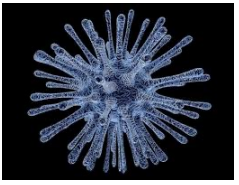
# Lecture 1



## 1 Biology of Mycobacteria

- **Acid-fast bacilli (AFB)** بحتاجها عشان مقاومة حمضية
- **Obligate aerobes**
- **Slow growth**: 15–20 hours per replication
- **Non-spore forming BUT extremely resistant**
- **Cell wall = key feature**
- Thick **mycolic acids**
- **Arabinogalactan + peptidoglycan core**
- Resistance to drying & disinfectants
- **Ability to persist intracellularly**

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## 2 Mycobacterial Cell Wall (Structure → Function)

chronicity and intracellular survival.

- **Inner cell membrane + periplasm**
- **Peptidoglycan** → structural rigidity
- **Arabinogalactan** → links PG to mycolic acids
- **Mycolic acid layer** لـ peptidoglycan
- Waxy, hydrophobic (cell wall)
- Responsible for **acid-fastness**
- Impermeable to many antibiotics
- **Surface lipids & glycolipids**
- **Cord factor (trehalose dimycolate)**
- Toxic to macrophages
- Drives **granuloma formation**
- **Capsule**
- Enhances survival inside phagocytes

**NTM vs. *Mycobacterium tuberculosis*: Key distinctions**

| NTM | *Mycobacterium tuberculosis* |
|---|---|
| Not obligate pathogens – normally live free in the environment [1] | Obligate pathogens: require host [1] |
| Low virulence: not usually pathogenic in the absence of predisposing conditions [2,3] | Pathogenic [3,4] |
| Human-to-human transmission extremely rare, but some evidence of this in the cystic fibrosis community [4] | Human-to-human transmission [5] |
| Infection rates increasing, especially in developed countries [6] | Infection rates decreasing, especially in developed countries [6] |
| Large heterogeneous group of species [4] | *Mycobacterium tuberculosis* complex contains small group of closely related subspecies [2,7] |

NTM and *Mycobacterium tuberculosis* differ in terms of pathogenicity, infection rates and transmission routes

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## 3 Mycobacterium tuberculosis Complex (MTBC)

- **M. tuberculosis** → main human pathogen
- **M. bovis**
- Zoonotic TB
- Unpasteurized milk, animal contact
- **BCG derived from attenuated strain** لقاح BCG مأخوذ من سلالة مُضعّفة من المتقطرة البقرية.
- **M. africanum**
- West Africa
- Less transmissible & less virulent
- **M. microti** → rodents
- **M. caprae** → goats & cattle (rare zoonosis)
- **M. canettii** → East Africa

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## 4 Non-tuberculous Mycobacteria (NTM)

- Environmental (soil, water)
- **No person-to-person transmission**
- **Groups**
- **Slow growers (>2 weeks)**

M. avium complex → MAC, M. kansasii, M. xenopi

- **Rapid growers (<7 days)** → growth in liquid media within 7 days

→ M. abscessus, M. fortuitum, M. chelonae

- **Clinical significance**
- Pulmonary disease (COPD, bronchiectasis)
- Disseminated disease in immunocompromised
- **High intrinsic drug resistance**

NTM Immunopathogenesis

- Predisposing factors: COPD, cystic fibrosis, immunodeficiency (severe AIDS)
- Control depends on cell-mediated immunity: IFN-γ → macrophage activation. Defects → poor intracellular killing → dissemination
- Chronic, indolent respiratory infection. Cough, sputum, fatigue, weight loss.

## 5 MTBC Immunopathogenesis – Early Infection

- Inhalation of **aerosolized droplet nuclei containing mycobacterium tuberculosis**
- Bacilli reach **terminal bronchioles & alveoli**

## 6 Initial Host–MTB Interaction

- Recognized by **Pattern Recognition Receptors (PRRs)**
- **TLRs**: 2, 4, 9
- **C-type lectin receptors**: Dectin-1, Mannose receptor, DC-SIGN
- **NOD-like receptors (NLRs)**
- Triggers **innate immunity**
- MTB = **facultative intracellular pathogen**

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## 7 Intracellular Survival Mechanisms (MTB)

- Inhibits **phagosome–lysosome fusion**
- Resists **oxidative stress**
- Alters **phagosomal pH** → prevents acidification

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## 8 Immune Evasion & Early Lesions

- **Lipoarabinomannan (LAM)**
- ↓ IL-1β
- ↓ TNF-α signaling
- ↓ macrophage activation
- Delays adaptive immunity **(2–4 weeks)**
- **Slow intracellular replication**
- Formation of **Ghon focus**
- Spread to lymph nodes → **Ghon complex** (Pulmonary + draining LN)

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## 9 Determinants of Clinical Outcome

**Effective Immune Response → Latent TB**

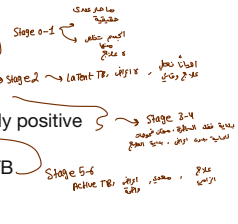
- Strong **Th1 immunity**
- **IFN-γ** → macrophage activation
- **TNF-α** → granuloma formation & maintenance
- Stable granulomas → infection contained

**Ineffective Immune Response → Active TB**

- Causes:
  Weak, delayed, or dysregulated immune response caused by immunosuppression
- HIV
- Malnutrition
- Diabetes
- Extremes of age
- Granuloma breakdown
- Uncontrolled replication

## 10 Clinical Spectrum of TB States

- **State 0**: Innate clearance (uninfected)
- **State I**: Adaptive clearance (LTBI reverter)
- **State II**: Latent TB (stable containment)
- **State III**: Incipient / subclinical TB
- **State IV**: Asymptomatic but bacteriologically positive
- **State V**: Active TB (symptomatic)
- **State VI**: Severe / cavitary / disseminated TB
- **State VII**: Past treated TB



| State | What it is | Symptoms | Tests | Treatment |
|---|---|---|---|---|
| 0 | Innate clearance (Uninfected) | None | TST / IGRA **negative** | ❌ No |
| I | Adaptive clearance (LTBI reverter) | None | TST / IGRA may revert to negative | ❌ No |
| II | **Latent TB (LTBI)** | Asymptomatic | **TST or IGRA positive**, normal CXR | ✅ **Preventive therapy (selected patients)** |
| III | Incipient / Subclinical TB | None or vague | IGRA/TST positive + subtle CXR | ✅ **Early intervention** |
| IV | Asymptomatic but bacteriologically + | No symptoms | **Sputum NAAT / culture positive**, abnormal CXR | ✅ **Full TB treatment** |
| V | Active TB | Cough, fever, weight loss | Symptoms + abnormal CXR + microbiology | ✅ **Mandatory TB treatment** |
| VI | Severe / cavitary / disseminated TB | Very ill, highly infectious | Smear-positive, cavitary disease | ✅ **Urgent intensive treatment** |
| VII | Past treated TB | None | Past TB + residual CXR changes | ❌ No (unless relapse) |

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## 11 Respiratory TB – Clinical Features

- Gradual onset (weeks–months)
- More acute in children & immunocompromised
- **Persistent cough (90–95%)**
- Dry → productive ± hemoptysis
- Systemic symptoms:
- Fever (75%)
- Night sweats (50%)
- Weight loss (60%)
- Fatigue, anorexia
- Distribution:
- 70–75% pulmonary TB
- 20% extrapulmonary TB
- 5–10% combined

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## 12 Diagnosis of TB

**AFB Smear** (Useful for determining infectiousness, not species.)

- Ziehl-Neelsen / Kinyoun
- Pink bacilli on blue background
- rapid & inexpensive
- **Cannot distinguish MTB vs NTM**
- Needs ≥$10^4$ organisms/mL

**GeneXpert MTB/RIF**

- PCR-based
- Detects MTB DNA
- Detects **rifampicin resistance (rpoB)**
- Turnaround ≈ 2 hours
- Best in smear-positive disease* High sensitivity in smear- positive disease.

Does not detect all resistance types (performs best for rifampicin).

**Culture (Gold Standard)**

- **Solid (Lowenstein-Jensen)**: 3–8 weeks
- **Liquid (MGIT)**: 7–14 days
- Confirms viable MTB
- Species ID + drug susceptibility

species identification (MTBC vs. NTM).
Limitations: Slow turnaround

**Immunologic Tests**

- **IGRA** (Interferon-γ Release Assay)
- Not affected by BCG
- Cannot distinguish latent vs active
- **Tuberculin Skin Test (TST):**
- Detect TB infection,False positives with BCG & some NTM

**Imaging**

- Upper-lobe infiltrates
- Cavities
- Hilar/mediastinal lymphadenopathy with or without consolidation

## 13 Treatment of TB

**Standard RIPE Regimen**

- **Intensive phase (2 months)**

Rifampicin + INH + Pyrazinamide + Ethambutol

- **Continuation phase (4 months)**

INH + Rifampicin

- **Total = 6 months**

**Resistance Mechanism**

- Spontaneous chromosomal mutations
- Risk factors:
- Monotherapy
- Poor adherence
- Incorrect dose/duration

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## 14 Drug-Resistant TB

- **INH resistance** → most common multidrug-resistant
- **Rifampicin resistance** → marker of MDR-TB
- **MDR-TB**: INH + Rifampicin resistant
- **XDR-TB:** Extensively drug-resistant TB
- Rifampicin resistant (and may also be resistant to INH)
- - fluoroquinolone (levofloxacin or moxifloxacin)
- - Group A drug (bedaquiline or linezolid)

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## 15 Adherence & Public Health

- Poor adherence = main cause of resistance
- **DOT (Directly Observed Therapy)**
- WHO-recommended
- Prevents MDR-TB
- Drug resistance →
- Longer treatment (≥18–24 months)
- More toxic drugs
- Higher mortality & transmission

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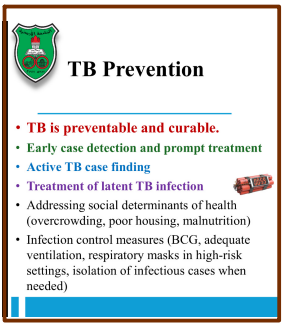
## 16 TB Prevention

- **BCG vaccine** (Bacillus Calmette-Guérin)
- Live attenuated *M. bovis* ,Administered intradermally
- Protects infants from meningitis & miliary TB
- ↓ severity NOT infection
- Causes false-positive TST
- Early detection & treatment
- Treat latent TB
- Infection control
- Improve social determinants (housing, nutrition)



**Q1**

Mycobacterium tuberculosis is a **facultative intracellular pathogen** that primarily survives inside macrophages.
**Answer:** True
**From file:** MTB survives and replicates intracellularly within macrophages.

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**Q2**

Initial recognition of MTB by the host innate immune system occurs mainly through **antibodies**.
**Answer:** False
**From file:** Recognition is mediated by PRRs (TLRs, CLRs, NLRs).

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**Q3**

TLR2, TLR4, and TLR9 are involved in recognizing MTB components.
**Answer:** True
**From file:** PRRs involved include TLRs 2, 4, and 9.

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**Q4**

C-type lectin receptors involved in MTB recognition include **Dectin-1 and DC-SIGN**.
**Answer:** True
**From file:** CLRs such as Dectin-1 and DC-SIGN recognize MTB.

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**Q5**

MTB enhances phagosome–lysosome fusion to promote intracellular killing.
**Answer:** False
**From file:** MTB inhibits phagosome–lysosome fusion.

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**Q6**

One survival mechanism of MTB is **alteration of phagosomal pH**, preventing acidification.
**Answer:** True
**From file:** MTB alters phagosomal pH to prevent acidification.

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**Q7**

Lipoarabinomannan (LAM) enhances IL-1β and TNF-α production.
**Answer:** False
**From file:** LAM suppresses IL-1β and reduces TNF-α signaling.

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**Q8**

The delay in effective adaptive immune response in TB infection is approximately **2–4 weeks**.
**Answer:** True
**From file:** Effective adaptive immunity is delayed 2–4 weeks.

**Q9**

The primary pulmonary lesion formed in TB is called the **Ghon focus**.
**Answer:** True
**From file:** Primary pulmonary lesion is the Ghon focus.

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**Q10**

The combination of Ghon focus and regional lymph node involvement is known as the **Ghon complex**.
**Answer:** True
**From file:** Ghon complex = pulmonary lesion + draining lymph nodes.

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**Q11**

Effective Th1-mediated immunity leads to progression toward active TB.
**Answer:** False
**From file:** Effective Th1 response → containment → latent TB.

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**Q12**

IFN-γ activates macrophages, while TNF-α is essential for granuloma formation and maintenance.
**Answer:** True
**From file:** IFN-γ activates macrophages; TNF-α maintains granulomas.

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**Q13**

Latent TB infection (LTBI) is characterized by **stable immune containment without symptoms**.
**Answer:** True
**From file:** LTBI = stable immune containment, asymptomatic.

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**Q14**

Subclinical TB is always associated with severe clinical symptoms.
**Answer:** False
**From file:** Subclinical TB may be asymptomatic or have vague symptoms.

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**Q15**

Ziehl–Neelsen stain detects acid-fast bacilli as **pink/red organisms on a blue background**.
**Answer:** True
**From file:** AFB appear pink/red against blue background.

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**Q16**

AFB smear microscopy can distinguish MTB from non-tuberculous mycobacteria (NTM).
**Answer:** False
**From file:** AFB smear cannot differentiate MTB from NTM.

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**Q17**

GeneXpert MTB/RIF detects rifampicin resistance through mutations in the **rpoB gene**.
**Answer:** True
**From file:** Rifampicin resistance detected via rpoB mutations.

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**Q18**

Culture is considered the **gold standard** for TB diagnosis and resistance profiling.
**Answer:** True
**From file:** Culture is the gold standard.

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**Q19**

IGRA tests can reliably distinguish latent TB from active TB.
**Answer:** False
**From file:** IGRA detects TB infection but cannot distinguish latent from active TB.

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**Q20**

BCG vaccination primarily prevents TB infection but has limited effect on disease severity.
**Answer:** False
**From file:** BCG reduces severity rather than acquisition of infection.