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# Aminoglycosides and Capreomycin in the Treatment of Multidrug-resistant Tuberculosis: Individual Patient Data Meta-analysis of 12 030 Patients From 25 Countries, 2009–2016

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**(See the Editorial Commentary by Hamilton on pages e3937–8.)**

***Background.*** As new drugs are developed for multidrug-resistant tuberculosis (MDR-TB), the role of currently used drugs must be reevaluated.

***Methods.*** We combined individual-level data on patients with pulmonary MDR-TB published during 2009–2016 from 25 countries. We compared patients receiving each of the injectable drugs and those receiving no injectable drugs. Analyses were based on patients whose isolates were susceptible to the drug they received. Using random-effects logistic regression with propensity score matching, we estimated the effect of each agent in terms of standardized treatment outcomes.

***Results.*** More patients received kanamycin (n = 4330) and capreomycin (n = 2401) than amikacin (n = 2275) or streptomycin (n = 1554), opposite to their apparent effectiveness. Compared with kanamycin, amikacin was associated with 6 more cures per 100 patients (95% confidence interval [CI], 4–8), while streptomycin was associated with 7 (95% CI, 5–8) more cures and 5 (95% CI, 4–7) fewer deaths per 100 patients. Compared with capreomycin, amikacin was associated with 9 (95% CI, 6–11) more cures and 5 (95% CI, 2–8) fewer deaths per 100 patients, while streptomycin was associated with 10 (95% CI, 8–13) more cures and 10 (95% CI, 7–12) fewer deaths per 100 patients treated. In contrast to amikacin and streptomycin, patients treated with kanamycin or capreomycin did not fare better than patients treated with no injectable drugs.

***Conclusions.*** When aminoglycosides are used to treat MDR-TB and drug susceptibility test results support their use, streptomycin and amikacin, not kanamycin or capreomycin, are the drugs of choice.

**Keywords.** aminoglycosides; capreomycin; multidrug-resistant tuberculosis; treatment; meta-analysis.

From the first randomized controlled trial (RCT) in history until the present, aminoglycosides have played a prominent role in the treatment of tuberculosis (TB) [1, 2]. Streptomycin was the first proven effective anti-TB drug and remained a first-line drug for decades [3]. Dozens of collaborative RCTs led by the British Medical Research Council and by the United States (US) Veterans Administration/US Armed Forces proved its efficacy [4, 5]. Kanamycin and capreomycin were discovered and developed in the 1950s for their broad-spectrum antibacterial activity, which included streptomycin-resistant *Mycobacterium tuberculosis* (*Mtb*) [6–8]. Amikacin was developed in the 1980s as a superior aminoglycoside against gram-negative bacilli, and it was also effective against *Mtb* in the laboratory [9]. Streptomycin, kanamycin, amikacin, and capreomycin were essentially equivalent in standardized laboratory tests in terms of in vitro bactericidal activity against *Mtb* [10]. Unlike streptomycin, however, there have been no definitive RCTs proving the efficacy of kanamycin, amikacin, and capreomycin against TB, although a RCT demonstrated amikacin to be effective against non-TB mycobacteria [11].

After all-oral, rifampin-based first-line treatment was established in the 1960s–1970s for drug-susceptible TB, parenterally administered agents were reserved for patients with drug-resistant TB or extensive cavitary lung disease. In addition to months of painful injections, these agents cause serious ototoxicity, nephroxicity, electrolyte imbalances, and other less common toxicities. The injectable drugs have been included in international guidelines for recurrent and drug-resistant TB since at least 1997 [12].

Treatment based on rifampin and isoniazid led to the emergence of multidrug-resistant TB; however, anti-TB drug

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discovery and development all but stopped after rifampin was approved. Except for the fortuitous effect of fluoroquinolones, treatment of multidrug-resistant TB (MDR-TB) was both unsatisfactory and relatively static from the 1970s to the 2000s. In the past decade, however, MDR-TB treatment changed due to increasing use of linezolid and clofazimine, as well as introduction of bedaquiline in 2012 and delamanid in 2013 [13–15]. Consequently, an individual patient data meta-analysis (IPDMA), based on data published during 2009–2016, led to new, markedly different recommendations and updated guidelines for MDR-TB treatment, especially regarding injectable agents [15–17]. Because of these changes, we report here detailed results of the IPDMA regarding the injectable drugs in modern chemotherapy for MDR-TB.

## METHODS

We carried out an IPDMA combining person-level data on 12 030 patients with MDR-TB from 50 cohorts treated in 25 countries and reported in studies published between 2009 and 2016 to investigate correlates of treatment success and of death with use of specific aminoglycosides [16]. De-identified individual patient data were transferred to McGill University where variables were harmonized and datasets combined. The high-level results were published [16]. This report focuses on the detailed analysis of aminoglycosides and capreomycin.

Using simple pooling, we compared demographic and clinical characteristics of patients receiving each of these drugs vs none of these drugs. Using random-effects multivariable logistic regression analysis, we compared patients receiving each of these drugs with patients who received no injectable drug and with patients receiving each other injectable drug in terms of (1) treatment success vs failure or relapse, excluding death and loss to follow-up, and (2) death vs survival. Analyses were repeated on the subsets of patients with fluoroquinolone-resistant TB with and without resistance to a second-line injectable drug. Those with additional resistance to a second-line injectable drug, by definition, have extensively drug-resistant TB (XDR-TB).

Patients receiving 2 or more injectable drugs were excluded unless the switch was based on drug susceptibility tests (DSTs) showing resistance to the first and susceptibility to the second; outcomes were ascribed to the second (susceptible) drug.

To control for the number of possibly effective drugs when DST results were absent, a drug was considered effective based on the prevalence of resistance in the nearest comparable group or population, in descending order: the rest of the same cohort, nationally representative data from that country, other published data from that country, and World Health Organization (WHO) estimates for that country or region. When the prevalence of resistance was < 10%, the drug was considered effective; if 10% or higher, the drug was considered ineffective. Bedaquiline, delamanid, clofazimine, and linezolid were considered effective. Analyses were based on patients whose cultures were susceptible to the injectable agent they received.

Using meta-analytic statistical methods with propensity score matching as previously reported [16], odds ratios were adjusted for age, sex, human immunodeficiency virus (HIV) status, acid-fast bacillus smear positivity, cavitation on chest radiograph, prior treatment history, resistance to fluoroquinolones, resistance to specific injectable drugs, and the number of effective drugs in the intensive phase. Adjusted risk differences were calculated from fixed-effects models since random-effects models would not converge. Statistical significance was defined as a 95% confidence interval (CI) that did not include the null value.

This analysis was approved by an ethics committee of the Research Institute of the McGill University Health Center. Ethics approval was obtained at participating sites, if considered necessary.

## RESULTS

In total, 10 560 patients received 1 injectable drug and 613 did not receive injections; 857 patients treated with ≥ 2 injectable drugs were excluded (Table 1). Kanamycin was used most frequently (n = 4330/10 560 [41%]), followed by capreomycin (n = 2401 [23%]), amikacin (n = 2275 [22%]), and streptomycin (1554 [15%]). The age and sex distributions were similar. HIV prevalence ranged from 8% of those treated with streptomycin to 23% of those treated with amikacin. Overall treatment outcomes in the no-injectable control group and the individual drug groups were similar except that capreomycin-treated patients had notably less success (49% vs 62%–69%) and more deaths (23% vs 8%–13%).

Compared with patients treated with aminoglycosides, the no-injectable control group had more patients previously treated with second-line drugs (35% vs 10%–15%), more fluoroquinolone resistance (36% vs 11%–26%), more resistance to second-line injectable drugs (46% vs 6%–16%), and more XDR-TB (26% vs 3%–10%). The capreomycin-treated group was like the no-injectable control group in these respects but with higher levels of fluoroquinolone resistance (42%), amikacin/kanamycin resistance (58%), and XDR-TB (35%).

Kanamycin-treated patients were much less likely to receive a later-generation fluoroquinolone (39%) compared with the other groups (60%–83%). Patients in the no-injectable control group were substantially more likely to receive linezolid (33%) vs any of the other groups (3%–13%).

### Each Drug Compared With No Injectable Drugs

As seen in Table 2 [16], compared with patients who received no injectable drug, streptomycin-treated patients had 50% higher odds of cure (adjusted odds ratio [aOR], 1.5 [95% CI, 1.1–2.1]). In terms of adjusted risk difference (aRD), for each 100 patients

**Table 1. Association of Clinical Characteristics and Outcomes With Injectable Agents Given (Simple Pooling)**

| Characteristic | No Injectable | | Streptomycin | | Amikacin | | Kanamycin | | Capreomycin | | ≥2 Injectables | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinical characteristics | | | | | | | | | | | | |
| No. in analysis | 613 | … | 1554 | … | 2275 | … | 4330 | … | 2401 | … | 857 | … |
| Mean age, y | 41.3 | … | 41.2 | … | 37.9 | … | 37.1 | … | 38.1 | … | 38.0 | … |
| Male sex | 361 | (59%) | 1079 | (69%) | 1320 | (58%) | 2700 | (62%) | 1571 | (65%) | 555 | (65%) |
| HIV positive | 86 | (16%) | 92 | (8%) | 509 | (23%) | 519 | (16%) | 471 | (21%) | 156 | (22%) |
| AFB smear positive | 366 | (62%) | 1172 | (79%) | 1779 | (80%) | 1346 | (80%) | 1346 | (70%) | 670 | (79%) |
| CXR cavitary | 264 | (54%) | 948 | (63%) | 1300 | (65%) | 1364 | (59%) | 986 | (63%) | 493 | (64%) |
| Prior treatment with first-line drugs[a] | 383 | (68%) | 625 | (75%) | 1335 | (80%) | 3508 | (83%) | 1717 | (73%) | 650 | (77%) |
| Prior treatment with second-line drugs[b] | 157 | (35%) | 97 | (15%) | 151 | (10%) | 351 | (12%) | 734 | (34%) | 128 | (17%) |
| DST results | | | | | | | | | | | | |
| Fluoroquinolone resistance on DST | 193 | (36%) | 123 | (18%) | 320 | (26%) | 400 | (11%) | 952 | (42%) | 176 | (24%) |
| Streptomycin resistance | 398 | (72%) | 131 | (9%) | 1340 | (68%) | 2618 | (63%) | 1760 | (93%) | 467 | (62%) |
| Amikacin/kanamycin resistance | 238 | (45%) | 118 | (16%) | 153 | (12%) | 231 | (6%) | 1302 | (58%) | 192 | (26%) |
| Capreomycin resistance | 146 | (34%) | 73 | (13%) | 100 | (11%) | 120 | (7%) | 322 | (19%) | 122 | (20%) |
| Any second-line injectable resistance | 248 | (46%) | 124 | (17%) | 181 | (15%) | 265 | (7%) | 1314 | (57%) | 202 | (27%) |
| XDR-TB[c] | 135 | (26%) | 65 | (10%) | 81 | (7%) | 103 | (3%) | 795 | (35%) | 102 | (14%) |
| Average number of pyrazinamide + ethambutol resistance | 1.1 | … | 0.7 | … | 1.1 | … | 1.2 | … | 1.4 | … | 1.2 | … |
| Average number of WHO group 4 drugs resistant[d] | 0.8 | … | 0.5 | … | 0.5 | … | 0.5 | … | 0.6 | … | 0.6 | … |
| Treatment given | | | | | | | | | | | | |
| Later-generation fluoroquinolone given[e] | 445 | (73%) | 1293 | (83%) | 1461 | (64%) | 1705 | (39%) | 1431 | (60%) | 444 | (52%) |
| Capreomycin given | 0 | … | 0 | … | 0 | … | 0 | … | 2401 | (100%) | 525 | (61%) |
| Linezolid given | 205 | (33%) | 40 | (3%) | 287 | (13%) | 131 | (3%) | 277 | (12%) | 71 | (8%) |
| Average number of WHO group 4 drugs given[d] | 1.7 | … | 1.5 | … | 1.5 | … | 2.1 | … | 2.4 | … | 2.3 | … |
| Average number of WHO group 5 drugs given[f] | 0.9 | … | 0.2 | … | 0.4 | … | 0.1 | … | 0.8 | … | 0.5 | … |
| Average number of possibly effective drugs[g] | 3.0 | … | 3.2 | … | 3.2 | … | 3.7 | … | 3.4 | … | 3.8 | … |
| Outcomes | | | | | | | | | | | | |
| Success | 406 | (66%) | 1079 | (69%) | 1531 | (67%) | 2675 | (62%) | 1175 | (49%) | 480 | (56%) |
| Fail/relapse | 49 | (8%) | 76 | (5%) | 115 | (5%) | 415 | (10%) | 251 | (10%) | 111 | (13%) |
| Died | 78 | (13%) | 130 | (8%) | 301 | (13%) | 528 | (12%) | 547 | (23%) | 145 | (17%) |
| Lost | 80 | (13%) | 269 | (17%) | 328 | (15%) | 712 | (16%) | 428 | (18%) | 121 | (14%) |

Data are presented as no. (%).

Abbreviations: AFB, acid-fast bacilli; CXR, chest radiograph; DST, drug susceptibility testing; HIV, human immunodeficiency virus; TB, tuberculosis; WHO, World Health Organization; XDR, extensively drug-resistant.

[a]First-line drugs: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin.

[b]Second-line drugs: fluoroquinolones, amikacin, kanamycin, capreomycin, ethionamide/prothionamide, cycloserine/terizidone, and para-aminosalicylic acid.

[c]XDR-TB defined as multidrug-resistant TB with additional resistance to a fluoroquinolone and a second-line injectable drug.

[d]WHO group 4 drugs: ethionamide, prothionamide, cycloserine, terizidone, and para-aminosalicylic acid.

[e]Later-generation fluoroquinolones: levofloxacin, moxifloxacin, and gatifloxacin.

[f]WHO group 5 drugs: amoxicillin/clavulanic acid, monobactams, and macrolides.

[g]Possibly effective drugs: all drugs with susceptibility testing results showing susceptibility or as defined in the Methods when test results not available, plus linezolid, clofazimine, bedaquiline, and delamanid.

so treated, treatment with streptomycin was associated with 2 more cures (95% CI, 0–4) per 100 patients. In the subgroup with fluoroquinolone resistance, streptomycin-treated patients had 3-fold higher odds of cure (aOR, 3.0 [95% CI, 1.3–6.6), and an aRD of 20 (95% CI, 5–34) more cures per hundred.

Amikacin-treated patients had twice the odds of cure (aOR, 2.0 [95% CI, 1.5–2.6]), independent of covariates, and an aRD of 6 (95% CI, 4–8) more cures per hundred. Among patients with quinolone resistance, amikacin was associated with a 3-fold higher odds of cure (aOR, 3.0 [95% CI, 1.6–5.6]), and an aRD of 14 (95% CI, 6–23) more cures per hundred.

In contrast, neither kanamycin nor capreomycin was associated with any meaningful benefit. Kanamycin treatment was associated with half the odds of cure (aOR, 0.5 [95% CI, .4–.6]) and 7 (95% CI, 5–8) fewer cures per hundred. Capreomycin was associated with increased odds of mortality (aOR, 1.4 [95% CI, 1.1–1.7]) and an aRD of 4 (95% CI, 1–7) more deaths per hundred.

### XDR-TB

In patients with XDR-TB (Table 2), amikacin was associated with nonsignificantly greater odds of cure (aOR, 2.5 [95% CI, .9–6.6]), significantly lower odds of death (aOR, 0.4 [95% CI, .2–.8]), and 16 (95% CI, 3–30) fewer deaths per hundred than those treated without an injectable agent. On the other hand, capreomycin was associated with less cure (aOR, 0.5 [95% CI, .4–.7]) and more deaths (aOR, 3.4 [95% CI, 2.7–4.3]), than

**Table 2. Outcomes of Patients Receiving Each Injectable Drug (Susceptible) Compared With Patients Receiving No Injectable Drug.**

| Drug | Injectable Given (Susceptible) Events/Total | No Injectable Given (All) Events/Total | Pairs, No. | Odds Ratio[a] (95% CI) | Risk Difference[a] (95% CI) |
|---|---|---|---|---|---|
| Streptomycin | | | | | |
| Cured | 959/1017 | 406/455 | 1017 | **1.5 (1.1–2.1)** | 0.02 (–.00 to .04) |
| Died | 104/1121 | 78/533 | 1121 | 0.8 (.6–1.1) | –0.02 (–.04 to .01) |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 61/73 | 115/144 | 73 | **3.0 (1.3–6.6)** | **0.20 (.05–.34)** |
| Died | 8/81 | 28/172 | 80 | 0.6 (.2–1.5) | –0.06 (–.17 to .04) |
| Amikacin | | | | | |
| Cured | 1302/1394 | 406/455 | 1393 | **2.0 (1.5–2.6)** | **0.06 (.04–.08)** |
| Died | 250/1644 | 78/533 | 1644 | 1.0 (.8–1.2) | –0.00 (–.03 to .02) |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 168/186 | 115/144 | 158 | **3.0 (1.6–5.6)** | **0.14 (.06–.23)** |
| Died | 43/229 | 28/172 | 201 | 1.1 (.7–1.9) | 0.02 (–.06 to .10) |
| Comparison in XDR tuberculosis[b] | | | | | |
| Cured | 62/69 | 384/551 | 68 | 2.5 (.9–6.6) | 0.09 (–.04 to .22) |
| Death | 15/84 | 395/946 | 83 | **0.4 (.2–.8)** | **–0.16 (–.30 to –.03)** |
| Kanamycin | | | | | |
| Cured | 2192/2523 | 406/455 | 2523 | **0.5 (.4–.6)** | **–0.07 (–.08 to –.05)** |
| Died | 435/2958 | 78/533 | 2958 | 1.1 (.9–1.2) | 0.01 (–.01 to .02) |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 178/213 | 115/144 | 212 | 1.5 (.9–2.4) | 0.06 (–.01 to .14) |
| Died | 39/252 | 28/172 | 250 | 1.0 (.6–1.7) | 0.00 (–.06 to .07) |
| Comparison in XDR tuberculosis[b] | | | | | |
| Cured | 52/74 | 394/546 | 73 | 0.9 (.5–1.9) | –0.01 (–.16 to .14) |
| Death | 19/93 | 391/937 | 93 | 0.9 (.5–1.9) | –0.01 (–.13 to .10) |
| Capreomycin | | | | | |
| Cured | 821/938 | 406/455 | 938 | 0.8 (.6–1.1) | **–0.03 (–.06 to –.00)** |
| Died | 176/1114 | 78/533 | 1114 | **1.4 (1.1–1.7)** | **0.04 (.01–.07)** |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 118/168 | 115/144 | 168 | 0.8 (.5–1.4) | –0.04 (–.14 to .05) |
| Died | 52/220 | 28/172 | 215 | 1.5 (.9–2.4) | 0.07 (–.01 to .15) |
| Comparison in XDR tuberculosis[b] | | | | | |
| Cured | 217/338 | 229/282 | 332 | **0.5 (.4–.7)** | **–0.14 (–.20 to –.07)** |
| Death | 354/692 | 56/338 | 675 | **3.4 (2.7–4.3)** | **0.25 (.20–.30)** |

Source: [16].

Excluded: 857 who received ≥2 injectables for no clear reason. Included: 613 who received no injectable, 10307 who received only 1 injectable, and 253 who were switched to an effective injectable drug based on drug susceptibility test results.

Values in bold are statistically significant ($P < .05$), meaning that 95% CI do not include 1.0 for odds ratios, or do not include 0 for risk differences.

Abbreviations: CI, confidence interval; XDR, extensively drug-resistant.

[a]Effect adjusted for age, sex, human immunodeficiency virus status, acid-fast smear microscopy results, cavities on chest radiograph, prior treatment with first- and second-line tuberculosis (TB) drugs, and resistance to fluoroquinolones or second-line injectable, and number of possibly effective drugs in initial phase. In all models, odds ratios were estimated with random-effects model (intercept and slope), but risk differences were estimated with fixed-effects models as random-effects models would not converge.

[b]For each injectable given to persons with XDR-TB, comparison is with any other injectable given or no injectable given to persons with XDR-TB. Only 8 persons were amikacin/kanamycin susceptible and received kanamycin; only 9 persons were amikacin/kanamycin susceptible and received amikacin. We could not analyze these separately due to the small number.

treatment with no injectable agent, including 25 (95% CI, 20–30) more deaths per hundred. Some of these patients may have had cultures resistant to the drug they received by definition of XDR-TB, so we repeated the analysis, restricting it to those with capreomycin-susceptible XDR-TB. In this subgroup, capreomycin treatment was associated with no practical difference in cures, but 11 (95% CI, 1–21) more deaths per hundred.

#### Second-line Injectable Drugs Compared With Streptomycin

Compared with streptomycin-treated patients, patients treated with amikacin had significantly higher odds of cure (aOR, 1.7 [95% CI, 1.3–2.2]) and 3 (95% CI, 0–5) more cures per hundred, whereas in the quinolone-resistant subgroup, these figures were an aOR of 1.7 (95% CI, .9–3.4), but 10 (95% CI, 3–17) more deaths per hundred—favoring streptomycin (Table 3).

Kanamycin and capreomycin were both significantly inferior to streptomycin in every respect, with less cure and more deaths overall and in each subgroup.

#### Second-line Injectable Drugs Compared With Each Other

Amikacin was superior to kanamycin and capreomycin in every respect with higher cure rates, lower mortality rates, or both. There was no meaningful difference between kanamycin and capreomycin (Table 4).

**Table 3. Comparing Use of Second-line Injectable Drugs to Streptomycin (Susceptible Only)**

| Drug and Outcome | Second-line Injectable Events/Total | Streptomycin Given Events/ Total | Pairs, No. | Odds Ratio (95% CI)[a] | Risk Difference (95% CI)[a] |
|---|---|---|---|---|---|
| Amikacin | | | | | |
| Cured | 1302/1394 | 959/1017 | 1365 | **1.7 (1.3–2.2)** | **0.03 (.00–.05)** |
| Died | 250/1644 | 104/1121 | 1644 | 1.0 (.8–1.2) | 0.01 (–.02 to .03) |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 168/186 | 61/73 | 169 | 1.7 (.9–3.4) | 0.06 (–.01 to .14) |
| Died | 43/229 | 8/81 | 226 | 1.2 (.7–2.0) | **0.10 (.03–.17)** |
| Kanamycin | | | | | |
| Cured | 2192/2523 | 959/1017 | 2523 | **0.4 (.4–.5)** | **–0.07 (–.08 to –.05)** |
| Died | 435/2958 | 104/1121 | 2958 | **1.8 (1.5–2.1)** | **0.05 (.04–.07)** |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 178/213 | 61/73 | 193 | 1.3 (.8–2.2) | 0.03 (–.05 to .11) |
| Died | 39/252 | 8/81 | 251 | 1.1 (.6–1.8) | **0.07 (.02–.13)** |
| Capreomycin | | | | | |
| Cured | 821/938 | 959/1017 | 938 | **0.2 (.1–.3)** | **–0.10 (–.13 to –.08)** |
| Died | 176/1114 | 104/1121 | 1114 | **2.9 (2.2–3.9)** | **0.10 (.07–.12)** |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 118/168 | 61/73 | 144 | **0.1 (.0–.2)** | **–0.30 (–.38 to –.21)** |
| Died | 52/220 | 8/81 | 210 | 1.2 (.8–1.9) | **0.16 (.10–.23)** |

Excluded: 857 who received ≥2 injectables for no clear reason. Included: 613 no injectables, 10307 who received only 1 injectable, and 253 who were switched to an effective drug based on drug susceptibility test results.

Values in bold are statistically significant ($P < .05$), meaning that 95% CI do not include 1.0 for odds ratios, or do not include 0 for risk differences.

Abbreviation: CI, confidence interval.

[a]Effect adjusted for age, sex, human immunodeficiency virus status, acid-fast smear microscopy results, cavities on chest radiograph, prior treatment with first- and second-line tuberculosis drugs, and resistance to fluoroquinolones or second-line injectables, and number of possibly effective drugs in the initial phase. In all models, odds ratios were estimated with random-effects models (intercept and slope), but risk differences were estimated with fixed-effects models as random-effects models would not converge.

**Table 4. Comparing Capreomycin, Amikacin, and Kanamycin (Susceptible Only)**

| Drug | Events/Total | Events/Total | Pairs, No. | Odds Ratio (95% CI) | Risk Difference (95% CI)[a] |
|---|---|---|---|---|---|
| Amikacin vs kanamycin | Amikacin | Kanamycin | | | |
| Cured | 1302/1394 | 2192/2523 | 1394 | **2.0 (1.5–2.5)** | **0.06 (.04–.08)** |
| Died | 250/1644 | 435/2958 | 1643 | **0.7 (.6–.8)** | –0.02 (–.04 to .01) |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 168/186 | 178/213 | 172 | **2.0 (1.0–3.8)** | **0.08 (.01–.15)** |
| Died | 43/229 | 39/252 | 216 | 0.8 (.5–1.3) | 0.02 (–.05 to .10) |
| Capreomycin vs amikacin | Capreomycin | Amikacin | | | |
| Cured | 821/938 | 1302/1394 | 938 | **0.3 (.2–.4)** | **–0.09 (–.11 to –.06)** |
| Died | 176/1114 | 250/1644 | 1113 | **1.7 (1.3–2.2)** | **0.05 (.02–.08)** |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 118/168 | 168/186 | 160 | **0.3 (.2–.5)** | **–0.20 (–.30 to –.11)** |
| Died | 52/220 | 43/229 | 216 | **1.8 (1.1–2.9)** | **0.04 (–.04 to .12)** |
| Capreomycin vs kanamycin | Capreomycin | Kanamycin | | | |
| Cured | 821/938 | 2192/2523 | 938 | 0.8 (.6–1.0) | –0.02 (–.05 to .01) |
| Died | 176/1114 | 435/2958 | 1114 | 0.8 (.6–1.0) | 0.01 (–.02 to .04) |
| Comparison in fluoroquinolone-resistant subgroup | | | | | |
| Cured | 118/168 | 178/213 | 168 | 0.8 (.5–1.2) | –0.05 (–.15 to .05) |
| Died | 52/220 | 39/252 | 220 | 1.0 (.7–1.6) | **0.12 (.05–.20)** |

Excluded: 857 who received ≥2 injectables for no clear reason. Included: 613 no injectables, 10307 who received only 1 injectable, and 253 who were switched to an effective second-line injectable drug based on drug susceptibility test results.

Values in bold are statistically significant ($P < .05$), meaning that 95% CI do not include 1.0 for odds ratios, or do not include 0 for risk differences.

Abbreviation: CI, confidence interval.

[a]Effect adjusted for age, sex, human immunodeficiency virus status, acid-fast smear microscopy results, cavities on chest radiograph, prior treatment with first- and second-line tuberculosis drugs, and resistance to fluoroquinolones or second-line injectables, and number of possibly effective drugs in the initial phase. In all models, odds ratios were estimated with random-effects model (intercept and slope), but risk differences were estimated with fixed-effects models as random-effects models would not converge.

Because these findings were contrary to experience, we went an additional step, beyond logic, of comparing capreomycin-treated patients whose isolates were susceptible to capreomycin with amikacin-treated patients whose isolates were resistant to amikacin. The numbers were small, but even under this extreme condition, capreomycin was associated with less cure (aOR, 0.7 [95% CI, .5–1.0]) and more deaths (aOR, 1.4 [95% CI, 1.1–1.8]) with 5 (95% CI, 3–8) more deaths per hundred. In the quinolone-resistant subgroup, capreomycin fared even worse as mortality was 12% higher (risk difference: 0.12, with 95% CI, .05, .20).

## DISCUSSION

This analysis reaffirms and quantifies the effect of streptomycin and amikacin, when supported by DST results, in treating MDR-TB, updating the older IPDMA with results from the current era of new and repurposed drugs. Surprisingly, kanamycin and capreomycin appeared worse than no injectable agent at all and much worse than amikacin or streptomycin.

How is this possible? There is no doubt they are effective on agar or in broth media at concentrations below typical serum concentrations. Their efficacies are similar in standardized laboratory tests [10]. Kanamycin and capreomycin are used extensively around the world, apparently with at least some positive results from the clinician's perspective.

On the other hand, this argument can be countered by noting the dismal cure rates for MDR-TB worldwide as reported by WHO (~50%–56%) and in peer-reviewed literature (~65%), so one certainly cannot claim they are *highly* effective [18]. Is there any other evidence these drugs are at least moderately effective?

Unlike treatment of drug-susceptible TB, there have been few RCTs of treatment of MDR-TB. Early clinical trials demonstrating the efficacy of streptomycin predated rifampin and the emergence of MDR-TB. It would be reasonable to expect these results to apply to MDR-TB, provided the isolates were susceptible to streptomycin, because the bactericidal action of streptomycin at the ribosomal and cellular levels should be the same. Thus, when supported by DST results, streptomycin remains an important agent for treatment of MDR-TB.

Amikacin was developed in the 1980s as a superior aminoglycoside for infections due to gram-negative rods, retaining that role to this day. Amikacin was effective against *Mtb* in vitro and in animal models and against nontuberculous mycobacteria in a RCT [11]. Within the limitations of observational data, amikacin was associated with better outcomes than no injectable drug, kanamycin, or capreomycin. Amikacin may be better than streptomycin, but the associations with cure vs mortality were in opposite directions, leading to uncertainty as to which is better. In practice, amikacin requires 2 separate injections each day to achieve an adequate dose in most patients. Using central venous catheters circumvents the pain of intramuscular injections but is associated with important risks of catheter-associated infections and thrombosis.

A 1958 volume of *Annals of the New York Academy of Science* devoted to kanamycin provides a comprehensive, authoritative summary of early work on kanamycin [7]. In vitro studies and experimental animal studies demonstrated the activity of kanamycin against *Mtb*, including strains resistant to streptomycin, isoniazid, and/or para-aminosalicylic acid (PAS) [6, 19–22]. Uncontrolled observational studies in the 1950s demonstrated improvement in some, but not all, patients with drug-resistant TB [21, 22]. We were unable to identify any clinical trials comparing kanamycin to placebo, alone or in combination, for the treatment of TB. In the present IPDMA, kanamycin-treated patients were less likely to receive a later-generation fluoroquinolone (39%) vs the other groups (60%–83%). Although multivariable analysis controlled for this disadvantage as best possible, residual confounding remains a possibility. To summarize, in humans there appears to be no strong evidence of kanamycin's superiority to no injectable drug or to any of the other injectable drugs. Unfortunately, based on cost and historical precedent, kanamycin was the most widely used aminoglycoside against MDR-TB in the IPD database.

Capreomycin is often used as the "last resort" injectable drug or when isolates are resistant to aminoglycosides because, as a cyclic polypeptide, it differs chemically as reflected in less cross-resistance. In the IPDMA database, overall treatment success for patients receiving capreomycin was only 48% (vs 62%–69% for the other injectables). Mortality was substantially higher at 23% (vs 8%–13%). Capreomycin-treated patients had more drug resistance, and the extent of drug resistance is a major determinant of outcome [23]. However, the analysis controlled for resistance to injectable drugs, fluoroquinolones, and the number of effective drugs. Even when the patient's isolate was susceptible in vitro to capreomycin and resistant to amikacin, capreomycin was associated with worse outcomes than amikacin. Four uncontrolled observational studies in TB patients, mainly with drug-resistant TB, showed modest benefit or benefit in a subset of patients only [24–27]. Two RCTs have examined capreomycin. In the US, a randomized trial in the 1960s compared capreomycin (1 g) + PAS to streptomycin (1 g) + PAS in a total of 138 patients [28]. Unfortunately, only 67 patients completed 6 months of treatment. There was no difference in radiographic improvement, but there was a small, consistent month-to-month increase in sputum conversion in the streptomycin group (95% vs 82% at 6 months). The difference was not statistically significant [28]. In the 1970s, 1 RCT from Japan with 209 patients compared capreomycin 1 g with streptomycin 1 g and with streptomycin 0.5 g. There were no meaningful differences between the 3 groups in terms of sputum conversion and radiographic improvement [29]. Unfavorable outcomes were observed in 2 of 72 (3%) patients treated with

1.0 g streptomycin, 7 of 72 (10%) patients treated with 0.5 g streptomycin, and 5 of 65 (8%) patients treated with 1.0 g capreomycin [29].

The 2010 IPDMA showed no clear benefit of capreomycin [30]. That IPDMA included 32 studies reporting 9153 patients published up to 2009. There was no significant difference between any of the 3 second-line injectable drugs in terms of treatment success vs failure/relapse or vs failure/relapse/death [30, 31]. The analysis "did not reveal any second-line parenteral agent—kanamycin, amikacin, or capreomycin—to be superior in effect to any other. Given its lower cost, kanamycin would be preferred. Amikacin may be used instead of kanamycin. In an analysis comparing patients who were cured or completed treatment to those who failed or relapsed, capreomycin was effective in case of resistance to kanamycin" [30].

Ahuja et al compared any second-line injectable vs no injectable [32]. Compared with no injectable agent, treatment with kanamycin, amikacin, or capreomycin did not significantly improve the odds of treatment success vs (1) treatment failure/relapse or (2) failure/relapse/death. Nevertheless, kanamycin appeared better than capreomycin, significantly increasing the odds of treatment success 1.6-fold vs failure/relapse/death in a direct 2-way comparison. These results did not take into account DST results.

In 2013, Falzon et al combined amikacin with kanamycin and kept capreomycin separate for purposes of analysis [33]. Patients with MDR-TB having no additional resistance besides isoniazid and rifampin who received 1 of these drugs had significantly better outcomes (aOR, 1.9 [95% CI, 1.1–3.1]) vs failure, relapse, or death, than patients receiving no injectable drug. In the group with additional resistance to at least 1 injectable drug, amikacin/kanamycin appeared superior to no injectable drug and to streptomycin but not among those with additional fluoroquinolone resistance. Capreomycin was associated with 2.2-fold (95% CI, 1.1–4.2) higher odds of treatment success vs no injectable drug, but not among patients with additional resistance to fluoroquinolones or injectables. There was no significant difference between amikacin/kanamycin vs capreomycin in any group. Paradoxically, among MDR-TB with additional fluoroquinolone resistance, in whom one might expect the injectable drugs to be more important, the injectable agents failed to show any benefit. Their results differ from ours in 3 important respects. First, their analyses combined amikacin and kanamycin. Second, their results were based on studies published up to 2009, whereas ours are based on research published after 2009. Third, the no-injectable group received a much weaker comparator regimen because bedaquiline and delamanid were not yet approved, while linezolid, clofazimine, and carbapenems were scarcely used—the main motivators for our updated IPDMA.

This study has important limitations. The most important is residual confounding including by indication and by the level of economic development in the countries contributing data. Second, the outcomes were composites: Cure and treatment completion are not the same; failure and relapse are not the same. Death is contrasted with survival, which includes treatment failure, but patients in whom treatment failed are likely to have high mortality in the near term. Some covariates were also composite: For example, the number of effective drugs does not distinguish newer highly effective drugs such as linezolid and bedaquiline.

## CONCLUSIONS

These findings differ from previous large IPDMAs because they reflect recent developments in the treatment of MDR-TB over the past 10 years [30, 31]. The detailed results presented here are based on an updated 2018 IPDMA [16] that served as evidence for developing 2018 and 2019 guidelines for drug-resistant TB treatment, including use of injectables [15, 17]. While amikacin and streptomycin were associated with better treatment outcomes than no injectable drug, patients who received kanamycin or capreomycin had worse outcomes than patients who received no injectable drug and worse outcomes than patients who received amikacin or streptomycin in analyses of composite treatment outcomes. Moreover, 64% of patients received the 2 worse drugs. One of the reasons MDR-TB treatment outcomes have been so poor over the years may be that the worst aminoglycoside (kanamycin) is the most widely used, and the weakest agent, capreomycin, is often reserved for patients with the worst resistance patterns. Given that these drugs also have serious toxicities, we urge physicians and programs to favor amikacin or streptomycin in patients with isolates susceptible to these agents who require parenteral treatment.

### Notes

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