JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

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Scale-up and impact of digital and molecular diagnostic technologies on TB diagnosis and timely linkage to care in Tajikistan

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Abstract

Introduction: Tajikistan is scaling up molecular diagnostic and digital technologies to strengthen its fight against drug-resistant TB (DR-TB). The study aimed to document national scale-up GeneXpert/GxAlert and Open MRS from 2012-2019 and compare time taken from TB diagnosis to treatment and quality of data recording before and after the introduction of GxAlert.

Methodology: This was a longitudinal study that included a comparison of historical cohorts. Continuous variables were compared using Wilcoxon Rank-Sum test and categorical variables using the chi square test.

Results: GeneXpert was introduced in 2011 and scaled up to 46 instruments in 43 (51%) diagnostic laboratories by May 2019. GxAlert was introduced in August 2018 and connected with all GeneXpert instruments by February 2019. Open MRS was introduced in 2014 and implemented in all 108 treatment centers by mid-2018. Time from diagnosis to treatment pre-GxAlert (range 0-749, median 3, days) was significantly longer than with GxAlert (range 0-273, median 3, days) (p <0.001). The proportion of patients whose time from diagnosis to treatment was > 2 weeks was 16% (282/1740) pre-GxAlert and 11% (206/1902) with GxAlert (p < 0.001). Between 31%-34% of patients with DR-TB results in Open MRS did not have results available in GeneXpert/GxAlert systems. Where results were present in both systems, there were discrepancies in 8.2% of patients pre-GxAlert and 4.3% with GxAlert (p = 0.25).

Conclusions: The scale-up of GeneXpert and digital technologies in Tajikistan was associated with a reduction in the proportion of patients with delays more than 2 weeks between diagnosis and treatment, but data quality recording improved only slightly.

Key words: Drug-resistant tuberculosis; Tajikistan; GeneXpert; GxAlert; Open; diagnosis and linkage to care; SORT IT.

J Infect Dev Ctries 2021; 15(9.1):58S-65S. doi:10.3855/jidc.13758

(Received 24 August 2020 – Accepted 05 July 2021)

Introduction

Early diagnosis of tuberculosis (TB) with rapid testing for drug resistance and prompt linkage to correct and effective treatment is one of the cornerstones of the World Health Organization (WHO) End TB Strategy [1]. For many years microbiological examination of sputum smears for acid-fast bacilli was the mainstay of TB diagnosis, with system inefficiencies frequently resulting in delays between diagnosis and treatment or complete pre-treatment loss to follow-up [2]. The advent and subsequent scale up of the commercial, automated Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) enables a bacteriological diagnosis of TB as well as information about the presence or absence of rifampicin-resistance to be made within 1-2 hours. The GeneXpert platform, which is easy to use, potentially opens the door to better and faster linkage to treatment and care. Unfortunately, this promise has yet to be realized, and in Africa and Asia there continues to be long turn-around times between diagnosis and treatment initiation as well as high pre-treatment losses to follow when the Xpert MTB/RIF assay is used [3-5]. GxAlert (SystemOne, Boston, MA, USA) is a remote, electronic cloud-based data monitoring system that allows the automatic connection of the Xpert instrument to the network and mobile channels, thus monitoring instrument status and removing the need for a paper-based interface to communicate the results of the Xpert MTB/RIF assay. The monitoring functionality provides visibility on readiness of the

instrument, calibration status, cartridge usage and supply and this information is used for planning and procurement. Additionally, the test results can be transmitted in real time over the internet as emails or through mobile channels as short message services (SMS) to the country's existing health information systems, treatment centers, referring clinicians and even patients themselves. This systematic approach should lead to patients being diagnosed and treated in a timely manner with potentially better treatment outcomes. The few published studies to date on GxAlert, however, have shown mixed results. Two studies in Mozambique and Papua New Guinea showed that GxAlert was associated with decreased time from Xpert testing to treatment initiation and a reduced pre-treatment loss to follow-up [6,7]. In Tanzania, the installation of Xpert MTB/RIF and GxAlert enhanced the rapid diagnosis of TB but did not improve linkage to care because of health system inefficiencies, inaccurate or incomplete patient data entry and communication breakdown among health care providers [8]. The potential effectiveness of this new technology is still unresolved. In 2012, Tajikistan received its first GeneXpert instrument. Scale up then occurred to diagnostic laboratories in the country, the main expansion taking place from 2017 onwards. From mid-2018, the instruments deployed around the country were connected to the GxAlert diagnostic system. The scale up of GeneXpert in Tajikistan coincided with the roll-out of the country's new Open MRS medical information system which potentially allows for better recording and reporting of TB diagnosis and treatment. Because TB-electronic medical record systems have met with mixed success in Asian and African countries [9-12], the Open MRS system was first piloted only in the capital city, Dushanbe, in 2011. Three years later, Open MRS was rolled out country-wide in a phased approach and full coverage was achieved in all TB treatment centers by 2018. All centers were mandated to back-enter their TB data to 2014, so that those initiating Open MRS later than 2014 had updated historical data back to that time.

There is no published information in Tajikistan about the scale up and national coverage of these two electronic systems (GxAlert and Open MRS) or whether they have made any difference to timely linkage between diagnosis and treatment or to the quality of TB diagnosis. The aim of this study therefore was to document the scale up and impact of GeneXpert / GxAlert and Open MRS in Tajikistan between 2012 and 2019. Specific objectives were to: i) describe the scale-up and national coverage of GeneXpert / GxAlert and Open MRS in the country; ii) determine the time taken between TB diagnosis and treatment before and after the introduction of GxAlert; and iii) assess whether there were discrepancies in the transcription of drug-resistant TB results in Open MRS before and after the introduction of GxAlert.

Methodology

Study design

This was a longitudinal study that included a comparison of historical cohorts.

Study setting

General setting

The Republic of Tajikistan is a landlocked mountainous country situated in Central Asia with an estimated population in 2019 of about 9.1 million [13]. The country is defined by the World Bank as low-income with a gross domestic product of USD$827 per capita [14]. The country is divided into four administrative regions in which there are 66 districts. Health care is delivered through regional hospitals, district hospitals for large districts and medical centers for smaller districts. In general, patients have to pay for health care with the exception of TB (after the diagnosis of TB has been made, all tests and treatment are free of charge) and HIV/AIDS. Currently, the country is in transition stage towards digitalization and is implementing electronic management systems in all national systems including healthcare.

Burden of TB and National TB Control Programme

Tajikistan is one of 18 countries in the WHO European Region with a high burden of TB and is one of the 27 countries globally with a high burden of drug resistant TB. In 2018, the incidence of TB was estimated at 7,600 (5,900-9,600) with 1,900 (1,400-2,400) having MDR/RR-TB (MDRTB = multidrug-resistant TB – resistant to rifampicin and isoniazid and RR-TB = rifampicin-resistant TB) [15]. In 2018 there were 5,975 notified TB cases, of which 74% had been tested with rapid molecular diagnostic technology. For the 2016/2017 cohorts, treatment success was 91% for drug-susceptible TB, 65% for MDR/RR-TB and 47% for extensively drug resistant TB [15].

The National TB Programme was established in 2002 and rigorously follows WHO guidelines for TB control [16]. Most of the TB control activities have been financed by international donor organizations, although domestic funding is gradually increasing to ensure sustainability. TB control measures are carried out by doctors and nurses working through a network of TB

facilities and the primary health care system. There are 108 TB treatment centers (some of which are combined): one national center, one prison TB hospital, four regional centers, 34 TB dispensaries and 68 TB outpatient centers. The total number of TB beds is 1,500. Within this network, there are 84 diagnostic TB laboratories based at national, regional and district levels. There are no set guidelines for how patients are managed once diagnosed with TB. Patients diagnosed with drug-susceptible TB are generally referred back to the hospital from which they were referred in the first place. Patients with drug-resistant TB are generally treated at the national and regional hospitals.

Initiation, development and management of GeneXpert MTB/RIF, GxAlert and Open MRS

The first GeneXpert MTB/RIF instrument was introduced in Tajikistan in 2012. In the following years, further instruments were then deployed around the country at the national TB center (including the national TB prison hospital), at national HIV centers, at the regional TB centers (including the regional TB prison hospital) and at district hospitals. These instruments mainly comprised two-module instruments, but there were also four-module instruments for busy centers. All specimens are tested by Xpert MTB/RIF assays, with specimens being sent from sites with no instruments to sites that have had instruments installed. The GxAlert diagnostic system was connected to every one of these GeneXpert instruments from mid-2018 onwards. There are plans to deploy GeneXpert instruments and GxAlert systems into diagnostic laboratories that do not have this technology in the future.

Open MRS was introduced into the National TB Programme in 2011 initially in the capital city, Dushanbe. The original model was supported financially and technically through the Global Fund and the WHO respectively, and piloted just in the capital city over the next three years. From 2014, with upgrading and improvement of the system through technical assistance and financial support from the USAID TB Control Programme, Open MRS was scaled up to all TB centers in the country, including all those with diagnostic laboratories.

Before the introduction of GxAlert, the results of the Xpert MTB/RIF assay were printed from the GeneXpert instrument and transcribed onto laboratory forms by the laboratory specialist. These forms were then sent to the clinician by various means available at that time (taxi, public transportation, through specialists visiting the laboratory facilities) and in some cases results were lost during the transfer. Once received, the results were transcribed to the paper-based TB register and into the Open MRS system by clinicians / Open MRS operators.

With the introduction of GxAlert, the results of the Xpert MTB/RIF assay were transmitted electronically straight from the server to the clinician and the patient, thus missing out the laboratory specialist. The electronic results were printed out from the receiver's computer or electronic device and then transcribed to the paper-based TB register and into the Open MRS system by clinicians / Open MRS operators. The system had the potential to reduce time from diagnosis to treatment because the clinician and patient were informed directly about the results and reduce transcription errors because of missing out the laboratory specialist.

Study population

The study population was as follows: *for objective 1*, the TB centers and TB diagnostic laboratories that used Open MRS, GeneXpert and GxAlert between 2012 and 2019; *for objective 2*, the patients diagnosed and initiated on treatment for TB using GeneXpert before and after the introduction of GxAlert between 2017 and 2019; *for objective 3*, the patients diagnosed with drug-resistant TB using GeneXpert before and after the introduction of GxAlert (Feb-Jun 2018 and Feb-Jun 2019).

Data sources and variables

Data variables included year and month for all objectives. *For Objective 1,* specific variables included names of TB treatment facilities, type of the facility (treatment, diagnostic or both) availability and dates of implementations of OpenMRS, GeneXpert and GxAlert. The source of data was National TB Control Programme records from 2012 to 2019. For *Objective 2,* specific variables included date of GeneXpert test result and date of start of TB treatment. The source of data was Open MRS. For *Objective 3*, specific variables included GeneXpert test results in GxAlert / GenXpert system print-outs and the Open MRS system. Sources of data were GeneXpert/GxAlert and Open MRS systems.

Statistical analysis

For *objective 1*, a descriptive analysis was performed using frequencies and proportions and annual trends of coverage of Open MRS, GeneXpert and GxAlert between 2012 and 2019. For *objective 2*, the analysis included plotting the median time (and interquartile range, IQR) as well as the mean time (and

standard deviation, SD) from diagnosis to start of treatment for each month from January 2017 to December 2019. Results before GxAlert (January-December 2017) were compared with those during GxAlert implementation (January-December 2019) using Wilcoxon rank-sum test for median values. Time frequently has a strongly skewed distribution, and simple comparisons of the median (and mean) do not give a completepicture. A further analysis was therefore carried out comparing the proportion of tests taking longer than 14 days from diagnosis to treatment before GxAlert and during GxAlert implementation using the chi square test and presented as odds ratios (OR) with 95% confidence intervals (95%CI). For *objective 3*, RR-TB results were obtained from the GeneXpert instrument print-out and the Open MRS system from February to June 2018 (pre GxAlert) and were compared with RR-TB results from the GxAlert print out and the Open MRS system from February to June 2019 (GxAlert implementation). Discrepancies in results for each period were compared using the chi square test. For all significance tests, the *P* value was set at <0.05.

Ethics

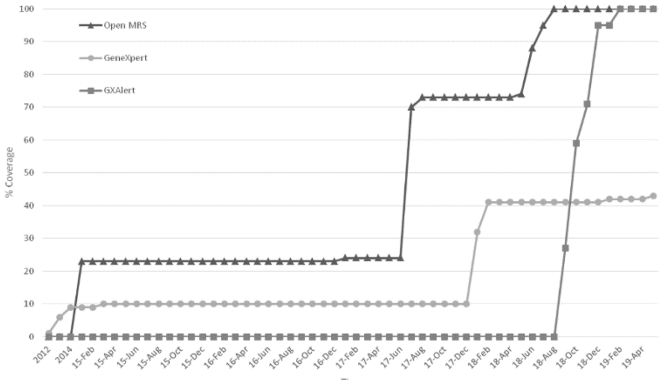
The National ethics committee of the Ministry of Health of the Republic of Tajikistan approved the implementation of the study. The study was also approved by the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France. As this study was a retrospective analysis of programme data and patient data was all anonymized with no identifying links. As such, informed patient consent was not required.

Results

The national scale-up of Open MRS, GeneXpert and GxAlert between 2012 and 2019 is shown in Figure 1, with the plots showing percentage coverage of treatment facilities or diagnostic laboratories. For GeneXpert, one instrument was deployed in 2011, and further expansion occurred with 46 instruments distributed in 43 diagnostic sites by May 2019. GxAlert was introduced in August 2018 and was connected with all GeneXpert instruments by February 2019. The scale up of Open MRS started in 2014 to 25 treatment centers, then in June 2017 to 76 centers and from there to all 108 treatment centers by mid-2018. The geographical distribution of Open MRS, GeneXpert and GxAlert in the country in 2019 is presented in Figure 2.

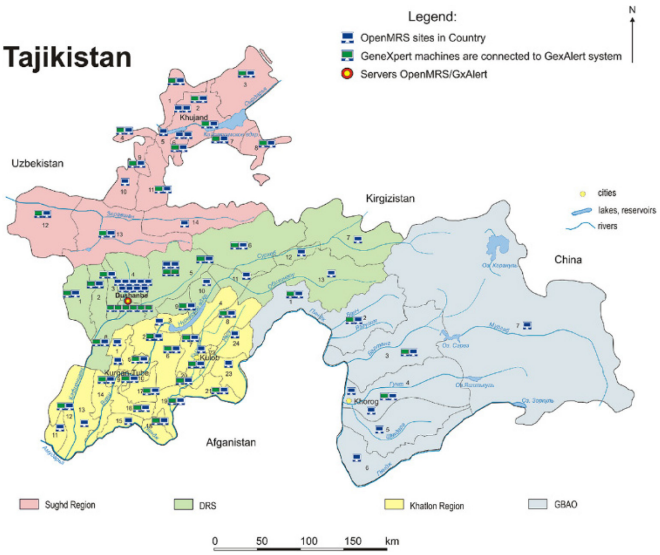
The time taken each month in days between the GeneXpert test result and treatment initiation is shown in Figure 3 for the period January 2017 to December 2019. One plot shows the median time in days each month between diagnosis and treatment. The median time was 3 (IQR 1–8, range 0-749) days in 2017 (before GxAlert) and 3 (IQR 1–7, range 0-273) days in 2019 (after GxAlert implementation), and comparison of these two sets of continuous variables was significantly different ($p < 0.05$). The other plot shows the mean time in days each month between diagnosis and treatment, which decreased from 13 (SD 37) days in 2017 (before GxAlert) to 7 (SD 15) days in 2019 (after GxAlert implementation). The proportion of patients whose time

Figure 1. Scale Up of GeneXpert, GxAlert and OpenMRS in Tajikistan, 2012 – 2019.



The graphs show the coverage of Open MRS, GeneXpert instruments and GxAlert over time. The denominators are different for each of these systems: for Open MRS the denominator = 108 TB treatment and diagnostic centers; for GeneXpert the denominator = 84 TB diagnostic laboratories; for GxAlert the denominator = number of Gene Xpert instruments.

Figure 2. Geographical distribution of GeneXpert, GxAlert and OpenMRS in Tajikistan in 2019.



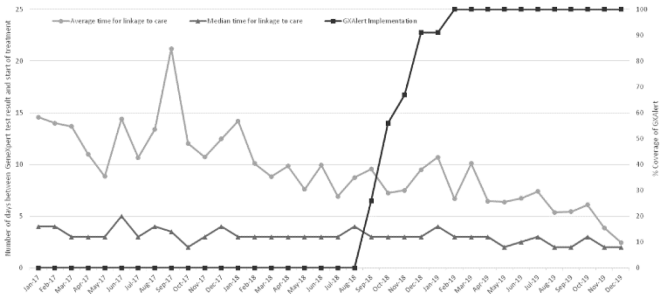
from diagnosis to treatment initiation was >2 weeks was 16% (282/1740) in 2017 and this declined to 11% (206/1902) in 2019 (OR 0.6, 95%CI 0.5-0.8), $p < 0.001$. Time-related comparisons are summarized in Table 1.

In the pre GxAlert period (February-June 2018), there were 286 patients recorded with RR-TB in Open MRS, of whom 90 (31.5%) did not have any results documented from the GeneXpert instrument print-out. This was no different from the GxAlert period (February-June 2019) where 209 patients were recorded in Open MRS, of whom 71 (34.0%) did not have any results from the GxAlert print-out. For those with results in both the print-outs and Open MRS, the comparisons are shown in Table 2. In the pre GxAlert period, there were 16 (8.2%) results that differed between the GeneXpert print-out and Open MRS which was not significantly different from the 6 (4.3%) different results observed between the GxAlert print-out and Open MRS in the GxAlert period.In pre GxAlert period there were mistakes in identification of *Mycobacterium tuberculosis* (5), instrument errors (3) and indeterminate results (2), while in GxAlert period these mistakes all disappeared.

Discussion

This is the first study in Tajikistan to document and evaluate the scale-up of digital technologies used with the GeneXpert Platform in the diagnosis of drug-resistant TB and the linkage to treatment and care. There were some interesting findings.

Figure 3. Time taken each month between GeneXpert test result and initiation of treatment, Tajkistan, 2017-2019.



The coverage of GxAlert is calculated by the number of functional GeneXpert instruments with GxAlert divided by the number of functional GeneXpert instruments (n=46 at the end of the observation period). Average time for linkage to care is the mean number of days per month between diagnosis by Xpert MTB/RIF and initiation on treatment. Standard deviations (SD) were calculated but are not presented Median time for linkage to care is the median number of days per month between diagnosis by Xpert MTB/RIF and initiation on treatment. Interquartile ranges (IQR) were calculated but are not presented.

First, after the introduction of 10 GeneXpert instruments between 2011 and 2013, no further instruments were brought to the country until January 2018. Over the next 16 months, further instruments were deployed reaching a total number of 46 by May 2019. Thus, just over half of the 84 diagnostic laboratories in the country were equipped with molecular technology to diagnose TB and RR-TB, and it has remained like this until now. The introduction and deployment of GxAlert from August 2018 was more

Table 1. Comparison of the time taken between the GeneXpert test result and treatment initiation in two periods: i) pre GxAlert (2017); ii) GxAlert implementation (2019).

Comparison of the time taken between the GeneXpert test result and treatment initiation	Pre GxAlert 2017 N = 1740	Gx Alert 2019 N = 1902	p value
Median time in days (Inter-Quartile Range)	3 (1 – 8)	3 (1 – 8)	< 0.05
Mean time in days (Standard Deviation)	13 (37)	7 (15)	-
Proportion of patients with > 2weeks delay in treatment initiation	16%	11%	< 0.001

Table 2. Comparison of Rifampicin-Resistant TB results in two periods: i) pre GxAlert (Feb-Jun 2018) GeneXpert instrument print-out and Open MRS; ii) GxAlert implementation (Feb-Jun 2019) GxAlert print-out and Open MRS.

Comparison of Rifampicin-Resistant TB results	Pre GxAlert 2018 February - June N = 196 N (%)	Gx Alert 2019 February - June N = 138 N (%)
Incorrect	16 (8.2)	6 (4.3)
Correct	180 (91.8)	132 (95.7)

P = 0.25; Pre GxAlert = GeneXpert instrument print out results compared with Open MRS results; GxAlert = GxAlert print-out results compared with Open MRS results; Pre GxAlert period, the incorrect results were: No identification of *Mycobacterium tuberculosis* (5); instrument errors (3); indeterminate rifampicin-resistance on instrument (2); rifampicin-sensitive result on instrument (6); GxAlert period, the incorrect results were: No identification of *Mycobacterium tuberculosis* (0); instrument errors (0); indeterminate rifampicin-resistance on instrument (0); rifampicin-sensitive result on instrument (6).

rapid, and within 6 months all GeneXpert instruments were equipped with GxAlert technology. Open MRS was introduced to all TB treatment centers, including diagnostic laboratories, from 2014 onwards. This was done in a staggered approach and full coverage was achieved by mid-2018.

Second, using both the median and average time per month, we found encouragingly that the time taken from diagnosis to treatment was significantly reduced during GxAlert implementation compared with the year before GxAlert was introduced. Overall, in Tajikistan the time from diagnosis to treatment was around 7-8 days or less for 75% of patients both before and after the GxAlert implementation. The improvements seen were in the upper quartile of patients and in extreme cases where patients had not started treatment and were potentially lost for extended periods of time after being diagnosed with TB. This improvement was observed in the results. The proportion of patients with a delay between diagnosis and treatment, defined as more than 2 weeks, declined by 37% between the pre GxAlert and the GxAlert period. A similar beneficial effect on time was observed in Papua New Guinea with the proportion of patients starting treatment > 30 days from diagnosis decreasing from 75% to 46% with the introduction of GxAlert [7]. However, in Mozambique, the time taken from diagnosis to treatment after GxAlert did not change, although the new technology resulted in an increased number of diagnosed RR-TB patients starting treatment [6]. In Nigeria, despite the introduction of GxAlert in 2012, by 2015 nearly 50% of patients with RR-TB were still started on treatment > 30 days after diagnosis [17].

Third, we assessed whether there were discrepancies in information on RR-TB between the instrument print-outs (from the GeneXpert/GxAlert system) and what had been recorded for the same patients in the Open MRS system. In both periods, about one third of results in the Open MRS system could not be traced to the GeneXpert/GxAlert system. In depth exploration revealed a common practice of archiving GeneXpert data after which the data could not be transferred through the GxAlert system. In some of the remote regions with diagnostic facilities, there were episodes of internet and power outage where archived data was lost or not transferred resulting in discrepancies with data in Open MRS. Furthermore, some of the data may have been incorrectly entered into OpenMRS making data matching with GeneXpert/GxAlert impossible. Where results could be matched in the instrument print-outs and Open MRS, discrepancies occurred in nearly 10% in the pre GxAlert period and declined to below 5% after GxAlert was implemented, although this difference was not statistically significant. A PubMed search revealed no previous studies examining this aspect of recording so no comparisons with other countries could be made.

While there was an impact of GxAlert on timeliness from diagnosis to treatment, there was a more modest effect on the quality of recording. This may be because with GxAlert there is still a human data entry component between the different electronic systems. The clinician has to receive the GeneXpert test results on the mobile phone, as well as paper print-outs of these results from the local laboratory and then transcribe them or have them transcribed by an operator into the Open MRS system. The further transcription of this data can take time and be prone to error. Although the observed decrease in transcription errors was not statistically significant, there was definite improvement with GxAlert with the only discrepancies being a mismatch in rifampicin resistance status compared with the pre GxAlert period when there were also mistakes in identification of *Mycobacterium tuberculosis,* instrument errors and indeterminate results.

The strengths of this study were the full national sample over an eight year period detailing the coverage of molecular diagnostic and digital technology in all TB diagnostic and treatment facilities in the country and the conduct and reporting of the study in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [18]. There were several limitations mainly related to missing data variables and lack of specific information about the functionality of the system, power and internet outages, server maintenance, regular funding and whether phone/SMS messages were always sent to patients/clinicians. We also did not collect data on how this new technology affected TB treatment outcomes.

Despite the limitations, there are two important programmatic implications from this study. First, additional GeneXpert instruments must be procured and deployed to all diagnostic facilities in the country. The WHO in 2020 updated its guidance recommending that Xpert MTB/RIF and Xpert Ultra be used as the initial diagnostic tests in all adults and children with symptoms of pulmonary TB [19]. The Xpert MTB/RIF Ultra is an assay with higher sensitivity than Xpert MTB/RIF, is run on the same instrument as Xpert, and requires only a software upgrade [20]. Sufficient funding, technical maintenance and support and good health system infrastructure must accompany the further scale up and deployment of GeneXpert instruments around the country. Regular supervision is

also essential to ensure that the instruments are fully functional and utilized to their maximum capacity [21,22].

Second, it is important that GxAlert is rapidly linked to the new GeneXpert instruments and further work conducted on how to optimize its utilization. Sufficient funding should be secured to support the routine maintenance for GxAlert and OpenMRS systems so that servers are always functioning and data can be transferred in a timely way to all stakeholders including patients. Research similar to that done in Uganda [23] must be carried out on how well health workers, health centers and patients themselves can receive, interpret and act upon SMS messages being sent from GxAlert systems. Digital technology experts need to link the two systems together and consider issues such as interoperability, confidentiality, data ownership, unique patient identifiers and data security [24], so that GeneXpert test results can be reliably and safely sent straight from the GxAlert system to Open MRS thus missing out the human element. Effective systems must also be put in place to ensure that OpenMRS TB data is accessed and acted upon each day. Implementation needs to go hand-in-hand with mixed-methods implementation research so that challenges and obstacles can be identified and solved. There is little evidence to date that digital health technologies have made any difference to TB treatment outcomes [25], and this aspect needs to be assessed in the future.

Conclusions

This study has documented the scale-up and coverage of molecular diagnostic and digital technology in the diagnosis and linkage to care of TB patients in Tajikistan. The introduction of GxAlert was associated with a decrease in the proportion of patients with delays more than 2 weeks between diagnosis and treatment. More modest benefits were observed with respect to data transcription discrepancies. Tajikistan needs to continue expanding GeneXpert and GxAlert to all diagnostic laboratories in the country and ensure a more streamlined connectivity with the Open MRS system.

Acknowledgements

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership coordinated by TDR (the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases). The specific SORT IT programme that led to these publications included a partnership between TDR and the European Tuberculosis Research Initiative (ERI-TB) at the WHO Regional Office for Europe, and was implemented by: the Tuberculosis Research and Prevention Center, Armenia; The Alliance for Public Health, Ukraine; The Centre for Operational Research, The Union, France; the Operational Research Unit (LuxOR), Médecins Sans Frontières, Brussels Operational Centre, Luxembourg; Sustainable Health Systems Sierra Leone; and TDR.

Funding

TDR and partners are able to conduct their work thanks to the commitment and support of a variety of funders. These include long-term core contributors from national governments and international institutions, as well as designated funding for specific projects within current priorities. A full list of TDR donors is available on our website at: https://www.who.int/tdr/about/funding/en/. This SORT IT program was funded by the United States Agency for International Development (USAID) and supported by implementing partners. Funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' Contributions

SK: Conception of the study; designing the protocol; data collection, analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. HD: designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. SA: data analysis and interpretation; critically reviewing the paper and giving approval for the final version to be published. AS: writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. ADH: designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. OK: designing the protocol; data collection; critically reviewing the paper and giving approval for the final version to be published. SA: designing the protocol; data collection; critically reviewing the paper and giving approval for the final version to be published. FS: designing the protocol; data collection; data analysis and interpretation; critically reviewing the paper and giving approval for the final version to be published. SS: designing the protocol; critically reviewing the paper and giving approval for the final version to be published. AR: designing the protocol; critically reviewing the paper and giving approval for the final version to be published.

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Conflict of interests: No conflict of interests is declared.