# DIAGNOSING CHILDHOOD TUBERCULOSIS IN INDIA

## 2014 - 2018

### Accelerating access to quality care for presumptive paediatric tuberculosis patients through improved diagnostic strategies

USAID FROM THE AMERICAN PEOPLE

KNCV TUBERCULOSIS FOUNDATION

DOTS Pura course, Pakka ilaaj

FIND Because diagnosis matters

CHALLENGE TB

Sabir, seen on the cover page in his home with his family, is 14 years old and lives in Surat, India. He loves studying and competed in the national Science Olympiad.

Sabir was diagnosed with TB after visiting five doctors. At the time of this photograph taken in December 2017, Sabir was receiving treatment for TB. His father died when he was young and his mother juggles two jobs to support the family and pay for Sabir's treatment.

Photo credit: FIND / Ben Phillips

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# Abbreviations

| | | |
|---|---|---|
| AC | – | Air conditioner |
| AMC | – | Annual maintenance contract |
| BAL | – | Bronchoalveolar lavage |
| CBNAAT | – | Cartridge-based nucleic acid amplification test (NTP's term for GeneXpert) |
| CFU | – | Colony Forming Units |
| CME | – | Continuing medical education |
| CSF | – | Cerebrospinal fluid |
| DBT | – | Direct benefit transfer |
| DEO | – | Data Entry Operator |
| DR | – | Drug resistant |
| EP | – | Extrapulmonary |
| FIND | – | Foundation for Innovative New Diagnostics |
| FNAC | – | Fine needle aspiration cytology |
| GA | – | Gastric aspirate |
| GL | – | Gastric lavage |
| GX IV | – | GeneXpert - Four module equipment |
| HR | – | Human resources |
| IEC | – | Information, education and communication |
| IAP | – | Indian Academy of Paediatrics |
| IMA | – | Indian Medical Association |
| IS | – | Induced sputum |
| LC | – | Laboratory coordinator |
| LN | – | Lymph node |
| LTBI | – | Latent tuberculosis infection |
| MDR | – | Multi-drug resistance |
| NTP | – | National TB programme |
| OPD | – | Out-patient department |
| PCC | – | Probe check control |
| PCR | – | Polymerase chain reaction |
| PPM | – | Public-private mix |
| QA | – | Quality Assurance |
| RNTCP | – | Revised National Tuberculosis Control Programme |
| RR | – | Rifampicin resistant |
| SPC | – | Sample processing control |
| SOP | – | Standard Operating Procedure |
| TAT | – | Turnaround time |
| TB | – | Tuberculosis |
| TST | – | Tuberculin skin test |
| USAID | – | United States Agency for International Development |
| UPS | – | Uninterrupted power supply |
| WHO | – | World Health Organization |
| XDR | – | Extensively drug resistant |
| ZN | – | Ziehl-Neelsen stain |

# Acknowledgements

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## About this document

The purpose of this document is to describe and report on the extensive experience derived from implementing upfront GeneXpert-based diagnosis for presumptive paediatric tuberculosis (TB) patients in India over the course of four years of the project duration (April 2014 to March 2018).

The Foundation for Innovative New Diagnostics (FIND), in collaboration with the Revised National TB Control Programme of India (RNTCP), and with financial support from USAID under the Challenge TB Project, launched a novel initiative to address the diagnostic challenges in paediatric TB by implementing upfront GeneXpert-based diagnosis. The project was initially implemented in four major cities of India (Delhi, Kolkata, Chennai, and Hyderabad). Subsequently, six additional cities were added – Bangalore, Guwahati, Surat, Nagpur, Visakhapatnam in 2016 and Indore in mid-2017.

The uniqueness of the project and its key findings are outlined in the **Summary**. The global and national paediatric TB burden, including the challenges associated with diagnosis of paediatric TB, is described in the section entitled **Epidemiology and challenges**. The GeneXpert system, together with the MTB/RIF assay, was implemented at designated sites for diagnosis of presumptive TB cases, and the section on the **Rationale** of this project highlights the research gap and relevance of implementing this project in India.

The project necessitated continuous brainstorming and dedicated effort and planning, described in the section **Planning and organization**. This section also covers site preparation, placement of and training on GeneXpert machines, linkage of laboratory sites with providers, sample transportation and related guidelines, standard operating procedures for processing of different samples, and guidelines for additional testing and discrepancy resolution.

As this initiative was to be implemented for improving the diagnosis of paediatric TB, it was necessary to engage healthcare workers providing care to children. The care providers were supplied with educational materials and information on the project (please refer to the **Implementation** section for the detailed project model). This section also details the sample extraction and collection points, testing on GeneXpert and linking the diagnosed TB cases to treatment.

The section on **Findings under the project** documents an overall analysis of collected data including specimen wise information, provider engagement, treatment details and the geographical impact within the scope of the project.

The section **Transition of paediatric project geographies** details the phased transition process of the project to NTP.

**Monitoring and supervision** describes the monitoring matrices, quality assurance, data management and lessons learnt. The document also elucidates the manner in which mapping of TB diagnostic pathways facilitated development of efficient referral mechanisms, while mapping of disease hot spots within the cities improved planning, targeted advocacy and short turnaround time in reporting results. This is elaborated under **Need for additional GeneXpert laboratories**.

Other sections included in the document are **Developing centers of excellence** as a model for non-sputum sample collection, **Lessons learnt and the road ahead**, and **Summaries of relevant publications**. The section on lessons learnt describes best practices under the project which led to its fruition, the challenges and how to mitigate them, and what is needed for the future.

References are indicated within the body of this document in the form of footnotes. The Annexes are provided in a separate document.

## Summary

Lack of accurate diagnosis of tuberculosis (TB) in children has been a major impediment in the management of childhood TB. Various diagnostic limitations pose serious challenges to laboratory-confirmed diagnosis of TB in children, adding to the potential for both under- and over-diagnosis. To address these diagnostic gaps, FIND, in collaboration with RNTCP, i.e., the National TB Programme (NTP) of India, and with funding support from USAID under the Challenge TB Project, implemented a novel paediatric initiative in April 2014 in four major cities of India (Delhi, Kolkata, Chennai and Hyderabad). This initiative initially focused on demonstrating the feasibility of rolling out upfront GeneXpert-based diagnosis of TB in the paediatric population.

High-throughput GeneXpert laboratories were established at NTP sites in each of the above-mentioned cities. At each location, potential referral institutions (public and private) were mapped and healthcare providers were engaged *via* outreach and information meetings. A hub-and-spoke model was established, with the labs acting as the hub and engaged providers as the spokes. Upfront GeneXpert testing was offered to all children under 15 years of age who showed symptoms of pulmonary and/or extrapulmonary TB (EP-TB) who sought care at these referral institutions. Linkage to testing was carried out, free-of-charge, *via* rapid specimen transport networks and results were delivered using electronic reporting (e-mail/SMS). Based on the remarkable impact seen over just two years, the project was scaled up to include five more cities (Bangalore, Guwahati, Surat, Nagpur, and Visakhapatnam) in 2016. A 10$^{th}$ city (Indore) was added in mid-2017.

The project was unique in several ways.

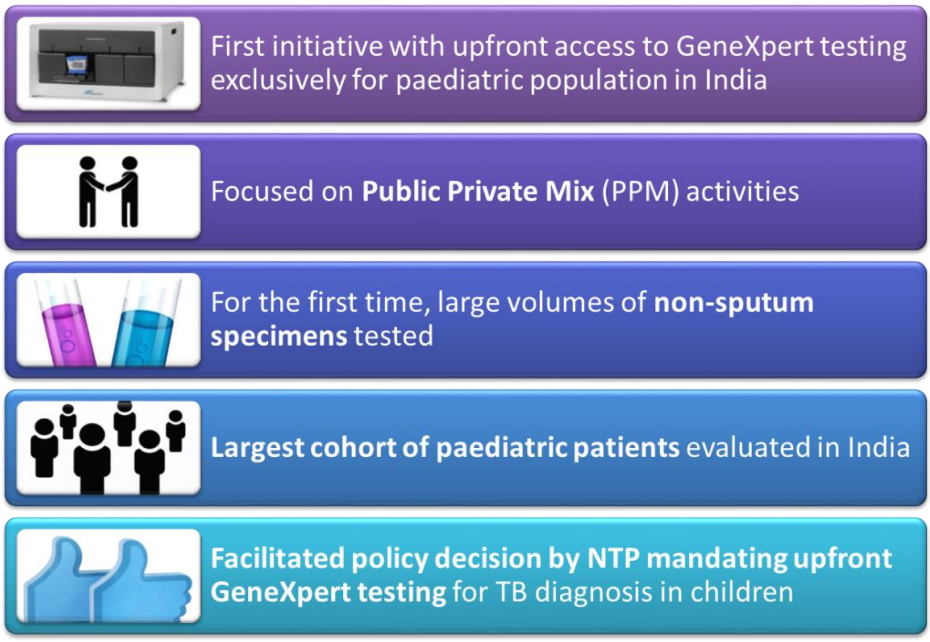


**Figure 1: Uniqueness of the project**

1. This was **the first time** that GeneXpert was offered as an upfront test for TB diagnosis among the paediatric population in India.
2. From the start, the focus was on **public-private mix** (PPM) activities targeting the paediatric population in key cities. The project was able to improve the diagnostic capacity for paediatric TB, not only in the public sector but also in the private sector, where a large proportion of patients seek medical care.
3. For the first time, a substantial number of **non-sputum specimens** from presumptive paediatric TB patients were collected systematically and tested using GeneXpert. The number of non-sputum samples tested under the project was nearly half of the total samples received.
4. This was the **largest cohort of paediatric patients** evaluated in India.
5. Project findings **facilitated a policy decision by India's NTP mandating the use of GeneXpert as a primary diagnostic tool** for TB in children.

**Key findings of the project (2014-2018):**

1. Overall, 94,415 presumptive paediatric patients (<15 years of age) were tested on GeneXpert across the 10 project intervention cities. This resulted in diagnosis of 6270 (6.6%) TB cases, including 545 drug (rifampicin) resistant cases.
2. Among the diagnosed patients, TB positivity in females (8.8%) was observed to be almost two-fold higher than in males (4.8%).
3. The project successfully engaged 1416 facilities/providers, 61% from the private sector, through information meetings, continued medical education (CME) sessions and outreach activities across the project cities.
4. For the first time under NTP of India, both sputum and non-sputum specimens from paediatric TB cases were tested on GeneXpert in a routine and systematic manner. 103,045 specimens (~50% non-sputum) from the 94,415 patients were tested using Xpert. Samples included gastric aspirate (GA), gastric lavage (GL), bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF), pleural fluid, and pus.
5. Overall, the project was highly successful in increasing detection rates. GeneXpert positivity under the project was close to 7%. The received specimens were also subjected to smear microscopy (the only decentralized lab test available before the start of the project) and the positivity rate observed with this diagnostic method was only around 2%, demonstrating a more than three-fold increase in the microbiological detection of paediatric TB when using upfront GeneXpert.
6. Of the total TB cases detected on GeneXpert, around 9% were diagnosed as rifampicin-resistant (RR)-TB. This highlights the additional benefit of using GeneXpert.

7. The project facilitated prompt access to quality diagnostic services. Average turnaround time for GeneXpert testing was one day including specimen collection, transportation, testing, and reporting.
8. Of the total diagnosed TB cases, around 89% were linked to treatment.

This intervention provided the necessary evidence to facilitate a policy decision by the NTP of India to mandate the use of upfront GeneXpert for diagnosis of TB in children. Based on the success of the project and leveraging its learnings, the intervention has now been scaled up across the country by the NTP.

## Epidemiology and challenges

Diagnosis of tuberculosis (TB) in children (under 15 years of age) traditionally had a lower priority than diagnosis of TB in adults in national TB programmes[1]. However, paediatric TB remains an important cause of juvenile morbidity and is one of the top ten causes of childhood mortality globally[2]. It is estimated that around 7.5 million children <15 years old are infected with TB every year[3], of which 1 million developed active TB in 2017 (Figure 2)[4]. This number represents 10% of the global incidence of TB, while high-burden settings report 15-20%. More than half of these cases are amongst children under five years of age[5]. However, 55% of children estimated to have TB were not reported to national TB programmes[3]. This gap is higher than observed in the adult age group. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) have also been documented in the paediatric age group[6], although there are no representative estimates of the overall burden because until now children have been excluded from most drug resistance surveys, and because difficulties with paediatric TB diagnosis has limited evidence of the number of actual cases.

*According to the Global TB Report 2018, 10% of the total TB positive population is in children between the ages of 0 to 14 years.*

According to the 2017 estimates on TB mortality, children accounted for 15% (0.2 million) of total deaths in HIV negative people (1.2 million), higher than their share of estimated cases, suggesting poorer access to diagnosis and treatment. A majority (80%) of these deaths were in children younger than 5 years of age[3,5,7]. Children accounted for 10% of total deaths in human immune-deficiency virus (HIV) positive people[3,7]. The high mortality rate may be a consequence of delayed

[1] Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clin Infect Dis. 2010;50 Suppl 3:S184-94.
[2] Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. The Lancet Global Health. 2017;5(9):e898-e906.
[3] Roadmap towards ending TB in children and adolescents, 2018. Available: http://apps.who.int/iris/bitstream/handle/10665/274374/9789241514668-eng.pdf?ua=1
[4] World Health Organization. Global tuberculosis report. Geneva, Switzerland; 2018. Available: http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1
[5] World Health Organization. Global Tuberculosis Report. Geneva, Switzerland; 2017. Available: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1
[6] Raizada N, Sachdeva KS, Swaminathan S, Kulsange S, Khaparde SD, Nair SA, et al. Piloting upfront GeneXpert MTB/RIF testing on various specimens under programmatic conditions for diagnosis of TB & DR-TB in paediatric population. PloS one. 2015;10(10):e0140375
[7] Lisa V Adams MRS, MD. Tuberculosis disease in children. Available: https://www.uptodate.com/contents/tuberculosis-disease-in-children

diagnosis and poor compliance to treatment, both of which can be improved by rapid diagnosis and promoting access to quality health care[8].

India is among the highest TB and drug-resistant (DR)-TB burden countries globally[9]. In 2017, the country accounted for around a quarter of the global TB burden, estimated to be 2.7 million (Figure 2). In the same year, TB incidence by age and sex in the Indian population was two-fold higher in males, with 1.8 million and 0.9 million cases in males and females, respectively[4]. The estimated proportion of TB cases with MDR/rifampicin resistant (RR)-TB cases were 2.8% and 12% in new and previously treated cases, respectively[4]. The National Drug Resistance Survey was completed and provides reliable estimates of national MDR-TB and XDR-TB burden.

India has close to 400 million children in the 0-14 year age group, which constitutes about one-third of the overall population[10]. Of the total TB incidence, 0.2 million TB cases are estimated to be from the 0-14 years age group[4,10]. In 2017, a little over 0.1 million childhood TB cases were notified, accounting for only 6% of the total notified TB cases[11]. In the same age-group, there was not much difference observed in TB incidence based on sex differentials. A recent retrospective study conducted in Mumbai (India) determined the prevalence of DR-TB in the paediatric population to be 9.6% (110/1,145 cases). There was an increase in the number in comparison with previous years, i.e., 5.6% pre-2010 and 7% in 2010-2013[12].

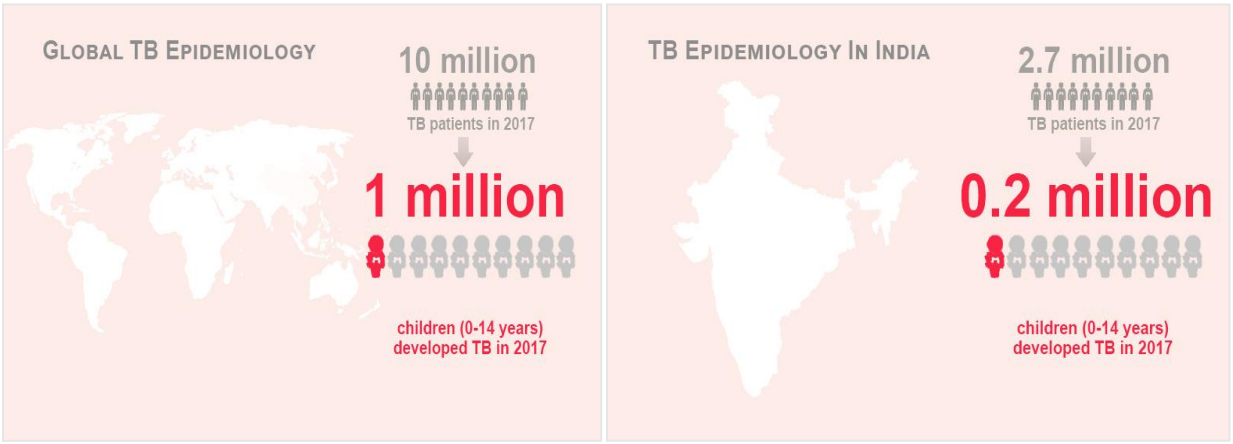


**Figure 2: Burden of paediatric TB at the global level and at the national level for India**

It is evident that in spite of recent progress in the availability of newer rapid TB diagnostics, a major gap between the estimated burden and diagnosis along with notification of paediatric TB

[8] Beyers N, Gie R, Schaaf H, Van Zyl S, Nel E, Talent J, et al. Delay in the diagnosis, notification and initiation of treatment and compliance in children with tuberculosis. 1994;75(4):260-5.
[9] Central TB Division. TB India, 2017: RNTCP annual status report. New Delhi: Government of India
[10] The World Bank Group. Population ages 0-14 (% of total). Available: https://data.worldbank.org/indicator/SP.POP.0014.TO.ZS
[11] India TB report, 2018. Available: https://tbcindia.gov.in/showfile.php?lid=3314
[12] Shah MA, Shah I. Increasing Prevalence of Pediatric Drug-Resistant Tuberculosis in Mumbai, India and its Outcome. 2018; The Pediatric infectious disease journal

cases still exists[13]. Official notification to NTP is necessary to understand the progression in disease incidence and the challenges associated with it.

Children run the risk of progressing from infection to disease within a year's span. Diagnosing TB in children is particularly challenging because children are often unable to produce sputum. Also, the sensitivity of smear microscopy for the diagnosis of childhood TB remains low. In addition, TB can mimic many other common childhood diseases including pneumonia, generalized bacterial and viral infections, malnutrition, and respiratory opportunistic infections associated with HIV. Hence, the diagnosis of childhood TB is primarily based on certain criteria such as (a) a positive history of contact with a TB case, (b) clinical and radiological findings and (c) positive tuberculin skin test (TST).

These criteria, however, have limited application in countries where TB is endemic and can potentially result in over and under diagnosis. Although culture growth is considered to be the gold standard for diagnosis of active TB and drug susceptibility, access to these tests is not always possible in resource-poor settings and time to results is overly long.

Delayed diagnosis of TB in children has been flagged in many studies in India and beyond[13,14] and this is more often accompanied by a delay in treatment initiation[15] which can have serious consequences on the child's health and overall well-being, despite TB being treatable and preventable.

*Challenges associated with paediatric TB diagnosis – non-specific clinical presentation (similar to other chest infections); unavailability of quality samples; poor sensitivity and longer turn-around time of available tests, limited access to rapid and highly sensitive diagnostic tests.*

## Rationale

Diagnosis of TB in children is challenging, as evidenced by the available literature and healthcare system data. This disease has devastating results for children, causing, among other complications, dropout from school and important financial setbacks for the families. The following factors explain the difficulties encountered in paediatric TB diagnosis:

- **Similarity of symptoms** to common childhood infections
- **Difficulty for children to produce quality specimens** for tests
- **Rapid disease progression in children** as compared with adults
- **Lack of access to quality diagnosis**

[13] Jenkins HEJP. Global burden of childhood tuberculosis. Pneumonia. 2016;8(1):24.
[14] Seddon JA, Jenkins HE, Liu L, Cohen T, Black RE, Vos T, et al. Counting children with tuberculosis: why numbers matter. Int J Tuberc Lung Dis. 2015;19 Suppl 1:9-16
[15] Kalra A. Care seeking and treatment related delay among childhood tuberculosis patients in Delhi, India. The International Journal of Tuberculosis. Lung Disease. 2017;21(6):645-50.

Prior to the introduction of this paediatric initiative by FIND and NTP India, there was less reliance on confirmation of TB in presumptive paediatric TB patients due to the limited availability of highly sensitivity, rapid diagnostic tests which could give prompt results. Prior to the introduction of GeneXpert, the common confirmatory paediatric diagnostic tests were:

- **Smear microscopy**: Low/variable sensitivity, unable to detect drug resistance
- **Bacterial culture** (gold-standard): High sensitivity, significantly longer time to results (at least 4-6 weeks)

Moreover, the available diagnostic tests require varying concentrations of bacteria in the sample to be tested (Figure 3), adding a complicating factor for TB diagnosis in children. These drawbacks, including over-reliance on clinical diagnosis, also limit diagnosing drug resistance in children.

The GeneXpert platform is a highly sensitive and specific tool with a quick turnaround time. In the global guidance document released by WHO[16], it was recommended that GeneXpert be used in place of conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB. The equipment requires only 50-150 cfu/mL to run a test, considerably less than for conventional liquid culture sampling. Upfront rapid testing with the GeneXpert TB test offers a promising solution for the early and accurate detection of TB and RR-TB among children. This, in turn, signifies that this vulnerable population can receive treatment rapidly.

Expanding the toolbox available to paediatricians by providing easy access to a rapid diagnostic test like GeneXpert could be one of the effective ways to shorten lengthy paediatric pathways to TB care and reduce the extent of suffering associated with paediatric TB, both clinically and in general.

Against this background, FIND, in consultation with India's NTP, implemented a novel paediatric TB project in April 2014 in Delhi, Kolkata, Chennai, and Hyderabad. Due to the success of the project, the additional cities of Bangalore, Guwahati, Surat, Nagpur, and Vizag also joined the project in 2016 and a tenth city, Indore, was added in mid-2017.

[16] World Health Organization. Policy update: automated real time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: GeneXpert MTB/ RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children, 2013. Available: http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf

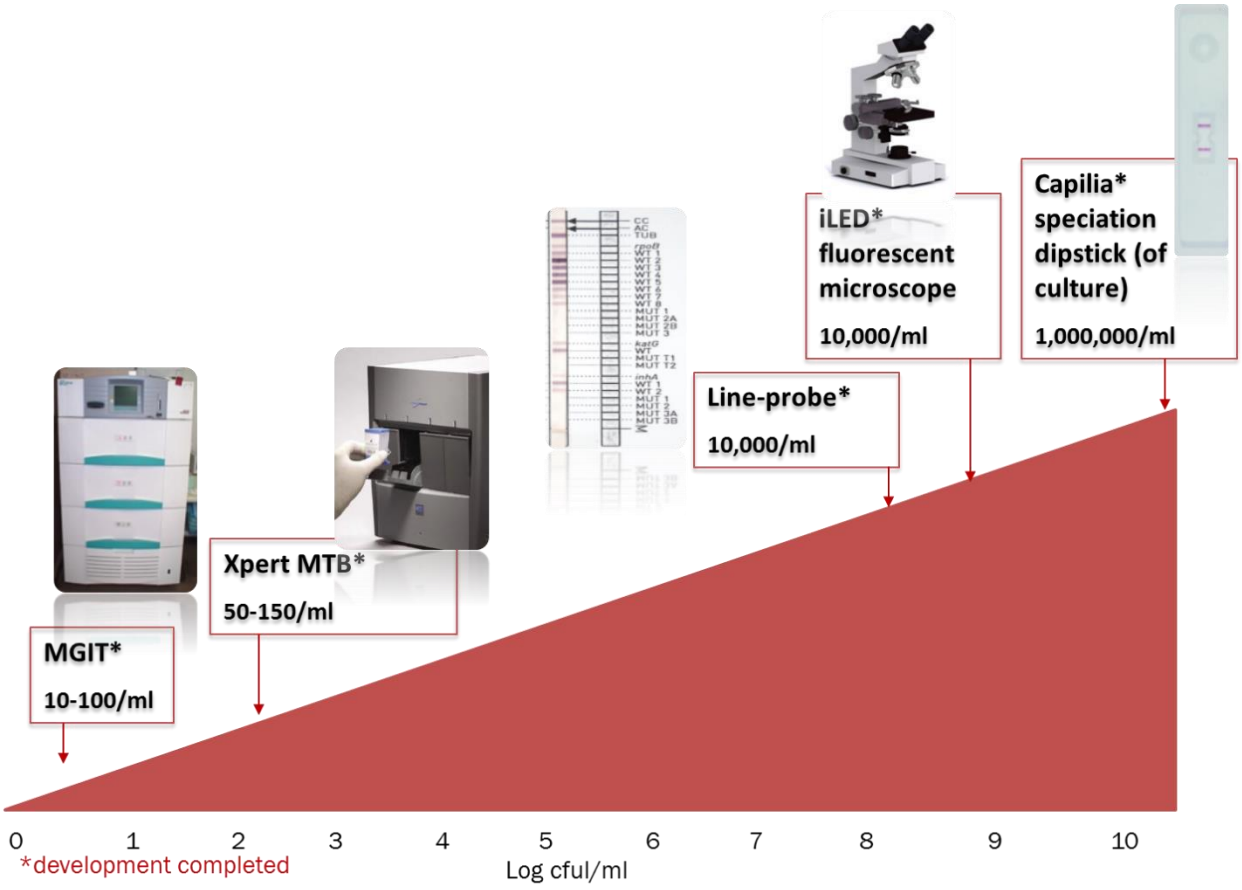


**Figure 3: Spectrum of available diagnostic tests with the concentration of bacteria required per ml of sample to be tested positive for each test; MGIT: Mycobacteria Growth Indicator Tube**

## Planning and organization

Before the project was launched in each of the intervention cities, multiple preparatory visits were made to assess the existing infrastructure, plan and check that other critical pre-requisites were in place, and ensure that the gaps which needed to be addressed before installation of the GeneXpert equipment had been identified. The assessments were carried out in consultation with both district and state-level NTP managers. The following key issues were covered on these visits:

- **Informing NTP programme officials** (both at the state and district level) of the technical background, aims, objectives, and structure of the project
- **Identification of a dedicated space/room** for placing GeneXpert equipment and storing MTB/RIF cartridges within the recommended temperature range. The space identified for

placement of the GeneXpert system and ancillary equipment was usually sufficient for accommodating a data entry operator (DEO) and the laboratory coordinators (LCs).

- **Identification of facilities** for sputum smear microscopy and extrapulmonary (EP) sample processing near the lab
- **Assessment of the power situation,** i.e., frequency and duration of power interruptions, the stability of voltage supply vis-à-vis planned power back-up provisions, if any
- **Identification of logistic requirements** for the lab, including personal protective equipment, disinfectants, and other related lab consumables
- **Assessment of provision for biomedical waste management** at the lab and laying out a plan for the management of lab-generated waste from the project (including human/biological waste, sharps waste, plastic waste like cartridges, etc.)
- **In-depth district/city profiling,** which includes the number of available GeneXpert machines, the actual testing load per machine per month and their distribution across the city, type of terrain and population coverage, existing health system structure and human resources (HR) available under NTP at the district/city level, availability of microscopy and culture/drug susceptibility testing (DST) services within the city
- **Situation analysis and preparing a detailed plan for mapping** the potential hospitals, prominent providers, standalone clinics and other health facilities to establish referral linkages under the project, for both the public as well as the private sector providers
- **Forecasting the monthly test loads** based on available data (both current as well as historic)
- **Planning of workflow** so as to minimize turnaround time for the test results
- **Developing an operational plan** with district and state officials for project implementation
- **Listing site preparatory activities** including civil work for establishing a GeneXpert facility and stipulating timeframe in order to forecast the launch of the project and related activities in the city
- **Other important tasks,** like the recruitment of manpower, minor (need-based) upgradation of the infrastructure, local procurement of various equipment, internet connectivity, etc. were also discussed with NTP officials and finalized

The site assessment checklist can be viewed in Annex I.

### a. Site preparation

A GeneXpert lab was established as per internationally accepted standards and WHO recommendations. Based on the findings of the initial site assessment, the following activities were undertaken:

- **Laboratory infrastructure:** The infrastructure was provisioned in the identified space and need-based modifications were undertaken. These included minor civil works, provision of lab furniture and ensuring a secure and dust free environment for the equipment.
- **Adequate and appropriate power back up units:** Completion of the ongoing test in case of power supply interruption was ensured by providing uninterrupted power supply (UPS) with batteries, in line with the recommended power requirements of the GeneXpert equipment.
- **Air conditioning:** To maintain an ambient temperature of below 28°C as per manufacturer's recommendations, an air conditioner (AC) unit (~ 1.5 ton) with stabilizer was installed at all the project sites. To monitor the efficacy of the AC unit, a maximum and minimum temperature gauge was installed in the GeneXpert lab room.
- **Equipment supply:** To begin with, each site was supplied with a single, four-module GeneXpert machine (GX IV)), MTB/RIF cartridges, and a laptop. A spare GX IV was kept in reserve. As the individual site workload increased, a second GX IV was provided to ensure minimum turnaround time for diagnostic results. All the GeneXpert machines were procured with a two-year warranty from the date of receipt for maintenance and trouble-shooting.
- **Cartridge supply and other lab consumables:** Ensuring an uninterrupted supply of cartridges and other consumables helped maintain rapid turnaround time and consequently gained provider trust. Preventing stockouts required estimating how many cartridges would be needed based on data from previous experience. One month's running stock and a minimum of three months' buffer stock were provided to each site based on estimates calculated in advance. Other lab consumables identified during the site assessment visits were also supplied, including additional Pasteur pipettes and 50 ml falcon tubes to facilitate smooth transportation of samples and personal protective equipment, like nitrile powder-free gloves, etc. Requirement of lab consumables was forecasted and supplied in the same manner as for cartridges.

  The project staff at each lab recorded and maintained stock details of cartridges and other consumables which were cross-verified by the NTP site in charge and monitored by the technical team at the national level on a monthly basis.
- **Micro-planning for efficient sputum transportation:** An appropriate specimen transport mechanism – from identified referral hospitals, standalone clinics, medical colleges and other health establishments (catering to paediatric populations) to GeneXpert labs – was established in consultation with local district officials.
- **Human resources support** (Figure 4)**:**
  - **National level:** Under the overall leadership and guidance of the Head of FIND India and NTP, the paediatric TB project leader was responsible for the overall project activities. The project leader was supported by a project coordinator who was assisted

by a technical coordinator and a data manager for the day-to-day activities, such as coordinating with district/city level teams as well as NTP officials, and critical review/monitoring.

- **District/city level:** Dedicated lab coordinators were appointed for each site to ensure adherence to the project protocol, to conduct daily lab activities and field visits. Their responsibility also included testing of samples received at the lab as well as smooth coordination of project activities with the site in charge and district level NTP officials. For optimal real-time data entry and rapid reporting of results by SMS and e-mail, DEOs were recruited at all the project sites. On average, each site had two lab coordinators and one DEO.

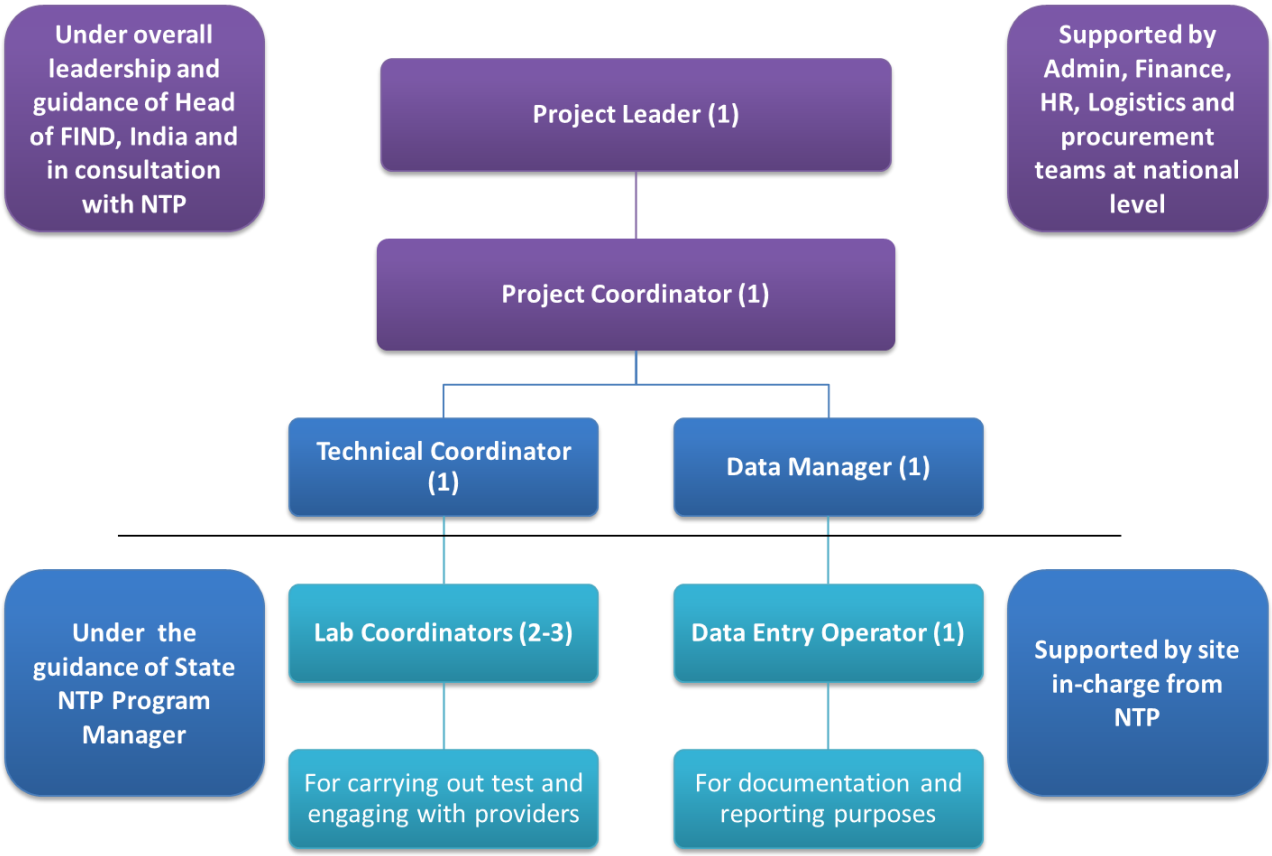


**Figure 4: Organogram under the project; NTP: National TB Programme**

In addition, support was also given by finance, HR, admin, logistics and procurement teams at national level for project-related activities.

## b. Identification of sites/cities and placement of GeneXpert machines

**Introduction of GeneXpert equipment and related policy recommendations:** The development of the Xpert® MTB/RIF assay for the GeneXpert platform was completed in 2009 and is considered an important breakthrough in combatting TB. In December 2010, WHO first recommended the use of the test (Figures 5 & 6) for TB diagnosis. In October 2013, WHO issued an updated Policy Guidance [17], providing revised recommendations on the use of GeneXpert to diagnose pulmonary TB, EP-TB, RR-TB, and paediatric TB. This policy update replaced the first edition and took into consideration the available body of evidence and operational experiences since the original policy recommendations. In 2014[18], WHO published a rapid implementation document which provided the technical "how-to" and operational considerations for rolling out the technology. The implementation document provided a simple checklist of prerequisites needed for employing the test, along with key action points.


**Figure 5: GeneXpert TB/RIF cartridge for the GeneXpert platform**

**Identification of sites/cities:** The selection of the project sites/cities was finalized in consultation with India's NTP. The identified sites were among India's most populous cities, lacked other similar initiatives and were selected to fast-track lessons learned since they were known to have a concentration of public and private sector providers, and could thus maximize the impact and uptake of the project interventions.

*In 2013, WHO recommended that GeneXpert be used rather than conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB*

**Placement of GeneXpert machines:** GeneXpert equipment was procured at the national level and was supplied to the identified sites by the vendor. Installation was undertaken by the regional representative/engineer of the vendor.

Upfront introduction of GeneXpert, particularly for the paediatric population in the initial four sites was intended to provide the NTP in India with early information on objectives related to feasibility. The additional six cities were included for phased expansion of the project to assess feasibility in

[17] Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: GeneXpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. Geneva, World Health Organization, 2013. Available: http://www.who.int/tb/laboratory/policy_statements/en/

[18] GeneXpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations. World Health Organization, 2014. Available: http://apps.who.int/iris/bitstream/handle/10665/112469/9789241506700_eng.pdf;jsessionid=A0EF757B089EA510B97B8580425149F1?sequence=1

different settings, based on the data produced in the initial two years which showed encouraging results for further scale-up.


**Figure 6: Four-module GeneXpert machines procured under the project (© FIND/B. Phillips)**

### c. Training on GeneXpert

A one-day, hands-on training on project protocol, aims, objectives, and outcome was held at each of the participating sites/cities for all project staff. They were instructed on performing the GeneXpert assay as well as on handling GeneXpert software and equipment. NTP staff at both state and district levels were also trained. Figure 7 summarizes the topics covered in the trainings.

Refresher trainings were also provided every year for the project staff where experts in the field guided the staff on standard operating procedures. This helped to update the staff on newer guidelines/recommendations relating to TB diagnosis and related matters, essential for the project implementation.

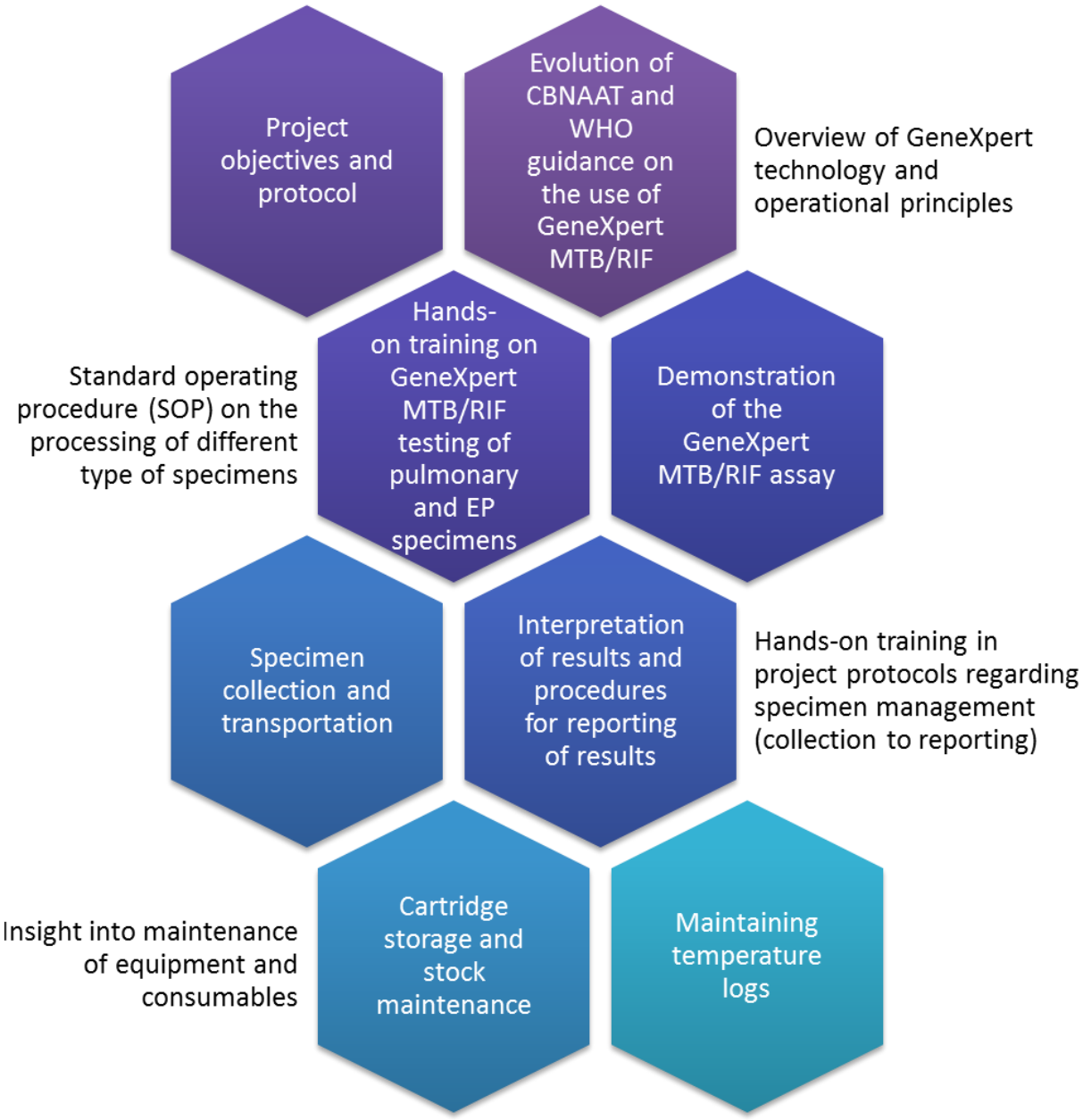


**Figure 7: Topics covered under GeneXpert training; EP: extrapulmonary; WHO: World Health Organization; CBNAAT: cartridge-based nucleic acid amplification test**

### d. Linkage of laboratories with providers

Providers in each of the project cities were mapped or located using various databases and approaches (see Mapping). They were informed about the project services through CME sessions, one-on-one meetings, and other advocacy interventions.

During the initial phase, the project team established linkages with the providers to build a good working relationship. Maintaining short turnaround time (TAT) of reporting results and taking regular feedback from the providers helped increase their confidence in the project and consequently their willingness to send referrals in a sustained manner. In each of the cities, the project gained significant momentum, with a growing number of providers becoming engaged with the initiative. The project was implemented in a manner to sustain and carry forward the interventions/activities so that the processes could be handed over to India's NTP in a phased manner. In due course, providers were encouraged to refer samples to the nearest GeneXpert/CBNAAT lab in the public sector for free testing. All the providers engaged under the project were apprised about the available GeneXpert/CBNAAT labs nearest to their clinic, where samples could be tested.

Linkages between labs and providers were established through:

- **Network of facilities and labs:** During CME and one-on-one meetings, providers (both private and public) were told about the location of the project lab and encouraged to refer samples to the lab for rapid testing.
- **Mapping of sites/routing:** The project and procedures for sample collection and referral to the GeneXpert lab established under the project were explained to providers.
- **Training:** The providers received onsite training on patient referrals and sending samples. They were given sterile falcon tubes and basic infection control protocols to follow during sample collection. Videos on sample collection for non-sputum samples, especially GA and induced sputum (IS), were shown and the process was described during CME sessions and one-on-one interactions. A simplified test request form was designed for private providers engaged under the project to enable ease of recording referrals (Annex II). The project provisioned for reimbursement of travel to the lab for testing of a sample incurred by the patient/parent/hospital attendant/volunteer/provider. This was disbursed at pre-decided fixed rates immediately upon receipt of the sample at the lab.
- **Management of the system/integration into other networks:** The project was planned and implemented in close coordination with the national/state/district NTP officials with a view to the eventual transition of these service to NTP. The services of NTP field staff were used for provider interactions, sample collection, sample transport and linkages to treatment.
- **Specimen collection and packaging:** The specimens were collected in sterile falcon tubes by the providers. These falcon tubes were given to all the providers (and replenished as per need) under the project. Training on sample collection and packaging was imparted through CMEs and during one-on-one meetings. The samples were then transported to the nearest lab for testing by GeneXpert.
- **Confidentiality of patient information:** Confidentiality was maintained throughout the course of the project. Other than the patient, provider, lab and NTP staff, patient details—including the results of testing—were not shared with anyone. This was strictly monitored

during onsite supervisory visits by project staff and NTP officials. The results were transmitted to the referring providers by e-mail and SMS only. The hard copies of the results were shared with the patient on request.

- **Communication of results:** It was ensured that the test results were transmitted/reported to the referring provider within 24 hours of receipt of a sample at the lab.

### e. Sample transportation and related guidelines

One of the key achievements of the project was rapid (within 24 hours) sample transportation from the referring facility to the GeneXpert lab in the intervention cities. **Mechanisms for appropriate sample transport** to the GeneXpert lab were put in place in consultation with district NTP officials. **Site-specific specimen collection and transportation plans** were developed which took into consideration distances, available transportation facilities, travel time and costs. Attempts were made **to encourage and facilitate all samples reaching the GeneXpert lab on the same day of specimen collection**, thus avoiding any pooling of specimens for several days at collection facilities. **Micro-planning** was done for efficient and sustainable sample transportation of public and private sector patients.

Specimens were collected in sterile tubes placed at the facility and packaged and transported with adequate biosafety precautions by the compounder/lab personnel. Every specimen was accompanied by a lab request form (Annex III) prescribed by NTP or an abridged form (Annex II) specifically designed for doctors in the private sector. The samples were transported by a human carrier, often the parents or relatives of the child, usually on the same day of collection. If timely transportation was not feasible, then it was advised to place samples in the refrigerator (but not in the freezer).

For precious samples like CSF, providers were encouraged to transport the sample promptly to the lab. In cases where the samples were transported from a remote area to the project lab by courier, for example from health centers in tribal belts at the Visakhapatnam site, then NTP guidelines were followed to ensure that the samples were packaged under biosafety precautions using the triple packaging system and ensuring that cold chain was maintained. Similarly, at the lab, in case same day testing was not feasible, the received samples were refrigerated after verifying patient details on the referral form.

The providers were asked to refer samples during the hours when the lab was operational. The providers were also informed in advance if the lab was not open, e.g., in the case of government holidays.

### f. Standard operating procedures for sample processing

Sputum specimens were tested by adding buffer in 1:2 proportions as recommended by the manufacturer (Cepheid manufacturer instructions). For non-sputum specimens, SOPs developed

by NTP and WHO were adopted[19]. Confirmatory DST for diagnosed RR cases was performed by repeat GeneXpert or line probe assay (LPA) or culture DST. Confirmatory DST was performed either on the remnant specimen, or on an additional specimen, if available. Protocols to process EP/non-sputum specimens on GeneXpert MTB/RIF have been described in Annex IV**.**

### g. Guidelines for additional testing and discrepancy resolution

In the case of an 'error' or 'no result' message using GeneXpert, a repeat test was performed on the remaining sample-buffer mix. In case of an 'invalid' or 'rifampicin resistance indeterminate' test result, repeat testing was performed on a second specimen—as per the updated WHO policy recommendations—due to the possibility that polymerase chain reaction (PCR) inhibitors were present in the original specimen.

The feasibility of GeneXpert implementation was assessed in terms of a few indicators, including the ability of the test to provide a valid result. The absence of a valid result for any given assay used was defined as a '**test failure'** regardless of the underlying reason. A test failure based on a single GeneXpert test was defined as '**initial test failure**'. Initial test failures that could not be resolved with a repeat assay, or which could not be re-tested for operational reasons, were defined as '**final test failure**'. The various reasons for the occurrence of test failures were reviewed at each site. Simultaneously, information on factors that may have affected failure rates, such as installation and training errors, ambient temperature, power failure, equipment reliability, or a defective cartridge manufacture lot were routinely collected, analyzed and acted upon. The national team assessed initial and final test failure rates across the project sites by compiling raw data directly extracted from every test run initiated and recorded by the GeneXpert software.

The manufacturer classified possible test failure causes as '**error'**, '**invalid'** or '**no result'** (see Figure 8).

*In case of an 'error' or 'no result' outcome, repeat testing was performed on the same sample; while for an 'invalid' result, repeat testing was performed on a second fresh sputum sample due to concern over the presence of PCR inhibitors in the original specimen.*

[19] Revised National Tuberculosis Control Program. Standard Operating Procedure, 2014. Available: https://tbcindia.gov.in/showfile.php?lid=3255

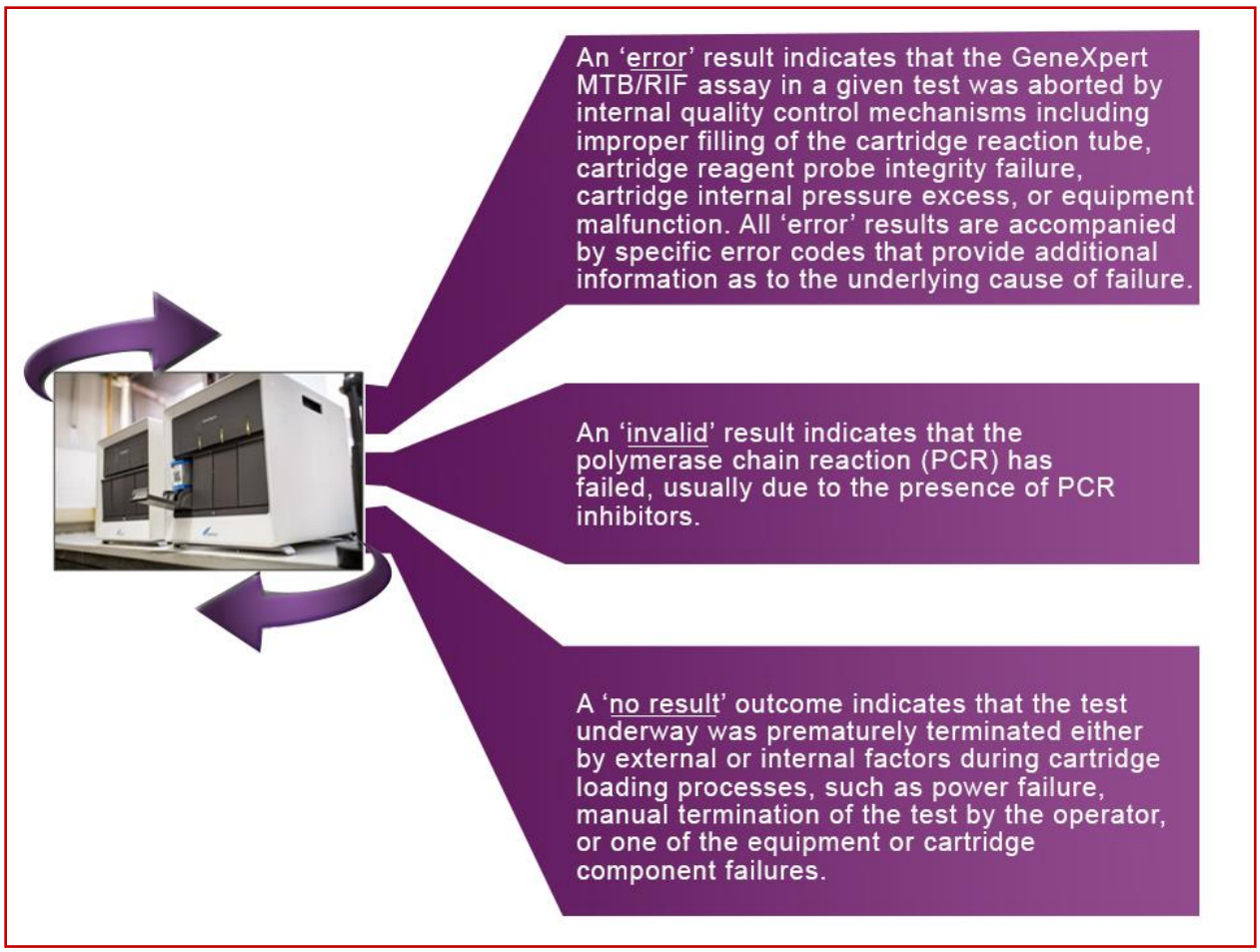


**Figure 8: Reasons for possible test failure**

## Implementation

Until recently, accurate diagnosis was uncommon in the early management of paediatric TB. For the most part, diagnosis was based on a positive history of contact with a TB case, or clinical and radiological findings, often without microbiological confirmation. Diagnostic efforts were also undermined by difficulty in specimen collection and limited availability of and access to highly sensitive, rapid diagnostic tests that can give results quickly.

The GeneXpert platform is a highly sensitive and specific diagnostic tool with a quick turn-around time and reliable results. This offers a viable solution for paediatric TB diagnosis, which is a lot more demanding than diagnosis of TB in adults. In 2013, WHO has recommended that GeneXpert be used instead of conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB.

For this paediatric TB project, upfront rapid testing with GeneXpert MTB/RIF seemed to provide a promising solution to achieve rapid and accurate detection of TB and rifampicin-resistance, critical for the timely initiation of appropriate treatment for this vulnerable population. In line with WHO recommendations on the use of GeneXpert, FIND, in collaboration with NTP, submitted a proposal to USAID in December 2013 to support such an initiative. The proposal was accorded fast track funding approval by USAID.

The objectives of the project were to provide direct access to free GeneXpert testing in the project cities to all children presumed to have TB as well as to strengthen the capacity of existing NTP labs to process paediatric specimens such as GA or GL, BAL, IS, lymph node (LN) aspirates, and CSF. This was done by providing tissue homogenizers, encouraging proper sample packing and transport, using trained project staff to triage samples, and training lab technicians under NTP in GeneXpert testing. High-throughput GeneXpert labs catering exclusively to the TB diagnostic needs of the paediatric population were set up in project cities. The expected outcome was accelerated access to improved TB diagnosis for children under 15 years of age seeking care in both the public and private sector, as well as establishment of better standards of TB care for paediatric patients by linking detected cases to a voluntary free treatment option available under NTP, thus paving the way for important public-private mix involvement.

In 2014, FIND, in consultation with India's NTP, began implementing this unique initiative for TB diagnosis in children. The project was first launched in four major cities of India – Delhi, Chennai, Hyderabad, and Kolkata – with one high-throughput GeneXpert lab established at a public sector facility in each of these cities.

Numerous public and private facilities were linked with this GeneXpert lab through rapid specimen transportation mechanism. The project was designed in a manner that the providers received test results within 24 hours of sample receipt at the laboratory, which was one of the key components contributing to the rapid uptake of project interventions.

GeneXpert testing was performed for all presumptive paediatric TB patients and on all types of specimens as per the 2013 WHO recommendations. Based on the outstanding outcomes observed over just two years of the project, it was decided to scale it up to include five additional Indian cities – Bangalore, Guwahati, Surat, Nagpur, and Visakhapatnam – in 2016 and a 10$^{th}$ city, Indore, in mid-2017 (Figure 9). The selection of intervention cities was planned in due consultation with NTP and the basis of selection of intervention cities included the estimated TB burden, population, and available TB diagnostic services along with interventions.

Systematic outreach and education initiatives were undertaken to engage with health care providers. The clearly defined steps – **mapping**, **approaching**, and **engaging providers** – are described below.

### a. Mapping

At the beginning of the project, providers catering to the healthcare needs of the paediatric population were systematically mapped or located at all the sites. Several approaches were adopted to effectively identify potential providers, including using district NTP lists, key informant and patient interviews, browsing web-based provider databases, liaising with chemists and medical representatives of pharmaceutical companies, etc. Other effective mapping approaches included liaising with professional associations of paediatricians (e.g., Indian Academy of Paediatrics (IAP)), chest physicians, and general practitioners (e.g., Indian Medical Association (IMA)).


**Figure 9: Map showing the geography of the project (red flags initial 4 project cities, blue flags cities added between 2016-2017)**

### b. Approaching providers

One-on-one meetings, trainings and continued medical education (CME) sessions were used to inform potential providers. The engagement and participation of the providers was tracked using a master call list. This list contained provider names, contact details, caseloads and referrals and was maintained by the Lab Coordinators at the sites.

**One-on-one meetings:** The most effective strategy for engaging providers was one-on-one meetings with regular follow-ups. This was vital for building a rapport with the providers and also for receiving real-time feedback, which ensured better service delivery. It also led to on-the-spot query resolution. One-on-one meetings with providers were relevant even following CME sessions.

Distributing or handing over information, education and communication (IEC) materials to providers followed by discussions helped to reinforce a better understanding of the project. IEC materials included flyers and brochures which were designed and printed under the project. These were periodically updated and given to mapped providers.

To plan follow-ups with providers, both those who were engaged and those who were approached, the project team classified providers based on high, moderate and low referrals. Providers with an average monthly referral of more than 10 patient samples were defined as ‘high quantum’ referral providers. Similarly, providers with a monthly average of more than 5 but less than 10 were ‘moderate quantum’ referral providers and those with less than 5 patient samples were categorized as ‘low quantum’ referral providers. All providers who referred from a single facility/hospital were clubbed together as a single unit. This helped in prioritizing visits in a strategic manner as well as for recording notifications.

**Outreach, training and CME**: Key interventions under the project included intensified trainings and CMEs to ensure better uptake of services by both the public and private sector providers. Efforts to drive demand for better quality TB diagnostic services included organizing various information and outreach activities involving prominent health experts, policy-makers and key opinion leaders. Project interventions were discussed in detail during the CMEs and information meetings, which were facilitated by the project's national team. These also included presentations on latest WHO guidelines on the use of GeneXpert as well as treatment aspects which were covered by key speakers, including state and district NTP officials, WHO RNTCP medical consultants, and prominent providers/peers. During the CMEs, well-known providers were invited to share their experience with the project. This served the purpose of engaging with other potential providers and informing them about the importance, necessity and usefulness of the project, including information on the availability of GeneXpert testing in their respective cities (Annex V). Peer to peer advocacy also helped to strengthen the engaged provider database under the project. The aim was to reach out to diverse groups of health care providers and stakeholders in each of the cities to encourage their participation in the project.

As a preparatory activity, state and district level NTP officials were trained on the utility of GeneXpert for the paediatric population and the services available under the project. A few outreach activities were conducted at the institutions/facilities where the TB load was suspected to be higher and where many children could be screened. The project team also ensured the sensitization of relevant individuals at these institutions/facilities about the initiative as well as diagnosis and management of TB. Distribution of IEC materials through CME events, organized under the project for targeted providers, followed by regular telephonic contact with the providers ensured broader coverage. Institutions like orphanages, officials from parallel government health-related programmes, NGOs working in the same geographical region and along similar lines were also educated. It was assumed that these institutions would serve as possible platforms for reaching people symptomatic of TB who have not sought care under NTP. Figure 10 shows where various stakeholders were reached/informed under the project.

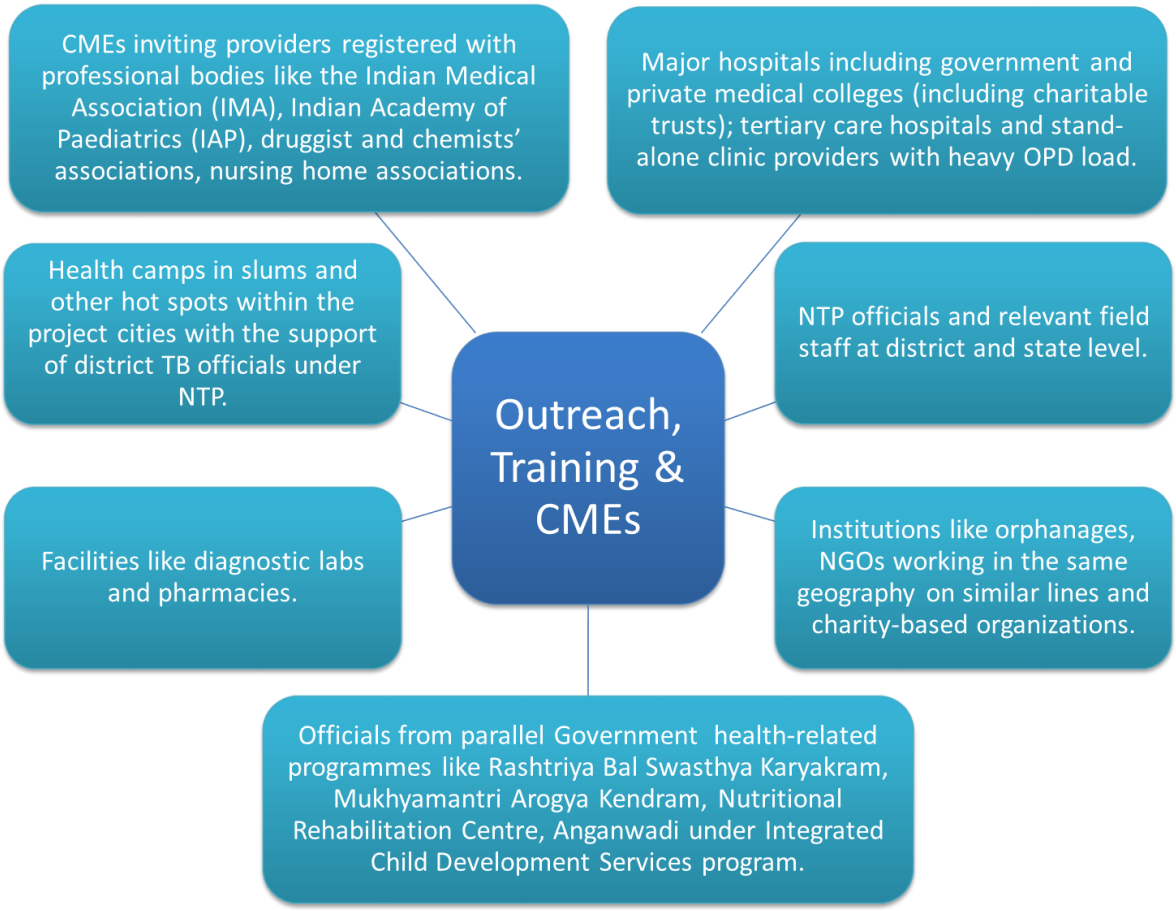


**Figure 10: Outreach, trainings & continuing medical education under the project & with different stakeholders.**

### c. Engaging providers

A provider was considered to be 'engaged' under the project only after they referred a patient and/or sample from a presumptive paediatric TB patient to a designated lab set up under the project. These engaged providers were followed up at regular intervals for feedback, resolution of issues, if any, and to maintain the connection.

To ensure effective and increasing uptake of project interventions, several of these outreach and education approaches were undertaken simultaneously and then repeated on a regular basis. The provider database was maintained in each of the project cities with details of mapped, approached and engaged providers. This dynamic database was updated on a day-to-day basis. The same has been enclosed under section **Monitoring and supervision**. Master call lists were also prepared and regularly updated to ensure effective provider engagement. Such lists included frequency of visits required along with a provider's contact details. Providers were categorized

from high- to low-referring based on the number of samples referred to the project lab and TB load. Subsequent visits or calls were planned based on the referral potential as well as the response from engaged providers.

For project monitoring purposes (including mapping, approaching, and engagement), facilities with single or multiple health care providers were considered as a single unit. For example, the paediatric and pulmonary medicine departments of a tertiary care facility were considered as a single unit. Similarly, a primary healthcare center with a single healthcare professional or a standalone clinic of a paediatrician was also considered to be a single unit.

### d. IEC materials

While the project aimed to establish successful linkages between the site labs and various public-private sector institutions, lack of a "pull" factor from providers was perceived to be a major deterrent to accelerated uptake of new diagnostic technologies during the initial period of the project. To address this, the uptake of services by the providers in both sectors was further enhanced through innovative outreach interventions for better engagement.

Project-specific information, education, communication (IEC) materials were developed, including flyers and brochures, which were used in support of the project. The materials were prepared by FIND in consultation with donor and NTP officials. The same were field tested to understand the response from providers. These were updated periodically based on the feedback received from providers, NTP officials and other stakeholders. The flyers and brochures, available as 1-page (Annex VI), 2-page (Annex VII), 3-page (Annex VIII) and 4-page documents (Annex IX), included information about available services and the process to follow under the project. The project-specific results and success stories were also highlighted in these materials to help providers make evidence-based decisions with respect to sample referrals from presumptive paediatric TB cases. It also served as a handy resource material for the providers with precise information about GeneXpert technology and its relevance in diagnosing paediatric TB.

At an advanced stage under the project, the project team observed that when these flyers and brochures were displayed in the clinic/hospital, a keen interest was shown by the patients to understand about the disease and available tests. To meet this need, one-page flyers were developed and translated in the local language with the support of the NTP district team so as to ensure the use of colloquial terms which patients could relate to and understand easily and effectively. A translated version in Telugu language is shown in Annex X. This version included basic information about TB symptoms, project modalities and available TB testing (via GeneXpert) at no cost to the patient.

*Informative IEC materials were designed for provider advocacy and one-page flyers describing TB symptoms and project modalities were developed for patients in the vernacular language of their respective regions.*

Provider-centric brochures were more technical in nature while patient-centric ones focused more on symptoms and possible actions to be taken, with an assumption that early

recognition of symptoms would lead to prompt and appropriate search for testing and treatment if found positive.

On similar lines, other sensitization and advocacy interventions were employed under the project. Letters were drafted on the letter head of designated NTP district or state official endorsing the project and encouraging providers to avail the services (Annex XI). This letter included basic protocols for sample collection and transportation for provider's reference. In addition, social media platforms like 'WhatsApp' (Annex XII) groups were utilized for circulating project-related messages. This was usually done by a champion provider or by one of the key professional body members engaged under the project. These mediums enabled project teams to reach out to a larger number of providers on a regular basis. Over the course, it was observed that engaged providers themselves advocated for the project among their medical fraternity and shared details during meetings, social media, conferences etc.

### e. Sample extraction and collection points

Presumptive paediatric TB cases were defined as per India's NTP guidelines. This included a child presenting with fever and/or a cough for ≥2 weeks, with or without weight loss or no weight gain in the past three months, history of contact with a TB patient or showing symptoms suggestive of pulmonary and/or extrapulmonary TB. Bacteriologically confirmed cases of TB were defined as having a pulmonary and/or extrapulmonary specimen positive for TB by smear microscopy, culture and/or GeneXpert MTB/RIF, or another WHO-approved rapid diagnostic test. RR-TB cases were defined as bacteriologically confirmed TB cases with an indication of rifampicin resistance on one or more of the following assays: GeneXpert MTB/RIF, LPA or phenotypic DST[20,21,22].

The sample was extracted at the hospital or clinic of the treating doctor where the parent / guardian sought care for his / her child. The sample collection procedure was simpler in case the patient could expectorate to produce a sputum sample. In such cases, the patients were explained about the steps to expectorate and parent/guardian was given falcon tubes for collection of samples. However, in general, a large proportion of children are unable to produce quality sputum samples. This is especially a challenge for younger children. For the non-

*Stand-alone clinics with no infrastructure to collect non-sputum samples were linked to nearby hospitals for extraction.. This ensured testing of all presumptive cases, irrespective of the type of sample.*

[20]Central TB Division Ministry of Health and Family Welfare, Managing the RNTCP in your area – A training course (Module 1–4). Available: https://tbcindia.gov.in/showfile.php?lid=2907.
[21] Amdekar Y. Consensus statement on childhood tuberculosis. Indian Pediatrics. 2010; 47(1): 41-55.
[22] Uria G A, Azcona J M, Midde M, Naik P, Reddy S, Reddy R. Rapid Diagnosis of Pulmonary and Extrapulmonary Tuberculosis in HIV-Infected Patients. Comparison of LED Fluorescent Microscopy and the GeneXpert MTB/RIF Assay in a District Hospital in India. Hindawi Publishing Corporation Tuberculosis Research and Treatment. 2012; 2012: 1-4.

sputum samples including pulmonary samples like GA and IS, provider's intervention with appropriate facility / infrastructure was essential. The tertiary care hospitals were fully equipped in terms of infrastructure and personnel to collect the non-sputum samples. However, this was not feasible for the stand-alone clinics. City wise mechanisms were established to link such clinics to a nearby hospital(s) where samples could be collected. Such facilities served the purpose of collection points which supported the extraction of samples. Patients visited these hospitals solely for sample collection and were charged a nominal fee by these hospitals for the procedure. For consultation and further treatment, the patient returned to the treating provider. In this way, the providers were not worried about referring their patients and proper coordination ensured that this trust could be sustained.

### f. Testing on GeneXpert

Specimens were collected at the referral facilities which were linked with the project GeneXpert (Xpert) lab in the city. The samples were then transported to the lab for testing where it was received by project staff. The transporter was provided reimbursement for travel at pre-fixed rates on receiving sample. Specimens were subjected to smear microscopy using Ziehl-Neelsen (ZN) staining for comparison, with the first available specimen being tested on GeneXpert. The testing procedure has been described in Annex XIII a and Annex XIII b. Smear microscopy was conducted using India's NTP smear microscopy guidelines, with all functional components of quality assurance in place.

GeneXpert testing was performed as per the project diagnostic algorithm (Figure 11). In cases where specimens were less than 1ml in volume, preference was given to GeneXpert testing ahead of smear microscopy, in line with WHO recommendations[23,24]. For a given patient, whenever multiple types of specimens were available, all of them were tested. In the case of 'error' and 'no result' test result on GeneXpert, a repeat test was performed on the remaining sample–buffer mix. In the case of 'invalid' and 'rifampicin resistance indeterminate' test result, repeat testing was performed on a second specimen as per the WHO recommendations[25].

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[23] Pai M. Extrapulmonary Tuberculosis: New Diagnostics and New Policies. Indian J Chest Dis Allied Sci. 2014; 56:71–73

[24] World Health Organization. Policy update: automated real time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: GeneXpert MTB/ RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children, 2013. Available: http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf

[25] GeneXpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations. World Health Organization, 2014. Available: http://apps.who.int/iris/bitstream/handle/10665/112469/9789241506700_eng.pdf;jsessionid=A0EF757B089EA510B97B8580425149F1?sequence=1

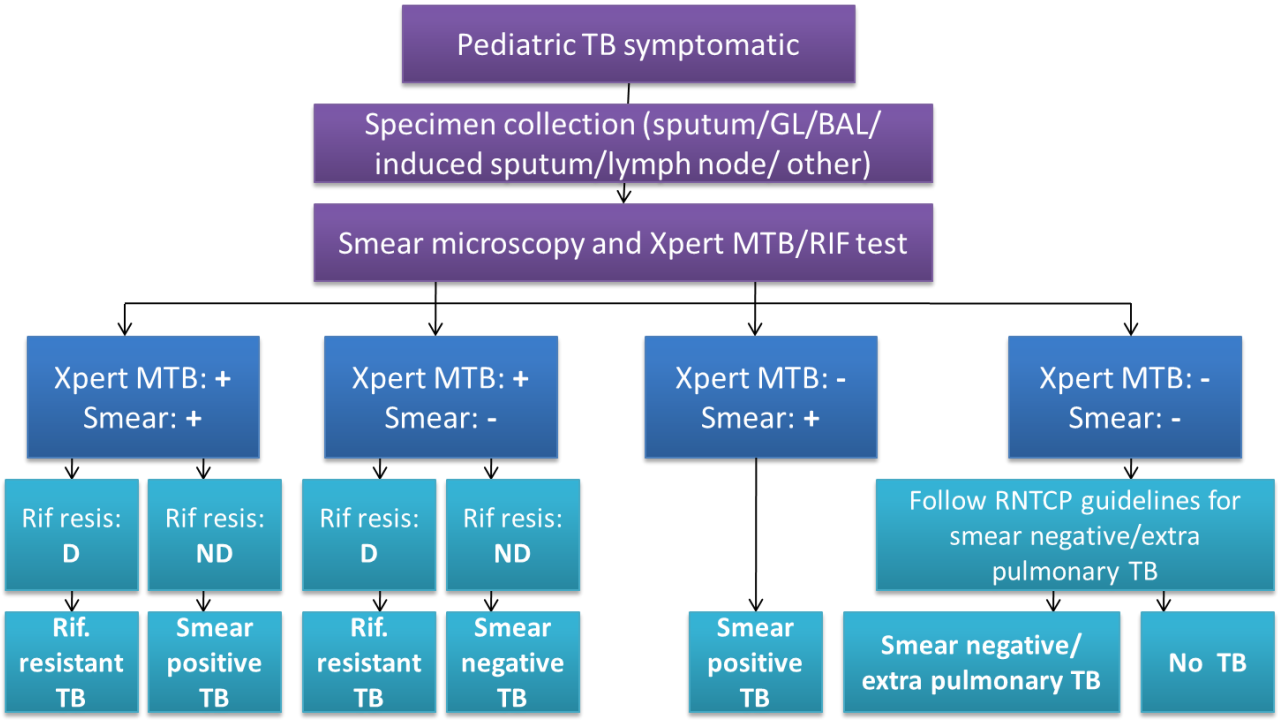


**Figure 11: Diagnostic algorithm followed under the project**

### g. Linkage to treatment

The project reached out to most of the potential facilities in the intervention cities including private clinics, corporate hospitals, medical colleges and hospitals (both public and private). Public sector patients detected positive on GeneXpert were tracked for information on treatment initiation over the phone with the concerned provider, NTP staff and from the NTP records (TB register). The treatment initiation information for patients referred through private sector was taken from treating provider or patient directly after taking provider's consent. If the private patient voluntarily opted for free drugs in the public sector, then the project team facilitated coordination of early treatment initiation at a center near to the patient's residence or at the treating provider's clinic.

## Findings under the project

Overall, 94,415 presumptive paediatric TB and DR-TB cases were given upfront GeneXpert testing across the ten project cities over the four-year project period. Of the referred cases, the proportion of males (51,003, 54.0%) was higher than females (43,406, 46.0%) (Figure 12). The highest proportion of presumptive TB cases from the three paediatric sub-age-groups were enrolled from the 10-14 years (38%) (Table 1). Overall, the median age of enrolled children was 8 years (IQR 4-11 years). Of the total presumptive cases tested through this project, a significantly

higher proportion of cases came from public sector (81,243, 86.0%) than from the private one (13,172, 14.0%).

Of the presumptive patients tested, 6,270 (6.6%) children were diagnosed with TB. Among these, TB positivity in females (8.8%) was observed to be almost two-fold higher than in males (4.8%); TB detection rates were mostly similar the public and private sectors (6.6% vs. 7.0%). TB positivity was the highest in 10-14 year age group (10.6%) compared to children in the 5-9 year (4.3%) and 0-4 year age group (4.2%).

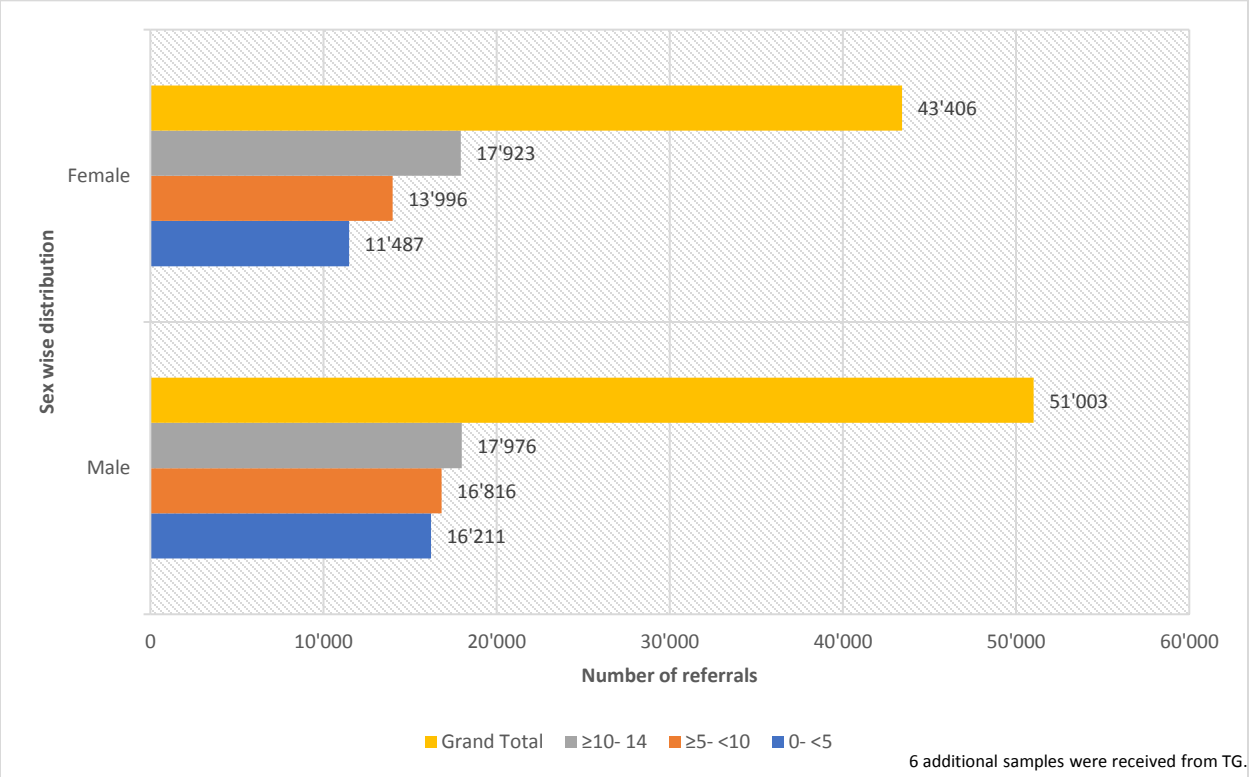


**Figure 12: Presumptive paediatric TB cases enrolled under the project stratified by age and sex (n = 94,415)**

| | Females* | | | | Males* | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall | 0-4yrs | 5-9yrs | 10-14yrs | Overall | 0-4yrs | 5-9yrs | 10-14yrs |
| Number of patients tested | 43406 | 11487 | 13996 | 17923 | 51003 | 16211 | 16816 | 17976 |
| Number of diagnosed TB cases on GX | 3807 | 521 | 702 | 2584 | 2463 | 636 | 613 | 1214 |
| Positivity rate, % | 8.8 | 4.5 | 5.0 | 14.4 | 4.8 | 3.9 | 3.6 | 6.8 |
| Number of DR cases | 328 | 32 | 55 | 241 | 217 | 40 | 61 | 116 |
| Positivity of all diagnosed TB cases, % | 8.6 | 6.1 | 7.8 | 9.3 | 8.8 | 6.2 | 9.9 | 9.6 |

*Samples were divided into 3 age groups: 0-4 yrs, 5-9 yrs and 10-14 yrs. TB: Tuberculosis, GX: GeneXpert, DR: Drug resistant

**Table 1: Presumptive paediatric TB cases enrolled under the project and TB cases diagnosed on GeneXpert: An analysis stratified by sex and age-group**

Amongst the 6,270 TB patients diagnosed positive for TB, 545 (8.7%) were found to be rifampicin resistant (RR). Of these only 28% had history of TB treatment. Higher levels of RR were observed in children in the age groups of 10-14 years (9.4%) and 5-9 years (8.8%) as compared to children in the 0-4 year age group (6.2%). Similar levels of RR were observed among males and females (8.8% vs. 8.6%).

Same-day turnaround for GeneXpert testing including specimen transportation, testing, and reporting was the norm under the project (Table 2). Overall, turnaround between sample collection and reporting of results was one day for 90% of the presumptive cases enrolled under the project. Of the 94,415 paediatric presumptive TB cases tested, valid test results were provided to 94,099 (99.7%) including retesting of those with invalid results.

| Variables | | Days between collection and receipt | Days between receipt and testing | Days between testing and reporting | Days between reporting and treatment initiation (for those who initiated treatment after reporting) | | Days between reporting and treatment initiation for DR TB (for those who initiated treatment after reporting) | |
|---|---|---|---|---|---|---|---|---|
| | N° | Median (IQR) | Median (IQR) | Median (IQR) | N° | Median (IQR) | N° | Median (IQR) |
| Total | 94415 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 5071 | 3 (1,6) | 425 | 7 (3,14) |
| Age | | | | | | | | |
| 0-4 | 27700 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 923 | 2 (1,5) | 48 | 6(2,16) |
| 5-9 | 30815 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 1083 | 3 (1,6) | 90 | 6(3,14) |
| 10-14 | 35900 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 3065 | 3 (1,6) | 287 | 7 (3,13) |
| Gender | | | | | | | | |
| Female | 43406 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 3099 | 3 (1,5) | 263 | 7(3,14) |
| Male | 51003 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 1972 | 2 (1,6) | 162 | 6 (3,11) |
| TG | 6 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 0 | NA | 0 | NA |
| Sector | | | | | | | | |
| Public | 81243 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 4371 | 3 (1,6) | 375 | 7(3,14) |
| Private | 13172 | 0 (0,0) | 0 (0,0) | 0 (0,0) | 700 | 1 (1,4) | 50 | 3 (1,8) |

**Table 2. Project turnaround time: Median time between events in the diagnostic cascade**

### a. Sample-wise analysis

For the 94,415 presumptive paediatric TB cases tested, a total of 103,045 specimens were tested on GeneXpert and 88,360 specimens were tested using smear microscopy. The overall specimen-wise TB positivity rate on GeneXpert was 6,808 / 103,045 (6.6%) and TB positivity rate on smear microscopy was 1,711 / 88,360 (1.9%). TB case detection was more than threefold higher on GeneXpert as compared to smear microscopy, which was independent of specimen type, thus indicating the higher utility of GeneXpert.

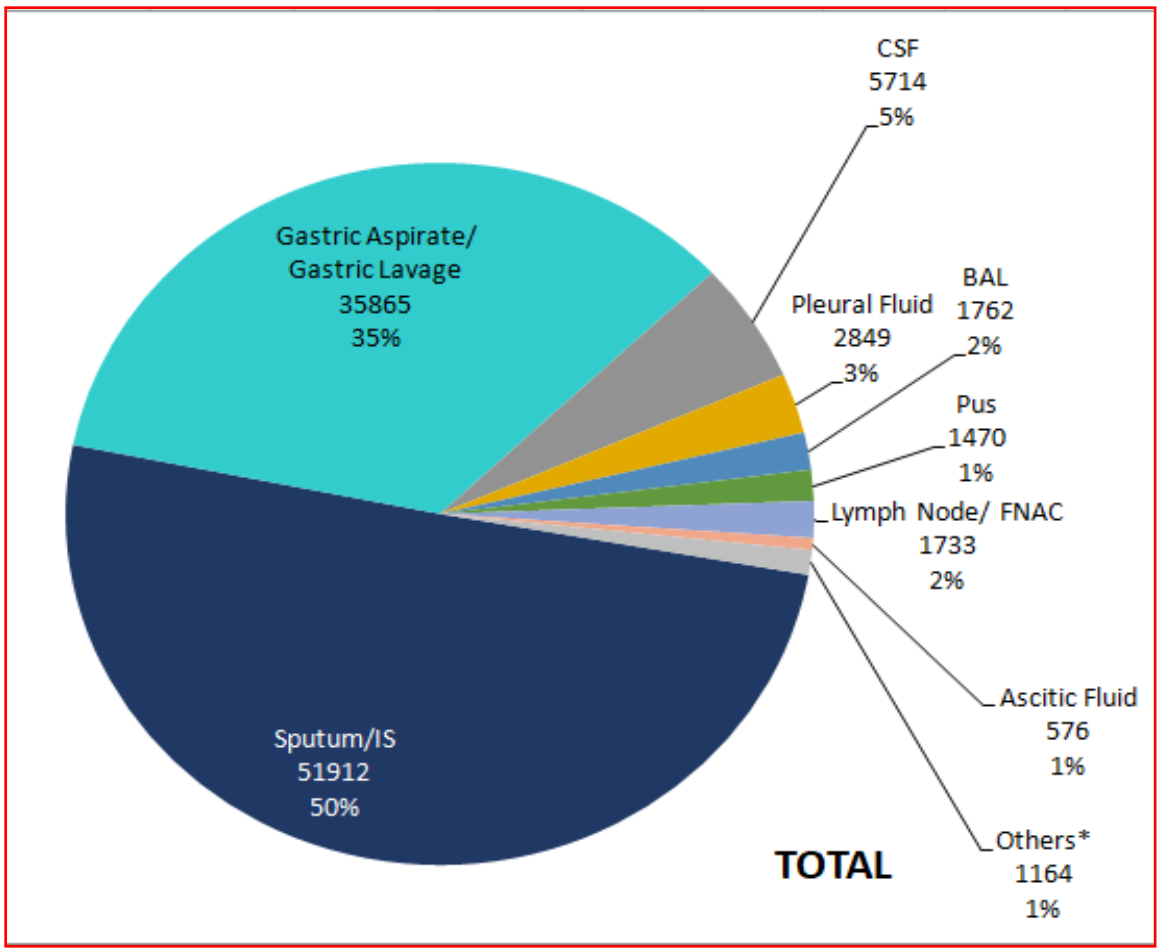


**Figure 13: Different specimens tested using GeneXpert under the paediatric TB project**

CSF: Cerebrospinal fluid; FNAC: Fine needle aspiration cytology; BAL: Broncho-alveolar lavage; *Others: Tissue, Pericardial Fluid, Cervical Aspirate, Peritoneal Fluid, Tracheal aspirate, Abscess, Synovial Fluid, Serum Bone, Chyle fluid, Nasal Aspirate, Pleural Biopsy, Thoracic swab, etc.

*Others: Tissue, Pericardial Fluid, Urine, Cervical Aspirate, Peritoneal Fluid, Tracheal aspirate, Abscess, Synovial Fluid, Serum Bone, Chyle fluid, Nasal Aspirate, Pleural Biopsy, Thoracic swab, etc.

Of the total 103,045 different specimens tested on GeneXpert, 51,912 (50.4%) were sputum and 51,133 (49.6%) were various kinds of non-sputum specimens (Figure 13). For the first time, a large proportion of extra-pulmonary specimens of presumptive paediatric TB patients were routinely tested under NTP. Among the sputum specimens tested with GeneXpert, 3,176 (6.1%) were found to be positive for TB. Of the non-sputum specimens tested under the project, TB positivity on GeneXpert was 3,632 (7.1%). Higher TB positivity on GeneXpert was observed on Pus (36.4%) and FNAC/LN (28.5%), followed by BAL (12.9%) specimens.

Specimen-wise analysis showed that of the 6,808 specimens found positive on GeneXpert, 760 (11.2%) were detected with RR-TB. More than half (51.2%) of the RR-TB cases were from non-sputum specimens (Table 3).

| | Specimens tested | Xpert MTB positives | Positivity (%) | Total Rifampicin resistant | Positivity (%) |
|---|---|---|---|---|---|
| **Sputum/IS** | 51,912 | 3,176 | 6.1 | 371 | 11.7 |
| **Gastric aspirate/ Gastric lavage** | 35,865 | 1,767 | 4.9 | 167 | 9.5 |
| **CSF** | 5,714 | 353 | 6.2 | 34 | 9.6 |
| **Pleural fluid** | 2,849 | 112 | 3.9 | 17 | 15.2 |
| **BAL** | 1,762 | 227 | 12.9 | 17 | 7.5 |
| **Pus** | 1,470 | 535 | 36.4 | 72 | 13.5 |
| **Lymph node/ FNAC** | 1,733 | 494 | 28.5 | 63 | 12.8 |
| **Ascites fluid** | 576 | 24 | 4.2 | 2 | 8.3 |
| **Other*** | 1,164 | 120 | 10.3 | 17 | 14.2 |
| **Total** | 103,045 | 6,808 | 6.6 | 760 | 11.2 |

*FNAC: Fine needle aspiration cytology; BAL: Broncho-alveolar lavage

**Table 3: Specimen type analysis of samples tested on GeneXpert**

## b. Treatment details on paediatric TB cases

Among all the positive patients, 5,563 patients (88.7%) initiated treatment for TB. Over 2% died before treatment initiation and nearly 9% were lost to follow up. Among the RR-TB cases, treatment initiation information was available for 467 patients (85.7%) (Table 4) with over 5% deaths before treatment and 9% lost to follow up. Less than 1% of the patients were referred out to another district.

| Category | Xpert MTB positives | % | Total Rifampicin Resistant | % | Total | % |
|---|---|---|---|---|---|---|
| **Patients diagnosed under the project** | 5,725 | | 545 | | 6,270 | |
| **Number initiated on treatment** | 5,096 | 89.0 | 467 | 85.7 | 5,563 | 88.7 |
| **Died before treatment initiation** | 113 | 2.0 | 28 | 5.1 | 141 | 2.2 |
| **Initial loss to follow up /Treatment refusal** | 492 | 8.6 | 49 | 9.0 | 541 | 8.6 |
| **Referred out** | 24 | 0.4 | 1 | 0.2 | 25 | 0.4 |

**Table 4: Treatment details of paediatric TB cases**

## c. Provider engagement

The total number of providers approached and sensitized were over 10, 000 through continuing medical education sessions (CMEs), one to one meetings and workshops. Of these 1416 providers/ facilities (61% were from private sector) were engaged in the project. Figure 14 represents provider engagement under the project classified by types of providers/facilities engaged.

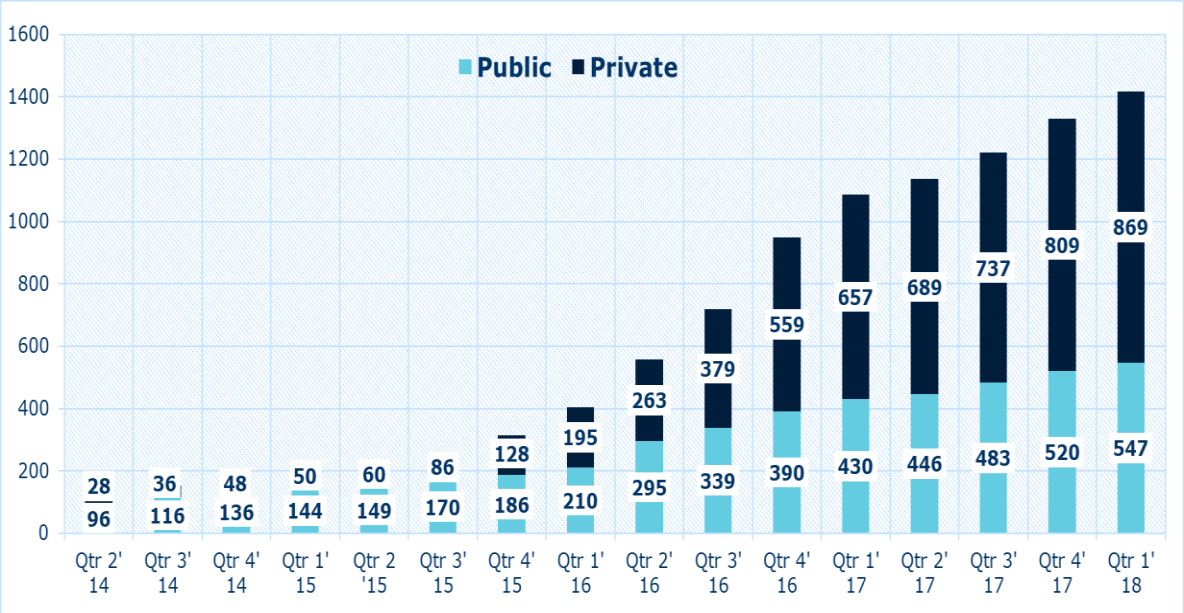


**Figure 14: Provider engagement classified by provider type/facilities engaged; The graph reflects data as follows: from Q2 14 to Q1 16- from 4 project cities; Q2 16 onwards -from 7 project cities; from Q3 16 - from 9 project cities; from Q3 17' onwards - from 6 cities (post transition of first 4 sites to the NTP and addition of 10th site to project)**

There was a continuous increase observed in the total referrals since the project initiation (Figure 15). An incremental uptake of project services was observed every successive quarter across the cities.

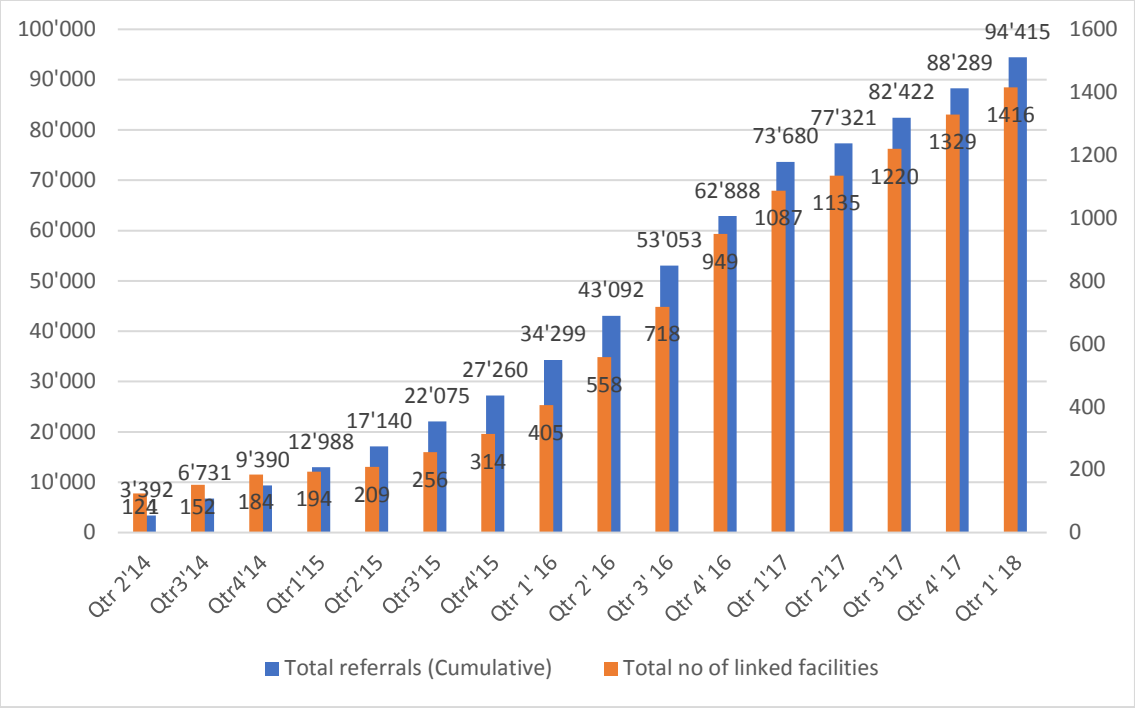


**Figure 15: Cumulative number of referrals and facilities linked to the project**

In 2014, project was initiated in 4 cities of India – Delhi, Chennai, Hyderabad and Kolkata. With increasing number of referrals in successive quarters, project was scaled up in 2016 (mid) to include 5 more cities- Vizag, Surat, Bangalore, Guwahati and Nagpur and a 10th city (Indore) was added in mid-2017 (Table 5). The initial 4 cities were transitioned to NTP by March 2017.

| Site/Project city | Number of referrals | Number positive on GeneXpert | % |
|---|---|---|---|
| Delhi | 24878 | 2794 | 11.2% |
| Kolkata | 10217 | 729 | 7.1% |
| Chennai | 11587 | 462 | 4.0% |
| Hyderabad | 17934 | 960 | 5.4% |
| Vizag | 10509 | 383 | 3.6% |
| Guwahati | 973 | 94 | 9.7% |
| Bangalore | 4868 | 219 | 4.5% |
| Surat | 7039 | 320 | 4.5% |
| Nagpur | 2990 | 179 | 6.0% |
| Indore | 3420 | 130 | 3.8% |
| Total | 94415 | 6270 | 6.6% |

**Table 5: Site/project city wise referrals and number of positives on GeneXpert**

## Transition of paediatric project geographies

The initial four sites (Delhi, Kolkata, Chennai, and Hyderabad) were transitioned to NTP by 31 March 2017 as per the project work plan. Since the activities at the remaining six project sites (Bangalore, Guwahati, Surat, Nagpur, Vizag, and Indore) had gained significant momentum, with an increasing number of referrals and providers being engaged in each successive quarter, it was planned to transition these site activities and other logistics to the National Programme by the end of March 2018.

Official communications from the Central TB Division/NTP were sent out to the concerned States well in advance, detailing the process to be followed. This was then followed by intensive interactions at the site / State level and handing over of the project inventory, along with details of engaged providers to the state / district NTP managers. The project team worked closely with the State TB Programme for coordinating the transition process. Based on the substantial data available under the project, recommendations were provided to the sites for consideration on placement of GeneXpert machines for optimal utilization post-transition of the project. All the major contributing providers/facilities were apprised about the transition plan from January 2018 onwards. The referring providers / facilities were provided with an option to refer samples either to the project lab or to the nearest NTP GeneXpert lab so that the providers become accustomed to sending samples to these labs as well as to sustain the referrals under programmatic conditions. On 31 March 2018, the activities and other processes at the six sites were handed over to the NTP.

Figure 16 shows a detailed, stepwise transition plan in the form of a Gantt chart. The transition was planned at least one quarter in advance of the handover date. Engaged providers had been informed about the specimen collection and referral process which will continue to address the needs of the paediatric population in the respective cities.

| Calender weeks | I month onwards | II month | III month | | | | Post-transition |
|---|---|---|---|---|---|---|---|
| | | | I week | II week | III week | IV week | |
| Letter from CTD to States regarding the transition of activities under the Peds Project to the NTP | | | | | | | |
| Email from FIND to sites regarding the transition of activities under the Peds Project to the NTP | | | | | | | |
| Informing all engaged facilities about transition plan | | | | | | | |
| Ensure engaged facilities know about contact details of the nearest GeneXpert lab under NTP | | | | | | | |
| Inventory sheets -updated and compiled - and handed over to NTP. Includes details of AMC status of all equipment being handed over | | | | | | | |
| Testing of samples at lab by project staff | | | | | | | |
| Closely work with RNCTP state and city level officials during transition | | | | | | | |
| Data based recommendation for GeneXpert machine placement | | | | | | | |
| Compiling financial, logistics and procurement data and handing over the same | | | | | | | |
| Follow-up with state-level NTP officials'post-transition | | | | | | | |

**Figure 16: Detailed stepwise transition plan in the form of a Gantt chart**

## Monitoring and supervision

Given the wide geographic spread of the sites in this project, there was heavy reliance on a number of widely available, free information technology tools such as team viewer, skype, web-transfer, Dropbox, and Microsoft Excel for remote access and web-based sharing of folders. These were used to track data and to monitor activities at the site level. The technical team was able to effectively resolve majority of issues through remote assistance supplemented by need-based site visits. The team focused on the points listed below (Figure 17).

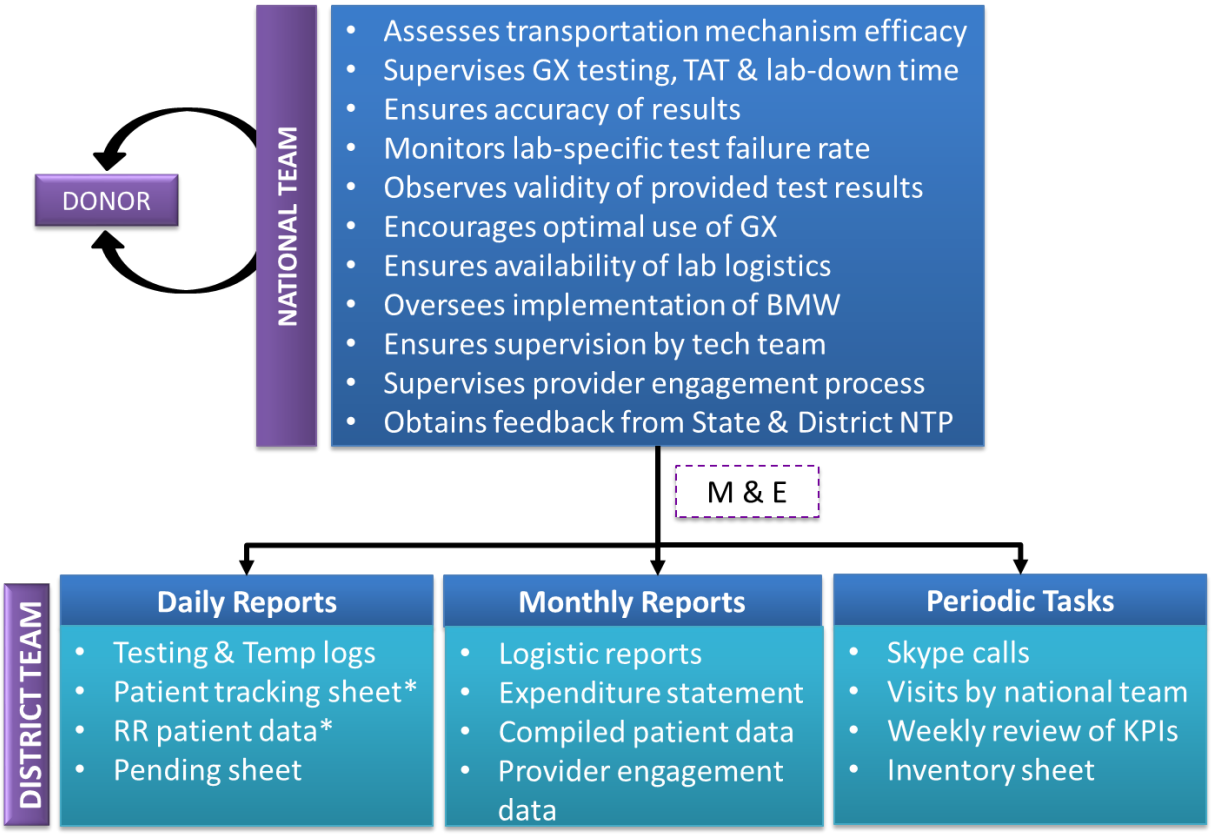


**Figure 17: Monitoring and supervision matrix under the project; *as and when the referral was sent to the project lab; RR: Rifampicin resistant; NTP: National TB Programme**

- Assessment of efficacy of the transportation mechanism with emphasis on decentralized collection points
- Periodic supervision of GeneXpert testing procedure by lab staff
- Assurance of accuracy of reported results and overall turnaround time of a given GeneXpert lab
- Examination of proportion of patients being provided with a valid test result
- Monitoring of lab-specific test failure rate, including trends and spikes in test failure rates
- Ensuring optimal utilization of GeneXpert lab capacity
- Ensuring availability of adequate buffer of lab logistics with an adequate shelf life
- Supervision of implementation of biomedical waste management procedures as per NTP guidelines

- Ensuring periodic supervision for the maintenance of GeneXpert equipment as per the manufactures' guidelines and monitor the maintenance status of other lab logistics including the functioning of AC and UPS
- Examination of lab-down time along with the contributing cause
- Supervision of provider engagement process and outcomes
- Obtaining feedback from state and district NTP officials and key engaged providers

To supervise the day-to-day performance of GeneXpert labs and other project activities remotely, the following tools were used:

- Daily testing logs in web shared folder (Dropbox) - used to cross-check the data and match the consumption of cartridges with physical stock
- Daily temperature logs (Annex XIV in web-shared folder (Dropbox) – this was recorded to monitor the optimal levels of temperature and humidity at the lab. A maximum and minimum temperature gauge was installed in the GeneXpert lab room for this purpose.
- Monthly logistic reports (Annex XV and XVI) in web shared folder (Dropbox). This was mainly used for tracking consumption of cartridges in adjunct to the stock register. The consolidated data was also maintained at National level to forecast requirements and understand transfers within cities.
- Frequent Skype calls with site staff to understand the reported trends in site performance
- Regular visits to sites by the national technical team – travel reports were prepared after each trip to summarize the visit and action points for follow-up.
- Weekly review of key performance indicators and monthly review of overall data to understand trends within and across cities so as to plan corrective actions, if required (Annex XVII)
- Patient data related sheets
  - Case-based Patient tracking sheet- This sheet was maintained to track the data of patients referred by public and private sector providers on a daily basis at each site. The results were also recorded in the sheet along with treatment information for patients detected with TB (Annex XVIII)
  - Case-based capturing of RR patient's data- The data of patients detected RR on GeneXpert was captured in detail including reconfirmation on other microbiological tests, history of contact with TB patients and history of TB treatment (Annex XIX).

- Daily Pending sheet to ensure maintenance of the rapid turnaround time – a key highlight of the project. To sustain this throughout the project period, the staff was asked to fill a pending sheet (Annex XX) and share with project team at the National level for review on a daily basis. This served as proxy verification of data in tracking sheet and a stock register. In addition, assisted in ensuring rapid result reporting and monitoring errors/invalids.
- Periodic stock list of all the supplied equipment at the lab maintained at the site level which was updated whenever there was a purchase or equipment was repaired or calibrated. The inventory sheet (Annex XXI) included lab equipment, electronic items, furniture and consumables supplied to the site under the project. The annual maintenance dates were carefully monitored to ensure equipment could run smoothly.
- Monthly expenditure statement for each site capturing all expenses and accordingly submit bills/expense sheets/invoices as per the organization and donor mandates

***Provider engagement through targeted tools***

*A provider database was created which included basic information about the facility (address, qualification, patient load etc.). This also included a master call list (which was regularly updated) to effectively plan visits and calls to providers depending upon the willingness of the provider and number of referrals (Annex XXII). After every sensitization meeting/workshop/training, project staff at the site level was responsible to document the details of the sessions with relevant photographs in a separate folder (Annex XXIII). A checklist was prepared for strategizing the efforts for engaging providers. This included monthly plans for approaching and targeting providers, outreach/sensitization activities, review meetings and reporting to the National team (Annex XXIV)*

In addition, at the national level, reporting to external stakeholders was carried out as per the specified frequency- monthly to states and monthly/quarterly/annually to the donor. Annual reviews were also planned where the activities were reviewed, and corrective actions discussed in detail. Relevant technical sessions were also conducted during such meetings.

### a. Quality assurance

In GeneXpert, quality control measures are internally built into each test cartridge. The Sample Processing Control (SPC) contains non-infectious spores in the form of a dry spore cake that is included in each cartridge to verify adequate processing of MTB. The machine-

- Verifies that lysis of MTB occurred if the organisms are present
- Verifies the adequacy of specimen processing
- Detects specimen associated inhibition of the real-time PCR assay

In a negative sample, SPC should be positive. In a positive sample, SPC is not relevant (can be positive or negative).SPC passes if it meets assigned acceptance criteria.

The other control is Probe Check Control (PCC). The PCC is automatically undertaken before the start of the PCR. The system measures the fluorescence signal from the probes to monitor bead rehydration, reaction-tube filling, probe integrity, and dye stability. PCC passes if it meets assigned acceptance criteria.

To ensure the quality of testing in the current project, the following measures were undertaken:

- On-site training of project staff was conducted by technical persons from the manufacturer and FIND. After training, proficiency testing of participants was done with regards to testing, handling software, generating reports, routine maintenance, and common troubleshooting
- Annual calibration of modules was done as per manufacturer recommendation

### b. Data analysis

Data were collected for all presumptive paediatric TB and DR-TB cases by the project staff (lab coordinators) using standardized format, through NTP-prescribed format (Annex III) in the case of public sector patients and through abridged referral forms (Annex II) from private sector patients. These date were entered into excel sheets specifically designed under the project to be uploaded onto a web-based tool (i.e., Dropbox) by a DEO. Data quality was ensured through regular scrutiny using cross-validation against programme records by the national team, including verification of completeness and consistency.

### c. Data based supervision and remedial action

Introduction of new technology was accompanied with an initial technical “mentoring” of the lab staff. The supervision plan for scale-up of the technology also included initial intensive onsite supervision with regular remote supervision in subsequent phases. The project demonstrated the usefulness of remote technical supervision and mentoring with a majority of the troubleshooting successfully conducted through remote assistance. Test failure rates at some of the sites could be captured for prompt analysis and corrective action. During the intervention period, this drastically reduced lab down-time, travel-related costs, and delays in providing results.

Furthermore, consumables were monitored for stock-outs and expiry dates with replacement transfers managed accordingly. Maintenance of AC, UPS, and batteries with prompt troubleshooting was of paramount importance to keep facilities functional. Communication and coordination with the manufacturer and supplier were essential for negotiating and rectification/replacement of equipment, modules and cartridges and for annual maintenance and calibration.

In summary, project participants learned that even fully automated technologies with simpler procedures cannot be left unsupervised. Smooth operations require monitoring, communication,

and coordination for efficient, quality service delivery. This is also needed to maintain the trust of patients and providers, especially those from the private sector.

## Need for additional GeneXpert laboratories

To further strengthen demand generation for quality diagnosis in the project cities, patient and provider data on TB positivity and drug resistance levels were collated. A structured approach was undertaken to map the TB diagnostic pathways to help the project team undertake a more targeted approach for provider engagement. This included:

- Mapping of all referring health facilities, screening and sample collection sites on google map.
- Data were collected to understand existing and potential testing capacity of the GeneXpert machines, their placement, workload, and utilization
- Mapping of current and alternative specimen referral patterns based on existing demand

Such an activity enabled the project to develop efficient referral mechanisms and to map disease hot spots within the cities, which consequently improved planning, targeted advocacy, and improved short turnaround time for reporting results. In addition, the mapping data was also used for optimization of available resources and planning for placement of additional GeneXpert machines to ensure proximity to hot spots and early diagnosis of presumptive TB patients. These recommendations were provided to the district NTP officials at regular intervals.

## Developing Centers of Excellence

Extra-pulmonary sample collection by an individual/stand-alone clinic (not based out of a hospital) was a challenge. To manage this, at least one tertiary care center within the same city, preferably a Medical College, was identified as the sample extraction site, also referred to as the **collection point**. The providers were informed about the availability of this site during one-on-one meetings and CMEs/trainings. The providers who wanted to avail themselves of sample collection services were encouraged to refer their patients to these centers. The sample, after collection, was sent to the project lab for testing and the results were intimated directly to the treating providers. However, there was a felt need for building capacity of the providers for the collection of non-sputum samples. The 'National Strategic Plan for Tuberculosis: 2017-25' released by the Ministry of Health and Family welfare also envisages the establishment of centers of excellence for a particular thematic area as paediatric TB or EP-TB. Considering this, it was proposed to develop non-sputum sample collection videos and disseminate them widely through an appropriate digital platform or through CMEs and workshops. During the project CMEs, sample collection videos were shown accompanied by discussions. Under the aegis of this project, videos have been

developed demonstrating the sample collection procedure for gastric aspirate, lymph node aspiration and induced sputum samples. The intention is to share the content with India's NTP for wider dissemination and to be used to build the capacity of the providers to evolve Centers of Excellence.

## Challenges

The following is a brief summary of the major challenges at the provider level encountered during the course of project implementation:

- **Awareness on the signs and symptoms** of TB, especially EP-TB, is generally low among the general practitioners. The ability to "THINK TB" while evaluating a paediatric case is sub-optimal.
- **Knowledge of the tools** available for the bacteriological confirmation of TB in presumptive paediatric TB cases leaves much to be desired. Clinicians still resort to the triad of clinical examination, chest x-rays, and TST to diagnose paediatric TB. Most were, at least to begin with, unaware of the availability and efficacy of the GeneXpert to diagnose TB and RR-TB in children.
- **Sample collection in presumptive EP-TB cases** is, by far, the biggest challenge faced by clinicians (except those in tertiary care setups). The providers were, by and large, hesitant to carry out even basic processes like IS or GL considering the additional complication involved in the process, especially in children. In addition, standalone clinics were also not equipped to extract non-sputum samples.
- **Awareness on appropriate drug regimens and duration of treatment**, especially for managing RR-TB, also appeared sub-optimal. Many of the engaged providers preferred referring the diagnosed RR-TB case to India's NTP for management.

For the operational challenges faced during implementation, certain ingenious locally available solutions were used. A brief summary of the major operational challenges faced, and solutions devised are as under:

| | Challenges | Solutions |
|---|---|---|
| **1** | Sub-optimal awareness on the diagnosis and management of TB | 1. CMEs were carried out for targeted providers in public and private sector. CMEs were also conducted for NTP Staff, providers in parallel government programmes which could be dealing with patients symptomatic for TB, etc. The resource persons used were experts from the State NTP and WHO (in addition to project staff). The professional associations' members, peer doctors were also called as speakers at the CMEs to share their experience with the project.<br>2. Latest developments in the diagnosis and management of TB, especially Paediatric TB, was shared and queries resolved. Services available under the NTP, free of cost, too were discussed and explained. |
| **2** | Challenges in engaging private sector providers | Simplified the engagement process with the project-<br>1. Abridged referral forms were provided for ease in sending samples<br>2. On the spot reimbursement of sample transport costs<br>3. Provision and replenishment of sterile collection tubes at the facilities<br>4. Zero paperwork for availing the benefits under the project<br>5. Ensuring strict TAT for reporting<br>6. Linkages with existing EP sample collection points<br>7. Taking regular feedback from the providers |
| **3** | Difficulty in sample collection in presumptive EP-TB cases | 1. Videos demonstrating the correct process of carrying out Gastric Lavage and Induced Sputum were shown in the CMEs and discussed.<br>2. Standalone clinics and providers were linked to nearby tertiary care centers, mostly a Medical College, where the presumptive EP-TB cases were referred for sample collection. The sample was then sent to the project site for testing and the referring providers were provided the results via email and SMS. |
| **4** | Challenges in sample transportation | 1. Sterile Conical Sample Collection Tubes (Falcon Tubes) were provided to the engaged providers. The sample collected was transported by the parent/guardian /relative of the presumptive case or the hospital staff to the project site for testing.<br>2. The person carrying the sample was reimbursed for his / her travel at a pre-decided rate on the spot. |
| **5** | Maintaining turnaround times | 1. The project staff ensured that the samples received at the project site was tested and the referring provider informed about the result within 24 hours. We used e-mail and SMS to transmit the result to the referring provider.<br>2. The providers were informed in advance about the working hours of the project site. They were also informed in case the Project Lab was could not remain open for any reason, e.g., National Holidays, etc. and the sample transportation was planned accordingly. |

| | | |
|---|---|---|
| | | 3. For high burden sites, the project staff either themselves or through the concerned NTP staff arranged for timely transportation of samples.<br>4. Ensured zero incidences of cartridge stock outs or machine downtimes |
| **6** | Challenges faced in ensuring a smooth transition of the project to the NTP | 1. Transition involved decentralization of referrals to other public sector GeneXpert labs. To ensure that providers continued to refer samples, processes were initiated a quarter ahead so that process is phased, and timely feedback could be taken.<br>2. Key providers were introduced to the field staff under NTP to give a point of contact (like lab coordinators)<br>3. Forecasting plan was prepared for cartridges and other consumables procurement and storage- to ensure there is no stock out post-transition<br>4. Recommendations were provided to place GeneXpert machines to continue uninterrupted referrals |

## Lessons learnt and the road ahead

Even today, in this modern day and age, nearly 650 children die from TB each day, close to 80% of whom succumb to the disease before the age of five. This is unthinkable as TB is a preventable and curable disease. Yet it continues to affect families of millions of children and adolescents worldwide. Although appropriate policies and tools are in place, they need to be given due priority and should be implemented, in letter and spirit, to achieve the End TB Goals in a timely manner.

Latest estimates suggest that each year approximately 3.6 million TB patients (including children) may not have been diagnosed and properly treated. In fact, around half the estimated paediatric TB cases are missing. This needs to be addressed as a health priority, particularly in high-burden countries.

Under the Paediatric Project, implemented in India from April 2014 to March 2018, we were able to test close to 94,500 presumptive paediatric TB patients by offering them upfront testing with GeneXpert and by conducting activities aimed at increasing awareness among healthcare providers, both in the private as well as the public sector, on the importance of early diagnosis of paediatric TB and the merits of bacteriological confirmation by GeneXpert.

This is probably the biggest cohort of paediatric patients tested and diagnosed under a project mode. The implementation of this extremely ambitious project threw up a lot of challenges and also enabled us to work out local solutions for most of the challenges. Based on our experience, the following represent key components of a successful intervention:

1. **Targeted communication incorporating regional variation:** City specific handouts and flyers in the local language were useful in demand generation via providers and direct engagement of patients. In addition, IEC materials should be developed according to the

needs of the patients (parents of the children) and be accompanied by a proper assessment and validation (pretesting) process.

2. **Simplified provider involvement process**: Continued engagement of time-starved private sector providers was successful through the introduction of tactics that reduced the time needed from these providers. The project introduced:
    - An abridged referral form;
    - A streamlined sample transport, testing and reporting pathway helping in confidence-building of the providers; and
    - High operational efficiency through timely reporting of results and building rapport with the providers.
3. **Maintenance of provider trust**: Ensuring uninterrupted supply of cartridges and other consumables helped in ensuring rapid turnaround time and consequently gaining the provider's trust. Preventing stock-outs required estimation of cartridges needs based on historical data. Based on these estimates, one-month running stock and a minimum of three months buffer stock was provided to the sites. Other laboratory consumables, as identified during the site assessment visits, were also provided and the stock was monitored in the same manner as for cartridges.
4. **Creation of relational capital through continuous provider engagement**: Regular follow-up with potential providers to seek and implement their feedback helped further fine tune the intervention.
5. **Analysis of ongoing paediatric TB practices as a basis for formulating remedial action**: Qualitative research was carried out as part of the project, including:
    - understanding how national guidelines on TB diagnosis and GeneXpert technology have been integrated into paediatric TB care practices of different health providers;
    - documenting pathways to microbiological confirmation for paediatric TB patients; and enabling researchers to understand current practices and identify gaps

All the above paved the way for future corrective steps incorporated into the intervention.

**Influencing policy change:** The Paediatric Project, although hugely successful, was implemented in a relatively small geography consisting of only 10 cities. However, the project and other such interventions were able to generate adequate evidence, leading the NTP into taking several positive steps towards the early diagnosis of the presumptive and treatment of the confirmed paediatric TB cases:

1. India's NTP has already made upfront testing on GeneXpert as a part of its policy for pan country implementation. This is now an integral part of the revised diagnostic algorithm to be followed across the country.
2. More than a thousand GeneXpert machines have already been deployed across the country catering to the pediatric population. All the districts now have at least one GeneXpert machine.
3. The anti TB drugs supplied under the programme have been made child-friendly and in line with the latest WHO recommendation. Daily FDCs are now the norm for management of TB (including paediatric TB).

4. Innovative e-based adherence tools like Medication event reminder monitor (MERM) have been rolled out by the NTP to ensure that the affected children complete the treatment regimen prescribed.
5. Mandatory notification of TB cases is being enforced throughout the country.
6. Mandatory recording of all Schedule H1 drugs too is being implemented across all pharmacies selling ATT.
7. Funds, through Direct Benefit Transfer (DBT) mechanisms, have been earmarked for all patients, including children, as well as providers notifying TB cases.
8. Currently, the paediatric TB guidelines are being revised. This is being spearheaded by the IAP. FIND is also contributing in updating the guidelines

As next steps, the following actions are recommended:

1. Set up of Centers of Excellence for non-sputum and EP-TB sample collection in all major cities of the country
2. Capitalizing on previous experiences to take forward advocacy efforts to engage all providers
3. Conducting advocacy meetings to increase the provider base with a focus on involving and engaging private providers
4. Out-reach to small clinic-based paediatricians
5. Operationalization and scale up of policy for management of LTBI – especially for children in contact with active cases -in line with the latest WHO guidelines
6. Disseminating learning from the project at various platforms for wider adoption
7. Validation of stool samples as an alternate specimen type can be explored which represents as a possible solution to the diagnostic challenge for paediatric TB diagnosis

## Summaries of relevant publications

Under the project, FIND published five manuscripts in peer-reviewed journals documenting the findings of this project. Two additional manuscripts are under review (as of 30 September 2018).

In September 2018, WHO published a new guidance document entitled “Best practices in child and adolescent tuberculosis” citing FIND’s childhood TB project as a model for replication.

This section highlights the work published under the project wherein a brief description has been provided for each publication followed by a few key points.

**Ref: Piloting Upfront GeneXpert MTB/RIF Testing on Various Specimens under Programmatic Conditions for Diagnosis of TB & DR-TB in Paediatric Population**[26]

*PLoS One ─ October 2015*

**Summary**: India accounts for one-fifth of the total TB incidence worldwide. However, the exact burden of paediatric TB is still unknown. Though there are various PCR based diagnostic tests available for TB diagnosis, the specificities and sensitivities of these tests are known to be quite variable. This is further augmented by challenges in terms of non-specific symptoms and specimen collection. A series of meta-analyses have shown GeneXpert assay has high specificity with variable sensitivity in different type of specimens for TB diagnosis. This paper describes the experience of using upfront GeneXpert testing, a WHO-recommended TB diagnostic tool, in 8,370 paediatric (0–14 years) presumptive TB cases & presumptive DR-TB cases tested between April and November 2014. Out of 9,149 specimens tested 4,445 (48.6%) were non-sputum specimens and GeneXpert was able to detect 9,083 (99.2%, CI 99.0–99.4) valid results. Among 8,143 presumptive TB cases, 517 (6.3%, CI 5.8–6.9) were confirmed via bacteriological test. GeneXpert detected two times more cases than smear microscopy. In addition, 60 RR-TB cases (38 among 512 presumptive TB cases and 22 out of 227 presumptive DR-TB cases) were also detected. Overall, GeneXpert is advantageous in terms of turnaround testing-time as well as for producing reliable and interpretable results. Moreover, it can detect RR-TB cases.

**Key points:**

- The study enrolled 8,370 paediatric presumptive TB cases & presumptive DR-TB cases of less than 15 years of age.
- GeneXpert detected two times more cases than smear microscopy.
- Xpert also diagnosed 60 RR-TB cases.
- Xpert gives valid and reliable results (99.2% cases) in shorter turnaround time.

[26] Raizada N, Sachdeva KS, Swaminathan S, Kulsange S, Khaparde SD, Nair SA, et al. Piloting upfront GeneXpert MTB/RIF testing on various specimens under programmatic conditions for diagnosis of TB & DR-TB in paediatric population. PLOS One. 2015;10(10):e0140375

**Ref: Accelerating access to quality TB care for paediatric TB cases through better diagnostic strategy in four major cities of India[27]**

*PLoS One – February 2018*

**Summary:** Paediatric TB diagnosis is associated with challenges in specimen collection, poor access and availability of highly sensitive and rapid diagnostic tools. Moreover, detection of TB in children is largely dependent upon contact history with a TB case, clinical and radiological findings, rather than microbiological confirmation. The study enrolled 42,238 paediatric presumptive TB cases (aged 0-14 years) from Delhi, Chennai, Kolkata, and Hyderabad to deal with paediatric TB diagnostic challenges and offered free of cost GeneXpert testing. Of total cases, 3340 cases were TB positive. A total of 295 (8.83%, CI 7.9±9.86) cases out of 3,340 were RR; the level of rifampicin resistance was high in the study population of 5-14 years of age. Among 295 RR-TB cases, 257 (87.1%; CI 82.6–90.6) cases initiated treatment. Of 3,340, 2,534 were pulmonary TB cases (with 210 RR-TB cases) and 734 were EP cases (with 71 RR-TB cases). A total of 72 cases were pulmonary and EP-TB cases (with 14 RR-TB cases). Specimen wise, a total of 46,879 specimens were tested on GeneXpert, while 41,918 specimens were tested using smear microscopy. TB positivity rate, specimen-wise, on GeneXpert and smear microscopy was 3,653/46,879 (7.8%; CI 7.6±8.0) and 1,062/41,918 (2.5%; CI 2.4±2.7), respectively. The study followed same-day turnaround [0 days (IQR 0±0 days)]. For GeneXpert testing including specimen collection, transportation, testing and reporting, while the median days between reporting of results and treatment initiation was 3 days (IQR 1±6 days) and 8 days (IQR 4±16 days) for TB cases and DR-TB cases, respectively. GeneXpert was able to detect TB among sputum as well as non-sputum specimens. The use of GeneXpert led to high TB detection rate (three times more than smear microscopy) and an early result which led to rapid/ appropriate treatment initiation.

**Key points:**

- The study enrolled 42,238 paediatric presumptive TB cases, aged 0-14 years
- Application of upfront GeneXpert testing led to three-fold higher TB detection as compared to smear microscopy
- Detection of significant number of paediatric drug-resistant TB cases was performed within short turnaround time, i.e., 295 cases out of 3,340 were RR
- Xpert was able to detect TB on sputum as well as non-sputum specimens.
- Project demonstrated the feasibility of rolling out rapid and upfront GeneXpert testing for paediatric presumptive TB cases through a single GeneXpert lab per city in an efficient manner.

[27] Raizada N, Khaparde SD, Salhotra VS, Rao R, Kalra A, Swaminathan S, et al. Accelerating access to quality TB care for pediatric TB cases through better diagnostic strategy in four major cities of India. PLOS One. 2018;13(2):e0193194.

**Ref: Upfront GeneXpert MTB/RIF testing on various specimen types for presumptive infant TB cases for early and appropriate treatment initiation[28]**

*PLoS One – August 2018*

**Summary:** Paediatric TB diagnosis particularly among infants is challenging due to non-specific symptoms and poor sensitivity of diagnostic tools which result in delayed TB treatment. Upfront access to GeneXpert /MTB RIF testing, a highly sensitive and specific rapid diagnostic tool, could potentially address some of these challenges. Under the project, utility and feasibility of applying upfront GeneXpert for diagnosis of TB in infants, including for testing of non-sputum specimens was assessed. Laboratories were established in four major cities of India and healthcare providers were linked to refer samples for free GeneXpert testing. A total of 7,994 presumptive infant TB cases were enrolled in the project from April 2014 to October 2016, detecting 465 (5.8%) TB cases. The majority (93.9%) of patient specimens were non-sputum and TB positivity was higher amongst non-sputum specimens. Further, a high proportion (5.6%) of infant TB cases were found to be rifampicin resistant. Case mortality observed in the project cohort of diagnosed TB cases was 11.0%, the majority of which was pre- or early treatment mortality, in spite of prompt access to treatment for most diagnosed cases. Overall, upfront GeneXpert testing is suitable for TB diagnosis among infants due to rapid results which can facilitate prompt and appropriate treatment initiation. In addition, GeneXpert detects RR-TB which offers an additional benefit in using the GeneXpert testing tool.

**Key points:**

- Sample size included in the study was high, i.e., 7,994 presumptive infant TB cases (<2 years of age)
- Xpert detected 465 TB positive cases, out of which a high proportion (5.6%) of cases were RR
- The project demonstrated the feasibility of same-day diagnosis with upfront GeneXpert testing
- Rapid diagnosis led to prompt and appropriate treatment initiation
- Case mortality observed in the TB positive study population was 11.0%, majority of which was pre- or early treatment mortality

[28] Raizada N, Khaparde SD, Rao R, Kalra A, Sarin S, Salhotra VS, et al. Upfront GeneXpert MTB/RIF testing on various specimen types for presumptive infant TB cases for early and appropriate treatment initiation. PLOS One. 2018;13(8):e0202085

**Ref: Catalysing progressive uptake of newer diagnostics by health care providers through outreach and education in four major cities of India[29]**

*PLoS One ─ March 2018*

**Summary:** Diagnosis of TB in children poses numerous challenges due to non-specific and similar (to other chest infections) clinical presentation. Though, advancement has been observed in diagnostic modalities, but, most of the paediatric cases are confirmed without laboratory tests. To deal with such challenges, WHO recommends the use of upfront GeneXpert MTB/RIF (Xpert) testing for the diagnosis of TB in paediatric presumptive pulmonary and EP-TB cases. The test is widely available; however, is not used commonly. Under a paediatric project ongoing since April 2014, the efforts were made to increase the use of GeneXpert test by reaching the healthcare providers catering to the paediatric population. More than 5,700 healthcare providers for children were systematically mapped from the four major cities of India and 3,670 of them were contacted using different outreach strategies. There was a 10-fold increase in the number of providers/facilities engaged, i.e., 43 at the initiation of the project (April 2014) and 466 at the end of the project (June, 2016). The healthcare providers referred 42,238 paediatric presumptive TB cases to the project labs. More than two-fold increase was observed in quarterly diagnostic uptake and paediatric TB cases detection rates. Scaling-up new diagnostics requires huge investments and this needs to be complemented with active provider engagement efforts which will assist in generating continuous demand. The paper reflects on the project findings/lessons which demonstrate the usefulness of outreach and education interventions for the effective uptake of newer diagnostics.

**Key points:**

- A high number of healthcare providers were mapped (5700) and contacted (3670)
- There was a 10-fold increase in number of providers/facilities engaged
- Over the project period, quarterly diagnostic uptake and paediatric TB cases detection rates increased more than two-fold
- This initiative is one of largest global efforts which exclusively focus to implement WHO guidelines on the use of upfront GeneXpert testing for paediatric population

[29] Raizada N, Khaparde SD, Swaminathan S, Sarin S, Salhotra VS, Kalra A, et al. Catalysing progressive uptake of newer diagnostics by health care providers through outreach and education in four major cities of India. PLOS One. 2018;13(3):e0193341

**Ref: Before GeneXpert, I only had my expertise: A qualitative study on the utilization and effects of GeneXpert technology among paediatricians in 4 Indian cities**[30]

*PLoS One ─ March 2018*

**Summary**: Diagnosis of TB in children is challenging, therefore, a highly sensitive and specific diagnostic method is warranted. The GeneXpert can be of particular benefit for diagnosing TB in paediatric populations because of (i) its higher sensitivity in comparison to smear microscopy and (ii) its ability to rapidly provide a result. The project implemented by FIND is dedicated to provide upfront free-of-cost GeneXpert diagnostic testing to presumptive children. This paper focused on the qualitative component captured during the project tenure. The aim was to qualitatively assess the understanding of health providers in integrating National guidelines of TB diagnosis and GeneXpert technology in paediatric TB diagnosis. Semi-structured interviews of 55 health care providers (20, 22, 5 and 8 from public sector, private sector, trust hospitals, and India's NTP, respectively) from Chennai (n=15), Delhi (n=12), Hyderabad (n=13) and Kolkata (n=15) were conducted based on practice, number of GeneXpert referrals, and rate of TB detection amongst referrals. Data were transcribed followed by thematic content analysis and narrative analysis by a medical anthropologist. The interviewees reported diversity in their understanding, perspective and implementation of GeneXpert in paediatric diagnostic algorithm, irrespective of the guidance provided by NTP. GeneXpert was utilized variably by physicians, i.e., to rule out TB, to confirm TB after getting other tests positive or in case of inconclusive diagnosis by other tests. Some physicians used GeneXpert frequently and reported its importance in paediatric TB diagnosis and providing insights on drug resistance. Overall, access to free and rapid GeneXpert testing for all presumptive pediatric TB patients has had multiple positive effects on pediatricians' diagnosis and treatment of TB. It has important effects on the speed of diagnosis, empirical treatment, and awareness of drug resistance among TB treatment-naive children. In addition, the study shows that access to public sector GeneXpert machines may be an important way to encourage Public-Private integration and facilitate the movement of patients from the private to the public sector for anti-TB treatment. However, the degree of diversity in using GeneXpert, even in the presence of clear evidence-based guidance, warrants the urgent need for concerted efforts to place GeneXpert early in diagnostic algorithms to positively impact the paediatric TB care pathway. Moreover, there is a need to standardize diagnostic practices across different settings to speed the positive effects of GeneXpert on paediatric TB care in India.

**Key points**:

- A total of 55 healthcare providers were interviewed across 4 major cities of India
- Xpert was utilized variably by physicians, i.e., to rule out TB, to confirm TB after getting other tests positive or in case of inconclusive diagnosis by other tests.
- Xpert has significantly influenced the speed of diagnosis, treatment planning and awareness of drug resistance

[30] McDowell A, Raizada N, Khaparde SD, Rao R, Sarin S, Kalra A, et al. "Before GeneXpert I only had my expertise": A qualitative study on the utilization and effects of GeneXpert technology among pediatricians in 4 Indian cities. PLOS One. 2018;13(3):e0193656


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