FIND

Because diagnosis matters

Evaluation trials in India: experiences and lessons

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Studies/trials undertaken by FIND in India

- LPA validation and demonstration study
  - 2008-09
- LC feasibility assessment study
  - 2008-09
- i-Led study
  - 2009
- GeneXpert feasibility and impact assessment study
  - 2012-14
- Paediatric Xpert project in 4 cities
  - 2014- ongoing

LPA validation and demonstration study

- Period: 2008-2009
- Background:
  - LJ C&DST standard of care under RNTCP
  - Average TAT: 3-4 months
  - Approx. 5-6 State C&DST labs delivering services
- Project components
  - Site assessment and preparedness
  - Pilot testing and proficiency assessment
  - LPA testing on direct sputum specimen
    - Validation phase (Blinded LPA testing)
    - Demonstration phase (LPA result- Pt management)

Introduction of LPA testing in RNTCP C&DST labs

- Redesigning specimen collection & transportation
  - Replacing McCartney Bottles with falcon tubes
  - Transportation of fresh specimen under cold chain to reference labs
- Introduction of Pipetting
- Establishing clean rooms & GLP for molecular testing
- Power back-up
- Training on LPA testing procedures

LPA testing pilot and proficiency assessment

- Purpose: Assessing site preparedness to conduct the test methodology

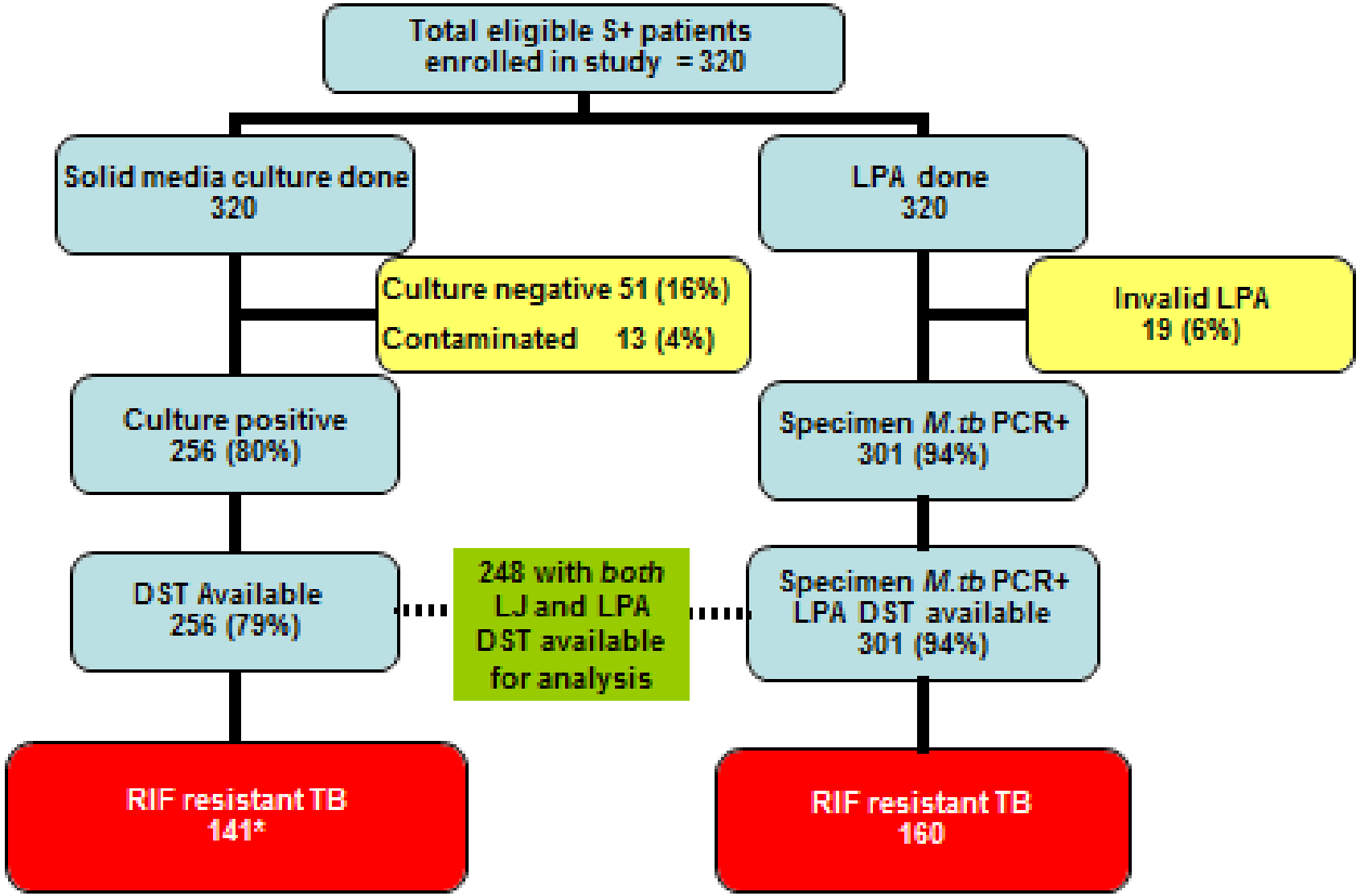
- After initial training, each site collected sputum specimens from 50 smear + pts for anonymous LPA testing
  - Results were assessed for predefined proficiency parameters

- Any site failing predefined proficiency benchmark
  - Reviewed practices and repeated another pilot round
  - Access to external lab experts
  - Site did not proceed with IVD validation till proficiency parameters achieved

LPA validation

- Conducted at C& DST Labs Ahd, Hyd & Jaipur
- Sample size: 250 specimens with valid LPA results & LJ DST results
- Patient enrollment: Oct, 08 – Feb, 09
- LJ C & DST conducted as per routine & results used for patient management
  - Blinded LPA testing undertaken from same sputum specimens
  - LPA results *not* used for patient management
- Discordance in results of LPA and LJ DST results
  - Sequencing & repeat DST on (LC) at NRL
- Minimum parameter to proceed with patient care
  - 95% Sensitivity to detect Rifampicin resistance

LPA validation



LPA validation : Initial results

Rif Resistance				INH Resistance			
	LJ DST Rif Resistant	LJ DST Rif Sensitive	Total Results		LJ DST INH Resistant	LJ DST INH Sensitive	Total Results
LPA Rif Resistant	127	7	134	LPA INH Resistant	133	2	135
LPA Rif Sensitive	9	105	114	LPA INH Sensitive	52	61	113
Total Results	136	112	248	Total Results	185	63	248
Concordance: 94%				Concordance: 78%			
Sensitivity: 93% (CI: 88% - 96%)				Sensitivity: 72% (CI: 65% - 78%)			
Specificity: 94% (CI: 88% - 97%)				Specificity: 97% (CI: 89% - 99%)			
PPV: 95% (CI: 90% - 97%)				PPV: 99% (CI: 95% - 99%)			
NPV: 92% (CI: 86% - 96%)				NPV: 54% (CI: 45% - 63%)			

LPA validation : Discordances

LAB	Speci. ID	LJ_RIF DST	LPA_RIF	Sequencing	Sequence alteration	Amino acid alteration	DST on liquid cultre	resolved
Jaipur	P-83	Resistant	Sens.					
Jaipur	P-89	Resistant	Sens.				Sens.	LPA
Jaipur	P-90	Resistant	Sens.				Res.	LJ
Jaipur	P-98	Resistant	Sens.	Sens.	Wild type		Res.	LJ
Jaipur	P-112	Resistant	Sens.	Sens.	Wild type		Sens.	LPA
Jaipur	P-213	Resistant	Sens.				Sens.	LPA
Jaipur	P-270	Resistant	Sens.					
Jaipur	P-81	Susceptib	Res.	Res.	CAC526AAC	His526Asn		LPA
Jaipur	P-208	Susceptib	Res.	Res.	TCG531TTG	Ser531Leu		LPA
Jaipur	P-235	Susceptib	Res.	Sens.	Wild type		Sens.	LJ
Ahmedabad	44	Susceptib	Res.				Res.	LPA
Ahmedabad	70	Susceptib	Res.				Res.	LPA
Hyderabad	175	Resistant	Sens.	Resistant	CAA513CCA	*Gln513Pro	Resistant	LJ
Hyderabad	236	Resistant	Sens.	Sens.	Wild type		Resistant	LJ
Hyderabad	269	Susceptib	Res.					
Hyderabad	301	Susceptib	Res.					

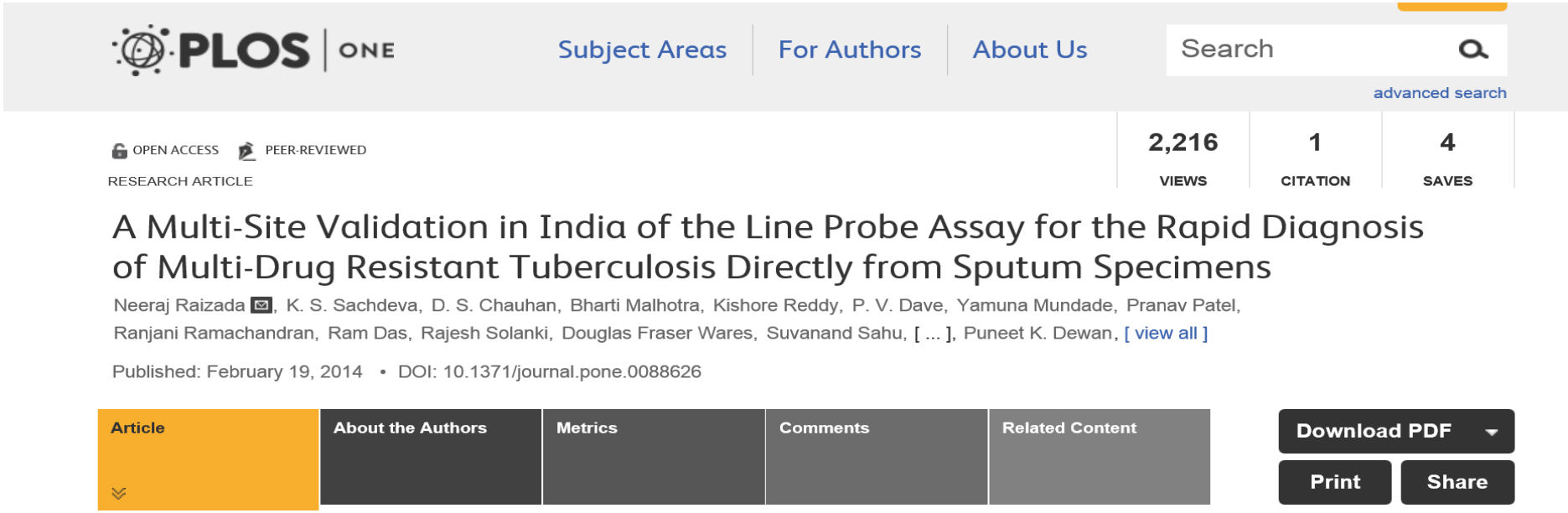
LPA validation : Reconciled results

	LJ C&DST reconciled with liquid culture & DST / sequencing at national reference laboratory		
	Resistant	Sensitive	Total
LPA Rif Resistant	133	1	134
LPA Rif Sensitive	6	108	114
Total	139	109	248
Concordance: 97%			
Sensitivity: 96% (CI: 90% - 98%)			
Specificity: 99% (CI: 95% - 99%)			
PPV: 99% (CI: 95% - 99%)			
NPV: 95% (CI: 89% - 98%)			

Outcome

- LPA endorsed by national Lab committee for patient care & subsequent rapid scale-up planned
  - http://tbcindia.nic.in/Pdfs/17th%20(July%202009).pdf
  - http://tbcindia.nic.in/Pdfs/18th_National_Laboratory_Committee_Meeting_Minutes.pdf

- Since, > 250,000 suspects screened on LPA under RNTCP



Outcome

Honorable Health Minister on occasion of inauguration of PMDT based on LPA

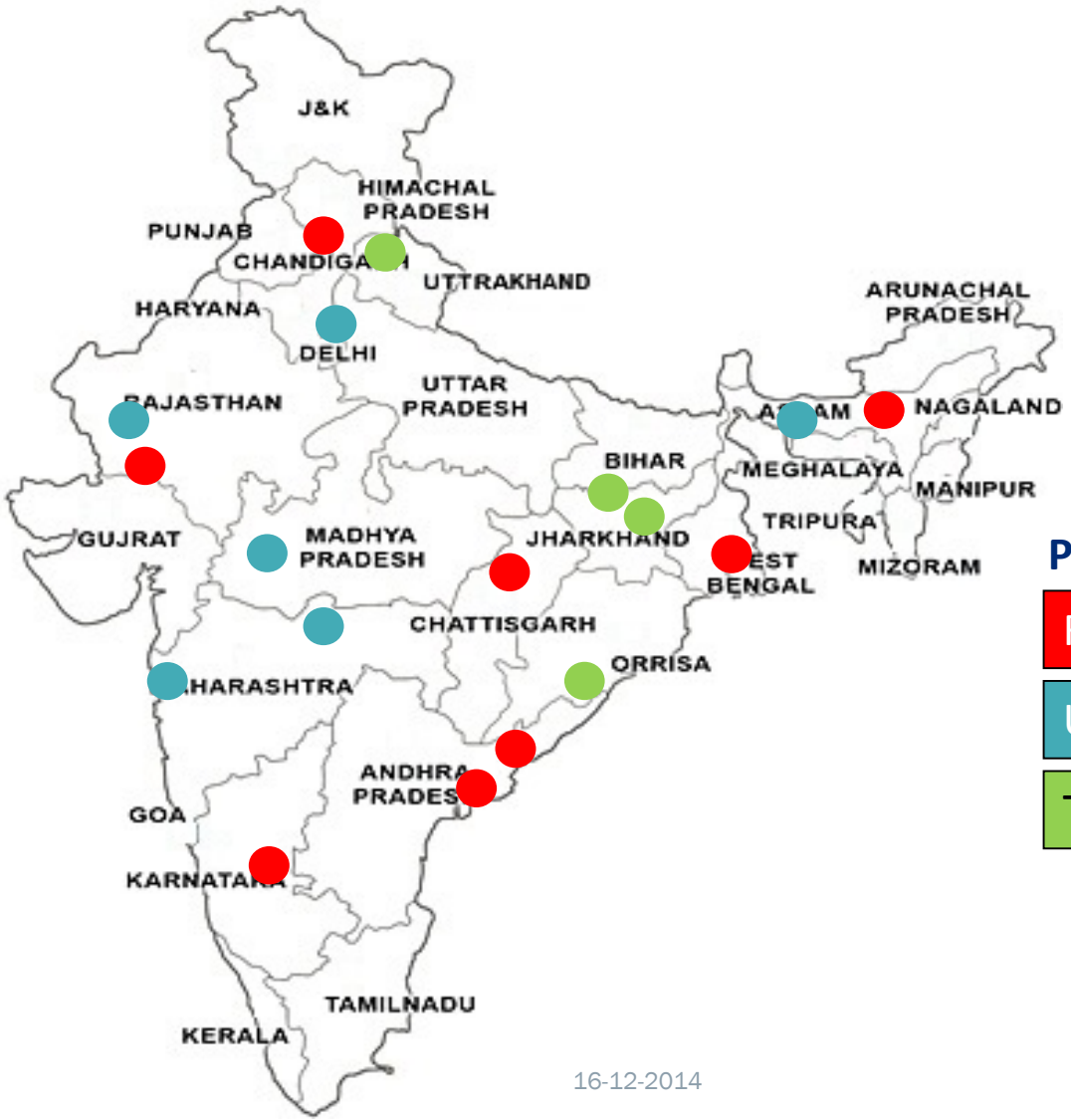
GeneXpert feasibility and impact assessment study

- Period: 2012- 2014

- Background:
  - Rapid LPA DST provided to > 10,000 suspects annually, for high risk cases
  - Increasing no. of LPA labs (>24)

- Objective: assess feasibility and impact of upfront decentralised Xpert MTB/RIF testing of all TB suspects
  - Settings:18 sub district TB Units (Approx. 0.5 mil. Pop. each)
  - Population: 8.8 million
  - **Impact assessment:** Before/after comparison at same sites & Smear vs. Xpert performance
  - **Feasibility assessment:** Ability to provide valid test results on a given patient specimen

Project Coverage



Population – 8.8 Mill (18 sites)

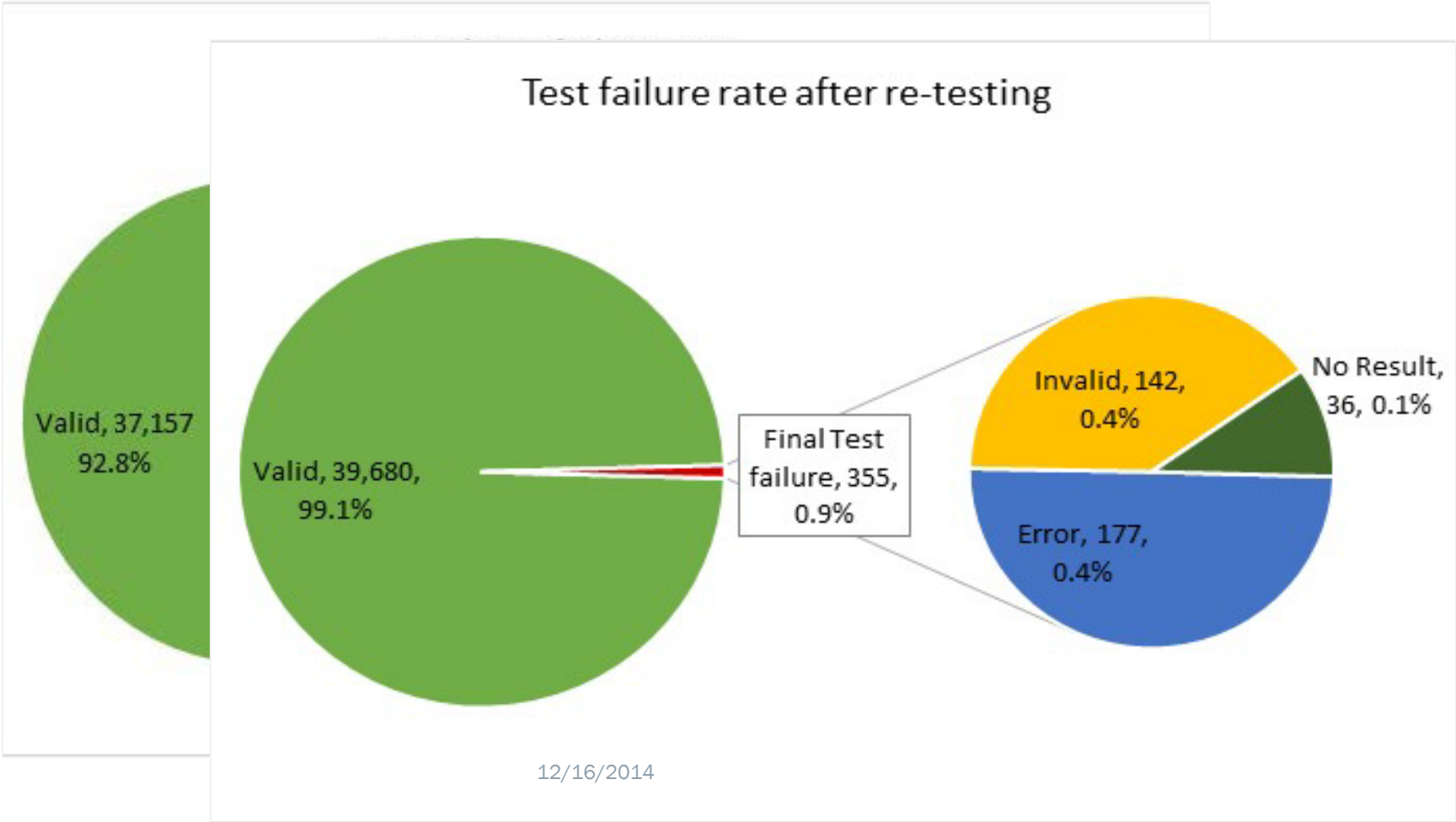
Rural - 3,946,148 (8)

Urban – 3,444,385 (6)

Tribal & Hilly – 1,456,241 (4)

Xpert feasibility Assessment

- Feasibility of Xpert was assess in terms of ability to provide valid test results
- Sub analysis of 40,035 patients tested till Mar,12- Jan'13

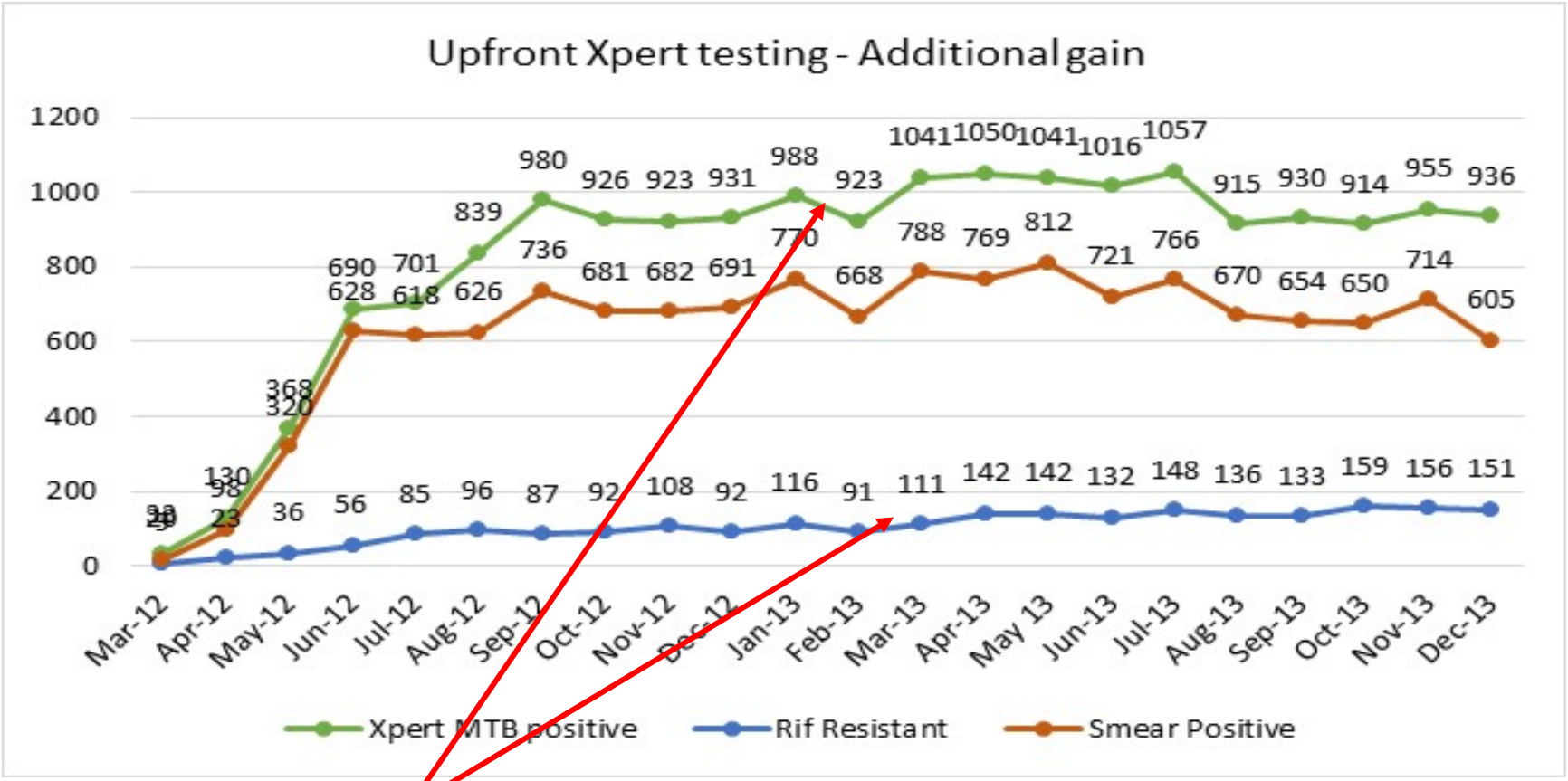


Xpert feasibility assessment

- Challenges related to equipment use at remote setting and reagent storage identified
  - High equipment failure rate documented
  - Transparent root cause analysis undertaken
  - Corrective actions to equipment performance documented
- Test performance across variable geographic settings studied and documented
- Concerns on ambient temp. conditions efficiently addressed
- Power supply and implication on cartridge & specimen losses
- Key challenges and solutions/adaptations documented and submitted to RNTCPs
  - Tech specs. defined
  - Adaptations costed

Solutions: Alternative powers source

Project Intervention: Upfront Xpert MTB/RIF testing of TB suspects



Xpert MTB/RIF 'additional' contribution of bacteriologically-confirmed cases and Rifampicin resistant -TB cases

Xpert Positivity – 20.2%
Smear Positivity – 13.5%
Rif Resistant - 2301 (10.2%)

Outcome

- Policy: Xpert included in lab-scale-up plan
- Decentralized Xpert scale-up planned by RNTCP
- Pilot for upfront Xpert testing of all pediatric & HIV infected suspects initiated
- Xpert scaled-up to > 100 sites under RNTCP; further scale-up planned

Liquid culture feasibility assessment study

- Period: 2008-09
- Objectives

- Assess feasibility of LC introduction under RNTCP
- Define infra. needs above existing RNTCP Lab norms

- Sites: Del, Ahd & Jaipur
- Project outcomes

- Key bottle-necks & solutions in LC introductions defined
  - » BSL-3 upgrades, additional specimen processing equipment, specimen handling, work flow, etc.
- Addl. lab infrastructure & equip needs
  - » Documented, tech specs. Developed & costed
- LC &DST Incorporated in RNTCP lab scale-up plan

Key lessons

Protocol & Trial Logistics

Elaborate study protocol

- Research Question????
  - Validation/feasibility/QA/Impact/level of deployment/Impact
- Study duration & sample size
- SOPs
  - Enrolment criteria, with due diligence in possible field realities
  - Discordance resolution
  - Predefined deliverables and performance benchmarks
  - Testing methodology
  - Supervision and monitoring
- Ethical approvals

Upfront availability of trial logistics

- T- Licence in-case IVD needs to be imported
- Other support specimen preparation & transportation logistics
- Micro-planning specimen flow
- Contingencies

Suspect enrolment

Define enrolment sites

- Training of site staff of study design
- Clarity on enrolment criteria
- Provide job-aids, contact person;
- Monitor
  - Enrolment biases

Define specific specimen collection needs and procedures

- Address gaps in the current field mechanism & provide account for logistics
  - Ex. LPA validation; Paediatric project
- Identification of personnel responsible for collection of specimen
- Define standard collection methodology & training of point persons

Data management

Define data management needs

- Need for blinding of test results
  - How the specimen are coded & who manages?
  - Implications for discordance resolution
- Double data entry
- Software for data management
- Data-entry and analytical support
- Support for possible complex statistical analysis
- Monitoring of data completeness and accuracy
- Archiving of hard copies
- Field monitoring team?

Result interpretation & Pt management

- Training of lab & clinicians in result interpretation
  - LPA validation
  - Xpert feasibility study
- Ensuring adequate drug supply
- Patient management in cases of discordance between test and reference methodology
- Reporting of results
  - Single/both
- Whom to contact in case of ambiguity

Laboratory quality management

- Quality of reference test results
- Variance in the bench procedures
  - Ex. LPA; Xpert
- Assess the need for mid-term correction
- Interaction between various sites participating in the study
- Waste management aspects

Quality assurance methodology

- Post validation QA needs
  - Parameters for monitoring test performance
  - Piloting QA methodology
  - Define corrective action
  - Establishing in-country team of experts with-in public & private sector
    - » Ex. LPA; LED microscopy; Xpert

Informed consent & Raw data archving

- Informed consent implementation
  - Training of staff on obtaining informed consent taking into account local language/literacy rate
  - Consent for minors
  - Witness ??
  - Documentation and dealing with drop-outs
- Publication
  - Maintaining raw data for institutional memory/possible distant analytical needs
  - International norm to have the raw data in public domain ahead of publication

Supervision & monitoring

- Roles & responsibilities
  - TORs, budget,
- Needs:
  - Enrolment & informed consent
  - Lab bench work; specimen storage
  - Reporting
  - Training/ retraining
  - Data recording & archiving
- **Risk: Repeat**

Identification of trial sites: Considerations

- Main activity of Lab: Research/ service delivery
- Lab resources:
  - Trained HR
  - Lab performance & QA of reference technology (accreditation)
  - Lab equipment: BSL-3 , Autoclave, centrifuge, storage facility for specimen
  - Microbiological techniques
- Population served
  - Average workload
  - Level of health system: Primary/ Tertiary health care/Referrals
  - Distance from the lab : Transportation time
  - MDR level; HIV positivity
- Cost to patient for treatment & testing
- Ethical committee

Summary

- Evidence based adoption/adaption of IVDs under RNTCP routinely happening
- Keys ingredients for adoption of IVDs as policy
  - Engage with NTP early; collaborate with partners
  - Identifying the unknown & systematic approach for evidence generation
  - Transparent evidence based approach
  - Perfect IVD = Myth; Document issues & solutions
  - Crucial complementary issues for policy makers:
    - » Accuracy
    - » Feasibility
    - » Cost

Thank You