98 (-- to --)</td><td>1.8%</td><td>1.8% (0.0 to 0.0)</td><td>0.0% fewer</td></tr>
</table>
a. The total number of studies measuring the effect of isolation on the incidence of LTBI in all settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Sinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
b. The total number of studies measuring the effect of isolation on the incidence of active TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.
</td><td>Evidence was not reviewed on the undesirable effects of isolation on the affected patient.

The Guideline Development Group notes that there are psychological harms of isolation. The Guideline Development Group also notes that there may be negative impacts on human rights and access to treatment, if individuals who are isolated are not given the same degree of care.

The Guideline Development Group noted that stigma and the lack of presence of family members in isolation rooms may be undesirable effects.

The Guideline Development Group notes that the undesirable effects will vary by type of isolation (individual, confined ward, TB wards, type of TB, e.g. MDR will lead to different isolation approaches).

No research evidence on undesirable outcomes was identified.

The Guideline Development Group agreed by consensus that the undesirable anticipated effects would be trivial.</td></tr>
</table>

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>CERTAINTY OF EVIDENCE</td>
<td>What is the overall certainty of the evidence of effects?
• Very low
○ Low
○ Moderate
○ High
○ No included studies</td>
<td>
<table>
<tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>Reduction in LTBI incidence/prevalence in all settings</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW[a,b,c]</td></tr>
<tr><td>Reduction in active TB incidence/prevalence in all settings</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW[d,e,f]</td></tr>
</table>
a. Indirectness was primarily through the implementation of multiple infection control measures together with isolation. Please see assessment of directness for details.
b. Imprecision exists: all except two studies (Fridkin and Roth) have fewer than 300 outcomes and three studies (Bangsberg, Behrman, and Wenger) have fewer than 20 outcomes.
c. Most studies included here have a high or unclear risk of bias. All are observational studies, some with high rates of loss to follow-up (e.g., Roth), low or unclear levels of participation, or incomplete reporting of outcomes (e.g., Blumberg). Two studies do not report results correctly or have missing results.
d. Very serious indirectness exists, for populations studied and in the nature of and fidelity to the intervention. Please see assessment of directness for details.
e. Both studies had fewer than 200 events; one had fewer than 100 events.
f. Under-ascertainment of outcome in at least one study. All studies implemented isolation/spatial separation in addition to a number of other TBIC interventions; the effect of isolation/separation on the outcome of interest cannot be determined. Poor reporting of loss to follow-up.
</td>
<td></td>
</tr>
<tr>
<td>VALUES</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
• No important uncertainty or variability</td>
<td>No research evidence was identified.</td>
<td>The Guideline Development Group agreed that there is no important uncertainty or variability.</td>
</tr>
<tr>
<td>BALANCE OF EFFECTS</td>
<td>Does the balance between desirable and undesirable effects favor the intervention or the comparison?
○ Favors the comparison
○ Probably favors the comparison
○ Does not favor either the intervention or the comparison
• Probably favors the intervention
○ Favors the intervention
○ Varies
○ Don't know</td>
<td>No research evidence was identified.</td>
<td>The Guideline Development Group agreed that the balance probably favours the intervention.</td>
</tr>
<tr>
<td>RESOURCES REQUIRED</td>
<td>How large are the resource requirements (costs)?
○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
• Varies
○ Don't know</td>
<td>No research evidence was identified.</td>
<td>The Guideline Development Group noted that if additional space or equipment are required, there would be an increase in costs related to the implementation of this recommendation. However, the Guideline Development Group agreed that any additional costs would vary by setting, and depending on existing infrastructure and complexity of the isolation system to be implemented.</td>
</tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • **No included studies**	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies • **No included studies**	No research evidence was identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact • **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that the impact of respiratory isolation may be affected by the effectiveness of other interventions such a triage – for instance, resources available and capacity of health workers to identify people with TB signs, symptom, or with TB disease.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes • **Varies** ○ Don't know	No research evidence was identified.	Patients and their families: may feel stigma is a serious issue related to isolation, and may feel disconnected from their family if they are treated in isolation rooms. Health workers may find the intervention acceptable if it reduces their incidence of TB. Depending on the setting and existing resources, policy-makers and hospital administrators may deliberate on the [significant] costs associated with this intervention. The Guideline Development Group agreed that the intervention acceptability would vary across key stakeholders.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes • **Varies** ○ Don't know	No research evidence was identified.	No evidence was identified to assess the feasibility, however, the Guideline Development Group judged that the widespread use of respiratory isolation rooms in current practice may be consider a proxy of feasibility. However, the Guideline Development Group acknowledged that in various settings isolation is either not feasible or increasing existing isolation facilities is not possible.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			The Guideline Development Group noted that feasibility of implementation relates to available resources to create isolation rooms. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 10 members voted in favour of 'probably yes'; 7 members voted in favour of 'varies'; there was 1 abstention, and 1 member of the panel were absent during the voting process.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the use of respiratory isolation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	Respiratory isolation / separation of people with presumed or demonstrated infectious TB is recommended to reduce TB transmission to health workers or other persons attending health care facilities (Conditional recommendation based on very low certainty in the evidence about the effects).				
JUSTIFICATION	The Guideline Development Group agreed on this recommendation by consensus. *Desirable Effects* The Guideline Development Group judged that the desirable anticipated effects were moderate, including a reduction in LTBI incidence by 24 per 1,000 and a reduction in active TB incidence/prevalence by 5 per 1,000. *Undesirable Effects* The Guideline Development Group judged that the undesirable anticipated effects were small, however, no research evidence was identified. *Balance of Effects* The Guideline Development Group agreed that the balance of effects probably favours the intervention. *Equity* The Guideline Development Group agreed that the impact of this intervention would probably increase health equity.				
SUBGROUP CONSIDERATIONS	None considered.				
IMPLEMENTATION CONSIDERATIONS	1. Health care systems must exhaust available patient care and support measures (including decentralised models of care, if applicable) prior to resorting to isolation of any person. 2. Implementation of this recommendation needs to include consultation and input from affected patients and health workers, in particular nurses. 3. Where local respiratory isolation facilities are not possible, consideration of referral systems to other health centres with respiratory isolation facilities should be considered. 4. Allocation of appropriate resources to pay for this intervention is necessary for implementation.				
MONITORING AND EVALUATION	1. Number of patients admitted into respiratory isolation. 2. Duration of patient stay in respiratory isolation.				
RESEARCH PRIORITIES	1. Further research should assess the cost-effectiveness of triage to reduce TB transmission. 2. Appropriate duration of respiratory isolation to prevent TB transmission. 3. High quality research studies are needed with a low risk of bias.				

PICO 1 - Administrative controls: Evidence-to-decision framework for the implementation of effective treatment

<table>
<tr><th colspan="3">CAN EFFECTIVE TREATMENT OF PATIENTS WITH TB DISEASE REDUCE TB TRANSMISSION TO HEALTH WORKERS (INCLUDING COMMUNITY HEALTH WORKERS) AND OTHER PERSONS ATTENDING HEALTH CARE SETTINGS WHEN COMPARED TO TRANSMISSION TO THE SAME POPULATIONS IN SETTINGS WHERE TREATMENT IS NOT YET ADMINISTERED?</th></tr>
<tr><td>POPULATION:</td><td>Health care settings to reduce TB transmission to health workers (including community health workers) when compared to transmission to health workers (including community health workers) in settings where treatment is not yet administered</td><td rowspan="5">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world’s leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>INTERVENTION:</td><td>Effective treatment of TB disease based on bacteriologic susceptibility</td></tr>
<tr><td>COMPARISON:</td><td>Treatment – [delayed or] not DST-based</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Four studies showed an absolute reduction in TST conversion after implementation of (composite) infection control measures, ranging from 0.1% to 21%, though all studies had small numbers of outcomes and all except one had small sample sizes. Only one study (conducted in a low TB burden setting) estimated the incidence of TB disease and found a change in incidence among HIV-positive individuals, from 8.8% before implementation of the (composite) intervention, to 2.6% after implementation.</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group was convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
• Yes
○ Varies
○ Don't know</td><td>Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with Mycobacterium tuberculosis while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic (1).

Reference
1. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.</td><td>The Guideline Development Group prioritized this PICO question for review.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
• Moderate
○ Large
○ Varies
○ Don't know</td><td rowspan="2"><table><tr><th rowspan="2">Outcomes</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="3">Anticipated absolute effects (95% CI)</th></tr><tr><th>Without treatment (or delayed)</th><th>With treatment</th><th>Difference</th></tr><tr><td>Reduction in LTBI incidence/prevalence in all settings</td><td>RR 0.29 (-- to --)</td><td>4.8%</td><td>1.4%</td><td>3.4% fewer</td></tr></table>See GRADE evidence summary table above.</td><td>No data was identified on TB disease incidence. Four articles were identified that assessed reduction in LTBI incidence/prevalence. The Guideline Development Group noted that these studies all identified composite interventions.

The Guideline Development Group based its judgement on the consideration that treating with appropriate drugs should be done anyway and has many other implicit benefits for the patient. The Guideline Development Group therefore judged that appropriate treatment has many other benefits for both the treated population and those at risk of TB disease.

The Guideline Development Group judged that 42 fewer per 1,000 individuals represented a moderate desirable anticipated effect.</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
• Trivial
○ Varies
○ Don't know</td><td>No research evidence was identified.

The Guideline Development Group judged that effective treatment initiated earlier for prevention of transmission had trivial desirable effects compared to effective treatment initiated later.</td></tr>
<tr><td>CERTAINTY OF EVIDENCE</td><td>What is the overall certainty of the evidence of effects?
• Very low
○ Low
○ Moderate
○ High
○ No included studies</td><td><table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Reduction in LTBI incidence/prevalence in all settings (n = 4 studies)</td><td>CRITICAL</td><td>⊕◯◯◯
VERY LOW[a,b,c,d]</td></tr></table>a. Indirectness is severe and from many sources: population, intervention, and comparators (please see assessment of directness for details).
b. Some inconsistency exists. In the study by Jarvis, in particular, certain results are reported as unavailable, but the site of origin of these results is not specified, so this cannot be accounted for in analysis. In addition, in the study by Welbel et al., overall denominators for at-risk individuals are provided, but not the time period for which these individuals were at risk, reducing confidence in the estimates of risk.
c. Serious imprecision exists. For a dichotomous outcome all studies have fewer than 110 cases (range 10–104). Samples sizes are also low in three studies (range 65–650; the exception is Welbel et al, with a sample size of 4,329).
d. There are design specific issues to these studies. Mainly, it is not possible to ascertain the effect of the intervention in question as the intervention is grouped with other interventions, which presents a serious risk of bias. There is also a serious design issue with the study by Wenger et al., as the intervention only differs slightly between before and after (3 agents vs. 4 agents). Though studies were not designed specifically to answer our question, the way they are designed does not give us confidence in the results of interest.</td><td></td></tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability • **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No research evidence was identified.	The Guideline Development Group agreed that there is probably no important uncertainty or variability in how much people value the main outcomes.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • **Favors the intervention** ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group agreed by consensus that the balance of effects favours the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings • **Moderate savings** ○ Large savings ○ Varies ○ Don't know	Overall cost of TB treatment is contributed by provider costs and patient-incurred costs as with any other treatment intervention. The cost of medicines is also part of these costs although its placement will depend on the way the health system is organized in specific country. The healthcare costs are very variable and depend on the local setting and country and the setup of the healthcare system, as well as costs of medicines. Due to its duration (and related healthcare and patient-incurred costs) and costs of medicines, treatment of DS-TB and DR-TB are very much different with DR-TB treatment being many times more costly. Since the anti-TB medicines are available from GDF, cost of medicines can be more standardized with DS-TB treatment course being less than 50 USD, treatment of DR-TB using shorter regimen ranging 500-900 USD, treatment of DR-TB using longer regimen 1'500-6'000 and higher for other, more complicated forms of MDR-TB.	The Guideline Development Group clarified that resource requirements relate to earlier treatment compared to later initiation of effective treatment. The Guideline Development Group noted that additional costs may relate to additional resources to facilitate more rapid diagnosis and initiation of treatment. The Guideline Development Group noted that cost savings for earlier effective treatment may relate to the management of less complicated TB cases (due to prevention of disease progression) to treat and cost savings due to prevented secondary transmission. The Guideline Development Group judged by consensus that the resources required conferred moderate savings.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • **No included studies**	No research evidence was identified.	

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • **Favors the intervention** ○ Varies ○ No included studies	No research evidence was identified.	The Guideline Development Group agreed that the economic case for investment in TB control is compelling: treatment is low cost and highly effective, and on average may give an individual in the middle of their productive life around 20 additional years, resulting in substantial economic and health returns. Additionally, the Copenhagen Consensus estimates that each US$1 invested in a package of TB interventions will lead to US$43 in economic benefits *(1)*. At US$6 per DALY averted, the treatment of cases under DOTS is the most cost-effective intervention considered by the WHO in an exercise named Choosing Interventions that are Cost Effective (WHO-CHOICE) *(2)*. References 1. http://www.copenhagenconsensus.com/post-2015-consensus 2. WHO | Cost-Effectiveness Results. World Health Organization. Available at: http://www.who.int/choice/results/en/. (Accessed: 7 March 2018)
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased • **Increased** ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that in addition to increasing equity for healthcare workers, this intervention will also increase equity for other individuals attending healthcare facilities. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 7 members voted in favour of 'probably increased'; 9 members voted in favour of 'increased'; there was 1 abstention, and 2 members of the panel were absent during the voting process.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group agreed by consensus that the intervention is probably acceptable to key stakeholders including patients, health workers and policy-makers.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that the feasibility may vary by setting and resources available for rapid diagnosis and treatment, however, the Guideline Development Group agreed by consensus that in general this intervention would probably be feasible across settings. The barriers to implementation have been identified as access to drug sensitivity testing and personnel resources for this intervention. The Guideline Development Group agreed by consensus that the intervention is probably feasible to implement.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the use of effective treatment

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	Prompt initiation of effective treatment of people with TB disease is recommended to reduce TB transmission to health workers, persons attending health care settings or other persons in high TB transmission risk settings (Strong recommendation based on very low certainty in the evidence about the effects).				
JUSTIFICATION	The Guideline Development Group made a strong recommendation based on very low certainty of the evidence, due to the life-threatening nature of TB (including possibly MDR-TB) for those health workers affected by transmission. *Desirable Effects:* The Guideline Development Group judged that the desirable anticipated effects were moderate, including evidence of 42 less LTBI incidence per 1,000. *Balance of Effects:* The Guideline Development Group agreed by consensus that the balance of effects favours the intervention. *Cost Effectiveness:* The Guideline Development Group noted that the cost-effectiveness of favours the intervention because effective treatment is cost-effective and results in significant benefits. *Acceptability:* The Guideline Development Group agreed that the intervention is probably acceptable to key stakeholders. *Feasibility:* The Guideline Development Group agreed that the intervention is probably feasible to implement.				
SUBGROUP CONSIDERATIONS	MDR-TB patients: the Guideline Development Group considered that the net benefit of effective treatment to prevent transmission may be greater due to the severity of the TB disease if transmitted, however, the benefit also exists for all TB patients not strictly drug-resistant patients.				
IMPLEMENTATION CONSIDERATIONS	1. The Guideline Development Group noted effective treatment, which is addressed in this recommendation implies initiation of treatment as early as possible based on drug-sensitivity testing to prevent complications or further transmission. 2. The Guideline Development Group noted testing-availability barriers to implementation including access to drug sensitivity testing and rapid diagnostic testing. Simultaneously the Guideline Development Group noted that rapid and accurate transmission of testing results 3. The Guideline Development Group also noted that increased personnel resources will be required for this intervention. 4. This may require additional treatment capacity, including isolation treatment facilities, and access to TB drugs for appropriate treatment. 5. The Guideline Development Group noted that access to second-line drug treatment may be limited to certain healthcare facilities and therefore effective treatment may take longer than first-line therapy. 6. The Guideline Development Group refers to the WHO Guidelines of Diagnosis of TB for further information on diagnosis. Available from: http://www.who.int/tb/publications/diagnosis/en/ 7. The Guideline Development Group suggests consideration of interventions that improve compliance to treatment, notably for patients with drug resistant TB. 8. Implementation of this recommendation needs to include consultation and input from affected patients and health workers.				
MONITORING AND EVALUATION	1. The Guideline Development Group suggested monitoring the quality and duration until initiation of effective treatment to prevent transmission. 2. Use surveillance data to evaluate how effective treatment.				
RESEARCH PRIORITIES	1. Duration of infectiousness on treatment of TB patients. 2. Research to better understand the incidence of TB and MDR-TB on healthcare workers. 3. Further research should assess the cost-effectiveness of effective treatment to reduce TB transmission. 4. Evaluation of individual interventions to reduce TB transmission, notably among healthcare workers. 5. Further research to assess treatment efficacy. 6. Research is suggested on the prevention of transmission of drug-resistant TB, including infection control strategies.				

PICO 2 - Administrative controls: Evidence-to-decision framework for the implementation of respiratory hygiene

<table>
<tr><th colspan="3">CAN RESPIRATORY HYGIENE (OR COUGH ETIQUETTE) IN PEOPLE WITH PRESUMED OR CONFIRMED TB REDUCE TB TRANSMISSION TO HEALTHCARE WORKERS IN HEALTHCARE FACILITIESN OR OTHER CONGREGATE SETTINGS TO REDUCE TB TRANSMISSION WHEN COMPARED TO SETTINGS WHERE THESE INTERVENTIONS ARE NOT IMPLEMENTED?</th></tr>
<tr><td>POPULATION:</td><td>Other healthcare or congregate settings to reduce TB transmission when compared to settings where these interventions are not implemented</td><td rowspan="6">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world's leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>INTERVENTION:</td><td>Respiratory hygiene (or cough etiquette)</td></tr>
<tr><td>COMPARISON:</td><td>No respiratory hygiene (or cough etiquette)</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Reduction in LTBI incidence/prevalence - all settings (n=2); Reduction in TB incidence/prevalence (n=2);</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group is being convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
• Yes
○ Varies
○ Don't know</td><td>Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with Mycobacterium tuberculosis while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic (1).

Reference
2. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.</td><td>The Guideline Development Group prioritized this PICO question for review.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
• Large
○ Varies
○ Don't know</td><td rowspan="2"><table><tr><th rowspan="2">Outcomes</th><th colspan="2">N° of patients</th><th rowspan="2">Certainty</th></tr><tr><th>Respiratory hygiene</th><th>No respiratory hygiene</th></tr><tr><td>Reduction in LTBI incidence/prevalence (n=1) (Animal study, surgical mask use by patient with TB)</td><td>36/90 (40.0%)</td><td>69/90 (76.7%)</td><td>⊕⊕◯◯ LOW</td></tr><tr><td>Reduction in TB incidence/prevalence (n=1)</td><td>0/44 (0.0%)</td><td>26/90 (28.9%)</td><td>⊕⊕◯◯ LOW</td></tr><tr><td>Reduction in TB incidence/prevalence in people living with HIV (n=1)</td><td>0/44 (0.0%)</td><td>26/90 (28.9%)</td><td>⊕⊕◯◯ LOW</td></tr></table>See GRADE evidence summary table above</td><td>The Guideline Development Group agreed by consensus that the desirable effects are large.</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
• Trivial
○ Varies
○ Don't know</td><td>The Guideline Development Group noted that discomfort and stigma are undesirable effects of the mask component of the respiratory hygiene intervention. The Guideline Development Group agreed by consensus that the undesirable effects are trivial.</td></tr>
<tr><td>CERTAINTY OF EVIDENCE</td><td>What is the overall certainty of the evidence of effects?
○ Very low
• Low
○ Moderate
○ High
○ No included studies</td><td></td><td></td></tr>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
• No important uncertainty or variability</td><td>No research evidence was identified.</td><td>The Guideline Development Group agreed by consensus that there is no important uncertainty or variability in how much people value the main outcomes.</td></tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • **Favors the intervention** ○ Varies ○ Don't know	No research evidence was identified.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings • **Moderate savings** ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that certain masks may have higher costs. The Guideline Development Group noted that the cost of most masks is very small. The Guideline Development Group noted that the cost savings with prevention of TB transmission, notably MDR-TB transmission would be significant. Overall, the Guideline Development Group judged that there would be moderate savings due to prevention of TB transmission. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 13 members voted in favour of 'moderate savings', 4 members voted in favour of 'large savings', there was 1 abstention, and 1 member of the panel was absent during the voting process.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • **No included studies**	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	The Guideline Development Group agreed by consensus that the cost-effectiveness probably favours the intervention.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact • **Probably increased** ○ Increased	No research evidence was identified.	The Guideline Development Group agreed by consensus that the intervention would probably increase health equity.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	○ Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Patients: The patient representative on the Guideline Development Group noted that the respiratory hygiene intervention of wearing a mask would create stigma for a patient. Other respiratory hygiene measures would be more acceptable because they are not as visible and stigmatizing. The Guideline Development Group noted that certain settings will implement a mask-wearing policy for patients with multiple medical conditions, thereby decreasing attention to patients with possible TB disease and decreasing stigma. The Guideline Development Group agreed by consensus that the intervention would probably be acceptable to key stakeholders.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes • **Yes** ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group agreed by consensus that the intervention would be feasible to implement.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the implementation of respiratory hygiene

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce TB transmission to health workers, persons attending health care facilities or other persons in high TB transmission risk settings (Strong recommendation based on low certainty in the evidence about the effects).				
JUSTIFICATION	The Guideline Development Group notes that the evidence reviewed was for wearing a mask, however, extended the application of this evidence to other respiratory hygiene measures based on Guideline Development Group judgement. The Guideline Development Group based its strong recommendation despite low certainty in the evidence about the effects on the judgement that TB transmission is a potentially fatal consequence. *Balance of Effects:* The Guideline Development Group judged that the balance of effects favours the intervention. *Resources Required:* The Guideline Development Group judged that the intervention would bring moderate savings due to the prevention of TB transmission. *Cost Effectiveness:* The Guideline Development Group judged that the cost-effectiveness probably favours the intervention. *Feasibility:* The Guideline Development Group judged that the intervention is feasible to implement.				
SUBGROUP CONSIDERATIONS	None considered.				
IMPLEMENTATION CONSIDERATIONS	1. Reducing stigma of patients through public education. 2. The Guideline Development Group also noted that increased personnel resources for the education and monitoring of respiratory hygiene may be required for this intervention. 3. Training of patients on how to wear masks or conduct other respiratory hygiene measures appropriately. 4. Access to and cost of large number of masks for this intervention. 5. The Guideline Development Group noted that the duration of mask use and when to discard masks should be directed. 6. Consideration of human cooperation and adherence to mask-use and other respiratory hygiene for patients. 7. The Guideline Development Group noted that this intervention may be more difficult to implement for children. 8. Implementation of this recommendation needs to include consultation and input from affected patients and health workers.				
MONITORING AND EVALUATION	1. The Guideline Development Group suggested monitoring the use of respiratory hygiene for the prevention of TB transmission.				
RESEARCH PRIORITIES	1. The Guideline Development Group suggests additional research on cost and resource use of the masks, including cost-effectiveness evidence. 2. Further research on the non-mask respiratory hygiene interventions. 3. Duration of infectiousness on treatment of TB patients. 4. Research to better understand the incidence of TB and MDR-TB on healthcare workers. 5. Further research should assess the cost-effectiveness of effective treatment to reduce TB transmission. 6. Evaluation of individual interventions to reduce TB transmission, notably among healthcare workers. 7. Research is suggested on the prevention of transmission of drug-resistant TB, including infection control strategies.				

PICO 3 - Environmental controls: Evidence-to-decision framework for the implementation of upper room ultraviolet germicidal irradiation systems

<table>
<tr><th colspan="3">CAN UPPER-ROOM GERMICIDAL ULTRAVIOLET (GUV) SYSTEMS REDUCE TB TRANSMISSION IN HEALTHCARE WORKERS IN HEALTH CARE FACILITIES OR OTHERS IN HIGH TB TRANSMISSION RISK SETTINGS WHEN COMPARED TO TRANSMISSION TO THE SAME POPULATIONS IN SETTINGS WITH NO INTERVENTION OR DIFFERENT INTERVENTIONS?</th></tr>
<tr><td>POPULATION:</td><td>Reducing TB transmission in persons in TB care or other high TB transmission risk settings</td><td rowspan="5">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world's leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>INTERVENTION:</td><td>Upper room GUV</td></tr>
<tr><td>COMPARISON:</td><td>No upper room GUV</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Reduction in LTBI incidence/prevalence (n=0); Reduction in TB incidence/prevalence (n=0); Reduction in LTBI incidence/prevalence (animal studies) (n=3); Reduction in TB incidence/prevalence (animal studies) (n=4);</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group is being convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes • **Yes** ○ Varies ○ Don't know	Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with *Mycobacterium tuberculosis* while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic *(1)*. Reference 1. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.	The Guideline Development Group prioritized this PICO question for review.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate • **Large** ○ Varies ○ Don't know	Three studies in humans evaluated the reduction in LTBI incidence/prevalence in healthcare workers in TB care or other high TB transmission risk settings. In Fella, a composite outcome including UVGI was associated with a reduction in TST conversion from 41/303 (13.5%) in the intervention group to 21/446 (4.7%) in the control group – a reduction of 8.8%. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Therefore, both studies demonstrated a reduction in TST conversions. Welbel 1995 showed that mechanical ventilation, in combination with other engineering measures, was associated with a reduction in TST conversions from 98/2,221 (4.4%) to 6/2108 (0.28%), a reduction of 4.1%. Heterogeneity in the interventions precluded meta-analysis (see GRADE evidence summary table above).	The Guideline Development Group noted that the effectiveness of upper room GUV may impacted by relative humidity. The Guideline Development Group agreed by consensus that the desirable anticipated effects were large.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate • **Small** ○ Trivial ○ Varies ○ Don't know		The Guideline Development Group agrees that there are undesirable effects of upper room GUV that largely relate to improper installation or maintenance. The adverse effects identified include eye and skin irritation if they are not turned off during cleaning or replacement. The eye and skin irritation are reported to be transient effects, resolving after 24-48 hours. Because this is UV-C type light, there have not been associations with skin cancers. Sleep disturbances may also be an undesirable effect. In practice the Guideline Development Group has noted that proper installation and maintenance is not conducted universally in practice. Additional evidence on safety of upper room GUV was discussed by the Guideline Development Group *(1)*. The Guideline Development Group could not agree by consensus, therefore voting was conducted:13 members voted in favour of 'small'; 2 members voted in favour of 'trivial', 1 members voted in favour of 'large'; 1 member voted in favour of 'varies'; there was 1 abstention (Chair), and 1 member of the panel was absent. Reference 1. Brickner PW, Vincent RL. Ultraviolet Germicidal Irradiation Safety Concerns: A Lesson from the Tuberculosis Ultraviolet Shelter Study Murphy's Law Affirmed. Photochemistry and photobiology. 2013 Jul;89(4):819-21.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low • **Moderate** ○ High ○ No included studies	No research evidence was identified.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability • **No important uncertainty or variability**	No research evidence was identified.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group agreed by consensus that the balance between the desirable and undesirable effects probably favours the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs • **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	Although no cost or cost-effectiveness studies were analysed for this review, the Guideline Development Group noted that the costs may vary by setting and the volume of purchasing. The cost of an effective UV fixture would range from $800-3000 USD, but the Guideline Development Group discussed that in some settings, GUV may cost as little as $100 USD. The Guideline Development Group emphasised that in the long run, the cost of such systems is not difficult to justify, given the main gain in the prevention of *M. tuberculosis* transmission (as well as other airborne pathogens). The Guideline Development Group could not agree by consensus, therefore voting was conducted: 2 members voted in favour of 'large costs'; 11 members voted in favour of 'moderate costs'; 3 members voted in favour of 'moderate savings'; there was 1 abstention (Chair), and 2 members of the panel were absent during the voting process.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CERTAINTY OF EVIDENCE OF REQUIRED	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • **No included studies**	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • **Favors the intervention** ○ Varies ○ No included studies	No research evidence was identified.	The Guideline Development Group could not agree by consensus, therefore voting was conducted: 5 members voted in favour of 'probably favours the intervention'; 11 members voted in favour of 'favours the intervention'; there was 1 abstention, and 2 members of the panel were absent during the voting process.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact • **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group judged that this intervention can be applied widely and that the benefits will impact other people attending healthcare settings. The Guideline Development Group agreed by consensus that health equity would probably increase.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Patients: may have concerns with sleep disturbance due to light at night. Policy-makers: consideration of the cost of this intervention may impact acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that the feasibility may be impacted by the cost of the installation of upper room GUV and ongoing maintenance. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 13 members voted in favour of 'probably yes'; 2 members voted in favour of 'varies'; there was 1 abstention, and 3 members of the panel were absent during the voting process.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the use of upper room ultraviolet air disinfection

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	Upper-room germicidal ultraviolet (GUV) irradiation is recommended to reduce TB transmission for health workers, persons attending health care facilities or other persons in high TB transmission risk settings (Conditional recommendation based on moderate certainty about the effects).				
JUSTIFICATION	The Guideline Development Group could not agree by consensus on the recommendation, therefore voting was conducted:5 members voted for a 'strong recommendation for the intervention', 11 members voted in favour of 'conditional recommendation for the intervention', there was 2 members absent and 1 member abstained (Chair). *Balance of Effects:* The Guideline Development Group judged that the balance of effects probably favours the intervention. *Resources Required:* The Guideline Development Group judged that the resources required for this intervention involve moderate costs. *Cost-Effectiveness:* The Guideline Development Group judged that the cost-effectiveness probably favours the intervention. *Equity:* The Guideline Development Group judged that the intervention would probably increase health equity. *Acceptability:* The Guideline Development Group judged that the invention would probably be acceptable to key stakeholders.				
SUBGROUP CONSIDERATIONS	None considered. The Guideline Development Group applies this conditional recommendation for all TB patients.				
IMPLEMENTATION CONSIDERATIONS	1. The Guideline Development Group recommends appropriate and safe installation and maintenance. 2. The Guideline Development Group noted that the intervention requires education regarding the safety of the upper room GUV with safe installation and use. 3. The Guideline Development Group noted that the effectiveness of upper room GUV may impacted by relative humidity. 4. The Guideline Development Group prioritized suggests risk assessments at the local level to identify priority areas for the use of upper room GUV. 5. The Guideline Development Group suggests consideration of movement of air through fan units to improve effectiveness of upper room GUV. 6. The Guideline Development Group notes that structural modifications or renovations may be necessary to meet performance parameters for upper room GUV.				
MONITORING AND EVALUATION	1. The Guideline Development Group noted that quality control measures for the effective and safe installation and maintenance should be implemented. 2. The Guideline Development Group notes that UV exposure for healthcare workers should be monitored.				
RESEARCH PRIORITIES	1. The Guideline Development Group notes that more direct research evidence, including program data, is broadly needed on the effectiveness of upper room GUV on patient-important outcomes. 2. Experiential evidence for upper room GUV in use should be shared and/or published. 3. Further research on UV dosing based on microenvironment, reported by space area (in cubic feet or metres) is necessary to guide implementation.				

PICO 3 - Environmental controls: Evidence-to-decision framework for the implementation of ventilation systems

<table>
<tr><th colspan="3">CAN NATURAL, MIXED-MODE, MECHANICAL OR RECIRCULATED THROUGH HIGH-EFFICIENCY PARTICULATE AIR VENTILATION SYSTEMS BE USED FOR REDUCING TB TRANSMISSION IN HEALTH WORKERS OR OTHER PERSONS IN TB CARE OR OTHER HIGH TB TRANSMISSION RISK SETTINGS?</th></tr>
<tr><td>POPULATION:</td><td>Reducing TB transmission in health workerss in TB care or other high TB transmission risk settings</td><td rowspan="6">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world's leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>INTERVENTION:</td><td>Natural, mixed-mode, mechanical ventilation or recirculated air with filtration.</td></tr>
<tr><td>COMPARISON:</td><td>No ventilation</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Reduction in LTBI incidence/prevalence (n= 6); Reduction in TB incidence/prevalence (n=0); Reduction in LTBI incidence/prevalence in TB laboratory workers (n=1);</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group is being convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
• Yes
○ Varies
○ Don't know</td><td>Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with Mycobacterium tuberculosis while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic (1).

Reference
1. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.</td><td>The Guideline Development Group prioritized this PICO question for review.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
• Moderate
○ Large
○ Varies
○ Don't know</td><td rowspan="2"><table><tr><th>Outcome</th><th>Use of ventilation systems (mixed)</th><th>No use of ventilation systems (mixed)</th><th>Certainty</th></tr><tr><td>Reduction in TB incidence/prevalence (n= 1)</td><td>19/4780 (0.4%)</td><td>30/4357 (0.7%)</td><td>⨁◯◯◯
VERY LOW</td></tr></table>See GRADE evidence summary table above</td><td>The Guideline Development Group discussed concern that the number of air changes per hour were not reported by a number of the included studies. Where studies report a number of ACH, it may be a target or estimate and not a measured number.

The Guideline Development Group could not agree by consensus, therefore voting was conducted: 9 members voted in favour of ‘moderate’, 7 members voted in favour of ‘large’, there was 1 abstention, and 2 members of the panel were absent during the voting process.</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
• Small
○ Trivial
○ Varies
○ Don't know</td><td>The Guideline Development Group did not identify any significant undesirable effects with an effective ventilation system.

The Guideline Development Group noted that lack of maintenance and/or design faults that create positive pressure may lead to harm for mechanical ventilation systems.

The Guideline Development Group additionally noted that there are climate-dependent consequences of ventilation options available (e.g. natural ventilation may not be feasible in cold climates).

The Guideline Development Group could not agree by consensus, therefore voting was conducted: 13 members voted in favour of ‘small’, 3 for ‘trivial’, 1 member abstained (Chair), and 2 members were absent.</td></tr>
<tr><td>CERTAINTY OF EVIDENCE</td><td>What is the overall certainty of the evidence of effects?
• Very low
○ Low
○ Moderate
○ High
○ No included studies</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
• No important uncertainty or variability</td><td>No research evidence was identified.</td><td>The Guideline Development Group agreed by consensus that there was probably no important uncertainty or variability in how much people value the main outcomes.</td></tr>
</table>

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group could not agree by consensus, therefore voting was conducted: 4 members voted in favour of 'favours the intervention'; 12 members voted in favour of 'probably favours the intervention'; 1 member abstained (Chair), and 2 members of the panel were absent during the voting process.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs • **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that there is variability in costs from moderate to large depending on the setting. The Guideline Development Group noted that in many settings mechanical ventilation for heating and cooling buildings is present already. For structures that do not currently have systems in place the incremental cost of mechanical or mixed-mode ventilation is higher. In addition to the incremental costs of upgrading to mechanical or mixed-mode ventilation the Guideline Development Group noted that maintenance cost must also be considered. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 10 members voted in favour of 'moderate costs'; 6 members voted in favour of 'large costs'; there was 1 abstention, and 2 members of the panel were absent during the voting process.
CERTAINTY OF EVIDENCE OF REQUIRED	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • No included studies	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	No research evidence was identified, however the Guideline Development Group agreed by consensus that the cost-effectiveness probably favours the intervention.
EQUITY	**What would be the impact on health equity?**	No research evidence was identified.	The Guideline Development Group agreed by consensus that there would probably be no impact on health equity.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	○ Reduced ○ Probably reduced • **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Patients and health workers: Probably yes acceptable. The Guideline Development Group noted the minor nuisance of noise for certain mechanical ventilation systems, however, felt that the benefits would make the intervention acceptable. Policy-makers: The Guideline Development Group agreed that due to the increased costs of mechanical ventilation, there may be less acceptability among certain policy-makers.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group judged that the intervention is probably feasible to implement.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the use of ventilation systems

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	Ventilation systems (including natural, mixed-mode, mechanical ventilation, and recirculated air through high-efficiency particulate air [HEPA] filtration) are recommended to reduce TB transmission to health workers, persons attending health care facilities or other persons in high TB transmission risk settings (Conditional recommendation based on very low certainty in the evidence about the effects). This recommendation applies to multiple ventilation strategies (See multi-comparison chart below), including natural, mixed-mode, mechanical ventilation and recirculated air with filtration.				
JUSTIFICATION	*Balance of Effects:* The Guideline Development Group judged that the balance of effects probably favours the intervention. *Resources Required:* The Guideline Development Group judged that the resources required included moderate costs. *Cost-Effectiveness:* The Guideline Development Group judged that the cost-effectiveness probably favours the intervention. *Acceptability:* The Guideline Development Group judged that the intervention was probably acceptable to key stakeholders. The Guideline Development Group agreed that this recommendation did not extend to portable room-air cleaners. The systematic review did not identify any evidence from studies that met inclusion/exclusion criteria. The Guideline Development Group did not feel they could extrapolate from other ventilation modes to room-air cleaners. The Guideline Development Group discussed indirect research evidence. Further research is recommended prior to the use of these devices.				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS	1. The Guideline Development Group noted that effective design and maintenance is very important for mechanical and mixed-mode ventilation or recirculated air with filtration to reduce TB transmission. 2. The Guideline Development Group noted across different settings there may be unique considerations ventilation systems due to security or safety concerns. Those identified included mechanical/mixed-mode ventilation systems in prisons or window-use for natural ventilation.				
MONITORING AND EVALUATION	1. The Guideline Development Group suggests monitoring and evaluation of maintenance for mechanical and mixed-mode ventilation and recirculated air with filtration systems.				
RESEARCH PRIORITIES	1. Studies assessing the air exchange rate in mechanical ventilation systems. 2. Additional research to assess the effect size of mechanical ventilation systems for the prevention of TB transmission. 3. Cost-effectiveness evidence and modelling studies to inform decision-making regarding mechanical ventilation settings. 4. The type of mechanical ventilation mode used and microclimate of mechanically-ventilated settings. 5. The Guideline Development Group suggests urgent development of target product profiles to better assess the evidence for room-air cleaners.				

	Natural ventilation	Mixed-mode ventilation	Mechanical ventilation	Recirculated air filtration
Balance of effects	★★★★☆	★★★★☆	★★★★☆	★★★☆☆
Resources required	★★★★☆	★★★☆☆	★☆☆☆☆	★★☆☆☆
Cost effectiveness	★★★★★	☆☆☆☆☆	☆☆☆☆☆	☆☆☆☆☆
Equity	★★★★☆	★★★☆☆	★★☆☆☆	★★☆☆☆
Acceptability	★★★★★	★★★★☆	★★★★☆	★★★★☆
Feasibility	★★★★☆	★★★☆☆	★★☆☆☆	★☆☆☆☆

PICO 4 – Respiratory protection: Evidence-to-decision framework for the implementation of particulate respirators

<table>
<tr><th colspan="3">CAN THE USE OF PARTICULATE RESPIRATORS REDUCE TB TRANSMISSION IN HEALTH WORKERS IN TB CARE OR IN OTHER HIGH TB TRANSMISSION RISK SETTINGS WHEN COMPARED TO TRANSMISSION TO THE SAME POPULATIONS IN SETTINGS WITH NO INTERVENTION OR DIFFERENT INTERVENTIONS?</th></tr>
<tr><td>POPULATION:</td><td>Reducing TB transmission in health workers in TB care or other high TB transmission risk settings</td><td rowspan="6">BACKGROUND: Tuberculosis (TB) remains a threat to global public health and the world's leading single-infectious cause of death. Approximately 1.7 billion people are believed to be infected with Mycobacterium tuberculosis. Although a relatively small proportion (5–15%) of the estimated people infected with M. tuberculosis will develop TB disease during their lifetime, the probability of developing TB disease is much higher among people with various risk factors, including HIV infection and others, such as under-nutrition, diabetes, smoking and alcohol consumption. In 2016, an estimated 10.4 million people developed TB, with1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people.

The implementation of effective infection control and prevention measures are essential to prevent transmission of M. tuberculosis, and these are vital to reaching the global goals and targets to end TB. The upcoming Guideline Development Group (Guideline Development Group) meeting seeks to evaluate available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community; also, the output of this Guideline Development Group meeting would be an updated set of guidelines to provide Member States with directions on the implementation of measures to reduce the risk of TB transmission in healthcare facilities, congregate settings and households, and how to prioritize TB infection prevention and control measures.

Between 2017-2018, evidence reviewers from the London School of Hygiene & Tropical Medicine and the University of Sydney, coordinated the search to identify relevant data that could informed the development of specific recommendations on infection control measures.</td></tr>
<tr><td>INTERVENTION:</td><td>Use of particulate respirators</td></tr>
<tr><td>COMPARISON:</td><td>No use of particulate respirators</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Reduction in LTBI incidence/prevalence (n=8); Reduction in TB incidence/prevalence (n=1);</td></tr>
<tr><td>SETTING:</td><td>International</td></tr>
<tr><td>PERSPECTIVE:</td><td>A WHO Guideline Development Group is being convened from 27-29 March 2018 to assess available evidence and update the 2009 recommendations on interventions to prevent or reduce TB transmission in health-care facilities, congregate settings and in the community. The PICO questions were formulated by the WHO Guidelines Steering Group and finalised in agreement with Members of the Guideline Development Group. These questions covered the all hierarchy of controls, including administrative measures; environmental controls; and use of respiratory protective equipment, with a focus on healthcare workers and other persons in TB care or other high TB transmission risk settings.</td></tr>
</table>

Assessment

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Tuberculosis (TB) is one of the top 10 causes of death worldwide. About one-quarter of the world's population is infected with *Mycobacterium tuberculosis* while about 10.4 million people developed TB disease, with 1.7 million more dying to the disease. Over 95% of TB deaths occur in low- and middle-income countries. Therefore, decreasing the risk of TB transmission is imperative to stemming the epidemic *(1)*. Reference 1. Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1. World Health Organization: Geneva. 2017.; 2017.	The Guideline Development Group prioritized this PICO question for review.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	Eight included studies, evaluating composite interventions that included fitted respirator use, found a reduction in TST conversion of between a 1% increase (Bangsberg 1997) and a 14.8% decrease (Yanai 2003). Fit testing was performed in three of these studies (Bangsberg, Yanai, Welbel).	The Guideline Development Group agreed by consensus that the desirable anticipated effects were moderate.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know		The Guideline Development Group noted that there may be stigmatization for patients when health workers are wearing respirators. The Guideline Development Group also noted that health workers communication with patients may be negatively impacted by respirator wearing. The Guideline Development Group also noted that there is discomfort and difficulty breathing for health workers wearing respirators, particularly in hotter climates. Difficulty breathing may be more significant for individuals with asthma or claustrophobia. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 11 members voted in favour of 'small', 4 members voted in favour of 'trivial', there was 1 abstention (Chair), and 3 members of the panel were absent during the voting process.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● **Very low** ○ Low ○ Moderate ○ High ○ No included studies		
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● **No important uncertainty or variability**	No research evidence was identified.	The Guideline Development Group agreed by consensus that there was no important uncertainty or variability in how much people value the main outcomes.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • **Favors the intervention** ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group could not agree by consensus, therefore voting was conducted: 7 members voted in favour of 'probably favours the intervention'; 8 members voted in favour of 'favours the intervention'; there was 1 abstention (Chair), and 3 members of the panel were absent during the voting process.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs • **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group noted that the resources required for this intervention are dependent on the cost of respirators and the frequency that health workers need to change their respirator. The Guideline Development Group also noted that effective fit testing is a significant additional cost, though the Guideline Development Group notes that effective fit testing averts wasted resources on ineffective respirators. The Guideline Development Group had substantial debate regarding the costs of the intervention in the context of the very high costs of TB disease as a consequence, and therefore the significant savings will accompany this intervention. The Guideline Development Group could not agree by consensus, therefore voting was conducted: 10 members voted in favour of 'moderate costs'; 5 members voted in favour of 'moderate savings'; and there was 1 abstention (Chair), and 3 members of the panel were absent during the voting process.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High • **No included studies**	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies • **No included studies**	No research evidence was identified.	
EQUITY	**What would be the impact on health equity?**	No research evidence was identified.	The Guideline Development Group agreed by consensus that there would probably be no impact on health equity.

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	○ Reduced ○ Probably reduced • **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Health workers: The Guideline Development Group also noted that there is discomfort and difficulty breathing for health workers wearing respirators, particularly in hotter climates. For this reason they may be less acceptable to wear. The Guideline Development Group noted that there are increased challenges for individuals with facial hair, notably those with facial hair for cultural reasons. The Guideline Development Group noted that alternative strategies are necessary for this population and this may impact the acceptability. Patients: The Guideline Development Group noted that there are increased communication difficulties for TB patients who have experienced hearing loss due to drug therapy adverse effects. The wearing of respirators will make lip-reading impossible. Administrators: The Guideline Development Group noted that they may require education about the downstream consequences and impact on TB transmission to increase acceptability of this intervention.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no • **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The Guideline Development Group judged that the cost implications may challenge the feasibility of the implementation of this intervention. However, this is currently in place in many settings. Therefore, the Guideline Development Group agreed by consensus that the intervention is probably feasible to implement.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions on the use of particulate respirators

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	Particulate respirators, within the framework of a respiratory protection programme, are recommended to reduce TB transmission to health workers, persons attending health care facilities or other persons in high TB transmission risk settings. (Conditional recommendation based on very low certainty in the evidence about the effects).				
JUSTIFICATION	The Guideline Development Group agreed by consensus to support a conditional recommendation for the intervention. *Balance of the Effects:* The Guideline Development Group judged that the balance of effects favours the intervention. *Resources Required:* The Guideline Development Group judged that there would be moderate costs associated with this intervention. The cost of respirators is small, however, the necessary adjunct, effective fit testing, was noted to have a significant additional cost. *Acceptability:* The Guideline Development Group judged that the intervention is probably acceptable by key stakeholders.				
SUBGROUP CONSIDERATIONS	Facial Hair: the Guideline Development Group considered that due to preferences or cultural considerations the use of respirators may not be effective in populations with facial hair such as beards. The Guideline Development Group suggests alternative respiratory protection for this population. Individuals who have not been fit tested: the Guideline Development Group noted that there is not reliability of respirators for this population and there may be a false sense of security and increased risk of TB transmission. Patients with hearing loss due to TB treatment: The Guideline Development Group noted that there are increased communication difficulties for TB patients who have experienced hearing loss due to drug therapy adverse effects. The wearing of respirators will make lip-reading impossible. Health workers in defined high-risk settings, including laboratory workers: for health workers in high-risk settings following a risk assessment, the Guideline Development Group felt that implementation of this recommendation is of particular importance for this population. The Guideline Development Group refers to the WHO biosafety guidelines *(1, 2)* for laboratory workers, who are considered to be health workers, however, there is additional evidence to support the respirator use for this high-risk work. Other high-risk settings identified by the Guideline Development Group included: aerosol generating procedures such as bronchoscopy or radiology. References 1. Laboratory biosafety manual, Third edition [WHO/CDS/CSR/LYO/2004.11]. Available from: http://www.who.int/csr/resources/publications/biosafety/Biosafety7.pdf. Geneva: World Health Organization. 2004. 2. Tuberculosis laboratory biosafety manual [WHO/HTM/TB/2012.11]. Available from: http://apps.who.int/iris/bitstream/handle/10665/77949/9789241504638_eng.pdf;jsessionid=B5B5D63637AC48EBB87FAD0D89A18828?sequence=1. Geneva: World Health Organization. 2012.				
IMPLEMENTATION CONSIDERATIONS	The Guideline Development Group suggested that respirators should be used in the context of respiratory protection programs If only have respirators available due to low resources and the incremental cost of a full respiratory protection program, the Guideline Development Group recommends to use respirators-alone, but otherwise the recommendation is to use respirators in the context of a broader respiratory protection program. 1. The Guideline Development Group referred to the definition of health workers utilized, which included broad healthcare working staff not strictly those involved in patient care. 2. The Guideline Development Group noted that use of respirators requires respirator fit testing programs to ensure effective respirator use. 3. The Guideline Development Group notes that legal requirements may impact respiratory fit testing policies in different settings. 4. The Guideline Development Group suggests that specifications for quality control is important for ensuring access to effective respirators. 5. The Guideline Development Group noted that a risk assessment for TB transmission is necessary for the implementation of particulate respirators.				

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
IMPLEMENTATION CONSIDERATIONS	6. The Guideline Development Group noted that respirator purchasing should be based on the specifications of respirators that are required for the fit testing specifications of health workers in a particular setting. 7. The Guideline Development Group noted that specifications for respirator-use are available, the implementation of respirator-use should be made in the context of these specifications.				
MONITORING AND EVALUATION	1. The Guideline Development Group suggests development of monitoring indicators for the effectiveness of respiratory protection programs, including particulate respirators, for the prevention of TB transmission.				
RESEARCH PRIORITIES	1. The Guideline Development Group suggests research on costs and cost-effectiveness to better inform decision-making regarding respirators. 2. The Guideline Development Group suggests that research on the duration of effectiveness of respirators, including with the patient-important outcome measures of LTBI and TB disease.				