Use of Xpert MTB/RIF and Xpert MTB/RIF Ultra on GeneXpert 10-colour instruments

WHO POLICY STATEMENT

2021

World Health Organization

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Contents

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Funding

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Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
Ct	cycle threshold
DR-TB	drug-resistant tuberculosis
FIND	Foundation for Innovative New Diagnostics
GTB	Global TB Programme
GXP	GeneXpert instrument
GXP6	GeneXpert 6-colour instrument
GXP10	GeneXpert 10-colour instrument
HIV	human immunodeficiency virus
MTB	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis* complex
PQ	prequalification
RIF	rifampicin
SRL	WHO TB Supranational Reference Laboratory
TAG	Technical Advisory Group
TB	tuberculosis
Tm	melting temperature
Ultra	Xpert MTB/RIF Ultra
USA	United States of America
WHO	World Health Organization
XDR	extensively drug-resistant

WHO policy statement

Introducing improved, rapid and more accurate diagnostic tools[1] is critical to achieving the global targets towards ending the tuberculosis (TB) epidemic. The World Health Organization (WHO) recommended the use of Xpert® MTB/RIF and Xpert MTB/RIF Ultra (Ultra) (Cepheid, Sunnyvale, United States of America [USA]) for the detection of TB and rifampicin-resistant TB in 2010 and 2017, respectively.[2] Both tests are widely implemented as initial tests for patients with presumptive TB and are performed on GeneXpert instruments with 6-colour optics. In 2021, WHO recommended the class of low complexity automated nucleic acid amplification tests (NAATs) to detect resistance to amikacin, ethionamide, fluoroquinolones and isoniazid.[3] The first-in-class test is the Xpert MTB/XDR (Cepheid, Sunnyvale, USA). In contrast to the Xpert MTB/RIF and Ultra, this test requires an instrument with 10-colour optics and cannot be performed on the existing 6-colour instrument systems. The performance of Xpert MTB/RIF and Ultra on the new GeneXpert 10-colour instruments has not been independently assessed. Having a single instrument that could be used to detect TB and resistance to first-line and second-line drugs would simplify workflow and facilitate implementation.

To evaluate the evidence on the performance of Xpert MTB/RIF and Xpert Ultra on GeneXpert 10-colour instruments, WHO convened a meeting of the Technical Advisory Group (TAG) on Tuberculosis Diagnostics and Laboratory Strengthening on 5–6 October 2021.[4] This document provides background information and describes the available evidence and discussions by the TAG.

Following review of the evidence and advice from the TAG, WHO makes the following policy statements:

1. Xpert MTB/RIF and Ultra cartridge performance on the GeneXpert 10-colour instrument is comparable to that of the GeneXpert 6-colour instrument for detection of TB and rifampicin resistance.
2. Current WHO recommendations for Xpert MTB/RIF and Ultra cartridge use on GeneXpert 6-colour instruments are also valid for their use on GeneXpert 10-colour instruments.

The guidance provided should facilitate procurement and uptake of these technologies and improve patient care. The statements above should be read in the context of the remarks and implementation considerations detailed in this report. In addition, further research questions are proposed that seek to address data gaps and inform models to improve effective implementation of the tests. The current WHO recommendations on the use of the Xpert MTB/RIF and Ultra on the GeneXpert 6-colour instrument and the use of the Xpert MTB/XDR on the GeneXpert 10-colour instrument are unchanged and remain valid. All products recommended by WHO are automatically eligible to be included in the WHO essential diagnostic list. Lastly, this policy document will be incorporated into existing WHO consolidated guidance when those guidelines are updated.

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[1] The End TB Strategy [website]. Geneva: World Health Organization; 2021 (https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy).

[2] WHO consolidated guidelines on tuberculosis, Module 3: Diagnosis – rapid diagnostics for tuberculosis detection. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240029415).

[3] WHO consolidated guidelines on tuberculosis, Module 3: Diagnosis – rapid diagnostics for tuberculosis detection. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240029415).

[4] Technical Advisory Group on Tuberculosis Diagnostics and Laboratory Strengthening [website]. Geneva: World Health Organization; 2021 (https://www.who.int/groups/technical-advisory-group-on-tuberculosis-diagnostics-and-laboratory-strengthening).

Background

The need to accelerate global efforts to end tuberculosis (TB), as outlined in the 2015–2035 End TB Strategy *(1, 2)*, was restated by the Heads of State and Government through the 2018 Political Declaration of the United Nations General Assembly high-level meeting on the fight against TB *(3)*. Strengthening health delivery systems, which includes introducing improved, rapid and more accurate diagnostic tools, is critical to achieving the global targets towards ending the TB epidemic.

There have been significant advances in the TB diagnostic pipeline. The biomedical sector has developed new diagnostic tools to detect TB infection, active TB disease and related drug resistance in recent years. Hence, the need for clear guidance to national TB programmes on implementing and using these new tools has increased. World Health Organization (WHO) evaluations of classes of TB diagnostic technologies are conducted by the Global TB Programme (GTB). Many new within-class products are emerging following the initial, class-based review, necessitating an additional pathway. Both pathways are managed through GTB for evaluating diagnostic technologies within the WHO framework.

- *Pathway A* – for all first-in-class technologies and updating of existing recommendations. This evaluation will follow the existing WHO guideline development process, based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. All products included in this assessment will automatically be eligible for the WHO prequalification (PQ) assessment.
- *Pathway B* – for all products that are not first-in-class technologies and have not already been assessed through Pathway A. Pathway B starts with a rapid assessment to determine whether a product belongs to a class of diagnostics already endorsed by GTB and, if so, could be referred to PQ for assessment. If it does not belong to an existing class of diagnostics, an assessment as a first-in-class technology through Pathway A may be performed.

A Technical Advisory Group (TAG) on Tuberculosis Diagnostics and Laboratory Strengthening was established in 2021 *(4)*. The TAG will oversee topics that are outside the scope of the WHO guideline development group process (Pathway A) but require critical evaluation and expert input. The scope of the TAG will include Pathway B assessments, and will address knowledge gaps that hinder the adoption and scale-up of WHO recommendations. The goal is to help WHO to adequately address the prevailing and foreseeable challenges, and provide input into technical aspects on implementing specific TB diagnostic technologies.

The TAG comprises 24 independent experts who serve in their personal capacities covering a spectrum of technical expertise, geographical representation and gender balance (Annex 1). Its terms of reference and brief biographies of members are available on the WHO website *(4)*.

GeneXpert 10-colour versus 6-colour instruments

Cepheid has improved the multiplexing capacity of the GeneXpert instrument (GXP) to detect a greater number of molecular targets in a single assay by upgrading the optics to a 10-colour detection system (GXP10).[1] The GXP using 6-colour optics (GXP6) is widely used to detect TB and rifampicin (RIF) resistance using Xpert® MTB/RIF and Xpert MTB/RIF Ultra (Ultra) cartridges. The newly recommended

[1] See https://www.cepheid.com/en/systems/Multiplexing.

Xpert MTB/XDR test detects resistance to amikacin, ethionamide, fluoroquinolones and isoniazid. However, it requires the latest instrument with 10-colour optics to support detection of additional molecular targets. Thus, the Xpert MTB/XDR test cannot be run on widely available GXP6 instruments.

The manufacturer claims compatibility of the new 10-colour optical system with the previously WHO-endorsed Xpert MTB/RIF and Ultra cartridges; however, no independent evaluations have confirmed this claim. Using a single Xpert instrument for all *Mycobacterium tuberculosis* complex (MTBC) initial diagnostic and drug susceptibility tests offers practical advantages, as countries have started implementing Xpert MTB/XDR on GXP10.

To support WHO policy development and country implementation, manufacturer-independent comparisons of Xpert MTB/RIF and Ultra tests on GXP6 and GXP10 are needed to ultimately determine how the systems compare for the detection of MTBC and RIF resistance. The current higher price of GXP10 modules also needs consideration.

The TAG on Tuberculosis Diagnostics and Laboratory Strengthening was convened on 5–6 October 2021 to review findings from an independent study that evaluated the comparability of GXP6 and GXP10 using the Xpert MTB/RIF and Ultra assays. The methodology and results were presented by the two evaluating centres: the WHO TB Supranational Reference Laboratory (SRL), Centre for Tuberculosis, National Institute for Communicable Diseases, Johannesburg, South Africa and the SRL, Emerging Bacterial Pathogens Unit, Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy. The group discussed all aspects of the evaluations and the results. The declaration of interests (Annex 2), agenda for the meeting (Annex 3) and full study report (Web Annex) are available in the respective annexes of this report.

Summary of methods

The SRLs performed laboratory-based evaluations using well-characterized clinical specimens and panels of RIF-resistant MTBC isolates, to evaluate the agreement of results on GXP10 compared with GXP6 using both the Xpert MTB/RIF and Ultra assays. The study comprised two parts:

- **Study 1** compared the performance of the Xpert MTB/RIF and Ultra assays between GXP6 and GXP10 with testing of clinical specimens. The outcome for Study 1 was positive and negative concordance for detection of MTBC and RIF resistance using Xpert MTB/RIF and Ultra testing on GXP10 and GXP6 for clinical specimens.
- **Study 2** compared the performance of the Xpert MTB/RIF and Ultra assays between GXP10 and GXP6 with well-characterized panels of RIF-resistant MTBC isolates. The outcomes for Study 2 were:
    - positive and negative concordance of Xpert MTB/RIF and Ultra testing on GXP10 and GXP6;
    - average difference in cycle threshold (Ct) values for each Xpert MTB/RIF and Ultra MTBC probe when testing on GXP10 compared with GXP6; and
    - average difference in melting temperature (Tm) values for each Ultra *rpoB* probe when testing on GXP10 compared with GXP6.

Study 1 was carried out on 320 concentrated, decontaminated sputum specimens (160 from each site's biobanks) based on convenience sampling. The overall selection included a total of 160 MTBC culture-positive specimens and 160 MTBC culture-negative specimens. The MTBC culture-negative

decontaminated sputum specimens were included to evaluate the negative concordance of the instruments for MTBC detection.

Study 2 was carried out with two independent panels (each of which carries the same set of *rpoB* mutations at the two sites) of 15 phenotypically and genotypically well-characterized RIF-resistant *M. tuberculosis* isolates. The 15 selected unique mutants spanned the entire RIF-resistance determining region (RRDR) and affected the binding of each *rpoB* probe at least once. The mutants were tested in triplicate on both the Xpert MTB/RIF and Ultra assays on GXP10 and GXP6. The sample size for both Study 1 and Study 2 was powered to assess concordance between the two systems.

Data were captured through manual entry at SRL Milan and SRL Johannesburg onto paper-based results reporting forms, then entered into a Microsoft Excel spreadsheet; at the end of the study, all Excel files were collated by Milan for analysis. In addition, daily exports from both GeneXpert instruments (.gxx files) were uploaded to a password-protected shared folder online, managed by SRL Johannesburg. Data quality checks were performed regularly. The .gxx files were shared with Cepheid (blinded) to reshape and convert them to .csv files, compatible with statistical software. Source data verification for all GeneXpert results was done by comparing the data entered on the reporting forms with files received from Cepheid. SRL Milan was ultimately responsible for compiling data and conducting the statistical analysis. The concordance between GXP10 and GXP6 was evaluated using the overall concordance and the Cohen's kappa coefficient (κ) with 95% confidence intervals. Linear mixed-effects models were employed to compare the Ct values between GXP10 and GXP6 separately for Xpert MTB/RIF and Ultra.

Summary of results

In **Study 1**, after removing results with errors, the final analysis was conducted on 154 MTBC culture-positive and 153 MTBC culture-negative specimens. The overall agreement for MTBC detection was 95.8% for Xpert MTB/RIF testing using GXP10 and GXP6, with a Cohen's κ of 0.91. Among culture-positive specimens that were discordant, all were either smear-negative or scantily positive. A total of 4.5% (7/154) of samples were detected as very low positive on GXP10 but missed on GXP6, and 3.9% (6/154) were detected as very low positive on GXP6 and missed by GXP10. Among culture-negative specimens, 99.3% (152/154) were correctly characterized by both instruments, and one sample tested MTBC positive ("MTB detected medium") on both GXP10 and GXP6.

The overall agreement for MTB detection was 98.4% for Xpert Ultra testing using GXP10 and GXP6, with a Cohen's κ of 0.97. Discordance was observed in 2.5% (4/159) of TB culture-positive sediments, all graded as smear-negative. Among these, all but one was detected as trace positive on GXP10 but missed on GXP6. Among culture-negative specimens, 99.4% (152/159) were correctly characterized by both systems; one sample tested MTB positive ("MTB detected medium, RIF resistance not detected") on both GXP10 and GXP6 (this was the same sample detected as MTB positive by Xpert MTB/RIF); and one sample that was correctly identified as MTB negative by GXP6 provided an MTB trace result on GXP10.

For RIF-resistance detection, among samples with an interpretable result, Xpert MTB/RIF correctly characterized 100% (56/56) of RIF-resistant and 100% (77/77) of RIF-susceptible samples on both instruments. When tested by Ultra, 98.1% (53/54) of RIF-resistant and 96.3% (77/80) of RIF-susceptible samples were correctly characterized by both instruments. For 1.9% (1/54) of resistant specimens, RIF was indeterminate on GXP10 but was correctly characterized on GXP6, and for 1.3% (1/80) of RIF-susceptible samples, resistance was erroneously detected by GXP6 only. For 2.5% (2/80)

of RIF-susceptible samples detected as MTB medium and high, RIF was indeterminate on one system (GXP6, N=1; or GXP10 N=1) and correctly characterized as "RIF resistance not detected" on the other. One susceptible sample was incorrectly detected as "RIF resistance detected" on GXP6.

In **Study 2**, all isolates were correctly characterized as RIF-resistant or RIF-susceptible by Xpert MTB/RIF on both instruments. In addition, there was no significant difference in the Ct values for all Xpert MTB/RIF probes demonstrated using a linear mixed effect (LME) analytical approach. For Ultra, a concordance of 97.8% for RIF-resistance detection was obtained between GXP10 and GXP6. Discordance was limited to one (1/45) replicate of the isolate carrying a Q432K mutation, mischaracterized as RIF-indeterminate on GXP10 only. Interestingly, both GXP10 and GXP6 failed to detect RIF resistance in all three replicates of three distinct isolates (Q432L, Q432P and D435G), although these are uncommon globally. The variation in the Ct and Tm values was negligible and did not affect the categorical interpretation of the final result. Web Annex provides the full study report with further details.

TAG meeting outcome

The TAG deliberated on the results comparing the performance of each assay on the two instrument types; made specific remarks on the study findings, implementation considerations and areas for further research; and provided the following concluding statements to WHO:

1. Xpert MTB/RIF and Xpert MTB/RIF Ultra cartridge performance on the GeneXpert 10-colour instrument is comparable with that of the GeneXpert 6-colour instrument for detection of TB and rifampicin resistance.
2. Current WHO recommendations for Xpert MTB/RIF and Xpert MTB/RIF Ultra cartridge use on GeneXpert 6-colour instruments are also valid for cartridge use on GeneXpert 10-colour instruments.

Remarks

- The evaluation was not powered as an equivalence study in a statistical sense; therefore, the term "comparable" is used rather than "equivalent".
- The studies used a convenience sampling approach of bio-banked, decontaminated and concentrated sputum samples (Study 1) and well-characterized isolates (Study 2) with limited geographical distribution, with the tests performed at SRLs. This selection was considered appropriate for determining comparability, owing to the urgent need for guidance and recognizing that the only change to the test system was the optics. Furthermore, the comparison is of the same test on a different type of instrument. The statements were made by extrapolating results to unprocessed sputum samples.
- The results of this evaluation can be extrapolated to people with signs and symptoms of extrapulmonary TB, following the WHO recommendations for the use of Xpert MTB/RIF and Xpert Ultra *(5)*.
- The semiquantitative output and the variability in Ct and Tm values had no major impact on the results.
- The proportion of errors were within the recommended limits (<3%) and were not instrument related.
- The current WHO recommendations on the use of the Xpert MTB/RIF and Ultra on GXP6 and the use of the Xpert MTB/XDR on GXP10 are unchanged and remain valid *(5)*.

Implementation considerations

National TB programmes and laboratory services need to consider several factors before implementing GXP10:

- Do local TB and drug-resistant TB (DR-TB) epidemiology merit the introduction of drug susceptibility testing for amikacin, ethionamide and fluoroquinolones that may be provided with Xpert MTB/XDR, and hence merit adoption of GXP10? The number of modules required should be guided by presumptive demand from patients with TB or DR-TB. The prevalence of resistance to fluoroquinolones and isoniazid also needs to be considered.
- One module can run up to four Xpert MTB/RIF or Ultra tests, and five Xpert MTB/XDR tests, in a single 8-hour shift.
- Installation options for GXP10 include the following *(6)*: replacing all 6-colour modules in a current GeneXpert system with 10-colour modules; daisy chaining a 10-colour satellite instrument to a current GXP6 (requiring a DAISYKIT); or purchasing a new GXP10. At present, the manufacturer does not support hybrid 6-colour and 10-colour GXP, so 10-colour modules must be purchased as freestanding instruments (with the required number of modules) and must then be connected to an existing GXP6.
- Additional financial resources are needed, because each GXP10 module costs more than a GXP6 module. Cost assessments for the installation options described above should consider specimen transport costs for referral routes to sites with a GXP10 versus all sites having access to GXP10 without referral.
- Specimen transportation networks will be essential to inform instrument placement and the capacity of the instrument selected.
- Knowledge is needed of the local epidemiology of other diseases that can be detected using either GXP6 or GXP10. Multidisease testing has the advantage of shared financial costs for equipment purchasing and maintenance, and for human resources. However, the daily testing volume for each disease needs to be considered and such testing should not compromise TB testing.
- General implementation requirements (e.g. regulatory registration, supply chain, training, documentation and modification of laboratory or health management information systems or diagnostic connectivity solutions) need special consideration.
- Other aspects are likely to be similar to any existing GXP6 instruments, such as GeneXpert infrastructure requirements, biosafety, diagnostic algorithms, quality assurance, service and maintenance, and monitoring and evaluation.

Further research

The TAG discussed the need for further research on the following topics:

- Additional clinical studies in different settings, comparing Xpert MTB/RIF or Ultra testing on GXP6 and GXP10 using unprocessed respiratory and non-respiratory specimen types.
- Reflex testing on GXP10 using the Xpert MTB/RIF or Ultra sample reagent buffer for the Xpert MTB/XDR test.
- Models of implementation, including the efficacy and efficiency of diagnostic algorithms and the impact of GXP10 module placement within the diagnostic network, to inform best practices for laboratory confirmation of TB and DR-TB within established turnaround times.
- Evaluation of robustness of GXP10 compared with GXP6.
- Cost–effectiveness and affordability of GXP10 implementation.

- Impact of synonymous single nucleotide polymorphisms (SNPs) in *rpoB* when tested on GXP10 versus GXP6.
- Equivalence of Tm and Ct values with statistically powered sample sizes between the two systems.
- Performance of GXP10 versus GXP6 in detecting RIF heteroresistance.

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4 Technical Advisory Group on Tuberculosis Diagnostics and Laboratory Strengthening [website]. Geneva: World Health Organization; 2021 (https://www.who.int/groups/technical-advisory-group-on-tuberculosis-diagnostics-and-laboratory-strengthening).

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6 10-color multiplexing technology. Sunnyvale, California: Cepheid (https://www.finddx.org/wp-content/uploads/2021/02/Cepheid-GeneXpert-10-Color-HBDC-Upgrade-Flyer-CE-IVD-3191-English-1.pdf).

Annex 1: List of participants

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Annex 2: Declaration of interests

NO CONFLICT OF INTEREST	
Expert name	Dr Patricia Hall (United States of America) Ms Lucia Barrera (Argentina) Dr Paulo Redner (Brazil) Dr Sabira Tahseen (Pakistan) Dr Alaine Umubyeyi Nyaruhirira (Rwanda) Prof Nguyen Van Hung (Viet Nam) Dr Valeriu Crudu (Republic of Moldova) Dr Siva Kumar Shanmugam (India) Dr Sandeep Meharwal (Thailand) Dr Vithal Prasad Myneedu (Nepal) Prof Yanlin Zhao (China) Dr Xin Shen (China)
Conflict identified	Nil
Conclusion	No conflict of interest
POTENTIAL CONFLICT OF INTEREST	
Expert name	Heidi Albert, South Africa
Conflict identified	**(1a) Employment**: Employment with FIND, the global alliance for diagnostics, but not closely involved in any recent diagnostic evaluations at FIND.
Conclusion	Non-significant

Expert name	Farzana Ismail, South Africa
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships, and other funding**: XDR Cartridge evaluation (Cepheid). Funds provided to research unit within the National Institute for Communicable Diseases in the amount of US$ 140 000; and bedaquiline post-marketing surveillance and emerging resistance (Janssen). Fund provided to the research unit in the amount of US$ 300 000. **(2b) Non-monetary support valued at more than US$ 1000 overall**: Activity (?) on latent TB infection in health care workers. Consumables and personnel were provided by Qiagen. This interest is still ongoing. Sponsorship to the International Union of TB and Lung Disease conference 2018 (Janssen). This included flight (to The Hague), accommodation and conference registration fee.
Conclusion	Significant: laboratory was involved in evidence generation and analysis to inform the current meeting and the individual was excluded from the deliberations.
Expert name	Madhukar Pai, Canada
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships, and other funding**: 1. Two ongoing grants from the Bill & Melinda Gates Foundation (none related to TB). 2. A grant from FIND: Tuberculosis diagnostics in conjunction with development of new regimens to fight TB and DR-TB. This grant is to support FIND by conducting market analyses of TB tests; uptake of TB tests; systematic reviews of TB diagnostics; product landscapes; and secondary analyses of data (e.g. TB biomarker database). The work now also involves COVID-19 diagnostics. No specific product evaluation is included.
Conclusion	Non-significant
Expert name	Thomas Shinnick, United States of America
Conflict identified	**(1b) Consulting, including service as a technical or other adviser**: As an independent consultant, [the participant] received contracts and travel support from WHO, FIND, USAID for work related to laboratory strengthening and developing global guidance documents.
Conclusion	Non-significant

Expert name	Sadia Shakoor, Pakistan
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships, and other funding**: Co-investigator of projects for which the expert's institution (Aga Khan University) has received funding support from Janssen. Research: The Bedaquiline DREAM programme and Bedaquiline EQA project. The funding covered 5% salary support for this expert from 2018 to 2020.
Conclusion	Non-significant
Expert name	Daniela Maria Cirillo, Italy
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships, and other funding**: The expert participated in the 2020 advisory board (Biomérieux) for which they received €1000 in financial gain (personal?). This engagement ended in 2020. The expert has also participated in the evaluation of diagnostic assays; for the evaluation of blood stability for VIDAS, the research unit in their institution received €11 200 from Biomérieux; and for the evaluation of the XDR test prototype for Cepheid and FIND, the research unit received €14 295 80 in 2018.
Conclusion	Significant: laboratory was involved in evidence generation and analysis to inform the current meeting and the individual was excluded from the deliberations.
Expert name	Claudia Denkinger, Germany
Conflict identified	**(1a) Employment**: The expert was employed by FIND until April 2019 and they have continued to have a collaboration agreement with FIND. **(2a) Research support, including grants, collaborations, sponsorships, and other funding**: The expert has implemented ongoing grants from various public funding agencies on work on TB diagnostics: • R2D2: multiple diagnostic solutions are evaluated for triage, TB diagnosis and comprehensive, rapid DST; • POC Ultrasound grant: Fujifilm instruments; • TB-CAPT: Omni from Cepheid; • SARS-CoV-2: Roche, SD Biosensor, Abbott, LumiraDx, Bioeasy, Mologic, PMC, Fujirebio (through FIND); and • Collaboration with FIND on evaluating FujiLAM, both as part of the prospective study, as well as the qualitative research and modelling work.
Conclusion	Non-significant

Expert name	Florian Maurer, Germany
Conflict identified	**(2b) Non-monetary support valued at more than US$ 1000 overall**: Instruments and reagents placed free of charge for evaluation (Becton Dickinson, Roche, Hain and Metasystems). No income was provided.
Conclusion	Non-significant
Expert name	Irina Lyadova, Russian Federation
Conflict identified	**(2b) Non-monetary support valued at more than US$ 1000 overall**: The expert was a lecturer at the "Recent advances in treatment and diagnosis of drug-resistant TB" in the Global Public Health meeting, sponsored by Johnson & Johnson. Travel expenses were covered. **(4a) Patents, trademarks, or copyrights**: Russian patents on TB diagnostics in 2012 and 2013, linked to the Central TB research institute where the expert worked. The patents belong to the expert's employer. This interest ceased in 2018.
Conclusion	Non-significant
Expert name	Christopher Coulter, Australia
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships, and other funding**: Research support from FIND to conduct LOD studies on TB molecular tests (Cepheid Xpert MTB/XDR; Bioneer). The monetary value of the contract was just over AUD 40 000 with 60% of the contract to fund the labour to do the studies and the balance consumables. The interest ceased in 2019.
Conclusion	Non-significant

Expert name	Mark Nicol, Australia
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships, and other funding**: Research support from NIH, Wellcome Trust, Bill & Melinda Gates Foundation, FIND, United Kingdom MRC and EDCTP to evaluate novel TB diagnostics (Xpert MTB/RIF; Xpert MTB/RIF Ultra; Epistem GeneDrive; BD MAX MDR-TB; Truenat TB; Determine TB-LAM; SILVAMP TB-LAM). No funding from commercial entities. Research grants belonged to the University of Cape Town and the University of Western Australia. Significant research funding (several million dollars). However, no personal income or income to family members. These activities are ongoing. The estimated total grant funding for this research programme would be in the order of US$ 10 million. **(4a) Patents, trademarks, or copyrights**: Provisional patent for novel method for extracting mycobacterial DNA from sputum. This patent is jointly owned by the University of Cape Town and the expert. This interest is ongoing.
Conclusion	Non-significant

DNA: deoxyribonucleic acid; DR-TB: drug-resistant TB: DST: drug susceptibility testing; EDCTP: European & Developing Countries Clinical Trials Partnership; FIND: Foundation for Innovative New Diagnostics; LOD: limit of detection; MRC: Medical Research Council; NIH: National Institutes of Health; POC: point of care; R2D2: Rapid Research in Diagnostics Development; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TB: tuberculosis; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USAID: United States Agency for International Development; WHO: World Health Organization.

Annex 3: Meeting agenda

Technical Advisory Group on Tuberculosis Diagnostics and Laboratory Strengthening

Virtual Zoom Meeting: 5-6 October 2021

Inaugural meeting and Task 1: Bioequivalence evaluation 10- vs 6-colour modules

Background

The need to accelerate global efforts to end tuberculosis (TB), as outlined in the 2015- 2035 End TB Strategy, was restated by the Heads of State and Government through the 2018 Political Declaration of the UN General Assembly High-Level Meeting on the Fight against TB. Strengthening health delivery systems, including introducing improved, rapid and more accurate diagnostic tools while leveraging on the experience of key stakeholders, is critical to achieving the global targets towards ending the TB epidemic.

Significant advances in the TB diagnostic pipeline have emerged. New tools for identifying TB infection, active TB disease and related drug resistance, and the optimisation of existing technologies. To keep pace with these developments and rapidly inform the Members States on their utility, the WHO Global TB Programme carries out evidence-informed guideline development processes as soon as evidence becomes available following the procedures established by the WHO Guideline Review Committee.

The WHO Global TB Programme recently added a rapid assessment pathway (Pathway B) for TB diagnostic interventions within pre-established and WHO-recommended classes of TB diagnostic technologies. In addition, other important aspects of TB diagnostics and laboratory strengthening are out of the scope of the WHO guideline development process and require a critical evaluation and expert input.

In this context, a Technical Advisory Group (TAG) on Tuberculosis Diagnostics and Laboratory Strengthening, composed of experts on TB diagnostics and clinical laboratory sciences, with the following functions:

- Advise WHO on priorities for TB diagnostic strategies that are identified by the WHO Secretariat in response to the needs of Member States and in line with the work of the existing Strategic and Technical Advisory Group for Tuberculosis (STAG-TB); and
- Provide rapid, independent evaluation and advice to WHO on scientific and technical aspects of TB diagnostic tools, technologies, methods and approaches which cannot be addressed within the scope of established WHO guideline development processes.

The Technical Advisory Group is established to help WHO adequately address the prevailing and foreseeable challenges and input into technical aspects on implementing specific TB diagnostic technologies, including addressing critical knowledge gaps that hinder the adoption and scale-up of WHO recommendations. The first part of the meeting will be the inauguration of this vital group.

A concrete example highlighting the need for such a technical advisory group is the emerging queries related to using previously endorsed WHO recommended tests on a new diagnostic platform. In the latest WHO guidelines, low complexity automated NAATs are recommended to detect resistance to isoniazid and second-line agents. The first-in-class test is the Xpert

MTB/XDR cartridge and performed on the new 10-colour fluorescent channel GeneXpert instrument, which allows increased multiplexing capabilities.

The previous WHO endorsed tests, the Xpert MTB/RIF and Xpert MTB/RIF Ultra, are extensively used as initial tests to detect TB and rifampicin resistance. In contrast, these are performed on the 6-colour fluorescent channel GeneXpert instrument. The company claims that the two previously endorsed tests could be used on the new instruments, though the evidence was limited and not independently generated. Two supranational reference laboratories undertook a bioequivalence study with the support of FIND to address this knowledge gap. The meeting will provide an opportunity for the TAG to review the results and give advice to WHO. The second part of this meeting will be dedicated to this technical query. The Zoom connection details are provided at the end of the document.

Objective

1. Inauguration of the Technical Advisory Group on Tuberculosis Diagnostics and Laboratory Strengthening
2. Review and provide advice on the bioequivalence of GeneXpert 6- vs 10-colour modules for the detection of TB and rifampicin resistance

Provisional agenda (CEST time)

Day 1 – Tuesday 5 October: Session 1		**Chair: M Zignol**
12:30 – 13:00	Registration	
The inauguration of the Technical Advisory Group		
13:00 – 13:10	Director's Welcome	Tereza Kasaeva
13:10 – 13:25	Introductions	
13:25 – 13:35	Strategic Focus of the Prevention, Care and Innovation Unit at GTB	Matteo Zignol
13:35 – 14:00	Update on the WHO diagnostic policies, norms and standards	Nazir Ismail
14:00 – 14:20	Dx TAG: Objectives, roles, responsibilities and procedures	Alexei Korobitsyn
14:20 – 14:25	Announcement of TAG Chair	Matteo Zignol
14:25 – 14:45	General Discussion	All
14:45 – 14:50	Break	

Day 1 – Tuesday 5 October: Session 2		Chair: P Hall
Bioequivalence of GeneXpert 6- vs 10-colour modules for TB and rifampicin resistance detection		
14:50 – 15:05	Summary of declarations of interest	Alexei Korobitsyn
15:05 – 15:20	Background, meeting objectives and working methods	Nazir Ismail
15:20 – 15:40	Bioequivalence study methodology comparing the GeneXpert 6- vs 10-colour modules	Shaheed Omar
15:40 – 15:55	Discussion	
15:55 – 16:00	Conclusion for the day	Nazir Ismail

Day 2 – Wednesday 28 October		Chair: P Hall
13:00 – 13:10	Welcome and summary of D1	Alexei Korobitsyn
13:10 – 13:55	Results of the studies on the bioequivalence of GeneXpert 6- vs 10-colour modules (Part 2)	Elisa Tagliani
13:55 – 14:40	Discussion	All
14:40 – 14:45	Break	
14:45 – 15:45	Formulating the recommendations	All
15:45 – 15:55	AOB	
15:55 – 16:00	Meeting Closure	Nazir Ismail

Web Annex: Study report

The web annex can be downloaded from the link below.

Use of Xpert MTB/RIF and Xpert MTB/RIF Ultra on GeneXpert 10-colour instruments: WHO policy statement. Web Annex. Study report

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