General Infectious Diseases

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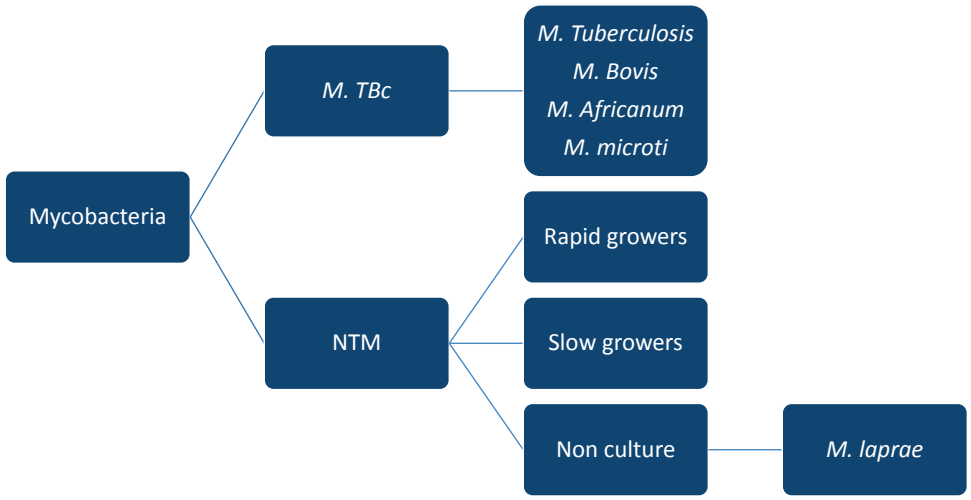
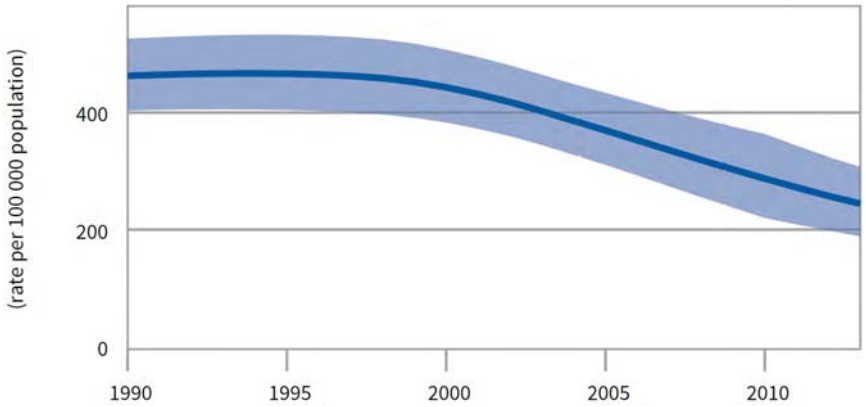


Mycobacterium tuberculosis

Epidemiology

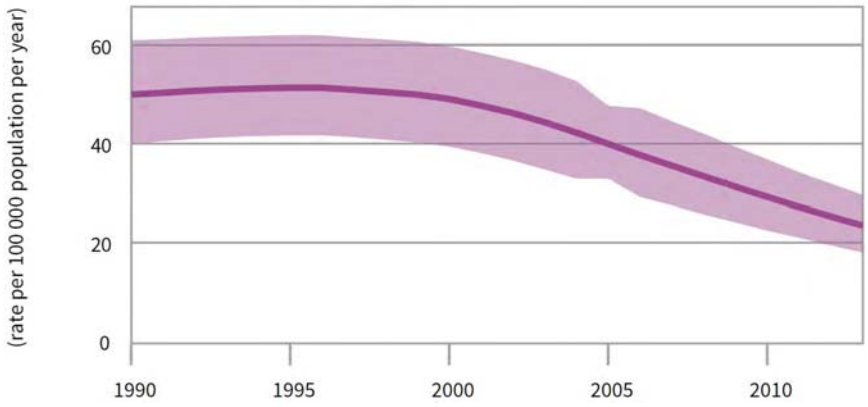
- Currently more than one-third of the world's population is infected with *M. tuberculosis*
- TB causes an estimated 8 million new cases and 2-3 million deaths annually worldwide

Prevalence in South-East Asia



www.who.int/tb/data Global Tuberculosis Report 2014

Mortality (excludes HIV+TB)



www.who.int/tb/data Global Tuberculosis Report 2014

WHO South-East Asia Region

Estimates of TB burden 2013		
	Number (thousands)	Rate (per 100,000 population)
Mortality (excludes HIV+TB)	440 (330–550)	23 (18–30)
Mortality (HIV+TB only)	48 (42–55)	2.6 (2.2–3)
Prevalence (includes HIV+TB)	4,500 (3,500–5,700)	244 (188–307)
Incidence (includes HIV+TB)	3,400 (3,200–3,600)	183 (175–192)
Incidence (HIV+TB only)	170 (150–190)	9 (8.1–10
Case detection, all forms (%)	62 (59–65)	

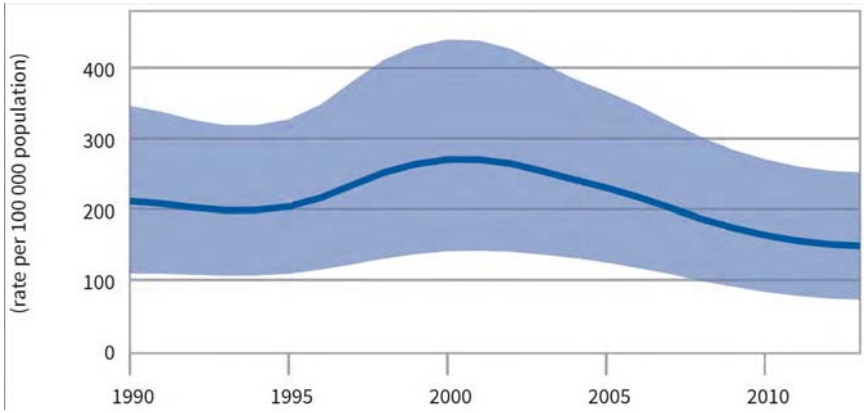
www.who.int/tb/data Global Tuberculosis Report 2014

WHO South-East Asia Region

Estimates of MDR-TB burden 2013		
	New	Retreatment
% of TB cases with MDR-TB	2.2 (1.8–2.7)	16 (12–20)
MDR-TB cases among notified pulmonary TB cases	36,000 (29,000–44,000)	53,000 (41,000–66,000)

www.who.int/tb/data Global Tuberculosis Report 2014

Prevalence in Thailand



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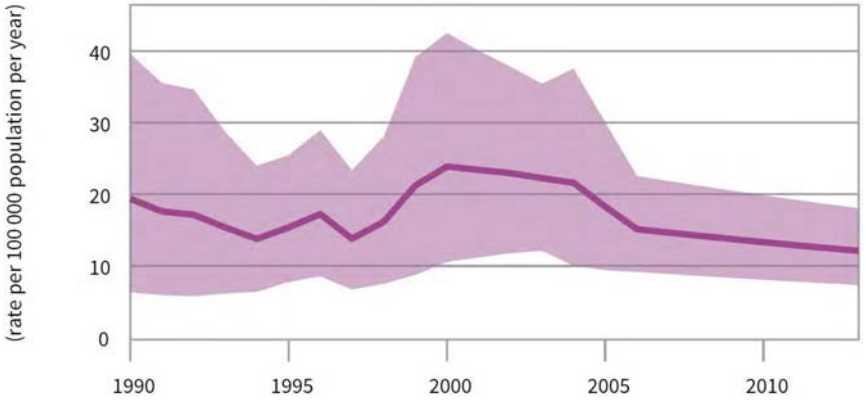
Mortality (excludes HIV+TB)



www.who.int/tb/data Global Tuberculosis Report 2014

WHO Thailand, 67 million

Estimates of TB burden 2013		
	Number (thousands)	Rate (per 100,000 population)
Mortality (excludes HIV+TB)	8.1 (4.9–12)	12 (7.3–18)
Mortality (HIV+TB only)	1.9 (1.3–2.4)	2.8 (2–3.6)
Prevalence (includes HIV+TB)	100 (48–170)	149 (72–252)
Incidence (includes HIV+TB)	80 (71–90)	119 (106–134)
Incidence (HIV+TB only)	12 (10–13)	17 (15–19)
Case detection, all forms (%)	80 (71–89)	

www.who.int/tb/data Global Tuberculosis Report 2014

WHO Thailand

Estimates of MDR-TB burden 2013		
	New	Retreatment
% of TB cases with MDR-TB	2 (1.4–2.8)	19 (14–25)
MDR-TB cases among notified pulmonary TB cases	1,000 (730–1,500)	880 (640–1 200)

www.who.int/tb/data Global Tuberculosis Report 2014

Tuberculosis (TB)

- **Synonyms**
- Consumption (pulmonary TB)
- Pott's disease (TB of the spine)
- **Causative organisms**
- *Mycobacterium tuberculosis* (common)
- *M. bovis* (rare)
- *M. africanum*, *M. microti*(rare)

Mode of Spread

- Inhalation of droplet nuclei
- Pulmonary tuberculosis
  - Aerosolized by coughing, sneezing, or talking
- *M. bovis* from ingestion of contaminated milk
- Skin inoculation of *M. tuberculosis* from contamination of an abrasion occurs in pathologists

Modified from Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Edition

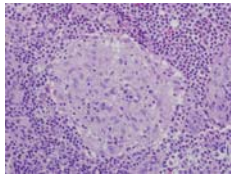
Immunology

- Cellular immune response
- An effective immune response relies on
  - CD4+ T cells
  - Cytokines interleukin (IL)-12
  - Interferon-γ
  - Tumor necrosis factor (TNF)
- *M. tuberculosis* multiply in alveolar spaces or within alveolar macrophages
- Several strategies to survive within macrophage
  - Antioxidants that detoxify reactive oxygen species

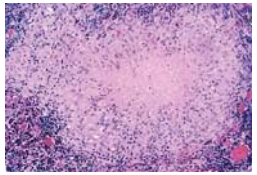
Modified from Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Edition

Immunology

- Small Ag load & High tissue hypersensitivity
- Lymphocytes, macrophages, Langhans giant cells, fibroblasts, and capillaries
- Granuloma formation



- Incomplete necrosis
- Solid or semisolid acellular material
- *Caseous* because of its cheesy consistency



Modified from Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Edition

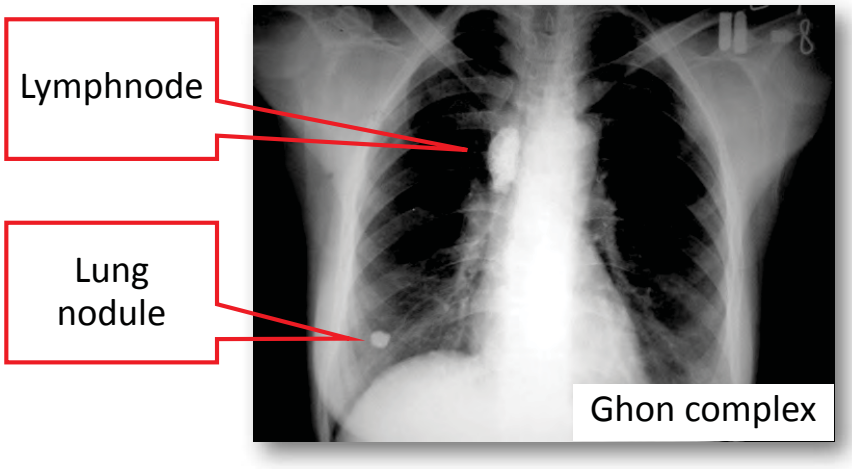
Pathogenesis of 4 stages

First stage

- 3 to 8 weeks
  - inhaled aerosols becomes implanted in alveoli
- Disseminated by the lymphatic circulation to regional lymph nodes in the lung
- Forming the so-called primary or Ghon complex
- Conversion to tuberculin reactivity

Isaar smith, Clin Microbiol Rev. 2003 Jul; 16(3): 463–496

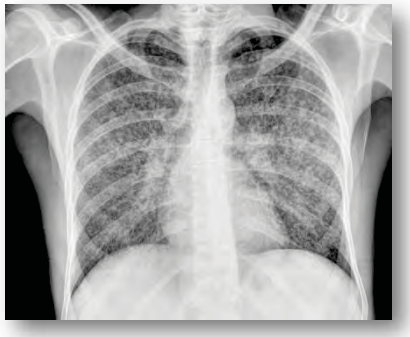
Primary TB infection



Pathogenesis of 4 stages

Second stage

- 3 months
- Hematogenous circulation
- Other parts of the lung
- Tuberculosis meningitis
- Miliary tuberculosis



Isaar smith, Clin Microbiol Rev. 2003 Jul; 16(3): 463–496

Pathogenesis of 4 stages

Third stage

- 3 to 7 months up to 2 years
- Pleurisy or inflammation of the pleural surfaces
- Severe chest pain
- Hematogenous dissemination or the release of bacteria into the pleural space
- Sensitized CD4+ T cells
  - proliferate and release inflammatory cytokines

Isaar smith, Clin Microbiol Rev. 2003 Jul; 16(3): 463–496

Pathogenesis of 4 stages

Fourth stage or resolution of the primary complex

- Disease does not progress
- Up to 3 years
- Slowly developing extrapulmonary lesions
  - e.g, those in bones and joints
- Most humans who are infected with TB do not exhibit progression of the disease

Isaar smith, Clin Microbiol Rev. 2003 Jul; 16(3): 463–496

Pathogenesis of 4 stages

- One-third of exposed HIV-negative individuals become infected
  - 3 to 5% develop TB in the first year
- An additional 3 to 5% develop TB later in their lives
- Most adult TB in non-HIV-infected patients
  - Reactivation
- HIV-positive
  - 50% chance of developing reactivation TB at some time in their lives
- Adult TB in HIV-infected patients
  - Pulmonary and is associated with differing degrees of lung

Isaar smith, Clin Microbiol Rev. 2003 Jul; 16(3): 463–496

Clinical Features

- Person-to-person transmission occurs by inhaled airborne particles 1-5 µm in diameter
- The probability that transmission will occur is related to:
  - Infectiousness of person with TB
  - Environment in which exposure occurred (e.g., close quarters)
  - Duration of exposure
  - Virulence of the organism

Clinical Features

- Primary TB is usually a self-limited
  - Undiagnosed
- Bacillemia and seeding of other organs sets the stage for reactivation in extrapulmonary sites
- TB symptoms are nonspecific and may be absent

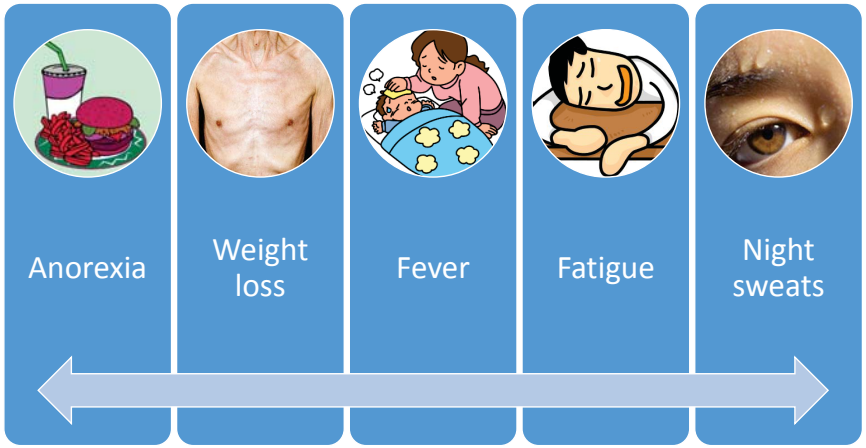
1. Batungwanayo J, et al. *Am Rev Respir Dis* 1992;146:53-6
2. Jones BE, et al. *Am Rev Respir Dis* 1993;148:1292-7
3. Cain KP, et al. *N Engl J Med.* Feb 25 2010

Conditions Increase Risk of TB

HIV (~10% each year)	IDU	Recent infection	Abnormal CXR (untreated)
Diabetes	Silicosis	Prolonged use of steroid	Anti TNF α, e.g., infliximab
Head and neck cancer	Hematologic diseases	ESKD	Intestinal bypass or gastrectomy
	Chronic malabsorption syndromes	LBW (> 10% IBW)	

1. Batungwanayo J, et al. *Am Rev Respir Dis* 1992;146:53-6. 2. Jones BE, et al. *Am Rev Respir Dis* 1993;148:1292-7
3. Cain KP, et al. *N Engl J Med.* Feb 25 2010

Classic Systemic Symptoms



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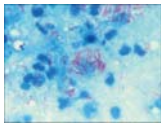
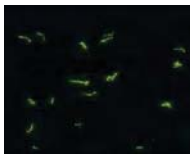
Organ-specific Symptoms of TB

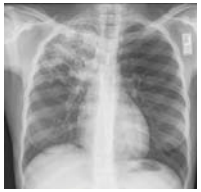
Pulmonary TB	Extrapulmonary TB
• Productive, prolonged cough • Pleuritic chest pain • Hemoptysis	• HIV infection • Immunosuppression • Lymph nodes, pleura, and bones or joints • Genitourinary system, central nervous system, abdomen, pericardium, • Miliary TB

Diagnosis

- Clinical and signs
- Lungs, lymph nodes, and CSF
  - AFB staining, TB culture (gold standard)
  - Fluorochrome staining with auramine-rhodamine
  - PCR
  - Histology
- CXR
  - Pulmonary involvement is common
- Immunological screening
  - TST and IGRA
  - Unusual situation and not rule out if test negative







Diagnosis

- Sputum (pus/tissue) for AFB smear and culture
- HIV negative patients
  - Smear x 1 = 63%
  - Smear x 2 = 84%
  - Smear x 3 = 86%
- More severe immunodeficiency
  - Sputum smear/culture become less sensitive
  - Yield of smear/culture from extrapulmonary sites are higher
- Nucleic acid amplification
  - Identify *M. tuberculosis* in new cases with smear positive
  - Especially high incidence of NTM
  - HIV, TB lymphadenitis in children

1. Smith L, et al. *Chest* 1994; 106:684-6
2. Karen S, et al. *Lancet Infect Dis* 2006; 6:664-674

Diagnosis of Active Tuberculosis

Diagnosis	Advantages	Limitations
Culture on solid media (Lowenstein-Jensen egg-ased or Middlebrook agar-based media)	• Gold standard	• Visible growth takes 3-8 weeks
Culture in liquid broth	• Sensitivity and specificity similar to solid media • Automated systems	• Does not show colony morphology, detect mixed cultures
Acid-fast stain	• Same-day results • Simple technology • Inexpensive	• Less sensitive than culture, requiring 10,000 organisms/mL • Cannot distinguish *M. TBc* from others
Nucleic acid amplification with GeneXpert MTB/RIF	• Sensitivity nearly approximates culture • 100 minutes • detects rifampin resistance mutations	• Expensive equipment; • Detects dead bacilli • susceptibility testing

Modified from Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Edition

Latent TB Infection

- Prevalence of latent infection is high
  - e.g., foreign-born persons from endemic area
- Risk of reactivated disease is high
  - e.g., patients with HIV infection or diabetes and patients receiving immunosuppressive therapy
- Both factors
  - e.g., recent contacts of patients with tuberculosis

Zumla A, et al. N Engl J Med. 2013 Feb 21;368(8):745-55

Tuberculin Skin Test, TST

TST induration	Interpretation
5 mm induration	• HIV-infected individuals • Recent contacts of active TB case • Old healed TB • Transplant patients • Chronic liver or renal failure patients • Immunosuppressed patients
10 mm induration	• Foreign born from high TB endemic regions • IV drug abusers • Laboratory or health personnel • Staff and residents of high congregate settings • Children less than 5 years or active TB case in the family
15 mm induration	• All cases

- TST is negative in at least 20% of active tuberculosis cases

Zumla A, et al. N Engl J Med. 2013 Feb 21;368(8):745-55

Culture and Drug Susceptibility Testing

- Solid or liquid cultures
  - differentiation of the *M. tuberculosis* complex from NTM
- Phenotypic DST (conventional DST)
  - Can be performed as direct or indirect tests on solid media or in liquid media
- Genotypic DST
  - Molecular LPA and the Xpert MTB/RIF

http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

Limitations of DST

- First-line DST
  - Most reliable for rifampicin and isoniazid
  - Less reliable and reproducible for streptomycin, ethambutol and pyrazinamide
  - Pyrazinamide testing can only be performed on liquid media after appropriate pH adjustment
- Second-line DST
  - Amikacin, kanamycin, capreomycin, fluoroquinolones
  - Other drugs; limited data, no standardized, no correlating with clinical outcome

http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

Xpert MTB/RIF

- In 2010, WHO endorsed the Xpert MTB/RIF assay
- Real-time PCR
  - *M. tuberculosis* complex with rifampicin resistance directly from sputum specimens
- < 2 hours
- Test of MDR-TB or HIV associated TB

http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

Line Probe Assays(LPA)

- Endorsed by WHO in 2008
- Rapid detection of resistance to rifampicin (alone or in combination with isoniazid)
- AFB smear-positive sputum specimens or on *M. tuberculosis* isolates grown by conventional culture methods

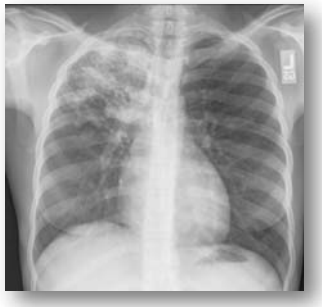
http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

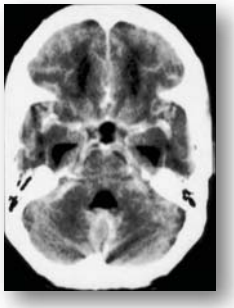
Radiology Features

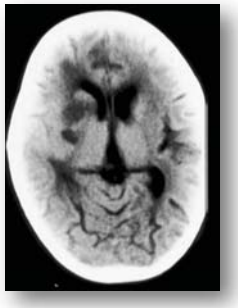
Chest radiograph

- Patchy or nodular infiltrates
  - Apical or posterior segments of upper lobe, or Superior segments of lower lobe
- Early chronic TB is likely if the above findings are:
  - Bilateral
  - Associated with cavity formation
- Cavities may be more apparent by CT or MRI

Imaging findings







- Enhancement in the basal cistern and meninges, dilatation of the ventricles, hydrocephalus
- Infarction from vasculitis

Risk factors for drug-resistant TB

- History of treatment with TB drugs
- Contacts of persons with drug resistant TB
- Foreign-born persons from high prevalence drug resistant areas
- Smears or cultures remain positive despite 2 months of TB treatment
- Received inadequate treatment regimens for >2 weeks
- Co-morbid conditions associated with malabsorption or rapid-transit diarrhoea

http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

Treatment of TB Disease

Basic principles of treatment

- Provide safest, most effective therapy in shortest time
- Use multiple drugs to which the organism is susceptible
- Never add just a single drug to a failing regimen
- Ensure adherence to therapy with case management and directly observed therapy
- Directly observed therapy (DOT)

Treatment

- 6 months: 2HRZE/4HR
  - Pulmonary TB & positive culture at 2 months: 9 months
  - Bone and joint infection: 6-9 months
  - CNS including meningitis: 9-12 months
  - DOTs should be implemented especially during first 2 months
- Prolonged treatment (up to 9 months) if
  - delayed clinical response
  - delayed micrological response

CDC 2014, http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb

Factors contributing to poor TB treatment outcomes

Heath care provider: Inappropriate treatment	Drugs: Inadequate supply/quality	Patients: Inadequate intake or response
• Inappropriate guidelines • Non-compliance with guidelines • Absence of guidelines • Poor training • Financial disincentives • Poor patient education • No monitoring of treatment • Poor management of S/E • Poor treatment support • Poorly organized or funded TB control programs	• Poor quality medicines • Unavailability of certain medicines Poor storage conditions • Wrong dose or combination • Poor regulation of medicines	• Lack of information • Lack of means to adhere to treatment Adverse effects • Social barriers • HIV • Diabetes mellitus • Undernutrition • Malabsorption • Substance abuse/dependency • Psychiatric condition

Modified from http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

Known Cross-resistance

Drugs	Cross-resistance
Rifamycins	• Rifamycins (rifampicin and rifabutin) have high levels of cross-resistance
Isoniazid	• high cross-resistance between isoniazid and ethionamide if the inhA mutation is present
Aminoglycosides and polypeptides	• Amikacin and kanamycin have (very) high cross-resistance • Amikacin/kanamycin and capreomycin cross-resistance; rrs mutation (clinical implications are not clear) • Streptomycin has low cross-resistance with amikacin/kanamycin and capreomycin
Fluoroquinolones	• Levofloxacin, gatifloxacin, moxifloxacin remain effective when ofloxacin are resistance (no clinical data) • Not known between moxifloxacin andgatifloxacin)
Thiamides	• Prothionamide and ethionamide, 100% cross-resistance

Modified from http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, WHO 2014

Vaccine; BCG

- *M. bovis* bacilli Calmette–Guérin (BCG) vaccine
- Estimated overall efficacy of approximately 50% for the prevention
- Disseminated infection in immunosuppressed patients
  - it should not be administered in HIV-infected newborns

Colditz GA, et al. JAMA 1994;271:698-702

Nontuberculous Mycobacteria(NTM)

Overview of NTM Infections

Synonyms

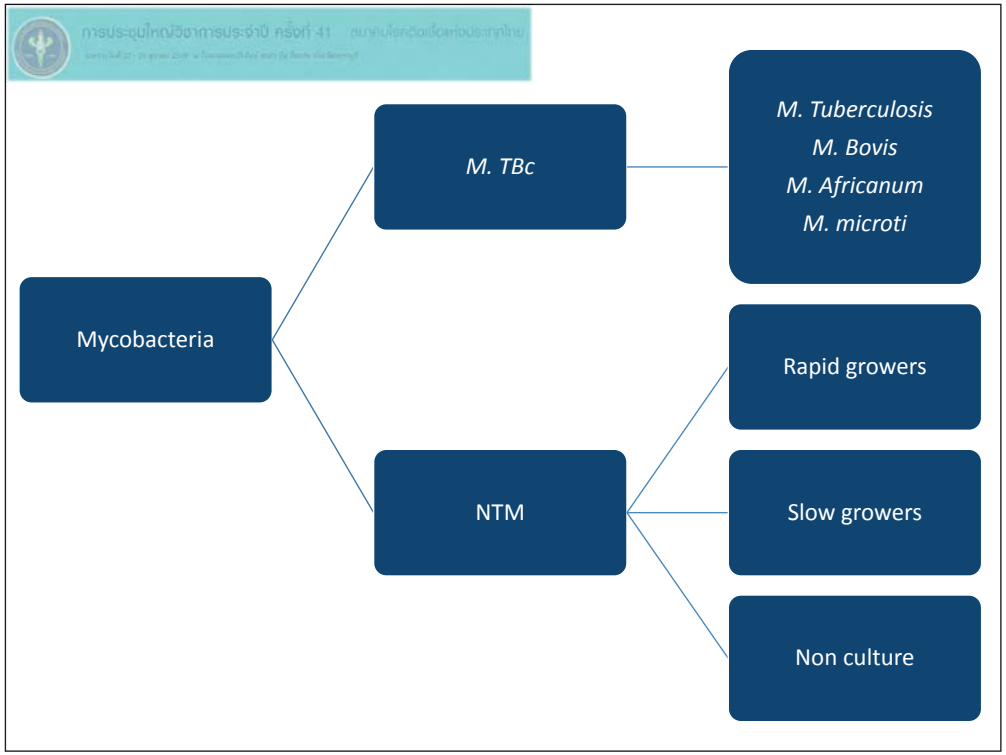
- Infections due to atypical mycobacteria
- Infections due to mycobacteria other than tubercle bacilli (MOTT)

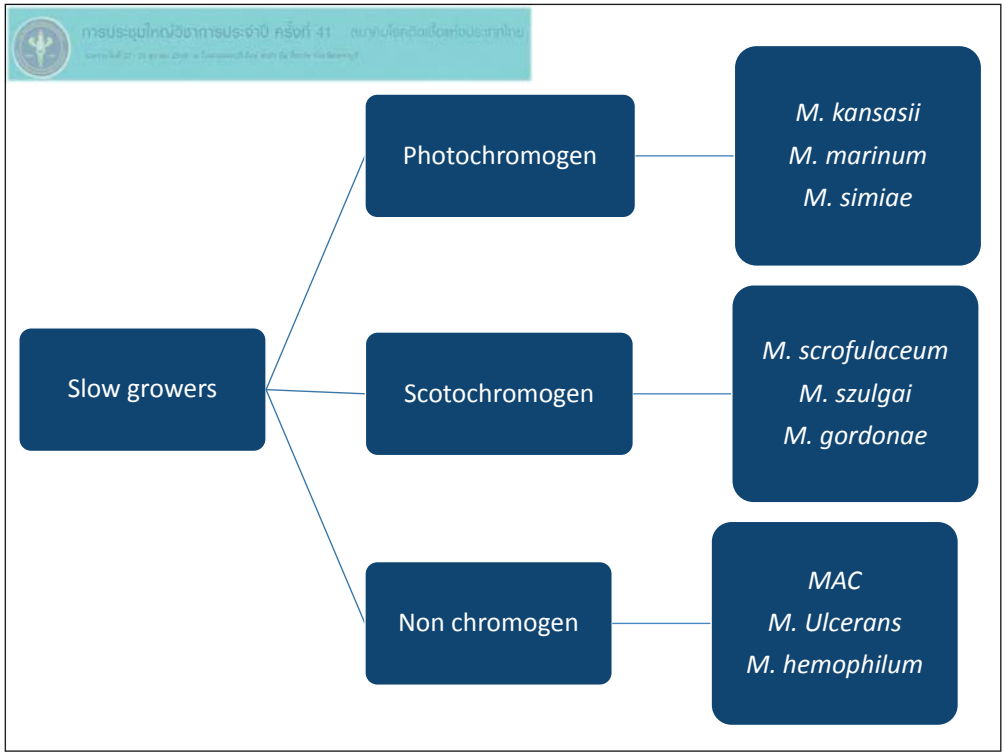
Causative Organisms

- The list of NTM pathogens continues to grow as new species are discovered
- Runyon classified NTM based on pigment production, growth rate, and colonial characteristics

Runyon Classification

Group I: Photochromogens	• Grow slowly on culture media (>7 days) • Colonies become yellow or orange after exposure to light
Group II: Scotochromogens	• Grow slowly on culture media • Colonies are pigmented in the dark or after light exposure
Group III: Nonpigmented	• Grow slowly and lack pigment in the dark or the light
Group IV: Rapid growers	• May grow slowly on initial culture but grow in 3-5 days on subculture • Lack pigment





Epidemiology

- Ubiquitous in nature, ground or tap water, soil, house dust, domestic and wild animals, and birds
- Inhalation or direct inoculation from environment
- Ingestion may be the source of infection for children and HIV
- Person-to-person transmission is extremely rare

Diagnosis

- Colonization and environmental contamination of specimens
- Cavitary infiltrate on chest radiogram when:
  - Two or more sputum samples (or sputum and a bronchial washing) are smear-positive for AFB and/or yield moderate to heavy growth on culture
- Exclude; fungal disease, tuberculosis, malignancy
- Transbronchial, percutaneous, or open lung biopsy

Etiologic Species

Clinical disease	Common	Less common
Pulmonary	*M. avium complex* *M. kansasii* *M. abscessus* *M. xenopi*	*M. simiae* *M. szulgai* *M. malmoense* *M. fortuitum* *M. Chelonae*
Lymphadenitis	*M. avium complex* *M. scrofulaceum*	*M. fortuitum* *M. chelonae* *M. abscessus* *M. Kansasii*
Cutaneous	*M. marinum* *M. fortuitum* *M. chelonae* *M. abscessus* *M. ulcerans*	*M. avium complex* *M. kansasii* *M. terrae* *M. smegmatis* *M. Haemophilum*
Disseminated	*M. avium complex* *M. kansasii* *M. chelonae* *M. abscessus* *M. haemophilum*	*M. fortuitum* *M. xenopi* *M. simiae* *M. gordonae* *M. terrae complex* *M. neoaurum* *M. celatum* *M. genavense*

Therapy

- Many NTM are resistant to conventional anti-TB agents
- For many NTM pathogens the optimal treatment regimen remains undefined

Mycobacterium avium-intracellulare (MAI)

- *M. avium* complex (MAC)
- MAI causes about 80% of NTM lymphadenitis
- **Pulmonary infection**
  - Underlying lung , indolent or slowly progressive course
- **Extrapulmonary or disseminated disease**
  - Occurs rarely in immunocompetent patients
  - HIV with CD4+ T-lymphocyte counts <50 cells/mm^3
  - Fever and/or weight loss, anorexia, abdominal pain, diarrhea
  - Hepatosplenomegaly, generalized lymphadenopathy

Treatment

Include at least two agents

- Every regimen should contain either azithromycin (600 mg once daily) or clarithromycin (500 mg twice daily)
- One or more of the following may be added:
  - Rifampicin (300-600 mg daily)
  - Ethambutol (15 mg/kg once daily)
  - Ciprofloxacin (750 mg twice daily)
  - Ofloxacin (400 mg twice daily)
  - And in some situations amikacin (7.5-15 mg/kg daily)
- Immunocompetent; minimum of 18-24 months
- INH and PZA are not effective

Mycobacterium kansasii

- Photochromogen
- Pulmonary infection is most common and resembles TB and MAI disease
- Extrapulmonary disease can involve any organ system
- Risks of dissemination are increased in immunocompromised patients

Treatment

- INH 300 mg daily, RIF 600 mg daily, and EMB daily (25 mg/kg for 2 months, then15 mg/kg for 18 months)
- Clarithromycin (500 mg twice daily) or RFB (150 mg once daily) can substitute for RIF in HIV patients receiving protease inhibitors
- Sulfamethoxazole (1 gram three times daily) may be used in regimens to treat RIF-resistant strains
- All strains are resistant to PZA

Mycobacterium marinum

- Free-living NTM
  - Fresh and saltwater fish and occasionally in humans
- Swimming pools and home aquariums
- Cutaneous infections commonly
  - Painless papules typically are found on an extremity
- Lesions may progress to shallow ulceration and scar
- Spontaneous healing can occur
  - May take months to years
- Tenosynovitis, osteomyelitis, arthritis, bursitis, and carpal tunnel syndrome

Treatment

- Simple observation or surgical excision for minor lesions
- Clarithromycin 500 mg twice daily as a single agent
- Doxycycline (100 mg twice daily)
- Trimethoprim-sulfamethoxazole(160/800 mg twice daily)
- Rifampin(600 mg daily) plus ethambutol (15 mg/kg daily)
- Linezolid and several fluoroquinolones show in vitro activity

Rapidly Growing Mycobacteria

- Ubiquitous in soil and water, including chlorinated municipal water systems
- Inoculation after accidental trauma, surgery, or injection
- Nosocomial epidemics or clusters have been reported in numerous settings
  - Augmentation mammaplasty
  - Hemodialysis
  - Plastic surgery
  - Long-term venous catheters
  - Cardiac surgery
  - Jet injector use

Rapidly Growing Mycobacteria

- Localized to disseminated with cutaneous involvement
- Acid fast bacilli
- Growth is rapid on subculture to solid media
  - <7 days
- Primary isolation from clinical specimens may require 2 to 30 days

Treatment

- Resistant to conventional antituberculous drugs
- Sensitive to traditional or newer antibiotics
- ***M. chelonae* ssp. *abscessus* infections**
  - Clarithromycin 500 mg twice daily for 6 months
  - Isolates may be susceptible to amikacin, cefoxitin, cefmetazole, clofazimine, or linezolid
- ***M. chelonae* ssp. *chelonae* infections**
  - Clarithromycin 500 mg twice daily for 6 months
  - Isolates may be susceptible to amikacin, cefoxitin, cefmetazole, clofazimine, or linezolid
- ***M. fortuitum* infections**
  - Amikacin plus cefoxitin plus probenecid for 2 weeks, then
  - Oral trimethoprim-sulfamethoxazole or doxycycline for 2-6 months
  - Isolates may be susceptible to imipenem, ciprofloxacin, ofloxacin, azithromycin, clarithromycin, or linezolid

Thank You