WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Drug-susceptible tuberculosis treatment

Web annexes

World Health Organization

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Design by Inis Communication

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Module 4: Treatment

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World Health Organization

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Web Annex 1. Expert panels

Web Annex 1a. Participants in the Guideline Development Group meeting. 27–30 April 2021

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Web Annex 2. Declarations of interest

Web Annex 2a. Guideline Development Group meeting. 2021

Twenty-five individuals from various areas of expertise were invited to attend. All the experts completed and submitted their Declaration of Interest (DOI) and Confidentiality Undertaking forms between March – April 2021.

On review of the completed DOIs, the following 8 experts declared interests that required further consideration and discussion with WHO Office of Compliance, Risk Management and Ethics (CRE): Susan ABDEL RAHMAN; Grania BRIGDEN; Daniela CIRILLO; Charles DALEY; Geraint DAVIES; Anneke HESSELING; Laia RUIZ MINGOTE; Carrie TUDOR. Following thorough assessment and review in collaboration with the CRE no competing interests were identified with the scope of the work being undertaken by the GDG. The note for the record with details of the assessment was filed.

Web Annex 2b. Guideline Development Group meeting. 2016

The following members declared no interests: Si Thu Aung; Frank Bonsu; Jeremiah Chakaya; Lucy Chesire; Daniela Cirillo; Poonam Dhavan; Kathy Fiekert; Andrei Mariandyshev; Nguyen Viet Nhung; Ejaz Qadeer; Abdul Hamid Salim; Holger Schünemann; Pedro Suarez; Justin Wong Yun Yaw.

The following GDG members declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting:

Kelly Dooley declared that she did not receive any salary support from drug companies for her work in the following roles and activities: Co-chair of the AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid for MDR-TB; principal investigator, assessing pretomanid for tuberculosis trial, assessing pretomanid (PA-824, investigational drug) for treatment of drug-sensitive TB; investigator on trials assessing rifapentine for pregnant women with latent TB infection, rifapentine for treatment shortening in patients with pulmonary TB, high-dose rifampicin and levofloxacin for pediatric TB meningitis, high-dose isoniazid for MDR-TB, and delamanid for MDR-TB in children with and without HIV.

Mike Frick declared that his organization received noncommercial support 1) to track investment made in TB research and development; 2) to host a symposium at the Union meeting; 3) to advocate for increased funding for TB research and development, research and access to evidence-based interventions; and 4) for the management of the community research advisors group.

Simon Schaaf declared receiving grants for pharmacokinetic drug studies in children of second-line drugs and for studying preventive therapy in MDR-TB.

Carrie Tudor declared that her organization receives funding from Eli Lilly Foundation for activities related to TB and MDR-TB projects.

Web Annex 2c. Guideline Development Group meeting. 2009

All members of the group completed a Declaration for the Conflict of Interest; there were no conflicts declared.

Web Annex 3. PICO questions

Research questions in a Population, Intervention, Comparator, Outcomes (PICO) format are listed below as they related to the recommendations retained in this policy consolidation.

Web Annex 3a. PICO questions. Guideline Development Group meetings in 2021

Recommendation 7. PICO question

In patients aged ≥ 12 years with drug-susceptible pulmonary TB, is a 4-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin as effective and safe as the standard drug-susceptible TB regimen composed according to WHO guidelines?

Population	Intervention	Comparator	Outcomes
Patients aged ≥ 12 years with drug-susceptible pulmonary TB, stratified by sub-populations: **a. with signs of extensive disease (i.e. bilateral cavitary disease or extensive parenchymal damage on radiography)*** **b. adults ≥20 years and adolescents aged 12–19 years** **c. persons with HIV (+/- ARVs)** **d. with comorbidities (e.g. diabetes mellitus; malnutrition)**	A 17-week regimen composed of two months of rifapentine, isoniazid, pyrazinamide and moxifloxacin followed by two months of rifapentine, pyrazinamide and moxifloxacin**	The currently WHO recommended standard drug-susceptible TB treatment regimen composed of two months of rifampicin, isoniazid, pyrazinamide and ethambutol followed by four months of rifampicin and isoniazid	• Cure (favourable outcome)*** • Absence of cure (unfavourable outcome)*** • Death • Adherence to treatment (or treatment interruption due to non-adherence) • Severe adverse events (defined as grade 3 or higher) • Acquisition (amplification) of drug resistance

* WHO defines extensive or advanced TB disease as: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

** Standard doses (i.e. those that are currently recommended, and weight based, where relevant) of pyrazinamide, isoniazid and moxifloxacin were used and the dose of rifapentine used was 1200mg.

*** In Study 31, a participant was classified as having a favorable outcome if any one of the following conditions was met and an unfavorable outcome did not occur:

1. Participants whose last culture result during the Month 12 analysis visit window was *M. tuberculosis* negative.

2. Participants who were seen during the Month 12 analysis visit window and were clinically without symptoms/signs of ongoing active TB (indicated by absence of initiation of possible poor treatment response (PPTR) evaluation or PPTR that did not indicate presence of symptoms/signs of ongoing active TB), and had achieved culture conversion prior to Month 12, and
   a) Were unable to produce a sputum specimen at any point during the Month 12 analysis visit window; or
   b) Produced a sputum specimen that was contaminated or unevaluable without evidence of *M. tuberculosis*, and no sputum specimens yielded positive or negative culture results during the Month 12 analysis visit window.

A participant was classified as having an unfavorable outcome if any one of the following conditions is met:

1. A participant was considered to have absence of bacteriological cure if he/she had a sputum sample, obtained at or after Week 17 and no later than the end of the Month 12 analysis visit window, that is *M. tuberculosis* Culture Positive that was indistinguishable from the initial isolate (see separate sequencing plan for definitions), and this was confirmed by a second sample that was *M. tuberculosis* culture positive. A second confirmatory sample, on a different day without an intervening *M. tuberculosis* negative culture result, was required, as a single positive sputum culture result in isolation was not considered absence of bacteriological cure. If results from strain analysis were inconclusive or unavailable, it was assumed that strains were indistinguishable.
2. Participants who died from any cause during study treatment ('study treatment phase' is defined in the protocol), except from violent or accidental cause (e.g. road traffic accident). Suicide during study treatment was classified as an unfavorable outcome.
3. Participants who were withdrawn from follow-up or lost to follow-up prior to the scheduled end of treatment of study treatment, except for pregnancies and violent or accidental death that were instead classified as having a Not Assessable outcome (see protocol for definition).
4. Participants who had an M. tuberculosis positive culture result when last seen during or prior to the Month 12 analysis visit window, whether confirmed by a second sample or not, unless determined to have been re-infected.
5. Participants receiving any one or more of the following, except when given for failure or recurrence subsequently shown to be a reinfection with a strain of *M. tuberculosis*, different from that or those identified at study entry through genotyping methods):
   a) Extension of treatment beyond that permitted by the protocol; excepting
      a. temporary drug re-challenge;
      b. over-treatment with drugs from assigned study kits;
      c. twenty-one days or fewer of non-study anti-TB medications given for treatment of active TB; or
      d. secondary isoniazid preventative therapy in HIV infected participants.
   b) Re-start of treatment for active TB;
   c) Change in treatment (including frequency or dosage) for any reason except re-infection, pregnancy, or temporary drug challenge.
6. Participants who died during the follow-up phase (as defined in the protocol) where the cause of death was considered related to TB.

Recommendation 8. PICO question

In children and adolescents with non-severe TB*, should a 4-month intervention regimen versus the standard 6-month regimen conforming to WHO guidelines be used?

Population	Intervention	Comparator	Outcomes
Children and adolescents with non-severe tuberculosis* Sub-populations: • children living with HIV; • children with lymph node TB (extrathoracic and intrathoracic). Stratify by age: • Infants aged 0–12 months; • Children aged 1–4 years; • Children aged 5–9 years; • Adolescents aged 10–14 years • Adolescents aged 15–19 years.	4 months of TB treatment comprised of 8 weeks of HRZ(E), followed by 8 weeks of HR	Currently recommended treatment regimen for drug susceptible TB comprised of 8 weeks HRZ(E), followed by 16 weeks of HR	• Treatment outcomes (treatment success, treatment failure, mortality, loss to follow-up) • Relapse • Treatment adherence • Adverse events

* Notes: children in whom the diagnosis of non-severe TB was established by a committee.

Non-severe TB is defined as sputum smear-negative TB, extrathoracic lymph node TB, intrathoracic lymph node TB with no significant airway obstruction, or uncomplicated forms of pulmonary TB, confined to one lobe and with no cavities.

Web Annex 3b. PICO questions. Guideline Development Group meeting in 2016

Recommendation 3. PICO questions

Does intermittent dosing in the intensive phase have outcomes similar to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients on intensive phase of treatment for drug-susceptible TB	3-times-weekly dosing of drugs throughout duration of treatment	Daily dosing of drugs throughout duration of treatment	• Cure or treatment completion • Treatment failure • Disease relapse • Death • Acquired drug resistance among patients who failed or relapsed

Does intermittent dosing in the continuation phase have outcomes similar to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients on continuation phase of treatment for drug-susceptible TB	3-times-weekly dosing of drugs throughout duration of treatment	Daily dosing of drugs throughout duration of treatment	• Cure or treatment completion • Treatment failure • Disease relapse • Death • Acquired drug resistance among patients who failed or relapsed

Recommendation 4. PICO question

In patients with active TB, is the use of fixed-dose combination (FDC) formulations as effective as the use of separate drug formulations?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients treated with first-line drugs (2HRZE/ 4HR)	FDC formulation with isoniazid plus rifampicin plus pyrazinamide plus ethambutol	Separate drug formulation: isoniazid, rifampicin, pyrazinamide and ethambutol	• Cure or completion of treatment • Treatment failure or disease relapse • Death • Smear conversion after 2 months of treatment • Acquired drug resistance • Adverse drug reaction • Patient adherence and satisfaction

Recommendation 10. PICO question

Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Population	Intervention	Comparator	Outcomes
Patients with tuberculous meningitis	First-line oral agents plus systemic corticosteroid therapy	First-line oral agents plus placebo	• Death • Adherence • Constrictive pericarditis

Recommendation 11. PICO question

Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Population	Intervention	Comparator	Outcomes
Patients with tuberculous pericarditis	First-line oral agents plus systemic corticosteroid therapy	First-line oral agents plus placebo	• Cure or treatment completion • Survival • Staying disease free after treatment; sustaining a cure • Acquisition or amplification of drug resistance • Smear or culture conversion during treatment • Drug adverse events

Web Annex 3c. PICO questions. Guideline Development Group meeting in 2009

Recommendation 1. PICO question

Should new pulmonary TB patients be treated with the 6-month or the 2-month rifampicin regimen?

Recommendation 2. PICO question

When a country selects 2HRZE/4HR, should patients be treated daily or three times weekly during the intensive phase?

Recommendation 5. PICO question

In new pulmonary TB patients, how effective is extension of treatment for preventing failure or relapse?

Recommendation 8. PICO question

Should intermittent regimens be used for persons living with HIV? What should be the duration of TB treatment in people living with HIV?

Web Annex 4. GRADE evidence profiles and evidence-to-decision tables

Web Annex 4a. Guideline Development Group meetings in 2021

PICO: In patients aged ≥ 12 years with drug-susceptible pulmonary TB is a 4 month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin as effective and safe as the standard drug-susceptible TB regimen composed according to WHO guidelines?

Author(s): Tuberculosis Trials Consortium Study 31 and AIDS Clinical Trials Group A5349

Question: A 4 month regimen with rifapentine and moxifloxacin compared to standard drug-susceptible TB regimen for patients aged ≥ 12 years with drug-susceptible pulmonary TB

Setting: An international, multicenter, randomized, open-label, phase 3, three-arm non-inferiority trial with sites in Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, United States of America, Vietnam, Zimbabwe

Bibliography: a 4 month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin vs the standard drug-susceptible TB regimen composed according to WHO guidelines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 4 month regimen with rifapentine and moxifloxacin	standard drug-susceptible TB regimen	Relative (95% CI)	Absolute (95% CI)		
Cure [Microbiologically eligible population] (follow-up: 12 months)[a]												
1	randomised trials	not serious	not serious	not serious	not serious	none	668/791 (84.5%)	656/768 (85.4%)	**RR 0.99** (0.95 to 1.03)[b]	**9 fewer per 1,000** (from 43 fewer to 26 more)	⨁⨁⨁⨁ High	CRITICAL
Acquisition (amplification) of drug resistance [Microbiologically eligible population]												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	1/791 (0.1%)	0/768 (0.0%)	**RR 3.13** (0.13 to 76.69)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Adverse events during treatment (grade 3 or higher) [Safety analysis population]												
1	randomised trials	not serious	not serious	not serious	serious[d,e]	none	159/846 (18.8%)	159/825 (19.3%)	**RR 0.97** (0.76 to 1.24)	**6 fewer per 1,000** (from 46 fewer to 46 more)	⨁⨁⨁◯ Moderate	CRITICAL
All-cause mortality (within 14 days after end of treatment) [Safety analysis population]												
1	randomised trials	not serious	not serious	not serious	very serious[f]	none	3/846 (0.4%)	7/825 (0.8%)	**RR 0.42** (0.11 to 1.61)	**5 fewer per 1,000** (from 8 fewer to 5 more)	⨁⨁◯◯ Low	CRITICAL
Retention in treatment [Microbiologically eligible population][g]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 4 month regimen with rifapentine and moxifloxacin	standard drug-susceptible TB regimen	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	789/791 (99.7%)	760/768 (99.0%)	**RR 1.01** (1.00 to 1.02)	**10 more per 1,000** (from 0 fewer to 20 more)	⨁⨁⨁⨁ High	CRITICAL
Absence of cure [microbiologically assessable mITT, adjusted for HIV and cavitation] (follow-up: 12 months)[h]												
1	randomised trials	not serious	not serious	not serious	serious[i]	none	123/791 (15.5%)	112/768 (14.6%)	**RR 1.07** (0.84 to 1.35)	**10 fewer per 1,000** (from 23 fewer to 51 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Definition of a favourable outcome ('cure'): a participant was classified as having a favourable outcome if any one of the following conditions was met and an unfavorable outcome did not occur: 1. Participants whose last culture result during the Month 12 analysis visit window was M. tuberculosis negative. 2. Participants who were seen during the Month 12 analysis visit window and were clinically without symptoms/signs of ongoing active TB (indicated by absence of initiation of possible poor treatment response (PPTR) evaluation or PPTR that did not indicate presence of symptoms/signs of ongoing active TB), and had achieved culture conversion prior to Month 12, and a) Were unable to produce a sputum specimen at any point during the Month 12 analysis visit window; or b) Produced a sputum specimen that was contaminated or unevaluable without evidence of M. tuberculosis, and no sputum specimens yielded positive or negative culture results during the Month 12 analysis visit window.

b. The outcome favourable is reported in table 2 in the Study 31 report. This outcome, named 'cure' in the evidence profile, is chosen as it was prioritised by the guideline group. The microbiologically eligible population is reported which excludes those with resistance to the medicines used for treatment; those with no baseline positive TB culture and others that were not eligible to participate in the trial. The choice of population, microbiologically eligible, minimises the chance of underestimating the effect of the RPT-MOX considering the non-inferiority trial design. For completeness, we provide results for the intention to treat (ITT) analysis and the per-protocol (assessable) population analysis for the favourable outcome (or 'cure') here: 1) ITT: RPT-MOX 78.7% (668/849) vs in standard care 79.1% (656/829) RR 0.99 (95% CI 0.95 – 1.04); 2) Assessable: RPT-MOX 88.4 % (668/756) vs standard treatment 90.4 % (656/726) RR 0.98 (95% CI 0.94 – 1.01).

c. Rated down by two levels for very serious imprecision. One event occurred. Further studies are required to answer this question. One participant on RPT-MOX arm had an isolate of recurrent Mycobacterium tuberculosis that showed phenotypic evidence of resistance to isoniazid plus rifampin but was susceptible to isoniazid and rifampin on line-probe molecular testing (WGS results were not available). 0 cases in the control arm.

d. Rated down by one level for serious imprecision. The confidence interval ranges from 24% reduction in adverse events to a 24% increase. In absolute terms this is reported as 6 fewer adverse events per 1000 people who receive the RPF-MOX treatment rather than the standard of care (ranging from 46 fewer to 46 more per 1000 people treated with the shorter regimen compared to the standard six month regimen).

e. The primary safety analysis included the intention to treat population excluding those who had not received a single dose of the regimen.

f. Rated down by two levels for serious imprecision. Few events occurred (10 total) and the confidence interval is wide (crossing both appreciable benefit and appreciable harm) suggesting that further evidence would provide greater confidence in the effect of RPT-MOX compared to standard treatment for the outcome all-cause mortality.

g. In Study 31, loss-to-follow-up at the end of study treatment is reported as part of the 'unfavourable' outcome: 2/791 (0.3%) in the RPT-MOX group vs 8/768 (1%) in the standard treatment group (RR 0.24 95% CI 0.05 - 1.14). The evidence profile reports the calculated 'retention in treatment' as the inverse of this. This number represents the number of trial participants that were not classified as loss to follow-up during the treatment phase in the primary outcome analysis; a specific analysis of retention on treatment within the trial has not been conducted and may therefore be slightly lower than that presented. In the trial report, retention is reported to the end of follow up as: 759/791 in the RPT-MOX group vs 728/768 in the standard treatment group (RR 1.01 95% CI 0.99 - 1.03).

h. This outcome was not presented as the GDG agreed at a preparatory webinar that as this is the inverse of the outcome cure (favourable outcome), it would not be necessary to review both outcomes.

i. Rated down by one level for serious imprecision. The confidence interval ranges from 16% reduction to a 35% increase in unfavourable (absence of cure) outcomes. In absolute terms this is reported as 10 fewer patients with unfavourable outcome (ranging from 23 fewer to 51 more per 1000 people treated with the shorter regimen compared to the standard six month regimen).

QUESTION

Should a 4 month regimen with rifapentine and moxifloxacin vs. standard drug-susceptible TB regimen be used for patients aged ≥ 12 years with drug-susceptible pulmonary TB?	
POPULATION:	patients aged ≥ 12 years with drug-susceptible pulmonary TB
INTERVENTION:	a 4 month regimen with rifapentine and moxifloxacin
COMPARISON:	standard drug-susceptible TB regimen
MAIN OUTCOMES:	Cure [Microbiologically eligible population]; Acquisition (amplification) of drug resistance [Microbiologically eligible population]; Adverse events during treatment (grade 3 or higher) [Safety analysis population]; All-cause mortality (within 14 days after end of treatment) [Safety analysis population]; Retention in treatment [Microbiologically eligible population]; Absence of cure [microbiologically assessable mITT, adjusted for HIV and cavitation];
SETTING:	An international, multicenter, randomized, open-label, phase 3, three-arm non-inferiority trial with sites in Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, United States of America, Vietnam, Zimbabwe
PERSPECTIVE:	Public health and health systems perspective
BACKGROUND:	The public health problem being addressed is the effective and safe treatment of drug susceptible tuberculosis (TB). Tuberculosis affects an estimated ten million people per year in 2019 (range 8.9-11.0 million) and is the world's leading infectious disease killer, responsible for an estimated 1.2 million TB deaths among HIV-negative people (range, 1.1–1.3 million), and an additional 208 000 deaths among HIV-positive people (range, 177 000–242 000) in 2019 *(World Health Organization, 2020)*. Of the estimated ten million TB cases, approximately 70% are diagnosed and treated, resulting in 7.1 million TB case notifications *(World Health Organization, 2020)*. The majority of these patients have drug susceptible TB and will have a positive treatment outcome when treated with the right combination of first line medicines, for the right duration. The current World Health Organization (WHO) recommendation for treating persons with drug susceptible TB is included in the WHO *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update (World Health Organization, 2017).* Here, a six month regimen composed of four first line TB medicines, namely isoniazid, rifampicin, ethambutol and pyrazinamide, is recommended *(2)*. In the first two months of treatment (i.e. the intensive phase) all four medicines are used and in the final two months of treatment (i.e. the continuation phase) two medicines are used, until treatment completion *(World Health Organization, 2017)*. This is a strong recommendation based on moderate certainty of the evidence. This regimen has been widely adopted worldwide, and using it, approximately 85% of patients will have a successful treatment outcome *(World Health Organization, 2017; World Health Organization 2020)*. The current four drug treatment regimen has been in use for approximately thirty years and is based on seminal TB treatment studies conducted by the British Medical Research Council in the 1980s *(Fox W et al., 1999)*. Therefore, the regimen is well known and has been widely used for decades. In recent years, there has been strong research interest in shortening the duration of TB treatment. This has resulted in a number of trials and other studies designed to assess whether treatment can be shortened, while remaining highly effective. A recent phase III trial (TBTC[1] study 31/ACTG[2] A5349, or S31/A5349, referred to as "Study 31" here) assessed the safety and effectiveness of two four month regimens for the treatment of drug susceptible TB *(Dorman S et al., 2020)*. Study 31 was an international, randomized, open-label, controlled, three-arm non-inferiority trial among adolescents and adults with smear and culture positive drug susceptible pulmonary tuberculosis *(Dorman S et al., 2020)*. The study objectives were to evaluate the efficacy of: a) a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to four months the duration of treatment for drug-susceptible pulmonary tuberculosis, and b) a rifapentine-containing regimen that additionally substitutes moxifloxacin for ethambutol and continues moxifloxacin throughout treatment, to determine whether the duration of treatment can be reduced. *(Dorman S et al., 2020)*. The rifapentine-moxifloxacin arm demonstrated non-inferiority when compared to the standard of cure (the current WHO recommendation of six months of treatment with rifampicin, isoniazid, pyrazinamide and ethambutol) and this the regimen being reviewed by the Guideline Development Group. This regimen consisted of eight weeks of daily rifapentine, isoniazid, pyrazinamide, and moxifloxacin (M), followed by nine weeks of daily rifapentine, isoniazid, and moxifloxacin (2PHZM/2PHM). The dose of rifapentine used was 1200mg. The primary efficacy end point was TB disease-free survival at twelve months after study treatment assignment, while the primary safety end point was the proportion of participants with grade 3 or higher adverse events during study drug treatment. [1] TBTC stands for Tuberculosis Clinical Trials Consortium, which is "a collaboration of researchers from the CDC, domestic and international public health departments, academic medical centers, and selected Veterans Administration medical centers whose mission is to conduct programmatically relevant research concerning the diagnosis, clinical management, and prevention of tuberculosis (TB) infection and disease." Information on TBTC is available at: https://www.cdc.gov/tb/topic/research/tbtc/default.htm

	[2] ACTG stands for the AIDS Clinical Trials Research Group, is the "the world's largest and longest running HIV clinical trials network. The ACTG conducts groundbreaking research to improve the treatment of HIV and its co-infections, including tuberculosis and viral hepatitis, as well as its co-morbidities. The ACTG also seeks to advance approaches to ultimately cure HIV. ACTG clinical trial units in 12 countries serve as major resources for HIV/AIDS research and training/education in their communities." Information on ACTG is available at: https://actgnetwork.org/
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis remains a pressing public health problem and is the world's leading infectious disease killer. Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years (WHO, 2020). There were an estimated 1.2 million (range, 1.1– 1.3 million) TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths (range, 177 000–242 000) among HIV-positive people (a reduction from 678 000 in 2000) (WHO, 2020). Men (aged ≥15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged <15 years) for 12% (WHO, 2020). Among all those affected, 8.2% were people living with HIV (WHO, 2020). Globally in 2019, 7.1 million people with a new episode of TB (new and relapse cases) were diagnosed and notified to national TB programmes (NTPs) and reported to WHO (WHO, 2020). This was an increase from 7.0 million in 2018 and 6.4 million in 2017 (WHO, 2020). Of the 7.1 million new and relapse cases notified in 2019, 5.9 million (84%) had pulmonary TB (WHO, 2020). Of these, 57% were bacteriologically confirmed (WHO, 2020). This was a slight increase from 55% in 2018, but the percentage has remained virtually unchanged since 2005 (WHO, 2020). A bacteriologically confirmed case is one from whom a biological specimen is positive by smear microscopy, culture or molecular WHO-recommended rapid diagnostic test, such as the Xpert MTB/RIF® assay (WHO, 2020). The currently recommended treatment for cases of drug-susceptible TB disease is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide (WHO, 2017). There has been strong research interest in shortening the duration of treatment in recent years. Shortened treatment has the potential to improve adherence and reduce health system costs. The treatment success rate for people newly enrolled on treatment (on a six month regimen) in 2018 was 85% (WHO, 2020).	Long treatment regimens present serious challenges to the programmatic management of TB globally. Since the discovery of first-line anti-TB medicines and treatment regimens, the TB community has been in search of shorter and more effective treatments for TB disease.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Study 31/A5349 was a randomized, multi-national, open-label, controlled phase 3 trial comparing two 4-month rifapentine-containing regimens to the standard 6-month control regimen. The intervention considered for this WHO guideline was a 4-month regimen that replaced rifampin with rifapentine and replaced ethambutol with moxifloxacin continued throughout treatment (rifapentine-moxifloxacin RPT-MOX regimen). The trial enrolled participants who were 12 years or older with newly diagnosed tuberculosis confirmed by culture and susceptible to isoniazid, rifampin and fluoroquinolones. The primary efficacy outcome was tuberculosis disease-free survival at 12	The panel discussed the applicability of the trial to the population that would be affected by a recommendation from this guideline process. The trial was considered a fair representation of tuberculosis patients in various country settings, however, several key populations were

months after randomization. The primary safety endpoint was the proportion of participants with grade 3 or higher adverse events during treatment with onset up to 14 days after the last dose of study medication.

Desirable effects reported here are: Cure and Retention in treatment

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without a 4 month regimen with rifapentine and moxifloxacin	With a 4 month regimen with rifapentine and moxifloxacin	Difference		
Cure [Microbiologically eligible population] follow up: 12 months № of participants: 1559 (1 RCT)[a]	**RR 0.99** (0.95 to 1.03)[b]	Study population			⨁⨁⨁⨁ HIGH	There is no difference in the outcome cure between those who received the four month regimen with rifapentine and moxifloxacin compared to the standard six month regimen.
		85.4%	**84.6%** (81.1 to 88)	**0.9% fewer** (4.3 fewer to 2.6 more)		
Retention in treatment [Microbiologically eligible population] № of participants: 1559 (1 RCT)[c]	**RR 1.01** (1.00 to 1.02)	Study population			⨁⨁⨁⨁ HIGH	There is a slight increase in retention at the end of the treatment comparing four month regimen with rifapentine and moxifloxacin compared to the standard six month regimen.
		99.0%	**99.9%** (99 to 100)	**1.0% more** (0 fewer to 2 more)		

a. Definition of a favourable outcome ('cure'): a participant was classified as having a favourable outcome if any one of the following conditions was met and an unfavorable outcome did not occur: 1. Participants whose last culture result during the Month 12 analysis visit window was M. tuberculosis negative. 2. Participants

mentioned that may require further consideration for implementation:

- People living with HIV infection (cd4)
- Diabetes Mellitus
- Extrapulmonary disease
- Children and adolescents
- Pregnant, breast-feeding and post partum women
- People under 40kg weight

Several panel members reflected that no major differences in desirable effects as both regimens performed in a very similar way.

It was mentioned that the intervention regimen has an advantage of shorter duration. All agreed with judgment of **Trivial** based on a similarity of desirable effects (cure-favourable, retention in treatment, including in the subgroups available for analysis).

Duration is a critical desirable consequence that cannot be directly captured by the trial outcomes, but perhaps represented by 'retention in treatment' (which is slightly increased in the intervention group) and covered by other criteria for consideration (e.g. acceptability).

who were seen during the Month 12 analysis visit window and were clinically without symptoms/signs of ongoing active TB (indicated by absence of initiation of possible poor treatment response (PPTR) evaluation or PPTR that did not indicate presence of symptoms/signs of ongoing active TB), and had achieved culture conversion prior to Month 12, and a) Were unable to produce a sputum specimen at any point during the Month 12 analysis visit window; or b) Produced a sputum specimen that was contaminated or unevaluable without evidence of M. tuberculosis, and no sputum specimens yielded positive or negative culture results during the Month 12 analysis visit window.

b. The outcome favourable is reported in table 2 in the Study 31 report. This outcome, named 'cure' in the evidence profile, is chosen as it was prioritised by the guideline group. The microbiologically eligible population is reported which excludes those with resistance to the medicines used for treatment; those with no baseline positive TB culture and others that were not eligible to participate in the trial. The choice of population, microbiologically eligible, minimises the chance of underestimating the effect of the RPT-MOX considering the non-inferiority trial design. For completeness, we provide results for the intention to treat (ITT) analysis and the per-protocol (assessable) population analysis for the favourable outcome (or 'cure') here: 1) ITT: RPT-MOX 78.7% (668/849) vs in standard care 79.1% (656/829) RR 0.99 (95% CI 0.95 – 1.04); 2) Assessable: RPT-MOX 88.4 % (668/756) vs standard treatment 90.4 % (656/726) RR 0.98 (95% CI 0.94 – 1.01).

c. In Study 31, loss-to-follow-up at the end of study treatment is reported as part of the 'unfavourable' outcome: 2/791 (0.3%) in the RPT-MOX group vs 8/768 (1%) in the standard treatment group (RR 0.24 95% CI 0.05 - 1.14). The evidence profile reports the calculated 'retention in treatment' as the inverse of this. This number represents the number of trial participants that were not classified as loss to follow-up during the treatment phase in the primary outcome analysis; a specific analysis of retention on treatment within the trial has not been conducted and may therefore be slightly lower than that presented. In the trial report, retention is reported to the end of follow up as: 759/791 in the RPT-MOX group vs 728/768 in the standard treatment group (RR 1.01 95% CI 0.99 - 1.03).

Results for the intention to treat (ITT) analysis, Microbiologically Eligible and the Assessable populations for the favourable outcome (or 'cure') are reported:

Table. Comparing favourable outcome* (cure) in analysis populations

Analysis population	Rifapentine-Moxifloxacin group n/N (%)	Standard treatment group n/N (%)	Effect estimate Relative risk (95% confidence interval)
Intention-to-treat (all randomised)	668/849 (78.7%)	656/829 (79.1%)	RR 0.99 (95% CI 0.95 – 1.04)
Microbiologically Eligible**	668/791 (84.5%)	656/768 (85.4%)	RR 0.99 (95% CI 0.95 – 1.03)
Assessable population***	668/756 (88.4%)	656/726 (90.4%)	RR 0.98 (95% CI 0.94 – 1.01)

	*Favorable is defined as a participant who does not meet criteria for unfavorable or not assessable, and either a) had their latest sputum cultures at month 12 negative for M. tuberculosis, or b) was without signs and symptoms of active tuberculosis at month 12, and either unable to produce sputum or produced sputum that was contaminated without evidence of M. tuberculosis. **Microbiologically Eligible: refers to participants with culture confirmation of drug-susceptible tuberculosis at study entry. ***Assessable population: includes the subset of Microbiologically Eligible participants who, in addition, are not classified as 'not assessable'. **Results for sub-group analysis:**	

Table. Population subgroup analyses for the outcome of Cure (favourable outcome) [iii] comparing the intervention regimen from Study 31 to the control regimen (standard of care)

Sub-population	Intervention regimen n/N (%)	Control regimen n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Extensive disease [iv] (based on extent of disease ≥ 50% on chest radiography)				
	226/270 (83.7%)	259/301 (86.0%)	0.97 (0.91-1.04)	-2.3% (-8.24-3.55)
No extensive disease (based on extent of disease < 50% on chest radiography)				
	436/515 (84.7%)	393/463 (84.9%)	0.99 (0.95-1.05)	-0.2% (-4.73-4.23)
Persons with HIV infection [v]				
	53/62 (85.5%)	50/64 (78.1%)	1.09 (0.93-1.29)	7.4% (-6.04-20.75)
Persons without HIV infection				
	615/729 (84.4%)	605/703 (86.1%)	0.98 (0.94-1.02)	-1.7% (-5.37-1.98)
Persons with diabetes mellitus [vi]				
	26/32 (81.3%)	22/31 (71.0%)	1.15 (0.87-1.52)	10.3% (-10.65-31.21)
Persons without diabetes mellitus				
	636/751 (84.7%)	630/730 (86.3%)	0.98 (0.94-1.02)	-1.6% (-5.20-1.97)
Persons with a Body Mass Index < 17.9 kg/m^2				
	441/519 (85.0%)	439/511 (85.9%)	0.99 (0.94-1.04)	-0.9% (-5.24-3.37)
Persons with a Body Mass Index ≥ 17.9 kg/m^2				
	226/270 (83.7%)	217/257 (84.4%)	0.99 (0.92-1.07)	-0.7% (-6.98-5.52)

[i] TBTC stands for Tuberculosis Clinical Trials Consortium, which is "a collaboration of researchers from the CDC, domestic and international public health departments, academic medical centers, and selected Veterans Administration medical centers whose mission is to conduct programmatically relevant research concerning the diagnosis, clinical management, and prevention of tuberculosis (TB) infection and disease." Information on TBTC is available at: https://www.cdc.gov/tb/topic/research/tbtc/default.htm

[ii] ACTG stands for the AIDS Clinical Trials Research Group, is the "the world's largest and longest running HIV clinical trials network. The ACTG conducts groundbreaking research to improve the treatment of HIV and its co-infections, including tuberculosis and viral hepatitis, as well as its co-morbidities. The ACTG also seeks to advance approaches to ultimately cure HIV. ACTG clinical trial units in 12 countries serve as major resources for HIV/AIDS research and training/education in their communities." Information on ACTG is available at: https://actgnetwork.org/

[iii] Definition of a favourable outcome: In Study 31, a participant was classified as having a favourable outcome if any one of the following conditions was met and an unfavorable outcome did not occur:

1. Participants whose last culture result during the Month 12 analysis visit window was M. tuberculosis negative.
2. Participants who were seen during the Month 12 analysis visit window and were clinically without symptoms/signs of ongoing active TB (indicated by absence of initiation of possible poor treatment response (PPTR) evaluation or PPTR that did not indicate presence of symptoms/signs of ongoing active TB), and had achieved culture conversion prior to Month 12, and
   1. Were unable to produce a sputum specimen at any point during the Month 12 analysis visit window; or
   2. Produced a sputum specimen that was contaminated or unevaluable without evidence of M. tuberculosis, and no sputum specimens yielded positive or negative culture results during the Month 12 analysis visit window.

A participant was classified as having an unfavourable outcome if any one of the following conditions is met:

1. A participant was considered to have absence of bacteriological cure if he/she had a sputum sample, obtained at or after Week 17 and no later than the end of the Month 12 analysis visit window, that is M. tuberculosis Culture Positive that was indistinguishable from the initial isolate (see separate sequencing plan for definitions), and this was confirmed by a second sample that was M. tuberculosis culture positive. A second confirmatory sample, on a different day without an intervening M. tuberculosis negative culture result, was required, as a single positive sputum culture result in isolation was not considered absence of bacteriological cure. If results from strain analysis were inconclusive or unavailable, it was assumed that strains were indistinguishable.
2. Participants who died from any cause during study treatment ('study treatment phase' is defined in the protocol), except from violent or accidental cause (e.g. road traffic accident). Suicide during study treatment was classified as an unfavorable outcome.
3. Participants who were withdrawn from follow-up or lost to follow-up prior to the scheduled end of treatment of study treatment, except for pregnancies and violent or accidental death that were instead classified as having a Not Assessable outcome (see protocol for definition).
4. Participants who had an M. tuberculosis positive culture result when last seen during or prior to the Month 12 analysis visit window, whether confirmed by a second sample or not, unless determined to have been re-infected.
5. Participants receiving any one or more of the following, except when given for failure or recurrence subsequently shown to be a reinfection with a strain of M. tuberculosis, different from that or those identified at study entry through genotyping methods):
   a) Extension of treatment beyond that permitted by the protocol; excepting
      a. Temporary drug re-challenge;
      b. Over-treatment with drugs from assigned study kits;
      c. Twenty-one days or fewer of non-study anti-TB medications given for treatment of active TB; or
      d. Secondary isoniazid preventative therapy in HIV infected participants.
   b) Re-start of treatment for active TB;
   c) Change in treatment (including frequency or dosage) for any reason except re-infection, pregnancy, or temporary drug challenge.
6. Participants who died during the follow-up phase (as defined in the protocol) where the cause of death was considered related to TB.

[iv] WHO defines extensive or advanced TB disease as: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. However the definition used in these sub group analyses is extent of disease on chest radiography <25%, 25 – 49%, ≥ 50%. In the table, we report ≥ 50%.

[v] Of all the persons with HIV who participated in the trial (in all three arms), 95.4% were receiving antiretroviral treatment. HIV-positive individuals not on ART at enrollment, had planned initiation of efavirenz-based ART before or at study week 8. Persons with HIV were excluded from enrollment in the trial if, at the time of enrollment, their CD4 T cell count was known to be <100 cells/mm^3. Overall there were nine patients who were not on ART in the microbiologically eligible analysis population (4.6%); the reasons for non-initiation of ART are not clear

[vi] In the trial, patients were screened for diabetes mellitus using hemoglobin A1C (the preferred test). If hemoglobin A1C testing was not available at the study site, then either fasting blood glucose (defined as no caloric intake for at least 8 hours) or random blood glucose was measured. The cut offs were for a diabetes diagnosis (i.e. for HbA1c etc.) were not specified in the protocol. Patients either reported a history of diabetes or site investigators made the diagnosis during trial enrollment according to local standards.

People living with HIV infection: The proportion of patients living with HIV infection in the intervention and control regimen arms was 8%. Of all the persons with HIV who participated in the trial (in all three arms), 95.4% were receiving antiretroviral treatment. HIV-positive individuals not on ART at enrollment, had planned initiation of efavirenz-based ART before or at study week 8. Persons with HIV were excluded from enrollment in the trial if, at the time of enrollment, their CD4 T cell count was known to be <100 cells/mm3. Overall there were nine patients who were not on ART in the microbiologically eligible analysis population (4.6%); the reasons for non-initiation of

	ART are not clear. Additional information from pharmacokinetic (PK) analyses will be available for this population in the future which may provide more nuanced evidence on the use of the intervention and control regimens in persons with diabetes mellitus. People with diabetes mellitus: Additional information from PK analyses will be available for this population in the future which may provide more nuanced evidence on the use of the intervention and control regimens in persons with diabetes mellitus. Patients with extensive TB disease: The trial reported on the presence of cavitation on chest radiograph (CXR), extent of disease on CXR as a percentage and cavity size (absent, < or >= 4cm). Children and adolescents: The trial aimed to recruit people aged 12 and above and the youngest participant was 13 years of age. Therefore there were no children included in the trial. In the microbiologically eligible population, there were 70 and 56 participants in the rifapentine-moxifloxacin and control arms respectively that were aged less than 20. Pregnant, breast-feeding and post-partum women: Pregnant or breast-feeding women were excluded from the study because of uncertainties about the safety of rifapentine, moxifloxacin, and pyrazinamide in these groups. Women who became pregnant while receiving study therapy were taken off of study treatment and were treated according to NTP or local guidelines. The women continue to receive scheduled study follow-up, were classified as being on a non-study regimen, and did not receive study radiographs. Women who became pregnant while on study follow-up (not on study treatment) continued to receive scheduled study follow-up and did not receive study radiographs. In all cases (i.e. whether pregnant during treatment or during follow up), the outcome of the pregnancy was reported on study forms. Other sub groups: Other sub group analyses conducted as part of the trial included analyses by: age group, sex, presence of cavities, cavity size, WHO smear grade, smoking history, Xpert CT and MGIT DTP (days).	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Undesirable effects include acquisition of drug resistance, adverse events and mortality.

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without a 4 month regimen with rifapentine and moxifloxacin	With a 4 month regimen with rifapentine and moxifloxacin	Difference		
Acquisition (amplification) of drug resistance [Microbiologically eligible population] № of participants: 1559 (1 RCT)	**RR 3.13** (0.13 to 76.69)	Study population			⨁⨁◯◯ LOW[a]	We are uncertain about the effect of the four month regimen compared to standard TB treatment on the outcome acqisition of resistance.
		0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)		
Adverse events during treatment (grade 3 or higher) [Safety analysis population] № of participants: 1671 (1 RCT)	**RR 0.97** (0.76 to 1.24)	Study population			⨁⨁⨁◯ MODERATE[b,c]	There is probably little or no difference in the outcome adverse effects comparing a four month regimen with rifapentine and moxifloxacin compared to the standard six month regimen.
		19.3%	**18.7%** (14.6 to 23.9)	**0.6% fewer** (4.6 fewer to 4.6 more)		
All-cause mortality (within 14 days after end of treatment) [Safety analysis population] (Death) № of participants: 1671 (1 RCT)	**RR 0.42** (0.11 to 1.61)	Study population			⨁⨁◯◯ LOW[d]	There may be little or no difference in the outcome mortality comparing a four month regimen with rifapentine and moxifloxacin compared to the
		0.8%	**0.4%** (0.1 to 1.4)	**0.5% fewer** (0.8 fewer to 0.5 more)		

The panel discussed the issue of whether a four-month regimen would be expected to have fewer adverse events. The issue of two types of adverse reactions were mentioned, those that are directly related to the effects of the medicine and generally occur in the first four months of treatment; and idiosyncratic adverse reactions that may happen at any time.

The panel discussed that the trial adverse event rates was likely higher than in the programme setting due to close active safety monitoring in a trial setting. Further, adverse events may or may not be causally related to the medicines in the regimen.

The panel discussed the lack of data about acquisition of drug resistance with only one event reported in the intervention group.

Further data are needed on this and may only be seen in the context of large programme implementation with this new regimen. Although the overall judgement for undesirable effects was agreed to be 'trivial,' the panel recognised that for the specific outcome of acquisition of drug resistance, we remain uncertain.

						standard six month regimen.

a. Rated down by two levels for very serious imprecision. One event occurred. Further studies are required to answer this question. One participant on RPT-MOX arm had an isolate of recurrent Mycobacterium tuberculosis that showed phenotypic evidence of resistance to isoniazid plus rifampin but was susceptible to isoniazid and rifampin on line-probe molecular testing (WGS results were not available). 0 cases in the control arm.
b. Rated down by one level for serious imprecision. The confidence interval ranges from 24% reduction in adverse events to a 24% increase. In absolute terms this is reported as 6 fewer adverse events per 1000 people who receive the RPF-MOX treatment rather than the standard of care (ranging from 46 fewer to 46 more per 1000 people treated with the shorter regimen compared to the standard six month regimen).
c. The primary safety analysis included the intention to treat population excluding those who had not received a single dose of the regimen.
d. Rated down by two levels for serious imprecision. Few events occurred (10 total) and the confidence interval is wide (crossing both appreciable benefit and appreciable harm) suggesting that further evidence would provide greater confidence in the effect of RPT-MOX compared to standard treatment for the outcome all-cause mortality.

Undesirable effects include acquisition of drug resistance, adverse events and mortality.

See Appendix 1

Safety and tolerability are reported in Table 3 of the trial report.

CAUSES OF DEATHS:

Rifapentine-moxifloxacin regimen: 1 thrombotic thrombocytopenia purpura, 1 congestive cardiac failure, 1 pulmonary tuberculosis

Control regimen: 1 Paracoccidioides infection, 1 sepsis, 1 papillary thyroid cancer, 1 central nervous system lesion, 1 hemoptysis, 1 pulmonary embolism, 1 unexplained death.

ANY ADVERSE EVENT RESULTING IN DISCONTINUATION OF THE STUDY TREATMENT

Rifapentine-moxifloxacin regimen: 11 hepatitis, 1 thrombocytopenia, 1 QT prolongation, 1 tendonitis, 1 pruritis, 1 maculopapular rash.

Control regimen: 6 hepatitis, 1 seizure.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The overall certainty of the evidence for the benefits is high, while the overall certainty of the evidence for the harms is moderate to low. The overall certainty is generally based on the lowest certainty for the agreed critical outcomes.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Patient values and preferences:** A patient values and preferences study was not conducted as part of the trial. Therefore, a separate study was conducted which included questions on patient values and preferences, feasibility, acceptability and equity. In April 2021, an online survey was conducted among patients and TB survivors in Cambodia and Pakistan. These countries were selected because they are in WHO's list of high TB burden countries (WHO, 2020) and because patient organizations within these countries responded to an invitation by WHO through the Civil Society Taskforce. Due to the short timeframe of the study, participants were purposively sampled and approached based on convenience through the participating patient organisations. Participants (n = 37) who had either completed TB treatment or were well into their TB treatment were the target group, and, where possible, aimed for equal numbers of participant in terms of their gender and marital status. The survey questions consisted of mostly open questions covering the background of the participant including type of TB, treatment and setting; overall treatment experience including difficulties experienced, forms of support, pill burden; as well as questions asking for preferences over shortened treatment length, additionally probing for the caveat of either increased risk of relapse, risk of side effects or higher pill burden. The outcomes considered as part of the GDG discussion align with the feedback from the patient values survey. With regards to patient values and preferences, the survey found:	Shorter treatment was thought to be something valued by patients, although avoiding relapse and adverse events was also thought to be valued at the same time. Based on the responses in the survey, patients spoke about adverse events that were of a lesser severity than the outcome of grade 3 or higher adverse events that is included in the outcomes of this study. A lower pill burden was an issue that may also be valued by patients, it was acknowledged that the pill burden in this regimen may change in the future. It was acknowledged that the persons who responded to the survey had a certain treatment experience and that this may have influenced their responses. The panel thought that further research on patients values and preferences is required to determine how much people value certain outcomes with regards to shortened treatment. A Community Advisory Board was consulted to inform various aspects of the trial.

	Most participants would prefer a shorter regimen, however, not at the expense of other risks. o **Avoiding risk of relapse:** participants value making full recovery over shortening treatment by two months o **Avoiding and minimizing adverse effects:** participants value minimizing adverse side effects over shortening treatment duration by two months o **Avoiding a higher pill burden:** participants value minimizing pill burden over shortening treatment duration by two months, because this is associated with a risk of more side effects and discomfort	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The GDG determined that, on balance neither intervention nor comparison was favoured over the other in people more than 12 years of age diagnosed with drug-susceptible tuberculosis because the differences in outcomes were trivial. The panel discussed extensively the importance of the issue of duration, not captured by the outcomes specifically, but by the importance of this issue to patients, programmes.	A vote was held to decide whether this judgement should be 'does not favour either the intervention or comparison' OR 'probably favours the intervention'. The majority of panel members agreed to 'does not favour either intervention or comparison' based on desirable and undesirable effects. However, the panel agreed that the importance of duration of treatment needs to be clearly expressed as an important benefit and also a desirable consequence when choosing the new shorter regimen.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know

Overall costs: The overall costs of the intervention regimen were not determined by study investigators. However, the costs of the medicines included in both the intervention and control regimens was calculated. The estimated price of the intervention regimen based upon weight average prices available through the Global Drug Facility for a 55-70kg person is $225-233 USD. Rifapentine makes up 90% of the estimated cost of the regimen. The analogous cost of the control regimen is 43 USD. Additional costs to be considered likely include drug susceptibility testing at baseline and any additional health care costs**.**

Regimen	Formulation	Number of Quality-Assured Suppliers	Estimated Weighted average Price USD
2HRZE/4HR	4-FDC (ethambutol/isoniazid/Pyrazinamide/Rifampicin 275mg/75mg/400mg/150mg)	5	$43
	2-FDC (isoniazid/rifampicin 75mg/150mg)	4	
2HPMZ/2HPM	Rifapentine 150mg	1	$225-$233
	Isoniazid 300mg	>5	
	Moxifloxacin 400mg	>5	
	Pyrazinamide 500mg	5	
	Pyrazinamide 400mg	3	
	3HP FDC (rifapentine/isoniazid 300mg/300mg)	1	

Table from Global Drug Facility report, April 2021

Patient costs: were not determined by study investigators. As the intervention regimen is two months shorter than the control regimen, patient costs may be lower. This may depend on the application of Directly Observed Treatment. Among 14 countries that reported disaggregated data to WHO in 2020, the pooled average of TB affected households experiencing catastrophic costs was 44% (95% CI: 31–58%) for drug-susceptible TB and the End TB Strategy target is 0%.

Panel members discussed a range of resourcing issues that may have an impact on implementation of the shorter regimen. Panel members discussed the extent of baseline DST that would be required before starting the shorter regimen and acknowledged that national TB programmes are expanding access to drug susceptibility testing overall and that WHO now recommends a WHO approved rapid molecular diagnostic test for TB diagnosis which also detects rifampicin resistance.

The panel agreed that it would be preferable to have drug susceptibility testing at baseline (for both regimens) but that it may not be necessary or feasible yet in all settings. Many national TB programmes are testing for rifampicin resistance at baseline anyway as they are using a WHO recommended rapid molecular diagnostic test. The panel felt that baseline drug susceptibility testing for fluoroquinolones should not be a standard requirement unless there are specific local concerns regarding background fluoroquinolone resistance. Globally, fluoroquinolone resistance is low for patients with rifampicin susceptible TB. The panel also acknowledged that universal drug susceptibility testing should be an eventual goal for all TB patients at baseline.

It was acknowledged that we don't know about all of the resource costs or savings involved in implementing the shorter regimen. At the present time there is an increased cost due to the medicines in the shorter regimen but these costs may be reduced over time. As well, other costs or savings may relate to drug susceptibility testing (although the panel noted that the same drug susceptibility testing requirements may apply to both regimens in most settings), health system costs and patient costs. The panel acknowledged that there are no available data on indirect costs to patients or the health system.

	Opportunity costs: may also need to be considered including potential acquisition of drug resistance, although there was only one patient with acquired drug resistance in this study, one participant who received the intervention regimen had an isolate of recurrent *Mycobacterium tuberculosis* that showed phenotypic evidence of resistance to isoniazid plus rifampicin but was susceptible to isoniazid and rifampicin on line-probe molecular testing (whole genome sequencing results were not available). Additional resources would include drug susceptibility testing prior to commencement of treatment and other healthcare costs.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No included studies. *Report from the Global Drug Facility is available.*	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No included studies.	Cost effectiveness was noted by the panel as a research gap. The panel recommended that additional costs effectiveness studied would be needed along with operational implementation studies in different settings.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Equity from the patient perspective:** A study was commissioned on patient values and preferences, feasibility, acceptability and equity. In April 2021, the online survey was conducted among patients and TB survivors in Cambodia and Pakistan. Participants who had either completed TB treatment or were well into their TB treatment were the target group, and, where possible, the survey aimed for equal numbers of participant in terms of their gender and marital status. The survey questions consisted of mostly open questions covering the background of the participant including type of TB, treatment and setting; overall treatment experience including difficulties experienced, forms of support, pill burden; as well as questions asking for preferences over shortened treatment length, additionally probing for the caveat of either increased risk of relapse, risk of side effects or higher pill burden. The survey found that: o **Treatment access:** Most participants reported taking treatment at home with limited or no supervision. If a new regimen requires more treatment monitoring, this could reduce access to treatment for those who live in more remote, rural, or under-resourced areas, and may be less acceptable than the current regimen that can be taken at home. o **Social and material support:** Those who face socioeconomic constraints, live in remote, rural or poorer communities and who have more difficulties in finding adequate emotional and material support, might be unjustly disadvantaged if a new regimen is harsher in terms of side effects or risk of relapse (even though shorter), as social support was reported by participants as being key in preventing treatment abandonment due to side effects. A reduced duration of treatment is another equity consideration as a shorter duration of treatment may allow patients to return to their normal lives sooner and it may have impacts on overall quality of life - this may increase equity. Additional considerations related to equity may include the cost of the intervention regimen, the need for and access to baseline drug susceptibility testing and the need for and national policies/ access to DOT - these may increase or decrease equity depending on access.	The panel felt that short term barriers may decrease equity, however that over the long term, the benefits may aim to increase equity (i.e. more patients may be able to access diagnosis and treatment). The panel recognized that there are some current access barriers including the cost of rifapentine, drug licensing and registration issues, availability of rifapentine. The panel recognized that any new regimen or innovation may be more costly at the start but that costs may decrease over time. The panel agreed that the impact on equity may vary and therefore felt that the judgement of varies may be best here as there were varied views regarding the impact of this intervention on equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Duration of treatment:** The intervention regimen is 4 months long whereas the control regimen is 6 months long. A shorter duration of treatment may be highly desirable for patients if effectiveness is not compromised and if adverse events are not increased. The shortened duration of treatment may also have other positive effects on patient costs, health care access, stigma, quality of life and education and employment (i.e. livelihoods). **Retention on treatment:** There is a slight increase in retention at the end of the treatment comparing four month regimen with rifapentine and moxifloxacin to the standard six month regimen (10 more per 1000 people treated with the shorter regimen, ranging from 0 more to 20 more). Loss to follow up was reported for 2 patients who received the intervention regimen (0.3%) and 8 patients who received the control regimen (1.0%). A shorter duration of treatment may feasibly increase retention. **Pill burden:** The intervention regimen would require 13 tablets per day in the intensive phase and 10 tablets per day in the continuation phase for a 55-70kg person using currently available formulations. With new formulations of rifapentine 300mg likely to be quality-assured in 2021, the number of tablets in the intensive phase will decrease from 13 to 9 tablets and in the continuation phase from 10 to 6 tablets. **Acceptability from the patient perspective:** From the patient values and preferences study conducted to inform the GDG discussions, when first asked how a shorter regimen would affect their treatment experience, most participants of this study stated that a 4-month regimen would be better than the current 6-month regimen as it would enable them to complete their treatment sooner and return back to their normal life. However, it was important that other factors (such as side effects, relapse) were not compromised. Concerns were raised about the pill burden in the context of concerns about adverse effects that are perceived related to the pill number. **Presence of nitrosamines in both rifampicin and rifapentine:** 1-cyclopentyl-4-nitrosopiperazine (CPNP) and 1-methyl-4-nitrosopiperazine (MeNP) are nitrosamine impurities that have been identified in rifapentine and rifampicin products, respectively. For these products, work on mitigation measures by manufacturers has started. Given the outcome of an initial risk assessment, WHO has not suspended any of the rifampicin prequalified APIs or medicines. No alert has been considered necessary for the time being. (WHO, Prequalification Unit - Medicines Assessment Team. FAQs. 2020: https://extranet.who.int/pqweb/sites/default/files/documents/FAQ_Nitrosamine_18Dec2020.pdf) **TAG Information Note: *N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine*; S Cloez and M Frick, Treatment Action Group, Technical Brief, February 2021** **Key Messages and Recommendations**	The panel acknowledged that a four-month regimen would be highly desirable. The panel discussed that cost is an important component of acceptability, particularly from the country perspective. Some panel members also felt that any requirement for drug susceptibility testing or ECG monitoring may decrease acceptability although cardiotoxicity was not frequently reported in the trial (and is elaborated further under feasibility). There was some concern about including moxifloxacin in a regimen for drug susceptible TB when it is used in many countries to treat drug resistant TB, so if a fluoroquinolone becomes a first line drug it may have an unknown impact on second line treatment and acquired resistance was a concern. Monitoring (ECG or otherwise) and drug susceptibility testing were thought to be feasibility considerations. The panel acknowledged the need for a fixed dose combination formulation to overcome the issue of the pill burden.

	1. Rifampicin and rifapentine are essential medicines for the treatment and prevention of TB. TB is a life-threatening infectious disease, and its prevention and treatment are personal and public health imperatives. 2. Everyone is exposed to some level of N-nitrosamines in daily life. N-nitrosamines are not unique to rifampicin and rifapentine, and their identification in medicines is not a new problem. Rather, in recent years health authorities and manufacturers have newly recognized the issue and taken action to document, understand, and reduce the level of N-nitrosamines in medicines. 3. The known risks of not treating or preventing TB outweigh the theoretical risk of cancer associated with N-nitrosamine exposures from rifampicin and rifapentine.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Bacteriological confirmation of TB:** Of the 7.1 million new and relapse cases notified in 2019, 5.9 million (84%) had pulmonary TB (WHO, 2020). Of these, 57% were bacteriologically confirmed (WHO, 2020). This was a slight increase from 55% in 2018, but the percentage has remained virtually unchanged since 2005 (WHO, 2020). A bacteriologically confirmed case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-recommended rapid diagnostic test, such as the Xpert MTB/RIF® assay (WHO, 2020). **Drug susceptibility testing**: There has been considerable progress in increasing the coverage of DST, especially since 2012. Globally in 2019, 2.2 million (61%) of the 3.6 million bacteriologically confirmed pulmonary TB cases notified globally were tested for rifampicin resistance, up from 1.7 million (51%) in 2018 and 0.2 million (7%) in 2012. In 2019, coverage was 59% for new and 80% for previously treated TB patients (WHO, 2020). Currently WHO recommends a molecular diagnostic test to be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum rather than smear microscopy/culture and phenotypic drug susceptibility testing (strong recommendation, high certainty of evidence for test accuracy; moderate certainty of evidence for patient-important outcomes, WHO 2021). As the intervention regimen contains both a rifampicin and a fluoroquinolone, and given that the microbiologically eligible population included only those who had confirmed drug susceptible TB (using Xpert MTB/RIF testing before treatment start and followed by phenotypic culture), there may be a need for baseline drug susceptibility testing. Given the lack of available MIC data Rifapentine, the complete cross-resistance with Rifampicin should be assumed until sufficient data to the contrary are available (i.e. gDST and pDST results for RIF should be used as the surrogate for Rifapentine) References:	The panel discussed that feasibility may depend on any additional requirements such as additional drug susceptibility testing requirements (particularly if fluoroquinolone testing is required). The panel agreed that ideally all patients should have access to high quality baseline drug susceptibility testing, but this is not yet always a reality. When comparing the current regimen to the intervention regimen the panel debated what are the consequences of having undiagnosed resistance? There may be serious consequences of missing moxifloxacin resistance, if this was missed then the regimen may behave like the third regimen in the Study 31 regimen where favourable outcomes were also good. If rifampicin resistance is missed, then the other drugs in the regimen are at risk and this is a more serious consequence which would be the same with standard six month treatment. **Therefore, there are consequence of missed resistance for both regimens.** The background prevalence of resistance in the population was also thought to be relevant i.e. in settings where there is a high comparative background of fluoroquinolone resistance. Ideally everyone should have baseline drug susceptibility testing for rifampicin. The panel agreed that baseline ECG should not be uniformly required based on the evidence from this trial. This may be different for MDR-TB treatment where more than one cardiotoxic drug is used, therefore the ECG considerations are not the same for this intervention regimen and treatment for MDR-TB Average QT prolongation for moxifloxacin is 6 milliseconds and the package labelling does not indicate that ECG monitoring is required especially if moxifloxacin is used without other

Technical report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine). Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Williams DL, Spring L, Collins L, et al. Contribution of rpoB mutations to development of rifamycin cross-resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother. 1998;42(7):1853-7. doi:10.1128/AAC.42.7.1853

Fluoroquinolone resistance in patients with drug-susceptible TB is usually low (below or just above 1% in both new and retreatment patients, based on several studies shown in table below). Results from a multi-country surveillance project show slightly higher rates (range 1-11.2% in new cases and 0.8-15.1% in retreatment cases) and unusually higher rates in some countries (Pakistan, Bangladesh, Belarus).

Fluoroquinolone resistance in patients with drug-susceptible TB

	New (%)	Previously treated (%)	Reference number
South Africa	1.2 (0.7-1.7)	1.5 (0.7-2.2)	(1)
DRC	0.1 (0.0-0.7)	0 (0.0-3.9)	(2)
Philippines	0.1 (0.0-0.4)	0.1 (0.0-4.2)	(3)
Eritrea	0.2 (0.0-1.1)	0 (0.0-6.7)	(4)
Azerbaijan	3.4	8.6	(5)*
Bangladesh	4.4	9.2	
Belarus	7	38	
Pakistan	11.2	15.1	
South Africa (Gauteng)	1	0.8	
South Africa (KZN)	1	2	

* Based on phenotypic testing using Ofloxacin 2.0 mg/ml

1. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018 Jul 1;18(7):779–87.

2. Kayomo MK, Mbula VN, Aloni M, André E, Rigouts L, Boutachkourt F, et al. Targeted next-generation sequencing of sputum for diagnosis of drug-resistant TB: results of a national survey in Democratic Republic of the Congo. Sci Rep. 2020 Jul 1;10(1):10786.

3. Lim DR, Dean AS, Taguinod-Santiago MR, Borbe-Reyes A, Cabibbe AM, Zignol M, et al. Low prevalence of fluoroquinolone resistance among patients with tuberculosis in the Philippines: results of a national survey. Eur Respir J [Internet]. 2018 Mar 1 [cited 2021 Apr 8];51(3). Available from: https://erj.ersjournals.com/content/51/3/1702571

4. Mesfin AB, Araia ZZ, Beyene HN, Mebrahtu AH, Suud NN, Berhane YM, et al. First molecular-based anti-TB drug resistance survey in Eritrea. Int J Tuberc Lung Dis. 2021 Jan 1;25(1):43–51.

5. Zignol M, Dean AS, Alikhanova N, Andres S, Cabibbe AM, Cirillo DM, et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry

potentially cardiotoxic drugs. Some patients may need a baseline ECG based on their individual circumstances (i.e. patients with a history of disease that predisposes to cardiac arrythmias).

The panel also discussed the current availability of rifapentine and some barriers to its importation into certain countries, but they agreed that this may change or improve in the future. The panel also discussed that they would not like to emphasise any additional monitoring requirements such as DOT.

Overall the panel agreed that this judgement should be 'varies'.

	surveillance project. Lancet Infect Dis [Internet]. [cited 2016 Jul 11]; Available from: http://www.sciencedirect.com/science/article/pii/S1473309916301906 **Availability:** There is currently one quality-assured supplier of the rifapentine 150mg tablet and one quality-assured supplier a 3HP Fixed Dose Combination (FDC) tablet of 300mg rifapentine and 300mg isoniazid. It is expected that a new supplier of a rifapentine 300mg tablet will be available be the end of 2021 and a second supplier of the 3HP FDC in early 2022. Rifapentine is also used in regimens for tuberculosis preventive treatment (TPT). The scale-up of rifapentine-based regimens for TPT over the past few years has significantly increased demand for rifapentine products, which in turn is increasing the number of quality-assured suppliers and formulations. In the very short term (the next 6 months or so), demand for rifapentine will likely stay higher than available supply. However, the work of the last few years on supplier engagement means that new formulations will be quality-assured by end 2021/early 2022 which will increase the available supply and create competition to lower the price. **DOT:** The lack of a FDC formulation for the intervention regimen may mean that some NTPs may prefer to use DOT. Community- or home-based DOT is recommended by WHO over health facility-based DOT or unsupervised treatment and Video Observed Treatment (VOT) may replace DOT when the video communication technology is available, and it can be appropriately organized and operated by health care providers and patients. However, not all NTPs are currently providing DOT or VOT and there may be some concerns about providing medications to patients in non FDC formulations. **Monitoring:** One of the known possible adverse events of Moxifloxacin is QT prolongation, when QT prolongation is significant it may predispose to torsades de points - a life-threatening condition. Therefore, when QT prolongation is shown to occur frequently on certain treatment regimens it may be advisable to monitor by regular ECGs. If ECG monitoring is needed, then training will be required for health care providers doing ECGs and for readers of the ECGs, also adding some additional costs. However based on the safety events reported in the trial, ECG monitoring may not be required (one person in the intervention arm experienced borderline QTcF prolongation to 461 msec from 402 msec prior to study treatment (change of 59 msec)).	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

People aged 12 years or older with drug-susceptible pulmonary tuberculosis, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (**Conditional** recommendation, **moderate** certainty evidence).

additional option to the current standard WHO-recommended 6-month regimen

Justification

The panel suggested that the benefits of a shorter regimen that is as effective as the current regimen (moderate certainty evidence) is the justification for the recommendation to introduce the shorter regimen as an option for treating DS TB patients.

Certain contextual issues were discussed that resulted in the conditional, rather than strong recommendation. These included:

Resources: Costs for the medicine are currently high and further research is needed on resource implications (e.g. patient and health system savings) and cost-effectiveness

Equity: Short term and longer term equity considerations were raised. In the short term issues regarding access to rifapentine, costs, pill burden and possible need for additional DST testing may decrease equity; however, in the longer term as costs reduce and access to rifapentine increases, the shorter regimen is considered to offer an increase in equity for patients who will have a shorter period in the health system and be able to return to work sooner.

Acceptability and feasibility: Although the shorter regimen may be preferred, the current pill burden relative to the standard regimen; the need for DST testing including in some settings with a high background prevalence of fluoroquinolone resistance and the possible need for additional DST testing for moxifloxacin resistance was a concern.

Subgroup considerations

The sub group analyses presented to the GDG included people living with HIV infection, people with diabetes mellitus, people with a low body weight (with a Body Mass index less than < 17.9 kg/m2) and patients with extensive disease (using a cut off of >50% lung parenchyma affected) on chest x-ray. The reported risk differences for these sub populations indicated no statistically significant differences when comparing the shorter regimen to the current standard of care, however in some sub-groups the overall numbers were small. Additional PK analyses being undertaken by the trial investigators will also be available in the coming months and may provide more nuanced information on drug exposures in these groups. Other sub group analyses conducted as part of the trial included analyses by: age group, sex, presence of cavities, cavity size, WHO smear grade, smoking history, Xpert CT and MGIT DTP (days).

The panel suggested that the shorter regimen can be used in the sub groups that were presented to the GDG including people living with HIV infection, persons with diabetes mellitus, those with a low body weight and those with extensive disease, however the panel also emphasized that additional research on the use of these shorter regimen is desirable. For some sub-groups there was limited or no evidence on the use of the shorter regimen, but the GDG members felt that the use of the shorter regimen could be considered as favourable outcomes were reported using the shorter regimen in patients with extensive disease. These patients include those with non-severe and minimal forms of TB such as lymph node TB.

However, there were also sub groups for which there was no evidence and therefore the use of the shorter regimen outside the research environment is not indicated. These groups include:

· Patients weighing less than 40kg

· Patients with forms of extra pulmonary TB (such as TB meningitis, disseminated TB, osteoarticular TB, abdominal TB)

· Persons living with HIV infection with a CD4 count less than 100 cells/mm3 (the panel expressed concerns about an increased risk of relapse in this group)

· Children less than 12 years of age

· Pregnant, breast-feeding and post-partum women

Implementation considerations

A number of implementation considerations were discussed by the GDG. These included:

· Drug susceptibility testing: The panel agreed that universal drug susceptibility testing should be something that national TB programmes strive for overall. In reality, however, universal drug susceptibility testing is not always available. With regards to implementation considerations it was also noted that the same sputum sample could be tested for drug susceptibility testing for rifampicin, moxifloxacin and isoniazid, so this may present less of an issue with regards to drug susceptibility testing but has cost and laboratory workload implications. Balancing the desired situation with the reality, the panel considered that while desirable, baseline drug susceptibility testing would not be necessary given that the majority of patients with TB receive a WHO approved rapid molecular diagnostic test which also tests for rifampicin resistance. The prevalence of fluoroquinolone resistance in the absence of rifampicin resistance is usually low. However in some countries resistance to fluoroquinolones may be comparatively high due to use for other conditions. In these settings DST for the fluoroquinolones would be highly recommended at baseline to exclude fluoroquinolone resistance. The background prevalence of fluoroquinolone resistance would be an important consideration for national TB programmes (although a prevalence was not discussed by the panel).

· In the trial patients received directly observed treatment (DOT) at least five days per week. In programmatic settings this may not be possible. DOT may be important given the pill burden and the lack of a fixed dose combination formulation.

· The overall pill burden is currently higher for patients who will receive the shorter regimen and a fixed dose combination tablet does not exist for this regimen. This may affect acceptability at the current time.

· The costs of medicines in the shorter regimen are higher, particularly due to rifapentine. Currently the cost of the shorter regimen is substantially higher than the standard of care, mainly due to the inclusion of rifapentine.

· Administration of the shorter regimen with food may present a challenge in some settings.

· Training of healthcare workers was another implementation consideration that the panel discussed would be necessary when introducing the shorter regimen into a programmatic setting.

· When making a choice between regimens eligibility criteria for the shorter regimen should guide regimen choice as well as other local factors such as availability of rifapentine etc.

Implementation considerations related to monitoring are described below under monitoring and evaluation.

Monitoring and evaluation

The current recommendation for monitoring the response to drug susceptible TB treatment stays the same. The panel did not recommend baseline ECG monitoring for those receiving the shorter regimen (unless clinically indicated) and laboratory monitoring such as liver function tests (LFT) would remain the same for both regimens. Some countries may have different requirements for LFT monitoring due to the 'black box' warnings for moxifloxacin.

Research priorities

The GDG discussed a number of research priorities, including:

· Acquisition of drug resistance for Mycobacterium tuberculosis and also for other bacteria.

· The efficacy of the regimen for patients with extra pulmonary TB.

· Pharmaco-kinetic studies and safety studies in younger adolescents and children. A PK sub study was initiated alongside the trial and results are expected in the coming months.

· The cost effectiveness of the shorter regimen.

· Considerations regarding the impact of this regimen on equity.

· The acceptability of the shorter regimen, particularly for patients.

· The use of this regimen in specific sub populations including pregnant and lactating women, children aged less than 12 years, HIV positive individuals with a CD4 count lower than 100 cells/ mm3 and people with a body weight less than 40kg.

· Dosing considerations for people weighing less than 40kg.

· The use of fixed dose combination formulations for the shorter regimen.

· Operational research on directly observed treatment versus self-administered therapy.

· Treatment adherence in operational settings.

Author(s): Turkova A, Wills, GH, Wobudeya E and the SHINE trial team

Question: A 4 month treatment regimen compared to currently recommended 6 month treatment regimen in children and adolescents with non-severe drug-susceptible tuberculosis

Setting: Uganda, Zambia, South Africa and India

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 4 month treatment regimen	currently recommended 6 month treatment regimen	Relative (95% CI)	Absolute (95% CI)		
Death (all-cause) (follow-up: mean 72 weeks; assessed with: mITT)[a]												
1	randomised trials	not serious	not serious	not serious[b]	serious[c]	none	7/572 (1.2%)	13/573 (2.3%)	**RR 0.54** (0.22 to 1.34)	**10 fewer per 1,000** (from 18 fewer to 8 more)	⨁⨁⨁◯ Moderate	CRITICAL
Treatment success (follow-up: mean 72 weeks; assessed with: mITT)[d]												
1	randomised trials	not serious	not serious	not serious[b]	not serious	none	556/572 (97.2%)	555/573 (96.9%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 19 fewer to 19 more)	⨁⨁⨁⨁ High	CRITICAL
Treatment failure (follow-up: mean 72 weeks; assessed with: mITT)[e]												
1	randomised trials	not serious	not serious	not serious	serious[f]	none	3/572 (0.5%)	1/573 (0.2%)	**RR 3.01** (0.31 to 28.81)	**4 more per 1,000** (from 1 fewer to 49 more)	⨁⨁⨁◯ Moderate	CRITICAL
Relapse (follow-up: mean 72 weeks; assessed with: mITT)[g]												
1	randomised trials	not serious	not serious	not serious	serious[f]	none	6/572 (1.0%)	4/573 (0.7%)	**RR 1.50** (0.43 to 5.30)	**3 more per 1,000** (from 4 fewer to 30 more)	⨁⨁⨁◯ Moderate	CRITICAL
Treatment adherence (follow-up: mean 72 weeks; assessed with: ITT)[h]												
1	randomised trials	not serious	not serious	not serious	serious[i]	none	572/602 (95.0%)	561/602 (93.2%)	**RR 1.02** (0.99 to 1.05)	**19 more per 1,000** (from 9 fewer to 47 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (follow-up: mean 72 weeks; assessed with: ITT)[j]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 4 month treatment regimen	currently recommended 6 month treatment regimen	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[c]	none	47/602 (7.8%)	48/602 (8.0%)	**RR 0.98** (0.67 to 1.44)	**2 fewer per 1,000** (from 26 fewer to 35 more)	⨁⨁⨁◯ Moderate	CRITICAL

Loss to follow up (follow-up: mean 72 weeks; assessed with: ITT)

1	randomised trials	not serious	not serious	not serious	serious[f]	none	11/602 (1.8%)	11/602 (1.8%)	**RR 1.00** (0.44 to 2.29)	**0 fewer per 1,000** (from 10 fewer to 24 more)	⨁⨁⨁◯ Moderate	CRITICAL

Treatment success children with TB LN (follow-up: mean 72 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	184/189 (97.4%)	177/183 (96.7%)	**RR 1.01** (0.97 to 1.04)	**10 more per 1,000** (from 29 fewer to 39 more)	⨁⨁⨁⨁ High	CRITICAL

Treatment success children living with HIV (follow-up: mean 72 weeks)

1	randomised trials	not serious	not serious	not serious	very serious[k]	none	55/59 (93.2%)	48/54 (88.9%)	**RR 1.05** (0.93 to 1.18)	**44 more per 1,000** (from 62 fewer to 160 more)	⨁⨁◯◯ Low	CRITICAL

Mortality children living with HIV (follow-up: mean 72 weeks)

1	randomised trials	not serious	not serious	not serious	very serious[k]	none	4/65 (6.2%)	9/62 (14.5%)	**RR 0.42** (0.14 to 1.31)	**84 fewer per 1,000** (from 125 fewer to 45 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. All-cause death reports deaths after 16 weeks of treatment in each group.

b. Not downgraded for indirectness. The trial population may be representative of TB patients seen in TB programmes in various countries globally. The trial enrolled 1204 children under 16 years of age from Uganda (n = 376), Zambia (n = 364), South Africa (n = 315), Pune (n = 86), Chennai (n = 63). These children were enrolled between July 2016 and July 2018; median age 3.5 years (range 2 months-15 years), 52% male, 11% HIV-infected, 14% bacteriologically-confirmed tuberculosis.

c. Downgraded by one level for serious imprecision, low event rate and wide confidence interval. The absolute values may be within a reasonable decision threshold around the null value - indicating probably no difference between groups.

d. The outcome 'treatment success' in TB is usually defined as 'cured and treatment completion'. This differs from the trial outcome 'favourable' which is defined as 'clinically well and without retreatment or otherwise unfavourable outcome'. As bacteriological confirmation was not required for trial inclusion, the use of 'clinically well' may be a surrogate for cure (bacteriological clearance).

e. Treatment failure is usually defined as a 'patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy' . In the trial the outcome 'unfavourable' is the composite endpoint of TB treatment failure, relapse (or re-infection) or death which is what is reported here.

f. Downgraded by one level for imprecision due to low number of events and very wide confidence interval.

g. Relapse includes recurrence or re-infection.

h. The definition of adequate treatment sets a limit for the amount of treatment missed. All children are required to have taken 80% of their allocated 8 weeks intensive phase treatment within 70 days of starting treatment. For children allocated to a 6 month regimen, they must also have taken at least 80% of their allocated 16 weeks treatment regimen for the continuation phase within 133 days of starting the continuation phase. For children allocated to a 4 month regimen, to meet the definition of adequate treatment they must also have taken at least 80% of their allocated 8 weeks treatment regimen for the continuation phase within 77 days of starting the continuation phase.

i. Downgraded by one level for imprecision due to very wide confidence interval around the absolute effects that may suggest different decisions at either end of the threshold.

j. Adverse events include patients with at least one Grade 3, 4 or 5 adverse event.

k. Downgraded by two levels for imprecision. Small numbers and wide confidence interval crossing appreciable benefit and the null value. The wide confidence intervals around the absolute value decreases our confidence in the effect size.

QUESTION

Should a 4-month treatment regimen vs. currently recommended 6-month treatment regimen be used for children and adolescents with non-severe drug-susceptible tuberculosis?	
POPULATION:	Children and adolescents with non-severe drug-susceptible tuberculosis
INTERVENTION:	A 4-month treatment regimen
COMPARISON:	Currently recommended 6-month treatment regimen
MAIN OUTCOMES:	Death (all-cause); Treatment success; Treatment failure; Relapse; Treatment adherence; Adverse events; Loss to follow up; Treatment success children with peripheral lymph node TB; Treatment success children living with HIV; Mortality children living with HIV
SETTING:	Global
PERSPECTIVE:	Clinical and public health perspectives
BACKGROUND:	It is estimated that approximately 1.2 million children develop TB annually and 230,000 die, most of them without having accessed care and treatment *(1)*. The majority of children with TB have less severe forms of the disease. Long treatment regimens can result in high costs to families and health services, potentially with added toxicity, risks of drug-drug interactions in children living with HIV, and problems with pill-burden and adherence. Shorter, safe and effective treatment regimens for children with both drug-susceptible and drug-resistant TB are a key intervention to achieve the WHO's End TB Strategy targets, as well as the targets related to children set during the United Nations General Assembly High Level Meeting on the Fight Against TB in 2018 *(2)*. This PICO question uses evidence from the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children). This was a multi-centre, open-label, parallel-group, non-inferiority, randomised controlled, two-arm trial comparing 4-month (16 weeks) versus standard 6-month (24 weeks) treatment durations using WHO-recommended paediatric anti-TB drug doses in children under 16 years with symptomatic, non-severe TB. Children and young adolescents were treated with rifampicin, isoniazid and pyrazinamide, with or without ethambutol. Minimal TB was defined as non-severe and respiratory-sample smear-negative TB. Non-severe TB included pulmonary TB confined to one lobe with no cavities, intra-thoracic lymph node TB with no significant airway obstruction and no bilateral airway narrowing and extra-thoracic (peripheral) lymph node TB *(3)*.
CONFLICT OF INTERESTS:	Chishala CHABALA Steve GRAHAM

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Globally, an estimated 1.19 million (range 1.05 -1.33 million) children (aged below 15 years) fell ill with TB in 2019, or about 12% of the global burden. Only 44% of these children were reported to national TB programmes. TB-related mortality in children below 15 years was estimated at 230,000 for 2019 *(1)*. Modelling has shown that 80% of TB-related deaths are among children aged under 5, and that 96% of children who die of TB, did not access treatment *(4)*. The treatment success rate for children (aged below 15 years) newly enrolled on treatment (on a six month regimen), reported by 123 countries (including 19 high TB burden countries) for the 2018 cohort was 85% *(1)*.	

	Long treatment regimens present serious challenges to the programmatic management of TB globally. Since the discovery of first-line anti-TB medicines and treatment regimens, the TB community has been in search of shorter and more effective treatments for TB disease. Long treatment regimens may lead to costs to children and their families, a burden to health services and added toxicity. In addition, children with HIV-co-infection risk suboptimal control of HIV resulting from drug-drug interactions between TB treatment and ART, and the increased pill-burden may have an effect on adherence. These factors could be ameliorated by shortening TB treatment *(3)*. There has been strong research interest in shortening the duration of treatment in recent years. Shortened treatment has the potential to improve adherence and reduce patient and health system costs.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

SHINE was a multicentre, open-label, parallel-group, non-inferiority, randomised controlled, two-arm trial comparing 4-month (16 weeks) versus standard 6-month (24 weeks) treatment durations using WHO-recommended paediatric anti-TB drug doses in children under 16 years with symptomatic minimal (non-severe) TB. Minimal TB was defined as non-severe and respiratory-sample smear-negative TB. Non-severe TB included pulmonary TB confined to one lobe with no cavities, intra-thoracic lymph node TB with no significant airway obstruction and no bilateral airway narrowing and extra-thoracic (peripheral) lymph node TB.

Desirable effects:

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without a 4-month treatment regimen	With a 4 -month treatment regimen	Difference		
Death (all-cause) assessed with: mITT follow up: mean 72 weeks № of participants: 1145 (1 RCT)[a]	**RR 0.54** (0.22 to 1.34)	Study population			⨁⨁⨁◯ MODERATE[b,c]	A 4-month treatment regimen probably results in little to no difference in death (all-cause). 10 fewer per 1,000 (from 18 fewer to 8 more)
		2.3%	**1.2%** (0.5 to 3)	**1.0% fewer** (1.8 fewer to 0.8 more)		
Treatment success (Cure and treatment completion) assessed with: mITT follow up: mean 72 weeks № of participants:	**RR 1.00** (0.98 to 1.02)	Study population			⨁⨁⨁⨁ HIGH[b]	A 4-month treatment regimen results in little to no difference in treatment success. 0 fewer per 1,000
		96.9%	**96.9%** (94.9 to 98.8)	**0.0% fewer** (1.9 fewer		

ADDITIONAL CONSIDERATIONS

The GDG highlighted the importance of clarifying the population included in the SHINE trial. The population consisted of: children and young adolescents aged below 16 years; weight ≥ 3kg; no known drug resistance; symptomatic but non-severe TB; smear negative on respiratory samples (Xpert positive result allowed); not treated for TB in previous 2 years; known HIV status (positive or negative). The definition of non-severe TB included the following: peripheral lymph node TB or respiratory TB, confined to one lobe, without cavities, without complicated airway obstruction, without complicated pleural effusion and no miliary TB.

The GDG also discussed that trial participants were unlikely to have drug-resistant (DR) TB. Known contact with an adult source case with drug-resistant TB (including mono-resistant TB) or known drug resistance in the child were exclusion criteria for the trial. The panel highlighted that rapid molecular diagnostics have low sensitivity in children with non-severe TB and can therefore not be definitively used to rule out TB. Most children with non-severe TB in the trial were therefore clinically diagnosed. The GDG emphasized that children with TB who are not responding to first-line anti-TB treatment should be evaluated for DR-TB.

The GDG judged that while the desirable effects are related to treatment outcomes, shortening the duration of treatment is also important and desirable (as reducing the length of treatment could make treatment easier for children and caregivers as well as reduce cost for families and the health system).

1145 (1 RCT)[d]				to 1.9 more)		(from 19 fewer to 19 more)
Treatment failure (A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy) assessed with: mITT follow up: mean 72 weeks № of participants: 1145 (1 RCT)[e]	**RR 3.01** (0.31 to 28.81)	Study population			⨁⨁⨁◯ MODERATE[f]	A 4 -month treatment regimen likely results in little to no difference in treatment failure. 4 more per 1,000 (from 1 fewer to 49 more)
		0.2%	**0.5%** (0.1 to 5)	**0.4% more** (0.1 fewer to 4.9 more)		
Relapse assessed with: mITT follow up: mean 72 weeks № of participants: 1145 (1 RCT)[g]	**RR 1.50** (0.43 to 5.30)	Study population			⨁⨁⨁◯ MODERATE[f]	A 4-month treatment regimen probably results in little to no difference in relapse. 3 more per 1,000 (from 4 fewer to 30 more)
		0.7%	**1.0%** (0.3 to 3.7)	**0.3% more** (0.4 fewer to 3 more)		
Treatment adherence assessed with: ITT follow up: mean 72 weeks № of participants: 1204 (1 RCT)[h]	**RR 1.02** (0.99 to 1.05)	Study population			⨁⨁⨁◯ MODERATE[i]	A 4-month treatment regimen probably results in little to no difference in treatment adherence. 19 more per 1,000 (from 9 fewer to 47 more)
		93.2%	**95.1%** (92.3 to 97.8)	**1.9% more** (0.9 fewer to 4.7 more)		

a. All-cause death reports deaths after 16 weeks of treatment in each group.
b. Not downgraded for indirectness. The trial population may be representative of TB patients seen in TB programmes in various countries globally. The trial enrolled 1204 children under 16 years of age from Uganda (n = 376), Zambia (n = 364), South Africa (n = 315), Pune (n = 86), Chennai (n = 63). These children were enrolled between July 2016 and July 2018; median age 3.5 years (range 2 months-15 years), 52% male, 11% HIV-infected, 14% bacteriologically-confirmed tuberculosis.

c. Downgraded by one level for serious imprecision, low event rate and wide confidence interval. The absolute values may be within a reasonable decision threshold around the null value - indicating probably no difference between groups.
d. The outcome 'treatment success' in TB is usually defined as 'cured and treatment completion'. This differs from the trial outcome 'favourable' which is defined as 'clinically well and without retreatment or otherwise unfavourable outcome'. As bacteriological confirmation was not required for trial inclusion, the use of 'clinically well' may be a surrogate for cure (bacteriological clearance).
e. Treatment failure is usually defined as a 'patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy'. In the trial the outcome 'unfavourable' is the composite endpoint of TB treatment failure, relapse (or re-infection) or death which is what is reported here.
f. Downgraded by one level for imprecision due to low number of events and very wide confidence interval.
g. Relapse includes recurrence or re-infection.
h. The definition of adequate treatment sets a limit for the amount of treatment missed. All children are required to have taken 80% of their allocated 8 weeks intensive phase treatment within 70 days of starting treatment. For children allocated to a 6-month regimen, they must also have taken at least 80% of their allocated 16 weeks treatment regimen for the continuation phase within 133 days of starting the continuation phase. For children allocated to a 4-month regimen, to meet the definition of adequate treatment they must also have taken at least 80% of their allocated 8 weeks treatment regimen for the continuation phase within 77 days of starting the continuation phase.
i. Downgraded by one level for imprecision due to very wide confidence interval around the absolute effects that may suggest different decisions at either end of the threshold.

Treatment duration is a critical desirable consequence that cannot be directly captured by the trial outcomes. The duration of treatment in the intervention arm was 16 weeks compared to the standard of care, which is 24 weeks. Duration is potentially represented by 'loss to follow up' or 'adherence' (the latter is slightly increased in the intervention group) and covered by other criteria for consideration (e.g. acceptability).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

The undesirable effects included adverse events and loss to follow up.

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without a 4 month treatment regimen	With a 4 month treatment regimen	Difference		
Adverse events assessed with: ITT follow up: mean 72	**RR 0.98** (0.67 to 1.44)	Study population			⨁⨁⨁◯ MODERATE[b]	A 4-month treatment regimen probably results in little to no difference in adverse events. 2 fewer per
		8.0%	**7.8%** (5.3 to 11.5)	**0.2% fewer** (2.6 fewer		

ADDITIONAL CONSIDERATIONS

The GDG discussed that since the SHINE trial was a non-inferiority trial, no difference in unfavourable outcomes between the two arms is what the trial aimed for. Therefore, both desirable and undesirable effects were judged by most GDG members as trivial.

weeks № of participants: 1204 (1 RCT)[a]				to 3.5 more)		1,000 (from 26 fewer to 35 more)
Loss to follow up assessed with: ITT follow up: mean 72 weeks № of participants: 1204 (1 RCT)	**RR 1.00** (0.44 to 2.29)	Study population			⨁⨁⨁◯ MODERATE[c]	A 4-month treatment regimen probably results in little to no difference in loss to follow up. 0 fewer per 1,000 (from 10 fewer to 24 more)
		1.8%	**1.8%** (0.8 to 4.2)	**0.0% fewer** (1 fewer to 2.4 more)		

a. Adverse events include patients with at least one Grade 3, 4 or 5 adverse event.
b. Downgraded by one level for serious imprecision, low event rate and wide confidence interval. The absolute values may be within a reasonable decision threshold around the null value - indicating probably no difference between groups.
c. Downgraded by one level for imprecision due to low number of events and very wide confidence interval.

Certainty of evidence

What is the overall certainty of the evidence of effects?

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

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There was no direct evidence from the SHINE trial about how much patients valued the outcomes.	Although there was no direct evidence on how much the population (children and their caregivers) value the outcomes for 4 months treatment versus 6 months treatment (mortality, adverse events etc.), the majority of the GDG judged that there is probably no important uncertainty or variability about this.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The GDG determined that, the balance of effects does not favour either the intervention or the comparison.	The GDG discussed that the balance of effects is focusing on efficacy and safety of the 4-month versus the 6-month regimen. Since non-inferiority of the 4-month regimen was demonstrated in the trial, the balance of effects was judged to not favour either the shorter or the longer duration of treatment. However, the GDG noted that treatment duration is a critical issue which is considered under contextual factors such as cost, acceptability and feasibility.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	The SHINE trial included a cost effectiveness study, in which detailed costs were collected on the cost of diagnostic and laboratory tests, medicines and health service use. Healthcare costs were reduced by $17.34 (95% CI $3.77 to $30.91, 2019 USD) when comparing the 4-month regimen to the 6 month one. However, patient costs were not determined by study investigators. As the intervention regimen is two months shorter than the control regimen, patient costs may be lower. Among 14 countries that reported disaggregated data to WHO in 2020, the pooled average of TB affected households experiencing catastrophic costs was 44% (95% CI: 31–58%) for drug-susceptible TB and the End TB Strategy target is 0%. Two separate analyses of the socio-economic impact of TB care on children, adolescents, families and households were undertaken. One was a study that pooled the results from national TB patient cost studies. This study found that if the TB patient was a child or an adolescent the proportion of households who experienced catastrophic costs was lower when compared to households where the adult was the index patient: 41.8% (95% confidence interval (CI): 22.9 - 60.8%) for a child, 45.3% (95% CI: 30.2 - 60.4%) for an adolescent and 56.2%, (95% CI: 44.4 - 68.1%) for an adult. However, the proportion of households with catastrophic costs was still way above the target of 0%. The second study was a literature review of the socioeconomic impact of TB on children, adolescents and families. This study found that the cost of transport to hospital was sometimes raised as a barrier to a child completing treatment. Loss of income and loss of employment for the family were also noted.	The GDG discussed how the trial evaluated the cost related to the health care system. In the trial, the difference in health care costs in the 4-month versus the 6-month arm was mainly related to reduced costs of medication, health care visits, and hospitalization. Cost related to diagnostic tests and laboratory services was also reduced, but to a lesser extent. It was judged important to also consider societal costs including direct and indirect patient costs, for example related to transport and loss of family income (opportunity cost). Such costs may vary across settings and further research to determine them would be useful. The GDG discussed that presumably, a shorter duration of treatment will reduce costs to both the health care system and the patient/family. The GDG ultimately agreed on ‘moderate savings’ despite varying views on the level of savings that could be incurred.

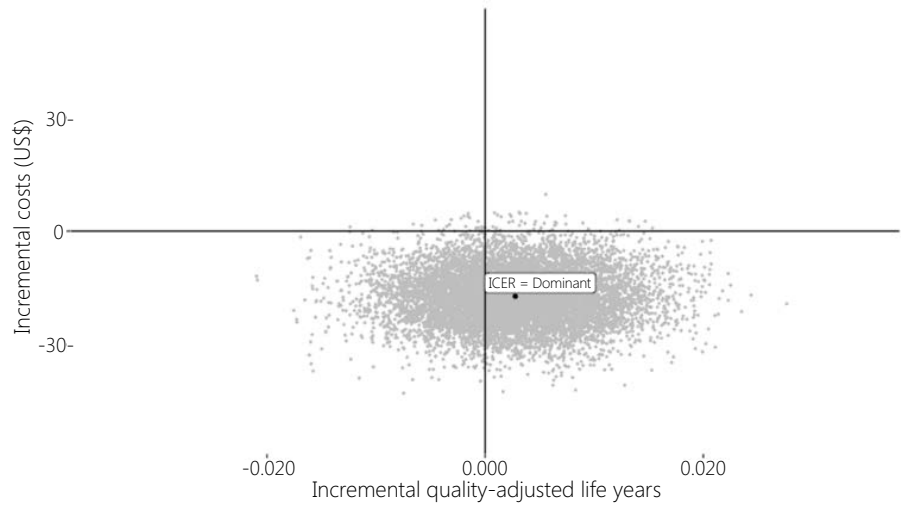
Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	The SHINE trial health economics analysis investigated the value of the shortened regimen in terms of healthcare cost savings and health outcomes (measured by quality-adjusted life years). Regression analysis was used to control for chance differences in demographic characteristics and symptom severity between the children in each treatment arm. Costs were estimated from a health sector perspective and QALYs were estimated by combing health-related quality of life scores, estimated using the EQ-5D, and survival. Costs and outcomes were discounted at 3% per annum. The cost effectiveness analysis showed that at 72 weeks, children treated for 16 weeks had both improved health (0.003 QALYs - 95% CI -0.009 to 0.0144) and reduced healthcare costs ($17.34 - 95% CI $3.77 to $30.91, 2019 USD) compared with those treated in the 24-week arm. A regression analysis controlling for chance differences in demographic characteristics and symptom severity estimated that quality-adjusted life years were improved by 0.003 (95% CI -0.009 to 0.0144) and healthcare costs reduced by $17.34 (95% CI $3.77 to $30.91, 2019 USD) (Turkova A et al., 2021). These results indicate that for every 1000 children treated with the shortened regimen, cost savings of up to $17,000 could be achieved. These could in turn be used to improve the implementation of the shortened regimen, such as the provision of diagnostics to identify children with mild TB.	The majority of the GDG felt that the data on cost-effectiveness favoured the shorter treatment duration.

	All costs included (scenario analysis)		
Predicted outcomes	**mITT (base case)**	**ITT**	**Pre protocol**
Costs - 6 mo	396.14 (7.66)	393.81 (7.87)	395.13 (7.58)
Costs - 4 mo	395.85 (7.74)	395.3 (7.78)	393.97 (7.36)
Life years - 6 mo	1.358 (0.004)	1.347 (0.006)	1.357 (0.004)
Life years - 4 mo	1.353 (0.004)	1.342 (0.006)	1.353 (0.004)
QALYs - 6 mo	1.364 (0.004)	1.354 (0.006)	1.364 (0.004)
QALYs - 4 mo	1.356 (0.004)	1.347 (0.006)	1.356 (0.004)
Incremental outcomes			
Costs	-0.3 (10.68)	1.49 (10.78)	-1.16 (10.5)
Life years	0.006 (0.006)	0.007 (0.009)	0.007 (0.006)
QALYs	0.003 (0.006)	0.004 (0.009)	0.003 (0.006)
Cost-effectiveness outcomes			
Cost-per-QALY	Dominant	342	Dominant

Cost-effectiveness plane



Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	A reduced duration of treatment is an equity consideration as a shorter duration of treatment may allow patients (and caregivers) to return to their normal lives sooner and it may have impacts on overall quality of life, including access to education, schooling and patient related costs - this may increase equity. As well it may allow more children to access treatment after diagnosis. Availability of CXR and other diagnostic services may also be an equity consideration; if these are not available, equity may be reduced but the same logic applies to the 6-month regimen. It can be assumed that access to the medicines for the intervention regimen is the same. Child-friendly fixed dose combination tablets (FDCs) are available through the Stop TB Partnership's Global TB Drug Facility in over 90 countries.	The GDG noted that approximately 40% of the children in the SHINE trial were clinically diagnosed, this was related to limited test accuracy, difficulty with collecting sputum and other specimens, and the fact that young children have paucibacillary disease. It was noted that the proportion of children who are clinically diagnosed may be as high as 90% in programmatic settings, where access to chest radiography and diagnostic tests may be insufficient. Interpretation of chest X-rays in children can also be challenging. It was noted that the SHINE trial was set up in a very pragmatic way, reflecting the everyday reality in many settings. One fifth of the children were later judged not to have TB but this was thought to also reflect the programmatic reality, where some level of over-diagnosis may occur and which may be hard to avoid. Restricting eligibility for shorter treatment to children with bacteriological confirmation would limit the number of children with TB being diagnosed and treated. Limiting eligibility would affect equity in a negative way.

		The GDG judged that equity was probably increased with the shorter treatment duration.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There was no direct evidence from the SHINE trial about acceptability of a shorter treatment duration compared to the standard 6-month regimen. However, a qualitative sub-study in the SHINE trial was conducted on acceptability of the child-friendly (dispersible, fruit-flavoured) fixed dose combination (FDC). The sub-study found that the FDC was acceptable. The FDC and the possibility of a shorter regimen was welcomed by caregivers who participated in the trial. Administering TB treatment to younger children was found to be more difficult than to older children. Among the few caregivers and patients who initially reported challenges with administration and lower levels of acceptability, almost all reported improved acceptability over time. There were no observed differences in acceptability by study arm (4 versus 6 months). Some practical challenges to TB treatment for children, often in difficult social contexts, remain, therefore the authors concluded that making improvements to regimens and formulations continues to be important. Overall, the FDC was also reported to be palatable *(5)*. A separate literature review on the socio-economic impact of TB care on children, adolescents and families noted that a TB diagnosis during childhood or adolescence (whether as a patient or as a household member of a TB-patient) appears to translate into significant socio-economic impacts. A shortened duration of treatment may be acceptable as these socio-economic impacts may be lessened. • *Financial impact*: The evidence suggests that the same pathways and issues, known for adult TB-patients, operate at the household level when a child is affected by TB (i.e. income loss, unemployment, increased expenditure and mainly for food). • *Educational impact:* A specific impact on children is the discontinuation of school during treatment, or because of reduced financial status in the household. • *Psychosocial impacts of TB disease:* Stigma and discrimination are prevalent, the disease influences household dynamics, parenting and caregiving; and children may be separated from their caregivers due to TB.	Although there was no direct evidence on acceptability, the GDG judged that the shorter regimen was acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Shorter treatment is presumably feasible to implement at patient and caregiver levels as the 6-month regimen is currently being implemented and has been implemented for many years. The acceptability sub-study conducted as part of the SHINE trial also yielded some results on feasibility. For example, the study found that administering TB treatment to younger children was found to be more difficult than to older children. However, the duration of the intervention is 8 weeks shorter than the current standard of care, which may mean that it is more feasible to implement, even when some challenges in administering treatment to younger children are reported.	In terms of feasibility, the GDG noted that it is important to be able to differentiate severe from non-severe disease to make a decision on the appropriate duration of treatment. The trial used smear microscopy and chest radiography to determine severity of disease. Currently, Xpert MTB/RIF or Ultra should be used as the initial bacteriological test to diagnose TB in children. The trial defined non-severe peripheral lymph node TB or respiratory TB as confined to one lobe; no cavities; no

		significant airway obstruction; no complicated pleural effusion; no miliary TB. The WHO definition of extensive disease is: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. The GDG felt that, in the absence of exposure to DR-TB, access to chest radiography would help distinguish between non-severe and severe disease. However the panel recognized that access to chest radiography is often limited or the quality of chest radiography and the capacity for it's interpretation is insufficient at lower levels of the health care system. Therefore, feasibility was judged to vary by setting. The GDG noted as critically important for the Operational Handbook to clearly define "non-severe or minimal disease" and that National TB Programmes are encouraged to scale up access to quality chest radiography and train health care providers in interpretation. Overall, the GDG judged that if the severity of TB disease in children can be adequately determined, then implementation of a 4-month regimen is highly feasible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.
(Strong recommendation, moderate certainty of evidence)

Remarks:

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary and non-cavitary disease confined to one lobe of the lungs, or without a miliary pattern
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.

Justification

A total of 1204 children were enrolled in the trial between July 2016 and July 2018. The median age of enrolled children was 3.5 years (range 2 months-15 years), 52% were male, 11% had HIV-infection, and 14% had bacteriologically-confirmed TB. Retention in the trial by 72 weeks and adherence* to allocated TB treatment were 95% and 94%, respectively. Sixteen (2.8%) versus 18 (3.1%) children reached the primary efficacy outcome (treatment failure) in the 16- versus 24-week arms respectively, with an unadjusted difference of -0.3% (95% CI: -2.3, 1.6). Treatment success was reported in 97.1% of participants receiving the 16 week regimen versus 96.9% of those who received the 24 week regimen (relative risk (RR): 1.00, 95% CI: 0.98-1.02). Non-inferiority of the 16-week regimen was consistent across all intention-to-treat, per-protocol and key secondary analyses. This included restricting the analysis to the 958 (80%) children that were independently adjudicated to have TB at baseline by the trial Endpoint Review Committee. A total of 7.8% of children

experienced a grade 3-5 adverse event in the 16 week arm, versus 8.0% in the 24 week arm (RR: 0.98, 95% CI: 0.67-1.44). A total of 95 (8%) children experienced grade 3-5 adverse events, including 17 adverse reactions (11 hepatic, all except three occurred within first 8 weeks, when treatment arms were the same).

The GDG judged that while the desirable effects related to this PICO question are related to treatment outcomes, shortening the duration of treatment is also important and desirable (as reducing the length of treatment could make treatment easier for children and caregivers as well as reduce cost for families and the health system). The GDG discussed that since the SHINE trial was a non-inferiority trial, no difference in unfavourable outcomes between the two arms is what the trial aimed for. Therefore, both desirable and undesirable effects were judged by most GDG members as trivial. Since non-inferiority of the 4-month regimen was demonstrated in the trial, the balance of effects was judged to not favour either the shorter or the longer duration of treatment. However, the GDG noted that treatment duration is a critical issue which was further considered in the context of issues such as cost, acceptability and feasibility.

The GDG also discussed that presumably, a shorter duration of treatment will reduce costs to both the health care system but also to patients and families. The GDG ultimately agreed on 'moderate savings' despite varying views of the level of these savings. The GDG judged that equity was probably increased with a shorter duration of treatment. Although there was no direct evidence on acceptability, the GDG judged that the shorter regimen was acceptable to stakeholders.

In addition, the GDG felt that, in the absence of exposure to DR-TB, access to chest radiography would help distinguish between non-severe and severe disease. However the panel recognized that access to chest radiography is often limited or quality of chest radiography and capacity for interpretation insufficient at lower levels of the health care system. Therefore, feasibility was judged to vary by setting. The GDG noted that it is critically important to clearly define "non-severe or minimal disease" and that National TB Programmes are encouraged to scale up access to quality chest radiography and train health care providers in interpretation. Overall, the GDG judged that if the severity of TB disease in children can be adequately determined, then implementation of a 4-month regimen is highly feasible.

* In the SHINE trial, adherence was defined as the proportion of children who received an adequate amount of treatment (as defined in the statistical analysis plan for both the intervention and control regimens; generally a cut off of 80% of the allocated doses was used, within a certain timeframe of starting each phase of treatment (i.e. intensive phase versus continuation phase).

Subgroup considerations

Children with peripheral lymph node TB: Although the numbers of children in the sub-group of children with peripheral lymph node TB in the SHINE trial were small (N=19 in the 4-month arm and N=21 in the 6-month arm), there was no difference in the proportion of unfavourable outcomes between the two arms and non-inferiority was consistent across all sub-groups. The SHINE trial also found that 4 months of treatment was non-inferior compared to 6 months of treatment in children with both peripheral lymph nodes and pulmonary disease (N=182 in the 4-months arm and N=171 in the 6-months arm). These results may provide reassurance for clinicians regarding a seemingly delayed clinical response to TB treatment, frequently seen in children with peripheral lymph node TB (where lymph nodes remain enlarged even after treatment).

Children living with HIV infection (CLHIV): Children and young adolescents living with HIV were included in the SHINE trial, 65 (11%) in the 4-month arm and 62 (10%) in the 6-month arm. 49% of CLHIV in the 4-month arm and 43% in the 6-month arm were on antiretroviral treatment (ART) at enrolment. 20% of CLHIV in both arms had a CD4 count of less than 200 cells per mm^3. 51% of CLHIV in the 4-month arm and 63% in the 6-month arm were classified as severe as per the WHO immunological classification for established HIV infection *(6)*. In this sub-group the 4-month regimen was non-inferior as compared to the 6-month regimen as well, although the 95% confidence interval for the difference from the control arm in the unfavourable rate was wide (risk difference -4.3, 95% CI -14.9 to 6.2).

In view of the limited evidence, clinicians may consider treating CALHIV with non-severe TB for 4 months, depending on the degree of immunosuppression and ART status, as well as the presence of other opportunistic infections. These children and adolescents will need to be closely monitored, especially at 4 months of treatment, and treatment extended to 6 months if there is insufficient progress.

Children with severe acute malnutrition (SAM): In the trial, SAM was defined as weight-for-height Z-score (WHZ) <−3 or MUAC <115 mm (World Health Organization, 2013). 30 children with SAM (5%) were included in the 4-month arm and 33 (5%) in the 6-month arm. No separate sub-group analysis was conducted for children with SAM.

In view of the insufficient evidence on this subgroup, children with SAM and non-severe TB should preferably receive 6 months of anti-TB treatment.

Infants below three months of age and or weighing < 3kg: Infants below three months of age and infants weighing less than 3 kg (including premature birth (<37 weeks) were not eligible for inclusion in the SHINE trial. Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low certainty of evidence)*

Children treated for TB in the past 2 years: These children were not eligible for inclusion in the SHINE trial and should be treated with the 6-month treatment regimen (2HRZ(E)/4HR).

Implementation considerations

The feasibility of assessing the severity of TB disease under programmatic circumstances, in particular in settings without access to chest radiography or interpretation capacity and to diagnostic tests was identified as a major implementation consideration. Chest radiography was identified as a critical tool to evaluate the severity of intrathoracic disease, considering the definition of non-severe disease used in the SHINE trial, which for intrathoracic or pulmonary disease was based on the presence of intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary and non-cavitary disease confined to one lobe of the lungs, or without a miliary pattern. National TB Programmes are encouraged to scale up access to quality chest radiography and provide capacity building to health care providers in interpretation. Scaling up access to chest radiography would not only help clinicians understand the extent of disease in the lungs but it may also serve to assist with follow up during TB treatment, as well as differential diagnosis, if needed. Charging fees for chest radiography poses a potential barrier to the diagnosis of TB and access to the shorter regimen for eligible children and young adolescents.

Detailed implementation guidance will be provided in the O*perational handbook on the management of tuberculosis in children and adolescents*, taking into consideration differences in the health care system and country context, including the availability of diagnostic tools to make a diagnosis and to assess disease severity. Implementation guidance includes criteria for assessing disease severity, including clinical criteria in the absence of chest radiography or rapid diagnostics or other bacteriological tests, to determine eligibility for the shorter treatment regimen and the definition of non-severe TB in programmatic settings. It also includes criteria for extending treatment beyond 6 months in case of insufficient clinical progress in children and young adolescents with non-severe TB. In determining eligibility for the shorter treatment regimen, the background prevalence of DR-TB is an important factor to be taken into account.

An additional implementation consideration discussed by the GDG is the concept that a continuum exists between TB infection, non-severe and more severe forms of TB disease in children. Shorter treatment regimens for drug susceptible TB are now very similar to recently recommended shorter regimens for the treatment of TB infection (in terms of duration and composition, in particular the regimen consisting of 3 months of daily rifampicin and isoniazid (3HR). This implies that incorrectly diagnosing a child who has TB infection as having non-severe TB disease may not have severe consequences.

Programmatic implementation considerations include scaling up active contact investigation approaches, which can dramatically improve early case detection of children with non-severe disease who can benefit from a 4-month regimen. National TB and child health programmes are encouraged to prioritize the use of child-friendly fixed dose combination (FDC) formulations for TB treatment in children up to 25 kg body weight, e.g. the 3-FDC HRZ 50/75/150mg, with or without the addition of dispersible ethambutol and the 2-FDC HR 50/75mg (available from the Stop TB Partnership's Global Drug Facility). Capacity building of healthcare workers at all levels of the health system on diagnostic approaches (including the use of treatment decision algorithms), eligibility for the 4-month regimen and monitoring of children on first-line TB treatment will be a critical factor in successful implementation of the shorter regimen.

Monitoring and evaluation

- The clinical monitoring requirements for the shorter regimen remain the same as for the 6-month regimen. Treatment outcomes are determined at the end of the 4-month regimen and the definition of successful treatment completion takes into account the reduced expected number of doses in the shorter regimen.
- Monitoring for potential relapse is a priority for shorter regimens especially when they are introduced into programmatic settings. Therefore, follow-up of children and young adolescents after completion of the 4-month regimen is important.

Research priorities

The following topics were identified as research priorities related to treatment shortening in children and young adolescents:

- Stronger evidence on the feasibility of making a diagnosis of non-severe drug-susceptible TB in children and adolescents in settings where there is no access to diagnostic tools, in particular to chest radiography
- Evaluation of societal costs, including direct and indirect patient costs, in implementation of shorter treatment regimens for drug-susceptible TB (including, but not limited to transport costs and loss of family income)

References

1 World Health Organization. Global tuberculosis report 2020. Geneva: 2020.

2 UN GENERAL ASSEMBLY HIGH-LEVEL MEETING ON ENDING TB. 26 September 2018, New York [website]. 2018 (http://www.who.int/tb/features_archive/UNGA_HLM_ending_TB/en/, accessed.

3 Chabala C, Turkova A, Thomason MJ, Wobudeya E, Hissar S, Mave V et al. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials. 2018;19(1):237 (https://www.ncbi.nlm.nih.gov/pubmed/29673395, accessed.

4 Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. The Lancet Global Health. 2017;5(9):e898-e906.

5 Wademan DT, Busakwe L, Nicholson TJ, van der Zalm M, Palmer M, Workman J et al. Acceptability of a first-line anti-tuberculosis formulation for children: qualitative data from the SHINE trial. Int J Tuberc Lung Dis. 2019;23(12):1263-8 (https://www.ncbi.nlm.nih.gov/pubmed/31931909, accessed.

6 World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. . Geneva, 2007 (https://apps.who.int/iris/bitstream/handle/10665/43699/9789241595629_eng.pdf?sequence=1&isAllowed=y, accessed.

Web Annex 4b. Guideline Development Group meeting in 2016

PICO 1

Author(s): Narges Alipanah and Payam Nahid

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

Setting:

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

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

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

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

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

PICO 2

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

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

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

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

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

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

CI: Confidence interval; RR: Risk ratio

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

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

c. 95% CI 2.6 to 5.8

d. 95% CI 1.9 to 4.2

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

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

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

h. 95% CI: 1.5 to 3.7

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

j. 95% CI: 5.5 to 9.1

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

l. 95% CI: 1.7 to 3.4

m. 95% CI 91 to 96%

n. 95% CI 89% to 92%

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

p. 95% CI: 85.7 to 91.0

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

r. Imprecision based on confidence interval for risk ratio

s. 95% CI 72 to 80

t. 95% CI 76 to 83

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

v. 95% CI 9 to 23

w. 95% CI 11 to 28

x. 95% CI 1.4 to 3.7

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

z. 95% CI 2.2 to 6.7

aa. 95% CI 81 to 87

ab. 95% CI 62 to 70

ac. Imprecision based on confidence interval for risk ratio.

ad. 95% CI 0 to 0.7

ae. 95% CI 0 to 0.4

ah. No explanation was provided

PICO 3

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

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

Setting: Numerous countries, mostly LMIC

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

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

CI: Confidence interval; RR: Risk ratio

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

PICO 4.1

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

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

Setting: Numerous countries, mostly LMIC

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

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

CI: Confidence interval; RR: Risk ratio

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

PICO 4.2

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

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

Setting: Numerous countries, mostly LMIC.

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

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

CI: Confidence interval; RR: Risk ratio

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

PICO 6

Author(s): Payam Nahid and Lelia Chaisson

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

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

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

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

CI: Confidence interval; RR: Risk ratio

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

PICO 7

Author(s): Lelia Chaisson

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

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

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

CI: Confidence interval; RR: Risk ratio

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

PICO 8

Author(s): Lelia Chaisson

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

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

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

CI: Confidence interval; RR: Risk ratio

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

PICO 9.1

Author(s): Dick Menzies

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

Setting: Multiple countries

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

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

CI: Confidence interval

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

PICO 9.2

Author(s): Dick Menzies

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

Setting: Multiple countries

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

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

CI: Confidence interval

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

PICO 1

Question

Should a less than 6-month fluoroquinolone (FQ)-containing regimen versus. the standard 6-month treatment regimen (2HRZE-4HR) be used for patients with drug-susceptible TB?		
Population:	Patients with drug-susceptible TB	Background:
Intervention:	A less than 6-month FQ-containing regimen	
Comparison:	Standard 6-month treatment regimen (2HRZE/4HR)	
Main outcomes:	Mortality all-cause; Mortality TB-related; Favourable outcome (end of treatment); Favourable outcome (end of follow-up); HIV-favourable - positive; HIV-favourable - negative; Relapse rate; Adverse effects - tx and fu - INH; Adverse effects - tx and fu - EMB; 2-month culture conversion; Unfavourable outcome (18 months); Unfavourable outcome (end of tx);	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Shortening the duration of TB treatment is a global research priority. However, the risk of developing resistance to fluoroquinolones (an essential element of the MDR-TB regimens) if used in an ineffective shortened regimen is a serious concern.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Desirable anticipated effects:** The less than 6-month FQ-containing regimen did trend towards better culture conversion at 2 months. However, this did not result in better treatment outcomes overall compared to standard treatment. **Undesirable anticipated effects** There are statistically significant higher rates of TB relapse and higher rates of unfavourable outcomes at 18 months in the patients treated with the less than 6-month FQ-containing regimen. Additionally, there are statistically significant worse outcomes in HIV-negative patients treated with the less than 6-month FQ-containing regimen. The higher rates of unfavourable outcomes were driven by the higher rates of relapse. **Summary of findings:**	The Guideline Development Group (GDG) felt that the shorter regimens were not at a "disadvantage" with regard to the discovery of relapse, as most relapses occur soon after stopping treatment, so most cases of relapse would be equally likely to be detected in the standard regimen and shorter regimen. The GDG also acknowledged that the comparator shorter FQ regimens varied with respect to the FQ used, the drug that the FQ replaced and the other drugs in the regimen. However, the EG believes that the FQ-based regimens at the doses tested still had similar outcomes, and those outcomes were inferior to the standard rifampicin-containing regimen. HIV-negative people did worse with the shortened FQ regimen, although this does not change the recommendations. There was no difference in mortality between the two regimens. The GDG expressed concern that a difference in mortality may not be seen between the two groups because the rates of mortality were low and a difference in mortality is not likely to be seen between a 4-month and a 6-month regimen and with the duration of follow-up seen in these studies. Mortality would be most likely to be influenced by treating patients with effective drugs early in the disease, which could have occurred in both the short FQ regimen and the standard regimen. Nevertheless, mortality after relapse is a concern, but this was not measured by the studies.

Outcome	With the standard 6-month treatment regimen (2HRZE/4HR)	With a less than 6-month FQ-containing regimen	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality all-cause	29 per 1000	**29 per 1000** (19 to 44)	**0 fewer per 1000** (from 10 fewer to 15 more)	**RR 1.00** (0.65 to 1.53)
Mortality TB-related	14 per 1000	**12 per 1000** (6 to 23)	**3 fewer per 1000** (from 9 fewer to 9 more)	**RR 0.82** (0.40 to 1.65)
Favourable outcome-(end of treatment)	912 per 1000	**922 per 1000** (912 to 940)	**9 more per 1000** (from 0 fewer to 27 more)	**RR 1.01** (1.00 to 1.03)
Favourable outcome (end of follow-up)	838 per 1000	**787 per 1000** (746 to 838)	**50 fewer per 1000** (from 0 fewer to 92 fewer)	**RR 0.94** (0.89 to 1.00)

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Outcome</th><th>With the standard 6-month treatment regimen (2HRZE/4HR)</th><th>With a less than 6-month FQ-containing regimen</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>HIV-favourable - positive</td><td>763 per 1000</td><td>725 per 1000 (630 to 802)</td><td>38 fewer per 1000 (from 39 more to 133 fewer)</td><td>OR 0.82 (0.53 to 1.26)</td></tr>
<tr><td>HIV-favourable - negative</td><td>884 per 1000</td><td>802 per 1000 (763 to 835)</td><td>82 fewer per 1000 (from 50 fewer to 122 fewer)</td><td>OR 0.53 (0.42 to 0.66)</td></tr>
<tr><td>Relapse rate</td><td>49 per 1000</td><td>135 per 1000 (88 to 209)</td><td>87 more per 1000 (from 39 more to 160 more)</td><td>RR 2.78 (1.81 to 4.29)</td></tr>
<tr><td>Adverse effects - tx and fu - INH</td><td>192 per 1000</td><td>194 per 1000 (156 to 243)</td><td>2 more per 1000 (from 37 fewer to 50 more)</td><td>RR 1.01 (0.81 to 1.26)</td></tr>
<tr><td>Adverse effects - tx and fu - EMB</td><td>98 per 1000</td><td>118 per 1000 (63 to 221)</td><td>20 more per 1000 (from 35 fewer to 123 more)</td><td>RR 1.20 (0.64 to 2.25)</td></tr>
<tr><td>Unfavourable outcome (18 months)</td><td>162 per 1000</td><td>234 per 1000 (190 to 289)</td><td>71 more per 1000 (from 28 more to 127 more)</td><td>RR 1.44 (1.17 to 1.78)</td></tr>
<tr><td>Unfavourable outcome (end of treatment)</td><td>88 per 1000</td><td>74 per 1000 (60 to 92)</td><td>13 fewer per 1000 (from 4 more to 28 fewer)</td><td>RR 0.85 (0.68 to 1.05)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
● Moderate
○ Small
○ Trivial

○ Varies
○ Don't know</td><td></td><td>Studies in this analysis excluded FQ-resistant patients</td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
○ Low
● Moderate
○ High

○ No included studies</td><td>The quality of the evidence for mortality ranks as moderate, most other recommendations rank as high as the studies analysed were randomized control trials.</td><td>The certainty of evidence grade was influenced by the grade for the mortality evidence, as mortality is a critical outcome. Adverse events did not affect overall rating of evidence and did not influence the direction of the recommendation, due to high levels of inconsistency and imprecision in the adverse event data.</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability

○ No known undesirable outcomes</td><td>Main outcomes are mortality, favourable (and unfavourable) outcomes, relapse and adverse events.</td><td>This is a complex question. Patient preferences probably depend on limiting the length of treatment versus reducing the risk of relapse combined with degree of adverse events during treatment. In this case, the relatively minor reduction of treatment duration (2 months) with no difference in reducition of adverse events, combined with the increased risk of relapse, would probably lead most patients to favour remaining with the standard 2HRZE/4HR regimen. The panel feels that a major concern for patients would be relapse of TB disease.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ● Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		Decision based mostly on increased rates of relapse among the shorter FQ-containing regimen.
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	If the 4-month FQ regimen is recommended, what is the impact on health equity?	The belief that the shortened FQ regimen may lead to a reduction in health equity is based on concerns that certain groups may not respond as well to a shorter FQ-containing regimen and that relapse may be higher in certain populations (e.g. men, people with severe disease, people with low BMI). Concerns were also raised about the increased cost of an FQ-containing regimen. However, WHO believes that the cost of a regimen should not be the driver of best treatment recommendations.
Acceptability	Is the intervention acceptable to key stakeholders? ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	A concern with using FQs in drug-susceptible TB treatment is that this may lead to a rise in FQ resistance and therefore to its loss as part of the drug-resistant TB regimen. This would be a very serious loss to the MDR-TB treatment armamentarium. Another concern would be that stakeholders may be reluctant to purchase a more expensive medication (FQ) that may not be as effective as the standard regimen. However, WHO believes that the cost of a regimen should not be the driver of best treatment recommendations.

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The feasibility of using a shorter FQ-containing regimen may be reduced by the fact that many locations cannot test for FQ resistance.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
Desirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	**Moderate**	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	**Favours the comparison**	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	**No**	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should a less than 6-month fluoroquinolone (FQ)-containing regimen versus the standard 6-month treatment regimen (2HRZE-4HR) be used for patients with drug-susceptible TB?

Type of recommendation	Strong recommendation against the intervention ●	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG recommends that the 6-month rifampicin-based regimen should be used rather than shorter 4-month FQ-containing regimens in drug-susceptible TB (strong recommendation, moderate certainty in the evidence).				
Justification	Although shortening the duration of tuberculosis therapy is a global research priority, the GDG strongly recommends against the use of a less than 6-month FQ-containing regimen and for the use of the standard 6-month rifampicin-containing regimen. The main reason behind the recommendation not to use a FQ-containing regimen of less than 6 months is that there are significantly higher rates of relapse at 18-month follow-up among patients treated with this regimen compared to the standard 6-month regimen (2HRZE/4HR). This higher rate of relapse was found despite that fact that there were higher rates of 2-month culture conversion with the less than 6-month FQ-containing regimen. Additionally, the evidence showed no reduction in adverse events with the FQ-containing regimen and no difference in all-cause and TB-related mortality. An additional concern (although not addressed specifically in these data) with using FQs in drug-susceptible TB treatment, especially given higher rates of relapse in the FQ regimen, is that this may lead to a rise in FQ resistance and therefore to the loss of FQ as part of the drug-resistant TB regimen. This would be a very serious loss to the MDR-TB treatment armamentarium. Consequently, the relatively minor reduction in treatment duration (2 months) with no reduction in adverse events or mortality, combined with the increased risk of relapse at 18 months, leads the EG to support the standard 2HRZE/4HR regimen and recommend against the shorter FQ-containing regimen. The GDG also acknowledges that the comparator shorter FQ regimens varied with respect to the FQ used, the drug that the FQ replaced and the other drugs in the regimen. However, the EG still believes that all the FQ-based regimens at the doses tested had similar outcomes and those outcomes were inferior to the standard rifampicin-containing regimen.				
Subgroup considerations	None.				
Implementation considerations	There are no implementation concerns as the 6-month rifampicin-based regimen is the standard regimen for the treatment of drug-susceptible tuberculosis.				
Monitoring and evaluation	There are no new monitoring or evaluation concerns beyond the standard recommendations.				
Research priorities	Certain subgroups may do equally well with a shortened FQ-containing regimen (i.e. women, people with BMI greater than 18, people with non-severe, non-cavitary disease). Therefore, further research may be warranted into whether a 4-month FQ-containing regimen could be non-inferior to the standard regimen in these populations. Suggested areas for research are: the mechanisms that lead certain groups to be more likely to do worse with a shortened FQ-containing regimen; the biological mechanisms behind why TB persists and then relapses despite more rapid culture conversion with certain regimens; the determination of optimal dosing of FQ, since higher doses may affect outcomes; more qualitative research or systematic review on patient values and preferences with regard to TB treatment regimens.				

PICO 2

Question

Should a fixed-dose combination, versus separate drug formulations, be used for patients with active drug-susceptible TB disease?		
Population:	Patients with active drug-susceptible TB disease	**Background:**
Intervention:	Fixed-dose combination formulation (FDC)	
Comparison:	Separate drug formulations	
Main outcomes:	Failure/relapse (per protocol analysis), Albanna & Menzies; Treatment failure, Cochrane study; Relapse, Cochrane study; Death, Cochrane study; 2-month culture conversion, Albanna & Menzies; Sputum smear or culture conversion at end of treatment, Cochrane study; Adherence versus non-adherence to treatment, Albanna & Menzies; Serious adverse reactions from TB drugs, Albanna & Menzies; Serious adverse events, Cochrane study; Adverse events leading to discontinuation of treatment, Cochrane study; Patient satisfaction, Albanna & Menzies; Acquisition (or amplification) of drug resistance, Albanna & Menzies.	
Setting:	Albanna & Menzies: Many countries – mostly low- to middle-income countries. Cochrane: adolescents and adults with bacteriologically confirmed TB.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Increasing rates of TB drug resistance are a major global health concern. Fixed-dose combination formulations (FDCs) have long been recommended by WHO and may reduce rates of drug resistance by improving adherence and minimizing the risk that a patient may receive an incomplete treatment regimen. However, concerns remain about the efficacy of FDCs, especially regarding the bioavailability of rifampicin.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Desirable anticipated effects:** The GDG decision on the degree of desirable anticipated effects is based on the balance of patient satisfaction and adherence. Patient satisfaction was higher in patients taking the FDCs. Two studies evaluated this outcome although how this evaluation was performed in these studies is not very clear. Patient adherence was slightly lower with FDCs but the difference was not significant and was not considered to be substantial enough to outweigh the effects of patient satisfaction. **Undesirable anticipated effects:** The review of evidence shows no significant difference in benefit or harm between the FDCs and separate drug formulations in terms of treatment failure, death, adherence or acquisition of drug resistance. There were slightly higher rates of acquired drug resistance and relapse among patients taking FDCs, although the differences were not significant. Rates of adverse events were not greater with the FDCs. There is general concern with the studies in this review in that FDCs or single drug formulations were not always used exclusively and uniformly throughout the entire treatment period. This may have caused inconsistencies in the results that may have masked a clear effect of one formulation over another. Regimens that used intermittent dosing were excluded from the analysis.	It is thought that the FDCs may improve patient adherence through reduction in pill burden, and may reduce drug resistance by preventing the patient from taking an incomplete regimen due to patient omission of medications and by reducing prescribing mistakes. However, these benefits were not supported by the data in these reviews. The slightly increased risk of acquired drug resistance may be biologically plausible in that decreased rifampicin bioavailability in FDCs may cause the loss of INH protection, leading to resistance mutations. Potential undesirable effects of FDCs include difficulty in adjusting the regimen in case of adverse events, inability to adjust individual medication dosing, and the risk of poor rifampicin bioavailability. However, FDCs provide programme benefits by making medication ordering easier and reduce the occurrence of stock-outs. FDCs are likely to facilitate more convenient programmatic administration of TB treatment for both patient and provider. The benefit-harm balance of FDCs may change under programme conditions.

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

○ Varies
○ Don't know</td><td colspan="2">Summary of findings:
<table>
<tr><th>Outcome</th><th>With separate drug formulations</th><th>With a FDC</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Failure/relapse (per protocol analysis): Albanna & Menzies</td><td>31 per 1000</td><td>40 per 1000(31 to 53)</td><td>11 more per 1000 (from 1 fewer to 21 more)</td><td>RR 1.28 (0.99 to 1.70)</td></tr>
<tr><td>Treatment failure: Cochrane study</td><td>19 per 1000</td><td>24 per 1000 (15 to 37)</td><td>5 more per 1000 (from 3 fewer to 19 more)</td><td>RR 1.28 (0.82 to 2.00)</td></tr>
<tr><td>Relapse: Cochrane study</td><td>55 per 1000</td><td>71 per 1000 (55 to 91)</td><td>16 more per 1000 (from 0 fewer to 36 more)</td><td>RR 1.28 (1.00 to 1.64)</td></tr>
<tr><td>Death: Cochrane study</td><td>25 per 1000</td><td>24 per 1000 (17 to 34)</td><td>1 fewer per 1000 (from 8 fewer to 10 more)</td><td>RR 0.96 (0.67 to 1.39)</td></tr>
<tr><td>Acquisition (or amplification) of drug resistance: Albanna & Menzies</td><td>1 per 1000</td><td>1 per 1000 (0 to 4)</td><td>2 more per 1000 (from 1 fewer to 5 more)</td><td>RR 1.6 (0.5 to 5.4)</td></tr>
</table></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
● Low
○ Moderate
○ High

○ No included studies</td><td>Overall, the quality of the evidence for the critical outcomes ranged from low to moderate, with most being of moderate quality.</td><td>The bioavailability of the drug formulations in FDCs were an ongoing concern. Studies in these reviews did not evaluate bioavailability of drugs in FDCs. However, previous studies did not indicate that the formulations used in these reviews had significant bioavailability issues. Additionally, when individual studies within the reviews were examined, there was no improvement in outcomes over time. Presumably formulations would have improved over time, so no improvement with better formulations indicates that the lack of superior treatment outcomes seen with the FDCs were not due to older, poorer formulations masking the effect of newer, better formulations. However, no pharmacokinetic (PK) studies were done, and it is known that the bioavailability of drugs, especially rifampin, in FDCs has historically been a concern. The bioavailability of FDCs versus single drug formulations remains unclear and controversial.

Programmes that receive drugs from quality-assured sources may not have as many complicating bioavailability issues.</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability</td><td></td><td></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
● Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>Justification of judgement: the GDG felt that the increase in patient satisfaction counterbalances the potential for relapse and adverse reactions.</td><td>Concerns with applying this review's evidence to current treatment circumstances are:

Many studies were done before the widespread use of HIV antiretroviral medications.

Many of the studies required the subjects to be AFB smear-positive, which could have limited the inclusion of HIV-positive persons.

The bioavailability of the component medications of the FDCs used in the studies is unclear.

Patients' comorbidities were not analysed.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	FDCs would be likely to lead to a reduction in stock-outs of TB medications, leading to increased health equity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	If NTPs are encouraged to use a new formulation, this may disrupt current manufacturing, production and TB drug dissemination chains. There is already wide experience with FDC use throughout the world.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should a fixed-dose combination, versus separate drug formulations, be used for patients with active drug-susceptible TB disease?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of FDCs or separate drug formulations in patients with drug-susceptible TB (conditional recommendation, low certainty in the evidence).				
Justification	Ascertaining the risks and benefits of FDCs versus separate formulations was complex, causing the GDG to be unable to recommend one over the other. Patient satisfaction was higher in patients taking FDCs but only two studies in the systematic review evaluated this and the method of evaluation was not clear. There was no inferiority with the FDCs compared with separate dose formulations in terms of treatment failure, death, adherence or acquisition of drug resistance. Separate formulations performed better on the basis of point estimates but these differences were not considered to be substantial by the GDG. The Cochrane review showed there may be a slightly higher risk of relapse among patients taking FDCs. Rates of adverse events were not greater with the FDCs. In general, it is thought that FDCs may improve patient adherence through reduction in pill burden and reduction in drug resistance by preventing the patient from taking an incomplete regimen due to patient omission of medications and by reducing prescribing mistakes. However, such benefits were not supported by the data in these reviews. The slightly increased risk of acquired drug resistance may be biologically plausible in that decreased rifampicin bioavailability in FDCs causes the loss of INH protection, leading to resistance mutations. The bioavailability of the drug formulations in the FDCs were an ongoing concern. Studies in these reviews did not evaluate bioavailability of drugs in FDCs, but previous studies did not indicate that the formulations used in these reviews had significant bioavailability issues. Additionally, when individual studies within the review were examined, there was no improvement in outcomes over time. Presumably formulations would have improved over time, so no temporal improvement suggests that the lack of better treatment outcomes seen with FDCs was not due to older, poorer formulations masking the effect of newer, better formulations. However, no PK studies were done, and it is known that the bioavailability of drugs, especially rifampin, in FDCs has historically been a concern. NTPs that receive drugs from quality-assured sources may not have as many complicating bioavailability issues. The bioavailability of FDCs versus separate dose formulations remains unclear and controversial. There is general concern about the systematic reviews presented to the GDG, in that FDCs or single-dose formulations were not always used exclusively and uniformly throughout the entire treatment period. This may have caused inconsistency in the results that may have masked a clear effect of one formulation over another. Regimens that used intermittent dosing were excluded from the analysis. Additional concerns with applying this review's evidence to current treatment circumstances are that many studies were done before the widespread use of HIV antiretroviral medications, many of the studies required the subjects to be AFB smear-positive, which could have limited the inclusion of HIV-positive persons, and patient comorbidities were not analysed. Potential undesirable effects of FDCs that were not included in the systematic review but that could impact their programmatic use include the difficulty in removing the offending drug in the case of adverse events and the inability to adjust individual medication dosing. However, FDCs may provide programme benefits by making medication ordering easier, reducing the occurrence of stock-outs, facilitating drug delivery and prescription preparation, reducing the need for additional health-care staff training on dosing and dispensing of medications, and contributing to a lower pill burden. It is likely that the true benefit-harm balance of the FDCs may change under programme conditions. In summary, the GDG believes that there is no clear advantage of FDCs over separate drug formulations or vice versa except with respect to greater patient satisfaction with FDCs and a reduced risk of relapse with separate dose formulations. The GDG felt that the increase in patient satisfaction counterbalances the small potential increase in relapse and other programmatic benefits of FDCs supporting the choice of FDCs over the separate dose formulations.				
Subgroup considerations	The reduced pill burden afforded by FDCs may be especially valuable in patients with comorbidities (notably HIV infection) and for pediatric patients (who may have particular difficulty in swallowing large amounts of medications). Patients with a specific medical condition such as intolerance for a specific TB drug, liver or renal malfunction may not benefit from an FDC, as they are more likely to require individual medication dose adjustment which can be done with separate formulations only.				
Implementation considerations	The inability to state clear guidelines for the preferred use of FDCs or separate drug formulations may confuse programmes concerning which drugs to purchase. This may affect drug manufacturing, production and supply chains. NTPs are encouraged to make decisions about which formulations to use on the basis of market availability, their treatment results and experience. However, whichever treatment regimen is chosen (particularly with the FDCs), the quality of drugs must be assured.				
Monitoring and evaluation					
Research priorities	Additional qualitative research could show the reasons why FDC formulations did not show a clear benefit. Therefore, suggested areas for research are: pharmacokinetic studies of the bioavailability of FDC versus separate drug formulation regimens; better development of weight banding categories for drug dosing (children and other special populations, particularly people living with HIV, would benefit the most from this); additional qualitative studies detailing medication adherence; additional work on FDC formulations to further decrease pill burden, especially among patients with co-morbidities.				

PICO 3

Question

Should daily dosing throughout treatment versus thrice-weekly dosing throughout treatment be used for treatment of drug-susceptible pulmonary tuberculosis?		
Population:	Patients with drug-susceptible pulmonary tuberculosis	Background:
Intervention:	Daily dosing throughout treatment	
Comparison:	Thrice-weekly dosing throughout treatment	
Main outcomes:	Risk of failure in drug-susceptible disease; Risk of relapse in drug-susceptible disease; Risk of acquired drug resistance in drug-susceptible disease; Risk of failure in drug-susceptible disease or susceptibility unknown; Risk of relapse in drug-susceptible disease or susceptibility unknown; Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown.	
Setting:	Numerous countries, mainly low- and middle-income.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Intermittent dosing of tuberculosis medications (either throughout treatment or in the continuation phase only) may have the ability to improve treatment adherence. However, there are risks with intermittent dosing of poor treatment outcomes and the development of drug resistance.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	This review included pulmonary TB only. When thrice-weekly dosing throughout treatment was compared to daily dosing throughout, there were higher rates of treatment failure, relapse and acquired drug resistance both in drug-sensitive disease and when the strain sensitivity was unknown. Adherence was not addressed adequately enough in the reviewed studies to be included as an outcome. However, in most studies included in the review, intermittent dosing used DOT while the use of DOT during daily dosing was variable. **Summary of findings:**	Possible anticipated benefits are less of a burden on the health-care system due to reduced need for DOT.

Outcome	With daily dosing throughout treatment	With thrice weekly dosing throughout treatment	Difference (95% CI)	Relative effect (RR) (95% CI)
Risk of failure in drug-susceptible disease	10 per 1000	27 per 1000 (3 to 221)	17 more per 1000 (from 7 fewer to 211 more)	RR 2.6 (0.3 to 21.2)
Risk of relapse in drug-susceptible disease	30 per 1000	63 per 1000 (33 to 120)	33 more per 1000 (from 3 more to 90 more)	RR 2.1 (1.1 to 4.0)
Risk of acquired drug resistance in drug-susceptible disease	2 per 1000	23 per 1000 (5 to 109)	21 more per 1000 (from 3 more to 107 more)	RR 10.0 (2.1 to 46.7)
Risk of failure in drug-susceptible disease or susceptibility unknown	14 per 1000	50 per 1000 (16 to 172)	37 more per 1000 (from 3 more to 158 more)	RR 3.7 (1.2 to 12.6)
Risk of relapse in drug-susceptible disease or susceptibility unknown	34 per 1000	75 per 1000 (41 to 136)	41 more per 1000 (from 7 more to 102 more)	RR 2.2 (1.2 to 4.0)
Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown	2 per 1000	23 per 1000 (5 to 109)	21 more per 1000 (from 3 more to 107 more)	RR 10.0 (2.1 to 46.7)

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes assessed (treatment failure, treatment relapse and acquired drug resistance) would probably be of importance to all patients.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Daily dosing is favoured.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Health equity would be increased with daily dosing and it would be reduced with dosing three times weekly. Certain populations would have inferior treatment for tuberculosis if intermittent dosing was used in the intensive phase. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment (the intervention) is acceptable to stakeholders. Thrice-weekly dosing is not acceptable to stakeholders, chiefly because of the concerns about equity outlined above. It is acknowledged that large countries, particularly India, use intermittent dosing frequently. However, the practice varies widely throughout India between daily and intermittent dosing. Given the findings in this review, all countries should be encouraged to use exclusively daily dosing in the intensive phase.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment is believed to be feasible. However, there were no representatives from India (the largest user of thrice-weekly treatment) present on the GDG.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should daily dosing throughout treatment versus thrice-weekly dosing throughout treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	Recommendation 3a: The GDG suggests the use of daily dosing rather than three times weekly dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis in all patients (conditional recommendation, very low certainty in the evidence).				
Justification	There was hope that intermittent dosing of tuberculosis medications may have the ability to improve treatment adherence and to be less of a burden on the health-care system because of the reduced need for DOT. However, when thrice-weekly dosing throughout treatment is compared to daily dosing throughout treatment, there is a higher risk of treatment failure, relapse and acquired drug resistance in both drug-sensitive disease and when the strain sensitivity was unknown. This review included pulmonary TB only. Adherence was not addressed adequately enough in the reviewed studies for it to be included as an outcome. However, in most studies included in the review, intermittent dosing used DOT while the use of DOT during daily dosing was variable. The GDG also felt that health equity would be increased with daily dosing and would be reduced with three times weekly dosing. Certain populations would have inferior treatment for tuberculosis if intermittent dosing was used in the intensive phase. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs. Given the findings in this review, all countries are encouraged to use exclusively daily dosing in the intensive phase of treatment.				
Subgroup considerations	These recommendations apply to HIV-negative people as well as people living with HIV. The data used in this review was based on pulmonary TB patients. Children were not considered specifically in this review. However, there is no biologically plausible reason why these recommendations should not apply to children as well as adults. It is recommended that all children receive daily dosing of TB medications during the intensive phase of treatment, for the same reason as adults. See the 2014 WHO guideline Guidance for National Tuberculosis Programmes on the management of tuberculosis in children for recommendations on the daily dosing of children with drug-susceptible tuberculosis.				
Implementation considerations	There are no new implementation considerations because the recommended treatment is already widespread practice. India is the main exception since intermittent dosing is widespread in that country. These recommendations to use exclusively daily dosing in the intermittent phase of TB treatment will therefore probably have implications in India for drug procurement, practitioner training, change of programme practice and patient support.				
Monitoring and evaluation	There are no new monitoring or evaluation recommendations, as the standard of care (daily dosing of medications during the intensive phase of treatment) is being recommended.				
Research priorities	It may be appropriate to analyse the utility of 5 days of treatment per weeks versus 7 days of treatment in the intensive phase of treatment (i.e. sparing weekend dosing). Suggested areas for research are: research into the optimal duration of the intensive phase of treatment; outcomes of DOT versus self-administered treatment.				

PICO 4.1

Question

Should daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase versus daily dosing throughout TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?		
Population:	Patients with drug-susceptible pulmonary tuberculosis	Background:
Intervention:	Daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase	
Comparison:	Daily dosing throughout TB treatment	
Main outcomes:	Risk of failure in drug-susceptible disease; Risk of relapse in drug-susceptible disease; Risk of acquired drug resistance in drug-susceptible disease; Risk of failure in drug-susceptible disease or susceptibility unknown; Risk of relapse in drug-susceptible disease or susceptibility unknown; Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown.	
Setting:	Numerous countries, mostly low- and middle income.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Intermittent dosing of tuberculosis medications (either throughout treatment or in the continuation phase only) may improve treatment adherence. However, there is a risk with intermittent dosing of poor treatment outcomes and the development of drug resistance.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	This review included pulmonary TB only. When thrice-weekly dosing during the continuation phase only was compared to daily dosing throughout, there were higher rates of treatment failure and relapse in the patients that received thrice-weekly treatment during the continuation phase. Rates of acquired drug resistance did not differ. However, it was felt that, since the confidence intervals were very wide, the difference between the two treatments were not as substantial as when intermittent dosing during the intensive phase of treatment was examined (PICO 3).	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:**	Treatment must be closely supervised if treatment with intermittent dosing is considered.

Outcome	With daily dosing throughout TB treatment	With daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase	Difference (95% CI)	Relative effect (RR) (95% CI)
Risk of failure in drug-susceptible disease	10 per 1000	40 per 1000 (5 to 315)	29 more per 1000 (from 5 fewer to 304 more)	RR 3.8 (0.5 to 30.2)
Risk of relapse in drug-susceptible disease	30 per 1000	39 per 1000 (18 to 87)	9 more per 1000 (from 12 fewer to 57 more)	RR 1.3 (0.6 to 2.9)
Risk of acquired drug resistance in drug-susceptible disease	2 per 1000	1 per 1000 (0 to 13)	1 fewer per 1000 (from 2 fewer to 11 more)	RR 0.6 (0.1 to 5.7)
Risk of failure in drug-susceptible disease or susceptibility unknown	14 per 1000	20 per 1000 (5 to 74)	7 more per 1000 (from 8 fewer to 60 more)	RR 1.5 (0.4 to 5.4)
Risk of relapse in drug-susceptible disease or susceptibility unknown	34 per 1000	41 per 1000 (20 to 78)	7 more per 1000 (from 14 fewer to 44 more)	RR 1.2 (0.6 to 2.3)
Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown	2 per 1000	1 per 1000 (0 to 13)	1 fewer per 1000 (from 2 fewer to 11 more)	RR 0.6 (0.1 to 5.7)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes assessed (treatment failure, treatment relapse and acquired drug resistance) would probably be of importance to all patients.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Daily dosing is probably favoured.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Health equity would be increased with daily dosing and would be reduced with dosing three times weekly. Certain populations would have inferior treatment for tuberculosis if intermittent dosing in the continuation phase was used. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.	

	Judgement	Research evidence	Additional considerations
Acceptability	Is the intervention acceptable to key stake-holders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment (the intervention) is acceptable to stakeholders. Three times weekly dosing during the continuation phase is not acceptable to stakeholders, chiefly because of the issues of equity outlined above. It is acknowledged that large countries, particularly India, use intermittent dosing frequently. However, practice varies widely throughout India between daily dosing and intermittent dosing. If intermittent dosing is considered, DOT must be done.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment is believed to be feasible. However, there were no representatives from India (the largest user of thrice-weekly treatment) present on the GDG.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evi-dence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evi-dence of required resources	Very low	Low	Moderate	High			No included studies	
Cost- effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase versus daily dosing throughout TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of daily dosing over twice-weekly or thrice-weekly dosing in the continuation phase of treatment for drug-susceptible pulmonary tuberculosis (conditional recommendation, very low certainty in the evidence).				
Justification	There was hope that intermittent dosing of tuberculosis medications may improve treatment adherence and may be less of a burden on the health-care system due to the reduced need for DOT. However, when thrice-weekly dosing in the continuation phase of treatment is compared to daily dosing throughout treatment, there is a higher risk of treatment failure and relapse. If thrice-weekly dosing during the continuation phase is used, then DOT must be adhered to. This review included pulmonary TB only. Adherence was not addressed adequately enough in the reviewed studies to be included as an outcome. However, in most studies included in the review, intermittent dosing used DOT while the use of DOT during daily dosing was variable. The GDG also felt that health equity would be increased with daily dosing and would be reduced with three times weekly dosing. Certain populations would have inferior treatment for tuberculosis if intermittent dosing in the intensive phase were to be used. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs. Given the findings in this review, all countries are encouraged to use daily dosing in the continuation phase of treatment.				
Subgroup considerations	No additional considerations beyond those outlined in PICO 3.				
Implementation considerations	No additional considerations beyond those outlined in PICO 3.				
Monitoring and evaluation	If thrice-weekly dosing during the continuation phase of treatment is used, then DOT must be adhered to.				
Research priorities	Additional research may show a benefit for thrice-weekly dosing in the continuation phase, as effect differences seen in this review between thrice-weekly dosing in the continuation phase and daily dosing during the continuation phase are small.				

PICO 4.2

Question

Should daily dosing throughout TB treatment versus daily dosing in the intensive phase followed by twice-weekly dosing in the continuation phase of TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?		
Population:	Patients with drug-susceptible pulmonary tuberculosis	Background:
Intervention:	Daily dosing throughout TB treatment	
Comparison:	Daily dosing in the intensive phase followed by twice-weekly dosing in the continuation phase of TB treatment	
Main outcomes:	Risk of failure in drug-susceptible disease: Johnston; Risk of relapse in drug-susceptible disease, Johnston; Risk of acquired drug resistance in drug-susceptible disease, Johnston; Risk of failure in drug-susceptible disease or susceptibility unknown, Johnston; Risk of Relapse in drug-susceptible disease or susceptibility unknown, Johnston; Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown, Johnston.	
Setting:	Numerous countries, mostly LMIC.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Intermittent dosing of tuberculosis medications (either throughout treatment or in the continuation phase only) may improve treatment adherence. However, there is the risk with intermittent dosing of poor treatment outcomes and the development of drug resistance.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Twice-weekly dosing in the continuation phase, versus daily dosing throughout, showed an increase risk of treatment failure and relapse. Acquired drug resistance did not differ. The rest of the findings regarding twice-weekly dosing in the continuation phase are the same as stated in the discussion surrounding thrice-weekly dosing in the continuation phase.	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With daily dosing throughout TB treatment	With daily dosing in the intensive phase followed by twice weekly dosing in the continuation phase of TB treatment	Difference (95% CI)	Relative effect (RR) (95% CI)
Risk of failure in drug-susceptible disease (Johnston)	10 per 1000	41 per 1000 (5 to 179)	30 more per 1000 (from 5 fewer to 169 more)	RR 3.9 (0.5 to 17.2)
Risk of relapse in drug-susceptible disease (Johnston)	30 per 1000	51 per 1000(27 to 102)	21 more per 1000 (from 3 fewer to 72 more)	RR 1.7 (0.9 to 3.4)
Risk of acquired drug resistance in drug-susceptible disease (Johnston)	2 per 1000	2 per 1000 (0 to 12)	0 fewer per 1000 (from 2 fewer to 9 more)	RR 1.0 (0.2 to 5.0)
Risk of failure in drug-susceptible disease or susceptibility unknown (Johnston)	14 per 1000	41 per 1000 (14 to 120)	27 more per 1000 (from 0 fewer to 106 more)	RR 3.0 (1.0 to 8.8)
Risk of relapse in drug-susceptible disease or susceptibility unknown (Johnston)	34 per 1000	61 per 1000 (34 to 112)	27 more per 1000 (from 0 fewer to 78 more)	RR 1.8 (1.0 to 3.3)
Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown (Johnston)	2 per 1000	2 per 1000 (0 to 12)	0 fewer per 1000 (from 2 fewer to 9 more)	RR 1.0 (0.2 to 5.0)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should daily dosing throughout TB treatment versus daily dosing in the intensive phase followed by twice-weekly dosing in the continuation phase of TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of daily dosing over twice-weekly or thrice-weekly dosing in the continuation phase of treatment for drug-susceptible pulmonary tuberculosis (conditional recommendation, very low certainty in the evidence).				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 5

Question

Should antiretrovirals started during TB treatment versus antiretrovirals started at the end of TB treatment be used for tuberculosis patients co-infected with HIV?		
Population:	Tuberculosis patients co-infected with HIV	Background:
Intervention:	Antiretrovirals started during TB treatment	
Comparison:	Antiretrovirals started at the end of TB treatment	
Main outcomes:	Adherence versus non-adherence to treatment; Successful treatment outcome (cure/completed treatment) versus failure/relapse/death; No severe adverse reactions from TB drugs versus severe drug reaction; No substantial cost versus substantial cost to patient; No substantial cost versus substantial cost to health-care system; Acquisition (or amplification) of drug resistance; Reduction of hospital stay; Reduction of clinical complications.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No research evidence was identified.	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should antiretrovirals started during TB treatment versus antiretrovirals started at the end of TB treatment be used for tuberculosis patients co-infected with HIV?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Recommendation	HIV antiretroviral medications should be started in all TB patients living with HIV regardless of their CD4 count (strong recommendation, high quality of evidence). TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high quality of evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment. From: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections (WHO, 2016).				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 6

Question

Should a treatment period greater than 8 months versus a treatment period of 6 months be used for patients with pulmonary drug-susceptible tuberculosis co-infected with HIV?

Population:	Patients with pulmonary drug-susceptible tuberculosis co-infected with HIV	**Background:**
Intervention:	A treatment period greater than 8 months	
Comparison:	A treatment period of 6 months	
Main outcomes:	Failure, relapse, death	
Setting:	From a systematic review of randomized trials plus controlled observational studies (i.e. retrospective or prospective cohort studies).	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	People co-infected with HIV and TB have greater risks of relapse and mortality. A systematic review and meta-analysis (Khan FA et al., CID 2010) found a trend towards higher rates of relapse if rifampicin were used for only 6 months (compared to a period greater than or equal to 8 months) or if ART was not used. However, in the face of WHO recommendations that all people with TB should also be treated with ART, the question of the duration of TB treatment needs to be revisited.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Many of the studies included in this review were conducted before the HIV antiretroviral medications became available. During the review, the data were also broken down in a subgroup analysis comparing persons who were treated with ART and those who were not. When people who were not on HIV antiretrovirals were examined, relapse rates were significantly higher among persons who received treatment with regimens that contained 6 months of rifampicin, as opposed to those who received a treatment regimen greater than or equal to 8 months of rifampicin. However, when people received at least some treatment with ART, these differences disappeared. Rates of failure and death did not differ between people treated with 6 months of rifampicin versus those treated with rifampicin for a period greater than or equal to 8 months. This was true whether or not patients were on ART. However, it is unclear from these data whether the observed cases were true relapse as opposed to reinfection. Possible undesirable effects include: The extension of treatment to 8 months from 6 months has the additional burden of 2 months more of medication Patients may face increased stigma if they are on the longer treatment and others find out that the longer duration of TB treatment is the regimen for people living with HIV (PLWH). There is a greater risk of drug-drug interactions with a longer treatment regimen.	In the studies analysed for these guidelines, the patients not on ART were driving the relapse rates.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:** See table below	
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	

Outcome	With a treatment period greater than 8 months	With the standard 6-month treatment regimen	Difference (95% CI)	Relative effect (RR) (95% CI)
Failure	44 per 1000	35 per 1000 (18 to 66)	9 fewer per 1000 (from 22 more to 26 fewer)	RR 0.8 (0.4 to 1.5)
Relapse	68 per 1000	164 per 1000 (82 to 341)	96 more per 1000 (from 14 more to 273 more)	RR 2.4 (1.2 to 5.0)
Death	140 per 1000	126 per 1000 (70 to 224)	14 fewer per 1000 (from 70 fewer to 84 more)	RR 0.9 (0.5 to 1.6)

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ● Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should a treatment period greater than 8 months versus a treatment period of 6 months be used for patients with pulmonary drug-susceptible tuberculosis co-infected with HIV?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that patients with drug-susceptible pulmonary TB who are living with HIV should receive 6 months of treatment rather than extended treatment of 8 months or more (conditional recommendation/very low quality of evidence).				
Justification	All people living with HIV, especially those with TB, should be receiving ART. Therefore, PLWH co-infected with drug-susceptible TB should only require 6 months of rifampicin-containing TB treatment (see PICO 6 and the WHO publications The use of antiretroviral drugs for treating and preventing HIV infection [2016] and WHO policy on collaborative TB/HIV activities: guidelines for National Programmes and other stakeholders [2012]). However, conditions may justify deviating from this recommendation (i.e. extending treatment). Such conditions include situations when people fail to receive ART, or when people have severe TB disease, very low CD4 counts or other immunocompromising conditions. While PLWH should ideally always be on ART, in reality people do not receive ART for a variety of reasons. Adverse consequences of an extended period of TB treatment include the burden of an additional 2 months of medications and the increased risk of drug-drug interactions with prolonged treatment. When the subgroup of people who were not being treated with HIV antiretrovirals was examined, relapse rates were significantly higher among persons who received treatment with regimens that contained 6 months of rifampicin, as opposed to those who received greater than or equal to 8 months of treatment with rifampicin. When people received at least some treatment with ART, these differences disappeared. Rates of failure and death did not differ between people treated with 6 months of rifampicin versus greater than or equal to 8 months of rifampicin. This held true whether or not they were on ART. It should be noted that it is unclear from these data whether the observed cases were true relapse – as opposed to reinfection – and many of these studies (and the evidence for prolonging TB treatment) were conducted before the availability of HIV antiretroviral medications. Possible undesirable effects of an extended duration of TB treatment include the additional burden of 2 months more of medications and a greater risk of drug-drug interactions.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Suggested areas for research are: the factors that may cause people, especially PLWH, not to respond well to TB treatment (i.e. starting ART late, low CD4 counts, etc.); exploration and description of etiological factors leading to higher death rates and rates of adverse events in HIV/TB co-infected persons.				

PICO 7

Question

Should adjuvent corticosteroids versus TB treatment without corticosteroids be used for tuberculous pericarditis?		
Population:	Patients with tuberculous pericarditis	Background:
Intervention:	Treatment with adjuvent corticosteroids	
Comparison:	TB treatment without corticosteroids	
Main outcomes:	Death; Treatment adherence; Constrictive pericarditis.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is controversy concerning the effectiveness of adjunctive corticosteroids in reducing mortality in tuberculous pericarditis.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Review of the data showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. However, when the studies were considered individually, the largest (1400 patients) and most recent study – i.e. the IMPI study (Mayosi BM et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014) – showed no benefit to steroids. However, HIV infection complicates these findings. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. In another smaller study of 58 subjects, in which all were HIV-positive, steroids reduced mortality (two other studies took place before the HIV era and one study had half of their subjects infected with HIV, but mortality was not analysed, although the other outcomes were). These immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative persons or people living with HIV(PLWH) who are on ART. In the IMPI study, there was a supplemental analysis of only the HIV-negative patients, and a small mortality benefit was shown with steroid treatment. Several other issues were raised regarding the analysis. A random-effects model was used in this analysis, which led to an unexpected finding that the relative risk of death was lower in the steroid treatment arm, despite the fact that similar numbers and proportions of patients in both the steroid and placebo arms had this outcome. When a fixed-effects model was applied, the difference in mortality tended to disappear. However, upon extensive discussion it was determined that the random-effects model was the most appropriate model to use, and so the findings stand. There was also a concern that publication bias may play a role in these results. Most of the studies were published in 2000 and before, so there was probably more of a publication bias at that time towards studies with positive findings. The undesirable effects were dictated by the increased rates of cancer in the steroid-treated group. These cancers were seen in the IMPI study, and were almost all HIV-related cancers (particularly Karposi sarcoma). Concerns still also exists in that the cancer findings in the IMPI study were also complicated by the fact that many patients who received steroids were also treated with immunotherapy (M. indicus pranii), the effects of which are unknown. Adjuvent corticosteroids compared to TB treatment without corticosteroids for tuberculous pericarditis	However, selective use of glucocorticoids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction (ATS guidelines, 2016).
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TB treatment without corticosteroids	Risk difference with adjuvent corticosteroids
Death	1779 (5 RCTs)	(⊕⊕◯◯) LOW 1,2	RR 0.54 (0.23 to 1.26)	161 per 1000	74 fewer per 1000 (124 fewer to 42 more)
Treatment adherence	1795 (2 RCTs)	(⊕◯◯◯) VERY LOW 1,3	RR 0.91 (0.75 to 1.12)	865 per 1000	78 fewer per 1000 (216 fewer to 104 more)
Constrictive pericarditis	1515 (3 RCTs)	(⊕⊕◯◯) LOW 2	RR 0.72 (0.32 to 1.58)	75 per 1000	21 fewer per 1000 (51 fewer to 43 more)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Dexamethasone may not be available in some settings due to its IV requirements. If an oral steroid formulation is not available in these cases, this would lead to inequity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should adjuvent corticosteroids versus TB treatment without corticosteroids be used for tuberculous pericarditis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests initial adjunctive corticosteroid treatment may be used in patients with tuberculous pericarditis (conditional recommendation, very low certainty in the evidence).				
Justification	The panel felt that the benefit in constrictive pericarditis, even if the latest and largest study did not show a reduction in mortality, outweighed the potential harms of corticosteroid treatment. Review of the data showed a benefit to steroid treatment with regards to death, constrictive pericarditis and treatment adherence. However, when the studies were considered individually, the largest (1400 patients) and most recent study – i.e. the IMPI study (Mayosi BM et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014) – showed no benefit to steroids. However, HIV infection complicates these findings. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. In another smaller study of 58 subjects, in which all were HIV-positive, steroids reduced mortality (the other studies did not address HIV and mortality). These immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative persons or PLWH who are on ART. In the IMPI study, there was a supplemental analysis of just the HIV negative patients, and a small mortality benefit was shown with steroid treatment. Several other issues were raised regarding the analysis. A random-effects model was used in this analysis, which led to an unexpected finding where the relative risk of death was lower in the steroid treatment arm, despite the fact that similar numbers and proportions of patients in both the steroid and placebo arms had this outcome. When a fixed-effects model was applied, the difference in mortality tended to disappear. However, upon extensive discussion it was determined that the random-effects model was the most appropriate model to use, and so the findings stand. There was also a concern that publication bias may play a role in these results. Most of the studies were published in the year 2000 and before, so there was probably more of a publication bias at that time towards studies with positive findings.				
Subgroup considerations	PLWH: In one study an increase in HIV-related cancers was observed. However, this increase appears to be caused by co-administration of immunotherapy (M. indicus pranii).				
Implementation considerations	Practitioners should give oral steroids if IV formulations are not available.				
Monitoring and evaluation					
Research priorities	Suggested areas for research are: different effects of steroids on people who are HIV-positive or not or who are being treated with ART or not; the relationship between steroid treatment and cancer risk.				

PICO 8

Question

Should adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks versus TB treatment without corticosteroids be used for tuberculous meningitis?		
Population:	Patients with tuberculous meningitis	Background:
Intervention:	Adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks	
Comparison:	TB treatment without corticosteroids	
Main outcomes:	Mortality; Death or severe disability; Relapse; Adverse events.	
Setting:		
Perspective:		

Assessment

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Tuberculous meningitis is a serious form of extrapulmonary TB that leads to high rates of death and severe disability. Steroids have been used in the treatment of tuberculous meningitis, but their role has been controversial.</td><td></td></tr>
<tr><td>Desirable Effects</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td>Analysis of the data shows statistically significantly lower rates of mortality or severe disability , and relapse in patients treated with steroids. The mortality benefit increased with increasing TB meningitis stage (i.e. increasing severity of disease). Additionally, rates of adverse events and severe adverse events were lower in the patients receiving steroids. All 8 of the episodes of severe hepatitis (one of which was fatal) occurred in the placebo arm.
There were no substantial undesirable anticipated effects due to steroid treatment.</td><td></td></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td>Summary of findings:
<table>
<tr><th>Outcome</th><th>With TB treatment without corticosteroids</th><th>With adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Mortality</td><td>348 per 1000</td><td>250 per 1000 (181 to 348)</td><td>97 fewer per 1000 (from 0 fewer to 167 fewer)</td><td>RR 0.72 (0.52 to 1.00)</td></tr>
<tr><td>Death or severe disability</td><td>489 per 1000</td><td>391 per 1000 (327 to 474)</td><td>98 fewer per 1000 (from 15 fewer to 161 fewer)</td><td>RR 0.80 (0.67 to 0.97)</td></tr>
<tr><td>Relapse</td><td>159 per 1000</td><td>134 per 1000 (92 to 198)</td><td>26 fewer per 1000 (from 38 more to 67 fewer)</td><td>RR 0.84 (0.58 to 1.24)</td></tr>
</table></td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
○ Low
● Moderate
○ High

○ No included studies</td><td>No research evidence was identified.</td><td>Usually, the overall certainty of evidence is graded on the basis of the lowest grade of the outcome evidence. In this case, the outcome of "relapse" is graded as low certainty of evidence. However, because the evidence for relapse is in the same direction as all the other evidence (and so therefore would not affect the overall decision) the overall certainty of evidence should not be downgraded to the level of the evidence of relapse (i.e. low).</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	Dexamethasone may not be available in some settings due to its IV requirements. If an oral steroid formulation is not available in these cases, this would lead to inequity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	Practitioners should give oral steroids if IV formulations are not available.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks versus TB treatment without corticosteroids be used for tuberculous meningitis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Recommendation	The GDG recommends that initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used for patients with tuberculous meningitis (strong recommendation, moderate certainty in the evidence).				
Justification	Analysis of the data shows statistically significantly lower rates of mortality or severe disability, and relapse in patients treated with steroids. Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.				
Subgroup considerations	Steroids should be given regardless of the severity of meningitis				
Implementation considerations	Practitioners should give oral steroids if IV formulations are not available.				
Monitoring and evaluation					
Research priorities	Suggested areas for research are: the optimal steroid dose for TB meningitis (including among different formulations); the optimal steroid duration for TB meningitis, and whether this duration differs between different grades of meningitis.				

PICO 9

Question

Should empiric re-treatment with the 5 first-line drugs HRZES (WHO category II regimen) be used for patients with a previous history of treatment, with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing?		
Population:	Patients with a previous history of treatment with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing	Background:
Intervention:	Empiric re-treatment with the 5 first-line drugs HRZES (WHO category 2 regimen)	
Comparison:	No comparator was defined for this comparison	
Main outcomes:	Adherence versus non-adherence to treatment; Successful treatment outcome (cure/completed treatment) versus failure/relapse/death; No severe adverse reactions from TB drugs versus severe drug reaction; No substantial cost versus substantial cost to patient; No substantial cost versus substantial cost to health-care system; Acquisition (or amplification) of drug resistance; Reduction of hospital stay; Reduction of clinical complications.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No research evidence was identified.	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should empiric re-treatment with the 5 first-line drugs HRZES (WHO category II regimen) be used for patients with a previous history of treatment, with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG recommends that TB patients who require retreatment for TB should be referred for drug-susceptibility testing and that the category II regimen should no longer be prescribed (ungraded good practice statement).				
Justification	In persons who require retreatment for TB due to treatment interruption or recurrence of disease, drug susceptibility testing (DST) should be carried out and category II treatment should not be used. There are several reasons why category II should no longer be used. With the advent of widespread DST, the standard of care is to perform a DST on people who have had treatment interruption or recurrence of disease and then to treat accordingly. Not doing this, and instead empirically treating with the substandard category II regimen, perpetuates treatment inequity (especially in low- to middle-income countries), delays proper treatment for drug-resistant tuberculosis (which fuels drug resistance and leads to worse outcomes for the patient and for the community) and, if patients have drug-sensitive disease, exposes them unnecessarily to the toxicities of streptomycin. One of the basic tenets of TB treatment is that one drug should not be added to an unsuccessful regimen. Adding streptomycin to the previously unsuccessful regimen of INH, rifampicin, ethambutol and PZA violates this principle and fuels the development of drug resistance and the loss of streptomycin as a second-line agent in MDR-TB treatment. Patients who have failed treatment may have done so because of drug resistance. Use of category II in these patients runs contrary to the WHO treatment principle that any patient who has failed treatment should be started on an empirical MDR-TB regimen (Treatment of tuberculosis: guidelines, fourth edition. World Health Organization, 2010) and will only accelerate drug resistance. In patients who have had treatment interruption, the reason for that interruption should be addressed, whether it be medication stock-outs, side-effects of medicines, the need for greater patient or provider education, etc. The data for this review demonstrated that the empiric use of category II in patients requiring retreatment for their TB disease led to unacceptably low rates of treatment success (median treatment success rates of 68%). In addition, when patients with known INH resistance who were treated with category II were examined, acquired drug resistance rates were significantly higher than in those who received an RZE regimen. Adverse events were not sufficiently well recorded in the literature to be analysed. The GDG expressed concern regarding treatment of patients with INH mono-resistant TB. Xpert® MTB/RIF is the most common method for drug susceptibility testing, but it lacks the current ability to test for INH resistance. Patients with INH resistance are at a higher risk of developing additional drug resistance. Providers must be vigilant about the possibility of INH resistance and, if it is suspected, they must test for INH susceptibility and treat accordingly, although category II should never be used. Further WHO guidance on treatment for patients with INH mono-resistance, particularly addressing the use of fluoroquinolones, is upcoming.				
Subgroup considerations					
Implementation considerations	Patients eligible for retreatment should be referred for a rapid molecular test or DST to determine at least the INH and RIF resistance status. Based on the drug susceptibility profile, a standard treatment regimen can be repeated if no resistance is documented, or a MDR-TB regimen will be prescribed according to WHO's recently published MDR-TB treatment guidelines.				
Monitoring and evaluation					
Research priorities					

Web Annex 4c. Guideline Development Group meeting in 2009

Not available

Web Annex 5. 2010 and 2017 DS-TB Guidelines

Treatment of Tuberculosis. Guidelines for National TB Programmes, fourth edition 2010 (https://www.who.int/publications/i/item/9789241547833)

Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update (https://www.who.int/publications/i/item/9789241550000)

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