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Reply to Soman et al, Alffenaar et al, Metcalfe et al, and Raoult

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To the Editor

We thank Metcalfe et al, Alffenaar et al, Soman et al, and Raoult for their interest in our study [1]. Metcalfe et al raise 2 issues about the analysis and reporting of results [2]. Alffenaar and colleagues raise issues related to drug dosing [3]. Soman and colleagues raise concern about standardized treatment regimens [4]. Raoult refers to the potential utility of existing drugs that are not standard antituberculosis drugs [5]. We respond to each of these letters in turn.

Metcalfe and colleagues suggest that patients who remain culture negative after 1 month of treatment could not have acquired drug resistance and therefore might have been included in the denominator when calculating the proportion of patients with acquired drug resistance [2]. However, the reality and the math are more complicated for at least 3 reasons. First, we disagree that the target population "is presented as all patients with MDR [multidrug-resistant] tuberculosis starting treatment with [second-line drugs]." The target population for this analysis was patients with at least one positive follow-up cultures as displayed in our Figure 1 [1]. Second, we described the excluded subset of patients as having no positive follow-up cultures rather than as having all negative follow-up cultures because these are not the same: 20.8% of the excluded group of patients did not complete treatment (ie, were classified as defaulting) after a median of <12 months (interquartile range, 5–16 months). Because "default" is a World Health Organization (WHO)–defined standard outcome category [6], it was the endpoint in our follow-up of these patients, and we cannot know whether these patients had any subsequent positive cultures. However, the duration of treatment for this group of patients is inadequate. These patients would be at high risk for

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again becoming culture positive and for acquired drug resistance. Third, many of these patients already had baseline resistance to fluoroquinolones, second-line injectable drugs, or both. It would not be appropriate to include them in the denominator when calculating the frequency of acquired resistance to these same drugs. The exact percentages are uncertain because we did not receive baseline cultures for all these patients and did not recover viable mycobacteria from all cultures received. However, of the 340 viable baseline isolates we received among patients with no positive follow-up cultures, 6.8% had fluoroquinolone resistance, 8.5% had resistance to 1 or more second-line injectable drugs, 11.8% had resistance to either, and 3.5% had resistance to both.

Metcalfe and colleagues also discuss our use of propensity scores to control for potential confounding factors. Unlike large randomized controlled trials, in observational studies there is always the possibility of unmeasured confounders. This does not preclude the use of multivariable regression and propensity score methods in analyzing data from observational studies. To the extent possible, we addressed this concern by measuring as accurately and completely as possible not only factors known to be associated with the main predictor and outcome variables, but also a broad range of factors that might possibly be associated with the main predictor and outcome variables. We also implemented a careful, systematic, step-by-step analytic strategy including sensitivity analyses to explore the robustness of the findings. Our data did not violate the so-called positivity assumption (ie, there were no known confounders in which everyone was either exposed or unexposed). Human immunodeficiency virus (HIV) infection was perhaps the most prominent risk factor affecting one country in particular in the “unexposed” (non–Green Light Committee [GLC]) group, but 10% of HIV-infected patients were in GLC-approved countries, and one-third of patients were not tested for HIV infection (distributed across all countries). When we stratified countries by HIV prevalence, HIV infection was not associated with acquired drug resistance. Nearly half of HIV-positive patients were receiving highly active antiretroviral treatment and therefore would be expected to have outcomes more similar to HIV-negative patients. Last, we carried out sensitivity analyses to test whether the results were dominated by the higher prevalence of HIV infection in South Africa, for example, by excluding patients with HIV (from all countries) from the analysis, and the results were very close to the results we reported. For the association between GLC status and acquired XDR (extensively drug-resistant) tuberculosis, the adjusted odds ratios with and without HIV-infected patients in the regression model were 0.21 (95% confidence interval [CI], .07–.63; $P = .004$) and 0.26 (95% CI, .09–.77; $P = .01$), respectively. For the association between GLC status and acquired fluoroquinolone resistance, the adjusted odds ratios were 0.23 (95% CI, .09–.59; $P = .001$) and 0.28 (95% CI, .11–.71; $P = .007$), respectively.

We thank Alffenaar and colleagues for raising important issues related to the interrelationship between emergence of drug resistance and drug dosing based on pharmacokinetic and pharmacodynamic considerations [3]. There remains a great deal to be learned about optimal drug dosing, and we are aware of 2 clinical trials currently under way to assess the effect of different doses of antituberculosis drugs (ClinicalTrials.gov NCT01918397 and NCT01408914). Therapeutic drug monitoring may benefit many patients. In our cohort, the detailed treatment data are complex because drugs and doses

change repeatedly over the course of treatment based on drug susceptibility testing (DST) results, drug toxicity, clinical response to treatment, and drug availability. We are currently analyzing the impact of drug dosing on acquired drug resistance.

Soman and colleagues call attention to the risk of acquired drug resistance associated with standardized treatment regimens [4]. Our data add to the evidence that preexisting resistance to other drugs in the treatment regimen is one of the strongest risk factors for further acquired drug resistance [1]. Because resistance to second-line drugs is widespread among patients with MDR tuberculosis [6], we support WHO's recommendations on DST for fluoroquinolones and second-line injectable drugs among patients with or suspected of having MDR tuberculosis [7, 8].

We agree with Raoult that many existing drugs with activity against *M. tuberculosis* have not been adequately studied, including some of the drugs classified by WHO as group 5 drugs [7]. We recently launched a study to better characterize the effect of such drugs on MDR *M. tuberculosis* isolates from the Preserving Effective Tuberculosis Treatment Study, including most of the drugs named by Raoult. New and more effective drugs will help efforts to control highly drug-resistant forms of tuberculosis. We did not intend to imply that "only new drugs can be effective on XDR tuberculosis" as Raoult suggests. Bedaquiline and delamanid have been provisionally approved in the past 2 years for the treatment of MDR tuberculosis, and we urge clinicians and programs to use these drugs in a manner that does not lead to acquired resistance to these same drugs, that is, by ensuring there are at least 3 other effective drugs in the treatment regimen.

Finally, we would like to thank again the authors of these 4 letters for raising important issues related to the treatment of MDR tuberculosis and the potential for further acquired resistance during treatment.

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