Reply to von Reyn and Horsburgh

To the Editor—We thank von Reyn et al [1] for their interest in our work and for providing pertinent data on the impact of nontuberculous mycobacteria (NTM) infection on the screening for latent tuberculosis infection, which support the results of our trial. We wholeheartedly agree with their conclusion on the value of using an interferon γ release test when screening for tuberculosis infection regardless of the presence of BCG vaccination.

In an ad hoc analysis of our data set, 28% of the non–BCG-immunized contacts with a positive tuberculin skin test (TST) result had a negative QuantiFERON-TB Gold In-Tube (QFT-GIT) test result, (18% for contacts with a TST reaction >15 mm, 23% for those with a reaction 11–15 mm, and 78% for those with a reaction 5–10 mm). Even considering that the TST result may have been positive in a substantial proportion of these contacts because of sensitization with NTM, our figures are below those obtained among healthcare workers in United States, probably owing first to the higher risk of tuberculosis infection among our contacts and second to the lower prevalence of NTM in our country. According to unpublished data, the prevalence rate of respiratory isolation of NTM in our region is 8 per 100 000 population, which is clearly lower than the US rates [2].

Together with the valuable data provided by von Reyn et al, our results strongly suggest that applying our strategy of using the QFT-GIT test in the tuberculosis household contact investigation in areas with high prevalence of NTM would reduce the number of preventive treatments even further. However, it should be kept in mind that the safety of this strategy has been proved only for screening immunocompetent persons with the QFT-GIT test, and presumably with the new-generation QuantiFERON-TB Gold Plus test.

Note

Potential conflicts of interest. All authors: No reported 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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2. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med **2012**; 185:881–6.

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C-Reactive Protein Response in Patients With Post-Treatment Lyme Disease Symptoms Versus Those With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

To the Editor—There is substantial overlap in symptoms, including fatigue, muscle and joint pain, and cognitive and memory deficits, between post-treatment Lyme disease syndrome (PTLDS) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [1]. Increasing evidence suggests a role for immunologic and inflammatory pathways in both PTLDS and ME/CFS [2–4]. However, in part owing to their etiologic complexity and the lack of established biomarkers, our understanding of the pathways involved and potential mechanistic differences between the 2 conditions is very limited.

In a 2016 study published in *Clinical Infectious Diseases,* Uhde et al [5] examined the concentrations of acute-phase response proteins, including C-reactive protein (CRP), in individuals with PTLDS. CRP is a highly sensitive marker of infection and inflammation that binds a variety of ligands present on the surface of pathogens or exposed during autologous cell stress or death, exerting its effect through opsonin deposition and activation of the complement pathway, in addition to direct interaction with phagocytic cells [6]. We found that the circulating levels of CRP, as well as the frequency of concentrations >3 mg/mL (generally considered to represent some degree of inflammation [7]) to be significantly higher in the PTLDS cohort than in a control group of subjects who had a history of Lyme disease but without persistent symptoms (both $P < .001$). The data provided evidence for increased expression of an objective marker of inflammation in PTLDS but suggested a mechanism of activation distinct from that in active infection, as previously discussed [5].

Using the same methods [5] in a new study, we screened plasma samples from 131 patients with ME/CFS (89 female; mean age [standard deviation], 50.0 [11.4] years; mean body mass index (BMI), 26.0 [5.5]) and 86 healthy controls (68 female; mean age, 50.0 [12.8] years; mean BMI, 26.5 [6.8]), provided by the SolveCFS BioBank [8]. Patients with ME/CFS met the criteria of Fukuda et al [9] and the Canadian criteria [10] for this condition [9, 10]. Screening questionnaires were used to evaluate the general health of the unaffected controls and to confirm that they did not meet ME/CFS case definition criteria. The ME/CFS and control sample sizes provided >95% power, with an α value <.05, to detect the same increase in CRP response as in the patients with PTLDS [5]. Group differences were assessed by the analysis of covariance, using the general linear model, to account for the potential confounding effect of age, sex, and BMI. This study was approved by the Institutional Review Board of Columbia University. In contrast to data from patients with PTLDS [5], we did not find a statistically significant difference in the circulating levels of CRP (Figure 1) or the frequency of CRP levels >3 mg/L (33 of 131 [25.2%] vs 22 of 86 [25.6%], respectively) between patients with ME/CFS and controls.

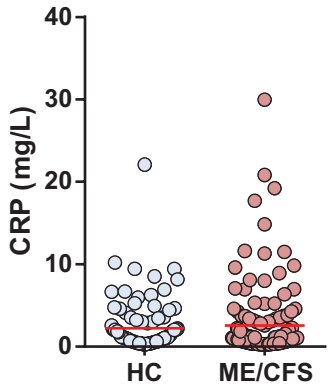

Figure 1. C-reactive protein (CRP) concentrations in the cohorts of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and healthy controls (HCs). The difference between the 2 groups was not statistically significant ($P = .55$). Horizontal red bars represent the mean for each group.

These data provide evidence for the likely existence of distinct inflammatory mechanisms in ME/CFS versus PTLDS, which may be driven in part by the potentially more heterogeneous etiology of ME/CFS symptoms in comparison with PTLDS. The absence of a significantly enhanced CRP response in ME/CFS, despite published data suggesting activation of various inflammatory pathways, warrants further examination.