glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014;371: 1285–1294.
7. Haque R, Hakim A, Moodley T, Torrego A, Essilfie-Quaye S, Jazrawi E, *et al*. Inhaled long-acting β2 agonists enhance glucocorticoid receptor nuclear translocation and efficacy in sputum macrophages in COPD. *J Allergy Clin Immunol* 2013;132:1166–1173.
8. Adcock IM, Maneechotesuwan K, Usmani O. Molecular interactions between glucocorticoids and long-acting β2-agonists. *J Allergy Clin Immunol* 2002;110(Suppl 6):S261–S268.
9. Hakim A, Younis K, Esteban I, Miller-Larsson A, Barnes PJ, Usmani OS. Effects of a single inhaled budesonide/formoterol dose on glucocorticoid receptor activity in sputum of COPD patients. *Eur Respir J* 2016;48:OA3313.
10. Hakim A, Adcock IM, Usmani OS. Corticosteroid resistance and novel anti-inflammatory therapies in chronic obstructive pulmonary disease: current evidence and future direction. *Drugs* 2012;72: 1299–1312.

Implications of Tuberculosis Sputum Culture Test Sensitivity on Accuracy of Other Diagnostic Modalities

To the Editor:

Yoon and colleagues (1) recently showed that using a C-reactive protein point-of-care test (CRP-POC) as the initial screening tool compared with using the World Health Organization symptom screener could lead to a substantial reduction in the total number of Xpert tests used to diagnose tuberculosis (TB) in a population with only a slight loss in the number of cases identified. Using two sputum samples as the "gold standard" for a pulmonary TB diagnosis, they found that there were seven false-positive cases using the conventional approach (World Health Organization screen followed by Xpert) and four using a CRP-POC screen followed by Xpert.

Although not a focus of their article, their results (Table E2 in their online supplement) illustrate an important problem with using TB sputum culture as a gold standard. A single culture had a sensitivity of only 79% (160 detected) out of the 203 individuals identified by two cultures as positive TB cases. As there is no reason to expect that the sensitivity of a second sputum sample would be better than the first sample, these results imply that some true TB cases will be missed even using two samples. In fact, if the sensitivity of each test were 79%, one would expect that 4.41% (21% × 21%) of true-positive cases would be missed using two cultures, equal to about 9 [203/(1 − 0.0441) − 203] additional cases in this study. Taking account of these additional cases of pulmonary TB, however, reduces the estimated sensitivity to 75% (160 detected out of 212 [203 identified and 9 missed] cases). Thus, an even higher fraction of pulmonary TB cases would be missed by the gold standard of two sputum cultures. Continuing the calculations above, the sensitivity is about 73% (160 detected out of 219 [203 detected and 16 missed] cases), implying that about 7.29% (27% × 27%) of cases are missed, which is consistent with 16 missed cases among 219 true TB cases (16/219 = 7.31%).

Moreover, this assumes that the second test, performed in a population for which the first test was negative, has the same sensitivity as the first test. However, results for Xpert (2) suggest that this is an overly optimistic assumption. For example, for sputum-negative, culture-positive specimens, sensitivity for a single sample is reported as 72.5%, whereas for three samples it is only 90.2% (estimated 95% confidence interval, 84.9–93.8%). If sensitivity for each separate test was 72.5%, however, then the expected sensitivity for three specimens would be 97.9% ($1 - 0.275^3$).

Importantly, if the sensitivity of a single Xpert test is about 60% (as reported in Table E2A of Yoon's paper), then one would expect Xpert to diagnose about 60% of the 16 cases missed by the gold standard, or about 10 individuals. Thus, it is possible that all 7 individuals positive by Xpert had pulmonary TB that was missed by the two sputum cultures, and incorrectly considered false positives. It seems advisable that such patients be followed clinically to determine whether they actually had TB (a true positive) or whether the clinical course suggests that they did not have TB (a false positive).

In the absence of such follow-up, it might be appropriate to consider any diagnostic test positive for pulmonary TB as diagnostic for the presence of TB, whether confirmed by the gold standard or not, especially if the false-positive rate of the diagnostic test is low. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Robert A. Parker, Sc.D.*
Massachusetts General Hospital
Boston, Massachusetts

*Corresponding author (e-mail: rparker4@mgh.harvard.edu).

References

1. Yoon C, Semitala FC, Asege L, Asege L, Katende J, Mwebe S, *et al*. Yield and efficiency of novel intensified tuberculosis case-finding algorithms for people living with HIV. *Am J Respir Crit Care Med* [online ahead of print] 7 Sept 2018; DOI: 10.1164/rccm.201803-0490OC. Published in final form as *Am J Respir Crit Care Med* 2019; 199:643–650 (this issue).
2. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, *et al*. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010;363:1005–1015.

This publication was made possible with help from the Harvard University Center for AIDS Research (CFAR), an NIH-funded program (P30 AI060354), which is supported by the following NIH Co-Funding and Participating Institutes and Centers: National Institute of Allergy and Infectious Diseases, National Cancer Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NHLBI, National Institute on Drug Abuse, National Institute of Mental Health, National Institute on Aging, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of General Medical Sciences, National Institute on Minority Health and Health Disparities, National Institute of Dental and Craniofacial Research, Office of AIDS Research, and Fogarty International Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Originally Published in Press as DOI: 10.1164/rccm.201811-2112LE on December 11, 2018