Tuberculosis

Core Course: Medical Microbiology
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A Brief History of Tuberculosis (TB)

- Tuberculosis (phthisis) described since the time of **Hippocrates (460 BC - 370 BC)**

- **1689: Doctor Richard Morton** used the term **"consumption"** to denote TB.

- Second half of the 17th century: high death rates from TB in Europe.

- **1722: Doctor Benjamin Marten** proposed that TB could be transmitted in the air and described TB as being caused by "wonderfully minute living creatures"

- End of 19th century to the start of 20th century: Principal cause of death in Europe was TB.
    - The romantic Era of TB

"Queen Guinevere" painted by William Morris

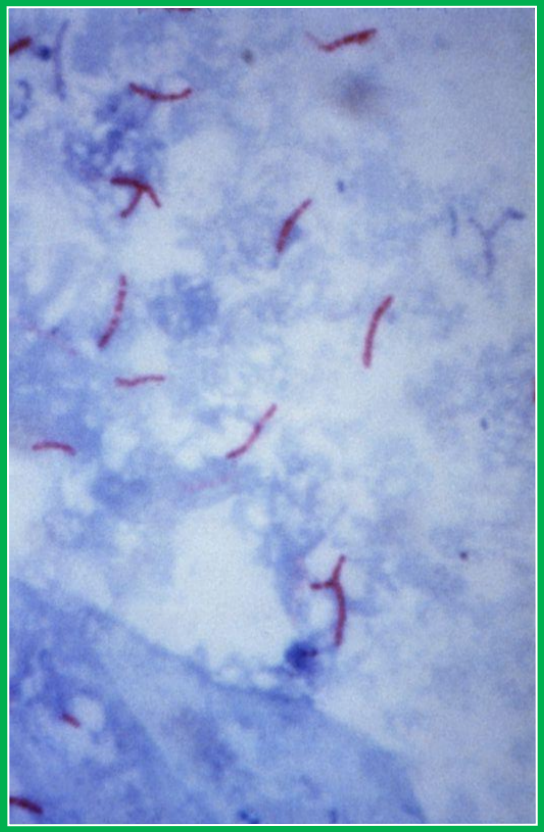
A Brief History of Tuberculosis (TB)

- **1865 Jean-Antoine Villemin:** confirmed that TB is contagious.

- **Robert Koch**:
  - **1882:** Isolated and cultured *M. tuberculosis*.
  - **1890:** Announced the discovery of tuberculin.
  - Developed staining methods used to identify the bacteria.
  - **1905:** Received the Nobel Prize

- Bacteriologist **Paul Ehrlich** developed **Ziehl-Neelsen staining**.

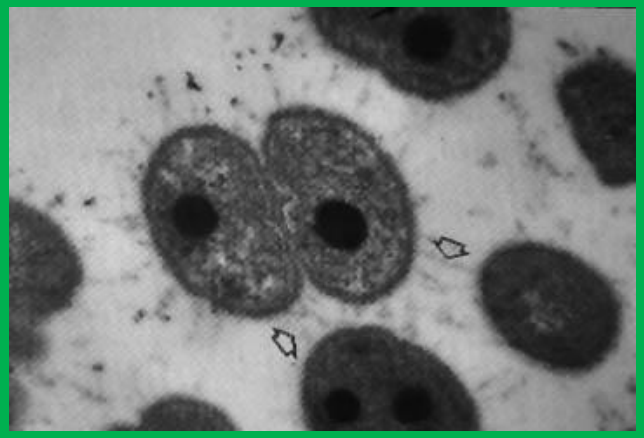
- Late 1800's: **Edward Livingston Trudeau** established "Adirondack Cottage Sanatorium", first TB sanatorium in the US.



Visualization of *M. tuberculosis* using the Ziehl-Neelsen stain

A Brief History of Tuberculosis (TB)

- **1896 Theobald Smith** demonstrated that bovine TB is caused by *M. bovis*.
- **1908 Albert Calmette** and **Camille Guérin** isolated *M. bovis* and grew it in ox bile.
  - Identified a morphological variant of *M. bovis* found to be avirulent, conferred immunity against *M. tuberculosis*.
  - Lead to the **BCG vaccine** (bacilli Calmette-Guérin).
- Development of antibiotics to combat infection:
  - **1947**: streptomycin, **1952**: isoniazid
  - The majority of drugs used to combat infection were identified between 1945 and 1967.
  - No new drugs developed since the 1980's
- Reoccurrence of TB for two main reasons:
  1) HIV/AIDS pandemic
  2) Development of drug resistance



M. bovis

Tuberculosis in Humans

- **Reservoir:** Humans
- **Transmission:** Airborne disease (aerosol transmission)
- **Symptoms**:

Latent TB infection:

No symptoms

*Cannot spread TB

Active TB infection:

Bad cough

Coughing up blood/sputum

Chest pain

Loss of appetite

Weight loss

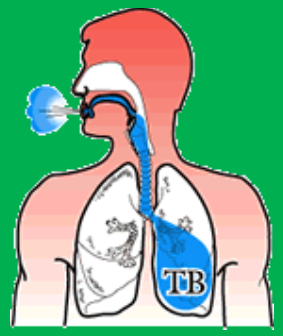
Fever

Chills

Night sweats

Swollen glands

*Contagious

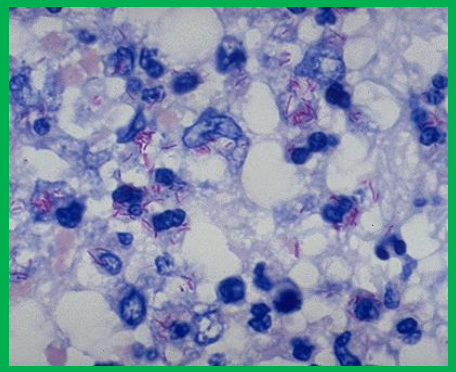


Extra-pulmonary TB: Symptoms depend on location of infection
General symptoms: fatigue, fever, loss of appetite, weight loss.

TB of **lymph nodes**: swelling of lymph nodes
TB **meningitis**: neurological symptoms including headache
Spinal TB: Mobility impairments, pain

Mycobacterium Tuberculosis

SEM of *M. tuberculosis*



M. Tuberculosis
(stained in purple)

General Characteristics

- Family – Myobacteria
- Gram-positive aerobic rod-shaped bacilli
- "Acid fast" bacteria
- Lack of spore formation and toxin production
- No capsule, flagellum (non-motile)
- Generation time of 18- 24 hours but requires 3-4 weeks for visual colonies

Pathological Features

- Principle cause of Human Tuberculosis
- Intracellular pathogen (alveolar macrophages)
- Waxy, thick, complex cellular envelope
- Cell envelope components ex) sulfolipids
- Produces **tubercles**, localized lesions of *M. tuberculosis*

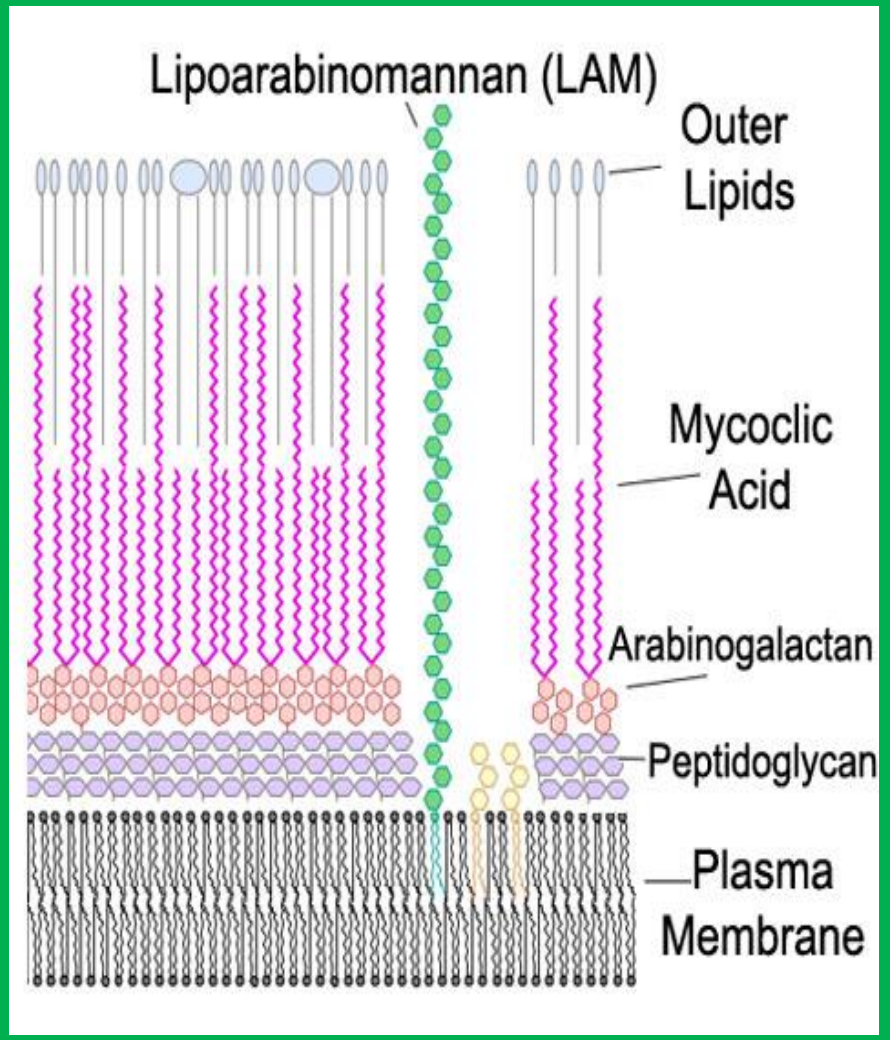
Mycobacterial Cellular Envelope

General Features

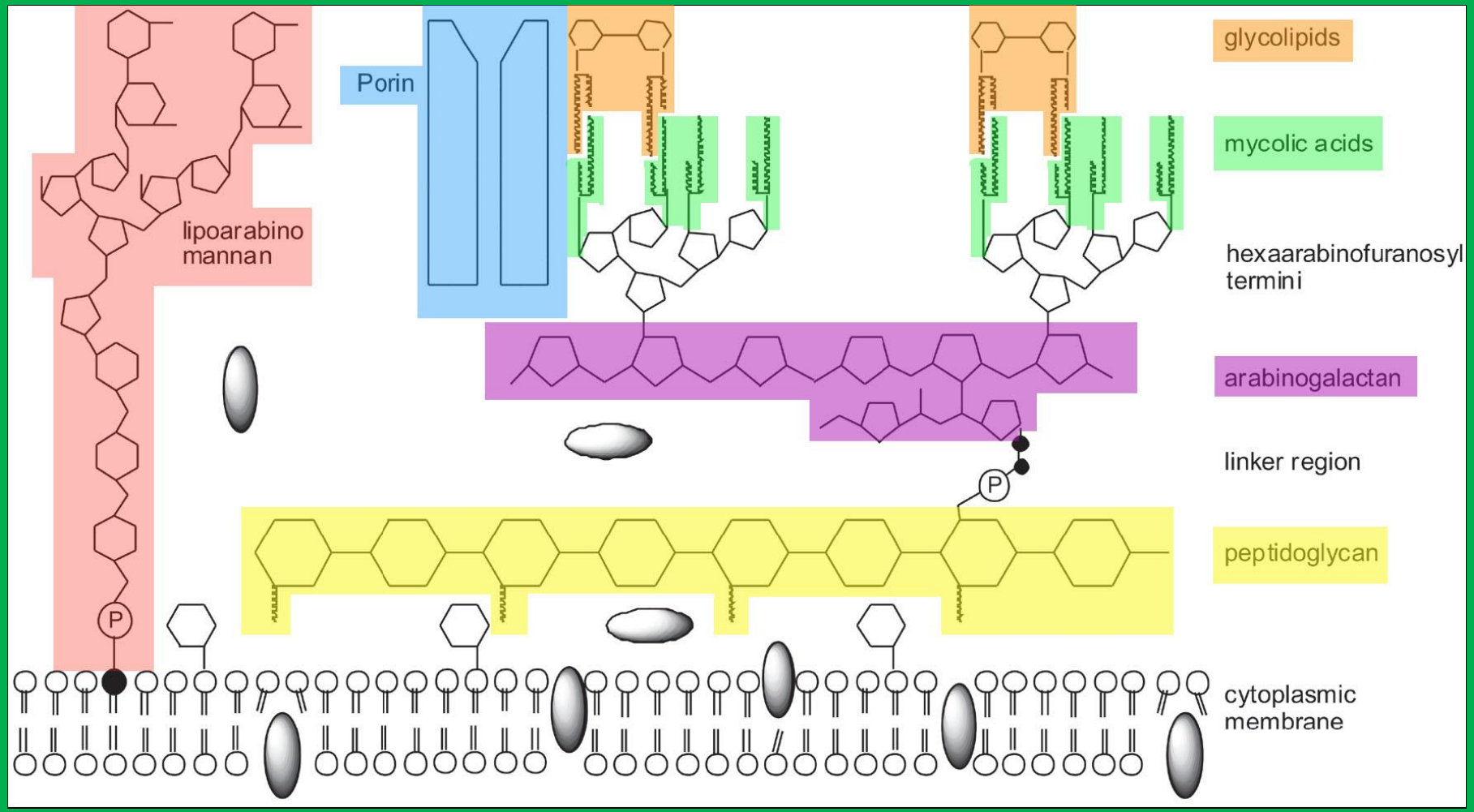
- Thick, waxy and complex
- Higher fluidity in more external regions than internal regions
- Relatively impermeable to hydrophilic solutes
- Contain porins (selective cationic channels)

Main Components

- Peptidoglycan
  → contains N-glycolylmuramic acid instead of N-acetylmuramic acid
- Arabinogalactan
- Mycolic Acids (60% of cellular envelope)
- Lipoarabinomannan (LAM)



Mycobacterial Cellular Envelope



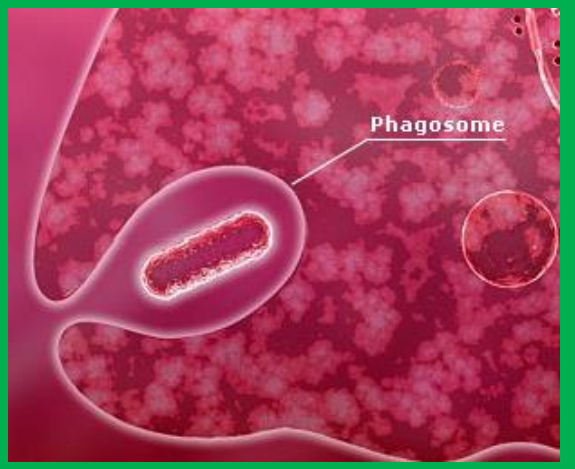
Contribution of Mycobacterial Cellular Envelope to Pathogenesis

Resistance to Drying and Other Environmental Factors

- Thick, waxy nature of cellular envelope protects M. tuberculosis from drying, alkali conditions, and chemical disinfectants
- Hinders entrance of antimicrobial agents

Entry into Host Cells

- Lipoarabinomannan (LAM) binds to mannose receptors on alveolar macropages leading to entry into the cell



Interference of Host Immune Response

- Glycolipids and sulfolipids decrease the effects of oxidative cytotoxic mechanism
- Inhibition of phagosome and lysosome fusion inside macrophage
- Waxy cellular envelope prevents acidification of the bacteria inside the phagosome

Factors Affecting Pathogenicity

Active Infection

- Only individuals with an active infection can transmit the disease

Transmission

- Aerosolized droplets need to be <10μm in order to evade the ciliated epithelium of the lung to establish infection in the terminal alveoli

Growth & Structure

- Only require a very few number of bacteria to establish an infection (1-10 bacteria)
- Slow generation time

M. Tuberculosis in sputum (stained in red)

Variability of Infection Rates

Exposure Time

- Most infected individuals expel relatively few bacilli, transmission of TB usually occurs only after prolonged exposure to someone with active TB.
- On average, 50% of people are likely to become infected with TB if they spend 8hrs/day for six months or 24hrs/day for two months working or living with someone with active TB.

Health of Individuals

- Active TB typically occur in individuals whose immune systems have been weakened by **age**, **disease**, **improper nutrition** or use of **immunosuppresive drugs**.

Tuberculosis – Disease Progression

Primary Infection

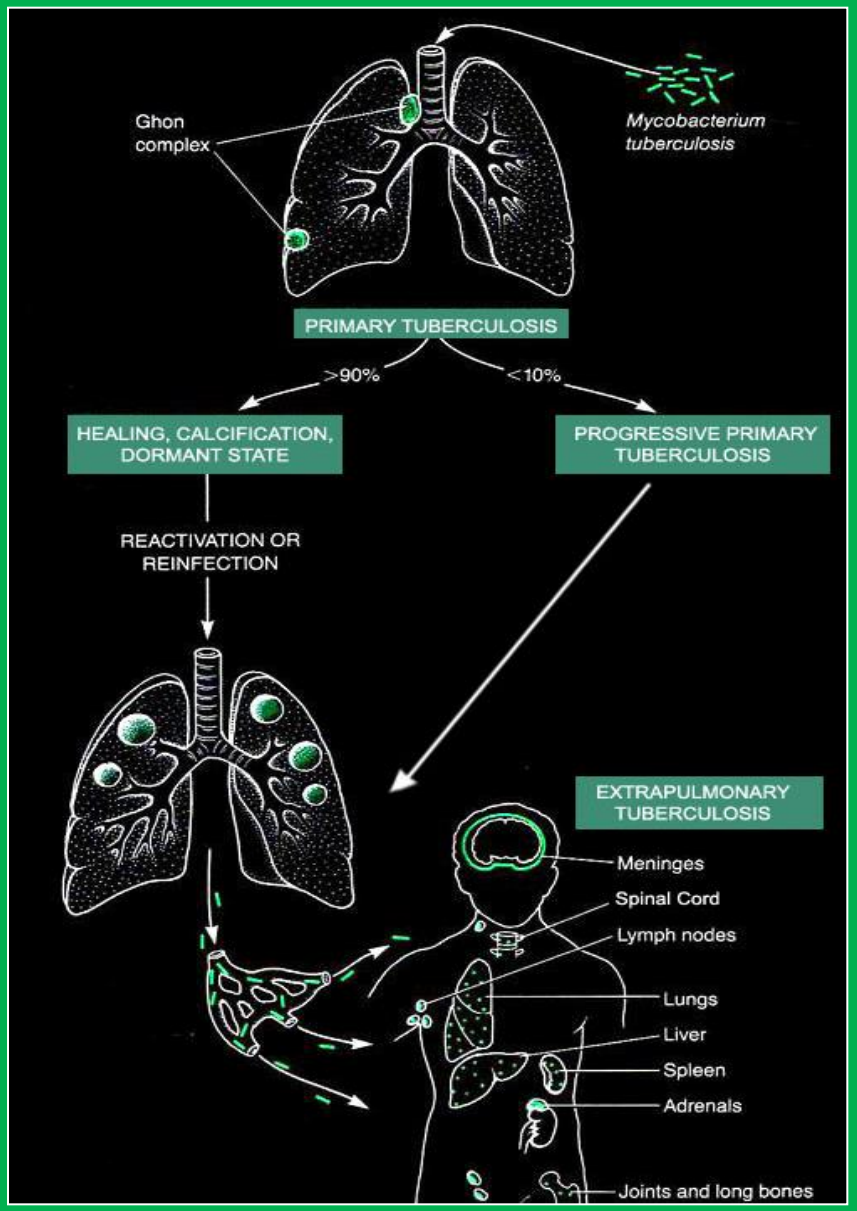
In healthy individuals…

- *M. tuberculosis* phagocytosed by alveolar macrophages leading to intracellular proliferation and **tubercle** formation
- Cell-mediated response develops and eliminates most of the bacilli in 2-6 weeks
- Commonly **asymptomatic**

OR

- *M. tuberculosis* can remain **dormant** intracellularly

Tuberculosis – Disease Progression



Primary Infection

Immunocomprimised Individuals…

- Infection leads usually leads to progressive primary tuberculosis, where the pathogen breaks out of the tubercles in the alveoli and cause active disease
- Active disease leads to chronic inflammation
- Death of pathogen and pulmonary cells can lead to **Gohn complex** and **granuloma** formation
- May lead to **extrapulmonary tuberculosis** (TB infection outside the lung in the CNS and lymph nodes)

Latent Tuberculosis Infections

- Following exposure to TB: Inhaled bacilli usually destroyed by **host's immune system** (90-95% of the time).
  - Healthy person: Recruitment of **T-cells** and **macrophages** which results in controlling the infection.
- Some bacilli can establish infection in **macrophages** (**phagosomes**) leading to host immune response
- Bacilli forced into an inactive (**latent**), non-replicating state.
  - Survive intracellularly: prevent **phagosome-lysosome fusion**.
  - Infection contained but not eradicated.
- The dormant bacteria are still viable, can be re-activated: Approximately 10% of latent infections will develop into active TB if left untreated.
- Factors that lead to re-activation of the bacteria: **HIV co-infection**, aging, cancer, diabetes etc

M. Tuberculosis colonies

Tuberculosis – Disease Progression

Note…

- Infection does not mean disease!
- Infection can lead to active disease or dormant state of pathogen
- Active disease develops differently (Healthy individuals VS. Immunocomprimised individuals)

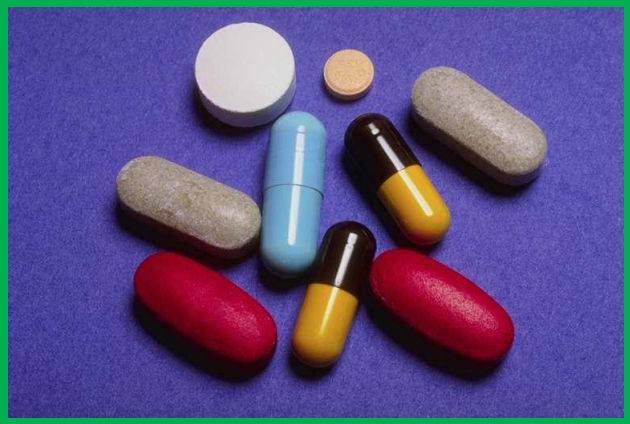
Summary of TB Infection in Alverolar Macrophages

http://www.nature.com/nrmicro/animation/imp_animation/index.html

Treatment

Antibacterial chemotherapy:

- Combination of **first** and **second line** drugs for the first 2 months which could include:
  - **Isoniazid**
  - **Rifampicin**
  - **Pyrazinamide**
  - **Streptomycin** or **Ethambutol**



- Next 4 months, combination of:
  - **Isoniazid**
  - **Rifampicin**

- Early resistance to **isoniazid**: other first-line drugs such as **ethambutol**, **streptomycin**, **pyrazinamide** and **fluoroquinolones** can be added to drug arsenal (treatment period also extended).
- These drugs are relatively effective in killing the bacteria, however, they also produce a wide variety of side effects.

Treatment

First line drugs:

- **Bactericidal agents**: kill active bacteria, important in the early stages of infection.

Second line drugs:

- **Bacteriostatic**: hinder bacterial growth.
  - Strengthen treatment in the case of resistant bacteria.
  - Less efficient and generally more toxic than first line drugs.

Inappropriate chemotherapy:

- Monotherapy (single drug treatment)
- Decreased treatment period
- Low absorption of drugs