TREATMENT OF TUBERCULOSIS

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

Annex 3
GRADE EVIDENCE PROFILES

World Health Organization

TREATMENT OF TUBERCULOSIS

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

Annex 3
GRADE EVIDENCE PROFILES

World Health Organization

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

Contents: Web Annex 3: GRADE evidence profiles – Web Annex 4: Evidence-to-decision tables – Annex 5: Reports of the systematic reviews – Annex 6: Essential first-line antituberculosis drugs

ISBN 978-92-4-155000-0

Designed by Genève Design.

Printed in Switzerland.

WHO/HTM/TB/2017.05

Contents

PICO 7

PICO 8

PICO 9

PICO 10

PICO 11

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 six-month fluoroquinolone-containing regimen compared with the standard six-month treatment regimen (2HRZE-4HR) for patients with drug-susceptible TB

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							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A less than six-month fluoroquinolone-containing regimen	The standard 6-month treatment regimen (2HRZE-4HR)	Relative (95% CI)	Absolute (95% CI)		
Mortality – all cause												
3	randomized 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 1000 (from 10 fewer to 15 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality – TB related												
2	randomized 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 1000 (from 9 fewer to 9 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Favourable outcome (end of treatment)												
4	randomized 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 1000 (from 0 fewer to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Favourable outcome (end of follow up)												
3	randomized 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 1000 (from 0 fewer to 92 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Favourable outcome – HIV positive												
3	randomized 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 1000 (from 39 more to 133 fewer)	⊕⊕◯◯ LOW	CRITICAL
Favourable outcome – HIV negative												
3	randomized 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 1000 (from 50 fewer to 122 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Relapse rate												
4	randomized 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 1000 (from 39 more to 160 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse effects – tx and fu – INH												
2	randomized 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 1000 (from 28 fewer to 35 more)	⊕⊕◯◯ LOW	
Adverse effects – treatment and follow-up – isoniazid												
3	randomized 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 1000 (from 43 fewer to 185 more)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A less than six-month fluoro-quinolone-containing regimen	The standard 6-month treatment regimen (2HRZE-4HR)	Relative (95% CI)	Absolute (95% CI)		
2–month culture conversion												
2	rand-omized 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 1000 (from 52 more to 143 more)	⊕⊕◯◯ LOW	IMPOR-TANT
Unfavourable outcome (18 months)												
3	rand-omized 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 1000 (from 28 more to 127 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Unfavourable outcome (end of therapy)												
4	rand-omized 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 1000 (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 fixed-drug combination compared with 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: Al-Banna et al. Eur Respir J. 2013; Gallardo: Gallardo CR et al. Cochrane Database Syst Rev. 2016 (systematic review of published and unpublished data). Mostly low- and middle-income countries, few HIV-positive patients.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-drug combination	Separate drug formulations	Relative (95% CI)	Absolute (95% CI)		
Failure or relapse (per protocol analysis): Al-Banna and Menzies												
15	randomized 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 1000 (from 1 fewer to 21 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Treatment failure: Cochrane study												
7	randomized 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 1000 (from 3 fewer to 19 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Relapse: Cochrane study												
10	randomized 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 1000 (from 0 fewer to 36 more)	⊕⊕◯◯ LOW	CRITICAL
Death: Cochrane study												
11	randomized 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 1000 (from 8 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
2 month culture conversion: Al–Banna and Menzies												
12	randomized 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 1000 (from 15 more to 45 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Sputum smear or culture conversion at end of treatment: Cochrane study												
7	randomized 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 1000 (from 36 fewer to 18 more)[af]	⊕⊕⊕⊕ HIGH	IMPORTANT
Adherence versus non–adherence to treatment: Al–Banna and Menzies												
5	randomized 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 1000 (from 20 fewer to 85 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Serious adverse reactions from TB drugs: Al-Banna and Menzies												
10	randomized 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 1000 (from 120 fewer to 40 more)	⊕⊕◯◯ LOW	IMPORTANT
Serious adverse events: Cochrane study												
6	randomized 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 1000 (from 2 fewer to 21 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adverse events leading to discontinuation of therapy: Cochrane study												
13	randomized 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 1000 (from 18 fewer to 26 more)	⊕⊕◯◯ LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed-drug combination	Separate drug formulations	Relative (95% CI)	Absolute (95% CI)		
Patient satisfaction: Al–Banna and Menzies												
2	rand-omized 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 1000 (from 85 fewer to 20 more)	⊕◯◯◯ VERY LOW	IMPOR-TANT
Acquisition (or amplification) of drug resistance: Al–Banna and Menzies												
4	rand-omized 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 1000 (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, since no studies were found that reported these outcomes (although economic analyses were not included – only randomized trials)

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

c. 95% CI 2.6–5.8.

d. 95% CI 1.9–4.2.

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, one side of the 95% CI does not exclude potential harm associated with fixed-drug combinations.

g. The risk in the intervention group (fixed-drug combination) (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: 1.5–3.7.

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

j. 95% CI: 5.5–9.1

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

l. 95% CI: 1.7–3.4

m. 95% CI 91–96%.

n. 95% CI 89–92%.

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: 85.7–91.0.

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

r. Imprecision based on confidence interval for risk ratio.

s. 95% CI 72–80.

t. 95% CI 76–83.

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 9–23.

w. 95% CI 11–28.

x. 95% CI 1.4–3.7.

y. Studies of highest risk of bias contribute to explain the large heterogeneity (I^2 statistic = 57%).

z. 95% CI 2.2–6.7.

aa. 95% CI 81–87.

ab. 95% CI 62–70.

ac. Imprecision based on confidence interval for risk ratio.

ad. 95% CI 0.0–0.7.

ae. 95% CI 0.0–0.4.

ah. No explanation was provided.

PICO 3

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

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

Setting: Numerous countries, mostly low- and middle-income countries

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:e1000146.[2]

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily dosing throughout treatment	Thrice-weekly dosing throughout 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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (from 10 more to 411 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

1. Only regimens with rifampicin 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 (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: 0.0–0.2.
7. Pooled effect estimate with 95% CI in subgroup analysis: 0.1; 0.0–0.3.
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: 0.0–0.2.
12. Pooled effect estimate with 95% CI in subgroup analysis: 0.3; 0.0–0.8.
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; 0.0–1.4.
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; 0.0–0.2.
18. Pooled effect estimate with 95% CI in subgroup analysis: 0.3; 0.0–0.8.
19. No explanation was provided.

PICO 4.1

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

Question: Daily dosing throughout TB treatment compared with 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 low- and middle-income countries

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: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 (not direct head-to-head comparisons)

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (from 2 fewer to 8 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

1. Only regimens with rifampicin 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: 0.0–0.2.
6. Pooled effect estimate with 95% CI in subgroup analysis; 0.2; CI: 0.0–0.8.
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: 0.0–4.2.
10. Pooled effect estimate with 95% CI in subgroup analysis; 0.1; CI: 0.0–0.2.
11. Pooled effect estimate with 95% CI in subgroup analysis; 0.1; 0.0–0.3.
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; 0.0–1.1.
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; 0.0–0.2.
17. Pooled effect estimate with 95% CI in subgroup analysis; 0.1; 0.0–0.3.

PICO 4.2

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

Question: Daily dosing throughout TB treatment compared with 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 low- and middle-income countries.

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:e1000146.[2]

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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: Johnston												
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 1000 (from 9 fewer to 276 more)[19]	⊕◯◯◯ VERY LOW	CRITICAL
Risk of relapse in drug-susceptible disease: Johnston												
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 1000 (from 8 fewer to 198 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug-susceptible disease: Johnston												
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 1000 (from 4 fewer to 21 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of failure in drug-susceptible disease or susceptibility unknown: Johnston												
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 1000 (from 0 fewer to 207 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of relapse in drug-susceptible disease or susceptibility unknown: Johnston												
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 1000 (from 0 fewer to 197 more)	⊕◯◯◯ VERY LOW	CRITICAL
Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown: Johnston												
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 1000 (from 4 fewer to 21 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

1. Only regimens with rifampicin duration ≥6 months included in analysis..
2. the systematic review performed across trial comparisons by treating the arms of trials as independent cohorts (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: 0.0–0.2.
7. Pooled effect estimate with 95% CI in subgroup analysis: 0.5; CI: 0.0–1.5.
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: 0.0–0.2.
12. Pooled effect estimate with 95% CI in subgroup analysis: 0.2; CI: 0.0–0.6.
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: 0.0–2.9.
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: 0.0–0.2.
18. Pooled effect estimate with 95% CI in subgroup analysis; 0.2; CI: 0.0–0.6.
19. No explanation was provided.

PICO 6

Author(s): Payam Nahid and Lelia Chaisson

Question: A treatment period greater than eight months compared with a treatment period of six months for patients with pulmonary drug-susceptible tuberculosis coinfected with HIV

Setting: From a systematic review of randomized trials plus controlled observational studies (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;55:1154–63.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment period greater than eight months	Treatment period of six 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 1000 (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 1000 (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 1000 (from 57 fewer to 69 more)[8]	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

1. Randomized trials and 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% (0.5–5.0).
7. Pooled estimate 95% CI: 2.6% (1.2–4.0).
8. No explanation was provided.
9. Dose–response gradient – with longer rifampicin duration there was a steady decline in rate of failure and relapse.
10. Pooled estimate 95% CI: 4.7% (0–11.2).
11. Pooled estimate 95% CI: 9.1% (0.4–17.8).
12. Pooled estimate 95% CI: 13.9% (7.3–20.4).
13. Pooled estimate 95% CI: 9.6% (5.9–12.5).

PICO 7

Author(s): Lelia Chaisson

Question: Adjuvant corticosteroids compared with 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							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant corticosteroids	TB treatment without corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Death												
5	randomized 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 1000 (from 42 more to 124 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment adherence												
2	randomized 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 1000 (from 104 more to 216 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Constrictive pericarditis												
3	randomized 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 1000 (from 43 more to 51 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; RR: risk ratio.

1. Inconsistent findings between studies. Death $I^2 = 70\%$; adherence $I^2 = 89\%$. Older studies show 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 reflecting the populations 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 show 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 with 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							Number of patients		Effect		Quality	Importance
Number 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	randomized 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 1000** (from 0 fewer to 167 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Death or severe disability												
4	randomized 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 1000** (from 15 fewer to 161 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Relapse												
2	randomized 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 1000** (from 38 more to 67 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
2	randomized 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 1000** (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: Retreatment with the five first-line drugs HRZES (WHO category II regimen) used with known isoniazid resistance compared with retreatment with the five first-line drugs HRZES (WHO category II regimen) used with known isoniazid susceptibility for patients with a previous history of treatment with first-line anti-TB drugs being considered for retreatment due to treatment interruption or recurrence

Setting: Multiple countries

Bibliography: Gegia M, Menzies D. Impact of isoniazid resistance on treatment outcomes, submitted.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Retreatment with the five first-line drugs HRZES (WHO category II regimen) used with known isoniazid resistance	Retreatment with the five first-line drugs HRZES (WHO category II regimen) used with known isoniazid susceptibility	Relative (95% CI)	Absolute (95% CI)		
Failure – Category 2 (2HRZES or 1HRZE or 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 1000** (from 5 fewer to 45 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse – Category 2 (2HRZES or 1HRZE or 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 1000** (from 36 fewer to 28 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure or Relapse – Category 2 (2HRZES or 1HRZE or 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 1000** (from 13 more to 98 more)	⊕◯◯◯ VERY LOW	CRITICAL
Acquisition (or amplification) of drug resistance – Category 2 (2HRZES or 1HRZE or 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 1000** (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 isoniazid-resistant versus 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, 0.4).

PICO 9.2

Author(s): Dick Menzies

Question: The five first-line drugs HRZES (WHO category II regimen) compared with 6- to 9-month RZE for patients with known isoniazid resistance requiring TB retreatment[1]

Setting: Multiple countries

Bibliography: Gegia M, Menzies D. Impact of isoniazid resistance on treatment outcomes, submitted.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	The five first-line drugs HRZES (WHO category II regimen)	6- to 9-month 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 1000** (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 1000** (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 1000** (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 1000** (from 29 fewer to 37 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval.

1. In most of the included trials, the isoniazid-resistant patients were a small subgroup of all treated patients.
2. Number of studies with category II: 24. Number of studies with 6- to 9-month RZE: 13.
3. RCT and cohort studies.
4. Risk, 95% CI: 6% (2, 10).
5. Risk, 95% CI: 2% (0, 5).
6. Number of studies with category II: 20. Number of studies with 6- to 9-month 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 category II: 17. Number of studies with 6- to 9-month 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
Bibliography: Adherence interventions for tuberculosis.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-administered therapy	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 1000 (from 0 fewer to 40 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs												
5	randomized 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 1000 (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 1000 (from 89 fewer to 208 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success – RCTs												
5	randomized 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 1000 (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 1000 (from 40 fewer to 80 more)	⊕◯◯◯ VERY LOW	CRITICAL
Completion – RCTs												
5	randomized 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 1000 (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 1000 (from 109 fewer to 252 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Cure – RCTs												
4	randomized 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 1000 (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 1000 (from 0 fewer to 50 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – RCTs												
6	randomized trials	serious[d]	not serious	not serious	serious[e]	none	21/1036 (2.0%)	24/1220 (2.0%)	not estimable	0 fewer per 1000 (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 1000 (from 20 more to 90 more)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-administered therapy	Directly observed therapy (DOT)	Relative (95% CI)	Absolute (95% CI)		
Loss to follow up – RCTs												
4	randomized trials	serious[d]	not serious	not serious	serious[e]	none	138/689 (20.0%)	166/914 (18.2%)	**RR 1.28** (0.93 to 1.76)	51 more per 1000 (from 13 fewer to 138 more)	⊕⊕◯◯ LOW	CRITICAL
Relapse – cohorts												
6	observational studies	serious[a]	serious[j]	not serious	serious[e]	none	103/937 (11.0%)	36/992 (3.6%)	not estimable	60 more per 1000 (from 30 fewer to 150 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse – RCTs (follow-up: mean 24 months)												
1	randomized trials	serious[k]	not serious	not serious	very serious[e,l]	none	15/290 (5.2%)	23/259 (8.9%)	**RR 0.58** (0.31 to 1.09)	37 fewer per 1000 (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 1000 (from 118 fewer to 169 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adherence – RCTs (follow-up: mean six months)												
1	randomized trials	serious[n]	not serious	not serious	serious[e]	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94** (0.87 to 1.02)	58 fewer per 1000 (from 19 more to 126 fewer)	⊕⊕◯◯ LOW	CRITICAL
Smear conversion – cohort studies												
2	observational studies	serious[o]	not serious	not serious	serious[e]	none	49/60 (81.7%)	324/407 (79.6%)	**RR 0.92** (0.78 to 1.08)	64 fewer per 1000 (from 64 more to 175 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Smear conversion – RCTs												
1	randomized 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 1000 (from 18 fewer to 115 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Acquisition of drug resistance												
3	observational studies	very serious[q]	very serious[r]	not serious	serious[e]	none	202/2644 (7.6%)	71/3284 (2.2%)	not estimable	50 fewer per 1000 (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. Three 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 Newcastle-Ottawa Scale 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							Number of patients		Effect		Quality	Importance
Number 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 or community versus 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 1000 (from 10 fewer to 20 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs (community versus clinic)												
2	randomized 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 1000 (from 103 fewer to 146 more)	⊕◯◯◯ VERY LOW	CRITICAL
Success – cohorts (home or community versus 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 1000 (from 47 more to 111 more)	⊕◯◯◯ VERY LOW	CRITICAL
Completion – cohort studies (home or community versus clinic)												
2	randomized 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 1000 (from 0 fewer to 76 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Completion – cohort studies (home or community versus 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 1000 (from 75 fewer to 94 more)	⊕◯◯◯ VERY LOW	CRITICAL
Completion– RCTs (community versus clinic)												
1	randomized 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 1000 (from 5 more to 215 more)	⊕⊕◯◯ MODERATE	CRITICAL
Cure – cohort studies (home or community versus 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 1000 (from 7 fewer to 160 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cure – RCTs (home or community versus clinic)												
2	randomized 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 1000 (from 48 fewer to 72 more)	⊕⊕◯◯ LOW	CRITICAL
Failure – cohort studies (home or community versus 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 1000 (from 30 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – RCTs (home versus community)												
1	randomized 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 1000 (from 1 fewer to 23 more)	⊕⊕◯◯ LOW	CRITICAL
Failure – RCTs (community versus clinic)												
1	randomized 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 1000 (from 12 fewer to 36 more)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 or community versus 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 1000 (from 14 fewer to 69 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up – RCTs (home or community versus clinic)												
2	randomized 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 1000 (from 88 fewer to 293 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence – cohort studies (home or community versus 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 1000 (from 112 more to 215 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Sputum conversion (second month) – Cohort studies (home or community versus 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 1000 (from 17 more to 251 more)	⊕◯◯◯ VERY LOW	CRITICAL
Sputum conversion (second month) – RCTs (home or community versus clinic)												
1	randomized 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 1000 (from 7 fewer to 153 more)	⊕⊕◯◯ LOW	CRITICAL
Unfavourable outcome (community versus 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 1000 (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 of 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 that 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 with self-administered therapy for TB treatment
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinic-based DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Mortality – 1: clinic DOT versus self-administered therapy – 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 1000** (from 36 fewer to 133 more)	⨁◯◯◯ VERY LOW	
Mortality – 1: clinic DOT versus self-administered therapy – RCTs												
3	randomized 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 1000** (from 8 fewer to 61 more)	⨁⨁◯◯ LOW	
Success – 1: clinic DOT versus self-administered therapy – 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 1000** (from 106 more to 276 fewer)	⨁◯◯◯ VERY LOW	
Success – 1: clinic DOT versus self-administered therapy – RCTs												
3	randomized 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 1000** (from 76 more to 82 fewer)	⨁⨁⨁◯ MODERATE	
Completion – 1: clinic DOT versus self-administered therapy – 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 1000** (from 84 fewer to 211 fewer)	⨁⨁◯◯ LOW	
Completion – 1: clinic DOT versus self-administered therapy – RCTs												
3	randomized 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 1000** (from 26 fewer to 70 more)	⨁⨁◯◯ LOW	
Cure – 1: clinic DOT versus self-administered therapy – 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 1000** (from 32 more to 128 fewer)	⨁◯◯◯ VERY LOW	
Cure – 1: Clinic DOT versus self-administered therapy – RCTs												
3	randomized 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 1000** (from 106 more to 151 fewer)	⨁⨁◯◯ LOW	
Failure – 1: clinic DOT versus self-administered therapy – 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 1000** (from 0 fewer to 40 more)	⨁◯◯◯ VERY LOW	
Failure – 1: clinic DOT versus self-administered therapy – RCTs												
3	randomized trials	serious[c]	not serious	not serious	not serious	none	3/281 (1.1%)	2/267 (0.7%)	not estimable	**10 fewer per 1000** (from 10 more to 20 fewer)	⨁⨁⨁◯ MODERATE	
Default – 1: clinic DOT versus self-administered therapy – 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 1000** (from 6 fewer to 131 more)	⨁◯◯◯ VERY LOW	

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinic-based DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Default – 1: clinic DOT versus self-administered therapy – RCTs												
3	randomized 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 1000** (from 53 more to 96 fewer)	⨁⨁◯◯ LOW	
Adherence – 1: home DOT versus self-administered therapy												
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 1000** (from 21 more to 207 more)	⨁⨁◯◯ LOW	
Adherence – 1: home DOT versus self-administered therapy – RCTs												
1	randomized 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 1000** (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- or community-based DOT compared with self-administered therapy for TB treatment

Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home- or community-based DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Mortality – 1: home-based DOT versus self-administered therapy – 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 1000 (from 38 fewer to 97 more)	⊕◯◯◯ VERY LOW	
Mortality – 1: home-based DOT versus self-administered therapy – RCTs												
2	randomized 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 1000 (from 7 fewer to 112 more)	⊕⊕◯◯ LOW	
Success – 1: home-based DOT versus self-administered therapy – 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 1000 (from 58 more to 167 more)	⊕◯◯◯ VERY LOW	
Success – 1: home-based DOT versus self-administered therapy – RCTs												
2	randomized 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 1000 (from 108 fewer to 235 more)	⊕⊕◯◯ LOW	
Completion – 1: home-based DOT versus self-administered therapy – 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 1000 (from 177 more to 204 fewer)	⊕◯◯◯ VERY LOW	
Completion – 1: Home-based DOT versus self-administered therapy – RCTs												
3	randomized 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 1000 (from 90 fewer to 302 more)	⊕⊕◯◯ LOW	
Cure – 1: home-based DOT versus self-administered therapy – 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 1000 (from 48 fewer to 665 more)	⊕◯◯◯ VERY LOW	
Cure – 1: home-based DOT versus self-administered therapy – RCTs												
2	randomized 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 1000 (from 178 fewer to 378 more)	⊕◯◯◯ VERY LOW	
Failure – 1: home-based DOT versus self-administered therapy – 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 1000 (from 0 fewer to 10 fewer)	⊕◯◯◯ VERY LOW	
Failure – 1: home-based DOT versus self-administered therapy – RCTs												
2	randomized trials	serious[d]	not serious	not serious	not serious	none	3/219 (1.4%)	2/206 (1.0%)	not estimable	0 fewer per 1000 (from 10 more to 10 fewer)	⊕⊕◯◯ MODERATE	
Default – 1: home-based DOT versus self-administered therapy												
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 1000 (from 101 fewer to 116 fewer)	⊕◯◯◯ VERY LOW	

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home- or community-based DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Default – 1: home-based DOT versus self-administered therapy – RCTs												
2	randomized 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 1000 (from 99 more to 127 fewer)	⨁⨁◯◯ LOW	
Adherence – 1: home-based DOT versus self-administered therapy												
2	observational studies	not serious	not serious	serious[f]	not serious	none	1332/1616 (82.4%)	961/1392 (69.0%)	**RR 1.15** (1.03 to 1.30)	104 more per 1000 (from 21 more to 207 more)	⨁◯◯◯ VERY LOW	
Adherence – 1: home-based DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 19 more to 126 fewer)	⨁⨁◯◯ MODERATE	

CI: confidence interval; RR: risk ratio.

a. Based on the Newcastle-Ottawa 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 and intervention groups.
f. Studies define the 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 with standard providers for TB treatment (2)
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 versus health-care workers												
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 1000 (from 11 fewer to 25 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality – lay provider versus health-care workers												
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 1000 (from 7 more to 28 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Success – family versus health-care workers												
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 1000 (from 43 more to 239 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Success – lay provider versus health-care workers												
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 1000 (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 1000 (from 7 more to 26 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Cure – family versus health-care workers												
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 1000 (from 312 more to 397 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Cure – lay provider versus health-care workers												
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 1000 (from 141 fewer to 350 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – family versus health-care workers												
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 1000 (from 0 fewer to 10 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – lay provider versus health-care workers												
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 1000 (from 13 more to 36 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow up – family versus health-care workers												
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 1000 (from 11 more to 44 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow-up – lay provider versus health-care workers												
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 1000 (from 32 more to 58 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence – family versus health-care workers (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 1000 (from 57 fewer to 198 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

a. Based on the 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 self-administered therapy for TB treatment

Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Family DOT	Self- administered therapy	Relative (95% CI)	Absolute (95% CI)		
Mortality – family DOT vs self-administered therapy – 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 1000 (from 43 fewer to 438 more)	⊕◯◯◯ VERY LOW	
Mortality – family DOT vs self-administered therapy – RCTs												
1	randomized 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 1000 (from 7 fewer to 143 more)	⊕⊕⊕⊕ HIGH	
Success – family DOT vs self-administered therapy – 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 1000 (from 35 more to 194 more)	⊕◯◯◯ VERY LOW	
Success–1 – family DOT vs self-administered therapy – RCTs												
1	randomized 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 1000 (from 84 more to 117 fewer)	⊕⊕⊕⊕ HIGH	
Completion – family DOT vs self-administered therapy												
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 1000 (from 205 fewer to 294 more)	⊕◯◯◯ VERY LOW	
Completion – family DOT vs self-administered therapy – RCTs												
2	randomized 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 1000 (from 177 fewer to 1000 more)	⊕◯◯◯ VERY LOW	
Cure – family DOT vs self-administered therapy												
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 1000 (from 82 fewer to 764 more)	⊕◯◯◯ VERY LOW	
Cure – family DOT vs self-administered therapy – RCTs												
1	randomized 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 1000 (from 43 more to 160 fewer)	⊕⊕⊕⊕ HIGH	
Failure – family DOT vs self-administered therapy												
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 1000 (from 8 fewer to 36 more)	⊕◯◯◯ VERY LOW	
Failure – family DOT vs self-administered therapy – RCTs												
1	randomized 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 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	
Default – family DOT vs self-administered therapy – 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 1000 (from 118 fewer to 138 fewer)	⊕◯◯◯ VERY LOW	

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Family DOT	Self- administered therapy	Relative (95% CI)	Absolute (95% CI)		
Default – family DOT vs self-administered therapy – RCTs												
1	randomized 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 1000 (from 92 fewer to 111 more)	⊕⊕⊕⊕ HIGH	
Adherence – family DOT vs self-administered therapy – 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 1000 (from 53 fewer to 167 more)	⊕⊕◯◯ LOW	
Adherence – family DOT vs self-administered therapy – RCTs												
1	randomized 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 1000 (from 19 more to 126 fewer)	⊕⊕⊕◯ MODERATE	

CI: confidence interval; RR: risk ratio.

a. Based on the Newcastle-Ottawa 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: Health-care worker DOT compared with self-administered therapy for TB treatment

Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Health-care worker DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Mortality – 1: health-care worker DOT versus self-administered therapy – 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 1000 (from 28 fewer to 32 more)	⊕◯◯◯ VERY LOW	
Mortality – 1: health-care worker DOT versus self-administered therapy – RCTs												
3	randomized trials	serious[d]	not serious	not serious	not serious	none	7/281 (2.5%)	4/267 (1.5%)	not estimable	10 fewer per 1000 (from 20 more to 40 fewer)	⊕⊕⊕◯ MODERATE	
Success – 1: health-care worker DOT versus self-administered therapy – 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 1000 (from 21 fewer to 247 more)	⊕◯◯◯ VERY LOW	
Success – 1: health-care worker DOT versus self-administered therapy – RCTs												
3	randomized 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 1000 (from 76 more to 82 fewer)	⊕⊕◯◯ LOW	
Completion – 1: health-care worker DOT versus self-administered therapy – 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 1000 (from 71 fewer to 167 fewer)	⊕◯◯◯ VERY LOW	
Completion – 1: health-care worker DOT versus self-administered therapy – RCTs												
3	randomized 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 1000 (from 26 fewer to 70 more)	⊕⊕◯◯ LOW	
Cure – 1: health-care worker DOT versus self-administered therapy – 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 1000 (from 131 more to 457 more)	⊕◯◯◯ VERY LOW	
Cure – 1: health-care worker DOT versus self-administered therapy – RCTs												
3	randomized 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 1000 (from 106 more to 151 fewer)	⊕⊕◯◯ LOW	
Failure – 1: health-care worker DOT versus self-administered therapy												
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 1000 (from 20 fewer to 20 more)	⊕◯◯◯ VERY LOW	
Failure – 1: health-care worker DOT versus self-administered therapy – RCTs												
3	randomized trials	serious[d]	not serious	not serious	not serious	none	3/281 (1.1%)	2/267 (0.7%)	not estimable	10 fewer per 1000 (from 10 more to 20 fewer)	⊕⊕⊕◯ MODERATE	
Default – 1: health-care worker DOT versus self-administered therapy – 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 1000 (from 5 more to 214 fewer)	⊕◯◯◯ VERY LOW	

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Health-care worker DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Default – 1: health-care worker DOT versus self-administered therapy – RCTs												
3	rand-omized 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 1000 (from 53 more to 96 fewer)	⨁⨁◯◯ LOW	
Relapse – health-care worker DOT versus self-administered therapy – cohorts												
2	obser-vational 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 1000 (from 33 fewer to 202 fewer)	⨁◯◯◯ VERY LOW	
Acquisition of drug resistance – health-care worker DOT versus self-administered therapy – cohorts												
1	obser-vational 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 1000 (from 67 fewer to 89 fewer)	⨁◯◯◯ VERY LOW	
Adherence – health-care worker DOT versus self-administered therapy – cohorts												
2	obser-vational 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 1000 (from 110 more to 179 more)	⨁⨁◯◯ LOW	

CI: confidence interval; RR: risk ratio.

a. Based on the Newcastle-Ottawa 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. Two 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 with self-administered therapy for TB treatment

Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lay provider DOT	Self-administered therapy	Relative (95% CI)	Absolute (95% CI)		
Mortality – 1: lay provider DOT versus self-administered therapy – 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 1000 (from 19 fewer to 80 more)	⊕◯◯◯ VERY LOW	
Mortality – 1: lay provider DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 19 fewer to 372 more)	⊕⊕◯◯ LOW	
Success – 1: lay provider DOT versus self-administered therapy – 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 1000 (from 0 fewer to 130 more)	⊕◯◯◯ VERY LOW	
Success – 1: lay provider DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 35 fewer to 402 more)	⊕⊕⊕◯ MODERATE	
Completion – 1: lay person DOT versus self-administered therapy – 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 1000 (from 11 fewer to 148 fewer)	⊕◯◯◯ VERY LOW	
Completion – 1: lay provider DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 111 fewer to 215 more)	⊕⊕◯◯ LOW	
Cure – 1: lay person DOT versus self-administered therapy – 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 1000 (from 73 more to 256 more)	⊕◯◯◯ VERY LOW	
Cure – 1: lay provider DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 33 fewer to 466 more)	⊕⊕◯◯ LOW	
Failure – 1: lay provider DOT versus self-administered therapy – 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 1000 (from 6 fewer to 104 more)	⊕◯◯◯ VERY LOW	
Failure – 1: lay provider DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 36 fewer to 272 more)	⊕⊕◯◯ LOW	
Default – 1: lay provider DOT versus self-administered therapy – 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 1000 (from 181 fewer to 394 more)	⊕◯◯◯ VERY LOW	
Default – 1: lay provider DOT versus self-administered therapy – RCTs												
1	randomized 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 1000 (from 85 more to 185 fewer)	⊕⊕◯◯ LOW	

CI: confidence interval; RR: risk ratio.

a. Based on the Newcastle-Ottawa 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: Self-administered therapy compared with DOT for patients with TB and HIV
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-administered therapy	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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (from 82 fewer to 1000 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 1000 (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 with none for TB treatment

Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 1000 (from 30 fewer to 66 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs												
2	randomized trials	not serious	not serious	not serious	serious[d]	none	151/2157 (7.0%)	139/2034 (6.8%)	**not estimable**	1 more per 1000 (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 1000 (from 61 more to 283 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success – RCTs												
3	randomized 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 1000 (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 1000 (from 17 fewer to 97 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion – RCTs												
2	randomized 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 1000 (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 1000 (from 138 more to 230 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cure – RCTs												
1	randomized 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 1000 (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 1000 (from 120 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment failure – RCTs												
1	randomized 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 1000 (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 1000 (from 130 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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	rand-omized 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 1000 (from 10 fewer to 41 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Acquisition of resistance												
1	rand-omized 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 1000 (from 1 fewer to 3 more)	⊕⊕◯◯ LOW	CRITICAL
Sputum conversion rate – RCTs												
1	rand-omized 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 1000 (from 16 more to 346 more)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: confidence interval; RR: risk ratio.

a. Based on the 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 with none for TB treatment
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 1000 (from 26 fewer to 343 more)	⊕◯◯◯ VERY LOW	CRITICAL
Success – RCTs (alcohol cessation counselling)												
1	randomized 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 1000 (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 1000 (from 38 more to 469 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment completion – RCTs (support groups)												
1	randomized 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 1000 (from 24 more to 317 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cure – RCTs (support groups)												
1	randomized 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 1000 (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 1000 (from 60 fewer to 30 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – RCTs (support groups)												
1	randomized 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 1000 (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 1000 (from 150 fewer to 345 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow-up – RCTs (support groups)												
1	randomized 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 1000 (from 44 fewer to 200 more)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

a. Based on the 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 the 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: Additional patient education and educational counselling compared with routine care for TB treatment
Setting: Multiple countries
Bibliography: Adherence Interventions for Tuberculosis.

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Additional patient education and educational counselling	Routine care	Relative (95% CI)	Absolute (95% CI)		
Mortality – RCTs												
2	randomized 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 1000 (from 27 fewer to 42 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success												
2	randomized 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 1000 (from 43 fewer to 498 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment completion												
1	randomized 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 1000 (from 134 more to 512 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure												
1	randomized 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 1000 (from 229 more to 759 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Failure												
1	randomized 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 1000 (from 38 fewer to 266 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow-up												
3	randomized 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 1000 (from 84 more to 390 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence – RCT												
1	randomized 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 1000 (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 1000 (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 with none for TB treatment

Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 1000 (from 30 more to 30 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs												
2	randomized 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 1000 (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 1000 (from 104 more to 381 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success – RCTs												
3	randomized 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 1000 (from 32 fewer to 76 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Completion – RCTs												
2	randomized 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 1000 (from 96 more to 115 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure – RCTs												
3	randomized 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 1000 (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 1000 (from 30 more to 30 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment failure – RCTs												
2	randomized trials	not serious	not serious	not serious	serious[d]	none	10/830 (1.2%)	6/665 (0.9%)	not estimable	0 fewer per 1000 (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 1000 (from 260 fewer to 100 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow-up – RCTs												
2	randomized 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 1000 (from 38 more to 50 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

a. Based on the Newcastle-Ottawa Scale.
b. No events in the intervention and 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 with none for TB treatment
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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-observed treatment (VOT) versus 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 1000 (from 7 fewer to 146 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success – RCTs (phone reminders)												
2	randomized 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 1000 (from 115 fewer to 265 more)	⨁⨁◯◯ LOW	CRITICAL
Completion – cohort studies (VOT versus 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 1000 (from 149 fewer to 511 more) [h]	⨁◯◯◯ VERY LOW	CRITICAL
Completion – RCTs (phone reminders)												
1	randomized trials	serious[f]	not serious	not serious	serious[d]	none	0/30 (0.0%)	6/31 (19.4%)	not estimable	190 fewer per 1000 (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 1000 (from 194 more to 762 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cure – RCTs (phone reminders)												
1	randomized 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 1000 (from 203 more to 679 more)	⨁⨁◯◯ LOW	CRITICAL
Failure (phone reminders)												
1	randomized trials	serious[f]	not serious	not serious	serious[d]	none	0/49 (0.0%)	6/50 (12.0%)	not estimable	120 fewer per 1000 (from 220 fewer to 20 fewer)	⨁⨁◯◯ LOW	CRITICAL
Sputum or culture conversion at two 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 1000 (from 35 more to 547 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sputum or culture conversion at two months – RCTs (phone reminders)												
1	randomized 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 1000 (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 1000 (from 39 fewer to 74 fewer)	⨁⨁◯◯ LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (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 1000 (from 122 fewer to 146 fewer)	⊕◯◯◯ VERY LOW	

CI: confidence interval; RR: risk ratio.

a. Based on the Newcastle-Ottawa Scale.
b. Studies conducted in high-income countries; extrapolation to low- and middle-income countries 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 with none for TB treatment
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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	16 375/182 194 (9.0%)	18 044/224 631 (8.0%)	not estimable	20 fewer per 1000 (from 70 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs												
1	randomized 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 1000 (from 13 more to 30 fewer)	⨁⨁◯◯ LOW	CRITICAL
Treatment success – cohort studies												
3	observational studies	serious[a]	serious[d]	not serious	serious[b]	none	129 645/182 194 (71.2%)	171 637/224 631 (76.4%)	**RR 1.03** (0.89 to 1.20)	23 more per 1000 (from 84 fewer to 153 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success – RCTs												
4	randomized 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 1000 (from 8 more to 203 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment completion – cohort studies												
1	observational studies	not serious	not serious	not serious	not serious	none	20 579/181 283 (11.4%)	19 697/224 390 (8.8%)	**RR 1.29** (1.27 to 1.32)	25 more per 1000 (from 24 more to 28 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment completion – RCT												
2	randomized 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 1000 (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	108 459/181 319 (59.8%)	151 810/224 496 (67.6%)	**RR 1.28** (0.59 to 2.79)	189 more per 1000 (from 277 fewer to 1000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Failure – cohort studies												
3	observational studies	serious[a]	not serious	not serious	not serious	none	4208/18 2194 (2.3%)	4687/22 4631 (2.1%)	not estimable	0 fewer per 1000 (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	20 935/182 822 (11.5%)	18 637/22 5259 (8.3%)	not estimable	50 fewer per 1000 (from 150 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow-up – RCTs												
2	randomized 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 1000 (from 66 more to 111 fewer)	⨁⨁◯◯ LOW	CRITICAL
Adherence												
2	randomized 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 1000 (from 66 more to 357 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tracers	None	Relative (95% CI)	Absolute (95% CI)		
Sputum or culture conversion at two months												
2	rand-omized 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 1000 (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/ 181 283 (0.3%)	1452/ 224 390 (0.6%)	**RR 0.50** (0.45 to 0.55)	3 fewer per 1000 (from 3 fewer to 4 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

a. Based on the 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 did 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 with none for TB treatment
Setting: Multiple countries

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 versus self-administered therapy)												
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 1000 (from 130 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality – cohort studies (enhanced DOT versus 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 1000 (from 17 more to 18 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs (mixed interventions versus self-administered therapy)												
2	randomized 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 1000 (from 45 fewer to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality – RCTs (enhanced DOT versus DOT)												
1	randomized 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 1000 (from 3 fewer to 26 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success – cohort studies (enhanced DOT versus self-administered therapy)												
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 1000 (from 111 more to 188 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success – cohort studies (enhanced DOT versus 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 1000 (from 64 more to 351 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success – RCTs (enhanced DOT versus self-administered therapy)												
1	randomized 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 1000 (from 41 more to 516 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment success – RCTs (enhanced DOT versus DOT)												
2	randomized 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 1000 (from 82 more to 165 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion – cohort studies (enhanced DOT versus self-administered therapy)												
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 1000 (from 158 more to 368 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion – cohort studies (enhanced DOT versus 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 1000 (from 156 more to 197 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion – RCTs (enhanced DOT versus self-administered therapy)												
1	randomized 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 1000 (from 76 more to 543 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 versus DOT)												
2	randomized 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 1000 (from 13 more to 30 fewer)	⊕⊕◯◯ LOW	CRITICAL
Cure – cohort studies (enhanced DOT versus 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 1000 (from 112 fewer to 665 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cure – RCTs (enhanced DOT versus DOT)												
1	randomized 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 1000 (from 91 more to 182 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure – cohort studies (enhanced DOT versus self-administered therapy)												
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 1000 (from 14 more to 700 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cure – RCTs (enhanced DOT versus self-administered therapy)												
1	randomized 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 1000 (from 41 more to 516 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cure – RCTs (mixed case management versus self-administered therapy)												
2	randomized 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 1000 (from 20 more to 197 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Failure – cohort studies (enhanced DOT versus 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 1000 (from 6 fewer to 6 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – cohort studies (enhanced DOT versus self-administered therapy)												
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 1000 (from 20 fewer to 10 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – RCTs (mixed case management versus self-administered therapy)												
1	randomized 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 1000 (from 40 fewer to 200 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure – RCTs (enhanced DOT versus DOT)												
1	randomized 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 1000 (from 2 fewer to 33 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow-up – cohort studies (enhanced DOT versus 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 1000 (from 102 more to 144 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to follow-up – RCTs (enhanced DOT versus DOT)												
2	randomized 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 1000 (from 77 fewer to 134 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number 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 versus self-administered therapy)												
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 1000 (from 38 more to 183 fewer)	⊕○○○ VERY LOW	CRITICAL
Loss to follow-up – RCTs (mixed case management versus self-administered therapy)												
2	randomized 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 1000 (from 13 fewer to 119 fewer)	⊕⊕○○ LOW	CRITICAL
Relapse – cohort studies (enhanced DOT versus self-administered therapy)												
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 1000 (from 30 more to 10 fewer)	⊕○○○ VERY LOW	CRITICAL
Adherence (enhanced DOT versus DOT)												
1	randomized 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 1000 (from 114 fewer to 228 more)	⊕⊕○○ LOW	CRITICAL
Adherence (mixed case management versus self-administered therapy)												
1	randomized 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 1000 (from 63 fewer to 411 more)	⊕⊕○○ LOW	CRITICAL
Sputum smear conversion rate (second month) – RCTs (enhanced DOT versus self-administered therapy)												
1	randomized 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 1000 (from 85 more to 712 more)	⊕⊕○○ LOW	CRITICAL
Acquired drug resistance – cohort studies (enhanced DOT versus self-administered therapy)												
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 1000 (from 30 more to 10 fewer)	⊕○○○ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

a. Based on the 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: Decentralized treatment and care compared with centralized treatment and care for patients on MDR-TB treatment

Setting: Countries that have decentralized treatment and care for patients with multidrug-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							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decentralized treatment and care	Centralized treatment and care	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure, death or loss 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 1000 (from 6 more to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow-up versus treatment success, treatment failure or 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 1000 (from 29 more to 138 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Death versus treatment success, treatment failure or 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 1000 (from 57 fewer to 91 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment failure versus treatment success, death or 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 1000 (from 22 fewer to 59 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

a. All the studies were observational studies. The method of allocating patients to intervention and control groups was not randomized. Not downgraded for this further because this was 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 was 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.

World Health Organization

World Health Organization
20 Avenue Appia, 1211-Geneva-27, Switzerland

Web site: www.who.int/tb
Information Resource Centre HTM: tbdocs@who.int