WHO treatment guidelines for isoniazid-resistant tuberculosis

Online Annexes: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

THE END TB STRATEGY

World Health Organization

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Contents

Annex 1. GRADE evidence summary tables

5-1. GRADE Table - 6 months of (H)REZ compared with more than 6 months of (H)REZ

Author(s): Dick Menzies, Federica Fregonese (McGill University, Montréal, Canada)
Date:
Question: 6 months of (H)REZ compared to more than 6 months of (H)REZ for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)
Setting: Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis
Bibliography: Fregonese F, Menzies D. Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis (UNDER REVIEW FOR PUBLICATION).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months of (H)REZ	6 months or more of (H)REZ	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/relapse 6 months of (H)REZ versus more than 6 months of (H)REZ												
15	observational studies	serious	not serious[a]	not serious	serious[b]	All plausible residual confounding would reduce the demonstrated effect	254/262 (96.9%)[c]	999/1088 (91.8%)[d]	**adjusted OR 2.4** (1.0 to 5.5)[e]	**40 more per 1,000** (from 0 fewer to 80 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL
Subgroup analysis : treatment success versus treatment failure/relapse of 6 months of REZ compared with more than 6 months of REZ												
13	observational studies	serious	not serious[a]	not serious	serious[b]	All plausible residual confounding would reduce the demonstrated effect	136/142 (95.8%)	701/785 (89.3%)	**adjusted OR 2.5** (0.9 to 7.5)[g]	**50 more per 1,000** (from 10 fewer to 100 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of resistance to rifampicin, for 6 months of (H)REZ versus more than 6 months of (H)REZ[h]												
10	observational studies	serious	serious[i]	not serious	serious	none	1/168 (0.6%)[j]	43/992 (4.3%)[k]	**adjusted OR 0.2** (0.0 to 1.7)[l]	**10 more per 1,000** (from 60 fewer to 40 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence Interval

Explanations

a. Inconsistency based on I squared.
b. Broad confidence interval.
c. Of the 262 treated, 120 had isoniazid for one month or more and 142 did not. Stratification by resistance to SM did not show any significant difference in treatment success between the intervention and comparator groups.
d. Of the 1088 treated, 303 had isoniazid for one month or more and 785 did not. Stratification by resistance to SM did not show any significant difference in treatment success between the intervention and comparator groups.
e. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 262 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
f. The risk difference (absolute effect) is estimated based on a fixed effects generalized linear mixed model, using propensity score matching method. The adjusted OR should be considered the more robust and correct estimate as it is based on a random effects PS matched model (random intercept and random slope).
g. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 140 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
h. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred, but not analysed).
i. Completeness of testing for the acquisition of resistance to rifampicin and the procedures followed for testing may have differed between individuals within the same cohort and between patient series.
j. Of the 168 treated, 84 had isoniazid for one month or more and 84 did not.
k. Of the 992 treated, 263 had isoniazid for one month or more and 729 did not.
l. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 168 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.

5-2. GRADE Table - 6 months or more of (H)REZ plus fluoroquinolone compared with 6 months or more of (H)REZ

Author(s): Dick Menzies, Federica Fregonese (McGill University, Montréal, Canada)
Date:
Question: 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017) [a]
Setting: Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis
Bibliography: Fregonese F, Menzies D. Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis (UNDER REVIEW FOR PUBLICATION).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months or more of (H)REZ plus fluoroquinolone	6 months or more of (H)REZ	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/relapse for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ												
15	observational studies	serious	not serious[b]	not serious	serious[c]	Strong association all plausible residual confounding would reduce the demonstrated effect[d]	245/251 (97.6%)[e]	1253/1350 (92.8%)[f]	**adjusted OR 2.8** (1.1 to 7.3)[g]	**50 more per 1,000** (from 0 more to 90 more)[h]	⨁⨁◯◯ LOW	CRITICAL
Death versus success/treatment failure/relapse in (H)REZ-FQ vs (H)REZ[i]												
15	observational studies	serious	not serious[b]	not serious	not serious	All plausible residual confounding would reduce the demonstrated effect[d]	25/524 (4.8%)[j]	97/2174 (4.5%)[k]	**adjusted OR 0.7** (0.4 to 1.1)[l]	**20 fewer per 1,000** (from 50 fewer to 0 fewer)[h]	⨁⨁◯◯ LOW	CRITICAL
Death versus success/treatment failure/relapse in REZ-FQ vs REZ (subgroup analysis in patients with no isoniazid use)[i]												
14	observational studies	serious	not serious[b]	not serious	very serious[m]	All plausible residual confounding would reduce the demonstrated effect[d]	8/219 (3.7%)	41/1054 (3.9%)	**adjusted OR 0.4** (0.2 to 1.1)[n]	**20 fewer per 1,000** (from 60 fewer to 20 more)[h]	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of resistance to rifampicin for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ[o]												
10	observational studies	serious	serious[p]	not serious	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect	1/221 (0.5%)	44/1160 (3.8%)	**adjusted OR 0.1** (0.0 to 1.2)[q]	**30 fewer per 1,000** (from 60 fewer to 0 fewer)[h]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse for 6 months or more of REZ plus fluoroquinolone compared to 6 months or more of REZ: subgroup analysis in patients without isoniazid												
14	observational studies	serious	not serious[b]	not serious	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect [d]	131/135 (97.0%)	837/927 (90.3%)	**adjusted OR 5.4** (1.8 to 16.6)[r]	**130 more per 1,000** (from 40 fewer to 230 more)[h]	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ: subgroup analysis in patients using moxifloxacin/levofloxacin/gatifloxacin as fluoroquinolones												
15	observational studies	serious	not serious[b]	not serious	very serious[m]	all plausible residual confounding would reduce the demonstrated effect[d]	161/165 (97.6%)[s]	1253/1350 (92.8%)[f]	**adjusted OR 2.9** (0.9 to 9.3)[t]	**60 more per 1,000** (from 20 fewer to 140 more) [h]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence Interval

Explanations

a. The median duration of use of fluoroquinolones in ≥6months (H)REZ+FQ regimens was of 6.1 months (interquartile range 3.5; 8.4); for rifampicin 9.0 (7.2; 11.1); for ethambutol 9.0 (7.3; 11.1) and for pyrazinamide 8.9 (6.8; 10.7). In one large database, with 137 patients with this regimen, start dates of each drug were available and therefore it was possible to calculate the delay between start of rifampicin and fluoroquinolones: median 1.4 months (IQR 0.9; 2.3)
b. Based on I squared
c. The confidence interval is broad.
d. Addition of FQ may represent confounding by indication.
e. Of the 251 treated, 116 had isoniazid for one month or more and 135 did not.
f. Of the 1350 treated, 423 had isoniazid for one month or more and 927 did not.
g. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 248 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
h. The risk difference (absolute effect) is estimated based on a fixed effects generalized linear mixed model, using propensity score matching method. The adjusted OR should be considered the more robust and correct estimate as it is based on a random effects PS matched model (random intercept and random slope).
i. Mortality analysis cannot take into account duration of specific regimens because death truncates duration (outcome determined the independent variable of duration). Mortality analysis thus includes all cases who received (H)REZ+FQ or (H)REZ regardless of duration. Observations contributing to mortality analysis are therefore different from those included in analysis of treatment success.
j. Of the 524 in intervention, 305 had isoniazid for one month or more and 219 did not.
k. Of the 2174 in control, 1120 had isoniazid for one month or more and 1054 did not.
l. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 522 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
m. The confidence interval is broad and includes one.
n. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 205 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
o. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred, but not analysed).
p. Completeness of testing for the acquisition of resistance to rifampicin and the procedures followed for testing may have differed between individuals within the same cohort and between patient series.
q. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 220 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
r. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 127 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
s. Of the 165 treated, 67 had isoniazid for one month or more and 98 did not.
t. Propensity scores odd ratio (aOR) based on matched pairs for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 164 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.

5-3. GRADE Table - 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ

Author(s): Dick Menzies, Federica Fregonese (McGill University, Montréal, Canada)
Date:
Question: 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)
Setting: Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis
Bibliography: Fregonese F, Menzies D. Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis (UNDER REVIEW FOR PUBLICATION).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S	6 months or more of (H)REZ	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/relapse for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ												
23	observational studies	serious	not serious[a]	not serious	not serious	none	271/325 (83.4%)[b]	1253/1350 (92.8%)[c]	**adjusted OR 0.4** (0.2 to 0.7)[d]	**120 fewer per 1,000** (from 190 fewer to 60 fewer)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse: subgroup analysis in patients without isoniazid												
14	observational studies	serious	not serious[a]	not serious	very serious[f]	none	89/107 (83.2%)	837/927 (90.3%)	**adjusted OR 0.5** (0.2 to 1.2)[g]	**80 fewer per 1,000** (from 170 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Death versus success/treatment failure/relapse in (H)REZ-S vs (H)REZ[h]												
23	observational studies	serious	not serious[a]	not serious	very serious[f]	none	40/763 (5.2%)[i]	103/2263 (4.6%)[i]	**adjusted OR 0.9** (0.6 to 1.3)[k]	**10 fewer per 1,000** (from 30 fewer to 20 more)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Death versus success/treatment failure/relapse: subgroup analysis in patients without isoniazid[l]												
14	observational studies	serious	not serious[a]	not serious	very serious[f]	none	6/136 (4.4%)	41/1054 (3.9%)	**adjusted OR 1.2** (0.4 to 4.1)[m]	**0 fewer per 1,000** (from 50 fewer to 60 more)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of resistance to rifampicin, for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ[n]												
14	observational studies	serious	serious	not serious	very serious[o]	none	6/58 (10.3%)	44/1160 (3.8%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence Interval

Explanations

a. Based on I squared.
b. Of the 325 treated, 218 had isoniazid for one month or more and 107 did not.
c. Of the 1350 treated, 423 had isoniazid for one month or more and 927 did not.
d. Propensity scores odd ratio (OR) adjusted for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used. Poly-resistance was 47% in the group taking 6 or more(H)RE 3Z 3SM as compared with <1% in the group taking 6 or more (H) REZ.) Adjusted OR was calculated on 296 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope.
e. The risk difference (absolute effect) is estimated based on a fixed effects generalized linear mixed model, using propensity score matching method. The adjusted OR should be considered the more robust and correct estimate as it is based on a random effects PS matched model (random intercept and random slope).
f. Confidence interval is broad.
g. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used. Adjusted OR was calculated on 105 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
h. Mortality analysis cannot take into account duration of specific regimens because of death truncated duration (outcome determined the independent variable of duration). Therefore the mortality analysis included all cases who received regimens with (H)REZ+SM vs (H)REZ regardless of duration. Hence the observations contributing to mortality (n=3026) analysis are different from observations included in analysis of treatment success (n=1675), even if analysis was done in the same datasets (n=23)- for mortality we consider all duration of regimens (and not only 6 or more (H)RE, up to 3m of Z and up to 3 months of SM, as we do for the success analysis), therefore we have more patients.
i. Of the 763 treated, 627 used isoniazid for one month or more and 136 did not.
j. Of the 2263 treated, 1209 used isoniazid for one month or more and 1054 did not.
k. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 756 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
l. Mortality analysis cannot take into account duration of specific regimens because of death truncated duration (outcome determined the independent variable of duration). Therefore the mortality analysis included all cases who received regimens with REZ+SM vs REZ regardless of duration. Hence the observations contributing to this mortality analysis are different from observations included in analysis of treatment success for 6 months RE, up to 3 months of Z and up to 3 months of SM versus 6 months or more of REZ.
m. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 133 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
n. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred but not analysed).
o. Not possible to calculate adjusted OR and 95% confidence interval as difficult matching for differences between groups. Annex 5. Evidence-to-Decision Tables.

Annex 2. GRADE evidence-to-decision tables

6-1. Evidence-to-Decision Table - 6 months of (H)REZ compared with more than 6 months of (H)REZ

<table>
<tr><td colspan="2">Should 6 months of (H)REZ vs more than 6 months of (H)REZ be used for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)?</td><td rowspan="6">BACKGROUND:
Tuberculosis (TB) remains a threat to global public health and the world's leading single infectious cause of death. In 2016, an estimated 10.4 million people developed TB and 1.7 million died from the disease. In the same year an estimated 600 000 TB patients developed rifampicin or multidrug-resistant TB (MDR/RR-TB), resistant to rifampicin and isoniazid – the two most important anti-TB medicines – and about 240 000 of these patients are estimated to have died. Patients with MDR/ RR-TB require second-line treatment regimens which are generally longer, more toxic and difficult to scale up than first-line regimens used in drug-susceptible TB. Apart from patients with MDR-TB, 8.5% of TB cases (7.3% in new and 14.0% in previously treated) worldwide are estimated to have isoniazid-resistant TB without MDR-TB (Hr-TB); this form of TB is associated with higher likelihood of treatment failure in patients who receive first-line regimens. The emergence of drug-resistant TB (DR-TB) has led to an increased demand for second-line anti-TB medicines in many parts of the world in recent years. WHO has released guideline for DR-TB treatment since 1997. Since 2006, WHO also included instructions on the treatment of Hr-TB in its implementation handbooks for the programmatic management of DR-TB. In October 2016, WHO updated its treatment guidelines for drug-resistant TB to incorporate the most recent evidence on the use of TB medicines, both old and new, and issued the first evidence-based recommendations for the use of a shorter MDR-TB regimen in selected patients. The Guideline Development Group which revised these guidelines also looked at the evidence for the treatment of Hr-TB. The evidence review could not trace cohorts or RCTs which included fluoroquinolones as part of standardized TB regimens designed primarily for Hr-TB. Fluoroquinolones, when used, were individualized and introduced at varying points in a patient's regimen when Hr-TB was detected. The GDG thus advised that no policy recommendation on the treatment of Hr-TB be formulated and that a meta-analysis is conducted using IPD from studies of subjects treated for Hr-TB using different regimens.

Through 2016, evidence reviewers from McGill University, Canada, coordinated the collection and assembling of an IPD for Hr-TB. By November 2016, data on 5,537 Hr-TB patients from 33 global datasets was obtained and an interim analysis for treatment outcome determinants was then conducted. The findings from this analysis suggest that an evidence-informed recommendation for the treatment of Hr-TB could now be formulated to replace previous guideline based largely on expert opinion.</td></tr>
<tr><td>POPULATION:</td><td>Adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded. The findings have been inferred primarily from the individual-patient data analysis of 2017.</td></tr>
<tr><td>INTERVENTION:</td><td>6 months of (H)REZ</td></tr>
<tr><td>COMPARISON:</td><td>More than 6 months of (H)REZ</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Treatment success versus treatment failure/relapse 6 months of (H)REZ versus more than 6 months of (H)REZ; Subgroup analysis : treatment success versus treatment failure/relapse of 6 months of REZ compared with more than 6 months of REZ; Acquisition of resistance to rifampicin, for 6 months of (H)REZ versus more than 6 months of (H)REZ;</td></tr>
<tr><td>SETTING:</td><td>Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis with 5417 observations from 33 datasets</td></tr>
<tr><td>PERSPECTIVE:</td><td>A GDG was convened on 27 April 2017 to consider the IPD meta-analysis and advise on changes to the current recommendations. The GDG meeting followed upon a three-day meeting on the critical concentrations, pharmacokinetics and pharmacodynamics of TB medicines, which will discuss "background questions" crucial to the implementation of the WHO DR-TB treatment guideline (e.g. dosage regimens in children and adults; therapeutic drug monitoring; substitution of medicines in the same class; formulations; use of medicines in the presence of resistance to them)</td></tr>
</table>

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	References: **1)** Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line medicines: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2017 Feb;17(2):223–34. **2)** Stagg HR, Harris RJ, Hatherell H-A, Obach D, Zhao H, Tsuchiya N, et al. What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax. 2016 Oct;71(10):940–9.	Isoniazid has been one of the backbone medicines for the management of TB patients. Resistance to isoniazid threatens the efficacy of TB treatment.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See GRADE tables.	Use of a regimen lasting more than 6 months to which a fluoroquinolone is added is expected to increase the likelihood of treatment success significantly. However, given that treatment success in patients with Hr-TB treated with first-line regimens is generally high the absolute effect of adding a fluoroquinolone is relatively modest on a population level.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	see GRADE tables.	While first-line TB medications have been associated with severe adverse reactions and even death, such occurrences are rare. The overall undesirable effect from the widespread use of these regimens are thus expected to vary from small to moderate in most patients. Toxicity is usually associated with longer duration of use of a drug. It is assumed that shorter duration is expected to give less adverse effects in general (reduced cumulative toxicity), even if the data could not be summarised in this analysis. Anticipated harms are expected to be small.

	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	Observational data only has been included in the IPD In three recent RCTs that investigated the potential for fluoroquinolones to shorten frst-line TB regimens, over 240 patients with non-MDR, isoniazid-resistant strains were placed on fluoroquinolone-containing regimens (1-3). Data for 66 of these patients enrolled in one of these RCTs showed similar levels of unfavourable outcome (treatment failure/relapse/death/loss to follow-up) in patients on fluoroquinolone-containing four-month regimens (20.7%) compared with the standard 2HRZE/4HR10 regimen (21.6%) (1). In a second trial, success rates in patients treated with four-month fluoroquinolone containing regimens were similar in subgroups with isoniazid-resistant strains and those with fully susceptible strains (2). References **1)** Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacincontaining regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588–98 **2)** Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371(17):1577–87 **3)** Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS One. 2013;8(7):e67030.	As the quality of the evidence presented in these studies was poor, the certainty in the estimates of effect was very low, increasing the need for further research. Additional studies will then be likely to have an important impact on the confidence in the estimates and are likely to change the estimates.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Reference 1) Khan FA, 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. Clinical Infectious Diseases. 2012 Jul 19:cis630.	All patients are likely to value the outcomes of successful treatment, death, acquired resistance and toxicity as critical. Some patients may value prolonged treatment or additional doses of rifampicin if this increases the likelihood of relapse-free successful outcome. However, not all patients would equally value having a longer duration of treatment (e.g. pregnant women, children taking extra ethambutol, people with HIV).

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></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>Given the substantial heterogeneity found in terms of safety /toxicities in present studies (e.g. in the way that AE data were collected and classified by the different studies – measurement and reporting bias), it was not possible to further analyse adverse events in the IPD meta-analysis.

<u>Reference</u>
1) Khan FA, 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. Clinical Infectious Diseases. 2012 Jul 19:cis630.</td><td>This treatment is the current standard of care. Recommendations to test for HIV and treat. There are some subgroups in which (duration) variation in the regimen may be indicated on a case by case basis.</td></tr>
<tr><td>RESOURCES REQUIRED</td><td>How large are the resource requirements (costs)?
○ Large costs
○ Moderate costs
○ Negligible costs and savings
● Moderate savings
○ Large savings
○ Varies
○ Don't know</td><td>No cost-effectiveness analysis done.

Comparative cost of regimens Approximate GDF prices for medicines needed for complete treatment of a 60kg adult, 16 March 2018.
<table><tr><th>Regimen</th><th>Approximate cost of medicines alone, USD</th></tr><tr><td>2HREZ/4HR</td><td>31.9 (22.36 - kit)</td></tr><tr><td>6HREZ</td><td>104.4 (47.8)</td></tr><tr><td>6REZLfx</td><td>122.26</td></tr><tr><td>6HREZLfx</td><td>125.8 (68.7)</td></tr><tr><td>9HREZLfx</td><td>186.8 (102.5)</td></tr></table>
Note.— Values in brackets are the price when the regimen is given in part or whole as a FDC.</td><td>Resource cost of medicines alone are affordable and comparable to usual first-line drug regimens. Use of FDCs, even for part of treatment, expected to lower costs further.

Only drug costs available. Service and patient costs are not factored in and will dwarf the drug costs. Sometimes patients have to pay for the medicines themselves. Indirect costs are estimated to be much greater than the direct cost of medicines.</td></tr>
<tr><td>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</td><td>What is the certainty of the evidence of resource requirements (costs)?
○ Very low
○ Low
○ Moderate
○ High
● No included studies</td><td>No cost-effectiveness analysis done.</td><td></td></tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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		Probably favours the intervention.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	It would be expected to increase equity (relative costs of regimen low, more patients likely to complete treatment, and may increase cure in a substantial proportion of TB patients).
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	It is a shorter regimen and the medicines used are already part of standard TB regimens. May not be acceptable if it is used in patients without laboratory confirmed Hr-TB. May not be acceptable to programmes where prolongation of treatment is associated with e.g. extent of disease or HIV positivity rather than drug resistance (resistance to change could be due to intellectual conviction). There may be some time (and training) required to ensure the transfer and adoption of new guidelines.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		The intervention is considered to be feasible and efficient even if a feasibility analysis was not performed. In some countries (e.g. Portugal) the 3-drug combination is HRZ and so ethambutol has to be given separately (most GDF supply is 4 drug). There has been extensive use of these regimens. Testing for H and R is widely available; testing for Z susceptibility also increasingly practised.

SUMMARY OF JUDGEMENTS								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 **6 months of (H)REZ** *vs* **more than 6 months of (H)REZ** be used for **adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)**?					
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	In adults and children with isoniazid-resistant, rifampicin-susceptible tuberculosis, combination treatment with rifampicin, ethambutol and pyrazinamide may be used for 6 months [very low certainty in the evidence].				
JUSTIFICATION	**Overall justification** The overall benefit of any of (i) prolonging RZE beyond 6 months, and (ii) adding high-dose isoniazid. **Detailed justification** *Desirable Effects:* There was a greater likelihood for successful outcome in patients who received at least 6 months of RZE and fluoroquinolones (following adjustment, although residual confounding is likely). Other adjustments may be justified on individual-patient considerations. *Undesirable Effects:* Additional harms from prolongation or additional medication need to be outweighed by the expected benefits of these deviations *Certainty of evidence:* Judged to be low or very low, so evidence from well-constructed observational series or clinical trials could reduce current uncertainties (see also Research Priorities below) *Feasibility :*The intervention and deviations from the main recommendation considered to be feasible and efficient even if a cost-effectiveness analysis was not performed. It would be expected to increase equity (relative costs of regimen low and increases likelihood of a relapse-free cure in a substantial proportion of TB patients)				
SUBGROUP CONSIDERATIONS	In the absence of evidence for children and based on the extrapolation from adult data, this recommendation applies to children (0-14 years) in the absence of evidence for children. The GDG found no reason to believe that the recommendation should not apply to children. Although there was no clear evidence to suggest that the addition of isoniazid would add benefit to this HREZ regimen, the 4-drug HREZ FDC may be more convenient for the patient and feasible for healthcare services given that it obviates the need to use single drugs.				
IMPLEMENTATION CONSIDERATIONS	In regimens containing REZ with or without isoniazid (standard dose), the addition of isoniazid did not appear to make a difference in the point estimates of the effect. Adding isoniazid had no demonstrable effect in the present analysis to inform these guidelines. However, for convenience and to improve adherence, the 4-drug FDC, with isoniazid, may be used to implement the recommendation. In settings where the 3-drug combination is HRZ (e.g. Portugal), ethambutol has to be given separately (most GDF supply is 4 drug). Possibility to undertake DST for isoniazid, rifampicin and fluoroquinolones at the start of treatment and have a reliable test result for pyrazinamide susceptibility Can treatment be given empirically based on individual risk (e.g. in close contacts) or should it wait until a definitive bacteriological diagnosis? Can treatment be given empirically based on background epidemiology? (e.g. in a TB patient subpopulation in whom Hr-TB >20%)? Under which conditions do regimens need to be prolonged from 6 to 9 months (previous treatment, extensive disease, polydrug resistance…) What is the upper limit for the duration of treatment (9 months?) Should PZA be given for 9 months? Likelihood that DST results are obtained *after* treatment has been started Under what conditions to use fluoroquinolones? (previous treatment, extensive disease, polydrug resistance) is Xpert/LPA testing for RR-TB required before adding FQs? Levofloxacin is the preferred fluoroquinolone (i.e. so that Mfx/Gfx are reserved for the treatment of M/XDR-TB). Specify the dose? Is there added benefit to keep H in the regimen, and if				

CONCLUSIONS Should **6 months of (H)REZ** *vs* **more than 6 months of (H)REZ** be used for **adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)**?	
	so under which conditions and at what dose? If streptomycin is indicated can it be replaced by another injectable agent? Is there a role for other SLDs? (under what conditions; exclude S resistance before use?) A statement proposed to underline that bedaquiline and delamanid are NOT recommended in the treatment of Hr-TB? Should medication adherence support (directly observed therapy or digital technologies) be required? In formulating "how to" advice on the implementation of the Hr-TB treatment regimens the GDG will be informed by the recent discussion on the CC/PK/PD of TB medicines which will immediately precede the 27 April meeting
MONITORING AND EVALUATION	**The intervention is considered feasible. However, as toxicity may be increased in some cases, supervision/monitoring of patients should be stressed.** • Bacteriological cure • Resolution of clinical manifestations by the end of prescribed treatment • Non-response (e.g. sputum smear positive at the end of month 2) or treatment failure as per the 2013 WHO definition • Relapse (what duration of follow-up) • Survival (or death) • Adverse reactions from anti-TB medicines by severity/seriousness, type, organ class • Acquisition (amplification) of additional drug resistance Continued surveillance for background H resistance (mutation studies), pyrazinamide, fluoroquinolones in a given setting • Individual-patient testing for Hr-TB; FQ; PZA; issues with testing for E and streptomycin • Can past exposure be used as a proxy of ineffectiveness, taking also into consideration that the rate of resistance-conferring mutations which occur spontaneously differs for the individual anti-TB medicines - e.g. E=1 to 6.4×10−7; S=2.95×10−8; Z= 1×10−5 (not a rate but estimated proportion of mutants in a M.tb population); Lfx in *M fortuitum*= 3.8×10−9) Reference **1)** McGrath M, Gey van Pittius NC, van Helden PD, Warren RM, Warner DF. Mutation rate and the emergence of drug resistance in Mycobacterium tuberculosis. Journal of Antimicrobial Chemotherapy. 2014 Feb 1;69(2):292–302.
RESEARCH PRIORITIES	• High-quality evidence on the optimization of the regimen composition in children and adults, particularly the role of high-dose isoniazid, fluoroquinolones and injectable agents • High-quality evidence on the duration of individual medicines in the regimens in children and adults • NNT for empirical use of an Hr-TB regimen, balancing risk to benefit. Studies of daily versus intermittent regimen. Feasibility of FDCs incorporating the fluoroquinolone • Monitoring of patient response and analysing for the genotyping patterns in isoniazid resistance • Critical concentrations (FQNs at 0.1-0.2 and 1.0) • Cost-effectiveness of different approaches to DST, including the rapid testing of all TB patients to both H & R resistance before start of treatment

6-2. Evidence-to-Decision Table - 6 months or more of (H)REZ plus fluoroquinolone compared with 6 months or more of (H)REZ

<table>
<tr><td colspan="2">Should 6 months or more of (H)REZ plus fluoroquinolone vs 6 months or more of (H)REZ be used for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)?</td><td rowspan="7">BACKGROUND:
Tuberculosis (TB) remains a threat to global public health and the world's leading single infectious cause of death. In 2016, an estimated 10.4 million people developed TB and 1.7 million died from the disease. In the same year an estimated 600 000 TB patients developed rifampicin or multidrug-resistant TB (MDR/RR-TB), resistant to rifampicin and isoniazid – the two most important anti-TB medicines – and about 240 000 of these patients are estimated to have died. Patients with MDR/ RR-TB require second-line treatment regimens which are generally longer, more toxic and difficult to scale up than first-line regimens used in drug-susceptible TB. Apart from patients with MDR-TB, 8.5% of TB cases (7.3% in new and 14.0% in previously treated) worldwide are estimated to have isoniazid-resistant TB without MDR-TB (Hr-TB); this form of TB is associated with higher likelihood of treatment failure in patients who receive first-line regimens. The emergence of drug-resistant TB (DR-TB) has led to an increased demand for second-line anti-TB medicines in many parts of the world in recent years. WHO has released guideline for DR-TB treatment since 1997. Since 2006, WHO also included instructions on the treatment of Hr-TB in its implementation handbooks for the programmatic management of DR-TB. In October 2016, WHO updated its treatment guidelines for drug-resistant TB to incorporate the most recent evidence on the use of TB medicines, both old and new, and issued the first evidence-based recommendations for the use of a shorter MDR-TB regimen in selected patients. The Guideline Development Group which revised these guidelines also looked at the evidence for the treatment of Hr-TB. The evidence review could not trace cohorts or RCTs which included fluoroquinolones as part of standardized TB regimens designed primarily for Hr-TB. Fluoroquinolones, when used, were individualized and introduced at varying points in a patient's regimen when Hr-TB was detected. The GDG thus advised that no policy recommendation on the treatment of Hr-TB be formulated and that a meta-analysis is conducted using IPD from studies of subjects treated for Hr-TB using different regimens.

Through 2016, evidence reviewers from McGill University, Canada, coordinated the collection and assembling of an IPD for Hr-TB. By November 2016, data on 5,537 Hr-TB patients from 33 global datasets was obtained and an interim analysis for treatment outcome determinants was then conducted. The findings from this analysis suggest that an evidence-informed recommendation for the treatment of Hr-TB could now be formulated to replace previous guideline based largely on expert opinion.</td></tr>
<tr><td>POPULATION:</td><td>Adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded. The findings have been inferred primarily from the individual-patient data analysis of 2017.</td></tr>
<tr><td>INTERVENTION:</td><td>6 months or more of (H)REZ plus fluoroquinolone</td></tr>
<tr><td>COMPARISON:</td><td>6 months or more of (H)REZ</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Treatment success versus treatment failure/relapse for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ; Death versus success/treatment failure/relapse in (H)REZ-FQ vs (H)REZ; Death versus success/treatment failure/relapse in REZ-FQ vs REZ (subgroup analysis in patients with no isoniazid use).; Acquisition of resistance to rifampicin for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ.; Treatment success versus failure/relapse for 6 months or more of REZ plus fluoroquinolone compared to 6 months or more of REZ: subgroup analysis in patients without isoniazid; Treatment success versus failure/relapse for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ: subgroup analysis in patients using moxifloxacin/levofloxacin/gatifloxacin as fluoroquinolones.</td></tr>
<tr><td>SETTING:</td><td>Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis with 5417 observations from 33 datasets</td></tr>
<tr><td>PERSPECTIVE:</td><td>A GDG was convened on 27 April 2017 to consider the IPD meta-analysis and advise on changes to the current recommendations. The GDG meeting followed upon a three-day meeting on the critical concentrations, pharmacokinetics and pharmacodynamics of TB medicines, which will discuss "background questions" crucial to the implementation of the WHO DR-TB treatment guideline (e.g. dosage regimens in children and adults; therapeutic drug monitoring; substitution of medicines in the same class; formulations; use of medicines in the presence of resistance to them)</td></tr>
</table>

Assessment

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	References **1)** Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2017 Feb;17(2):223–34. **2)** Stagg HR, Harris RJ, Hatherell H-A, Obach D, Zhao H, Tsuchiya N, et al. What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax. 2016 Oct;71(10):940–9.	Isoniazid has been one of the backbone medicines for the management of TB patients. Resistance to isoniazid threatens the efficacy of TB treatment.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See GRADE tables.	Use of a regimen lasting more than 6 months to which a fluoroquinolone is added is expected to increase the likelihood of treatment success significantly. However, given that treatment success in patients with Hr-TB treated with first-line regimens is generally high the absolute effect of adding a fluoroquinolone is relatively modest on a population level. There is reduction in death and acquired rifampicin resistance (uncertainty about how the acquired intervention was applied) and therefore the effect considered moderate.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		While first-line TB medications have been associated with severe adverse reactions and even death, such occurrences are rare. The overall undesirable effect from the widespread use of these regimens are thus expected to vary from small to moderate in most patients. The inclusion of a fourth or a fifth medicine may increase the risk of adverse drug reactions and drug-drug interactions. In patients with HIV or other comorbidity these effects could be accentuated. Relative hepatotoxicity of Lfx compared with anti-TB medicines is very small. However the cardiotoxicity effect may be more important and is unknown in this group. If Lfx it could be trivial. Rifampicin and moxifloxacin may interact and the RMP may have effectively lowered the Mfx in the regimen (in this case ECG monitoring would be needed). References (hepatotoxicity) **1)** Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. Journal of Antimicrobial Chemotherapy. 2011 Jul 1;66(7):1431–46. **2)** Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008;149:689-697

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	Observational data only has been included in the IPD In three recent RCTs that investigated the potential for fluoroquinolones to shorten frst-line TB regimens over 240 patients with non-MDR, isoniazid-resistant strains were placed on fluoroquinolone-containing regimens (1-3). Data for 66 of these patients enrolled in one of these RCTs showed similar levels of unfavourable outcome (treatment failure/relapse/death/loss to follow-up) in patients on fluoroquinolone-containing four-month regimens (20.7%) compared with the standard 2HRZE/4HR10 regimen (21.6%) (1). In a second trial, success rates in patients treated with four-month fluoroquinolone containing regimens were similar in subgroups with isoniazid-resistant strains and those with fully susceptible strains (2). References 1) Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacincontaining regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588–98 2) Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371(17):1577–87. 3) Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS One. 2013;8(7):e67030.	The implication of low or very low certainty in the estimates of effect is that the quality of the evidence is poor and that further research is very likely to have an important impact on the confidence in the estimates and is likely to change the estimates. Uncertainty about WHEN to introduce the fluoroquinolone. Median duration of FQ in the studies was very similar to the duration of R and therefore likely to have been given from the start.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	All patients are likely to value the outcomes of successful treatment, death, acquired resistance and toxicity as critical. Some patients may value prolonged treatment or additional doses of rifampicin/fluoroquinolones if this increases the likelihood of relapse-free successful outcome. However, not all patients would equally value having a longer duration of treatment (e.g. pregnant women, children taking extra ethambutol, people with HIV).

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></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>Given the substantial heterogeneity found in terms of safety /toxicities in present studies (e.g. in the way that AE data were collected and classified by the different studies – measurement and reporting bias),it was not possible to further analyse adverse events in the IPD meta-analysis.</td><td>Combination chemotherapy with RHEZ has been safely administered to millions of patients worldwide in the past decades. Likewise, treatment with fluoroquinolones lasting many months has been given to many thousands of TB patients with an overall beneficial sum effect.</td></tr>
<tr><td>RESOURCES REQUIRED</td><td>How large are the resource requirements (costs)?
○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
● Varies
○ Don't know</td><td>No cost-effectiveness analysis done.

Comparative cost of regimens Approximate GDF prices for medicines needed for complete treatment of a 60kg adult, 16 March 2018.
<table><tr><th>Regimen</th><th>Approximate cost of medicines alone, USD</th></tr><tr><td>2HREZ/4HR</td><td>31.9 (22.36 - kit)</td></tr><tr><td>6HREZ</td><td>104.4 (47.8)</td></tr><tr><td>6REZLfx</td><td>122.26</td></tr><tr><td>6HREZLfx</td><td>125.8 (68.7)</td></tr><tr><td>9HREZLfx</td><td>186.8 (102.5)</td></tr></table>
Note.— Values in brackets are the price when the regimen is given in part or whole as a FDC.</td><td>One of the major costs would be that associated with diagnosis (which does not exist in many places) to rule-out resistance to fluoroquinolones and rifampicin.

The cost may be higher in settings where the frequency of fluoroquinolones resistance is high among rifampicin-sensitive cases, and therefore testing is more indicated. In addition, because of cardiotoxicity, ECG monitoring is required at baseline. Considerable costs to diagnose FQ resistance, and implement ECGs. If Lfx used no need for ECGs.

The cost of 100 tabs of Lfx 750mg is USD10 and Mfx 400mg USD31-39 (GDF 27.04.2017).</td></tr>
<tr><td>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</td><td>What is the certainty of the evidence of resource requirements (costs)?
○ Very low
○ Low
○ Moderate
○ High
● No included studies</td><td>No research evidence was identified.</td><td>Testing algorithms may vary and can affect cost at country level. Cost of drug is known in many settings (See also above).</td></tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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.	There will be additional costs associated with the rule-out of resistance to fluoroquinolones, especially for areas with a high prevalence of fluoroquinolones resistance.
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.	Lfx may not be available in some settings. It would be expected to increase equity (relative costs of regimen low and increases likelihood of a relapse-free cure in a substantial proportion of TB patients).
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	NTPs may resist the recommendation because it increases costs and the timing of the addition of the FQ may not be clear. Many managers would want to reserve FQs for use in cases with MDR-/XDR-TB. In places like Russian Fed they would favour using the FQ. In Swaziland there is concern that use of FQs in such patients can generate FQ resistance. In Cameroon, adding fluoroquinolones, would potentially increase costs and this is the major concern (much of the funding depends on donors); not clear in which patients to apply the recommendation. In general, acceptability would also depend on countries' capacity to implement second-line DST.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		In some settings the DST may still be a challenge. Intervention considered to be feasible and efficient even if a cost-effectiveness analysis was not performed. Most of the medicines are widely available to programmes (RZE as an FDC; FQ as an add on) There has been extensive use of these regimens Testing for H,R and FQs is widely available; testing for Z susceptibility also increasingly practised.

SUMMARY OF JUDGEMENTS								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	

<table>
<tr><td colspan="6">CONCLUSIONS
Should 6 months or more of (H)REZ plus fluoroquinolone vs 6 months or more of (H)REZ be used for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)?</td></tr>
<tr><td>TYPE OF RECOMMENDATION</td><td>Strong recommendation against the intervention
○</td><td>Conditional recommendation against the intervention
○</td><td>Conditional recommendation for either the intervention or the comparison
○</td><td>Conditional recommendation for the intervention
●</td><td>Strong recommendation for the intervention
○</td></tr>
<tr><td>RECOMMENDATION</td><td colspan="5">In adults and children with isoniazid-resistant, rifampicin-susceptible tuberculosis, levofloxacin may be included in a treatment regimen composed of rifampicin, ethambutol, and pyrazinamide (with or without isoniazid) [very low certainty in the evidence]</td></tr>
<tr><td>JUSTIFICATION</td><td colspan="5">Overall justification
The overall benefit of adding a fluoroquinolone to the (H)RZE regimen outweighs potential harms.
Detailed justification
Desirable Effects
Patients who received FQs were 3.7 times more likely to have treatment success and 50% reduction in risk of death as compared to patients who did not received any FQs. Additionally, they also had a 90% risk reduction in the acquisition of resistance to rifampicin.
Undesirable Effects
Although there were minor concerns about hepatotoxicity and information on other toxicities (e.g. QT prolongation) was limited, it was noted that additional harms from adding FQ are outweighed by the expected benefits of incorporating FQs in a regimen
Certainty of evidence
Judged to be low or very low, so evidence from well-constructed observational series or clinical trials could reduce current uncertainties.
Feasibility
The intervention and deviations from the main recommendation considered to be feasible and efficient even if a cost-effectiveness analysis was not performed. It would be expected to increase equity (relative costs of regimen low and increases likelihood of a relapse-free cure in a substantial proportion of TB patients).</td></tr>
<tr><td>SUBGROUP CONSIDERATIONS</td><td colspan="5">The recommendation applies equally to (i) patients, both adult and children, detected with Hr-TB and in whom RR-TB was excluded at the start of treatment.

Under certain conditions: Previously treated; Hr-TB detected after 2 months from start of current regimen; extensive disease; suspected ineffectiveness of E/Z.

The 6-month (H)REZ-Lfx regimen is recommended in HIV-positive patients.
The regimen composition proposed is likely to be effective in patients with extrapulmonary disease. However, the treatment of this group of patients should be designed in close consultation with respective specialists.
Prolongation of (H)REZ-Lfx beyond six months could be considered on an individual basis for patients with extensive disease, as determined by cavitary disease and persistence of bacteriologically positive sputum at or after month 3.

The addition of levofloxacin to (H)REZ is recommended in all patients with Hr-TB, with exception of the following: (i) in cases where resistance to rifampicin cannot be excluded; (ii) known or suspected resistance to levofloxacin; (iii) known intolerance to fluoroquinolones; (iv) known or suspected risk for prolonged QTc interval; and (v) pregnancy or during breastfeeding (not an absolute contraindication). In Hr-TB cases in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ.
In situations where E & Z are likely to be ineffective Lfx could be added systematically if Z resistance is not tested in the individual-patient. Patients not responding should not have a single drug (Lfx) added to the regimen.</td></tr>
<tr><td>IMPLEMENTATION</td><td colspan="5">The standard of care should be to run Xpert on everyone. FQ can only be added if R resistance has been reliably excluded (genotypical or phenotypical). In the field the genotypic tests</td></tr>
</table>

CONCLUSIONS Should **6 months or more of (H)REZ plus fluoroquinolone** *vs* **6 months or more of (H)REZ** be used for **adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)**?	
CONSIDERATIONS	preferred given reliability and rapidity. The practice is to retest for a whole DST panel when an unexpected resistance is detected in the course of treatment. The recommendation should not be implemented in a manner whereby the FQ is added to a failing or inadequate regimen. Which fluoroquinolone to use? Prefer Lfx to Mfx so as to reserve Mfx/Gfx are reserved for M/XDR. Put in conditions on when Mfx/Gfx can substitute Lfx. The dose of Lfx will be in the 750-1gm.
MONITORING AND EVALUATION	Monitoring the acquisition of additional resistance adequately (not just use previous treatment as a proxy). Some of the RR-TB testing with Xpert, LPA and MGIT may be missed (e.g. one third of RR-TB strains in Swaziland) Reference Sanchez-Padilla E, Merker M, Beckert P, Jochims F, Dlamini T, Kahn P, Bonnet M, Niemann S. Detection of drug-resistant tuberculosis by Xpert MTB/RIF in Swaziland. New England Journal of Medicine. 2015 Mar 19;372(12):1181-2.
RESEARCH PRIORITIES	

6-3. Evidence-to-Decision Table - 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ

<table>
<tr><td colspan="2">Should 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S vs. 6 months or more of (H)REZ be used for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)?</td><td rowspan="6">BACKGROUND:
Tuberculosis (TB) remains a threat to global public health and the world's leading single infectious cause of death. In 2016, an estimated 10.4 million people developed TB and 1.7 million died from the disease. In the same year an estimated 600 000 TB patients developed rifampicin or multidrug-resistant TB (MDR/RR-TB), resistant to rifampicin and isoniazid – the two most important anti-TB medicines – and about 240 000 of these patients are estimated to have died. Patients with MDR/ RR-TB require second-line treatment regimens which are generally longer, more toxic and difficult to scale up than first-line regimens used in drug-susceptible TB. Apart from patients with MDR-TB, 8.5% of TB cases (7.3% in new and 14.0% in previously treated) worldwide are estimated to have isoniazid-resistant TB without MDR-TB (Hr-TB); this form of TB is associated with higher likelihood of treatment failure in patients who receive first-line regimens. The emergence of drug-resistant TB (DR-TB) has led to an increased demand for second-line anti-TB medicines in many parts of the world in recent years. WHO has released guideline for DR-TB treatment since 1997. Since 2006, WHO also included instructions on the treatment of Hr-TB in its implementation handbooks for the programmatic management of DR-TB. In October 2016, WHO updated its treatment guidelines for drug-resistant TB to incorporate the most recent evidence on the use of TB medicines, both old and new, and issued the first evidence-based recommendations for the use of a shorter MDR-TB regimen in selected patients. The Guideline Development Group which revised these guidelines also looked at the evidence for the treatment of Hr-TB. The evidence review could not trace cohorts or RCTs which included fluoroquinolones as part of standardized TB regimens designed primarily for Hr-TB. Fluoroquinolones, when used, were individualized and introduced at varying points in a patient's regimen when Hr-TB was detected. The GDG thus advised that no policy recommendation on the treatment of Hr-TB be formulated and that a meta-analysis is conducted using IPD from studies of subjects treated for Hr-TB using different regimens.

Through 2016, evidence reviewers from McGill University, Canada, coordinated the collection and assembling of an IPD for Hr-TB. By November 2016, data on 5,537 Hr-TB patients from 33 global datasets was obtained and an interim analysis for treatment outcome determinants was then conducted. The findings from this analysis suggest that an evidence-informed recommendation for the treatment of Hr-TB could now be formulated to replace previous guideline based largely on expert opinion.</td></tr>
<tr><td>POPULATION:</td><td>Adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded. The findings have been inferred primarily from the individual-patient data analysis of 2017.</td></tr>
<tr><td>INTERVENTION:</td><td>6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S</td></tr>
<tr><td>COMPARISON:</td><td>6 months or more of (H)REZ</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>Treatment success versus treatment failure/relapse for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ.; Treatment success versus failure/relapse: subgroup analysis in patients without isoniazid.; Death versus success/treatment failure/relapse in (H)REZ-S vs (H)REZ- using the same datasets used for success versus treatment failure/relapses analysis.; Death versus success/treatment failure/relapse in (H)REZ-S vs (H)REZ- using all datasets with these regimens.; Death versus success/treatment failure/relapse: subgroup analysis in patients without isoniazid- in all datasets with REZ and REZ-SM regimens.; Acquisition of resistance to rifampicin, for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ.;</td></tr>
<tr><td>SETTING:</td><td>Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis with 5417 observations from 33 datasets</td></tr>
<tr><td>PERSPECTIVE:</td><td>A GDG was convened on 27 April 2017 to consider the IPD meta-analysis and advise on changes to the current recommendations. The GDG meeting followed upon a three-day meeting on the critical concentrations, pharmacokinetics and pharmacodynamics of TB medicines, which will discuss "background questions" crucial to the implementation of the WHO DR-TB treatment guideline (e.g. dosage regimens in children and adults; therapeutic drug monitoring; substitution of medicines in the same class; formulations; use of medicines in the presence of resistance to them)</td></tr>
</table>

Assessment

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
● Yes
○ Varies
○ Don't know</td><td><u>References:</u>
1) Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2017 Feb;17(2):223–34.

2) Stagg HR, Harris RJ, Hatherell H-A, Obach D, Zhao H, Tsuchiya N, et al. What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax. 2016 Oct;71(10):940–9.</td><td>Isoniazid has been one of the backbone medicines for the management of TB patients. Resistance to isoniazid threatens the effectiveness of first-line TB treatment.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know</td><td rowspan="2">Analysis of mortality for (H)REZ-S vs (H)REZ, stratified for streptomycin resistance
<table><tr><th rowspan="2">Outcomes</th><th colspan="2">Anticipated absolute effects* (95% CI)</th><th rowspan="2">Difference</th><th rowspan="2">Relative effect (95% CI)</th></tr><tr><th>Risk with 6 months or more of (H)REZ</th><th>Risk with 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of Sm</th></tr><tr><td>Treatment success versus treatment failure/relapse for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of Sm compared to 6 months or more of (H)REZ.</td><td>928 per 1,000</td><td>371 per 1,000 (186 to 650)</td><td>557 fewer per 1,000 (743 fewer to 278 fewer)</td><td>adjusted OR 0.4 (0.2 to 0.7)[a]</td></tr><tr><td>Treatment success versus failure/relapse: subgroup analysis in patients without isoniazid.</td><td>903 per 1,000</td><td>451 per 1,000 (181 to 1,083)</td><td>451 fewer per 1,000 (722 fewer to 181 more)</td><td>adjusted OR 0.5 (0.2 to 1.2)[b]</td></tr><tr><td>Death versus success/treatment failure/relapse in (H)REZ-Sm vs (H)REZ.[c]</td><td>46 per 1,000</td><td>41 per 1,000 (27 to 59)</td><td>5 fewer per 1,000 (18 fewer to 14 more)</td><td>adjusted OR 0.9 (0.6 to 1.3)[d]</td></tr><tr><td>Death versus success/treatment failure/relapse: subgroup analysis in patients without isoniazid.[e]</td><td>39 per 1,000</td><td>47 per 1,000 (16 to 159)</td><td>8 more per 1,000 (23 fewer to 121 more)</td><td>adjusted OR 1.2 (0.4 to 4.1)[f]</td></tr><tr><td>Acquisition of resistance to rifampicin, for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of Sm compared to 6 months or more of (H)REZ.[g]</td><td>38 per 1,000</td><td>0 per 1,000 (0 to 0)</td><td>38 fewer per 1,000 (38 fewer to 38 fewer)</td><td>not estimable</td></tr></table></td><td>The only benefit that can be expected is in certain subgroups, such as patients with polydrug resistant TB (limited data available in the IPD - not shown - could not support this effect). Treatment success appears to be worse in patients receiving streptomycin although this is likely to be partly confounded by indication. Fluoroquinolones could be used in the place of streptomycin; other second-line TB medicines could in theory be used too but there are no data to support this. Any expected benefit is likely to be overshadowed by the inconvenience of repeated painful injections and toxicity.</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know</td><td>The addition of streptomycin is likely to increase the frequency of serious AEs and will also have an effect on overall treatment adherence.</td></tr>
</table>

JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		a. Propensity scores odd ratio (OR) adjusted for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used. Poly-resistance was 47% in the group taking 6 or more(H)RE 3Z 3SM as compared with <1% in the group taking 6 or more (H) REZ.) Adjusted OR was calculated on 296 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope. b. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used. Adjusted OR was calculated on 105 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs. c. Mortality analysis cannot take into account duration of specific regimens because of death truncated duration (outcome determined the independent variable of duration). Therefore the mortality analysis included all cases who received regimens with (H)REZ+SM vs (H)REZ regardless of duration. Hence the observations contributing to mortality (n=3026) analysis are different from observations included in analysis of treatment success (n=1675), even if analysis was done in the same datasets (n=23)- for mortality we consider all duration of regimens (and not only 6 or more (H)RE, up to 3m of Z and up to 3 months of SM, as we do for the success analysis), therefore we have more patients. d. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 756 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs. e. Mortality analysis cannot take into account duration of specific regimens because of death truncated duration (outcome determined the independent variable of duration). Therefore the mortality analysis included all cases who received regimens with REZ+SM vs REZ regardless of duration. Hence the observations contributing to this mortality analysis are different from observations included in analysis of treatment success for 6 months RE, up to 3 months of Z and up to 3 months of SM versus 6 months or more of REZ. f. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 133 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs. g. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred but not analysed).	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	Only observational data have been included in the IPD	The implication of low or very low certainty in the estimates of effect is that the quality of the evidence is poor and that further research is very likely to have an important impact on the confidence in the estimates and is likely to change the estimates.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	All patients are likely to value the outcomes of successful treatment, death, acquired resistance and toxicity as critical. It is also likely that many patients would prefer to avoid an injectable medicine unless this is absolutely necessary.

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	The IPD meta-analysis did not analyse the adverse events because of heterogeneity in the way the AE data were collected by the different studies.	The balance may tip more in favour of the intervention in patients in whom streptomycin may be expected to be an important component of the regimen (e.g. polydrug resistance) but there is uncertainty in the data.
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 cost-effectiveness analysis done. The price for 100 vials of streptomycin 1g powder for injection on the Global Drug Facility catalogue is USD64 and water for injection and syringes would add about USD15 more (15 December 2017; http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=623). Three months use in an average patient may thus be expected to add a cost of USD45 to the price of HREZ (six months of HREZ FDC by itself would cost another USD45)	The addition of the injectable would double the price of the regimen although the overall costs in medicines alone would still be relatively low and affordable (GDF prices). However, this depends on the country and setting given that in some places streptomycin is expensive. Sometimes patients may have to pay for certain medicines out of their own pockets. Indirect costs are estimated to be much greater than the direct cost of medicines. Compared with the price of medicines, the service and patient costs are expected to dominate the overall implementation costs. This is particularly the case for streptomycin which is the only injectable agent in the regimen, requiring skilled staff to ensure safe administration. Making these staff available in a decentralised setting and ensuring that there is adequate monitoring and management of adverse reactions incurs additional resource mobilisation.
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 cost-effectiveness analysis done.	

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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 included studies.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The availability of the drug for the patients who need it may vary. The administration issues are likely to be the main barrier because of lack of skills to administer the injectable agent on a daily basis in a decentralised setting. Availability may thus be influenced by variations in resource among the patient population and would thus be expected to lower 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.	Most patients are expected to prefer not to have the injectable agent (although unsubstantiated beliefs in the therapeutic superiority of parenteral agents may prevail among certain patients and health care staff).
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		Streptomycin and HREZ have been in use worldwide in the treatment of TB for many years. In recent decades, streptomycin has been reserved for treatment of previously treated patients, and, more recently, only for multidrug-resistant TB patients in whom other injectable agents cannot be used. This is making access to it less widespread than before. Reintroducing the drug now for broader use is likely to challenge the logistics of many programmes. Testing for susceptibility to streptomycin is still not considered a reliable way to exclude *in vivo* resistance even in well-performing diagnostic laboratories.

SUMMARY OF JUDGEMENTS							
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

<table>
<tr><td colspan="6">CONCLUSIONS
Should 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S vs. 6 months or more of (H)REZ be used for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)?</td></tr>
<tr><td>TYPE OF RECOMMENDATION</td><td>Strong recommendation against the intervention
○</td><td>Conditional recommendation against the intervention
●</td><td>Conditional recommendation for either the intervention or the comparison
○</td><td>Conditional recommendation for the intervention
○</td><td>Strong recommendation for the intervention
○</td></tr>
<tr><td>RECOMMENDATION</td><td colspan="5">In tuberculosis patients (adults and children) with isoniazid-resistant, rifampicin-susceptible strains, it is suggested not to add streptomycin to the treatment regimen [very low certainty in the evidence]</td></tr>
<tr><td>JUSTIFICATION</td><td colspan="5">Overall justification
Available data do not support the use of streptomycin in regimens for patients with isoniazid-resistant TB.

Detailed justification
Problem
Patients with isoniazid polydrug resistance may be more likely to sustain a treatment failure if treated with HRZE. Adding a fluoroquinolone by itself when Hr-TB is detected after the start of HREZ may violate the principle of adding a single drug to a "failing" regimen. In many settings, resistance to pyrazinamide may be high and therefore an additional drug could protect the fluoroquinolone
Desirable Effects
There is no evidence or low certainty in available evidence for a substantial benefit of adding streptomycin to regimens composed of rifampicin, pyrazinamide, ethambutol and levofloxacin (plus or minus isoniazid)
Undesirable Effects
Although not quantified in this analysis, the likelihood of increasing harms when adding streptomycin is high. The certainty of this relies on existing experience about this from patients who have been administered the medicine as part of TB treatment</td></tr>
<tr><td>SUBGROUP CONSIDERATIONS</td><td colspan="5">Polydrug resistance and other options (no evidence base); the benefit is marginal and so it is not recommended. Streptomycin is contraindicated in pregnancy and in patients who develop SAE (eg ototoxicity, nephrotoxicity)</td></tr>
<tr><td>IMPLEMENTATION CONSIDERATIONS</td><td colspan="5">Not applicable</td></tr>
<tr><td>MONITORING AND EVALUATION</td><td colspan="5">The likelihood of resistance to streptomycin reducing further the possible beneficial effect.
The likelihood of generating resistance to streptomycin and thus compromising its potential value in second-line regimens</td></tr>
<tr><td>RESEARCH PRIORITIES</td><td colspan="5">The benefit of second-line medicines other than fluoroquinolones and streptomycin in patients with isoniazid-resistant TB
Alternatives to injection in the effective delivery of aminoglycosides</td></tr>
</table>