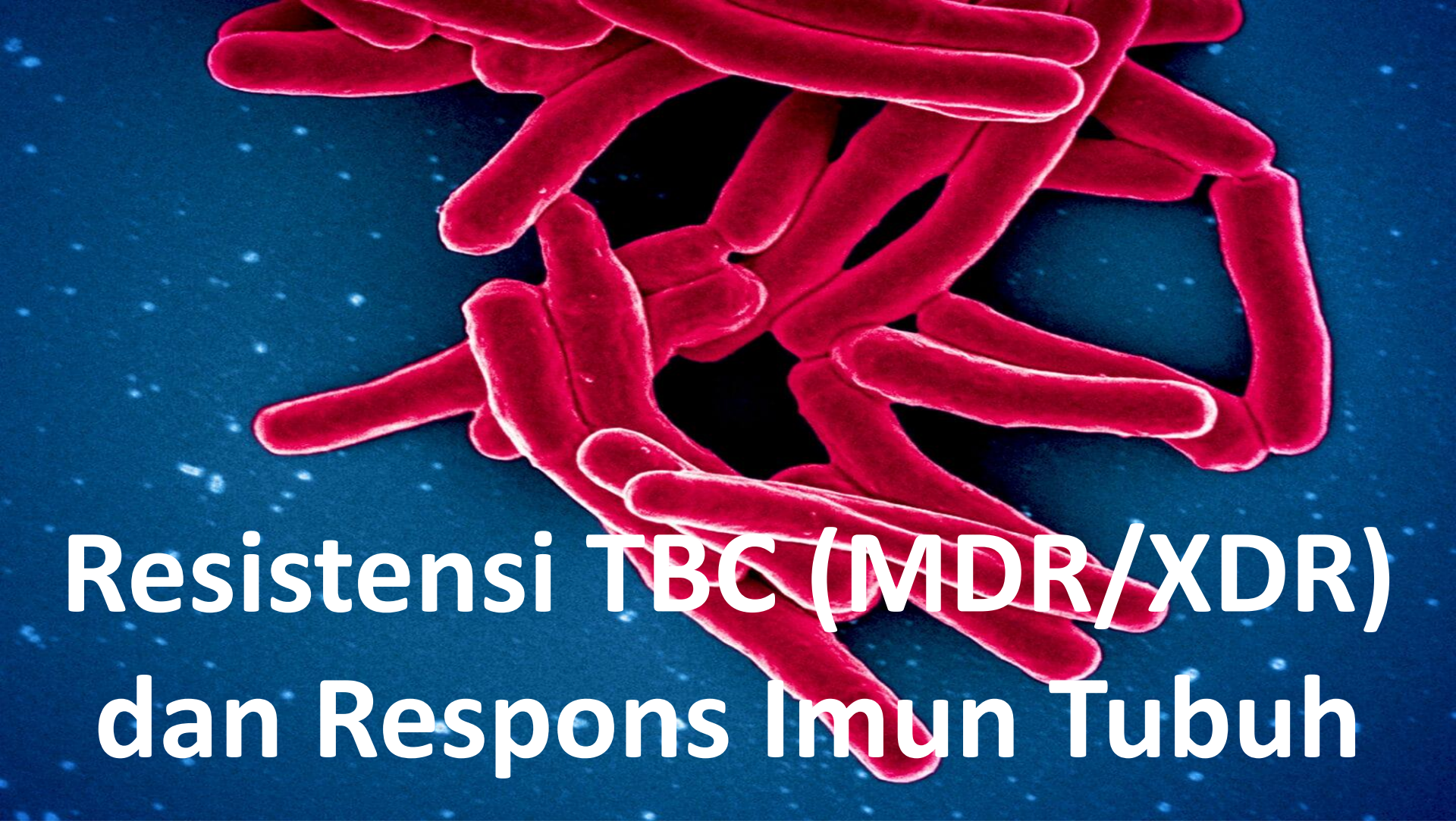
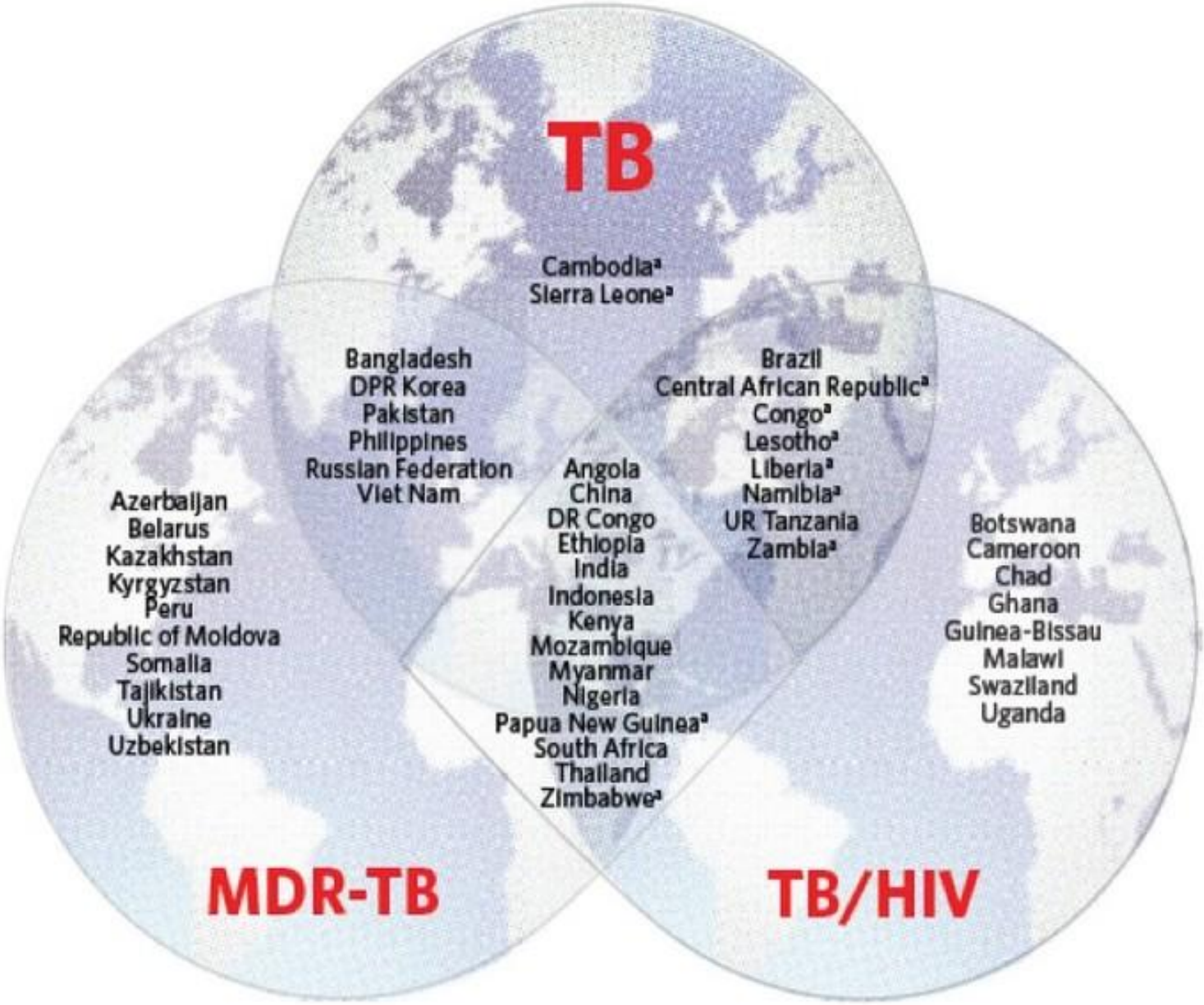


Resistensi TBC (MDR/XDR) dan Respons Imun Tubuh

Agung Dwi Wahyu Widodo
Departemen Mikrobiologi dan Parasitologi Kedokteran,
Fakultas Kedokteran Unair Surabaya

Subyek

- Konsep Resistensi TB
- Resistensi TB dan Respon Imun


TB
Cambodia[a]
Sierra Leone[a]
Bangladesh
DPR Korea
Pakistan
Philippines
Russian Federation
Viet Nam
Brazil
Central African Republic[a]
Congo[a]
Lesotho[a]
Liberia[a]
Namibia[a]
UR Tanzania
Zambia[a]
Azerbaijan
Belarus
Kazakhstan
Kyrgyzstan
Peru
Republic of Moldova
Somalia
Tajikistan
Ukraine
Uzbekistan
Angola
China
DR Congo
Ethiopia
India
Indonesia
Kenya
Mozambique
Myanmar
Nigeria
Papua New Guinea[a]
South Africa
Thailand
Zimbabwe[a]
Botswana
Cameroon
Chad
Ghana
Guinea-Bissau
Malawi
Swaziland
Uganda
MDR-TB
TB/HIV

Concept of Drug-Resistant Tuberculosis (MDR & XDR)

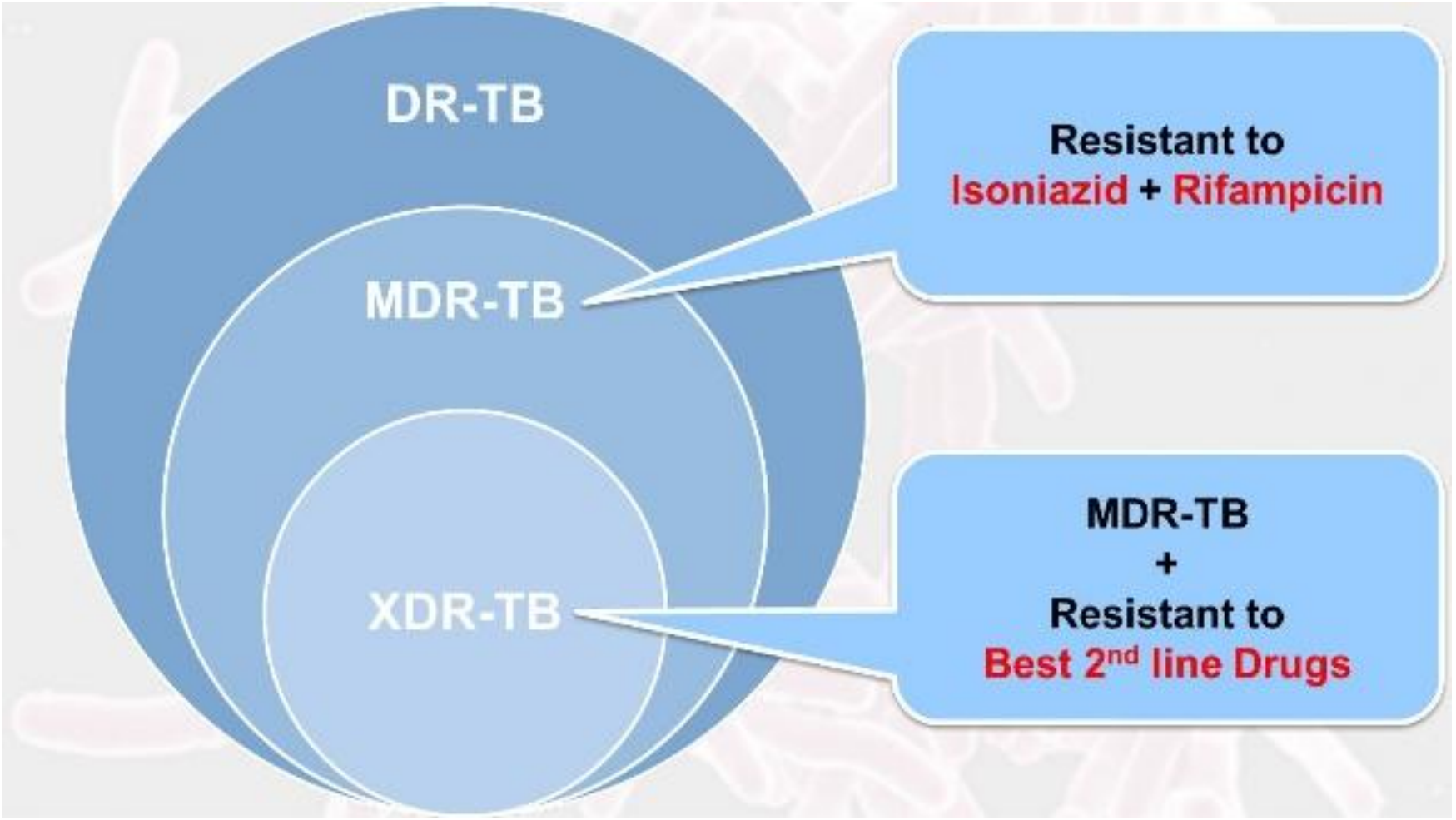
- **1. What is Drug-Resistant TB?**
- TB becomes drug-resistant when *Mycobacterium tuberculosis* continues to grow despite the correct use of anti-TB drugs, due to genetic mutations that prevent drugs from killing the bacteria.
- Drug resistance can be:
  - **Primary**: patient is infected with a resistant strain from the start
  - **Acquired**: resistance develops during treatment due to inadequate therapy, poor adherence, incorrect regimen, drug quality issues

Concept of Drug-Resistant Tuberculosis

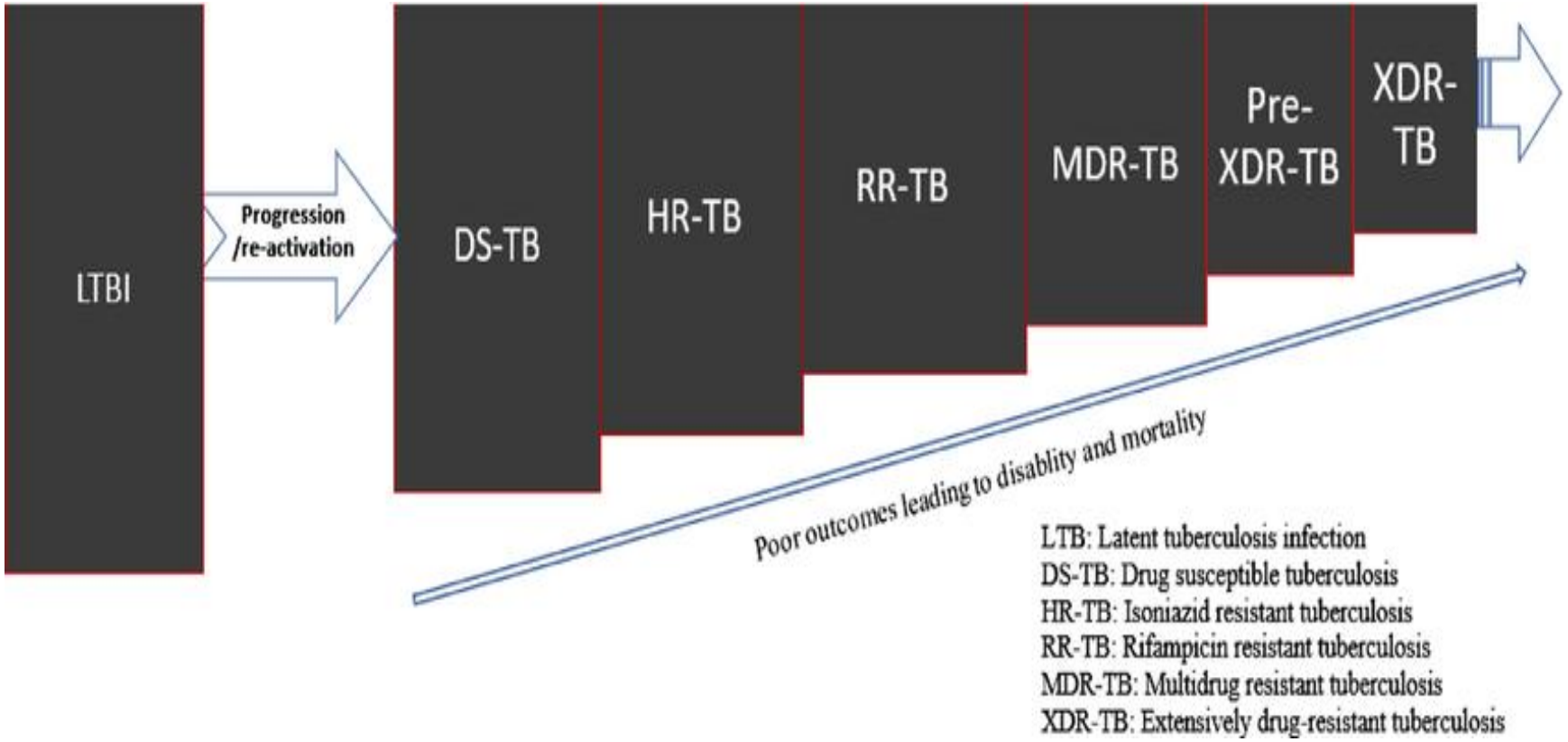
- 2. Definitions (Core Concept)
- Meaning: XDR-TB is a more severe, difficult-to-treat form of MDR-TB.

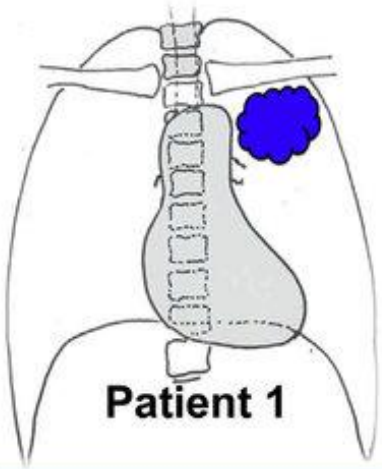
Type	Definition
MDR-TB	Resistant to **at least** Isoniazid (INH) **and** Rifampicin (RIF)
XDR-TB	**MDR-TB +** resistance to **any fluoroquinolone** (e.g. levofloxacin/moxifloxacin) **and** at least **one injectable second-line drug** (amikacin, kanamycin, or capreomycin)

Concept of Drug-Resistant Tuberculosis

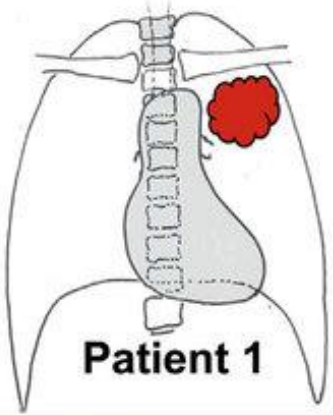


The activation and different resistance profiles of tuberculosis





- Susceptible bacillus
- Resistant bacillus

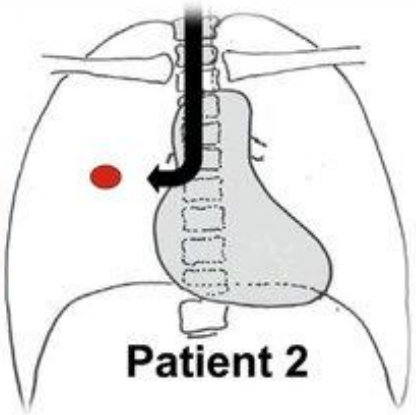


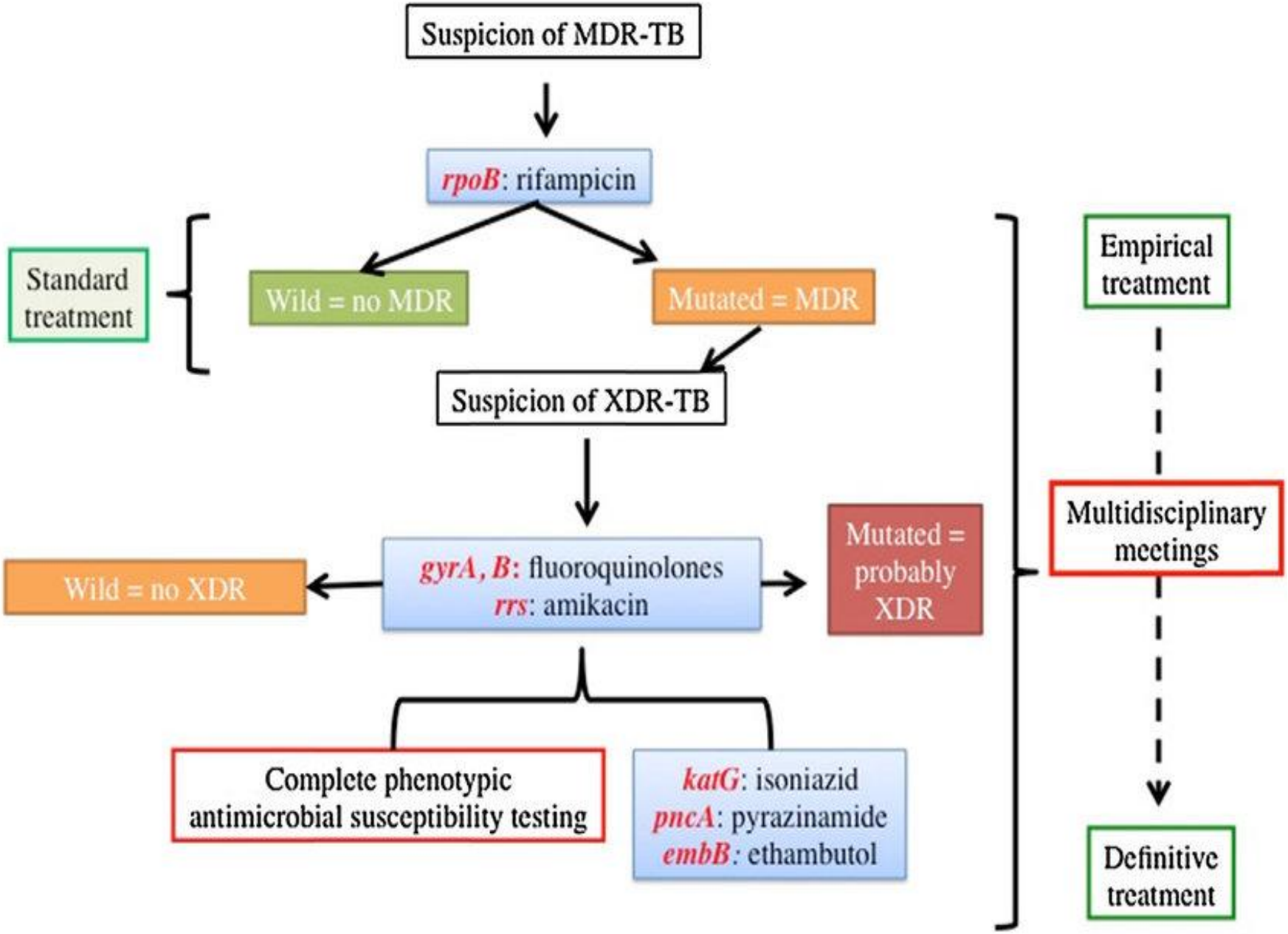
Population that became resistant: secondary resistance

Pulmonary cavity: susceptible population: 10^8 bacilli

Transmission to close contacts

Primary resistant infection: primary resistance




Suspicion of MDR-TB
rpoB: rifampicin
Standard treatment
Wild = no MDR
Mutated = MDR
Suspicion of XDR-TB
gyrA, B: fluoroquinolones
rrs: amikacin
Wild = no XDR
Mutated = probably XDR
Complete phenotypic antimicrobial susceptibility testing
katG: isoniazid
pncA: pyrazinamide
embB: ethambutol
Empirical treatment
Multidisciplinary meetings
Definitive treatment

3. Genetic Mechanisms of Resistance

- Drug resistance occurs due to spontaneous chromosomal mutations.
- TB does not acquire resistance via plasmids like many bacteria.
- When multiple mutations accumulate → MDR → XDR

Genetic Mechanisms of Resistance

- Common mutation sites:

Drug	Gene mutation	Result
Isoniazid (INH)	**katG**, **inhA**	Prevents INH activation or target binding
Rifampicin (RIF)	**rpoB**	Alters RNA polymerase binding site
Fluoroquinolones	**gyrA/gyrB**	Alters DNA gyrase
Injectable drugs	**rrs**, **eis promoter**	Aminoglycosides fail to bind ribosome

Mechanism of resistant

Antibiotic-Resistant Genes Associated with MDR/XDR-TB

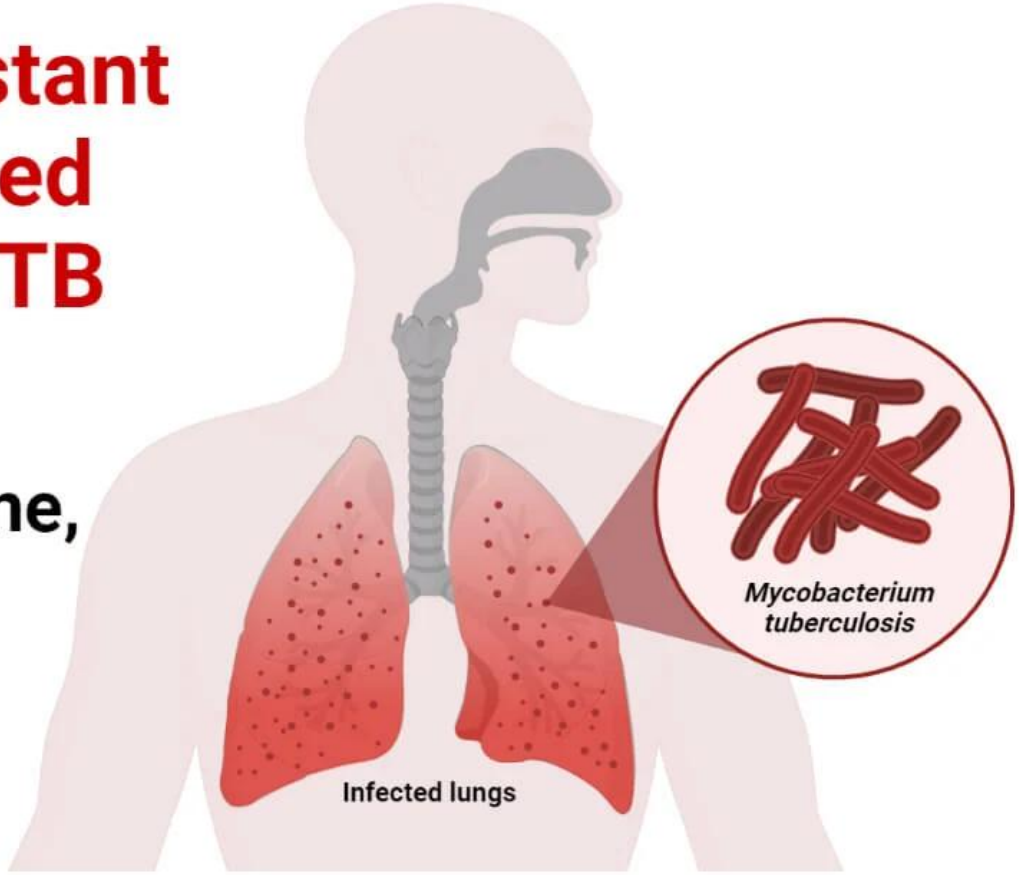
Mutated *atpE* Gene,

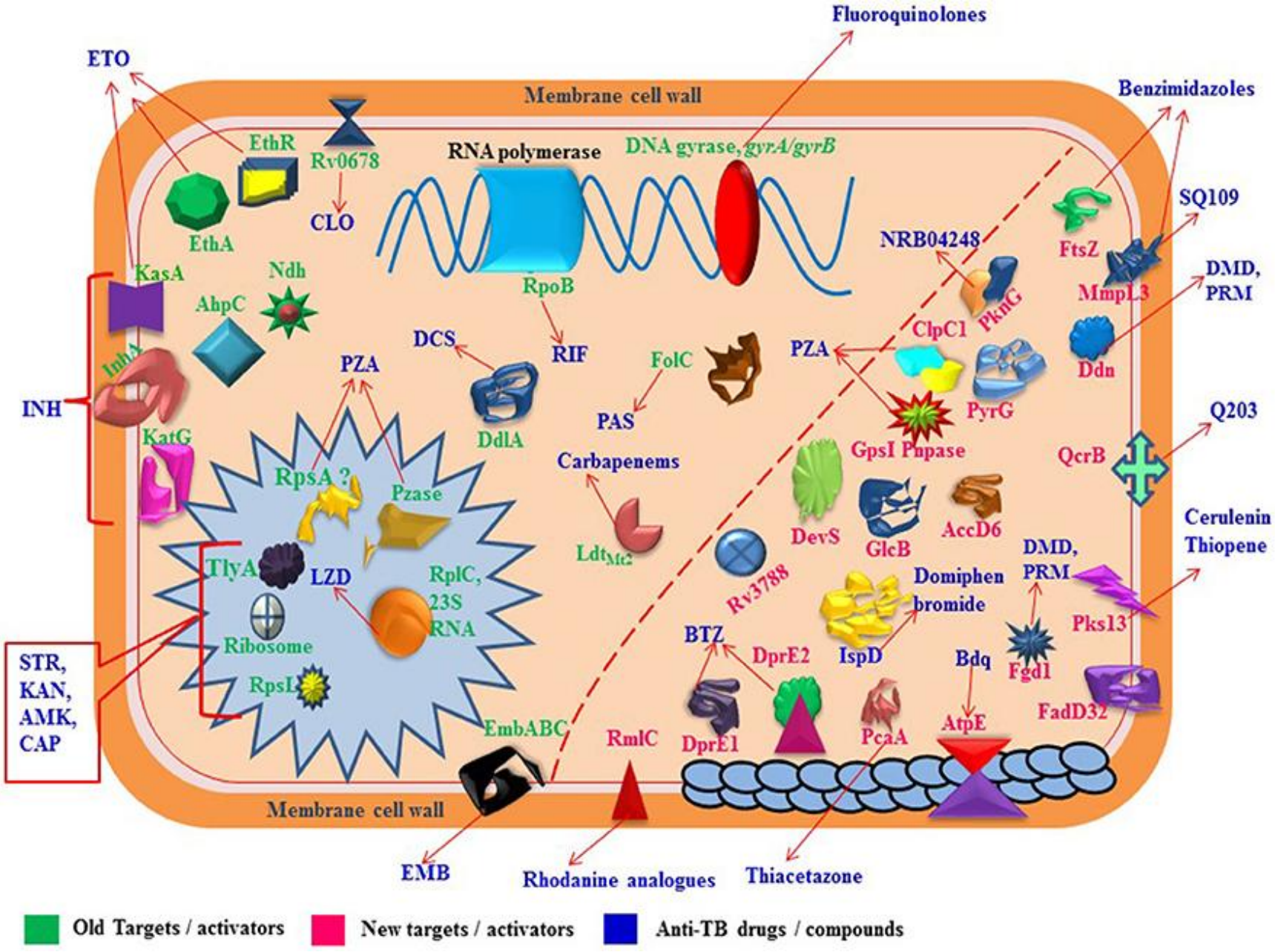
Mutated *Rv0678* Gene,

Mutated *rpoB* Gene,

Mutated *katG* Gene,

Mutated *ethA* Gene




Fluoroquinolones
ETO
Membrane cell wall
Benzimidazoles
EthR
Rv0678
RNA polymerase
DNA gyrase, gyrA/gyrB
SQ109
EthA
CLO
NRB04248
FtsZ
KasA
Ndh
RpoB
MmpL3
DMD, PRM
AhpC
ClpC1
PknG
DCS
RIF
PZA
FolC
Ddn
InhA
PZA
PyrG
INH
PAS
Q203
KatG
DdlA
GpsI Ppase
QcrB
Carbapenems
RpsA ?
Pzase
DevS
AccD6
GlcB
Cerulenin
Thiopene
LdtMt2
DMD, PRM
TlyA
LZD
RplC, 23S RNA
Rv3788
Domiphen bromide
Pks13
Ribosome
BTZ
DprE2
IspD
Bdq
Fgd1
STR, KAN, AMK, CAP
RpsL
FadD32
EmbABC
RmlC
DprE1
PcaA
AtpE
Membrane cell wall
EMB
Rhodanine analogues
Thiacetazone
Old Targets / activators
New targets / activators
Anti-TB drugs / compounds

4. How TB Becomes Resistant

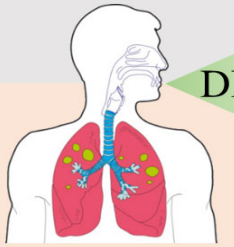
- Two pathways:
- **A. Acquired Resistance**
  - Poor adherence (patient stops early)
  - Wrong combination of drugs
  - Poor drug quality / supply interruption
  - Incorrect dosing
  - Malabsorption (HIV, DM, GI disease)
    ➞ Bacteria exposed to low drug levels → survive → mutate
- **B. Primary Resistance**
  - Patient is infected directly by another MDR/XDR TB case
    ➞ This is becoming increasingly common worldwide

5. Biological Characteristics of MDR/XDR Strains

- Survive inside macrophages longer
- Often associated with high bacillary load
- Cause more destructive lung disease
- Persist despite immune responses and therapy
- Transmit the same as drug-sensitive TB (airborne droplets)
- ➞ Resistant TB is **not less contagious**—just harder to treat.

- **Programmatic Strengthening Across TB Care Continuum**
- **Case Finding:**
  - Rigorous deployment of cough analysis technologies
  - Investigation of breath sampling/skin patch approaches
  - Use of GIS mapping approaches to identify transmission hotspots
- **Case Notification**
  - Increase notification in private sector
- **Improve Diagnostic Methods:**
  - Rapidly progress point of care detection of resistance
  - Whole genome sequencing / Targeted sequencing
    Eliminate cost restraints
    Increase data pool regards genotype:phenotype associations
    Further investigations to detect heteroresistance as a proxy for transmission leading to poor outcomes

- **Prophylaxis, Increase Available Treatments:**
  - in adults
  - in vulnerable populations (HIV, children)
- **Who Transmits the Disease?**
  - Investigate fundamental differences in transmission of drug sensitive vs. drug resistant TB
  - Investigate role of sub-clinical TB in driving transmission of drug resistant TB
- **Impact of Covid-19 on:**
  - Diagnostic pickup
  - TB-Covid-19 coinfections
  - Further transmission of drug resistant TB due to effects on heath systems



DR-TB

Environmental transmission of drug resistant bacteria

Bacterial mechanisms driving drug resistance

- **Tolerance Factors**
  - The pathway from tolerance to resistance
    Investigating efflux pumps, pathway redundancies, drug target modifications
- **Dormancy (role in drug tolerance and persistent infection)**
- **Heterogeneity**
  - Division and cell cycle, heterogeneity in cell size
  - LamA and others
- **Transcription/Translation**
  - Sigma factors
  - Mistranslation
- **Toxin-Antitoxin Systems**
  - Antibiotics targeting all redundant systems
- **Biofilms**
  - Overcoming reduced antibiotic accessibility
  - Further evaluating relevance in TB disease and DR strains

- **Metabolism**
  - TCA Cycle and related; respiration
    TAG and Lipid Droplets (new clinical endpoints?)
    Is carbon metabolism different in drug resistant TB?
- **Macrophage Activation**
  - Are there specific differences with DR strains?
  - Host-directed therapies
- **Differentially Culturable Tubercle Bacteria**
  - Appropriate testing for all possible bacteria present in the lungs
  - Better definitions of sterilising cure endpoints
- **Host Factors**
  - Immunometabolism
    Specific changes in immune responses with DR strains

6. Clinical Impact

Parameter	Drug-Sensitive TB	MDR-TB	XDR-TB
Drugs used	First-line	Second-line	Limited options
Treatment duration	6 months	9–24 months	≥ 18–24 months
Cure rate	High (>90%)	Lower	Much lower
Toxicity	Low/Moderate	High	Very high
Cost	Low	10–20× higher	>20× higher

7. Key Concepts

- MDR = resistance to INH + RIF
- XDR = MDR + fluoroquinolone + one injectable second-line agent
- Caused by gene mutations, not plasmids
- Can be primary or acquired
- Drug resistance increases mortality, transmission, cost, and toxicity

Summary

- MDR-TB is resistance to INH and Rifampicin due to chromosomal mutations.
- XDR-TB is MDR plus resistance to fluoroquinolones and one injectable second-line drug.
- Resistance arises from improper treatment or transmission of resistant strains, making therapy longer, more toxic, and less effective.

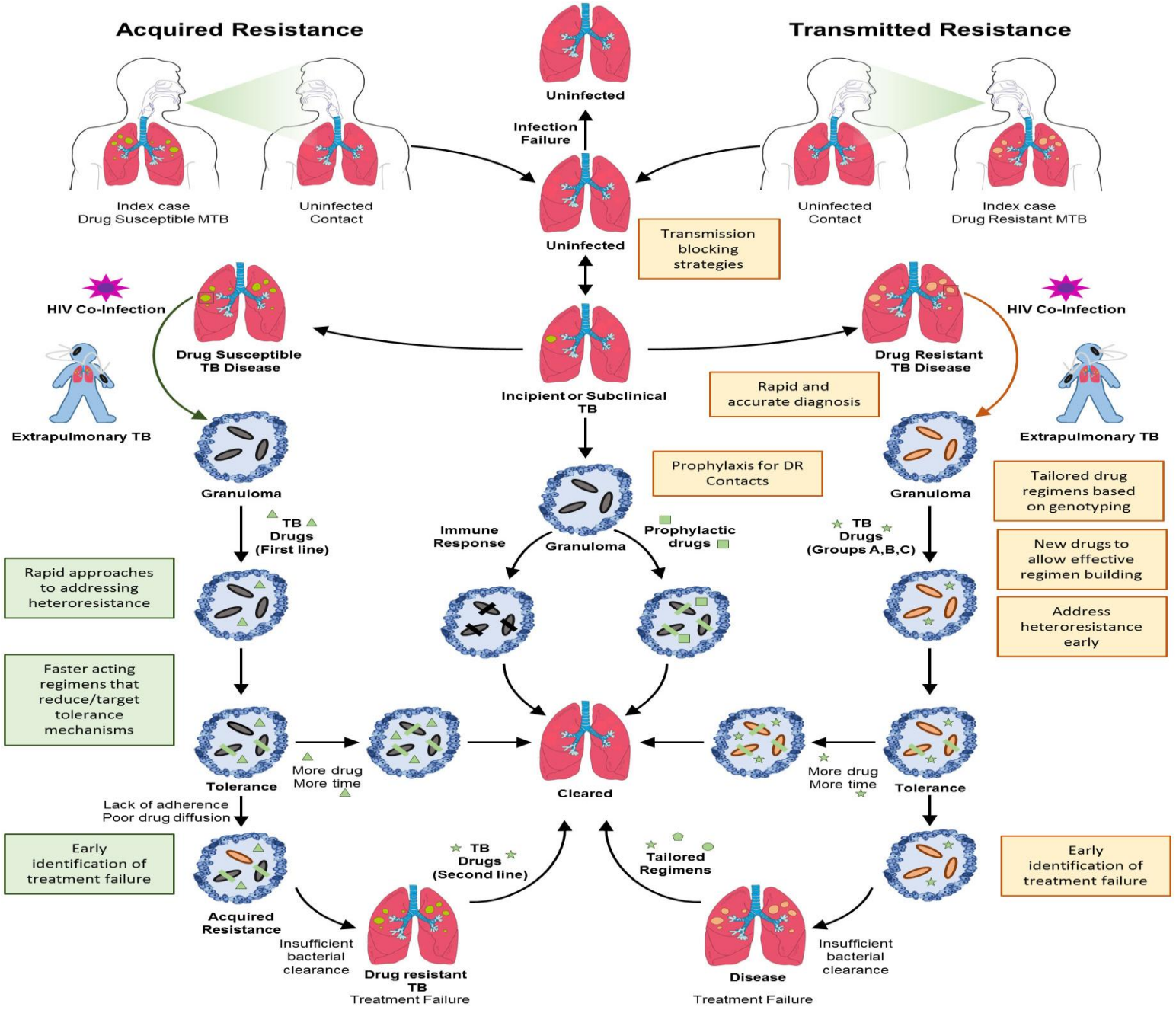
Tuberculosis Resistance (MDR/XDR) and Immune Responses

- **MDR-TB = resistant to at least INH + Rifampicin**
  XDR-TB = MDR + resistance to any fluoroquinolone + ≥1 injectable (amikacin/kanamycin/capreomycin)
  These strains are often more virulent, persist longer, and produce **altered immune responses** that help them survive inside the host.

1. Normal Immune Response to TB

1. Macrophages ingest MTB
2. Antigen → IL-12 → activates Th1
3. Th1 produces **IFN-γ** → macrophage activation
4. **TNF-α + IFN-γ** → granuloma formation
5. Latent TB remains contained

- ✓ Immune control depends on **macrophage killing + T-cell response + stable granuloma**


Acquired Resistance
Transmitted Resistance
Uninfected
Infection Failure
Index case
Drug Susceptible MTB
Uninfected
Contact
Uninfected
Contact
Index case
Drug Resistant MTB
Uninfected
Transmission blocking strategies
HIV Co-Infection
Drug Susceptible TB Disease
Incipient or Subclinical TB
Drug Resistant TB Disease
HIV Co-Infection
Rapid and accurate diagnosis
Extrapulmonary TB
Granuloma
Prophylaxis for DR Contacts
Granuloma
Extrapulmonary TB
Tailored drug regimens based on genotyping
TB Drugs (First line)
Immune Response
Granuloma
Prophylactic drugs
TB Drugs (Groups A,B,C)
New drugs to allow effective regimen building
Rapid approaches to addressing heteroresistance
Address heteroresistance early
Faster acting regimens that reduce/target tolerance mechanisms
Tolerance
More drug
More time
Cleared
More drug
More time
Tolerance
Lack of adherence
Poor drug diffusion
Early identification of treatment failure
Early identification of treatment failure
TB Drugs (Second line)
Tailored Regimens
Acquired Resistance
Insufficient bacterial clearance
Drug resistant TB
Treatment Failure
Disease
Treatment Failure
Insufficient bacterial clearance

2. Why MDR/XDR TB Survives the Immune System Better

- **A. Enhanced Ability to Survive Inside Macrophages**
- Drug-resistant MTB strains:
  - Inhibit phagosome–lysosome fusion more effectively
  - Resist nitric oxide and oxidative killing
  - Persist in intracellular niches
- **➞ Chronic intracellular survival = long infectious period**

Why MDR/XDR TB Survives the Immune System Better

- **B. Altered Cell Wall + Virulence Factors**
- Genetic mutations (katG, rpoB, efflux pumps, cell-wall changes) are not only drug-resistance–related but also:
  - Make bacilli less immunogenic
  - Reduce antigen presentation
  - Increase immune evasion
- ➞ The immune system “sees” them less

Why MDR/XDR TB Survives the Immune System Better

- **C. Prolonged Antigenic Stimulation → Chronic Inflammation**
- Long-standing infection causes:
  - Persistent macrophage activation
  - Excess TNF-α, IL-1, IL-6
  - **Tissue damage → cavitation**
- ➞ Explains **extensive lung destruction** seen in MDR-TB

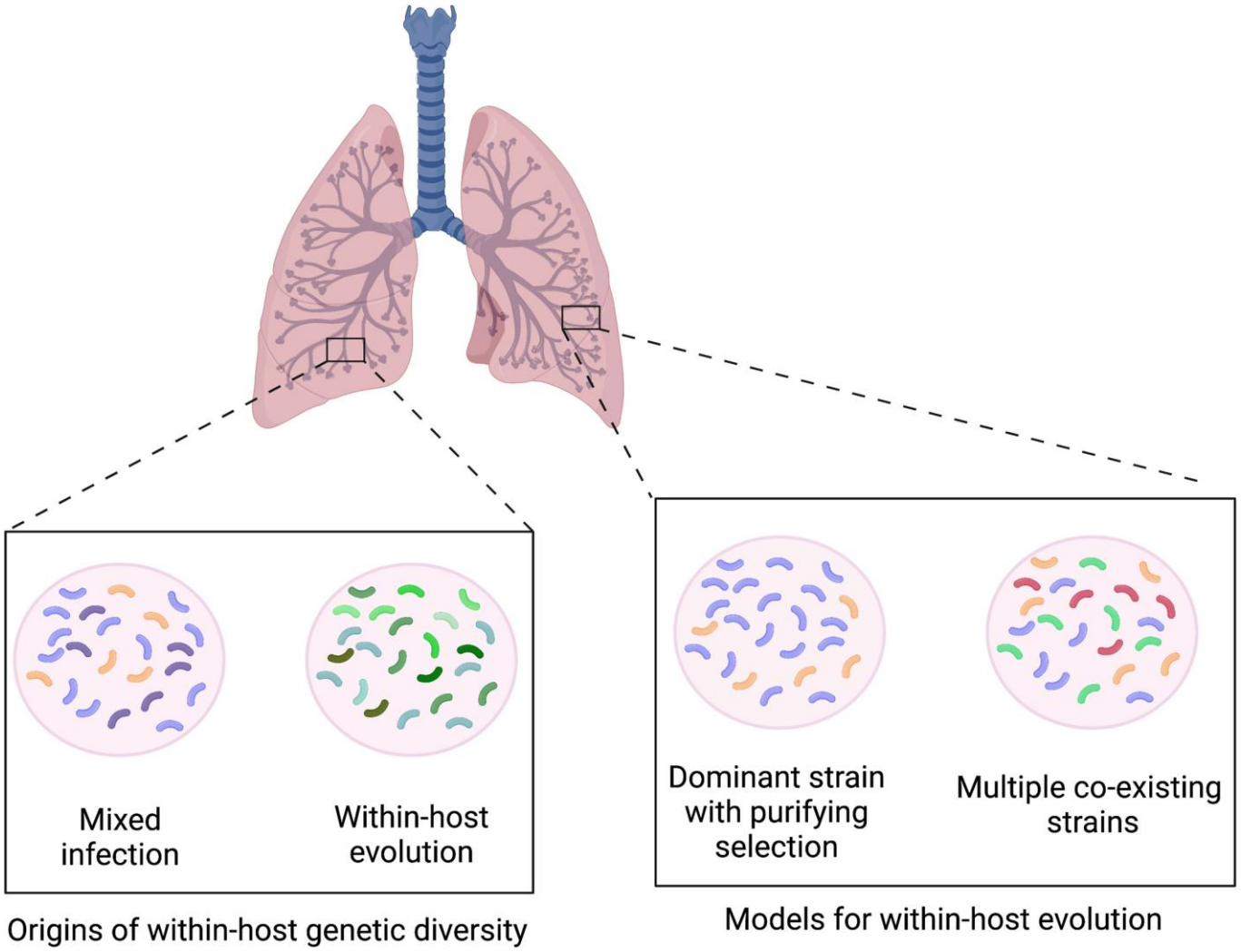
Why MDR/XDR TB Survives the Immune System Better

- **D. T-cell Exhaustion**
- Chronic exposure causes:
  - CD4+ and CD8+ T-cell exhaustion
  - Upregulated inhibitory receptors (PD-1, CTLA-4)
  - Reduced IFN-γ and IL-2 over time
- ➡ The immune system gradually loses control

Why MDR/XDR TB Survives the Immune System Better

- **E. Regulatory T cells (Tregs) Increase**
- MDR/XDR TB patients show:
  - Higher Treg counts (CD4+CD25+FOXP3+)
  - ↑ IL-10, ↑ TGF-β
- ➞ Suppresses Th1 immune clearance
  ➞ Favors persistence of bacilli

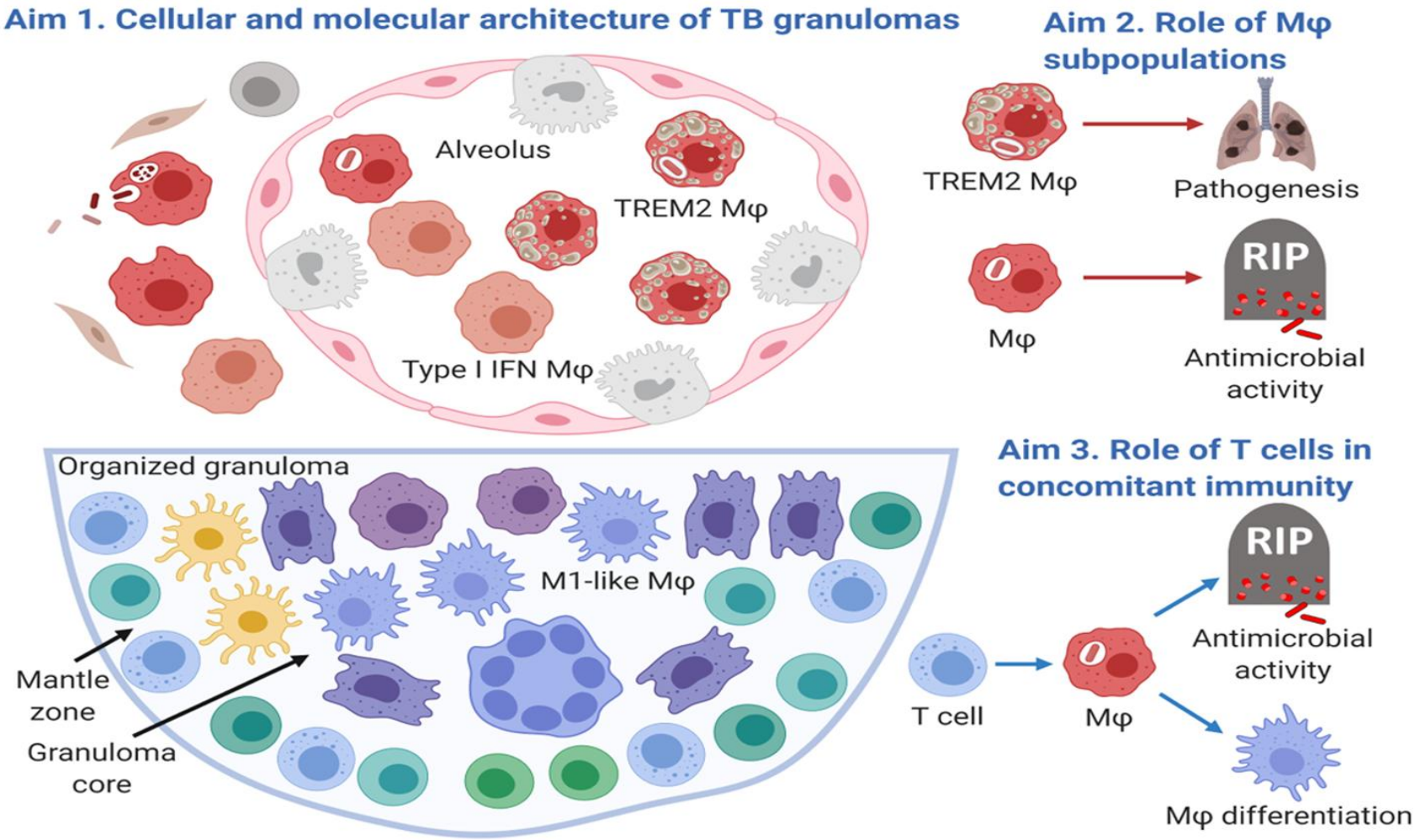
within-host genetic diversity



3. Granuloma Behavior in Drug-Resistant TB

- Granulomas are **more necrotic and cavitating**
- Higher bacterial load inside granulomas
- Multidrug-resistant strains survive even in “hostile” granuloma environments
- ✓ Necrosis spills bacilli → **high transmission**

TB Granuloma



4. Immune Response Differences: Drug-Sensitive vs MDR/XDR TB

Feature	Drug-Sensitive TB	MDR/XDR TB
Macrophage killing	Often adequate	Resistant to killing mechanisms
T-cell response	Th1 strong	Becomes exhausted/suppressed
Cytokines	Balanced TNF-α/IFN-γ	Chronic high TNF-α → tissue damage
Granuloma	Organized, fibrotic	Necrotic, cavitary, unstable
Bacillary load	Lower	Higher, prolonged persistence

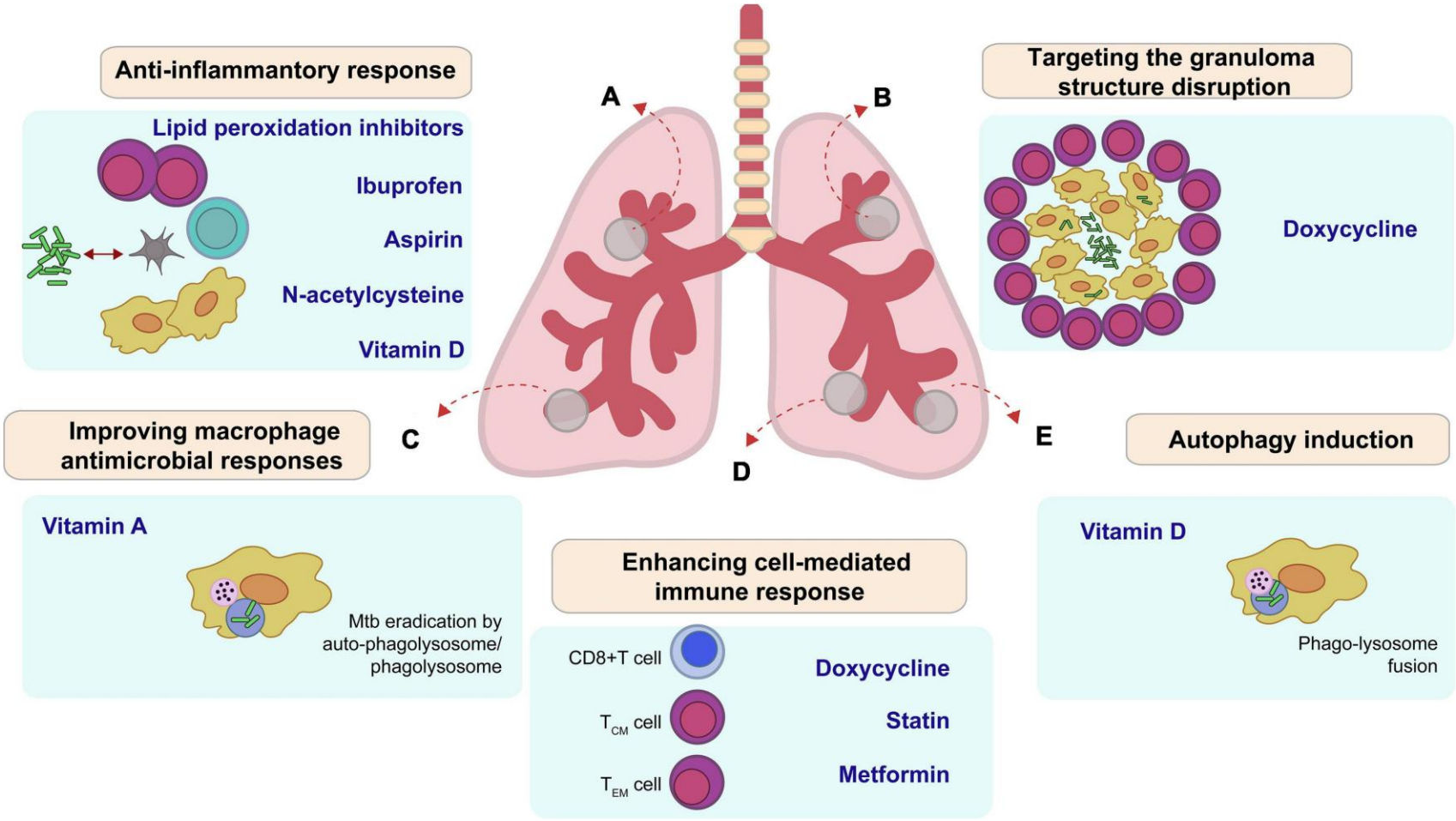
5. Impact of Host Immunity on MDR/XDR TB Outcomes

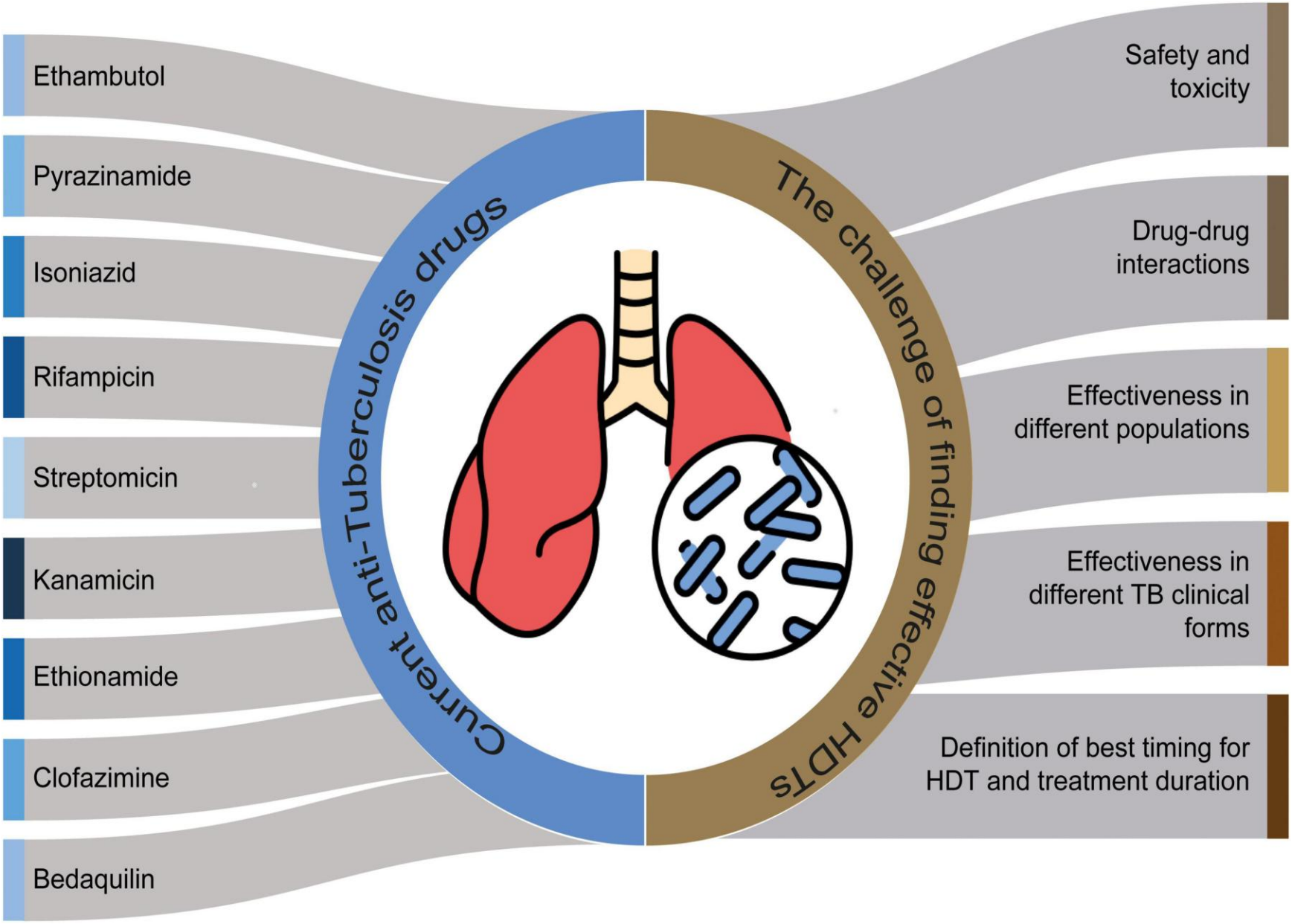
- Weak immunity **accelerates failure of drug therapy**
- HIV, diabetes, malnutrition, and corticosteroids worsen outcomes
- Even with drugs, **immune control is essential**
- ✓ Treatment success depends on **antibiotics + host immune function**

6. Newer Concepts
Host-Directed Therapy (HDT)

- Enhances immunity to help clear resistant strains:
  - IFN-γ therapy (to boost macrophage activation)
  - TNF-α modulation
  - Vitamin D supplementation (induces antimicrobial peptide cathelicidin)
  - PD-1 blockade (reduces T-cell exhaustion)
- Still experimental but promising.

Host-Directed Therapy (HDT)




Ethambutol
Pyrazinamide
Isoniazid
Rifampicin
Streptomicin
Kanamicin
Ethionamide
Clofazimine
Bedaquilin
Current anti-Tuberculosis drugs
The challenge of finding effective HDTs
Safety and toxicity
Drug-drug interactions
Effectiveness in different populations
Effectiveness in different TB clinical forms
Definition of best timing for HDT and treatment duration

7. Summary

- MDR/XDR TB strains evade immunity by surviving inside macrophages, resisting oxidative killing, altering antigen presentation, inducing chronic inflammation, and causing T-cell exhaustion.
- They produce unstable, necrotic granulomas with high bacillary load and persistent cytokine activation, leading to severe lung destruction and prolonged infectivity.

Summary

- MDR/XDR TB persists due to enhanced intracellular survival
- Chronic infection → high TNF-α, IL-1 → tissue damage
- T-cell exhaustion and ↑ Tregs reduce Th1 response
- Granulomas become necrotic → high bacillary burden➡ Severe disease and high transmission

Arigatou
Gozaimasu