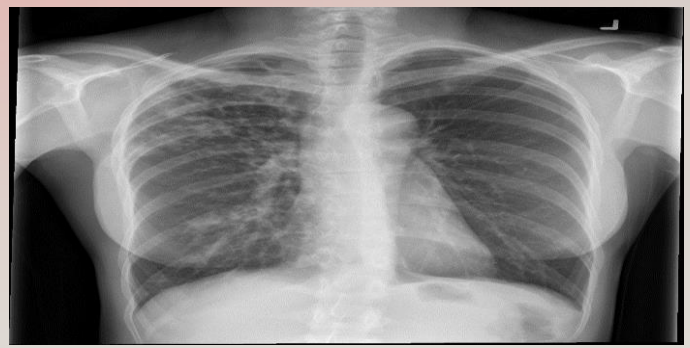
OUR RECENT CASE

- This patient , 30 year old , G4 P2 presented to the OB clinic or her pre - natal visit;
- TST was 25 mm ,
- CXR shown;

- She was totally asymptomatic ; had no history of contact with any TB patient personally or professionally; Had a negative TST 8 yrs. ago ;
- 3 sputum tests of 6 were positive for AFB



- T-Spot TB TEST WAS NEGATIVE

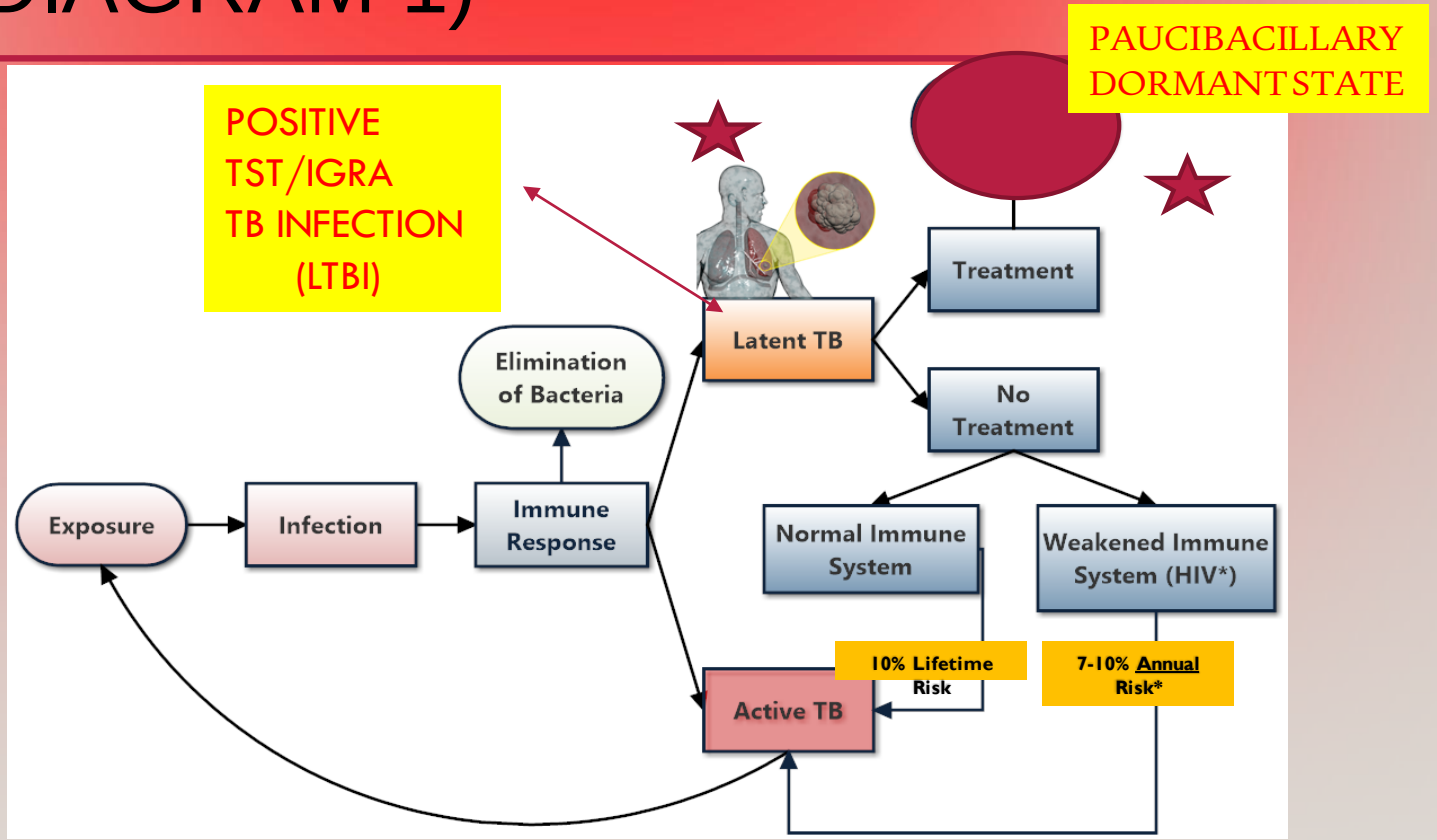
PATHWAY OF PATHOGENESIS IN NON-IMMUNE COMPROMISED PATIENTS WITH A CONNECTION AND YET A DISCONNECT BETWEEN INFECTION, IMMUNE RESPONSE AND DISEASE

- Inhalation
- Macrophage phagocytosis
- Shedding and macrophage turnover
- Alveolar Dendritic Cell migration to regional LN
- MTB Antigens ESAT -6; CFP-10 with CD_4 /CD_8 interaction
- Differentiate into INF-G, TNF TH_1 or cytotoxic Tc_1 cells respectively IL 17 21, 22
- DTH Reaction- positive TST with Intragranuloma necrosis called Ghon Complex **LATENT PHASE**
  - Ghon Complex is not necessarily limited to lung
- Post Primary IL- 4 IL -13 TH 2 response with central caseation and DISEASE

LATENT TB AKA LTBI AKA LASTING TB IMMUNITY HAS NO CLINICAL ACTIVITY BUT GRANULOMAS ARE DYNAMIC LESIONS WITH CONTINOUS TURNOVER AND VARIABLE BACILLARY POPULATION AND DISEASE ACTIVITY RANGING FROM DORMANCY TO STUNDED GROWTH TO ACTIVE MULTIPLICATION

Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J*. 2009;33(5):956-973. doi:10.1183/09031936.00120908

TB INFECTION FLOW CHART (DIAGRAM 1)



Adapted from Core *Curriculum on Tuberculosis: What the Clinician Should Know*, 5th ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. with addenda and modifications by authors

Pregnancy suppresses the T-helper 1 (Th1) proinflammatory response, which may mask symptoms while increasing susceptibility to new infection and reactivation of tuberculosis (like Influenza) After delivery, Th1 suppression reverses—similar to immune reconstitution syndrome in HIV patients starting antiretroviral therapy (ART)—and symptoms are exacerbated

A large study recently found that early postpartum women are twice as likely to develop tuberculosis as non-pregnant women .

Practitioners should be cognizant of the unpredictable symptomatology of tuberculosis during pregnancy. Clin Infect Dis. Déc. 1, 2012; 55(11): 1532–1549.

- Prevalence of active TB in pregnancy 0.25 – 7 % In low burden countries
- Prevalence of LTBI probably matches the population (4.2 % LTBI)

- Clin Infect Dis. Déc. 1, 2012; 55(11): 1532–1549. **Tuberculosis in Pregnant and Postpartum Women: Epidemiology, Management, and Research Gaps**
  Kenneth H. Mayer, Section Editor
  Jyoti S. Mathad[1] and Amita Gupta

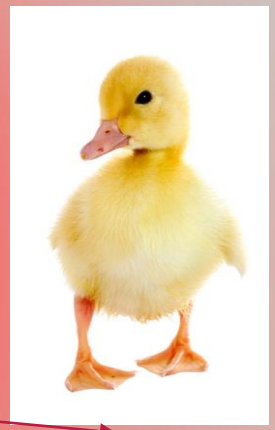
Tuberculosis increases mortality during pregnancy or postpartum, especially in HIV-positive women
Pregnant women with pulmonary or extrapulmonary tuberculosis, other than lymphadenitis, also have increased risk of complications including antenatal hospitalization and miscarriages

Risk of tuberculosis in pregnancy: a national, primary care-based cohort and self-controlled case series study. Zenner D, Kruijshaar ME, Andrews N, Abubakar I
Am J Respir Crit Care Med. 2012 Apr 1; 185(7):779-84.

MODIFIED PUBLIC HEALTH CLASSIFICATION

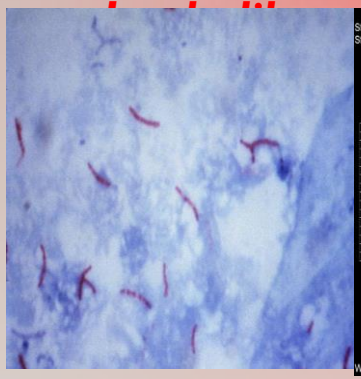
- 0 No Exposure; Not Infected
- 1 Exposure; Not Infected
- 2 Infected; No Active Disease
- 3 Active Disease Pulmonary and or Extra-Pulmonary
- 4 Old Disease or "UDA"
- 5 Under Evaluation for Active TB
- 6 "TB wannabes"/Atypical/NTM
- 7 Associate Involvement
- 8 Exposed Contacts

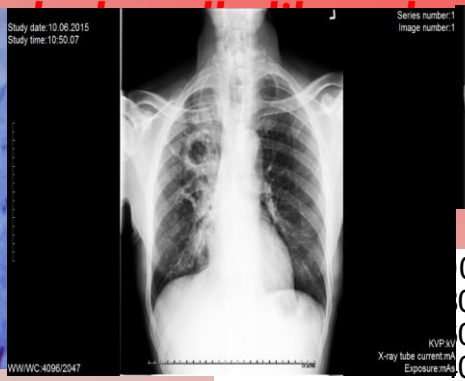
"To Be or Not To Be"

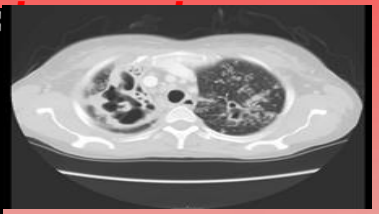


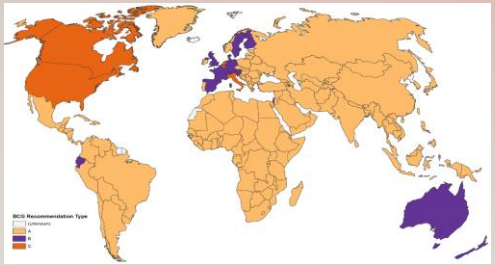
Risk, Signs, Symptoms, Micro (Smear, NAAT, Culture, Probe, Final Culture) Images Tissue Dx

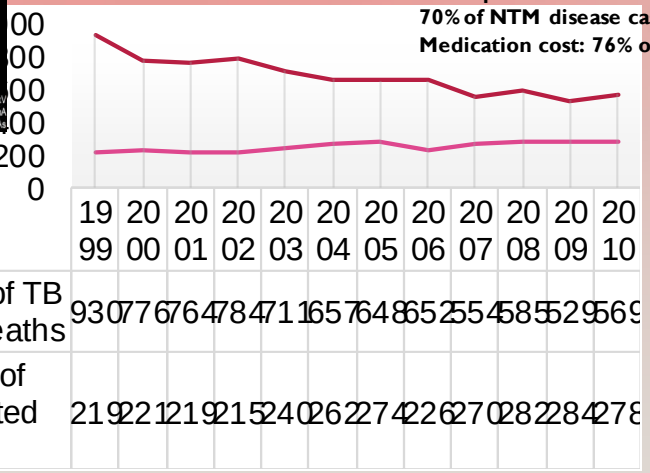
...BUT IS IT?











Based on 2003 – 2007 Medicare data
Projected 8% annual increase in prevalence
Estimated 86,244 cases in 2010 at an annual cost $815 million; 87% inpatient
70% of NTM disease cases occurred in oceanic coast line & gulf states
Medication cost: 76% of all total cost

BCG – Does that matter?
NTM - Is that important?
WHICH NTM THE MOST : MAC

Public Health Image Library. ID#5789 Ziehl-Neelsen stain

TESTS FOR IMMUNE RESPONSE[1]

TB Skin Testing

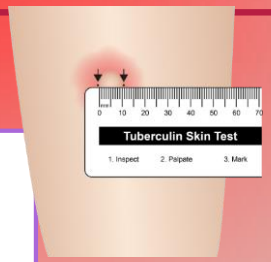
- ***In vivo*** **measurement of cell-mediated immunity to mycobacterium antigens in the form of a delayed-type hypersensitivity reaction**
- Previous exposure to mycobacterium results in production of **sensitized lymphocytes**
- Sensitized lymphocytes secrete cytokines to attract neutrophils, **memory CD4 T cells, CD8 T cells,** which cause induration and erythema
- Induration measured 48−72 hours post implantation
- Sensitivity of the tuberculin skin test is limited in **immunocompromised** individuals
- Specificity is limited because of cross-reactivity due to prior infection with **environmental mycobacteria or BCG vaccination**

Interferon-Gamma Release Assay

- ***In vitro*** **measurement of INF-gamma released by effector T cells responding to specific TB antigen stimulation, such as ESAT-6 and CFP10**
- Previous exposure to *M. tuberculosis* results in production of **sensitized T cells**
- **Sensitized T cells secrete IFN-γ (cytokine) when they reencounter specific *M. tuberculosis* antigens**
- IFN-γ secreted by effector T cells measured ~20 hours poststimulation
- **Antigens used in IGRAs (ESAT-6 , CFP10, TB7.7) are not present *M. bovis* BCG and in most environmental mycobacteria**

1. Mack U, Migliori GB, Sester M, et al. *Eur Respir J.* 2009;33(5):956-973.

TESTING METHODOLOGIES FOR IMMUNE RESPONSE



Tuberculin skin testing (TST)

- Mantoux test, Purified Protein Derivative (PPD)

Interferon-gamma release assay (IGRA)

- T-SPOT®.*TB* test
- QuantiFERON®-TB Gold/Plus

Advantages & Disadvantages

T-SPOT is a registered trademark of Oxford Immunotec, Ltd.
QuantiFERON is a registered trademark of the QIAGEN Group.

J 4 100

NTM/MOTT BCG Technique Anergy?

What are the drawbacks of TST/Mantoux test/PPD?

J 4

ISSUES AFFECTING THE USE OF TST

Limitations

- Need for trained personnel to administer the intradermal injection and also interpret the test
- Inter- and intra-reader variability in interpretation
- Need for a return visit to have the test read
- False-positive results due to cross-reactivity of antigens within the PPD to both BCG and nontuberculous mycobacteria
- False-negative results due to infections and other factors, rare adverse effects, and complicated interpretation

False-Negative Results

- In persons with clinical conditions associated with immunosuppression or overwhelming illness
- After recent viral and bacterial infections
- In association with treatment with immunosuppressive drugs

False-Positive Results

- Repeat TST can restore reactivity in persons whose TST reactivity has decreased over time
- Cross-reactivity with BCG vaccine
- Cross-reactivity for non-tuberculous mycobacteria (NTM) is increased for persons living in areas where nontuberculous mycobacteria is common
- Errors in TST placement or reading

Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. December 2016:ciw694.

J5 300

This is based on mycobacterial genomics and antigen specific T cell response, Antigenic targets include ESAT-6 and CFP-10

This is performed in homeless/transient resident population and has a higher PPV and NPV

What is IGRA and what is it based on?

J5

In vitro **measurement of INF-gamma released by effector T cells responding to specific TB antigen stimulation, such as ESAT-6 and CFP10**

TB-SPECIFIC ANTIGENS USED IN IGRAS

- Produce measureable immunologic responses in TB-infected persons
- Are present in
  - *Mycobacterium tuberculosis* complex organisms, including *M. tuberculosis, M. bovis, M. africanum, M. microti,* and *M. canetti*
  - *M. kansasii, M. szulgai,* and *M. marinum* (nontuberculous mycobacteria)
- Are absent in and do not cross-react with
  - *M. bovis* BCG sub strains
  - *M. avium* and most other nontuberculous mycobacteria

JA note: except "KMSGF"

T-SPOT.*TB* Package Insert PI-TB-US-V5. Oxford Immunotec Ltd. Abingdon, UK. March 2015.
QuantiFERON-TB Gold (QFT) ELISA Package Insert, 1075116 Rev. 02. Cellestis, Inc. Valencia, CA., April 2015.

IGRAs demonstrate only fair concordance with the TST in pregnancy. Two US studies screening pregnant women for latent tuberculosis found that most discordance was IGRA negative/TST positive attributed to previous BCG vaccination among the foreign-born.

In contrast, in India, discordance was largely IGRA positive/TST negative
Epidemiological (eg, recent tuberculosis exposure) and biological factors (eg, malnutrition, immune changes of pregnancy) may explain this, although the significance of this discordance needs further study

TARGETED TST OR IGRA: CAN BE PERFORMED IN PREGNANCY

- Identified increased risks
- Foreign born
- Recent immigrants
- Frequent travelers
- HIV / immune compromised

TARGETTED TST

Clin Inf Disease 2012; 55:1532/ATS etc …but what happened to our case

OTHER APPROACHES

- Counselling
- \LTBI testing prior to pregnancy if indicated

J 2 300

- Silicosis**…… 30% ** silica exposure
- DM…… 2-4 %
- CRF…….. 10-25%
- Gastrectomy…… .2-5%
- J-I Bypass…… 27-63%
- Solid Organ Transplant….37% / 70%
- Carcinoma of head or neck 16%

J 2

- What is the relative Increased Risk for developing Active TB by selected conditions :

- NOTE NOT PREGANCY

J 7 200

HIV 5 mm

Contact 5mm

Congregate setting 10 mm

No risk 15mm

What are the criteria for a positive TST requiring consideration for chemoprophylaxis?

J 7

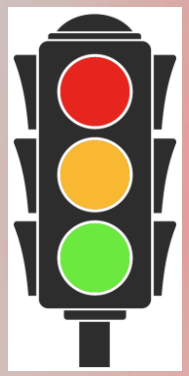
JEOPARDY 1

Must check for active TB

Do not forget to look for Extrapulmonary TB

What do you do before starting treatment for latent TB/TB Infection?

…Remember the one definitive contraindication**



POSITIVE TST/IGRA: SUGGESTED TRAFFIC LIGHT PLAN*

Driving Path

A: DATA	B: EVALUATE	C: SCAN		D: TREAT LTBI
Quantify; Assess Borderline Indeterminate Discordant Results	Rule Out Active TB Disease Based on Symptoms and Risk	Rule out Extra-Pulmonary Disease		**Dx; LTB Infection Should we Offer Rx? Assess Risk Benefit Ratio and patient engagement , understanding and adherence to treatment.**
Document	Symptoms History / Physical	Detailed Review of Systems: **"ROS 101";** Repeat Physical exam specially LN Exam		**Be aware of risk of adverse drug reactions and potential side effects**
Check HIV Other Immune status	Chest Radiograph CT Scan if needed	Correlate with Chest and other imaging if applicable		**Pre-Rx start : Lab Check**
Risk Stratify Check Source Case Culture/ Sensitivity	Sputum Smear/NAAT; Induce Sputum if needed May need Direct Observed Sputum Evaluation (DOSE)	Assess Background History again ?		Treat for TB Infection based on Risk Benefit Ratio
Conclude after Full Evaluation: Proceed to Steps B-E	Assess Pre-Test Probability; Treat for active TB disease f index of suspicion is high	Treat for active TB disease f index of suspicion is high		**Monitor Side Effects; Drug-Drug Interaction; Establish Care Coordination with Primary Care Team**

**Designed by JA

RX FOR LTBI IN PREGNANCY IF RECENT INFECTION/ CLOSE HOUSEHOLD CONTACTS SEVERE IMMUNE COMPROMISED HOSTS HIV

OTHERWISE DEFER**** BUT REPEAT PROCESS AND RULE OUT ACTIVE TB PROCESS POST DELIVERY******

**** *WHY? RISK OF INH HEPATOTOXICITY POST PARTUM*
****ADHERENCE TO FOLLOW UP LOW 42 % ..CRUZ ET AL AM J OBST GYN 2005;192:1455*

**** *HOWEVER NEEDS STRICTER STRUCTURED POST PARTUM FOLLOW UP CLOSE THE LOOP BY CARE COORDINATION*

******* *USE OF RIF AND D-D INTERACTION RELATED TO CONTRACEPTION MEASURES*

RX OPTIONS; USUALLY RX DEFERRED , BUT IF STARTED PRIOR TO PREGNANCY , THAT SHOULD BE CONTINUED; WATCH LFTS AND FOR HIV HEP B/C

- INH 6 months*
- INH 9 months*
- RIF 4 months**
- RIF& INH 4 months
- RPT and INH weekly **

Completion rate 20-60%

If index case MDRTB or XDRTB , then a big problem

** *DOT*

The Real Life Algorithm*

.. 2/4 or 2/7 or 3/3

Dx of TB (Class 3 or 5 Start RIPE DOT DAILY/Bi weekly*

RIPE*** (RIF INH PZA ETM)

****

Culture back

****

Pan sensitive

***RIP(drop E)

2 month Sputum culture negative

***Drop PZA

| *** RI ******

0…… 2-4 weeks……..6 weeks 8-12 wks …….6mths

……9mths

* Check dosage; ***Watch for ADR/LFTs/DILI

J 14 300

No SM

No PZA in USA

9 months at least

Vitamin B6 a must

What is

TB treatment in pregnant women?

J 14

- INH HEPATOXICITY
- RIF *** Watch for hemorrhagic complications peri delivery
- RB in case of HIV & Pregnancy and use of PI ; watch levels
- ETM

DRUGS FOR RX IN PREGNANCY

*REF **ATS GUIDELINES** **MMWR 2003***
*VERSUS **IUAT AND WHO***

NO PZA,
NO SM OR ANY AMINOGLYCODIDES;
FQS … ONLY IF NO OTHER ALTERNATIVES

- J 16

- Rare
- Associated with maternal HIV infection, miliary disease and tuberculous endometriosis**
- ** needs a high index of suspicion ..a true ILH/UMC story
- Hematogenous spread
- Multiorgan involvement with low APGAR
- TST unhelpful
- High mortality

- J 16
- What is Congenital TB?

- ** Note Neonatal TB on the other hand follows exposure to mother's resp secretions.

J 15

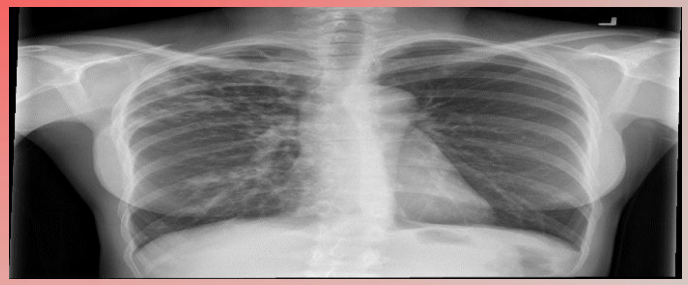
- Not contraindicated; concentrations small; no toxic effects
- AVOID Rifabutin AND FQs
- Not recommended when treatment with second line drugs

J 15

GUIDELINES ABOUT BREAST FEEDING

OUR RECENT CASE AND THE REST OF THE STORY

- This patient , 30 year old , G4 P2 presented to the OB clinic or her pre - natal visit;
- TST was 25 mm ,
- CXR shown;



- She was totally asymptomatic ; had no history of contact with any TB patient personally or professionally; Had a negative TST 8 yrs. ago ;
- 3 sputum tests of 6 were positive for AFB
- T-Spot TB TEST WAS NEGATIVE

DOTS YES, BUT ALSO

……..

REFER TO

1. Wetmore Clinic Fax referral print through Epic

2. NTM - ELD/UMC Clinic EPIC direct

Use TB Hot line 504 638-7053 Ms. Maureen

JA 504 875 7680 jali@lsuhsc.edu

HELP LINE

Juzar Ali MD; FRCP(C); FCCP

Cell : 504 875 7680

LSU Alumni Klein Professor of Medicine , Section Pulm/CC/A&I at LSU HEALTH SCIENCES CENTER

Director LSUHSC -Wetmore Mycobacterial Disease Program

Academic Office : MEB Suite 3205 , 1901 Perdido Street, New Orleans 70112 Phone : 504 568 4634 ; 504 568 4295

LSU HealthCare Network Pulmonary Clinic: 3700 St Charles Avenue, NOLA 70115 Clinic 504 412 1366 ; CLINIC FAX 412 1367

University Medical Center NTM (Non-Tuberculosis Mycobacterial) Disease Program Clinic, New Orleans

UMC CLINIC NURSE 504 702 4574 ; fax 504 702 -5728

WETMORE TB CLINIC /Office of Public Health Region 1 New Orleans Phone : 504 826 2063 FAX 504 826 2052

TB/Mycobacterial Disease program HOT LINE: Ms. Maureen Vincent 504 568 4581 or CELL 504 638 7053

LSU Health NEW ORLEANS

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www.lsudocs.com **www.lsuhsc.edu**

http://www.medschool.lsuhsc.edu/tb/

http://ntm.lsuhsc.edu