Editorial

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There Is More than One Way to Catch a Bug

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Tuberculosis (TB) kills. In 2007 there were an estimated 9.27 million new TB cases worldwide and about 1.78 million people died from the disease in the same year. Sputum smear microscopy remains the primary tool for TB diagnosis in most countries, but only an estimated 44% of TB cases are smear positive [1]. Though culture of TB bacteria is more sensitive, it may take several weeks to diagnosis due to low growth rates. Research is ongoing to develop the best diagnostic strategy for smear-negative cases (still 5.2 million people after all), with 'best' in this context implying highly sensitive, specific, fast, reliable and, last but not least, cost effective.

Recently published papers on the diagnosis of smear-negative pulmonary TB focus on the improvement in clinical judgment, specimen collection or specimen processing, and innovative laboratory technologies. A score based on demographic data, symptoms, past medical history and chest X-ray findings for rapid identification of patients with pulmonary TB reached a sensitivity of 93%, but had a very low specificity (42%) questioning its clinical significance [2]. New technologies such as LED fluorescence microscopy and bleach microscopy might improve sensitivity of smear microscopy [3]. In developed countries, flexible bronchoscopy in patients unable to produce sputum or with smear-negative sputum might accelerate the diagnostic procedure, especially when TB-specific nucleic acid amplification techniques or enzyme-linked immunospot assays are performed on bronchoalveolar lavage fluid or mononuclear cells [4, 5]. Single serologic antibody detection tests for TB lack sensitivity, but might be promising when used as multiple-antigen tests in combination with other procedures [6]. There are many other diagnostic tools under investigation, such as volatile organic compounds, gold nanoparticle probes, biomarkers in QuantiFERON supernatants for example. However, none of the above-mentioned strategies reaches sufficient diagnostic yield to replace sputum smear microscopy and TB culture.

In this issue of *Respiration*, Lee et al. [7] propose another approach for the rapid diagnosis of sputum smear-negative pulmonary TB. In their retrospective analysis of 84 patients with confirmed active pulmonary TB and with a negative sputum smear, they compared the diagnostic value of clinical findings, chest high-resolution (HR) CT, sputum TB-PCR and the IFN-γ release assay (IGRA) for the diagnosis of active pulmonary TB. As has been shown previously, they found none of these parameters alone to be of sufficient diagnostic value. However, they describe a high positive and negative predictive value for the combined utilization of IGRA and chest HR-CT. A congruent result of HR-CT and IGRA, i.e. HR-CT findings suggestive of pulmonary TB and a positive IGRA, predicted the correct diagnosis in 23 of 24 patients (positive predictive value 96%). The negative predictive value of congruent negative HR-CT findings and IGRA was 92%: in 23 of 25 patients pulmonary TB was correct-

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ly excluded. Despite some limitations of the study (retrospective analysis, some variables missing and small sample size), the HR-CT-IGRA combination is a promising approach that might assist clinicians in their decision to start TB therapy or isolate hospitalized patients when sputum smear is negative.

It must be kept in mind that the results of this study are of little value for the countries with the highest burden of TB. HR-CT and IGRA are expensive, require expertise and are unavailable in developing countries. Furthermore, HIV co-infection is frequent in these countries, and this study was performed in HIV-negative patients. In the appropriate setting, i.e. intermediate- to low-burden countries with sufficient health care resources to perform HR-CT and IGRA in patients with suspected pulmonary TB and negative sputum smear, the combined use of HR-CT and IGRA might substantially improve decision making, and obviate the need for further diagnostic procedures in cases with congruent results. We are now waiting for prospective evaluation of this approach.

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