cross-resistance between isoniazid and ethionamide/prothionamide (153).

***Conclusions.*** When the individualized treatment regimen for patients with MDR-TB contains newer-generation, more-effective drugs, the addition of ethionamide/prothionamide does not appear to provide benefit.

***Research needs.*** Research efforts are underway to identify potential boosters of potency for ethionamide, which, if successful when coadministered, may result in improved therapeutic index and overall better risk-benefit ratio for use (154).

### Fluoroquinolones: Levofloxacin, Moxifloxacin, Ciprofloxacin, and Ofloxacin

The fluoroquinolones are a family of chemically related drugs characterized by a common core dual-ring structure (155). Ofloxacin, then levofloxacin, then moxifloxacin sequentially improved on earlier generation's spectrum of activity, including mycobacteria, and their antimycobacterial action increased as evidenced by lower minimum inhibitory concentrations (MICs) and increasing success in clinical use (156, 157). Physicians began using these drugs to treat MDR-TB on the basis of *in vitro* data, with subsequent case series and observational studies showing efficacy (158), although none of the fluoroquinolones are currently indicated by regulatory authorities for the treatment of TB. In general, these drugs are well absorbed orally, have favorable pharmacological profiles for once-daily dosing, are generally well tolerated, and now are available in generic formulations (155).

***Summary of the evidence.*** 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. In our PS-matched IPDMA, ofloxacin was used most commonly ($n = 4{,}020$), followed by levofloxacin ($n = 3{,}872$), moxifloxacin ($n = 2{,}132$), and ciprofloxacin ($n = 431$); 734 patients did not receive a fluoroquinolone, the comparison group for subsequent analyses, and 828 patients received two or more quinolones and were excluded (3). The groups were similar in age, sex, proportion AFB smear positive, proportion with cavitary disease on chest radiograph, and prior treatment with first-line drugs. However, the no-quinolone group had substantially more HIV coinfection (44% vs. 13–28%; proportion with HIV coinfection across different quinolones), more past treatment with second-line drugs (52% vs. 8–25%), more quinolone resistance (86% vs. 6–33%), more second line injectables resistance (74% vs.12–34%), and more XDR TB (73% vs. 4–19%). In terms of treatment, the no-fluoroquinolone group received less amikacin (7% vs. 18–43%) and kanamycin (13% vs, 26–65%) and more capreomycin (66% vs. 6–34%). Therefore, the median number of effective drugs (intensive phase) was lower in the no-fluoroquinolone group (2.1) than in the other groups (3.3–4.0). Thus, treatment success was lower in the no-fluoroquinolone group (35% vs. 55–68%) and failure/relapse was higher than but not greatly different from the others (13% vs. 2–10%); mortality, however, was much higher (40% vs. 11–15%).

***Benefits.*** In our PS-matched IPDMA, among patients with susceptible isolates, levofloxacin-containing regimens compared with no quinolone were associated with significantly more treatment successes (aOR, 4.2; 95% CI, 3.3–5.4) and significantly fewer deaths (aOR, 0.6; 95% CI, 0.5–0.7). Moxifloxacin, compared with no quinolone, was also associated with significantly more treatment successes (aOR, 3.8; 95% CI, 2.8–5.2) and significantly fewer deaths (aOR, 0.5; 95% CI, 0.4–0.6). In the subgroup with resistance to an injectable drug(s), levofloxacin or moxifloxacin were associated with a significant improvement in treatment success (aOR, 1.8; 95% CI, 1.2–2.8) and reduction in death (aOR, 0.6; 95% CI, 0.4–0.8), although the corresponding adjusted risk differences were not statistically significant. In pairwise comparisons, both levofloxacin and moxifloxacin were associated with significantly better treatment outcomes than ofloxacin. The aORs of death were lower for the two later-generation quinolones when compared with ofloxacin (levofloxacin: aOR, 0.8; 95% CI, 0.6–0.9; moxifloxacin: aOR, 0.8; 95% CI, 0.6–1.0) (data not shown). Ofloxacin and ciprofloxacin are considered inferior quinolones against *M. tuberculosis* (144, 149, 159, 160). Levofloxacin and moxifloxacin did not differ significantly from each other.

In a recent IPDMA describing treatment outcomes in children treated for MDR-TB (113), new and repurposed TB drugs, including late-generation fluoroquinolones, were not used enough to adequately evaluate efficacy, but most experts and emerging evidence suggest that the efficacy of fluoroquinolones noted in adults should be similar in children (83, 161).

***Harms.*** In our PS-matched IPDMA, grade 3 adverse events were recorded systematically in a subset of 1,962 patients from a cohort study of MDR-TB at 27 sites in nine countries. Permanent discontinuation of fluoroquinolones due to adverse events was uncommon. Among 150 patients treated with levofloxacin, the drug was stopped permanently because of adverse events in 6 (4.0%). Among 398 patients treated with moxifloxacin, the drug was stopped permanently in 14 (3.5%) patients. Among 1,167 patients treated with ofloxacin, the drug was stopped permanently in 56 (4.8%) patients. An analysis of 56 clinical trials comparing quinolones against placebo or against other antimicrobial agents found generally similar adverse event profiles (3). Seven studies reported more frequent adverse events and six studies reported fewer adverse events in fluoroquinolone-treated patients. The most frequent adverse effects reported are those of the gastrointestinal tract in 3% to 17% and CNS in 0.9% to 11% of patients (155, 162). Allergic and other hypersensitivity reactions and other skin reactions occur in 0.5% to 2.8% of patients. Other adverse effects that occur in >1% of patients are cardiac (QT interval prolongation) and endocrine (hypoglycemia). Recently, FDA strengthened warnings in the prescribing information for the entire class of fluoroquinolones on risks of severe hypoglycemia, certain mental health side effects, and tendonitis, as well as risks of ruptures or tears in the aorta (163). Safety concerns persist for long-term pediatric use of fluoroquinolones, especially regarding arthropathy. However, several long-term prospective and retrospective studies in children have confirmed that severe adverse effects with the fluoroquinolones are rare, including musculoskeletal, neurological, and QT interval prolongation adverse effects (164–166).

***Additional considerations.*** As later-generation fluoroquinolones have become generic, their cost has decreased greatly and their use has expanded to many different indications, so procurement and availability have not been problematic, but resistance is more common than among aminoglycosides. Some foods or beverages and antacids high in content of divalent or