Impact of Point-of-Care Xpert MTB/RIF on Tuberculosis Treatment Initiation

A Cluster-randomized Trial

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Abstract

Rationale: Point-of-care (POC) diagnostics have the potential to reduce pretreatment loss to follow-up and delays to initiation of appropriate tuberculosis (TB) treatment.

Objectives: To evaluate the effect of a POC diagnostic strategy on initiation of appropriate TB treatment.

Methods: We conducted a cluster-randomized trial of adults with cough who were HIV positive and/or at high risk of drug-resistant TB. Two-week time blocks were randomized to two strategies: (1) Xpert MTB/RIF test (Cepheid, Sunnyvale, CA) performed at a district hospital laboratory or (2) POC Xpert MTB/RIF test performed at a primary health care clinic. All participants provided two sputum specimens: one for the Xpert test and the other for culture as a reference standard. The primary outcome was the proportion of participants with culture-positive pulmonary tuberculosis (PTB) initiated on appropriate TB treatment within 30 days.

Measurements and Main Results: Between August 22, 2011, and March 1, 2013, 36 two-week blocks were randomized, and 1,297 individuals were enrolled (646 in the laboratory arm, 651 in the POC arm), 159 (12.4%) of whom had culture-positive PTB. The proportions of participants with culture-positive PTB initiated on appropriate TB treatment within 30 days were 76.5% in the laboratory arm and 79.5% in the POC arm (odds ratio, 1.13; 95% confidence interval, 0.51–2.53; $P = 0.76$; risk difference, 3.1%; 95% confidence interval, –16.2 to 10.1). The median time to initiation of appropriate treatment was 7 days (laboratory) versus 1 day (POC).

Conclusions: POC positioning of the Xpert test led to more rapid initiation of appropriate TB treatment. Achieving one-stop diagnosis and treatment for all people with TB will require simpler, more sensitive diagnostics and broader strengthening of health systems.

Clinical trial registered with www.isrctn.com (ISRCTN 18642314) and www.sanctr.gov.za (DOH-27-0711-3568).

Keywords: tuberculosis; drug-resistant tuberculosis; molecular diagnostics; point-of-care systems; clinical trial

(Received in original form February 3, 2017; accepted in final form July 20, 2017)

Supported by Wellcome Trust grant 090999/Z/09/Z (www.wellcome.ac.uk) (R.J.L.), the Biomedical Research Centre of Imperial College Healthcare NHS Trust and the National Institute for Health Research Point of Care Diagnostics Diagnostic Evidence Co-operative (G.S.C.), and Wellcome Trust grant WT083495MA (N.M.). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions: Conception and design: R.J.L., G.S.C., N.M., M.P.N., M.-L.N., and P.G.-F.; randomization and cluster allocation: N.M.; acquisition of data: R.J.L.; preparation of statistical analysis plan and data analysis: R.J.L. and N.M.; interpretation of data: R.J.L., G.S.C., N.M., M.P.N., M.-L.N., and P.G.-F.; drafting of the manuscript: R.J.L.; revision of the manuscript for important intellectual input: G.S.C., N.M., M.P.N., M.-L.N., and P.G.-F.; approval of the final version of the manuscript: R.J.L., G.S.C., N.M., M.P.N., M.-L.N., and P.G.-F.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 196, Iss 7, pp 901–910, Oct 1, 2017

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Originally Published in Press as DOI: 10.1164/rccm.201702-0278OC on July 20, 2017

Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the

Subject: Centralized, laboratory-based diagnostic systems for tuberculosis (TB) are associated with substantial loss to follow-up and delays prior to treatment. Whether decentralized, point-of-care diagnostic systems can reduce loss to follow-up and treatment delay has not been adequately investigated.

What This Study Adds to the

Field: To our knowledge, this is the first randomized trial to make a direct comparison between point-of-care and laboratory use of a molecular TB diagnostic test. The point-of-care strategy shortened the time to appropriate treatment for people with rifampicin-susceptible TB; three-fourths of Xpert-positive/rifampicin-susceptible participants received same-day diagnosis and treatment. Under both strategies, there were delays for people with drug-resistant TB and people with Xpert-negative/culture-positive TB, highlighting the need for more sensitive rapid diagnostics and further strengthening of health and laboratory systems.

Tuberculosis (TB) remains one of the most important causes of global mortality, causing around 5,000 deaths every day (1). In sub-Saharan Africa, the HIV epidemic and the spread of drug-resistant tuberculosis (DR-TB) contributed to a failure to achieve targets for reduction in TB prevalence and mortality expressed in the United Nations Millennium Development Goals (2). Timely detection and treatment of adult patients with pulmonary tuberculosis (PTB) is important, not only to limit individual morbidity and mortality but also to interrupt transmission. Centralized laboratory-based TB diagnostic systems are associated with substantial loss to follow-up and delays prior to treatment (3, 4). Although diagnostics with improved sensitivity for detecting TB disease could have substantial clinical and public health impact, additional benefit might be achieved by positioning diagnostics at more peripheral levels of the health system (5, 6); however, there is

little high-quality evidence regarding whether implementation of diagnostics at the point of care (POC) improves patient-relevant outcomes.

This evidence is important to inform the scaleup of existing technologies and to guide the development of new diagnostics (7, 8). The aim of this trial was to determine whether a diagnostic strategy involving a rapid molecular test positioned at a rural primary health care (PHC) clinic would reduce delays and loss to follow-up prior to TB treatment compared with a strategy of centralized laboratory testing.

Methods

Trial Design

This study was a cluster-randomized trial of adults with possible PTB and DR-TB in which we evaluated the impact of Xpert MTB/RIF test (Cepheid, Sunnyvale, CA) positioning on the initiation of appropriate TB treatment (9). The unit of randomization was a time period (2-week block), with each time period randomized either to a strategy with the Xpert MTB/RIF system placed in a centralized, subdistrict-level laboratory (laboratory strategy) or to a strategy with the same system positioned at the clinic (POC strategy). A cluster represented the group of participants enrolled during the 2-week block. The unit of observation was the individual participant.

The trial was conducted in Hlabisa health subdistrict, uMkhanyakude district, northern KwaZulu-Natal province, South Africa, a predominantly rural area with a high burden of TB, DR-TB, and HIV. In 2011, the TB notification rate for the subdistrict was 1,050 per 100,000, and HIV seroprevalence was 29% in the adult population aged 15–49 years (10). HIV and TB services are provided at 17 PHC clinics and 1 district hospital through decentralized collaborative programs. Participants were recruited from the largest PHC clinic, situated approximately 55 km by road from the district hospital.

The trial was approved by the biomedical research ethics committee of the University of KwaZulu-Natal (reference BF033/11), the ethics committee of the London School of Hygiene and Tropical Medicine (reference 5926), and the health research committee of the KwaZulu-Natal

Department of Health (reference 084/11). The trial was registered with Current Controlled Trials (ISRCTN Registry) on June 17, 2011 (ISRCTN 18642314), and with the South African National Clinical Trials Register on July 10, 2011 (DOH-27-0711-3568).

Participants

Adults (aged ≥ 18 yr) with possible PTB (defined as cough of any duration) were recruited at the clinic if they were HIV positive and/or had a high risk of DR-TB. These two groups were specified on the basis of their high risk for mortality and prioritization for Xpert MTB/RIF testing at the time of the study (11). High risk of DR-TB was defined as per World Health Organization case finding recommendations and South African national TB guidelines: failure of standard treatment regimen or retreatment regimen, smear nonconversion at Month 2 or 3 of standard treatment regimen or retreatment regimen, relapse or return after loss to follow-up, any other previous TB treatment, household exposure to a person with known multidrug-resistant or extensively drug-resistant TB, health care worker, or prison inmate in the previous 12 months (12, 13). Individuals were excluded if they had a previous diagnosis of multidrug-resistant or extensively drug-resistant TB, were severely unwell and required immediate admission to the hospital, or were unable to give informed consent. In the event of enrollment of a participant on more than one occasion, only the data from the first enrollment were included in the analysis.

Procedures

Potential participants were identified by clinic staff and referred to a research nurse for assessment. Individuals who were eligible for the study were given information about the study in the local language (isiZulu), and consent was indicated by signature or thumbprint. Clinical and demographic information was collected at enrollment by the research nurse. The research nurse at the study site collected two spontaneously expectorated sputum specimens (the first for Xpert MTB/RIF testing and the second for culture). With both strategies, the nurse instructed participants to wait 1 hour between producing the first and second specimens. Under the POC strategy,

participants were advised to wait for their result or, if not possible, to return the next day. Under the laboratory strategy, participants were requested to return to the clinic for results after 3 working days, based on the typical turnaround time for receipt of sputum results at the time of the study.

A four-module GeneXpert system (Cepheid) was installed for each 2-week time period at either the district hospital laboratory or the clinic according to the randomization strategy. With the laboratory strategy, both sputum specimens were transported daily to the National Health Laboratory Service laboratory at the district hospital using the routine specimen transport system. A laboratory technician

performed Xpert MTB/RIF testing, and results were returned to the clinic using the routine transport system. For POC blocks, the research nurse performed Xpert MTB/RIF testing on site in a dedicated room. N95 respirator masks were used, but no biosafety cabinet was used. If no valid result was obtained from the first test and there was sufficient sputum-buffer mix remaining, the test was repeated. If there was insufficient sputum-buffer mix or still no valid result, an additional sputum specimen was obtained from the participant at the earliest opportunity.

Sputum specimens for culture were forwarded from the clinic via the routine specimen transport system to the district

hospital laboratory and then the following day to the provincial reference laboratory in Durban. Mycobacterial growth indicator tubes were inoculated and incubated at 37°C for up to 6 weeks. Positive cultures were identified as *Mycobacterium tuberculosis* complex using routine tests. The Genotype MTBDR_{plus} assay (Hain Lifescience, Nehren, Germany) was performed indirectly on culture isolates to identify mutations associated with rifampicin and isoniazid resistance. For isolates demonstrating rifampicin and/or isoniazid resistance, phenotypic drug susceptibility testing for rifampicin, isoniazid, ofloxacin, and kanamycin was performed.

Figure 1. Study flow diagram for clusters and individual participants. DR-TB = drug-resistant tuberculosis; MDR/XDR-TB = multidrug-resistant/extensively drug-resistant tuberculosis; TB = tuberculosis.

Clinical management was carried out following standardized diagnostic and treatment algorithms (*see* Figures E1 and E2 in the online supplement). The research nurse worked in parallel with the TB nurses at the clinic, but in a separate room; the research nurse coordinated further management for trial participants following routine clinic practice (*see* further details in the online supplement). X-ray facilities were not available at the clinic; they were available only at the district hospital. A medical officer was present at the clinic 1 day per week, but any adults who required further evaluation for TB were referred to the district hospital. Throughout the study period, all participants with rifampicin-resistant TB were admitted to the district hospital and referred to the provincial DR-TB unit in Durban for initiation of DR-TB treatment (14). (Further details are provided in the online supplement.)

Clinic review for outcome evaluation was scheduled 2 months after the enrollment visit. The research nurse collected information regarding initiation of TB treatment, antiretroviral therapy (ART), and hospitalization. Outcome evaluation was not blinded to randomization group. If the participant did not attend the clinic for follow-up evaluation, information was obtained by telephone or from clinic registers.

Outcomes

The primary outcome was the proportion of participants with culture-positive PTB initiated on appropriate TB treatment within 30 days of enrollment. Appropriate treatment was defined according to the results of genotypic and phenotypic tests on the culture isolate (*see* Table E1). Secondary outcomes were time to initiation of appropriate TB treatment for participants with culture-positive PTB, time to initiation of appropriate DR-TB treatment (for participants with rifampicin-resistant TB), all-cause mortality at 60 days, proportion of participants with at least one hospital admission within 60 days, and time to initiation of ART for HIV-positive participants.

Sample Size

The study was designed to detect a 10% increase in the proportion of participants with culture-positive PTB initiated on appropriate treatment within 30 days (from 85% in the laboratory arm).

Sample size was calculated using the coefficient of variation (κ) with the equation of Hayes and Bennett (15). With $\kappa = 0.05$ and a cluster size of 12 culture-positive participants, we needed 16 clusters and 188 participants with culture-positive TB in each arm to detect this difference with 95% confidence and 80% power. We assumed that 10% of individual participants would be lost to follow-up, so we needed 208 participants with culture-positive TB in each arm. Based on the assumption that 25% of adults with possible PTB would have a positive culture, the study was initially planned for enrollment of 1,664 participants.

Randomization

The allocation schedule for random assignment of 2-week blocks was computer generated

using random permuted blocks of eight. Because of extension of the trial, an extra four blocks were randomized. Allocation for each clinic block was placed into sequentially numbered, opaque, sealed envelopes; the envelope was opened on the Friday before the start of a new 2-week block, and the allocated strategy for the next time block was communicated to study staff.

Statistical Methods

Analysis of baseline characteristics was performed to characterize the trial population and to identify any baseline imbalances between the study arms. All analyses were individual-level intention-to-treat analyses that took account of within-cluster correlation. The primary analysis excluded participants with TB

Table 1. Baseline Demographic and Clinical Characteristics of Participants with Possible Tuberculosis or Drug-Resistant Tuberculosis

Variable	Laboratory (n = 640)	Point of Care (n = 641)
Female sex, n (%)	393 (61.4)	422 (65.8)
Age, yr, median (IQR)	36 (30–43)	36 (28–45)
Body mass index, kg/m ² , median (IQR)	22.6 (20.2–26.5)	22.9 (20.1–27.0)
Current symptoms, n (%)		
Cough only	157 (24.5)	147 (22.9)
Weight loss	332 (51.9)	335 (52.3)
Fever	269 (42.0)	256 (40.0)
Night sweats	295 (46.2)	298 (46.7)
Duration of cough, wk*, median (IQR)	2 (1–4)	3 (1–4)
Current IPT use, n (%)	8 (1.3)	11 (1.7)
Risk of drug resistance, n (%)		
None	351 (54.8)	353 (55.1)
Treatment failure	4 (0.6)	7 (1.1)
Smear nonconversion	18 (2.8)	21 (3.3)
Previous TB treatment	253 (39.5)	247 (38.5)
Household contact	22 (3.4)	15 (2.3)
Health care worker	12 (1.9)	9 (1.4)
Prison in last 12 mo	7 (1.1)	10 (1.6)
HIV status, n (%)		
Positive	589 (92.0)	596 (93.0)
Negative	39 (6.1)	39 (6.1)
Never tested	6 (0.9)	3 (0.5)
Not disclosed	5 (0.8)	3 (0.5)
Missing	1 (0.2)	0
Current antiretroviral therapy†, n (%)	238 (40.4)	222 (37.3)
CD4 ⁺ cell count‡, cells/μl		
Median (IQR)	280 (147–455)	247 (119–415)
≤50, n (%)	41 (6.4)	66 (10.3)
51–200, n (%)	152 (23.8)	150 (23.4)
201–350, n (%)	149 (23.3)	158 (24.6)
351–500, n (%)	85 (13.3)	81 (12.6)
>500, n (%)	108 (16.9)	92 (14.4)
Missing, n (%)	54 (8.4)	49 (7.6)

Definition of abbreviations: IPT = isoniazid preventive therapy; IQR = interquartile range; TB = tuberculosis.

*Cough duration missing for 11 participants (laboratory, n = 3; point of care, n = 8).

†Proportions are of HIV-positive participants.

‡CD4⁺ cell count up to 18 months prior to or 30 days after enrollment.

who were on treatment at the time of enrollment with an *M. tuberculosis* culture isolate susceptible to rifampicin and isoniazid, because appropriate treatment for these participants would involve continuation of the same drug regimen. Regression modeling using generalized estimating equations with a binomial distribution function and a logit link was applied, specifying an exchangeable working correlation matrix. Any important individual-level characteristics that were unbalanced between arms were considered in the model as covariates. For the secondary outcomes with binary variables, generalized estimating equation models were also fitted with a binomial distribution function and a logit link. For the secondary outcomes with time-to-event measures, Cox proportional hazards models were used with the shared frailty option to account for clustering by time block. All times were measured from the enrollment date. The proportional hazards assumption was examined graphically using the log-log plot and using the score test based on scaled Schoenfeld residuals (16). Time-to-event data were also plotted as Kaplan-Meier survival curves, and the two groups were compared using the log-rank test. For the Kaplan-Meier analysis, deaths were censored at 60 days (17). All analyses were performed using Stata version 13.1 software (StataCorp, College Station, TX).

Results

Between August 22, 2011, and March 1, 2013, 36 two-week blocks were randomized to one of the two diagnostic strategies (Figure 1). In July 2012, following the identification of a shortfall in the enrollment of culture-positive participants, the trial steering committee recommended measures to optimize recruitment and to maximize the yield from sputum cultures. Despite implementation of these measures, enrollment remained below target, but owing to time and logistical constraints, the enrollment phase could not be extended beyond March 2013. With the numbers recruited, the power of the study to detect a 10% difference in the primary endpoint was 55%.

A total of 1,526 individuals were screened, and 1,297 were enrolled in the trial (Figure 1). Data from 16 participants were excluded from all analyses because of

duplicate enrollment ($n = 14$) or incorrect criteria for TB drug resistance risk ($n = 2$), giving 1,281 individuals for analysis (mean, 36 per cluster; range, 19–56). Altogether, 1,185 (92.5%) were HIV positive, and 577 (45.0%) had a documented risk of DR-TB. The baseline characteristics of the individual participants were well balanced (Table 1).

Overall, 1,235 participants (96.4%) submitted two sputum specimens. The proportion of initial specimens from which no Xpert MTB/RIF test result was obtained was higher with the laboratory strategy than with the POC strategy (7.8% vs. 1.1%; $P < 0.001$), mostly due to specimen leakage in transit (Table 2). The overall proportion of participants with a culture positive for *M. tuberculosis* was 12.9% (159 of 1,235); this was higher in the POC arm than in the laboratory arm (14.8% vs. 11.0%; $P = 0.06$) (see Table E2). Thirty-two (20.1%) *M. tuberculosis* isolates were rifampicin resistant (see Tables E3 and E4). Almost one in four specimens (281 of 1,235 [22.8%]) did not yield a valid culture result: 133 (10.8%) specimens leaked in transit, 103 (8.3%) cultures were contaminated, and 46 (3.7%) had no documented result. Participants with and without a valid culture result had similar baseline characteristics (see Table E5).

Outcomes were evaluated for all 159 culture-positive participants a median of 90 days (interquartile range [IQR], 72–153) after enrollment. Three culture-positive participants were excluded from the primary analysis because they were on TB treatment at enrollment and the *M. tuberculosis* culture isolate was susceptible to rifampicin and isoniazid. The population for analysis therefore included 156 participants with culture-positive PTB (68 in the laboratory arm, 88 in the POC arm). The baseline characteristics of the culture-positive participants were well balanced (Table 3). The proportions of participants with culture-positive PTB initiated on appropriate TB treatment within 30 days of enrollment were 76.5% (52 of 68) with the laboratory strategy and 79.5% (70 of 88) with the POC strategy (odds ratio [OR], 1.13; 95% confidence interval [CI], 0.51–2.53; $P = 0.76$; risk difference, 3.1%; 95% CI, –16.2 to 10.1). The estimated value of the coefficient of variation (κ) was 0.11.

For Xpert-positive/culture-positive participants, 51 of 57 (89.5%; 95% CI, 78.9–95.1) in the laboratory arm and 65 of 68 (95.6%; 95% CI, 87.8–98.5) in the POC arm started appropriate TB treatment within 30 days (Table 4). The majority of Xpert-negative/culture-positive participants did not start appropriate treatment within 30 days (see further

Table 2. Xpert MTB/RIF Test Results

Xpert MTB/RIF Result	Laboratory ($n = 619$)	Point of Care ($n = 616$)
First sputum specimen		
<i>Mtb</i> detected	98 (15.8)	108 (17.5)
Rif resistance not detected	82 (13.2)	91 (14.8)
Rif resistance detected	16 (2.6)	17 (2.8)
<i>Mtb</i> not detected	473 (76.4)	501 (81.3)
Invalid	6 (1.0)	4 (0.6)
Error	5 (0.8)	2 (0.3)
Not processed (specimen leaked)	37 (6.0)	1 (0.2)
All sputum specimens		
<i>Mtb</i> detected	105 (17.0)	108 (17.5)
Rif resistance not detected	87 (14.1)	91 (14.8)
Rif resistance detected	18 (2.9)	17 (2.8)
<i>Mtb</i> not detected	505 (81.6)	502 (81.5)
Invalid	1 (0.2)	3 (0.5)
Error	1 (0.2)	2 (0.3)
Not processed (specimen leaked)	7 (1.1)	1 (0.2)

Definition of abbreviations: *Mtb* = *Mycobacterium tuberculosis*; Rif = rifampicin.

Forty of 48 participants in the laboratory arm with no valid result from the first sputum specimen submitted a second specimen after a median of 5 days (interquartile range, 4–8); all but one of the repeat specimens yielded a valid result. One participant in the point-of-care arm with an invalid result for the first sputum specimen submitted a second specimen on the same day, which yielded a valid result; six other participants in the point-of-care arm with no valid result from the first sputum specimen did not submit a second specimen.

Table 3. Baseline Demographic and Clinical Characteristics of Culture-Positive Tuberculosis Participants Included in Primary Analysis

Variable	Laboratory (n = 68)	Point of Care (n = 88)
Female sex, n (%)	32 (47.1)	53 (60.2)
Age, yr, median (IQR)	34 (28–41)	33 (27–41)
Body mass index, kg/m ² , median (IQR)	20.5 (18.2–22.0)	21.0 (18.6–25.0)
Current symptoms, n (%)		
Cough only	9 (13.2)	10 (11.4)
Weight loss	53 (77.9)	67 (76.1)
Fever	28 (41.2)	34 (38.6)
Night sweats	39 (57.4)	50 (56.8)
Duration of cough, wk, median (IQR)	3 (1–6)	3 (2–4)
Current IPT use, n (%)	1 (1.5)	1 (1.1)
Risk of drug resistance, n (%)		
None	33 (48.5)	52 (59.1)
Treatment failure	1 (1.5)	2 (2.3)
Smear nonconversion	3 (4.4)	3 (3.4)
Previous TB treatment	30 (44.1)	31 (35.2)
Household contact	6 (8.8)	4 (4.6)
Health care worker	—	—
Prison in last 12 mo	1 (1.5)	2 (2.3)
HIV status, n (%)		
Positive	64 (94.1)	87 (98.9)
Negative	3 (4.4)	1 (1.1)
Never tested	1 (1.5)	—
Not disclosed	—	—
Missing	—	—
Current antiretroviral therapy*, n (%)	19 (29.7)	31 (35.6)
CD4 ⁺ cell count*†, cells/μl		
Median (IQR)	219 (98–371)	203 (99–328)
≤50, n (%)	6 (8.8)	10 (11.4)
51–200, n (%)	21 (30.9)	29 (33.0)
201–350, n (%)	14 (20.6)	24 (27.3)
351–500, n (%)	12 (17.6)	8 (9.1)
>500, n (%)	7 (10.3)	9 (10.2)
Missing, n (%)	8 (11.8)	8 (9.1)

Definition of abbreviations: IPT = isoniazid preventive therapy; IQR = interquartile range; TB = tuberculosis.

*Proportions are of HIV-positive participants.

†CD4⁺ cell count up to 18 months prior to or 30 days after enrollment.

details in the online supplement). Overall, 215 participants started TB treatment within 60 days: 154 (71.6%) on the basis of a positive Xpert result, 14 (6.5%) on the basis of a positive culture, and 45 on clinical or radiological grounds (3.5% of all enrolled or 20.9% of those who started treatment). For two participants, the basis for starting treatment was not known. Seven (15.6%) of the participants treated empirically had a subsequent positive culture.

For the analysis of time to appropriate treatment, 156 participants with culture-positive TB contributed 2,413 days follow-up (median, 5.5 d; IQR, 1.0–22.5). In the Cox regression model for time to appropriate TB treatment, the proportional hazards assumption was not met. Time to appropriate TB treatment was plotted as Kaplan-Meier survival curves (Figure 2).

Six participants (all in the POC arm) died prior to initiation of appropriate TB treatment. The estimated median time to appropriate treatment was 7 days (95% CI, 6–10) under the laboratory strategy and 1 day (95% CI, 1–2) under the POC strategy. Under the POC strategy, 34 participants commenced appropriate treatment on the day of enrollment (50.0% of Xpert-positive/culture-positive participants, 75.6% of rifampicin-susceptible Xpert-positive/culture-positive participants).

Thirty-two rifampicin-resistant participants contributed 976 days follow-up (median, 23.5 days; IQR, 14.5–56.0). In the Cox regression model for time to appropriate TB treatment, the proportional hazards assumption was not met. Two participants died before the initiation of appropriate treatment. Kaplan-Meier

curves for time to appropriate TB treatment by arm for the rifampicin-resistant participants are shown in Figure 3.

The estimated median time to treatment was 27 days (95% CI, 22–51) under the laboratory strategy and 17 days (95% CI, 10–60) in the POC arm.

For the analyses involving all participants with possible TB or DR-TB, 28.3% (362 of 1,281) had no postenrollment follow-up (28.0% for laboratory arm vs. 28.5% for POC arm). Participants with no postenrollment follow-up were less likely to be on ART and had marginally higher CD4⁺ cell counts at enrollment, but they were otherwise similar to those whose outcomes were evaluated (see Table E6). Figure E3 shows the outcomes at Day 60 for all trial participants. Overall, 24 (2.6%) participants died within 60 days of enrollment, a greater proportion in the POC arm (3.5%; 95% CI, 2.2–5.6) than in the laboratory arm (1.7%; 95% CI, 0.9–3.4), with an OR of 2.33 (95% CI, 1.13–4.80; *P* = 0.022); risk difference, –1.8% (95% CI, –3.8 to 0.3). After adjustment for baseline CD4⁺ T-cell count and culture result, this difference did not reach statistical significance (adjusted OR, 1.92; 95% CI, 0.89–4.16; *P* = 0.096). Similar proportions of participants in the two arms were admitted to the hospital within 60 days of enrollment (2.0% in the laboratory arm vs. 3.1% in the POC arm), with an OR of 1.60 (95% CI, 0.68–3.77; *P* = 0.286); risk difference, –1.1% (95% CI, –3.1 to 0.9). The estimated median times to ART initiation for HIV-positive participants eligible for but not yet receiving ART were 24.1 days (95% CI, 22.1–32.1) in the laboratory arm and 20.1 days (95% CI, 17.1–22.1) in the POC arm. There was no evidence that time to ART initiation was different according to Xpert placement (hazard ratio, 1.22; 95% CI, 0.91–1.64; *P* = 0.184).

An exploratory *post hoc* analysis was performed to explore the effect of POC positioning on treatment initiation at different time thresholds (2 d, 5 d, and 14 d from enrollment). The proportion of culture-positive participants who had initiated appropriate treatment was greater in the POC arm at all three time points (Table 5).

Discussion

To our knowledge, this is the first randomized trial to evaluate the effect of

Table 4. Proportion of Culture-Positive Patients with Pulmonary Tuberculosis Who Started Appropriate Tuberculosis Treatment within 30 Days, according to Xpert MTB/RIF Result

	Laboratory	Point of Care
30 d		
Xpert positive	51/57 (89.5%)	65/68 (95.6%)
Xpert-positive/rifampicin-susceptible	42/45* (93.3%)	55/56 [†] (98.2%)
Xpert-positive/rifampicin-resistant	9/12 [‡] (75.0%)	10/12 (83.3%)
Xpert-negative	0/10	5/20 [§] (25.0%)
Xpert no result	1/1 (100%)	—
Total	52/68 (76.5%)	70/88 (79.6%)
60 d		
Xpert-positive	53/57 (93.0%)	65/68 (95.6%)
Xpert-positive/rifampicin-susceptible	42/45 (93.3%)	55/56 (98.2%)
Xpert-positive/rifampicin-resistant	11/12 (91.7%)	10/12 (83.3%)
Xpert-negative	4/10 (40.0%)	11/20 (55.0%)
Xpert no result	1/1 (100%)	—
Total	58/68 (85.3%)	76/88 (86.4%)

Definition of abbreviations: Mtb = *Mycobacterium tuberculosis*; Rif = rifampicin; TB = tuberculosis.

*One participant with multidrug resistance based on culture isolate but rifampicin susceptibility based on Xpert test result initiated inappropriate TB treatment after 3 days (switched to appropriate treatment beyond 30 d).

[†]One participant with multidrug resistance based on culture isolate but rifampicin susceptibility based on Xpert test result initiated inappropriate TB treatment on the day of enrollment (switched to appropriate treatment beyond 30 d).

[‡]One participant with isoniazid monoresistance based on culture isolate but rifampicin resistance based on Xpert test result initiated inappropriate TB treatment after 15 days.

[§]Four participants with negative Xpert test results started treatment on the basis of chest X-ray (after 1, 8, 11, and 14 d, respectively); one participant started treatment on the basis of a positive culture (at 30 d).

^{||}One participant with no Xpert test result (specimen leaked) started treatment on the basis of clinical features (after 1 d).

providing POC molecular diagnostics for adults with possible PTB and DR-TB in a rural PHC setting. Our data complement those from randomized trials in which researchers have compared Xpert with

smear microscopy in similar southern African settings (18–20) and other nonrandomized studies in which researchers have explored the impact of decentralized Xpert testing (21–23).

Number at risk							
Laboratory	68	(45)	23	(10)	13	(9)	10
Point-of-care	88	(68)	20	(3)	17	(7)	12

Figure 2. Kaplan-Meier failure estimate curves for time to initiation of appropriate tuberculosis treatment before death among culture-positive participants.

POC placement shortened the time to initiation of appropriate TB treatment and enabled same-day diagnosis and treatment for half of the Xpert-positive/culture-positive participants. With POC placement, almost all Xpert-positive/rifampicin-susceptible participants started treatment within the national target of 2 days (13). The failure to achieve same-day treatment for all people with a positive Xpert test result was partly explained by people choosing not to wait for same-day results and restricted Xpert operating hours. Other studies have also shown that POC implementation does not automatically translate to same-day treatment, and collectively this evidence highlights the need for innovation in both technology and health systems to enable same-day treatment for all patients with TB (21–24).

Although the proportion of individuals initiating appropriate treatment within 30 days was higher in the POC arm, this did not reach statistical significance. Our ability to detect a difference between the two strategies at 30 days was limited by low statistical power. The power of the study was reduced primarily by the lower than expected proportion of participants with culture-positive TB, as well as slightly higher than expected between-cluster variability. Our *post hoc* analysis showed a significant difference in proportions of individuals starting treatment (at Days 2, 5, and 14), suggesting that the POC strategy did have the intended effect in facilitating earlier treatment. We selected the threshold of 30 days on the basis of our considered opinion of what would be seen to be of clinical and public health relevance, but with the benefit of hindsight, this was probably not the ideal endpoint. Many different study designs and outcomes have been used in TB diagnostic research, and this is an area that would certainly benefit from more consensus (25).

Pretreatment loss to follow-up was lower than expected under the laboratory strategy. Of the Xpert-positive, rifampicin-susceptible participants in the laboratory arm, only two (4%) did not start any treatment within 30 days. This suggests that the routine measures to recall those with a positive test who did not initially return functioned well during the trial. It is possible that this was partly due to the Hawthorne effect (26) or that the study personnel helped to improve the routine systems. However, analysis of routine laboratory and

Figure 3. Kaplan-Meier failure estimate curves for time to initiation of appropriate tuberculosis treatment before death among culture-positive, rifampicin-resistant participants.

program data has shown that pretreatment loss to follow-up has declined in this area in the last few years and is lower than other published data from South Africa (19); in 2014, in seven clinics in the same area (including the study clinic), pretreatment loss to follow-up for people with positive Xpert test results (rifampicin susceptible) was 5% (R.J.L., unpublished data). Under the standard-of-care strategy, the laboratory and specimen transport systems worked better than we had expected. This suggests that although the results may be generalizable within South Africa, POC systems may have greater impact in settings where logistics and laboratory systems preclude the prompt return of results.

Whether the shorter time to treatment initiation and fewer pretreatment clinic visits observed in this study could result in public health benefit, in terms of reducing transmission, is a question that remains to be tested. Given that the median reported duration of cough was 2 weeks, shortening

the time to appropriate TB treatment by 6 days could have an important effect on the overall infectious time. A reduction in time to appropriate treatment is of particular importance for DR-TB; yet, rifampicin resistance was the main reason for treatment delay in both arms. During preparation for the trial, it was anticipated that the district hospital would become a fully decentralized DR-TB treatment site (27). However, this did not happen according to anticipated time lines, and throughout the study period, people with DR-TB had to be referred to the provincial DR-TB unit in Durban (approximately 250 km) for treatment initiation. The delay between referral and the initial visit at the provincial DR-TB unit was the main component of the overall delay to DR-TB treatment initiation. Nevertheless, the time to initiation of DR-TB treatment for both strategies was comparable to that of other programs in South Africa (28, 29) but longer than the median time of 7 days achieved by one decentralized DR-TB

program in Cape Town (30). These data emphasize how novel molecular diagnostics may have greatest impact when access to treatment is not limited.

Cost-effectiveness analyses have suggested that POC placement of Xpert MTB/RIF at current prices would need to produce substantial clinical benefits to offset the increased costs associated with PHC clinic deployment in South Africa, although these analyses were only of health system costs without consideration of patient costs (31). In that analysis, the increased costs were related to the need for more instruments and staff and to the decreased operational efficiency at the clinic level. Although economic analysis is beyond the scope of this paper, our findings to some extent support this notion because even in this busy PHC clinic, the system was never operating at full capacity. However, the nurse was easily trained in use of the system and was able to do this among other duties. The big difference for POC deployment would therefore be the capital expenditure costs for instruments, which would be depreciated over the next few years. Given that the benefits could be greater with further decentralization of DR-TB care or in settings with weaker laboratory systems, better understanding of the cost drivers is still needed to inform diagnostic systems in different settings. With respect to patient costs, the shorter time to treatment and fewer clinic visits, particularly same-day treatment, could have particular benefit in rural communities such as this, where one in two people with TB incurs catastrophic costs (32, 33).

With new technologies being developed that may be more convenient for decentralized use (34), this study provides rare real-world evidence of the benefits and limitations of POC diagnostics. The findings derived from this cluster-randomized trial suggest that strengthening of the diagnostic cascade to get all people

Table 5. Exploratory Analyses with Different Time Thresholds for Initiation of Appropriate Antituberculosis Treatment

Time Threshold	Laboratory Arm (n = 68)		Point-of-Care Arm (n = 88)		Odds Ratio (95% CI)	P Value
	n	% (95% CI)	n	% (95% CI)		
2 d	5	7.4 (2.4–16.3)	53	60.2 (49.2–70.5)	17.1 (5.3–55.1)	<0.001
5 d	22	32.4 (21.5–44.8)	56	63.6 (52.7–73.6)	3.6 (1.8–7.3)	<0.001
14 d	42	61.8 (49.2–73.3)	66	75.0 (64.6–83.6)	1.9 (1.0–3.6)	0.057

Definition of abbreviation: CI = confidence interval.

with TB on treatment in a timely fashion will require a combination of technological advances (simpler, more sensitive diagnostics better suited for POC use [34, 35]) allied with broader strengthening of health systems to limit treatment delays, especially for DR-TB (36). There remains a need to push for the development of simple diagnostic technologies suitable for true POC use and affordable for widespread use (7, 8, 37). ■

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

Acknowledgment: The authors thank the community members who participated in the study and the Community Advisory Board of the Africa Health Research Institute. The authors also thank the study team (N. Hlophe, C. Makhanya, T. Mtshali, P. Dlamini, and M. Mabaso) and the health care workers at the study site for care of the study participants. In addition, the authors thank the Department of Health and National Health Laboratory Service for

Hlabisa subdistrict, uMkhanyakude district, and KwaZulu-Natal province for allowing the authors to work at the study site and for supporting the research. The authors acknowledge Cepheid and the Foundation for Innovative New Diagnostics for the concessionary pricing of Xpert MTB/RIF cartridges. The authors thank the independent members of the trial steering committee (D. Moore, K. Fielding, and M. Moosa) for their support and scientific guidance. The authors also acknowledge the support of the Wellcome Trust – Bloomsbury Centre for Global Health Research.

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