Operational Research in TB Diagnostics

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TB Diagnostics Workshop

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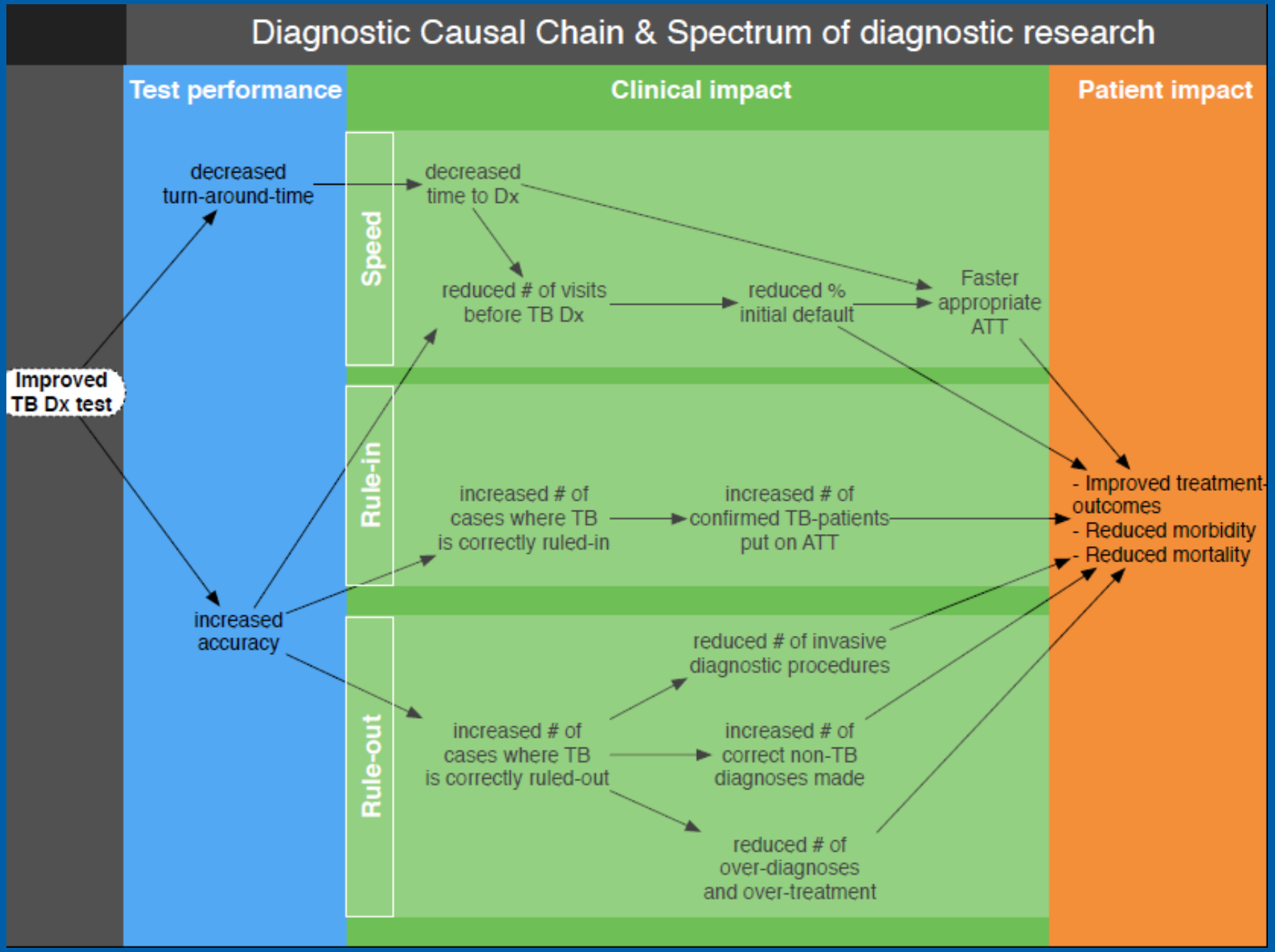
‘What’ is operational research..?

Research into
interventions, strategies, tools or *knowledge*
that can enhance **the quality or coverage** of disease control programs, health services or health systems

Zachariah et al, Lancet Infect Dis 2009; 9: 711- 717

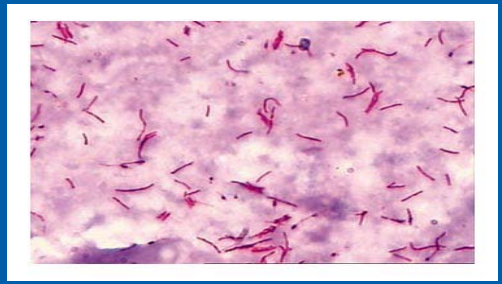


Acknowledgement: Samuel Schumacher's presentation

Guiding principles in conducting operational research

- Define program / health system *objectives*
- *Identify constraints* to meeting objectives
- *Ask research questions* around constraints

Example: Sputum smears for diagnosing PTB



- Objective of NTP = high quality sputum smear diagnosis using three sputum smears per patient
- Constraint = three smears per patient are demanding for the laboratory technicians (shortages, high caseloads)
- Research question = are *two smears* as efficient as three smears for diagnosing smear-positive pulmonary TB
- Answer the question in a number of different ways

Is One Sputum Specimen as Good as Two during Follow-Up Cultures for Monitoring Multi Drug Resistant Tuberculosis Patients in India?

Sharath Burugina Nagaraja[1,2]*, Ajay M. V. Kumar[3], Kuldeep Singh Sachdeva[2], Ranjani Ramachandran[1], Srinath Satyanarayana[3], Avi Bansal[1,2], Malik Parmar[1,2], Sarabjit Chadha[3], Sreenivas Nair[1], Ashok Kumar[2], Sven Gudmund Hinderaker[4], Mary Edginton[5], Puneet K. Dewan[1]

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- Sputum Cultures are done at 11 different times (3, 4, 5, 6, 7, 9, 12, 15,18, 21, 24)- each time 2 specimens
- One sputum specimen culture is as efficient as 2 specimens
- **“Policy change”**

Research methodology

Usually observational studies

- Ecological studies **(aggregate data)**
- Descriptive or cross-sectional studies
- Case-control studies
- Cohort studies (prospective, retrospective)

Research is performed within the routine system; within a sound ethics framework; follows STROBE guidance

(*Lancet 2007; 370: 1453-57)*

Examples..1

LED Florescent microscopy Project

LED FM- project

- Implemented by The Union-South East Asia Regional Office in collaboration with RNTCP, Medical colleges-National Task Force, WHO India
- Technical assistance: Lab experts from National Institutes, FIND and Medical colleges
- Funding support from TB REACH (Wave-2 grant)- 1 Million USD

Key intervention

- Replace ZN microscopy with LED-FM in 200 Medical college microscopy centers in North, South, East and North-East Zones of the country
- West Zone not included due to budgetary constraints

Key interventions under the project (Oct 2011 to Sept 2012)

- Procurement and placement of 200 LED-FM
- Training of all Lab technicians and their supervisors
- Procurement and provision of lab consumables
- Support implementation of external quality assurance mechanism as per RNTCP guidelines
- Support documentation and demonstration of impact (at least 5000 additional cases detected)

- **Setting:** Medical college hospitals are tertiary care centers catering to large number of patients including TB patients
- **Programme objective**: Maximise the number of sputum smear positive pulmonary TB cases detected in these settings
- **Constraint/opputunity** = high case load/ LED-FM
- **Operations Research question**
  - Did LED-FM result in change in the number of suspects examined?
  - How many additional cases did we detect by implementing LED-FM?

Methods

- **Before and after comparison study (Ecological study)**
  - **July to December 2011 with ZN Microscopy (Before period)**
  - **July to December 2012 with LED-FM (After period)**

- **Study Population**
  - **Presumptive TB patients examined for Sputum smear microscopy in 190 medical college microscopy centers**
  - **Data collected from the lab registers (summaries) and reports**
  - **Data was endorsed by all the District TB Officers**

Quasi-experimental studies

Types & Features

1. **pre-post implementation studies**
   - without control group
   - with control group (difference in differences)
   - interrupted time-series
2. **instrumental-variable estimation**
   - exploit natural experiment
3. **regression-discontinuity**
   - exploit discontinuity

Acknnowledgement: Samuel Schumacher's presentation

Data from 190 microscopy centers

Period	Total TB symptomatics examined	Sputum Smear Positive TB Cases detected	Proportion found sputum positive
July-December 2011 (Conventional Microscopy)	222,658	28,042	12.6%
July-December 2012 (LED Fluorescent Microscopy)	224,714	33,552	14.9%
Absolute and incremental change between 2012 and 2011	+2,056 (1% increase)	+ 5,510 (20% increase)	+ 2.3%

Applying 12.6% positivity (observed in 2011) for the extra number of TB symptomatics examined in 2012, LED-FM services still resulted in an additional yield of 5251 cases

Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

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SHORT COMMUNICATION

LED fluorescence microscopy increases the detection of smear-positive pulmonary tuberculosis in medical colleges of India

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Next set of questions

- **How does the increase compare with the other DMCs who continued to implement ZN?**

- **In which age, sex and sputum smear grade group was the increase more?**

We selected 15 medical college DMCs randomly and for each of these we selected a comparison DMC (DTC DMC)

Quasi-experimental studies

Types & Features

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Acknnowledgement: Samuel Schumacher's presentation

Results : Control Vs Intervention DMC's

DMC Type	Year/Type *	Number of Patient Examined **	Number of Positive	Positivity Rate	P - Value
Control DMC	2011/ZN	16,531	2152	13.0	0.31
	2012/ZN	16,403	2064	12.6	

* ZN = Ziehl Neelson staining method based Light Microscopy
* FM = Auramine – Phenol staining method based LED fluorescence Microscopy
** Patient with TB symptoms underwent for microscopy

Result : Age - Sex wise distribution in Intervention DMC

Table : Sputum smear examination results, by age and sex, in selected medical college microscopy centres in India, before (July-December 2011) and after (July-December 2012) introduction of LED-FM

Attribute		2011, ZN Microscopy			2012, LED Microscopy			Change			
		Yield of positives			Yield of positives						
		Examined	Number	%	Examined	Number	%	Total	%	(95% CI)	p-value*
Total		25,159			26,426						
Sex	Male	16,576			17,435						
	Female	8550			8950						
	Unknown	33			41						
Age group											
	0-14	1038			1,109						
	15-24	3255			3,535						
	25-34	3785			4,014						
	35-44	4257			4,527						
	45-54	4703			4,869						
	55-64	4218			4,388						
	65+	3535			3,565						
	Unknown	368			419						

*Chi-square test; ZN = Ziehl Neelsen staining microscopy; LED-FM = Light Emitting Diode fluorescence microscopy

Comparing % Change by Smear Grading

Table: Sputum smear examination results, by smear grading, in selected medical college Designated microscopy centres in India, before (July-December 2011) and after (July-December 2012) introduction of LED-FM.

Highest Grade of patient	ZN Microscopy 2011		LED-FM 2012		Change
	Number	%	Number	%	%
Negatives	21727	86.4	21720	82.2	- 4.9
Scanty	377	1.5	777	2.9	93.3
1+ Positive	1036	4.1	1236	4.7	14.6
2+ Positive	714	2.8	886	3.4	21.4
3+ Positive	1305	5.2	1807	6.8	30.8
Total	25159	100	26426	100	

Chi square test = 57.69 (df-3, for positive grades) p-value <0.001; ZN = Ziehl Neelsen staining microscopy; LED-FM = Light Emitting Diode fluorescence microscopy

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PLOS ONE

LED-Fluorescence Microscopy for Diagnosis of Pulmonary Tuberculosis under Programmatic Conditions in India

Lord Wasim Reza[1]*, Srinath Satyanarayna[1], Donald A. Enarson[2], Ajay M. V. Kumar[1], Karuna Sagili[1], Sujeet Kumar[1], Levi Anand Prabhakar[1], N. M. Devendrappa[1], Ashish Pandey[1], Nevin Wilson[1], Sarabjit Chadha[1], Badri Thapa[1], Kuldeep Singh Sachdeva[3], Mohan P. Kohli[1,3]

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What is end users opinion on LED FM?

Who are end users?

- Laboratory Technician (LT) and Senior TB Laboratory Supervisor (STLS) of RNTCP
- Trained in LED FM from 200 project sites
- 1 LT & 1 STLS from each site
- Eligibility
  - Current user of LED FM for AFB detection
  - Used LED FM for at least 3 months

Methods

- **Study Period : Jan – March 2013**
- **Data was collected by Qualitative Methods**
- **Semi structured self administered questionnaire was sent via E-mail to 400 LT/STLS**
- **Themes covered in the questionnaire**
  - **Handling of Microscopes**
  - **Reagent preparation**
  - **Smear Staining, reading, grading**
  - **Ease of Efficiency**
  - **Ease of operation**

Methods Cont …

- Ethics approval was obtained from Union EAG and permission from CTD to conduct this survey
- Received response with written consent from 116 respondents via e-mail
- Response to Questionnaire was voluntary.
- Additionally face to face in-depth interviews were also conducted for at least 20s person including LT/STLS/DTO's

Result

- Proportion Responded – 29% (n=116; LT - 67; STLS – 49)
- Lab experience – Mean 10.6 (median 10.0) Years
- LED-FM experience – Mean 7.9 (Median 8) Months
- As compared to BFM, LED FM
  - Technically more user friendly – 99% (n=115)
  - Improved visibility – 89% (n=103)
  - Less stress to shoulder/back – 70% (n = 81)
  - Less stress to eyes in slide examination – 80% (n=93)

Results

- AO Stain as compared ZN
  - Preparation - Easier for 82%
  - Storage – Easier for 67%

- AO Slide Staining, Reading, and Grading Vs ZN
  - Staining Easy for 89% (n=103)
  - **Staining process time consuming for 69% (n=80)**
  - Slide Reading Easy for 97% (n=112)
  - Slide Grading easy for 95% (n=110)
  - Average reported reading time 1.89 minute (Median 2 min) compared to 5 minutes in ZN

Result

- Would you prefer to switch back to ZN in future?
  - No 90% (n=104) Yes 6% (n=5)
- Is LED FM time efficient
  - Yes 84% (n=97)
- LED FM helped in more Case detection
  - Yes 89% (n=103)

Qualitative Outcome

- “Heating is not required, hence this technique is safer as the aerosol generation is minimum” - LT/STLS
- “Increases the quality of slide reading and helped in more case detection” LT/STLS
- “Due to longer staining time, it is not possible to process sample received in last hour” - LT/STLS
- “The primary staining time (which is of 20 minutes) can be used for other laboratory activities like, recording and reporting” – LT/STLS

Qualitative Outcome

- “I am single trained person in LED FM in the district and due to which I am facing difficulty in availing leaves.” – LT

- “In case of power cut, we can continue our work with Solar back-up. Patient do not suffer” LT/STLS

- District Programme Managers appreciating the technologies however worried about cost and future.

Summary

- **Changing the diagnostic tool to LED FM resulted in significant increase in smear positive case detection**

- **Other contributory factors**
  - **Training of LT**
  - **New Microscope**
  - **Quality reagent**
  - **Continuous technical support, intensified supervision and monitoring, increased enthusiasm in project mode**

- **Programme decision**
  - **LED-FM will be sustained beyond the project period and the services will be expanded to other high work load DMCs**

Example ….2

Assessed the strategy for diagnosis

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PLoS one

Operational Challenges in Diagnosing Multi-Drug Resistant TB and Initiating Treatment in Andhra Pradesh, India

Sarabjit S. Chadha[1]*, Sharath BN[2], Kishore Reddy[3], Jyothi Jaju[2], Vishnu PH[3], Sreenivas Rao[4], Malik Parmar[2], Srinath Satyanarayana[1], Kuldeep Singh Sachdeva[6], Nevin Wilson[1], Anthony D. Harries[5]

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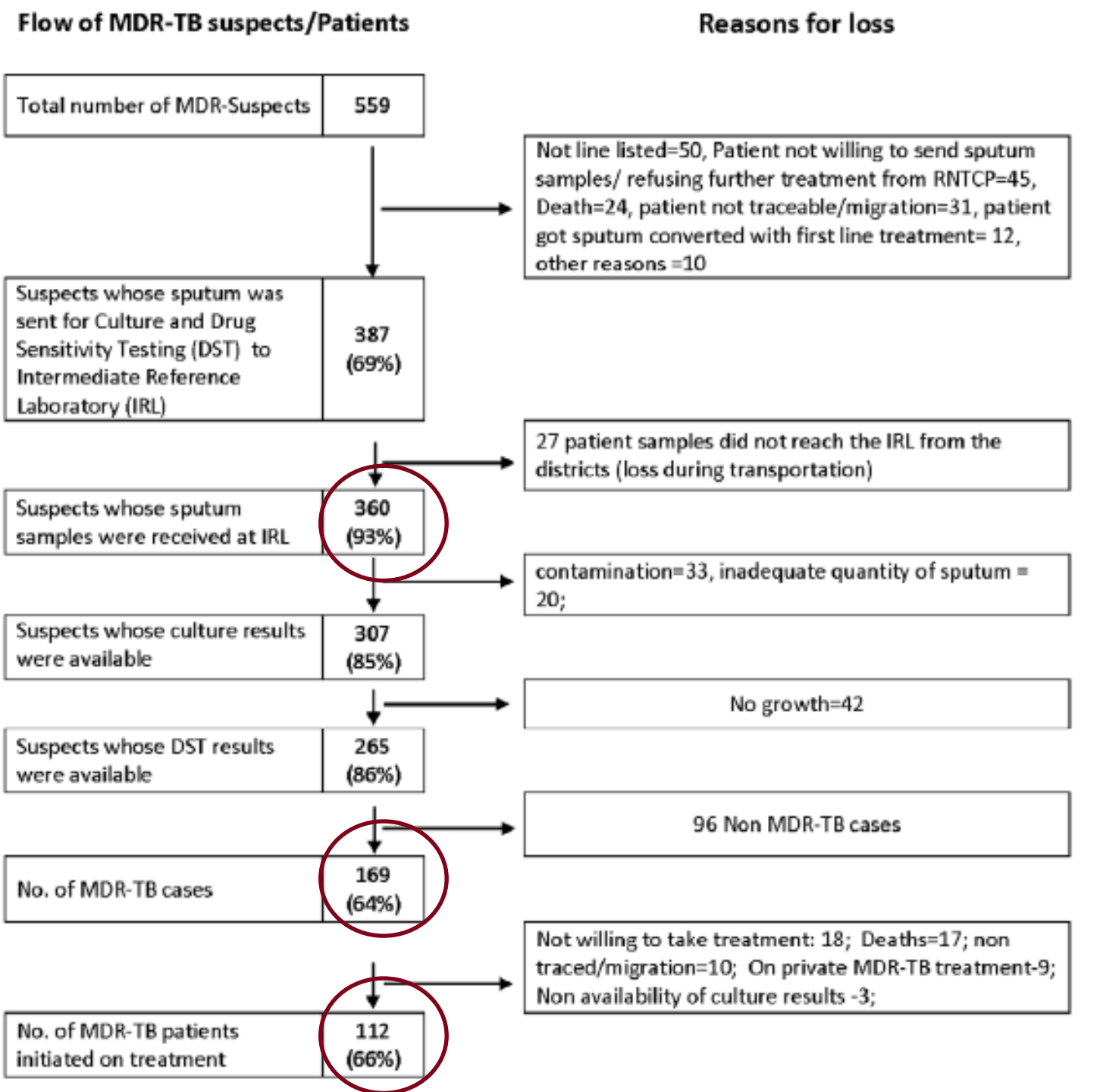
- **Setting:** Andhra Pradesh, MDR-TB roll out

- **Programme objective**:
  - To provide culture and DST services to all patients who were not responding to treatment
  - To provide Cat-IV treatment to all those with MDR-TB

- **Constraint** = Lack of information,
  - we had info on 1) no. tested 2) no. initiated on treatment

- **Operations research question**:
  - What proportion of all eligible patients were tested?
  - What proportion of all diagnosed MDR-TB patients were intiated on treatment?


Flow of MDR-TB suspects/Patients
Reasons for loss
Total number of MDR-Suspects
559
Not line listed=50, Patient not willing to send sputum samples/ refusing further treatment from RNTCP=45, Death=24, patient not traceable/migration=31, patient got sputum converted with first line treatment= 12, other reasons =10
Suspects whose sputum was sent for Culture and Drug Sensitivity Testing (DST) to Intermediate Reference Laboratory (IRL)
387 (69%)
27 patient samples did not reach the IRL from the districts (loss during transportation)
Suspects whose sputum samples were received at IRL
360 (93%)
contamination=33, inadequate quantity of sputum = 20;
Suspects whose culture results were available
307 (85%)
No growth=42
Suspects whose DST results were available
265 (86%)
96 Non MDR-TB cases
No. of MDR-TB cases
169 (64%)
Not willing to take treatment: 18; Deaths=17; non traced/migration=10; On private MDR-TB treatment-9; Non availability of culture results -3;
No. of MDR-TB patients initiated on treatment
112 (66%)

Changes in policy and practice

- All sites implementing PMDT to report on
  - Number of MDR-TB suspects
  - Number of MDR-TB suspects whose sputum was sent for culture and DST and received at IRL
  - Number of MDR-TB patients diagnosed
  - Of those diagnosed the number initiated on treatment

- Lab technician also responsible for identifying MDR-TB suspects

Example..3

Impact of introduction of LPA on

Time to diagnosis
Time to treatment initiation
Pre-treatment loss to follow-up

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PLOS ONE

Impact of Introducing the Line Probe Assay on Time to Treatment Initiation of MDR-TB in Delhi, India

Neeta Singla[1]*, Srinath Satyanarayana[2], Kuldeep Singh Sachdeva[3], Rafael Van den Bergh[4], Tony Reid[4], Katherine Tayler-Smith[4], V. P. Myneedu[1], Engy Ali[4], Donald A. Enarson[5], Digamber Behera[6], Rohit Sarin[1]

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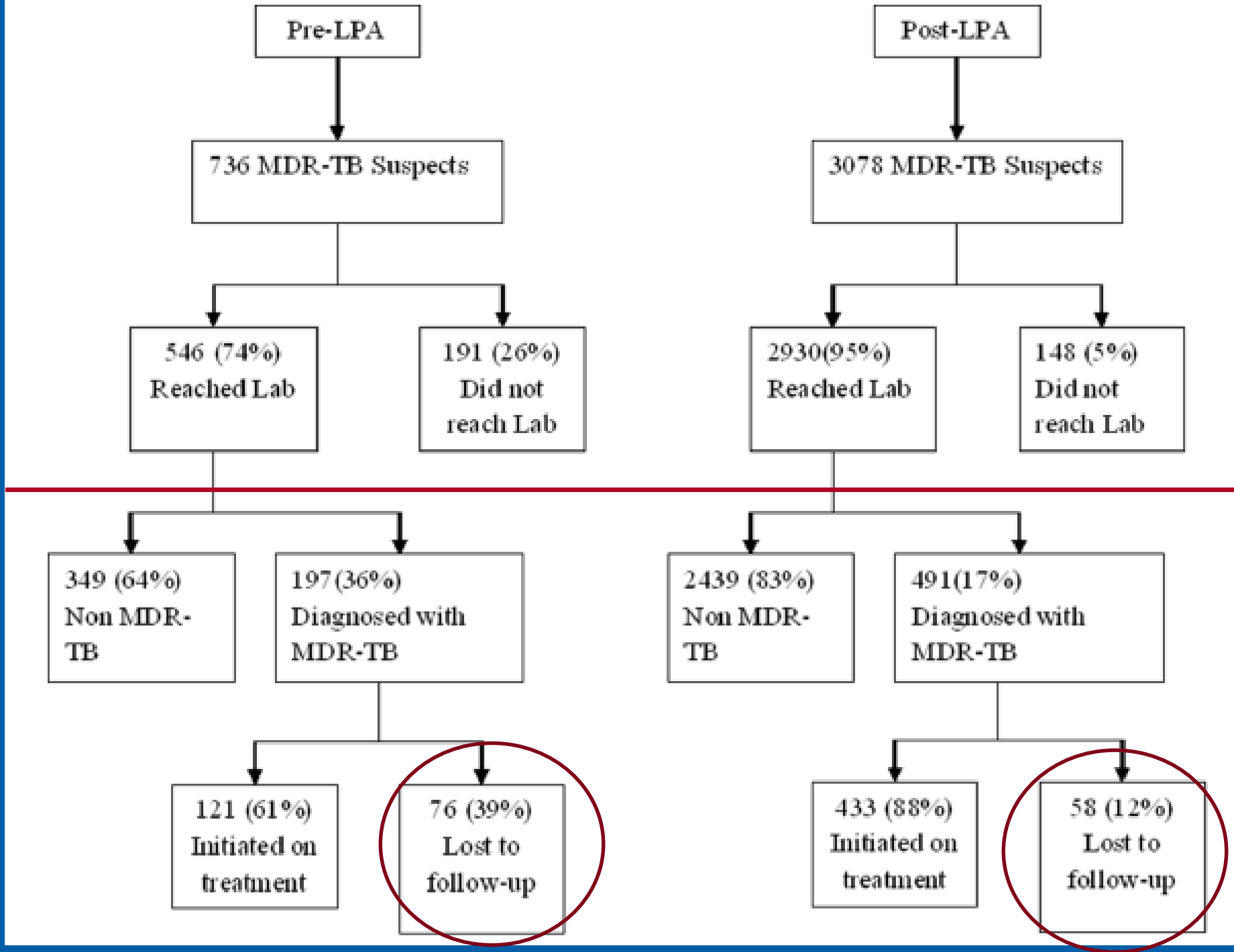
Study methods

- **Study undertaken in LRS Institute**
- **LPA introduced in 2011**
- **Before and after comparison study**
  - **2009 to mid 2011 (pre LPA Phase)**
  - **Mid-2011 to 2012 (Post LPA phase)**

	Median Time in days (IQR)		
Steps	Pre-LPA	Post-LPA	P-Value
Identification as MDR-TB suspects to submission of samples	12 (7-29)	9 (4-31)	0.07
Receipt of samples at lab to reporting	107 (79-131)	5 (3-6)	<0.0001
Time taken for patient to visit DRTB Center	12 (4-26)	7 (5-13)	0.3
Time taken by DR-TB center to initiate the patient on treatment	8 (7-13)	12 (9-17)	<0.001
Total time	157 (127-200)	38 (30-79)	<0.001


Pre-LPA
736 MDR-TB Suspects
546 (74%) Reached Lab
191 (26%) Did not reach Lab
349 (64%) Non MDR-TB
197 (36%) Diagnosed with MDR-TB
121 (61%) Initiated on treatment
76 (39%) Lost to follow-up
Post-LPA
3078 MDR-TB Suspects
2930(95%) Reached Lab
148 (5%) Did not reach Lab
2439 (83%) Non MDR-TB
491(17%) Diagnosed with MDR-TB
433 (88%) Initiated on treatment
58 (12%) Lost to follow-up

Example.. 4

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PLOS ONE

Comparing Same Day Sputum Microscopy with Conventional Sputum Microscopy for the Diagnosis of Tuberculosis – Chhattisgarh, India

Priyakanta Nayak[1*], Ajay M. V. Kumar[2], Mareli Claassens[3], Donald A. Enarson[2], Srinath Satyanarayana[2], Debashish Kundu[1], Kshitij Khaparde[1], Tarun K. Agrawal[4], Shankar Dapkekar[1], Sachin Chandraker[5], Sreenivas Achuthan Nair[1]

Conclusion: Same-day microscopy method missed 17% of smear-positive cases and contrary to prior perception, did not increase the proportion of suspects providing the second sample. These findings call for an urgent need to revisit the WHO recommendation of switching to same-day diagnosis over the current policy.

In Conclusion..

Operational research helps in

Answering questions related to interventions, strategies, tools or *knowledge* that can enhance **the quality or coverage** of disease control programs, health services or health systems

- **Records and reports are a valuable source of information, need to identify variables for which errors/missing information are minimal and use them efficiently**

Thank You

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