reproduction number sufficiently to reduce the size of outbreaks. Chain-binomial models (Figure 1) show that reduced HSAR leads to remarkable reductions in secondary household cases—an HSAR of 30% creates an estimated 1.3 secondary infections, whereas 12% creates just 0.4. Given the need to reduce transmission to less than 1 secondary case per index case for epidemic control, otherwise described as an effective R_0 of below 1, this difference may explain why the epidemic continues to run amok in the United States.

For infection control of methicillin-resistant *Staphylococcus aureus* in hospitals, it is established that colonized cases (ie, those without disease and at low risk of complications) should be cohorted to prevent onward transmission, which protects potentially vulnerable inpatients. This principle is not to benefit colonized patients, who may never develop disease, but those around them. Using the same principle, mild COVID-19 cases ought to be moved out of the household until they no longer pose a threat of transmitting infection.

If a country does not follow fundamental infection control principles in the COVID-19 pandemic, it is scarcely a surprise if it fails to control infection.

Notes

Financial support. B. L. D. and A. R. C. were supported by funding from Singapore's National Medical Research Council through grants COVID19RF-004 and NMRC/CG/C026/2017_NUHS.

Potential conflicts of interest. The authors declare no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2021;72(12):e1166–7

DOI: 10.1093/cid/ciaa1842

How Second-Line Injectable Drugs Work

To the Editor—The meta-analysis by Cegielski and colleagues on the effectiveness of second-line injectable drugs (SLID) adds nuance to the previously published meta-analysis, which showed a surprising lack of activity [1, 2]. However, we have concerns with regards to the outcomes evaluated and thus with the conclusions of both meta-analyses.

The meta-analyses studied recurrence (treatment failure or relapse) and mortality [1, 2]. These outcomes are almost entirely dependent on the core drug, for example, fluoroquinolone or bedaquiline, driving the efficacy of rifampicin-resistant tuberculosis (RR-TB) treatment [3]. Without active core drug in the regimen, success is rare [4]. SLID are not core drugs because they have no sterilizing power [3]. SLID act only in alkaline environment where they rapidly kill actively replicating bacilli. They provide the most effective protection of the core drug against acquired drug resistance (ADR) [5], by preventing the selection of newly emergent or initially present core drug-resistant bacilli [3]. When evaluating the effect of SLID, the endpoint should thus be acquired core drug resistance in patients with initially core drug-susceptible TB. This explains why no or little effect of SLID on recurrence was seen in patients with initially fluoroquinolone-resistant RR-TB treated with a fluoroquinolone-based regimen [1]. Indeed, SLID are only successful when combined with an active core drug [5, 6].

The authors acknowledge that their finding of kanamycin's ineffectiveness could be due to its infrequent use with a more potent later generation fluoroquinolone, which were more frequently combined with amikacin [1]. The type of fluoroquinolone that acts as core drug must be taken into account when assessing the effect of SLID because of the different resistant mutant suppression windows [7, 8]. Almost nonexistent for the earlier drugs, it is considerable for fourth-generation fluoroquinolones, with differences also within the group [9]. Gatifloxacin was better than levofloxacin or moxifloxacin in overcoming its own lower-level resistant mutants. Used with kanamycin for the first 4 months, it ensured that none of the 859 patients successively treated with the standard short RR-TB regimen experienced recurrence with fluoroquinolone ADR [10]. However, reduction of standard 4-month administration of kanamycin to 2 months significantly increased the risk of gatifloxacin ADR [5]. That kanamycin

protects as well as amikacin against fluoroquinolone ADR was reported by a multicountry study [11].

Amikacin, the most powerful SLID [12], probably will have the same excellent effect. Capreomycin is weaker than amikacin due to its lower peak serum/minimal inhibitory concentration (MIC) ratio [12]. More importantly, amikacin resistance, caused by rrs1401 or rrs1484 mutations, confers complete cross-resistance to kanamycin as well as capreomycin. The original report of amikacin-resistant/capreomycin-susceptible strains [13] was recently corrected after MIC testing [14]. Because capreomycin is the only SLID rendered inactive also by tlyA mutations, it is least indicated.

In conclusion, when measuring the effect of TB drugs, researchers should take into account their specific action within a well-defined combination. Until a new drug proves to be as powerful, amikacin as well as kanamycin remain essential safeguards of the effectiveness of the core drug, currently the fluoroquinolones and/or bedaquiline for RR-TB treatment.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2021;72(12):e1167–8

DOI: 10.1093/cid/ciaa1874

Reply to van Deun and Decroo

To the Editor—We thank Drs. van Deun and Decroo for their letter regarding our article on aminoglycosides and capreomycin in the treatment of multidrug-resistant (MDR) tuberculosis (TB) [1, 2]. In 2019, the World Health Organization [3], as well as the American Thoracic Society/U.S. Centers for Disease Control, and Prevention/European Respiratory Society/Infectious Diseases Society of America [4] issued new guidelines for the treatment of MDR-TB that demoted amikacin and streptomycin from first-choice to third-choice drugs, removing kanamycin and capreomycin from the list of recommended drugs, based on the results of a large individual patient data meta-analysis (IPDMA) [5]. Experienced clinicians everywhere, including ourselves, were surprised these drugs had such limited effect on successful treatment and mortality, as they had been mainstays of treatment for decades. Indeed, that was the reason for reporting our extended analysis of these data.

Van Deun and Decroo posit these drugs should be evaluated not by treatment failure, relapse, or death, but by preventing acquired resistance to core drugs (defined as those having sterilizing activity), such as fluoroquinolones, because aminoglycosides work mainly against rapidly dividing mycobacteria at alkaline (to neutral) pH. While this argument is valid, acquired resistance to core sterilizing drug(s) has a devastating effect on final treatment outcomes [6]. Those final treatment outcomes—cure versus treatment failure, relapse, or death—are the outcomes ultimately important to patients and, therefore, should be primary endpoints in evaluating the utility of any antimicrobial agent.

Moreover, the risk of acquired fluoroquinolone resistance as a function of one specific drug is difficult to measure in MDR-TB regimens because that risk increases exponentially with the extent of pretreatment drug resistance and decreases with the number of other effective drugs in the regimen; it also differs sharply by program characteristics [7]. Our analysis controlled for other drugs in the treatment regimens and susceptibility test results, as well as for disease severity and program differences.