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The uncertainty of tuberculosis diagnosis

Tuberculosis is estimated to affect 10 million people each year, but this statistic is remarkably uncertain: 30% are countries' estimates of undiagnosed, untreated, or unreported cases. Furthermore, about half of tuberculosis diagnoses globally are uncertain because they rely entirely on the non-specific clinical features of tuberculosis, without any laboratory confirmation.[1]

Laboratory tests for tuberculosis generally perform poorly and are scarcely available in resource-constrained settings where most cases of tuberculosis occur.[1] Consequently, when assessing a patient who is unwell with symptoms such as prolonged productive cough for whom rapid laboratory tests for tuberculosis are unavailable or negative, it is often difficult to discern whether the 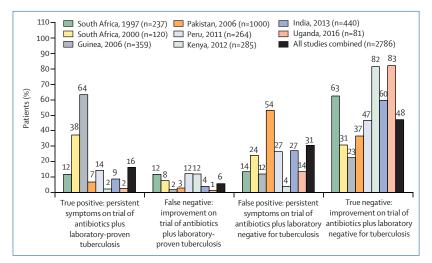patient has tuberculosis or a more common disease such as a bacterial pneumonia. In this situation, some guidelines recommend a trial of antibiotics, a widely practiced approach entailing a few days of broad-spectrum antibiotics that are inactive against tuberculosis. This approach assumes that symptom persistence despite a trial of antibiotics implies that tuberculosis is probable, and that improvement on a trial of antibiotics rules out tuberculosis.[2] However, these assumptions have been the subject of remarkably little research and are undermined by issues such as antibiotic resistance and the placebo effect.

In a systematic review and meta-analysis in *The Lancet Infectious Diseases*, Titus Divala and colleagues[3] evaluated a trial of antibiotics as if it were a diagnostic test for tuberculosis. After screening 9410 publications, they identified eight studies in which patients with initially negative rapid tuberculosis tests were treated with a trial of antibiotics, the response to which was compared with the subsequent results of more sensitive laboratory testing for tuberculosis. Of the 2786 patients who had a trial of antibiotics, overall 608 patients (22% [range 4–65]) were later found to have laboratory-proven tuberculosis. The crude results of these eight studies are summarised in the figure, which shows that whether patients' symptoms persisted on a trial of antibiotics did not usefully predict laboratory-proven tuberculosis. For example, overall, 1307 (47% [range 6–76]) of 2786 patients had symptoms that persisted despite a trial of antibiotics, implying that they had tuberculosis, but remarkably only 454 (35% [range 11–84]) of 1307 patients with persistent symptoms were later found to have laboratory-confirmed tuberculosis. Furthermore, 154 patients (25% [range 3–85]) of

Figure: Crude data from the eight studies analysed by Divala and colleagues,[3] adapted from their figure 2
If the response to a trial of antibiotics reliably indicated whether a patient had tuberculosis, then almost all of the patients would have true-positive or true-negative responses, and few patients would have false-positive or false-negative responses. Labels above each bar are the crude percentages reported in each study. Thus, the bars for all studies combined indicate the crude sum of the data from each of the eight studies. n=number of patients receiving a trial of antibiotics for suspected tuberculosis.

608 patients later found to have laboratory-confirmed tuberculosis paradoxically improved on a trial of antibiotics, an improvement that should have ruled out this tuberculosis diagnosis. These crude percentages are complementary to the rigorous random effects meta-analysis reported by Divala and colleagues, which suggested that a trial of antibiotics had pooled sensitivity of 67% (95% CI 42–85) and specificity of 73% (58–85) versus mycobacteriology tests. This poor performance of a trial of antibiotics has important implications for policy and practice.[3]

The methods and results of these eight studies varied so greatly that the combined statistics and pooled meta-analyses have questionable precision.[4] Despite this variability, the trial of antibiotics performed poorly for ruling tuberculosis in or out in each of the eight studies. These findings are approximations because tuberculosis laboratory testing might be false positive,[5] and because false-negative laboratory tests in patients who have tuberculosis are frequent.[6] Furthermore, molecular testing was only included in the initial rapid testing in one of these eight studies,[7] but it has since become widely used for diagnosing tuberculosis.[1] None of these issues are likely to challenge Divala and colleagues' conclusion that a trial of antibiotics is unreliable for informing tuberculosis diagnosis.

Importantly, broad-spectrum antibiotics might still be necessary, not to inform tuberculosis diagnosis, but rather because the patient's illness requires antibiotic treatment, ideally guided by laboratory testing.[8] However, there is compelling evidence that broad-spectrum antibiotic therapy for patients with a suspected respiratory tract infection might often be safely withheld initially, potentially reducing the risk of side-effects and antibiotic resistance.[9]

Divala and colleagues' findings show that a trial of antibiotics should not generally be used to decide whether to commence tuberculosis therapy in patients with negative, pending, or unavailable laboratory tests for tuberculosis. But what should health systems, clinicians, and patients do instead? When should empirical treatment be commenced rather than doing additional tests or waiting to see how the illness evolves? There is an urgent need for operational research to address this knowledge gap, which will depend on local epidemiology, the severity of the patient's illness, and the availability of repeat and more accurate laboratory tests.

More than a century after Robert Koch identified *Mycobacterium tuberculosis*, why do policy and practice still often include non-evidence-based algorithms for people with tuberculosis? Why are we clarifying the poor diagnostic reliability of a trial-of-antibiotics for tuberculosis only after they have been used millions of times during several decades? Both questions are answered in part by the chronic severe underfunding of tuberculosis research.[1,10] The coronavirus disease 2019 (COVID-19) emergency and resultant socioeconomic crisis will inevitably worsen the global tuberculosis pandemic by increasing tuberculosis risk factors and social determinants, and challenging health systems and access to them. It is striking that long before mortality attributed to COVID-19 approaches 1·5 million—the number of deaths caused by tuberculosis each year—there has been unprecedented investment in research that is rapidly defining how best to care for people with suspected COVID-19. This should be an inspiration to the fight for tuberculosis elimination. Similar urgency and investment are also desperately needed to inform improved care for people suspected of having the most frequent infectious cause of death, tuberculosis.

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Assessment of patients who tested positive for COVID-19 after recovery

See Online for appendix

Since the start of the outbreak in December 2019, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), has led to an increasing number of infections worldwide, with an estimated overall mortality of 5·7%.[1] Meanwhile, many patients who were hospitalised have recovered and were discharged to self-quarantine. However, some patients have tested positive for COVID-19 again after recovery. An explanation of why patients tested positive for COVID-19 on a retest remains unclear.

In the Wuhan Pulmonary Hospital (Wuhan, China), 651 patients were classified as recovered between Jan 11, 2020, and April 1, 2020. The standard hospital discharge criteria[2] were applied: patients were haemodynamically stable and afebrile for longer than 3 days, with radiological evidence of substantial resolution of pneumonia with a CT scan, two negative SARS-CoV-2 RT-qPCR tests done at least 1 day apart on nasopharyngeal and oropharyngeal swabs, and no concurrent acute medical issues requiring transfer to another medical facility. All discharged patients were followed up by two medical teams; the median follow-up duration was 48 days (IQR 18–50), and the longest follow-up was 91 days.

During this follow-up, 23 (3%) of 651 patients tested positive on a retest for SARS-CoV-2 by RT-qPCR assay in a routine health check (appendix). The median age of this retest-positive group was 56·0 years (range 27·0–89·0, IQR 48·5–74·0), with slightly more women (12 [52%] of 23 patients) than men (11 [48%]). In this retest-positive group, 12 patients (52%) had moderate, nine (39%) severe, and two (9%) critical conditions during their previous hospitalisation. The median duration from hospital discharge to a positive retest was 15·0 days

(range 4–38, IQR 11·0–16·5; appendix). The median duration from a positive retest to hospital re-admission was 1·5 days (IQR 1·0–2·0). At the time of the positive retest, a colloidal gold-based immunochromatographic strip assay for anti-SARS-CoV-2 viral immunoglobulins showed that seven patients (30%) were positive for both IgM and IgG, whereas five (22%) were IgG-positive but IgM-negative; the remaining 11 patients (48%) were negative for both antibodies. Among this retest-positive group, 15 patients (65%) were asymptomatic at the time of the retest whereas eight (35%) had at least one symptom associated with active COVID-19. Specifically, six patients (26%) presented with fever, two (9%) had a cough, one (4%) reported fatigue, one (4%) dyspnoea, and one (4%) chest tightness. Although a positive PCR test in asymptomatic patients who were retested might only reflect residual non-pathogenic viral components, the positive retest in symptomatic patients suggests the potential for recurrence of active disease and its transmission.

At the time of the last follow-up, on April 4, 2020, all 23 patients with a positive retest were alive, 18 (78%) had recovered and were again discharged from the hospital, four (17%) remained in hospital for additional medical care, and one (4%) remained at home for self-isolation. In this retest-positive group, one 80-year-old patient had thoughts of suicide. No new viral transmission could be ascribed to these patients with a positive retest. This might be due to the precautionary measure of the hospital to discharge patients into intermediary Fangcang shelter hospitals[3] or other related health centres for 14-day clinical monitoring. Fangcang shelter hospitals are large-scale and temporary hospitals rapidly built