TREATMENT OF TUBERCULOSIS

Annex 3

GRADE EVIDENCE PROFILES

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

World Health Organization

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Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update

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Abbreviations & acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ATS	American Thoracic Society
BMI	body mass index
CDC	United States Centers for Disease Control and Prevention
DOT	directly observed treatment
E	Ethambutol
FDC	fixed-dose combination
GDG	Guideline Development Group
Gfx	Gatifloxacin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	Global TB Programme
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IRIS	Immune Reconstitution Inflammatory Syndrome
KNCV	Royal Dutch Tuberculosis Foundation
MDR-TB	multidrug-resistant tuberculosis
Mfx	Moxifloxacin
NGO	non-government organization
PICO	Patients, Intervention, Comparator and Outcomes
RIF or R	Rifampicin
RFP	Rifapentine
SAT	self-administered treatment or unsupervised treatment
SMS	Short Message Service or text message
TB	tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
VOT	video-observed treatment
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

PICO 1

Author(s): Narges Alipanah and Payam Nahid

Question: A less than 6 month fluoroquinolone containing regimen compared to the standard 6 month treatment regimen (2HRZE-4HR) for patients with drug susceptible TB

Setting:

Bibliography: Gillespie SH et al. REMoxTB. N Engl J Med 2014; Jindani A et al. RIFAQUIN N Engl J Med 2014; Merle CS et al. OFLOTUB N Engl J Med 2014; Jawahar MS et al. PLoS One 2013; Ziganshina LE et al. Cochrane Database Syst Rev. 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A less than 6 month fluoroquinolone containing regimen	The standard 6 month treatment regimen (2HRZE-4HR)	Relative (95% CI)	Absolute (95% CI)		
Mortality-all cause												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	63/2357 (2.7%)	49/1708 (2.9%)	**RR 1.00** (0.65 to 1.53)	0 fewer per 1,000 (from 10 fewer to 15 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality-TB related												
2	randomised trials	not serious	not serious	not serious	serious [a,b]	none	20/1566 (1.3%)	13/914 (1.4%)	**RR 0.82** (0.40 to 1.65)	3 fewer per 1,000 (from 9 fewer to 9 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Favorable outcome- (end of treatment)												
4	randomised trials	not serious	not serious	not serious	not serious	none	2161/ 2339 (92.4%)	1543/1691 (91.2%)	**RR 1.01** (1.00 to 1.03)	9 more per 1,000 (from 0 fewer to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Favorable outcome (end of follow up)												
3	randomised trials	not serious	not serious	not serious	not serious	none	1544/ 1925 (80.2%)	1177/1405 (83.8%)	**RR 0.94** (0.89 to 1.00)	50 fewer per 1,000 (from 0 fewer to 92 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Favorable outcome - HIV positive												
3	randomised trials	not serious	serious [c]	not serious	serious [a]	none	176/242 (72.7%)	164/215 (76.3%)	**OR 0.82** (0.53 to 1.26)	38 fewer per 1,000 (from 39 more to 133 fewer)	⊕⊕◯◯ LOW	CRITICAL
Favorable outcome - HIV negative												
3	randomised trials	not serious	not serious	not serious	not serious	none	1365/ 1679 (81.3%)	1010/1142 (88.4%)	**OR 0.53** (0.42 to 0.66)	82 fewer per 1,000 (from 50 fewer to 122 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Relapse rate												
4	randomised trials	not serious	not serious	not serious	not serious	none	268/ 2236 (12.0%)	76/1560 (4.9%)	**RR 2.78** (1.81 to 4.29)	87 more per 1,000 (from 39 more to 160 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse effects-tx and fu - INH												
2	randomised trials	not serious	serious [c]	not serious	serious [a]	none	138/930 (14.8%)	135/914 (14.8%)	**RR 1.00** (0.81 to 1.24)	0 fewer per 1,000 (from 28 fewer to 35 more)	⊕⊕◯◯ LOW	
Adverse effects during treatment and follow up - EMB												
3	randomised trials	not serious	serious [c]	not serious	serious [a]	none	253/1735 (14.6%)	177/1648 (10.7%)	**RR 1.28** (0.60 to 2.72)	30 more per 1,000 (from 43 fewer to 185 more)	⊕⊕◯◯ LOW	CRITICAL
2-month culture conversion												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A less than 6 month fluoroquinolone containing regimen	The standard 6 month treatment regimen (2HRZE-4HR)	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	serious [c]	not serious	serious [a]	none	1097/1466 (74.8%)	495/764 (64.8%)	**RR 1.15** (1.08 to 1.22)	97 more per 1,000 (from 52 more to 143 more)	⊕⊕◯◯ LOW	IMPORTANT
Unfavorable outcome (18 months)												
3	randomised trials	not serious	not serious	not serious	not serious	none	462/2006 (23.0%)	228/1405 (16.2%)	**RR 1.44** (1.17 to 1.78)	71 more per 1,000 (from 28 more to 127 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Unfavorable outcome (end of treatment)												
4	randomised trials	not serious	not serious	not serious	not serious	none	178/2339 (7.6%)	148/1691 (8.8%)	**RR 0.85** (0.68 to 1.05)	13 fewer per 1,000 (from 4 more to 28 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

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

a. Wide CI does not exclude benefit or harm.
b. Few events in the intervention and control group
c. Significant heterogeneity between studies.

PICO 2

Author(s): Dick Menzies, Amr Al-Banna. Cochrane review

Question: A FDC combination compared to separate drug formulations for patients with active drug susceptible TB disease

Setting: Menzies and Al-Banna: Many countries – mostly low- to middle-income countries Cochrane: adolescents and adults with bacteriologically confirmed TB [a]

Bibliography: Menzies and Al-Banna: AlBanna et al Eur Respir J 2013 Gallardo: Gallardo CR et al. Cochrane database of systematic reviews 2016 (systematic review of published and unpublished data). Mostly low to middle income countries, few HIV positive patients.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a FDC combination	Separate drug formulations	Relative (95% CI)	Absolute (95% CI)		
Failure/relapse (per protocol analysis): Al-Banna and Menzies												
15	randomised trials	serious [b]	not serious	not serious	not serious	none	116/2750 (4.2%) [c]	89/2880 (3.1%) [d]	**RR 1.28** (0.99 to 1.70)	11 more per 1,000 (from 1 fewer to 21 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Treatment failure: Cochrane study												
7	randomised trials	not serious	not serious	not serious [e]	serious [f]	none	44/1833 (2.4%) [g,h]	33/1773 (1.9%) [g]	**RR 1.28** (0.82 to 2.00)	5 more per 1,000 (from 3 fewer to 19 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Relapse: Cochrane study												
10	randomised trials	serious [i]	not serious	not serious [e]	serious [f]	none	126/1855 (6.8%) [g,j]	98/1766 (5.5%) [g]	**RR 1.28** (1.00 to 1.64)	16 more per 1,000 (from 0 fewer to 36 more)	⊕⊕◯◯ LOW	CRITICAL
Death: Cochrane study												
11	randomised trials	not serious	not serious	not serious [e]	serious [k]	none	52/2373 (2.2%) [g,l]	60/2427 (2.5%) [g]	**RR 0.96** (0.67 to 1.39)	1 fewer per 1,000 (from 8 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
2 month culture conversion: Al-Banna and Menzies												
12	randomised trials	serious [b]	not serious	not serious	not serious	none	2213/ 2354 (94.0%) [m]	2223/ 2443 (91.0%) [n]	**RR 1.03** (1.01 to 1.04)	30 more per 1,000 (from 15 more to 45 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Sputum smear or culture conversion at end of treatment: Cochrane study												
7	randomised trials	not serious	not serious	not serious [e]	not serious [o]	none	1119/ 1250 (89.5%) [g,p]	954/1069 (89.2%) [g]	**RR 0.99** (0.96 to 1.02)	9 fewer per 1,000 (from 36 fewer to 18 more) [af]	⊕⊕⊕⊕ HIGH	IMPORTANT
Adherence versus non-adherence to treatment: Al-Banna and Menzies												
5	randomised trials	serious [b]	serious [q]	not serious	serious [r]	none	378/496 (76.2%) [s]	367/462 (79.4%) [t]	**RR 0.96** (0.95 to 0.97) [u]	32 fewer per 1,000 (from 20 fewer to 85 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Serious adverse reactions from TB drugs: Al-Banna and Menzies												
10	randomised trials	serious [b]	not serious	not serious	serious [r]	none	387/2416 (16.0%) [v]	439/2195 (20.0%) [w]	**RR 0.88** (0.75 to 1.03)	40 fewer per 1,000 (from 120 fewer to 40 more)	⊕⊕◯◯ LOW	IMPORTANT
Serious adverse events: Cochrane study												
6	randomised trials	not serious	not serious	not serious [e]	serious [k]	none	38/1735 (2.2%) [g,x]	26/1653 (1.6%) [g]	**RR 1.45** (0.90 to 2.33)	7 more per 1,000 (from 2 fewer to 21 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adverse events leading to discontinuation of therapy: Cochrane study												
13	randomised trials	serious [i]	not serious [y]	not serious [e]	serious [f]	none	89/2760 (3.2%) [g,z]	111/2770 (4.0%) [g]	**RR 0.96** (0.56 to 1.66)	2 fewer per 1,000 (from 18 fewer to 26 more)	⊕⊕◯◯ LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a FDC combination	Separate drug formulations	Relative (95% CI)	Absolute (95% CI)		
Patient satisfaction: Al-Banna and Menzies												
2	ran-domised trials	serious [b]	serious	not serious	serious [r]	none	475/565 (84.1%) [aa]	379/575 (65.9%) [ab]	**RR 1.28** (1.25 to 1.30)	182 more per 1,000 (from 85 fewer to 20 more)	⊕◯◯◯ VERY LOW	IMPOR-TANT
Acquisition (or amplification) of drug resistance: Al-Banna and Menzies												
4	ran-domised trials	serious [b]	not serious	not serious	serious [ac]	none	3/1113 (0.3%) [ad]	1/1405 (0.1%) [ae]	**RR 1.6** (0.5 to 5.4)	2 more per 1,000 (from 1 fewer to 5 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. The outcomes of patients' or health system costs are not shown as no studies found reporting these outcomes (although economic analyses were not included - only randomized trials)

b. Risk of bias is considered serious because in the majority of randomized trials the method of allocation and allocation concealment were either unclear, not stated or inadequate

c. 95% CI 2.6 to 5.8

d. 95% CI 1.9 to 4.2

e. differences in doses probably do not affect the comparability of groups

f. The optimal information size considering an absolute > 0.5%non-inferiority margin as clinically meaningful, is not reached. In addition 1 side of the 95% CI does not exclude potential harm associated to FDCs.

g. The risk in the intervention group (FDC) (and its 95%CI) is based on the assumed risk in the comparison group (single dose) and the relative effect of the intervention (and its 95%CI)

h. 95% CI: 1.5 to 3.7

i. Exclusion of studies at highest risk of bias heavily affects the pooled estimate of effect.

j. 95% CI: 5.5 to 9.1

k. The optimal information size considering an absolute > 0.1%non-inferiority margin as clinically meaningful, is not reached.

l. 95% CI: 1.7 to 3.4

m. 95% CI 91 to 96%

n. 95% CI 89% to 92%

o. Although the optimal information size (considering an absolute > 0.5%non-inferiority margin as clinically meaningful) is not reached, the total sample size and number of events are very large

p. 95% CI: 85.7 to 91.0

q. In the five trials that assessed adherence, all used different methods to measure this outcome. Therefore, pooling for meta-analysis not appropriate. Summary effect estimate should be interpreted with GREAT caution.

r. Imprecision based on confidence interval for risk ratio

s. 95% CI 72 to 80

t. 95% CI 76 to 83

u. Risk ratio and confidence interval for risk ratio estimated with exact binomial method, based on simple pooling of numbers from each study. Estimate NOT from random effect meta-analysis effect – so should be interpreted with great caution due to heterogeneity of study methods and results.

v. 95% CI 9 to 23

w. 95% CI 11 to 28

x. 95% CI 1.4 to 3.7

y. Studies of highest risk of bias contribute to explain the large heterogeneity (I2 statistic = 57%).

z. 95% CI 2.2 to 6.7

aa. 95% CI 81 to 87

ab. 95% CI 62 to 70

ac. Imprecision based on confidence interval for risk ratio.

ad. 95% CI 0 to 0.7

ae. 95% CI 0 to 0.4

ah. No explanation was provided

PICO 3

Author(s): James Johnston, Jonathon Campbell, Dick Menzies

Question: Daily dosing throughout treatment compared to thrice weekly dosing throughout treatment for treatment of drug-susceptible pulmonary tuberculosis [1]

Setting: Numerous countries, mostly LMIC

Bibliography: 2016 update of systematic review of randomized control trials in first-line therapy: Menzies D et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009; 6(9): e1000146.[2]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily dosing through out treatment	Thrice weekly dosing through out treatment	Relative (95% CI)	Absolute (95% CI)		
Risk of Failure in drug susceptible disease												
68	observational studies	not serious [3]	serious [4]	not serious	serious [5]	none	62/5947 (1.0%) [6]	5/1950 (0.3%) [7]	**RR 2.6** (0.3 to 21.2) [8]	4 more per 1,000 (from 2 fewer to 52 more) [19]	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Relapse in drug susceptible disease												
67	observational studies	not serious [3]	serious [4]	not serious	not serious	none	164/ 5457 (3.0%) [9]	89/1801 (4.9%) [10]	**RR 2.1** (1.1 to 4.0) [8]	54 more per 1,000 (from 5 more to 148 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug susceptible disease												
58	observational studies	not serious [3]	serious [4]	not serious	not serious	none	11/4700 (0.2%) [11]	16/1778 (0.9%) [12]	**RR 10.0** (2.1 to 46.7) [8]	81 more per 1,000 (from 10 more to 411 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Failure in drug susceptible disease or susceptibility unknown												
81	observational studies	not serious [3]	serious [4]	not serious	not serious [5]	none	112/ 8223 (1.4%) [13]	28/2310 (1.2%) [14]	**RR 3.7** (1.2 to 12.6) [8]	33 more per 1,000 (from 2 more to 141 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Relapse in drug susceptible disease or susceptibility unknown												
78	observational studies	not serious [3]	serious [4]	not serious	not serious	none	254/ 7475 (3.4%) [15]	128/ 2130 (6.0%) [16]	**RR 2.2** (1.2 to 4.0) [8]	72 more per 1,000 (from 12 more to 180 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug susceptible disease or susceptibility unknown												
58	observational studies	not serious [3]	serious [4]	not serious	not serious	none	11/4700 (0.2%) [17]	16/1778 (0.9%) [18]	**RR 10.0** (2.1 to 46.7) [8]	81 more per 1,000 (from 10 more to 411 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

1. Only regimens with rifampin duration ≥6 months included in analysis.
2. Systematic review of 64 randomized trials published between 1965 and 2016; the systematic review performed across trial comparisons by treating the arms of trials as independent cohorts (i.e. not direct head-to-head comparisons)
3. Comparisons performed across trials rather than within trials
4. There was considerable heterogeneity of results between studies
5. The effects at the ends of the confidence interval would lead to different clinical decisions
6. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; CI: 0-0.2
7. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; 0-0.3
8. Relative adjusted effect estimate with negative binomial regression, interpret with extreme caution
9. Pooled effect estimate with 95%CI in subgroup analysis: 2.2; CI: 1.5-3.1
10. Pooled effect estimate with 95%CI in subgroup analysis: 5.4; 2.3-8.4
11. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; CI: 0-0.2
12. Pooled effect estimate with 95%CI in subgroup analysis: 0.3; 0-0.8
13. Pooled effect estimate with 95%CI in subgroup analysis: 0.2; CI: 0.1-0.4
14. Pooled effect estimate with 95%CI in subgroup analysis: 0.6; 0-1.4
15. Pooled effect estimate with 95%CI in subgroup analysis: 2.5; CI: 1.8-3.2
16. Pooled effect estimate with 95%CI in subgroup analysis: 6.8; 3.8-9.9
17. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; 0-0.2
18. Pooled effect estimate with 95%CI in subgroup analysis: 0.3; 0-0.8
19. No explanation was provided

PICO 4.1

Author(s): James Johnston, Jonathon Campbell, Dick Menzies

Question: Daily dosing throughout TB treatment compared to daily dosing during the intensive phase followed by thrice weekly dosing during the continuation phase for treatment of drug susceptible pulmonary tuberculosis[1]

Setting: Numerous countries, mostly LMIC

Bibliography: 2016 update of systematic review of randomized control trials in first-line therapy: Menzies D et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009; 6(9): e1000146. Systematic review of 64 randomized trials published between 1965 and 2016; the systematic review performed across trial comparisons by treating the arms of trials as independent cohorts (i.e. not direct head-to-head comparisons)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily dosing throughout TB treatment	Daily dosing during the intensive phase followed by thrice weekly dosing during the continuation phase	Relative (95% CI)	Absolute (95% CI)		
Risk of Failure in drug susceptible disease												
62	observational studies	not serious [2]	serious [3]	not serious	serious [4]	none	62/5947 (1.0%) [5]	2/642 (0.3%) [6]	**RR 3.8** (0.5 to 30.2) [7]	9 more per 1,000 (from 2 fewer to 91 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Relapse in drug susceptible disease												
61	observational studies	not serious [2]	serious [3]	not serious	serious [4]	none	164/5457 (3.0%) [8]	16/614 (2.6%) [9]	**RR 1.3** (0.6 to 2.9) [7]	8 more per 1,000 (from 10 fewer to 50 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug susceptible disease												
52	observational studies	not serious [2]	serious [3]	not serious	serious [4]	none	11/4700 (0.2%) [10]	1/588 (0.2%) [11]	**RR 0.6** (0.1 to 5.7) [7]	1 fewer per 1,000 (from 2 fewer to 8 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Failure in drug susceptible disease or susceptibility unknown												
80	observational studies	not serious [2]	serious [3]	not serious	serious [4]	none	112/8223 (1.4%) [12]	19/2075 (0.9%) [13]	**RR 1.5** (0.4 to 5.4) [7]	5 more per 1,000 (from 5 fewer to 40 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Relapse in drug susceptible disease or susceptibility unknown												
77	observational studies	not serious [2]	serious [3]	not serious	serious [4]	none	254/7475 (3.4%) [14]	72/2007 (3.6%) [15]	**RR 1.2** (0.6 to 2.3) [7]	7 more per 1,000 (from 14 fewer to 47 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug susceptible disease or susceptibility unknown												
52	observational studies	not serious [2]	serious [3]	not serious	serious [4]	none	11/4700 (0.2%) [16]	1/588 (0.2%) [17]	**RR 0.6** (0.1 to 5.7) [7]	1 fewer per 1,000 (from 2 fewer to 8 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

1. Only regimens with rifampin duration ≥6 months included in analysis.
2. Comparisons performed across trials rather than within trials.
3. There was considerable heterogeneity of results between studies
4. The effects at the ends of the confidence interval would lead to different clinical decisions
5. Pooled effect estimate with 95%CI in subgroup analysis; 0.1; CI: 0-0.2
6. Pooled effect estimate with 95%CI in subgroup analysis; 0.2; CI: 0-0.8
7. Relative adjusted effect estimate with negative binomial regression, interpret with extreme caution
8. Pooled effect estimate with 95%CI in subgroup analysis; 2.4; CI: 1.6-3.0
9. Pooled effect estimate with 95%CI in subgroup analysis; 2.1; CI: 0-4.2
10. Pooled effect estimate with 95%CI in subgroup analysis; 0.1; CI: 0-0.2
11. Pooled effect estimate with 95%CI in subgroup analysis; 0.1; 0-0.3
12. Pooled effect estimate with 95%CI in subgroup analysis; 0.2; CI: 0.1-0.4
13. Pooled effect estimate with 95%CI in subgroup analysis; 0.4; 0-1.1
14. Pooled effect estimate with 95%CI in subgroup analysis; 2.5; CI: 1.8-3.2
15. Pooled effect estimate with 95%CI in subgroup analysis; 3.0; CI: 1.0-5.1
16. Pooled effect estimate with 95%CI in subgroup analysis; 0.1; 0-0.2
17. Pooled effect estimate with 95%CI in subgroup analysis; 0.1; 0-0.3

PICO 4.2

Author(s): James Johnston, Jonathon Campbell, Dick Menzies

Question: Daily dosing throughout TB treatment compared to daily dosing in the intensive phase followed by twice weekly dosing in the continuation phase of TB treatment for treatment of drug susceptible pulmonary tuberculosis[1]

Setting: Numerous countries, mostly LMIC.

Bibliography: 2016 update of systematic review of randomized control trials in first-line therapy; Systematic review of 64 randomized trials published between 1965 and 2016; Menzies D et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009; 6(9): e1000146.[2]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily dosing throughout TB treatment	Daily dosing in the intensive phase followed by twice weekly dosing in the continuation phase of TB treatment	Relative (95% CI)	Absolute (95% CI)		
Risk of Failure in drug susceptible disease												
58	observational studies	not serious [3]	serious [4]	not serious	serious [5]	none	62/5947 (1.0%) [6]	8/470 (1.7%) [7]	**RR 3.9** (0.5 to 17.2) [8]	49 more per 1,000 (from 9 fewer to 276 more) [19]	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Relapse in drug susceptible disease												
57	observational studies	not serious [3]	serious [4]	not serious	serious [5]	none	164/5457 (3.0%) [9]	33/399 (8.3%) [10]	**RR 1.7** (0.9 to 3.4) [8]	58 more per 1,000 (from 8 fewer to 198 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug susceptible disease												
48	observational studies	not serious [3]	serious [4]	not serious	serious [5]	none	11/4700 (0.2%) [11]	2/377 (0.5%) [12]	**RR 1.0** (0.2 to 5.0) [8]	0 fewer per 1,000 (from 4 fewer to 21 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Failure in drug susceptible disease or susceptibility unknown												
71	observational studies	not serious [3]	serious [4]	not serious	not serious [5]	none	112/8223 (1.4%) [13]	21/793 (2.6%) [14]	**RR 3.0** (1.0 to 8.8) [8]	53 more per 1,000 (from 0 fewer to 207 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of Relapse in drug susceptible disease or susceptibility unknown												
68	observational studies	not serious [3]	serious [4]	not serious	not serious [5]	none	254/7475 (3.4%) [15]	49/572 (8.6%) [16]	**RR 1.8** (1.0 to 3.3) [8]	69 more per 1,000 (from 0 fewer to 197 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug susceptible disease or susceptibility unknown												
48	observational studies	not serious [3]	serious [4]	not serious	serious [5]	none	11/4700 (0.2%) [17]	2/377 (0.5%) [18]	**RR 1.0** (0.2 to 5.0) [8]	0 fewer per 1,000 (from 4 fewer to 21 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

1. Only regimens with rifampin duration ≥6 months included in analysis
2. the systematic review performed across trial comparisons by treating the arms of trials as independent cohorts (i.e. not direct head-to-head comparisons)
3. Comparisons performed across trials rather than within trials
4. There was considerable heterogeneity of results between studies
5. The effects at the ends of the confidence interval would lead to different clinical decisions
6. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; CI: 0-0.2
7. Pooled effect estimate with 95%CI in subgroup analysis: 0.5; CI: 0-1.5
8. Relative adjusted effect estimate with negative binomial regression, interpret with caution.
9. Pooled effect estimate with 95%CI in subgroup analysis: 2.2; CI: 1.5-3.0
10. Pooled effect estimate with 95%CI in subgroup analysis: 7.0; CI: 2.4-11.6
11. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; CI: 0-0.2
12. Pooled effect estimate with 95%CI in subgroup analysis: 0.2; CI: 0-0.6
13. Pooled effect estimate with 95%CI in subgroup analysis; 0.2; CI: 0.1-0.4
14. Pooled effect estimate with 95%CI in subgroup analysis; 1.3; CI: 0-2.9
15. Pooled effect estimate with 95%CI in subgroup analysis; 2.5; CI: 1.8-3.2
16. Pooled effect estimate with 95%CI in subgroup analysis; 7.3; CI: 3.5-11.1
17. Pooled effect estimate with 95%CI in subgroup analysis: 0.1; CI: 0-0.2
18. Pooled effect estimate with 95%CI in subgroup analysis; 0.2; CI: 0-0.6
19. No explanation was provided

PICO 6

Author(s): Payam Nahid and Lelia Chaisson

Question: A treatment period greater than 8 months compared to a treatment period of 6 months for patients with pulmonary drug-susceptible tuberculosis co-infected with HIV

Setting: From a systematic review of randomized trials plus controlled observational studies (i.e., retrospective or prospective cohort studies).

Bibliography: Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clin Infect Dis 2012; 55(8): 1154-63.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A treatment period greater than 8 months	A treatment period of 6 months	Relative (95% CI)	Absolute (95% CI)		
Failure												
47	observational studies [1]	serious [2,3]	serious [4]	not serious	not serious	publication bias strongly suspected [5]	29/658 (4.4%) [6]	55/1620 (3.4%) [7]	**RR 0.8** (0.4 to 1.5)	7 fewer per 1,000 (from 17 more to 20 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse												
27	observational studies [1]	serious [2,3]	serious [4]	not serious	not serious	publication bias strongly suspected [5,8,9]	29/425 (6.8%) [10]	119/830 (14.3%) [11]	**RR 2.4** (1.2 to 5.0)	96 more per 1,000 (from 14 more to 273 more) [8]	⨁◯◯◯ VERY LOW	CRITICAL
Death												
47	observational studies [1]	serious [2,3]	serious [4]	not serious	not serious	publication bias strongly suspected [5]	107/765 (14.0%) [12]	209/1829 (11.4%) [13]	**RR 0.9** (0.5 to 1.6)	11 fewer per 1,000 (from 57 fewer to 69 more) [8]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

1. randomized trials & observational
2. Some studies had incomplete confirmation of active cases and some failed to confirm relapse or failure
3. In the systematic review, several comparisons were done across trials (treating different arms as independent cohorts) rather than within trials; however, the panel decided that this was not serious enough to warrant further downgrading the quality of evidence
4. There was considerable heterogeneity of results between studies
5. Possible reporting bias
6. Pooled estimate 95% CI: 2.7% (0.5 to 5.0)
7. Pooled estimate 95% CI: 2.6% (1.2 to 4.0)
8. No explanation was provided
9. Dose response gradient - with longer Rifampin duration there was a steady decline in rate of failure and relapse.
10. Pooled estimate 95% CI: 4.7% (0 to 11.2)
11. Pooled estimate 95% CI: 9.1% (0.4 to 17.8)
12. Pooled estimate 95% CI: 13.9% (7.3 to 20.4)
13. Pooled estimate 95% CI: 9.6% (5.9 to 12.5)

PICO 7

Author(s): Lelia Chaisson

Question: Adjuvent corticosteroids compared to TB treatment without corticosteroids for tuberculous pericarditis

Bibliography: Strang JI et al. Lancet 1987; Strang JI et al. Lancet 1988; Hakim JG et al. Heart 2000; Mayosi BM et al. N Engl J Med 2014; Reuter H et al. Cardiovasc J S Afr. 2006

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvent corticosteroids	TB treatment without corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Death												
5	randomised trials	not serious	serious [1]	serious [2]	serious [3]	none [4]	142/897 (15.8%)	142/882 (16.1%)	**RR 0.54** (0.23 to 1.26)	74 fewer per 1,000 (from 42 more to 124 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment adherence												
2	randomised trials	serious [5]	very serious [1]	serious [5]	not serious	none	744/888 (83.8%)	785/907 (86.5%)	**RR 0.91** (0.75 to 1.12)	78 fewer per 1,000 (from 104 more to 216 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Constrictive pericarditis												
3	randomised trials	not serious	not serious	not serious	very serious [3]	none	36/768 (4.7%)	56/747 (7.5%)	**RR 0.72** (0.32 to 1.58)	21 fewer per 1,000 (from 43 more to 51 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

1. Inconsistent findings between studies. Death I2= 70% Adherence I2=89%. Older studies showing larger effects.
2. Although not alone a reason for downgrading (only in context of the concern for publication bias), we considered the older studies not necessarily reflective of populations who are seen in practice today.
3. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
4. Publication bias is possible - small studies showing a large effect. However, these studies are also older and the enrolled populations may differ accounting for the difference in the effects
5. Different definitions of adherence were used by different studies

PICO 8

Author(s): Lelia Chaisson

Question: Adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks compared to TB treatment without corticosteroids for tuberculous meningitis

Bibliography: Chotmongkol V et al. J Med Assoc Thai 1996; Kumarvelu S et al. Tuber Lung Dis 1994; Malhotra HS et al. Ann Trop Med Parasitol 2009; Schoeman JF et al. Pediatrics 1997; Thwaites GE et al. N Engl J Med 2004

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks	TB treatment without corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomised trials	not serious	not serious	not serious	serious [1]	none	118/454 (26.0%)	147/423 (34.8%)	**RR 0.72** (0.52 to 1.00)	**97 fewer per 1,000** (from 0 fewer to 167 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Death or severe disability												
4	randomised trials	serious [2]	not serious	not serious	not serious	none	172/425 (40.5%)	192/393 (48.9%)	**RR 0.80** (0.67 to 0.97)	**98 fewer per 1,000** (from 15 fewer to 161 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Relapse												
2	randomised trials	serious [2]	not serious	not serious	serious [1]	none	41/303 (13.5%)	48/301 (15.9%)	**RR 0.84** (0.58 to 1.24)	**26 fewer per 1,000** (from 38 more to 67 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
2	randomised trials	serious [2]	not serious	not serious	not serious	none	211/335 (63.0%)	231/301 (76.7%)	**RR 0.85** (0.77 to 0.94)	**115 fewer per 1,000** (from 46 fewer to 177 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio

1. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
2. Not all studies blinded

PICO 9.1

Author(s): Dick Menzies

Question: Re-treatment with the 5 first-line drugs HRZES (WHO category 2 regimen) be used with known INH resistance compared to Re-treatment with the 5 first-line drugs HRZES (WHO category 2 regimen) be used with known INH susceptibility for patients with a previous history of treatment with first-line anti-TB drugs being considered for re-treatment due to treatment interruption or recurrence

Setting: Multiple countries

Bibliography: Medea Gegia, Nicholas Winters, Andrea Benedetti, Dick van Soolingen, Dick Menzies. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Vol. 17, No. 2, p223–234, February 2017

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Re-treatment with the 5 first-line drugs HRZES (WHO category 2 regimen) be used with known INH resistance	Re-treatment with the 5 first-line drugs HRZES (WHO category 2 regimen) be used with known INH susceptibility	Relative (95% CI)	Absolute (95% CI)		
Failure – Category 2 (2HRZES/1HRZE/5HRE)												
24 [1]	observational studies [2]	serious	not serious	not serious	not serious	none [3]	41/505 (8.1%) [4]	40/2609 (1.5%) [5]	**risk difference (%) 2** (0 to 4)	**20 more per 1,000** (from 5 fewer to 45 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse – Category 2 (2HRZES/1HRZE/5HRE)												
20 [6]	observational studies [2]	serious	not serious	not serious	not serious	none [3]	13/277 (4.7%) [7]	115/2205 (5.2%) [8]	**risk difference (%) 0** (-3 to 4)	**4 fewer per 1,000** (from 36 fewer to 28 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure or Relapse - Category 2 (2HRZES/1HRZE/5HRE)												
24 [1]	observational studies [2]	serious	not serious	not serious	not serious	none [3]	54/506 (10.7%) [9]	155/2609 (5.9%) [10]	**risk difference (%) 6** (1 to 10)	**55 more per 1,000** (from 13 more to 98 more)	⊕◯◯◯ VERY LOW	CRITICAL
Acquisition (or amplification) of drug resistance - Category 2 (2HRZES/1HRZE/5HRE)New outcome												
17 [11]	observational studies [2]	serious	not serious	not serious	not serious	none [3]	7/284 (2.5%) [12]	7/2091 (0.3%) [13]	**risk difference (%) 3** (0 to 6)	**27 more per 1,000** (from 3 fewer to 57 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

1. 21 studies included drug sensitive arms.
2. RCT and cohort studies
3. Pooled across all studies for risk difference estimate of INHR vs DS TB - not from within study comparisons
4. risk, 95% CI: 3% (0, 6) based on a random effects model. Raw estimate is about 8%
5. risk, 95% CI: 1% (0, 2)
6. 18 studies included drug sensitive arms
7. risk, 95% CI: 5% (2, 8)
8. risk, 95% CI: 5% (4, 7)
9. risk, 95% CI: 12% (7, 17)
10. risk, 95% CI: 6% (4, 9)
11. 16 studies included drug sensitive arms
12. risk, 95% CI: 3% (0, 5)
13. risk, 95% CI: 0.2% (0, 0.4)

PICO 9.2

Author(s): Dick Menzies

Question: The 5 first-line drugs HRZES (WHO category 2 regimen) compared to 6-9 months RZE for patients with known INH resistance requiring TB retreatment 1

Setting: Multiple countries

Bibliography: Medea Gegia, Nicholas Winters, Andrea Benedetti, Dick van Soolingen, Dick Menzies. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Vol. 17, No. 2, p223–234, February 2017

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	The 5 first-line drugs HRZES (WHO category 2 regimen)	6-9 months RZE	Relative (95% CI)	Absolute (95% CI)		
Failure												
24 [2]	observational studies [3]	serious	serious	not serious	not serious	none	41/505 (8.1%) [4]	82/911 (9.0%) [5]	**risk difference (%) 3** (-2 to 8)	**30 more per 1,000** (from 20 fewer to 80 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse												
20 [6]	observational studies [3]	serious	serious	not serious	not serious	none	13/277 (4.7%) [7]	11/157 (7.0%) [8]	**risk difference (%) -2** (-6 to 2)	**18 fewer per 1,000** (from 57 fewer to 27 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure or Relapse												
24 [2]	observational studies [3]	serious	serious	not serious	not serious	none	54/505 (10.7%) [9]	93/911 (10.2%) [10]	**risk difference (%) 4** (-2 to 10)	**42 more per 1,000** (from 19 fewer to 102 more)	⊕◯◯◯ VERY LOW	CRITICAL
Acquisition (or amplification) of drug resistance												
17 [11]	observational studies [3]	serious	serious	not serious	not serious	none	7/284 (2.5%) [12]	3/164 (1.8%) [13]	**risk difference (%) 0** (-3 to 5)	**4 fewer per 1,000** (from 29 fewer to 37 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

1. In most of the included trials, the INH resistant patients were a small sub-group of all treated.
2. Number of studies with cat2: 24. Number of studies with 6-9 Mos RZE: 13
3. RCT+Cohort studies
4. risk, 95% CI: 6% (2 ,10)
5. risk, 95% CI: 2% (0, 5)
6. Number of studies with cat2: 20. Number of studies with 6-9 Mos RZE: 9
7. risk, 95% CI: 5% (2, 8)
8. risk, 95% CI: 7% (2, 11)
9. risk, 95% CI: 12% (7, 16)
10. risk, 95% CI: 8% (3, 12)
11. Number of studies with cat2: 17. Number of studies with 6-9 Mos RZE: 9
12. risk, 95% CI: 2% (0, 5)
13. risk, 95% CI: 2% (0, 4)

PICO 10.1

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 10.2.1

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	ran-domised 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	obser-vational 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	ran-domised 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)	⨁⨁◯◯ MODER-ATE	

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 10.3.1

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

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

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

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

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

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

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

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

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

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

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