Immunology Team

Respiratory Block

431

Team Members

Afnan AlRashoud

Abdullah Almazyad

Hadeel Helmi

Ibrahim Alsaleem

Rand Alhaweal

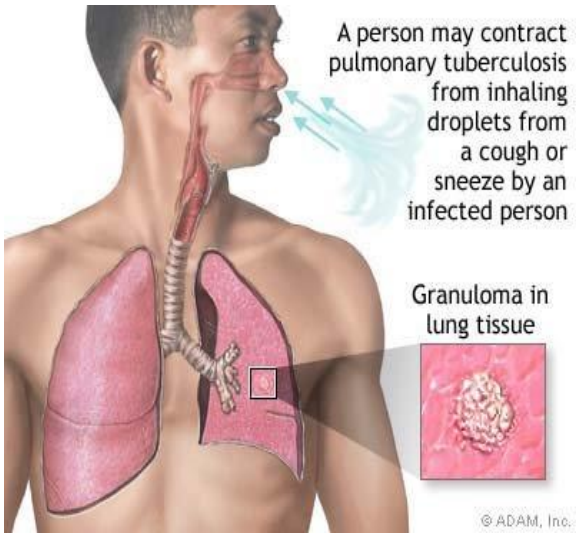
Fahad Alshuweishi

Jumanah Mirah

Abdulrahman Alshaya

- The different manifestations of infection with *Mycobacterium tuberculosis* reflect the balance between the bacillus and host defense mechanisms .

* TB is an example of an infection in which the immune state of both the host(defense) and the microbe affects the manifestations.



Droplet nuclei → comes from someone was infected (by inhaling droplets from a cough or sneeze).

Mycobacterium tuberculosis is inhaled on droplet nuclei into the lungs and deposits in the terminal bronchioles and distal alveoli.

After inhalation of *M. tuberculosis* (MTB) several scenarios may follow :

1. Mycobacteria may be destroyed "completely" by alveolar macrophages → no infection

2. *M. tuberculosis* may not be immediately killed → a primary complex will develop.

3. In a minority of cases → active disease develops (primary tuberculosis) [TB]

4.Months or years afterwards , usually under conditions of failing immune surveillance → latent infection may reactivate (post-primary TB).

- In the 2nd scenario: host is infected, however is asymptomatic
- In the 3rd scenario: there are signs and symptoms
- In the 4th scenario: reactivation of TB (+ development of symptoms) after many years of infection, could be of latent TB or in patient who has been cured of primary TB
- The 2nd scenario may become 4th scenario.

Chronological events after inhalation of M. Tuberculosis:

When the result of PPD test is :

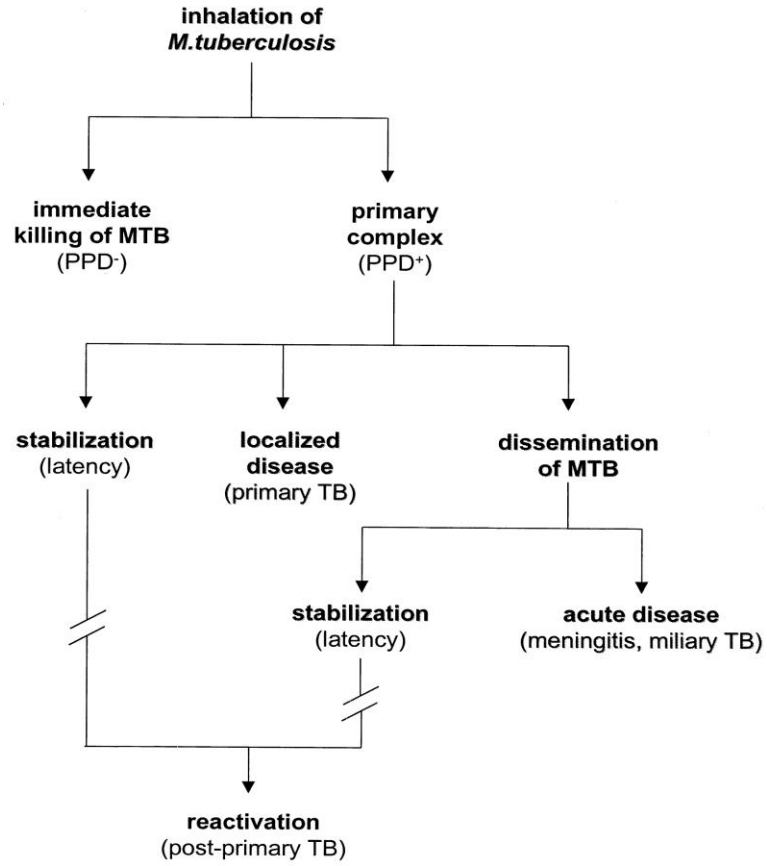
1) **–ve** → no TB infection, or there will be infection but killed immediately by alveolar macrophages (natural defense mechanisms) with NO immune response.

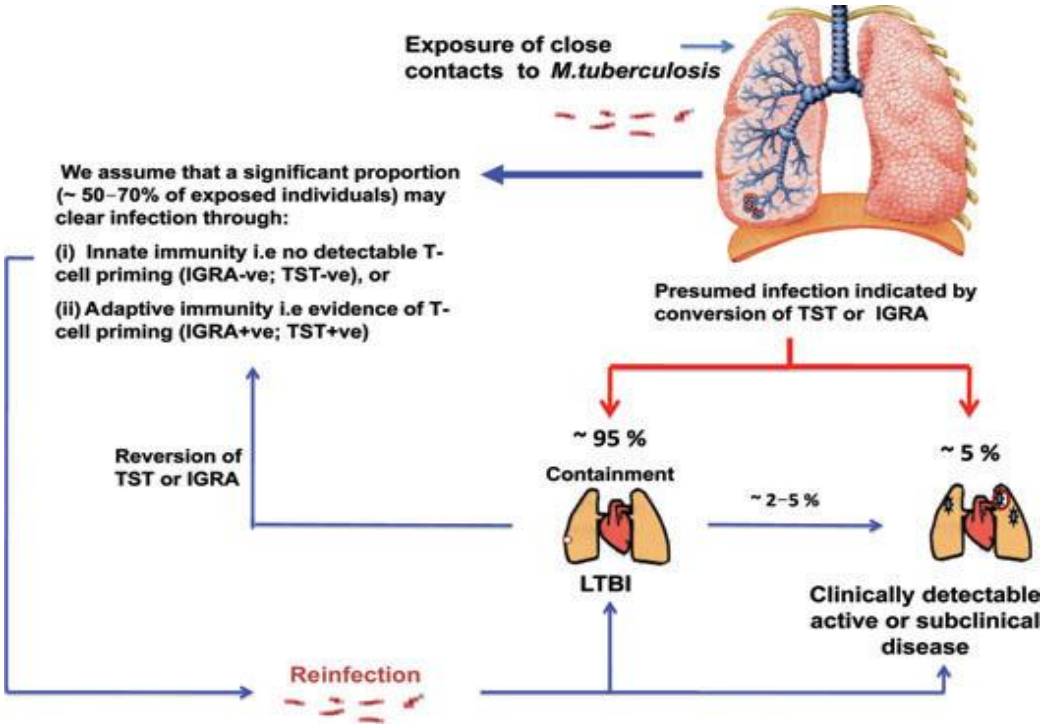
(*the results of the test will be negative because they don't develop any immune response)

2) **+ve** → immune response is produced

Miliary TB → infection involve many organs in the body, not only the lung

Post-primary TB → involve the lung only





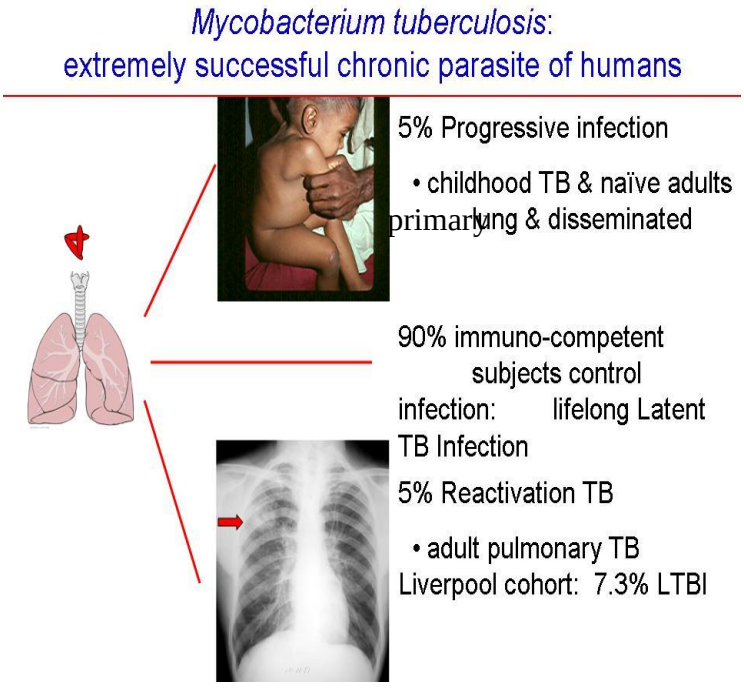
Outcomes of primary infection :

- In most patients (90%), primary infection heal to to leave a small visible scar on radiograph.
- The PPD skin test (Mantoux), as a marker of T-cell response, becomes positive.
- The Ghon (or primary) complex, most often, infection is stabilized at this point.

The Gohn complex consist of :

- The lung lesions (tubercles = small granulomas) plus the enlarged lymph nodes .
- Tubercles may become fibrotic or calcified, and persist as such for a lifetime.
- Show up on chest x- ray as radio-opaque nodules. ← (appears on radiograph as consolidation/ dense mass)

PHAGOCYTOSIS OF *M. TUBERCULOSIS* :



Alveolar resident macrophages are the cell type involved in the initial uptake of *M. tuberculosis*.

After this first encounter, dendritic cells and monocyte-derived macrophages also take part in the phagocytic process.

Various receptors have been identified for phagocyosis of *M. tuberculosis* (MTB) by macrophages and dendritic cells:

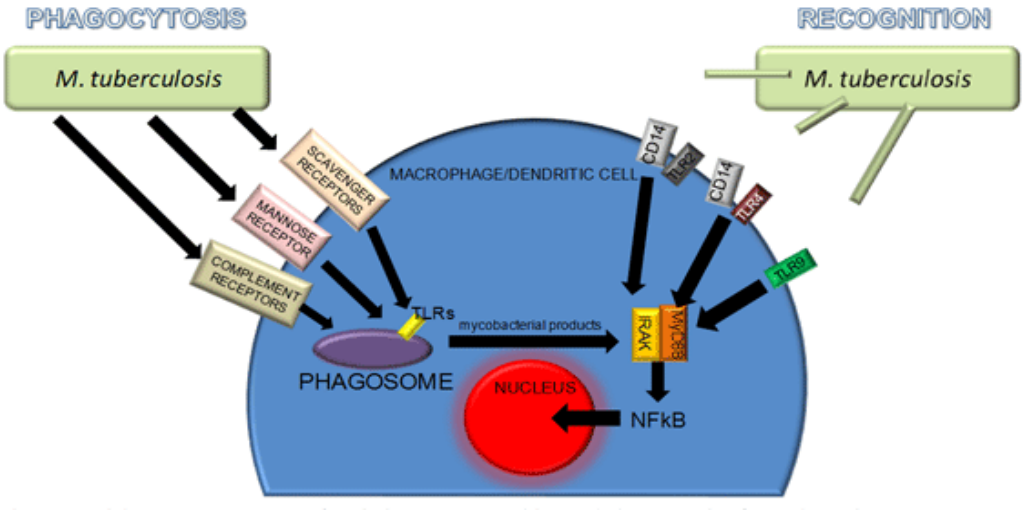
1. complement receptors are primarily responsible for uptake of opsonized *M. tuberculosis*

Opsonization : The process by which bacteria are altered to become more readily to engulfed by phagocytes.

2. mannose and scavenger receptors for uptake of nonopsonized *M. tuberculosis*.

3. TLRs play a central role in immune recognition of *M. tuberculosis.* (*TLRs=Toll-like Receptos)

Phagocytosis and immune recognition of M. Tuberculosis



Phagocytosis of *M. tuberculosis* is followed by: an inflammatory response with a crucial role for cytokine production, most important are :

- Tumor Necrosis Factor (TNF- **α**).
- Interferon-gamma (INF- γ).

Inflammatory response of phagocytic cells upon activation with *M. tuberculosis.*

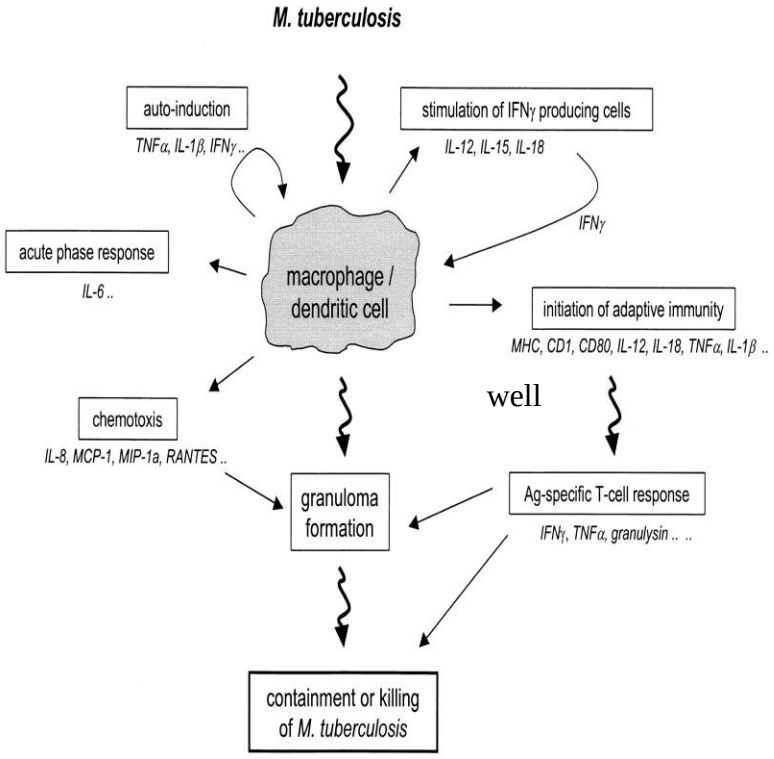
- **TNF-α :** a proinflammatory cytokine, plays a key role in:

1. granuloma formation,
2. induces macrophage activation,
3. immunoregulatory properties.
4. induction of apoptosis.

- **IFN-γ:**

Its protective role in tuberculosis is established primarily in the context of antigen- specific T-cell immunity .

IFN-γ production in vitro can be used as a marker of infection with *M. tuberculosis*



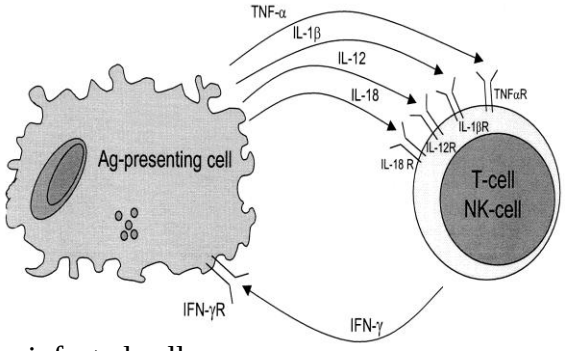
EFFECTOR MECHANISMS FOR KILLING OF *M. TUBERCULOSIS :*

1.Macrophages → are the main effector cells involved in killingof *M. tuberculosis*.

Activated by : - IFN-γ

- TNF-α

-vitamin D.



2. CD8 cytolytic T lymphocytes (CTL) secrete :

granulysin, granzymes and perforins to kill mycobacteria-infected cells.

3. Apoptosis of phagocytic cells:

Apoptosis may constitute another effector mechanism for the infected host to limit outgrowth of *M. tuberculosis* .

Apoptosis may prevent dissemination of infection.

Granulysin → it functions to create holes in the membrane of microbe and destroy.

granzymes → induce apoptosis

perforins→ attacking the membrane and forming pore.

M. tuberculosis resist killing by macrophages by many mechanisms :

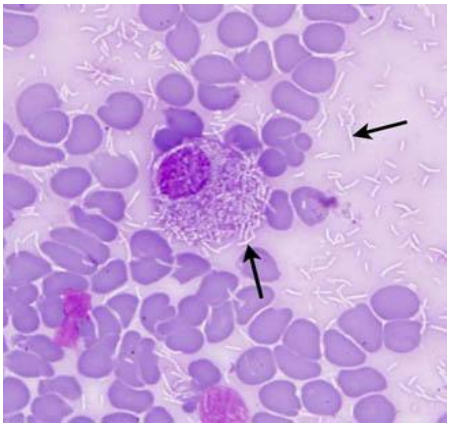
1. delay or inhibit fusion of phagosomes and lysosomes .

2. prevents phagosomal maturation and acidification of phagosomes,

3. catalase enzyme prevent the respiratory burst .

Numerous *Mycobacteria sp.* visualized as negative rod-shaped images with a Romanowsky stain (arrows).

Organisms are both free in the background and within a macrophage.



Initiation Of Adaptive Immunity To *M. Tuberculosis.* :

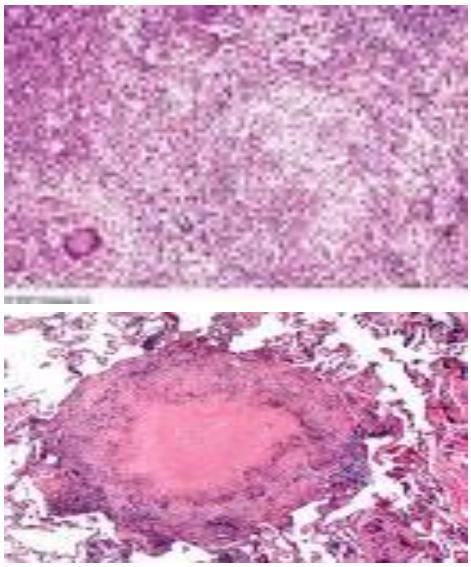
Excessive activation of cell-mediated immunity due to persistence of mycobacteria in macrophages ⇒ DTH (Delayed -Type Hypersensitivity) reactions in tuberculosis.

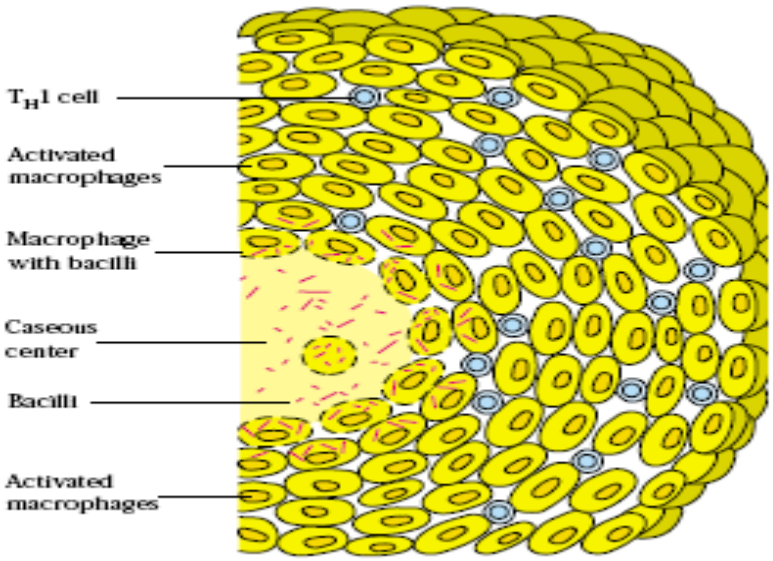
DTH reactions in tuberculosis :

Chronic DTH reactions develop when the TH_1 response activates macrophages but fails to eradicate phagocytosed microbes .

This will lead to granulomatous inflammation which is a form of DTH reactions to the bacilli .

Tuberculous Granuloma





Outcomes of T.B In individuals with defective IMMUNITY (immunodeficiency ID) :

1) **Mild I.D** ⇒ lead to reactivation, usually in the apices of the lung .

2) **Sever I.D** ⇒ leads to more widespread infection beyond the lungs .

In patients with excessive TNF production , lesions break down leading to open T.B.

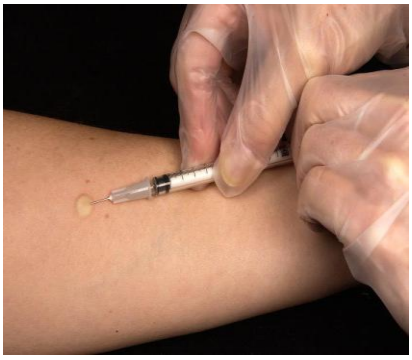
> excessive TNF may cause breakdown of lesion > cough contains microbe > any contact will lead to direct infection . i.e VERY SERIOUS

In a small proportion of young patients ,widespread primary T.B. may occur, present as :

miliary T.B OR tuberculous meningitis .

Reactivation is a consequence of impaired immune function which may result from :

1. malnutrition . ← * particularly in children
2. infections (e.g. AIDS).
3. chemotherapy.
4. corticosteroids.

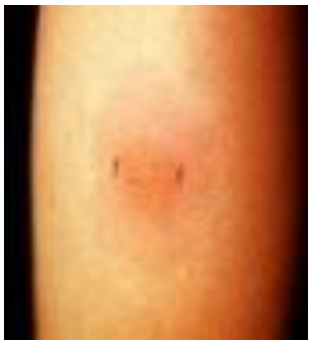


Test for immunity against T.B :

1. Delayed hypersensitivity skin test.
2. Tuberculin test (or Mantoux text) :
   Intradermal injection of PPD (purified protein derivative).

Tuberculin test reading after 48hours (delayed type IV).

Measure diameter of induration.



Blood test for T.B. exposure :

Measures interferon – gamma secreted in response to mycobacterial antigen .

Mycobacterial peptides are added to patients blood which is then incubated for 12 hours .

The amount of (IFN) produced is then measured by ELISA test .

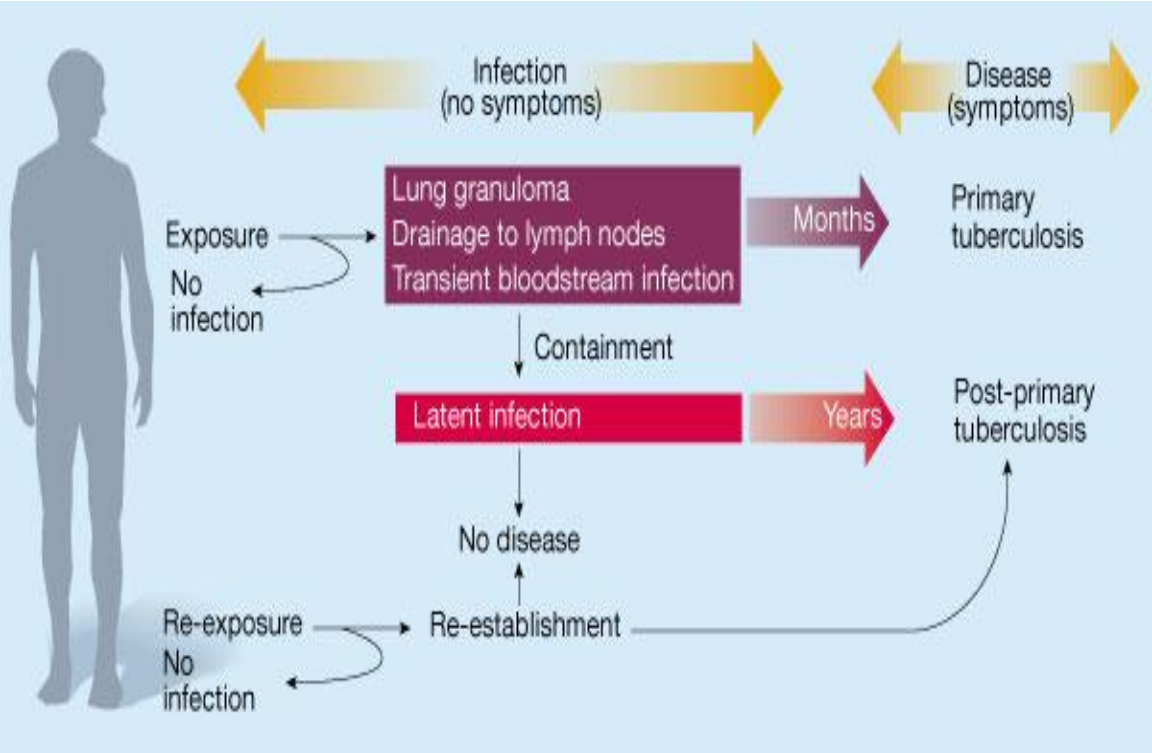
Prevention :

1.Immunoprophylaxis:

vaccination (BCG).

2. Chemoprophylaxis: [given to patients with latent TB to avoid reactivation]

anti- tuberculous drugs .



Summary

1. The interplay between *M. tuberculosis* and host immunity determines the outcome after infection.

2. With respect to the human host, both innate and adaptive defense mechanisms are involved.

3. At many stages in the host response, *M. tuberculosis* has developed mechanisms to circumvent or antagonize protective immunity.