

ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

Article

Cattamanchi A, Reza TF, Nalugwa T, et al. **Multicomponent Strategy with Decentralized Molecular Testing for Tuberculosis.** *N Engl J Med.* 2021;385(26):2441-2450

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Study Summary

The cluster-randomized XPEL-TB trial evaluated whether on-site molecular testing for tuberculosis (TB), combined with guided restructuring of clinic workflows and monthly performance feedback, improved TB diagnosis and treatment, compared to routine care.

Study Setting

- Twenty community health centers in Uganda.
- All sites performed on-site sputum-smear microscopy as the primary method of TB diagnosis at the time of trial initiation and were linked to a central health facility (hub) that performed Xpert testing.

Methods

- Adults (≥ 18 years of age) were included in the study if they underwent evaluation for TB at one of the study sites, defined as having been entered into at least one national register for patients who screen positive for TB symptoms, are tested for TB, or are treated for TB.
- Health centers were randomly assigned (1:1) to the intervention group or the control group, stratified by the proportion of patients treated for TB within 14 days after presentation for evaluation at baseline.
- Health centers in the intervention group:
 - Received one GeneXpert Edge device to enable on-site molecular testing with Xpert as the first-line test for TB.
 - Underwent a structured process to redesign and streamline their clinic, laboratory, and pharmacy workflows to facilitate same-day testing and treatment initiation.
 - Received a monthly report card with performance indicators related to TB diagnostic evaluation to encourage continuous quality improvement.
- Health centers in the control group continued to follow national guidelines for TB diagnostic evaluation with on-site sputum-smear microscopy, plus referral of sputum samples obtained from high-risk patients to Xpert testing hubs.
- Demographic, clinical, and outcome data were abstracted from the TB registers.

- The primary outcome was the number of individuals who were treated for confirmed TB (defined as a positive result on sputum-smear microscopy or molecular testing) within 14 days after presentation to the health center for TB evaluation during the 16-month intervention period.
- Secondary outcomes included the number and proportion of individuals who were tested for TB according to national guidelines; who received a diagnosis of confirmed TB on the same day or within 14 days after presentation; who were treated for confirmed TB on the same day or within 14 days; time to diagnosis of TB and time to treatment for TB.

Study Population and Follow-up

- Ten health centers were assigned to each group.
- From October 2018 to February 2020, 12,934 individuals underwent evaluation for TB at the study sites, of whom 10,644 were eligible and included in the trial, including 5,546 at health centers in the intervention group and 5,098 at health centers in the control group.
- The median age of individuals was 40 years, 60.1% were women, and 43.8% were living with HIV, with similar characteristics between the trial groups.

Primary Outcome

- During the 16-month intervention period, 342 patients were treated for confirmed TB within 14 days after presenting for evaluation at health centers in the intervention group, as compared with 220 patients at health centers in the control group (adjusted rate ratio [aRR], 1.56; 95% confidence interval [CI], 1.21 to 2.01).
- In sub-group analyses, the number of patients treated for confirmed TB within 14 days was greater in the intervention group among people living with HIV (aRR, 1.78; 95% CI, 1.15 to 2.77), and among those without HIV infection (aRR, 1.46; 95% CI, 0.98 to 2.18), although in the latter group, this comparison did not reach statistical significance.

Secondary TB Testing Outcomes

- The number of individuals tested for TB in accordance with national guidelines was higher at health centers in the intervention group than at health centers in the control group (aRR, 1.85; 95% CI, 1.21 to 2.82), as were the number of individuals who received a diagnosis of confirmed TB on the same day (aRR, 1.89; 95% CI, 1.39 to 2.56) or within 14 days (aRR, 1.28; 95% CI, 0.99 to 1.66).
- Among all individuals evaluated for TB, a greater proportion completed testing in accordance with national guidelines (aRR, 1.57; 95% CI, 1.39 to 1.78) and were diagnosed with confirmed TB on the same day (aRR, 1.42; 95% CI, 0.99 to 2.02) at the intervention sites, compared to control sites, whereas the proportion who received a diagnosis within 14 days was not significantly different (aRR, 0.98; 95% CI, 0.73 to 1.31).
- The adjusted geometric mean number of days to diagnosis of TB was 51% (95% CI, 38 to 61) lower in the intervention group than in the control group.

Secondary TB Treatment Outcomes

- The number of individuals treated for confirmed TB on the same day was greater at health centers in the intervention group than at health centers in the control group (aRR, 2.38; 95% CI, 1.57 to 3.61), as was the number treated within 14 days (aRR, 1.56; 95% CI, 1.21 to 2.01).
- Among the individuals evaluated for TB, a greater proportion were treated for confirmed TB at the intervention sites, compared to the control sites, on the same day (aRR, 2.18; 95% CI, 1.17 to 4.05) and at 14 days (aRR, 1.15; 95% CI, 0.80 to 1.64), although the latter was not significant.
- The adjusted geometric mean number of days to treatment for TB was 65% (95% CI, 44 to 79) lower in the intervention group than in the control group.

Critical Analysis

This cluster-randomized trial found that a multicomponent intervention, including the availability of on-site molecular TB testing, restructuring of clinic workflow, and monthly feedback, resulted in a higher rate of treatment for confirmed TB within 14 days of presentation, when compared to routine care at community health clinics. In addition, the intervention improved the completion and timeliness of earlier steps along the cascade of care, which led to more individuals being tested for TB in accordance with national guidelines and receiving a diagnosis of confirmed TB.

The following points should be considered when interpreting the study findings:

- The intervention was a multicomponent strategy; therefore, the effects of each separate component could not be evaluated.
- The primary outcome was changed six months after the trial began. The original primary outcome was the proportion of individuals who were treated for confirmed TB within 14 days after presentation among those evaluated for TB, and there was no difference in this outcome by study arm. However, this change was made before data analysis, because investigators thought the number treated was a better reflection of the intended effect of the intervention, which was designed to close gaps across the entire TB diagnostic evaluation cascade of care.
- The trial period was also changed, from 18 months to 16 months, due to the anticipated impact of COVID-19 on the care and treatment of individuals with TB. This likely reduced the intended sample size and power to detect significant differences between the groups.
- Children and adults with extrapulmonary TB were excluded, and therefore the impact of this intervention on these populations is unknown.
- The median number of individuals evaluated for TB per health center was 617 at intervention sites and 394 at control sites. This suggests that there was an imbalance among the sites in the prevalence of TB or other factors, or that the intervention increased the number of people who underwent TB evaluation. To minimize the possibility of imbalance between study arms, investigators collected pre-randomization data from the sites that

informed stratified and restricted randomization; however, the number of health centers was small.

- The effects of the trial strategy on TB diagnosis and treatment outcomes were less robust at day 14 than on day 1, which was likely due to more people returning after the initial visit for additional testing or to initiate treatment.
- This trial was highly pragmatic, with minimal eligibility criteria, waiver of informed consent, minimal study staff presence at sites, and reliance on routinely collected data to assess study outcomes. This increases the generalizability of trial findings to real-world settings.

Implications

The cluster-randomized XPEL-TB trial found that a multicomponent intervention that decentralized molecular testing and addressed site-level barriers to TB evaluation improved the number of people diagnosed and treated for confirmed TB at community health centers in Uganda. As additional platforms for decentralized molecular testing become available, these results support their implementation at community health centers in countries with a high prevalence of TB, in combination with other feasible strategies to promote quality TB services.

This article synopsis was written by Dr. Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at caw2208@columbia.edu.