To the Editor—Fierer’s editorial, “One Small Step,” presented useful information on the roles and limitations for the Coccidioides antigen detection enzyme immunoassay [1]. He noted that the antigen test performed best in immunocompromised patients living with human immunodeficiency virus (HIV)/AIDS (PLHIV). PLHIV comprised 39.5% of cases, potentially biasing our assessment toward a higher sensitivity (57%) for antigen detection. A prospective study is planned at an institution with PLHIV to address this concern.

He indicated that assessment of sensitivity in probable cases was biased by inclusion of positive antigen results as a basis for determination of sensitivity. We have analyzed 34 probable cases diagnosed using antibody testing that excluded antigen results, of which antigen was detected in 38.2%.

He commented that antigen detection could identify infection sooner than antibody detection. The patients evaluated in the VHMC retrospective study presented late, and serial testing was not performed. We have planned prospective studies at 2 institutions in highly endemic areas to address this hypothesis.

We agree with Fierer that antigen detection is less sensitive than antibody detection; however, antigen alone was detected in 11.3% of cases, in which delayed or missed diagnoses may have serious consequences [3]. We thank Fierer for his insightful and helpful comments that we plan to evaluate in prospective clinical trials.

Note
Potential conflicts of interest. L. J. W. is an owner and president of MiraVista Diagnostics. All authors report no potential conflicts.

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.

Christelle Kassis, and L. Joseph Wheat

1Arizona Pulmonary and Medical Specialists, Phoenix, Arizona, USA; and 2MiraVista Diagnostics, Indianapolis, Indiana, USA

References
1. Fierer J. One small step. Clin Infect Dis 2021; 72:976–8.
2. Kassis C, Zaidi S, Kuberski T, et al. Role of coccidioides antigen testing in the cerebrospinal fluid for the diagnosis of coccidiodal meningitis. Clin Infect Dis 2015; 61:1521–6.
3. Donovan FM, Wightman P, Zong Y, et al. Delays in coccidioidomycosis diagnosis and associated healthcare utilization. Tucson, Arizona, USA. Emerg Infect Dis 2019; 25:1745–7.

Correspondence. L. J. Wheat, MiraVista Diagnostics, 4705 Decatur Boulevard, Indianapolis, IN 46241 (jwheat@miravistalabs.com).

Clinical Infectious Diseases® 2022;74(3):560 © The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com DOI: 10.1093/cid/ciab482

It Is Time to Determine Tocilizumab’s Place in Coronavirus Disease 2019 (COVID-19)

To the Editor—We read with great interest the meta-analysis by Huang et al [1]. Huang et al conducted a meta-analysis of the first 5 randomized clinical trials (RCTs) with tocilizumab in COVID-19 and concluded that tocilizumab (TCZ) does not provide mortality benefit for patients with severe coronavirus disease 2019 (COVID-19). Since the meta-analysis by Huang et al, 3 new RCTs [2–4] have been published or are at a pre-publication stage. Veiga et al’s [2] trial was stopped early in July 2020 after an increase in deaths in opposition to REMAP-CAP and RECOVERY results [3, 4] which showed a positive benefit of tocilizumab on mortality. We think that an updated meta-analysis and discussion are necessary. In this context, we aimed to perform a meta-analysis on these 8 RCTs [2–9] on the impact of TCZ administration on mortality. We selected through a systematic search on PubMed and the preprint server medRxiv (until 3 March 2021) all RCTs that compared the clinical outcome of patients with COVID-19 treated with TCZ versus standard of care or placebo. Our primary endpoint was 28-day mortality. Secondary endpoints were mechanical ventilation incidence and safety endpoints (adverse events and serious infections).

We included 8 RCTs. A total of 6303 patients were included: 3266 randomized to TCZ and 3037 to placebo (Figure 1). Overall, there were 810 (24.8%) deaths at day 28 in the TCZ group and 893 (29.4%) deaths in the placebo group (pooled odds ratio [OR], .86; 95% confidence interval [CI], .76–.96; P = .008). Mechanical ventilation incidence had a pooled OR (.72; 95% CI, .62–.84; P < .001) in favor of TCZ. There were 88 of 705 (12.5%) serious infections in the TCZ group and 60 of 353 (17%) serious infections in the placebo group (pooled OR, .67; 95% CI, .47–.97; P = .03) and no significant differences in adverse events (Figure 1).

A few assumptions can be discussed to explain this contradiction on mortality effect in these RCT results. First, a lack of statistical power seems manifest in some RCTs. For example, Stone et al [6] and Salvarini et al [7] showed a mortality rate of less than 5% in their population and the required number of patients to conclude for the lack of impact on mortality in COVID-19 with tocilizumab used was not reached; Veiga et al’s [2] results must be interpreted with caution due to the sample size of the trial and considering that there were no significant differences in mortality at day 28.

Second, we only have the results of short-term mortality. For example, in COVACTA [5], at day 28, 72% (83/115) of the patients who were still hospitalized required a high level of oxygen support: 17% (50/294) in the TCZ arm versus 23% (33/144) in the placebo arm. We can possibly expect a lower number of deaths in the TCZ arm in long-term mortality.

Third, these RCTs included heterogeneous populations, which may explain the heterogeneity of results [10]. We have recently defined the optimal group who is susceptible to have the greatest benefit from TCZ as severe/critical COVID-19.