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COUNTERPOINT

Why do clinical trials of Xpert® MTB/RIF fail to show an effect on patient relevant outcomes?

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THE WORLD HEALTH ORGANIZATION (WHO) recommends that Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) should be used instead of conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults with suspected multidrug-resistant tuberculosis (MDR-TB) or human immunodeficiency virus (HIV) associated TB (strong recommendation, high-quality evidence).[1] This advice is based primarily on a systematic review and meta-analysis of diagnostic accuracy studies, which found a pooled sensitivity of 88% (95% credibility interval [CrI] 83–92) and pooled specificity of 98% (95%CrI 97–99) when Xpert replaces microscopy as the initial diagnostic test.[2] This equates to a positive likelihood ratio (LR+) of 44 and a negative LR (LR–) of 0.12.

There have now been eight trials evaluating the impact of Xpert on patient-relevant outcomes such as morbidity and mortality, and all have shown no benefit.[3–10] This not only calls the WHO guidance into question, it also raises the question as to why a test with seemingly impressive diagnostic accuracy should fail in impact trials. A number of theories have been advanced, including deficiencies in trial design and trial conduct and the weaknesses of the health systems in which the trials were conducted.[11] Application of the threshold approach to clinical decision making may also be helpful in solving this conundrum.[12]

The threshold model of disease describes two thresholds for clinical decision making (Figure). The test threshold is the point at which the clinician is at equipoise regarding the decision to rule out the disease or gather additional data. The treatment threshold is the point at which the clinician is at equipoise regarding the decision to gather additional data or rule in the disease and initiate treatment. There are thus three options for any patient presenting with an undifferentiated symptom: the probability of disease falls below the test threshold and it can be ruled out; the probability falls above the treatment threshold and treatment may be initiated; or it falls between the thresholds and more information is needed in the form of test(s).[13]

It follows that testing is unnecessary if the probability of disease lies above the treatment threshold, as treatment will be initiated even if the test is negative, and the reverse is true if the probability of disease is below the test threshold. For example, a patient with HIV who has been coughing for 2 weeks and is unable to walk unaided, with temperature 39°C, haemoglobin 8.3 g/dl, white cell count 6.5 x10^9/l and chest X-ray highly suggestive of TB, has a pre-test probability of TB of 90.5%, according to a validated prediction rule.[14] If Xpert on sputum is negative, the post-test probability of TB is still 53%. Although the threshold for initiating treatment in such cases has not been formally determined, it is likely, given how unwell the patient is and the lack of further immediate testing options, that anti-tuberculosis treatment should be started. Therefore, such a patient should be initiated on treatment regardless of the Xpert result.

Inclusion of such patients in randomised trials is problematic for a number of reasons. First, the appropriate treatment for these patients is independent of the group into which they are randomised, which diminishes the power of the study. Second, it might lead to inappropriate treatment of patients: if they were randomised to the intervention arm but the test was negative, the clinician might inappropriately withhold therapy; if the same patient were randomised to the control arm they would probably be initiated on therapy based on the high probability of disease. As such, being randomised to the intervention arm has the potential to cause harm and reduce any overall observed benefit of the test. A similar argument can be made for patients with a pre-test probability of disease below the test threshold.

The magnitude of these effects is currently unknown, as validated clinical prediction rules have not generally be used in impact studies, and the test and treatment thresholds for TB have not been formally determined. There have, however, been recent ad-

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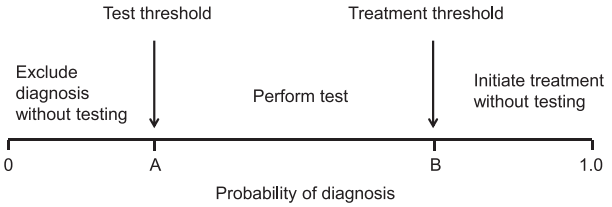

Figure The threshold model of clinical decision making.

vances in the methods of determining thresholds for other diseases. For example, Ebell et al. have determined decision thresholds for common diseases such as influenza, acute coronary syndrome and urinary tract infection by randomly varying the probability of disease presented to clinicians in clinical scenarios and creating threshold curves.[13] A similar approach may be used for determining decision thresholds for TB. The test threshold is likely to be low due to the high reported specificity, but will be slightly higher in treatment-experienced patients due to the lower specificity in this group.[15] Treatment thresholds are likely to vary depending on how clinically unstable the patient is, as treatment at a lower probability is usually indicated when patients are very unwell and time to assess response to treatments is limited.

Separate thresholds must be determined for each type of extra-pulmonary TB. The treatment threshold is likely to be lower for TB meningitis, due to the severe consequences of delaying treatment and because the sensitivity of Xpert on cerebrospinal fluid is lower than on sputum.[1] The converse is true for isolated lymph node disease, as short delays in treatment are less likely to be harmful and the sensitivity of Xpert is high when performed on lymph node tissue.[1]

It should be noted that Xpert detects not only the presence of TB but also rifampicin resistance, and this may add to its value, particularly in high-prevalence areas. However, the approach should be no different, in that thresholds for starting treatment for rifampicin-resistant TB should be determined and compared with the prevalence in the given population.

While validated clinical decision rules to determine the probability of disease prior to testing have been developed,[14] it is imperative that test and treatment thresholds are also determined prior to any future impact trials of Xpert. Patients should then be excluded if test results are unlikely to influence treatment decisions. Only once this is done will we have a clearer picture of the value of Xpert in clinical decision making.

Conflicts of interest: none declared.

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