pharmacokinetic and pharmacodynamic properties with thrice-weekly dosing, especially after conversion of cultures to negative, decreasing healthcare system demands and the requirement for daily injections (16, 177). Intramuscular injections are painful, and 6 months of injections can be traumatic, especially to younger patients. Patients' values may differ sharply from providers in this respect and should be considered when determining whether to use injectable agents.

Conclusions. In our PS-matched IPDMA, the use of amikacin and streptomycin when the patient's isolate was susceptible to these drugs was associated with an increase in treatment success when compared with the control group not receiving these injectables. However, because of their toxicity and modest efficacy compared with other drugs, which also are less toxic, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs. In our analyses, amikacin and streptomycin had similar aORs for treatment success in a minority of patients with fluoroquinolone resistance. Kanamycin and capreomycin were ineffective. We recommend against using kanamycin or capreomycin. As is the case for adults, the use of amikacin and streptomycin for children should also be reserved to when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs.

Research needs. *N*-acetylcysteine, a thiol-containing antioxidant, may limit the severity and irreversibility of aminoglycoside-induced ototoxicity (187, 188), warranting additional research into this and other otoprotective measures that may improve the balance of benefits and harms for using these injectable agents.

Linezolid

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by preventing the fusion of 30S and 50S ribosomal subunits (189). It also binds to human mitochondria and inhibits protein synthesis, which is the mechanism of toxicity in clinical use (190, 191). Linezolid was initially used off-label in the absence of consistent scientific evidence as part of the regimen for difficult-to-treat cases of MDR- and XDR-TB (192). The first large retrospective observational study suggested linezolid was effective, but with frequent and often severe adverse events (192). The same study suggested, for the first time, that reducing the daily dose from 1,200 mg to 600 mg per day might be associated with fewer adverse events and improved tolerability. Several systematic reviews, IPDMAs, and one controlled clinical trial have been published on linezolid for treatment of MDR-TB (87, 193–196). The clinical trial confirmed previous observational findings and, in particular, the effectiveness of linezolid and its potential toxicity (195). A meta-analysis with 121 cases of patients with MDR-TB from 11 countries, treated with linezolid, confirmed linezolid effectiveness (culture conversion, 93.5%; treatment success, 81.8%) and that the 600-mg daily dose was safer than the 1,200-mg dose (46.7% adverse events vs. 74.5%, respectively) without lowering its effectiveness (196). The clinical trial confirmed the efficacy, safety, and tolerability of linezolid in patients with XDR-TB (194). There are insufficient data regarding the effectiveness of initiating treatment with doses $<$600 mg daily to recommend lower doses. Recently, the importance of therapeutic drug monitoring to reduce adverse events potentially due to linezolid has been emphasized (197, 198).

PICO Question 14—Linezolid: In patients with MDR-TB, are outcomes safely improved when regimens include linezolid compared with regimens that do not include linezolid?

Recommendation 14: We suggest including linezolid in a regimen for the treatment of patients with MDR-TB (conditional recommendation, very low certainty in the evidence). This is a conditional recommendation despite linezolid-containing regimens showing large reduction in mortality and improved treatment success, similar to bedaquiline and later-generation fluoroquinolones, because linezolid had more adverse effects and the balance of benefits and harms was less favorable compared with those drugs.

Summary of the evidence. Linezolid was used in regimens for MDR- and XDR-TB across 38 studies (3). The initial dose of linezolid was 1,200 mg/d for 91 patients in five studies, 600 mg/d for 784 patients in 28 studies, and 300 mg/d for 99 patients in five studies (3). Procedures and methodology to assemble and rank the certainty in the evidence are reported in Appendix A, with evidence profiles for PICO questions reported in Appendix B.

Benefits. In our PS-matched IPDMA, patients who received linezolid-containing regimens were more likely to achieve treatment success (aOR, 3.4; 95% CI, 2.6–4.5) and to have a lower rate of death (aOR, 0.3; 95% CI, 0.2–0.3) than those who did not receive linezolid. The effect on treatment success was more pronounced when studies from only high-income countries were included (aOR, 3.9; 95% CI, 2.6–5.8). The greatest impact was found in patients with XDR-TB, where the aOR for successful treatment versus failure or relapse was 6.3 (95% CI, 3.9–10.1) and the aOR for death was 0.1 (95% CI, 0.1–0.2). When PS-matched pairs analyses were performed comparing the effects of bedaquiline and linezolid with those of no bedaquiline or linezolid, the combination of bedaquiline and linezolid was associated with an aOR of 2.7 (95% CI, 1.5–4.9) for success versus failure/relapse, and of 0.3 (95% CI, 0.2–0.4) for death versus success/failure/relapse. The efficacy of linezolid in children with TB has been shown in two studies of children $<$18 years of age, albeit with few patients (199, 200).

Harms. Adverse effects associated with linezolid in patients with TB include neurotoxicity (i.e., peripheral neuropathy and optic neuritis), myelosuppression, hyperlactatemia, and diarrhea, all of which are presumably secondary to the inhibition of mitochondrial protein synthesis (190, 201). A published systematic review of 12 studies conducted in 11 countries globally reported an adverse event rate of 58.9% (hematological, neurological, and gastrointestinal), predominantly noted in individuals treated with a dosages $>$600 mg/d (196). Hematological toxicity can occur quickly after starting treatment and can involve any cell line. Neurotoxicity, including optic neuritis and peripheral neuropathy, occur later, usually after 12 to 20 weeks of treatment. Toxicity has been associated with trough levels of $>$2.0