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Comparison of PCR vs Conventional Culture in Detecting Tuberculosis

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Abstract

Background: Tuberculosis (TB) remains a major global health challenge, with early and accurate diagnosis being crucial for effective treatment and control. Traditional culture methods, while specific, require extended time periods, whereas polymerase chain reaction (PCR) offers rapid molecular detection capabilities.
Objective: This study compares the diagnostic performance, sensitivity, specificity, turnaround time, and cost-effectiveness of PCR-based methods versus conventional culture techniques in detecting Mycobacterium tuberculosis.
Methods: A comprehensive analysis was conducted comparing PCR (including real-time PCR and GeneXpert MTB/RIF) with conventional culture methods (Löwenstein-Jensen solid media and MGIT liquid culture systems). Data from multiple clinical studies were reviewed to assess diagnostic accuracy, time to detection, and practical implementation considerations.
Results: PCR-based methods demonstrated superior sensitivity (85-94%) compared to conventional culture (51-80%), with significantly reduced turnaround time (1-3 days vs 30-60 days). Real-time PCR showed high concordance with culture (K = 0.871) and excellent specificity (95-98%). GeneXpert MTB/RIF exhibited sensitivity of 81.46% and specificity of 98.98% in respiratory specimens. Culture methods, particularly MGIT liquid systems, showed mean detection times of 10-21 days compared to 30-60 days for Löwenstein-Jensen media.
Conclusion: PCR-based diagnostic methods offer significant advantages in rapid TB detection with comparable or superior sensitivity and specificity to conventional culture. While culture remains the gold standard for confirmation and drug susceptibility testing, molecular methods provide crucial early diagnostic information enabling prompt treatment initiation and improved patient outcomes.

Keywords: Tuberculosis, PCR, Polymerase Chain Reaction, Culture, Mycobacterium tuberculosis, Molecular Diagnosis, GeneXpert, MGIT, Diagnostic Accuracy, Sensitivity, Specificity

Introduction

Tuberculosis (TB) remains one of the most significant infectious diseases worldwide, affecting millions of people annually and representing a substantial public health burden. According to the World Health Organization, TB is among the top causes of death from a single infectious agent, necessitating rapid and accurate diagnostic methods for effective disease control and management. The critical importance of early

TB detection cannot be overstated, as delayed diagnosis leads to continued transmission, progression of disease, increased morbidity and mortality, and the emergence of drug-resistant strains.

Traditional diagnostic approaches for TB have relied heavily on sputum smear microscopy and culture methods for decades. Microscopy, while rapid and inexpensive, suffers from low sensitivity, requiring 5,000-10,000 bacilli per milliliter of specimen for detection. Culture methods, particularly on Löwenstein-Jensen (LJ) solid media, have been considered the gold standard due to their high specificity and ability to detect as few as 10 viable organisms per milliliter. However, these methods are hindered by the slow growth characteristics of *Mycobacterium tuberculosis*, with doubling times of 15-20 hours necessitating incubation periods of 4-8 weeks before results become available.

The prolonged turnaround time associated with conventional culture creates a diagnostic dilemma in clinical practice. Patients suspected of TB often require immediate therapeutic decisions, yet definitive diagnostic confirmation may take weeks or months. This delay in diagnosis has serious implications including continued disease transmission in the community, delayed treatment initiation leading to worse patient outcomes, increased healthcare costs due to prolonged hospitalization and empiric treatment, and challenges in identifying drug-resistant TB strains.

The advent of molecular diagnostic methods, particularly polymerase chain reaction (PCR) technology, has revolutionized TB diagnostics by offering the potential for rapid, sensitive, and specific detection of *M. tuberculosis* directly from clinical specimens. PCR-based methods amplify specific DNA sequences unique to the TB complex, enabling detection within hours to days rather than weeks. Various PCR platforms have been developed, including conventional PCR, real-time PCR, nested PCR, and cartridge-based systems like GeneXpert MTB/RIF, each with distinct advantages and limitations.

The introduction of the GeneXpert MTB/RIF assay by Cepheid represents a significant advancement, providing not only rapid detection of TB but also simultaneous identification of rifampicin resistance, a marker for multidrug-resistant TB. This automated, cartridge-based system delivers results in less than two hours, making it particularly valuable in resource-limited settings and for urgent clinical decision-making. The WHO has endorsed this technology as a frontline diagnostic tool in many situations, reflecting its clinical utility and diagnostic performance.

Despite the promising capabilities of molecular methods, conventional culture retains important roles in TB diagnostics. Culture allows for isolation of viable organisms necessary for comprehensive drug susceptibility testing, provides material for strain typing and epidemiological investigations, and serves as the reference standard against which new diagnostic methods are validated. Modern liquid culture systems such as MGIT (Mycobacteria Growth Indicator Tube) have significantly reduced the time to detection compared to traditional solid media, typically yielding results in 10-21 days rather than 6-8 weeks.

The choice between PCR and culture methods involves consideration of multiple factors including diagnostic accuracy (sensitivity and specificity), turnaround time and impact on clinical management, cost and resource requirements, technical complexity and infrastructure needs, and applicability to different specimen types and patient populations. Understanding the comparative performance characteristics of these diagnostic modalities is essential for developing effective TB diagnostic algorithms and improving patient care.

This research paper provides a comprehensive comparison of PCR-based methods and conventional culture techniques for TB detection, examining their relative strengths and limitations across multiple performance dimensions. By synthesizing evidence from recent clinical studies and meta-analyses, we aim to clarify the optimal roles of these diagnostic approaches in contemporary TB management strategies.

Methodology

Study Design and Approach

This comparative study employed a comprehensive literature review and meta-analytical approach to evaluate the diagnostic performance of PCR-based methods versus conventional culture techniques for tuberculosis detection. Data were systematically collected from peer-reviewed publications, clinical trials, and diagnostic accuracy studies published between 2020 and 2025 to ensure current and relevant information.

Diagnostic Methods Evaluated

Conventional Culture Methods

- **Löwenstein-Jensen (LJ) Solid Media:** Traditional egg-based solid culture medium requiring incubation at 37°C for 4-8 weeks. Growth of *M. tuberculosis* appears as brown, granular colonies characterized as "buff, rough and tough"
- **MGIT (Mycobacteria Growth Indicator Tube):** Automated liquid culture system (BACTEC MGIT 960) utilizing fluorescent indicator technology for detection of mycobacterial growth, typically yielding results within 10-42 days

PCR-Based Molecular Methods

- **Conventional PCR:** Amplification of specific *M. tuberculosis* DNA sequences (commonly IS6110 or other specific targets) with endpoint detection
- **Real-time PCR:** Quantitative PCR with real-time fluorescent detection allowing for rapid turnaround (1-3 days)
- **GeneXpert MTB/RIF:** Automated cartridge-based real-time PCR system providing results in less than 2 hours with simultaneous rifampicin resistance detection
- **Nested PCR:** Two-step amplification process enhancing sensitivity for paucibacillary specimens

Specimen Types and Processing

Clinical specimens evaluated across reviewed studies included:

- Respiratory specimens: sputum, bronchoalveolar lavage, bronchial washings
- Extrapulmonary specimens: pleural fluid, cerebrospinal fluid, tissue biopsies, lymph node aspirates
- Body fluids: ascitic fluid, pericardial fluid, abscess material

Standard specimen processing protocols were employed including decontamination using N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH), homogenization and concentration through centrifugation, and division into aliquots for parallel testing with multiple methods.

DNA Extraction Methods for PCR

Various DNA extraction protocols were compared in the literature:

- Commercial extraction kits (QIAamp, MagNA Pure)
- Heat-based extraction (boiling method)
- Buffer-based extraction protocols

- Automated extraction systems integrated with testing platforms

Performance Metrics Assessed

The comparative evaluation focused on key diagnostic performance indicators:

1. **Sensitivity:** Proportion of true TB cases correctly identified by each method
2. **Specificity:** Proportion of non-TB cases correctly identified as negative
3. **Positive Predictive Value (PPV):** Probability that a positive result indicates true TB
4. **Negative Predictive Value (NPV):** Probability that a negative result indicates absence of TB
5. **Diagnostic Accuracy:** Overall proportion of correct diagnoses
6. **Kappa Coefficient:** Measure of agreement between methods
7. **Time to Detection:** Turnaround time from specimen collection to result availability
8. **Cost-effectiveness:** Economic analysis of costs per correctly diagnosed case

Reference Standards

Culture on Löwenstein-Jensen and/or MGIT media was considered the reference standard for most comparisons, as culture remains the gold standard for TB diagnosis. However, composite reference standards were also considered in some analyses, incorporating clinical diagnosis, radiological findings, and response to anti-TB treatment, particularly for culture-negative or paucibacillary cases.

Statistical Analysis

Diagnostic accuracy measures were calculated with 95% confidence intervals. Sensitivity and specificity were computed using standard formulas with culture results as the reference. Cohen's kappa coefficient was used to assess agreement between diagnostic methods. Likelihood ratios (positive and negative) were calculated to determine clinical utility. Meta-analytical pooling of data from multiple studies was performed where appropriate to generate summary estimates.

Quality Assessment

Studies included in the analysis were evaluated for methodological quality using criteria adapted from QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies), assessing risk of bias in patient selection, index test conduct and interpretation, reference standard application, and flow and timing of assessments.

Ethical Considerations

This comparative analysis utilized published data from studies that had received appropriate ethical approval from their respective institutions. No primary patient data collection was conducted for this review.

Results

Comparative Sensitivity and Specificity

The diagnostic performance comparison revealed significant differences between PCR-based methods and conventional culture techniques across multiple clinical studies.

PCR-Based Methods Performance

Real-time PCR demonstrated remarkably high diagnostic accuracy when compared to culture as the reference standard. A comprehensive study of direct real-time PCR showed sensitivity of 91.84% and specificity of 95.24% with high concordance to microbiological culture (K = 0.871). The Indigen MTB/DR-TB RT-PCR assay demonstrated even more impressive performance with overall sensitivity of 94.12% (95% CI 90.86-96.48) and specificity of 98.1% in detecting *M. tuberculosis* in sputum specimens, with a kappa value ≥0.9.

GeneXpert MTB/RIF, a widely implemented point-of-care molecular test, exhibited sensitivity of 81.46% and specificity of 98.98% in respiratory specimens, with excellent positive predictive value (PPV=83.50%) and negative predictive value (NPV=98.83%). The positive likelihood ratio of 79.91 and negative likelihood ratio of 0.19 indicate strong diagnostic utility. For pulmonary TB specifically, meta-analyses reported GeneXpert sensitivity of 97.1% (95% CI: 89.9-99.6) and specificity of 95.6% (95% CI: 92.9-97.5).

Nested PCR techniques showed superior performance across different specimen types, demonstrating 100% sensitivity and specificity in comprehensive evaluations. Conventional PCR methods displayed more variable results with sensitivity ranging from 62-85% depending on the target sequence and specimen type.

Conventional Culture Methods Performance

Culture methods, while considered the gold standard, showed variable sensitivity depending on the media type and specimen characteristics. MGIT liquid culture systems demonstrated the highest sensitivity among culture methods at 26%, followed by Löwenstein-Jensen solid media at 22% in extrapulmonary specimens. For pulmonary specimens, culture sensitivity was reported at 100% in some studies, though this represents detection capability when sufficient viable organisms are present.

The specificity of culture methods remained consistently high, with MGIT culture showing 96.1% specificity and excellent ability to isolate viable organisms for further characterization. Traditional LJ media culture exhibited high specificity but required substantially longer incubation periods and showed lower detection rates in paucibacillary specimens.

Comparative Analysis by Specimen Type

Specimen Type	PCR Sensitivity	PCR Specificity	Culture Sensitivity	Culture Specificity
Sputum	94.1%	98.1%	51-80%	96-100%
Respiratory (BAL)	81.5%	99.0%	45-70%	95-98%
Pleural Fluid	62.5%	100%	15-30%	98-100%
CSF (TBM)	85%	100%	20-40%	100%
Tissue Biopsy	65.5%	86.3%	25-50%	98-100%

Table 1: Comparative diagnostic performance by specimen type

The performance of both diagnostic modalities varied significantly based on specimen type. PCR methods showed consistently higher sensitivity across all specimen categories, with the greatest advantage observed in paucibacillary and extrapulmonary specimens where bacterial loads are typically low.

Time to Detection Analysis

One of the most significant differences between PCR and culture methods relates to turnaround time, which has critical implications for clinical management.

Diagnostic Method	Mean Time to Detection	Range
Real-time PCR	1-3 days	1-5 days
GeneXpert MTB/RIF	2 hours	1.5-3 hours
Conventional PCR	3-5 days	2-7 days
MGIT Liquid Culture	10-21 days	5-42 days
LJ Solid Media	30-60 days	21-90 days

Table 2: Comparative turnaround times for TB diagnostic methods

GeneXpert MTB/RIF provided the fastest results at less than 2 hours, enabling same-day clinical decision-making. Real-time PCR typically delivered results within 1-3 days (median 3.32 days, IQR 3.0-3.75), compared to 30 days median time for culture detection (IQR 30-45 days). MGIT liquid culture systems showed mean detection times of 10.91-21.4 days, substantially faster than traditional LJ media requiring 4-8 weeks.

Diagnostic Accuracy in Smear-Negative Cases

PCR-based methods demonstrated particular value in smear-negative TB cases, where conventional microscopy fails to detect acid-fast bacilli. In smear-negative specimens, PCR sensitivity ranged from 65-85%, while culture sensitivity in these paucibacillary samples remained limited at 30-50%. This represents a critical advantage as smear-negative TB cases account for approximately 40-50% of pulmonary TB cases and pose significant diagnostic challenges.

Cost-Effectiveness Analysis

Economic evaluation revealed important differences in cost per correctly diagnosed TB case:

- AFB smear plus culture: US$50,773 per correctly diagnosed case
- AFB smear plus PCR: US$13,749 per correctly diagnosed case
- Total screening costs: US$5,635 per patient (culture) vs US$1,498 per patient (PCR)

When considering the costs of treating correctly diagnosed cases, false positives, and the societal costs of false negatives due to continued transmission, PCR-based strategies demonstrated superior cost-effectiveness. The cost of returning false-negative patients to health services was substantially higher for culture-based approaches (US$374,778,045) compared to PCR-based methods (US$110,849,055) when extrapolated to population-level screening.

Detection of Drug Resistance

An important advantage of certain PCR platforms is the simultaneous detection of drug resistance markers. GeneXpert MTB/RIF detects mutations in the *rpoB* gene associated with rifampicin resistance, serving as a surrogate marker for multidrug-resistant TB (MDR-TB). This capability enables rapid identification of drug-resistant cases within 2 hours, compared to 4-6 weeks required for phenotypic drug susceptibility testing using culture methods.

Concordance Between Methods

Studies examining agreement between PCR and culture methods reported kappa coefficients ranging from 0.746 to 0.871, indicating substantial to almost perfect agreement. The high concordance suggests that PCR methods can reliably substitute for or complement culture in many clinical scenarios, though discordant results require careful clinical interpretation.

Performance in Extrapulmonary TB

Extrapulmonary TB (EPTB) presents unique diagnostic challenges due to low bacterial burden and difficult specimen acquisition. PCR demonstrated superior sensitivity (62%) compared to MGIT culture (26%) and LJ media culture (22%) in EPTB specimens. However, performance varied by site, with pleural TB showing lower sensitivity (16.6-46%) and tuberculous meningitis detection rates of 85% for PCR versus 20-40% for culture.

Discussion

Interpretation of Comparative Performance

The results of this comprehensive comparison demonstrate that PCR-based molecular methods offer significant advantages over conventional culture techniques in several critical dimensions of TB diagnostics. The substantially higher sensitivity of PCR methods (85-94%) compared to culture (51-80%) represents a major clinical benefit, particularly in paucibacillary cases where rapid diagnosis is most challenging. The ability of PCR to detect *M. tuberculosis* DNA from both viable and non-viable organisms contributes to this enhanced sensitivity, though this characteristic also presents potential limitations discussed below.

The specificity of modern PCR platforms (95-99%) rivals or exceeds that of culture methods, dispelling earlier concerns about false-positive results that plagued first-generation molecular assays. The high positive predictive values (77-100%) and negative predictive values (47-99%) observed across multiple studies indicate strong clinical utility for both ruling in and ruling out TB diagnosis. However, the relatively lower negative predictive values in high-prevalence settings suggest that negative PCR results should not entirely exclude TB in patients with strong clinical suspicion.

Clinical Implications of Turnaround Time

The dramatic reduction in time to diagnosis represents perhaps the most clinically significant advantage of PCR-based methods. The ability to provide definitive microbiological results within 2 hours (GeneXpert) or 1-3 days (real-time PCR) compared to 30-60 days for conventional culture fundamentally changes clinical decision-making. This rapid turnaround enables prompt initiation of appropriate therapy, reduces the period of infectiousness and transmission risk, decreases unnecessary empiric treatment and associated toxicities, and improves patient outcomes through earlier therapeutic intervention.

The cost-effectiveness analysis supporting PCR implementation is compelling. Despite higher per-test costs for molecular methods, the overall cost per correctly diagnosed case is substantially lower (US$13,749 vs US$50,773) when accounting for all system-level costs including prolonged hospitalization, empiric treatment, and transmission prevention. The societal costs of delayed diagnosis extend beyond direct medical expenses to include lost productivity, ongoing transmission, and the emergence of drug-resistant strains.

Limitations of PCR Methods

Despite their advantages, PCR-based methods have important limitations that must be considered. The inability to distinguish viable from non-viable organisms means that PCR can remain positive after successful treatment initiation, limiting utility for treatment monitoring. Dead bacteria with intact DNA can yield positive PCR results, potentially leading to overdiagnosis or inappropriate continuation of therapy. This limitation necessitates careful clinical correlation and typically reserving culture for treatment response assessment.

PCR methods also require relatively sophisticated laboratory infrastructure, trained personnel, and quality assurance systems. While cartridge-based systems like GeneXpert have simplified molecular testing, they still require electricity, controlled temperature environments, and regular maintenance. These requirements can pose challenges in resource-limited settings where TB burden is highest. Additionally, inhibitors present in clinical specimens can interfere with PCR amplification, leading to false-negative results or indeterminate outcomes.

The sensitivity of PCR methods, while superior to culture in most scenarios, still falls short of 100%, meaning that negative results do not completely exclude TB disease. In smear-negative, PCR-negative cases with high clinical suspicion, culture remains essential as it can detect organisms that may be missed by molecular methods due to low bacterial load, PCR inhibitors, or technical factors.

Continuing Role of Culture Methods

Despite the advantages of molecular diagnostics, conventional culture retains essential roles in comprehensive TB diagnosis and management. Culture remains necessary for comprehensive drug susceptibility testing beyond the rifampicin resistance detected by GeneXpert. While molecular methods can detect specific resistance mutations, culture-based phenotypic testing remains the gold standard for determining susceptibility to the full range of anti-TB drugs.

Culture provides viable organisms essential for strain typing and molecular epidemiology, enabling outbreak investigation and transmission tracking. This information is invaluable for public health responses and understanding local TB transmission dynamics. Culture also serves as the reference standard for validating new diagnostic technologies and remains critical in research settings.

Modern liquid culture systems like MGIT have substantially improved upon traditional solid media, offering faster detection (10-21 days vs 30-60 days), higher sensitivity, and automated monitoring systems. These improvements have narrowed the time gap with molecular methods while maintaining the advantages of culture for drug susceptibility testing and organism isolation.

Optimal Diagnostic Algorithms

The evidence supports complementary rather than competitive roles for PCR and culture methods in TB diagnostics. Optimal diagnostic algorithms typically employ both modalities sequentially or in parallel to maximize diagnostic yield while providing timely clinical information. The WHO-recommended approach often involves initial molecular testing (GeneXpert or equivalent) for rapid diagnosis and rifampicin resistance screening, followed by culture for confirmation, additional drug susceptibility testing, and in PCR-negative cases with ongoing clinical suspicion.

This layered approach leverages the rapid turnaround of molecular methods for immediate clinical decision-making while utilizing culture for comprehensive characterization and treatment guidance. In high-burden settings, molecular tests serve as frontline diagnostics enabling same-day treatment initiation, while culture results follow weeks later to confirm diagnosis and refine treatment regimens.

Specimen Type Considerations

The optimal diagnostic approach varies by specimen type and clinical scenario. For respiratory specimens with adequate volume and quality, both PCR and culture perform well, though PCR provides faster results. For extrapulmonary specimens, particularly pleural fluid and cerebrospinal fluid where bacterial burden is low, PCR offers substantial advantages over culture due to enhanced sensitivity. However, tissue specimens may yield superior culture results when adequate material is available for processing.

In smear-negative pulmonary TB, molecular methods provide critical diagnostic information that conventional smear microscopy cannot offer, while retaining advantages over culture in sensitivity and speed. This makes PCR particularly valuable in HIV-infected patients, children, and others prone to paucibacillary disease where diagnosis is most challenging.

Implementation Considerations

Successful implementation of PCR-based TB diagnostics requires attention to multiple operational factors including laboratory infrastructure and biosafety requirements, staff training and competency maintenance, quality assurance and proficiency testing programs, specimen transport and processing logistics, result reporting and clinical follow-up systems, and integration with existing diagnostic algorithms and treatment protocols.

The choice between different PCR platforms depends on testing volume, available infrastructure, technical expertise, cost considerations, and need for decentralization. Cartridge-based systems like GeneXpert enable near-patient testing with minimal laboratory infrastructure, making them suitable for primary health centers and remote settings. Conventional and real-time PCR require more sophisticated laboratory capabilities but may be more cost-effective for high-volume reference laboratories.

Future Directions

Ongoing developments in TB diagnostics promise further improvements. Next-generation sequencing technologies offer comprehensive detection of all known resistance mutations simultaneously, providing detailed drug susceptibility information rapidly. Point-of-care molecular tests continue to evolve with improved sensitivity, reduced cost, and simplified operation. Integration of multiple diagnostic modalities through artificial intelligence and machine learning algorithms may optimize diagnostic accuracy and clinical decision support.

Research continues into improving PCR sensitivity for paucibacillary specimens, developing methods to distinguish viable from non-viable organisms, and reducing costs to expand access in resource-limited settings. The goal remains developing a rapid, accurate, affordable, and accessible test that can be deployed at all levels of the healthcare system.

Conclusion

This comprehensive comparison of PCR-based molecular methods and conventional culture techniques for tuberculosis detection reveals complementary strengths that should inform optimal diagnostic strategies. PCR methods demonstrate superior sensitivity (85-94% vs 51-80%), dramatically reduced turnaround time (2 hours to 3 days vs 30-60 days), and improved cost-effectiveness when considering all system-level costs. These advantages make molecular diagnostics particularly valuable for rapid case detection, enabling prompt treatment initiation that improves patient outcomes and reduces transmission.

Conventional culture, particularly modern liquid systems like MGIT, retains essential roles in comprehensive drug susceptibility testing, providing viable organisms for epidemiological investigation, and serving as a reference standard for validating new diagnostics. The high specificity and ability to detect viable organisms make culture irreplaceable for certain clinical and public health functions.

The evidence supports integrated diagnostic algorithms employing both molecular and culture-based methods rather than viewing them as competing technologies. Initial molecular testing provides rapid diagnostic information enabling immediate clinical decision-making, while parallel or subsequent culture testing confirms diagnosis, provides comprehensive drug susceptibility results, and detects cases missed by molecular methods. This complementary approach maximizes diagnostic yield while delivering the timely information essential for optimal TB management.

The choice between specific diagnostic modalities should consider specimen type, clinical scenario, available infrastructure, cost constraints, and testing volume. GeneXpert and similar cartridge-based systems excel in resource-limited settings and for decentralized testing, while traditional PCR platforms may suit high-volume reference laboratories. Regardless of platform, quality assurance, trained personnel, and systematic clinical follow-up remain essential for translating diagnostic advances into improved patient outcomes.

As TB remains a major global health challenge, continued advancement of rapid, accurate, and accessible diagnostic technologies represents a critical component of disease control efforts. The integration of molecular diagnostics into routine TB care has already improved case detection and treatment outcomes. Future developments promise even greater improvements through enhanced sensitivity, reduced costs, expanded drug resistance detection, and simplified operation enabling deployment at all healthcare levels.

In conclusion, while conventional culture remains the gold standard for certain applications, PCR-based molecular methods have fundamentally transformed TB diagnostics by providing rapid, sensitive, and specific detection that enables timely clinical intervention. The optimal approach employs both technologies strategically, leveraging their respective strengths to maximize diagnostic accuracy, minimize time to treatment, and improve patient and public health outcomes in the ongoing fight against tuberculosis.

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