WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Tuberculosis care and support

Web annexes

World Health Organization

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Design by Inis Communication

WHO consolidated guidelines on tuberculosis

Module 4: Treatment

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Web Annex 1.1. Guideline update 2011

Question 7: Among MDR-TB patients, is ambulatory therapy compared to inpatient treatment more or less likely to lead to the outcomes of interest?

							Indirect comparison of generalized cost-effectiveness results[1]								
							Outpatient model of care[2]			Control: Inpatient model of care					
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies [patients]	Resistance profile (# drugs:% patients)	Resource use/ cost (2005 I$)[3,4]	Number of studies [patients]	Resistance profile (# drugs: % patients)	Resource use/ cost (2005 I$)[3,4]	Absolute effect/ difference[3]	Relative effect/ difference[3]	Quality
Viewpoint: health system															
Resource use per patient[5]	Observational	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	2 [415]	2:8 3:26 4:38 ≥5:28	bed-days: 0–7 hospital visits: 0–18 clinic visits: 253–450	2 [249]	2:1 3:14 4:26 ≥5:59	Bed-days: 192–321 Hospital visits: 0–250 Clinic visits: 85–171	Bed-days: outpatient 185–321 lower	Bed-days: outpatient 96–100% lower	⊕⊕◯◯[6]
Cost per patient	Observational	No serious limitations	No serious inconsistency	Serious indirectness[7]	No serious imprecision	None	2 [415]	2:8 3:26 4:38 ≥5:28	Diagnosis:[8] 125 Drugs: 1914 GHS:[9] 3400 Other: 5687 Total: 11126 (3201–29556)	2 [249]	2:1 3:14 4:26 ≥5:59	Diagnosis:[8] 251 Drugs: 4838 GHS:[9] 27068 Other: 3882 Total: 36039 (8349–103127)	Outpatient 24912 (4152–79315) better	Outpatient 63% (33–85%) better	⊕◯◯◯[10]
Cost per compliant[11] patient	Observational	No serious limitations	No serious inconsistency	Serious indirectness[7]	No serious imprecision	None	2 [415]	2:8 3:26 4:38 ≥5:28	12854 (3843–34037)	2 [249]	2:1 3:14 4:26 ≥5:59	40834 (9475–116820)	Outpatient 28119 (4616–89758) better	Outpatient 63% (33–85%) better	⊕◯◯◯
Cost per death averted[12]	Observational	No serious limitations	No serious inconsistency	Serious indirectness[13]	No serious imprecision	None	2 [415]	2:8 3:26 4:38 ≥5:28	17105 (4431–48540)	2 [249]	2:1 3:14 4:26 ≥5:59	48458 (10722–143102)	Outpatient 33099 (3821– 109169) better	Outpatient 62% (22–86%) better	⊕◯◯◯
Cost per DALY[14] averted	Observational	No serious limitations	No serious inconsistency	Serious indirectness[13]	No serious imprecision	None	2 [415]	2:8 3:26 4:38 ≥5:28	589 (137–1689)	2 [249]	2:1 3:14 4:26 ≥5:59	1859 (401–5445)	Outpatient 1271 (146–4173) better	Outpatient 62% (22–86%) better	⊕◯◯◯
Viewpoint: patient[15]															
Resource use per patient[5]	Observational	Serious limitations[16]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2 [415]	2:8 3:26 4:38 ≥5:28	Hours: 365–468	2 [249]	2:1 3:14 4:26 ≥5:59	Hours: 3158–5429	Outpatient 2690–5064 better	Outpatient 85–93% better	⊕◯◯◯

1. No two models of MDR-TB care are directly compared in the included studies and no two alternatives are the same. In order to (indirectly) compare cost per death averted and cost per DALY averted across the studies, we modelled a standard alternative of no intervention based on a standard distribution of death rate in the absence of second-line treatment and an assumption of zero cost. We re-calculate cost-effectiveness with regard to this null set for each of the studies. The results are then (partially) generalized for setting, using a standard distribution of DALYs averted per death averted and a global distribution of unit costs [adjusted for inflation, purchasing power parity (PPP), and Gross Domestic Product (GDP) per capita, as appropriate]. The results are not corrected for differences in the basic demography and epidemiology of disease across settings (See Footnote 13). The indirect comparison therefore assumes that effect sizes (death rates) achieved in one setting can be replicated in any other given setting by exactly reproducing the model of care–at local costs.
2. For the purposes of this review, the model of care described by a study is classified as "outpatient" if the average duration of hospitalization among the cohort of patients is no more than seven days. Three of the four included studies had some mix of inpatient and outpatient care; only in one study was the model of care entirely outpatient-based. Within the outpatient models of care, there were no studies looking at community-based care.
3. Numbers in parentheses are the 5th and 95th percentiles, representing the plausible range of values obtained in probabilistic, multivariate uncertainty analyses.
4. A 2005 international dollar (I$) is worth in any given country what 1 US$ could have bought in the United States of America in 2005.
5. Ranges in resource use per patient are lowest and highest cohort averages (mean or median) from across all of the included studies.
6. Low quality: Further research is likely to have an impact on the estimate of effect.
7. Results for the outpatient model of care represent a mix of standardized (298 patients) and individualized regimens (117 patients); whereas results for the inpatient model of care represent individualized regimens only (all 249 patients). The standardized regimen would today be considered substandard. The standardized regimen described by Suarez et al. (2002) is a 18-month daily regimen consisting of kanamycin (1 g injectable) for the first three months, ciprofloxacin (1 g orally), ethionamide (750 mg orally), pyrazinamide (1500 mg orally), and ethambutol (1200 mg orally). If we assumed the cost of an individualized regimen, the cost per patient under the outpatient model of care would increase by 19% (10%-38%), but the relative effect would still be 54% (13%-82%) less than the inpatient-based models of care.
8. Diagnosis costs include smear microscopy, culture, and drug-susceptibility testing using culture; none of the included studies were conducted in sites where or at a time when molecular or genetic testing for MDR-TB was available.
9. General Health-care Services (GHS): the cost associated with utilization of general health-care services (bed-days, hospital visits and clinic visits).
10. Very low quality: We are very uncertain about the estimates of effect.
11. Includes all patient outcomes except default.
12. Cost per death averted per index case and cost per DALY averted include transmission benefits (i.e. reductions in the number of deaths and DALYs from secondary cases infected by the index cases), and well as long-term deaths among defaults and relapses.
13. We know that there are differences between the study settings in terms of basic demography and epidemiology of disease, not least with respect to the resistance profile (see column "Resistance profile"). The fact that there is a higher proportion of patients showing resistance to more than five drugs in the studies of inpatient models of care may confound the results in favor of outpatient-based models. At the same time, the results may be confounded in favor of inpatient-based models, since the outcomes of the outpatient-based models reflect (in part) a substandard regimen. See Footnote 7. It is unclear which confounder predominates.
14. Disability-adjusted life-year (DALY).
15. Only costs of resources used to access the health intervention are included (e.g. transportation, nutrition); within these access costs, time losses are described, but not costed. Productivity losses due to illness are not considered.
16. None of the studies describes losses times in units. We estimate time losses at 16 hours per bed-day, 1 hour per hospital visit and 0.5 hours per clinic visit.

Web Annex 1.2. Guideline update 2017

PICO 10.1 Should self-administered treatment versus directly observed treatment be used for TB patients?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Self administered therapy (SAT) compared to directly observed therapy (DOT) for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self administered therapy (SAT)	Directly observed therapy (DOT)	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies												
19	observational studies	very serious [a]	very serious [b]	not serious	serious [c]	none	471/6955 (6.8%)	2681/81500 (3.3%)	not estimable	20 more per 1,000 (from 0 fewer to 40 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality - RCTs												
5	randomised trials	serious [d]	not serious	not serious	very serious [c,e]	none	27/731 (3.7%)	43/961 (4.5%)	not estimable	10 fewer per 1,000 (from 30 fewer to 10 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success - Cohort studies												
15	observational studies	very serious [a]	very serious [f]	not serious	not serious	none	3370/5061 (66.6%)	10311/13858 (74.4%)	**RR 0.79** (0.72 to 0.88)	156 fewer per 1,000 (from 89 fewer to 208 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success - RCTs												
5	randomised trials	serious [d]	not serious	not serious	not serious	none	566/775 (73.0%)	747/1001 (74.6%)	**RR 0.94** (0.89 to 0.98)	45 fewer per 1,000 (from 15 fewer to 82 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Completion - Cohort studies												
14	observational studies	very serious [a]	very serious [f]	not serious	serious [c]	none	1193/2997 (39.8%)	2276/8682 (26.2%)	not estimable	20 more per 1,000 (from 40 fewer to 80 more)	⊕◯◯◯ VERY LOW	CRITICAL
Completion - RCTs												
5	randomised trials	serious [d]	not serious	not serious	serious [c]	none	139/842 (16.5%)	267/1140 (23.4%)	**RR 0.79** (0.56 to 1.11)	49 fewer per 1,000 (from 26 more to 103 fewer)	⊕⊕◯◯ LOW	CRITICAL
Cure - Cohort studies												
17	observational studies	very serious [a]	very serious [g]	not serious	not serious	strong association	1083/3689 (29.4%)	5067/10676 (47.5%)	**RR 0.61** (0.47 to 0.77)	185 fewer per 1,000 (from 109 fewer to 252 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Cure - RCTs												
4	randomised trials	serious [d]	serious [h]	not serious	serious [c]	none	432/689 (62.7%)	587/914 (64.2%)	**RR 0.98** (0.83 to 1.17)	13 fewer per 1,000 (from 109 fewer to 109 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - Cohort studies												
17	observational studies	very serious [a]	very serious [i]	not serious	serious [c]	none	422/4511 (9.4%)	519/11802 (4.4%)	not estimable	20 more per 1,000 (from 0 fewer to 50 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - RCTs												
6	randomised trials	serious [d]	not serious	not serious	serious [e]	none	21/1036 (2.0%)	24/1220 (2.0%)	not estimable	0 fewer per 1,000 (from 10 more to 10 fewer)	⊕⊕◯◯ LOW	CRITICAL
Loss to follow up - Cohorts												
20	observational studies	very serious [a]	very serious [j]	not serious	not serious	none	2590/27540 (9.4%)	2544/81897 (3.1%)	not estimable	60 more per 1,000 (from 20 more to 90 more)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self administered therapy (SAT)	Directly observed therapy (DOT)	Relative (95% CI)	Absolute (95% CI)		
Loss to follow up - RCTs												
4	randomised trials	serious [d]	not serious	not serious	serious [c]	none	138/689 (20.0%)	166/914 (18.2%)	**RR 1.28** (0.93 to 1.76)	51 more per 1,000 (from 13 fewer to 138 more)	⊕⊕◯◯ LOW	CRITICAL
Relapse - Cohorts												
6	observational studies	serious [a]	serious [j]	not serious	serious [c]	none	103/937 (11.0%)	36/992 (3.6%)	not estimable	60 more per 1,000 (from 30 fewer to 150 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse - RCTs (follow up: mean 24 months)												
1	randomised trials	serious [k]	not serious	not serious	very serious [c,l]	none	15/290 (5.2%)	23/259 (8.9%)	**RR 0.58** (0.31 to 1.09)	37 fewer per 1,000 (from 8 more to 61 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence - Cohorts												
2	observational studies	not serious	not serious	serious [m]	not serious	strong association	961/1392 (69.0%)	1634/1936 (84.4%)	**RR 0.83** (0.80 to 0.86)	143 fewer per 1,000 (from 118 fewer to 169 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adherence - RCTs (follow up: mean 6 months)												
1	randomised trials	serious [n]	not serious	not serious	serious [c]	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94** (0.87 to 1.02)	58 fewer per 1,000 (from 19 more to 126 fewer)	⊕⊕◯◯ LOW	CRITICAL
Smear conversion - Cohort studies												
2	observational studies	serious [o]	not serious	not serious	serious [c]	none	49/60 (81.7%)	324/407 (79.6%)	**RR 0.92** (0.78 to 1.08)	64 fewer per 1,000 (from 64 more to 175 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Smear conversion - RCTs												
1	randomised trials	serious [p]	not serious	not serious	not serious	none	345/422 (81.8%)	366/414 (88.4%)	**RR 0.92** (0.87 to 0.98)	71 fewer per 1,000 (from 18 fewer to 115 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Acquisition of drug resistance												
3	observational studies	very serious [q]	very serious [r]	not serious	serious [c]	none	202/2644 (7.6%)	71/3284 (2.2%)	not estimable	50 fewer per 1,000 (from 0 fewer to 90 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Multiple studies with lack of comparability of intervention and control groups, poor outcome assessment, and selection of intervention and control groups from different populations

b. Significant heterogeneity across the studies with p <0.00001, I^2 = 90%

c. Confidence interval does not exclude appreciable benefit or appreciable harm.

d. All studies identified are unblinded. One study has poor random sequence generation. 3 studies had loss to follow up >20%

e. Relatively small number of events in the intervention and control groups. The estimate of effect suggests no benefit or harm.

f. Significant heterogeneity across the studies with p <0.00001, I^2 = 93%

g. Significant heterogeneity across the studies with p <0.00001, I^2 = 97%

h. Significant heterogeneity between studies, p = 0.04, I^2 = 64%

i. Significant heterogeneity between studies with p<0.00001, I^2 = 90%

j. Significant heterogeneity across the studies with p <0.00001, I^2 = 95%

k. No information on random sequence generation, allocation concealment, or blinding.

l. Only 15 (5.2%) events in the intervention and 23 (8.9%) events in the control groups. Estimate of effect suggests potentially large benefit or no effect.

m. One study defined adherence as anyone with an outcome in the continuous phase, the other study defined it as completing >90% of treatment doses

n. Not a robust randomization method, unblinded

o. One study with no data on comparability of intervention and control cohorts.

p. Unblinded study. No information on allocation concealment or blinding of outcome assessment.

q. Studies with low NOS ratings on selection, comparability, and outcome

r. Significant heterogeneity between studies with p<0.00001, I^2 = 94%

PICO 10.2 Should directly observed treatment at different locations versus clinic or routine care be used for TB treatment?

PICO 10.2.1

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: DOT at different locations compared to clinic-based DOT

Setting: Multiple countries

Bibliography: Adherence Interventions for Tuberculosis.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOT at different locations	Clinic or routine care	Relative (95% CI)	Absolute (95% CI)		
Mortality-Cohorts (home/community vs clinic)												
10	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	195/4148 (4.7%)	263/5793 (4.5%)	not estimable	0 fewer per 1,000 (from 10 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality-RCTs (community vs clinic)												
2	randomised trials	serious [d]	serious [b]	not serious	serious [c]	none	29/481 (6.0%)	69/628 (11.0%)	**RR 0.36** (0.06 to 2.33)	70 fewer per 1,000 (from 103 fewer to 146 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success-Cohorts (home/community vs clinic)												
8	observational studies	serious [a]	serious [b]	not serious	not serious	none	4464/5654 (79.0%)	7384/9340 (79.1%)	**RR 1.10** (1.06 to 1.14)	79 more per 1,000 (from 47 more to 111 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success-RCTs (home/community vs clinic)												
2	randomised trials	not serious	not serious	not serious	not serious	none	540/618 (87.4%)	736/876 (84.0%)	**RR 1.04** (1.00 to 1.09)	34 more per 1,000 (from 0 fewer to 76 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Completion - Cohort studies (home/community vs clinic)												
6	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	657/3336 (19.7%)	810/4754 (17.0%)	**RR 0.93** (0.56 to 1.55)	12 fewer per 1,000 (from 75 fewer to 94 more)	⨁◯◯◯ VERY LOW	CRITICAL
Completion- RCTs (community vs clinic)												
1	randomised trials	not serious	not serious	not serious	serious [e]	none	14/143 (9.8%)	6/179 (3.4%)	**RR 2.92** (1.15 to 7.41)	64 more per 1,000 (from 5 more to 215 more)	⨁⨁◯◯ MODERATE	CRITICAL
Cure - Cohort studies (home/community vs clinic)												
9	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	2086/3405 (61.3%)	3933/5912 (66.5%)	**RR 1.11** (0.99 to 1.24)	73 more per 1,000 (from 7 fewer to 160 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cure - RCTs (home/community vs clinic)												
2	randomised trials	serious [d]	not serious	not serious	serious [c]	none	228/364 (62.6%)	289/480 (60.2%)	**RR 1.01** (0.92 to 1.12)	6 more per 1,000 (from 48 fewer to 72 more)	⨁⨁◯◯ LOW	CRITICAL
Failure - Cohort studies (home/community vs clinic)												
7	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	38/3348 (1.1%)	185/4762 (3.9%)	not estimable	10 fewer per 1,000 (from 30 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Failure - RCTs (home vs community)												
1	randomised trials	not serious	not serious	not serious	very serious [c,e]	none	1/662 (0.2%)	1/664 (0.2%)	**RR 1.00** (0.06 to 16.00)	0 fewer per 1,000 (from 1 fewer to 23 more)	⨁⨁◯◯ LOW	CRITICAL
Failure - RCTs (community vs clinic)												
1	randomised trials	serious [d]	not serious	not serious	very serious [c,e]	none	2/221 (0.9%)	4/301 (1.3%)	**RR 0.68** (0.13 to 3.69)	4 fewer per 1,000 (from 12 fewer to 36 more)	⨁◯◯◯ VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOT at different locations	Clinic or routine care	Relative (95% CI)	Absolute (95% CI)		
Loss to follow up-Cohorts (home/community vs clinic)												
9	observational studies	serious [a]	serious [b]	not serious	not serious	none	445/4089 (10.9%)	641/5681 (11.3%)	**RR 0.59** (0.39 to 0.88)	46 fewer per 1,000 (from 14 fewer to 69 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow up-RCTs (home/community vs clinic)												
2	randomised trials	serious [d]	serious [b]	not serious	serious [c]	none	92/481 (19.1%)	84/628 (13.4%)	**RR 1.04** (0.34 to 3.19)	5 more per 1,000 (from 88 fewer to 293 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - Cohort studies (home/community vs clinic)												
2	observational studies	serious [a]	not serious	serious [f]	serious [c]	none	126/152 (82.9%)	336/360 (93.3%)	**RR 0.93** (0.77 to 1.12)	65 fewer per 1,000 (from 112 more to 215 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Sputum conversion (2nd month) - Cohort studies (home/community vs clinic)												
5	observational studies	serious [a]	serious [b]	not serious	not serious	none	1063/1158 (91.8%)	2369/2737 (86.6%)	**RR 1.15** (1.02 to 1.29)	130 more per 1,000 (from 17 more to 251 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sputum conversion (2nd month) - RCTs (home/community vs clinic)												
1	randomised trials	serious [d]	not serious	not serious	serious [c]	none	168/221 (76.0%)	209/301 (69.4%)	**RR 1.09** (0.99 to 1.22)	62 more per 1,000 (from 7 fewer to 153 more)	⨁⨁◯◯ LOW	CRITICAL
Unfavorable outcome (community vs clinic)												
1	observational studies	serious [a]	not serious	serious [g]	not serious	strong association	309/1646 (18.8%)	332/1123 (29.6%)	**RR 0.63** (0.55 to 0.73)	109 fewer per 1,000 (from 80 fewer to 133 fewer)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale
b. Significant heterogeneity between studies
c. Wide CI that does not exclude benefit or harm
d. One trial with significantly more people who dropped out f the intervention arm
e. Few events in the intervention and control groups
f. One trial defined adherence as taking >90% of doses prescribed, the other defined it as >80% of pills taken
g. Composite measure which includes outcomes of failure, default, death, transfer out, or out of control.

PICO 10.2.2

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: Clinic based DOT compared to SAT for TB treatment

Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinic based DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Mortality - Clinic DOT vs SAT - cohorts												
2	observational studies	not serious	serious [a]	not serious	serious [b]	none	25/951 (2.6%)	37/896 (4.1%)	**RR 0.75** (0.14 to 4.21)	**10 fewer per 1,000** (from 36 fewer to 133 more)	⊕○○○ VERY LOW	
Mortality - Clinic DOT vs SAT - RCTs												
3	randomised trials	serious [c]	not serious	not serious	serious [b,d]	none	7/281 (2.5%)	4/267 (1.5%)	**RR 1.57** (0.49 to 5.06)	**9 more per 1,000** (from 8 fewer to 61 more)	⊕⊕○○ LOW	
Success - Clinic DOT vs SAT - cohorts												
2	observational studies	not serious	serious [a]	not serious	serious [b]	none	709/951 (74.6%)	728/896 (81.3%)	**RR 0.86** (0.66 to 1.13)	**114 fewer per 1,000** (from 106 more to 276 fewer)	⊕○○○ VERY LOW	
Success - Clinic DOT vs SAT - RCTs												
3	randomised trials	serious [c]	not serious	not serious	not serious	none	173/281 (61.6%)	168/267 (62.9%)	**RR 0.99** (0.87 to 1.12)	**6 fewer per 1,000** (from 76 more to 82 fewer)	⊕⊕⊕○ MODERATE	
Completion - Clinic DOT vs SAT - Cohorts												
1	observational studies	not serious	not serious	not serious	not serious	none	51/225 (22.7%)	115/300 (38.3%)	**RR 0.59** (0.45 to 0.78)	**157 fewer per 1,000** (from 84 fewer to 211 fewer)	⊕⊕○○ LOW	
Completion - Clinic DOT vs SAT - RCTs												
3	randomised trials	serious [c]	not serious	not serious	serious [b]	none	23/281 (8.2%)	19/267 (7.1%)	**RR 1.12** (0.63 to 1.98)	**9 more per 1,000** (from 26 fewer to 70 more)	⊕⊕○○ LOW	
Cure - Clinic DOT vs SAT - cohorts												
1	observational studies	not serious	not serious	not serious	serious [b]	none	90/225 (40.0%)	137/300 (45.7%)	**RR 0.88** (0.72 to 1.07)	**55 fewer per 1,000** (from 32 more to 128 fewer)	⊕○○○ VERY LOW	
Cure - Clinic DOT vs SAT - RCTs												
3	randomised trials	serious [c]	not serious	not serious	serious [b]	none	150/281 (53.4%)	149/267 (55.8%)	**RR 0.93** (0.73 to 1.19)	**39 fewer per 1,000** (from 106 more to 151 fewer)	⊕⊕○○ LOW	
Failure - Clinic DOT vs SAT - cohorts												
2	observational studies	not serious	not serious	not serious	serious [b,d]	none	23/951 (2.4%)	11/896 (1.2%)	**RR 2.02** (0.96 to 4.23)	**13 more per 1,000** (from 0 fewer to 40 more)	⊕○○○ VERY LOW	
Failure - Clinic DOT vs SAT - RCTs												
3	randomised trials	serious [c]	not serious	not serious	not serious	none	3/281 (1.1%)	2/267 (0.7%)	not estimable	**10 fewer per 1,000** (from 10 more to 20 fewer)	⊕⊕⊕○ MODERATE	
Default - Clinic DOT vs SAT - cohorts												
3	observational studies	serious [e]	serious [a]	not serious	serious [b]	none	325/2068 (15.7%)	125/1239 (10.1%)	**RR 1.47** (0.94 to 2.30)	**47 more per 1,000** (from 6 fewer to 131 more)	⊕○○○ VERY LOW	

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinic based DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Default - Clinic DOT vs SAT - RCTs												
3	randomised trials	serious [c]	not serious	not serious	serious [b]	none	78/281 (27.8%)	83/267 (31.1%)	**RR 0.90** (0.69 to 1.17)	**31 fewer per 1,000** (from 53 more to 96 fewer)	⨁⨁◯◯ LOW	
Adherence - Home DOT vs SAT												
2	observational studies	not serious	not serious	not serious	not serious	none	1332/1616 (82.4%)	961/1392 (69.0%)	**RR 1.15** (1.03 to 1.30)	**104 more per 1,000** (from 21 more to 207 more)	⨁⨁◯◯ LOW	
Adherence - Home DOT vs SAT - RCTs												
1	randomised trials	serious [f]	not serious	not serious	serious [b]	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94** (0.87 to 1.02)	**58 fewer per 1,000** (from 19 more to 126 fewer)	⨁⨁◯◯ LOW	

CI: Confidence interval; RR: Risk ratio

a. Significant heterogeneity between studies
b. Wide CI that does not exclude significant benefit or harm
c. Two studies with more than 20% patients lost to follow up and no information on blinding
d. Few events in the intervention and/or control groups
e. Based on NOS scale
f. No information on blinding, allocation concealment, or randomization

PICO 10.2.3

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: Home/community based DOT compared to SAT for TB treatment

Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home/community based DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Mortality - Home based DOT vs SAT - Cohorts												
4	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	594/5405 (11.0%)	105/2319 (4.5%)	**RR 0.70** (0.15 to 3.14)	14 fewer per 1,000 (from 38 fewer to 97 more)	⊕◯◯◯ VERY LOW	
Mortality - Home DOT vs SAT - RCTs												
2	randomised trials	serious [d]	not serious	not serious	serious [c,e]	none	9/219 (4.1%)	4/206 (1.9%)	**RR 2.11** (0.66 to 6.75)	22 more per 1,000 (from 7 fewer to 112 more)	⊕⊕◯◯ LOW	
Success - Home based DOT vs SAT - cohorts												
4	observational studies	serious [a]	serious [b]	not serious	not serious	none	3744/5405 (69.3%)	1486/2319 (64.1%)	**RR 1.17** (1.09 to 1.26)	109 more per 1,000 (from 58 more to 167 more)	⊕◯◯◯ VERY LOW	
Success - Home DOT vs SAT - RCTs												
2	randomised trials	serious [d]	not serious	not serious	serious [c]	none	143/219 (65.3%)	131/206 (63.6%)	**RR 1.07** (0.83 to 1.37)	45 more per 1,000 (from 108 fewer to 235 more)	⊕⊕◯◯ LOW	
Completion - Home based DOT vs SAT - cohorts												
3	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	1274/4916 (25.9%)	664/1723 (38.5%)	**RR 0.83** (0.47 to 1.46)	66 fewer per 1,000 (from 177 more to 204 fewer)	⊕◯◯◯ VERY LOW	
Completion - Home DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	serious [c]	none	105/306 (34.3%)	91/292 (31.2%)	**RR 1.18** (0.71 to 1.97)	56 more per 1,000 (from 90 fewer to 302 more)	⊕⊕◯◯ LOW	
Cure - Home DOT vs SAT - cohorts												
3	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	2028/4916 (41.3%)	346/1723 (20.1%)	**RR 1.82** (0.76 to 4.31)	165 more per 1,000 (from 48 fewer to 665 more)	⊕◯◯◯ VERY LOW	
Cure - Home DOT vs SAT - RCTs												
2	randomised trials	serious [d]	serious [b]	not serious	serious [c]	none	122/219 (55.7%)	118/206 (57.3%)	**RR 1.07** (0.69 to 1.66)	40 more per 1,000 (from 178 fewer to 378 more)	⊕◯◯◯ VERY LOW	
Failure - Home DOT vs SAT - cohorts												
4	observational studies	serious [a]	not serious	not serious	not serious	none	87/5405 (1.6%)	24/2319 (1.0%)	not estimable	0 fewer per 1,000 (from 0 fewer to 10 fewer)	⊕◯◯◯ VERY LOW	
Failure - Home DOT vs SAT - RCTs												
2	randomised trials	serious [d]	not serious	not serious	not serious	none	3/219 (1.4%)	2/206 (1.0%)	not estimable	0 fewer per 1,000 (from 10 more to 10 fewer)	⊕⊕◯◯ MODERATE	
Default - Home DOT vs SAT												
4	observational studies	serious [a]	not serious	not serious	not serious	none	435/5405 (8.0%)	403/2319 (17.4%)	**RR 0.37** (0.33 to 0.42)	109 fewer per 1,000 (from 101 fewer to 116 fewer)	⊕◯◯◯ VERY LOW	

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home/community based DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Default - Home DOT vs SAT - RCTs												
2	randomised trials	serious [d]	not serious	not serious	serious [c]	none	61/219 (27.9%)	64/206 (31.1%)	**RR 0.88** (0.59 to 1.32)	37 fewer per 1,000 (from 99 more to 127 fewer)	⨁⨁◯◯ LOW	
Adherence - Home DOT vs SAT												
2	observational studies	not serious	not serious	serious [f]	not serious	none	1332/1616 (82.4%)	961/1392 (69.0%)	**RR 1.15** (1.03 to 1.30)	104 more per 1,000 (from 21 more to 207 more)	⨁◯◯◯ VERY LOW	
Adherence - Home DOT vs SAT - RCTs												
1	randomised trials	serious [g]	not serious	not serious	not serious	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94** (0.87 to 1.02)	58 fewer per 1,000 (from 19 more to 126 fewer)	⨁⨁◯◯ MODERATE	

CI: Confidence interval; RR: Risk ratio

a. Based on NOS scale
b. Significant heterogeneity between studies
c. Wide CI that does not exclude significant benefit or harm
d. One study without blinding and more than 20% loss to follow up.
e. Few events in the control/intervention groups
f. Studies define outcome of interest differently
g. No information on random sequence generation, allocation concealment, or blinding

PICO 10.3 Should different directly observed treatment providers versus standard providers be used for TB treatment?

PICO 10.3.1

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: Different DOT providers compared to standard providers for TB treatment (2)

Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Different DOT providers	Standard providers	Relative (95% CI)	Absolute (95% CI)		
Mortality - Family DOT vs HCW												
2	observational studies	serious [a]	not serious	not serious	not serious	none	589/4774 (12.3%)	281/2357 (11.9%)	**RR 1.05** (0.91 to 1.21)	6 more per 1,000 (from 11 fewer to 25 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality - Lay provider vs HCW												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	113/2875 (3.9%)	135/2599 (5.2%)	**RR 0.73** (0.47 to 1.13)	14 fewer per 1,000 (from 7 more to 28 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Success - Family vs HCW												
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	3161/4774 (66.2%)	1705/2357 (72.3%)	**RR 0.85** (0.67 to 1.06)	109 fewer per 1,000 (from 43 more to 239 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Success - Lay provider vs HCW												
3	observational studies	serious [a]	serious [c]	not serious	serious [b]	none	1200/1411 (85.0%)	1658/2173 (76.3%)	**RR 1.09** (0.93 to 1.27)	69 more per 1,000 (from 53 fewer to 206 more)	⊕◯◯◯ VERY LOW	CRITICAL
Completion - Cohort studies												
3	observational studies	serious [a]	not serious	not serious	not serious	none	2513/6513 (38.6%)	879/2409 (36.5%)	**RR 0.97** (0.93 to 1.02)	11 fewer per 1,000 (from 7 more to 26 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Cure - Family vs HCW												
2	observational studies	serious [a]	serious [c]	not serious	serious [b]	none	1944/4774 (40.7%)	1115/2357 (47.3%)	**RR 0.52** (0.16 to 1.66)	227 fewer per 1,000 (from 312 more to 397 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Cure - Lay provider vs HCW												
2	observational studies	serious [a]	serious [c]	not serious	serious [b]	none	662/745 (88.9%)	1292/1736 (74.4%)	**RR 1.09** (0.81 to 1.47)	67 more per 1,000 (from 141 fewer to 350 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - Family vs HCW												
2	observational studies	serious [a]	not serious	not serious	serious [d]	none	74/4774 (1.6%)	20/2357 (0.8%)	not estimable	10 more per 1,000 (from 0 fewer to 10 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - Lay provider vs HCW												
3	observational studies	serious [a]	serious [c]	not serious	very serious [b,d]	none	38/1411 (2.7%)	94/2173 (4.3%)	**RR 0.47** (0.17 to 1.29)	23 fewer per 1,000 (from 13 more to 36 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up - Family vs HCW												
2	observational studies	serious [a]	not serious	not serious	not serious	none	403/4774 (8.4%)	128/2357 (5.4%)	**RR 1.48** (1.21 to 1.81)	26 more per 1,000 (from 11 more to 44 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up - Lay provider vs HCW												
3	observational studies	serious [a]	serious [c]	not serious	serious [b]	none	129/1411 (9.1%)	218/2173 (10.0%)	**RR 0.75 (0.42 to 1.32)**	25 fewer per 1,000 (from 32 more to 58 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence - Family vs HCW (village doctor)												
1	observational studies	not serious	not serious	not serious	not serious	none	95/117 (81.2%)	302/320 (94.4%)	**RR 0.86 (0.79 to 0.94)**	132 fewer per 1,000 (from 57 fewer to 198 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle-Ottawa Scale
b. Wide CI does not exclude significant benefit or harm
c. Significant heterogeneity between studies
d. Very few events in the intervention and control groups

PICO 10.3.2

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: Family DOT compared to SAT for TB treatment

Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Family DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Mortality - Family DOT vs SAT - Cohorts												
2	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	584/4861 (12.0%)	78/1706 (4.6%)	**RR 0.89** (0.07 to 10.59)	5 fewer per 1,000 (from 43 fewer to 438 more)	⊕◯◯◯ VERY LOW	
Mortality - Family DOT vs SAT - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	7/165 (4.2%)	3/162 (1.9%)	**RR 2.29** (0.60 to 8.71)	24 more per 1,000 (from 7 fewer to 143 more)	⊕⊕⊕⊕ HIGH	
Success - Family DOT vs SAT - Cohorts												
2	observational studies	serious [a]	serious [b]	not serious	not serious	none	3264/4861 (67.1%)	1001/1706 (58.7%)	**RR 1.19** (1.06 to 1.33)	111 more per 1,000 (from 35 more to 194 more)	⊕◯◯◯ VERY LOW	
Success-1 - Family DOT vs SAT - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	103/165 (62.4%)	105/162 (64.8%)	**RR 0.96** (0.82 to 1.13)	26 fewer per 1,000 (from 84 more to 117 fewer)	⊕⊕⊕⊕ HIGH	
Completion - Family DOT vs SAT												
2	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	1265/4861 (26.0%)	659/1706 (38.6%)	**RR 0.91** (0.47 to 1.76)	35 fewer per 1,000 (from 205 fewer to 294 more)	⊕◯◯◯ VERY LOW	
Completion - Family DOT vs SAT - RCTs												
2	randomised trials	serious [d]	serious [b]	not serious	serious [c]	none	96/252 (38.1%)	83/248 (33.5%)	**RR 1.47** (0.47 to 4.53)	157 more per 1,000 (from 177 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	
Cure - Family DOT vs SAT												
2	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	1999/4861 (41.1%)	342/1706 (20.0%)	**RR 1.68** (0.59 to 4.81)	136 more per 1,000 (from 82 fewer to 764 more)	⊕◯◯◯ VERY LOW	
Cure - Family DOT vs SAT - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	91/165 (55.2%)	100/162 (61.7%)	**RR 0.89** (0.74 to 1.07)	68 fewer per 1,000 (from 43 more to 160 fewer)	⊕⊕⊕⊕ HIGH	
Failure - Family DOT vs SAT												
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	75/4861 (1.5%)	19/1706 (1.1%)	**RR 1.12** (0.29 to 4.25)	1 more per 1,000 (from 8 fewer to 36 more)	⊕◯◯◯ VERY LOW	
Failure - Family DOT vs SAT - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/165 (0.0%)	0/162 (0.0%)	**RR 0.00** (-0.01 to 0.01)	-- per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	
Default - Family DOT vs SAT - Cohorts												
2	observational studies	serious [a]	not serious	not serious	not serious	none	402/4861 (8.3%)	341/1706 (20.0%)	**RR 0.36** (0.31 to 0.41)	128 fewer per 1,000 (from 118 fewer to 138 fewer)	⊕◯◯◯ VERY LOW	

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Family DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Default - Family DOT vs SAT - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	53/165 (32.1%)	53/162 (32.7%)	**RR 0.98** (0.72 to 1.34)	7 fewer per 1,000 (from 92 fewer to 111 more)	⊕⊕⊕⊕ HIGH	
Adherence - Family DOT vs SAT - cohorts												
1	observational studies	not serious	not serious	not serious	not serious	none	95/117 (81.2%)	86/113 (76.1%)	**RR 1.07** (0.93 to 1.22)	53 more per 1,000 (from 53 fewer to 167 more)	⊕⊕◯◯ LOW	
Adherence - Family DOT vs SAT - RCTs												
1	randomised trials	serious [d]	not serious	not serious	not serious	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94** (0.87 to 1.02)	58 fewer per 1,000 (from 19 more to 126 fewer)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; RR: Risk ratio

a. Based on NOS scale
b. Significant heterogeneity between studies
c. Wide CI that does not exclude appreciable benefit or harm
d. No information by one trial on allocation concealment, random sequence generation, or blidning

PICO 10.3.3

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: HCW DOT compared to SAT for TB treatment

Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCW DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Mortality - HCW DOT vs SAT - cohorts												
6	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	355/5672 (6.3%)	147/3415 (4.3%)	**RR 0.78** (0.35 to 1.75)	9 fewer per 1,000 (from 28 fewer to 32 more)	⊕◯◯◯ VERY LOW	
Mortality - HCW DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	not serious	none	7/281 (2.5%)	4/267 (1.5%)	not estimable	10 fewer per 1,000 (from 20 more to 40 fewer)	⊕⊕⊕◯ MODERATE	
Success - HCW DOT vs SAT - cohorts												
6	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	4380/5672 (77.2%)	2346/3415 (68.7%)	**RR 1.15** (0.97 to 1.36)	103 more per 1,000 (from 21 fewer to 247 more)	⊕◯◯◯ VERY LOW	
Success - HCW DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	serious [c]	none	173/281 (61.6%)	168/267 (62.9%)	**RR 0.99** (0.87 to 1.12)	6 fewer per 1,000 (from 76 more to 82 fewer)	⊕⊕◯◯ LOW	
Completion - HCW DOT vs SAT - cohorts												
3	observational studies	serious [a]	not serious	not serious	not serious	none	539/2038 (26.4%)	742/1775 (41.8%)	**RR 0.71** (0.60 to 0.83)	121 fewer per 1,000 (from 71 fewer to 167 fewer)	⊕◯◯◯ VERY LOW	
Completion - HCW DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	serious [c]	none	23/281 (8.2%)	19/267 (7.1%)	**RR 1.12** (0.63 to 1.98)	9 more per 1,000 (from 26 fewer to 70 more)	⊕⊕◯◯ LOW	
Cure - HCW DOT vs SAT - cohorts												
4	observational studies	serious [a]	serious [b]	not serious	not serious	none	1091/2185 (49.9%)	285/1828 (15.6%)	**RR 2.69** (1.84 to 3.93)	263 more per 1,000 (from 131 more to 457 more)	⊕◯◯◯ VERY LOW	
Cure - HCW DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	serious [c]	none	150/281 (53.4%)	149/267 (55.8%)	**RR 0.93** (0.73 to 1.19)	39 fewer per 1,000 (from 106 more to 151 fewer)	⊕⊕◯◯ LOW	
Failure - HCW DOT vs SAT												
6	observational studies	serious [a]	serious [b]	not serious	not serious	none	64/3348 (1.9%)	35/2452 (1.4%)	not estimable	0 fewer per 1,000 (from 20 fewer to 20 more)	⊕◯◯◯ VERY LOW	
Failure - HCW DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	not serious	none	3/281 (1.1%)	2/267 (0.7%)	not estimable	10 fewer per 1,000 (from 10 more to 20 fewer)	⊕⊕⊕◯ MODERATE	
Default - HCW DOT vs SAT - Cohorts												
6	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	291/3355 (8.7%)	792/3036 (26.1%)	**RR 0.43** (0.18 to 1.02)	149 fewer per 1,000 (from 5 more to 214 fewer)	⊕◯◯◯ VERY LOW	

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCW DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Default - HCW DOT vs SAT - RCTs												
3	randomised trials	serious [d]	not serious	not serious	serious [c]	none	78/281 (27.8%)	83/267 (31.1%)	**RR 0.90** (0.69 to 1.17)	31 fewer per 1,000 (from 53 more to 96 fewer)	⨁⨁◯◯ LOW	
Relapse - HCW DOT vs SAT - cohorts												
2	observational studies	serious [a]	not serious	not serious	not serious	none	33/728 (4.5%)	95/460 (20.7%)	**RR 0.13** (0.02 to 0.84)	180 fewer per 1,000 (from 33 fewer to 202 fewer)	⨁◯◯◯ VERY LOW	
Acquisition of drug resistance - HCW DOT vs SAT - cohorts												
1	observational studies	serious [a]	not serious	not serious	not serious	none	8/581 (1.4%)	39/407 (9.6%)	**RR 0.14** (0.07 to 0.30)	82 fewer per 1,000 (from 67 fewer to 89 fewer)	⨁◯◯◯ VERY LOW	
Adherence - HCW DOT vs SAT - cohorts												
2	observational studies	not serious	not serious	not serious	not serious	none	1539/1819 (84.6%)	961/1392 (69.0%)	**RR 1.21** (1.16 to 1.26)	145 more per 1,000 (from 110 more to 179 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; RR: Risk ratio

a. Based on NOS scale

b. Significant heterogeneity between the studies

c. Wide CI that does not exclude significant benefit or harm

d. All studies identified are unblinded. One study has poor random sequence generation. 2 studies had loss to follow up >20%

PICO 10.3.4

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

Question: Lay provider DOT compared to SAT for TB treatment

Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lay provider DOT	SAT	Relative (95% CI)	Absolute (95% CI)		
Mortality - Lay provider DOT vs SAT - Cohorts												
2	observational studies	serious [a]	serious [b]	not serious	serious [c,d]	none	26/990 (2.6%)	8/380 (2.1%)	**RR 0.67** (0.09 to 4.81)	7 fewer per 1,000 (from 19 fewer to 80 more)	⊕○○○ VERY LOW	
Mortality - Lay provider DOT vs SAT - RCTs												
1	randomised trials	serious [e]	not serious	not serious	serious [d]	none	2/54 (3.7%)	1/44 (2.3%)	**RR 1.63** (0.15 to 17.38)	14 more per 1,000 (from 19 fewer to 372 more)	⊕⊕○○ LOW	
Success - Lay provider DOT vs SAT - Cohorts												
2	observational studies	serious [a]	not serious	not serious	not serious	none	768/990 (77.6%)	261/380 (68.7%)	**RR 1.09** (1.00 to 1.19)	62 more per 1,000 (from 0 fewer to 130 more)	⊕○○○ VERY LOW	
Success - Lay provider DOT vs SAT - RCTs												
1	randomised trials	serious [e]	not serious	not serious	not serious	none	40/54 (74.1%)	26/44 (59.1%)	**RR 1.25** (0.94 to 1.68)	148 more per 1,000 (from 35 fewer to 402 more)	⊕⊕⊕○ MODERATE	
Completion - Lay person DOT vs SAT - Cohorts												
1	observational studies	serious [a]	not serious	not serious	not serious	none	150/324 (46.3%)	193/352 (54.8%)	**RR 0.84** (0.73 to 0.98)	88 fewer per 1,000 (from 11 fewer to 148 fewer)	⊕○○○ VERY LOW	
Completion - Lay provider DOT vs SAT - RCTs												
1	randomised trials	serious [e]	not serious	not serious	serious [c]	none	9/54 (16.7%)	8/44 (18.2%)	**RR 0.92** (0.39 to 2.18)	15 fewer per 1,000 (from 111 fewer to 215 more)	⊕⊕○○ LOW	
Cure - Lay person DOT vs SAT - Cohorts												
1	observational studies	serious [a]	not serious	not serious	not serious	none	92/324 (28.4%)	47/352 (13.4%)	**RR 2.13** (1.55 to 2.92)	151 more per 1,000 (from 73 more to 256 more)	⊕○○○ VERY LOW	
Cure - Lay provider DOT vs SAT - RCTs												
1	randomised trials	serious [e]	not serious	not serious	serious [c]	none	31/54 (57.4%)	18/44 (40.9%)	**RR 1.40** (0.92 to 2.14)	164 more per 1,000 (from 33 fewer to 466 more)	⊕⊕○○ LOW	
Failure - Lay provider DOT vs SAT - Cohorts												
2	observational studies	serious [a]	not serious	not serious	serious [c,d]	none	35/990 (3.5%)	3/380 (0.8%)	**RR 1.59** (0.18 to 14.13)	5 more per 1,000 (from 6 fewer to 104 more)	⊕○○○ VERY LOW	
Failure - Lay provider DOT vs SAT - RCTs												
1	randomised trials	serious [e]	not serious	not serious	serious [c,d]	none	3/54 (5.6%)	2/44 (4.5%)	**RR 1.22** (0.21 to 6.99)	10 more per 1,000 (from 36 fewer to 272 more)	⊕⊕○○ LOW	
Default - Lay provider DOT vs SAT - Cohorts												
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	154/990 (15.6%)	104/380 (27.4%)	**RR 0.92** (0.34 to 2.44)	22 fewer per 1,000 (from 181 fewer to 394 more)	⊕○○○ VERY LOW	
Default - Lay provider DOT vs SAT - RCTs												
1	randomised trials	serious [e]	not serious	not serious	serious [c]	none	8/54 (14.8%)	11/44 (25.0%)	**RR 0.59** (0.26 to 1.34)	103 fewer per 1,000 (from 85 more to 185 fewer)	⊕⊕○○ LOW	

CI: Confidence interval; RR: Risk ratio

a. Based on NOS scale

b. Significant heterogeneity between studies

c. Wide CI that does not exclude significant benefit or harm

d. Few events in the intervention and/or control group

e. No blinding, study with >20% loss to follow up

PICO 10.4 Should self-administered treatment versus directly observed treatment be used for TB/HIV patients?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: SAT compared to DOT for TB/HIV patients
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAT	DOT	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies												
3	observational studies	serious [a]	not serious	not serious	very serious [b,c]	none	27/181 (14.9%)	13/193 (6.7%)	**RR 2.74** (1.51 to 4.99)	117 more per 1,000 (from 34 more to 269 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success - Cohort studies												
3	observational studies	serious [a]	not serious	not serious	not serious	strong association	45/158 (28.5%)	710/865 (82.1%)	**RR 0.41** (0.29 to 0.59)	484 fewer per 1,000 (from 337 fewer to 583 fewer)	⨁⨁◯◯ LOW	CRITICAL
Completion - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	none	1/39 (2.6%)	11/44 (25.0%)	**RR 0.10** (0.01 to 0.76)	225 fewer per 1,000 (from 60 fewer to 248 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Cure - Cohort studies												
2	observational studies	serious [a]	not serious	not serious	not serious	strong association	35/151 (23.2%)	85/145 (58.6%)	**RR 0.40** (0.29 to 0.55)	352 fewer per 1,000 (from 264 fewer to 416 fewer)	⨁⨁◯◯ LOW	CRITICAL
Failure - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	not serious	strong association	71/112 (63.4%)	20/101 (19.8%)	**RR 3.20** (2.11 to 4.86)	436 more per 1,000 (from 220 more to 764 more)	⨁⨁◯◯ LOW	CRITICAL
Loss to follow up - Cohort studies												
2	observational studies	serious [a]	serious [d]	not serious	serious [e]	none	229/1156 (19.8%)	66/387 (17.1%)	**RR 1.94** (0.52 to 7.17)	160 more per 1,000 (from 82 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	serious [e]	none	2/112 (1.8%)	2/101 (2.0%)	**RR 0.90** (0.13 to 6.28)	2 fewer per 1,000 (from 17 fewer to 105 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale.
b. Wide confidence interval.
c. Very few events in the intervention and/or control groups.
d. Significant heterogeneity between studies.
e. Wide CI that does not exclude significant benefit or harm.

PICO 10.5 Should incentives and enablers versus none be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Material support compared to none for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Material support	None	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies												
3	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	37/482 (7.7%)	219/2101 (10.4%)	**RR 0.51 (0.37 to 0.71)**	51 fewer per 1,000 (from 30 fewer to 66 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - RCTs												
2	randomised trials	not serious	not serious	not serious	serious [d]	none	151/2157 (7.0%)	139/2034 (6.8%)	**not estimable**	1 more per 1,000 (from 3 fewer to 4 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment success - Cohort studies												
4	observational studies	serious [a]	serious [b]	not serious	not serious	none	974/1353 (72.0%)	2021/2999 (67.4%)	**RR 1.25 (1.09 to 1.42)**	168 more per 1,000 (from 61 more to 283 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success - RCTs												
3	randomised trials	serious [e]	not serious	not serious	not serious	none	1752/2291 (76.5%)	1543/2162 (71.4%)	**RR 1.07 (1.03 to 1.11)**	50 more per 1,000 (from 21 more to 79 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion - Cohort studies												
3	observational studies	serious [a]	serious [b]	not serious	serious [d]	none	206/345 (59.7%)	185/1586 (11.7%)	**RR 1.25 (0.85 to 1.83)**	29 more per 1,000 (from 17 fewer to 97 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion - RCTs												
2	randomised trials	not serious	not serious	not serious	not serious	none	960/2157 (44.5%)	735/2034 (36.1%)	**RR 1.23 (1.15 to 1.31)**	83 more per 1,000 (from 54 more to 112 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Cure - Cohort studies												
2	observational studies	serious [a]	not serious	not serious	not serious	none	173/191 (90.6%)	1158/1509 (76.7%)	**RR 1.24 (1.18 to 1.30)**	184 more per 1,000 (from 138 more to 230 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cure - RCTs												
1	randomised trials	not serious	not serious	not serious	serious [d]	none	695/2107 (33.0%)	708/1984 (35.7%)	**RR 0.92 (0.85 to 1.01)**	29 fewer per 1,000 (from 4 more to 54 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment failure - Cohort studies												
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	2/309 (0.6%)	141/2008 (7.0%)	**not estimable**	50 fewer per 1,000 (from 120 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment failure - RCTs												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	79/2107 (3.7%)	113/1984 (5.7%)	**RR 0.66 (0.50 to 0.87)**	19 fewer per 1,000 (from 7 fewer to 28 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Loss to follow up - Cohort studies												
5	observational studies	serious [a]	serious [b]	not serious	not serious	none	1788/16892 (10.6%)	236/2326 (10.1%)	**not estimable**	80 fewer per 1,000 (from 130 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Material support	None	Relative (95% CI)	Absolute (95% CI)		
Loss to follow up - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	158/2107 (7.5%)	202/1984 (10.2%)	**RR 0.74 (0.60 to 0.90)**	26 fewer per 1,000 (from 10 fewer to 41 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Acquisition of resistance												
1	randomised trials	not serious	not serious	not serious	very serious [c,f]	none	1/2107 (0.0%)	3/1984 (0.2%)	**RR 0.31 (0.03 to 3.01)**	1 fewer per 1,000 (from 1 fewer to 3 more)	⊕⊕◯◯ LOW	CRITICAL
Sputum converstion rate - RCTs												
1	randomised trials	not serious	not serious	not serious	not serious	none	35/36 (97.2%)	29/36 (80.6%)	**RR 1.21 (1.02 to 1.43)**	169 more per 1,000 (from 16 more to 346 more)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale.
b. Significant heterogeneity between the studies.
c. Few events in the intervention and control arms
d. CI does not exclude significant benefit or harm.
e. One study provides no information on random sequence generation or allocation concealment
f. Wide confidence interval that does not exclude benefit or harm.

PICO 10.6 Should psychological interventions versus none be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Psychological interventions compared to none for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	psychological interventions	none	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	none	11/64 (17.2%)	6/64 (9.4%)	**RR 1.83** (0.72 to 4.66)	78 more per 1,000 (from 26 fewer to 343 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success - RCTs (ETOH cessation counseling)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	80/92 (87.0%)	83/104 (79.8%)	**RR 1.09** (0.96 to 1.23)	72 more per 1,000 (from 32 fewer to 184 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion - Cohort studies (support groups)												
1	observational studies	serious [d]	not serious	not serious	not serious	none	44/64 (68.8%)	30/64 (46.9%)	**RR 1.47** (1.08 to 2.00)	220 more per 1,000 (from 38 more to 469 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion - RCTs (support groups)												
1	randomised trials	not serious	not serious	not serious	not serious	none	43/44 (97.7%)	35/43 (81.4%)	**RR 1.20** (1.03 to 1.39)	163 more per 1,000 (from 24 more to 317 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Cure - RCTs (support groups)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	40/43 (93.0%)	35/43 (81.4%)	**RR 1.14** (0.97 to 1.35)	114 more per 1,000 (from 24 fewer to 285 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Failure - Cohort studies (support groups)												
1	observational studies	serious [d]	not serious	not serious	very serious [b,c]	none	0/64 (0.0%)	1/64 (1.6%)	not estimable	20 fewer per 1,000 (from 60 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Failure - RCTs (support groups)												
1	randomised trials	not serious	not serious	not serious	very serious [b,c]	none	0/43 (0.0%)	5/43 (11.6%)	not estimable	1 fewer per 1,000 (from 2 fewer to 0 fewer) [e]	⨁⨁◯◯ LOW	CRITICAL
Loss to follow up - Cohort studies (support groups)												
1	observational studies	serious [d]	not serious	not serious	serious [c]	strong association	8/64 (12.5%)	26/64 (40.6%)	**RR 0.31** (0.15 to 0.63)	280 fewer per 1,000 (from 150 fewer to 345 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow up - RCTs (support groups)												
1	randomised trials	not serious	not serious	not serious	very serious [b,c]	none	1/43 (2.3%)	2/43 (4.7%)	**RR 0.50** (0.05 to 5.31)	23 fewer per 1,000 (from 44 fewer to 200 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale
b. Wide CI that does not exclude significant benefit or harm.
c. Very few events in the intervention and/or control groups.
d. Based on Newcastle Ottawa Scale
f. No explanation was provided

PICO 10.7 Should additional patient education and counselling versus routine care be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Patient education and educational counseling compared to none for TB treatment
Setting: Multiple countries
Bibliography: Adherence Interventions for Tuberculosis.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Additional patient education and educational counseling	Routine care	Relative (95% CI)	Absolute (95% CI)		
Mortality - RCTs												
2	randomised trials	serious [a]	not serious	not serious	very serious [b,c,d]	none	17/537 (3.2%)	24/596 (4.0%)	**RR 0.83** (0.34 to 2.05)	7 fewer per 1,000 (from 27 fewer to 42 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success												
2	randomised trials	serious [e]	serious [f]	not serious	serious [b]	none	321/604 (53.1%)	262/615 (42.6%)	**RR 1.40** (0.90 to 2.17)	170 more per 1,000 (from 43 fewer to 498 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment completion												
1	randomised trials	serious [e]	not serious	not serious	not serious	none [d]	72/100 (72.0%)	42/100 (42.0%)	**RR 1.71** (1.32 to 2.22)	298 more per 1,000 (from 134 more to 512 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure												
1	randomised trials	serious [a]	not serious	not serious	not serious	none [d]	28/33 (84.8%)	32/81 (39.5%)	**RR 2.15** (1.58 to 2.92)	454 more per 1,000 (from 229 more to 759 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Failure												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,c]	none	2/33 (6.1%)	4/81 (4.9%)	**RR 1.23** (0.24 to 6.38)	11 more per 1,000 (from 38 fewer to 266 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up												
3	randomised trials	serious [a,e]	serious [f]	not serious	serious [b]	none	254/637 (39.9%)	344/696 (49.4%)	**RR 0.49** (0.21 to 1.17)	252 fewer per 1,000 (from 84 more to 390 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence - RCT												
1	randomised trials	serious [a]	not serious	not serious	serious [c,g]	none	30/56 (53.6%)	17/58 (29.3%)	**RR 1.83** (1.14 to 2.92)	243 more per 1,000 (from 41 more to 563 more)	⊕⊕◯◯ LOW	CRITICAL
Adherence - Cohort studies												
1	observational studies	not serious	not serious	not serious	not serious	none	57/60 (95.0%)	47/60 (78.3%)	**RR 1.21** (1.05 to 1.40)	164 more per 1,000 (from 39 more to 313 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. No information provided on randomization methods or blinding strategy by one study.
b. CI does not exclude significant benefit or harm.
c. Few events occurred in the intervention and control groups
d. Large effect. It was felt that this does not mitigate the risk of bias (also for upgrading GRADE typically requires two studies with narrow confidence intervals.
e. One study has inferior randomization technique with no concealment or blinding.
f. Significant heterogeneity between the studies.
g. Wide CI

PICO 10.8 Should staff education versus none be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Staff education compared to none for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Staff education	None	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	0/54 (0.0%)	0/101 (0.0%)	not estimable	0 fewer per 1,000 (from 30 more to 30 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality - RCTs												
2	randomised trials	not serious	not serious	not serious	very serious [c,d]	none	20/630 (3.2%)	33/657 (5.0%)	**RR 0.76** (0.44 to 1.31)	12 fewer per 1,000 (from 16 more to 28 fewer)	⊕⊕◯◯ LOW	CRITICAL
Treatment success - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	not serious	none	50/54 (92.6%)	70/101 (69.3%)	**RR 1.34** (1.15 to 1.55)	236 more per 1,000 (from 104 more to 381 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success - RCTs												
3	randomised trials	not serious	not serious	not serious	serious [c]	none	586/860 (68.1%)	472/745 (63.4%)	**RR 1.03** (0.95 to 1.12)	19 more per 1,000 (from 32 fewer to 76 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Completion - RCTs												
2	randomised trials	not serious	not serious	not serious	serious [c]	none	46/260 (17.7%)	52/168 (31.0%)	**RR 0.91** (0.63 to 1.31)	28 fewer per 1,000 (from 96 more to 115 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure - RCTs												
3	randomised trials	not serious	serious [e]	not serious	serious [c]	none	446/860 (51.9%)	338/745 (45.4%)	**RR 1.08** (0.86 to 1.36)	36 more per 1,000 (from 64 fewer to 163 more)	⊕⊕◯◯ LOW	CRITICAL
Treatment failure - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	0/54 (0.0%)	0/101 (0.0%)	not estimable	0 fewer per 1,000 (from 30 more to 30 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment failure - RCTs												
2	randomised trials	not serious	not serious	not serious	serious [d]	none	10/830 (1.2%)	6/665 (0.9%)	not estimable	0 fewer per 1,000 (from 10 fewer to 20 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Loss to follow up - Cohort studies												
1	observational studies	serious [a]	not serious	not serious	serious [d]	none	0/54 (0.0%)	18/101 (17.8%)	not estimable	180 fewer per 1,000 (from 260 fewer to 100 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up - RCTs												
2	randomised trials	not serious	not serious	not serious	very serious [c,d]	none	17/260 (6.5%)	13/168 (7.7%)	**RR 0.74** (0.36 to 1.49)	20 fewer per 1,000 (from 38 more to 50 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale
b. No events in the intervention/control groups
c. Wide CI that does not exclude significant benefit or harm.
d. Very few events in the intervention and/or control groups.
e. Significant heterogeneity between studies.

PICO 10.9 Should mobile telephone interventions be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Mobile phone and medication monitoring interventions compared to none for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mobile phone and medication monitoring interventions	None	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies (video DOT vs in-person DOT)												
1	observational studies	serious [a]	not serious	serious [b]	very serious [c,d]	none	1/61 (1.6%)	3/329 (0.9%)	**RR 1.80** (0.19 to 17.00)	7 more per 1,000 (from 7 fewer to 146 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success - RCTs (phone reminders)												
2	randomised trials	serious [e]	not serious	not serious	serious [c]	none	66/68 (97.1%)	60/68 (88.2%)	**RR 1.06** (0.87 to 1.30)	53 more per 1,000 (from 115 fewer to 265 more)	⨁⨁◯◯ LOW	CRITICAL
Completion - Cohort studies (video DOT vs in-person DOT)												
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	77/119 (64.7%)	283/399 (70.9%)	**RR 1.17** (0.79 to 1.72)	121 more per 1,000 (from 149 fewer to 511 more) [h]	⨁◯◯◯ VERY LOW	CRITICAL
Completion - RCTs (phone reminders)												
1	randomised trials	serious [f]	not serious	not serious	serious [d]	none	0/30 (0.0%)	6/31 (19.4%)	not estimable	190 fewer per 1,000 (from 340 fewer to 50 fewer)	⨁⨁◯◯ LOW	CRITICAL
Cure - Cohort studies (phone reminder)												
1	observational studies	serious [a]	not serious	not serious	serious [d]	strong association	18/24 (75.0%)	31/96 (32.3%)	**RR 2.32** (1.60 to 3.36)	426 more per 1,000 (from 194 more to 762 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cure - RCTs (phone reminders)												
1	randomised trials	serious [f]	not serious	not serious	serious [c,d]	none	49/49 (100.0%)	29/50 (58.0%)	**RR 1.71** (1.35 to 2.17)	412 more per 1,000 (from 203 more to 679 more)	⨁⨁◯◯ LOW	CRITICAL
Failure (phone reminders)												
1	randomised trials	serious [f]	not serious	not serious	serious [d]	none	0/49 (0.0%)	6/50 (12.0%)	not estimable	120 fewer per 1,000 (from 220 fewer to 20 fewer)	⨁⨁◯◯ LOW	CRITICAL
Sputum/culture conversion at 2 months - Cohort studies (phone reminders)												
1	observational studies	serious [a]	not serious	not serious	serious [c,d]	none	15/24 (62.5%)	37/96 (38.5%)	**RR 1.62** (1.09 to 2.42)	239 more per 1,000 (from 35 more to 547 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sputum/culture conversion at 2 months - RCTs (phone reminders)												
1	randomised trials	serious [e]	not serious	not serious	very serious [c,d]	none	5/7 (71.4%)	6/8 (75.0%)	**RR 0.95** (0.51 to 1.76)	38 fewer per 1,000 (from 368 fewer to 570 more)	⨁◯◯◯ VERY LOW	CRITICAL
Poor outcome (phone reminders)												
1	observational studies	not serious	not serious	not serious	not serious	none	53/966 (5.5%)	121/1066 (11.4%)	**RR 0.48** (0.35 to 0.66)	59 fewer per 1,000 (from 39 fewer to 74 fewer)	⨁⨁◯◯ LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mobile phone and medication monitoring interventions	None	Relative (95% CI)	Absolute (95% CI)		
Poor outcome (medication monitor)												
1	observational studies	not serious	not serious	not serious	not serious	none	68/955 (7.1%)	121/1066 (11.4%)	**RR 0.63** (0.47 to 0.83)	42 fewer per 1,000 (from 19 fewer to 60 fewer)	⊕⊕◯◯ LOW	CRITICAL
Poor outcome (combined medication monitor and phone reminders)												
1	observational studies	not serious	not serious	not serious	not serious	none	99/992 (10.0%)	121/1066 (11.4%)	**RR 0.88** (0.68 to 1.13)	14 fewer per 1,000 (from 15 more to 36 fewer)	⊕⊕◯◯ LOW	CRITICAL
Loss to follow up (phone reminders)												
1	observational studies	not serious	not serious	not serious	not serious	none	41/954 (4.3%)	112/1057 (10.6%)	**RR 0.41** (0.29 to 0.57)	63 fewer per 1,000 (from 46 fewer to 75 fewer)	⊕⊕◯◯ LOW	CRITICAL
Loss to follow up (medication monitor)												
1	observational studies	not serious	not serious	not serious	not serious	none	59/946 (6.2%)	112/1057 (10.6%)	**RR 0.59** (0.43 to 0.80)	43 fewer per 1,000 (from 21 fewer to 60 fewer)	⊕⊕◯◯ LOW	CRITICAL
Loss to follow up (combined medication monitor and phone reminders)												
1	observational studies	not serious	not serious	not serious	not serious	none	89/982 (9.1%)	112/1057 (10.6%)	**RR 0.86** (0.66 to 1.11)	15 fewer per 1,000 (from 12 more to 36 fewer)	⊕⊕◯◯ LOW	CRITICAL
Poor adherence (phone reminders)												
1	observational studies	not serious	not serious	serious [g]	not serious	none	1518/5284 (28.7%)	1834/6013 (30.5%)	**RR 0.94** (0.89 to 1.00)	18 fewer per 1,000 (from 0 fewer to 34 fewer)	⊕◯◯◯ VERY LOW	
Poor adherence (medication monitor)												
1	observational studies	not serious	not serious	serious [g]	not serious	none	943/5430 (17.4%)	1834/6013 (30.5%)	**RR 0.57** (0.53 to 0.61)	131 fewer per 1,000 (from 119 fewer to 143 fewer)	⊕◯◯◯ VERY LOW	
Poor adherence (phone reminder and medication monitor)												
1	observational studies	not serious	not serious	serious [g]	not serious	none	981/5782 (17.0%)	1834/6013 (30.5%)	**RR 0.56** (0.52 to 0.60)	134 fewer per 1,000 (from 122 fewer to 146 fewer)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale.
b. Studies conducted in HIC, extrapolation to LMIC is uncertain
c. Wide CI that does not exclude significant benefit or harm.
d. Very few events in the intervention and/or control arms.
e. In one trial, 47% of the control group were lost to follow up.
f. No information provided on randomization, blinding, or allocation strategies.
g. Study evaluating patient months where 20% of doses were missed
h. No explanation was provided

PICO 10.10 Should reminders and tracers versus none be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Tracers compared to none for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tracers	None	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies												
3	observational studies	serious [a]	not serious	not serious	serious [b]	none	16375/182194 (9.0%)	18044/224631 (8.0%)	not estimable	20 fewer per 1,000 (from 70 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - RCTs												
1	randomised trials	not serious	not serious	not serious	very serious [b,c]	none	3/240 (1.3%)	8/240 (3.3%)	**RR 0.38** (0.10 to 1.40)	21 fewer per 1,000 (from 13 more to 30 fewer)	⨁⨁◯◯ LOW	CRITICAL
Treatment success - Cohort studies												
3	observational studies	serious [a]	serious [d]	not serious	serious [b]	none	129645/182194 (71.2%)	171637/224631 (76.4%)	**RR 1.03** (0.89 to 1.20)	23 more per 1,000 (from 84 fewer to 153 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success - RCTs												
4	randomised trials	serious [e]	serious [d]	not serious	not serious	none	361/389 (92.8%)	303/389 (77.9%)	**RR 1.12** (1.01 to 1.26)	93 more per 1,000 (from 8 more to 203 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment completion - Cohort studies												
1	observational studies	not serious	not serious	not serious	not serious	none	20579/181283 (11.4%)	19697/224390 (8.8%)	**RR 1.29** (1.27 to 1.32)	25 more per 1,000 (from 24 more to 28 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment completion - RCT												
2	randomised trials	serious [f]	serious [d]	not serious	serious [b]	none	59/94 (62.8%)	115/158 (72.8%)	**risk difference (%) -0.06** (-0.31 to 0.19)	60 fewer per 1,000 (from 310 fewer to 190 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cure - Cohort studies												
2	observational studies	serious [a]	serious [d]	not serious	very serious [b]	none	108459/181319 (59.8%)	151810/224496 (67.6%)	**RR 1.28** (0.59 to 2.79)	189 more per 1,000 (from 277 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Failure - Cohort studies												
3	observational studies	serious [a]	not serious	not serious	not serious	none	4208/182194 (2.3%)	4687/224631 (2.1%)	not estimable	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow up - Cohort studies												
4	observational studies	serious [a]	serious [d]	not serious	serious [b]	none	20935/182822 (11.5%)	18637/225259 (8.3%)	not estimable	50 fewer per 1,000 (from 150 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow up - RCTs												
2	randomised trials	not serious	not serious	not serious	very serious [b,c]	none	7/304 (2.3%)	42/367 (11.4%)	**RR 0.23** (0.03 to 1.58)	88 fewer per 1,000 (from 66 more to 111 fewer)	⨁⨁◯◯ LOW	CRITICAL
Adherence												
2	randomised trials	serious [f]	not serious	not serious	not serious	none	361/547 (66.0%)	94/200 (47.0%)	**RR 1.41** (1.14 to 1.76)	193 more per 1,000 (from 66 more to 357 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tracers	None	Relative (95% CI)	Absolute (95% CI)		
Sputum/culture conversion at 2 months												
2	ran-domised trials	serious [e]	not serious	not serious	not serious	none	209/247 (84.6%)	166/248 (66.9%)	**RR 1.26** (1.14 to 1.40)	174 more per 1,000 (from 94 more to 268 more)	⊕⊕⊕◯ MODER-ATE	CRITICAL
Development of drug resistance - Cohort studies												
1	obser-vational studies	not serious	not serious	not serious	not serious	none	581/ 181283 (0.3%)	1452/ 224390 (0.6%)	**RR 0.50** (0.45 to 0.55)	3 fewer per 1,000 (from 3 fewer to 4 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale.

b. CI does not exclude significant benefit or harm.

c. Very few events in the intervention and/or control groups.

d. Significant heterogeneity between studies.

e. In one study, 47% of the control arm were lost to follow up. Multiple studies did not report data on blinding and allocation strategies.

f. One study does not provide data on randomization or allocation strategies.

PICO 10.11 Should mixed patient case management interventions versus none be used for TB treatment?

Author(s): Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
Question: Mixed case management interventions compared to none for TB treatment
Setting: Multiple countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed case management interventions	None	Relative (95% CI)	Absolute (95% CI)		
Mortality - Cohort studies (Enhanced DOT vs SAT)												
4	observational studies	serious [a]	serious [b]	not serious	very serious [c,d]	none	64/2063 (3.1%)	64/1311 (4.9%)	not estimable	50 fewer per 1,000 (from 130 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - Cohort studies (Enhanced DOT vs DOT)												
2	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	285/6411 (4.4%)	575/11739 (4.9%)	**RR 0.93** (0.64 to 1.35)	3 fewer per 1,000 (from 17 more to 18 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - RCTs (mixed interventions vs SAT)												
2	randomised trials	serious [e]	not serious	not serious	very serious [c,d]	none	15/219 (6.8%)	19/236 (8.1%)	**RR 0.88** (0.44 to 1.75)	10 fewer per 1,000 (from 45 fewer to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - RCTs (Enhanced DOT vs DOT)												
1	randomised trials	serious [e]	not serious	not serious	very serious [c,d]	none	12/778 (1.5%)	25/744 (3.4%)	**RR 0.46** (0.23 to 0.91)	18 fewer per 1,000 (from 3 fewer to 26 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success - Cohort studies (Enhanced DOT vs SAT)												
2	observational studies	serious a	not serious	not serious	not serious	none	1607/1920 (83.7%)	747/1075 (69.5%)	**RR 1.22** (1.16 to 1.27)	153 more per 1,000 (from 111 more to 188 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success - Cohort studies (Enhanced DOT vs DOT)												
3	observational studies	not serious	serious [b]	not serious	not serious	none	5371/6611 (81.2%)	8546/11929 (71.6%)	**RR 1.27** (1.09 to 1.49)	193 more per 1,000 (from 64 more to 351 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success - RCTs (Enhanced DOT vs SAT)												
1	randomised trials	serious [f]	not serious	not serious	not serious	none	30/32 (93.8%)	22/32 (68.8%)	**RR 1.36** (1.06 to 1.75)	248 more per 1,000 (from 41 more to 516 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment success - RCTs (Enhanced DOT vs DOT)												
2	randomised trials	serious [f]	not serious	not serious	not serious	none	720/828 (87.0%)	594/794 (74.8%)	**RR 1.16** (1.11 to 1.22)	120 more per 1,000 (from 82 more to 165 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion - Cohort studies (Enhanced DOT vs SAT)												
2	observational studies	serious [a]	not serious	not serious	not serious	none	97/179 (54.2%)	177/582 (30.4%)	**RR 1.84** (1.52 to 2.21)	255 more per 1,000 (from 158 more to 368 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion - Cohort studies (Enhanced DOT vs DOT)												
2	observational studies	not serious	serious [b]	not serious	serious [g]	none	2407/6411 (37.5%)	4823/11739 (41.1%)	**RR 0.85** (0.52 to 1.38)	62 fewer per 1,000 (from 156 more to 197 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion - RCTs (Enhanced DOT vs SAT)												
1	randomised trials	serious [f]	not serious	not serious	not serious	none	31/32 (96.9%)	22/32 (68.8%)	**RR 1.41** (1.11 to 1.79)	282 more per 1,000 (from 76 more to 543 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed case management interventions	None	Relative (95% CI)	Absolute (95% CI)		
Treatment completion - RCTs (Enhanced DOT vs DOT)												
2	randomised trials	serious [f]	not serious	not serious	serious [g]	none	47/828 (5.7%)	56/794 (7.1%)	**RR 0.83** (0.58 to 1.19)	12 fewer per 1,000 (from 13 more to 30 fewer)	⊕⊕◯◯ LOW	CRITICAL
Cure - Cohort studies (Enhanced DOT vs DOT)												
2	observational studies	not serious	serious [b]	not serious	serious [g]	none	2803/5637 (49.7%)	3640/10725 (33.9%)	**RR 1.41** (0.67 to 2.96)	139 more per 1,000 (from 112 fewer to 665 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cure - RCTs (Enhanced DOT vs DOT)												
1	randomised trials	serious [f]	not serious	not serious	not serious	none	649/778 (83.4%)	520/744 (69.9%)	**RR 1.19** (1.13 to 1.26)	133 more per 1,000 (from 91 more to 182 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure - Cohort studies (Enhanced DOT vs SAT)												
2	observational studies	serious [a]	serious [b]	not serious	serious [g]	none	164/179 (91.6%)	179/253 (70.8%)	**RR 1.42** (1.02 to 1.99)	297 more per 1,000 (from 14 more to 700 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cure - RCTs (Enhanced DOT vs SAT)												
1	randomised trials	serious [f]	not serious	not serious	not serious	none	30/32 (93.8%)	22/32 (68.8%)	**RR 1.36** (1.06 to 1.75)	248 more per 1,000 (from 41 more to 516 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure - RCTs (mixed case management vs SAT)												
2	randomised trials	serious [f]	not serious	not serious	not serious	none	169/215 (78.6%)	160/236 (67.8%)	**RR 1.15** (1.03 to 1.29)	102 more per 1,000 (from 20 more to 197 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Failure - Cohort studies (Enhanced DOT vs DOT)												
2	observational studies	not serious	not serious	not serious	very serious [d,g]	none	34/6017 (0.6%)	93/11268 (0.8%)	**RR 0.64** (0.23 to 1.77)	3 fewer per 1,000 (from 6 fewer to 6 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - Cohort studies (Enhanced DOT vs SAT)												
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	2/1920 (0.1%)	4/1075 (0.4%)	not estimable	0 fewer per 1,000 (from 20 fewer to 10 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - RCTs (mixed case management vs SAT)												
1	randomised trials	serious [f]	not serious	not serious	very serious [c,d]	none	2/42 (4.8%)	4/81 (4.9%)	**RR 0.96** (0.18 to 5.05)	2 fewer per 1,000 (from 40 fewer to 200 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure - RCTs (Enhanced DOT vs DOT)												
1	randomised trials	serious [f]	not serious	not serious	very serious [c,d]	none	12/778 (1.5%)	6/744 (0.8%)	**RR 1.91** (0.72 to 5.07)	7 more per 1,000 (from 2 fewer to 33 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up - Cohort studies (Enhanced DOT vs DOT)												
2	observational studies	not serious	serious [b]	not serious	serious [g]	none	673/6411 (10.5%)	1962/11739 (16.7%)	**RR 0.47** (0.14 to 1.61)	89 fewer per 1,000 (from 102 more to 144 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up - RCTs (Enhanced DOT vs DOT)												
2	randomised trials	serious [f]	not serious	not serious	not serious	none	52/828 (6.3%)	142/794 (17.9%)	**RR 0.38** (0.25 to 0.57)	111 fewer per 1,000 (from 77 fewer to 134 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed case management interventions	None	Relative (95% CI)	Absolute (95% CI)		
Loss to follow up - Cohort studies (Enhanced DOT vs SAT)												
4	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	150/2099 (7.1%)	445/1657 (26.9%)	**RR 0.61** (0.32 to 1.14)	105 fewer per 1,000 (from 38 more to 183 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow up - RCTs (mixed case management vs SAT)												
2	randomised trials	serious [f]	not serious	not serious	serious [d]	none	23/219 (10.5%)	44/236 (18.6%)	**RR 0.58** (0.36 to 0.93)	78 fewer per 1,000 (from 13 fewer to 119 fewer)	⨁⨁◯◯ LOW	CRITICAL
Relapse - Cohort studies (Enhanced DOT vs SAT)												
1	observational studies	serious [a]	not serious	not serious	serious [d]	none	0/149 (0.0%)	3/223 (1.3%)	not estimable	10 more per 1,000 (from 30 more to 10 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence (Enhanced DOT vs DOT)												
1	randomised trials	serious [f]	not serious	not serious	serious [c]	none	40/50 (80.0%)	38/50 (76.0%)	**RR 1.05** (0.85 to 1.30)	38 more per 1,000 (from 114 fewer to 228 more)	⨁⨁◯◯ LOW	CRITICAL
Adherence (mixed case management vs SAT)												
1	randomised trials	serious [f]	not serious	not serious	serious [g]	none	29/41 (70.7%)	24/42 (57.1%)	**RR 1.24** (0.89 to 1.72)	137 more per 1,000 (from 63 fewer to 411 more)	⨁⨁◯◯ LOW	CRITICAL
Sputum smear converstion rate (2nd month) - RCTs (Enhanced DOT vs SAT)												
1	randomised trials	serious [f]	not serious	not serious	serious [h]	none	28/32 (87.5%)	17/32 (53.1%)	**RR 1.65** (1.16 to 2.34)	345 more per 1,000 (from 85 more to 712 more)	⨁⨁◯◯ LOW	CRITICAL
Acquired drug resistance - Cohort studies (Enhanced DOT vs SAT)												
1	observational studies	serious [a]	not serious	not serious	serious [d,g]	none	0/149 (0.0%)	2/223 (0.9%)	not estimable	10 more per 1,000 (from 30 more to 10 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Based on Newcastle Ottawa Scale.
b. Significant heterogeneity between the studies.
c. CI does not exclude significant benefit or harm.
d. Few events in the intervention and/or control arms.
e. Studies do not provide data on randomization, blinding, or allocation strategies.
f. No information provided on methodology of randomization, allocation, and concealment.
g. Wide CI that does not exclude benefit or harm.
h. Wide confidence interval.

PICO 11 Should decentralized treatment and care versus centralized treatment and care be used for patients on MDR-TB treatment?

Author(s): Jennifer Ho and Greg Fox

Question: Decentralised treatment and care compared to centralized treatment and care for patients on MDR-TB treatment

Setting: Countries which have decentralised treatment and care for patients with multi-drug resistant tuberculosis

Bibliography: Loveday M, et al. Int J Tuberc Lung Dis; 2015; Chan PC et al.. PloS one 2013 Kerschberger B. Community-based drug resistant TB care: opportunities for scale-up and remaining challenges. 2016 (unpublished). Narita M et al. Chest 2001 Gler MT et al. Int J Tuberc Lung Dis; 2012 Cox H et al. Int J Tuberc Lung Dis; 2014

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	decentralised treatment and care	centralized treatment and care	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/death/lost to follow up												
5	observational studies	serious [a]	not serious [b]	not serious [c]	not serious [d]	none	1035/1695 (61.1%) [e]	979/1710 (57.3%) [f]	**RR 1.13** (1.01 to 1.27)	74 more per 1,000 (from 6 more to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to Follow-Up vs Treatment Success/ Treatment Failure / Death												
4	observational studies	serious [a]	serious [b]	not serious [c]	not serious [d]	none	278/1549 (17.9%) [g]	384/1727 (22.2%) [h]	**RR 0.66** (0.38 to 1.13)	76 fewer per 1,000 (from 29 more to 138 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Death vs Treatment Success / Treatment Failure / Loss to Follow-Up												
4	observational studies	serious [a]	serious [b]	not serious [c]	not serious [d]	none	250/1405 (17.8%) [i]	232/1349 (17.2%) [j]	**RR 1.01** (0.67 to 1.53)	2 more per 1,000 (from 57 fewer to 91 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment Failure vs Treatment success / Death / Loss to Follow-Up												
3	observational studies	serious [a]	serious [b]	not serious [c]	not serious [d]	none	90/1382 (6.5%) [k]	55/1311 (4.2%) [l]	**RR 1.07** (0.48 to 2.40)	3 more per 1,000 (from 22 fewer to 59 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. All of the studies were observational studies. The method of allocating patients to intervention and control groups was not randomised. Not downgraded for this further because already accounted for in the initial certainty in the evidence. The studies did not adjust for baseline imbalances or possible confounders and therefore the evidence were further downgraded.

b. Based on estimated I2

c. the study interventions and outcomes were directly relevant to the objective of this review

d. Based on 95% CIs

e. pooled proportion 0.67, 95% CI 0.54-0.79

f. pooled proportion 0.61, 95% CI 0.49-0.72

g. pooled proportion 0.12, 95% CI 0.06-0.23

h. pooled proportion 0.18, 95% CI 0.09-0.32

i. pooled proportion 0.18, 95% CI 0.16-0.20

j. pooled proportion 0.19, 95% CI 0.15-0.24

k. pooled proportion 0.04, 95% CI 0.01-0.12

l. pooled proportion 0.04, 95% CI 0.02-0.08

Web Annex 1.3. Guideline update 2022

Table 6a. In children and adolescents with signs and symptoms of TB, should decentralization of child and adolescent TB services versus centralized child and adolescent TB services (at referral or tertiary hospital level) be used?

Author(s): Yuen C, Hussain H, Hirsch-Moverman Y and Szkwarko D

Question: Decentralization TB services compared to centralized TB services in children and adolescents with signs and symptoms of TB

Setting: Bangladesh, Cameroon, Cote d'Ivoire, Democratic Republic of Congo, India, Kenya, Lesotho, Malawi, Nepal, Nigeria, Pakistan, Papua New Guinea, Peru, South Africa, Tanzania. Uganda, Zimbabwe

Bibliography: See reference list

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	decentralization TB services	centralized TB services	Relative (95% CI)	Absolute (95% CI)		
TB case notifications (population) – strengthening diagnostic capacity in primary-level facilities and via community-facility linkages												
1[1,a]	randomised trials	serious[b]	not serious	not serious	not serious	none	175/-	130/-	**Rate ratio 1.87** (1.28 to 2.71)	**-- per 1000 patient(s) per years** (from – to --)	⨁⨁⨁◯ MODERATE	CRITICAL
TB case notifications (population) – Strengthening diagnostic capacity in primary-level facilities and via community–facility linkages												
8[2,3,4,5,6,7,8,9,c]	observational studies	serious[d]	not serious	not serious	not serious	none	Eight multifaceted studies including community-activities to bring people with signs/symptoms into facilities and enhanced primary care facility components. • Khan: 205 vs 28 cases, IRR 7.32 (95% CI 4.39–10.87) • Malik: 1391 vs 417 cases, IRR* 2.96 (95% CI 2.49–3.50) • Zawedde-Muyanja: 647 vs 271 cases, IRR 2.39 (95% CI 2.07–2.75) • Maha: 295 vs 140 cases, IRR 2.11 (95% CI 1.72–2.58) • Islam: 231 vs 65 cases, IRR 1.78 (95% CI 1.35–2.34) • Cap-TB: 5865 vs 2295 cases, IRR 1.49 (95% CI 1.42–1.56) • Oshi: 1590 vs 1210 cases, IRR 1.31 (95% CI 1.22–1.42) • Joshi: 360 vs 113 cases, IRR* 1.14 (95% CI 0.83–1.56)				⨁◯◯◯ VERY LOW	CRITICAL
TB case notifications (population) – home-based screening of household contacts												
1[10,e]	randomised trials	serious[f]	not serious	serious[g]	serious[h]	none	189/-	216/-	**Rate ratio 0.88** (0.31 to 2.46)	**-- per 1000 patient(s) per years** (from – to --)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	decentralization TB services	centralized TB services	Relative (95% CI)	Absolute (95% CI)		
TB diagnoses (cohort) – home-based screening every 3 months												
1[11,i,j]	randomised trials	not serious	not serious	not serious	not serious	none	89/2381	36/2382	**Rate ratio 2.6** (1.8 to 4.0)	**13 more per 1000 patient(s) per years** (from 8 more to 19 more)[k]	⨁⨁⨁⨁ HIGH	
TB diagnoses (cohort) – home-based screening with sputum collection vs with referral												
1[12,j]	randomised trials	not serious	not serious	serious[l]	serious[m]	none	8/216 (3.7%)	10/227 (4.4%)	**RR 0.84** (0.34 to 2.09)	**7 fewer per 1,000** (from 29 fewer to 48 more)	⨁⨁◯◯ LOW	
TB case notifications (population) or diagnoses (cohort) – Home-based screening for contacts and at-risk populations												
3[13,14,15]	observational studies	serious[n]	not serious	serious[o]	serious[p]	none	Three studies evaluated home-based symptom screening + sputum collection in the home or referral to health facilities for evaluation. • Fatima: 13,288 vs 12,506 case notifications, IRR 1.06 (95% CI 1.03–1.08) • Reddy: 7 vs 2 case notifications, aIRR 0.71 (95% CI 0.04–12.07) adjusted for change in control area • Bayona: 1/151 vs 3/118 cases among MDR contacts, RR 0.26 (95% CI 0.02–2.56)		⨁◯◯◯ VERY LOW	CRITICAL
TB diagnoses (cohort) – Introduction of Xpert into decentralized diagnostic centers												
1[16,q]	observational studies	not serious	not serious	not serious	serious[h]	none	271/2570 (10.5%)	46/428 (10.7%)	**RR 0.98** (0.72 to 1.33)	**2 fewer per 1,000** (from 30 fewer to 35 more)	⨁◯◯◯ VERY LOW	

CI: confidence interval; RR: risk ratio

Explanations

a. This cluster-randomized trial reported number of TB diagnoses at population-based diagnostic centers before and after intervention. The effect estimate is the incidence rate ratio for the change in diagnoses at the intervention centers divided by the incidence rate ratio at the control centers. The study also reported numbers of children evaluated at the centers, so another way to analyze the data would have been to calculate a risk ratio for diagnosis among children evaluated. However, we felt that the PICO outcome is really about population-level notifications, and the effect estimate we report is both most reflective of the PICO outcome and also the most conservative outcome possible in terms of magnitude. However, no information about underlying population size is given, so no absolute effect estimate can be determined.

b. This trial was rated as having "some concerns" over bias in the RoB2 because lack of access to a protocol meant that there was no information available on most of the key items in the RoB2. While we have no reason to believe that there was any systematic bias, the absence of so much key information caused us to downgrade.

c. Pre- and post-intervention periods are not equal in all studies. Asterisk (*) indicates IRR adjusted for changes in notifications in a control area.

d. Only 2 out of the 8 pre-post studies adjusted for secular changes over time via use of a control area.

e. This cluster randomized trial was designed with case notifications as the outcome and an analysis plan based on a Poisson regression fitted to facility-level counts. No information on the underlying size of the at-risk population is given or assumed. Therefore, it is not possible to calculate a rate difference.

f. There were serious concerns about bias for this facility-randomized trial because of imbalance in the size and level of the health facilities in the two arms.

g. There were serious concerns with indirectness because the intervention arm comprised a mixture of two interventions, one of which we consider decentralized (home visits for contact screening) and the other of which we do not (cash incentives for contacts who came to the health facility).

h. Confidence interval is wide and crosses 1.

i. Events out of participants is entered into the "Number of patients" section, but effect estimates are rate ratio and rate difference, which is how the trial assessed the outcome of interest.

j. This trial was rated as having "some concerns" over risk of bias via the RoB2. This rating was driven mostly by the fact that it would have been impossible to blind trial participants and the people making the household visits to intervention allocation, but we thought it unlikely that this could affect outcome ascertainment,. Therefore, we did not downgrade the trial for risk of bias concerns.

k. The intervention arm had 89 cases detected out of 4109 person-years of observation, while the control arm had 36 cases detected out of 4372 person-years of observation.

l. Intervention population is not all children and adolescents with signs/symptoms of TB, but its restricted to household contacts. Results do not provide a direct measure of population-level case notifications.

m. There were serious concerns with imprecision due to small numbers of events in the child/adolescent age group.

n. Only 1 of the studies adjusted for possible confounding

o. Two sources of indirectness were identified for the two smaller studies. Reddy assessed only smear-positive TB diagnoses, which is not the same as all TB notifications. The population of Bayona was limited to MDR-TB contacts, which is not necessarily representative of all people with TB signs/symptoms. Of note, the largest study (Fatima) did not suffer from these concerns.

p. Very small numbers of children diagnosed with TB in two of the studies resulted in wide confidence intervals

q. We considered downgrading for indirectness because the population reached by the intervention is not all people with TB signs/symptoms but only those who accessed the diagnostic centers (since the intervention contained no community component). However, because diagnostic center attendance did not change during the intervention and the effect estimates would have been almost identical if analyzed as a population-level case notification rate ration, we chose not to downgrade.

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Table 6b. In children and adolescents exposed to TB, should decentralization of child and adolescent TB prevention and care services versus centralized prevention and care services (at referral or tertiary hospital level) be used to increase coverage of TB preventive treatment in eligible children and adolescents?

Author(s): Yuen C, Hussain H, Hirsch-Moverman Y and Szkwarko D

Question: Decentralization of child and adolescent TB prevention and care services compared to centralized (tertiary/ referral centre) in children and adolescents exposed to TB

Setting: Cameroon, Cote d'Ivoire, Democratic Republic of Congo, Ethiopia, India, Kenya, Lesotho, Malawi, Tanzania, Uganda, Zimbabwe

Bibliography: See reference list

Certainty assessment							No of patients		Effect		Cer-tainty	Impor-tance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	decentralization TB services	centralized TB services	Relative (95% CI)	Absolute (95% CI)		
Coverage of TPT initiation among contacts (0–5 years old)												
1[1]	obser-vational studies	serious[a]	not serious	not serious	serious[b]	none	25/113 (22.1%)	22/126 (17.5%)	**RR 1.27** (0.76 to 2.12)	**47 more per 1,000** (from 42 fewer to 196 more)	⨁◯◯◯ VERY LOW	CRITICAL
Population TPT initiation rate for contacts (0–4 years old)												
2[2,3]	obser-vational studies	serious[c]	not serious	not serious	not serious	none	Two studies of multifaceted interventions to strengthen decentralized TPT services: Yassin: 698 vs 0 TPT initiations, IRR undefined Cap-TB: 12,634 vs 1,758 TPT initiations, 8-fold increase in median monthly TPT initiations per site, p<0.001				⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. The study was considered to have a serious risk of bias, as it did not report adjustment for secular changes over time or other sources of confounding.

b. There were serious concerns about imprecision as confidence interval crosses 1; the low number of events suggests that larger sample size might increase precision.

c. These studies were considered to have a serious risk of bias, as they were pre-post studies without any adjustment for secular changes over time or other sources of confounding.

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Table 6c. In children and adolescents with signs and symptoms of TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used?

Author(s): Yuen C, Hussain H, Hirsch-Moverman Y and Szkwarko D

Question: Family-centred, integrated services compared to standard, non-family-centred, non-integrated services in children and adolescents with signs and symptoms of TB

Setting: Ethiopia and Zambia

Bibliography: See reference list

Certainty assessment							No of patients		Effect		Cer-tainty	Impor-tance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	family-centred, integrated services	standard, non-family-centred, non-integrated services	Relative (95% CI)	Absolute (95% CI)		
TB diagnoses (cohort) – TB screening in IMNCI												
1[1,a]	ran-domised trials	serious[b]	not serious	not serious	not serious	none	38/95618 (0.0%)	9/85278 (0.0%)	**RR 3.77** (1.82 to 7.79)	**0 fewer per 100** (from 0 fewer to 0 fewer)[c]	⨁⨁⨁◯ MODERATE	CRITICAL
Case notifications (population) – co-location of ART												
1[2,d]	obser-vational studies	serious[e]	not serious	not serious	serious[f]	none	40/-	12/-	**Rate ratio 2.67** (1.05 to 6.76)	**-- per 1000 patient(s) per years** (from – to --)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. This stepped-wedge trial evaluated a multi-component intervention including screening in IMNCI and in the TB DOTS clinic of 30 health facilities.

b. The stepped wedge trial was deemed to have a serious risk of bias because the analysis method did not account for potential time trends over the course of the trial.

c. The event rate is the number of TB diagnoses out of the number of children attending the IMNCI clinic. The relative effect is the relative risk of TB diagnosis, calculated without accounting for clustering. The absolute effect, as reported by the study, was 0.5 (95% CI 0.2–0.7) additional diagnoses per facility per 4-month study period (i.e. period of each "step" in the stepped wedge), corresponding to an absolute increase in TB notifications.

d. This study reported TB notifications at intervention facilities before and after co-location of ART services, and at control facilities in the same region that never received co-located ART services. Only the intervention facility counts are shown (before and after co-location of ART services). The number of cases in the control facilities was very small, and decreased substantially between the two periods, raising the possibility of population shifting from one set of facilities to the other. The unadjusted notification rate ratio presented here is more conservative than the one that adjusts for the change in the control facilities.

e. There were serious concerns about bias, as it is not clear whether increase in TB cases at intervention facilities was due population shifting from control facilities to intervention facilities, as they are in the same area and not specified as being tied to specific catchment populations.

f. There were serious concerns about imprecision due to the small numbers of events, which led to a wide confidence interval, even though the confidence interval did not cross 1.

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Table 6d. In children and adolescents exposed to TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used to increase coverage of TB preventive treatment in eligible children and adolescents?

Author(s): Yuen C, Hussain H, Hirsch-Moverman Y and Szkwarko D

Question: Family-centred, integrated services compared to standard, non-family-centred, non-integrated services in children and adolescents exposed to TB

Setting: Peru

Bibliography:

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	family-centred, integrated services	standard, non-family-centred, non-integrated services	Relative (95% CI)	Absolute (95% CI)		
Coverage of TPT initiation among contacts (0–19 years)												
1[1,a]	randomised trials	not serious	not serious	not serious	not serious	none	91/206 (44.2%)	53/206 (25.7%)	**RR 1.70** (1.10 to 2.64)	**180 more per 1,000** (from 26 more to 422 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Coverage of TPT initiation among contacts (0–19 years)												
1[2,b]	observational studies	serious[c]	not serious	not serious	not serious	none	476/542 (87.8%)	1116/2829 (39.4%)	**RR 2.23** (2.11 to 2.36)	**485 more per 1,000** (from 438 more to 537 more)	⨁◯◯◯ VERY LOW	CRITICAL
TPT completion among contacts (0–19 years)												
1[2,d]	observational studies	serious[c]	not serious	not serious	not serious	none	383/441 (86.8%)	301/1116 (27.0%)	**RR 3.22** (2.90 to 3.57)	**599 more per 1,000** (from 512 more to 693 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. This household-randomized trial of a socioeconomic support package included social support activities and conditional cash transfers to offset hidden costs of care. Although this trial was rated as having "some concerns" for bias via the RoB2, these were related to the unblinded nature of the intervention and the lack of access to a protocol to assess adherence to a pre-defined analysis plan. We chose not to downgrade because we did not feel that the lack of blinding was likely to affect the outcome given the nature of the intervention, and the presentation of results suggested a pre-defined analysis plan for this primary trial outcome.

b. A multifaceted support package included social, economic, and psychological support; patients and their families were free to accept or decline individual components. Event counts were calculated from reported percentages and are thus approximate; the possible range of intervention events is 474–479 and the possible range for control events is 1116–1117. While this could be a source of imprecision, the amount of imprecision is not sufficient to substantively change the magnitude of the effect estimate.

c. This study was a pre-post study without any adjustment for secular trends over time or other sources of confounding, leading to serious concerns about bias.

d. A multifaceted support package included social, economic, and psychological support; patients and their families were free to accept or decline individual components. Event counts were calculated from reported percentages and are thus approximate; the possible range of intervention events is 382–385 and the possible range for control events is 296–306. While this could be a source of imprecision, the amount of imprecision is not sufficient to substantively change the magnitude of the effect estimate.

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Web Annex 2. Evidence-to-decision tables

Web Annex 2.1. Guideline update 2017

PICO 10.1

Question

Should self-administered treatment versus directly observed treatment be used for TB patients?		
Population:	TB patients	Background:
Intervention:	Self-administered treatment (SAT)	
Comparison:	Directly observed treatment (DOT)	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Completion - cohort studies; Completion - RCTs; Cure - cohort studies; Cure - RCTs; Failure - cohort studies; Failure - RCTs; Loss to follow-up – cohort studies; Loss to follow-up - RCTs; Relapse – cohort studies; Relapse - RCTs; Adherence – cohort studies; Adherence - RCTs; Smear conversion - cohort studies; Smear conversion - RCTs; Acquisition of drug resistance.	
Setting:		
Perspective:		

Assessment

<table>
<tr><th></th><th>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>No research evidence was identified.</td><td>DOT is defined as any person observing the patient taking medications in real time. It may include real-time video recording.</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>SAT is considered the intervention. Results from RCTs were considered preferentially.
Patients on SAT had slightly lower mortality rates and lower relapse rates but had higher rates of loss to follow-up and higher rates of acquired drug resistance.
Patients who were on DOT had better rates of treatment success, cure, treatment completion, 2-month sputum conversion, and had better adherence.</td><td>The GDG focused preferentially on randomized control trial data. DOT included any form of observation of administration of treatment.
Some patients were "double counted" in treatment success and in cure or treatment completion.
In these studies, DOT was administered at a daily health clinic or was home-administered.
Adherence definitions varied, but in general it was defined as taking > 90% of medications.</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 colspan="2">Summary of findings:
<table>
<tr><th>Outcome</th><th>With directly observed treatment (DOT)</th><th>With self administered treatment (SAT)</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Mortality - Cohort studies</td><td>33 per 1000</td><td>0 per 1000 (0 to 0)</td><td>20 more per 1000 (from 0 fewer to 40 more)</td><td>not estimable</td></tr>
<tr><td>Mortality - RCTs</td><td>45 per 1000</td><td>0 per 1000 (0 to 0)</td><td>10 fewer per 1000 (from 30 fewer to 10 more)</td><td>0.73 (0.45-1.19)</td></tr>
<tr><td>Treatment success - Cohort studies</td><td>744 per 1000</td><td>588 per 1000 (536 to 655)</td><td>156 fewer per 1000 (from 89 fewer to 208 fewer)</td><td>RR 0.79 (0.72 to 0.88)</td></tr>
<tr><td>Treatment success - RCTs</td><td>746 per 1000</td><td>701 per 1000 (664 to 731)</td><td>45 fewer per 1000 (from 15 fewer to 82 fewer)</td><td>RR 0.94 (0.89 to 0.98)</td></tr>
<tr><td>Completion - Cohort studies</td><td>262 per 1000</td><td>0 per 1000 (0 to 0)</td><td>20 more per 1000 (from 40 fewer to 80 more)</td><td>not estimable</td></tr>
<tr><td>Completion - RCTs</td><td>234 per 1000</td><td>185 per 1000 (131 to 260)</td><td>49 fewer per 1000 (from 26 more to 103 fewer)</td><td>RR 0.79 (0.56 to 1.11)</td></tr>
</table>
</td></tr>
</table>

	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, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ● Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	DOT is comparison	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	SAT is treatment intervention.	DOT definition broadened to include any person who observes the patient taking the medications in real time. This does not have to be a health care worker (HCW), but could be friend, relative, etc. Other patient-related factors (e.g. daily wage workers) may prevent access to DOT. The feeling of being "watched over" may be disempowering for patients. It may be stigmatizing to have an HCW coming to a patient's house. Other forms of DOT (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may also be stigmatizing.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	SAT is treatment intervention.	See comments on stigma, above.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	SAT is treatment intervention.	

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should self-administered treatment versus directly observed treatment be used for TB 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	The GDG suggests either directly observed treatment (DOT) or self-administered treatment (SAT) (conditional recom-mendation, low certainty of evidence).				
Justification	If SAT is used, it must be used in conjunction with proper medical care, including patient counselling and education on the disease and its treatment.				
Subgroup considerations					
Implementation consider-ations	DOT may refer to observation by relatives and other caregivers. The systematic review defined DOT as any form of directly observed treatment by a health worker, social worker, relative or neighbour.				
Monitoring and evaluation					
Research priorities					

PICO 10.2

Question

Should directly observed treatment at different locations versus clinic or routine care be used for TB treatment?		
Population:	Patients undergoing TB treatment	Background:
Intervention:	DOT at different locations	
Comparison:	DOT at health facility/clinic or unsupervised treatment	
Main outcomes:	Mortality - cohorts (home/community versus clinic); Mortality - RCTs (community versus clinic); Success - cohorts (home/community versus clinic); Success - RCTs (home/community versus clinic); Completion - cohort studies (home/community versus clinic); Completion- RCTs (community versus clinic); Cure - cohort studies (home/community versus clinic); Cure - RCTs (home/community versus clinic); Failure – cohort studies (home/community versus clinic); Failure - RCTs (home versus community); Failure - RCTs (community versus clinic); Loss to follow-up - cohorts (home/community versus clinic); Loss to follow-up - RCTs (home/community versus clinic); Adherence - cohort studies (home/community versus clinic); Sputum conversion (2nd month) - cohort studies (home/community versus clinic); Sputum conversion (2nd month) - RCTs (home/community versus clinic); Unfavourable outcome (community versus clinic).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The GDG focused on the data presented from RCTs, when available. This question compared community/home DOT versus clinic DOT. In general, these locations were grouped by distance, with community/home DOT being closer to the patient, and clinic-based DOT being more distant. There were some instances of community-based DOT being provided by health-care workers. Community/home-based DOT had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. It also had lower rates of mortality and overall lower rates of unfavourable outcomes. However, community-based DOT also had higher rates of loss to follow-up and lower adherence rates.	

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With clinic or routine care	With DOT at different locations	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohorts (home/community versus clinic)	45 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 10 fewer to 20 more)	not estimable
Mortality - RCTs (community versus clinic)	110 per 1000	40 per 1000 (7 to 256)	70 fewer per 1000 (from 103 fewer to 146 more)	RR 0.36 (0.06 to 2.33)
Success - cohorts (home/community versus clinic)	791 per 1000	870 per 1000 (838 to 901)	79 more per 1000 (from 47 more to 111 more)	RR 1.10 (1.06 to 1.14)
Success - RCTs (home/community versus clinic)	840 per 1000	874 per 1000 (840 to 916)	34 more per 1000 (from 0 fewer to 76 more)	RR 1.04 (1.00 to 1.09)
Completion - cohort studies (home/community versus clinic)	170 per 1000	158 per 1000 (95 to 264)	12 fewer per 1000 (from 75 fewer to 94 more)	RR 0.93 (0.56 to 1.55)
Completion - RCTs (community versus clinic)	34 per 1000	98 per 1000 (39 to 248)	64 more per 1000 (from 5 more to 215 more)	RR 2.92 (1.15 to 7.41)
Cure - cohort studies (home/community versus clinic)	665 per 1000	738 per 1000 (659 to 825)	73 more per 1000 (from 7 fewer to 160 more)	RR 1.11 (0.99 to 1.24)
Cure - RCTs (home/community versus clinic)	602 per 1000	608 per 1000 (554 to 674)	6 more per 1000 (from 48 fewer to 72 more)	RR 1.01 (0.92 to 1.12)
Failure - cohort studies (home/community versus clinic)	39 per 1000	0 per 1000 (0 to 0)	10 fewer per 1000 (from 30 fewer to 0 fewer)	not estimable
Failure - RCTs (home versus community)	2 per 1000	2 per 1000 (0 to 24)	0 fewer per 1000 (from 1 fewer to 23 more)	RR 1.00 (0.06 to 16.00)
Failure - RCTs (community versus clinic)	13 per 1000	9 per 1000 (2 to 49)	4 fewer per 1000 (from 12 fewer to 36 more)	RR 0.68 (0.13 to 3.69)
Loss to follow-up - cohorts (home/community versus clinic)	113 per 1000	67 per 1000 (44 to 99)	46 fewer per 1000 (from 14 fewer to 69 fewer)	RR 0.59 (0.39 to 0.88)
Loss to follow-up - RCTs (home/community versus clinic)	134 per 1000	139 per 1000 (45 to 427)	5 more per 1000 (from 88 fewer to 293 more)	RR 1.04 (0.34 to 3.19)
Adherence - cohort studies (home/community versus clinic)	933 per 1000	868 per 1000 (719 to 1000)	65 fewer per 1000 (from 112 more to 215 fewer)	RR 0.93 (0.77 to 1.12)
Sputum conversion (2nd month) - cohort studies (home/community versus clinic)	866 per 1000	995 per 1000 (883 to 1000)	130 more per 1000 (from 17 more to 251 more)	RR 1.15 (1.02 to 1.29)
Sputum conversion (2nd month) - RCTs (home/community versus clinic)	694 per 1000	757 per 1000 (687 to 847)	62 more per 1000 (from 7 fewer to 153 more)	RR 1.09 (0.99 to 1.22)

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, the extent to which 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.	

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	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	As per previous discussion on DOT versus self-administered treatment (SAT)	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	There is probably more acceptability and accessibility with community/home based-DOT than with other forms of DOT. Stigma may continue to be a concern. However, given complex family social dynamics, family members may not always be the best people to monitor treatment. Evidence from another PICO question showed that loss to follow-up is higher and adherence is lower if a family member is administering DOT.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Training of local staff will still be needed since family members cannot be the only options for care. Patients will still need psychosocial support and social service support even if family members are providing DOT.

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	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should directly observed treatment at different locations versus clinic or routine care be used for TB 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	The GDG suggests community-based or home-based DOT over clinic-based or hospital-based DOT (conditional recommendation, moderate certainty in the evidence).				
Justification	Following the meeting the Steering Group asked for further clarification of the data relating to home/community-based DOT versus SAT. Additional analysis directly comparing home/community-based DOT versus SAT (cohort studies only, see corresponding evidence table) showed higher rates of treatment success and treatment adherence and lower rates of loss to follow-up with home/community-based DOT. Comparison of health facility-based DOT versus SAT (both RCTs and cohort studies, see corresponding evidence table) showed no difference in outcomes between these two methods. These analyses led to the recommendation that community/home-based DOT is the preferred option rather than health facility-based DOT or SAT.				
Subgroup considerations					
Implementation considerations	Community/home-based DOT should be done in combination with psychosocial support. Careful identification and training of persons conducting DOT is required. There is a need to define community-based DOT (this should not be confused with community clinics).				
Monitoring and evaluation					
Research priorities					

PICO 10.3

Question

Should different directly observed treatment providers versus standard providers be used for TB treatment (2)?		
Population:	Patients undergoing TB treatment (2)	Background:
Intervention:	Different DOT providers	
Comparison:	Standard providers (health-care workers, or HCW) or unsupervised treatment	
Main outcomes:	Mortality - family DOT versus HCW; Mortality - lay provider versus HCW; Success - family versus HCW; Success - lay provider versus HCW; Completion - cohort studies; Cure - family versus HCW; Cure - lay provider versus HCW; Failure - family versus HCW; Failure - lay provider versus HCW; Loss to follow-up - family versus HCW; Loss to follow-up - lay provider versus HCW; Adherence - family versus HCW (village doctor).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	In this analysis, family members were compared to HCW and lay providers were compared to HCW. Among family providers, compared to HCW, there were higher rates of mortality, loss to follow-up, failure and default, and lower rates of successful treatment, cure and adherence among patients who had DOT administered by family members. Among lay providers compared to HCW, there were higher rates of success and cure and lower mortality and failure among patients who had DOT administered by a lay person compared to an HCW.	

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
● Moderate
○ Small
○ Trivial

○ Varies
○ Don't know</td><td>Summary of findings:
<table><tr><th>Outcome</th><th>With standard providers</th><th>With different DOT providers</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr><tr><td>Mortality - family DOT versus HCW</td><td>119 per 1000</td><td>125 per 1000 (108 to 144)</td><td>6 more per 1000 (from 11 fewer to 25 more)</td><td>RR 1.05 (0.91 to 1.21)</td></tr><tr><td>Mortality - lay provider versus HCW</td><td>52 per 1000</td><td>38 per 1000 (24 to 59)</td><td>14 fewer per 1000 (from 7 more to 28 fewer)</td><td>RR 0.73 (0.47 to 1.13)</td></tr><tr><td>Success - family versus HCW</td><td>723 per 1000</td><td>615 per 1000 (485 to 767)</td><td>109 fewer per 1000 (from 43 more to 239 fewer)</td><td>RR 0.85 (0.67 to 1.06)</td></tr><tr><td>Success - lay provider versus HCW</td><td>763 per 1000</td><td>832 per 1000 (710 to 969)</td><td>69 more per 1000 (from 53 fewer to 206 more)</td><td>RR 1.09 (0.93 to 1.27)</td></tr><tr><td>Completion - cohort studies</td><td>365 per 1000</td><td>354 per 1000 (339 to 372)</td><td>11 fewer per 1000 (from 7 more to 26 fewer)</td><td>RR 0.97 (0.93 to 1.02)</td></tr><tr><td>Cure - family versus HCW</td><td>473 per 1000</td><td>246 per 1000 (76 to 785)</td><td>227 fewer per 1000 (from 312 more to 397 fewer)</td><td>RR 0.52 (0.16 to 1.66)</td></tr><tr><td>Cure - lay provider versus HCW</td><td>744 per 1000</td><td>811 per 1000 (603 to 1000)</td><td>67 more per 1000 (from 141 fewer to 350 more)</td><td>RR 1.09 (0.81 to 1.47)</td></tr><tr><td>Failure - family versus HCW</td><td>8 per 1000</td><td>0 per 1000 (0 to 0)</td><td>10 more per 1000 (from 0 fewer to 10 more)</td><td>not estimable</td></tr><tr><td>Failure - lay provider versus HCW</td><td>43 per 1000</td><td>20 per 1000 (7 to 56)</td><td>23 fewer per 1000 (from 13 more to 36 fewer)</td><td>RR 0.47 (0.17 to 1.29)</td></tr><tr><td>Loss to follow-up - family versus HCW</td><td>54 per 1000</td><td>80 per 1000 (66 to 98)</td><td>26 more per 1000 (from 11 more to 44 more)</td><td>RR 1.48 (1.21 to 1.81)</td></tr><tr><td>Loss to follow-up - Cohort studies</td><td>100 per 1000</td><td>75 per 1000 (42 to 132)</td><td>25 fewer per 1000 (from 32 more to 58 fewer)</td><td>RR 0.75 (0.42 to 1.32)</td></tr><tr><td>Adherence - Cohort studies</td><td>944 per 1000</td><td>812 per 1000 (746 to 887)</td><td>132 fewer per 1000 (from 57 fewer to 198 fewer)</td><td>RR 0.86 (0.79 to 0.94)</td></tr></table></td><td></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, the extent to which 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></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
● Probably favours the comparison
○ Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>Comparison is DOT being provided by standard providers (HCW).</td><td></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.	
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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours 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	As per previous DOT discussion.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Family-based providers may have lower stigma, as their provision of DOT to the patient is less obvious to other people, such as neighbours.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Feasibility may be reduced with health-care workers in the community because it requires an increased number of health-care workers placed in the community, with an increased associated costs.

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours 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 resourc-es	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours 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

Should different directly observed treatment providers versus standard providers be used for TB treatment (2)?

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	The GDG suggests the use of health-care providers or trained lay providers, rather than family members, to administer DOT (conditional recommendation, very low certainty in the evidence).				
Justification	Following the meeting, the Steering Group asked for further clarification of the data surrounding different providers delivering DOT versus self-administered treatment (SAT). Additional analysis directly comparing HCW provided DOT versus SAT (RCTs and cohort studies, see corresponding evidence table) showed higher rates of treatment completion with SAT but higher rates of cure and adherence and lower rates of relapse and acquisition of drug resistance with HCW DOT. Comparison of lay provider-supplied DOT versus SAT, which included both RCTs and cohort studies (see corresponding evidence table) showed lower rates of treatment completion but higher rates of cure with a lay provider DOT. Comparison of family-provided DOT versus SAT showed higher rates of treatment success and lower rates of loss to follow-up with family-provided DOT compared with SAT (see corresponding evidence tables). These analyses led to the recommendation that DOT should be administered by trained lay providers or health-care workers. This is recommended over DOT administered by family members or unsupervised treatment.				
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities					

PICO 10.4

Question

Should self-administered treatment versus directly observed treatment be used for TB/HIV patients?		
Population:	TB/HIV patients	Background:
Intervention:	Self-administered treatment (SAT)	
Comparison:	DOT	
Main outcomes:	Mortality - cohort studies; Success - cohort studies; Completion - cohort studies; Cure - cohort studies; Failure - cohort studies; Loss to follow-up - cohort studies; Relapse - cohort studies.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Only cohort studies were available for this review. Self-administered treatment (SAT) is the intervention. TB/HIV co-infected patients on SAT had lower rates of treatment success, treatment completion and cure. They had higher rates of mortality, treatment failure and loss to follow-up. **Summary of findings:**	
Undesirable Effects	How substantial are the undesirable anticipated effects? ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
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, the extent to which 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.	

Outcome	With DOT	With SAT	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies	67 per 1000	185 per 1000 (102 to 336)	117 more per 1000 (from 34 more to 269 more)	RR 2.74 (1.51 to 4.99)
Success - cohort studies	821 per 1000	337 per 1000 (238 to 484)	484 fewer per 1000 (from 337 fewer to 583 fewer)	RR 0.41 (0.29 to 0.59)
Completion - cohort studies	250 per 1000	25 per 1000 (3 to 190)	225 fewer per 1000 (from 60 fewer to 248 fewer)	RR 0.10 (0.01 to 0.76)
Cure - cohort studies	586 per 1000	234 per 1000 (170 to 322)	352 fewer per 1000 (from 264 fewer to 416 fewer)	RR 0.40 (0.29 to 0.55)
Failure - cohort studies	198 per 1000	634 per 1000 (418 to 962)	436 more per 1000 (from 220 more to 764 more)	RR 3.20 (2.11 to 4.86)
Loss to follow-up - cohort studies	171 per 1000	331 per 1000 (89 to 1000)	160 more per 1000 (from 82 fewer to 1000 more)	RR 1.94 (0.52 to 7.17)
Relapse - cohort studies	20 per 1000	18 per 1000 (3 to 124)	2 fewer per 1000 (from 17 fewer to 105 more)	RR 0.90 (0.13 to 6.28)

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ● Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	DOT is the comparison.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		DOT definition broadened to include any person who observes the patient taking the medications in real time. This does not have to be a health care worker (HCW), but could be friend, relative, etc. Other patient-related factors (daily wage workers, etc.) may prevent access to DOT. The feeling of being "watched over" may be disempowering for patients. It may be stigmatizing to have an HCW coming to a patient's house. Other forms of DOT (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may also be stigmatizing.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The possibility of increased drug-drug interactions between TB and HIV medications may make DOT (and the increased patient support) more acceptable to stakeholders.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

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	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should self-administered treatment versus directly observed treatment be used for TB/HIV patients?

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	The GDG suggests the use of DOT rather than self-administered treatment (SAT) in HIV-infected patients with TB (conditional recommendation, very low certainty of evidence).				
Justification	The GDG felt that HIV-positive people as a subgroup benefited more from DOT than the general TB population. The reasons for this are unclear but increased rates of drug-drug interactions and more severe disease in this cohort may cause DOT to offer a significant advantage over SAT.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 10.5

Question

Should incentives and enablers versus none be used for TB treatment?		
Population:	Patients receiving TB treatment	Background:
Intervention:	Incentives and enablers	
Comparison:	None	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Treatment completion - cohort studies; Treatment completion - RCTs; Cure - cohort studies; Cure - RCTs; Treatment failure - cohort studies; Treatment failure - RCTs; Loss to follow-up - cohort studies; Loss to follow-up - RCTs; Acquisition of resistance; Sputum conversion rate - RCTs.	
Setting:		
Perspective:		

Assessment

<table>
<tr><th></th><th>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></td><td></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>Data from the RCT were preferentially considered.
There were higher rate of treatment success, completion and sputum conversion with incentives/enablers.
There were lower rate of treatment failure and loss to follow-up with incentives/enablers.</td><td>Examples of incentives and enablers included food, food vouchers, food supplements, financial support, transport subsidies, living allowance, housing incentives, and financial bonus if study objectives met. All but one of the studies were in low- to middle-income countries, so presumably these incentives were of significant value for the subjects.
Food may be given as an incentive but it may also biologically improve outcomes through a reduction in malnutrition and consequent improvement in immune function.
It should be noted that outcomes were exclusive, so cure may appear to be lower if treatment completion is higher. Treatment success is therefore probably the most reliable outcome.</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>Summary of findings:
<table>
<tr><th>Outcome</th><th>With none</th><th>With incentives and enablers</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Mortality - RCTs</td><td>68 per 1000</td><td>-7 per 1000 (-3 to 2)</td><td>1 fewer per 1000 (from 40 fewer to 30 more)</td><td>risk difference (%) -0.10 (-0.04 to 0.03)</td></tr>
<tr><td>Treatment success - RCTs</td><td>714 per 1000</td><td>764 per 1000 (735 to 792)</td><td>50 more per 1000 (from 21 more to 79 more)</td><td>RR 1.07 (1.03 to 1.11)</td></tr>
<tr><td>Treatment completion - RCTs</td><td>361 per 1000</td><td>444 per 1000 (416 to 473)</td><td>83 more per 1000 (from 54 more to 112 more)</td><td>RR 1.23 (1.15 to 1.31)</td></tr>
<tr><td>Cure - RCTs</td><td>357 per 1000</td><td>328 per 1000 (303 to 360)</td><td>29 fewer per 1000 (from 4 more to 54 fewer)</td><td>RR 0.92 (0.85 to 1.01)</td></tr>
<tr><td>Treatment failure - RCTs</td><td>57 per 1000</td><td>38 per 1000 (28 to 50)</td><td>19 fewer per 1000 (from 7 fewer to 28 fewer)</td><td>RR 0.66 (0.50 to 0.87)</td></tr>
<tr><td>Loss to follow up - RCTs</td><td>102 per 1000</td><td>75 per 1000 (61 to 92)</td><td>26 fewer per 1000 (from 10 fewer to 41 fewer)</td><td>RR 0.74 (0.60 to 0.90)</td></tr>
<tr><td>Sputum conversion rate - RCTs</td><td>806 per 1000</td><td>975 per 1000 (822 to 1000)</td><td>169 more per 1000 (from 16 more to 346 more)</td><td>RR 1.21 (1.02 to 1.43)</td></tr>
</table></td><td></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>
</table>

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	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.	These incentives were usually given to the most vulnerable groups, so health equity was improved. However, if the incentives are not applied equitably, health disparities may be increased. The distribution of incentives and enablers is likely to depend on the country context. Incentives and enablers may have different effects within countries and between countries.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	There may be reluctance on the part of implementers (e.g. governments, health partners) to pay for incentives. Implementers may be more willing to pay for incentives/enablers for particularly high-risk smaller subgroups (e.g. patients with MDR-TB). One of the components of WHO's END TB Strategy is to provide "social protection and poverty alleviation" for patients with tuberculosis. The strategy specifically calls for measures to "alleviate the burden of income loss and non-medical costs of seeking and staying in care". Included in these suggested protections are social welfare payments, vouchers and food packages. The benefit of incentives and enablers found in this review supports these components of the END TB Strategy (See: WHO END TB Strategy, http://www.who.int/tb/post2015_strategy/en/).
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Incentives and enablers may not be feasible in all settings if the implementers are reluctant to pay for such programmes. Feasibility may also vary according to the type of the proposed incentive. In order to distribute the incentives and enablers, a government and/or NGO infrastructure would need to be in place, including anti-fraud mechanisms and appropriate accounting to ensure that incentives are distributed equitably and to the people who need them the most.

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should incentives and enablers vs. none be used for TB 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	The GDG suggests that incentives and enablers* be provided to patients on tuberculosis treatment (conditional recommendation, moderate certainty in the evidence). *Incentives and enablers include different types of material support such as food, transportation subsidies or living allowances.				
Justification					
Subgroup considerations					
Implementation considerations	Countries should choose incentives that are the most appropriate to their situation.				
Monitoring and evaluation	Programmes should attempt to measure whether the provision of incentives improves programme performance.				
Research priorities	Suggested areas for research are: incentives that are best suited to specific populations; incentives that are most effective in low- and middle-income countries: analysis of the cost effectiveness of different types of incentives.				

PICO 10.6

Question

Should psychological interventions versus none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Psychological interventions	
Comparison:	None	
Main outcomes:	Mortality - cohort studies; Success - RCTs (ETOH cessation counseling); Treatment completion - cohort studies (support groups); Treatment completion - RCTs (support groups); Cure - RCTs (support groups); Failure - cohort studies (support groups); Failure - RCTs (support groups); Loss to follow-up - cohort studies (support groups); Loss to follow-up - RCTs (support groups).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Based on data from RCTs, patients who had access to support groups had higher rates of treatment completion and cure and lower rates of treatment failure and loss to follow-up. **Summary of findings:**	One RCT included alcohol cessation counselling as the intervention.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The panel did not believe that the increased mortality seen in the cohort study had plausible results due to the following reasons: There were concerns about confounding due to severity of illness in the support groups. Allocation of patients to the support groups (the TB clubs) was based on where they lived so it was not randomized. Within this cohort study, the control group had substantially more patients lost to follow-up (40%), so many patient outcomes are unclear and this degree of loss to follow-up may make the study invalid. Causes of mortality in the two groups were not described, so causal relationship could not be determined.

Outcome	With none	With psychological interventions	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies	94 per 1000	172 per 1000 (68 to 437)	78 more per 1000 (from 26 fewer to 343 more)	RR 1.83 (0.72 to 4.66)
Success - RCTs (ETOH cessation counseling)	798 per 1000	870 per 1000 (766 to 982)	72 more per 1000 (from 32 fewer to 184 more)	RR 1.09 (0.96 to 1.23)
Treatment completion - cohort studies (support groups)	469 per 1000	689 per 1000 (506 to 938)	220 more per 1000 (from 38 more to 469 more)	RR 1.47 (1.08 to 2.00)
Treatment completion - RCTs (support groups)	814 per 1000	977 per 1000 (838 to 1000)	163 more per 1000 (from 24 more to 317 more)	RR 1.20 (1.03 to 1.39)
Cure - RCTs (support groups)	814 per 1000	928 per 1000 (790 to 1000)	114 more per 1000 (from 24 fewer to 285 more)	RR 1.14 (0.97 to 1.35)
Failure - cohort studies (support groups)	16 per 1000	0 per 1000 (0 to 0)	20 fewer per 1000 (from 60 fewer to 30 more)	not estimable
Failure - RCTs (support groups)	116 per 1000	0 per 1000 (0 to 0)	1 fewer per 1000 (from 2 fewer to 0 fewer)	not estimable
Loss to follow-up - cohort studies (support groups)	406 per 1000	126 per 1000 (61 to 256)	280 fewer per 1000 (from 150 fewer to 345 fewer)	RR 0.31 (0.15 to 0.63)
Loss to follow-up - RCTs (support groups)	47 per 1000	23 per 1000 (2 to 247)	23 fewer per 1000 (from 44 fewer to 200 more)	RR 0.50 (0.05 to 5.31)

	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, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	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 range of types of psychological support is very broad and may not be represented adequately in this review. Within this review, counselling sessions and peer support were included. Equity will be increased if the support is targeted at the most marginalized populations.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should psychological interventions versus none be used for TB 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	The GDG suggests that psychological support* should be provided to patients with TB (conditional recommendation, low certainty of evidence).				
Justification	*Psychological support includes counselling sessions and peer-group support.				
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities	Suggested area for research is: what type of psychological support is most appropriate?				

PICO 10.7

Question

Should additional patient education and counselling versus routine care be used for TB treatment?		
Population:	Patients on TB treatment	Background:
Intervention:	Additional patient education and counselling	
Comparison:	Routine care	
Main outcomes:	Mortality - RCTs; Treatment success; Treatment completion; Cure; Failure; Loss to follow-up; Adherence - RCT; Adherence - cohort studies.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Patients who received education and counselling had better treatment success, treatment completion, cure and adherence rates. They had lower rates of loss to follow-up. It should be noted in this case that "counselling" refers to educational counselling and not psychological counselling. **Summary of findings:**	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	The certainty of the evidence would usually be the grade of the lowest ranked outcome (in this case very low or low). However, in this instance the evidence was graded as having overall a moderate certainty because the outcomes with very low or low certainty were not determined by the GDG as being critical outcomes. Two of the critical outcomes were rated as moderate and all the effects point in the same direction (i.e. in support of patient education).	

Outcome	With routine care	With additional patient education and counselling	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - RCTs	40 per 1000	33 per 1000 (14 to 83)	7 fewer per 1000 (from 27 fewer to 42 more)	RR 0.83 (0.34 to 2.05)
Treatment success	426 per 1000	596 per 1000 (383 to 924)	170 more per 1000 (from 43 fewer to 498 more)	RR 1.40 (0.90 to 2.17)
Treatment completion	420 per 1000	718 per 1000 (554 to 932)	298 more per 1000 (from 134 more to 512 more)	RR 1.71 (1.32 to 2.22)
Cure	395 per 1000	849 per 1000 (624 to 1000)	454 more per 1000 (from 229 more to 759 more)	RR 2.15 (1.58 to 2.92)
Failure	49 per 1000	61 per 1000 (12 to 315)	11 more per 1000 (from 38 fewer to 266 more)	RR 1.23 (0.24 to 6.38)
Loss to follow-up	494 per 1000	242 per 1000 (104 to 578)	252 fewer per 1000 (from 84 more to 390 fewer)	RR 0.49 (0.21 to 1.17)
Adherence - RCT	293 per 1000	536 per 1000 (334 to 856)	243 more per 1000 (from 41 more to 563 more)	RR 1.83 (1.14 to 2.92)
Adherence - cohort studies	783 per 1000	948 per 1000 (823 to 1000)	164 more per 1000 (from 39 more to 313 more)	RR 1.21 (1.05 to 1.40)

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	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.	It is important to make sure that education and counselling are done in a culturally appropriate manner. Specific marginalized populations may require special educational efforts.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Staff time needs to be freed up for this intervention and staff should be appropriately trained to provide health education. As staff time increases for this, it is necessary to ensure that staff time for other key activities is not affected.

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should additional patient education and counselling versus routine care be used for TB 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	The GDG recommends additional patient education and counselling for patients with TB (strong recommendation, moderate certainty of evidence).				
Justification					
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities					

PICO 10.8

Question

Should staff education versus none be used for TB treatment?		
Population:	Patients on TB treatment	Background:
Intervention:	Staff education	
Comparison:	None	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Completion - RCTs; Cure - RCTs; Treatment failure - cohort studies; Treatment failure - RCTs; Loss to follow-up - cohort studies; Loss to follow-up – RCTs.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There were higher rates of treatment success, slightly lower rates of mortality and lower rates of loss to follow-up with staff education. **Summary of findings:**	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
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.	

Outcome	With none	With staff education	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies	0 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 30 more to 30 fewer)	not estimable
Mortality - RCTs	50 per 1000	38 per 1000 (22 to 66)	12 fewer per 1000 (from 16 more to 28 fewer)	RR 0.76 (0.44 to 1.31)
Treatment success - cohort studies	693 per 1000	929 per 1000 (797 to 1000)	236 more per 1000 (from 104 more to 381 more)	RR 1.34 (1.15 to 1.55)
Treatment success - RCTs	634 per 1000	653 per 1000 (602 to 710)	19 more per 1000 (from 32 fewer to 76 more)	RR 1.03 (0.95 to 1.12)
Completion - RCTs	310 per 1000	282 per 1000 (195 to 405)	28 fewer per 1000 (from 96 more to 115 fewer)	RR 0.91 (0.63 to 1.31)
Cure - RCTs	454 per 1000	490 per 1000 (390 to 617)	36 more per 1000 (from 64 fewer to 163 more)	RR 1.08 (0.86 to 1.36)
Treatment failure - cohort studies	0 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 30 more to 30 fewer)	not estimable
Treatment failure - RCTs	9 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 10 fewer to 20 more)	not estimable
Loss to follow-up - cohort studies	178 per 1000	0 per 1000 (0 to 0)	180 fewer per 1000 (from 260 fewer to 100 fewer)	not estimable
Loss to follow-up - RCTs	77 per 1000	57 per 1000 (28 to 115)	20 fewer per 1000 (from 38 more to 50 fewer)	RR 0.74 (0.36 to 1.49)

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	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.	Training of staff may not be possible with all health-care workers in all communities. All health-care workers, regardless of their place in the health-care structure, need to have equal access to education. Patient equity may increase with increased staff education. With better staff education, treatment of patients should improve as health-care providers understand the disease better and place less stigma on patients.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Training and resources are required to train health staff adequately.

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should staff education vs. none be used for TB 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	The GDG suggests that staff education should be used to optimize the treatment of patients with TB (conditional recommendation, low certainty of evidence).				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 10.9.1

Question

Should mobile telephone interventions versus. none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Mobile health interventions	
Comparison:	None	
Main outcomes:	Mortality - cohort studies (video DOT versus in-person DOT); Treatment success - RCTs (telephone reminders); Completion - cohort studies (video DOT versus in-person DOT); Completion - RCTs (telephone reminders); Cure - cohort studies (telephone reminder); Cure - RCTs (telephone reminders); Failure (telephone reminders); Sputum/culture conversion at 2 months - cohort studies (telephone reminders); Sputum/culture conversion at 2 months - RCTs (telephone reminders); Poor outcome (telephone reminders); Poor outcome (medication monitor); Poor outcome (combined medication monitor and telephone reminders); Loss to follow-up (telephone reminders); Loss to follow-up (medication monitor); Loss to follow-up (combined medication monitor and telephone reminders); Poor adherence (telephone reminders); Poor adherence (medication monitor); Poor adherence (telephone reminder and medication monitor).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The mobile telephone interventions could be SMS reminders, telephone calls or video observed treatment (VOT). Since VOT was examined only by cohort studies, VOT was considered separately. Otherwise, RCT data were considered preferentially. For telephone reminders (SMS and telephone calls), there were higher rates of successful treatment outcomes and cure, and lower rates of treatment failure with telephone reminders as opposed to no intervention. Telephone reminders marginally lowered 2-month sputum conversion rates. It should be noted however, that these data are based on only one RCT.	

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td>Summary of findings:
<table>
<tr><th>Outcome</th><th>With none</th><th>With mobile health interventions</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Treatment success - RCTs (telephone reminders)</td><td>882 per 1000</td><td>935 per 1000 (768 to 1000)</td><td>53 more per 1000 (from 115 fewer to 265 more)</td><td>RR 1.06 (0.87 to 1.30)</td></tr>
<tr><td>Completion - RCTs (telephone reminders)</td><td>194 per 1000</td><td>0 per 1000 (0 to 0)</td><td>190 fewer per 1000 (from 340 fewer to 50 fewer)</td><td>not estimable</td></tr>
<tr><td>Cure - cohort studies (telephone reminder)</td><td>323 per 1000</td><td>749 per 1000 (517 to 1000)</td><td>426 more per 1000 (from 194 more to 762 more)</td><td>RR 2.32 (1.60 to 3.36)</td></tr>
<tr><td>Cure - RCTs (telephone reminders)</td><td>580 per 1000</td><td>992 per 1000 (783 to 1000)</td><td>412 more per 1000 (from 203 more to 679 more)</td><td>RR 1.71 (1.35 to 2.17)</td></tr>
<tr><td>Failure (telephone reminders)</td><td>120 per 1000</td><td>0 per 1000 (0 to 0)</td><td>120 fewer per 1000 (from 220 fewer to 20 fewer)</td><td>not estimable</td></tr>
<tr><td>Sputum/culture conversion at 2 months - Cohort studies (telephone reminders)</td><td>385 per 1000</td><td>624 per 1000 (420 to 933)</td><td>239 more per 1000 (from 35 more to 547 more)</td><td>RR 1.62 (1.09 to 2.42)</td></tr>
<tr><td>Sputum/culture conversion at 2 months - RCTs (telephone reminders)</td><td>750 per 1000</td><td>712 per 1000 (383 to 1000)</td><td>38 fewer per 1000 (from 368 fewer to 570 more)</td><td>RR 0.95 (0.51 to 1.76)</td></tr>
</table></td><td></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, the extent to which 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></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Equity</td><td>What would be the impact on health equity?
○ Reduced
○ Probably reduced
○ Probably no impact
○ Probably increased
○ Increased

● Varies
○ Don't know</td><td>No research evidence was identified.</td><td>These interventions may increase equity if travel to a clinic or to the patient's home is reduced.
These interventions may decrease ability of patients to participate if the patients are in an area with limited communication infrastructure.</td></tr>
</table>

	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.	There may be trepidation about using new technology. There are significant privacy issues surrounding security of telephone data. Encryption and other privacy technology will need to be considered. HCWs may not like the use of this intervention if their fee structure is lower when telephone communication is used.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	Feasibility depends on the communication infrastructure, telephone availability and connection costs.

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	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should mobile health interventions versus none be used for TB 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	The GDG suggests that mobile telephone interventions should be used with patients undergoing TB treatment (conditional recommendation, very low certainty in the evidence).				
Justification	Patient support and the ability to interact with HCWs should be preserved.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Research into the effectiveness of video DOT in low- to middle-income countries is encouraged since existing data are from high-income countries.				

PICO 10.9.2

Question

Should video observed treatment versus DOT be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Video observed treatment (VOT)	
Comparison:	DOT	
Main outcomes:	Mortality - cohort studies (VOT versus in-person DOT); Treatment success - RCTs (telephone reminders); Completion - cohort studies (VOT versus in-person DOT); Completion - RCTs (telephone reminders); Cure - cohort studies (telephone reminder); Cure - RCTs (telephone reminders); Failure (telephone reminders); Sputum/culture conversion at 2 months - cohort studies (telephone reminders); Sputum/culture conversion at 2 months - RCTs (telephone reminders); Poor outcome (telephone reminders); Poor outcome (medication monitor); Poor outcome (combined medication monitor and telephone reminders); Loss to follow-up (telephone reminders); Loss to follow-up (medication monitor); Loss to follow-up (combined medication monitor and telephone reminders); Poor adherence (telephone reminders); Poor adherence (medication monitor); Poor adherence (telephone reminder and medication monitor);	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For VOT there were only cohort studies. These studies were from high-income countries. There were no data from low- and middle-income countries. Patients whose treatment included VOT had minimally higher mortality than those using regular DOT but, due to the rarity of mortality events, these findings may not be significant. The GDG expressed concerns at the uncertainty of evidence surrounding the use of VOT. This uncertainty fueled the conditional recommendation for this intervention.	There is concern at the indirectness of evidence for VOT, given that the studies were done in low-burden countries. There are many varieties of VOT, so many different options are likely to be available to TB programmes. VOT may be particularly useful in low- and middle-income countries where the health-care system is overburdened.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:** Outcome: Mortality - cohort studies (VOT versus in-person DOT); With none: 9 per 1000; With mobile health interventions: 16 per 1000 (2 to 155); Difference (95% CI): 7 more per 1000 (from 7 fewer to 146 more); Relative effect (RR) (95% CI): RR 1.80 (0.19 to 17.00) Outcome: Completion - cohort studies (VOT versus in-person DOT); With none: 709 per 1000; With mobile health interventions: 830 per 1000 (560 to 1000); Difference (95% CI): 121 more per 1000 (from 149 fewer to 511 more); Relative effect (RR) (95% CI): RR 1.17 (0.79 to 1.72)	
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.	

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	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.	See mobile technology intervention.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	See mobile technology intervention.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	See mobile technology intervention.

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should video observed treatment versus DOT be used for TB 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	The GDG suggests that VOT or DOT could be used in patients undergoing TB treatment (conditional recommendation, very low certainty of evidence).				
Justification					
Subgroup considerations					
Implementation consider-ations	Other support should be provided together with VOT.				
Monitoring and evaluation					
Research priorities	Suggested areas for research are: efficacy of VOT in low- and middle-income countries; utilization of data from other medical programmes that use telephone technology (especially the in the field of HIV).				

PICO 10.10

Question

Should reminders and tracers versus none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Reminders and tracers	
Comparison:	none	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Treatment completion - cohort studies; Treatment completion - RCT; Cure - cohort studies; Failure - cohort studies; Loss to follow-up - cohort studies; Loss to follow-up - RCTs; Adherence; Sputum/culture conversion at 2 months; Development of drug resistance - cohort studies.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Data from RCTs showed: There were higher rates of treatment success, treatment adherence, and 2-month sputum conversion with reminders/tracers. There were lower rates of mortality and loss to follow-up with reminders/tracers.	Higher rates of culture conversion benefit the community by decreasing the spread of TB.

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Reminders and tracers compared to none for TB treatment**	

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with none	Risk difference with reminders and tracers
Mortality - cohort studies	406825 (3 observational studies)	(⊕◯◯◯) VERY LOW 1,2	not estimable	80 per 1000	80 fewer per 1000 (80 fewer to 80 fewer)
Mortality - RCTs	480 (1 RCT)	(⊕⊕◯◯) LOW 2,3	RR 0.38 (0.10 to 1.40)	33 per 1000	21 fewer per 1000 (30 fewer to 13 more)
Treatment success - cohort studies	406825 (3 observational studies)	(⊕◯◯◯) VERY LOW 1,2,4	RR 1.03 (0.89 to 1.20)	764 per 1000	23 more per 1000 (84 fewer to 153 more)
Treatment success - RCTs	778 (4 RCTs)	(⊕⊕◯◯) LOW 4,5	RR 1.12 (1.01 to 1.26)	779 per 1000	93 more per 1000 (8 more to 203 more)
Treatment completion - cohort studies	405673 (1 observational study)	(⊕⊕◯◯) LOW	RR 1.29 (1.27 to 1.32)	88 per 1000	25 more per 1000 (24 more to 28 more)
Treatment completion - RCT	252 (2 RCTs)	(⊕◯◯◯) VERY LOW 2,4,6	not estimable	728 per 1000	728 fewer per 1000 (728 fewer to 728 fewer)
Cure - cohort studies	405815 (2 observational studies)	(⊕◯◯◯) VERY LOW 1,2,4	RR 1.28 (0.59 to 2.79)	676 per 1000	189 more per 1000 (277 fewer to 1,210 more)
Failure - cohort studies	406825 (3 observational studies)	(⊕◯◯◯) VERY LOW 1	not estimable	21 per 1000	21 fewer per 1000 (21 fewer to 21 fewer)
Loss to follow-up - cohort studies	408081 (4 observational studies)	(⊕◯◯◯) VERY LOW 1,2,4	not estimable	83 per 1000	83 fewer per 1000 (83 fewer to 83 fewer)
Loss to follow-up - RCTs	671 (2 RCTs)	(⊕⊕◯◯) LOW 2,3	RR 0.23 (0.03 to 1.58)	114 per 1000	88 fewer per 1000 (111 fewer to 66 more)
Adherence	747 (2 RCTs)	(⊕⊕⊕◯) MODERATE 6	RR 1.41 (1.14 to 1.76)	470 per 1000	193 more per 1000 (66 more to 357 more)
Sputum/culture conversion at 2 months	495 (2 RCTs)	(⊕⊕⊕◯) MODERATE 5	RR 1.26 (1.14 to 1.40)	669 per 1000	174 more per 1000 (94 more to 268 more)
Development of drug resistance - cohort studies	405673 (1 observational study)	(⊕⊕◯◯) LOW	RR 0.50 (0.45 to 0.55)	6 per 1000	3 fewer per 1000 (4 fewer to 3 fewer)

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, the extent to which 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.	

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	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.	Health equity would be increased unless the patient lives in an area that cannot be reached by a communication network.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

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	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should reminders and tracers versus none be used for TB 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	The GDG suggests that reminders or tracers* should be used for patients on tuberculosis treatment (conditional recommendation, very low certainty of evidence).				
Justification	Reminders or tracers include text messages, telephone calls, medicine monitors or home visits.				
Subgroup considerations					
Implementation considerations	Multiple organizations have initiated programmes like these, so TB programmes may find it helpful to collaborate and communicate with other medical service delivery programmes that have already set up the infrastructure.				
Monitoring and evaluation					
Research priorities					

PICO 10.11

Question

Should mixed patient case management interventions versus none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Mixed case management interventions	
Comparison:	none	
Main outcomes:	Mortality - cohort studies (enhanced DOT versus SAT); Mortality - cohort studies (enhanced DOT versus DOT); Mortality - RCTs (mixed interventions versus SAT); Mortality - RCTs (enhanced DOT versus DOT); Treatment success - cohort studies (enhanced DOT versus SAT); Treatment success - cohort studies (enhanced DOT versus DOT); Treatment success - RCTs (enhanced DOT versus SAT); Treatment success - RCTs (enhanced DOT versus DOT); Treatment completion - cohort studies (enhanced DOT versus SAT); Treatment completion - cohort studies (enhanced DOT versus DOT); Treatment completion - RCTs (enhanced DOT versus SAT); Treatment completion - RCTs (enhanced DOT versus DOT); Cure - cohort studies (enhanced DOT versus DOT); Cure - RCTs (enhanced DOT versus DOT); Cure - cohort studies (enhanced DOT versus SAT); Cure - RCTs (enhanced DOT versus SAT); Cure - RCTs (mixed case management versus SAT); Failure - cohort studies (enhanced DOT versus DOT); Failure - cohort studies (enhanced DOT versus SAT); Failure - RCTs (mixed case management versus SAT); Failure - RCTs (enhanced DOT versus DOT); Loss to follow-up - cohort studies (enhanced DOT versus DOT); Loss to follow-up - RCTs (enhanced DOT versus DOT); Loss to follow-up - cohort studies (enhanced DOT versus SAT); Loss to follow-up - RCTs (mixed case management versus SAT); Relapse - cohort studies (enhanced DOT versus SAT); Adherence (enhanced DOT versus DOT); Adherence (mixed case management versus SAT); Sputum smear conversion rate (2nd month) - RCTs (enhanced DOT versus SAT); Acquired drug resistance - cohort studies (enhanced DOT versus SAT).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	In this review, enhanced DOT was compared to DOT (or SAT) without any other services. Enhanced DOT was DOT combined with some form of incentive or reminder or patient education. There is a lot of variation surrounding what "enhanced" means. Mixed interventions were a combination of some forms of support, whether incentives, reminders or patient education. Data from the RCTs showed: When enhanced DOT was compared to DOT alone, enhanced DOT had higher rates of treatment success, treatment completion, cure and adherence, and lower rates of mortality and loss to follow-up. There was a minimal increase in risk of failure with enhanced DOT. When enhanced DOT was compared to SAT, enhanced DOT had higher rates of treatment success, treatment completion, cure and 2-month sputum conversion. When mixed patient support interventions were compared to SAT, mixed patient support interventions had higher rates of cure and adherence, and lower rates of mortality and loss to follow-up.	

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With none	With mixed case management interventions	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies (enhanced DOT versus SAT)	49 per 1000	0 per 1000 (0 to 0)	50 fewer per 1000 (from 130 fewer to 30 more)	not estimable
Mortality - cohort studies (enhanced DOT versus DOT)	49 per 1000	46 per 1000 (31 to 66)	3 fewer per 1000 (from 17 more to 18 fewer)	RR 0.93 (0.64 to 1.35)
Mortality - RCTs (mixed interventions versus SAT)	81 per 1000	71 per 1000 (35 to 141)	10 fewer per 1000 (from 45 fewer to 60 more)	RR 0.88 (0.44 to 1.75)
Mortality - RCTs (enhanced DOT versus DOT)	34 per 1000	15 per 1000 (8 to 31)	18 fewer per 1000 (from 3 fewer to 26 fewer)	RR 0.46 (0.23 to 0.91)
Treatment success - cohort studies (enhanced DOT versus SAT)	695 per 1000	848 per 1000 (806 to 883)	153 more per 1000 (from 111 more to 188 more)	RR 1.22 (1.16 to 1.27)
Treatment success - Cohort studies (enhanced DOT versus DOT)	716 per 1000	910 per 1000 (781 to 1000)	193 more per 1000 (from 64 more to 351 more)	RR 1.27 (1.09 to 1.49)
Treatment success - RCTs (enhanced DOT versus SAT)	688 per 1000	935 per 1000 (729 to 1000)	248 more per 1000 (from 41 more to 516 more)	RR 1.36 (1.06 to 1.75)
Treatment success - RCTs (enhanced DOT versus DOT)	748 per 1000	868 per 1000 (830 to 913)	120 more per 1000 (from 82 more to 165 more)	RR 1.16 (1.11 to 1.22)
Treatment completion - cohort studies (enhanced DOT versus SAT)	304 per 1000	560 per 1000 (462 to 672)	255 more per 1000 (from 158 more to 368 more)	RR 1.84 (1.52 to 2.21)
Treatment completion - cohort studies (enhanced DOT versus DOT)	411 per 1000	349 per 1000 (214 to 567)	62 fewer per 1000 (from 156 more to 197 fewer)	RR 0.85 (0.52 to 1.38)
Treatment completion - RCTs (enhanced DOT versus SAT)	688 per 1000	969 per 1000 (763 to 1000)	282 more per 1000 (from 76 more to 543 more)	RR 1.41 (1.11 to 1.79)
Treatment completion - RCTs (enhanced DOT versus DOT)	71 per 1000	59 per 1000 (41 to 84)	12 fewer per 1000 (from 13 more to 30 fewer)	RR 0.83 (0.58 to 1.19)
Cure - cohort studies (enhanced DOT versus DOT)	339 per 1000	479 per 1000 (227 to 1000)	139 more per 1000 (from 112 fewer to 665 more)	RR 1.41 (0.67 to 2.96)
Cure - RCTs (enhanced DOT versus DOT)	699 per 1000	832 per 1000 (790 to 881)	133 more per 1000 (from 91 more to 182 more)	RR 1.19 (1.13 to 1.26)
Cure - cohort studies (enhanced DOT versus SAT)	708 per 1000	1000 per 1000 (722 to 1000)	297 more per 1000 (from 14 more to 700 more)	RR 1.42 (1.02 to 1.99)
Cure - RCTs (enhanced DOT versus SAT)	688 per 1000	935 per 1000 (729 to 1000)	248 more per 1000 (from 41 more to 516 more)	RR 1.36 (1.06 to 1.75)
Cure - RCTs (mixed case management versus SAT)	678 per 1000	780 per 1000 (698 to 875)	102 more per 1000 (from 20 more to 197 more)	RR 1.15 (1.03 to 1.29)
Failure - cohort studies (enhanced DOT versus DOT)	8 per 1000	5 per 1000 (2 to 15)	3 fewer per 1000 (from 6 fewer to 6 more)	RR 0.64 (0.23 to 1.77)
Failure - cohort studies (enhanced DOT versus SAT)	4 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 20 fewer to 10 more)	not estimable
Failure - RCTs (mixed case management versus SAT)	49 per 1000	47 per 1000 (9 to 249)	2 fewer per 1000 (from 40 fewer to 200 more)	RR 0.96 (0.18 to 5.05)
Failure - RCTs (enhanced DOT versus DOT)	8 per 1000	15 per 1000 (6 to 41)	7 more per 1000 (from 2 fewer to 33 more)	RR 1.91 (0.72 to 5.07)
Loss to follow-up - cohort studies (enhanced DOT versus DOT)	167 per 1000	79 per 1000 (23 to 269)	89 fewer per 1000 (from 102 more to 144 fewer)	RR 0.47 (0.14 to 1.61)
Loss to follow-up - RCTs (enhanced DOT versus DOT)	179 per 1000	68 per 1000 (45 to 102)	111 fewer per 1000 (from 77 fewer to 134 fewer)	RR 0.38 (0.25 to 0.57)
Loss to follow-up - cohort studies (enhanced DOT versus SAT)	269 per 1000	164 per 1000 (86 to 306)	105 fewer per 1000 (from 38 more to 183 fewer)	RR 0.61 (0.32 to 1.14)
Loss to follow-up - RCTs (mixed case management versus SAT)	186 per 1000	108 per 1000 (67 to 173)	78 fewer per 1000 (from 13 fewer to 119 fewer)	RR 0.58 (0.36 to 0.93)
Relapse - cohort studies (enhanced DOT versus SAT)	13 per 1000	0 per 1000 (0 to 0)	10 more per 1000 (from 30 more to 10 fewer)	not estimable
Adherence (enhanced DOT versus DOT)	760 per 1000	798 per 1000 (646 to 988)	38 more per 1000 (from 114 fewer to 228 more)	RR 1.05 (0.85 to 1.30)
Adherence (mixed case management versus SAT)	571 per 1000	709 per 1000 (509 to 983)	137 more per 1000 (from 63 fewer to 411 more)	RR 1.24 (0.89 to 1.72)
Sputum smear conversion rate (2nd month) - RCTs (enhanced DOT versus SAT)	531 per 1000	877 per 1000 (616 to 1000)	345 more per 1000 (from 85 more to 712 more)	RR 1.65 (1.16 to 2.34)
Acquired drug resistance - Cohort studies (enhanced DOT versus SAT)	9 per 1000	0 per 1000 (0 to 0)	10 more per 1000 (from 30 more to 10 fewer)	not estimable

	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.	Because all the effects point in the same direction and the majority of the outcomes of interest are graded as having moderate or low certainty of evidence, the outcomes graded as moderate certainty drive the overall evidence grade. Therefore, instead of grading the evidence at the lowest grade of the outcome of interest (mortality at a grade of very low), the preponderance of moderate certainty of evidence improves the overall evidence grade to low. The GDG also believed that the quality of the mortality data should not affect the overall data grading to a great degree because the mortality data was weak due to rarity of events and a large confidence interval.
Values	Is there important uncertainty about, or variability in, the extent to which 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 favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	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.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The same financial concerns apply here as outlined in the section on incentives/enablers.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

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	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
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

Should mixed case management interventions versus none be used for TB 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	The GDG suggests that a combination of DOT or organized self-administered treatment (SAT) plus other treatment adherence interventions* should be provided instead of DOT alone or SAT (conditional recommendation, low certainty of evidence).				
Justification	*Other treatment adherence interventions include: relevant DOT provider, staff education, digital health reminders (SMS, telephone calls), different types of social support such as material support for the patient (e.g. financial incentives, food, transport subsidies), and health education or psychological support.				
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities					

PICO 11

Question

Should decentralized treatment and care versus centralized treatment and care be used for patients on MDR-TB treatment?		
Population:	Patients on MDR-TB treatment	Background:
Intervention:	Decentralized treatment and care	
Comparison:	Centralized treatment and care	
Main outcomes:	Treatment success versus treatment failure/death/loss to follow-up; Loss to follow-up versus treatment success/treatment failure/death; Death versus treatment success/treatment failure/loss to follow-up; Treatment failure versus treatment success/death/loss to follow-up.	
Setting:	Countries which have decentralized treatment and care for patients with multi-drug resistant tuberculosis.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	WHO recommendations from 2011 state that patients with MDR-TB should be treated mainly in an ambulatory setting rather than in a system based mainly in the hospital. This is an update of that guidance.	As Xpert rolls out more patients will be diagnosed in decentralized centres, requiring more treatment in decentralized areas.
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Decentralized care was defined as care in the local community where the patient lives provided by non-specialized or periphery health centres, by community health workers or nurses, by non-specialized doctors, community volunteers or treatment supporters. There may have been a brief phase of initial hospitalization up to 1 month. Care could occur at local venues or at the patient's home or workplace. Treatment and care included DOT and patient support, and injections during the intensive phase. Centralized care was defined as treatment and care provided solely by specialized DR-TB centres or teams. This care was usually delivered by specialist doctors or nurses and could include centralized outpatient clinics (outpatient facilities located at or near the site of the centralized hospital). The care was defined as inpatient care for the duration of the intensive phase of treatment or until culture smear conversion. After that, patients could have received decentralized care. Both HIV-negative and HIV-positive persons were included in the studies examined. However, the studies did not stratify patients on the basis of HIV status. Treatment success and loss to follow-up improved with decentralized care versus centralized care. The risk of death and treatment failure showed minimal difference between patients undergoing decentralized care or centralized care. There were limited data on adverse reactions, adherence, acquired drug resistance and cost. No studies examined injections during the intensive phase or support for co-morbidities. The study by Narita et al. was excluded from sensitivity analysis due to concerns that it was very different from the other studies. For instance, it was conducted in the USA in the 1990s and the patients selected for hospitalized care in the study were failing their treatment or were non-adherent. The results of this study differed significantly from the other studies and had wide confidence intervals. Exclusion of this study did not significantly affect the treatment success or risk of death.	The GDG expressed concern that health-care workers may have selected patients that they thought might have a worse prognosis into the centralized care groups. None of the studies controlled for this risk of bias.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td>Decentralized treatment and care compared to centralized treatment and care of patients on MDR-TB treatment
<table>
<tr><th>Outcomes</th><th>No of participants (studies) Follow-up</th><th>Quality of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects</th></tr>
<tr><th></th><th></th><th></th><th></th><th>Risk with centralized treatment and care</th><th>Risk difference with decentralized treatment and care</th></tr>
<tr><td>Treatment success versus treatment failure/death/loss to follow-up</td><td>3405 (5 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 1.13 (1.01 to 1.27)</td><td>573 per 1000</td><td>74 more per 1000 (6 more to 155 more)</td></tr>
<tr><td>Loss to follow-up versus treatment success/treatment failure/death</td><td>3276 (4 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 0.66 (0.38 to 1.13)</td><td>222 per 1000</td><td>76 fewer per 1000 (138 fewer to 29 more)</td></tr>
<tr><td>Death versus treatment success/treatment failure/loss to follow-up</td><td>2754 (4 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 1.01 (0.67 to 1.53)</td><td>172 per 1000</td><td>2 more per 1000 (57 fewer to 91 more)</td></tr>
<tr><td>Treatment failure versus treatment success/death/loss to follow-up</td><td>2693 (3 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 1.07 (0.48 to 2.40)</td><td>42 per 1000</td><td>3 more per 1000 (22 fewer to 59 more)</td></tr>
</table></td><td></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, the extent to which 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></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>No research evidence was identified.</td><td></td></tr>
</table>

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></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 cost estimates were based on limited studies. This would be an area for further research.
Although hospitalization is generally thought of as being more expensive than outpatient care, good outpatient programmes have significant costs as well. These costs in outpatient programmes may vary significantly depending on the services provided.
A cost-saving measure with decentralized care may be that patients are able to access treatment faster. Treating patients before they are very ill and require more medical care, and making public health savings by treating people before TB can be transmitted to contacts could be benefits of decentralized care.
The resource requirements probably vary because country programmes are highly variable and so the costs of these programmes in different countries are variable.</td></tr>
<tr><td>Certainty of evidence of required resources</td><td>What is the certainty of the evidence of resource requirements (costs)?
● Very low
○ Low
○ Moderate
○ High

○ No included studies</td><td>Of the eight studies eligible for inclusion in the review, three (two modelling studies and one cohort study) reported on treatment costs. Table 6 compares the treatment cost to the health-care system for one MDR-TB patient in the decentralized and centralized setting. The two modelling studies showed significant cost savings using a decentralized compared with a centralized model. Whereas, the study by Kerschberger et al showed similar treatment costs for both treatment models.
Treatment cost to the health-care system for one MDR-TB patient in decentralized and centralized care settings (in US$)
<table><tr><th>Study</th><th>Study design</th><th>Country</th><th>Description of decentralized care</th><th>Cost of decentralized care</th><th>Description of centralized care</th><th>Cost of centralized care</th></tr><tr><td>Musa 2015</td><td>Modelling</td><td>Nigeria</td><td>Home-based care for entire duration of treatment</td><td>$1535</td><td>Hospital-based care for intensive phase then home-based care for continuation phase</td><td>$2095</td></tr><tr><td>Sinanovic 2015</td><td>Modelling</td><td>South Africa</td><td>Primary health-care clinic for entire duration of treatment</td><td>$7753</td><td>Hospital-based care for intensive phase (until 4-month culture conversion) then clinic-based care</td><td>$13,432</td></tr><tr><td>Kerschberger 2016</td><td>Retrospective cohort</td><td>Swaziland</td><td>Home-based care for entire duration of treatment</td><td>$13,361</td><td>Clinic-based care for intensive phase then home-based care for continuation phase</td><td>$13,006</td></tr></table></td><td></td></tr>
<tr><td>Cost-effectiveness</td><td>Does the cost-effectiveness of the intervention favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention

○ Varies
○ No included studies</td><td>No research evidence was identified.</td><td></td></tr>
</table>

	Judgement	Research evidence	Additional considerations
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.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	In some places it may be illegal to treat MDR-TB patients in a decentralized setting. These legal issues need to be addressed.

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	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours 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	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours 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	

Web Annex 2.2. Guideline update 2022

Table 6a. Should decentralization TB services vs. centralized TB services be used for children and adolescents with signs and symptoms of TB and for children and adolescents exposed to TB?

POPULATION:	Children and adolescents with signs and symptoms of TB and children and adolescents exposed to TB
INTERVENTION:	Decentralization TB services
COMPARISON:	Centralized TB services (tertiary /referral centre)
MAIN OUTCOMES:	PICO 6a: TB case notifications (population) – strengthening diagnostic capacity in primary-level facilities and via community-facility linkages; TB case notifications (population) – Strengthening diagnostic capacity in primary-level facilities and via community–facility linkages; TB case notifications (population) – home-based screening of household contacts; TB diagnoses (cohort) – home-based screening every 3 months; TB diagnoses (cohort) – home-based screening with sputum collection vs with referral; TB case notifications (population) or diagnoses (cohort) – Home-based screening for contacts and at-risk populations; TB diagnoses (cohort) – Introduction of Xpert into decentralized diagnostic centres PICO 6b: Coverage of TPT in eligible child TB contacts (0–5 years old); Population TPT initiation rate for child contacts (0–4 years old)
SETTING:	Global
PERSPECTIVE:	Health systems and primary health care
BACKGROUND:	Capacity for paediatric TB is often highly centralized at secondary/tertiary level, and children may present seriously ill, after delays in accessing care. Capacity at higher levels of care is often managed in a vertical, non-integrated way. Healthcare workers at primary health care (PHC) level may have limited capacity and confidence in managing paediatric TB, although this is where most children with TB or at risk of TB seek care. In addition, TB screening is often not systematically part of clinical algorithms for child health (e.g. IMCI and iCCM). Private sector providers play an increasing role as first point of care in many countries. There are many missed opportunities for contact tracing, TB prevention, detection and care of TB as a result of weak integration of child and adolescent TB services with other programmes and services. Decentralization and family-centred, integrated care are highlighted as one of ten key actions in the 2018 Roadmap *(1)*. This set of PICO questions looks at the impact of i. decentralization and ii. family-centred, integrated approaches of child and adolescent TB services on case detection in children who present with signs and symptoms of TB. They also examine the impact of these approaches on coverage of TB preventive treatment in children and adolescents exposed to TB. Decentralization is defined as: provision of/access to/capacity for child and adolescent TB services at a lower level of the health system than the lowest level where this is currently routinely provided (in most settings, district hospital (first referral level hospital) and/or primary health care level and/or community level). Family-centred, integrated services are defined as: Family-centred models of care: interventions selected on the basis of the needs, values and preferences of the child or adolescent and his or her family or caregiver. This can include health education, communication, material or psychological support. Integrated services: approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health related programmes and services.
CONFLICT OF INTERESTS:	Steve GRAHAM Farhana AMANULLAH

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Globally, an estimated 1.19 million (range 1.05 -1.33 million) children (aged below 15 years) fell ill with TB in 2019, or about 12% of the global burden. Only 44% of these children were reported to national TB programmes. TB-related mortality in children below 15 years was estimated at 230,000 for 2019 *(2)*. Modelling has shown that 80% of TB-related deaths are among children aged under 5, and that 96% of children who die of TB, did not access treatment *(3)*. A systematic review and meta-analysis to investigate the risk of TB in children after close exposure found that children not receiving preventive treatment who have a positive TB infection test (TST or IGRA) had significantly higher 2-year cumulative TB incidence rates than children with a negative TB infection test *(4)*. This incidence was highest among children below 5 years of age (19·0% [95% CI 8·4–37·4]). The effectiveness of preventive treatment was 63% (adjusted HR 0·37 [95% CI 0·30–0·47]) among all exposed children, and 91% (adjusted HR 0·09 [0·05–0·15]) among those with a positive TB infection test. Among all children <5 years of age who developed TB, 83% were diagnosed within 90 days of the baseline visit. The authors concluded that the risk of developing TB among exposed infants and young children is very high.	

	In 2019, only 433,000 (33%) of 1.3 million eligible children under the age of 5 (contacts of patients with infectious TB) received TB preventive treatment globally. Among contacts over the age of 5 (including older children and adolescents) only 105,000 (no estimates are available for eligible contacts in these age groups) were provided with TPT in 2019 *(2)*.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PICO 6a (case detection) ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know PICO 6b (TPT provision) ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The desirable effects for PICO 6a (case detection) include increased TB case notifications and case detection rates in children and adolescents, reduced time to diagnosis (and time to treatment) and treatment success among children and adolescents started on anti-TB treatment after being diagnosed.	The GDG expressed different judgements regarding the desirable effects as small or moderate, but with acknowledgement that this may vary by setting and by interventions or approaches to decentralize services. The evidence base also indicates varied efficacy. For the impact on TPT initiation, the GDG expressed varied judgements as well, with the majority in favour of moderate desirable effects. Overall, the GDG agreed to proceed with a judgement of 'varies' for PICO 6a (case detection) and 'moderate' for PICO 6b (TPT provision).

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with centralized TB services	Risk with decentralization TB services				
TB case notifications – strengthening diagnostic capacity in primary-level facilities and via community-facility linkages (Case notif)	Study population ∞ per 1,000	Infinity per 1,000 (∞ to ∞)	**Rate ratio 1.87** (1.28 to 2.71)	(1 RCT)[1,a]	⨁⨁⨁◯ MODERATE[b]	
TB case notifications – Strengthening diagnostic capacity in primary-level facilities and via community–facility linkages	Eight multifaceted studies including community-activities to bring people with signs/ symptoms into facilities and enhanced primary care facility components. Khan: 205 vs 28 cases, IRR 7.32 (95% CI 4.39-10.87) Malik: 1391 vs 417 cases, aIRR 2.96 (95% CI 2.49-3.50) Zawedde-Muyanja: 647 vs 271 cases, IRR 2.39 (95% CI 2.07-2.75) Maha: 295 vs 140 cases, IRR 2.11 (95% CI 1.72-2.58) Islam: 231 vs 65 cases, IRR 1.78 (95% CI 1.35-2.34) Cap-TB: 5865 vs 2295 cases, IRR 1.49 (95% CI 1.42-1.56) Oshi: 1590 vs 1210 cases, IRR 1.31 (95% CI 1.22-1.42) Joshi: 360 vs 113 cases, aIRR 1.14 (95% CI 0.83-1.56)		-	(8 observational studies)[2,3,4,5,6,7,8,9,c]	⨁◯◯◯ VERY LOW[d]	
TB case notifications - home-based screening of household contacts	Study population ∞ per 1,000	**Infinity per 1,000** (∞ to ∞)	**Rate ratio 0.88** (0.31 to 2.46)	(1 RCT)[10,e]	⨁◯◯◯ VERY LOW[f,g,h]	
TB diagnoses in a household cohort - home-based screening every 3 months (children 0-26 months)	Study population 15 per 1,000	**39 per 1,000** (27 to 60)	**Rate ratio 2.6** (1.8 to 4.0)	4763 (1 RCT)[11,i,j]	⨁⨁⨁⨁ HIGH	
TB diagnoses in a household cohort - home-based screening with sputum collection vs with referral	Study population 44 per 1,000	**37 per 1,000** (15 to 92)	**RR 0.84** (0.34 to 2.09)	443 (1 RCT)[12,j]	⨁⨁◯◯ LOW[k,l]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with centralized TB services	Risk with decentralization TB services				
TB case notifications or diagnoses – Home-based screening for contacts and at-risk populations	Three studies evaluated home-based symptom screening + sputum collection in the home or referral to health facilities for evaluation. Fatima: 13,288 vs 12,506 case notifications, IRR 1.06 (95% CI 1.03-1.08) Reddy: 7 vs 2 case notifications, aIRR 0.71 (95% CI 0.04-12.07) adjusted for change in control area Bayona: 1/151 vs 3/118 cases among MDR contacts, RR 0.26 (95% CI 0.02-2.56)		-	(3 observational studies)[13,14,15]	⨁◯◯◯ VERY LOW[m,n,o]	
TB diagnoses – Introduction of Xpert into decentralized diagnostic centers	Study population		**RR 0.98** (0.72 to 1.33)	2998 (1 observational study)[16,p]	⨁◯◯◯ VERY LOW[g]	
	107 per 1,000	**105 per 1,000** (77 to 143)				

Talukder K, Salim MAH,Jerin I,Sharmin F,Talukder MQK,Marais BJ,et al. Intervention to increase detection of childhood tuberculosis in Bangladesh. Int J Tuberc Lung Dis; 2012.

Khan AJ, Khowaja S,Khan FS,Qazi F,Lotia I,Habib A,et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis; 2012.

Malik AA, Amanullah F,Codlin AJ,Siddiqui S,Jaswal M,Ahmed JF,et al. Improving childhood tuberculosis detection and treatment through facility-based screening in rural Pakistan. Int J Tuberc Lung Dis; 2018.

Zawedde-Muyanja S, Nakanwagi A,Dongo JP,Dekadde MP,Nyinoburo R,Ssentongo G,et al.. Decentralisation of child tuberculosis services increases case finding and uptake of preventive therapy in Uganda. Int J Tuberc Lung Dis; 2018.

Maha A, Majumdar SS,Main S,Philip W,Witari K,Schulz J,et al.. The effects of decentralisation of tuberculosis services in the East New Britain Province, Papua New Guinea. Public Health Action; 2019.

Islam Z, Sanin KI,Ahmed T. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation research. BMC Public Health; 2017.

Oshi DC, Chkwu JN,Nwafor CC,Meka AO,Madichie NO,Ogbudebe CL, et al.. Does intensified case finding increase tuberculosis case notification among children in resource-poor settings? A report from Nigeria. Int J Mycobacteriol; 2016.

Joshi B, Chinnakali P,Shrestha A,Das M,Kumar AMV,Pant R,et al.. Impact of intensified case-finding on childhood TB case registration in Nepal. Public Health Action; 2015.

Lemaire J, Casenghi M. Catalyzing Pediatric TB Innovation (CaP-TB) project, unpublished data.

Hanrahan CF, Nonyane BAS,Mmolawa L,West NS,Siwelana T,Lebina L,et al. Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). . PLOS Med; 2019.

Moyo S, Verver S,Hawkridge A,Geiter L,Hatherill M,Workman L et al.. Tuberculosis case finding for vaccine trials in young children in high-incidence settings: a randomised trial. . Int J Tuberc Lung Dis; 2012.

Davis JL, Turimumahoro P,Meyer AJ,Ayakaka I,Ochom E,Ggita J,et al. Home-based tuberculosis contact investigation in Uganda: a household randomized trial. ERJ Open Res; 2019.

Fatima R, Qadeer E,Yaqoob A,Ul Haq M,Majumdar SS,Shewade HD,et al.. Extending 'contact tracing' into the community within a 50-metre radius of an index tuberculosis patient using Xpert MTB/RIF in urban Pakistan: did it increase case detection? . PLOS One; 2016.

Reddy KK< Anathakrishnan R, Jacob AG,Das M,Isaakidis P,Kumar AMV. Intensified tuberculosis case finding amongst vulnerable communities in southern India. . Public Health Action; 2015.

Bayona J, Chavez-Pachas AM,Palacios E,Llaro K,Sapag R,Becerra MC. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. Int J Tuberc Lung Dis; 2003.

Sachdeva KS, Raizada N,Sreenivas A,Van't Hoog AH,van den Hof S,Dewan PK,et al.. Use of Xpert MTB/RIF in decentralized public health settings and its effect on pulmonary TB and DR-TB case finding in India. PLOS One; 2015.

This cluster-randomized trial reported number of TB diagnoses at population-based diagnostic centers before and after intervention. The effect estimate is the incidence rate ratio for the change in diagnoses at the intervention centers divided by the incidence rate ratio at the control centers. The study also reported numbers of children evaluated at the centers, so another way to analyze the data would have been to calculate a risk ratio for diagnosis among children evaluated. However, we felt that the PICO outcome is really about population-level notifications, and the effect estimate we report is both most reflective of the PICO outcome and also the most conservative outcome possible in terms of magnitude. However, no information about underlying population size is given, so no absolute effect estimate can be determined.

This trial was rated as having "some concerns" over bias in the RoB2 because lack of access to a protocol meant that there was no information available on most of the key items in the RoB2. While we have no reason to believe that there was any systematic bias, the absence of so much key information caused us to downgrade.

Adjusted IRR's adjust for changes in notifications in a control area. Pre- and post-intervention periods are not equal in all studies.

Only 2 out of the 8 pre-post studies adjusted for secular changes over time via use of a control area

This cluster randomized trial was designed with case notifications as the outcome and an analysis plan based on a Poisson regression fitted to facility-level counts. No information on the underlying size of the at-risk population is given or assumed. Therefore, it is not possible to calculate a rate difference.

There were serious concerns with indirectness because the intervention arm comprised a mixture of two interventions, one of which we consider decentralized (home visits for contact screening) and the other of which we do not (cash incentives for contacts who came to the health facility).

Confidence interval is wide and crosses 1.

There were serious concerns about bias for this facility-randomized trial because of imbalance in the size and level of the health facilities in the two arms.

Events out of participants is entered into the "Number of patients" section, but effect estimate is the trial-reported outcome of events per person-years.

This trial was rated as having "some concerns" over risk of bias via the RoB2. This rating was driven mostly by the fact that it would have been impossible to blind trial participants and the people making the household visits to intervention allocation, but we thought it unlikely that this could affect outcome ascertainment,. Therefore, we did not downgrade the trial for risk of bias concerns.

Intervention population is not all children and adolescents with signs/symptoms of TB, but its restricted to household contacts. Results do not provide a direct measure of population-level case notifications.

There were serious concerns with imprecision due to small numbers of events in the child/adolescent age group.

Two sources of indirectness were identified for the two smaller studies. Reddy assessed only smear-positive TB diagnoses, which is not the same as all TB notifications. The population of Bayona was limited to MDR-TB contacts, which is not necessarily representative of all people with TB signs/symptoms. Of note, the largest study (Fatima) did not suffer from these concerns.

Very small numbers of children diagnosed with TB in two of the studies resulted in wide confidence intervals

Only 1 of the studies adjusted for possible confounding

We considered downgrading for indirectness because the population reached by the intervention is not all people with TB signs/symptoms but only those who accessed the diagnostic centers (since the intervention contained no community component). However, because diagnostic center attendance did not change during the intervention and the effect estimates would have been almost identical if analyzed as a population-level case notification rate ration, we chose not to downgrade.

The desirable effects for PICO 6b (TPT coverage) include increased TPT coverage in children and adolescents exposed to TB, decreased time to TPT initiation, prevention of TB and reduction of TB incidence among these age groups.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with centralized (tertiary/ referral centre)	Risk with decentralization of child and adolescent TB prevention and care services				
Coverage of TPT in eligible child TB contacts (0–5 years old)	Study population		**RR 1.27** (0.76 to 2.12)	239 (1 observational study)[1]	⨁◯◯◯ VERY LOW[a,b]	
	175 per 1,000	**222 per 1,000** (133 to 370)				
Population TPT initiation rate for child contacts (0–4 years old)	Two studies of multifaceted interventions to strengthen decentralized TPT services: Yassin: 698 vs 0 TPT initiations, IRR undefined Cap-TB: 12,634 vs 1,758 TPT initiations, 8-fold increase in median monthly TPT initiations per site, p<0.001		-	(2 observational studies)[2,3]	⨁◯◯◯ VERY LOW[c]	

Zachariah R, Spielmann MP,Harries AD,Gomani P,Graham SM,Bakali E,et al.. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. Int J Tuberc Lung Dis; 2003.

Yassin MA, Datiko DG,Tulloch O,Markos P,Aschalew M,Shargie EB,et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLOS One; 2013.

Lemaire J, Casenghi M. Catalyzing Pediatric TB Innovation (CaP-TB) project, unpublished data.

The study was considered to have a serious risk of bias, as it did not report adjustment for secular changes over time or other sources of confounding.

Confidence interval wide and crosses 1; low number of events suggest that larger sample size could increase precision.

These studies were considered to have a serious risk of bias, as they were pre-post studies without any adjustment for secular changes over time or other sources of confounding.

Other desirable effects that were rated by the GDG as being critical were: *treatment success, time to TB treatment initiation, time to diagnosis, coverage of TB preventive treatment in eligible child and adolescent TB contacts, time to TB preventive treatment initiation, TB preventive treatment completion, treatment adherence and access to schooling.* However studies including these outcomes were not identified as a result of the systematic review, with the exception of treatment adherence where 5 studies were identified. These studies all included Directly Observed Treatment (DOT) as the intervention and were not further pursued as a WHO recommendation on DOT already exists based on a previous systematic review.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	The undesirable effects for PICO 6a (case detection) are reductions in TB case notifications and case detection rates in children and adolescents, delays in TB diagnosis and treatment initiation and unsuccessful treatment outcomes among those started on TB treatment. The undesirable effects for PICO 6b (TPT coverage) are decreased TPT coverage, delays in TPT initiation. Other undesirable effects that were rated by the GDG as being critical were: *death, treatment failure, relapse, loss to follow up, adverse events, poor treatment adherence and interrupted schooling*. However, studies including these outcomes were not identified as a result of the systematic review.	Two trials and one observational study of home-based screening (without facility-based strengthening) had fewer diagnoses or notifications in children aged 0–14 years in the intervention group compared to the control group, but confidence intervals were wide and crossed 1 (i.e. none of these differences were statistically significant).The GDG discussed that although there may be a reduction in case notifications documented at higher levels of care, but if services are decentralized to more peripheral levels, children will have the opportunity to be reviewed by a clinician close to where they access care, which will improve the chance of TB detection. The evidence overall was recognized as uncertain and while there is potential for overdiagnosis and overtreatment, the benefit of increased case finding and an increased number of children with TB started on TB treatment was considered to outweigh the concern for overtreatment. Therefore, the GDG agreed to a judgement of 'trivial' undesirable effects. The GDG discussed some potential risks of provision and management of TPT at the peripheral level: in the case of drug-related adverse events (AE) such as hepatotoxicity these may go undetected or lead to a more severe adverse event. There may be insufficient capacity at peripheral levels to manage severe AEs. In addition, there is a risk of TB disease being treated with TPT as opposed to getting a complete treatment regimen. In this case the child would likely come back with symptoms, and hopefully be referred for evaluation and initiated on a TB treatment regimen. The GDG judged that some of these undesirable events can happen, but are also rare. Therefore, the GDG concluded that for TPT provision the undesirable effects are 'trivial' as well.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There were no included studies on values. However, a qualitative evidence synthesis on community views on active case finding (ACF) for tuberculosis in low- and middle-income countries was undertaken and presented to the GDG, this review focused on children. The authors found that people valued their health, which could be supported through their own economic efforts or through TB services, but these two routes sometimes undermined each other. Seeking TB services accrued costs and interfered with employment through missing work or through discrimination at work. They therefore valued the lower costs of tuberculosis care nearer home and often sought care first from local pharmacies or traditional health providers. Persistence despite difficulty with securing follow up care also underscored health as a widely shared value. People valued privacy and discretion in all settings for tuberculosis screening and for all aspects of subsequent TB care for themselves and for their children. Sometimes individual values (i.e., individual health or employment) conflicted with the widely shared community values of social integration and of family solidarity and harmony. Discrimination due to TB and HIV stigma sometimes isolated people from their wider community; enabled fractious or frustrating treatment in clinics; or led to discord and divisiveness within families. People also had to balance tuberculosis care seeking according to their individual health against their fears of infecting others (i.e., threatening community health). Likewise, parents had to balance the health of their children against their fears of medications. Tuberculosis active case finding and contact tracing improved access to health services for those with worse health and fewer resources. ACF found this population exposed to deprived living conditions, but without being sensitive to additional dimensions of their plight, such as their marginalisation or their information needs. Lack of information impacted community members and health workers alike and sometimes led to harm. Many community members expressed fears related to tuberculosis active case finding and contact tracing. People were afraid infecting others in their family or workplace, of painful side effects of treatment for themselves or for their children, and of dying from tuberculosis. People were also afraid of being labelled with tuberculosis or with HIV. The reviewers of the evidence for the background question on engaging adolescents in TB care, found that adolescents fear disclosure of TB and cited this as a central barrier to engagement in treatment and adherence. Daily facility-based DOT was considered disruptive to schooling or work and community-based DOT models of care (community health worker, trained family member, video DOT) were preferred. Adolescents treated for TB reported loss of interpersonal relationships, education disruptions, and depression that are greatly exacerbated by prolonged isolation and/or hospitalization for TB treatment.	The GDG judged that there was probably no important uncertainty in how much people value the main outcomes for both case detection and the provision of TPT.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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		The GDG agreed that the balance of desirable and undesirable effects probably favours decentralized TB services for children and adolescents with signs and symptoms of TB, as well as for the provision of TPT. The panel noted that consideration of differences in the settings in which decentralisation might be implemented and the need for adequate resourcing for this to happen.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No studies were included on the cost of decentralized approaches for case detection or provision of TPT. However, costing data are available from the CaP TB project (Catalyzing Pediatric Tuberculosis Innovations), which focused on implementation and integration of New TB Care and Treatment Models in 9 sub-Saharan Africa countries and was presented to the GDG. The project aimed to: 1) improve detection of children (0–14 years) through facility-based intensified case-finding (ICF); 2) improve provision of TPT among household contacts aged below 5 and children living with HIV attending HIV clinics. The ICF intervention included implementation of systematic TB screening in different child health entry points (OPD, IPD, HIV, MCH, and nutrition clinic), among others. TB screening was performed using a symptom-based screening tool, by community health care workers in waiting areas. The TPT interventions used community-based household contact screening where possible and included referral of symptomatic children aged 0–14 years for TB evaluation, as well as asymptomatic 0–4 years for TPT. Enhanced paediatric TB training and site-support and supervision was provided to support paediatric TB management and project interventions. The comparator was standard of care (SoC) in each country.	The GDG discussed the issues of costs which were anticipated to be relevant for both the health system and for patients. Overall, health systems costs are likely increased with increased decentralization (e.g. infrastructure, human resources, training, equipment, community engagement etc.), but patient costs may decrease (e.g. transport to healthcare facilities). Initial costs to establish decentralized services may be high, but costs are likely to decrease over time, assuming that patients are effectively managed and TPT provided at the peripheral level, leading to a reduction in TB incidence. Equity was considered an important cross-cutting issue impacting on cost as well. The GDG also emphasized that the level of decentralization should consider the context, including for example the local burden of TB, availability of domestic or donor funding and of technical and programmatic support. The GDG highlighted that TPT implementation can be very challenging with high levels of loss to follow-up in centralized programmes, considering that children who are eligible for TPT are not sick. The panel felt that decentralization of prevention can potentially increase equity and enhance the success of the programme. It was noted that in the past two years, country training programmes have moved to virtual trainings due to COVID-19, which reduces programmatic costs.

The following table provides a comparison of activities and costs per child started on anti-TB treatment for the standard of care versus the intervention:

	Standard of care cascade (per child treated)						Intervention cascade (per child treated)					
Country	Screened	Presumptive TB	Tested with Xpert	TB diagnosed	TB treated	Cost, $ (SD)	Screened	Presumptive TB	Tested with Xpert	TB diagnosed	TB treated	Cost, $ (SD)
1	164.54	2.13	1.34	1.05	1	139 (48)	363.32	4.69	4.07	1.05	1	2025 (69)
2	29.81	0.91	0.91	1.03	1	90 (37)	65.82	2.01	1.18	1.03	1	601 (41)
3	388.55	3.17	3.17	1.03	1	97 (36)	817.98	6.67	1.38	1.03	1	1171 (38)
4	213.24	5.89	5.89	1.01	1	193 (61)	244.38	6.75	4.09	1.01	1	1350 (60)
5	168.71	2.82	2.82	1.01	1	145 (49)	569.05	9.52	7.9	1.01	1	3670 (133)

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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	There were no included studies on cost effectiveness. However, cost-effectiveness data are available from the CaP TB project (Catalyzing Pediatric Tuberculosis Innovations), which focused on implementation and integration of New TB Care and Treatment Models in 9 sub-Saharan Africa countries (see under resources required). The project included a programme evaluation ('TIPPI') that recorded before/after data at a site-level on anti-TB treatment (ATT) and TPT rates. These data were available for 5 of 9 countries with regulatory approval granted so far. Project financial and cascade data were analysed to estimate the cost of the intervention relative to baseline rates, capturing changes in resources used and additional investments in training and M&E. Changes in mortality and discounted expected life-years lost (3% discount rate) were modelled to estimate the interventions' impact on health and the incremental cost-effectiveness ratios (ICERs) in terms of US$ per DALY (disability-adjusted life year) averted. For the ICF intervention, country central estimates of deaths averted per 100 children starting ATT under SoC *varied between 11 and 46* (excluding one country, with negative effect). Country ICERs ranged between 238 & 646 US$/DALY (excluding one country). ICERs were less than GDP and comparable or less than 0.5 x GDP, except for 2 countries. For the TPT interventions (including household case-finding), country central estimates of deaths averted per 100 children starting TPT under SoC *varied between 3 and 21*. Country ICERs ranged between 301 and 1529 US$/DALY. ICERs were less than GDP and comparable or less than 0.5 x GDP in one country, and over GDP in other countries. Analysing both ICF and TPT intervention components as a single intervention gave ICERs similar to those of the ICF component, which accounted for most of the incremental costs and health benefits of the combined package. Interventions were more cost-effective among children aged 0–4 years than among children 5–14 years. Limitations of the analyses include confounding with before/after comparisons, omission of patient costs, difficulty in isolating project costs that may exceed analogues under implementation (e.g. wage rates) and modelled rather than measured health outcomes. Most limitations are on the side of biasing ICERs upwards (i.e. towards being less cost-effective).	While there were no separate studies included on the cost-effectiveness of decentralization, the CaP-TB project (which provided data for the systematic review for both PICO 6a and 6b) provided cost-effectiveness data on intensified TB case finding interventions focused on decentralization to the lower levels of the health system. Intensified case finding interventions in this project were more cost-effective than the TPT interventions. Both interventions were more cost-effective in the age group under 5 compared to older children and young adolescents up to 15 years. The GDG discussed that cost-effectiveness was setting specific with variability depending on available resources. The GDG judged that cost-effectiveness probably favours decentralized approaches for both case finding and provision of TPT.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	There were no included studies on equity. However, a qualitative evidence synthesis on community views on active case finding for tuberculosis in low- and middle-income countries was undertaken, this review focused on children. This study found that *community- based tuberculosis services improved access to screening and subsequent care for some, including for children.* However, many people living in areas selected for tuberculosis active case finding or contact tracing experienced material deprivation. Sometimes this marginalisation was exacerbated by difficult geography, environmental pollution, or unstable populations. For example, tuberculosis services for children were compromised when community health workers could not trace families that had moved, or when parents and families were unable to pay out of pocket costs. In contrast, those community members with greater economic security felt less vulnerable to tuberculosis. Tuberculosis programmes that aim to improve equity must consider both individual and community resources. Access to services is an important component of health equity, but equity also encompasses fairness and human rights norms. A commitment to equity addresses discrimination by changing laws or "social relationships" (WHO, 2021). The researchers found that tuberculosis stigma led to discrimination following three pathways: isolation in the community, discord within families, and problems at work or lost employment. Tuberculosis stigma set people apart, whether they were targeted for screening or received diagnosis and treatment. This setting apart exposed people to discrimination along distinct pathways: isolation from their wider community, lost employment, fraught social interaction with health care workers both in the clinic and on the doorstep, and discord and divisiveness within families. HIV stigma compounded tuberculosis stigma and heightened vulnerability to discrimination along these same pathways. In many settings, lack of resources restricted what services were available for TB, and this had implications for the care of children. Programme health workers and community members described a skeleton service in competition for resources, infrastructure, and staff. *In this context of low investment, tuberculosis health services sometimes reinforced, rather than alleviated, deprivation and discrimination.* Parents and children faced repeated tests and clinic visits, wasted time and fraught social interaction with health providers. It can be assumed that, considering the current low coverage of TPT in child contacts under 5 and the extremely low TPT coverage of older child as well as adolescent contacts, providing TPT services at lower levels of the health system will improve equity.	Most GDG members felt that equity is probably increased with decentralization for both case detection as well as provision of TPT, despite the absence of data related to the impact regarding TPT.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	However, a qualitative evidence synthesis on community views on active case finding for tuberculosis in low- and middle-income countries was undertaken, this review focused on children. This study found that several aspects of programme delivery reduced its acceptability for service users and other community members. First, *community-based active case finding and contact tracing created expectations for treatment that were not always met.* TB programmes that were committed to early case detection in settings with low investment were not acceptable to people because they could not deliver on the expectations for follow up care for people with, and without, tuberculosis. People across diverse settings documented difficult follow up care due to low investment, and health workers reported competition for health resources. Second, *community members were aware of the consequences of tuberculosis screening and subsequent care, in terms of out-of-pocket costs and risks of discrimination.* Both reduced the acceptability of community-based tuberculosis programmes. Until adequate mitigating strategies are in place, the well-known barriers of costs and discrimination will persist. Finally, *the association of tuberculosis services with deprivation made outreach less effective amongst those better off economically, and their association with HIV reinforced stigma and the possibility for discrimination* – both had implications for programme acceptability. As well, the TB-Speed decentralization study assessed acceptability of decentralizing TB diagnosis from the *healthcare worker (HCW) perspective.* This was an operational research study in children with presumptive TB, evaluating an innovative childhood TB diagnosis package (including systematic screening, clinical evaluation, Xpert Ultra on stool and nasopharyngeal aspirate [NPA] and optimized chest X-ray) at district hospital (DH) and primary health care (PHC) levels. The objectives of the sub-study were to assess the knowledge, attitudes and practices (KAP) of HCWs on childhood TB (comparing pre-intervention the post-intervention period) and to assess the point of view, experience, and perceptions of HCWs regarding the childhood TB diagnosis approach implemented in their facility (post-intervention only). This was done through self-administered questionnaires among HCWs involved in childhood TB management. 55% of respondents were based at PHC level. 18% versus 70% of the HCWs were trained on TB in the past 2 years, pre- and post-intervention. *Knowledge scores improved* from 10.2 out of 18 to 11.0 out of 18 before and after the intervention, with the *score for diagnosis improving* from 2.2 to 2.6 out of 5 and for *prevention this remained the same* (4 out of 4). At both PHC and DH levels, 94% of respondents agreed or strongly agreed that systematic TB screening contributed to find children with presumptive TB. 95 and 97% of respondents at PHC and DH level (strongly) agreed that systematic TB screening should continue after the end of the TB-Speed project. 77% and 63% (strongly) agreed that systematic TB screening was easy. 79% and 82% (strongly) agreed that stool sampling contributed to increasing the number of children diagnosed with TB. For NPA, these proportions were 97% and 95% at PHC and DH level, respectively. *Overall, there was high acceptability with positive attitudes towards decentralized child TB diagnosis at DH and PHC levels and clinical diagnosis at decentralized levels of care played an important role in child TB case detection.* The reviewers of the evidence for the background question on engaging adolescents in TB care, reported that adolescents, because they have particular epidemiological risks for TB exposure and increased biological risk for developing TB disease, had indicated that they should be a priority group for preventive treatment. The reviewers also reported that because adolescents have an increased risk of poor treatment adherence, including loss to follow-up, and TB treatment often interferes with their education, adolescents should preferentially receive shorter regimens for TB infection.	The GDG highlighted that the potential impact of stigma should be taken into consideration, when services for active case finding in children and adolescents are decentralized to lower levels. The panel judged that decentralized approaches are probably acceptable to key stakeholders, but may also vary depending on the setting.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There were no included studies on feasibility. However, a qualitative evidence synthesis on community views on active case finding for tuberculosis in low- and middle-income countries was undertaken, this review focused on children. The logic of tuberculosis active case finding and contact tracing is that community activities lead to early detection and, in turn, better treatment outcomes for individuals and less transmission within communities. The qualitative evidence synthesis found that *community tuberculosis outreach operated in contexts where there was* ***low investment in health services,*** *including staff, facilities, tests, and medicines,* which left programmes in competition with other diseases and public health priorities. *Lack of investment also led to* ***difficult follow up care for parents and children,*** *who faced repeated visits, wasted time, fractious interactions with health staff, and burdensome out of pocket costs. Low investment compromises the feasibility of programmes.* All parties involved in community-based tuberculosis services had ***unmet information needs,*** which also compromised the feasibility and effectiveness of tuberculosis programmes. Based on another review undertaken to determine the socioeconomic impact of TB on children, adolescents and families, the general financial impact of TB was mentioned in 15 qualitative papers, 5 quantitative studies and two reviews. The impact was on the family in general, closely linked to spending and nutrition. *The cost of transport to hospital was raised as sometimes a barrier to a child completing treatment, and* ***decentralised services may make accessing care more feasible.*** As well, the TB-Speed decentralization study assessed feasibility (uptake) and yield of deploying systematic screening and an innovative TB diagnostic package at District Hospital (DH) and Primary Health care (PHC) in resource limited countries with (very) high TB incidence. 111,944 children attended OPD, of whom 78.1% were screened (65% at DH and 84% at PHC level). Of the children who were screened, 3229 (3.7%) were identified as presumptive TB (8.4% at DH and 2.0% at PHC level). 1746 children with presumptive TB were enrolled in the study. TB was diagnosed in 237 (13.6%) of the enrolments (18.3% at DH and 5.6% at PHC). Chest X-ray uptake was 76% at DH level. The proportion of valid results for Ultra testing on stool samples was slightly lower at PHC level compared to DH level (68% versus 72%), whereas valid NPA results were lower at DH level compared to PHC (89% versus 93%). The decentralization study also assessed feasibility of decentralizing TB diagnosis to DH and PHC from the *healthcare worker (HCW) perspective.* As part of the KAP survey conducted after the intervention, 86% of respondents at PHC level felt that TB diagnosis and making a decision to treat were feasible in their facility. This was 96% at DH level. 96% and 97%, respectively, (strongly) agreed that the TB diagnostic approaches should continue to be implemented after the end of the project. TB Speed also reported early findings from an implementation research study to describe successes and challenges of implementing the childhood TB diagnostic approach in DH and PHCs from support supervision and clinical mentoring activities. Reported challenges around screening included the fact that screening questions were complex to understand for HCWs and parents, and had to be simplified; the stigma associated with TB screening in waiting areas and non-recording of presumptive cases in registers. Labelling and recording of laboratory samples and registers was a challenge in some countries as well. In 5 out of 6 countries, turn-around times were long (up to 8 days), mainly due to staff attitudes. Sample transport was affected by poor transport conditions in 3 out of 6 countries. Challenges related to chest radiography performance and interpretation included breakdown of machines, unavailability of radiographers or trained clinicians, image quality issues, delays in receiving reports (in PHC facilities) and poor internet connectivity for up- and download. Challenges around referrals included issues around transport to the DH (in terms of distance, time and cost), refusal from parents to be referred, poor means of communication and follow-up between PHC and DH levels and delays in referral or lack of referral documentation. Some countries reported a lack of trained staff (due to staff rotation or transfers) and a lack of motivation (linked to incentives). There were no major differences in terms of the feasibility challenges between the DH and PHC levels.	The GDG highlighted that feasibility varies by setting, infrastructure, and the structure of the national TB control programme, among others, for both case detection and TPT provision. In urban settings increasing community involvement may be more feasible and access may be less challenging than in rural areas. Overall, the panel judged that decentralization is probably feasible to implement.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
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
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

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
○	○	○	●	○

CONCLUSIONS

Recommendation

In TB high burden settings, decentralized TB services may be used in children and adolescents with signs and symptoms of TB and/or in those exposed to TB (conditional recommendation, very low certainty evidence).

Remarks:

This recommendation concerns children and adolescents with signs and symptoms of TB in terms of the impact on case detection. It also concerns children and adolescents who are exposed to TB (TB contacts) who are eligible for TB preventive treatment (TPT), in terms of the impact on provision of TPT. Children and adolescents with signs and symptoms who need evaluation for TB disease may also have a history of exposure to TB (TB contact). Children and adolescents who are TB contacts who do not have signs and symptoms need to be evaluated for TPT eligibility.

This recommendation refers to enhancing child and adolescent TB services at peripheral levels of the health system and closer to the community, not to replacing specialized paediatric TB services at higher levels of the health system.

Decentralization should be prioritized for settings and populations with poor access to existing services and/or in high TB prevalence areas.

Justification

This set of PICO questions examine the impact of i. decentralization and ii. family-centred, integrated approaches of child and adolescent TB services on case detection in children who present with signs and symptoms of TB. They also examine the impact of these approaches on coverage of TB preventive treatment in children and adolescents exposed to TB.

Definitions related to this PICO question:

Decentralization: provision of/access to/capacity for child and adolescent TB services at a lower level of the health system than the lowest level where this is currently routinely provided (in most settings, district hospital (first referral level hospital) and/or primary health care level and/or community level).

Family-centred, integrated services:

Family-centred models of care: interventions selected on the basis of the needs, values and preferences of the child or adolescent and his or her family or caregiver. This can include health education, communication, material or psychological support.

Integrated services: approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health related programmes and services.

A systematic review of studies assessing the impact of decentralized, integrated, or family-centred care models on TB diagnostic, treatment, or prevention outcomes for individuals 0–19 years old, comprising both children (0–9 years old) and adolescents (10–19 years old), was conducted to answer this group of PICO questions. The PubMed, Embase, Web of Science, Global Index Medicus, Global Health, and Cochrane Central databases were searched, as well as the references of 17 related reviews. 3,265 abstracts from databases and 129 additional references from related reviews were identified and assessed. 516 full-text articles were assessed for eligibility, from which 25 comparative studies (7 randomized, 18 observational) were identified; one unpublished observational was added for a total of 26 studies. 4 studies (1 randomized, 3 observational) were excluded after review because the care model described was community-based directly observed therapy, for which a WHO recommendation already exists (REF 2017 DS-TB guidelines). Of the remaining included studies, 16 had elements of decentralization, 5 had elements of integration, and 3 had elements of family-centred care; 4 studies had elements of more than one care model of interest, but were only included based on their main model, e.g. either decentralization or family-centred, integrated care. Most focused on the 0–14 year age group.

Studies where the primary intervention was decentralization mostly assessed diagnosis or case notification outcomes (n=16), with fewer assessing TPT outcomes (n=3). In general, interventions that included both strengthening diagnostic capacity in primary care settings as well as strengthening linkages between communities and facilities consistently showed increases in case notifications and TPT initiations, while interventions that involved only community-based activities did not.

Two studies of service integration were identified, which showed limited impact on case notifications of screening in integrated management of childhood illness clinics or co-location of TB and antiretroviral therapy (ART) services. Two studies of family-centred care were identified, which showed that provision of socioeconomic support packages to families affected by TB was associated with increased TPT initiation and completion. The reviewers noted that, while substantial wider literature on integration and family-centred care is available, evidence for the specific impact on child and adolescent TB outcomes is limited. Some overlap was noted between integration of TB services into non-specialized settings such as general outpatient or primary care services, and decentralization. For the evidence review this was a slightly artificial separation, while in practice decentralization and integration into primary health care may go hand in hand.

Regarding the evidence reviewed for the PICO question on the impact of decentralization on TB case detection, the GDG observed that two trials and one observational study of home-based screening (without facility-based strengthening) had fewer diagnoses or notifications in children aged below 15 years in the intervention group compared to the control group, but that none of these differences was statistically significant. The GDG discussed that while there may be a reduction in case notifications at higher levels of care, given that services are being decentralized to more peripheral levels, making sure that children are seen by a competent clinician where they access care, improves the chances of TB detection. The overall certainty of the evidence was very low. The benefit of increased case finding and an increased number of children with TB who are initiated on TB treatment was considered to outweigh the concern for overtreatment. Therefore, undesirable effects for case detection were considered trivial. The GDG discussed potential risks of provision and management of TPT at the peripheral level: in case of drug-related adverse events (AE) such as hepatotoxicity, these may go undetected or lead to a more severe AE. There may be insufficient capacity at peripheral level to manage severe AEs. In addition, there may be a risk of TB disease being treated with a course of TB preventive treatment (TPT) rather than with a complete treatment regimen. All of these undesirable events can happen, but are also rare. Therefore, the undesirable effects for TPT provision were considered trivial. Overall, the GDG agreed that the balance of desirable and undesirable effects probably favours decentralized TB services for children and adolescents with signs and symptoms of TB, as well as for the provision of TPT. The panel noted that consideration of differences in the settings in which decentralisation might be implemented and the need for adequate resourcing for this to happen.

Regarding the evidence reviewed for the PICO question on the impact of decentralization on TB case detection, the GDG observed that two trials *(5, 6)* and one observational study of home-based screening (without facility-based strengthening) *(7)* had fewer diagnoses or notifications in children aged below 15 years in the intervention group compared to the control group, but that none of these differences were statistically significant. The GDG discussed that while there may be a reduction in case notifications at higher levels of care, given that services are being decentralized to more peripheral levels, making sure that children are seen by a competent clinician at the point of access may improve the chances of TB detection. The evidence overall was recognized as uncertain. The benefit of increased case finding and an increased number of children with TB who are initiated on TB treatment was considered to outweigh the concern for overtreatment. Therefore, undesirable effects for case detection were considered trivial. The GDG discussed potential risks of provision and management of TPT at the peripheral level, including undetected drug-related adverse events (AE) such as hepatotoxicity and insufficient capacity to manage these. In addition, there may be a risk of TB disease being treated with a course of TB preventive treatment (TPT) rather than with a complete treatment regimen. All of these undesirable events can potentially happen, but were considered rare and not of major concern. Therefore, undesirable effects for TPT provision were considered trivial as well. Overall, the GDG agreed that the balance of desirable and undesirable effects probably favours decentralized TB services for children and adolescents with signs and symptoms of TB, as well as for the provision of TPT. The panel noted that consideration of differences in setting and adequate resources are important requirements.

The GDG discussed that setting specific factors related to TB burden or the organization of health services may impact feasibility, acceptability, and equity considerations. They also discussed that initial health system costs to establish decentralized and family-centred, integrated services may be relatively high (e.g. related to infrastructure, human resources, training, equipment, community engagement etc.), but that costs are likely to decrease over time, assuming that cases are effectively managed and TPT provided at the peripheral level, leading to a reduction in TB incidence. Decentralized and family-centred, integrated services may result in important savings for affected families. Equity was considered an important cross-cutting issue impacting cost as well. The GDG highlighted that TPT implementation can be very challenging with high levels of loss to follow-up in programmes implemented at higher levels of the health system, considering that children who are eligible for TPT are not sick. The panel agreed that decentralization and integration of services can potentially increase equity and enhance the success of the programme and judged that cost-effectiveness probably favours decentralized and family-centred, integrated approaches to both case finding and provision of TPT.

While the GDG stressed the importance of taking into consideration the potential impact of stigma, when decentralizing TB services for children and adolescents to lower levels, the panel judged that decentralized approaches are probably acceptable to key stakeholders. Overall decentralized and family-centred, integrated approaches were judged feasible to implement, although feasibility may vary depending on infrastructure, available funding and the structure of the national TB control programme, among others. However, adequate investment is critical to enable the acceptability, equity and feasibility of decentralized approaches.

Subgroup considerations

Adolescents have a disease presentation that is similar to adults, and therefore may need different interventions than young children.

The provision of TPT has historically focused on children under 5 years of age. In 2018, target groups for the provision of TPT were expanded to include contacts of all ages *(8)*.

CLHIV may derive particular benefit from decentralised TB service provision considering their need for TPT, ongoing care for HIV and early treatment of TB. In many high TB/HIV burden countries there is already a high level of integration or coordination between TB and HIV services.

Implementation considerations

Training of healthcare workers at decentralized levels is a critical requirement to ensure adequate implementation. Similarly, resources are needed at the peripheral level, especially initially, as services are established. It is expected that as services are established and effectively implemented, the long-term impact will result in a decrease in TB incidence with an associated reduction in resource requirements.

A phased approach to decentralisation may be applied if this is most appropriate in the country or area, depending on the local burden of TB, availability of domestic or donor funding and of technical and programmatic support.

Active contact investigation at community and household level is a critical intervention for enhancing both case finding and provision of TPT in children and adolescents.

Factors to consider in decentralizing child and adolescent TB services include the existing infrastructure (e.g. baseline health infrastructure, needs for expansion or upgrading), the applicable regulatory framework, financing, choosing between an operational research setting or programmatic implementation, human resource issues (e.g. staffing requirements and HR development such as capacity building/training and consultation skills), monitoring and evaluation, conducting qualitative research into community needs and perceptions (including views on stigma). Decentralization of services to the primary health care level requires child and adolescent TB services to be integrated within general primary health care services and therefore there may be significant overlap between decentralization and family-centred, integrated approaches. The operational handbook will provide practical guidance and examples on this.

Decentralization should not only concern the levels of the health system, but should ideally also take place within the same structure, by training all health care providers of all child and adolescent care services in the recognition and management of TB. This so-called task shifting was mentioned by the GDG as an important implementation factor.

Monitoring and evaluation

Moving to decentralized, family-centred, integrated services requires careful planning, and regular monitoring of implementation against the plan. The capacity needs of national programmes interested in implementing the proposed interventions need to be identified and addressed.

Enhanced data collection around child and adolescent TB potentially takes a substantial amount of additional time and detailed data collection may only be feasible in specific operational research settings. Programmes generally have registers in place for contact investigation, treatment registration and outcomes, as well as TPT registers. The use of these (preferably electronic) tools is important as programmes move to a more decentralized and family-centred, integrated approach, to ensure comprehensive management and treatment. The use of these tools needs to be evaluated and enhanced, including through operational research.

It will be important to monitor the number of children diagnosed at different levels of the health system, including the proportion of children that have bacteriological confirmation, the proportion that were clinically diagnosed as well as the number of children initiated on and completing TPT. Evaluating the quality of services (covering the quality of all steps in the patient pathway, from screening, to diagnosis and treatment) as well as client satisfaction are important components as well.

Research priorities

Cost effectiveness of decentralization/integration for case detection and provision of TPT

Impact of decentralization of services on health equity

Acceptability and feasibility of decentralized approaches to child and adolescent TB care for case detection and for TPT provision

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Table 6b. Should family-centred, integrated services vs. standard, non-family-centred, non-integrated services be used for children and adolescents with signs and symptoms of TB and for children and adolescents exposed to TB?

POPULATION:	Children and adolescents with signs and symptoms of TB
INTERVENTION:	Family-centred, integrated services
COMPARISON:	Standard, non-family-centred, non-integrated services
MAIN OUTCOMES:	Case notifications – TB screening in IMNCI; Case notifications (intervention = co-location of ART) Prevention – TPT coverage; TPT completion rate
SETTING:	Global
PERSPECTIVE:	Health systems and primary care
BACKGROUND:	Capacity for paediatric TB is often highly centralized at secondary/tertiary level, and children may present seriously ill, after delays in accessing care. Capacity at higher levels of care is often managed in a vertical, non-integrated way. Healthcare workers at primary health care (PHC) level may have limited capacity and confidence in managing paediatric TB, although this is where most children with TB or at risk of TB seek care. In addition. TB screening is often not systematically part of clinical algorithms for child health (e.g. IMCI and iCCM). Private sector providers play an increasing role as first point of care in many countries. There are many missed opportunities for contact tracing, TB prevention, detection and care of TB as a result of weak integration of child and adolescent TB services with other programmes and services. Decentralization and family-centred, integrated care are highlighted as one of ten key actions in the 2018 Roadmap *(1)*. This set of PICO questions looks at the impact of i. decentralization and ii. family-centred, integrated approaches of child and adolescent TB services on case detection in children who present with signs and symptoms of TB. They also examine the impact of these approaches on coverage of TB preventive treatment in children and adolescents exposed to TB. Decentralization is defined as: provision of/access to/capacity for child and adolescent TB services at a lower level of the health system than the lowest level where this is currently routinely provided (in most settings, district hospital (first referral level hospital) and/or primary health care level and/or community level). Family-centred, integrated services are defined as: Family-centred models of care: interventions selected on the basis of the needs, values and preferences of the child or adolescent and his or her family or caregiver. This can include health education, communication, material or psychological support. Integrated services: approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health related programmes and services.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Globally, an estimated 1.19 million (range 1.05 -1.33 million) children (aged below 15 years) fell ill with TB in 2019, or about 12% of the global burden. Only 44% of these children were reported to national TB programmes. TB-related mortality in children below 15 years was estimated at 230,000 for 2019 *(2)*. Modelling has shown that 80% of TB-related deaths are among children aged under 5, and that 96% of children who die of TB, did not access treatment *(3)*.	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The desirable effects for **case detection** include increased notifications and case detection rates, reduction in delays in diagnosis and initiation of TB treatment, as well as treatment success in children started on TB treatment. **No data for case detection rates, reduction in delays in diagnosis and initiation of TB treatment, treatment success.**	The GDG noted that no data were available related to case detection on the outcomes of delays in diagnosis and initiation of TB treatment and treatment success. Similarly, in the review related to TPT coverage there were no data available for reduction in the time to initiation of TPT and TB incidence. It was clarified that for the Ketema trial *(4)* the case detection outcome was not well reflected in GRADEpro, but this is reflected in the risk ratios in the table (e.g. 0.04% versus 0.01% of attendees or 0.5 additional TB notification per facility over a 4-month period). The GDG discussed that family-centred, integrated care also includes interventions at household level to identify members of the household requiring evaluation for TB disease, TPT, treatment support etc. In addition, there is overlap between integration of TB services into non-specialized settings such as general outpatient or primary care services, and decentralization. For the evidence review this was a slightly artificial separation, while in practice decentralization and integration into primary health care may go hand in hand. This meant that the studies reviewed for PICO 6a and b may also inform PICO 6c and d and merging the recommendations could be considered. Overall, the GDG judged that desirable effects are moderate for both case detection and provision of TPT.

Outcomes	No. of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard, non-family-centred, non-integrated services	Risk difference with family-centred, integrated services
Case notifications – TB screening in IMNCI	180896 (1 RCT)[1,a]	⨁⨁⨁◯ MODERATE[b]	**RR 3.77** (1.82 to 7.79)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 1 more)
Case notifications (intervention = co-location of ART)	0 (1 observational study)[2,c]	⨁◯◯◯ VERY LOW[d,e]	**Rate ratio 2.67** (1.05 to 6.76)	Study population	
				∞ per 1,000	**-- per 1,000** (-- to --)

Ketema L, Dememew ZG,Assefa D,Gudina T,Kassa A,Letta T,et al.. Evaluating the integration of tuberculosis screening and contact investigation in tuberculosis clinics in Ethiopia: A mixed method study. PLOS One; 2020.

Miyano S, Dube C,Kayama N,Ishikawa N,Nozaki I,Syakantu G. Association between tuberculosis treatment outcomes and the mobile antiretroviral therapy programme in Zambia. Int J Tuberc Lung Dis. Int J Tuberc Lung Dis; 2013.

This stepped-wedge trial evaluated a multi-component intervention including screening in IMNCI and in the TB DOTS clinic of 30 health facilities. The relative effect estimate is the % of IMNCI attendees who were diagnosed with TB while the absolute effect is the trial-reported outcome of mean additional diagnoses per clinic per 4-month study period (i.e. period of each "step" in the stepped wedge).

The stepped wedge trial was deemed to have a serious risk of bias because allocation to the intervention could not be concealed (all facilities knew they would receive the intervention before they enrolled), and because the analysis method did not account for potential time trends over the course of the trial.

This study reported TB notifications at intervention facilities before and after co-location of ART services, and at control facilities in the same region that never received co-located ART services. Only the intervention facility counts are shown (before and after co-location of ART services). The number of cases in the control facilities was very small, and decreased substantially between the two periods, raising the possibility of population shifting from one set of facilities to the other. The unadjusted notification rate ratio presented here is more conservative than the one that adjusts for the change in the control facilities.

The small numbers of events led to a wide confidence interval, even though it does not cross 1.

It is not clear whether increase in TB cases at intervention facilities was due population shifting from control facilities to intervention facilities, as they are in the same area and not specified as being tied to specific catchment populations.

Desirable effects for **TB prevention** include increased TPT coverage, reduction in the time to initiation of TPT, improved TPT completion rates and ultimately a reduction in TB incidence among children and adolescents.

No data for reduction in the time to initiation of TPT and TB incidence

Outcomes	No. of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard, non-family-centred, non-integrated services	Risk difference with family-centred, integrated services
Coverage of TPT in eligible contacts (0-19 years)	412 (1 RCT)[1,a]	⨁⨁⨁⨁ HIGH	**RR 1.70** (1.10 to 2.64)	Study population	
				257 per 1,000	**180 more per 1,000** (26 more to 422 more)
Coverage of TPT in eligible contacts (0-19 years)	3371 (1 observational study)[2,b]	⨁◯◯◯ VERY LOW[c]	**RR 2.23** (2.11 to 2.36)	Study population	
				394 per 1,000	**485 more per 1,000** (438 more to 537 more)
TPT completion among contacts (0-19 years)	1557 (1 observational study)[2,d]	⨁◯◯◯ VERY LOW[e]	**RR 3.22** (2.90 to 3.57)	Study population	
				270 per 1,000	**599 more per 1,000** (512 more to 693 more)

Wingfield T, Tovar MA,Huff D,Boccia D,Montoya R,Ramos E,et al.. A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. Bull World Health Organ; 2017.

Rocha C, Montoya R,Zevallos K,Curatola A,Ynga W,Franco J,et al.. The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. . Int J Tuberc Lung Dis; 2011.

Household-randomized trial of a socioeconomic support package including social support activities and conditional cash transfers to offset hidden costs of care. Although this trial was rated as having "some concerns" for bias via the RoB2, these were related to the unblinded nature of the intervention and the lack of access to a protocol to assess adherence to a pre-defined analysis plan. We chose not to downgrade because we did not feel that the lack of blinding was likely to affect the outcome given the nature of the intervention, and the presentation of results suggested a pre-defined analysis plan for this primary trial outcome.

Multifaceted support package included social, economic, and psychological support; patients and their families were free to accept or decline individual components. Event counts were calculated from reported percentages and are thus approximate; the possible range of intervention events is 474–479 and the possible range for control events is 1116–1117. While this could be a source of imprecision, the amount of imprecision is not sufficient to substantively change the magnitude of the effect estimate.

This study was a pre-post study without any adjustment for secular trends over time or other sources of confounding, leading to serious concerns about bias.

Multifaceted support package included social, economic, and psychological support; patients and their families were free to accept or decline individual components. Event counts were calculated from reported percentages and are thus approximate; the possible range of intervention events is 382–385 and the possible range for control events is 296–306. While this could be a source of imprecision, the amount of imprecision is not sufficient to substantively change the magnitude of the effect estimate.

This study was a pre-post study without any adjustment for secular trends over time or other sources of confounding, leading to serious concerns about bias.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	The undesirable effects for case detection include decreased notifications and case detection rates, delays in diagnosis and initiation of TB treatment, as well as unfavourable treatment outcomes in children started on TB treatment. Undesirable effects for prevention include decreased TPT coverage, increases in the time to initiation of TPT, non-adherence to TPT and reduced TPT completion rates.	The GDG highlighted that information on undesirable effects was not available from the evidence review and it was therefore hard to make a judgement on undesirable effects. Potential undesirable effects were discussed, including missing a diagnosis of drug-resistant TB, possible under- or over-diagnosis, and treating a child with TB disease with TPT. It was noted that several GDG members thought undesirable effects were insignificant.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Overall, the certainty of the evidence of effects was very low for the effect on TB diagnosis and TB prevention	The GDG highlighted the variability of certainty from the reviews for specific outcomes and that many outcomes rated as critical by the GDG had no data available. This was noted as a research gap.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There were no included studies on values. However, a qualitative evidence synthesis on community views on active case finding for tuberculosis in low- and middle-income countries was undertaken, this review focused on children. This review found that people valued their health, which could be supported through their own economic efforts or through TB services, but these two routes sometimes undermined each other. Seeking TB services accrued costs and interfered with employment through missing work or through discrimination at work. They therefore valued the lower costs of TB care nearer home and often sought care first from local pharmacies or traditional health providers. Persistence despite difficulty with securing follow up care also underscored health as a widely shared value. People valued privacy and discretion in all settings for TB screening and for all aspects of subsequent TB care for themselves and for their children. Sometimes individual values (i.e., individual health or employment) conflicted with the widely shared community values of social integration and of family solidarity and harmony. Discrimination due to TB and HIV stigma sometimes isolated people from their wider community; enabled fractious or frustrating treatment in clinics; or led to discord and divisiveness within families. People also had to balance TB care seeking according to their individual health against their fears of infecting others (i.e., threatening community health. Likewise, parents had to balance the health of their children against their fears of medications. In addition, the study found: Children were part of the population sought by TB active case finding (ACF) and contact tracing programmes. Their contact with TB and ACF programmes depended largely on adults, many of whom responded to TB outreach according to their own priorities. Both sick and well adults prioritised employment over TB health services, which had direct implications for children. Community-based TB active case finding and contact tracing improved access for those missed with previous case finding strategies TB active case finding and contact tracing improved access to health services for those with worse health and fewer resources. ACF found this population exposed to deprived living conditions, but without being sensitive to additional dimensions of their plight, such as their marginalisation or their information needs. Lack of information impacted community members and health workers alike and sometimes led to harm. Children relied on adults, who had to navigate practical consequences of illness: out-of-pocket costs for travel, diagnostic tests and treatment, and adequate food to enable tolerance of drugs and speed recovery. Many community members expressed fears related to TB active case finding and contact tracing. People were afraid infecting others in their family or workplace, of painful side effects of treatment for themselves or for their children, and of dying from TB. People were also afraid of being labelled with TB or with HIV Relevant for prevention: Children were put at risk by contact with parents and teachers who, if they felt well, avoided TB screening. Some people with symptoms waited until their illness became severe, in part to avoid the social consequences of disease.	The GDG judged that there was probably no important uncertainty in how much people value the main outcomes for both case detection and the provision of TPT.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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	The balance of effects probably favours the intervention as an additional option.	The GDG expressed that, although there was no data on undesirable effects, and the certainty of the evidence was very low, the balance of effects probably favours the intervention, as there is evidence of positive effects of family-centred integrated care. The panel discussed that family-centred integrated care could be an addition to the standard of care as well as to specialized services which do not have an integration component. Family-centred care in the sense of family involvement was highlighted as a core principle of child health care.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	No studies were included on the costs of family-centred, integrated services. However, costing data are available from the CaP TB project (Catalyzing Pediatric Tuberculosis Innovations), which focused on implementation and integration of New TB Care and Treatment Models in 9 sub-Saharan African countries. The project aimed to: 1) improve detection of children (0–14 years) through facility-based intensified case-finding (ICF); 2) improve provision of TPT among household contacts aged below 5 and children living with HIV attending HIV clinics. The ICF intervention included implementation of systematic TB screening integrated in different child health entry points (OPD, IPD, HIV, MCH, and nutrition clinic), among others. TB screening was performed using a symptom-based screening tool, by community health care workers in waiting areas. The TPT interventions used community-based household contact screening where possible and included referral of symptomatic children aged 0–14 years for TB evaluation, as well as asymptomatic 0–4 years for TPT. Enhanced paediatric TB training and site-support and supervision was provided to support paediatric TB management and project interventions. The comparator was the standard of care (SoC) in each country. The following table provides a comparison of activities and costs per child started on anti-TB treatment for the standard of care versus the intervention:	Many of the GDG members anticipated moderate costs for programmes, but settled for 'varies' because of setting-specific costs, for example for training of healthcare providers, social protection schemes etc. The panel discussed that implementing family-centred, integrated approaches requires substantial initial investment from the health programme but could result in important savings for affected families. In addition, while investments are needed in the short term, in the long-term savings may be possible, depending on the setting and on the impact on TB incidence.

	Standard of care cascade (per child treated)						Intervention cascade (per child treated)					
Country	Screened	Presumptive TB	Tested with Xpert	TB diagnosed	TB treated	Cost, $ (SD)	Screened	Presumptive TB	Tested with Xpert	TB diagnosed	TB treated	Cost, $ (SD)
1	164.54	2.13	1.34	1.05	1	139 (48)	363.32	4.69	4.07	1.05	1	2025 (69)
2	29.81	0.91	0.91	1.03	1	90 (37)	65.82	2.01	1.18	1.03	1	601 (41)
3	388.55	3.17	3.17	1.03	1	97 (36)	817.98	6.67	1.38	1.03	1	1171 (38)
4	213.24	5.89	5.89	1.01	1	193 (61)	244.38	6.75	4.09	1.01	1	1350 (60)
5	168.71	2.82	2.82	1.01	1	145 (49)	569.05	9.52	7.9	1.01	1	3670 (133)

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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	Cost-effectiveness data are available from the CaP TB project (Catalyzing Pediatric Tuberculosis Innovations). The project included a programme evaluation ('TIPPI') that recorded before/after data at a site-level on anti-TB treatment (ATT) and TPT rates. These data were available for 5 of 9 countries with regulatory approval granted so far. Project financial and cascade data were analysed to estimate the cost of the intervention relative to baseline rates, capturing changes in resources used and additional investments in training and M&E. Changes in mortality and discounted expected life-years lost (3% discount rate) were modelled to estimate the interventions' impact on health and the incremental cost-effectiveness ratios (ICERs) in terms of US$ per DALY (disability-adjusted life year) averted. For the ICF intervention, country central estimates of deaths averted per 100 children starting ATT under SoC varied between 11 and 46 (excluding one country, with negative effect). Country ICERs ranged between 238 & 646 US$/DALY (excluding one country). ICERs were less than GDP and comparable or less than 0.5 x GDP, except for 2 countries. For the TPT interventions (including household case-finding), country central estimates of deaths averted per 100 children starting TPT under the SoC varied between 3 and 21. Country ICERs ranged between 301 and 1529 US$/DALY. ICERs were less than GDP and comparable or less than 0.5 x GDP in one country, and over GDP in other countries. Analysing both ICF and TPT intervention components as a single intervention gave ICERs similar to those of the ICF component, which accounted for most of the incremental costs and health benefits of the combined package. Interventions were more cost-effective among children aged 0–4 years than among children 5–14 years. Limitations of the analyses include confounding with before and after comparisons, omission of patient costs, difficulty in isolating project costs that may exceed analogues under implementation (e.g. wage rates) and modelled rather than measured health outcomes. Most limitations are on the side of biasing ICERs upwards (i.e. towards being less cost-effective).	The reviewers clarified that some studies outside of the evidence review showed that cash transfers avert catastrophic costs for families. Data from the CaP-TB project was included in the review for PICO 6a and b only, but also included integration and family-centred components. Some countries included vouchers for chest X-ray to improve access to radiography for families. This was however not standardized across all countries. The GDG agreed that cost-effectiveness probably favours the intervention.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	There were no included studies on equity. However, a qualitative evidence synthesis on community views on active case finding for TB in low- and middle-income countries was undertaken, this review focused on children. The authors found that *community-based TB services improved access to screening and subsequent care for some, including for children.* That said, many people living in areas selected for TB active case finding or contact tracing experienced material deprivation. Sometimes this marginalisation was exacerbated by difficult geography, environmental pollution, or unstable populations. For example, TB services for children were compromised when community health workers could not trace families that had moved, or when parents and families were unable to pay out of pocket costs. In contrast, those community members with greater economic security felt less vulnerable to TB. Tuberculosis programmes that aim to improve equity must consider both individual and community resources. Access to services is an important component of health equity, but equity also encompasses fairness and human rights norms. A commitment to equity addresses discrimination by changing laws or "social relationships" (WHO, 2021). The authors of the review found that *TB stigma led to discrimination along three pathways: isolation in the community, discord within families, and problems at work or lost employment.* In addition, the study found: Tuberculosis stigma set people apart, whether they were targeted for screening or received diagnosis and treatment. This setting apart exposed people to discrimination along distinct pathways: isolation from their wider community, lost employment, fraught social interaction with health care workers both in the clinic and on the doorstep, and discord and divisiveness within families. HIV stigma compounded tuberculosis stigma and heightened vulnerability to discrimination along these same pathways. In many settings, *lack of resources restricted what services were available for TB*, and this had implications for the care of children. Programme health workers and community members described a skeleton service in competition for resources, infrastructure, and staff. In this context of low investment, tuberculosis health services sometimes reinforced, rather than alleviated, deprivation and discrimination. Parents and children faced repeated tests and clinic visits, wasted time and fraught social interaction with health providers	The GDG judged that family-centred, integrated care for children and adolescents with signs and symptoms or exposure to TB probably increases health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One of the studies included in the systematic review reported on the acceptability of integrating TB into IMNCI *(4)*. The authors reported that at the health care facilities where the study was conducted, *more than 95.0% of the parents/guardians, health care providers and heads of the health facilities indicated they were comfortable with an integrated service delivery of TB screening and evaluation at IMNCI clinics and contact investigation at TB DOTS clinics*. More than 94.0% of the clients and HCWs, and all facility heads said that they had a positive perception of the integration. A separate qualitative evidence synthesis on community views on active case finding for TB in low- and middle-income countries was undertaken, this review focused on children. These authors found that several aspects of programme delivery reduced its acceptability for service users and other community members. First, community-based active case-finding and contact tracing created expectations for treatment that were not always met. TB programmes that were committed to early case detection in settings with low investment were not acceptable to people because they could not deliver on the expectations for follow up care for people with, and without TB. People across diverse settings documented difficult follow up care due to low investment, and health workers reported competition for health resources. Second, community members were aware of the consequences of TB screening and subsequent care, in terms of out-of-pocket costs and risks of discrimination. Both reduced the acceptability of community-based TB programmes. The authors concluded that until adequate mitigating strategies are in place, the well-known barriers of costs and discrimination will persist. Finally, the association of TB services with deprivation made outreach less effective amongst those better off economically, and their association with HIV reinforced stigma and the possibility for discrimination – both had implications for programme acceptability.	The majority of the GDG judged that family-centred, integrated care is probably acceptable to key stakeholders, including healthcare providers and families.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One of the studies included in the systematic review reported on acceptability of integrating TB into IMNCI *(4)*. The authors reported that the health care providers (95.0%) as well as the heads of the healthcare facilities (100.0%) indicated that the implementation of TB symptom screening and contact investigation at IMNCI and TB DOTS clinics was easy to implement. Integration was feasible and practical after intensive training and awareness creation on childhood TB among healthcare providers at the primary health care units. The authors noted that required capacity building needs to involve community health care workers as well, to facilitate the integration of childhood TB into the integrated community case management (iCCM) platform. In a separate qualitative evidence synthesis conducted on the topic of TB screening and case finding, the reviewers noted that the logic of TB active case finding and contact tracing is that community activities lead to early detection and, in turn, better treatment outcomes for individuals and less transmission within communities. They found that community TB outreach operated in contexts where there was low investment in health services, including staff, facilities, tests, and medicines, which left programmes in competition with other diseases and public health priorities. Lack of investment also led to difficult follow up care for parents and children, who faced repeated visits, wasted time, fractious interactions with health staff, and burdensome out of pocket costs. Low investment compromises the feasibility of programmes. All parties involved in community-based TB services had unmet information needs, which also compromised the feasibility and effectiveness of tuberculosis programmes.	The GDG highlighted that, while family-centred, integrated care is probably feasible to implement, substantial investment is needed to ensure ongoing capacity building of healthcare providers. It was also highlighted that practical implementation guidance is important to ensure equity, acceptability and feasibility are increased and family-centred, integrated interventions achieve what they intend to do, which is bringing child and adolescent services closer to patients and to reduce the burden and cost for them.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
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
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

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
○	○	○	●	○

CONCLUSIONS

Recommendation

Family-centred, integrated services in addition to standard TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB (conditional recommendation; very low certainty evidence).

Remarks:

Family-centred, integrated approaches are recommended as an additional option to standard TB services, for example alongside specialized services that may have a limited level of integration with other programmes or linkages to general health services

Family-centred care is a cross-cutting principle of child care at all levels

Justification

Capacity for paediatric TB is often highly centralized at secondary/tertiary level, where children may present seriously ill, after delays in accessing care. Capacity at higher levels of care is often managed in a vertical, non-integrated way. Healthcare workers at primary health care (PHC) level may have limited capacity and confidence in managing paediatric TB, although this is where most children with TB or at risk of TB seek care. In addition. TB screening is often not systematically part of clinical algorithms for child health (e.g. IMCI and iCCM). Private sector providers play an increasing role as first point of care in many countries. There are many missed opportunities for contact tracing, TB prevention, detection and care of TB as a result of weak integration of child and adolescent TB services with other programmes and services. Decentralization and family-centred, integrated care are highlighted as one of ten key actions in the 2018 Roadmap *(1)*.

This set of PICO questions looks at the impact of i. decentralization and ii. family-centred, integrated approaches of child and adolescent TB services on case detection in children who present with signs and symptoms of TB. They also examine the impact of these approaches on coverage of TB preventive treatment in children and adolescents exposed to TB.

Definitions related to this PICO question:

Decentralization: provision of/access to/capacity for child and adolescent TB services at a lower level of the health system than the lowest level where this is currently routinely provided (in most settings, district hospital (first referral level hospital) and/or primary health care level and/or community level).

Family-centred, integrated services:

Family-centred models of care: interventions selected on the basis of the needs, values and preferences of the child or adolescent and his or her family or caregiver. This can include health education, communication, material or psychological support. As part of the evidence review, patient-provider partnerships and participatory decision-making were aspects of family centred care that were added to the definition.

Integrated services: approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health related programmes and services.

A systematic review of studies assessing the impact of decentralized, integrated, or family-centred care models on TB diagnostic, treatment, or prevention outcomes for individuals 0–19 years old, comprising both children (0–9 years old) and adolescents (10–19 years old), was conducted to answer this group of PICO questions. The PubMed, Embase, Web of Science, Global Index Medicus, Global Health, and Cochrane Central databases were searched, as well as the references of 17 related reviews. 3,265 abstracts from databases and 129 additional references from related reviews were identified and assessed. 516 full-text articles were assessed for eligibility, from which 25 comparative studies (7 randomized, 18 observational) were identified; one unpublished observational was added for a total of 26 studies. 4 studies (1 randomized, 3 observational) were excluded after review because the care model described was community-based directly observed treatment, for which a WHO recommendation already exists (World Health Organization, 2017). Of the remaining included studies, 16 had elements of decentralization, 5 had elements of integration, and 3 had elements of family-centred care; 4 studies had elements of more than one care model of interest, but were only included based on their main model, e.g. either decentralization or family-centred, integrated care. Most focused on the 0–14 year age group.

Studies where the primary intervention was decentralization mostly assessed diagnosis or case notification outcomes (n=16), with fewer assessing TPT outcomes (n=3). In general, interventions that included both strengthening diagnostic capacity in primary care settings as well as strengthening linkages between communities and facilities consistently showed increases in case notifications and TPT initiations, while interventions that involved only community-based activities did not. Two studies of service integration were identified, which showed limited impact on case notifications of screening in integrated management of childhood illness clinics or co-location of TB and antiretroviral therapy (ART) services. Two studies of family-centred care were identified, which showed that provision of socioeconomic support packages to families affected by TB was associated with increased TPT initiation and completion. The reviewers noted that, while a substantial amount of literature on integration and family-centred care is available, evidence for the specific impact on child and adolescent TB outcomes is limited. Some overlap was noted between integration of TB services into non-specialized settings such as general outpatient or primary care services, and decentralization. For the evidence review this was a slightly artificial separation, while in practice decentralization and integration into primary health care may go hand in hand.

The GDG discussed that family-centred, integrated care includes interventions at household level to identify members of the household requiring evaluation for TB disease, TPT, treatment support etc. Some overlap between integration of TB services into non-specialized settings such as general outpatient or primary care services, and decentralization was noted. For the evidence review this was a slightly artificial separation, while in practice decentralization and integration into primary health care may go hand in hand. Overall, despite a lack of evidence on undesirable effects and low quality of the data, the panel agreed that there is evidence of positive effects of family-centred integrated care. It was suggested that family-centred, integrated care could be an addition to the standard of care as well as to specialized services which do not have an integration component. Family-centred care in the sense of family involvement was highlighted as a core principle of child health care.

The GDG discussed that setting specific factors related to TB burden or the organization of health services may impact feasibility, acceptability, and equity considerations. They also discussed that initial health system costs to establish decentralized and family-centred, integrated services may be relatively high (e.g. related to infrastructure, human resources, training, equipment, community engagement etc.), but that costs are likely to decrease over time, assuming that cases are effectively managed and TPT provided at the peripheral level, leading to a reduction in TB incidence. Decentralized and family-centred, integrated services may result in important savings for affected families. Equity was considered an important cross-cutting issue impacting cost as well. The GDG highlighted that TPT implementation can be very challenging with high levels of loss to follow-up in programmes implemented at higher levels of the health system, considering that children who are eligible for TPT are not sick. The panel agreed that decentralization and integration of services can potentially increase equity and enhance the success of the programme and judged that cost-effectiveness probably favours decentralized and family-centred, integrated approaches to both case finding and provision of TPT.

While the GDG stressed the importance of taking into consideration the potential impact of stigma, when decentralizing TB services for children and adolescents to lower levels, the panel judged that decentralized approaches are probably acceptable to key stakeholders. Overall decentralized and family-centred, integrated approaches were judged feasible to implement, although feasibility may vary depending on infrastructure, available funding and the structure of the national TB control programme, among others. However, adequate investment is critical to enable the acceptability, equity and feasibility of decentralized approaches.

Subgroup considerations

In children with illnesses that present with overlapping signs and symptoms of TB, approaches to integrate TB care into other services can be beneficial to improve case detection and provision of TPT.

These sub-groups include:

Children with severe acute malnutrition

Children with severe pneumonia (including inpatient management – where the prevalence of TB may be higher compared to outpatients)

Children with other chronic diseases

There are specific sub-group considerations for adolescents which were not discussed extensively during the GDG meeting but additional guidance on providing care for adolescents will be provided in the operational handbook on the management of TB in children and adolescents.

Implementation considerations

Although in child health, care evolves around the family, the concept of family-centred care has not been well defined. Family-centred care is related to the more common concept of patient-centred care. Patient-centred care in the End TB Strategy *(5)* is defined as follows: "Patient-centred care involves systematically assessing and addressing the needs and expectations of patients. The objective is to provide high-quality TB diagnosis and treatment to all patients – men, women and children – without their having to incur catastrophic costs. Depending on patients' needs, educational, emotional and economic support should be provided to enable them to complete the diagnostic process and the full course of prescribed treatment." Multiple definitions of family centred care exist, and these include components of support and education based on individual needs, building a patient-provider partnership and participatory decision-making. Family-centred care also includes interventions at the level of the household to identify members of the household requiring evaluation for TB disease, TPT, treatment support etc.

As the concept of family-centred, integrated care may be setting specific, one of the first steps in implementation includes clarifying which definition applies to the setting in which it is to be implemented. Similarly, the implementation strategy varies by setting and needs to be country- or region-specific, informed by social, cultural and societal values.

The package of TB services to be provided needs to be defined and developed by the national TB programme, in close coordination with other relevant programmes, for example through an existing child and adolescent TB technical working group. This package needs to be based on identifying and addressing capacity needs for national programmes interested in implementing proposed interventions, and ideally based on family and community perceptions on the ideal family-centred model of care. For example, it could include community-based models for contact investigation, identifying children with TB signs and symptoms or exposure as part of routine growth monitoring services or an integrated model for Integrated Management of Childhood Illnesses (IMCI) integration, starting with the sick child and identifying signs and symptoms that demonstrate a high likelihood of TB.

Integration can start within the family, by equipping the family with the knowledge to recognize signs and symptoms, to understand the importance of a history of contact, to know when to seek help at the healthcare facility and how to minimize stigma related to TB. High yield entry points provide a good starting point within the health system. For example, child and adolescent TB services can be integrated in malnutrition clinics, antenatal care, immunisation services, inpatient settings, adult TB and chest clinics, general paediatric clinics. Ideally TB care should be integrated into general health services, rather than be limited to enhanced coordination between two programmes. In the early phase, pilot programmes could be considered, which should be evaluated and adjusted as needed and then scaled up.

Factors to consider in designing an integrated approach to child and adolescent TB care include the existing infrastructure (e.g. baseline health infrastructure, needs for expansion or upgrading), the applicable regulatory framework, financing, choosing between an operational research setting or programmatic implementation, human resource issues (e.g. staffing requirements and HR development such as capacity building/training and consultation skills), monitoring and evaluation, conducting qualitative research into community needs, perceptions (including views on stigma) and suggestions.

Differentiated service delivery is a person-centred approach developed in the HIV programme that simplifies and adapts HIV services across the cascade in ways that both serve the needs of people living with and vulnerable to HIV and optimize the available resources in health systems. The principles of differentiated service delivery can be applied to prevention, testing, linkage to care, ART initiation and follow-up and integration of HIV care and coinfections and comorbidities (World Health Organization, 2021). This approach embraces the idea that families are given choices to interact with the health system and could provide a possible mechanism for integration of child and adolescent TB services within primary health or other programmes.

Monitoring and evaluation

Moving to decentralized, family-centred, integrated services requires careful planning, and regular monitoring of implementation against the plan. The capacity needs of national programmes interested in implementing the proposed interventions need to be identified and addressed.

Enhanced data collection around child and adolescent TB potentially takes a substantial amount of additional time and detailed data collection may only be feasible in specific operational research settings. Programmes generally have registers in place for contact investigation, treatment registration and outcomes, TPT registers. The use of these (preferably electronic) tools is important as programmes move to a more decentralized and family-centred, integrated approach, to ensure comprehensive management and treatment. The use of these tools needs to be evaluated and enhanced, including through operational research.

It will be important to monitor the number of children diagnosed at different levels of the health system, including the proportion of children who have bacteriological confirmation, the proportion who were clinically diagnosed as well as the number of children initiated on and completing TPT. Evaluating the quality of services (covering the quality of all steps in the patient pathway, from screening, to diagnosis and treatment) as well as client satisfaction are important components as well.

Research priorities

Detailed description of currently operating family-centered and integrated services; associated costs and cost-effectiveness

Implementation research on the components of these interventions; assessment of real-world implementation of these programmes

Feasibility and acceptability of family-centred, integrated and/or decentralized approaches to child and adolescent TB care for case detection and for TPT provision in different settings

Costs and catastrophic costs

Cost-effectiveness evaluations of family-centred, integrated and/or decentralized approaches, considering currently available resources (some models assume that these interventions are built upon existing structures that do not exist)

Outcomes of interest: initiation of preventive treatment; number of additional children and adolescents diagnosed; delay, retention in care, treatment completion, clinical outcomes (e.g., treatment success); Qualitative research related: stigma, mental health outcome, school interruption, equity

Evaluation of outcomes of interest using randomized, non-randomized designs, qualitative design

Baseline needs assessment in the community, community perceptions regarding TB care and prevention for children and adolescents

Research on the quality of TB diagnosis in children – addressing both under-diagnosis and over-diagnosis.

References

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4 Ketema L, Dememew ZG, Assefa D, Gudina T, Kassa A, Letta T et al. Evaluating the integration of tuberculosis screening and contact investigation in tuberculosis clinics in Ethiopia: A mixed method study. PLoS One. 2020;15(11):e0241977 (https://www.ncbi.nlm.nih.gov/pubmed/33211710, accessed.

5 World Health Organization. The END TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. 2014.

Web Annex 3. Reports of the systematic reviews

Web Annex 3.1. Guideline update 2011

Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed in Table 2 of the guidelines?

DATA SOURCES

The search strategy was developed to include studies (or systematic reviews of studies) from both health and economics databases, in both published and unpublished (grey) literature and in four of the six official languages of the World Health Organization (English, French, Spanish and Russian). Portuguese search terms were also included. No search was conducted in Chinese or Arabic, due to lack of capacity. The search was initiated on 15 January and concluded on 16 January 2010 for all languages other than Russian. The Russian-language search was conducted on 21 January. There were no restrictions on the years to be searched.

The search was limited to online databases, including PubMed, EMBASE, ISI Web of Knowledge, CABI Global Health, Health Economic Evaluations Database, NHS Economic Evaluation Database (NHSHEED), the Cost-Effectiveness Analysis Registry, and the European Network of Health Economic Evaluation Databases. In order to minimize publication bias in our sources of data, special efforts were made to identify grey literature from WHO regional databases and Google Scholar. Each online database required slight adaptation of the search terms, and these are presented in detail in Annex 1.

English, French, Spanish and Portuguese studies were assessed directly by at least one of the authors. In the case of Russian studies, abstracts were first translated using online translation software (Google Translate) to assess relevance. If relevant and not available in other languages, the full study was fully translated before being assessed as per the non-Russian studies.

If searches conducted in any of the five included languages returned an article in another language, the study was translated and included if applicable. In practice, two such studies were identified, one in Turkish and the other in Macedonian.

We also checked whether articles from ISI Web of Knowledge had been cited in more recent studies. On 1 February, a search was done for systematic reviews of treatment outcomes for MDR-TB. See Annex 2 for databases and search terms used. References of the two systematic reviews (*3*, *4*) thus identified were verified for any additional studies. The search strategy and preliminary list of articles were peer-reviewed by the group responsible for the revision of the *WHO Guidelines for the programmatic management of drug-resistant TB*. We did not receive any requests to include additional studies. Finally, Katherine Floyd provided one unpublished manuscript with results from two studies.

Time constraints prevented hand searching or the contacting of authors for papers that were not available electronically.

Citations were collected and managed electronically using EndNoteWeb 2.7 (online) and EndNote X (offline). 497 citations were imported. A total of 82 duplicates were identified by EndNote, leaving a total of 419 studies to be assessed for selection.

STUDY SELECTION

In order to be considered for the review, studies had to involve MDR-TB cases with resistance to at least isoniazid and rifampicin. Furthermore, interventions had to describe in detail at least one of the options for MDR-TB care described above. We had no restrictions on patient characteristics (e.g. drug resistance profile, or HIV-status).

We set out to provide a critical review of full economic evaluations: "the comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes, effects)" (ref. Cochrane Handbook)" including cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis.

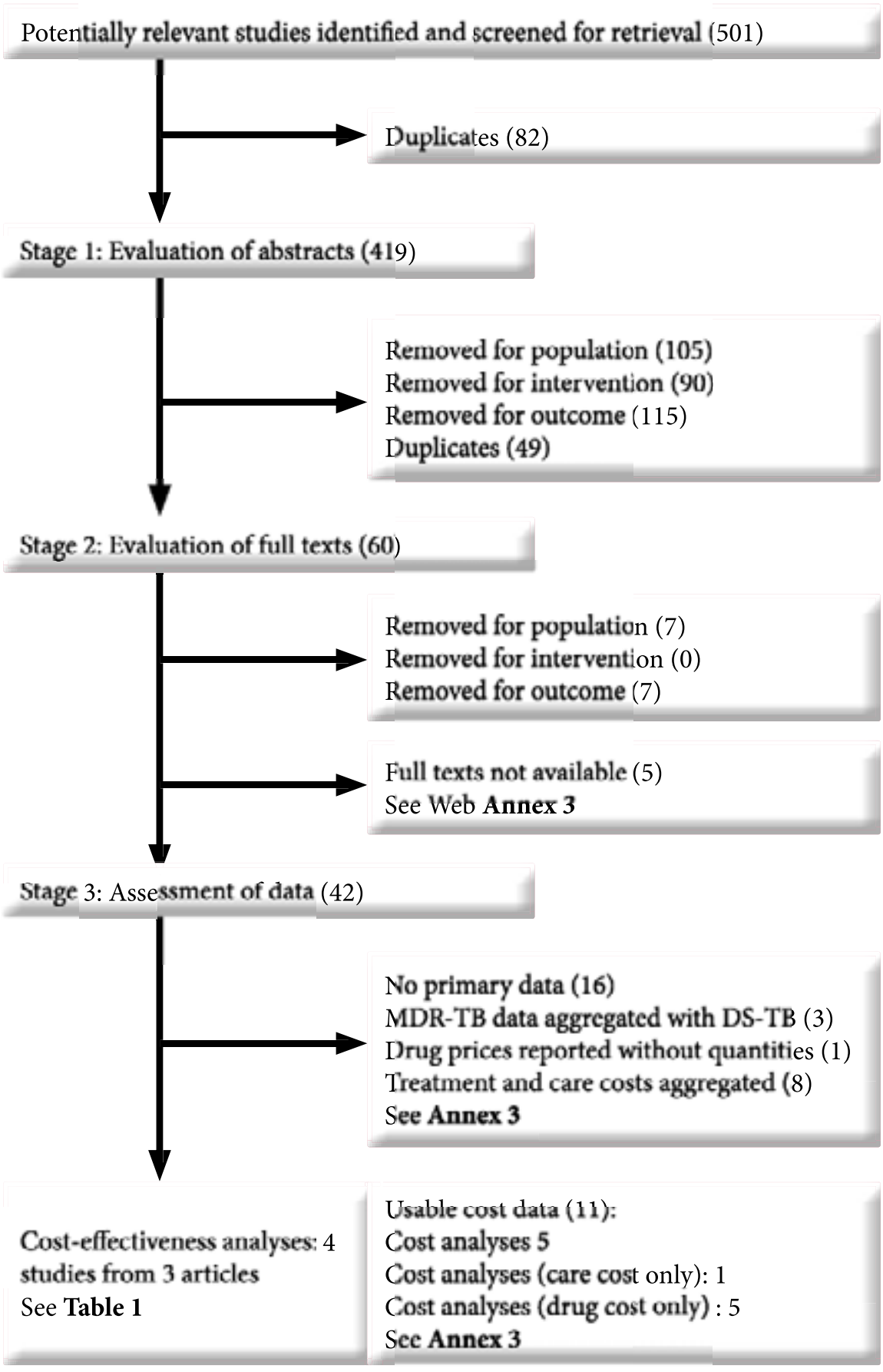
We considered full economic evaluations conducted alongside effectiveness studies, as well as those based upon data sourced from effectiveness studies. However, we excluded studies if both costs and effects were based entirely on secondary sources.

The main outcome of interest was the cost per disability-adjusted life year (DALY) averted. Costs considered for inclusion could be from any of the following perspectives: cost from the health service provider perspective, cost from the patient perspective (including direct medical costs as well as indirect costs related to transportation), and total societal cost.

In addition to cost per DALY averted, we documented, whenever possible, the following outcomes: compliance rate and long-term number of deaths (including secondary, default and relapse cases). We do not report these intermediate outcomes in this paper because they are implicit in the cost per DALY (averted) measures. They are, however, reported in supplementary digital content.

A diagram of the flow of included studies is provided in Figure 1.

Figure 1. Flow of included studies



In reviewing abstracts (Stage 1) and full texts (Stage 2), any one of the following criteria provided sufficient justification for exclusion:

- Population: Abstract/full text does not refer to MDR-TB cases resistant to at least isoniazid and rifampicin. Excluded were studies that referred only to: single drug-resistance, resistance of the individual to the disease, or drug-resistance in a general way (e.g. DS-TB cases have implications for MDR-TB).
- Intervention: Abstract/full text does not refer to treatment and/or care options for MDR-TB. Excluded were studies that referred only to diagnosis, infection control, chemoprevention, treatment of latent infection, or treatment in a general way (e.g. diagnostic intervention has implications for treatment).
- Outcome: Abstract/full text does not refer to either cost nor cost-effectiveness or economic evaluation. Excluded were studies that referred only to: "fitness cost"; the cost of not treating MDR-TB, or to cost in a general way (e.g. MDR-TB treatment is likely to have higher costs).

Duplicates not initially captured by EndNote were also removed at this point.

In reviewing the data (Stage 3), the assessment sought to answer the following question: Assuming that the results are valid, is it possible to assess on the basis of the data reported the extent to which they may apply to other settings? Applicability to other settings is an issue of critical concern to any systematic review of cost or cost-effectiveness analysis.

There were 8 studies in which resource use was not described, and/or costs were not reported with the necessary disaggregation or sensitivity analyses to say anything about applicability to other settings. In one study, only drug costs were considered, with no mention of the costs of care. Finally, there were three studies in which MDR-TB and non-MDR-TB data were not disaggregated.

Also at this stage, we excluded 16 studies that were based entirely on secondary sources of data. Excluded studies are listed, with reasons, in Annex 3.

INCLUDED STUDIES

The Summary of Findings table is restricted to studies which have data on our primary outcome of interest: cost per DALY averted. This final list of studies included is listed in Table 1, with a summary of their major characteristics.

Table 1. Summary characteristics of included studies

Lead author and year of publication; study design, economic, epidemiological[a], geographic and/or organizational setting; year(s) of cost and effect data	Intervention: **Model of MDR-TB treatment and care[b]**	**Comparison: Usual (pre-intervention) treatment and care[c]**
Floyd et al. (personal observation)[d]; Observational study; High income country; EUR C Estonia; 1995-1997 (comparison), 2001-2002 (intervention)	**Strategy:** individualized second-line drug treatment by expert committee of 4–5 physicians; Diagnosis/DST: drug susceptibility results for both first and second-line drugs; **Duration:** 12–18 month long continuation phase started 6 months after culture conversion; **Regimen:** daily, 6–7 drugs in the intensive phase of treatment, including a second-line injectable and any first-line drugs to which the patient was susceptible, in continuation, the injectable drug was removed from the regimen. **Setting:** committee determined whether patients should be treated in hospital or as an outpatient; average hospitalization was 192 days, with 171 clinic visits. **DOT:** throughout treatment. **Adherence:** Transport vouchers and food packages. **Training:** Clinical and laboratory staff were trained through international and national courses. **Other:** Patient progress was monitored using periodic X-rays and monthly sputum and culture examinations. Management and supervision: A small management team was established to provide overall supervision of clinical and laboratory work and to maintain a TB register.	**Strategy:** empirical and individualized treatment determined by individual physicians. **Diagnosis:** Incomplete drug susceptibility. **Regimen:** limited availability of second-line drugs; surgery sometimes formed part of treatment. **Duration:** discharged when cavity closure was documented. **Setting** Patients almost always hospitalized throughout treatment. Average 132 days inpatient treatment and 12 clinic visits. DOT: throughout treatment.
Floyd et al. (personal observation)[d]; Observational study; Upper-middle income country, EUR C; Tomsk Oblast (Russian Federation); 1998-1999 (comparison), 2001-2002 (intervention)	Same as above, except: **Setting:** average hospitalization was 321 days, with 250 hospital day-stays and 85 clinic visits. Adherence: Food parcels or free provision of meals were provided at outpatient facilities.	Same as above, except: **Setting** Patients almost always hospitalized throughout treatment. Average 120 days inpatient treatment, 109 hospital visits and 69 clinic visits.

Suarez 2002[e,f]**;** Observational study; Upper-middle income country AMR D Peru; 1997-1999	**Strategy:** standardized; expert committee of 12 lung specialists, public health specialists, and laboratory specialists approves or reject requests from the general health facilities to enroll patients; **Diagnosis/DST:** Drug susceptibility testing of first-line drugs at reference laboratory; **Duration:** 18 months; **Regimen:** daily regimen, consisting of kanamycin (1 g injectable), ciprofloxacin (1 g orally), ethionamide (750 mg orally), pyrazinamide (1500 mg orally), and ethambutol (1200 mg orally). Kanamycin was administered only for the first 3 months. **Setting:** outpatient, local health clinic, with 18 hospital visits and 450 clinic visits; **DOT:** throughout, daily by nurses for administration of drugs and monitoring of any adverse effects associated with treatment, and monthly by doctors for a medical check-up; **Adherence:** patients were provided, for example, with an appointment card and a weekly food parcel. **Other:** Baseline and monthly follow-up sputum smears at periphery level. Baseline and monthly follow-up cultures of sputum samples at district level.	Strategy: standardized; Regimen: Treatment with (negligeable cost) isoniazid monotherapy; Setting: unknown, but infrequent use of health services.
Tupasi 2006[g]**;** Observational study; Lower-middle income country, WPR B the Philippines Makati Medical Center in Manila,; 1999-2002	**Strategy:** Individualized; **Diagnosis/DST:** drug susceptibility testing results for all first-line drugs, three second-line drugs (kanamycin, ciprofloxacin, and ofloxacin), and previous use of other drugs as reported by patients.; **Setting:** 7 days hospitalization followed by 253 clinic visits during outpatient treatment; **Regimen:** In the intensive phase of treatment, a daily five-drug regimen was used. This typically consisted of an injectable drug, a fluoroquinolone, other oral second-line drugs, and first-line drugs to which the patient was not resistant. In the continuation phase, started after six consecutive months of negative culture results, the injectable was dropped from the regimen. **Duration:** until cultures were negative for 18 consecutive months. **DOT:** throughout — during the intensive phase, direct observation of treatment (DOT) was provided by MMC staff. In the continuation phase, alternating clinic and home-based DOT was used. **Adherence:** Patients who defaulted were followed up by telephone, telegram, and/or home visits.	**Strategy:** empirical/standardized; **Regimen:** for chronic cases, no or limited treatment determined by on what patients could afford to pay for in the private sector; for new and retreatment cases, standard first-line retreatment regimen. **Setting:** unknown.

[a] The WHO regions are: AMR — The Americas, EUR — Europe, WPR — Western Pacific. WHO subregions are classified according to mortality strata: B. Low child, low adult; C. Low child, high adult; D. High child, high adult.

[b] We documented, whenever explicitly described in the study, the following aspects of a "model of care", from the WHO MDR-TB Guidelines : Chapter 7: diagnosis / DST, treatment strategy (standardized, empirical, individualized or other), drug regimen (inclusion or not of fluoroquinolones, injectables), number of drugs, number of months of treatment (past culture conversion), adjunct therapies (surgery, nutritional, corticosteroids); Chapter 12: treatment delivery setting (community-based care, clinic-based/outpatient treatment, hospitalization/inpatient treatment), disease education, DOT, socioeconomic support, psychosocial and emotional support, management of adverse effects, monitoring systems to improve adherence. "Other" includes details, if available, on monitoring of treatment and management of adverse side effects (Chapter 11), management of contacts of MDR-TB patients (Chapter 14), infection control (Chapter 15) or recording and reporting (Chapter 18), if reported.

[c] All studies provide intervention-mix constrained cost-effectiveness results — that is, comparisons of the MDR-TB intervention to usual (pre-intervention) treatment and care, which may or may not have been a cost-effective allocation. These results are later generalized for comparisons to a null set of no intervention.

[d] An unpublished manuscript by Floyd et al. contains a comparison of results from two separate studies conducted in two countries of the former Soviet Union.

[e] This study has not been evaluated by the Centre for Review and Dissemination (CRD); no structured abstract is available in the National Health Service Economic Evaluation Database (NHSEED).

[f] The study calculates cost-effectiveness of another two interventions: 1) Standardized second-line drug treatment plus individualized drug treatment strategy for patients not responding to treatment with standardized second-line drug regimen; 2) Same as 1) but standardized second-line drug regimen for patients who do not respond to the treatment regimen with first-line drugs and who are diagnosed with MDR, instead of the first-line re-treatment regimen. However, these were hypothetical interventions, not actually implemented, and we therefore do not include these interventions in our systematic review and data synthesis.

[g] This study has been evaluated by a health economist for CRD and is listed in NHSEED; for reasons not stated, it is considered to be a cost study, not an economic evaluation.

The major differences between the interventions relate to treatment strategy, drug regimen, number of drugs and treatment delivery setting. A standardized treatment strategy was used in Peru, whereas an individualized strategy was used in the Philippines, Tomsk and Estonia. The drug regimen and number of drugs used in the Peru study would, by today's standards, be considered substandard. In Peru and the Philippines, treatment was delivered under a clinic-based, outpatient-focussed model; in Tomsk and Estonia, treatment was delivered under a hospital-based, inpatient-focussed model. There is no example among the included studies of community-based treatment and care.

There is comparatively little difference between the studies in terms of diagnosis, drug-susceptibility testing (DST), number of months of treatment (past culture conversion), and directly observed therapy (DOT). Differences in terms of adjunct therapies, disease education, socioeconomic support, psychosocial and emotional support, management of adverse effects, and monitoring systems to improve adherence could not be quantified on the basis of reported information on resource use.

This paper is not a systematic review of effectiveness, but of cost-effectiveness. To the extent that economic evaluations are conducted in some settings more than others—such as in developed countries, where effectiveness may be higher—the studies included in this review will not provide the best available estimate of effect-size across all settings.

In theory, there is a possibility of publication bias arising from the fact that economic evaluations are more likely to be based on published (usually larger effect-size) results than on unpublished (usually small effect-size) results. We had attempted to mitigate these potential biases by extending our search to non-English language and regional databases, as well as to the so-called "grey literature". We compared included studies to those assessed elsewhere in a systematic review of effectiveness (*3*). Confidence intervals from Tupasi et al seem to reflect confidence interval on individualized treatment success as a whole; the Peru result from Suarez, appears to be on the low end of treatment success among standardized treatment regimens. In practice, there is therefore little to suggest the presence of effect-size bias in the included studies. The Tomsk and Estonia results were not included in the Orenstein et al. (2009) systematic review of effectiveness, because they were not published at the time.

There is also a theoretical possibility of publication bias arising from a preference for low-cost settings. We compared unit costs from the four included studies plus eleven other studies with usable cost data (see Annex 3) with cost data to planned (preliminary) 2011 budgets divided by expected numbers of MDR-TB patients in high TB burden and high MDR-TB burden countries, as reported to WHO for the Global TB Report (*5*). We found that the per patient costs from these studies are at the very low end of the per patient budgets currently being planned for MDR-TB scale-up, even after adjusting for inflation. Part of the reason may be buffer stocks of drugs and other non-recurring costs such as buildings, which are not annualized in country-reported budgets. But

even so, study costs are very low compared to country-reported budgets. We attempt to mitigate this bias by generalizing the results, as described in the Data Synthesis section, to reflect a wider distribution of unit costs.

DATA EXTRACTION

The methods employed in this paper are broadly consistent with the structure and methods proposed in the Cochrane Handbook (*6*), especially with regards to Chapter 15, on integrating critical reviews of health economic studies into systematic reviews.

Assessment of the quality of the economic evaluations was guided by checklists as developed by Drummond et al. (2005) and the Consensus Health Economic Criteria (CHEC) list. Unfortunately, no Centre for Review and Dissemination (CRD) / National Health Service Economic Evaluation Database (EED) structured abstracts were available for comparison.

The quality of the overall evidence was graded was performed using the GRADE approach and GRADEprofiler (GRADEpro) software v.3.2.2. A GRADE profile and Summary of Findings (SoF) table was produced.

This paper was then itself assessed against PRISMA and MOOSE checklists, for systematic reviews and meta-analysis of observational studies, respectively.

DATA SYNTHESIS

All studies provide intervention-mix constrained (IMC) cost-effectiveness results—that is, comparisons of the MDR-TB intervention to usual (pre-intervention) treatment and care, which may or may not have been a cost-effective allocation. In order for results to be comparable, we standardized results by comparing each intervention not to usual treatment and care, but to a common null of no intervention at all. The latter assumption allows for a re-allocation of existing resources, from a potentially cost-ineffective allocation in the pre-intervention period.

Furthermore, we enhanced the applicability of the results by generalizing the input variables. We performed multivariate uncertainty analysis based on Monte Carlo methods, using effect results and resource use results from the included studies, but replacing setting-specific unit costs with distributions from other sources, in a simulation of 10,000 iterations. In order words, we expand simple parameter uncertainty (as contained in the individual studies), to both parameter and generalizability uncertainty.

We thereby mitigated some of the factors that would otherwise have reduced the comparability of results from the different studies :

- **Relative prices or costs:** Drug costs were adjusted for inflation; with an uncertainty interval determined by high and low buyer prices cited in the International Drug Price Indicator Guide 2009. Unit costs for hospital beddays, hospital visits and clinic visits

(these were resources for which quantities had been reported in the studies) were generalized using a distribution of unit costs in 2005 international dollars (I$) from WHO-CHOICE. Correlations between these variables and GDP per capita (2005 I$) were also derived from WHO-CHOICE data. Unit costs for smears, cultures and DST were standardized across the four studies using the distribution implied by unit costs from these very studies; these unit costs were assumed to be highly correlated (rho=0.75). We assumed, in the absence of information to the contrary, no specific correlation between unit costs and effect sizes. Other non-drug costs were assumed to be non-traded commodities and were therefore converted to 2005 international dollars (2005 I$) using GDP implicit price deflators and purchasing power parity (PPP) exchange rates.

- **Availability of health care resources and variations in clinical practice.** As per WHO-CHOICE, a standard utilization rate of 80% is implicit in the unit cost for hospital beddays; we allow for hospitalization to take place in either first, secondary or tertiary level hospitals, hospital day-stays in either primary, secondary or tertiary level hospitals, and clinic visits at population coverage levels of 50-95%. We do not assume any correlation between facility type and effect size.
- **Population values:** The rate at which the population discounts future health outcomes was already standard in the four studies, at 3% per annum, and all studies used disability-adjusted life years (DALY) as the measure of morbidity. No further adjustments were required.
- **Incentives to health care workers and institutions:** All other non-drug costs (for quantities had not been reported in the studies) were adjusted by GDP per capita (2005 I$), as a proxy for the complexity and quantity of inputs required.
- **Basic demography and epidemiology of disease:** The numbers of deaths under the null is entirely modelled, with the same level of uncertainty across all models; in fact, we assume that health outcomes in the absence of any intervention would be similar across demographic and epidemiological settings. Furthermore, we standardized the number of DALYs per death averted under both the null and the intervention. We did no additional modelling of the numbers of deaths under the intervention.

In order to distinguish the country from the model of treatment and care, we refer in this table and throughout the rest of the paper to the models of treatment and care as Es, To, Pe and Ph for Estonia, Tomsk, Peru and Philippines, respectively.

Even with adjustments made to increase the generalizability of the study results, caution is warranted. Cost-effectiveness results remain specific to the countries in which the studies were undertaken primarily because of differences in basic demography and epidemiology of disease. Patient characteristics differ between the studies; it is therefore not known to what extent the health outcomes would be similar in different settings, even using the exact same model of treatment and care.

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Web Annex 3.2. Guideline update 2017

Report on Systematic Review for Adherence Interventions in TB Treatment

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Background

The current treatment for drug-susceptible pulmonary tuberculosis (PTB), for most types of extra-pulmonary TB, and for human immunodeficiency virus (HIV) associated TB is a 6-month multidrug regimen. Ensuring adherence to long-duration treatment regimens is challenging and incomplete treatment may lead to poor outcomes including treatment failure, relapse, and acquisition of drug resistance. Several adherence strategies have been implemented over the years to improve adherence with therapy. Perhaps the most commonly known such intervention is directly observed therapy (DOT) introduced in the early 1960s in which a health worker, family member, or community member observes the patient taking TB medications(1). Other interventions have included financial incentives, implementing reminder or tracking systems, improving patient and staff education, and most recently the use of mobile technology for video observed therapy and SMS tracking. The resources necessary for such interventions vary and many centers across the world have been using a combination of these strategies to improve TB treatment outcomes. Here, we set out to determine which of these interventions, alone or in conjunction with a package of interventions, leads to improved TB treatment outcomes.

The specific terms of reference for the current systematic review were as follows.

- Undertake systematic reviews and analysis evaluating the following PICO question: In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the following outcomes: treatment adherence, conventional treatment outcomes, adverse reactions, acquired drug resistance, patient costs and health service costs?
- Work in close liaison with WHO/Global TB Programme and, where necessary, other contributors to the studies and data in carrying out this work; and invite WHO/GTB technical focal points and others who are significant contributors to be co-authors in subsequent publication of the systematic reviews contracted;
- Deliver the findings per agreed timelines including submitting the report of findings and presenting the findings at the guideline meeting; and
- Sign and comply with the confidentiality agreement with WHO for not releasing or publishing results of the systematic reviews prior to the approval of the WHO Guideline Review Committee for the publication of WHO TB treatment guideline.

PICO Question

In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?

Table 1. Breakdown of the PICO question

Population	Intervention	Comparator	Outcome
Patients on treatment for DS-TB Patients on MDR-TB treatment Children (0-14y) and adults HIV-infected and HIV-uninfected TB patients	Any intervention to promote treatment adherence • Supervising treatment (DOT, VOT) • Measures to improve treatment adherence (e.g. medication monitors and/or SMS or phone call reminders) • Social support (educational, psychological, material) • Combinations of the above interventions	Routine practice*	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death • Adverse reactions from TB drugs (severity, type, organ class) • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to health services

* Routine practice: regular TB drugs pick-up and consultations with physician or other health-care workers are available when necessary; TB treatment is free of charge; essential information/health education in relation to TB treatment is provided.

Review methodology

A protocol for this systematic review was generated prior to conducting the literature search and conducted in accordance with the PRISMA guidelines.

All aspects of the terms of reference have been completed, including this final report.

Study Selection

We searched pubmed through February 6th, 2016. Title and abstract review was performed by one reviewer (NA) and full text reviews were done by multiple reviewers. We included all randomized controlled trials, quasi-randomized studies, and prospective or retrospective cohort studies that met the inclusion criteria. Articles were excluded if they were conducted on patients with latent tuberculosis, did not have a current or historical control group, or if the article was not published in English. Two foreign language articles were included as data from them was previously abstracted by a different systematic review. Studies that specifically compared DOT delivered in a hospital setting versus clinic setting were excluded from this review due to a different systematic review dedicated to the comparison being conducted at the time of our review.

Table 2. Search protocol for adherence interventions in TB

Step	Search Terms (Pubmed)
1	TB
2	tuberculosis
3	1 OR 2
4	"directly observed therapy"
5	"directly observed treatment"
6	"supervised therapy"
7	"supervised treatment
8	DOT*
9	VOT
10	"video observed"
11	SMS
12	Text messag*
13	phone
14	telephone
15	Patient adherence
16	video
17	Patient participation
18	motivation
19	Decision support techniques
20	Default*
21	Adheren*
22	Supervis*
23	4-22/OR
24	3 AND 23
Date conducted	12/12/2015
Results	6394
Date search repeated	2/6/2016
Final results	6467

A separate search was conducted for video/SMS interventions in TB through June 28th, 2016 using the following search strategy.

Table 3. Search protocol for SMS/video interventions

Step	Search Terms (Pubmed)
1	TB
2	tuberculosis
3	1 OR 2
4	Text message
5	SMS
6	Cell phone
7	Video
8	4-7/OR
9	3 AND 8
Date conducted	6/28/2016
Results	425

Analysis

The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials (reference) and the Newcastle-Ottawa Scale was used for observational studies (reference). The types of information abstracted from each article included setting, average age of patients enrolled, type of tuberculosis (pulmonary vs extapulmonary), drug resistance, co-infection with HIV, type of adherence intervention, and conventional TB treatment outcomes including cure, success, treatment failure, default or loss to follow up, adverse reactions, and death. The standard WHO definition was used for all outcomes of interest. One reviewer (NA) abstracted all data for analysis. Data was abstracted and analyzed using RevMan. Where two or more studies reported on similar outcomes, data was pooled using random effects meta-analysis. Heterogeneity was assessed using Chi-squared test available in RevMan with p<005 used to determine statistical significance. Where more than 15 studies were available for a particular question, we used funnel plots to determine publication bias.

Results

Characteristics of the included studies are summarized in the tables provided below. The complete slide set is provided as a companion to this report and includes a summary of the methodology as well as forest plots and GRADE evidence profiles for each comparison.

Figure 1. PRISMA diagram

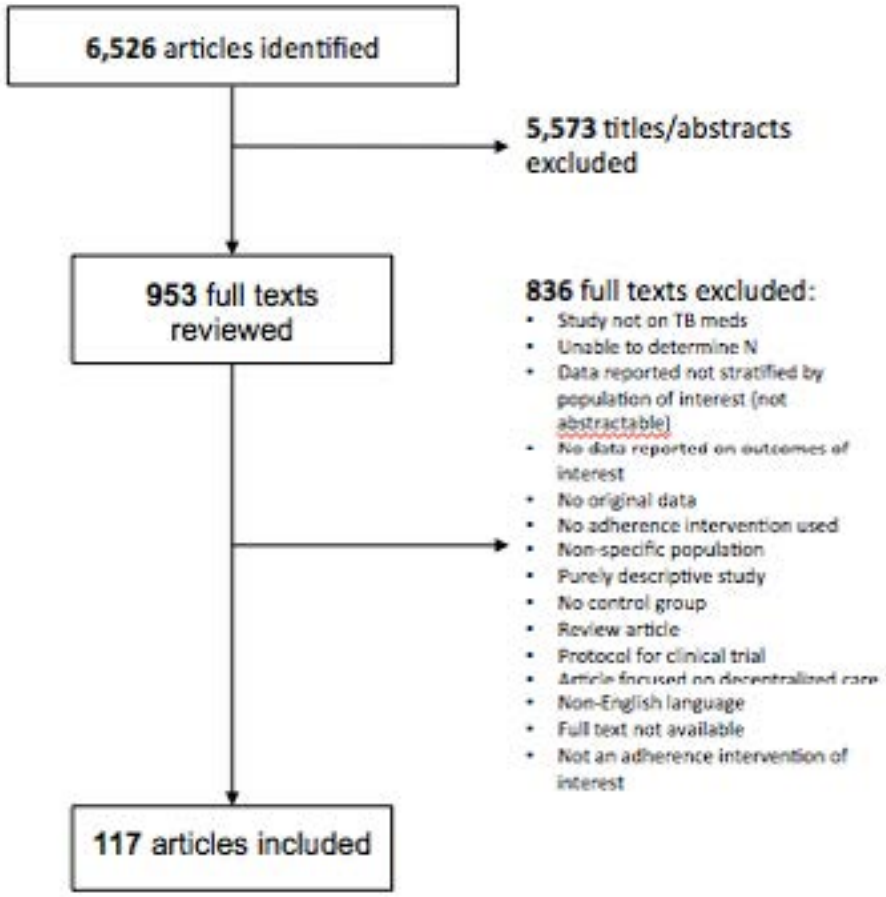


Table 4. Characteristics of included studies: SAT vs DOT

Comparison: Self-administered therapy as an intervention versus directly observed therapy

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Kamolratanakul (2)	1999	RCT	Thailand	836	-PTB (smear +) ->15 years	-Daily -Clinic, community member, Family member
MacIntyre(3)	2003	Quasi-RCT	Australia	173	-Excluded MDR, relapse, HIV+ ->14 years	-Daily -Family member
TRC Chennai(4)	1997	Clinical trial, not rand-omized	India	825	-PTB (smear +) -excluded those who missed >25% of rx. -Included INH/RIF mono-resistant ->12 years	-Twice weekly -Clinic.
Walley(5)	2001	RCT	Pakistan	497	-PTB (smear +) ->15 years	-Daily -Clinic, Home (health worker or family member)
Zwarenstein(6)	1998	RCT	South Africa	216	-PTB (smear +) -Excluded MDR, h/o ATT>2wks ->15 years	-Daily -Clinic
Zwarenstein(7)	2000	RCT	South Africa	156	-PTB (smear +) -Excluded MDR, h/o ATT>2wks ->15 years	-Daily -Clinic, Home (health worker or family member)
Tandon(8)	2002	RCT	India	400	-PTB (smear +) -Excluded HIV+ ->20 years	-Provided by patient attendant or school teacher
Akkslip(9)	1999	Prospective	Thailand	779	-PTB (smear +/-) -EPTB	-DOT, family member or village volunteer
Balasubramanian (10)	2000	Retrospec-tive	India	200	-New -PTB (smear +)	-DOT by health workers -Thrice weekly intensive phase -Once weekly continuation phase
Mathema(11)	2001	Prospective	Nepal	759	-PTB (smear +/-) -EPTB (4%) -Adults & children	-DOT by health workers, community, or family -Intensive phase only, daily
Ormerod(12)	2002	Mixed	UK	205	-PTB (smear +/-) -Adults	-Thrice weekly regimen
Tsuchida(13)	2003	Retrospec-tive	Japan	80	-PTB (smear +) -Excluded DR -New & retreatment -Adults	-Hospital until sputum conversion -Daily DOT by clinic nurse
Nirupa(14)	2005	Retrospec-tive	India	865	-PTB (smear +) -New -Adults & children	-DOT by CHWs, teachers, community volunteers
Daniel(15)	2006	Retrospec-tive	Nigeria	467	-PTB (Smear +/-) -EPTB ->15 years	-No info
Okanurak(16)	2007	Prospective	Thailand	931	-> 15 years	-Clinic, family, community DOT

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Abassi(17)	2007	Prospective	Iran	260	-PTB (smear +) -New	-Clinic DOT
Szczesniak(18)	2009	Retrospec-tive	Poland	100	-PTB (smear +/-) -New	-DOTS (not defined)
Cayla(19)	2009	Prospective	Spain	1490	-PTB (smear +/-) -EPTB ->18 years -No drug resistance -TB/HIV -New & retreatment	-Provided to those at higher risk of default
Zvavamwe(20)	2009	Prospective	Namibia	332	-Post-hospital discharge	-Community or clinic DOT -Continuation phase only
Xu(21)	2009	Prospective	China	670	-PTB (smear +) -Adults -New & retreatment	-DOT by family member, health worker, or village doctor
Abuaku(22)	2010	Retrospec-tive	China	68430	-PTB (smear +/-) -EPTB -Adults & children -New & retreatment	-DOT -Modified DOT (intensive phase only)
Ershova(23)	2014	Retrospec-tive	South Africa	741	-Adults & children -TB/HIV (60%) -PTB (smear +/-) -EPTB -New & retreatment	-Full DOT vs partial DOT
Weis(24)	1995	Retrospec-tive	USA	988	-Adults & children -MDR/TB -TB/HIV (data only available for the DOT group) -PTB -EPTB	-DOT offered at multiple locations, daily for 2-4 wks, then twice weekly for 2-4 wks.
Bashar(25)	2001	Retrospec-tive	USA	28	-Diabetics vs non-diabetics -PTB -TB/HIV -MDR-TB (100%) -Adults & 2 children	-No info
Olle-Goig(26)	2001	Retrospec-tive	Haiti	281	-PTB (smear +/-) -TB/HIV -New & retreatment -EPTB -Adults	-First 2 wks inpatient, rest at home with DOT by HCW -Meds + food delivered twice weekly
Pungrassami(27)	2002	Prospective	Thailand	411	-MDR-TB -TB/HIV -Adults & children	-HCW, community member, or family member DOT
Jasmer(28)	2004	Retrospec-tive	USA	372	-PTB (culture +) -Excluded EPTB -TB/HIV -Adults & children	-DOT + incentives/ enablers -Home, clinic, or workplace
Cayla(29)	2004	Prospective	Spain	1515	-PTB (smear +) -EPTB -TB/HIV -Adults & children	-Provided to those at higher risk of default

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Cavalcante(30)	2007	Retrospective	Brazil	1811	-PTB (smear +/-) -EPTB -TB/HIV -New & retreatment -Adults	-Home or local clinic DOT -CHWs
Radilla-Chavez(31)	2007	Retrospective	Mexico	629	-TB/HIV -New & retreatment -Adults & children -Excluded EPTB	-Daily clinic DOT (intensive phase), thrice weekly continuation phase
Anuwatnonthakate (32)	2008	Prospective	Thailand	8031	-PTB (smear +/-) -TB/HIV -Adults & children -New & retreatment	-HCW or family DOT -Intensive phase only
Kapella(33)	2009	Retrospective	Thailand	791	-Adults & children -TB/HIV -New & retreatment -PTB (smear +/-) -EPTB -MDR-TB	-HCW DOT during intensive phase
Vieira(34)	2011	Retrospective	Brazil	218	-PTB (smear +/-) -EPTB -New & retreatment -Excluded MDR and TB meningoencephalitis -Adults & children -TB/HIV	-Clinic DOT thrice weekly intensive phase, then twice weekly continuation phase
Ong'ang'o(35)	2014	Retrospective	Kenya	2778	-Adults & children -New & retreatment -PTB (smear +/-) -EPTB (24%) -?TB/HIV	-CHW DOT once/wk at home intensive phase, once/month during continuation phase
Mac(36)	1999	Retrospective	USA	50	-Vietnamese ->18 years -PTB (smear +/-) -Excluded TB/HIV, EPTB -MDR-TB	-DOT (no info provided)
Juan(37)	2006	Mixed	Spain	213	-PTB (smear +/-) -EPTB -TB/HIV (70%) -Drug resistant -New & retreatment -Adults & children	-Initial 2 wks inpatient -District based DOT
Chung(38)	2007	Retrospective	Taiwan	399	-PTB (smear +) -Excluded EPTB and MDR/TB -New & retreatment	-Clinic DOT
Yen(39)	2013	Retrospective	Taiwan	3487	->18 years -PTB (smear +/-) -MDR-TB -New & retreatment	-Daily DOT at home or workplace
Chien(40)	2013	Retrospective	Taiwan	2160	-PTB (smear +/-) -M/XDR-TB -Excluded TB/HIV	-DOTS & DOTS-PLUS
Alvarez-Uria(41)	2014	Retrospective	India	1460	-TB/HIV (100%) -PTB (smear +/-) -EPTB except TB meningitis -New & retreatment -Adults	-Inpatient initially -Thrice weekly DOT at hospital

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Das(42)	2014	Retrospective	India	89	-New -PTB (smear +/-) -EPTB -TB/HIV (100%) -Adults	-Daily DOT by CHW at home
Alwood(43)	1994	Retrospective	USA	78	-TB/HIV (100%) -PTB (smear +/-) -Adults -INH and streptomycin resistant (n=1)	-Daily DOT for 9 months

Table 5. Characteristics of included studies: DOT offered by different providers

Comparison: DOT provided by family member, community member, or lay health worker versus DOT provided by healthcare providers

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Mathema(11)	2001	Prospective	Nepal	759	-PTB (smear +/-) -EPTB	-DOT by health workers, community, or family -Intensive phase only, daily
Colvin(44)	2003	Retrospective	South Africa	1816	-PTB (smear +/-) -New & retreatment -EPTB	-DOT by health clinic, CHW, LHW, or traditional healer -First few weeks inpatient
Singh(45)	2004	Retrospective	India	617	-PTB (smear +) -New	-DOT by CHW (gov fscilities) or community volunteer (lay ppl)
Nirupa(14)	2005	Retrospective	India	865	-PTB (smear +) -New	-DOT by CHWs, teachers, community volunteers
Anuwatnonthakate(32)	2008	Prospective	Thailand	8031	-PTB (smear +/-) -TB/HIV -Adults & children -New & retreatment	-HCW or family DOT -Intensive phase only
Kungkaew(46)	2008	Prospective	Thailand	506	-New -PTB (smear +/-) -Adults & children -TB/HIV	-DOT by family member or HCW
Xu(21)	2009	Prospective	China	670	-PTB (smear +)	-DOT by family member, health worker, or village doctor
Tripathy(47)	2013	Retrospective	India	1769	-New -PTB (smear +) -Adults & children	-DOT by community volunteers (CHWs, physicians, alternative medicine doctors, shopkeepers, teachers) vs institutional providers (TB health visitors, staff nurses, auxiliary nurse midlves)
Wilkinson(48)	1997	Retrospective	South Africa	1890	-No info -High HIV prevalent setting	-Choice of HW, CHW, or volunteer lay people. No distinction provided between HW & CHW.

Table 6. Characteristics of included studies: DOT offered at different locations

Comparison: DOT offered at home or in the community versus clinic-based DOT

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Lwilla(49)	2003	RCT	Tanzania	522	-New -PTB (smear +)	-Community based vs institution based DOT
Wandwa-lo(50)	2004	RCT	Tanzania	587	-Adults & children -New -PTB (smear +/-) -EPTB	-Community (family or former TB patient) vs health clinic DOT
Wright(51)	2004	RCT	Swaziland	1353	-Adults & children -PTB (smear +/-) -EPTB -New & retreatment	-DOT by CHW (not at home) vs family member
Newell(52)	2006	RCT	Nepal	907	-PTB (smear +) ->15 years old -New	-Community based DOT vs family member DOT
Akkslip(9)	1999	Prospective	Thailand	779	-PTB (smear +)	DOT, family member or village volunteer
Banerjee(53)	2000	Prospective	Malawi	600	-PTB (smear +/-) -EPTB -New	-DOT at home vs health center vs hospital
Becx-Ble-umink(54)	2001	Prospective	Indonesia	2353	-PTB (smear +) -New	-DOT in community vs clinic -6 times/week DOT by fam member during intensive phase, 5 times/fortnight during continuation phase
Caval-cante(30)	2007	Retrospec-tive	Brazil	1811	-PTB (smear +/-) -TB/HIV -EPTB	-DOT in community (home or church by CHW) vs clinic
Dobler(55)	2015	Retrospec-tive	Mongolia	2181	-PTB (smear +) -> 15 years old	-Daily DOT at home by volunteers -DOT at cafeterias -Clinic DOT
Dudley(56)	2003	Prospective	South Africa	2873	-PTB -EPTB -> 15 years -New & retreatment	-Daily DOT at clinic or community (at CHW's home)
Maciel(57)	2010	Prospective	Brazil	171	-New -TB/HIV -PTB (smear +/-) -EPTB	-Daily DOT by a domiciliary supervisor at home or by CHW at clinic
Miti(58)	2003	Prospective	Zambia	168	-> 15 years -TB/HIV only -New -PTB (smear +)	-Daily DOT delivered at home + AIDS home care program -Daily DOT at clinic
Moalosi(59)	2003	Retrospec-tive	Botswana	633	-TB/HIV -PTB (smear +/-)	-Daily DOT by family at home -Clinic DOT
Niazi(60)	2003	Prospective	Iraq	172	-New -PTB (smear +)	-Daily home vs clinic DOT
Wares(61)	2001	Prospective	Nepal	327	-New & retreatment -PTB (smear +/-) -EPTB	-Daily DOT via health post, clinic, or hostel

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Arora(62)	2003	Prospective	India	2573	-Adults & children -PTB (smear +/-) -EPTB	-DOT by community member at patient's or member's house vs center based DOT
Kironde(63)	2002	Prospective	South Africa	505	-New & retreatment -> 15 years -PTB (smear +)	-Daily clinic or community-based DOT
Van den Boogaard (64)	2009	Retrospec-tive	Tanzania	2769	-Adults & children -New & retreatment -PTB (smear +/-) -EPTB -TB/HIV	-Daily community vs clinic DOT
Manders(65)	2001	Prospective	Malawi	75	-> 18 years -PTB (smear +/-) -EPTB	-Guardian-based (family) DOT vs health-center based vs inpatient
Xu(21)	2009	Prospective	China	670	-PTB (smear +)	-DOT by family member, health worker, or village doctor
Akhtar(66)	2011	Prospective	Pakistan	582	-PTB (smear +) ->15 years -New & retreatment -Excluded drug resistant	-Clinic DOT 5x/wk intensive phase, then 3x/wk continuation phase -Family DOT

Table 7. Characteristics of included studies: Patient education & counseling

Comparison: patient education and counseling in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Clark(67)	2007	RCT	Turkey	114	-New -MDR -Adult	-Oral and written education via clinical pharmacist before d/c -intensive phase inpatient
Janmeja(68)	2004	RCT	India	200	-New -PTB (smear +) -EPTB -Excluded MDR	-Behavioral/psychotherapy at 8 drug collection visits
Liefooghe (69)	1999	RCT	Pakistan	1019	-New -Adults -PTB (smear +/-) -EPTB	-Counseling provided to patients each time they presented for follow up appointment. Also involved social network and family members.
Baral(70)	2014	RCT	Nepal	156	-MDR (100%) -Adults	-Counseling -Counseling plus financial support -None
Dick(71)	1997	Prospec-tive	South Africa	120	-PTB (smear +/-) -> 15 years -Excluded EPTB, MDR -New & retreatment	Oral and written education via clinical pharmacist before d/c

Table 8. Characteristics of included studies: Incentives & enablers

Comparison: Incentives and enablers in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Martins(72)	2009	RCT	East Timor	270	-New -PTB (smear +/-) -Adults	-Daily mid-day food with DOT.
Lutge(73)	2013	RCT	KwaZulu-Natal, South Africa	4,091	New drug-sensitive pulmonary TB, high HIV prevalence	Monthly food voucher on treatment collection
Jahnavi(74)	2010	RCT	India	100	-New ->18 years -PTB (smear +/-) -EPTB -Wasting (BMI <20) -Excluded HIV	-Food supplements and dietary plan -General advice to increase food intake
Sudarsanam (75)	2011	RCT	India	97	->12 years -TB/HIV -New -PTB (smear +/-) -EPTB	-Food supplements & multivitamin vs none
Dobler(55)	2015	Retrospec-tive	Mongolia	2181	-PTB (smear +) -> 15 years old	-Daily DOT at home by volunteers -DOT at cafeterias -Clinic DOT
N-Yanai(76)	2013	Retrospec-tive	Thailand	759	-TB/HIV -Adults & children	-Financial support -Financial support + home visits -None
Zou(77)	2013	Prospective	China	787	-New	-Living subsidy + transport incentive, low SES -Living subsidy + transport incentive, all patients
Lu(78)	2013	Prospective	China	2006	->15 years old -New -PTB	-Transportation subsidies + living allowance
Wei(79)	2012	Prospective	China	183	-PTB (smear +/-) -No EPTB	-Transportation for all -Living allowance for low income patients
Cantalice(80)	2009	Retrospec-tive	Brazil	142	-TB/HIV -PTB (smear +/-) -> 15 years	-Monthly baskets of food
Sripad(81)	2014	Mixed	Ecuador	191	-DR-TB only (including MDR) -TB/HIV -Adults	-Financial bonus after each month of adherence up to 24 months
Tsai(82)	2010	Retrospec-tive	Taiwan	17061	-No info	-Pay for performance
Bock(83)	2001	Retrospec-tive	USA	107	-History of non-adherence -Adults & children -TB/HIV -INH mono-resistant	-Financial incentive

Table 9. Characteristics of included studies: Reminders & tracers

Comparison: Reminders and tracers in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Iribarren(84)	2013	RCT	Argentina	37	-New -Excluded DR or HIV -> 18 years -PTB (smear +)	Patients text daily after taking meds and received reminder texts.
Krishnaswami (85)	1981	RCT	South India	150	-PTB (smear -) -INH mono-resistant (n=3)	SAT, monthly collection. Reminder health visit on 4th day of not picking up meds.
Kunawarak (86)	2011	RCT	Thailand	61	-New -PTB (smear +) ->15 years -TB/HIV -MDR/B (62%) -Excluded XDR/TB	Family-DOT + daily phone call reminder to take meds
Mohan(87)	2003	RCT	Iraq	480	-New -PTB (smear +)	Home visits to patients late for med pick up
Parama-sivan(88)	1993	RCT	India	200	-New -PTB (smear +)	Sent reminder letter to patients late for pick up.
Tanke(89)	1994	Quasi-RCT	USA	2008	-Adults & children -Anyone registered for TB treatment	Automated message reminder before first treatment appointment
Moulding(90)	2002	RCT	Haiti	2002	-> 15 years old -New -PTB (smear +)	-Med monitors with feedback -Med monitors w/o feedback -None
Bronner(91)	2012	Retrospec-tive	South Africa	405673	-PTB (smear +) -New & retreatment -TB/HIV -MDR/TB	-CHWs traced patients who interrupted treatment
Snidal(92)	2015	Prospective	Uganda	142	-> 18 years -PTB (smear +/-) -New & retreatment -TB/HIV -EPTB	-Computer system to ensure CHWs see all patients and keep visit logs
Thomson(93)	2011	Retrospec-tive	Kenya	1369	-TB/HIV (100%) -PTB -Adults & children	-Social worker traced people who missed scheduled clinic appointments
Al-Hajjaj(94)	2000	Retrospec-tive	Saudi Arabia	628	-New & retreatment -PTB -EPTB	-Phone call, then home visit for missed appointments

Table 10. Characteristics of included studies: Mixed interventions

Comparison: Combination package of adherence interventions versus curative therapy alone

Author	Year	Study design	Country	# of patients	Population	Intervention
Khortwong (95)	2013	Qua-si-RCT	Thailand	100	-Undocumented migrant -New TB cases ->70% smear positive	-DOT + patient education and monthly home visits vs DOT alone
Morisky(96)	1990	RCT	USA	88	-New -> 18 years	-Health education and $10 voucher at each monthly visit and $40 if no missed treatment vs monthly clinic follow up alone
Baral(70)	2014	RCT	Nepal	156	-MDR-TB -Adults	-Counseling + financial incentive ($28/mo) q2-3 wks vs none
Drabo(97)	2009	RCT	Burkina Faso	333	-PTB (smear +)	-Food + home visit +psychosocial support vs SAT
Thiam(98)	2007	RCT	Senegal	1522	-Adults -PTB (smear +) -New	-Counseling, choice of DOT supporter, and reinforcement activities vs clinic based DOT
Hsieh(99)	2008	RCT	Taiwan	96	-> 18 years -Excluded EPTB	-DOT in intensive phase, home visit continuation phase and health education -Control: initial ward care followed by monthly clinic follow up
Atkins(100)	2011	Prospec-tive	South Africa	5833	-> 18 years old -PTB (smear +/-) -EPTB -New & retreatment -TB/HIV (>50%) -Excluded M/XDR-TB	-Enhanced DOT with staff training, treatment supporters, and counseling vs standard DOT
Farmer(101)	1991	Prospec-tive	Haiti	60	-PTB -EPTB -TB/HIV	-Daily home visits, monthly reminder visits, food, financial incentive vs SAT
Jasmer (102)	2004	Retro-spective	USA	372	-PTB (culture +) -Excluded EPTB -TB/HIV -Adults & children	-DOT + incentives/enablers at home, clinic, or workplace vs SAT
Soares(103)	2013	Prospec-tive	Brazil	2623	-Adults & children -PTB (smear +/-) -EPTB -New & retreatment -TB/HIV	-DOT + psychosocial intervention + counseling and education + food incentives vs SAT
Yassin(104)	2013	Prospec-tive	Ethiopia	5090	-PTB (smear +/-) -EPTB -Adults & children	-Hospital capacity strengthening, staff education, mobile phone for HCWs, home-based DOT vs clinic/community based DOT
Chan(105)	2013	Retro-spective	Taiwan	390	-MDR-TB (100%) -PTB -New & retreatment -Adults	-Home DOT + incentives/ enablers, optional inpatient component vs hospital and then clinic DOT.
Garden(106)	2012	Prospec-tive	Russia	518	-Adults -New & retreatment (77%) -PTB (smear +/-)	-DOT + food incentive, psychosocial support vs SAT
David-son(107)	1998	Retro-spective	USA	319	-Adults & children -TB/HIV -EPTB -PTB -MDR-TB	-Clinic or home DOT, 5 x/wk, intensive phase, included food coupons, bus tokens vs SAT

Table 11. Characteristics of included studies: Psychosocial interventions.

Comparison: Psychosocial interventions in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Shin(108)	2013	RCT	Russia	196	-> 18 years old -TB/HIV -New & retreatment	Brief counseling intervention for ETOH cessation
Alvarez(109)	2003	RCT	Mexico	87	->15 years old -PTB	Self-help groups
Demissie (110)	2003	Prospective	Ethiopia	128	-Adults & children -PTB (smear +/-)	TB clubs as a support network

Table 12. Characteristics of included studies: Staff education.

Comparison: Staff education in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Lewin(111)	2005	RCT	South Africa	1177	->14 years -PTB (smear +) -New -Excluded MDR-TB	-Adherence education for staff
Ritchie(112)	2015	RCT	Malawi	178	-New -Adults & children -PTB -EPTB -TB/HIV (45%)	-Peer training of LHW -Laminated chart/visual reminder to initiate adherence discussions
Datiko(113)	2009	RCT	Ethiopia	318	-New -PTB (smear +) -Adults & children	-Education for HCW and lab techs
Safdar(114)	2011	Prospective	Pakistan	194	-Children (100%) -PTB (smear +/-) -EPTB	-Staff educational tool and desktop aid for decision making and red flags

Table 13. Characteristics of included studies: Mobile health interventions

Comparison: Use of mobile health interventions in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Iribarren(84)	2013	RCT	Argentina	37	-New -> 18 years -PTB (smear +)	Patients text daily after taking meds and received reminder texts.
Kunawarak (86)	2011	RCT	Thailand	61	-New -PTB (smear +)	Family-DOT + daily phone call reminder to take meds
Liu(115)	2015	RCT	China	4173	-New -PTB (smear +/-) -> 18 years	-SMS -Med monitor -Both -Control
Chuck(116)	2016	Prospective	USA	390	->18 years -PTB (smear +/-) -Included drug resistant -Included TB-HIV	-VDOT vs in-person DOT
Broomhead (117)	2012	Case-control	South Africa	120	-PTB (smear +) -New	-Wireless pill box with alarm system sends SMS -DOTS
Wade(118)	2012	Retrospective	Australia	128	-Anyone receiving DOT	-home videophone DOT vs in-person DOT

Table 14.1 Summary of meta-analysis findings of all included adherence interventions

	SAT vs DOT (all)	SAT vs DOT (TB/HIV)	DOT provider-family/community vs HCW	DOT provider-lay provider vs HCW	DOT location-home/community vs clinic	Patient education vs curative therapy alone	Incentives/enablers vs curative therapy alone	Reminders/tracers vs curative therapy alone
Mortality-cohorts	No effect[1]	--[2]	No effect	No effect	No effect	--	↓[3]	No effect
Mortality-RCTs	No effect	--	--	--	No effect	No effect	No effect	No effect
Success-cohorts	↓	↓	No effect	No effect	No effect	--	↑[4]	No effect
Success-RCTs	↓	--	--	--	↑	No effect	↑	↑
Completion-cohorts	No effect	↓	No effect	--	No effect	--	No effect	↑
Completion-RCTs	No effect	--	--	--	↑	↑	↑	No effect
Cure-cohorts	↓	↓	No effect	No effect	No effect	--	↑	No effect
Cure- RCTs	No effect	--	--	--	No effect	↑	No effect	No effect
Failure-cohorts	No effect	↑	No effect	No effect	No effect	--	No effect	No effect
Failure-RCTs	No effect	--	--	--	No effect	No effect	↓	--
Loss to follow up-cohorts	↑	--	↑	No effect	↓	--	No effect	No effect
Loss to follow up-RCTs	↑	--	--	--	No effect	No effect	↓	No effect
Relapse-cohorts	No effect	No effect	--	--	--	--	--	--
Relapse-RCTs	No effect	--	--	--	--	--	--	--
Adherence-Cohorts	↓	--	↓	--	No effect	↑	--	--
Adherence-RCTs	No effect	--	--	--	--	↑	--	↑
Smear conversion-cohorts	No effect	--	--	--	↑	--	--	--
Smear conversion-RCTs	↓	--	--	--	No effect	--	↑	↑
Acquisition of drug resistance-cohorts	↑	--	--	--	--	--	--	↓
Acquisition of drug resistance-RCTs	No effect	--	--	--	--	--	No effect	--
Unfavorable outcome-cohorts	--	--	--	--	↓	--	--	--

1 No effect: There is no statistically significant difference in the rate of outcome occurrence between the intervention and control groups.

2 -- : No outcome data available for the comparison.

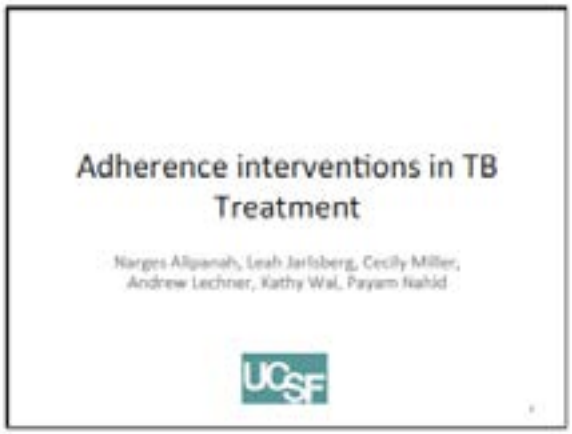
3 ↓: Overall estimate of effect shows a significantly lower rate of outcome occurrence in the intervention group compared to the control group.

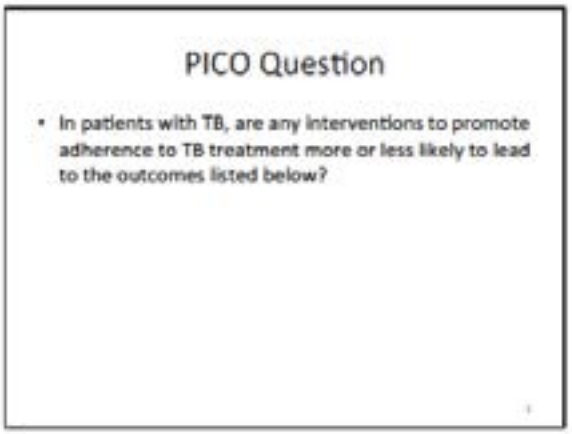
4 ↑: Overall estimate of effect shows a significantly higher rate of outcome occurrence in the intervention group compared to the control group.

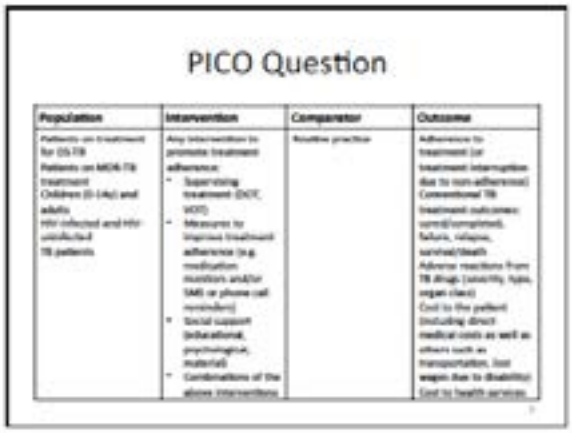
Table 14.2 Summary of meta-analysis findings of all included adherence interventions

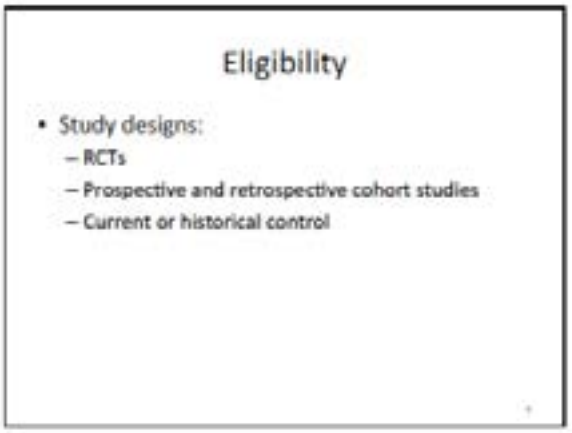
	Mixed interventions/ Enhanced DOT vs SAT	Mixed interventions/ Enhanced DOT vs DOT	Mixed case management/ Mixed interventions vs SAT	Psychosocial interventions vs curative therapy alone	Staff education vs curative therapy alone	Phone reminders vs no reminders	VOT vs in-person DOT
Mortality-cohorts	No effect	No effect	--	No effect	No effect	No effect	No effect
Mortality-RCTs	--	↓	No effect	--	No effect	--	--
Success-cohorts	↑	↑	--	--	↑	--	--
Success-RCTs	↑	↑	--	No effect	No effect	No effect	--
Completion-cohorts	↑	No effect	--	↑	--	No effect	No effect
Completion-RCTs	↑	No effect	--	↑	No effect	↓	--
Cure-cohorts	↑	No effect	--	--	--	↑	--
Cure-RCTs	↑	↑	--	No effect	No effect	↑	--
Failure-cohorts	No effect	No effect	--	No effect	No effect	--	--
Failure-RCTs	--	No effect	No effect	↓	No effect	↓	--
Loss to follow up-cohorts	No effect	No effect	--	↓	↓	↓	--
Loss to follow up-RCTs	--	↓	↓	No effect	No effect	--	--
Relapse-cohorts	No effect	--	--	--	--	--	--
Relapse-RCTs	--	--	--	--	--	--	--
Adherence-Cohorts	--	--	--	--	--	--	--
Adherence-RCTs	--	No effect	No effect	--	--	--	--
Smear conversion-cohorts	--	--	--	--	--	↑	--
Smear conversion-RCTs	↑	--	--	--	--	No effect	--
Acquisition of drug resistance-cohorts	No effect	--	--	--	--	--	--
Acquisition of drug resistance-RCTs	--	--	--	--	--	--	--
Unfavorable outcome-cohorts	--	--	--	--	--	↓	--
Unfavorable outcome-RCTs	--	--	--	--	--	--	--
Poor adherence-cohorts	--	--	--	--	--	↓ (phone reminder and med monitor combined)	--

Slidesets


Adherence interventions in TB Treatment
Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid
UCSF


PICO Question
• In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?


PICO Question
Population
Intervention
Comparator
Outcome
Any intervention to promote treatment adherence:
Routine practice


Eligibility
• Study designs:
– RCTs
– Prospective and retrospective cohort studies
– Current or historical control


Outcomes of interest
CRITICAL
IMPORTANT
Adherence
Adverse reactions from TB drugs
Failure
Relapse
Survival (or death)
Loss to follow up


Search methods
• Medline database
• Search through 2/6/16
• Title and abstract review by one reviewer
• Full text review by multiple reviewers

Analysis

- Data abstraction by one reviewer
- Cochrane risk of bias tool for RCTs
- Newcastle-Ottawa Scale for cohort studies
- Data synthesis in Rev-Man
  - Pool estimates if ≥ 2 studies
  - Random effects meta-analysis

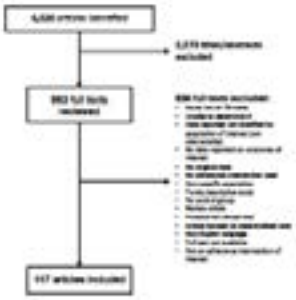
Newcastle Ottawa Scale

- 9 point scale:
  - Selection (4)
    - Representativeness of exposed cohort
    - Selection of non-exposed cohort
    - Ascertainment of exposure
    - Demonstration that outcome of interest was not present at start of study
  - Comparability (2)
    - Comparability of cohorts on the basis of design or analysis
  - Outcome (3)
    - Assessment of outcome
    - Length of follow up long enough to ensure outcome occurrence
    - Adequacy of follow up of cohorts

Adherence interventions

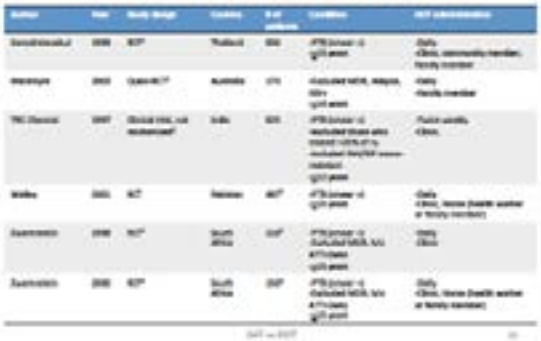
- SAT vs DOT
- DOT provider
- DOT location
- Reminders & tracers
- Incentives & enablers
- Patient education & counseling
- Mixed case management
- Mobile health (SMS, VOT)
- Psychosocial
- Staff education

PRISMA Summary

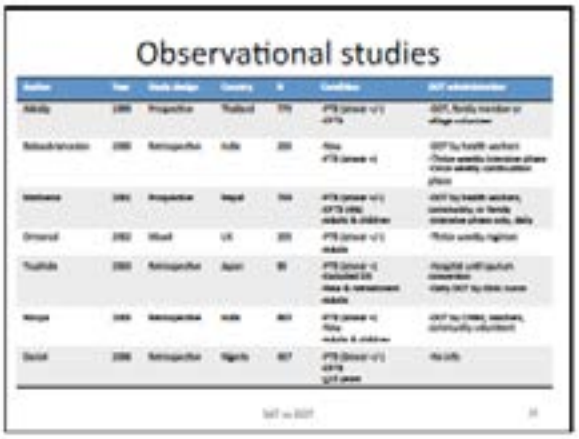


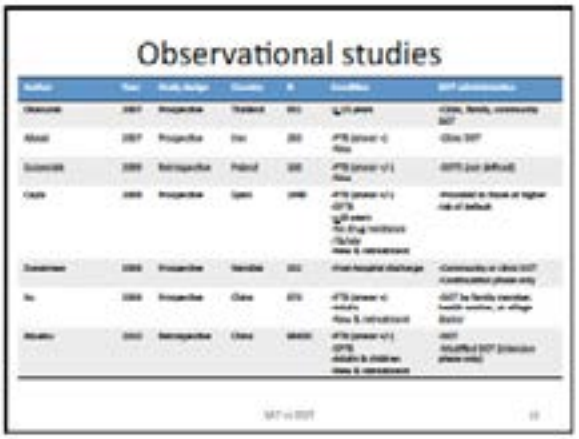
SAT vs DOT

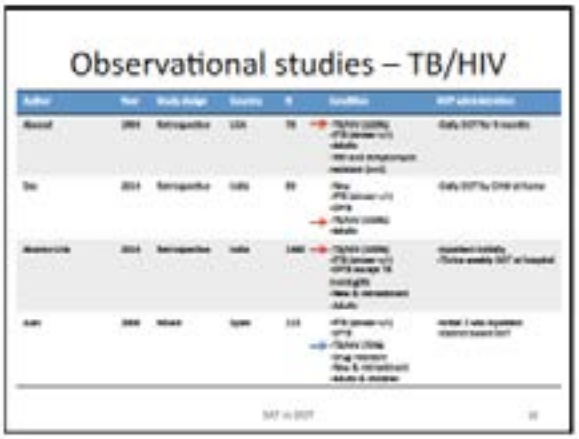
Randomized controlled trials

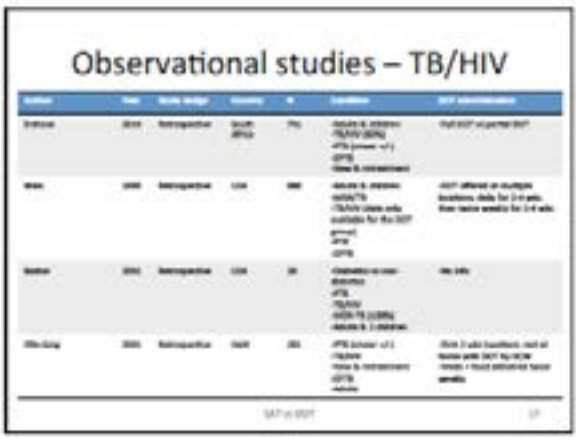


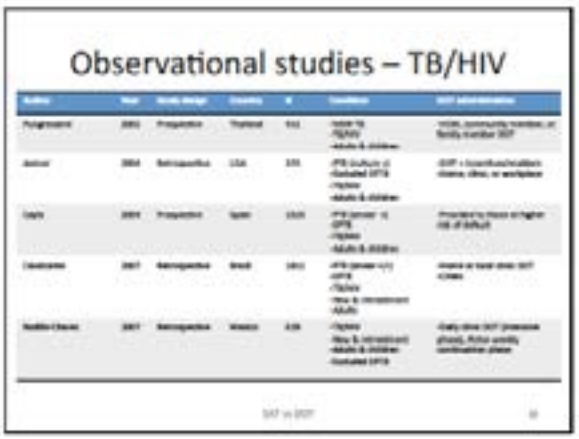

Randomized controlled trials


Observational studies


Observational studies

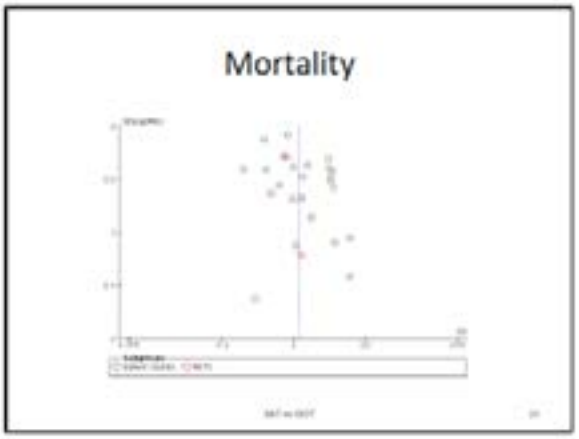

Observational studies – TB/HIV

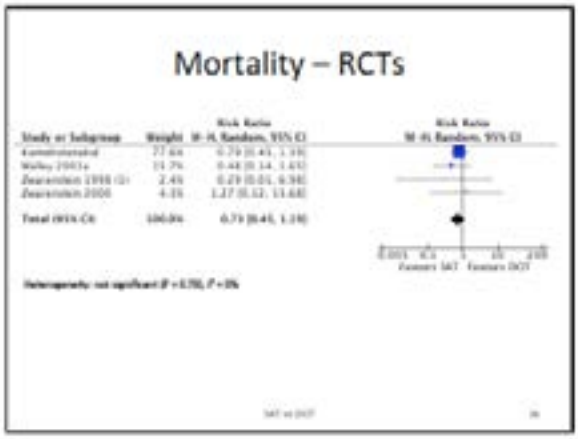

Observational studies – TB/HIV

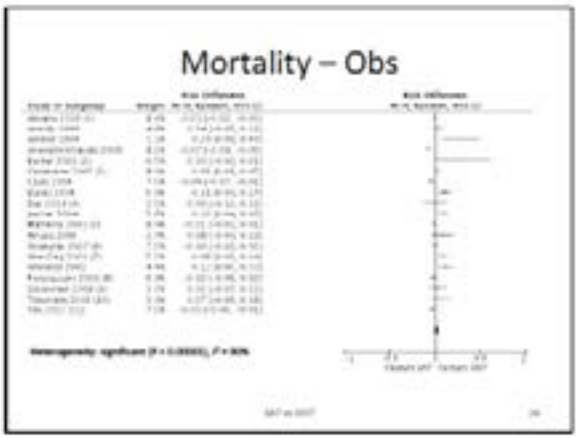

Observational studies – TB/HIV

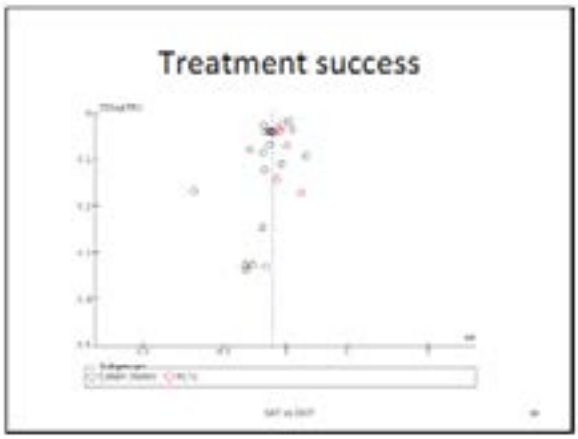

Quality – Obs


Quality – Obs


Mortality


Mortality – RCTs

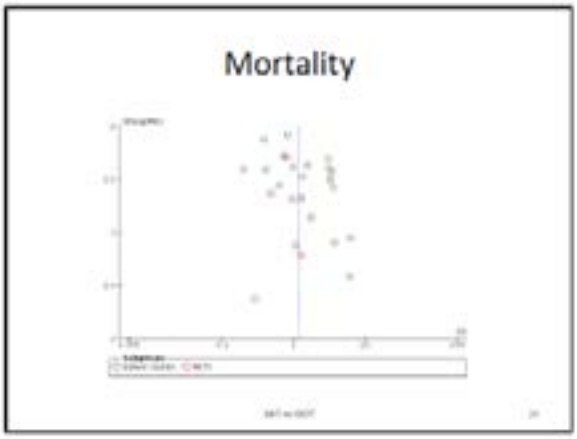

Mortality – Obs


Treatment success

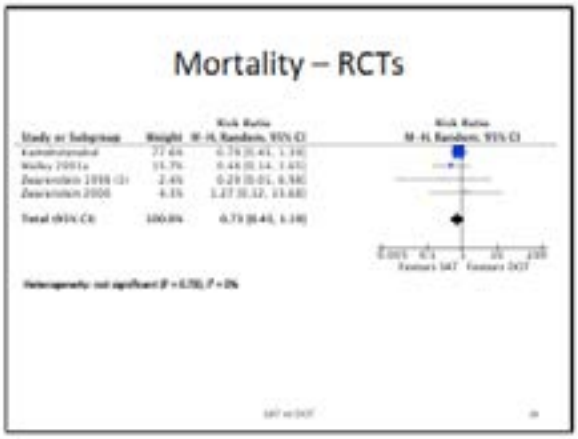
Quality – Obs

Quality – Obs

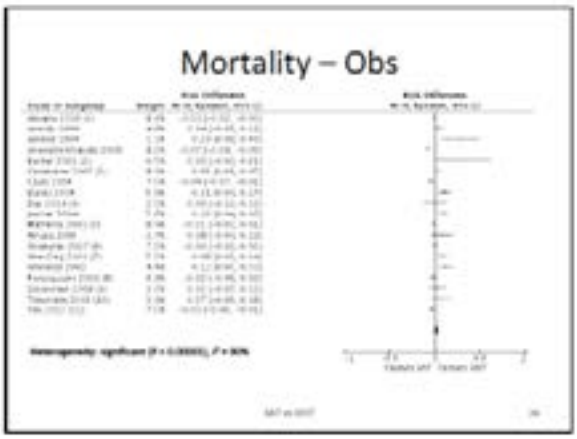
Mortality



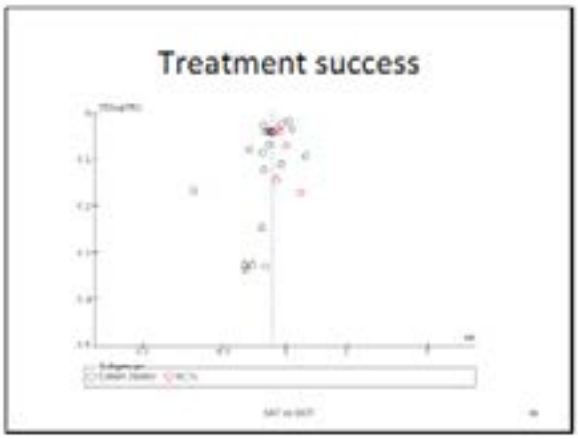
Mortality – RCTs



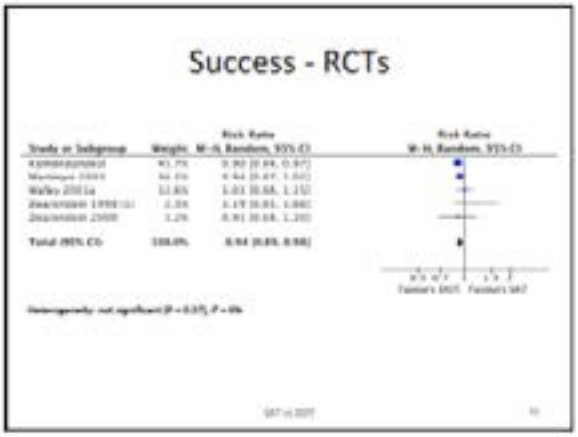
Mortality – Obs



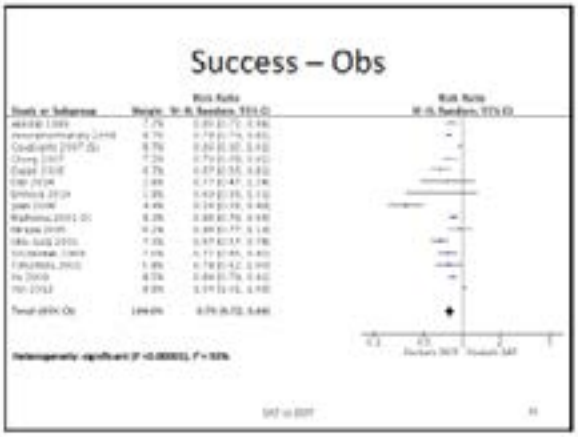
Treatment success



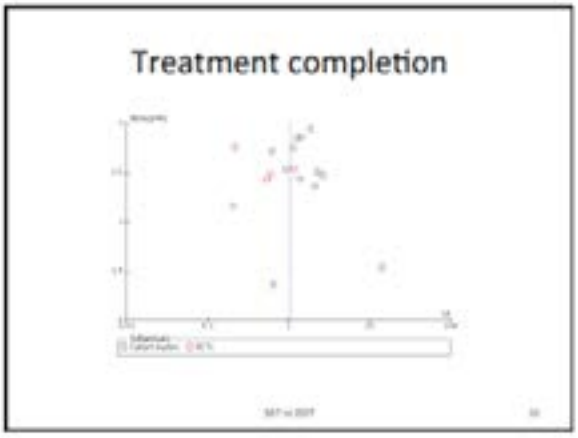
Success - RCTs



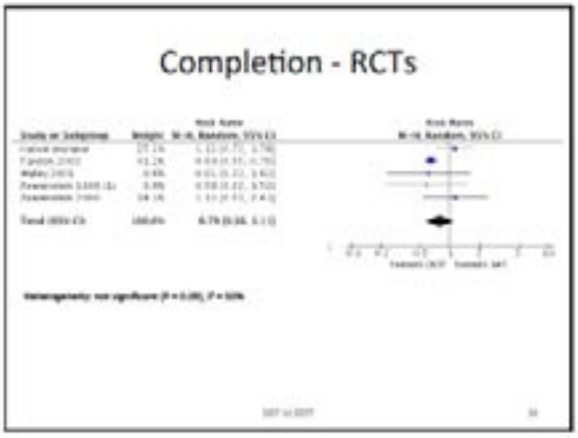
Success – Obs



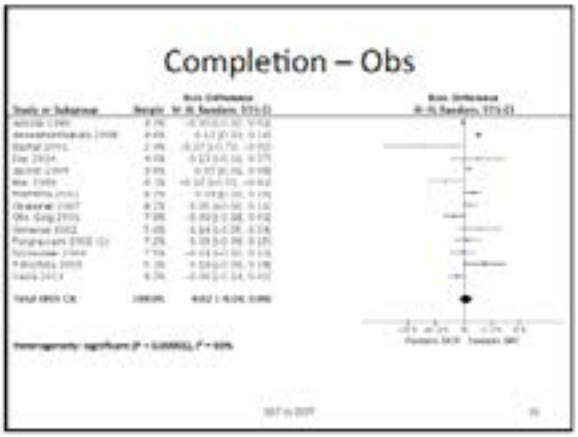
Treatment completion



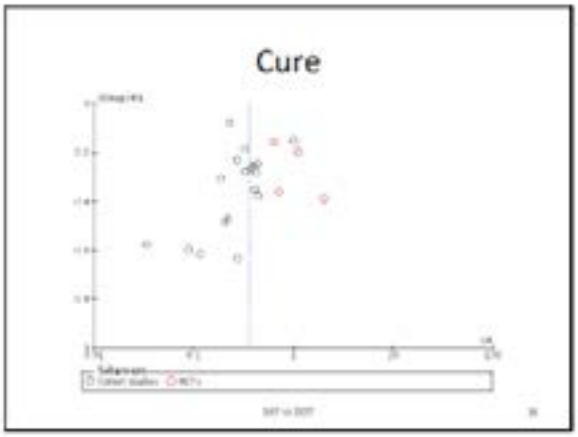
Completion - RCTs



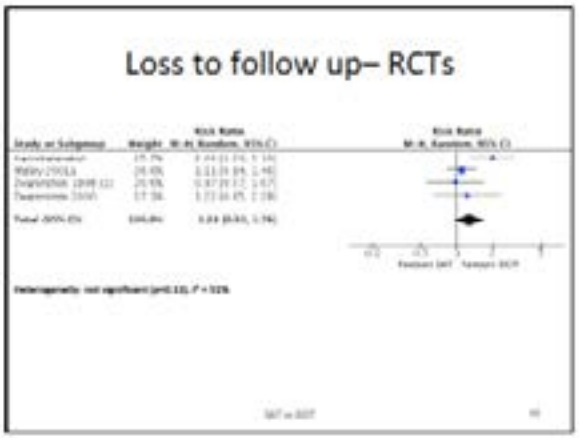
Completion – Obs



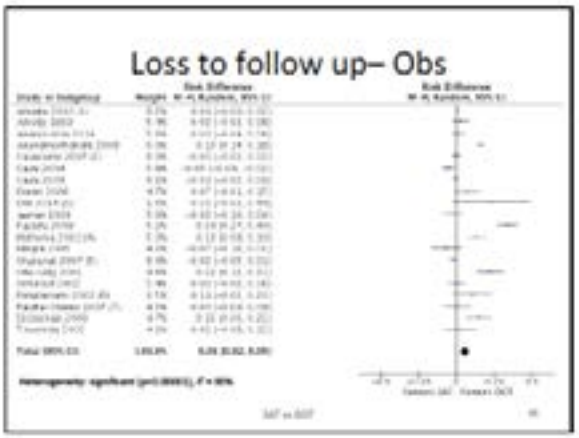
Cure



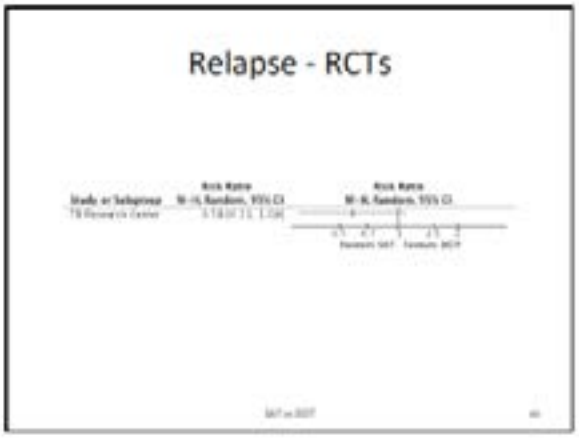
Loss to follow up– RCTs



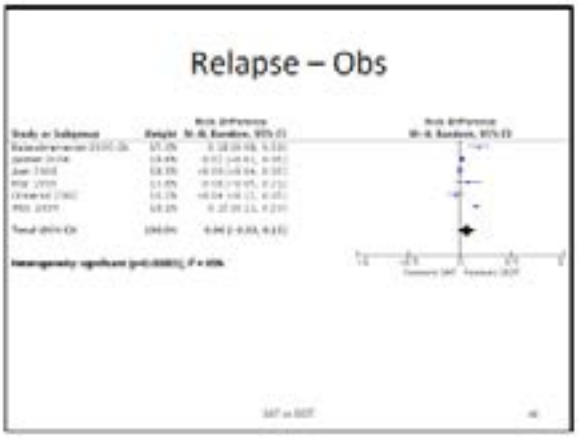
Loss to follow up– Obs



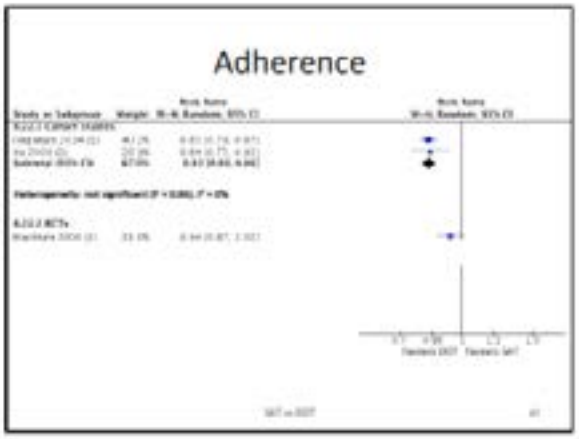
Relapse - RCTs



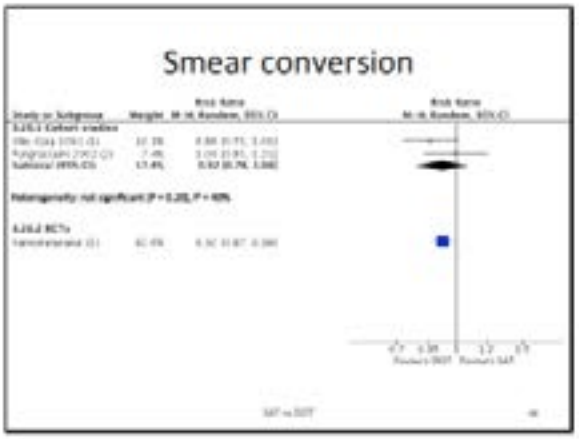
Relapse – Obs



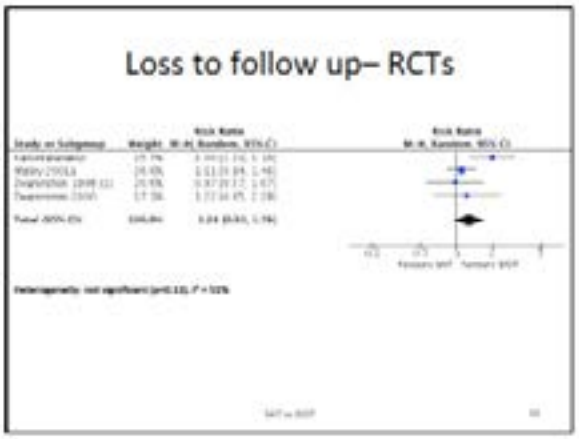
Adherence



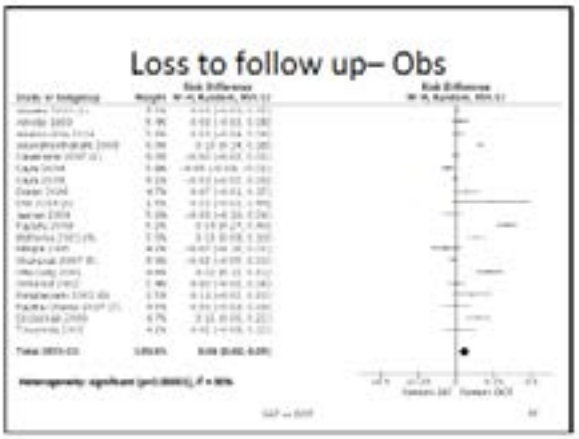
Smear conversion



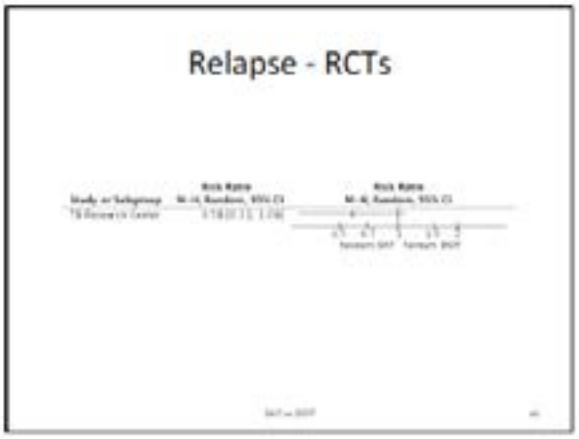
Loss to follow up– RCTs



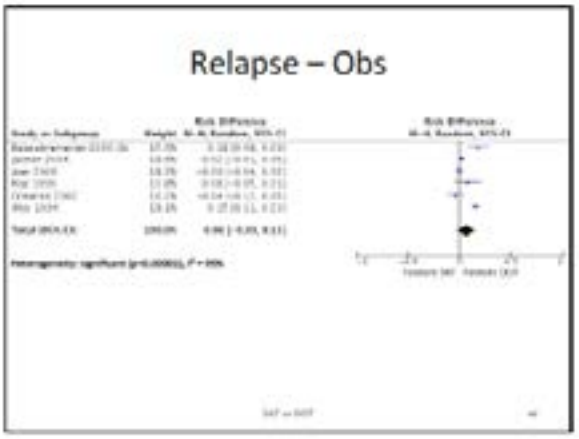
Loss to follow up– Obs



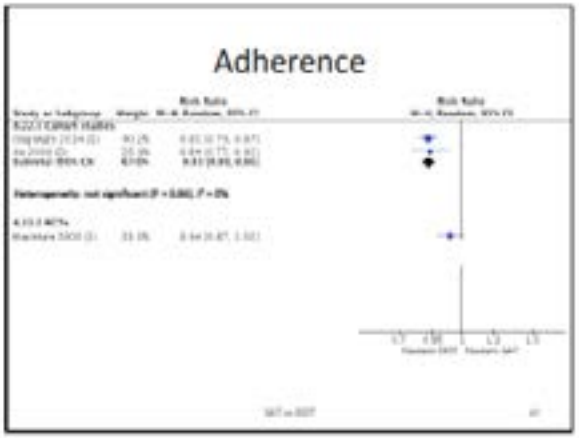
Relapse - RCTs



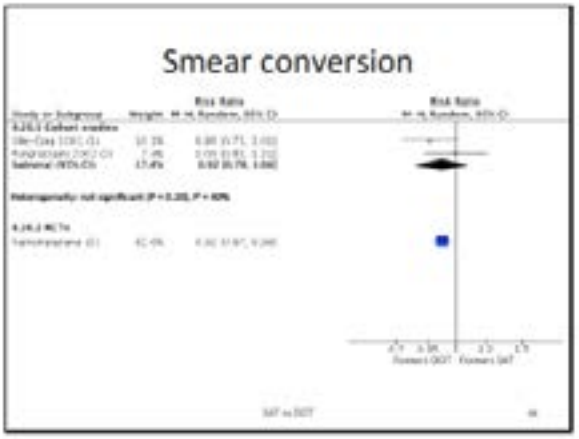
Relapse – Obs



Adherence



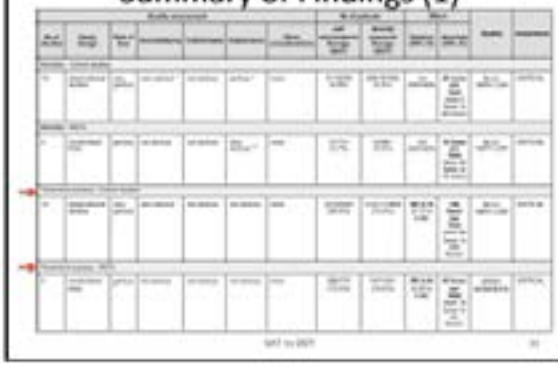
Smear conversion



Time to smear conversion

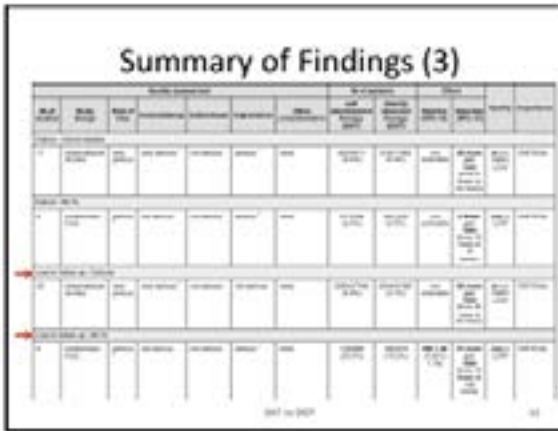
Acquisition of drug resistance

Summary of Findings (1)

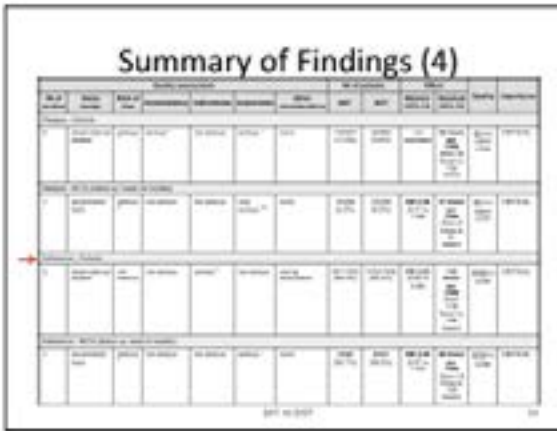


Summary of Findings (2)

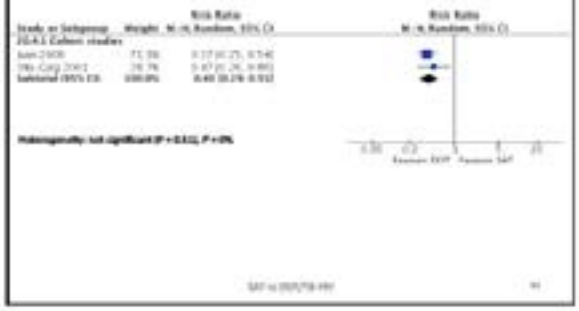
Summary of Findings (3)



Summary of Findings (4)



Cure



Failure

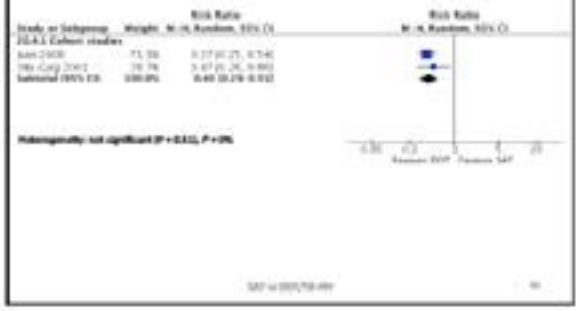
Loss to follow up

Relapse

Summary of Findings (1)

Summary of Findings (2)

Cure



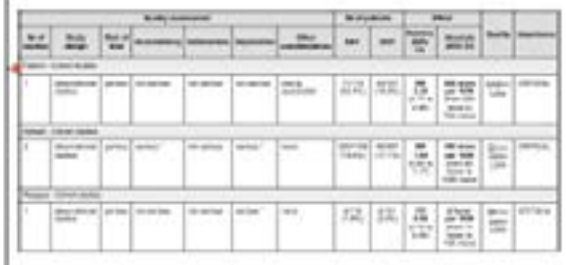
Failure

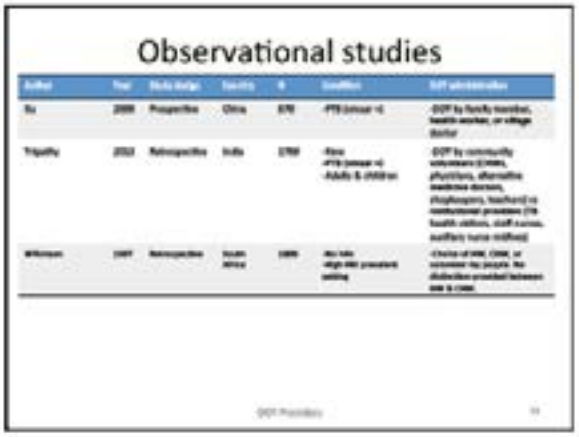
Loss to follow up

Relapse

Summary of Findings (1)

Summary of Findings (2)



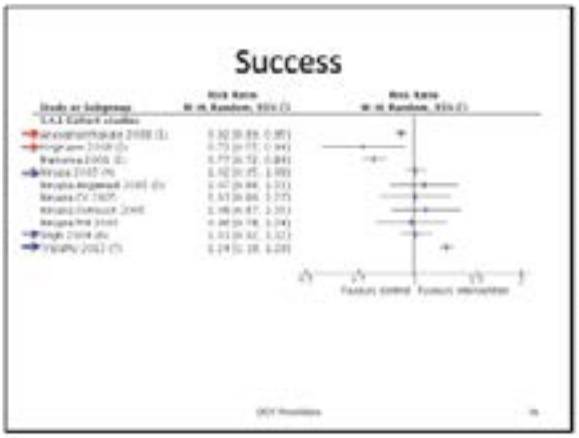

Observational studies

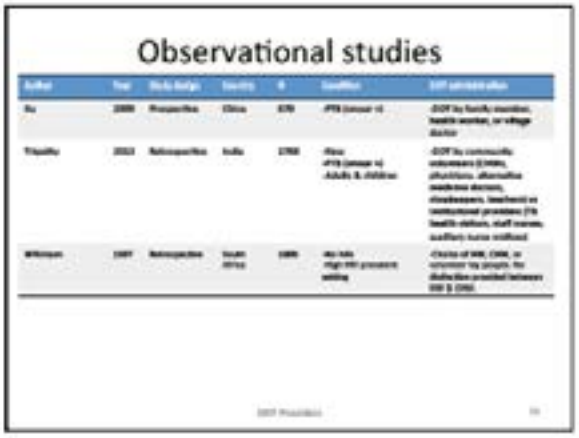

Quality – Obs


Mortality


Mortality

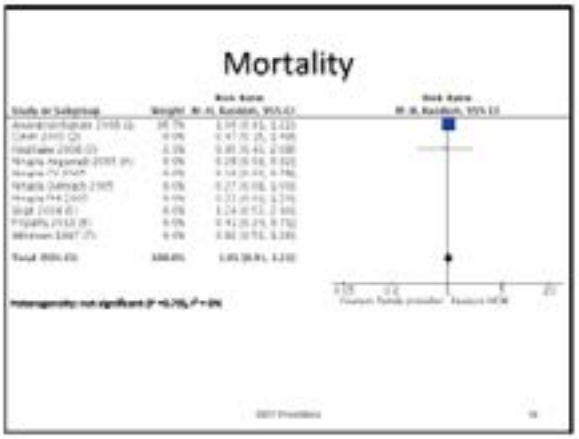

Mortality


Success

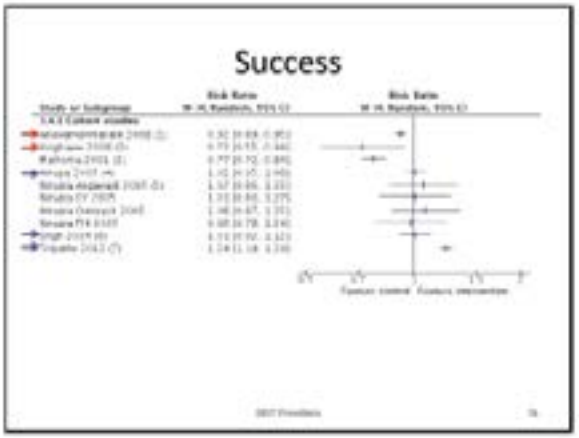

Observational studies


Quality – Obs


Mortality


Mortality


Mortality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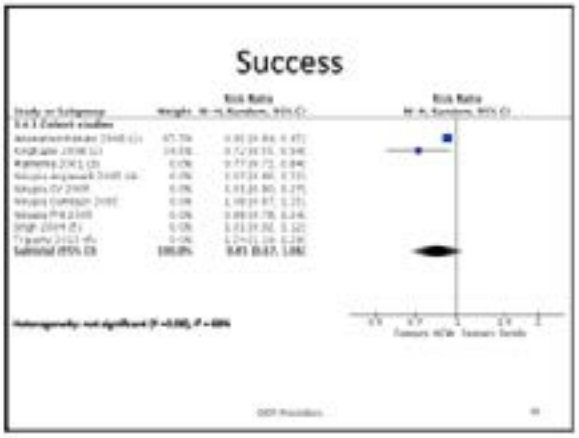
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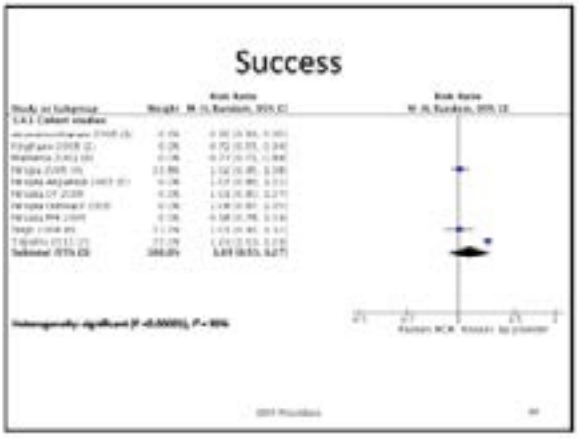
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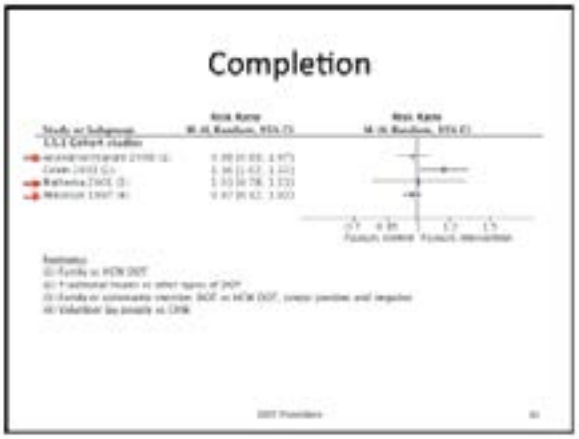
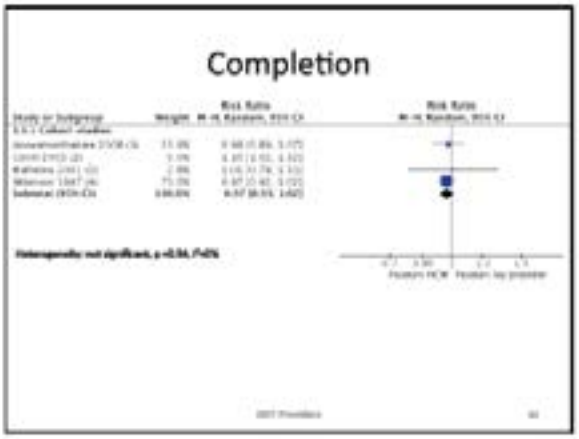
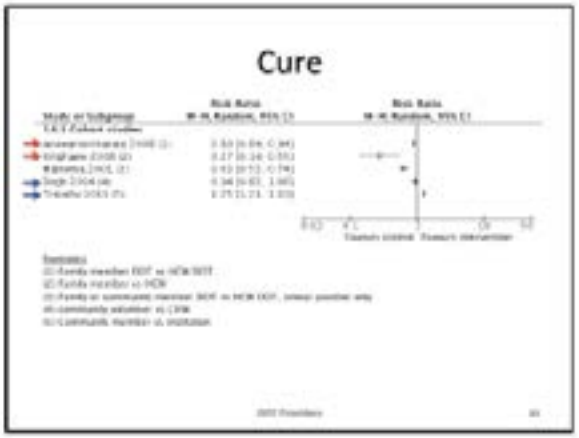
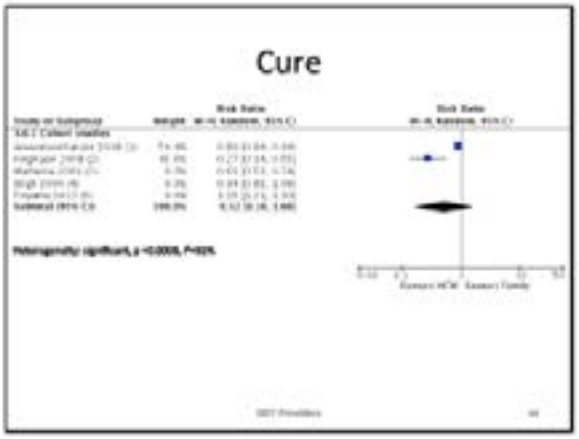
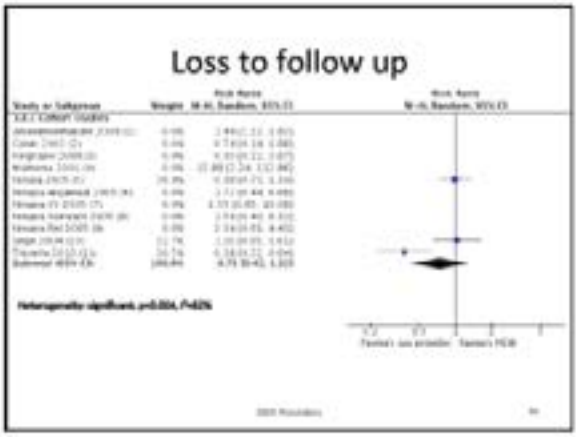
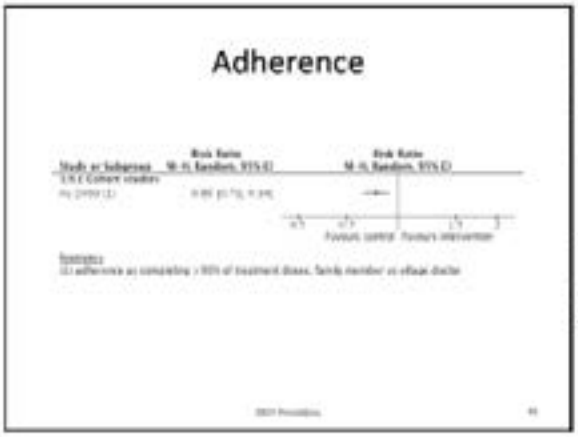

Completion

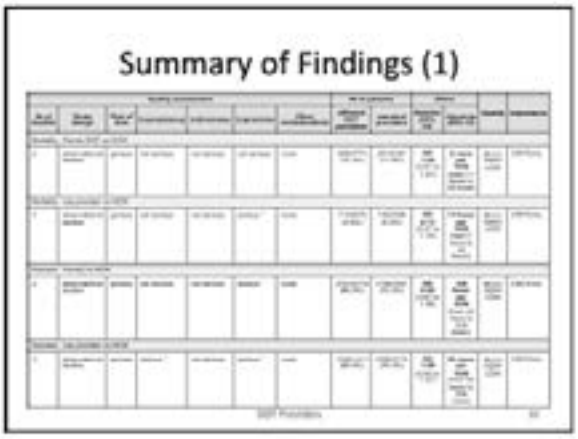

Completion

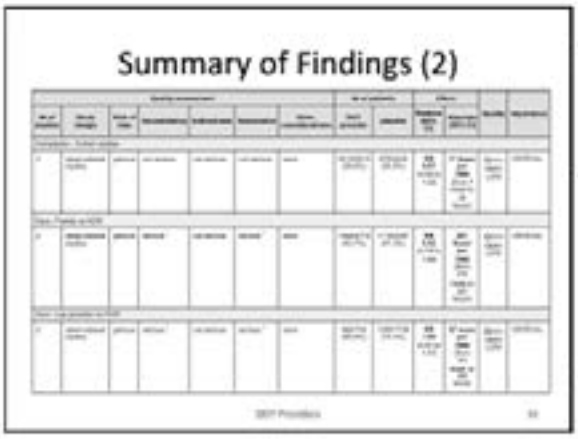

Cure

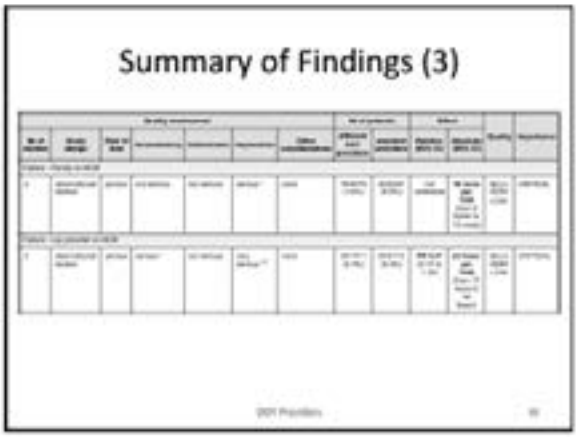

Cure

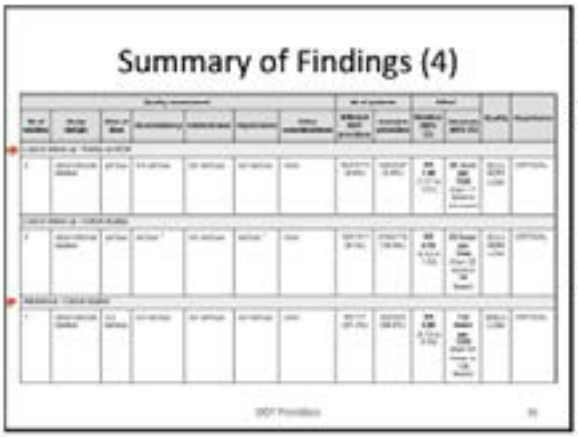

Loss to follow up


Adherence

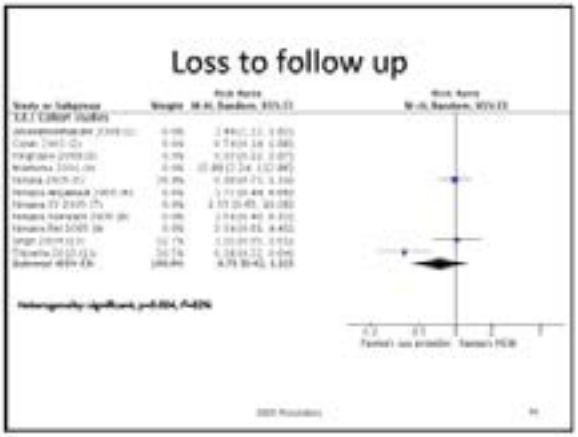

Summary of Findings (1)


Summary of Findings (2)

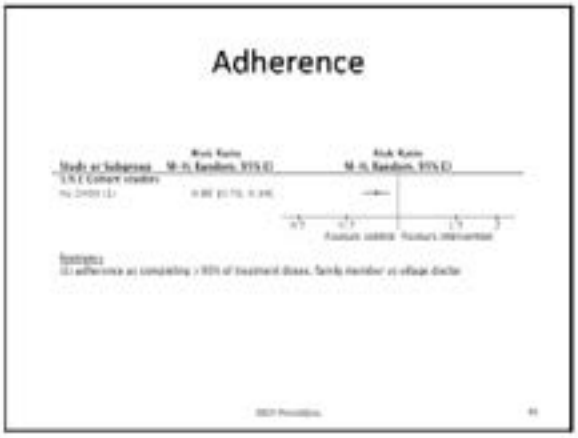

Summary of Findings (3)


Summary of Findings (4)

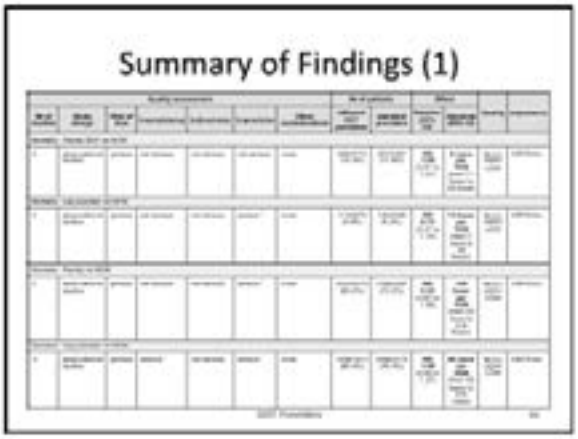
Loss to follow up



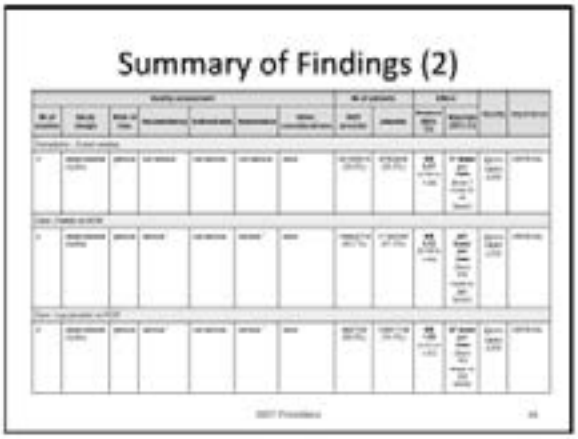
Adherence



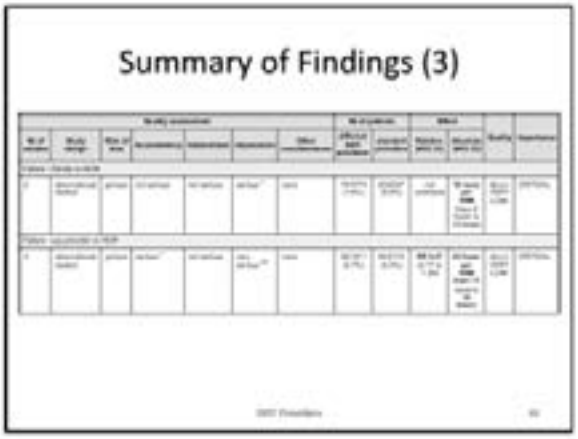
Summary of Findings (1)



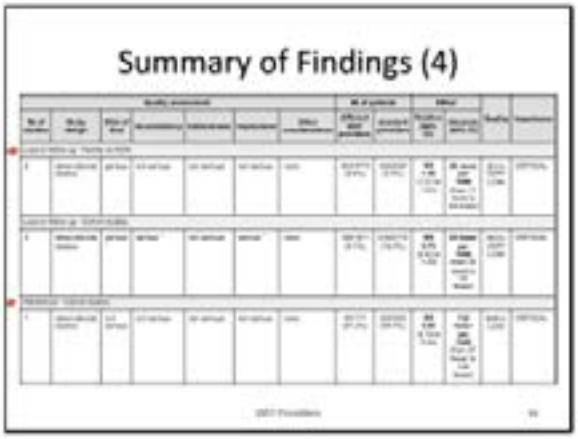
Summary of Findings (2)



Summary of Findings (3)



Summary of Findings (4)



Conclusion

- Similar performance of family or lay providers compared to institutional providers for most outcomes of interest.
- Higher rate of loss to follow up and lower rate of adherence with family DOT providers

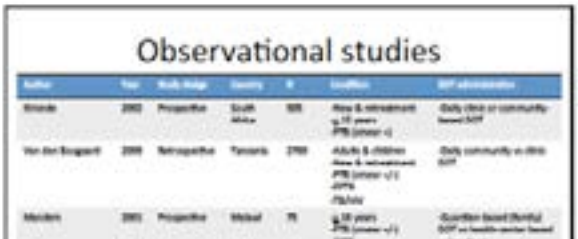
DOT location

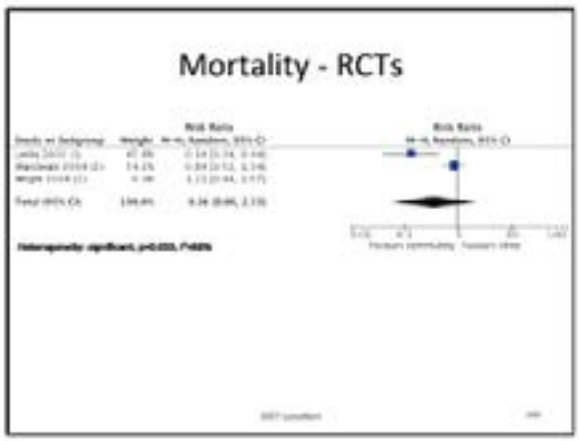
Randomized controlled trials

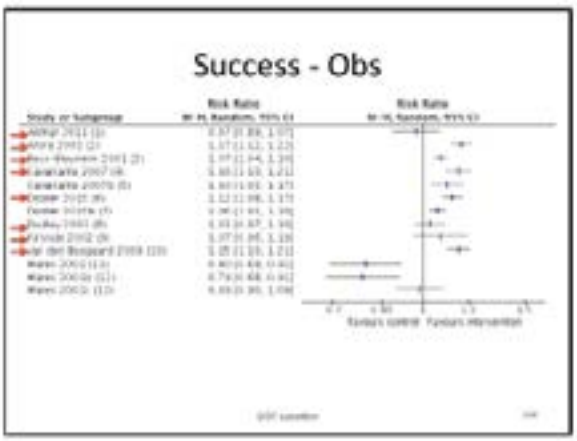
Observational studies

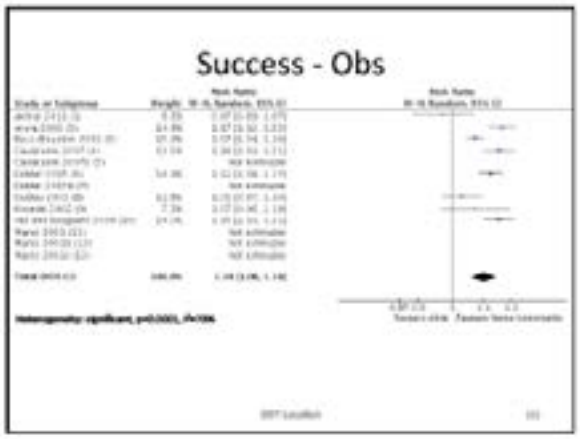
Observational studies

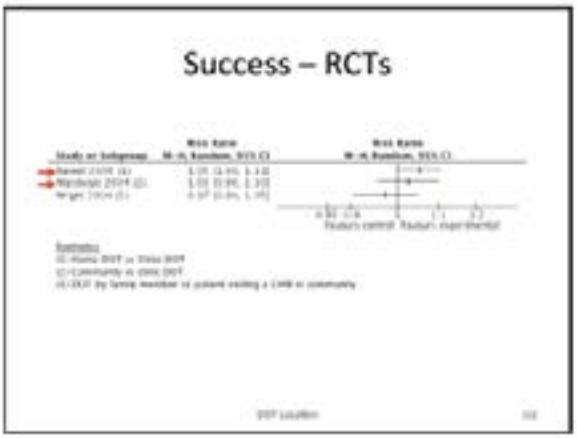
Observational studies

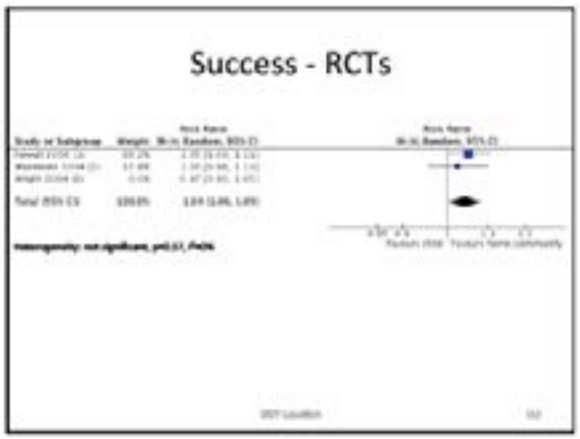


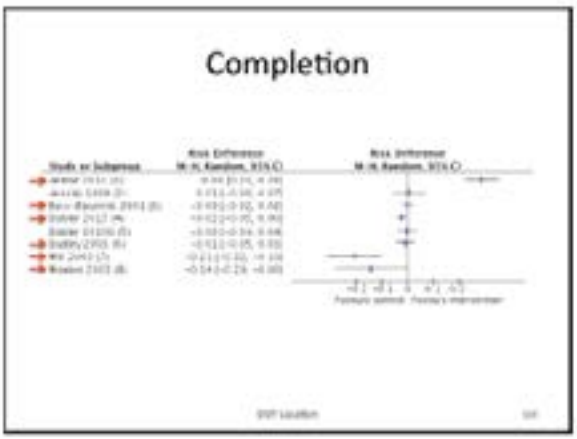

Mortality - RCTs

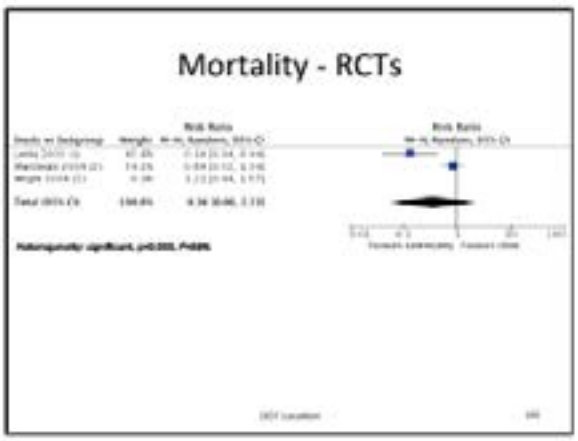

Success - Obs

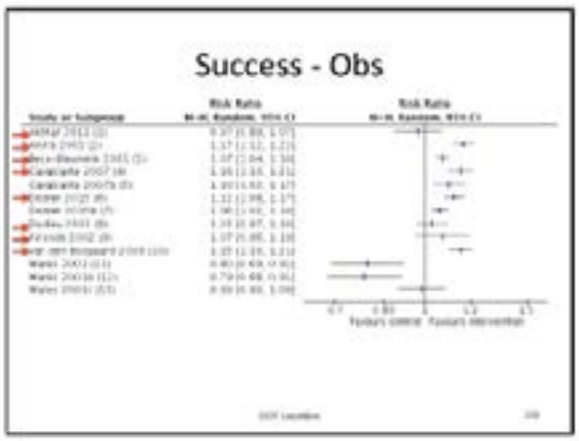

Success - Obs


Success – RCTs

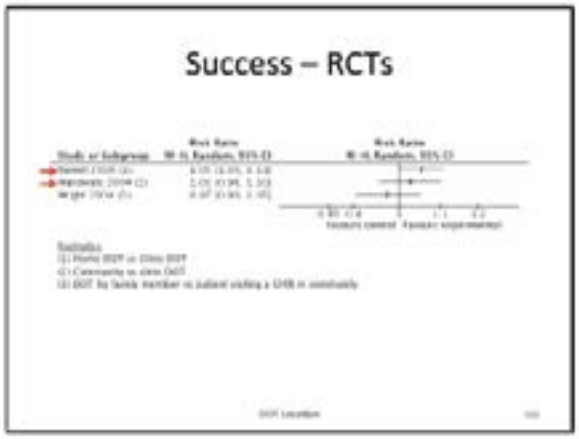

Success - RCTs

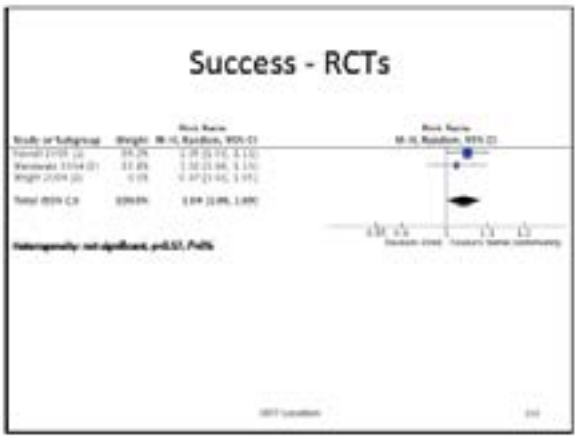

Completion

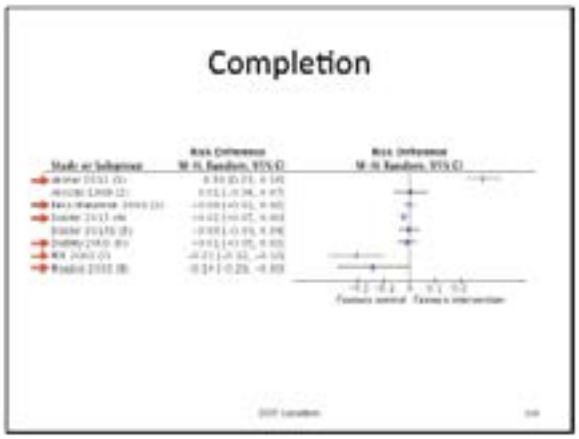

Mortality - RCTs


Success - Obs


Success - Obs

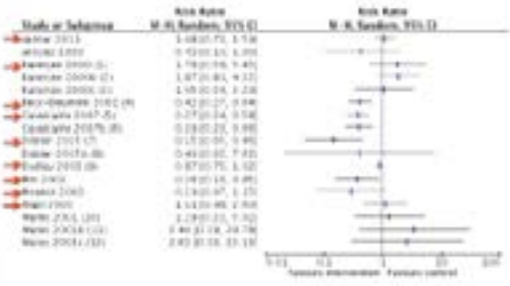

Success – RCTs


Success - RCTs

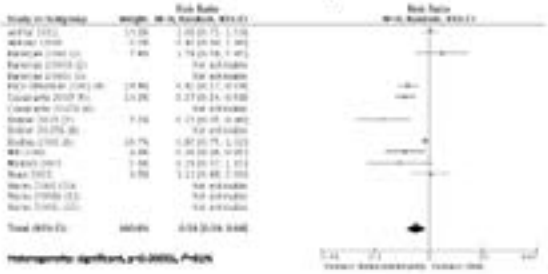

Completion

Failure – RCTs

Loss to follow up – Obs



Loss to follow up – Obs



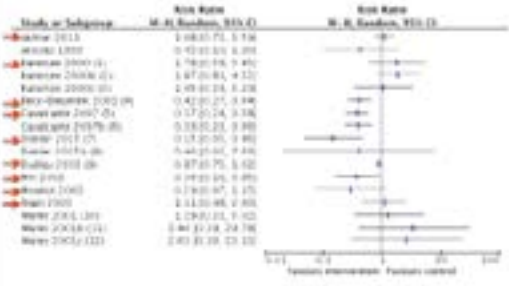
Loss to follow up – RCTs

Loss to follow up – RCTs

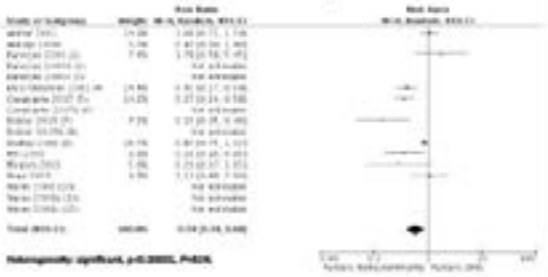
Adherence

Failure – RCTs

Loss to follow up – Obs



Loss to follow up – Obs

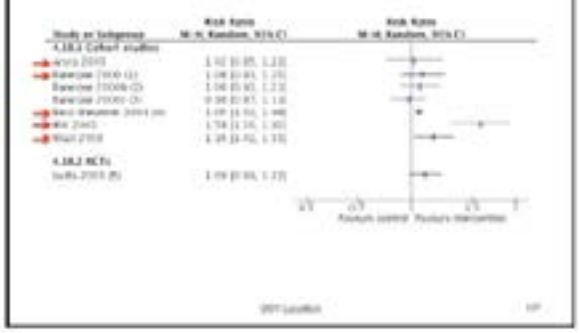


Loss to follow up – RCTs

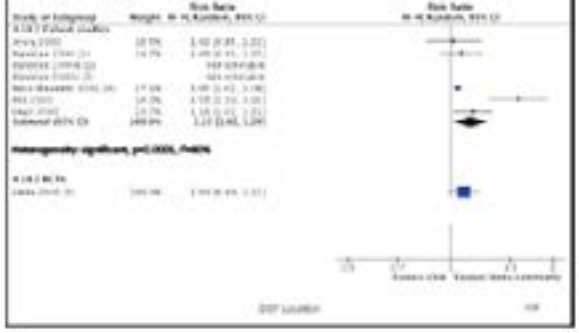
Loss to follow up – RCTs

Adherence

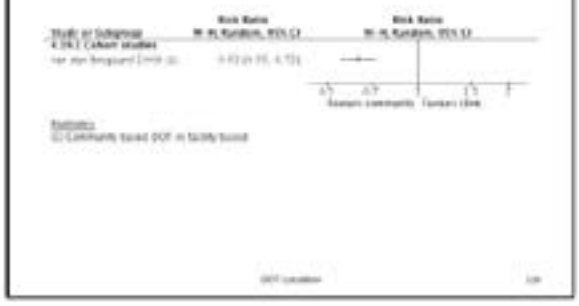
Sputum conversion rate



Sputum conversion rate

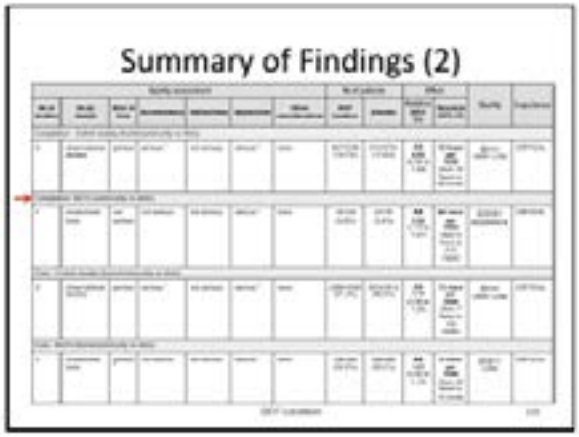


Unfavorable outcome

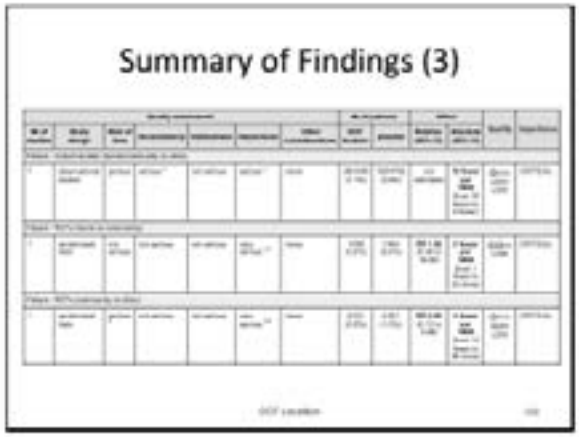


Summary of Findings (1)

Summary of Findings (2)



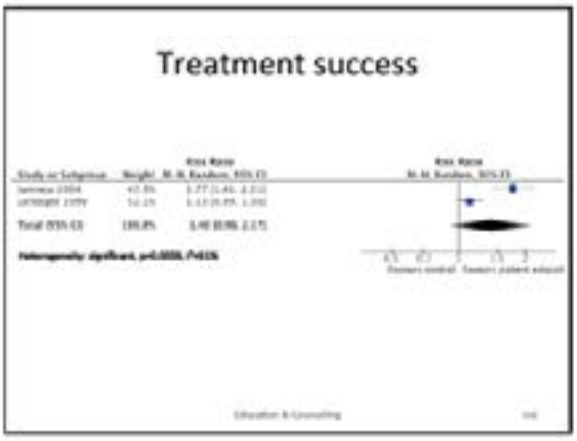
Summary of Findings (3)



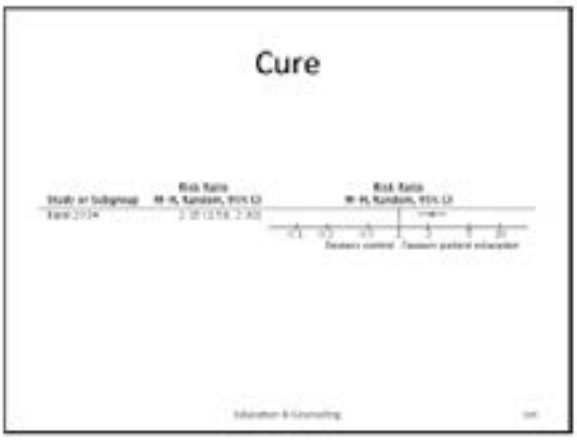

Quality – RCTs
Cochrane risk of bias tool


Quality – Obs
Newcastle Ottawa Scale

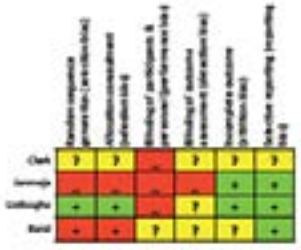

Mortality


Treatment success


Treatment completion


Cure

Quality – RCTs



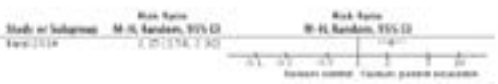
Quality – Obs

Mortality

Treatment success

Treatment completion

Cure

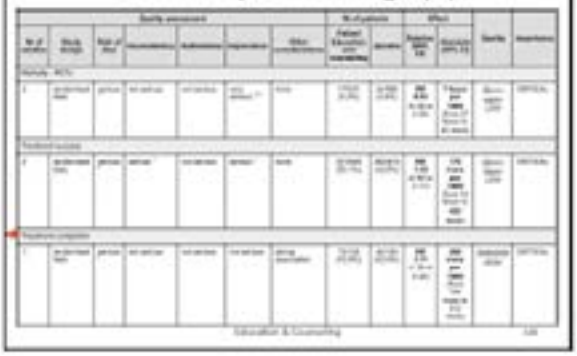


Failure

Loss to follow up

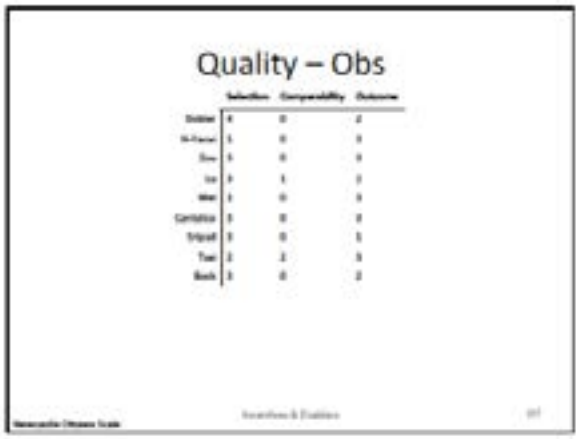
Adherence

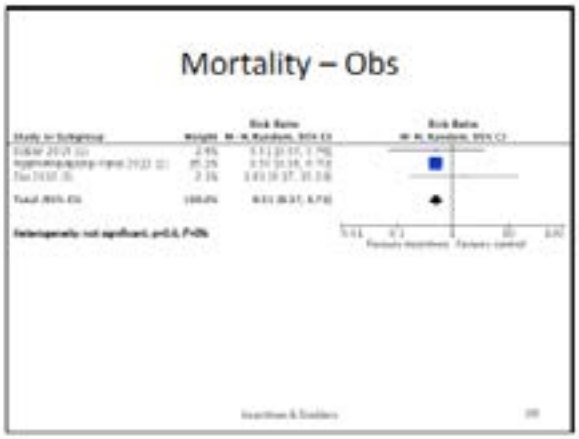
Summary of Findings (1)

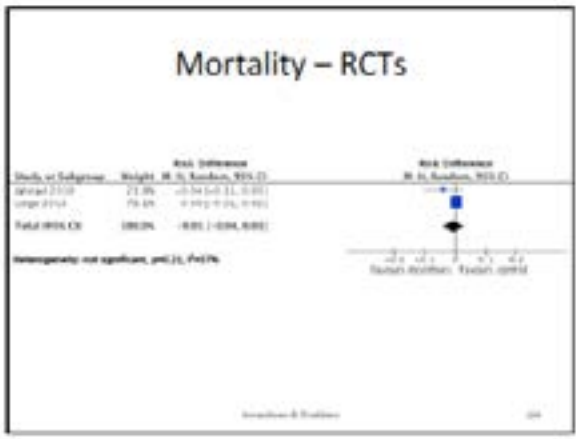


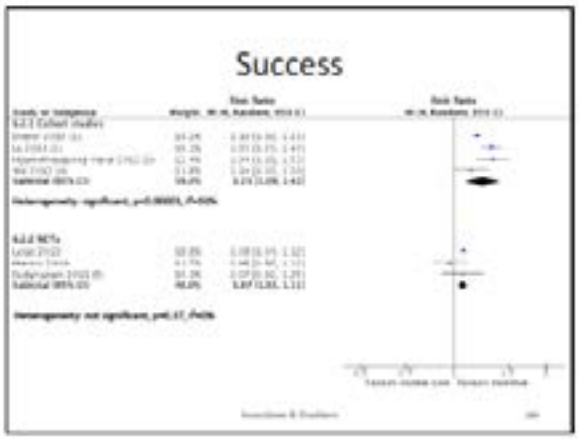
Summary of Findings (2)

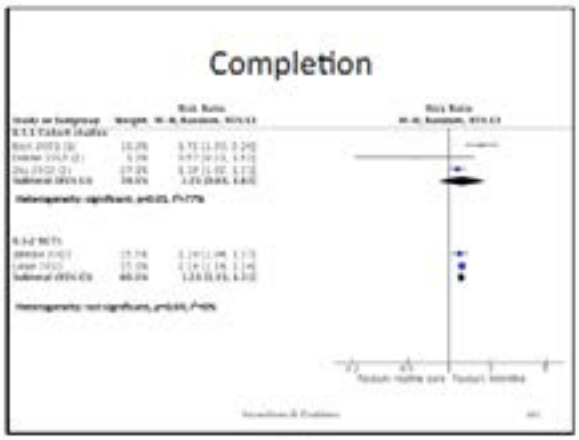
Summary of Findings (3)

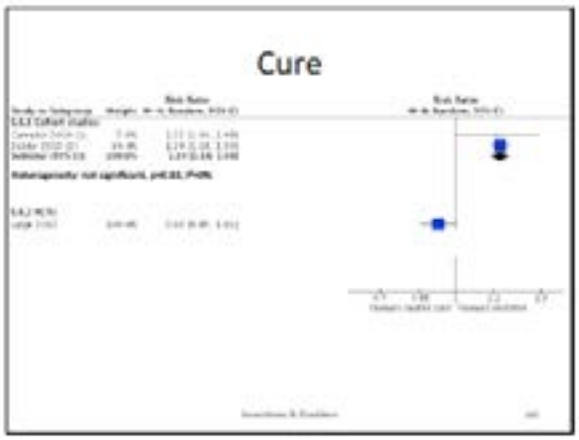

Quality – Obs

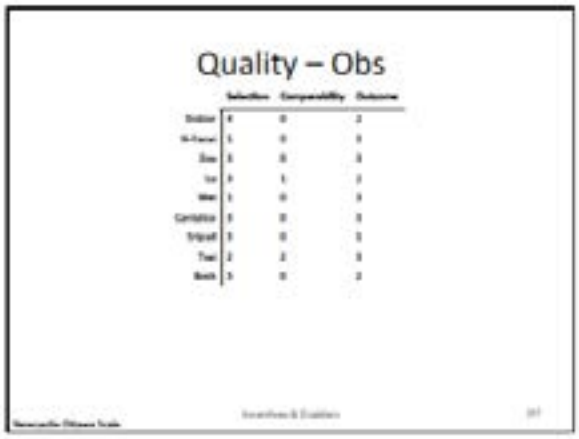

Mortality – Obs

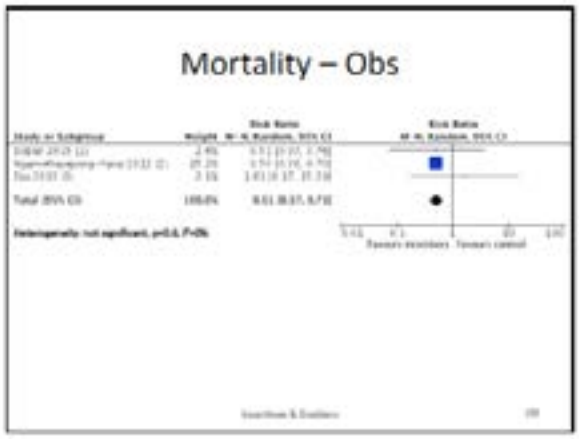

Mortality – RCTs

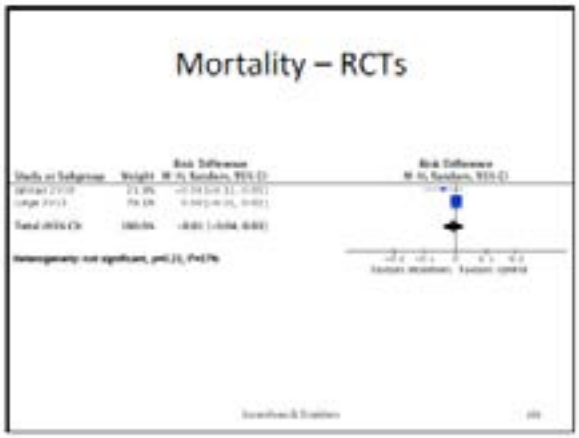

Success

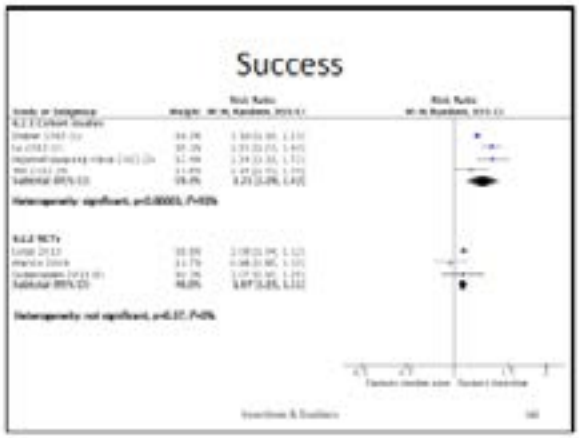

Completion

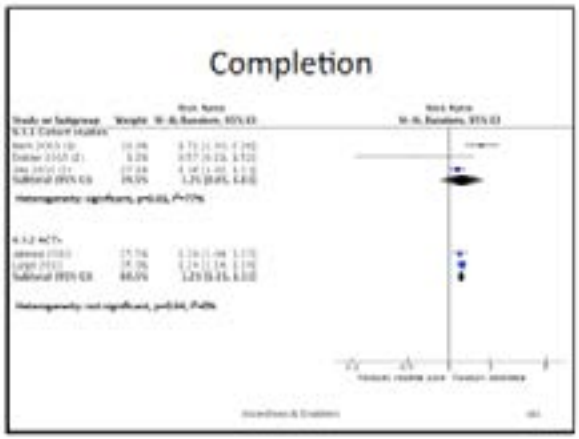

Cure


Quality – Obs


Mortality – Obs


Mortality – RCTs


Success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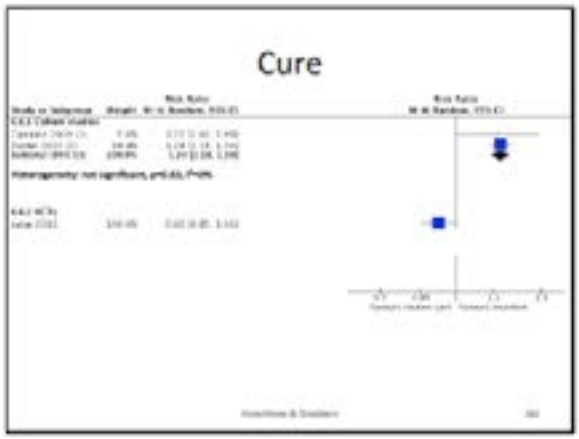
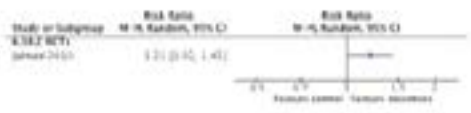

Cure

Adverse events

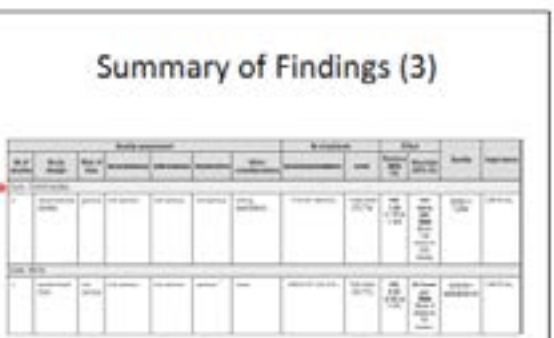
Sputum conversion rate



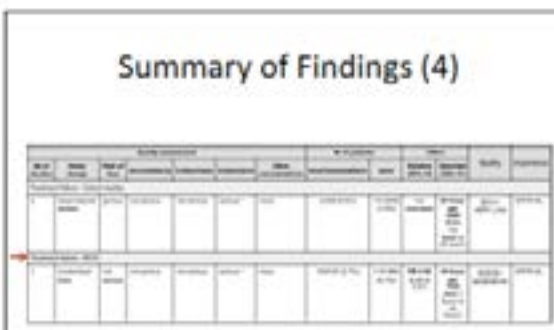
Summary of Findings (1)

Summary of Findings (2)

Summary of Findings (3)



Summary of Findings (4)



Adverse events

Sputum conversion rate

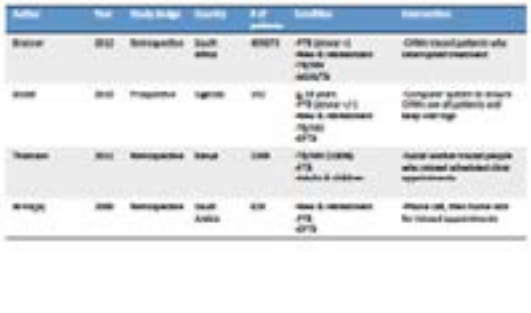
Summary of Findings (1)

Summary of Findings (2)

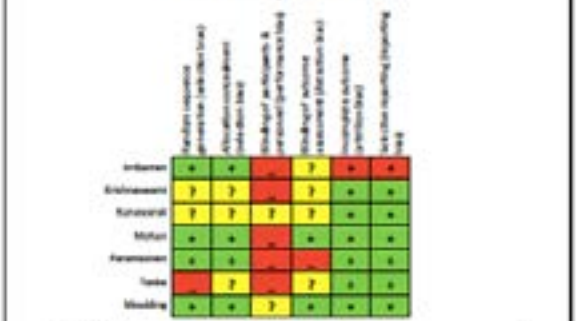
Summary of Findings (3)

Summary of Findings (4)

Observational studies

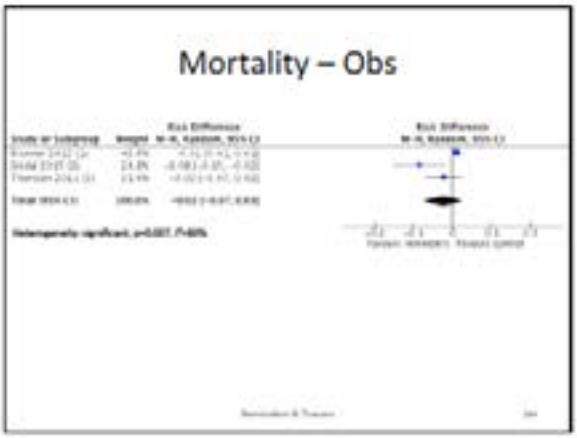


Quality – RCTs

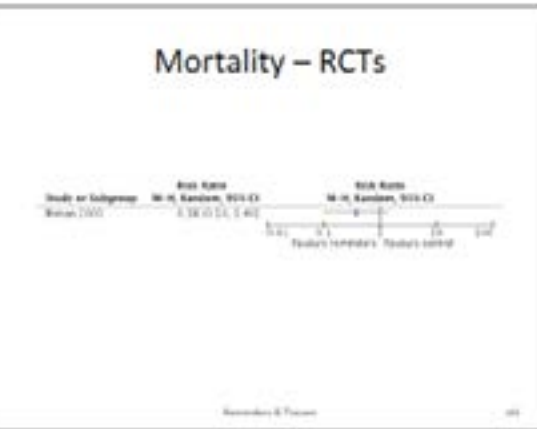


Quality – Obs

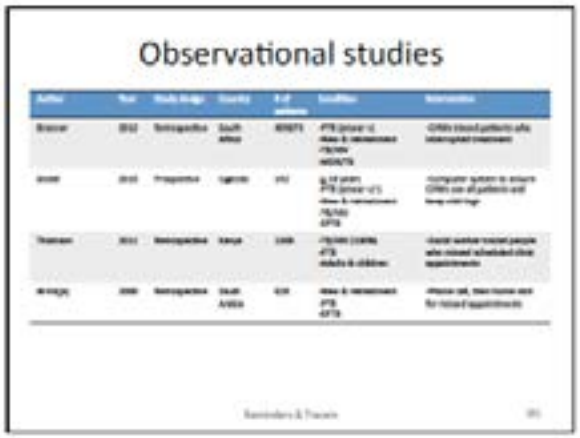
Mortality – Obs



Mortality – RCTs

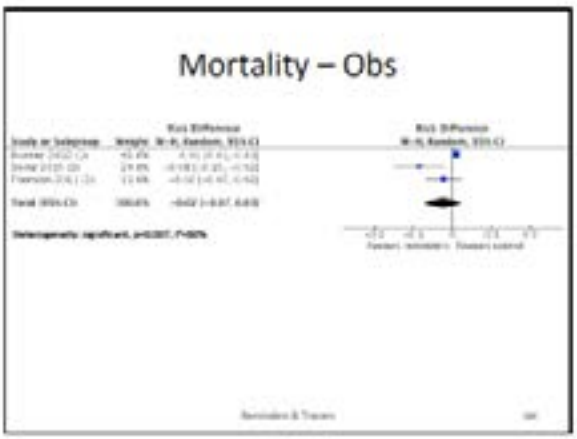


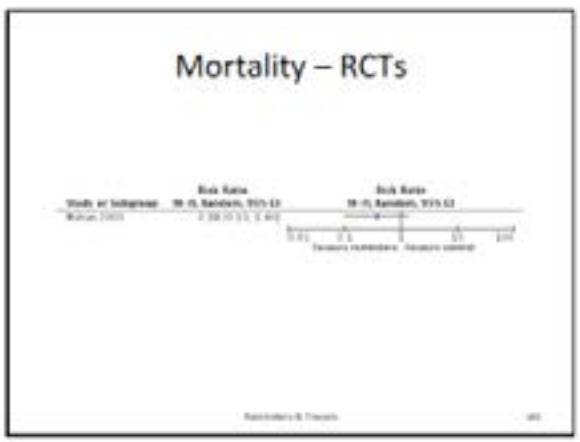
Success – Obs


Observational studies


Quality – RCTs

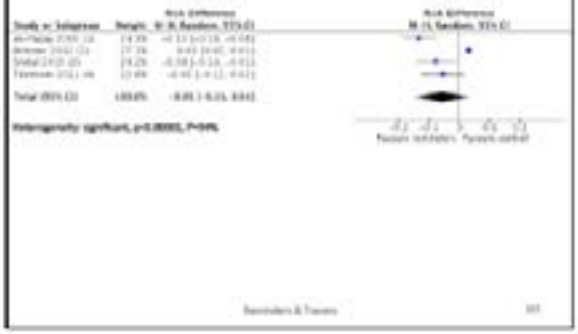

Quality – Obs


Mortality – Obs


Mortality – RCTs

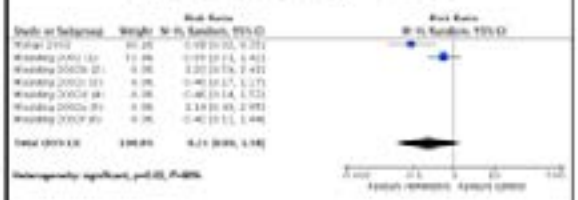

Success – Obs

Loss to follow up – Obs



Loss to follow up – RCTs

Loss to follow up – RCTs



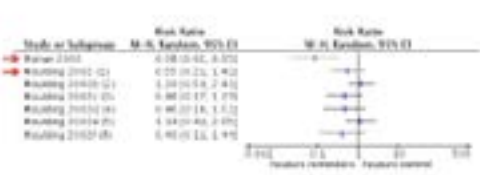
Adherence – RCTs

Culture conversion at 2 months

Acquisition of drug resistance

Loss to follow up – Obs

Loss to follow up – RCTs



Loss to follow up – RCTs

Adherence – RCTs

Culture conversion at 2 months

Acquisition of drug resistance

Summary of Findings (1)

Summary of Findings (2)

Summary of Findings (3)

Summary of Findings (4)

Conclusion

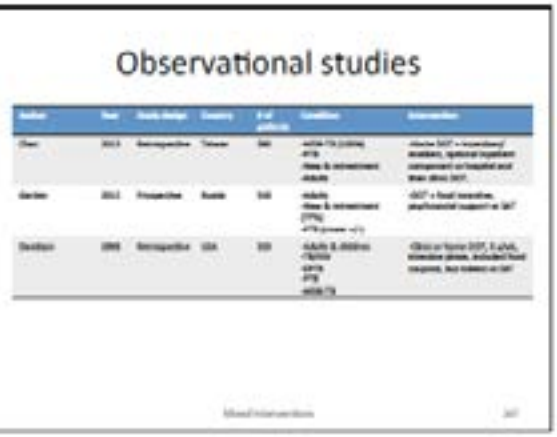
- Higher rate of treatment success, completion, adherence, and sputum conversion with reminders/tracers
- Lower rate of drug resistance development with reminders/tracers

Mixed interventions

Randomized controlled trials

Observational studies

Observational studies

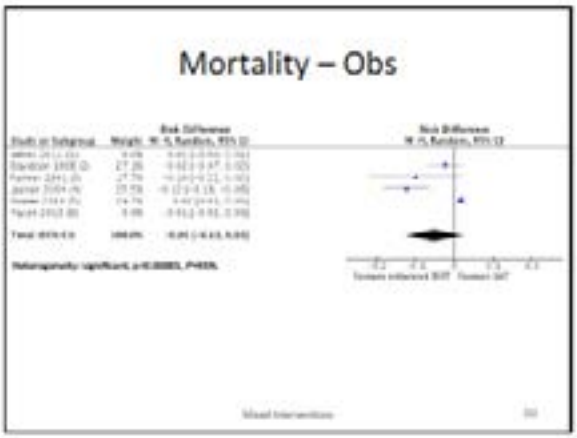


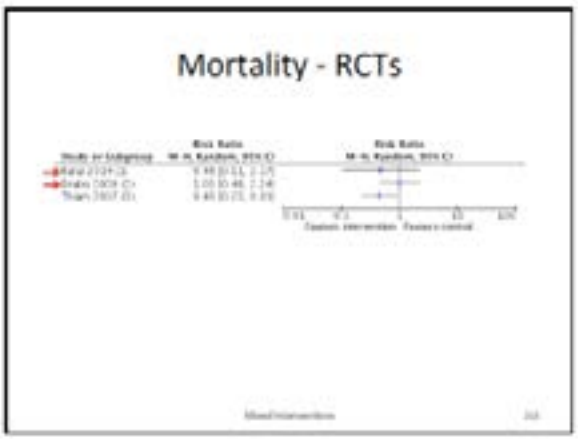
Quality – RCTs

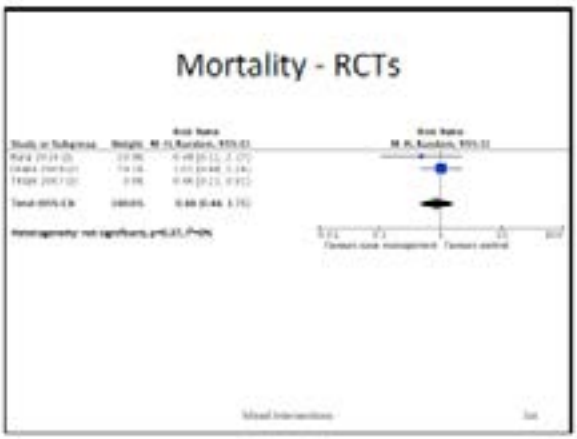
Quality – Obs

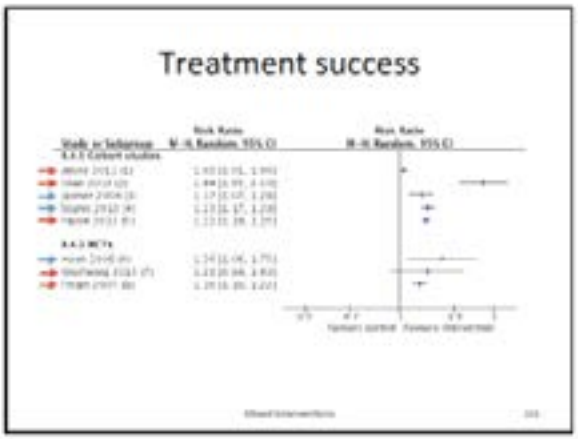
Mortality – Obs

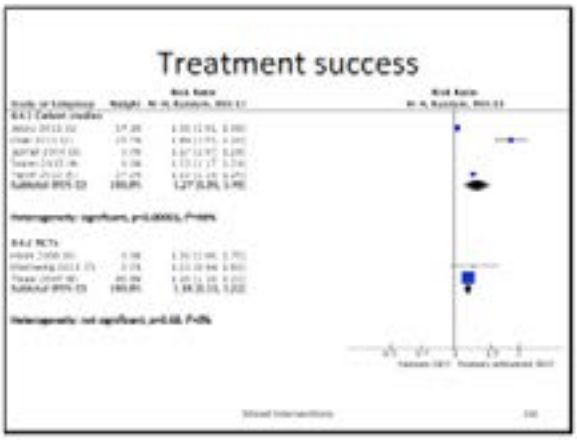

Mortality – Obs

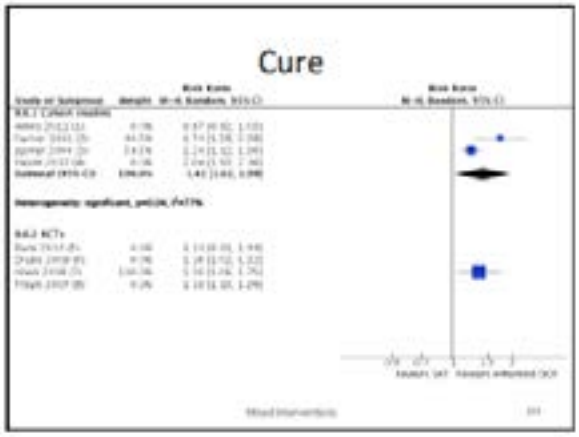

Mortality – Obs

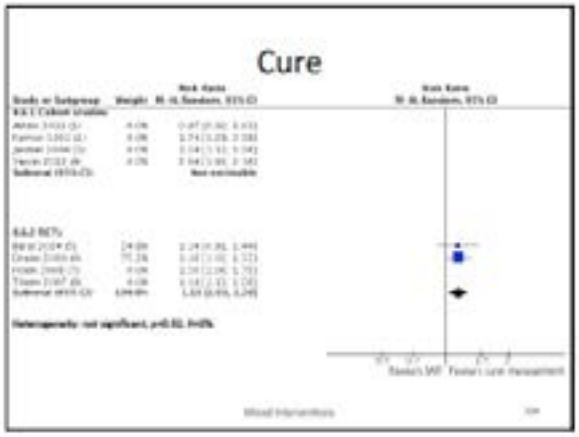

Mortality - RCTs

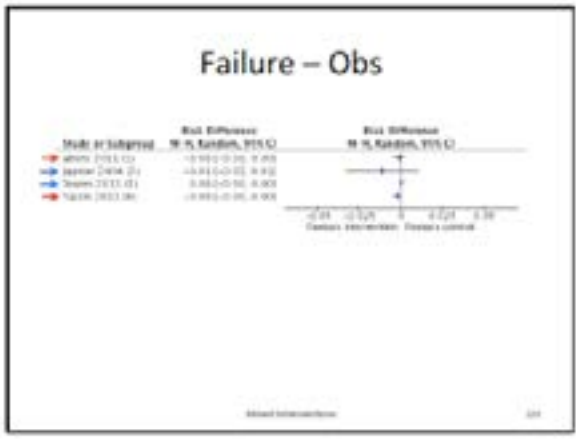

Mortality - RCTs

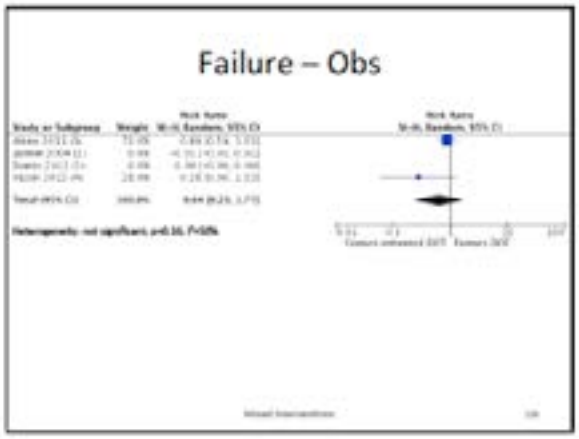

Treatment success


Treatment success

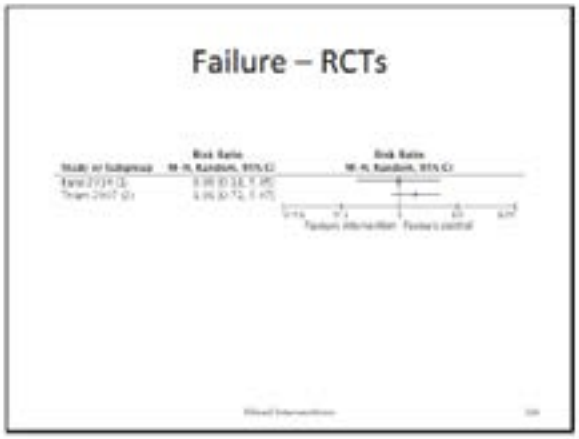

Cure

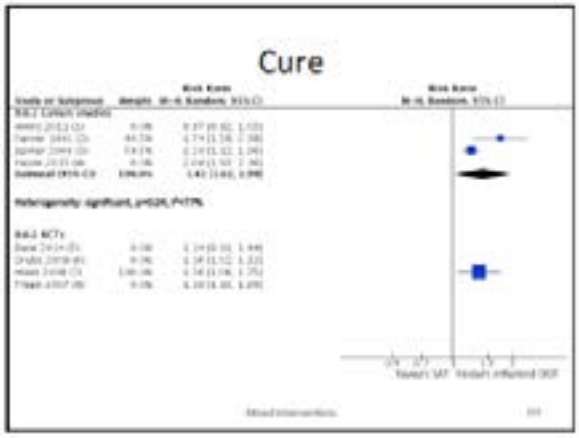

Cure

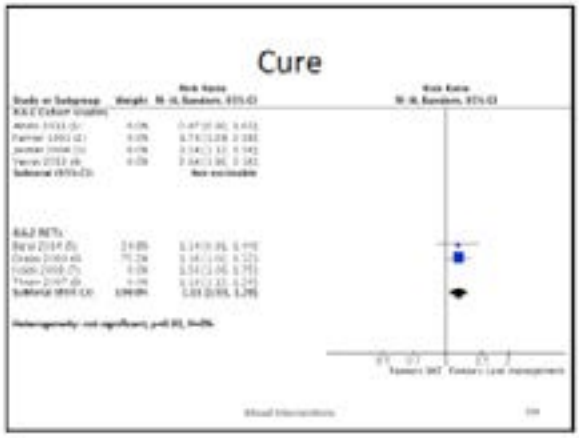

Failure – Obs

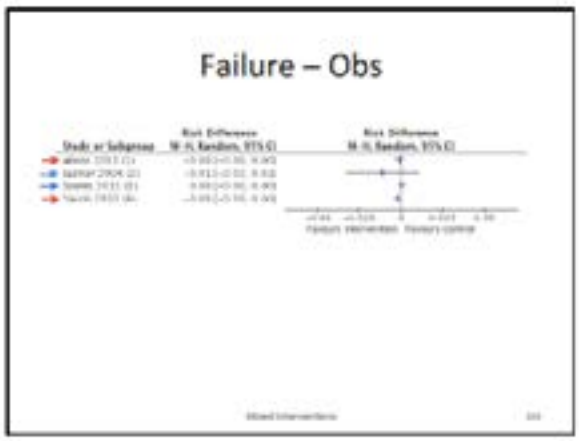

Failure – Obs

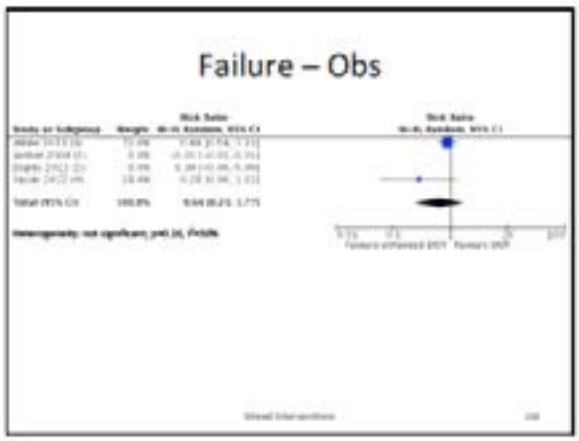

Failure – Obs


Failure – RCTs

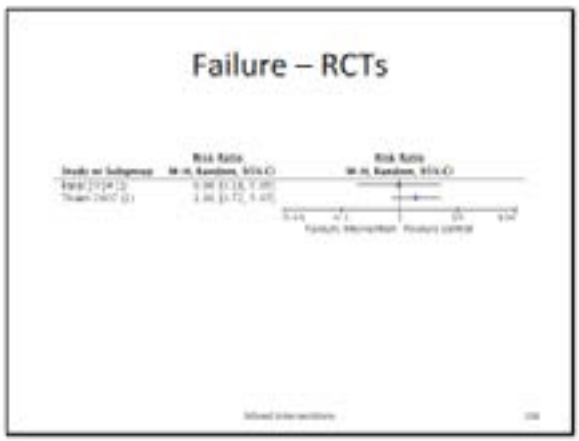

Cure


Cure


Failure – Obs


Failure – Obs


Failure – Obs


Failure – RCTs

Sputum conversion rate

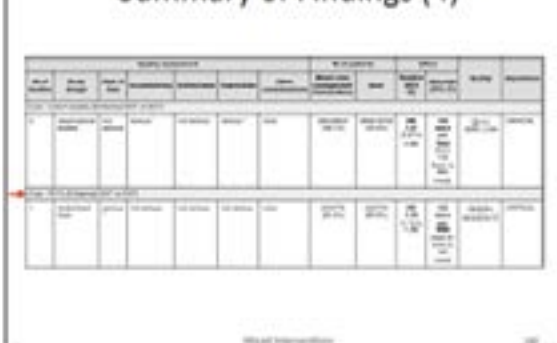
Acquired drug resistance

Summary of Findings (1)

Summary of Findings (2)

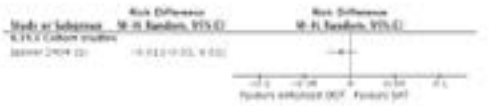
Summary of Findings (3)

Summary of Findings (4)



Sputum conversion rate

Acquired drug resistance

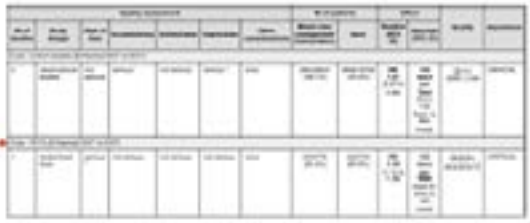


Summary of Findings (1)

Summary of Findings (2)

Summary of Findings (3)

Summary of Findings (4)



Psychosocial

Randomized controlled trials

Observational study

Quality – RCTs

Quality – Obs

Mortality

Psychosocial

Randomized controlled trials

Observational study

Quality – RCTs

Quality – Obs

Mortality

Summary of Findings (2)

Summary of Findings (3)

Conclusions

- Higher rate of treatment completion and lower rate of treatment failure and loss to follow up with psychosocial interventions (support groups)

Staff education

Randomized controlled trials

Observational study

Summary of Findings (2)

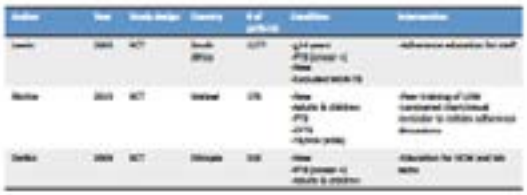
Summary of Findings (3)

Conclusions

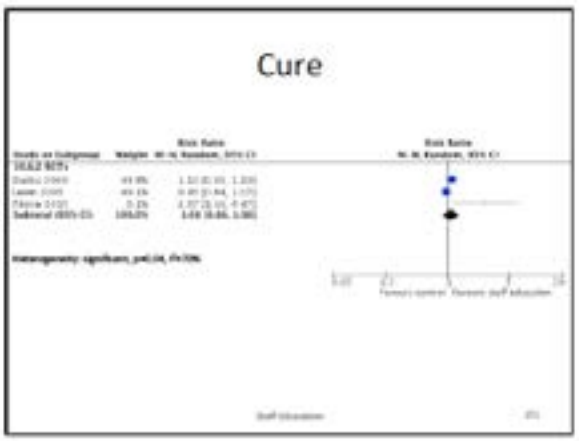
- Higher rate of treatment completion and lower rate of treatment failure and loss to follow up with psychosocial interventions (support groups)

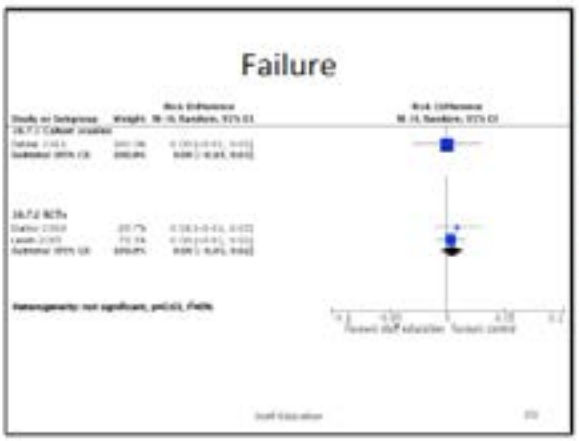
Staff education

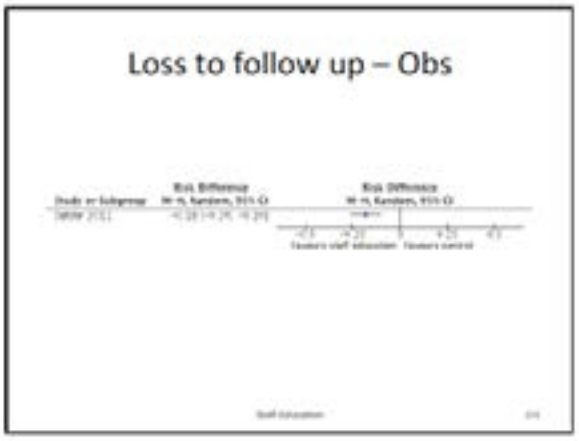
Randomized controlled trials

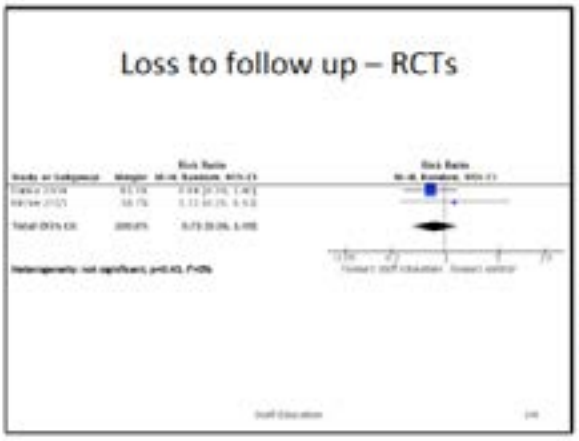


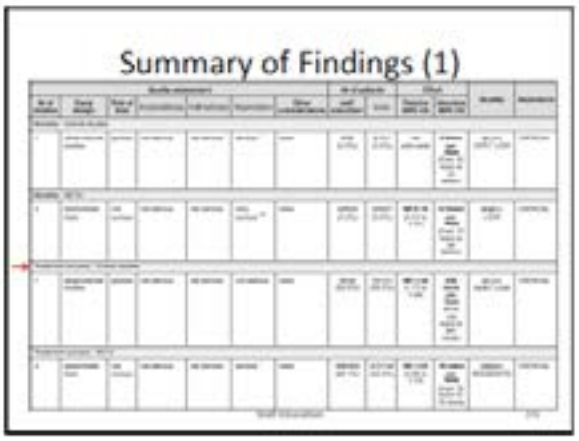
Observational study

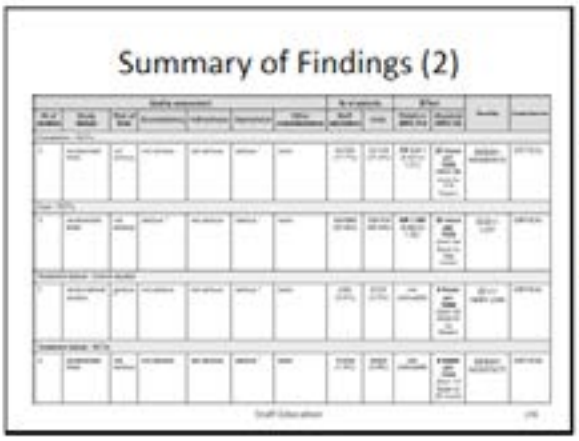

Cure


Failure

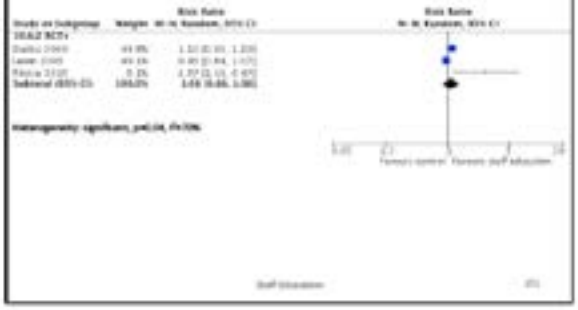

Loss to follow up – Obs


Loss to follow up – RCTs

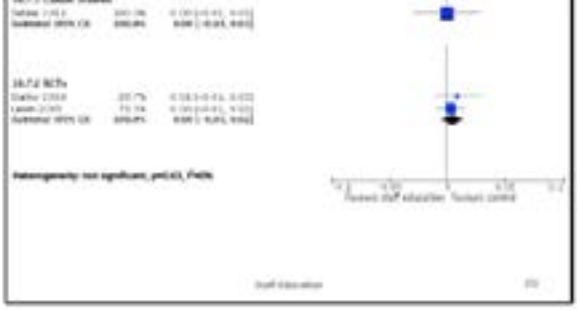

Summary of Findings (1)


Summary of Findings (2)

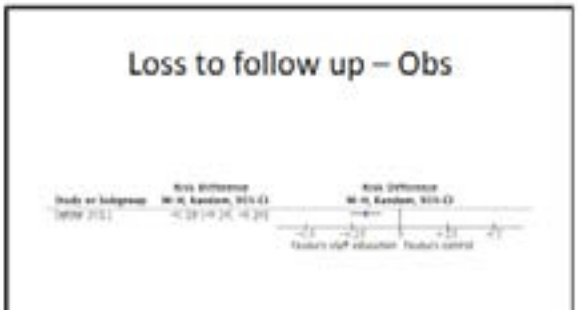
Cure



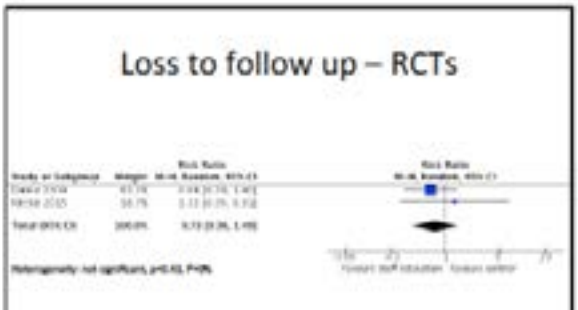
Failure



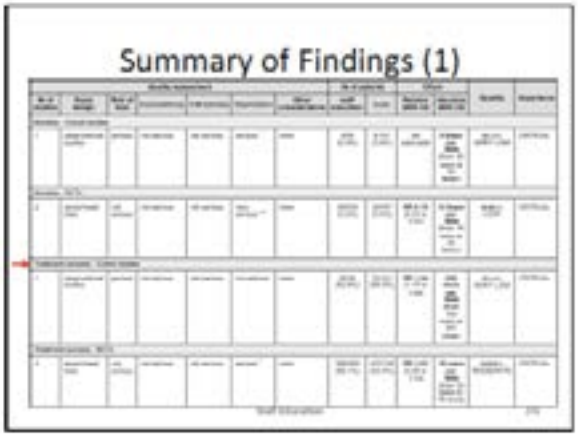
Loss to follow up – Obs



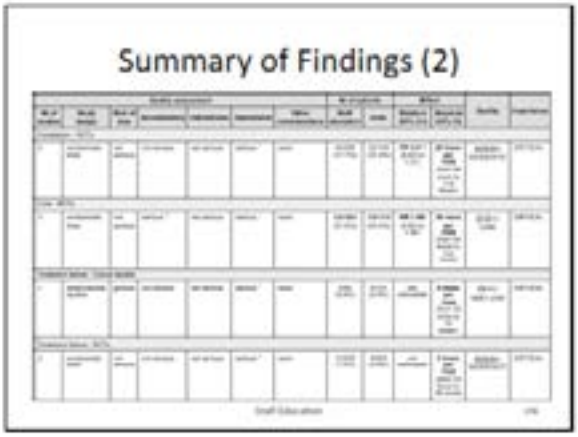
Loss to follow up – RCTs



Summary of Findings (1)



Summary of Findings (2)



Summary of Findings (3)

Conclusion

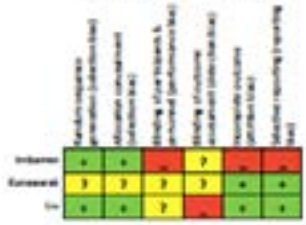
- Higher rate of treatment success and lower rate of loss to follow up with staff education interventions

Mobile health

Randomized controlled trials

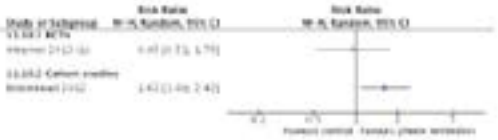
Observational study

Quality – RCTs

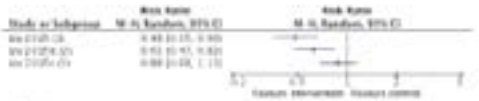


Failure

Sputum conversion rate



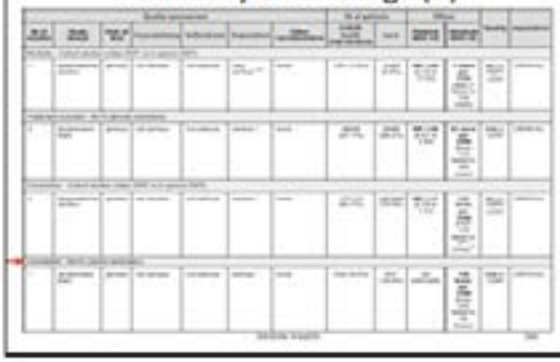
Poor outcome



Loss to follow up

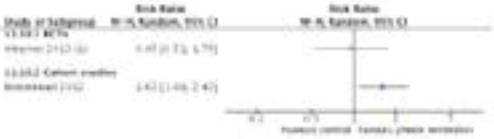
Poor adherence

Summary of Findings (1)

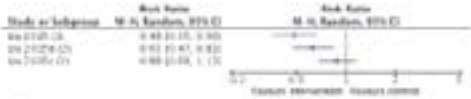


Failure

Sputum conversion rate



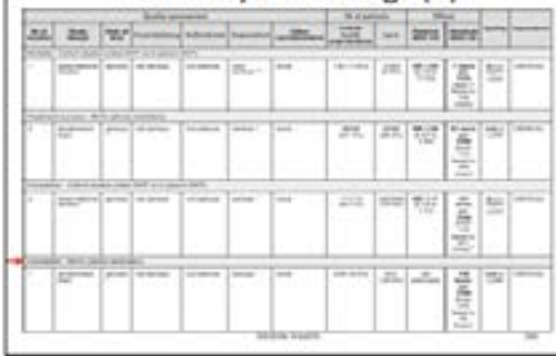
Poor outcome



Loss to follow up

Poor adherence

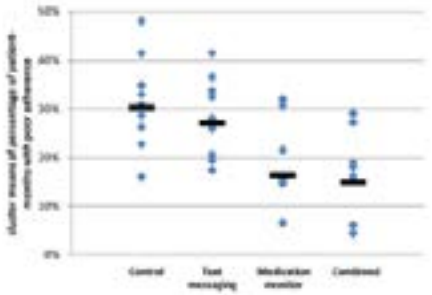
Summary of Findings (1)



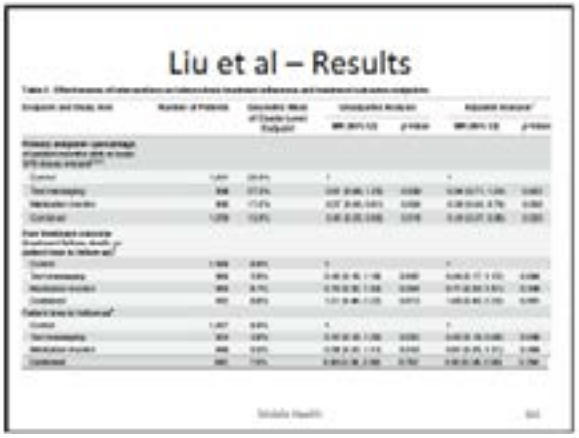
Liu et al – Study design

- PLoS One. 2015
- RCT, cluster randomized
- Inclusion criteria:
  - New patients
  - ≥18 years
- Intervention:
  - SMS reminder
  - Med monitor box reminder
  - Both
- Control:
  - SAT, family DOT, or HCW DOT (per patient preference)
- Outcomes:
  - Number of missed doses based on pill count
  - Poor adherence = Percentage of patient-months where ≥ 20% of doses were missed

Liu et al – Results



Liu et al – Results



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Decentralised Treatment and Care for Multi-Drug Resistant Tuberculosis Patients

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Executive summary

Background

Multi-drug resistant tuberculosis (MDR-TB) poses a major threat to the control of TB worldwide. Management of MDR-TB is complex and prolonged, and has traditionally been provided in centralised specialised treatment centres. However, such treatment centres are insufficient to meet the needs of the large and growing burden of MDR-TB patients in most settings. Decentralised treatment typically utilises facilities close to the patient's residential location (including home-based care), and trained personnel in the community to administer and monitor treatment, thereby overcoming the resource limitations in centralised, specialised facilities. In this review we summarise the evidence for the use of decentralised treatment and care for patients with MDR-TB.

Methods

We performed a comprehensive database search for relevant studies on decentralised treatment and care for patients with MDR-TB, which compared treatment outcomes, treatment adherence and cost to health services, to centralised treatment facilities. For outcome measures which had sufficient studies, a meta-analysis was performed to obtain pooled relative risk (RR) estimates.

Results

Eight studies comprising of 4,493 patients with MDR-TB were eligible for review inclusion. Two studies modelled cost-effectiveness, whilst the remaining six cohort studies reported on treatment outcomes and/or cost of health-care. The pooled RR estimates for decentralised versus centralised care for the outcomes of treatment success, loss to follow-up, death and treatment failure were: 1.13 (95% CI 1.01-1.27), 0.66 (95%CI 0.38-1.13), 1.01 (95% CI 0.67-1.52) and 1.07 (95%CI 0.48-2.40) respectively. Considerable study heterogeneity was seen amongst the studies for each pooled estimate.

Conclusions

Treatment success for MDR-TB patients improved when patients were treated in a decentralised, compared to centralised, setting. Further studies, in a range of different settings, are required to improve the evidence base for recommending decentralised care for patients with MDR-TB.

Background

Multi-drug resistant tuberculosis (MDR-TB) (i.e. resistance to both rifampicin and isoniazid) poses a major threat to the control of TB worldwide. In 2014, there were an estimated 480,000 new cases of MDR-TB worldwide and approximately 190,000 deaths from MDR-TB.[1] An estimated 9.7% of people with MDR-TB have extensively drug resistant TB (XDR-TB) (i.e. MDR-TB that is also resistant to a second line injectable drug and a fluoroquinolone). Of all MDR-TB cases from the 2012 cohort, only 50% completed treatment, 16% died, 16% were lost to follow-up and treatment failed for 10%.[1] Recommended therapy for MDR-TB requires a combination of second-line drugs that are more costly, less efficacious, more toxic and must be taken for much longer than first-line TB therapy.[2] Historically MDR-TB treatment has been provided through specialised, centralised programmes, and involved prolonged inpatient care.[3] This approach is based on the view that treatment adherence, the management of adverse events and infection control may be superior in the hospital setting compared to in the community.[4, 5] However, prolonged treatment in centralised facilities is impractical in resource-limited settings, with a substantial number of patients with MDR-TB. Paradoxically, the reliance on centralised treatment for MDR-TB may inadvertently increase transmission of this infection by delaying treatment commencement until inpatient beds become available. In addition, centralised approaches have been associated with poorer rates of retention in care.[6] Decentralised care for the treatment of drug susceptible TB is well-established, with treatment outcomes shown to be at least as good as hospital-based approaches.[7-9] This review aims to evaluate the existing evidence for decentralised care to treat MDR-TB.

Current World Health Organisation Policy

The World Health Organisation (WHO) currently recommends that 'patients with MDR-TB should be treated using mainly ambulatory care, rather than models of care based principally on hospitalization'.[10] These recommendations are 'conditional', reflecting the very low quality evidence upon which they were based. Two published systematic reviews have compared treatment outcomes for hospital and ambulatory-based management of MDR-TB, reporting similar treatment outcomes for centralised and decentralised approaches[11, 12] However, an important limitation of both these reviews was the inclusion of studies without an appropriate comparator group (i.e. a control group, where standard centralised care was provided). The review by Weiss et al,[12] compared pooled treatment outcomes of a community-based MDR-TB management intervention to pooled treatment outcomes from other previously published systematic reviews. Just one of the 41 studies included in one or both of these reviews directly compared hospital and ambulatory MDR-TB care.[13] The approach used in these systematic reviews likely results in substantial bias – given that the control and intervention populations were largely drawn from different study populations. Where possible, direct comparisons should be used to draw conclusions about complex health system interventions.[14] Therefore, more robust evidence is required to evaluate the effect of decentralised care upon treatment outcomes, compared to standard centralised treatment.

Objective of this review

The objective of this review is to examine the effect of decentralized treatment and care upon treatment outcomes among patients with MDR-TB. This review addresses some of the limitations of previous systematic reviews on this topic[11, 12] by including studies that directly compare decentralised and centralised MDR-TB treatment models in the same study setting. This review will contribute to revised WHO guidelines for the treatment of drug resistant TB.

Table 1 provides information about previous related systematic reviews and how these differ from this current review.

Table 1: Summary of related systematic reviews on treatment outcomes for MDR-TB and/or decentralised care for TB

Review	Objective	Main study findings	How this review differs from ours
Studies of DS-TB			
Karumbi et al[15] (2015) (Cochrane review)	Compared treatment outcomes using DOT versus SAT	Found no difference in treatment outcomes for - DOT versus SAT - home versus health facility DOT - family member versus CHW provider	Did not focus on MDR-TB
Wright et al[16] (2015)	Compared treatment outcomes for community based and clinic DOT	Greater treatment success for community versus clinic based DOT	Did not focus on MDR-TB
Kangovi et al[17] (2009)	Compared treatment outcomes using community based DOT programs that do and do not offer financial rewards	No difference in treatment outcomes with and without financial rewards	Did not focus on MDR-TB
Studies of MDR-TB			
Yin et al[18] (2016)	Compared treatment success with DOT to SAT for MDR-TB	Greater treatment success for DOT over the entire treatment course. No difference found between health facility and home based DOT	Did not specifically focus on decentralised versus centralised treatment. The only outcome measured was treatment success.
Toczek et al[6] (2012)	Identified strategies for reducing treatment default in DR-TB	Lower default rates for patients where: CHW provided care, and DOT was given for the entire treatment course	Did not specifically focus on decentralised versus centralised treatment. The only outcome measured was treatment default.
Orenstein et al[19] (2009)	Identified factors associated with improved treatment outcomes in MDR-TB	Improved treatment success with at least 18 months of treatment and DOT for entire course	Did not compare decentralised and centralised treatment.
Johnston et al[20] (2009)	Identified factors associated with poor treatment outcomes in MDR-TB	Factors associated with lower success rates were: male, alcohol abuse, low BMI, smear positive at diagnosis, FQ resistance.	Did not compare decentralised and centralised treatment.
Fitzpatrick et al[21] (2012)	Summarized evidence regarding the cost-effectiveness of MDR-TB treatment.	Treatment for MDR-TB can be cost effective in low- and middle income countries	Did not compare decentralised and centralised treatment.

Weiss et al[12] (2014)	Reviewed treatment outcomes from community based MDR-TB treatment programs	Treatment outcomes of community based MDR-TB treatment were similar to pooled outcomes in published systematic reviews of MDR-TB treatment	Only one included study had a control group. The control group was derived from published systematic reviews on MDR-TB (i.e. different studies)
Bassili et al[11] (2013)	Compared treatment outcomes using ambulatory versus hospital-based MDR-TB treatment	No difference in treatment success between the ambulatory and hospital-based treatment.	Included studies reported either hospital or ambulatory treatment. They did not directly compare outcomes from these two treatment interventions

DS-TB = drug susceptible tuberculosis; DOT = directly observed therapy; SAT = self-administered treatment; CHW = community health worker; MDR-TB = multi-drug resistant tuberculosis; DR-TB = drug resistant tuberculosis; BMI = body mass index; FQ = fluoroquinolone

Definitions

The following definitions are modified from the WHO guidelines for the programmatic management of MDR-TB, 2012.[10] In this review, centralised vs decentralised treatment is defined according to (a) the location of treatment; and/or (b) community-based personnel delivering the treatment. This acknowledges the potential impact of the distance between the treatment facility and patients' residential location upon treatment outcomes and cost, as well as the limited personnel available to provide treatment and care in centralised, specialised settings.

- *Decentralised MDR-TB treatment and care*:
  This refers to treatment and care located in the local community in which the patient resides. This includes treatment delivery based at community health centres, clinics, religious and other community venues, as well as in the patient's home or workplace. The entire treatment period typically occurs in the ambulatory setting, or alternatively, there is a brief period of hospitalisation in a centralised facility (i.e. less than 1 month) that occurs in the intensive phase in order to observe initial response to therapy, manage severe medication side effects or other co-morbid conditions. Decentralised care is delivered primarily by trained volunteers (including family members), community nurses or non-specialised doctors.
- *Specialised/centralised MDR-TB treatment and care*:
  This includes treatment and care in a centralised and/or specialised hospital. Centralised care is usually provided by doctors and nurses with specialist training in MDR-TB management. It also includes treatment and care provided by 'centralised outpatient clinics' i.e. out-patient facilities which are located at or near to the site of the specialised, central facility.

Additional definitions:

- *Directly observed therapy (DOT):*
  A treatment program where a health worker, community volunteer or family member, routinely observes participants taking their anti-tuberculous drugs.[15]
- *Treatment outcomes:*
  MDR-TB treatment outcomes were defined according to standard WHO definitions.[10]

Research question

Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the following outcomes: treatment adherence, improved treatment outcomes, adverse reactions, acquired drug resistance, reduced patient costs and health service costs; compared to treatment and care provided solely by specialized drug resistant TB (DR-TB) treatment centres? (WHO PICO Question 2)

PICO framework

The PICO framework for this research question is as follows:

- Population: All patients commencing treatment for MDR-TB
- Intervention: Decentralised treatment and care, provided by non-specialised or periphery health centres, by community health workers, community volunteers or treatment supporters. Treatment and care includes: DOT and patient support; administration of injectable antibiotics during the intensive phase; specialist care for co-morbidities (e.g. Human Immunodeficiency Virus (HIV) infection, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology)
- Comparator: Treatment and care provided solely by centralised and/or specialized DR-TB centres or teams.
- Outcomes: Adherence to treatment (or treatment interruption due to non-adherence); conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death; adverse reactions from TB drugs (severity, type, organ class); acquisition (amplification) of drug resistance; cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability); cost to health services

Methods

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses: guidance for reporting of systematic reviews and meta-analyses).[22]

Search terms

The authors developed and agreed on the comprehensive search terms in consultation with WHO counterparts. The search terms are listed in Table 1.

Table 2: Search terms applied using Medline search engine

Area	MeSH headings	Free text
Population	Tuberculosis, Multidrug-Resistant [MeSH]	((tuberculosis OR TB) AND (multidrug-resistan* OR multidrug resistan* OR multi-drug resistan* OR "drug resistan*" OR drug-resistan* OR multiresistan* OR "multi resistan*" OR "rifampicin resistan*" OR "extensively drug-resistan*" OR "extensively-drug resistan*" OR "extensively resistan*" OR MDR OR XDR OR TDR)) OR MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR "MDR TB" OR "XDR TB" OR "TDR TB"
Intervention		(directly observed OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment) AND (community OR outpatient OR public participation OR community-based OR decentralized OR non-specialized OR perhiph* health centres OR home-based OR ambulatory OR clinic OR community OR community health worker OR CHW OR volunteer*)

Population terms were combined using the Boolean operator "OR". Intervention terms were combined using "OR". Population and intervention term groupings were then combined using "AND". Comparator and outcome terms were not included in the search strategy, as a sufficiently small number of hits were achieved using only the population and intervention terms. By sifting for comparator and outcome during the manual sift, the likelihood of missing a potentially relevant paper was reduced.

Search sources and limits

We searched electronic health care databases, evidence based reviews, and hand searched the "grey literature". Search terms in Table 2 were adapted to the requirements of each database (see Annex 1).

Sources searched to identify relevant literature are detailed in Table 3. Each search was limited to publications from 1995-onwards, given that this is the time-frame in which DOT for TB has been widely used. Searches were not restricted by language, publication type or study design.

Table 3: Information sources searched to identify relevant literature

Category	Sources
Healthcare databases	MEDLINE EMBASE LILACS Web of Science Google scholar
Evidence based reviews	Cochrane library (includes CENTRAL, DARE, HTA, CDSR)
Grey literature	OpenSIGLE International Union of Tuberculosis and Lung Disease conference electronic abstract database
Unpublished studies	ClinicalTrials.gov WHO portal of clinical trials Consultation with expert in the field

Eligibility criteria for studies

The following inclusion and exclusion criteria were applied to the searches:

Inclusion criteria

- *Types of participants:*
  Studies recruiting individuals of all ages with MDR-TB.
  - » Given the limited availability of microbiological confirmation of MDR-TB in some settings, MDR-TB was defined as microbiological (phenotypic or genotypic) evidence of MDR-TB or, a clinical diagnosis of MDR-TB
  - » Studies which included individuals with XDR-TB or totally drug resistant (TDR-TB) were included
- *Types of interventions*:
  Studies including any of the following interventions (or any similar intervention but named differently): decentralised treatment and care provided by non-specialised or peripheral health centres, by community workers, community volunteers or treatment supporters.
  - » Treatment and care includes: DOT and patient support, injection during the intensive phase, and specialist care for co-morbidities (e.g. HIV, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology).
  - » No restrictions were placed on the timing of the intervention within the treatment period e.g. whether the intervention occurred in the intensive phase, continuation phase or throughout the treatment period.
- *Types of studies*:
  The following study types were included: randomized controlled-trials, prospective cohorts, retrospective cohorts, case control studies including at least 10 patients, or modelling studies
- *Types of comparators:*
  Treatment and care provided solely by specialist DR-TB centres or teams
- *Types of outcome measures:*
  Studies including one or more of the following outcome measures: adherence to treatment (or treatment interruption due to non-adherence); conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death; adverse reactions from TB drugs (severity, type, organ class); acquisition (amplification) of drug resistance; cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability); cost to health services

Exclusion criteria

- Any study that did not report one or more of the above-stated outcomes of interest
- Any study reporting solely on primary outcomes of interest without a control/comparator group.
- Narrative reviews and commentaries/editorials
- Number of enrolled subjects in the intervention arm <10

For studies that were in a language other than English, we consulted an individual fluent in that language for interpretation and translation.

For studies where only an abstract was available, the study authors were contacted to obtain additional study information. Contactable, consenting authors were asked to complete a data collection form, specifically designed for this review, to obtain relevant study data.

Study selection and data extraction

In the first stage of study selection, titles and abstracts of papers identified from the above search were screened independently by two reviewers (JH and AB), for suitability for subsequent full text review.

In the second stage of study selection, full-text papers identified from the first stage were reviewed independently by two reviewers (JH and AB). A standardised extraction form was developed and pilot tested. Two reviewers (JH and GF) independently extracted the data from the papers selected for final inclusion. Data were compared, and unresolved disagreements in study selection or extraction were resolved consensus. An additional search of reference lists of all included articles, a search of all articles citing included articles, and review articles related to the research question were also conducted, to identify any further articles eligible for inclusion. For studies where interim findings were reported in one paper, and then more completely in a subsequent paper, the latter was selected for review inclusion. Study authors were contacted to clarify or obtain missing data where necessary.

Data extracted included: study design; study objective; study population characteristics (sample size, method of diagnosing MDR-TB, HIV prevalence, co-morbidities); details of intervention (organisation initiating decentralised care, method of selection of intervention group, time period intervention occurred, treatment regimen, nature of DOT, provider and location of treatment, duration/timing of decentralised treatment, additional support provided); details of control group (derived from the same population and/or same time period); event numbers for each outcome measure (as detailed above under "Types of interventions" in the Inclusion Criteria, above).

Study quality assessment

Risk of bias was assessed using the Newcastle Ottawa Scale for assessing the quality of nonrandomized studies[23] and the GRADE methodology.[24]

Analysis

A meta-analysis of relative risk and 95% confidence intervals for each treatment outcome, where sufficient studies (3 or more) were identified, comparing the intervention to the comparator group, were calculated using a generalised linear mixed model with study as a random effect, using RevMan 5.2. Forest plots summarised the data for individual trials. Outcomes were estimated as pooled proportions using the exact binomial method.[25] For each comparison, an I2 statistic was calculated to evaluate heterogeneity between studies.

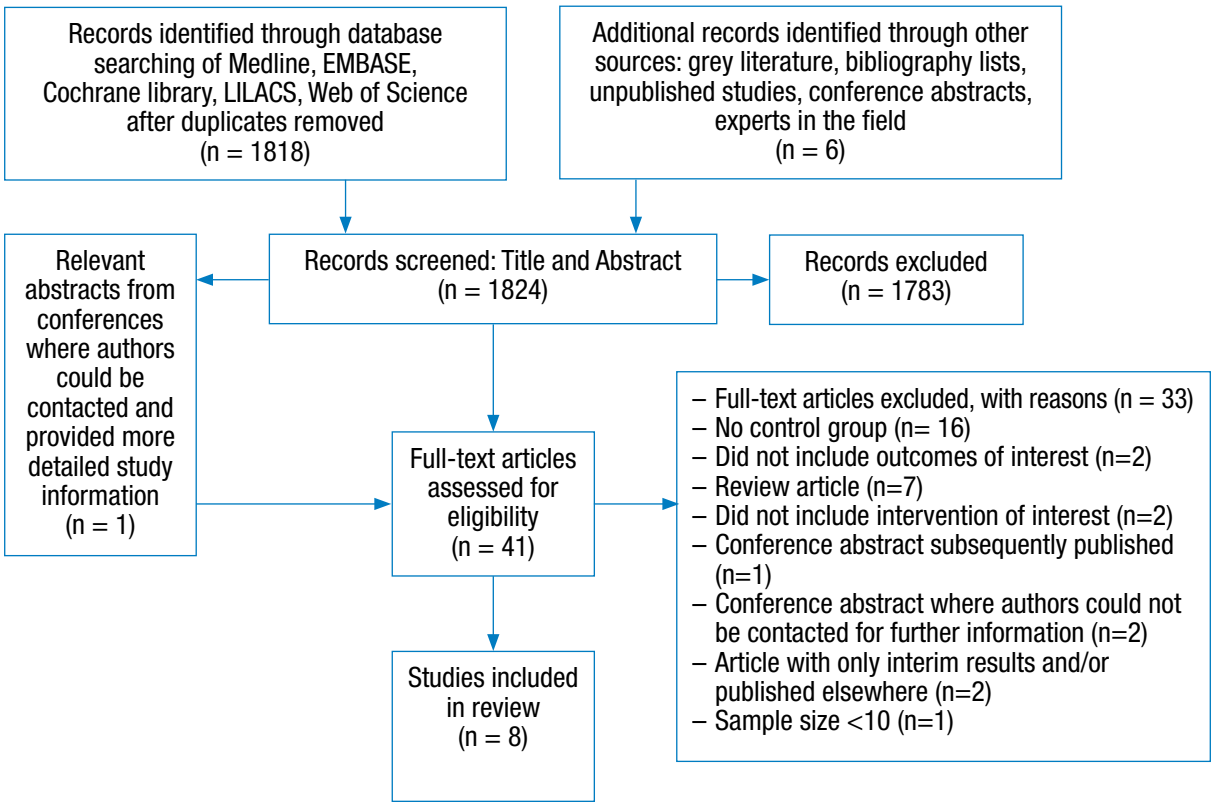
[26, 27] Where there were sufficient studies (five or more with the same end-point),[28] publication bias was assessed by funnel plot. Where available, costings were converted to $US 2015, based upon published World Bank conversion rates. Where insufficient studies were available to perform a meta-analysis, or where substantial heterogeneity precluded meta-analysis, we presented a table of findings of individual included studies. Statistical analysis was performed using SAS 9.3 (Cary, NC, USA). Forest plots of proportions were created using R version 3.2.5. An assessment of the overall study outcomes were performed using the GRADE methodology and summarized using GRADEPro software.

Results

Search results

The database search identified 1818 non-duplicate records. An additional six records were identified from searching conference abstracts (two) and bibliography lists of relevant papers (four). The title and abstract of 1824 records were reviewed identifying 41 articles for full-text review. Of these, 33 did not meet the inclusion criteria (see Figure 1 and Annex 2 for reasons for exclusion), leaving eight eligible studies (one unpublished) for review inclusion. [13, 29-35] Figure 1 shows the flow of search results and selection of eligible studies. The search was performed in January 2016.

Figure 1: Diagram of search results for eligible studies included in review of decentralised care of MDR-TB, compared to centralised care.



Findings

Key characteristics of the eight included studies are presented in Table 3. Of these studies, which included 4,493 patients with MDR-TB, two were performed in high income countries - Taiwan and the United States. The remainder were from low and middle income countries - South Africa, Swaziland, the Philippines and Nigeria. Two studies modelled cost-effectiveness, whilst the remaining six were cohort studies and reported on treatment outcomes (six) and/or cost of health-care (one). Of the studies that reported on treatment outcomes, five evaluated treatment success, four - loss to follow-up, four – death, and three - treatment failure. There were no randomised controlled trials evaluating decentralised MDR-TB treatment and care. Decentralised care described in the different studies included both home-based and decentralised clinic-based care. In one study, decentralised care occurred in a rural hospital.[32] In all except for one study, centralised care occurred in a specialised hospital. The (unpublished) study by Kerschberger et al [35] compared home-based DOT by trained community volunteers to a control cohort of clinic-based care by nurses. Based on a consensus of reviewers, this study was judged to be eligible for review inclusion given that the intervention provided decentralised care aimed to overcome the limitations of the existing treatment program which was clinic based care. Most decentralised and centralised management approaches used DOT. Importantly, patient selection for decentralised care was not randomised in any of the included cohort studies. Instead, treatment allocation was based upon patient factors likely to make centralised care more difficult or less successful e.g. residential location far from a centralised facility. No studies reported on treatment adherence, the acquisition of drug resistance or treatment costs for individual patients.

Pooled treatment outcome estimates

Table 4 shows the results of the pooled estimates for treatment outcomes. There were five studies which evaluated treatment success. The pooled relative risk (RR) from these five studies showed improved treatment success with decentralised compared to centralised treatment - pooled RR = 1.13 (95% CI 1.01-1.27). Pooled proportions of studies evaluating treatment success for decentralised and centralised care were 67.3% (95%CI: 53.8-78.5%) and 61.0% (95%CI: 49.0-71.7%) respectively. The pooled analysis of the four studies evaluating loss to follow up for MDR-TB patients showed a trend towards reduced loss to follow up with decentralised versus centralised care – pooled RR = 0.66 (95%CI 0.38-1.13). Pooled proportions of studies evaluating loss to follow-up for decentralised and centralised care were 11.9% (95%CI: 5.7-23.3%) and 18.0% (95%CI: 9.3-31.8%) respectively. The pooled RR from the four studies which evaluated death with decentralised, compared to centralised treatment was 1.01 (95% CI: 0.67-1.52). Pooled proportions of studies evaluating death for decentralised and centralised care were 17.8% (95%CI: 15.9-19.9%) and 18.6% (95%CI: 14.5-23.6%) respectively. The three studies evaluating treatment failure resulted in a pooled RR of 1.07 (95%CI 0.48-2.40) for decentralised versus centralised care. Pooled proportions of studies evaluating treatment failure for decentralised and centralised care were 4.2% (95%CI: 1.4-11.9%) and 4.3% (95%CI: 2.3-8.1%) respectively. There was considerable heterogeneity observed between studies. Figure 2 shows forest plots of these four outcome measures for

decentralised versus centralised MDR-TB treatment and care. Figure 3 shows a forest plot of proportions for treatment success. Owing to the small number of eligible studies, we did not formally assess publication bias.

Sensitivity analysis (analysis excluding Narita *et al*) for treatment outcomes

Of the studies eligible for review inclusion, the study by Narita *et al*[13] differs from the other studies with respect to: the income level of the country (high income versus predominantly low income), the years in which the intervention was conducted (1990s versus 2000s), the small sample size and the method of selection into the intervention and control groups (patients were selected for specialised TB hospital care if they were failing treatment or non-adherent) (Table 3). The results for treatment success and death for this study differ significantly from the other studies, and have wide confidence intervals (forest plots in Figure 2 and 3). Due to the marked heterogeneity of this study compared to the other included studies, we compared pooled proportions and relative risk estimates of the studies reporting on treatment success and death, with and without inclusion of the Narita *et al* study (Table 5). There was no significant difference in these estimates when this study was or was not included in the analysis. The study by Narita *et al* did not report treatment failure or loss to follow-up.

Treatment costs

Of the eight studies eligible for review inclusion, three (two modelling[33, 34] and one cohort study[35]) reported on treatment costs. Table 6 compares the treatment cost to the health-care system for one MDR-TB patient in the decentralised and centralised setting. The two modelling studies showed significant cost savings using a decentralised compared with a centralised model. Whereas, the study by Kerschberger *et al[35]* showed similar treatment costs for both treatment models.

Methodological quality of included studies

Table 4 and 7 shows the risk of bias assessment for the six included studies (excluding modelling studies). In all studies, a non-random method was used to select the intervention and control cohorts. In four of the six studies, the patients were chosen for decentralised treatment based on patient factors, such as residential location, socio-economic factors and risk factors for loss to follow-up. In the remaining two studies, treatment of the intervention and control groups occurred consecutively (not concurrently) reflecting the implementation of a new decentralised treatment program. Heterogeneity (inconsistency) was observed for all treatment outcomes, as indicated by the high I^2 values (from 74 to 88%) for pooled RR estimates. For all treatment outcomes, except for treatment success, there were wide variances in the point estimates (Figure 2). These risk of bias and heterogeneity factors reduced the overall quality of the evidence (rated as very low) for all treatment outcomes (Table 4).

Uncontrolled studies

Table 8 shows a summary of the key characteristics for the studies evaluating treatment outcomes using decentralised care for MDR-TB, which do not have a control group. Our search found 16 such studies where decentralised treatment alone, without direct comparison to centralised treatment, was evaluated. Although these studies did not met the eligibility criteria for review inclusion, this summary has been included to provide additional information to the studies which were eligible for review inclusion, and includes all of the more recent studies compared to the last systematic review on this subject.[12]. We excluded one study[36] from the pooled analysis that reported on treatment outcomes of MDR-TB patients treated in a field hospital after an earthquake, as this unique study setting is not representative of routine programmatic conditions.

(i) Treatment outcomes

Table 9 shows the event frequency and pooled proportion estimates for the studies that reported on treatment outcomes. Included in this table for comparison, are the pooled proportions for the studies in this review which did include a control group, and also data from an individual patient data meta-analysis (9,153 patients from 32 observation studies) of MDR-TB treatment outcomes.[37]. The latter serves as a comparison of the pooled results from the uncontrolled studies of MDR-TB treatment, in a decentralised setting, with a 'control' group - studies evaluating MDR-TB treatment in a non-specific setting (this may include both decentralised and centralised care models). Figure 4 shows the forest plots of proportions for treatment success of the studies evaluating decentralised care for MDR-TB, without a control group.

(ii) Adverse events from TB medications

There were no studies eligible for review inclusion (i.e. included a control group), that evaluated adverse events associated with TB medications. Of the 16 uncontrolled studies, nine studies reported on adverse drug events. Table 10 shows the adverse event frequency (any adverse event, severe adverse event or any adverse event requiring discontinuation of therapy) and pooled proportion estimates for these studies.

Strengths and weaknesses of this review

The results of this review are based on comprehensive database and other information source searching. This review had strict eligibility criteria which only permitted studies which directly compared intervention and control cohorts from the same study population to be included. This substantially reduced the risk of bias due to indirectness, and is a defining feature of this review compared to other systematic reviews on this subject. However, including only studies with both an intervention and control group reduced the final number of included studies and potentially reduced the precision of the estimates. In addition there was an absence of data for a number of *a priori* outcomes of interest. Substantial heterogeneity was also observed between included studies. This likely reflects the important differences between the study settings and the specific interventions used in each setting. We addressed

the limitation of the small number of eligible studies by presenting additional data from studies on decentralised care for MDR-TB that did not include a control group. W

Authors conclusions

In conclusion, this review demonstrated that treatment success for MDR-TB patients improved with decentralised care. Loss to follow-up was also reduced with decentralised models of care, although the confidence limits crossed the null. No difference was seen between the rate of death or treatment failure between these two groups.

These findings are consistent with previous systematic reviews.[11, 12]. Given the diversity of each setting in which MDR-TB patients are managed (e.g. cultural and socio-economic differences and the availability of infrastructure and personnel), heterogeneity of decentralised care amongst different studies is to be expected. This underpins the importance of further research in different settings. As national TB programs from TB endemic countries throughout the world increasingly adopt decentralised approaches for managing patients with MDR-TB, careful and thorough reporting of program interventions and outcomes (e.g. using 'before and after' or stepped-wedge study designs) should be undertaken out so that the benefit of such interventions can be accurately determined and reported.

Finally, whilst a decentralised approach to MDR-TB management may improve treatment outcomes at the level of the population, management of each patient with MDR-TB should be tailored, where possible, to the individual's requirements and circumstances. Clinicians and health services will need to tailor policies to maximise treatment outcomes, and minimise socioeconomic hardship. Thus, TB treatment programmes should aim for a combination of available treatment models, in order to serve the needs of all patients.

Declaration of interests

The review authors have no financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the review.

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Table 4: Key characteristics of included studies in systematic review of decentralised versus centralised treatment for MDR-TB

Author; Year; Country	Study design	Year of inter-vention	Sample size: inter-vention, control	HIV prevalence in study population	Description of control arm	Description of inter-vention arm	Method of selection of intervention group	Timing of intervention within TB treatment	Intervention and control: concurrent or consecutive	Outcomes measured
Loveday;[32] 2015; South Africa (KwaZulu-Natal)	Prospec-tive cohort	2008-2010	736, 813	75%	Treatment in central specialised TB hospital	Treatment in rural hospital followed by outpatient DOT (home or clinic based) by health workers	Based on residential location	Intensive phase	Concurrent	Treatment success Death Loss to follow-up Treatment failure
Chan;[29] 2013; Taiwan	Prospec-tive cohort	2007-2008	290, 361	0.9%	Hospital and out-patient clinics	Home based DOT by 'observers' and nurses	Time period	Entire duration of treatment	Consecutive	Treatment success
Kersch-berger;[35] 2016; Swaziland	Prospec-tive cohort	2008-2013	157; 298	81%	Clinic based care (patients visited nearest health facility daily)	Home based DOT by trained community volunteers	Based on residential location and socio-economic status	Intensive phase	Concurrent	Treatment success Death Loss to follow-up Treatment failure Cost to health care
Narita;[13] 2001; US (Florida)	Retro-spective cohort study	1994-1997	31,39	44.3%	Treatment in specialised TB hospital	Outpatient therapy (DOT and/or SAT)	Selected for control if: failing treatment, needed treatment of other medical condition, non-adherent	Entire duration of treatment	Concurrent	Treatment completion Death
Gler;[31] 2012; Philippines	Retro-spective cohort study	2003-2006	167, 416	Not stated	Treatment in central hospital	Community based DOT by trained health care workers.	Time period	After sputum culture conversion	Consecutive	Loss to follow-up
Cox;[30] 2014; South Africa (Khaye-litsha)	Retro-spective cohort study	2008-2010	512, 206	72%	Hospital based care	Community based care integrated into existing primary care TB and HIV services.	Based on residential location	Entire duration of treatment	Consecutive	Treatment success Death Loss to follow-up Treatment failure
Musa;[33] 2015; Nigeria	Mod-elling study	N/A	N/A	Not stated	Hospital based care	Home based DOT by trained health-care providers	Random selection	Intensive phase	N/A	Cost to health-care
Sinanovic;[34] 2015; South Africa (Khayelitsha)	Mod-elling study	N/A	467 total	72%	Fully hospitalised model (stay in hospital until culture conversion)	1 fully decentralised model (in primary health care clinics); 2 partially decentralised models	N/A	Entire duration of treatment	N/A	Cost to health-care

DOT = directly observed therapy; TB = tuberculosis; HIV = human immunodeficiency virus; SAT = self-administered therapy; MDR = multi-drug resistant; N/A = not applicable
Intensive phase defined by inclusion of an injectable antibiotic in the treatment regimen

Table 5: GRADE table of included studies in systematic review of decentralised versus centralised treatment for MDR-TB, showing pooled estimates for treatment outcomes and quality assessment of studies

Quality assessment							No of patients		Effect Estimate		Qua-lity	Impor-tance
No of studies	Design	Limi-tations*	Inconsistency**	Indirect-ness***	Imprecision ****	Other	Decentralised care N events/N patients (pooled proportion, 95% CI)	Centralised care N events/N patients (pooled proportion, 95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)		
Treatment Success vs Treatment Failure / Death / Loss to Follow-Up												
5	Obser-vatio-nal Studies	Serious con-cerns	No con-cerns	No con-cerns	No con-cerns	None	1035 / 1695 (0.67, 0.54-0.79)	979 / 1710 (0.61, 0.49-0.72)	1.13 (1.01-1.27)	74 more per 1,000 (from 6 more to 155 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to Follow-Up vs Treatment Success/ Treatment Failure / Death												
4	Obser-vational Studies	Serious con-cerns	Serious con-cerns	No con-cerns	No con-cerns	None	278 / 1549 (0.12, 0.06-0.23)	384 / 1727 (0.18, 0.09-0.32)	0.66 (0.38-1.13)	76 fewer per 1,000 (from 29 more to 138 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Death vs Treatment Success / Treatment Failure / Loss to Follow-Up												
4	Observa-tional Studies	Serious con-cerns	Serious con-cerns	No con-cerns	No con-cerns	None	250 / 1405 (0.18, 0.16-0.20)	232 / 1349 (0.19, 0.15-0.24)	1.01 (0.67-1.52)	2 more per 1,000 (from 57 fewer to 91 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment Failure vs Treatment success / Death / Loss to Follow-Up												
3	Observa-tional Studies	Serious con-cerns	Serious con-cerns	No con-cerns	No con-cerns	None	90 / 1382 (0.04, 0.01-0.12)	55 / 1311 (0.04, 0.02-0.08)	1.07 (0.48-2.40)	3 more per 1,000 (from 22 fewer to 59 more)	⊕◯◯◯ VERY LOW	CRITICAL

* Limitations - All of the studies were observational studies.
The method of allocating patients to intervention and control groups was not randomised.

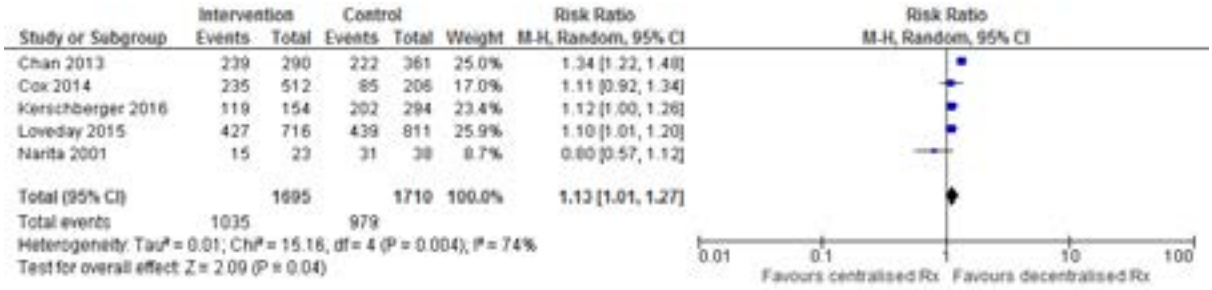
** Inconsistency - Based on estimated I^2

*** Indirectness – the study interventions and outcomes were directly relevant to the objective of this review

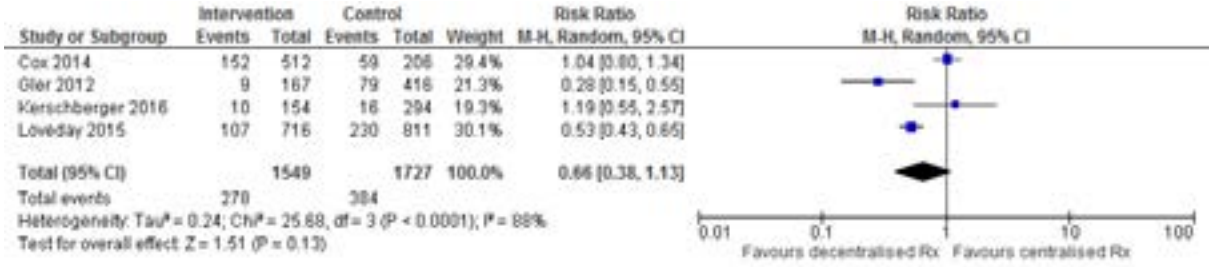
**** Imprecision – Based on 95% CIs

Figure 2:

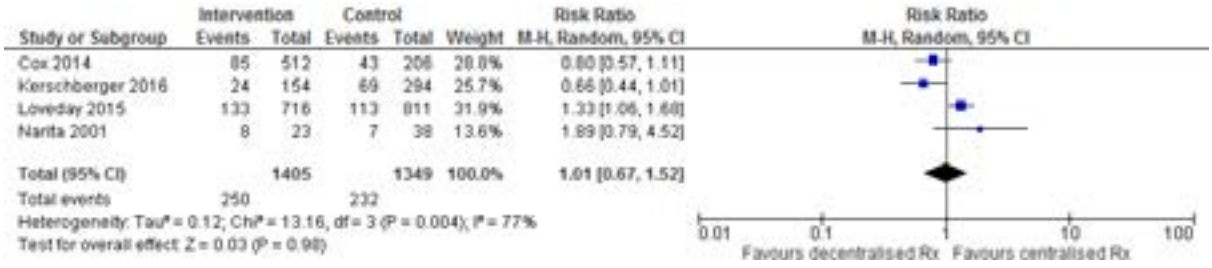
Forest Plot of Treatment Success for Decentralised versus Centralised MDR-TB treatment and care



Forest Plot of Loss to Follow-up for Decentralised versus Centralised MDR-TB treatment and care



Forest Plot of Death for Decentralised versus Centralised MDR-TB treatment and care



Forest Plot of Treatment Failure for Decentralised versus Centralised MDR-TB treatment and care

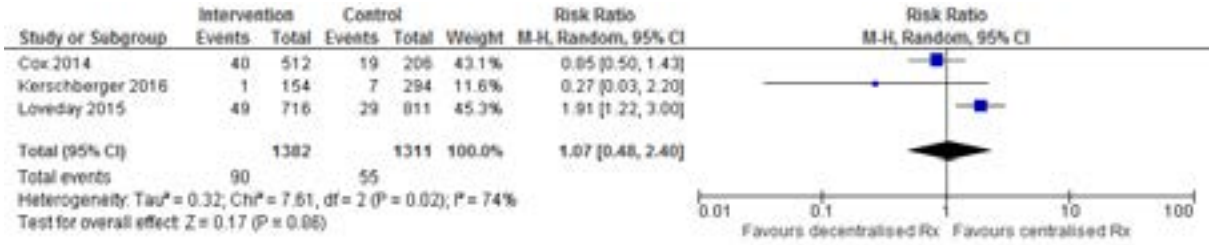
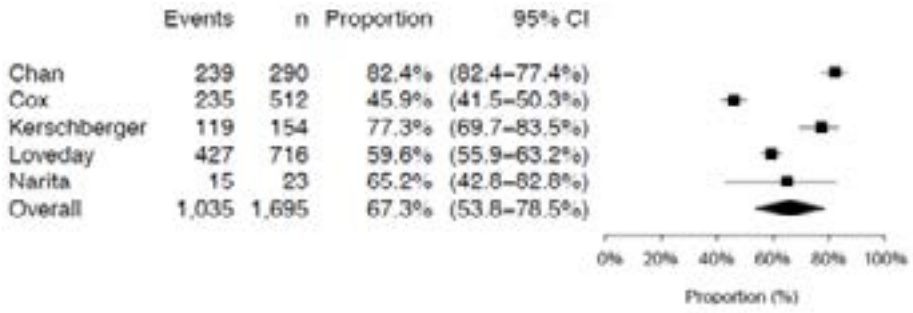


Figure 3: Forest plots of proportions for treatment success

(i) Decentralised treatment and care (intervention)



(ii) Centralised treatment and care (control)

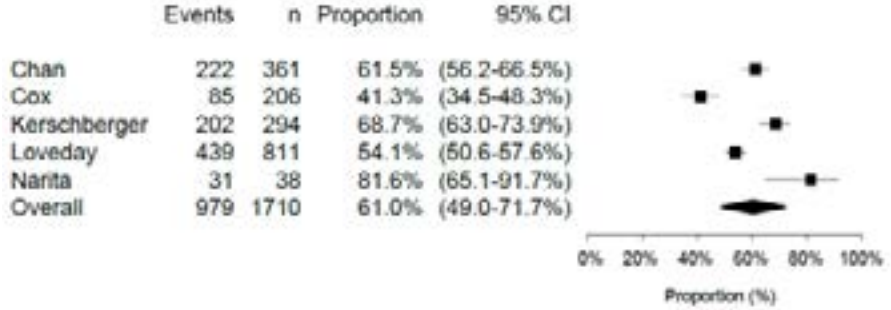


Table 6: Comparison of pooled proportion and relative risk estimates for studies evaluating treatment success and death, including and excluding Narita *et al[13]*

(a) Treatment success

Studies included in analysis	Studies (n)	Pooled proportion (95% CI) decentralised care	I^2	Pooled proportion (95% CI) centralised care	I^2	Pooled relative risk (95% CI) decentralised vs centralised care	I^2
Narita included	5	0.67 (0.54-0.79)	97.4%	0.61 (0.49-0.72)	93.4%	1.13 (1.01-1.27)	74%
Narita excluded	4	0.68 (0.52-0.63)	98.1%	0.57 (0.47-0.66)	92.8%	1.17 (1.05-1.30)	71%

(b) Death

Studies included in analysis	Studies (n)	Pooled proportion (95% CI) decentralised care	I^2	Pooled proportion (95% CI) centralised care	I^2	Pooled relative risk (95% CI) decentralised vs centralised care	I^2
Narita included	4	0.18 (0.16-0.20)	49.5%	0.19 (0.15-0.24)	82.3%	1.01 (0.67-1.52)	77%
Narita excluded	3	0.18 (0.16-0.20)	0.0%	0.19 (0.14-0.24)	88.3%	0.91 (0.59-1.42)	82%

Table 7: Treatment cost to the health-care system for one MDR-TB patient in the decentralised and centralised care setting (in US dollars)

Study	Study Design	Country	Description of decentralised care	Cost of decentralised care	Description of centralised care	Cost of centralised care
Musa[33] 2015	Modelling	Nigeria	Home-based care for entire duration of treatment	$1,535	Hospital-based care for intensive phase then home-based care for continuation phase	$2,095
Sinanovic[34] 2015	Modelling	South Africa	Primary health-care clinic for entire duration of treatment	$7,753	Hospital-based care for intensive phase (until 4 month culture conversion) then clinic based care	$13,432
Kerschberger [35] 2016	Retrospective cohort	Swaziland	Home-based care for entire duration of treatment	$13,361	Clinic-based care for intensive phase then home-based care for continuation phase	$13,006

Table 8: Risk of Bias Assessment[23] of Included Studies (excluding modelling studies)

Study	Selection (max = 4)	Comparability (max = 2)	Outcome (max = 3)	Total score[1] (max = 9)
Loveday 2015	3	0	3	6
Chan 2013	4	1	3	8
Kerschberger 2016	3	0	3	6
Narita 2001	2	0	3	5
Gler 2012	4	1	3	8
Cox 2014	3	0	3	6

[1] A higher score is associated with a lower risk of bias

Table 9: Key characteristics of the 16 studies on decentralised treatment and care for MDR-TB patients, without a comparator group

Author; year; country	Study design	Number receiving intervention	HIV prevalence	Description of intervention	Outcome measures reported	Overall findings/conclusion
Brust;[38] 2013; South Africa (KwaZulu-Natal)	Prospective cohort	91	81%	Home based care: nurses, CHWs, and family supporters trained to administer injections, provide adherence support, and monitor for adverse reactions.	Adverse events	In MDR-TB/HIV co-infected patients AE's to medications were common but most mild. Those on ART did not experience more AE's. Co-infected pts can be treated safely in a home-based setting
Brust;[39] 2012; South Africa (KwaZulu-Natal)	Prospective cohort	80	82.5%	Home based care: nurses, CHWs, and family supporters trained to administer injections, provide adherence support, and monitor for adverse reactions.	Treatment outcomes	Integrated, home-based treatment for MDR-TB and HIV may improve Rx outcomes in rural, resource-poor, high-HIV prevalent settings
Burgos;[4] 2005; US (San Francisco)	Retrospective cohort	48	23%	DOT was provided in the field by unlicensed public health personnel or at the clinic by an assigned nurse	Treatment outcomes; Adverse events Health-care cost	Treatment of MDR-TB in HIV negative patients as an outpatient is feasible and associated with high cure rates and lower cost than in other published studies. Patients with HIV infection had very poor treatment outcomes
Cavanaugh;[40] 2016; Bangladesh	Retrospective cohort	77	0%	Home based DOT by trained paraprofessionals who administer medications (including injections), and monitor for adverse events.	Adverse events (documentation versus patient interview recollection)	The programme appears to be feasible and clinically effective however there is inadequate monitoring of adverse events
Charles;[36] 2014; Haiti	Retrospective cohort	110	25%	Field hospital established after the hospital was destroyed in the earthquake for the management of MDR-TB patients in Port-au-Prince.	Treatment outcomes	Good outcomes for MDR-TB patients in the field hospital setting despite the adverse conditions
Drobac;[41] 2005; Peru (Lima)	Retrospective cohort	38	6%	Community-based DOTS for children with MDR-TB	Treatment outcomes; Adverse events	Percentage cured in this community-based treatment program (94%) was at least as high as any reported for a referral hospital setting and was higher than that for adults enrolled in the DOTS program in Peru
Furin;[42] 2001; Peru (Lima)	Retrospective cohort	60	1.7%	Community-based DOTS	Adverse events	In young patients with little comorbid disease, MDR-TB Rx rarely caused life-threatening adverse effects. Common side effects may be managed successfully on an out-patient basis
Isaakidis;[43] 2012; India (Mumbai)	Prospective cohort	67	100%	Community-based program for Rx of patients with HIV/MDR-TB co-infection	Adverse events	AE's occurred frequently in this MDR-TB/HIV cohort but not more frequently than in non-HIV patients on similar TB medications. Most AE's can be successfully managed on an outpatient basis through a community-based treatment program
Isaakidis;[44] 2011; India (Mumbai)	Prospective cohort	58	100%	Outpatient care for HIV/MDR-TB co-infected patients involving public-private ARV centres and a network of community NGOs	Treatment outcomes	Encouraging rates of survival, cure and culture conversion were found with this Rx program

Author; year; country	Study design	Number receiving intervention	HIV prevalence	Description of intervention	Outcome measures reported	Overall findings/conclusion
Malla;[45] 2009; Nepal	Prospective cohort	175	Not stated	DOT on an ambulatory basis through a decentralized network of clinics	Treatment outcomes	There were high MDR-TB cure rates in this ambulatory-based treatment programme
Mitnick;[46] 2003; Peru (Lima)	Retrospective cohort	75	1.3%	Community-based DOT	Treatment outcomes; Adverse events	There were high MDR-TB cure rates in this community-based treatment programme
Mohr;[47] 2015; South Africa (Khayelitsha)	Retrospective cohort	853	70.9%	Community-based Rx for DR-TB in the patient's nearest primary care clinic.	The impact of HIV and other factors on DR-TB treatment outcomes	Response to DR-TB treatment did not differ with HIV infection in a programmatic setting with access to ART
Satti;[48] 2012; Lesotho	Retrospective cohort	19	74%	Community-based Rx for children with MDR-TB	Treatment outcomes; Adverse events	Paediatric MDR-TB and MDR-TB/HIV co-infection can be successfully treated using a combination of social support, close monitoring by community health workers and clinicians, and inpatient care when needed
Seung;[5] 2009; Lesotho	Retrospective cohort	76	74%	Community-based DOT that included social and nutritional support	Treatment outcomes; Adverse events	This program was successful in reducing mortality in MDR-TB patients
Thomas;[49] 2007; India (Chennai)	Prospective cohort	66	Not stated	MDR-TB management under field conditions where DOTS programme has been implemented	Feasibility; Treatment outcomes; Adverse events	Rx outcomes in this program were suboptimal. The main challenge was identifying providers close to patient's residential location who were able to administer injections, and manage of drug AE's
Vaghela;[50] 2015; India (Delhi)	Prospective cohort	113	Not stated	Home based MDR-TB treatment and care with counselling support.	Treatment outcomes	Home based care with counselling support is an important intervention in management of MDR-TB patients

CHW = community health worker; MDR-TB = multi-drug resistant tuberculosis; HIV = Human Immunodeficiency Virus; AE = adverse event; DOT = directly observed therapy; DOTS= directly observed therapy short course; NGO = non-government organisation; TB = tuberculosis; DR-TB = drug resistant tuberculosis; ART = anti-retroviral therapy

Table 10: Event frequency and pooled proportion estimates for treatment outcomes of studies without a comparator group, evaluating decentralised treatment and care for MDR-TB patients. Included for comparison, are studies that do include a comparator group, and a meta-analysis of MDR-TB treatment outcome in a non-specific setting[37]

a) Treatment success (vs death, treatment failure, loss to follow-up)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	13	955	1,570	76.1%	62.7%	85.9%	97.0%
Decentralized [b]	5	1,035	1,695	67.3%	53.8%	78.5%	97.4%
Centralized [b]	5	979	1,710	61.0%	49.0%	71.7%	93.4%
Non-specific [c]	15	NR	4,637	64%	52%	76%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

b) Death (vs treatment success, treatment failure, loss to follow-up)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	13	228	1,570	11.8%	7.3%	18.3%	84.1%
Decentralized [b]	4	250	1,405	17.8%	15.9%	19.9%	49.5%
Centralized [b]	4	232	1,349	18.6%	14.%	23.6%	82.3%
Non-specific [c]	15	NR	4,637	8%	3%	12%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

c) Treatment failure (vs treatment success, death, loss to follow-up)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	12	85	1,526	3.0%	1.3%	6.5%	90.4%
Decentralized [b]	3	90	1,382	4.2%	1.4%	11.9%	93.7%
Centralized [b]	3	55	1,311	4.3%	2.3%	8.1%	87.0%
Non-specific [c]	15	NR	4,637	5%	1%	8%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

d) Loss to follow-up (vs treatment success, treatment failure, death)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	13	300	1,570	6.1%	2.9%	12.4%	98.2%
Decentralized [b]	4	278	1,549	11.9%	5.7%	17.8%	98.1%
Centralized [b]	4	384	1,727	18.0%	9.3%	31.8%	97.0%
Non-specific [c]	15	NR	4,637	15%	8%	22%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

Figure 4: Forest plots of proportions for treatment success of the studies evaluating decentralised care for MDR-TB without a control group

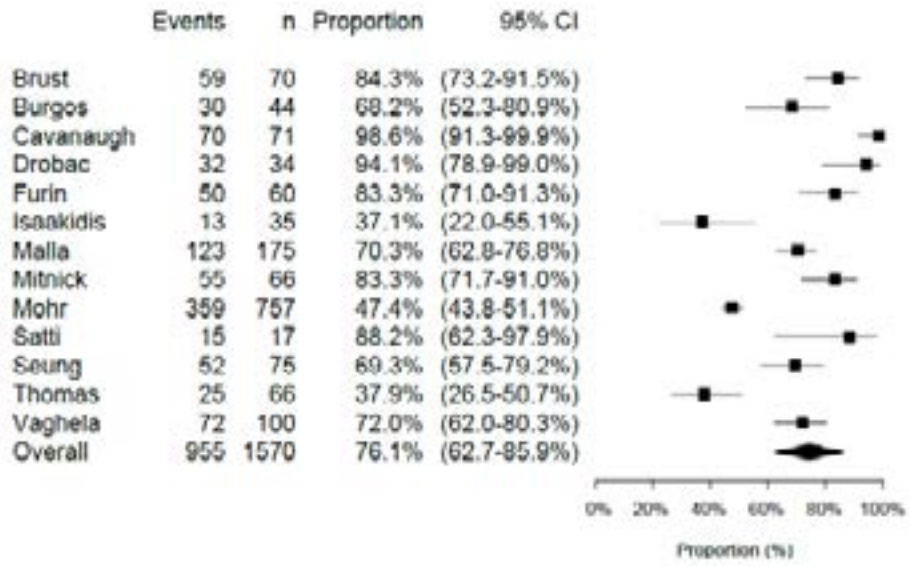


Table 11: Event frequency and pooled proportion estimates for studies evaluating decentralised care for MDR-TB, reporting on adverse events from TB medications

MDR-TB treatment model	Studies (n)	Outcome	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	9	Any adverse events	410	521	86.3%	65.0%	95.6%	94.4%
Decentralized [a] (no control)	3	Severe adverse events	47	175	22.2%	7.4%	50.5%	92.1%
Decentralized [a] (no control)	8	Adverse events requiring discontinuation of therapy	76	445	7.4%	1.9%	25.0%	95.6%

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

Appendixes

Appendix 1: Search terms used and reference retrieval success

Medline

URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: January 2016

1) Tuberculosis, Multidrug-Resistant [MeSH]
» OR
» ((tuberculosis OR TB) AND (multidrug-resistan* OR multidrug resistan* OR multi-drug resistan* OR "drug resistan*" OR drug-resistan* OR multiresistan* OR "multi resistan*" OR "rifampicin resistan*" OR "extensively drug-resistan*" OR "extensively-drug resistan*" OR "extensively resistan*" OR MDR OR XDR OR TDR)) OR mdrtb OR xdr tb OR mdrtb OR mdr-tb OR xdr-tb OR tdr-tb OR "MDR TB" OR "XDR TB" OR "TDR TB"

AND

2) ("directly observed" OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR "patient support")
» AND
» (community OR outpatient OR "public participation" OR community-based OR decentralized OR non-specialized OR "periph* health centres" OR home-based OR ambulatory OR clinic OR "community health worker" OR CHW OR volunteer)

1030 search results returned → title and abstract reviewed → 24 identified for full-text review

EMBASE

URL: http://www.embase.com

Search date: January 2016

1. Multidrug resistant tuberculosis.sh
2. (tuberculosis or TB).af
3. (multidrug-resistan* or multidrug resistan* or multi-drug resistan* or drug resistan* or drug-resistan* or multiresistan* or multi resistan* or rifampicin resistan* or extensively drug-resistan* or extensively-drug resistan* or extensively resistan* or MDR or XDR or TDR).af
4. 2 and 3
5. (MDRTB or XDRTB or TDRTB or MDR-TB or XDR-TB or TDR-TB or MDR TB or XDR TB or TDR TB).af
6. 1 or 4 or 5
7. (directly observed OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR patient support).af
8. (community OR outpatient OR public participation OR community-based OR

decentralized OR non-specialized OR periph* health centres OR home-based OR ambulatory OR clinic OR community health worker OR CHW OR volunteer).af.

9. 7 AND 8
10. 6 AND 9

1109 search results returned → title and abstracts reviewed → 18 identified for full text review → 10 relevant repeat studies from Medline search found (no additional studies found) and 2 relevant conference abstracts found

Cochrane Library including: Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Database of Systematic Reviews (CDSR)

URL: http://onlinelibrary.wiley.com/cochranelibrary/search/

Search date: January 2016

1. MeSH descriptor: [Tuberculosis, Multidrug-Resistant] explode all trees OR
2. ((tuberculosis OR TB) AND (multidrug-resistan* OR "multidrug resistan*" OR multi-drug resistan* OR "drug resistan*" OR drug-resistan* OR multiresistan* OR "multi resistan*" OR "rifampicin resistan*" OR "extensively drug-resistan*" OR "extensively-drug resistan*" OR "extensively resistan*" OR MDR OR XDR OR TDR)) OR (MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR "MDR TB" OR "XDR TB" OR "TDR TB")
3. #1 OR #2
4. ("directly observed" OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR "patient support") AND (community OR outpatient OR "public participation" OR community-based OR decentralized OR non-specialized OR "peripheral health centres" OR home-based OR ambulatory OR clinic OR "community health worker" OR CHW OR volunteer)
5. #3 AND #4

13 search results returned → no relevant reviews found

WHO portal of clinical trials

URL: http://apps.who.int/trialsearch/

Search date: January 2016

multi-drug resistant tuberculosis OR multidrug resistant tuberculosis OR multi drug resistant tuberculosis AND treatment (status=ALL)

64 records for 53 trials returned → no relevant studies found

LILACS

URL: http://lilacs.bvsalud.org/en/

Search date: January 2016

((MH: tuberculosis OR TB) AND (multidrug-resistan$ OR "multidrug resistan$" OR "multi-drug resistan$" OR "drug resistan$" OR drug-resistan$ OR multiresistan$ OR "multi resistan$" OR "rifampicin resistan$" OR "extensively drug-resistan$" OR "extensively-drug resistan$" OR "extensively resistan$" OR MDR OR XDR OR TDR)) OR MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR "MDR TB" OR "XDR TB" OR "TDR TB"

AND

(MH: "directly observed" OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR "patient support") AND (community OR outpatient OR "public participation" OR community-based OR decentralized OR non-specialized OR "periph$ health centres" OR home-based OR ambulatory OR clinic OR "community health worker" OR CHW OR volunteer)

7 search results returned → no relevant studies identified

Web of Science

URL: http://wokinfo.com/

Search date: January 2016

((Multidrug-Resistant Tuberculosis) OR ((tuberculosis OR TB) AND ((multidrug-resistan*) OR (multidrug resistan*) OR (multi-drug resistan*) OR (drug resistan*) OR (drug-resistan*) OR (multiresistan*) OR (multi resistan*) OR (rifampicin resistan*) OR (extensively drug-resistan*) OR (extensively-drug resistan*) OR (extensively resistan*) OR MDR OR XDR OR TDR)) OR (MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR (MDR TB) OR (XDR TB) OR (TDR TB))) AND ((directly observed OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR patient support) AND (community OR outpatient OR public participation OR community-based OR decentralized OR non-specialized OR peripheral health centres OR home-based OR ambulatory OR clinic OR community health worker OR CHW OR volunteer))

753 search results returned → title and abstracts reviewed → 19 relevant studies identified → Nil studies in addition to those from Medline identified

OpenSIGLE

URL: http://www.opengrey.eu/search/

Search date: January 2016

Multidrug-Resistant Tuberculosis OR ((tuberculosis OR TB) AND ((multidrug-resistan*) OR (multidrug resistan*) OR (multi-drug resistan*) OR (drug resistan*) OR multiresistan* OR (multi resistan*) OR MDR OR XDR) OR MDRTB OR XDRTB OR MDR-TB OR XDR-TB

No search terms used for intervention or outcomes.

76 search results returned → no relevant studies found

Google scholar

URL: https://scholar.google.com/

Search date: January 2016

multidrug resistant tuberculosis; community treatment

First 10 pages screened – 5 relevant studies identified. Nil studies in addition to those from Medline identified

International Union of Tuberculosis and Lung Disease conference electronic abstract database

URL: http://www.theunion.org/what-we-do/journals/ijtld/conference-abstract-books

Search date: January 2016

Hand searching of pdf's from the past 10 years (2006-2015) for abstracts related to MDR-TB and decentralised treatment.

2 relevant abstracts found → Author of 1 abstract contacted to obtain further information. Unable to contact the authors from the other abstract.

ClinicalTrials.gov

URL: https://clinicaltrials.gov/ct2/home

Search date: January 2016

multi drug resistant tuberculosis OR multi-drug resistant tuberculosis OR MDR TB OR MDR-TB

90 studies found → title and abstract reviewed → no relevant studies found

Review of reference lists from related review papers and from relevant papers identified from the database search → 1 additional study identified

Appendix 2: Full-text papers reviewed but excluded from review inclusion and reasons for exclusion

Reason for exclusion	References excluded from main analysis (N = 33)
No comparator group included in study	[4, 5, 36, 38-50]
Did not include outcomes in interest	[51, 52]
Review article (not an original study)	[6, 11, 12, 15-17, 21]
Did not include intervention of interest	[53, 54]
Conference abstract - subsequently published	[55]
Conference abstract - author uncontactable for further study information	[56]
Study published elsewhere	[57, 58]
Sample size <10 participants	[59]

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Web Annex 3.3. Guideline update 2022

PICO 6: Evidence review on decentralized, integrated, and family-centered care for children and adolescents affected by TB in high-burden settings

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1. Background

Tuberculosis (TB) remains a leading infectious cause of morbidity and mortality in children and adolescents worldwide. In 2019, 10 million people fell ill with TB, and an estimated 1.2 million of these were children < 15 years old.[1] However, approximately half of these children were diagnosed and treated, and only 27% of child contacts <5 years old eligible for TB preventive treatment in fact received it. Thus, major gaps persist in the detection and prevention of childhood TB. The effectiveness of TB detection and prevention programs for children and adolescents could be affected by the model of care delivery. As part of the process for updating the WHO guidelines on the management of child and adolescent TB, the WHO Guideline Development Group (GDG) requested a systematic review to evaluate the evidence for different models of care in high-TB burden settings. Specifically, we assessed the evidence whether or not decentralized, integrated, and family-centered care models should be recommended over traditional services to decrease the burden of TB in children and adolescents globally. The terms of reference were:

- Conduct a systematic review on models of care for TB case detection and TB prevention in children and adolescents in high TB burden settings
- Draft a systematic review report for WHO and WHO GDG
- Create GRADE profiles in GradePro, based on the PICO question, incorporating the systematic review results as well as any non-published trial data, including a summary of accuracy data, quality assessment of the evidence, justification of the quality grading
- Powerpoint presentation for the session of the WHO GDG models of care
- Final systematic review report incorporating edits and revisions suggested by WHO and GDG members

All aspects of the terms of reference have been completed.

2. PICO question

The 4-part PICO question was focused on "models of care for TB case detection and TB prevention in high TB burden settings (prevalence of TB in the general population of 100 per 100,000 or more)" (Table 1).

Table 1: PICO question

Population	Intervention	Comparator	Outcome/s
Children and adolescents aged 0–19 years with signs and symptoms of TB in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Decentralization of TB diagnostic, treatment and/or care services to district hospital or primary healthcare or community level	Centralized paediatric TB diagnostic, treatment and care services (at referral or tertiary hospital level)	• TB case notifications • Time to diagnosis • Treatment outcomes (treatment success, treatment failure, death, loss to follow up) • Patient costs • Barriers to access • Access to schooling
Children and adolescents aged 0–19 years exposed to TB (i.e. TB contacts) in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Decentralization of TB prevention services to district hospital or primary healthcare or community level	Centralized paediatric TB prevention services (at referral or tertiary hospital level)	• Coverage of TB preventive treatment in eligible child and adolescent TB contacts • Time to TPT initiation • TPT completion rate
Children and adolescents aged 0–19 years with signs and symptoms of TB in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Family-centred, integrated services	Standard, non-family-centred, non-integrated services	• TB case notifications • Time to diagnosis • Treatment outcomes (treatment success, treatment failure, death, loss to follow up) • Patient costs • Barriers to access • Access to schooling
Children and adolescents aged 0–19 years exposed to TB (i.e. TB contacts) in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Family-centred, integrated services	Standard, non-family-centred, non-integrated services	• Coverage of TB preventive treatment in eligible child and adolescent TB contacts • Time to TPT initiation • TPT completion rate

Decentralized care was defined as "child and adolescent TB services at a lower level of the health system than the lowest level where this is currently routinely provided. In most settings, decentralization would apply to district hospital…and/or primary health care level and/or community level." Integrated care was defined as "approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health related programmes and services." Family-centered models of care "refer to interventions selected on the basis of the needs, values, and preferences of the child or adolescent and his or her family or caregiver."

3. Review methods

Study selection

To develop our search strategy, we first defined key features of decentralized, integrated, and family-centered care in consultation with the World Health Organization and stakeholders with experience working in TB programs of middle-income countries. We developed search terms based on the results of these discussions. We also consulted existing systematic reviews on these care models and added search terms used in these reviews. We executed the abstract search in PubMed, Embase, Web of Science, the WHO regional databases of the Global Index Medicus, Global Health, and Cochrane Central. We reviewed a sample of 400 abstracts and 45 full text articles to better define the care models, and we consulted stakeholders to resolve ambiguity. Based on our refined definitions, we supplemented our database search with manual searches of the references from 17 additional systematic and non-systematic reviews to identify articles that might have been incompletely captured by our database

search.[2–18] Additionally, WHO GDG members reached out to investigators with unpublished data related to the care models of interest and requested the sharing of preliminary findings.

Our database search terms included four blocks of terms (Table 2). The first block specified TB, the second block specified children and adolescents, the third block specified terms related to the care models, and the fourth block, which was used for the Pubmed, Embase, Web of Science, and Global Health searches, specified the countries of interest. To limit the review to countries with high TB burdens, we created a list of 74 countries of interest comprising those that either had an estimated TB incidence of ≥100 per 100,000 in the 2020 WHO Global TB Report (N=64) or appeared on the WHO's list of TB priority countries in 2020 based on overall TB, drug-resistant TB, or TB/HIV burden (N=48).[1]

Table 2: Summary of search terms and database searches

Search term block	Concepts	Number of search terms*	Example search terms
1	Tuberculosis	3	• Tuberculosis (MeSH or Emtree) • Tuberculosis (text) • TB (text)
2	Children and adolescents	17	• Child (MeSH or Emtree) • Pediatrics (MeSH or Emtree) • Adolescent (MeSH or Emtree) • Child* (text) • Adolescen* (text)
3	Decentralized care	26	• Primary health care (MeSH or Emtree) • Community health services (MeSH) • Community health (Emtree) • Decentral* (text) • Nonspecialized (text) • Primary level (text) • Home based (text)
	Integrated care	10	• Delivery of health care, integrated [MeSH} • Integrated health care system (Emtree) • Integrat* (text) • Coordinat* (text) • Colocat* (text)
	Family-centered care	15	• Patient-centered care (MeSH) • Family-centered care (Emtree) • Patient-centered (text) • Family-centered (text) • Person-centered (text) • Individualiz* (text) • Holistic (text)
4	Countries of interest	88	Text terms for names of each country (including variants), plus MeSH and Emtree terms for Africa region
Search	**Database**	**Search date**	**Number of results**
1–4/ AND	Pubmed	5 February, 2021	1761
1–4/ AND	Embase	5 February, 2021	1429
1–4/ AND	Web of Science	9 February, 2021	623
1–4/ AND	Global Health	15 February, 2021	606
1–3/ AND	Cochrane Central Register of Controlled Trials	15 February, 2021	67
1–3/ AND	Global Index Medicus	15 February, 2021	451

* Numbers of search terms are given for the Pubmed search. This number differed slightly across databases because of difference in indexing search terms; all search terms in a block were linked by "OR" logic

Abstracts and full-text articles were double-reviewed with disagreements arbitrated by a third reviewer. We included articles in any language that reported a program or intervention with a decentralized, integrated, or family-centered care model, and from which we could extract outcome data as counts or notification rates for an age group ≤19 years old.

Analysis

We used the Cochrane Risk of Bias 2 tool for cluster-randomized trials to assess risk of bias for randomized studies and an adapted Newcastle-Ottawa scale to assess risk of bias in non-randomized studies. For cohort studies, effect estimates were calculated as risk ratios (RR) and risk differences based on extracted count data. For studies where the outcome was case notifications, we estimated annual incidence rate ratios (IRR) based on the number of events and the duration of the intervention and pre-intervention periods, assuming the size of the underlying population to remain constant between the pre-intervention and intervention periods. Where possible, we calculated IRRs adjusted for changes in case notification rate over time in a control area (i.e. the ratio of IRRs between the intervention and control area). A large normal approximation was used to estimate 95% confidence intervals for unadjusted IRRs.

4. Results

We identified 26 studies that met our inclusion criteria (Figure 1). However, four studies[19–22] included only treatment completion outcomes and assessed community-based directly observed therapy (DOT) or DOT-like interventions. Given an existing WHO recommendation for community-based DOT, the WHO GDG decided to exclude these studies from the current evidence synthesis. The remaining 22 studies are summarized in Table 3. The interventions in the identified studies were heterogeneous and often comprised multifaceted approaches. Due to the heterogeneity of interventions, we did not perform a meta-analysis to create pooled estimates.

Figure 1: PRISMA flow diagram for study selection

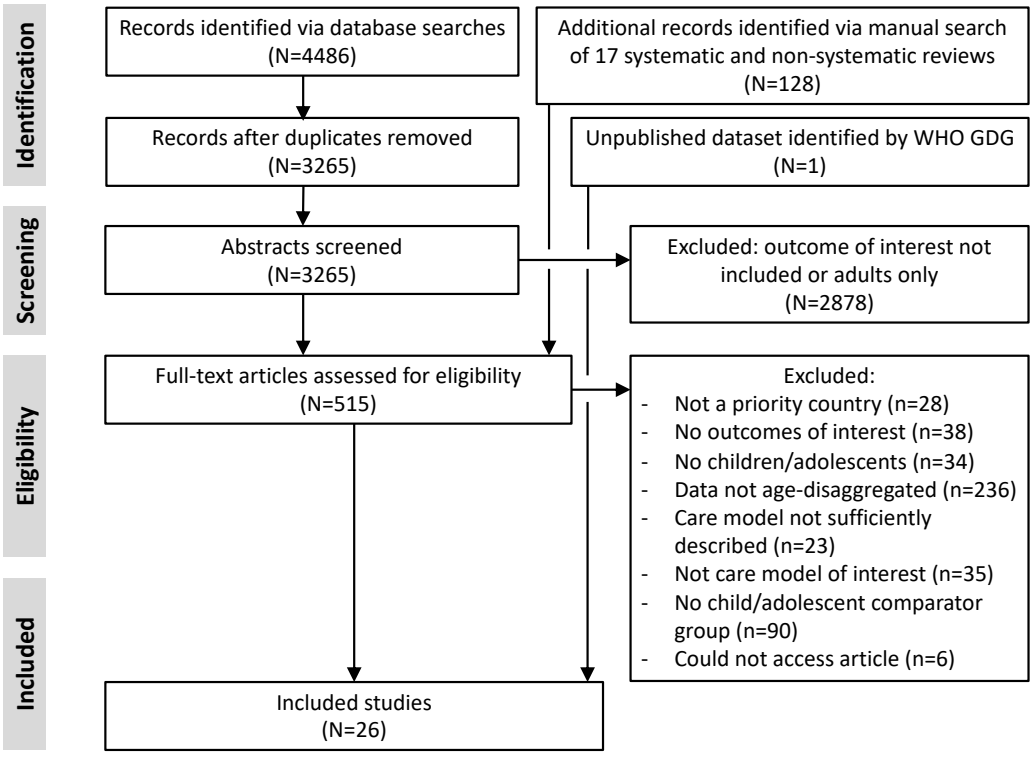

Table 3: Included studies

Authors	Year	Study design	Country	Primary care model	Key intervention components	Outcome(s) reported
Talukder et al[23]	2012	Cluster-randomized trial	Bangladesh	Decentralized	Primary-level provider training, supplies given to diagnostic centers, community awareness activities	TB diagnoses
Khan et al[24]	2012	Pre-post	Pakistan	Decentralized	Screeners in primary care (private sector), community awareness activities	TB notifications
Malik et al[25]	2018	Pre-post	Pakistan	Decentralized	Screeners in primary care, primary-level provider training, transport enablers for contacts, community awareness activities	TB notifications
Zawedde-Muyanja et al[26]	2018	Pre-post	Uganda	Decentralized	Primary-level provider training, home visits for contact screening and referral, procurement support	TB notifications
Maha et al[27]	2019	Pre-post	Papua New Guinea	Decentralized	Primary-level provider training, community awareness activities	TB treatment initiations
Islam et al[28]	2017	Pre-post	Bangladesh	Decentralized	Primary-level provider training, community awareness activities, procurement support	TB diagnoses
CaP-TB study unpublished data[29]	N/A	Pre-post	Cameroon, Cote D'Ivoire, DR Congo, Kenya, Lesotho, Malawi, Tanzania, Uganda, Zimbabwe, India	Decentralized	Primary-level provider training, screeners in primary care settings, screeners in integrated settings (HIV, MCH, nutrition clinics), home visits for contact screening and referral, supplies for sputum collection provided	TB treatment initiations, TPT initiations
Oshi et al[30]	2016	Pre-post	Nigeria	Decentralized	Primary-level provider training, screeners in primary care settings, screeners in ART clinics, home visits for contact screening, community awareness activities, purified protein derivative provided	TB notifications
Joshi et al[31]	2015	Pre-post	Nepal	Decentralized	Screeners in communities, schools, MCH clinics; home visits for contact screening with sputum collection or referral; private sector engagement;	TB notifications
Hanrahan et al[32]	2019	Cluster-randomized trial	South Africa	Decentralized	Home visits for contact screening with sputum collection	TB treatment initiations
Moyo et al[33]	2012	Randomized trial	South Africa	Decentralized	Home visits for screening and referral	TB diagnoses
Davis et al[34]	2019	Cluster-randomized trial	Uganda	Decentralized	Home visits for contact screening with sputum collection	TB diagnoses
Fatima et al[35]	2016	Pre-post	Pakistan	Decentralized	Home visits for screening and referral	TB notifications
Reddy et al[36]	2015	Pre-post	India	Decentralized	Home visits for screening with sputum collection or referral	TB notifications (smear positive)
Bayona et al[37]	2013	Prospective cohort	Peru	Decentralized	Home visits for contact screening and referral	TB diagnoses

Authors	Year	Study design	Country	Primary care model	Key intervention components	Outcome(s) reported
Sachdeva et al[38]	2015	Pre-post	India	Decentralized	Xpert MTB/RIF introduced into decentralized microscopy centers	TB diagnoses
Yassin et al[39]	2013	Pre-post	Ethiopia	Decentralized	Field supervisors screened household contacts and initiated TPT	TPT initiations
Zachariah et al[40]	2003	Pre-post	Malawi	Decentralized	Home visits for contact screening and referral	TPT initiations
Ketema et al[41]	2020	Stepped-wedge trial	Ethiopia	Integrated	Screening in IMNCI clinics	TB diagnoses
Miyano et al[42]	2013	Pre-post	Zambia	Integrated	Co-location of ART services in health facilities that already had TB services	TB treatment initiations
Wingfield et al[43]	2017	Cluster-randomized trial	Peru	Family-centered	Social support, conditional cash transfers to defray hidden costs of treatment	TPT initiations
Rocha et al[44]	2011	Pre-post	Peru	Family-centered	Psychosocial support, poverty reduction activities including food and cash transfers	TPT initiations, TPT completion

Abbreviations: MCH = maternal and child health, ART = antiretroviral therapy, IMNCI = Integrated maternal, neonatal, and child illnesses

Studies where the primary intervention was decentralization mostly assessed diagnosis or case notification outcomes (n=16), with fewer assessing TPT outcomes (n=3). In general, interventions that included both strengthening diagnostic capacity in primary care settings as well as strengthening linkages between communities and facilities consistently showed increases in case notifications, while interventions that involved only home-based screening did not. Across nine studies[23–31] of interventions that both strengthened diagnostic capacity in primary care settings and strengthened linkages between communities and facilities, notifications among individuals 0–14 years old increased by 1.14 to 7.32-fold, with varying degrees of precision. In contrast, four of the six interventions that involved home-based screening alone failed to increase overall notifications in the 0–14 age group or diagnoses among contacts.[32,34,36,37] The only study in this group that showed a substantial impact of the intervention was a randomized trial showing that home screening visits every 3 months increased TB diagnoses among a cohort of children 0–26 months old (IRR 2.6, 95% CI 1.8–4.0).[33] Notably, in this study, children with TB signs/symptoms were evaluated by a study team that performed X-ray and culture for all children evaluated, while all other studies relied on the routine health services to make TB diagnoses.

Three studies assessed interventions to increase the number of young child contacts initiating TPT through decentralized care. Two studies of multifaceted interventions that included strengthening TPT services in primary-level health facilities as well as household visits for contact management observed substantial increases in the numbers of child contacts initiating TPT.[29,39] The third study found that household visits did not significantly increase the proportion of child contacts initiating TPT because existing barriers to accessing x-ray prevented children from completing the evaluation required to prescribe TPT.[40]

We identified two studies of service integration, which showed limited impact on case notifications. A stepped-wedge trial found that integrating TB screening into 30 Integrated Maternal, Neonatal and Childhood Illnesses (IMNCI) clinics significantly increased the number of children 0–4 years old diagnosed with TB among IMNCI clinic attendants, although the absolute effect size was small (0.5 additional diagnosis per facility per each 4 months of intervention).[41] A non-randomized study assessed the effect of introducing ART services into rural health centers that were already providing

TB treatment.[42] While there was an increase in notifications (IRR 2.67, 95% 1.05–6.76), the confidence intervals were wide due to small numbers of diagnoses in the 0–14 age group.

We did not identify any studies specifically evaluating the effect of family-centered care on diagnostic or treatment outcomes. However, four studies included an integrated or family-centered component in a multifaceted intervention that also involved decentralization.[25,29–31] Because the primary intervention was decentralization, we included them among the decentralized studies. We identified two studies of family-centered care, showing that provision of socioeconomic support packages to families affected by TB was associated with increased TPT initiation and completion. In a randomized trial, provision of a package including empowerment meetings and conditional cash transfers to defray expenses incurred by seeking care was associated with an absolute increase of an additional 18% (95% CI 4–33%) of contacts initiating TPT.[43] The non-randomized study, which included a wider range of socioeconomic and psychosocial support interventions, observed an additional 48% (95% CI 45–52%) of contacts initiating TPT and an additional 59% (95% CI 56–64%) completing TPT.[44]

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