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Test and Treat: A New Standard for Smear-Positive Tuberculosis

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Abstract

Optimizing sputum smear microscopy, the principal method of tuberculosis (TB) diagnosis in high-burden settings around the world, is a critical priority for global TB control. To improve rates of testing, completion, and reporting, the World Health Organization (WHO) recently endorsed a policy of same-day diagnosis of TB by microscopy. Unfortunately, the implementation of this policy has emphasized same-day sputum collection alone, with patients required to return on a subsequent day to collect results. We use a simple decision analysis to demonstrate that the timing of results reporting has a greater impact on treatment initiation for smear-positive TB cases than the timing of specimen collection. Same-day diagnosis of smear-positive TB, including sputum collection and reporting of smear results, should be the new global standard.

Keywords

Tuberculosis; modeling; decision analysis; smear microscopy; same-day diagnosis; same-day treatment

The Problem

Despite its limited sensitivity, sputum smear microscopy is the principal method of tuberculosis (TB) diagnosis in high-burden settings around the world. It will likely remain so for many years, because more cost-effective and affordable diagnostic techniques are unlikely to be developed soon. Optimizing smear microscopy by improving rates of testing, completion, and reporting is therefore a critical priority for global TB control: even a 10% increase in case-detection and treatment-initiation rates could save thousands of lives and transform a stable TB epidemic into one trending toward elimination.[1]

In the past several years, the World Health Organization (WHO) has endorsed a number of changes to improve the efficiency of smear microscopy, including a recommendation for same-day diagnosis in which two sputum specimens are collected on the first day of patient evaluation rather than on successive days.[2] Although this policy recommendation explicitly states that the advantages of same-day diagnosis are maximized if “laboratory results are

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received back at the health facility and patients start treatment on the same day," the implementation of this policy has emphasized same-day sputum collection alone. Unfortunately, when reporting and treatment initiation occur on a subsequent day, the principal goals of the policy - eliminating the need for poor patients to make multiple visits to health centers and not losing smear-positive patients to follow-up before they start treatment -are frustrated.

As studies of new TB diagnostic tests and strategies proliferate, there is growing recognition that treatment initiation, rather than diagnostic accuracy, is the outcome of greater relevance for patients with TB and for populations at risk of developing TB following exposure.[3] Although preparing and examining a sputum smear takes less than 30 minutes, delays in reporting smear results are common, and treatment initiation for smear-positive patients frequently takes weeks.[4] During this time, patients are regularly lost to follow-up because the costs of a return visit are unaffordable; in HIV-endemic regions, many die.[5] Further, while much has been made of the fact that only 40% of people living with HIV know their status[6], and that these individuals contribute to the majority of ongoing HIV transmission even in low-burden settings[7], it is less widely publicized in the HIV community that over 30% of people with smear-positive TB *never* learn of their diagnosis and yet continue to transmit TB.[8] To illustrate how the standard TB diagnostic approach enables this public health failure, we use a simple decision analysis to demonstrate that the timing of results reporting has a greater impact on treatment initiation for smear-positive TB cases than the timing of specimen collection.

Impact of Same-day Results Reporting

We consider a hypothetical population of 1,000 individuals with active TB, presenting for diagnosis in a center with access to smear microscopy. We assume that each member of the population starts the diagnostic process by submitting one initial sputum specimen, and we evaluate the relative effectiveness of three strategies for completing the diagnostic evaluation:

- **a.** Standard TB diagnosis – collecting and preparing a second sputum for smear microscopy on the following day, and requiring patients to return for results and treatment initiation (if smear-positive) one or more days after the last sputum sample is submitted;
- **b.** Same-day sputum collection – collecting a second sputum for smear microscopy immediately, but reporting results and initiating treatment (if smear-positive) according to standard practice, as described above;
- **c.** Same-day diagnosis – collecting a second sputum for smear microscopy immediately, and reporting results and initiating treatment (if smear-positive) on the same day.

For purposes of this illustration, we ignore false-positive smear results and decisions to treat despite negative sputum smear(s). We assume a 54% sensitivity of the first smear[9], a 6% absolute increase in sensitivity for a second morning sputum[9], a 4% absolute increase in sensitivity for a second spot sputum on the same day[10], and a 15% initial-default proportion (proportion of smear-positive patients not starting treatment with delayed results reporting).[11] Based on data reported in a recent clinical trial[10], we conservatively assume 2% loss to follow-up before providing a second sputum specimen on the same day, and 4% additional loss to follow-up (total 6% loss) before providing a second sputum specimen at a subsequent visit. Similarly, we assume 4% loss to follow-up between sputum collection and results reporting for same-day reporting strategies. Our primary outcome is TB treatment initiation.

Under the conditions above, same-day diagnosis results in a 15% relative increase in smear-positive TB cases being placed on treatment compared with the standard diagnostic strategy (54.5% vs. 47.9%, Table). In contrast, focusing "same-day" efforts on sputum collection alone, without completing the diagnostic pathway through to reporting results and initiating treatment, generates relatively little benefit over the standard strategy (48.3% vs. 47.9%, Table). For the standard or same-day sputum collection strategies to outperform same-day diagnosis, the additional yield of the second sputum smear, as collected under those strategies, must be greater than the number of patients lost to follow-up before initiating treatment – a condition that is unlikely to occur in most routine settings.

This analysis does have important limitations; it does not account for repeat diagnostic attempts, treatment of smear-negative TB, or initial default for reasons unrelated to timing of sputum results (*e.g.*, mistrust of the public health system – which may be partially alleviated by same-day treatment initiation). However, we also biased this comparison in favor of delayed reporting by not accounting for secondary transmission or mortality prior to treatment initiation and by using optimistic follow-up rates observed in a clinical trial. In routine settings, where drop-out rates are commonly reported to be many-fold higher, the benefits of same-day diagnosis are likely to be even greater.

A Call to Action

We have used a simple decision analysis to show that same-day reporting of results is more likely to result in successful treatment initiation than either same-day or two-day collection with delayed reporting. These results suggests that unless we move quickly to adopt all aspects of the WHO recommendation for same-day TB diagnosis, we will contribute to ongoing – and preventable – TB transmission and mortality, much of which continues to be borne by people living with HIV. Recently, there has been substantial enthusiasm expressed for using rapid antiretroviral therapy with prompt linkage to care to prevent HIV transmission.[12] If we advocate a "test and treat" policy for HIV, why not for TB, the leading killer of people living with HIV/AIDS? Diagnosis without linkage to care is as ineffective - and should be as unacceptable - for TB as it is for HIV. Although high-quality post-implementation data on the impact of same-day reporting on patient- and public-health-important outcomes is important to evaluate this new policy, we cannot, in good conscience, persist with a system that requires poor patients to return for results and treatment when we know many will not be able to do so.

Developing systems for same-day reporting of smear results and treatment initiation poses staffing, logistical, and technological challenges, but several simple measures to re-center the process around the needs of patients could catalyze new solutions. For example, since guidelines recommend TB screening of patients with cough, fever, chills, or night sweats[13], routine algorithms should be developed to refer patients with these symptoms (especially in HIV testing or treatment centers) directly to laboratories for sputum collection without requiring them to see a clinician first. Laboratories could perform AFB smears according to the same streamlined workflow used to prepare, examine, and report other lab tests, so that patients suspected of having TB receive the same level of service as other patients. Importantly, the advent of LED fluorescence microscopy and rapid fluorescent staining kits make batched testing, which is common with Ziehl-Neelsen staining, unnecessary. Outside of diagnostic centers, innovative technologies such as mobile-phone-based microscopy could facilitate rapid interpretation and communication of sputum smear results.[14] Systems developed to report smear results rapidly will be critical for harnessing the potential of new TB diagnostic tests (*e.g.*, the Xpert MTB/RIF nucleic acid amplification assay). Moreover, these approaches can also be applied to other clinical data, thereby providing ancillary benefits to health systems in the same way that scale-up of antiretroviral therapy has

motivated overall improvements previously considered infeasible in other health sectors.[15] By emphasizing same-day results reporting and treatment initiation for smear-positive TB patients as the international standard, the TB control community can motivate global change in healthcare systems, to the benefit of the poor.

Failure to prioritize same-day reporting of microscopy results and treatment of smear-positive TB endangers individuals every day, many of whom are living with HIV. By facilitating ongoing transmission of TB, current practices will have a negative impact far into the future, from the dual perspectives of the disease itself, as well as the enormous economic toll it exacts. Same-day TB diagnosis should not be optional simply because it is challenging; we cannot wait for a point-of-care TB test to make same-day diagnosis the standard of care when we have the tools to do so today. We owe it to our patients to immediately make same-day diagnosis of smear-positive TB not just a recommendation, but a new global standard.

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JLD and AC conceived of the study. JLD, DWD, and AC drafted the manuscript. DWD, SDB, and NDW performed the data analysis. AK critically revised the manuscript. All authors read and approved the text as is being submitted to AIDS.

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Table

Projected Outcomes of 1,000 Active TB Cases Presenting for Diagnosis in a Facility with Smear Microscopy.

Strategy[a]	**Number of Patients Completing Each Step in TB Diagnosis**			
	Provide First Sputum	**Provide All Sputa**	**Produce ≥1 Positive Sputum**	**Initiate Treatment**
Standard TB diagnosis	**1000**	**940** (1000*0.94)	**564** (940*0.60)	**479** (564*0.85)
Same-day sputum collection	**1000**	**980** (1000*0.98)	**568** (980*0.58)	**483** (568*0.85)
Same-day diagnosis	**1000**	**980** (1000*0.98)	**568** (980*0.58)	**545** (568*0.96)

[a]See text for explanations of each strategy and relevant assumptions.