51ST ANNUAL MEDICAL SYMPOSIUM

Paediatric specialty meeting

TITLE: Gene Xpert testing in children suspected of PTB

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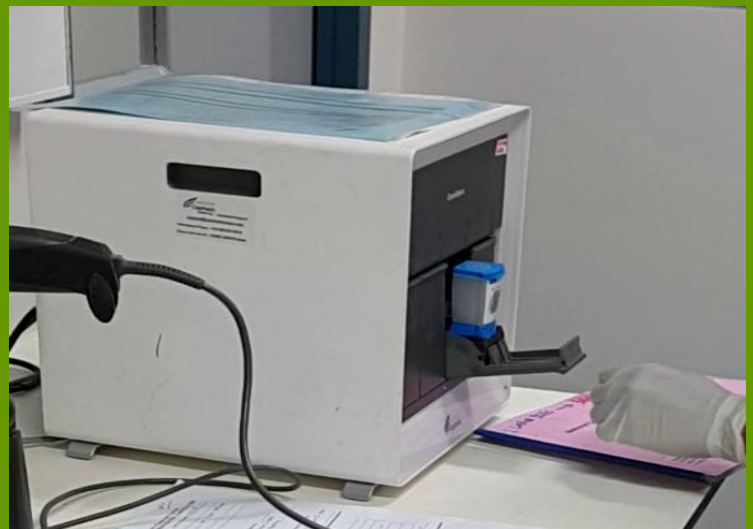
DATE: 02/9/2015

GENE XPERT MTB/RIF ASSAY

Step 1

Step 2

Step 3



Step 4

INTRODUCTION

- **Gene Xpert assay endorsed by WHO in Dec 2010 [WHO Policy updates 2013]**

- **WHO recommendations for children- 2013**
  - **Initial diagnostic test for HIV co-infection and MDR suspects (strong recommendations)**
  - **Initial diagnostic test in all PTB suspects (conditional recommendation)**

- **Most studies assessing the Gene Xpert assay in children have been done in Sub-saharan Africa and Asia [Nicol 2011, Rachow 2012, Bates 2012, Giang 2015]**

AIM

- **Assess the diagnostic performance of the Gene Xpert assay in children suspected of PTB**

- **Describe rifampicin resistance and MDR TB among children who have rifampicin resistance**

METHOD

STUDY TYPE: Prospective descriptive study

LOCATION: PMGH

PERIOD: 6 month Period (Sept 2014 to Mar 2015)

INCLUSION CRITERIA

- **All admitted children (14 years and less) with suspected PTB**

(PTB suspected on the basis of a symptom/sign/risk factor and chest radiographic screen)

Definition of suspected PTB

A child who had been unwell for more than 2 weeks [Graham MS et al 2012 - revised]

- **WITH 2 OR MORE OF THE FOLLOWING:**
  - **Persistent non-remitting cough for more than 2 weeks**
  - **Weight loss/Failure to thrive/PEM syndromes**
  - **Persistent unexplained fever**
  - **Persistent unexplained lethargy or reduced playfulness**
  - **History of exposure to Tuberculosis**
- **AND/OR**
  - **CXR consistent with TB (CXR were read by 2 independent readers)**

CHEST RADIOGRAPHIC REVIEW TOOL

Technical Quality

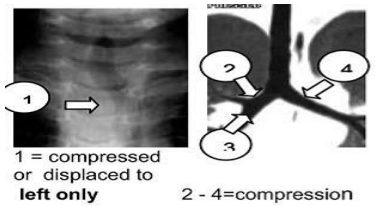
Acceptable ☐ Poor but readable ☐ Not acceptable not readable ☐

Instructions:

- Please indicate any number of locations of abnormality, using an 'X' in the appropriate numbered circle/box.
- Then tick only one of 'yes' or 'No' or 'Not visible' for each category of abnormality identified (numbered 1-8)

1. Airway compression and/or Tracheal displacement

Yes ☐ No ☐ Not visible ☐

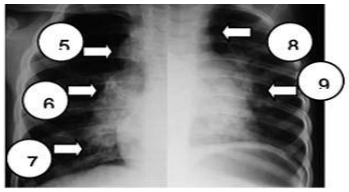


1 = compressed or displaced to **left only**

2 - 4=compression

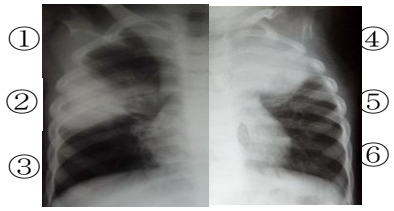
2. Soft Tissue density suggestive of lymphadenopathy

Yes ☐ No ☐ Not Visible ☐



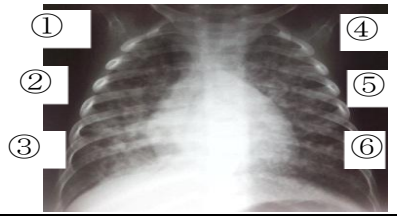
3. Localised homogenous opacity

Yes ☐ No ☐ Not visible ☐



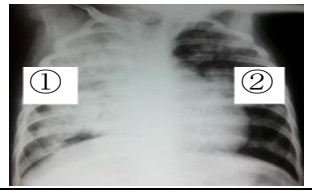
3. Heterogeneous opacities

Yes ☐ No ☐ Not visible ☐



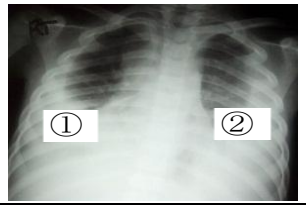
4. Generalized wide spread opacity or complete white out

Yes ☐ No ☐ Not visible ☐



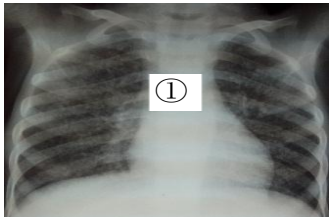
5. Pleural effussion

Yes ☐ No ☐ Not visible ☐



6. Milliary Pattern

Yes ☐ No ☐ Not visible ☐

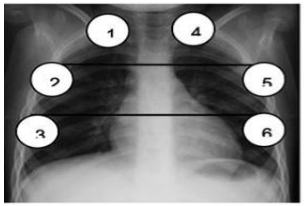


7. Cavities

Yes ☐ No ☐ Not visible ☐

8. Calcified parenchyma (Ghon focus)

Yes ☐ No ☐ Not Visible ☐



(not visible on this CXR)

CXR consistent with Tuberculosis: Yes ☐ No ☐

[Graham MS et al 2012-revised]

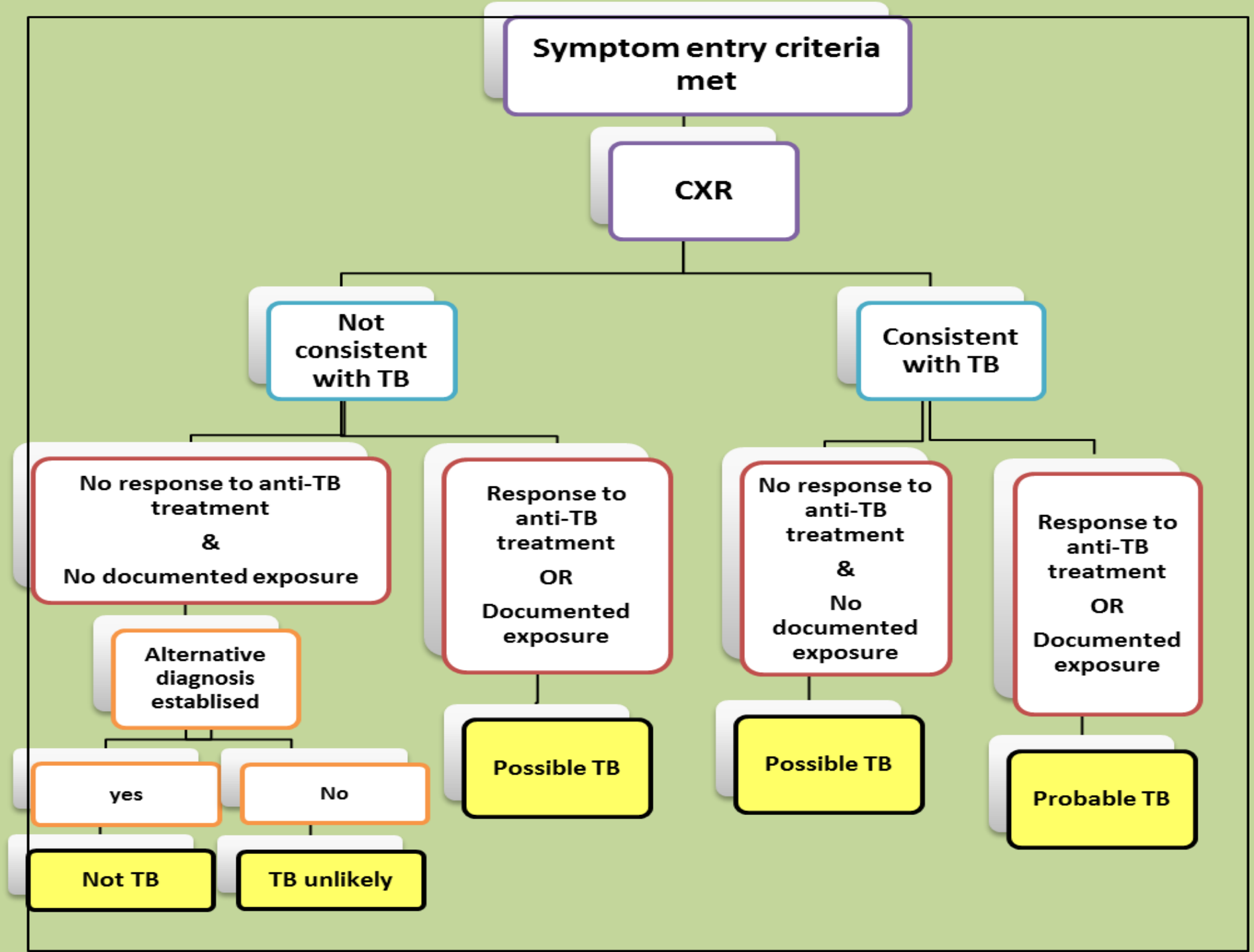
METHOD

EXCLUSION CRITERIA

- Patients in whom sputum or GA cannot be obtained
- Patients in whom guardians or parents do not give informed written consent

RECRUITMENT

- Children screened and recruited during admission
- Standardized Data collection forms used on all
- Classified into clinical diagnostic groups (Probable, Possible, TB unlikely or Not TB) [Graham MS et al 2012]


Symptom entry criteria met
CXR
Not consistent with TB
Consistent with TB
No response to anti-TB treatment
&
No documented exposure
Response to anti-TB treatment
OR
Documented exposure
No response to anti-TB treatment
&
No documented exposure
Response to anti-TB treatment
OR
Documented exposure
Alternative diagnosis establised
Possible TB
Possible TB
Probable TB
yes
No
Not TB
TB unlikely

SAMPLE HANDLING AND TESTING

- Sputum or Gastric aspirate obtained
- Both AFB smear and Gene Xpert done on all samples
- Sample handling and testing done as per the WHO manual for Gene Xpert testing and PMGH Lab protocol
- Rifampicin resistant and a group of the MTB negative samples sent to QMRL for culture and DST

METHOD OF ANALYSIS

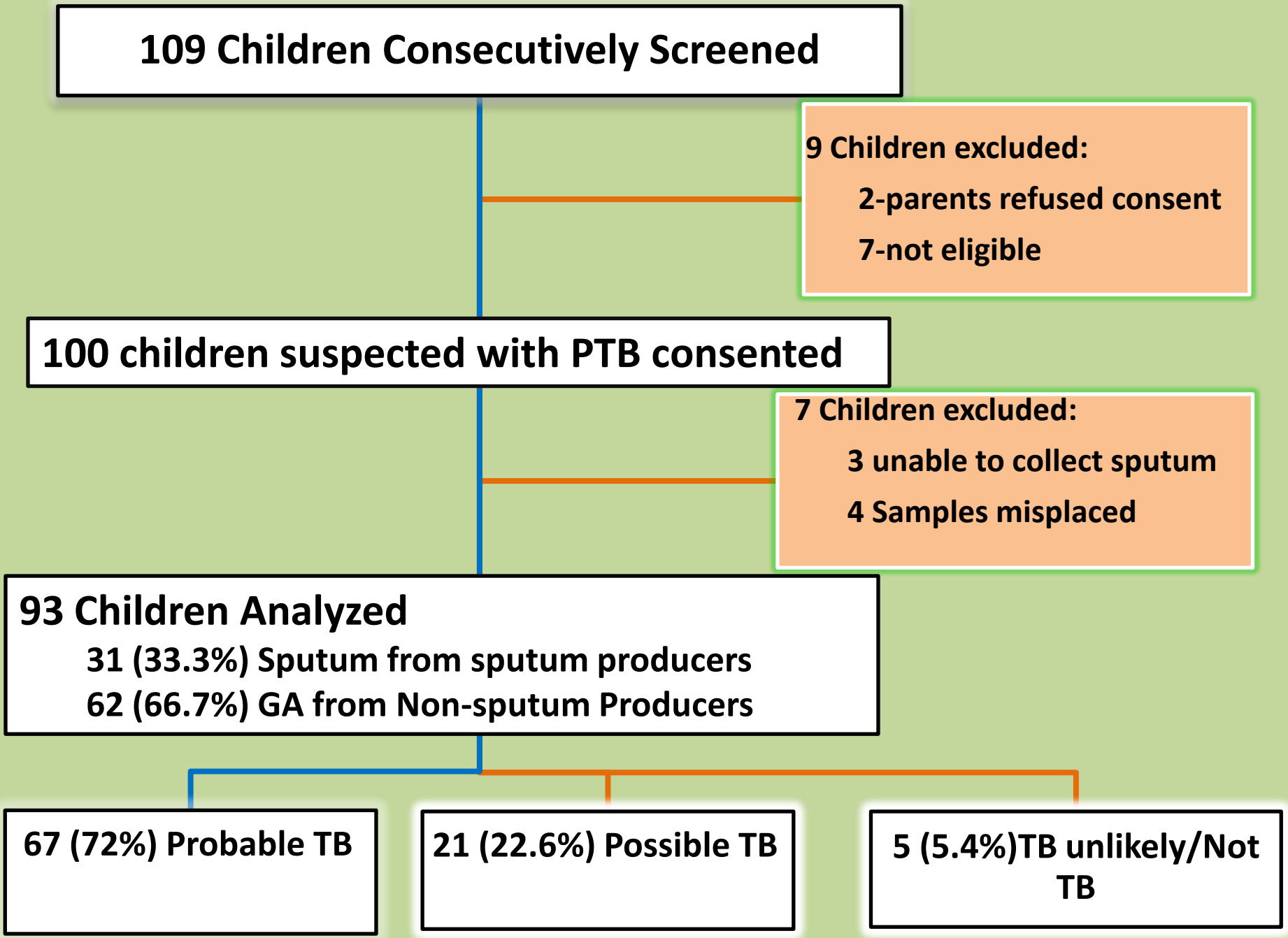
- Analysis done using Microsoft excel and SPSS V20

- Sensitivity, specificity, PPV and NPV done for
  - Gene Xpert Yield
  - AFB smear Yield
  - TB score > 7

Primary Reference standard: Clinical TB diagnosis requiring treatment

[Based on a signs and symptoms, risk factors, radiological (X-ray, USS, Echo, CT scan), microbiological (CSF analysis)and histopathology (FNAB smear) evaluation]

[Study was approved by MRAC, NDOH]


109 Children Consecutively Screened
9 Children excluded:
2-parents refused consent
7-not eligible
100 children suspected with PTB consented
7 Children excluded:
3 unable to collect sputum
4 Samples misplaced
93 Children Analyzed
31 (33.3%) Sputum from sputum producers
62 (66.7%) GA from Non-sputum Producers
67 (72%) Probable TB
21 (22.6%) Possible TB
5 (5.4%)TB unlikely/Not TB

BASELINE CHARACTERISTICS

Clinical characteristics	All (n=93)	Probable TB (n=67)	Possible TB (n=21)	Not TB (n=5)
Sex (Male)	60 (64.5%)	42 (62.7%)	15 (71.4%)	4 (80%)
Median (IQR) age (months)	36 (17 to 72)	36 (25 to 75)	48 (9 to 97)	41 (10 to 57)
*Severe acute malnutrition (<-3SD or Kwashiorkor)	45 (48.4%)	34 (50.7%)	10 (47.6%)	1 (20%)
Cut off TB score for TB diagnosis				
TB score of less than 7	12 (12.9%)	7 (10.4%)	4 (19%)	1 (20%)
TB score of 7 and above	81 (87.1%)	60 (89.6%)	17 (81%)	4 (80%)
HIV status				
HIV positive	17 (18.3%)	14 (21%)	2 (9.5%)	1 (20%)
HIV negative	76 (81.7%)	53 (79.1%)	19 (90.5%)	4 (80%)
Commenced on Anti-TB treatment	80 (86%)	67 (100%)	13 (61.9%)	0

* WFH z scores used for <60 months & BMI for age z scores used for > 60 months

POSITIVE RESULTS FOR GENE XPERT & AFB SMEAR

	All(n=93)	Probable (n=67)	Possible (n=21)
Gene Xpert	26 (28%)	22 (32.8%)	4 (19%)
AFB smear	13 (14%)	12 (17.9%)	1 (4.8%)

	Xpert Positive	Xpert Negative	Total
AFB smear Positive	12	1	13
AFB Smear Negative	14	66	80
Total	26	67	93

DIAGNOSTIC (%) YIELD

Diagnostic Method	Sensitivity	Specificity	PPV	NPV
Gene Xpert	25/80 **(31.25%)**	12/13 **(92.3%)**	25/26 **(96.1%)**	12/67 **(17.91%)**
AFB smear	13/80 **(16.3%)**	13/13 **(100%)**	13/13 **(100%)**	13/80 **(16.3%)**
TB score >7	72/80 **(90%)**	4/13 **(30.7%)**	72/81 **(88.9%)**	4/12 **(33%)**

Primary Ref standard: Clinical TB Diagnosis requiring treatment (n= all 80: 67 Probable TB Cases and 13/21 Possible TB Cases)

RIFAMPICIN RESISTANCE & DST

	All (n=26)	Probable TB (n=22)	Possible TB (n=4)
Rifampicin sensitive	23 (88.5%)	19 (86%)	4 (100%)
Rifampicin resistant	3 (11.5%)	3 (14%)	0

Rifampicin Resistant cases

- 2 -re-treatment cases
- 1 – Confirmed MDR TB contact
- HIV status:
  - 1 positive
  - 2 Negative

- **Culture and DST for the 3 Rif resistant samples**
  - 2-Negative for MTB
  - 1- Positive for MTB
    - DST- sensitive to all 1st line drugs [false positive]

CONCLUSION

- **Xpert had a higher positive yield and was more sensitive than AFB smear**
  - **Positive yield: Xpert 26/93 and AFB smear 13/26 [p=0.019]**
  - **Sensitivity: Xpert: 31.25% (25/80) and AFB smear 16.3% (13/80)**

- **Sensitivity for Xpert remains generally low [31.25%(25/80)]and it should be used and interpreted in light of its limitations**

- **A clinical diagnostic algorithm (including clinical findings, X-rays and other available tests) should remain the way to diagnose TB in children**

- **Practical guide lines should be used to identify the children who will benefit most from a gene Xpert assay**

ACKNOWLEDGEMENT

Peadiatric Team

Dr Welch, Dr Kilalang, Prof Duke, Prof Tefuarani, Prof Vince, Dr Amini, Dr Sobi, Dr Ripa

Peadiatric TB 2D ward Nursing Staff

Sr Minjiau, Sr Kakana and team

CPHL Team

Dr Lavu, Karen Johnson, Ruth Magaye , Jeniffer Banamu and team

All the study participants and their guardians/Parents

Dr Lino Tom

PRIMARY REFERENCE STANDARD: Clinical TB Diagnosis requiring treatment

Constitutional symptoms of TB (Chronic cough, Persistent fever/night sweats, weight loss and lethargy) with or without a close TB contact AND**:**

For PTB

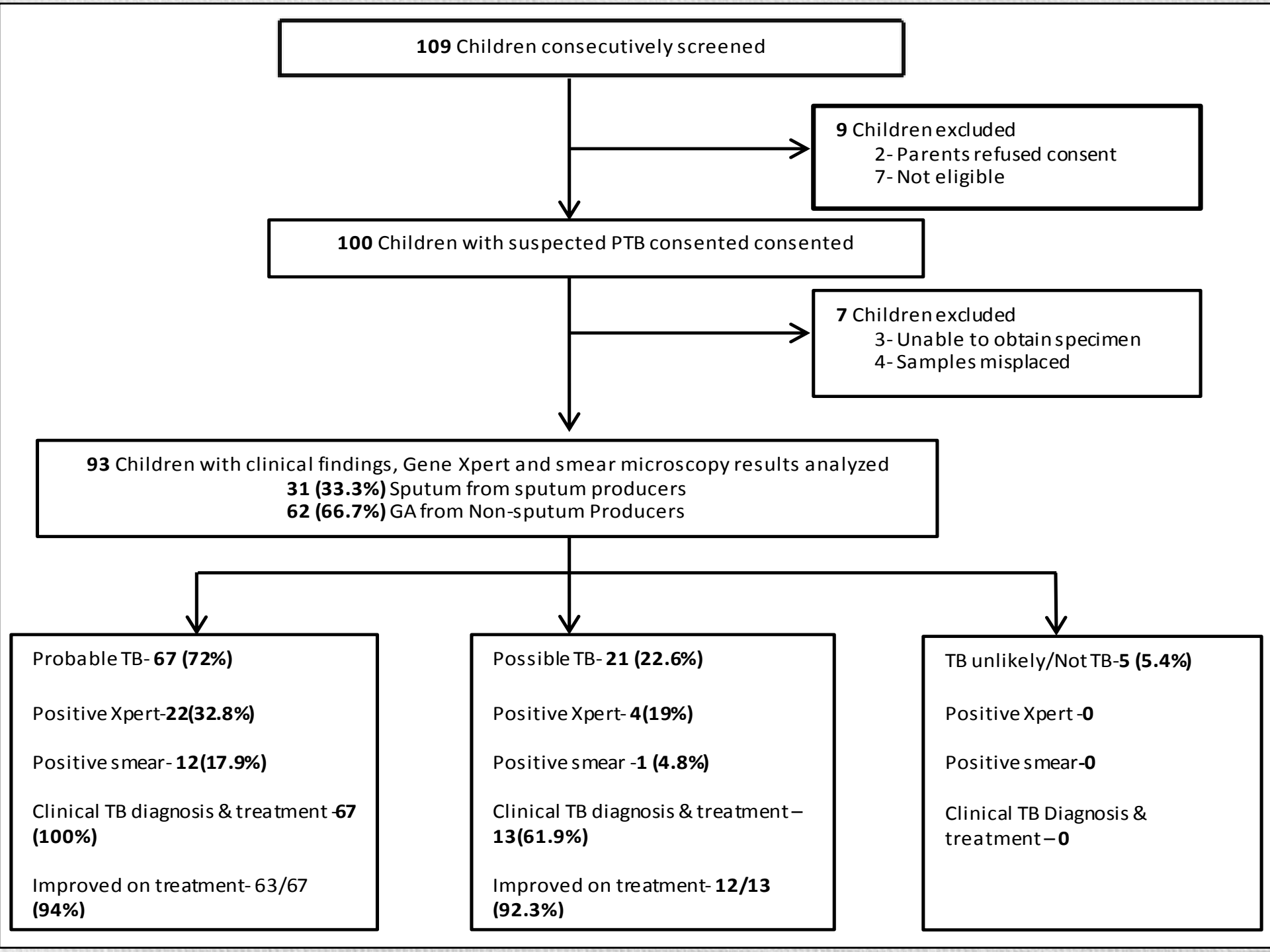
- [a] Clinical signs of chest infection and/or a [b] CXR highly suggestive of TB

For EXPTB

- **TB Pleural effusion**: [c] clinical signs of pleural effusion with a [d] CXR showing an effusion with or without an USS confirming Pleural effusion and a straw colored pleural aspirate
- **TB Pericardial effusion**: muffled heart sounds and a CXR showing a globular enlarged cardiac shadow, with a subsequent Echocardiogram showing pericardial effusion with fibrin strands
- **TBLN**: Large, matted, firm non-tender lymph nodes or soft sinus in the neck, axilla or inguinal area with an FNAB showing caseous granuloma or smear staining positive for acid fast bacilli
- **Abdominal TB**: Abdominal distention with or without [e] clinical signs of ascites with Ultrasound scan showing Ascites and intra-abdominal lymphadenopathy
- **Spinal TB**: Spinal gibus with spinal X-ray showing angle deformity of the spine and/or vertebral destruction with or without [f] distal neurological signs
- **TBM**: [g] Clinical signs of meningitis with Cerebrospinal fluid showing a high protein, low glucose and high lymphocyte count or CT scan showing lesion consistent with tuberculoma

For Both PTB and EXPTB:

- **Clinical signs and investigations consistent with PTB** and **disease affecting one or more of the extra pulmonary sites**
- **Milliary TB (Disseminated infection):** CXR shows Milliary pattern


109 Children consecutively screened
9 Children excluded
2- Parents refused consent
7- Not eligible
100 Children with suspected PTB consented consented
7 Children excluded
3- Unable to obtain specimen
4- Samples misplaced
93 Children with clinical findings, Gene Xpert and smear microscopy results analyzed
31 (33.3%) Sputum from sputum producers
62 (66.7%) GA from Non-sputum Producers
Probable TB- **67 (72%)**
Positive Xpert-**22(32.8%)**
Positive smear- **12(17.9%)**
Clinical TB diagnosis & treatment -**67 (100%)**
Improved on treatment- 63/67 **(94%)**
Possible TB- **21 (22.6%)**
Positive Xpert- **4(19%)**
Positive smear -**1 (4.8%)**
Clinical TB diagnosis & treatment – **13(61.9%)**
Improved on treatment- **12/13 (92.3%)**
TB unlikely/Not TB-**5 (5.4%)**
Positive Xpert -**0**
Positive smear-**0**
Clinical TB Diagnosis & treatment – **0**

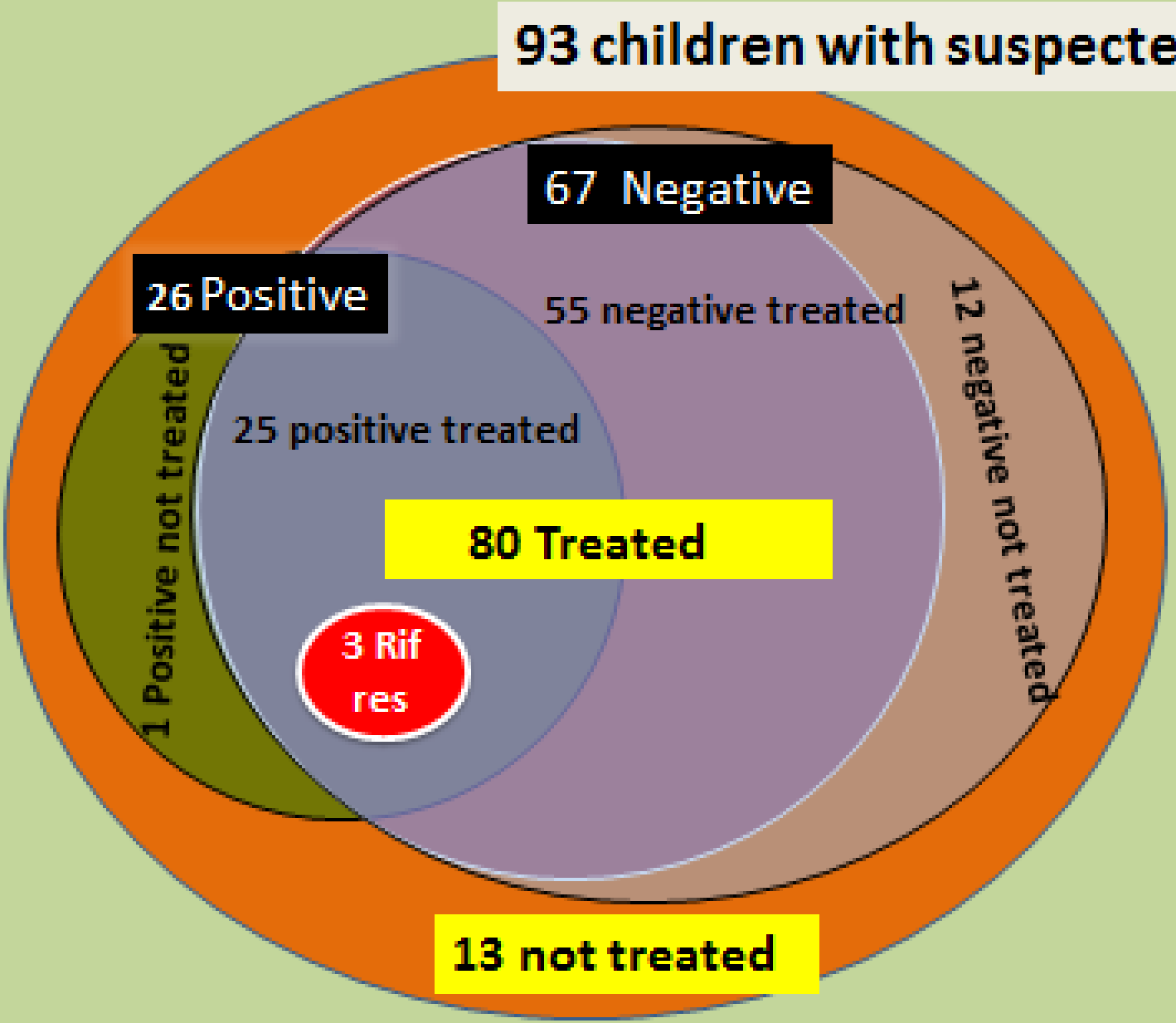
Sputum & GA combined	Result	All(n=93)	Probable (n=67)	Possible (n=21)	TB unlikely/Not TB (n=5)
Gene Xpert MTB/RIF assay	Positive	26 (28%)	22 (32.8%)	4 (19%)	0
	Negative	67 (72%)	45 (67.2%)	17 (81%)	5 (100%)
AFB smear microscopy	Positive	13 (14%)	12 (17.9%)	1 (4.8%)	0
	Negative	80 (86%)	55 (82%)	20 (95.2%)	5 (100%)

GA	Result	All(n=62)	Probable (n=45)	Possible (n=13)	TB unlikely/Not TB (n=4)
Gene Xpert MTB/RIF assay	Positive	19 (30.6%)	16 (35.6%)	3 (23%)	0
	Negative	43 (69.4%)	29 (64.4%)	10 (77%)	4 (100%)
AFB smear microscopy	Positive	8 (12.9%)	7 (15.6%)	1 (7.7%)	0
	Negative	54 (87%)	38 (84.4%)	12 (92.3%)	4 (100%)

	TB score	
	TB Score < 7 (n=12)	TB Score > 7 (n=81)
Xpert Positive	3 (25%)	23 (28.4%)
AFB Smear Positive	1 (8%)	12 (14.8%)

Diagnostic Method	Sensitivity	Specificity	PPV	NPV
Gene Xpert MTB/RIF assay				
Combined Sputum and GA	25/80 **(31.25%)**	12/13 **(92.3%)**	25/26 (96.1%)	12/67 **(17.91%)**
Sputum	7/29 **(24.13%)**	2/2 **(100%)**	7/7 (100%)	2/24 **(8.33%)**
GA	18/51 **(35.3%)**	10/11 **(90.9%)**	18/19 **(94.7%)**	10/43 **(23.25%)**
AFB smear microscopy				
Combined sputum and GA	13/80 **(16.3%)**	13/13 **(100%)**	13/13 **(100%)**	13/80 **(16.3%)**
Sputum	5/29 **(17.2%)**	2/2 **(100%)**	5/5 **(100%)**	2/26 **(7.7%)**
GA	8/51 **(15.7%)**	11/11 **(100%)**	8/8 **(100%)**	11/54 **(20.4%)**
TB score >7	72/80 **(90%)**	4/13 **(30.7%)**	72/81 **(88.9%)**	4/12 **(33%)**

GENE XPERT ADDS VALUE TO CLINICAL DX



DR TB Suspects

1. Retreatment cases
2. DOT non-converters (Cat 1 & 11)
3. Symptomatic contacts of known DR TB patients
4. TB/HIV co-infection

Gene Xpert will be used as the initial diagnostic test for DR TB suspects