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Xpert MTB/RIF versus Sputum Smear Microscopy: Microscopy Needs a Level Playing Field

To the Editor:

Theron and colleagues observed that Xpert MTB/RIF is significantly better than sputum smear microscopy in the diagnosis of pulmonary tuberculosis in high HIV prevalence setting (1). Diagnostic outcome of sputum smear microscopy depends on the number of sputum smears examined. A study in similar HIV prevalence settings has shown that the diagnostic yield of smear microscopy increase 12.2% and 4.4% with second and third examined smears, respectively (2). World Health Organization guidelines also assert that the chances of finding tuberculosis bacilli are greater with three samples than with two samples or one sample (3). However, the authors in the existing study did not mention the average number of smears examined per patient, which is an important factor in optimizing performance of smear microscopy, hence its unbiased comparison with other diagnostic modalities.

In high-burden settings, up to 30% of tuberculosis cases occur in children. There are difficulties in diagnosis in children, particularly those less than 10 years of age, as they do not produce sputa. The study did not study Xpert MTB/RIF performance in the children.

Author Disclosures are available with the text of this article at www.atsjournals.org.

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From the Authors:

We thank Drs. Dutt and Mohapatra for their letter pertaining to our recent publication (1). We agree that the diagnostic accuracy of smear microscopy increases with the number of specimens examined. We compared the performance of a single Xpert MTB/RIF assay to smear microscopy using two specimens from each patient. This was done in accordance with the World Health Organization recommendation (2). Patients who were unable to provide two sputum specimens were excluded from our study. The incremental diagnostic yield of smear microscopy performed on a third sputum specimen is small (2–5%) (3), and, given the additional workload, is thus generally not recommended in resource-limited settings (2, 4).

The assessment of Xpert MTB/RIF performance in children was not an objective of this study, which is why individuals younger than 18 years of age were not recruited. However, there are data on the performance of Xpert MTB/RIF in this group: Zar and colleagues recently assessed the utility of the assay in induced sputum samples collected from children (5), where the sensitivity of Xpert MTB/RIF for the detection of culture-confirmed tuberculosis was significantly better than smear microscopy (sensitivity of 74.3% versus 52%, respectively; $P = 0.01$).

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Areataeus of Cappadocia and the First Clinical Description of Asthma

To the Editor:

Asthma is derived from the Greek verb *aaazein*, meaning short-drawn breath or panting (1).

Areataeus of Cappadocia, a Greek physician, who studied in Alexandria and practiced in Rome probably in the second century CE, is credited with the first accurate description of asthma, as we know it today (2).

Areataeus is considered one of the most valuable medical writers of antiquity, an original observer that included in his work his personal experience and also the achievements of anatomy and physiology. His prevailing but incomplete treatises are: *De Causis et Signis Morborum Acutorum et Diuturnorum* (*On the Causes and Symptoms of Acute and Chronic Diseases*), in four books, and *De Curatione Morborum Acutorum et Diuturnorum* (*On the Cure of Acute and Chronic Diseases*), also in four books (2).

In Chapter XI of his essay *On the Causes and Symptoms*, entitled *On Asthma*, Areataeus defined the disease, emphasizing the association with exercise: "If from running, gymnastic exercises or from any other work, the breathing becomes difficult, it is called asthma" (3).

Follower of the Pneumatic school of medicine, he supported that health was preserved by *pneuma* or "vital air," and he attributed asthma to a "thick and viscid phlegm caused by coldness and humidity of the *pneuma*" (3, 4). Also, he noted that women were more prone to asthma, men were more likely to die of it, and children had a better outlook for recovery (3).

In his writings, the heart is the source of life and strength that attracts the *pneuma* into the lungs for subsequent dispersion through the body. Any imbalance in this condition could be fatal. He located asthma in the lungs, supporting the idea that if the patient has simultaneous heart disease, he or she will not survive very long (3).

Areataeus, in an excellent clinical sense, described the paroxysm of the disease. The symptoms include chest heaviness, tiredness, and difficulty of breathing. If the patient's condition gets worse, the symptoms will become more prominent, the cough is frequent and laborious, the expectoration small and thin, the cheeks intensely red, the eyes protuberant, and the voice liquid without resonance. The patient also has a desire to get into open air: "They open the mouth since no house is sufficient for their respiration, they breathily standing, as if desiring to draw in all the air which they possibly can inhale... the neck swells with the inflation of the breath, the precordia retracted, the pulse becomes small and dense," and if the symptoms persist the patient "may produce suffocation after the form of epilepsy" (3).

However, as the paroxysm ceases, he states, the cough becomes less urgent and less frequent, the voice sonorous, and the body relaxes. "Thus," he concludes, "asthmatics escape death, but in the intervals between severe attacks or even when they are walking on ground level, they bear in mind the symptoms of the disease" (3).

Reading that description, we should realize the value of Areataeus's vivid and clear portrayal of asthma over 1,800 years ago, as it remains a landmark in medical history.

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Lung Function Decrements with 0.06 ppm Ozone Exposure Are of Limited Clinical and Public Health Significance

Kim and coworkers (1) exposed 59 healthy, exercising young adults to 0.06 ppm ozone for 6.6 hours under controlled chamber conditions and observed a mean percent-change in FEV₁ (clean-air adjusted) of −1.75 (95% confidence interval, −3.0 to −0.5) and an increase in neutrophilic inflammation of the airways, with no statistically significant increase in total symptom score. Even though the observed effects for lung function are statistically significant, the essential condition for clinical relevance is that they be significant with respect to broadly recognized clinical guidelines (2).

The American Thoracic Society judges a reversible loss of lung function *in combination with symptoms* to be adverse (3). The European Respiratory Society suggests that only short-term changes in FEV₁ exceeding 12% "may be clinically important," and that changes in FEV₁ measurements should exceed 5% to overcome the intra-day variability of FEV₁ in normal subjects (4). The percent-change reported by Kim and colleagues (1) is much smaller than these standards, and is also smaller than the previously reported percent-changes of −3.52% (5) and −2.86% (6), neither of which were statistically significant. Hence, the results of Kim and coworkers are consistent with earlier reports that the effect of 0.06 ppm ozone exposure for 6.6 hours is not clinically adverse.

In arguing for the public health significance of their findings, Kim and colleagues suggested that because a small proportion of their subjects (3 of 59; 5.1%) had a FEV₁ decrement greater than 10%, a similar proportion of the healthy young adult population will have comparable FEV₁ decrements at 0.06 ppm ozone. The authors sought to augment their "estimate" by including two of the 30 subjects from the study by Adams (5). This number of subjects is far too small to generalize to the entire young adult population.

Moreover, Kim and coworkers overlooked the fact that the observed proportion of subjects with the most extreme responses to ozone exposure is driven substantially by individual variability in FEV₁ response. For example, one subject improved more than 10% with ozone exposure, while another declined by about 18% with filtered air. The *improved* FEV₁ measurements at 0.06 ppm ozone were most likely attributable to individual variability rather than any "beneficial" effects of ozone. The findings of Kim and colleagues should not be the basis for claims about the population-wide cost (much less benefit) of exposure to 0.06 ppm ozone.

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