Interpreting evidence on deprescribing in the context of guideline evidence synthesis frameworks: GRADE and deprescribing

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HUMANITAS UNIVERSITY

WHO Collaborating Center for Evidence-based Decision-making in Health

GRADE working group

Disclosures

- No direct financial conflicts
- GRADE Working Group Chair
  - GRADEpro GRADE's official app
- Guidelines International Network – chair of the board
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- Views expressed my own

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The way I understand deprescribing

Deprescribing is the planned and supervised process of dose reduction or stopping of medication that might be causing harm, or no longer be of benefit. Deprescribing is part of good prescribing – backing off when doses are too high, or stopping medications that are no longer needed (deprescribing.org).

I will take both a guideline developer and user perspective (as a clinician)

If you are a believer in evidence-based recommendations…

… you will be influenced by the evidence that support them.

Recommendation of lower versus higher blood pressure targets in the elderly

- Reduce doses of existing drugs or eliminate antihypertensive (perhaps together with other drugs) if higher values are the target or "OK"

It's a balance issue (of desirable and undesirable consequences)

- **Balance may be in favour of less (medication)**
- **Or of removing an intervention**

this is a general issue and not restricted to this example, similar to when multiple conditions are treated: polypharmacy is an issue of balance of desirable and undesirable consequences

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What drives this balance

Net harm or net benefit (a combination of desirable and undesirable health effects comprised of the absolute risk difference an intervention achieves and how important the affected outcomes or change in outcomes are)

10% increase in harm of high importance (disutility 0.8)

10% increase in benefit of low importance (utility change 0.2)

But there are nearly never only two outcomes (makes it more complicated but doable): stroke, MI, falls, libido, death, headache, quality of life

Values already incorporated here on a recommendation level. But may need to do **shared decision-making**.

Are we sure?

ACP Recommendations	Strength of Recommendation	Overall Certainty of Evidence
ACP **recommends** adding an SGLT-2 inhibitor or a GLP-1 agonist to metformin and lifestyle modifications in adults with type 2 diabetes and inadequate glycemic control (strong recommendation; high-certainty evidence). • Use an SGLT-2 inhibitor to reduce the risk for all-cause mortality, major adverse cardiovascular events (MACE), progression of chronic kidney disease (CKD), and hospitalization due to congestive heart failure (CHF). • Use a GLP-1 agonist to reduce the risk for all-cause mortality, MACE, and stroke.	Strong	High CoE
ACP **recommends against** adding a DPP-4 inhibitor to metformin and lifestyle modifications in adults with type 2 diabetes and inadequate glycemic control to reduce morbidity and all-cause mortality (strong recommendation; high-certainty evidence).	Strong	High CoE

More desirable than undesirable consequences?

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GRADE is a transparent and structured approach that helps us judge how certain we are about a body of evidence by addressing questions such as:

- What are the limitations of the studies?
- Are results consistent?
- Are results precise?
- How directly the evidence apply to the population/setting, interventions, and outcomes?
- Is this all the research that exists?
- Any issues that increase our confidence in the results (e.g., large effects, dose response)?

Evidence

But evidence is not enough. GRADE also offers a framework to help reaching decisions and making recommendations, by evaluating:

What is the net balance between benefits & harms? Including:

- Priority of the problem
- Magnitude of effects
- The value people place on outcomes

Benefits vs harms

Equity?

Decision Recommendation

Feasible?

Resource$

Acceptable?

Also, by addressing cost-effectiveness, and issues of equity, acceptability, and feasibility

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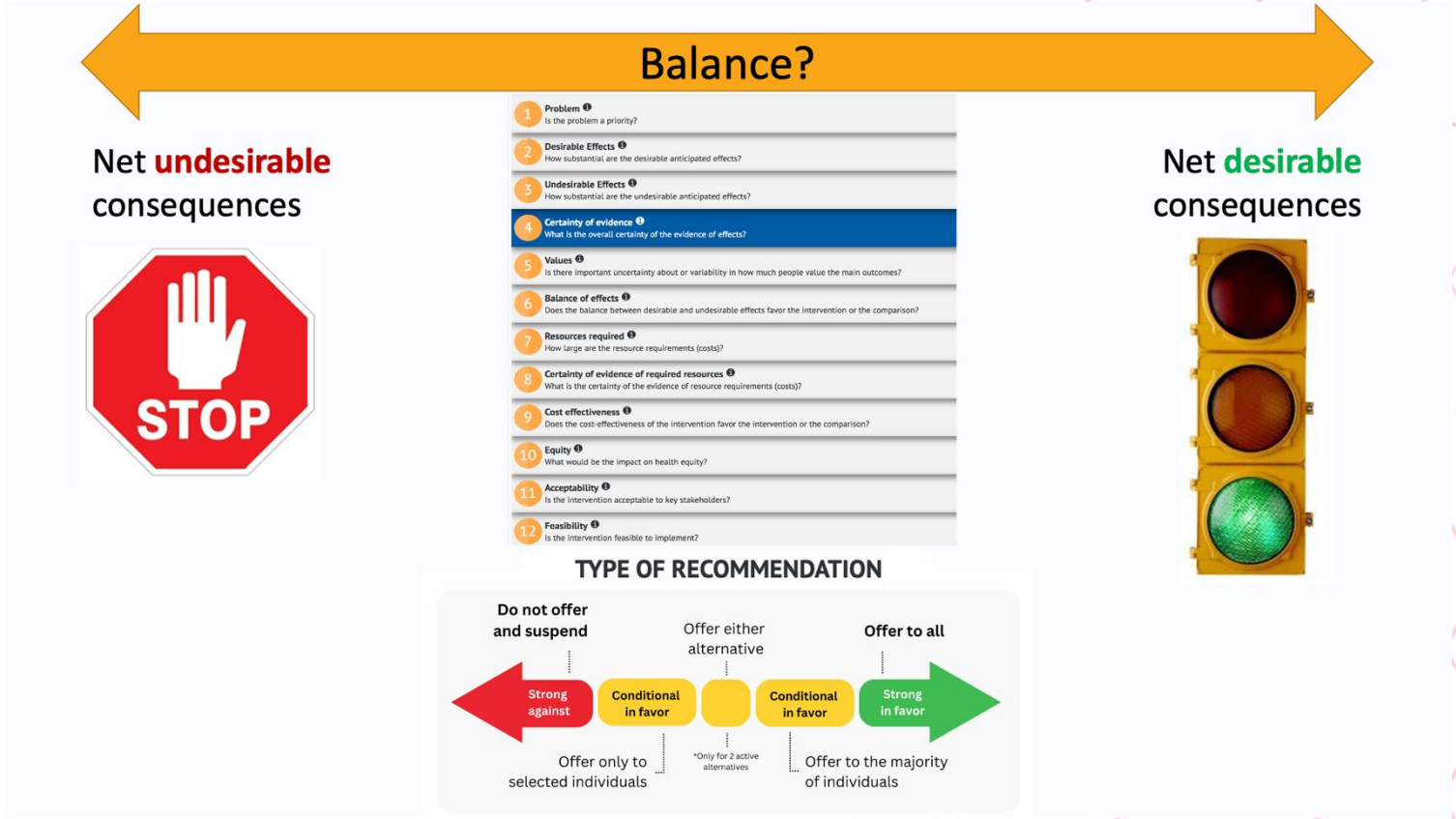
If true me as a straightforward "negative recommendation" issue

With my perspective of the guideline developer and user:

If the guideline recommends a higher blood pressure target it should be because of a presumed net balance that favours higher values, less medication, less burden etc, etc.

A good guideline recommendation explicitly describes all of that based on evidence reviews for

- Risk difference of all important outcomes
- Values of all important outcomes
- Cost
- Equity
- Acceptability
- Feasibility



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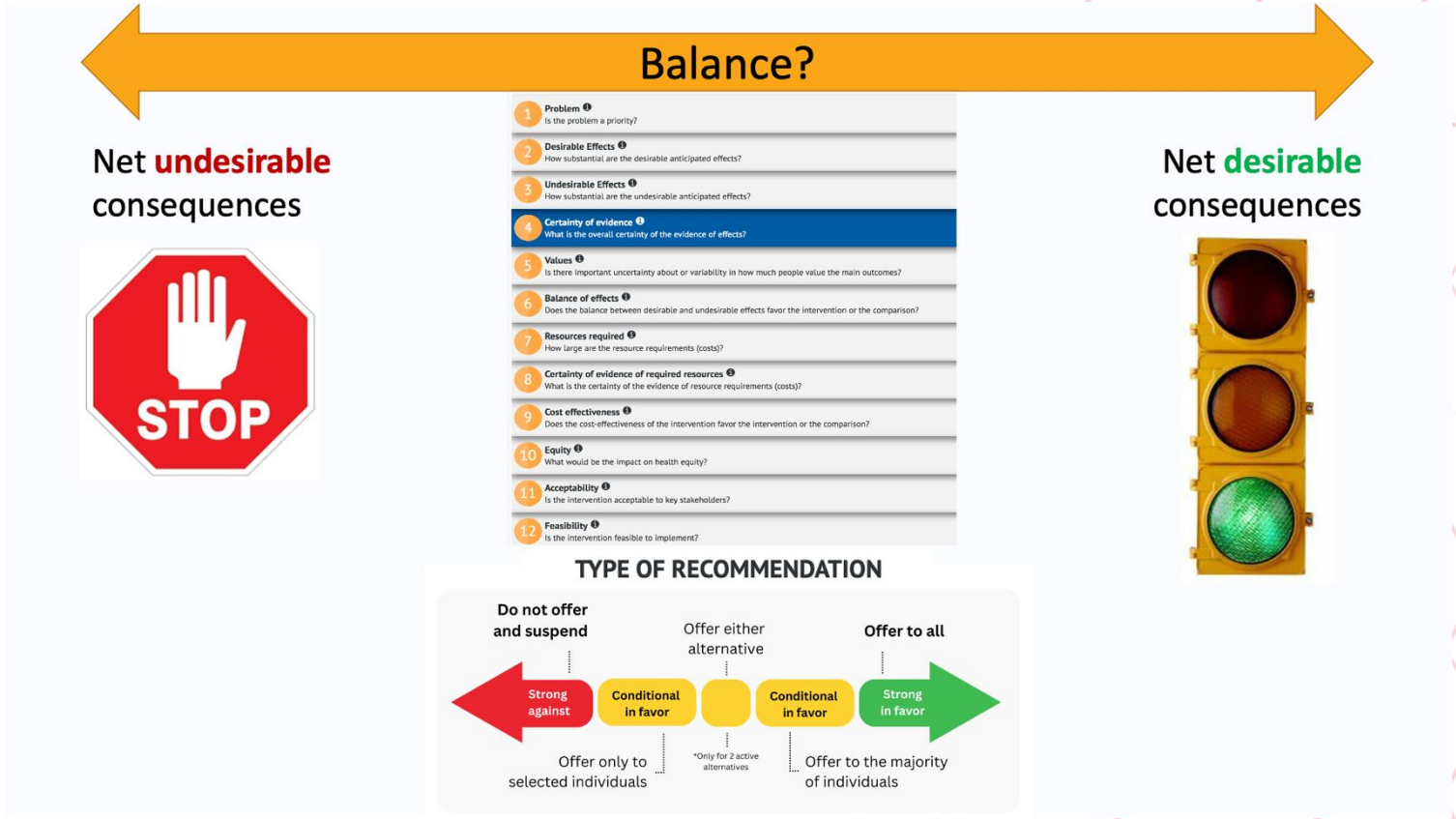

What's missing for deprescribing (using common criteria) that is not considered in a typical guideline recommendation?

Comprehensive medication review - obvious

Prioritization of medicines for discontinuation (there are frameworks for prioritization based on which outcomes matter most and what baseline risk is highest or lowest – again values and still net health benefits or harms) but challenging

Monitoring and follow-up (ongoing assessment, still balance of benefits and harms) – actually included in a typical EtD

How to interpret that recommendation about DPP-4 inhibitor in the context of people already in it

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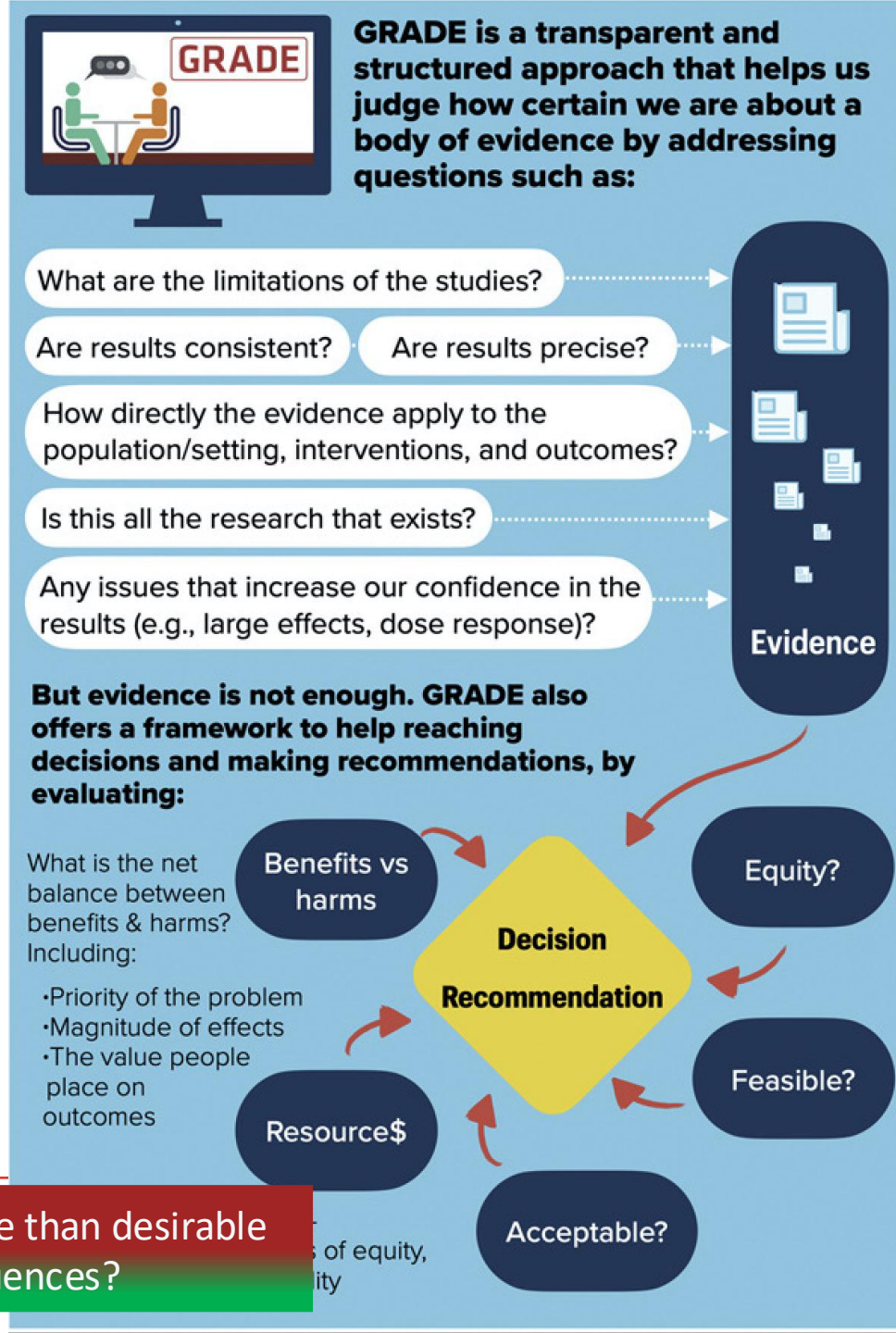

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Another quick example

END TB

World Health Organization

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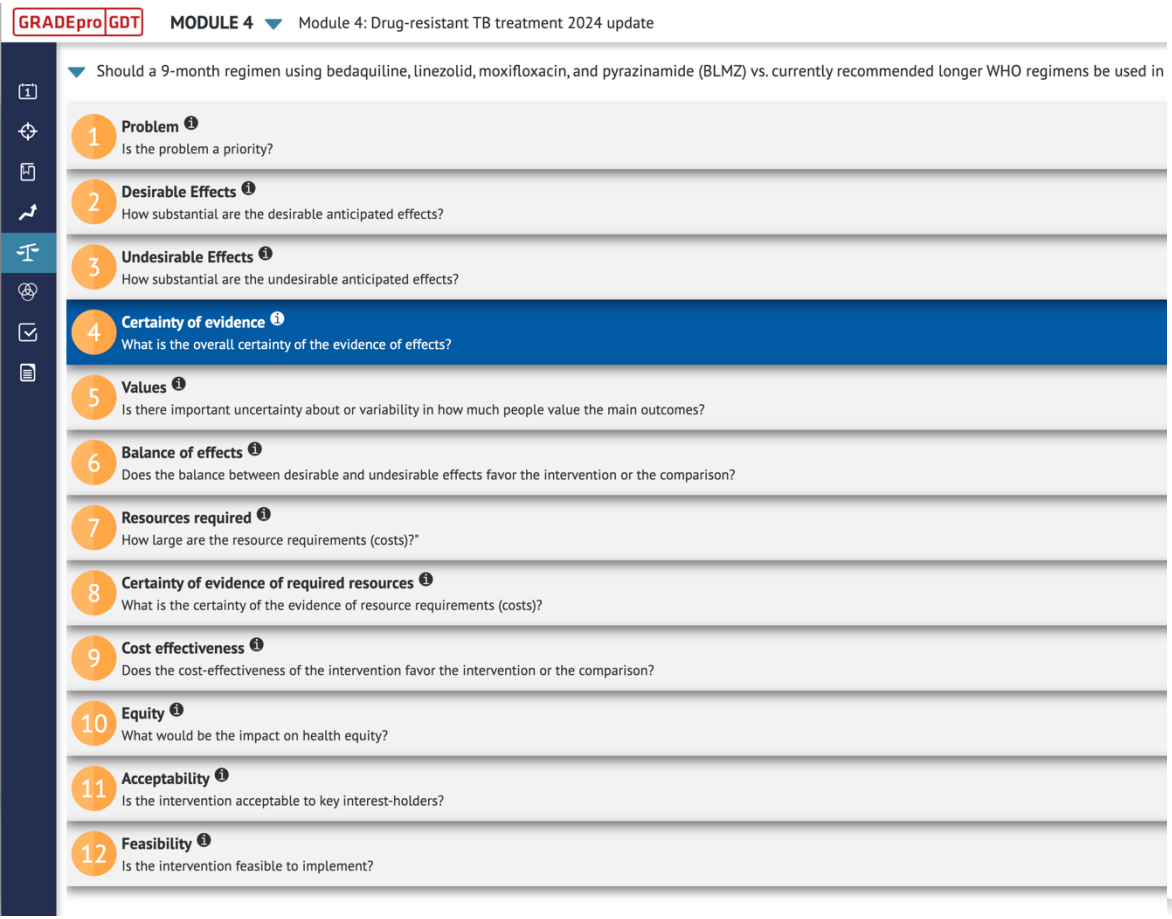
Longer versus shorter regimens for multi-drug resistant tuberculosis

3,500 deaths a day…., over 1,000,000 a year

Shorter regimens with less long terms side effects versus longer with perhaps better cure but more side effects

Many patients also live with HIV

Deprescribing is shortening the medication, perhaps fewer



CRITERIA	SUMMARY OF JUDGEMENTS			
PROBLEM	No	Probably no	Probably yes	**Yes**
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High
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
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High
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
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes
FEASIBILITY	No	Probably no	Probably yes	**Yes**

Shorter regimen (9 months) is better than 18 months – on balance (deprescribing)

Less sustained treatment success but less adverse events and less loss to follow up

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Recommendation*

WHO suggests using BLMZ over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.
(Conditional recommendation, very low certainty of evidence)

9 months versus more than 18 months

Remarks

1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.
2. This recommendation applies to the following:
a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.
b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.
d. People with MDR/RR-TB and less than 1 month of previous exposure to any of the component medicines of the regimen (apart from pyrazinamide and fluoroquinolones). When exposure is greater than 1 month, these patients may still receive one of the regimens if resistance to the specific medicines with such exposure has been ruled out.
e. Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

+ Add remarks

Add related evidence | Add related recommendations | Add recommendation metadata

Justification

The GDG issued a conditional recommendation based on very low certainty of evidence (due to imprecision in the effect estimates) based on a moderate benefit, with trivial harms, and cost savings. The GDG also highlighted the importance of a lower pill burden with the 9-month regimen.

Implementation considerations

Patient selection and decisions to start the 9-month regimens

sed patients should be made through an informed decision-making process that includes patient preference and clinical judgement, and DST results available before the

treated with bedaquiline, delamanid, or linezolid for more than a month and have no fluoroquinolone resistance, a 9-month regimen is generally preferred over longer, 18-month options. Priority is given to modified 9-month regimens, with the choice guided by the patient's eligibility and DST results to ensure optimal safety and efficacy.
If none of the modified 9-month regimens are to be used, the alternative choice is 9-month regimens with either ethionamide or linezolid. Based on the available evidence, this regimen can be used in patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin) in whom resistance to fluoroquinolones has been ruled out, in the following situations: no exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed); or no extensive TB disease and no severe extrapulmonary TB.

Drug susceptibility testing

DST for bedaquiline and linezolid is an important implementation consideration that will need to be enhanced in many countries, given the increasing use of these medicines in all regimens for MDR/RR-TB and the possible further inclusion of new medicines in MDR-TB treatment regimens. The implementation of these recommendations must be accompanied by continued efforts to increase access to DST for all medicines for which reliable methods are currently available, and for the development and roll-out of DST methods for newer medicines.
Access to WHO-recommended rapid DST is essential, especially for detecting resistance to rifampicin and fluoroquinolones, before starting the 9-month regimens. Baseline DST will confirm eligibility for different regimen options; therefore, the establishment and strengthening of DST services is a vital consideration for implementation. The DST methods for identifying resistance to bedaquiline and linezolid have been developed on available phenotypic platforms and need to be implemented in all settings where these medicines are being used. Resistance to other anti-TB drugs should be monitored in accordance with WHO recommendations.
One of the exclusion criteria for all shorter regimens in the datasets from South Africa was mutations in both *inh*A promoter and *kat*G regions, confirmed using a line probe assay (LPA). This means that patients with only *inh*A or only *kat*G mutations were included. A first-line LPA (MTBDRplus) and Xpert MTB/XDR cartridge can determine mutations in the *inh*A promoter or *kat*G regions; both mutations confer resistance to isoniazid, with the resistance being low level when *inh*A mutations alone are present, or high level with *kat*G gene mutations alone or *inh*A promoter and *kat*G gene mutations combined. Mutations at the *inh*A promoter are also associated with resistance to ethionamide and prothionamide. The presence of mutations in both the *inh*A promoter and *kat*G suggests that isoniazid at high dose and thioamides are not effective, and that the 9-month regimen may not therefore be used. In the absence of information on mutation patterns for an individual patient, the decision can be informed by knowledge of the frequency of the concurrent occurrence of both mutations, obtained from drug-resistance surveillance *(61)*. Phenotypic DST for some medicines included in the regimen (e.g. ethambutol and ethionamide) is not considered reliable and reproducible; therefore, this testing should be employed with caution to inform the use of this regimen.[1]
Currently, there is limited capacity globally to carry out DST for bedaquiline; however, laboratory capacity should be strengthened in this area as new medicines and regimens begin to be used more widely. National and reference laboratories will need to have the relevant reagents available to enable DST to be carried out and will need data on the MIC distribution of all *M. tuberculosis* lineages that are circulating globally. The WHO TB SRL Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in 2017 established critical concentrations for susceptibility testing for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid *(41)*.

Selection of fluoroquinolones

Selection of fluoroquinolones may take into account the evidence from South Africa available for the review – 83% of patients analysed using the 2017 dataset received levofloxacin and the rest received moxifloxacin at standard dose (400 mg daily). Both levofloxacin and moxifloxacin have shown similar efficacy for treating DR-TB. The choice between levofloxacin and moxifloxacin was guided by the potential risk of cumulative cardiotoxicity, using moxifloxacin in a shorter regimen with injectables and levofloxacin in an all-oral shorter regimen. Levofloxacin is often preferred because of moxifloxacin's slightly higher potential for cardiotoxicity; however, levofloxacin has been associated with musculoskeletal disorders in paediatric populations. Therefore[SS1] [FM2] , irrespective of the choice of fluoroquinolone, NTPs need to implement aDSM in all patients enrolled on treatment of DR-TB *(51, 63)*.

Justification

The GDG issued a conditional recommendation, rather than a strong recommendation, based on the very low certainty evidence (due to imprecision in the absolute effect estimates) that the balance of effects probably favours the intervention, as well as the resource considerations. While the included trial was designed as a non-inferiority trial the GDG considered the magnitude of effects in relation to specific thresholds the group agreed on for the desirable and undesirable effects. There was additionally a lack of information on the value that people place on outcomes associated with the interventions.

Subgroup considerations

Based on research evidence and expert experience, the panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were PLHIV, children, pregnant women, breastfeeding women, patients with extrapulmonary TB and patients with extensive TB disease. The recent new recommendation for use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(29)*. The panel noted specific considerations for the subpopulations listed below.

People living with HIV

The data evaluated corresponded to a setting with a high prevalence of HIV; of particular significance was that most PLHIV (>90%) who started the 9-month regimens were receiving ART. In view of the treatment outcomes described in the analysis, there were no grounds to believe that the regimen would perform any differently in PLHIV. It is necessary to consider significant clinical interactions that may increase bedaquiline exposure or that of other agents with potential for cardiotoxicity when these are co-administered with antiretroviral drugs. However, because the data evaluated did not include information on changes to the regimen as a result of management of adverse drug reactions, or complications from drug–drug interactions, the GDG reiterated that it is worth paying attention to any potential drug–drug interactions or overlapping drug toxicities that may not have been captured. For example, bedaquiline concentrations can be reduced by efavirenz (these drugs should not be co-administered) or increased by boosted protease inhibitors (resulting in a need for greater vigilance in monitoring for drug-related QT effects) *(55-57)*. Neuropathy, liver enzyme elevations and CNS side-effects can be attributed to HIV or TB drugs or their interactions *(58)*.

Children and adolescents

The datasets included only small numbers of people aged below 15 years (n=69), and thus did not allow for reliable comparisons in both datasets from South Africa (n=69 and n=7) and in the 2021 IPD (n=7). However, analysis in the subgroup aged below 15 years showed a relative increase in treatment success of 42% (aRR=1.42, 95% CI: 0.7 to 2.89) in sub-PICO 1.1 and a 5% relative reduction (RR=0.95, 95% CI: 0.78 to 1.15) in sub-PICO 1.2. Although a small number of participants were aged between 10 and 15 years (19/50, 38% in the intervention group, and 75/162, 46% in the comparator group), extrapolation of the findings to children was deemed reasonable for efficacy because components of the regimen had been used safely in children based on other available data regarding linezolid use in children. This extrapolation was considered applicable to children of all ages, taking into account the recommendation for use of bedaquiline in children aged below 6 years *(29)*.

Pregnant and breastfeeding women

In the research studies analysed, pregnant women were not identified, and subgroup data were unavailable. Ethionamide is usually contraindicated in pregnancy (because animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans), and this is the main reason that the 9-month regimen has not been recommended for this subgroup in the past. There is experience in using linezolid during pregnancy *(59, 60)*. For pregnant and breastfeeding women, it is therefore recom

Extrapulmonary TB

A subgr pulmonary TB were included in the research studies (81 in the regimen containing linezolid and 23 in the regim iew of the unavailability of evidence on surrogates for severity or extent of dise

Monitoring and evaluation

The importance of monitoring for drug-drug interactions with other medications was noted by th

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Research priorities

Summary

Challenges the same as for other guideline recommendations

Full EtD will help with making decisions and shared decision-making

Evidence will never be perfect and will have to be generated **BUT FOR ALL** EtD criteria and all outcomes (can never be single outcome driven)

Primary issue is one with implementation and related monitoring, not with methods