Tuberculosis (TB)

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Infectious Disease Consultant

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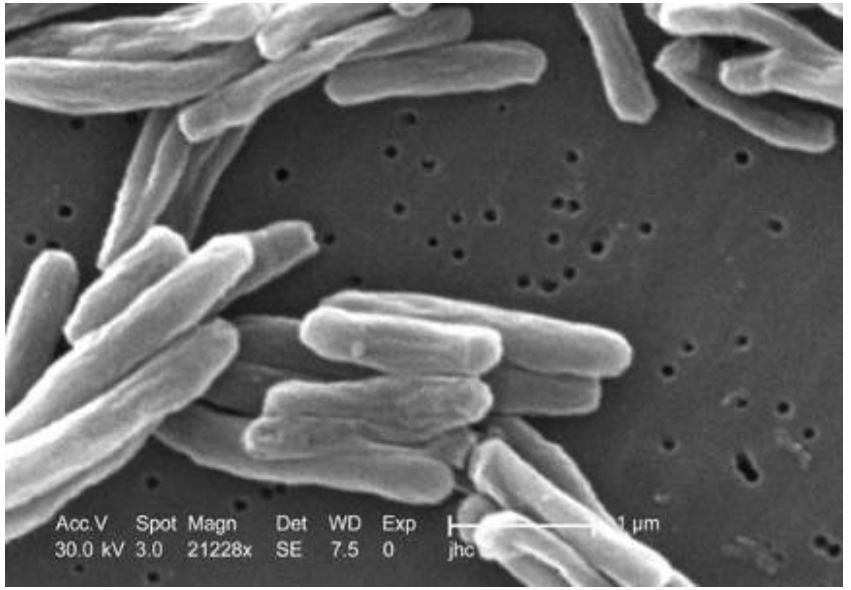
History of TB

- TB has affected humans for millennia
- Historically known by a variety of names e.g:
  - Consumption
  - Wasting disease
  - White plague
- TB was a death sentence for many

History of TB

Scientific Discoveries in 1800s

- Until mid-1800s, many believed TB was hereditary
- 1865 Jean Antoine-Villemin proved TB was contagious
- 1882 Robert Koch discovered *M. tuberculosis* the bacterium that causes TB



Mycobacterium tuberculosis

Robert Koch

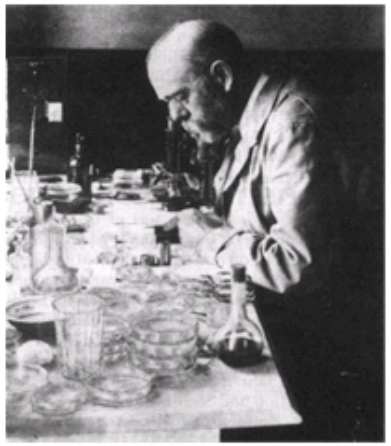
The Nobel Prize in Physiology or Medicine 1905

- Koch discovered the tubercle bacillus in 1882
- He developed a staining and destaining method for acid-fast bacilli
- He also discovered a method of growing it in pure culture.
- He sought to cure TB by means of a preparation, which he called tuberculin, made from cultures of tubercle bacilli.
- The curative value of this was disappointing; but it led, nevertheless, to the discovery of substances of diagnostic value (tuberculin skin test).

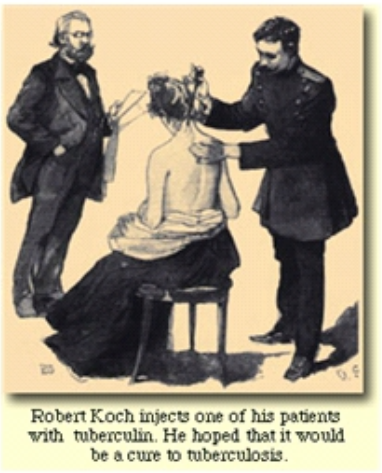
http://nobelprize.org/nobel_prizes/medicine/laureates/1905/koch-bio.html

Diagnostic tools that Koch used…

Microscopy



Culture



Tuberculin test

END TB

Stop TB Partnership

Global Plan to End TB: 2018–2022

TB Globally

- TB is the world's leading cause of death from a single infectious agent.
- In 2018, an estimated 10 million people became ill with TB and an estimated 1.5 million died
- More than 3 million people with TB each year are not diagnosed

SDG Target 3.3	By 2030, end the epidemics of AIDS, TB, malaria and neglected tropical diseases, and combat hepatitis, water-borne diseases and other communicable diseases
WHO End TB Strategy	80% reduction in the TB incidence rate (new and relapse cases per 100 000 population per year) by 2030, compared with 2015 *2020 milestone:* 20% reduction; *2025 milestone:* 50% reduction
	90% reduction in the annual number of TB deaths by 2030, compared with 2015 *2020 milestone:* 35% reduction; *2025 milestone:* 75% reduction
	No households affected by TB face catastrophic costs by 2020
UN high-level meeting on TB, 2018	40 million people treated for TB from 2018 to 2022, including: • 3.5 million children • 1.5 million people with drug-resistant TB, including 115 000 children
	At least 30 million people provided with TB preventive treatment from 2018 to 2022, including: • 6 million people living with HIV • 4 million children under 5 years of age and 20 million people in other age groups, who are household contacts of people affected by TB
	Funding of at least US$ 13 billion per year for universal access to TB prevention, diagnosis, treatment and care by 2022
	Funding of at least US$ 2 billion per year for TB research from 2018 to 2022

Tuberculosis incidence trends in Saudi Arabia over 20 years: 1991-2010

Ibrahim Al-Orainey, Mogbil A. Alhedaithy, Awad R. Alanazi, Mazin A. Barry,

Table 1: Annual TB patient numbers and incidence rate/100,000 in Saudi Arabia (1991-2010)

Year	Saudis		Non-Saudis		Total	
	No.	Rate	No.	Rate	No.	Rate
1991	1294	10.7	1220	26.6	2514	15
1993	1105	8.6	1281	27.2	2386	13.6
1995	1168	8.6	1536	31.7	2644	14.3
1997	1675	11.6	1646	29.4	3139	16.2
1999	1854	12.2	1653	32.3	3507	17.2
2000	1778	11.3	1566	30.2	3334	16
2002	1736	10.7	1535	29.2	3271	15.2
2004	1733	10.4	1494	24.3	3227	14.2
2006	1992	11.5	1654	25.8	3646	15.4
2008	2033	11.2	1785	26.7	3818	15.4
2010	2216	11.8	2078	24.6	4294	15.8
P value	<0.01		<0.001		>0.05	

Overview of TB epidemiology:

→After exposure to TB the patient will either present with an active TB or will just remain in a dormant latent phase of TB.

→Weather the patient had the infection or developed latent TB, TST or IGRA will be positive.

→The rate of progression from latent TB to active disease:

- Non-HIV patients is 5-10% lifetime.
- HIV positive patients: 5-10% per year.

Prevalence of Latent Tuberculosis Infection in the Middle East and North Africa: A Systematic Review

Mazin Barry

Department of Internal Medicine, Division of Infectious Diseases, College of Medicine, King Saud University, Riyadh, Saudi Arabia

- The overall prevalence is 41.78%

Balkhy et al. [34]	July 2010 to March 2013	2017	Saudi Arabia	Primary healthcare workers	TST QFT-GIT	Cross-sectional	1369	<15 to ≥65 years	Chi-square test, McNemar test	146	10.66% (9.07, 12.42)	Low prevalence of LTBI
El-Helaly et al. [35]	August 2009 to May 2011	2014	Saudi Arabia	Preemployment screening of tertiary healthcare workers	TST QFT-GIT	Cross-sectional	1372	18-60 years	Kappa coefficient, chi-square test	421	30.68% (28.25, 33.20)	Fair agreement between TST and QFT-G tests
Hassan and Diab et al. [36]	January to June 2012	2014	Saudi Arabia	Laboratory personnel at a university hospital	QFT-GIT	Cross-sectional	134	21-60 years (33 ± 9.2)	Standardized questionnaire, chi-square test, Fisher's exact test	26	19.4% (13.08, 27.12)	Assessed risk factors involved with LTBI
Abbas et al. [37]	January 2008 to December 2009	2010	Saudi Arabia	Healthcare workers in tertiary care hospital	TST	Cross-sectional	2650	10 to >50 years	ANOVA	291	10.98% (9.81,12.23)	Highest LTBI rates in physicians and nurses

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Risk factors for TB infection:

1. Exposure to TB cases.
2. From TB endemic area.
3. Homelessness.
4. Incarceration.
5. Works in a healthcare or corrections.
6. Injection drug use.

Risk factors for progression to TB disease:

1. Recent infection (The most important risk factor).
2. HIV infection.
3. TNF alpha inhibitors.
4. Immunosuppression.
5. End stage renal disease.
6. Diabetes.
7. Silicosis.
8. CXR showing fibrotic lesions consistent with prior TB.
9. Intestinal bypass/ gastrectomy/ chronic malabsorption.
10. Cancer of the head or neck, Hodgkin, leukemia.

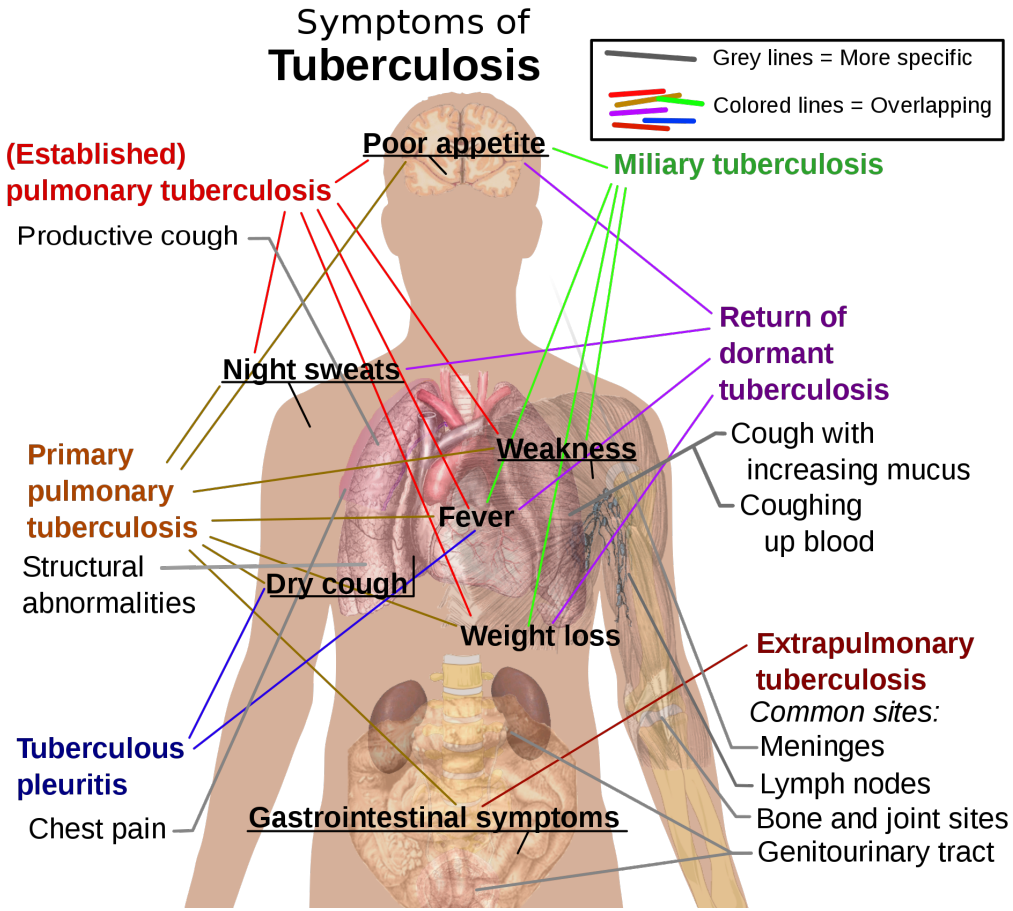
Active TB Clinical presentation:

→Fever, sweats, weight loss.

→Cough If pulmonary with hemoptysis in cases of cavitation (However the absence of hemoptysis should not exclude TB as it usually develops if there was a cavitary lesion).

→Subacute in onset (can be acute in immunocompromised patients).

TB Symptoms



Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014

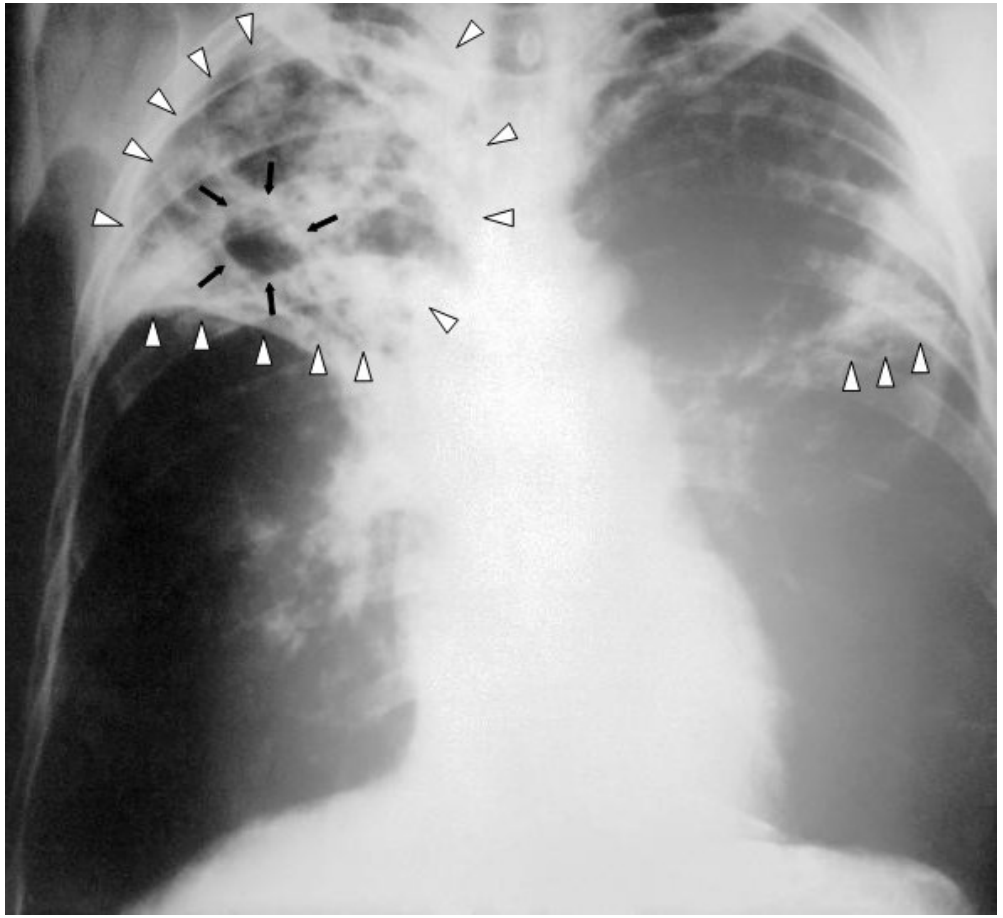
Chest Imaging:

→Upper lobe/Apical cavity is typical with surrounding infiltrate +/- adenopathy.

→Miliary TB is a hematogenous spread TB.

CXR

Bilateral pulmonary infiltrate (white triangles), and „caving formation“ (black arrows) present in the right apical region, in far-advanced TB.



Extrapulmonary TB:

→ TB can virtually affect any organ and any system.
→ It is reasonable to think about when patients do not respond to the typical therapy.
→ It is important to obtain clinical specimens from the site affected for mycobacteriological cultures, PCR, smears and pathology.

→ **Examples of extrapulmonary syndromes:**

1. CNS: Meningitis, focal tuberculomas.
2. Lymphadenitis (Cervical, thoracic, abdominal).
3. Bone and joint:
   - Vertebral (Thoracic- most common, lumbar, anterior wedging, +/- psoas abscess).
   - Osteomyelitis and arthritis.
4. Pleural.
5. Abdominal/ Pelvic:
   - GU: sterile pyuria, can cause infertility.
   - GI: A great mimicker for inflammatory bowel disease.

Contents lists available at ScienceDirect

The Knee

Case report

Miliary tuberculosis with delayed-onset total knee arthroplasty *Mycobacteria tuberculosis* infection successfully treated with medical therapy alone: A case report and literature review

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Author and year	Sex, age in years	Time from TKA to disease	Diagnostic method	Other sites of disease	Medical treatment (months)	Surgical intervention	Outcome at follow-up
[4]						arthroplasty	6 months
Uhel, 2018 [4]	F, 85	14 years	Synovial fluid culture	None	INH/RMP [16], EMB [2], PZA [1]	Resection arthroplasty	Good 2 months
Uhel, 2018 [4]	M, 86	9 years	Synovial fluid PCR	None	INH/RMP/OFX [11], EMB [4]	Resection arthroplasty	Good 3 months
Uhel, 2018 [4]	M, 84	11 years	Synovial tissue PCR and culture	Liver, spleen	INH/RMP [13], EMB [2]	Debridement	Dead
Uhel, 2018 [4]	M, 79	7 years	Synovial fluid culture	Pericardiac, pulmonary, liver	INH/RMP [16] EMB [4] PZA [2]	None	Good 1 year
Veloci, 2018 [31]	F, 34	3 years	Synovial fluid culture	None	INH/RMP [22] EMB/PZA [2]	None	Good, 2 years
Veloci, 2018 [32]	M 62	3 years	Synovial fluid culture and histopathology	None	INH/RMP [22] PZA [2]	None	Good 1 months

Table 1
Cases reported in medical literature of total knee arthroplasty tuberculosis prosthetic joint infection with author name and year published, patients' age and sex, time of onset of disease from total knee arthroplasty, diagnostic method, other sites of disease, type of medical treatment with duration, surgical intervention, and outcome at follow-up duration.

Author and year	Sex, age in years	Time from TKA to disease	Diagnostic method	Other sites of disease	Medical treatment (months)	Surgical intervention	Outcome at follow-up
Besser, 1980 [10]	M, 65	<1 month	Synovial tissue histopathology	None	NM	None	Good 1 year
Bryan, 1982 [11]	F, 72	8 years	Synovial fluid culture	Elbow	INH/RMP/PZA [9]	Arthrodesis	Good 3 years
Zeiger, 1984 [26]	F, 40	4 years	Synovial tissue culture	None	NM	Resection arthroplasty	Good 2.5 months
Wolfgang, 1985 [12]	M, 61	13 months	Synovial fluid culture	None	INH/RMP [9]	Staged exchange	Good 1 year
Wray, 1987 [13]	M, 62	<1 month	Synovial tissue histopathology and culture	Pulmonary	INH/RMP/EMB [16]	None	Good 5 years
Wray, 1987 [13]	M, 63	<1 month	Synovial tissue histopathology and sputum culture	Pulmonary	INH/RMP [16]	None	Good 1.5 years
Eskola, 1988 [14]	M, 47	18 months	Synovial fluid culture	None	INH/RMP/EMB [16]	Debridement	Good 2 years
Gale, 1991 [15]	M, 67	<1 month	Synovial tissue histopathology, sputum culture	Pulmonary	INH/RMP [16], EMB [11]	None	Good 10 years
Spinner, 1996 [16]	M, 79	10 years	NM	None	NM	Revision arthroplasty	NM
Lusk, 1995 [17]	F, 75	15 years	Synovial tissue histopathology and culture	None	INH/PZA [11], RMP [1], EMB [10]	Resection arthroplasty	Died at 6 months
Tokumoto, 1995 [18]	F, 71	20 months	Synovial aspirate culture	None	INH/EMB [22]	Resection arthroplasty	NM
Tokumoto, 1995 [18]	F, 70	38 years	Synovial aspirate culture	None	INH/RMP [16]	Resection arthroplasty	Good 2 years
Spinner, 1996 [19]	F, 70	4 years	Synovial tissue culture	None	INH/RMP/EMB [16]	Debridement	Good 2 years
Al Shaikh, 2003 [20]	F, 73	8 months	Synovial tissue culture	None	INH/RMP/PZA [16] EMB [13]	Debridement, delayed arthrodesis	Good 1 years
Marmor, 2004 [21]	M, 66	2 months	Synovial aspirate and blood cultures	Disseminated	INH/RMP/PZA [11]	Two-stage revision arthroplasty	Good 5 years
Marmor, 2004 [21]	F, 65	3 months	Synovial aspirate culture	Urinary tract	INH/RMP/PZA [11]	Two-stage revision arthroplasty	Good 7 years
Marmor, 2004 [21]	F, 77	4 months	Synovial aspirate culture	None	INH/EMB/PZA [12]	Debridement	Good 1 years
Kadakia, 2007 [22]	F, 85	1 month	Synovial aspirate AFB smear	Lungs	NM	None	Good NM
Khater, 2007 [23]	F, 75	3 months	Synovial tissue histopathology and culture	None	INH/EMB [22] RMP (NM)	Resection arthroplasty	Good 18 months
Wang, 2007 [3]	M, 72	3 years	Synovial tissue culture	lungs	NH/RMP/EMB/PZA [1]	Debridement	Dead
De Haan, 2008 [24]	F, 75	3 months	Synovial tissue culture	None	INH/RMP/EMB/PZA [13]	Debridement	Good NM
Marschall, 2008 [5]	M, 48	9 months	Synovial aspirate culture	Lungs, brain	INH/EMB/PZA [1], MOX (0.5), RMP (0.5)	None	Dead
Lee, 2009 [7]	F, 79	2 months	Synovial tissue histopathology	None	INH/RMP/EMB/PZA [16]	Debridement	Good 13 months
Neogi, 2009 [9]	F, 73	14 years	Synovial tissue PCR	NM	INH/RMP [22], EMB [4], PZA [27]	None	Good 3 years
Klein, 2012 [25]	F, 36	11 months	Synovial tissue culture	None	INH/RMP/EMB/PZA/MOX [23]	Two-stage revision arthroplasty	Good 3 years
Carrega, 2013 [6]	F, 80	<1 month	Synovial tissue histology and culture	None	INH/RMP [18], PZA [2]	Two-stage revision arthroplasty	Dead
Harwin, 2013 [27]	F, 60	7 months	Synovial tissue culture	None	INH/RMP [24], EMB/PZA [16]	Revision arthroplasty	Good 2 years
Tekin Koruk, 2013 [28]	M, 55	20 days	Synovial aspirate culture	None	INH/RMP [16], EMB/PZA [2]	None	Good 18 months
Seng, 2016 [29]	NM	NM	NM	NM	NM	NM	NM
von Keudell, 2016 [30]	M, 84	5 months	NM	None	INH/RMP (> 15), EMB/PZA [16]	Revision arthroplasty (partial)	Good 15 months
Uhel, 2018 [4]	F, 84	3 years	Synovial fluid culture	None	INH/RMP [16], EMB/PZA [2]	None	Good, NM
Uhel, 2018	F, 82	9 years	Synovial tissue culture	None	INH/RMP [19], PZA (0.5)	Resection	Good

Disseminated TB:

→Can present with an acute sepsis like syndrome especially in heavily immunocompromised patients.

→Obtain mycobacterial blood cultures and respiratory specimens.

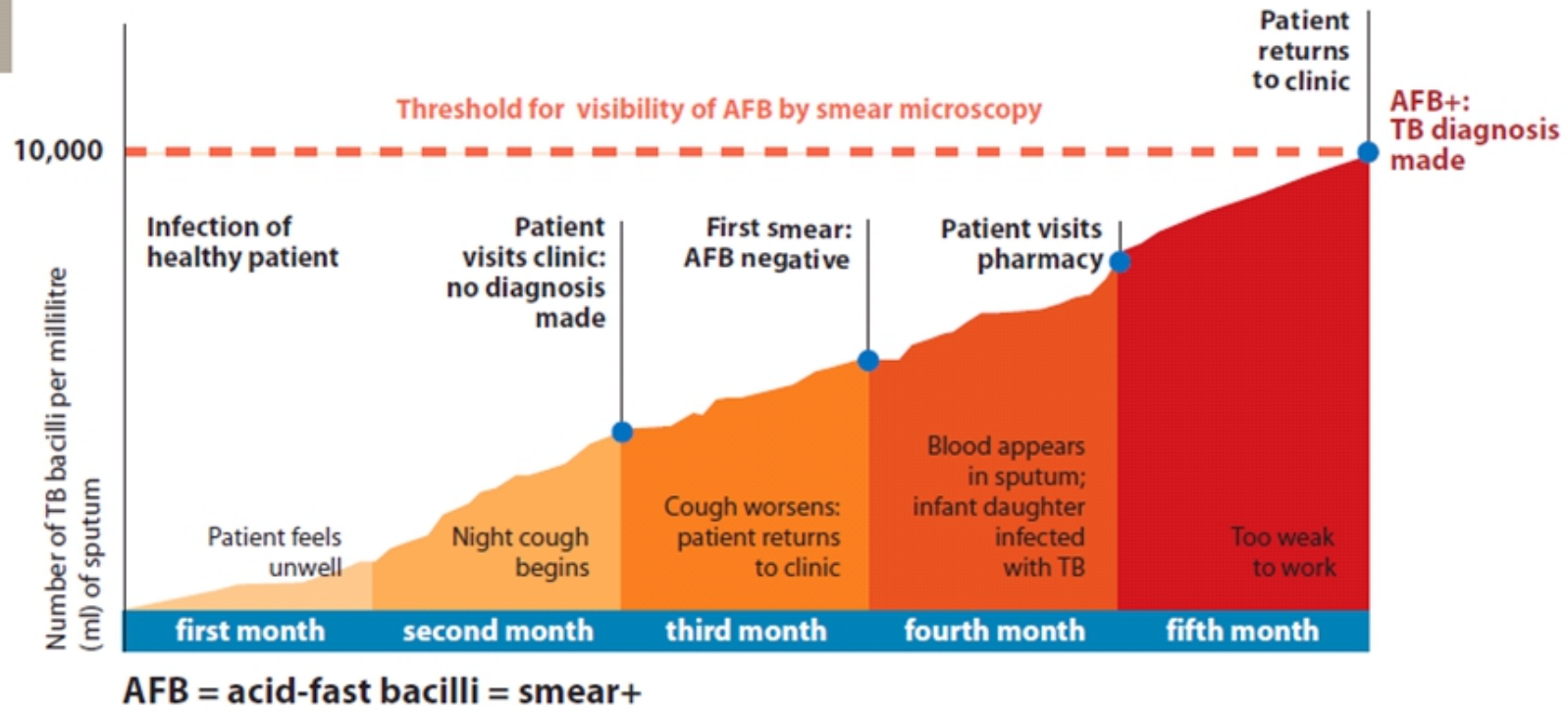
Active TB diagnosis:

→Smear microscopy AFB Stain Ziehl-Neelsen (ZN):

- Has a low sensitivity overall around 50-60% sensitivity in pulmonary TB.
- In pulmonary TB the yield of test is increased with multiple specimens
- Typically we order three sputum samples at least eight hours apart, one early morning.
- Less sensitive in advanced HIV (30-50%).
- Needs 10,000 cfu/ml.
- A negative smear does not exclude the diagnosis of active TB.
- Not specific for MTB (Most *mycobacteria* look alike).
- Good PPV in TB endemic regions.

Figure 6

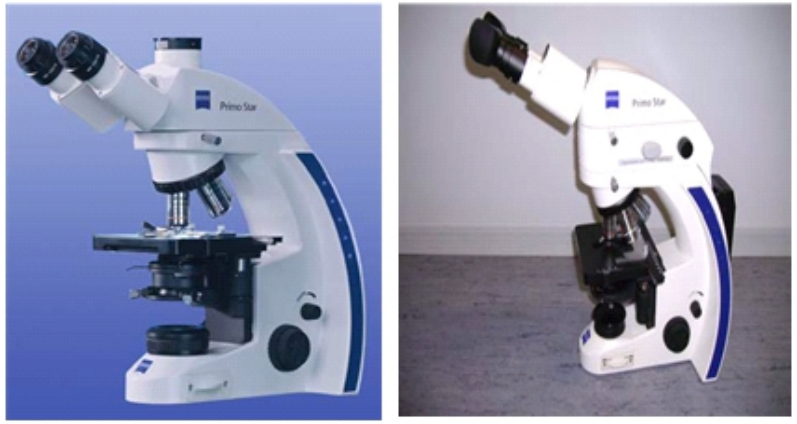
A TB PATIENT'S JOURNEY FROM SYMPTOMS TO DIAGNOSIS



AFB = acid-fast bacilli = smear+

FIND/TDR/WHO

Fluorescent Light Emitting Diode (LED) microscopy



Courtesy: FIND, Geneva

Zeiss PrimoStar iLED

Lumin

LW Scientific

www.lwscientific.com/

Fluorescence microscopy (FM)

- Fluorescence microscopy (FM) detects 10% more TB cases than light microscopy (LM)
- Requires only 25% of the time taken to read a Ziehl-Neelsen (ZN) stained smear
- FM requires equipment that is expensive and non-robust

Fluorescent Light Emitting Diode (LED) microscopy

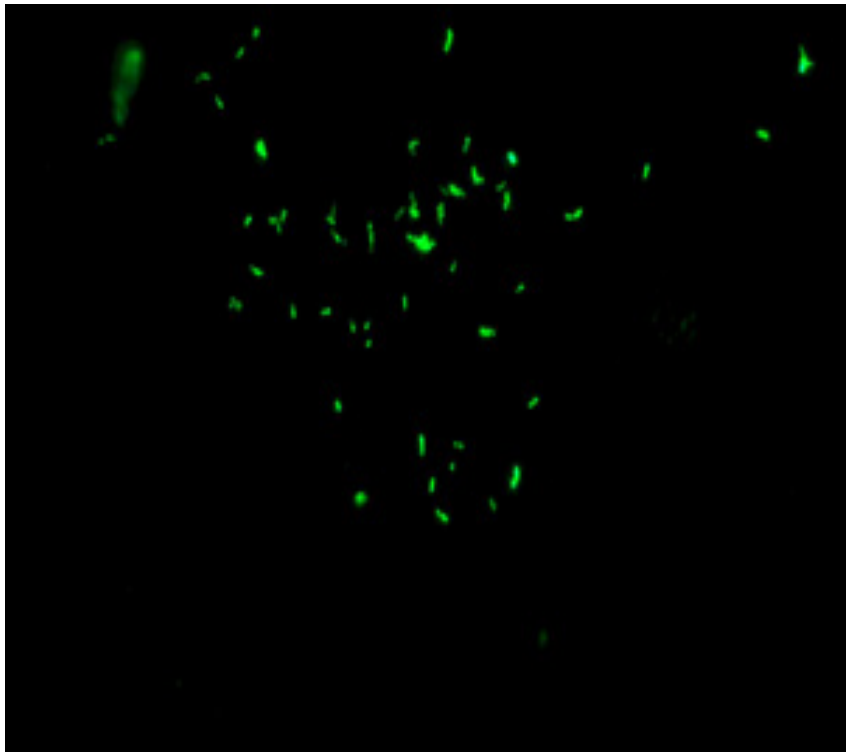
- Inexpensive
- Life span more than 10,000-50,000 hours
- Energy-efficient
- Does not require a dark room
- Can be used for both FM and LM with the flick of switch
- Provides bright and clear images.

Fluorescent Light Emitting Diode (LED) microscopy

- LED microscopy has 93% sensitivity, 99% specificity compared to conventional LM
- LED microscopy is statistically significantly more sensitive by 6% with no loss in specificity, when compared with direct Ziehl-Neelsen microscopy
- LED microscopy is 5% more sensitive and 1% more specific than conventional FM

Fluorescent Light Emitting Diode (LED) microscopy

- WHO recommends that conventional fluorescent microscopy be replaced by LED microscopy
- LED microscopy be phased in as an alternative for conventional ZN light microscopy



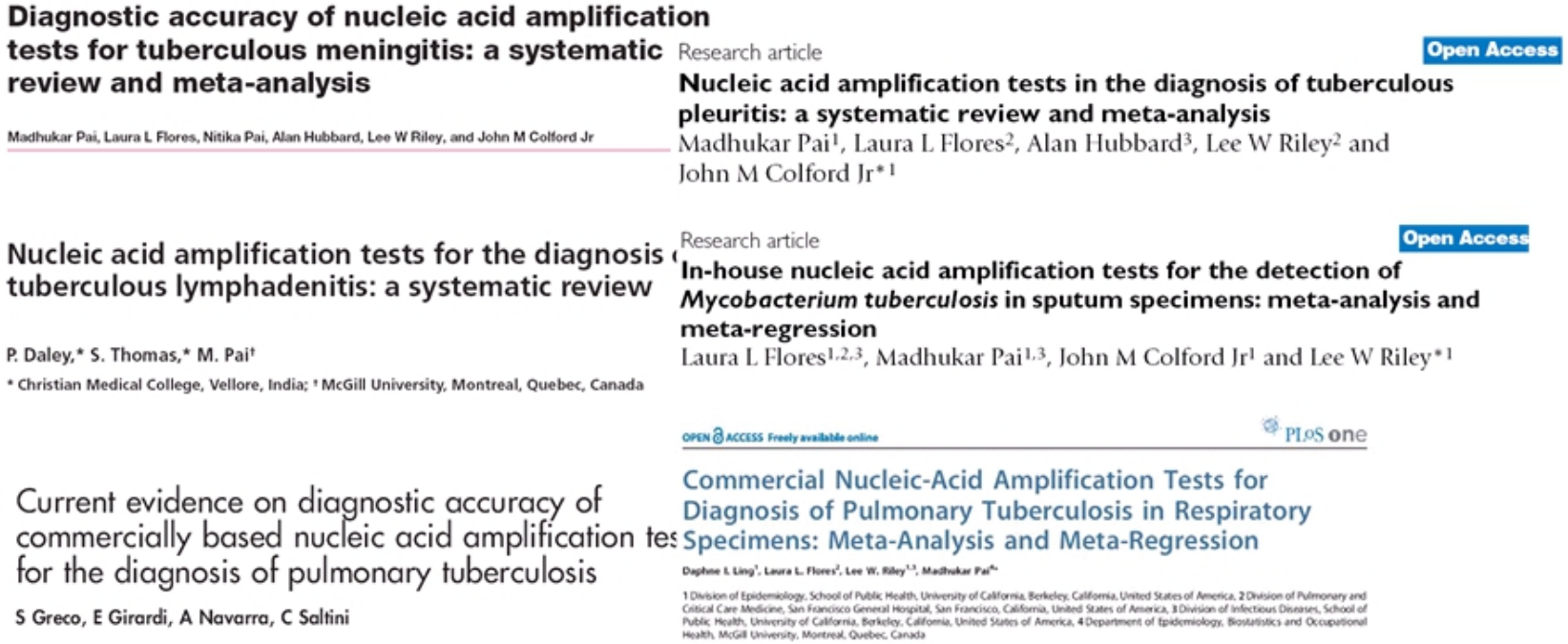
Active TB diagnosis:

→Rapid MTB PCR:

- Needs 100 cfu/ml for detection.
- A negative test does not rule out TB.
- High specificity for MTB.
- PCR based tests are designed to be specific mycobacterial TB and rifampicin resistance.
- Does not detect other *mycobacteria*.
- Does not predict resistance to other anti Tb medications.
- Once the rapid MTB/RIF test is reported as MTB detected RIF undetected this is by definition NOT a multidrug resistant TB.
- The test is validated to be done on sputum but can be done on non-sputum specimen (However can have false negative tests for the presence of inhibitors).

Nucleic acid amplification tests (NAAT)

- NAATs have high specificity and PPV
- Sensitivity is lower and highly variable across studies
  - Sensitivity lower in extra-pulmonary and smear-neg pulmonary TB
  - Negative test does not rule out TB
- Expensive



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Research article

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OPEN ACCESS Freely available online

PLoS one

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Daphne I. Ling[1], Laura L. Flores[2], Lee W. Riley[1,3], Madhukar Pai[4]*

1 Division of Epidemiology, School of Public Health, University of California, Berkeley, California, United States of America, 2 Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, San Francisco, California, United States of America, 3 Division of Infectious Diseases, School of Public Health, University of California, Berkeley, California, United States of America, 4 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

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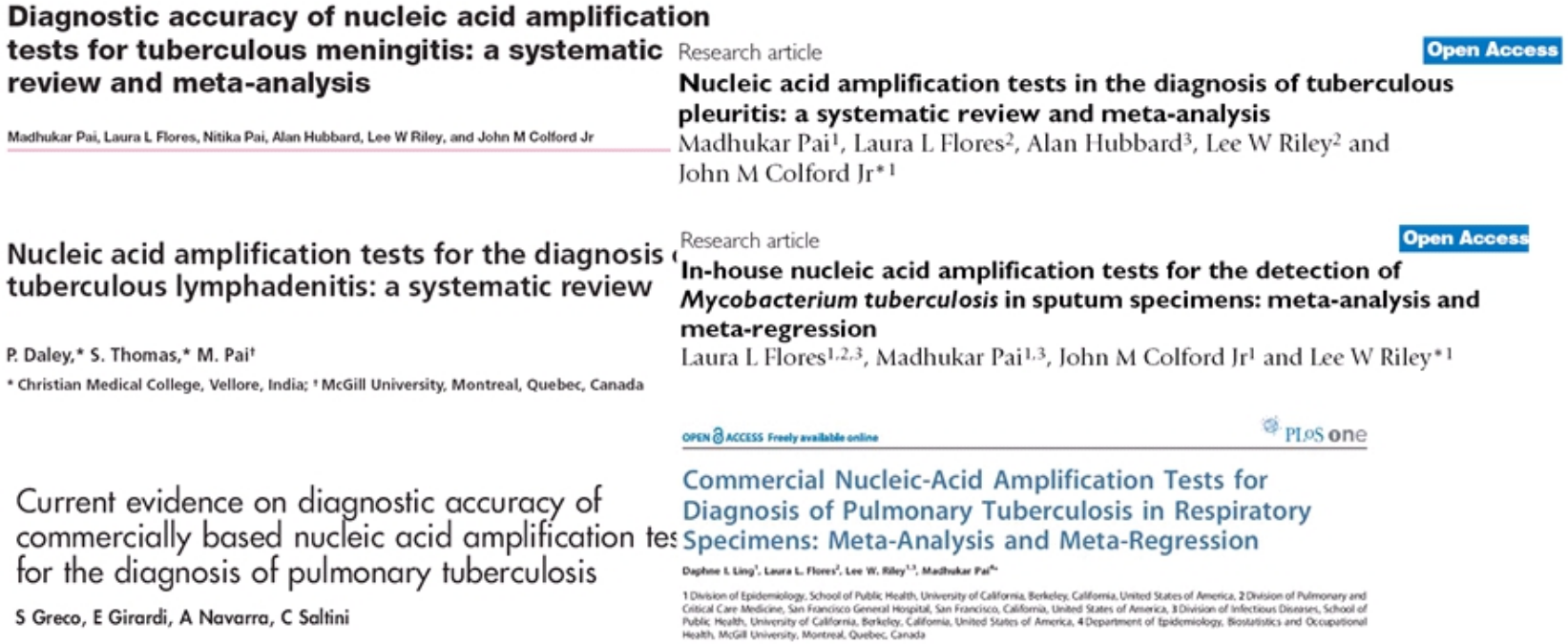

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1 Division of Epidemiology, School of Public Health, University of California, Berkeley, California, United States of America, 2 Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, San Francisco, California, United States of America, 3 Division of Infectious Diseases, School of Public Health, University of California, Berkeley, California, United States of America, 4 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

NAAT: Cepheid GeneXpert

- All steps automated
- Uses cartridges;
  MTB-specific primers
- Result in 2 hours
- Simultaneous drug susceptibility testing (DST)
- Resistance to rifampin uses PCR to amplify an MTB specific sequence of the *rpoB* gene
- In HIV-infected patients it yields up to a 45% increase in tuberculosis case detection compared with smear microscopy

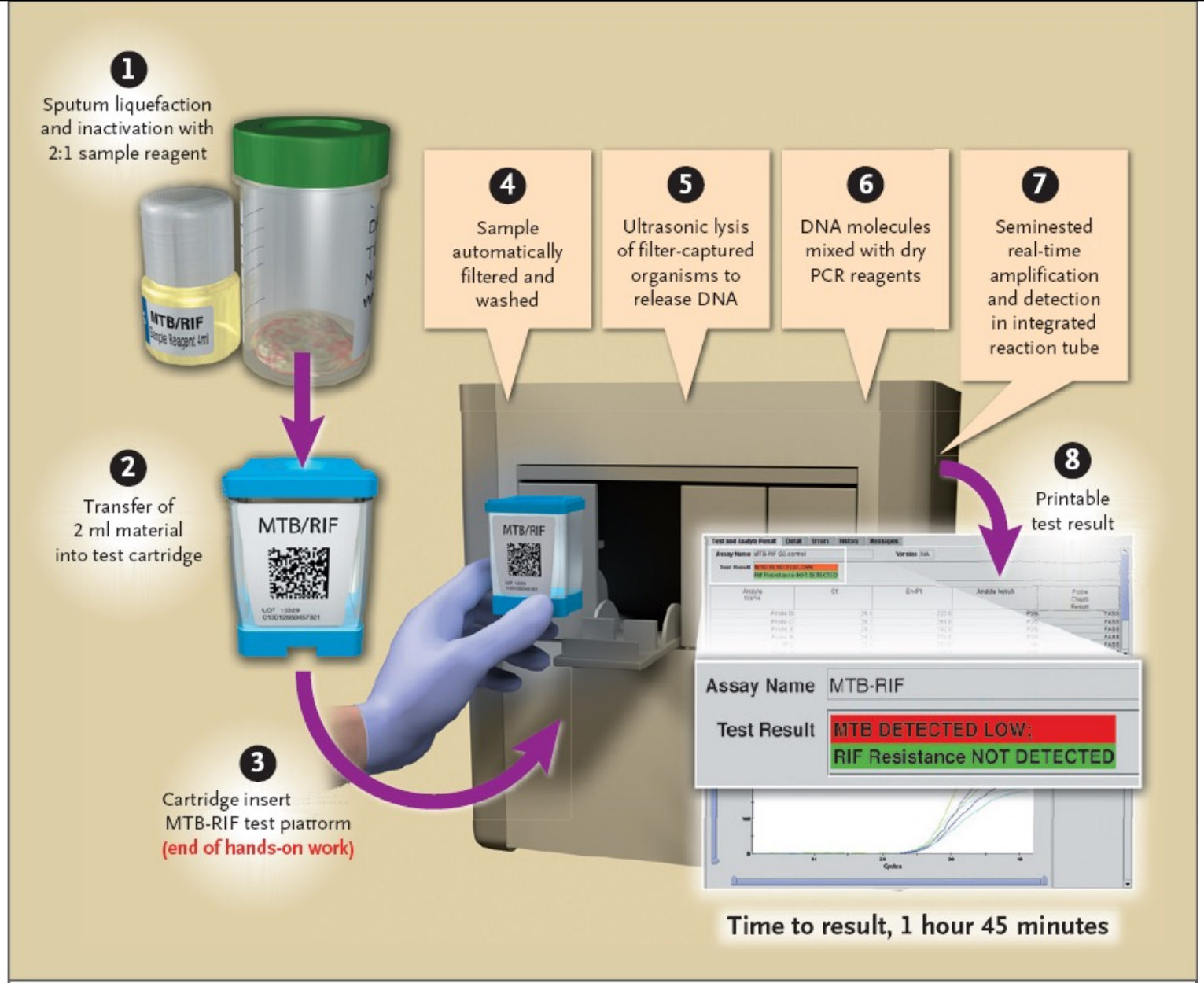

Figure 2. Assay Procedure for the MTB/RIF Test.

Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected; RIF resistance not detected." PCR denotes polymerase chain reaction.

Evaluation of GeneXpert MTB/RIF for detection of Mycobacterium tuberculosis complex and *rpo* B gene in respiratory and non-respiratory clinical specimens at a tertiary care teaching hospital in Saudi Arabia

Ali M. Somily, MD, FRCPC, Mazin A. Barry, MD, FRCPC,

Table 1 - Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Xpert MTB/RIF on various sample types as it compared to mycobacterium culture.

AFB smear	Samples sites	Total	MTB positive culture	Sensitivity	Specificity	PPV	NPV
Smear positive	Respiratory	15	15	100%*	-	100%	-
	Non-respiratory	9	8	100%*	-	88.8%*	-
Smear negative	Respiratory	88	0	-	98.9%#	-	100%
	Non-respiratory	128	3	100%*	100%*	100%	100%

#One sample was false positive GeneXpert, **p*-value <0.05, MTB - Mycobacterium tuberculosis, RIF - rifampin, AFB - Acid-fast bacilli

Active TB diagnosis:

→Culture:

- Has the highest sensitivity.
- Needs 1-10 cfu/ml.
- Mycobacterial culture is the most sensitive however it is a slow method (3-6 weeks).
- The median time for positivity is around 21 days in liquid *Mycobacteria* Growth Indicator Tube (MGIT).
- Once positive, additional tests need to be done to identify the species.
- Considered the gold standard:
  - Pulmonary TB 90-95% sensitive.
  - Extrapulmonary TB much less sensitive.

Culture

- High sensitivity
- But tedious, time-consuming and expensive
- Liquid cultures have emerged as the standard

BACTEC MGIT 960 SIRE kit (Becton Dickinson, Franklin Lakes, New Jersey, USA)

BacT/ALERT MB (bioMerieux Inc., Durham, North Carolina, USA)

VersaTREK system (Trek Diagnostic Systems, West Lake, Ohio, USA)

Liquid Culture

- Liquid culture systems reduce delays in obtaining results to days rather than weeks
  - For DST, delay may be as little as 10 days vs. 28-42 days with solid media
- Liquid systems are more sensitive - increase the case yield by ~10% over solid media
- Liquid systems are, however, more prone to contamination by other micro-organisms.
  - In experienced laboratories, ~5-10% of specimens cannot yield results because of contamination

http://www.who.int/tb/dots/laboratory/policy/en/index3.html

MTB/RIF test

- Culture-positive TB: Overall sensitivity 97.6%
- Smear- and culture-positive sensitivity 99.8%
- Smear-negative and culture-positive 90.2%
- Specificity 99.2%

Table 2. Overall Sensitivity and Specificity of the MTB/RIF Test, According to the Number of Tests per Patient, as Compared with Three Smears and Four Cultures.*

Site and No. of Tests	Sensitivity			Specificity
	All Culture-Positive	Smear-Positive and Culture-Positive	Smear-Negative and Culture-Positive	No Tuberculosis
Site				
Lima, Peru				
Correct — no./total no. (%)	209/211 (99.1)	199/199 (100)	10/12 (83.3)	102/102 (100)
95% CI	96.6–99.7	98.1–100.0	55.2–95.3	96.4–100.0
Baku, Azerbaijan				
Correct — no./total no. (%)	144/149 (96.6)	80/80 (100.0)	64/69 (92.8)	68/70 (97.1)
95% CI	92.4–98.6	95.4–100.0	84.1–96.9	90.2–99.2
Cape Town, South Africa				
Correct — no./total no. (%)	142/148 (95.9)	95/96 (99.0)	47/52 (90.4)	186/189 (98.4)
95% CI	91.4–98.1	94.3–99.8	79.4–95.8	95.4–99.5
Durban, South Africa				
Correct — no./total no. (%)	43/45 (95.6)	30/30 (100.0)	13/15 (86.7)	213/219 (97.3)
95% CI	85.2–98.8	88.6–100.0	62.1–96.3	94.2–98.7
Mumbai, India				
Correct — no./total no. (%)	185/188 (98.4)	162/162 (100.0)	23/26 (88.5)	35/36 (97.2)
95% CI	95.4–99.5	99.7–100.0	71.0–96.0	85.8–99.5
No. of MTB/RIF tests				
3 Samples (2 pellet and 1 direct)				
Correct — no./total no. (%)	723/741 (97.6)	566/567 (99.8)	157/174 (90.2)	604/616 (98.1)
95% CI	96.2–98.5	99.0–100.0	84.9–93.8	96.6–98.9
2 Samples (1 pellet and 1 direct)				
Correct — no./total no. (%)†	1423/1482 (96.0)	1127/1134 (99.4)	296/348 (85.1)	1215/1232 (98.6)
95% CI	94.6–97.1	98.6–99.7	79.7–89.2	97.5–99.2
1 Sample (direct)				
Correct — no./total no. (%)	675/732 (92.2)	551/561 (98.2)	124/171 (72.5)	604/609 (99.2)
95% CI	90.0–93.9	96.8–99.0	65.4–78.7	98.1–99.6

Active TB diagnosis:

- Histopathology:
  - Typically cause a caseating granuloma with a ZN stain for bacilli.
  - The granuloma formation requires a good immune system to form and therefore this histopathological feature may not be present in immunocompromised hosts.

→ PPD and IGRA:

- Do not distinguish latent from active TB.
- Negative test does not rule out active disease.

Active TB treatment:

→ **First line treatment:**

→ Induction phase:

- Rifampin, Isoniazid (Use B6 to prevent neurotoxicity of INH) Ethambutol, Pyrazinamide for two months.
- Continuation phase: Rifampicin + INH for four more months.

→ Extend the continuation phase in the following situations:

- Pulmonary disease if cavitation and culture positive at the end of the second month of treatment (9 months total).
- CNS TB (usually 9-12 months total duration).
- Bone and joint TB (6-9 months total duration).

Active TB treatment

→ **Corticosteroids indicated in:**

- TB meningitis: improved morbidity and mortality.
- TB pericarditis: Previously recommended but recent trials showed no difference in outcome. Can be considered in cases of inflammatory fluid analysis.

→ **General rules:**

- Daily regimen is more efficacious than intermittent (2 or 3 times a week).
- IN HIV positive, intermittent treatment is associated with Rifampin resistance.

ATT side effects:

→ Hepatotoxicity:
- Main ATT: INH, Rif, PYZ.
- INH and pyrazinamide are more hepatotoxic than rifampicin. Ethambutol is the least hepatotoxic of all 4 anti TB.
- Rifampicin mostly causes cholestatic liver derangement.

→ Ethambutol:
- retrobulbar neuritis (Color vision is the first affected, visual acuity will later be affected, unlikely to occur with the doses and duration of therapy given in TB).

→ Rifampin:
- A potent enzyme inducer and decreases the level of other drugs of particular importance warfarin ART (Integrase inhibitor, PI, NNRTI) hormonal contraceptives, corticosteroids.
- Of the four anti TB drugs Rifampicin is the most important and if it was dropped for side effect or intolerance short course (6 months therapy) can no longer be used.

→ PYZ:
- Arthralgias.

→ Aminoglycosides:
- Ototoxicity, vestibular toxicity, nephrotoxicity.

→ Bedaquiline:
- A novel drug with a novel mechanism of action targeting (MTB ATP synthase).
- Approved for pulmonary drug resistant TB when effective therapy cannot be provided.
- QT prolongation is a serious adverse effect of the medication.
- Has a long half-life 4 months.

Summary of ATT mechanism of action/resistant/ common side effec

Drug	Mechanism of action	Mechanism of resistance	Dose	Side effect
Isoniazid	Inhibits mycolic acid synthesis. Penetrates well even to the brain.	Loss of katG overexpression. Alteration in inhA encoded reductase.	5 mg/kg/day Maximum dose: 300	Hepatotoxicity. Peripheral neuropathy.
Rifampin	Inhibits DNA dependent RNA polymerase, blocking RNA transcript	rpoB (RNA polymerase subunit beta) mutation.	10 mg/kg/day Maximum dose: 600.	Rash. Hepatoxicity. Thrmobocytopenia Potent enzyme inducer.
Ethambutol	Inhibits arabinosyl transferase enzyme which will inhibit cell wall arabinogalactan and lipoarabinomannan.	embB gene mutation causing enzymatic alteration in ethambutol binding site.	15 mg/kg/day	Optic neuritis. Peripheral neuritis. Hepatotoxicity.
Pyrazinamide	Unknown. Pyrizinoic acid lowers the PH below the level necessary for mycobacterial growth.	pncA gene mutation. M. Bovis and M. Leprae are intrinsically resistant.	20 mg/kg/day	Hepatotoxicity. Asymptomatic hyperuricemia. Polyarthralgia.
Bedaquiline	Inhibits ATP synthetase by binding to subunit c. Prevents mycobacterium from ATP synthesis and eventually lead to cell death.	Point mutation in the atpE gene, efflux pump. mmpR mutation.	400 mg daily for 14 days followed by 200 mg thrice weekly to complete 24 weeks.	QTc prolongation.

Resistance

- Risk factors for drug resistant TB:

→ Contact with a known case of drug resistant TB.

→ Previous history of treatment especially if the patient was non adherent.

→ Travel to an area known to have drug resistant TB (Eastern Europe).

- Definitions:

→ MDR TB: Resistance to ***both*** Rifampin ***and*** INH.

→ XDR TB: MDR plus resistance to fluroquinolones plus at least one of the injectable 2nd line drugs (Amikacin, kanamycin, capreomycin).

HIV and TB considerations:

→ HIV increases the risk of progression from latent to active TB.
→ CD4 influences the severity and clinical manifestations of TB.
→ TB can increase HIV viral load.
→ TB is associated with more rapid progression of HIV.
→ In HIV patients it is less likely to see a cavitary lung disease.
→ With advancing immunosuppression there is increased risk for:
  - Smear negative pulmonary TB.
  - Extrapulmonary TB +/- Pulmonary disease.
  - CNS TB.
  - Widely disseminated TB/ Mycobacteremia.
→ A negative CXR and a negative smear does not exclude TB.

- Extrapulmonary TB, CNS TB and widely disseminated TB are the usual forms in advanced HIV.

HIV- TB treatment:

→ Despite the drug-drug interaction rifampicin cause, a rifamycin based therapy is still the preferred regimen.
→ ART guidelines recommend efavirenz based combination with higher doses of integrase inhibitors.
→ Rifampin:
- Accelerate clearance of PI, NNRTI, INSTI, CCR5 inhibitors.
- Integrase inhibitor: Need to give BID dosing.
- TAF: If used need to closely monitor HIV viral load while on therapy.
- Should not combine PI with Rifampin.

→ Rifabutin:
- Weaker enzyme inducer than rifampin.
- A CYP450 substrate (Rifabutin metabolism affected by NNRTI and PIs).
- If a PI based ART will be used decrease the Rifabutin dose to 150 mg daily or 300 mg every other day.

→ When to start ART:
- CD4< 50: Within 2 weeks of starting TB treatment.
- CD4> 50: Within 8 weeks of starting TB treatment.
- HIV infected pregnant women with active TB should be started on ART as soon as feasible (For maternal health and Prevention of mother to child transmission).
- In TB meningitis ART should not be given until after 8 weeks of anti TB medications.

Immune reconstitution inflammatory syndrome (IRIS):

- **Two forms:**
  - Paradoxical worsening of TB when ART is started after TB treatment.
  - Unmasking TB when ART started in setting of not yet recognized TB.
- Typically occurs 2 weeks to 3 months after starting ART.

- **Risk Factors:**

1. CD4< 50.
2. High pre-ART viral load.
3. Severe TB.
4. Short interval between initiation of TB treatment and ART.

- **Protean manifestation:**

- Fever, new lesion, extension of prior lesions.

- **Management approach in IRIS:**

- Deal promptly with any limited space issue: CNS inflammation, obstructing adenopathy), corticosteroid, surgery if needed.
- Consider other differential diagnosis:
- Give NSAID in mild cases.
- Give corticosteroids in more severe and refractory cases: Prednisone 1.5 mg/kg/day for two weeks then 0.75 mg/kg/day for two weeks.
- Continue both TB plus ART.

TB in transplant recipients:

→ Transplant associated immunosuppression increases the risk of active TB disease if the person is infected.

→ Presents atypically and therefore diagnosis is delayed:

- One third to half is disseminated or extrapulmonary.
- The ability of granuloma formation is lost by immunosuppression and therefore patients are unable to contain the infection and they rapidly progress and disseminate.
- 4% are thought to be donor derived.

→ Can rapidly progress and carry high mortality.

→ Small proportion are donor derived.

→ There is a drug-drug interaction with:

- MTOR inhibitors (Sirolimus/everolimus).
- Calcineurin inhibitors (Cyclosporin, tacrolimus).
- Frequent drug levels of calcineurin and MTORs is advised.
- Corticosteroid and hence they are at risk for graft rejection.

→ Rifabutin based regimen is preferred to minimize interaction.

TB and TNF alpha inhibitor inhibits:

→ TNF alpha inhibitors markedly increase the risk of active TB if infected.
→ Can present with atypical TB (e.g., non-cavitary pulmonary disease, extrapulmonary disseminated).
→ Increased TB morbidity and mortality.
→ Full monoclonal IgG1 monoclonal antibody most potent (i.e., infliximab, adalimumab, golimumab).
→ It is recommended to do a PPD or IGRA prior to starting anti TNF:
- If any is positive, patient should be started on latent TB management before starting therapy (2-8 weeks).

Latent TB:

→ Tuberculin skin test:
→ A mix of antigens.
→ It is a delayed type IV hypersensitivity reaction.
→ Intradermal inoculation, measure induration at 48-72 hours (positive reaction lasts a few days).
→ Adjunctive in the diagnosis of TB.
→ False positive results may be seen with NTM or prior BCV vaccine or NTM.
→ A booster effect can be mistaken for positive PPD test:
  - TST maybe initially negative if there is a remote history of infection. However, TST stimulates immune response to MTB antigens and a subsequent TST can be positive and mistaken for seroconversion.
  - For that a 2 step TST for individuals who may be tested periodically (e.g., HCW).

- Cutoffs are based on likelihood of true exposure, risk of progression to active TB if infected (5 mm; 10 mm; 15 mm)

46 - Tuberculosis in Normal and Abnormal Hosts (Dorman)

Latent TB infection (LTBI): classification of tuberculin skin test results

≥ 5 mm is POS	≥ 10 mm is POS	≥ 15 mm is POS
HIV-infected Recent TB contact CXR with fibrotic changes Organ transplantation Prednisone ≥ 15 mg/d x 1 month or more TNF alpha antagonists	Recent arrival (w/in 5 years) from TB high prevalence area Injection drug use Residents & employees of high-risk settings (HWC, corrections, homeless shelters) Mycobacteriology lab staff Children < 5 years old Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel bypass, solid organ transplant, CA head and neck	Persons with no known risk factors for TB

Interferon gamma release assays- IGRA:

→ Two tests are currently available: QuantiFERON-TB; T-SPOT.TB.
→ Blood based, in vitro stimulation of WBC with protein antigens specific for M. TB.
→ The advantage of IGRA over PPD is that there is no cross reactivity with BCG vaccine.
→ IGRA is as sensitive as PPD but more specific.
→ *M. Kansasii* and *M. Marinum* can cause a false positive IGRA.
→ It might be negative in immunocompromised.

Latent tuberculosis infection among health-care workers using Quantiferon-TB Gold-Plus in a country with a low burden for tuberculosis: prevalence and risk factors

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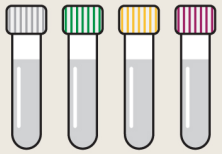
Health-care workers in general wards, ER, and ICU have greater risk of TB infection than workers in other areas

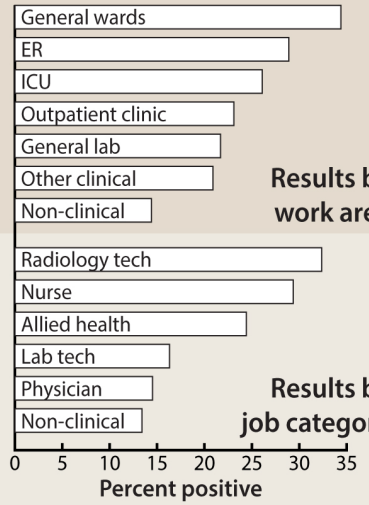
Analysis of latent tuberculosis infection at a hospital in Riyadh using QuantiFERON-TB Gold Plus



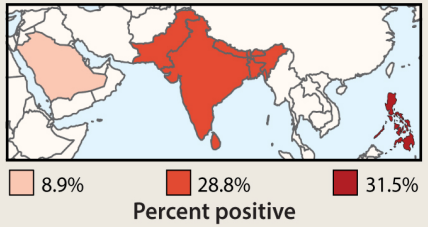
Cross-sectional analysis
3024 health-care workers (HCWs)

Case-control analysis
294 positive cases, 294 controls

24% of all HCWs tested positive



Results by region of origin



Independent predictors for positive test

	adjusted OR (95% CI)
Age > 50 years	2.96 (1.56, 5.62)
Known TB exposure	1.97 (1.41, 2.76)
No BCG vaccination at birth	3.08 (1.18, 8.05)

A. Almohaya, *et al.*, Latent tuberculosis infection among health-care workers using Quantiferon-TB Gold-Plus in a country with a low burden for tuberculosis: prevalence and risk factors. *Ann. Saudi Med.* 2020; 40(3): 191-199 DOI: 10.5144/0256-4947.2020.191.

Management of latent TB:

→ Excluding active TB is a key component of the diagnosis of latent TB infection:
- Review of system: Fever, weight loss, cough, night sweats, focal signs/symptoms that could be associated with extrapulmonary TB).
- Chest X-ray to exclude occult pulmonary TB.

→ **Regimens for latent TB include:**

- Preferred:

1. INH + Rifapentine once weekly for 12 doses.
2. Rifampin daily for 4 months.
3. INH+ Rifampin daily for 3 months.

- Alternative:
  - INH daily for 6 or 9 months.

- Rifampin + PYZ is NO longer used because of the risk of hepatotoxicity.
- Perform LFTs prior to treatment in adults with risks for hepatotoxicity (Ethanol, risk for viral hepatitis, other hepatotoxic medications).
- Monthly review of systems for adverse effects:
  - Peripheral neuropathy if on INH (Can be avoided by B6 supplements).
  - Hepatotoxicity (Nausea/vomiting, abdominal discomfort, jaundice).

BCG vaccine:

→ Live attenuated vaccine (from M. Bovis).

→ Neonatal vaccination:

- Decreases the incidence of severe forms of childhood TB.
- No very limited impact on adult TB.
- Regional lymphadenitis can occur after vaccination, typically no treatment is indicated.
- Disseminated infection can occur in immunocompromised (Treatment is needed).

→ Immunotherapy for bladder cancer:

- Intravesicular administration.
- Complications:
  - Granulomatous prostatitis or hepatitis, epididymitis-orchitis, spondylitis, psoas abscess, military pulmonary, disseminated/sepsis.
  - Contemporaneous with BCG treatment or up to years later.
    -
- Treatment:
  - Inherent resistance to PZA.
  - Treat with rifampin+ INH + Ethambutol.