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ORIGINAL ARTICLE

Proportions of Xpert MTB/RIF Ultra 'trace' results vary widely among different populations with presumptive TB

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SUMMARY

BACKGROUND: Microbiological confirmation of *Mycobacterium tuberculosis* (MTB) with Xpert® MTB/RIF Ultra is recommended, but the interpretation of a 'trace' result is uncertain. We aimed to determine the proportion of Xpert Ultra-positive results reported as 'trace' and how the 'trace' result informed patient care.

METHODS: We searched MEDLINE OVID, EMBASE, PubMed, Scopus, and Web of Science. All studies until September 2023 that reported Xpert Ultra 'trace' and non-trace MTB-positive results were included for analysis. The Joanna Briggs Institute tool evaluated methodological quality.

RESULTS: The review identified 62 studies conducted across 23 countries with 124,749 participants. The proportions of 'trace' varied widely from 3.1% to 80%; this proportion was 30% or higher in 26 (42%) studies. Higher 'trace' proportions were reported among children and in extrapulmonary samples. MTB culture, when done, was positive in 23.5% of 'trace' compared to 60.5% of non-trace positive results. Data on treatment decisions for those with 'trace' results were usually not reported, although some who were not treated developed TB.

CONCLUSION: Xpert Ultra 'trace' results are common, with wide variation between populations and inconsistencies in interpretation. The implications of a 'trace' result for clinical management and reporting categorisation require greater clarity.

KEY WORDS: tuberculosis; treatment decision; *Mycobacterium tuberculosis;* systematic review

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ORIGINAL ARTICLE

An estimated 10.6 million people became ill from TB in 2022, and 1.3 million people died.[1] It is estimated that almost one-third of those with TB are neither diagnosed nor notified. Increasing case detection with early initiation of effective treatment is critical to improve treatment outcomes, reduce TB-related morbidity and mortality, and reduce transmission. Rapid diagnostic tests increase detection of microbiologically confirmed TB and facilitate early initiation of effective treatment.[2]

In 2017, Xpert® MTB/RIF Ultra (Xpert Ultra) (Cepheid, Sunnyvale, CA, USA) was endorsed by WHO as an initial diagnostic test for *Mycobacterium tuberculosis* (MTB) in persons with presumptive TB.[3] The MTB detection limit of Xpert Ultra is 16 colony-forming unit (CFU)/mL, compared to 114 CFU/mL for its predecessor Xpert MTB/RIF assay (Cepheid), and as low as 10 CFU/mL for MTB culture (culture).[4] Xpert Ultra has a higher sensitivity of 90.9% (compared to 84.7% for Xpert MTB/RIF) against culture for pulmonary TB (PTB) diagnosis in adults.[5] However, the specificity of Xpert Ultra is reported as lower (95.6%) than Xpert MTB/RIF (98.4%), especially in persons with paucibacillary TB and those previously treated for TB, noting that determining specificity for the disease is challenged by imperfect reference standards.[5,6] Xpert Ultra has the same MTB detection categories as Xpert MTB/RIF (i.e. high, medium, low or very low) but includes an additional category of 'trace' for bacillary quantities less than 'very low'. Rifampicin resistance cannot be ascertained on samples with 'trace' positive results.

Currently, WHO recommends that a 'trace' positive result represents microbiologically confirmed TB in persons who are known or presumed to be living with HIV, children under 10 years, persons with positive extrapulmonary TB (EPTB) samples, and HIV-negative adults with presumptive PTB and no previous TB treatment; and therefore should be treated.[7] However, uncertainty remains about interpreting an Xpert Ultra 'trace' result. Persons with previous TB may have false-positive results on Xpert Ultra, as the assay does not differentiate between non-viable and active bacilli.[5,8] It is also plausible that a person without previous TB disease has MTB detectable on respiratory tract samples following recent exposure.[9] This uncertainty impacts patient management decisions, patient outcomes, and health system costs.[10] Furthermore, the frequency of 'trace' results is likely to vary between different populations, age groups, clinical presentations and settings.

This systematic review aimed to determine the proportion of all Xpert Ultra-positive results that are reported as 'trace' and to compare between different populations. In addition,

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we sought to explore how 'trace' results were interpreted within these study populations to inform the clinical management of persons with presumptive TB.

METHODS

We conducted the review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] We searched for studies in EMBASE, MEDLINE OVID, PubMed, Scopus, and Web of Science using a predetermined search: '(tuberculosis OR TB OR Mycobacterium tuberculosis OR pulmonary tuberculosis) AND (Xpert Ultra OR Xpert MTB/RIF Ultra) AND (trace positive OR (trace AND positive))'. This review was registered with the Prospective Register of Systematic Reviews (PROSPERO) (CRD42023460766).

All identified articles were imported into EndNote v20 (Clarivate; Philadelphia, PA, USA).[12] Duplicate articles were removed in EndNote before exporting the folder to Covidence.[13] A further screening was conducted in Covidence to remove any remaining duplicates, and uniquely identified studies were retained. Two researchers (MAA and KC) independently screened the articles by title and abstract in Covidence and independently screened the full-text publications using the eligibility criteria below. Any discordance was resolved by consensus between the two researchers. A third researcher was available if consensus could not be reached. We contacted authors to get information not available in the publications, particularly treatment decisions for persons with 'trace' results.

Inclusion criteria

The Xpert Ultra test was first introduced in 2017. We therefore included studies that reported the number of Xpert Ultra 'trace' and non-trace MTB-positive results that were published from January 2017 to September 2023. We included cross-sectional, case-control, cohort and diagnostic accuracy studies published in English.

Systematic reviews[5,6] were not included but were used to identify any eligible studies not identified by the initial search. We did not include conference abstracts, posters, scientific correspondence, case reports, case series, studies for which full texts could not be accessed, and pre-publication print or unpublished data. The study also excluded those articles reporting 'trace' results without non-trace positive results, as the denominator of all Xpert Ultra-positive results was required to determine the proportions with 'trace'.

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Data management and study quality assessment

Data extraction was conducted by KC and MAA into a standardised MS Excel 2016 spreadsheet (Microsoft, Redmond, WA, USA). The tool was pilot-tested and revised before full extraction was done. The national TB incidence estimates were accessed from WHO reports1 for the year of data collection or last year when the data collection period spanned more than 1 year. The study assessed whether national TB incidence influenced the proportion of Xpert Ultra results reported as 'trace'. In this study, high TB incidence was defined as a TB notification rate of ≥100 per 100,000 population, while low incidence was a rate of less than 100. The complete list of variables extracted is listed in Supplementary Data 1. The Joanna Briggs Institute (JBI) critical appraisal tool was used to evaluate the quality of studies and representativeness of study populations.

We cleaned the data captured in the spreadsheet tool and exported it to STATA v17 (Stata Corp, College Station, TX, USA).[14] We contacted the corresponding authors of the included studies to request key missing data, such as 'trace' results for persons with and without prior TB and treatment decisions. A study was excluded from analysis if key data were missing. Meta-analysis was performed using the random effects model to estimate pooled proportions for 'trace' positive in different population groups. We anticipated that 'trace' results would be heterogeneous by population groups and sample type. Heterogeneity was evaluated and reported using I^2 statistics. The results were displayed in a Forest Plot showing a 'trace' proportion estimate and 95% confidence intervals (CIs) for each included study. The proportion of 'trace' results was calculated over the total Ultra-positive results and stratified by age group, national TB incidence, proportion of participants living with HIV, history of TB treatment, study site, sample type and type of TB. The 'trace' proportions were presented in tabular and graphical formats. For the age group analysis, the study participants were classified as children (<10 years) and adolescents (10–17 years) or adults (≥18 years). Respiratory samples included expectorated sputum, induced sputum, nasopharyngeal aspiration, bronchoalveolar lavage, or gastric aspiration/lavage. Non-respiratory samples included EPTB samples such as lymph node aspirates, pleural aspirates, cerebrospinal fluid, urine, stool or tongue swabs. An arbitrary threshold of 'trace' results, as more than 30% of all results were chosen, indicated that 'trace' results were very common and to compare different study population characteristics.

Ethical approval

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Ethical approval was deemed not necessary for this study as it included published secondary data only.

RESULTS

A total of 62 unique publications were included in the review and qualitative synthesis after full-text screening (Figure 1). The 62 studies included 31 diagnostic accuracy studies, 16 cross-sectional, 11 cohort and 4 prevalence studies, representing a total of 124,749 study participants with ages ranging from 0 to 95 years; 46.5% were male. They included people from 23 countries, with 52 (85%) studies conducted in Asia and Africa and 13 (56.4%) in high TB incidence countries. The study characteristics and Xpert Ultra results for each study are listed in Supplementary Data 2. Of 124,749 study participants, 95,381 (76.5%) had at least 1 sample tested by Xpert Ultra, of which 10,749 (11.3%) were positive, and 2,602 (24.2%) of Ultra-positive results were 'trace'. Table 1 shows the ranges of proportions that were 'trace' and the numbers of studies that commonly reported 'trace' (>30% of results) by population characteristics. 26 (41.9%) focused exclusively on adults, while 23 (37.1%) included adults, children and adolescents, and 9 (14.5%) included both children and adolescents, while 3 (4.8%) included children only. There was inconsistency between studies defining the age limits for adults (15 years and older to 19 years and older), adolescents, and children (varied from less than 10 years, less than 15 years, and less than 18 years). A higher proportion of studies in children and adolescents (<18 years) than in adults reported 'trace' as >30%, including in all three studies that reported children (<10 years) alone. Most (80.6%) studies were based in health facilities. HIV results were reported by 45 studies, of which 24 were in Africa; 78,796 participants had HIV status reported, and 25,281 (32.1%) of these were living with HIV.

Most studies (56%) included individuals with PTB, while 26% focused on EPTB, and 15% included both. Results by specific sample type are listed in Table 1, with 15 studies evaluating a mixture of 2 or more samples. Table 2 lists cumulative numbers of trace results from across studies when available by specific sample type and as a proportion of Xpert Ultra-positive for that sample. Sputum was the most common sample with 25% trace positive, while trace positive was >40% in cerebrospinal fluid, stool, pleural, and vitreous fluid. 32 (56%) of the studies reported previous TB, and of these, 6,155 (5.5%) participants were documented as having previous TB. The number of participants with 'trace' results among those with previous TB could not be compiled for 18 studies as the data were not always reported. In 14 studies

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that did report the number of participants with 'trace' among those with previous TB, 231 (16.6%) of 1,390 'trace' results were in those with previous TB. In the studies with complete data, 217 (6.7%) out of 3,240 individuals with prior TB were 'trace' positive, while 1,019 (3.2%) out of 31,458 individuals without a history of TB were 'trace' positive. The highest proportion – 27 (81.8%) 'trace' of 33 results – was reported from a study in South Africa where 75% of all samples tested were from persons with previous TB.[14] It was also not possible to determine the proportion of non-trace positive results among people with previous TB.

The proportion of 'trace' results among all Xpert Ultra-positive findings ranged widely between studies from 3.1% to 80.0%. Due to the high heterogeneity (I^2 = 96%) of the studies, pooled proportions of 'trace' are not presented, as the results would be misleading (Supplementary Data 5). Culture results for samples with 'trace' results were reported in 38 studies. A total of 1,914 (73.6%) of all 2,602 persons with 'trace' results reported had MTB culture results, and 450 (23.5%) of these reported culture-positive. This compares to 2,616 (60.5%) that were culture-positive of 4,321 non-trace positive results.

Figure 2 shows that 'trace' proportion ranges were wide in all populations. Of the 62 studies, 26 (42%) reported that 'trace' represented more than 30% of positive results, and this finding was more common in studies of children and adolescents (67% of studies) or people with EPTB (69% of studies) compared to studies of adults (33%) or PTB (34%) respectively. Interpretation of 'trace' result for treatment decisions

Not all study participants were initiated on treatment, and data on treatment decisions were available for seven studies.[15–21] Several studies observed clinical improvement after more than 2 months of follow-up in 41 (74.5%) of 55 participants with 'trace' positive and culture-negative results who were not treated. Of the remaining 14 participants, 4 were lost to follow-up, 1 remained symptomatic, and the outcomes of the others were not reported.15–20 However, 10 out of 30 persons with 'trace' positive culture-negative results were later treated for TB – 5 after testing MTB culture-positive and 5 due to worsening of symptoms.[15,16,20,21]

Some studies also reported on the approach to retesting. A study by Biswas et al. retested 16 (40%) of 42 persons with a 'trace' result: MTB was detected in 3, 5 had another 'trace' result, and 8 were negative.[22] A South African cohort study followed participants who were Ultra-positive and culture-negative (most of them with 'trace' results and previous TB) for up to a year.[15] The researchers recommended retesting the same samples as it reduced non-actionable culture-negative results from 10% to about 6% in their study. A multi-country study

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retested 32 participants with a trace positive result on a subsequent sputum specimen – 14 (44%) tested positive on the second sample and were considered microbiologically confirmed.[16] A recent study by Sung et al. in Uganda, a high TB prevalence setting, found additional value in repeat testing for those with trace positive culture-negative results.[23] Zar et al. reported incremental yield from testing additional specimens in South Africa,[24] while Jagannath et al. reported improved diagnostic accuracy in a cohort with two respiratory samples tested in Uganda.[25] Both studies were conducted in children and adolescents.

DISCUSSION

The key findings of this systematic review are that a 'trace' result is common in people with presumptive TB and that there is wide variability in the proportion of Xpert Ultra results reported as 'trace'. The included studies represented a wide spectrum of study populations, which is important because the microbial load is known to vary according to factors such as age, disease site, and severity. In some study populations, 'trace' was either the most common or very common, result reported, representing more than 30% of Xpert Ultra-positive results. Higher 'trace' proportions tended to be reported among children and in EPTB samples. TB in children and EPTB samples, except for lymph node aspirates, usually have a low microbial load detectable.[7,25–32]

It is also notable that, when reported, most 'trace' positive samples were culture-negative and that culture positivity was lower in those with a 'trace' result compared to a non-trace result. While not surprising, given that this would reflect the microbial load, it highlights the challenges for interpretation and treatment decision-making. It is well recognised – predominantly for adults – that an Xpert test may remain positive for years following successful treatment and cure, as determined by follow-up cultures.[8] However, we have found that only a minority (17%) reported previous TB.[15,19] A history of previous TB treatment is important in the interpretation of results from molecular diagnostics but will not be the explanation for a 'trace' result in the majority of people with presumptive TB.

Our review had important limitations. The high heterogeneity of methodological approaches and reporting among the included studies did not allow for meta-analyses to determine tendency measures in pooled sub-populations and directly compare the diverse population groups. As the ranges of proportions for all groups were wide, we arbitrarily decided that a proportion of over 30% represented that a 'trace' result was very common in a population.

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It was also not possible to determine the association between Xpert Ultra results and culture or previous TB treatment from most studies. Pre-test probability is critical for interpretation, but the study population and epidemiological context were not always apparent or consistently reported. Data were often not reported for key variables, including comorbidities, age disaggregation, descriptions as per WHO definitions, details of treatment decisions, and follow-up in individuals with 'trace' results. Almost half of the studies did not report previous TB status or HIV results. Another limitation includes not searching unpublished data and trial registries.

These limitations, along with a lack of testing results in a population without presumptive TB, restricted the ability to critically analyse for associations that might better inform the interpretation of a 'trace' result. As the implementation of novel future molecular diagnostics will have similar challenges, we urge that future evaluation studies report data using age groups defined by the WHO, specific sample types, consistent reference standards, and clarity on the study population to determine pre-test probability. Evaluation in populations in various contexts, such as active case finding, diagnostic evaluation, and eligibility for preventive treatment with defined comparison groups, will be informative and should ideally report clinical outcomes with follow-up, including those not treated for TB disease.

The WHO recommends considering TB treatment for symptomatic persons with 'trace' results. This would include a person previously treated for TB as the onset of recent symptoms would still indicate presumptive TB, warranting further evaluation and retesting of samples.[20,33,34] A 'trace' and culture-negative result may be due to inactive DNA particles in someone previously treated but may also be due to poor quality samples and processing methods in a person with active TB.[7,19] It is important to actively look for TB among those with previous TB, particularly those who were not evaluated to determine treatment outcomes or did not have a successful treatment outcome.[35]

Not all participants with 'trace' results were initiated on treatment. Some were retested and treated, while others were not and remained well at follow-up. Given the inconsistency in reporting, it was not possible to identify characteristics that would guide practice, such as the decision to initiate treatment or to retest. Although we observed only marginal improvement in diagnostic yield or certainty from retesting the same or different samples, this may still be beneficial, especially for those patients at risk of poor outcomes if they clinically progress. If a decision is made not to treat TB, clinical monitoring and follow-up for up to 12 months would

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be appropriate. Although based on a small sample, our review indicates that a third of persons with 'trace' positive culture-negative results developed TB within 12 months. Similar findings were reported by Sung et al.[36] in a community TB screening study in Uganda, where 28% of those with 'trace' positive culture-negative results at baseline were diagnosed and treated for TB within 24 months of follow-up. Another prospective study conducted in Uganda and South Africa found that nearly half with 'trace' positive sputum were diagnosed within 3 months.[37] These findings underscore the importance of monitoring persons with 'trace' positive results.

There are other challenges for interpretation. Active case-finding studies and prevalence surveys that collect sputum irrespective of symptoms commonly detect subclinical disease.[38–40] Three studies in high TB incidence settings included in this review reported rates of subclinical disease ranging from 40% to 63% detected by chest X-ray (CXR).[33,34] The appropriate management of a 'trace' result is uncertain in a symptom- and CXR-screen negative person. The other uncertainty may be the interpretation of reporting data. As Xpert Ultra is rolled out in countries, the inclusion of 'trace' in the reporting definition will result in a sharp increase in microbiologically confirmed case notifications, especially in children and those with EPTB. This review does not provide evidence as to whether or not a person with a 'trace' result should be reported as microbiologically confirmed TB when the culture result is not positive or available.

In conclusion, a 'trace' result is common, especially in populations with paucibacillary disease, but there are inconsistencies and uncertainties in interpreting these results as microbiological confirmation of active disease. Further research, such as longitudinal studies that also include asymptomatic individuals with and without evidence of infection, is required to understand better the implications of a 'trace' result for diagnosis, management and reporting of TB.

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Conflict of interest: none declared.

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Table 1. Ranges of proportions that were 'trace' positive by study population characteristics.

Characteristics	Studies *n*	Range of proportions %	Studies with trace >30% *n* (%)
All studies	62	3.1–80.0	26 (41.9)
Age group			
Children aged <10 years	3	40.6–73.3	3 (100)
Children and adolescents aged <18 years	9	23.1–80.0	5 (55.6)
Adults aged ≥18 years	26	3.1–62.8	9 (34.6)
Mixed	23	8.3–50.0	8 (34.8)
Not recorded	1	38.7	
Continent*			
Asia	28	8.3–80.0	12 (42.9)
Africa	24	6.0–62.8	10 (41.7)
Europe	5	20.6–45.2	2 (40.0)
South America	4	3.1–50.0	2 (50.0)
National TB incidence, /100,000 population			
Low (<100)	27	3.1–50.0	12 (44.4)
High (≥100)	35	6.0–80.0	13 (37.1)
Site of TB			
Pulmonary	35	3.1–80.0	12 (34.3)
Extrapulmonary	16	16.7–73.3	11 (68.8)
Pulmonary and extrapulmonary	9	14.4–50.0	3 (33.3)
Not recorded	2	16.7–19.8	0
Sample type			
Sputum	24	3.1–62.8	5 (20.8)
Cerebrospinal fluid	7	20.0–73.3	6 (85.7)
Stool	4	20.7–80.0	3 (75.0)
Gastric aspirate	2	25.6–31.5	1 (50.0)
Tissue/biopsy	3	26.0–37.6	2 (66.7)
Urine	1	20.7	0
Tongue swab	1	16.7	0
Oropharyngeal saliva	1	23.2	0
Nasopharyngeal swab	1	14.3	0
Bronchoalveolar lavage	1	16.7	0
Pus (osteoarthritis)	1	19.8	0
Vitreous fluid	1	52.0	1 (100)
Mixed†	15	14.4–55.6	8 (53.3)
Study setting			
Health facility	50	3.1–80.0	21 (42.0)
Community-based	5	14.3–62.8	2 (40.0)
Health facility and community-based	3	10.3–50.0	1 (33.3)
Not recorded	4	10.0–50.0	1 (25.0)
Participants with HIV, %			
<1	6	8.3–45.2	4 (66.7)
1–10	5	3.1–55.6	2 (40.0)
11–50	14	7.1–73.3	5 (35.7)
>50	12	6.0–38.6	5 (41.7)
Not recorded	25	10.0–80.0	10 (40.0)
Participants with previous TB, %			
<1	2	3.1–45.2	1 (50.0)
1–10	8	8.3–80.0	4 (50.0)
11–50	20	6.8–62.8	7 (35.0)
>50	2	6.0–21.2	0 (0)
Not recorded	30	10.0–73.3	14 (46.7)

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*One study was conducted in four continents: Africa, Asia, Europe and South America. The study has been included in all the sections of the table. †Represents a variety of combination of samples with multiple respiratory, multiple non-respiratory or a combination or respiratory and non-respiratory samples. Available results by sample type rather than by study are listed in Table 2.

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Table 2. Numbers of specific samples that were Xpert Ultra and 'trace' positive in studies with data available by sample.

Sample type	Ultra-positive *n*	Trace-positive *n* (%)
Sputum	5,437	1,364 (25.1)
Cerebrospinal fluid	390	160 (41)
Oropharyngeal saliva	194	45 (23.2)
Stool	180	86 (47.8)
Gastric aspirate	174	48 (27.6)
Pleural fluid	169	74 (43.8)
Lymph node aspirate	144	43 (29.9)
Pus (osteoarthritis)	121	24 (19.8)
Lung biopsy	85	32 (37.6)
Bronchoalveolar lavage	44	9 (20.5)
Tongue swab	42	7 (16.7)
Urine	35	8 (22.8)
Vitreous fluid	25	13 (52)
Nasopharyngeal swab	21	3 (14.3)

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FIGURE LEGENDS

Figure 1. Study search, identification and selection flow chart.

Figure 2. Range of proportions of all Xpert Ultra results that were 'trace' by study population and proportion of studies in which trace represented more than 30% of all results. PTB = pulmonary TB; EPTB = extrapulmonary TB.