

Spirochetes

- **Slender**, motile, flexible, **undulating**, gram-negative bacteria
- Characteristic **corkscrew (helical) shape**
- Can be aerobic, anaerobic or facultative anaerobic
- Pathogenic spirochetes are included in
3 genera: *Treponema*, *Borrelia* and *Leptospira*

Syphilis - aetiology and transmission

- spirochaete ***Treponema pallidum*** (thin, helical (0.1 to 0.5 × 5 to 20 µm), gram-negative bacteria
- 3 periplasmic **flagellae** are inserted at each end. These spirochetes **do not grow in cell-free cultures**
- too thin to be seen with light microscope by Gram or Giemsa staining, but **dark-field microscopy** or **fluorescent microscopy** is suitable

Note: related to *T. pallidum* subspecies *endemicum* causes endemic syphilis (bejel); *T. pallidum* subspecies *pertenue* causes yaws; and *T. carateum* causes pinta. Bejel, yaws, and pinta are nonvenereal diseases

Virulence factors

- **Generally classical virulence factors are not known**
- **Outer membrane proteins** promote adherence to host cells
- **Hyaluronidase** may facilitate **perivascular infiltration**
- **Tissue destruction** primarily results **from host's immune response** to infection

Syphilis - pathogenesis

- the organism **enters** the body through **minute abrasions** (skin, mucous membranes)
- local slow multiplication – infiltration the lesion with plasma cells and macrophages (endarteritis)
- incubation period – 3 weeks
- **stages**
- 1. **primary (skin lesion – chancre)**
 2. **secondary (skin lesions disperse over the body – rash, pailoma-like lesions in anogenital or oral area - condylomata lata)**
 3. **tertiary – late phase** (all tissues may be involved , local multiplication and destruction of the tissue - arteritis, dementia, blindness, granulomatous lesions (gummas) may be found in bone, skin)

Note: not all patients go through all the stages, after 1. and 2. stages patients usually remains free of the disease)

Syphilis – congenital syphilis

- **In utero infections** can lead to serious **fetal disease**, resulting in **latent infections**, **multiorgan malformations**, or **death of the fetus**.
- *Treponema pallidum* is strong biological **teratogen!!!**
- Most infected infants are **born without clinical evidence** of the disease, but **rhinitis** then develops and is followed by a widespread desquamating **maculopapular rash**. **Teeth and bone malformation**, **blindness**, **deafness**, and **cardiovascular syphilis** are common in untreated infants who survive the initial phase of disease.

Syphilis – congenital syphilis

- **Most teratogenic**—meaning it has the **highest risk of vertical transmission** and **severe developmental consequences**—when the mother is in the **primary or secondary stages of syphilis**, and when the infection is present during the **first or second trimesters of pregnancy (transmission in 60-100%.**

Summary:

- **Early Infection (1st/2nd Trimester): catastrophic developmental outcomes**, e.g. fulminant congenital syphilis, severe bone abnormalities, hepatosplenomegaly, or intrauterine fetal stillbirth.
- **Late Infection (3rd Trimester):** While the transmission rate itself remains very high if the mother is untreated, the **fetus is often born asymptomatic** because organogenesis is already complete. However, they will develop symptoms postnatally if left untreated.

Syphilis – primary stage



Syphilis – secondary stage



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1. Primary Stage

- **Incubation** period: appears 10 to 90 days after exposure.
- Symptoms: A firm, round, and usually painless sore called a **chancre** (usually painless) develops **at the site of infection** (genitals, anus, or mouth). **Swollen lymph nodes** often occur nearby.
- **Infectiousness: highly contagious**; the sore heals on its own within 3 to 6 weeks, but the infection remains if untreated.

2. Secondary Stage

- Timing: begins **few weeks to months after the chancre fades**.
- Symptoms: A non-itchy rash often appears, including characteristic rough, reddish-brown spots on the palms of the hands and soles of the feet. Other signs include mucous membrane sores, fever, sore throat, patchy hair loss, and fatigue.
- Infectiousness: Highly contagious during this phase. Symptoms eventually clear without treatment.

3. Latent Stage

- **Follows the secondary stage and can last for years.**
- **Symptoms:** There are no visible signs or symptoms, but the bacteria remain dormant in the body. It is detected only through serology tests.
- **Infectiousness:** Generally **non-contagious through casual contact**, though pregnant individuals can still transmit congenital syphilis to an unborn baby.

4. Tertiary (Late) Stage

- **Develops 1 to 30+ years after the initial infection if left untreated.**
- **Symptoms:** causes **severe and life-threatening damage to internal organs**, including the **brain, nerves, eyes, heart, and blood vessels (cardiovascular syphilis and neurosyphilis)** along with **destructive tissue lesions called gummata.**
- ***Infectiousness:*** Not generally contagious to sexual partners at this point, but extremely dangerous to health²³

A late-stage cardiovascular complication of untreated syphilis that causes **inflammation, weakening, and potential aneurysm of the main artery**



Fig. left: mass on the anterior chest; right: transthoracic echocardiography, showing severe aneurysmal dilatation of the aortic arch and an extraluminal aneurysmal sac (pseudoaneurysm) with a narrow neck, with flow contained by what appears to be a thrombus (ref: Rev Port Cardiol. 2015;34(11):691.e1---691.e4).

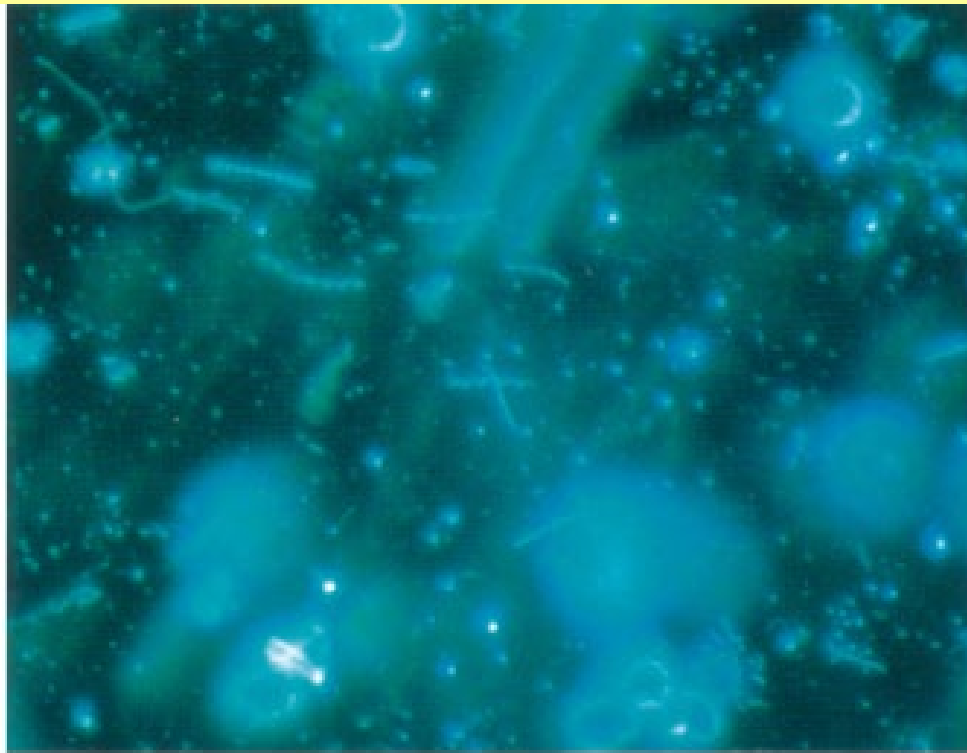
Note: Treponema pallidum infection causes vascular damage primarily through obliterative endarteritis, endothelial activation, and the disruption of the blood-brain barrier

Syphilis – tertiary stage



Laboratory dg - microscopy

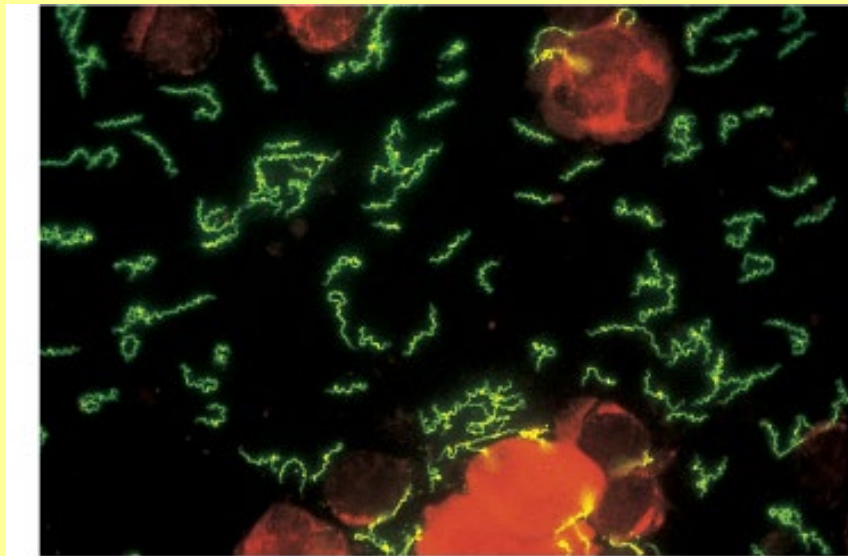
- the diagnosis of **primary, secondary, or congenital syphilis** can be made **rapidly** by **dark-field examination** of the exudate from skin lesions



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Laboratory dg – fluorescent microscopy

- **spirochetes do not survive transport to the laboratory, and tissue debris can be mistaken for spirochetes.** Material collected from oral and rectal lesions should not be examined because nonpathogenic spirochetes can contaminate the specimen. A more useful test for detecting *T. pallidum* is the **direct fluorescent antibody test**



Laboratory dg – serology, nontreponemal tests

• **Nontreponemal tests** measure immunoglobulin (Ig)G and IgM antibodies (also called **reaginic antibodies**). The antigen used for the nontreponemal tests is **cardiolipin**, which is derived from beef heart. The two tests used most commonly are the **Venereal Disease Research Laboratory (VDRL) test** and the **Rapid Plasma Reagin (RPR) test**.

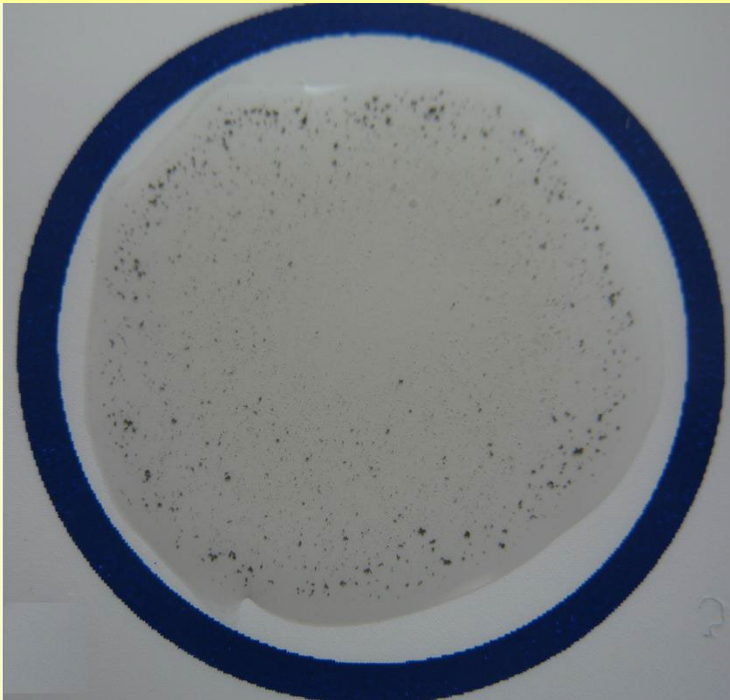


Fig. Positive agglutination in reagin test

Laboratory dg – serology, treponemal tests

- The tests **most commonly used** are the fluorescent **treponemal antibody-absorption (FTA-ABS) test** is an indirect fluorescent antibody test. *T. pallidum* immobilized on glass slides is used as the antigen. The slide is overlaid with the patient's serum, which has been mixed with an extract of nonpathogenic treponemes. The fluorescein-labeled antihuman antibodies are then added to detect the presence of specific antibodies in the patient's serum.
- Treponema pallidum* particle **agglutination (TP-PA)** test. The TP-PA test is a microtiter agglutination test. Gelatin particles sensitized with *T. pallidum* antigens are mixed with dilutions of the patient's serum. If antibodies are present, the particles agglutinate. A variety of specific **enzyme immunoassays (EIAs)** have been developed recently and appear to have sensitivities and specificities similar to the FTA-ABS and TP-PA tests.

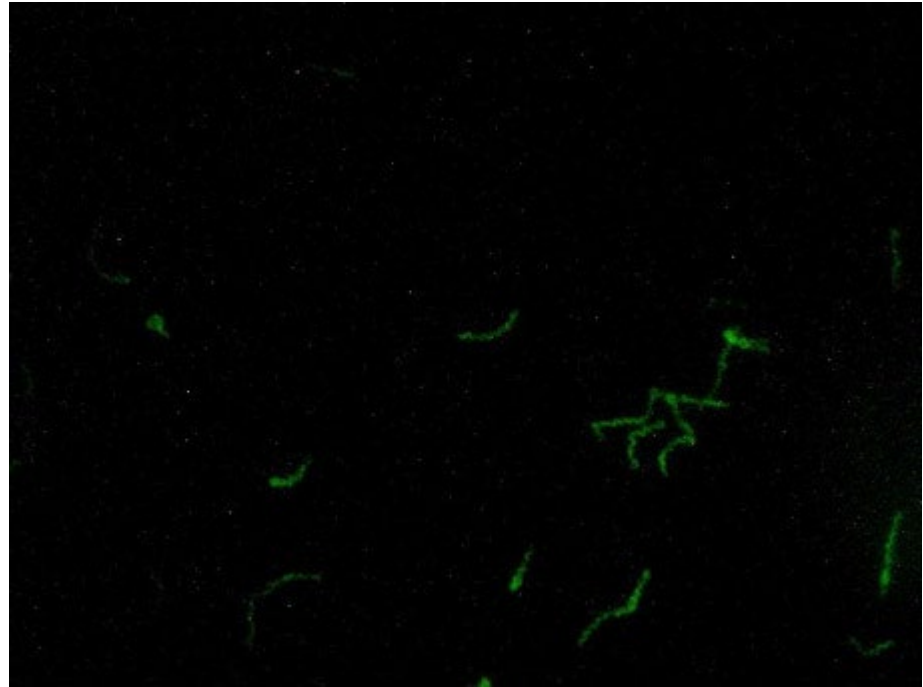
Laboratory dg – serology, treponemal tests

- The tests **most commonly used** are the fluorescent **treponemal antibody-absorption (FTA-ABS) test**



Procedure:

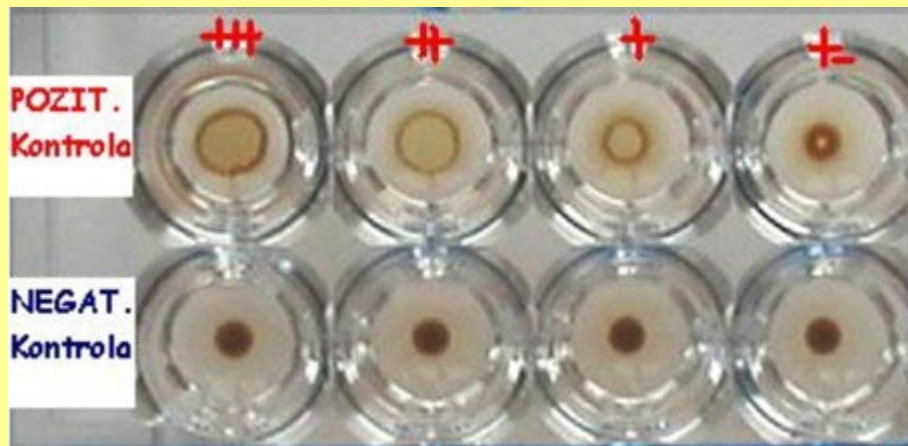
1. Dilution of patients' sera (Ab) and inoculation on slide where Ag is fixed
2. Add antihuman Ab labeled by fluorochrom
3. Observe using fluorescent microscope



Positive result

Laboratory dg – serology, treponemal tests

- Treponema pallidum particle **agglutination** (TP-PA) test. The TP-PA test is a microtiter agglutination test. Gelatin particles (or erythrocytes TPHA) sensitized with T. pallidum antigens are mixed with dilutions of the patient's serum. If antibodies are present, the particles agglutinate. A variety of specific **enzyme immunoassays** (EIAs) have been developed recently and appear to have sensitivities and specificities similar to the FTA-ABS and TP-PA tests.



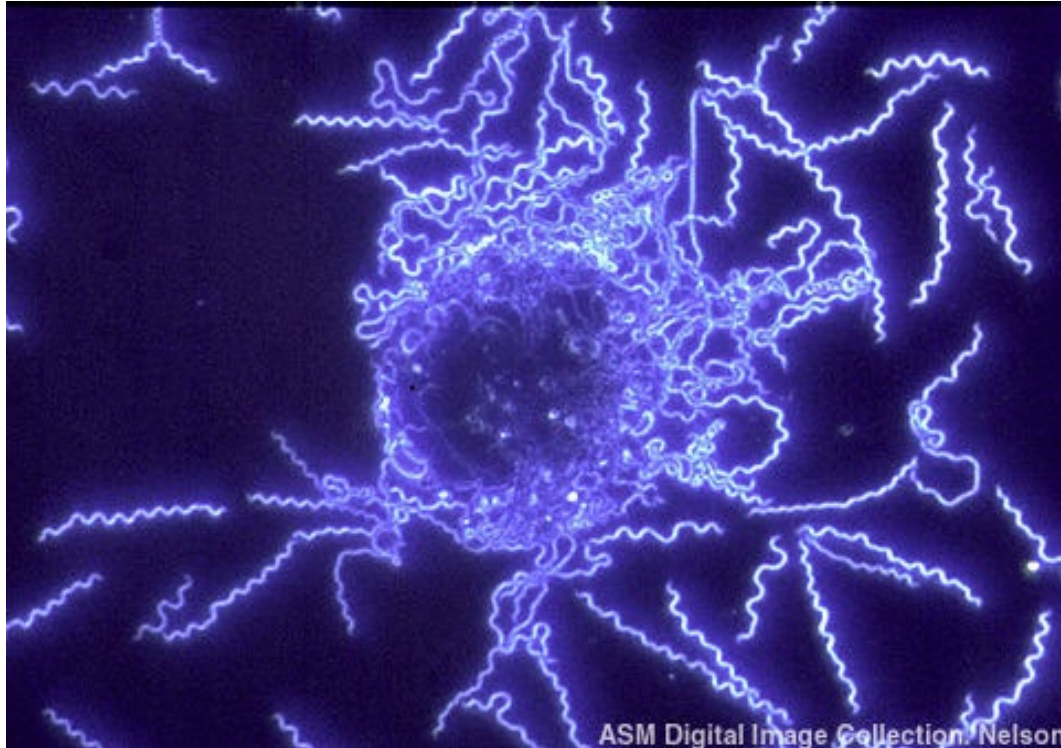
TPHA test

Treatment, prevention, control

- **penicillin** is the **drug of choice**
- long-acting **benzathine penicillin** is used for the **early stages**
- **penicillin G** is recommended for **congenital and late syphilis**.
- **tetracycline** and **doxycycline** can be used as alternative antibiotics for patients allergic to penicillin. Only penicillin can be used for the treatment of neurosyphilis; thus, **penicillin-allergic patients** must undergo **desensitization**. This is also true for pregnant women, who should not be treated with the tetracyclines. Because protective vaccines are not available, syphilis can be **controlled** only through the practice of **safe-sex techniques** and adequate contact and treatment of the sex partners of patients who have been documented with infection.



Lyme disease



This image is a dark-field microscopic image of the **spirochete** ***Borrelia burgdorferi*** taken from a culture of the organism in the laboratory. The dark-field microscopy allows visualization of these tightly curled spiral bacteria that **do not stain well with conventional bacterial stains** (Nelson, American society for microbiology).

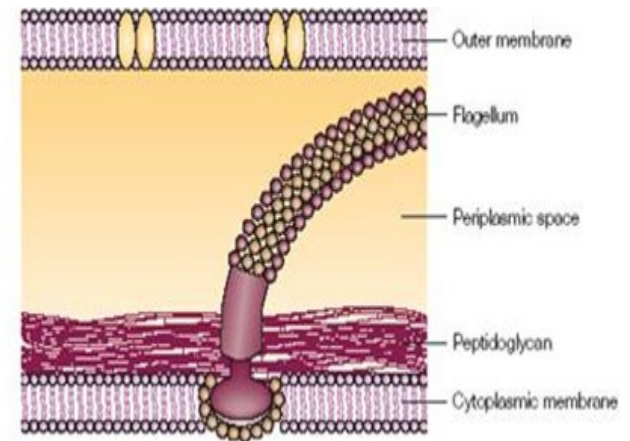
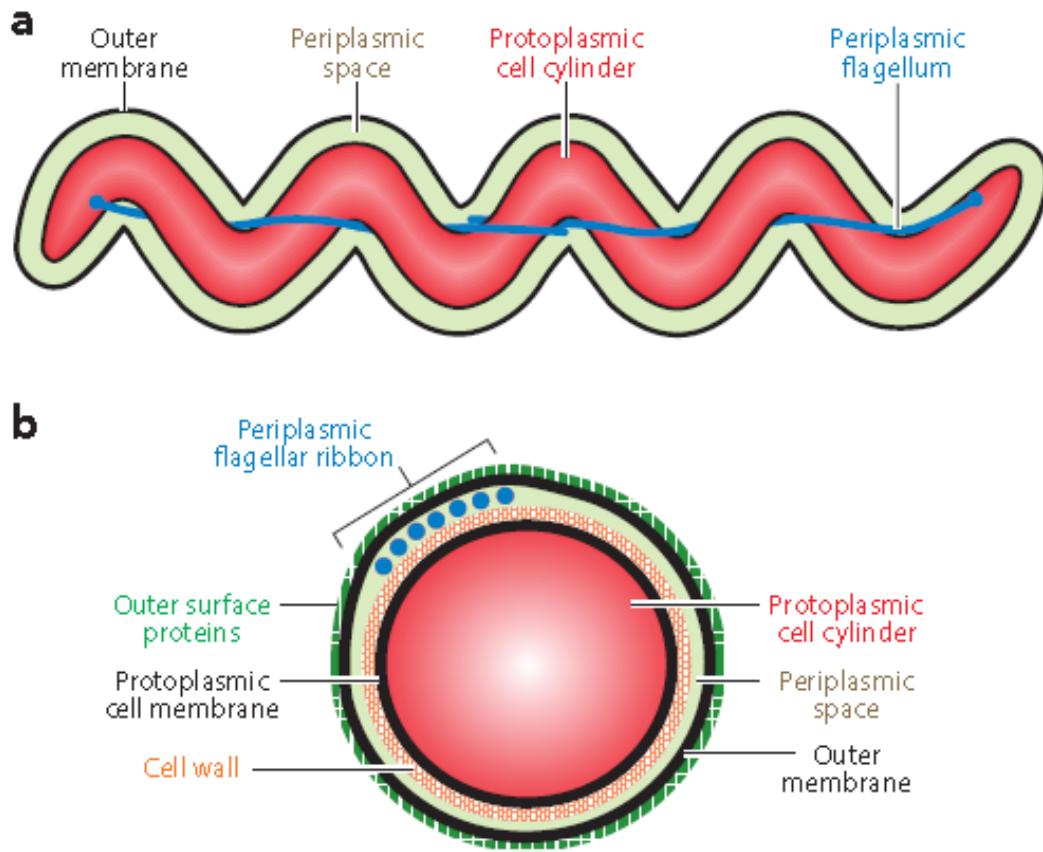
Borrelia burgdorferi infection - history

- * **1764** - reverend Walker, Scotland, first described *erythema migrans* (EM) and vector - tick
- * **1883** - *acrodermatitis chronica atrophicans* (skin inflammation on acral parts – e.g. fingers, thin blue skin), German dermatologist Buchwald, Breslau (Wroclaw)
- * **1909** – Swedish dermatologist Afzelius described symptoms of EM
- * **1976**, Steere – epidemic arthritis, Lyme disease (Connecticut, USA), proved infection, agent unknown
- * **1981** – agent described by Burgdorfer, Switzerland

Taxonomy and properties of *Borrelia burgdorferi*

- * order **Spirochaetales**
- * **screwed** (4-15x), gram-negative, velikost 2-05 x 5-30 μm
- * **motile** – rotation around axis, **corkscrew motility**
- * **generation time: 7-20h**
- * **morphology**
 - amorphous surface layer (S)
 - periplasmic space (3-8 flagella)
 - small linear **chromosom** (cca 1000 kb)
 - **plasmids**: 17-21 linear or circular (genes e.g. determined e.g. **surface proteins OspA a OspB**)

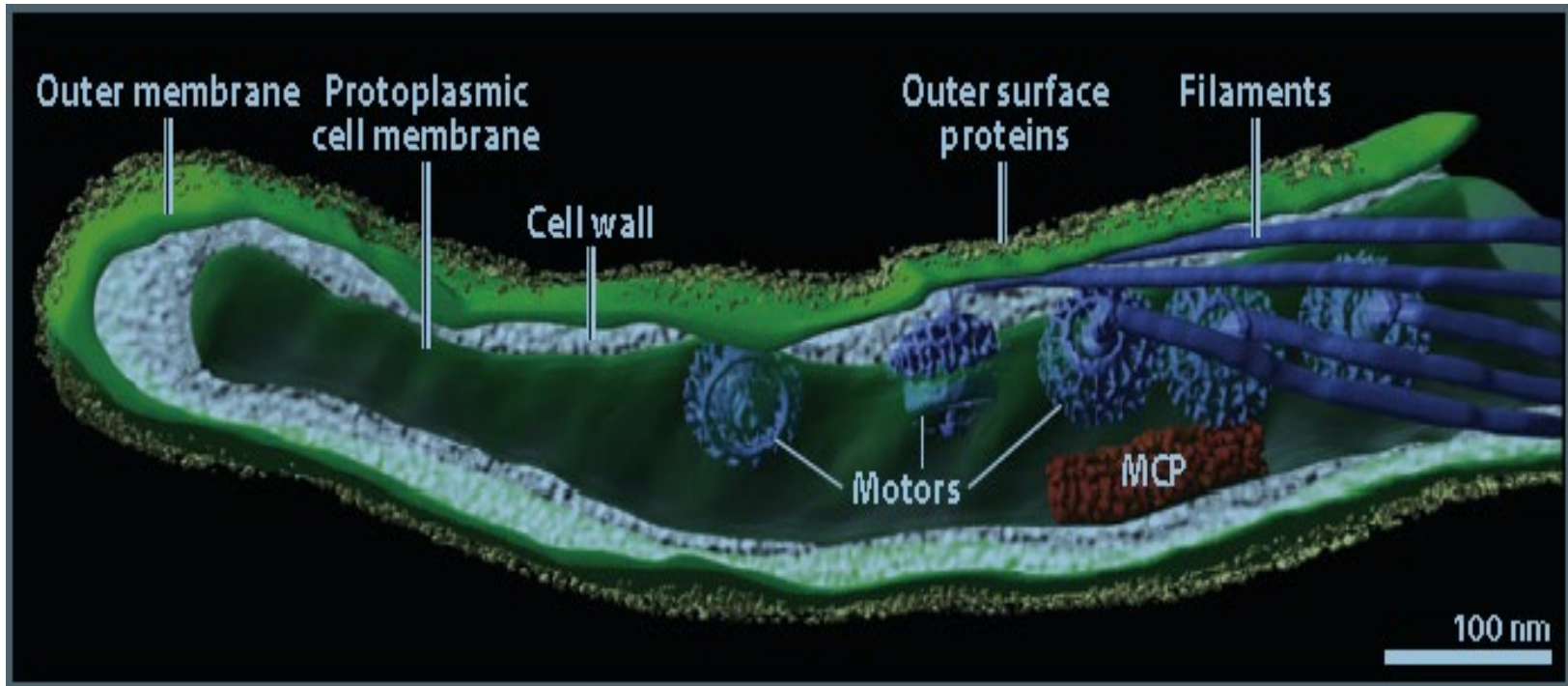
Morphology



(a) Longitudinal section - diagram of typical spirochaete. Flagella in the centre are covered.

(b) Transversal section - diagram of *Borrelia burgdorferi*. Seven flagella built solid ribbon, protruded from outer membrane (Charon et al., Annu. Rev. Microbiol. 2012. 66:349–70)

Apical morphology



Cryo-elektron tomography (ref: Charon et al., Annu. Rev. Microbiol. 2012. 66:349–70)

Agents of lyme disease

- * ***Borrelia burgdorferi sensu stricto*** (often USA; Europa) – in majority affected motion apparatus
- * ***Borrelia burgdorferi sensu lato***
 - ***Borrelia afzelii*** (*Europa, Asia...*), most frequently affected skin
 - ***Borrelia garinii*** (*Europa, Asia...*), most frequent affected nervous system
- * **tick-borne infection**: 30-50% patients, (*Ixodidae* – *I. ricinus*, *I. persulcatus* – east Europe, Asia; *I. scapularis* - USA)
 - Isolated **also** – from **other ticks** and **blood sucking insects**

Note: In the Czech Republic, *Borrelia afzelii* slightly predominating over *Borrelia garinii* in both the population of infected ticks and clinical findings. The myth that Lyme disease is transmitted by mosquitoes has been conclusively debunked by an extensive studies. The research confirmed that mosquitoes of the genus *Culex* lack the biological capacity to transmit the bacterium.

Ixodes ricinus life cycle

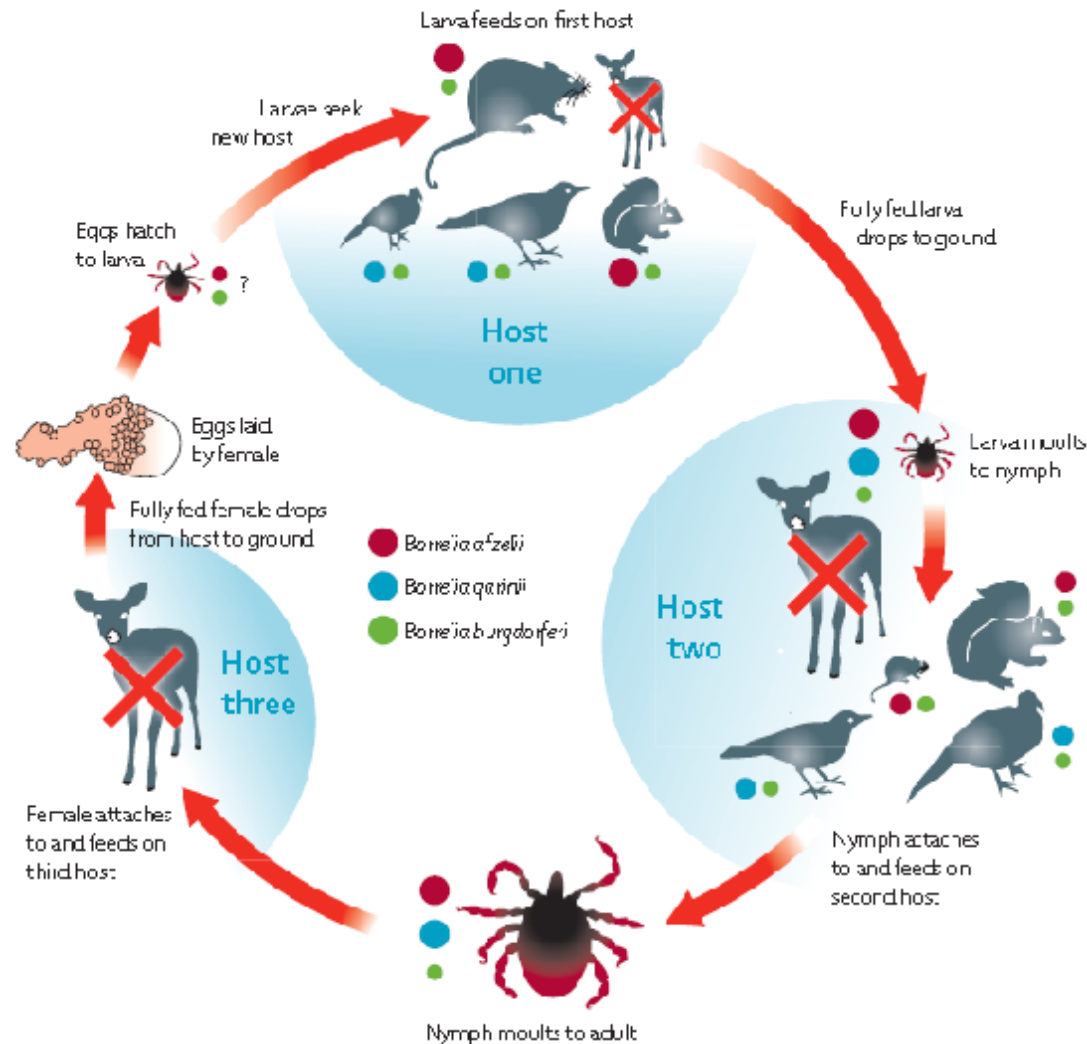


From the left: larvae (6 legs), nymphae (8 legs), imago (8 legs) – female (sac-like sac grow up to 100 times her original weight after infestation), imago – male (ref: *Stanek, Lancet, 2012, 379:461*)

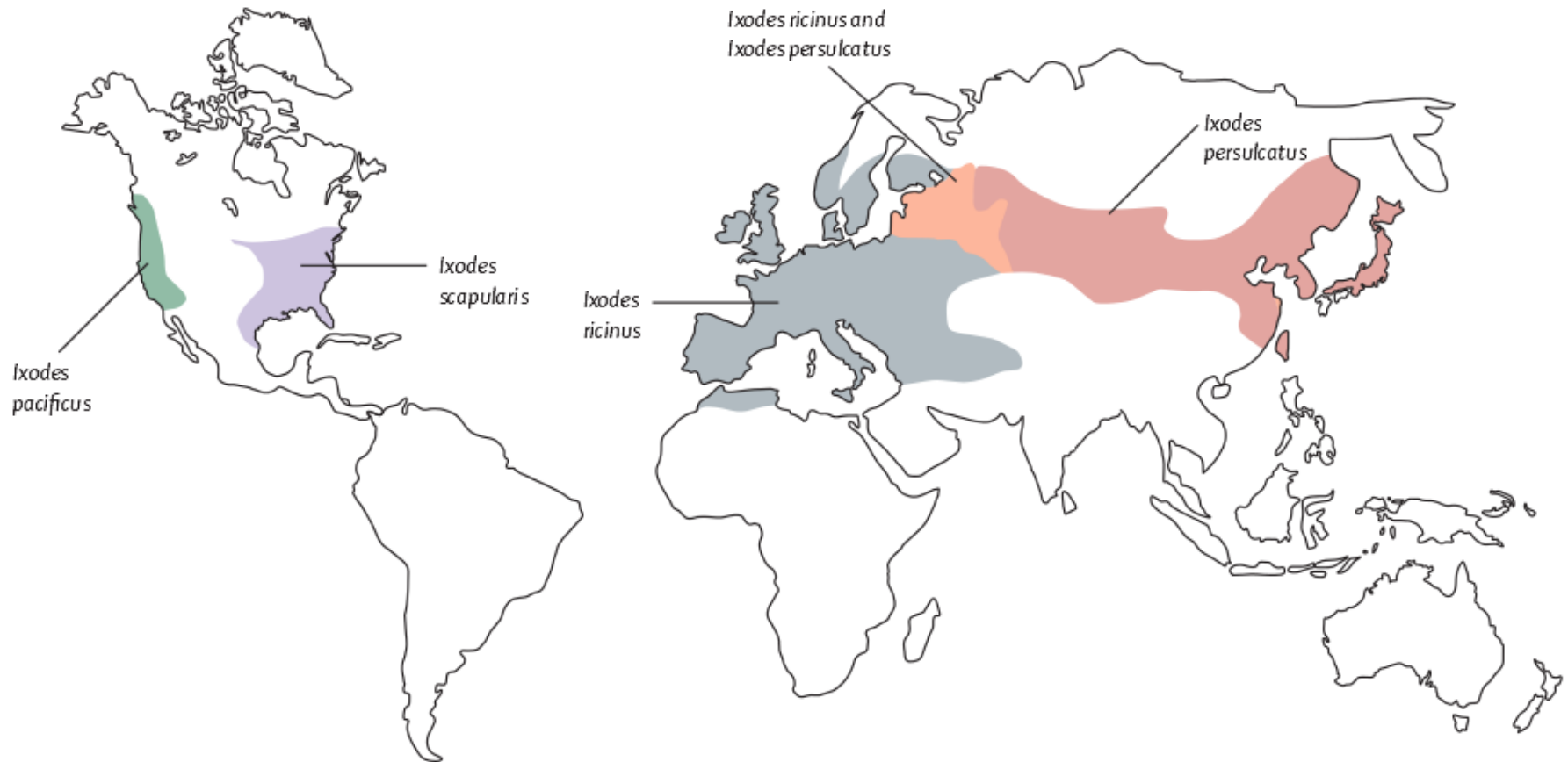
Tick life cycle

- * In average take 2 years, **each stadium suck blood only once** (on a different host)
- * **eggs** – laid in spring (autumn), larvae for 6-8 weeks
- * **larvae** 0,8 mm grey-yellowish, **suck 3-6 d, rodents**
- * **nymfae** – 2nd year, 1,2 mm, **suck 3-6 d** (e.g. **hedgehogs, squirrels, birds...**)
- * **imago** – after 3 months, male 2,5 mm, female 4 mm, **suck – e.g. deers**, after mating and blood sucking (6-14d), after 8-30d **laying eggs** (2 000 eggs)

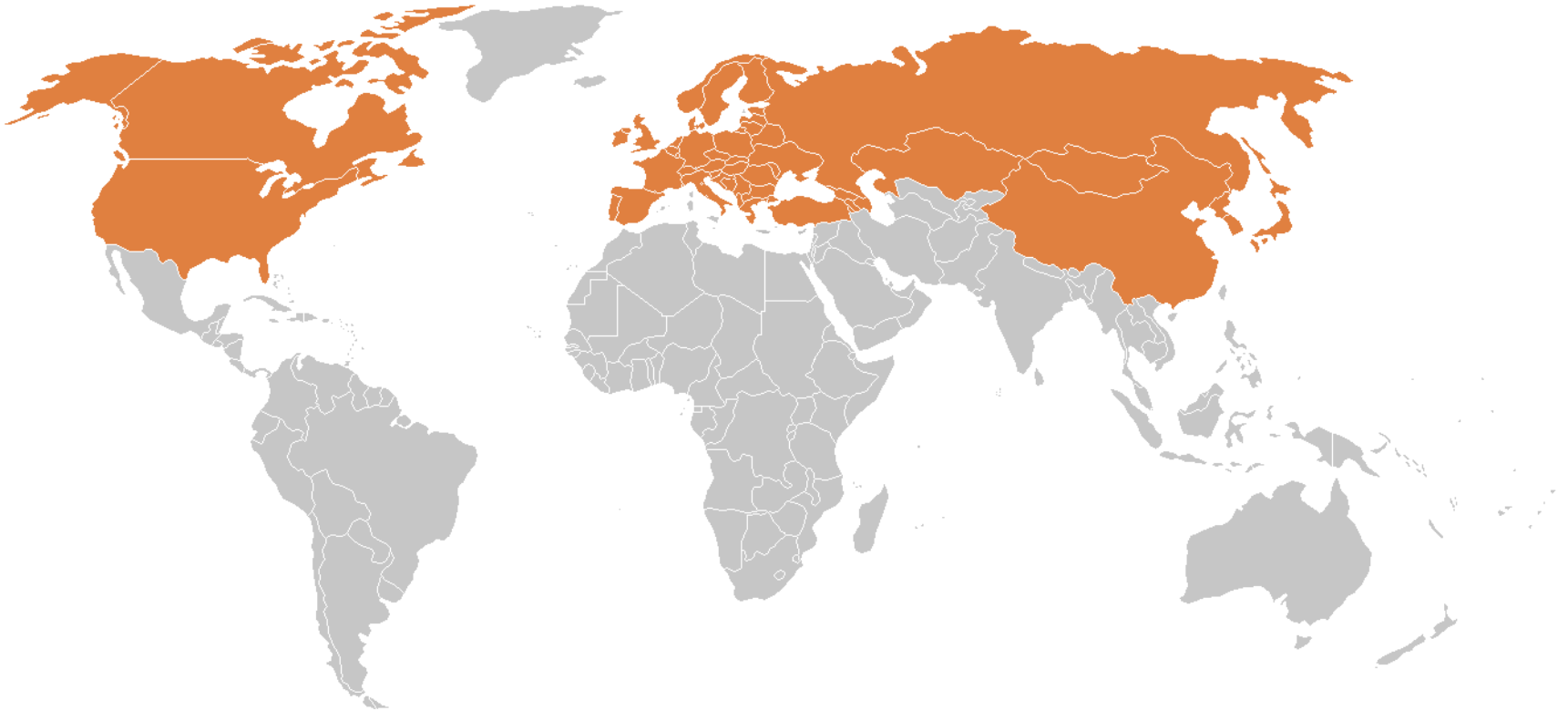
Life cycle of European *B. burgdorferi* sensu lato genomospecies



Vectors of lyme borreliosis (*Ixodes ricinus* species komplex) – global distribution



Distribution of lyme borreliosis



Lyme borreliosis is endemic in temperate latitude of North globe (wikipedia)

Classification of lyme borreliosis

Early	1. stadium	erytema migrans (EM) flu-like symptoms lymfadenitis
	2. stadium	acute neuroborreliosis cardiologic symptoms lymfocytoma
Late	3. stadium	chronic neuroboreliosis chronic arthritis acrodermatitis atroficans



Specimen collection, microscopy, cultivation

- **erytema migrans** – microbiological diagnostics are not performed
- **CSF, blood, joint puncture, other tissue** – PCR (culture low sensitivity)
- microscopy – dark-field (tick analysis), electron microscopy (clinical material after concentration using centrifugation – plasma, puncture, CSF)

Serology

- * Most useful for dg, **IgM** and **IgG** (3-6 weeks after infection, early IgM)
- * **Antigens** – cellular, recombinant, usually used ELISA
- * **Indirect immunofluorescence (IFA)** – subjective interpretation
- * **Western blot** – most specific, should **confirm ELISA** positive results

Therapy

- Depending on stadium and symptomatology, usually **14-21days**
- Antibody Index (AI): comparing antibody levels in your CSF and your blood (using a paired serum sample). This calculation checks for **intrathecal antibody synthesis**, meaning the antibodies are actively being produced inside your central nervous system rather than just leaking from your blood through the blood-brain
- **acute, mild neurol. and cardialogic symptoms - male, female (nonpregnant) and older children (> 8 years)**
tetracyclines (tetracyklin, doxycyklin)
- **children, pregnant women – amoxicilin or penicilin**
- **alternatives – macrolides** (e.g. azithromycin)

Therapy

- **Late neurological stadium, serious arthritis or serious cardiological symptoms** – PNC G i.v. or ceftriaxon
- doxycyklin –acute stadium, prevention of chron.stad.
- amoxicillin – pregnant, breast-feeding, children up to age 8 years
- azitromycin - breast-feeding
- ceftriaxon (cephalosporin 3rd generation) – **excellent penetration to CSF, synovial fluid** (i.v.1x day)
- **PNC G – megadoses 2. and 3. stadium**, disadvantages – alergisation, flebitis, week penetration through blood-brain barrier

Borrelia reccurentis

- **Agent of relapsing fever** (several cycles of recovery followed by a relapse caused by ability to change its surface protein antigens)
- **Pathogenesis** – usually **epidemic** disease transmitted from human to human by **body lice** (developing countries)(fatality up to 30% if untreated)
- **Symptoms** – incubation period 3-10 days, febrile period (spirochetes in the blood) – abrupt onset of high fever, headache, muscle pain, recovery 4-10 days and reccurence (up to 10 reccurences) with decreasing severity

Borrelia reccurentis

- **Diagnosis**

Giemsa stained spirochetes in the blood during febrile stage

- **Treatment**

tetracyclin, macrolides, penicillin

Prevention – by protecting against lice, no vaccine is available

Leptospira interrogans

- Cause **leptospirosis (Weil disease)**, worldwide
- **Sensitive to drying** and broad range of **desinfectants**
- **Epidemiology and pathogenesis**

Zoonosis coincidentally infect humans primary by **water** or food contaminated with **animal urine**, incidence in developed countries- very low

Entrance – **small abrasions** or the conjunctiva, but **also intact skin** which *leptospira* can actively go through

Leptospira interrogans

- **Clinical significance**

1-2 weeks after infection – spirochetes in the blood, fever, symptoms decrease after **1 week**, biphasic disease, spirochetes reappear – invasion of the liver, kidneys, CNS causing **jaundice, hemorrhage, tissue necrosis and/or aseptic meningitis** (second stage - **3 or more weeks**)(mortality up to 10%)

Microbiological diagnosis

Early-Stage Testing (First Week)

- **PCR.** It works best during the first 5 to 7 days of illness using blood or urine. It is fast and accurate before your body builds up antibodies.
- (• **Blood Culture:** Doctors try to grow the bacteria from a blood sample. Could prove the infection, but it takes a long time and is rarely ready soon enough to help with initial medical care).

Later-Stage Testing (Second Week and Onward)

- **MAT (Microscopic Agglutination Test):** gold standard method measures antibodies in blood by mixing your serum with live bacteria. Test 2 samples taken weeks apart to watch for a rising antibody level.
- **IgM ELISA:** A common screening test that quickly checks for specific infection-fighting antibodies. It is easy to run, but positive results usually need confirmation with a MAT test because false positives can happen.

Treatment

Leptospirosis treatment relies on prompt antibiotic therapy, tailored to the severity of the infection.

Mild Leptospirosis

- **Oral antibiotics:** Standard care includes oral [doxycycline](#) (taken for about a week).
- **Alternatives:** Oral [amoxicillin, ampicillin], or [azithromycin] are used if doxycycline is not suitable.
- **Special populations:** Doxycycline is generally avoided in children and pregnant patients; alternatives like [amoxicillin] or [azithromycin] are preferred.

Severe Leptospirosis

- **Intravenous (IV) therapy:** Severe cases with organ dysfunction or [Weil syndrome] require hospital care and IV [penicillin G] or [ceftriaxone] for about a week. Alternatives include IV [ampicillin] or [meropenem].
- **Supportive care:** fluid and electrolyte management, lung-protective mechanical ventilation, or renal replacement therapy (dialysis) for acute kidney injury.

Prevention and prophylaxis

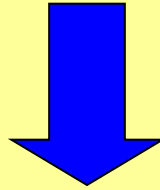
- **Chemoprophylaxis:** Oral [doxycycline] once a week can prevent infection during temporary, high-risk exposure.
- **General safety:** Avoid contact with potentially contaminated water, soil, and animal urine.



Mycobacteria

Why acid-fast?

**Dont stain readily, resist decolorization by
acid or alcohol**

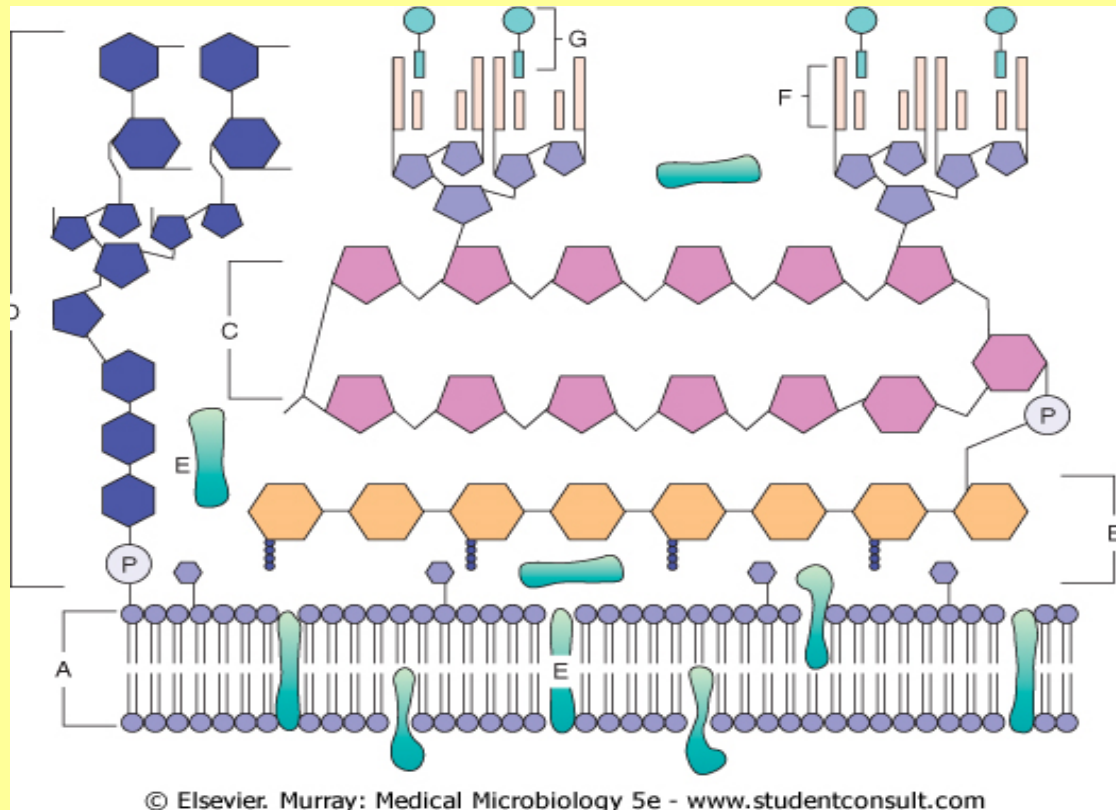


acid-fast bacteria

Biological properties

- **rod-shaped**
- **nonesporeforming**
- **aerobic**
- **saprophytic or pathogenic species**
(cause chronic diseases - lesions of the infectious granuloma type)

Cell wall structure - rich in lipids



Mycobacterial cell wall structure. The components include the (A) plasma membrane, (B) peptidoglycans, (C) arabinogalactan, (D) mannose-capped lipoarabinomannan, (E) plasma-associated and cell wall-associated proteins, (F) **mycolic acids**, and (G) **glycolipid surface molecules associated with the mycolic acids**. (Redrawn from Karakousis et al: *Cell Microbiol* 6:105-116, 2004.)

Because of the lipid rich cell wall structure

- acid-fastness
- **slow growth**
- resistance to detergents
- **resistance to common antibacterial antibiotics**
- antigenicity
- clumping

Cell wall protein

- extracted from *M. tuberculosis* (purified protein derivatives, or PPDs, **tuberculin**)
- **used as skin test reagents to measure exposure to *M. tuberculosis***

Classification of Mycobacteria

Pathogenicity

- **strictly** - *M. tuberculosis*, *M. bovis*, *M. leprae*
- **usually** - e.g. *M. avium* complex
- **sometimes** - e.g. *M. xenopi*

Growth of Mycobacteria

- **slow growers - weeks or months**
- **rapid growers - days**
- **media**
 - agars (e.g. egg based **Löwenstein-Jensen**)
 - broth (e.g. Šula broth)



M. tuberculosis growing 2 months on **Löwenstein-Jensen medium** cultured from patient sputum (<https://www.google.com/search>)

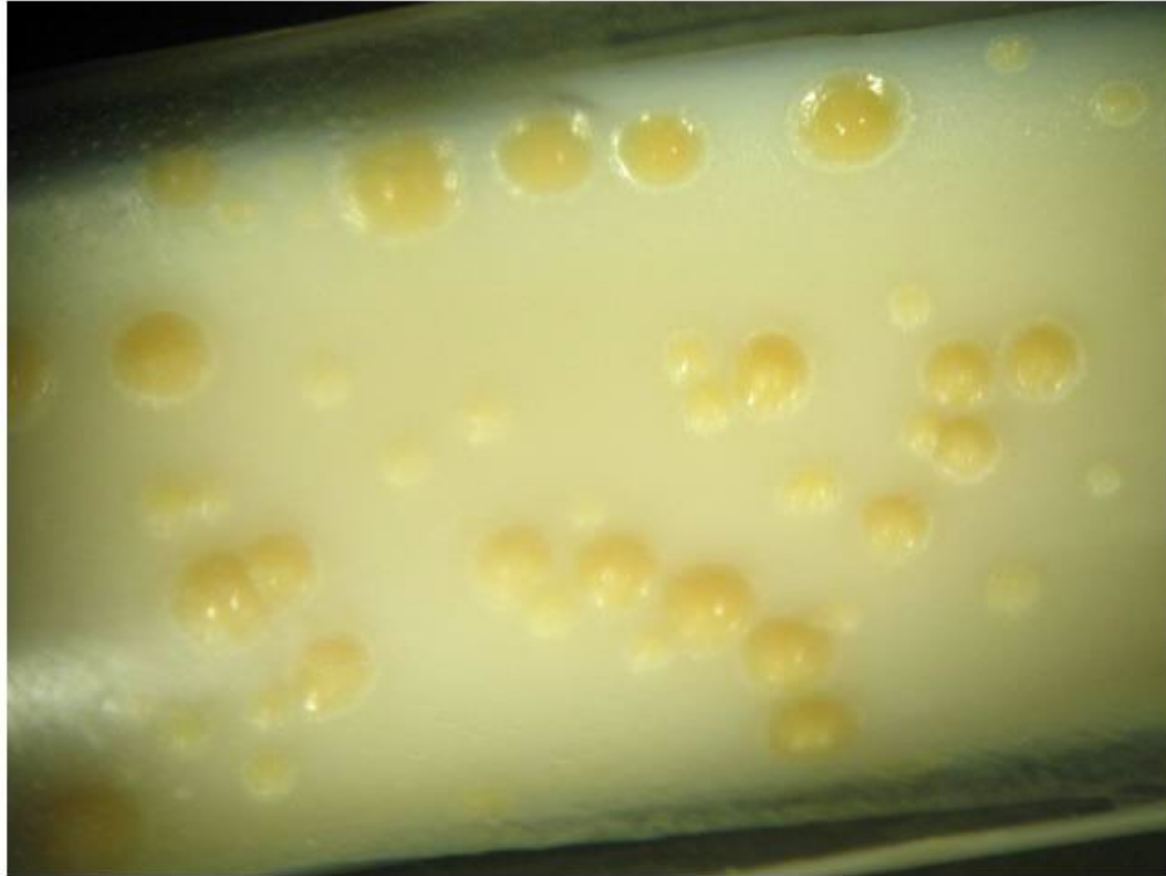
Growth of clinically significant Mycobacteria



M. avium
(Löwenstein-Jensen medium)

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Charles University, Prague

Growth of clinically significant Mycobacteria



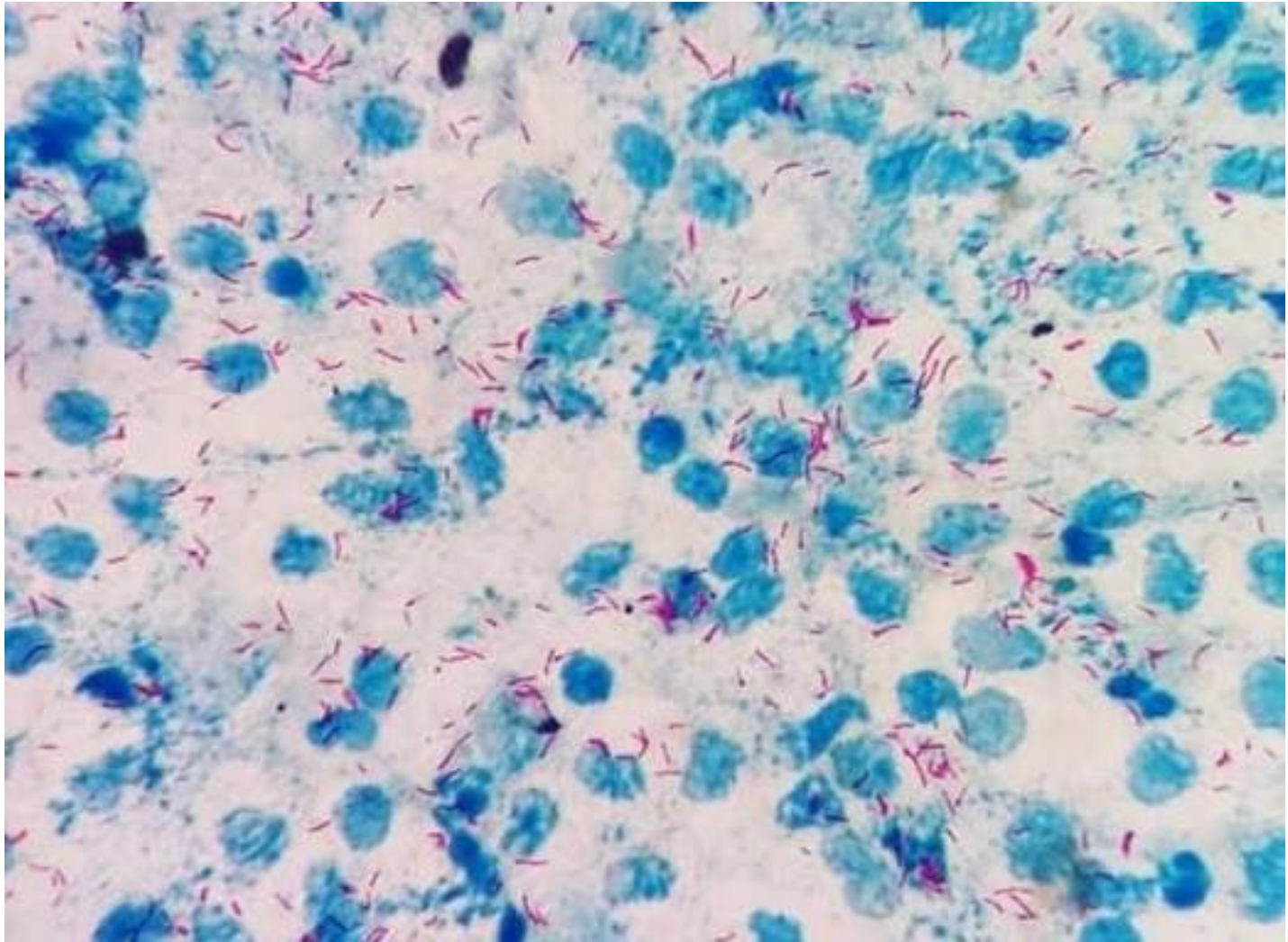
***M. kansasii* (photochromogenic)
(Löwenstein-Jensen medium)**

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Ziehl-Neelsen staining

- also known as the **acid-fast stain**, was first described by two German doctors; Franz Ziehl (1859 to 1926), a bacteriologist and Friedrich Neelsen (1854 to 1894), a pathologist
- **procedure**
 1. Flood slide with carbolfuchsin, for 2 minutes while heating with steam
 2. Decolorize slide with a mixture of hydrochloric acid and ethanol
 3. Counter stain with methylene blue (or malachite green)

Lung tuberculosis, sputum - Ziehl-Neelsen staining, *M. tuberculosis*



Ref: <https://www.google.com/search>

***M. tuberculosis* - pathogenesis**

- **can establish life long infection**
- **how?(disease primarily from host response to infection)**
 1. enter respir. tract & phagocytized by alveolar macrophages
(prevent fusion to phagolysosome)
 2. replicate in macrophage
 3. macrophages & Ly are attracted to the inf. focus
(multinucleated giant cells - Langhans cells)
 4. Infected macrophages to
 - a) regional lymph nodes
 - b) bloodstream & tissue
 5. origination of granulomas (localized activated macrophages)
 - a) prevent spread of the agent (encapsulated with fibrin) into the host
 - b) protect mycobacteria against killing by macrophages
 6. could be dormant in this stage for decades

***M. tuberculosis* - symptoms**

The **clinical signs** and symptoms of tuberculosis **reflect the site of infection**, with **primary** disease usually restricted to the **lower respiratory tract**. The disease is **insidious at onset**. Patients typically have **nonspecific complaints of malaise, weight loss, cough, and night sweats**. **Sputum** may be **scant or bloody and purulent**. Sputum production with **hemoptysis** is associated with tissue destruction (e.g., **cavitary disease**). The clinical diagnosis is supported by (1) **radiographic evidence** of pulmonary disease (2) **positive skin test reactivity**, and (3) the **laboratory detection of mycobacteria**, either with **microscopy** or in **cultures**. One or both upper lobes of the lungs are usually involved in patients with active disease that includes **pneumonitis or abscess formation and cavitation**.

Microbiological diagnosis

- * **tuberculin skin test** (PPD tuberkulin - is a sterile, cell-free solution used in the Mantoux test to screen for tuberculosis. It contains a complex mixture of proteins extracted from the bacteria that cause TB) intradermally
- * **QuantiFERON-TB test** sensitive marker for exposure to organism (how the immune system reacts) – fresh **whole blood** drawn directly into a specific set!!!
- * **microscopy** and **culture** less sensitive and specific
- * identification by rapid molecular tests – **PCR** (e.g. Xpert MTB/RIF, less than 2 hours)

***M. tuberculosis* - Epidemiology**

- **Worldwide; a third of the world's population is infected with this organism**
- **A total of 8.8 million new cases each year and 2 million deaths** (comparing with malaria cases - 282 million malaria cases and 610,000 malaria deaths each year)
- **Most common in Southeast Asia, sub-Saharan Africa, and Eastern Europe**
- **Populations at greatest risk for disease are immunocompromised patients** (particularly those with HIV infection), **drug or alcohol abusers, homeless persons, and individuals exposed to diseased patients**
- **Humans are the natural reservoir** (also non-human primates)
- **Person-to-person spread by infectious aerosols**

***M. tuberculosis* - treatment, prevention & control**

- * **multiple-drug regimens and prolonged treatment** are required to prevent development of drug-resistant strains
- * isoniazid (INH), ethambutol, pyrazinamide, and rifampin for 2 months followed by 4 to 6 months of INH and rifampin or alternative combination drugs
- * prophylaxis for exposure to tuberculosis can include INH for 9 months, rifampin for 4 months, or rifampin and pyrazinamide for 2 months; pyrazinamide and ethambutol or levofloxacin are used for 6 to 12 months after exposure to drug-resistant *M. tuberculosis*
- * **immunoprophylaxis with BCG (Bacille Calmette-Guérin) is a live vaccine primarily used to protect infants and young children against severe, life-threatening forms of tuberculosis)** in endemic countries
- * control of disease through active surveillance, prophylactic and therapeutic intervention, and careful case monitoring
- * problem **MDR-TB** (multidrug resistant strains), **XDR-TB** (extensively drug-resistant tuberculosis) is a highly resistant form of tuberculosis caused by *Mycobacterium tuberculosis* bacteria that does not respond to first- and second-line drugs against *M. tuberculosis*.

***M. tuberculosis* - treatment, prevention & control**

- **MDR-TB** (multidrug resistant strains). Multidrug-resistant tuberculosis (MDR-TB) is treated using specialized, all-oral medicine **combinations that last between 6 and 20 months**, depending on the specific regimen and drug resistance profile
- **XDR-TB** (extensively drug-resistant tuberculosis) is treated using customized, all-oral combination regimens of specialized second-line medications chosen based on drug-susceptibility testing.

Modern Treatment Regimens

- **6-Month All-Oral Regimens:** Modern medical guidelines prioritize short, all-oral courses like BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin) or BPaL (omitting moxifloxacin for cases with confirmed fluoroquinolone resistance). These have largely replaced older, painful daily injection regimens.
- **9-Month All-Oral Regimens:** Recommended for certain eligible patients where resistance to fluoroquinolones has been excluded, utilizing a combination of bedaquiline, fluoroquinolones, and other companion drugs.
- **Longer Individualized Regimens: Lasting 18 to 20 months**, these are designed for complex cases, extensive drug resistance, or patients ineligible for shorter courses. They rely on a prioritized hierarchy of effective second-line drugs (Group A, B, and C agents).

***M. avium* complex & diseases**

- consists of two mycobacterial species: *M. avium* & *M. intracellulare*
- **ubiquitous**, present in water (fresh, brackish, ocean, drinking water), plants, and soil
- **immunocompetent & immunodeficient patients**
- often - pulmonary diseases

***M. avium* complex & diseases**

Pulmonary Infection (Lungs)

This is the most common form, often affecting people with pre-existing lung conditions or older adults.

Chronic cough with sputum (mucus)

- **Shortness of breath** (dyspnea)
- **Fatigue** and low energy
- **Fever** and night sweats
- **Weight loss** and loss of appetite
- **Coughing up blood** (hemoptysis, less common, more nodules, could be milliar inf.)

Disseminated Infection (often milliary)

This occurs mainly in people with severe immune system weakness, such as advanced HIV/AIDS.

High or persistent fevers

- **Severe fatigue**
- **Abdominal pain**
- **Diarrhea**
- **Anemia** (low red blood cell count)
- **Enlarged liver or spleen**

Lymphadenitis (Lymph Nodes)

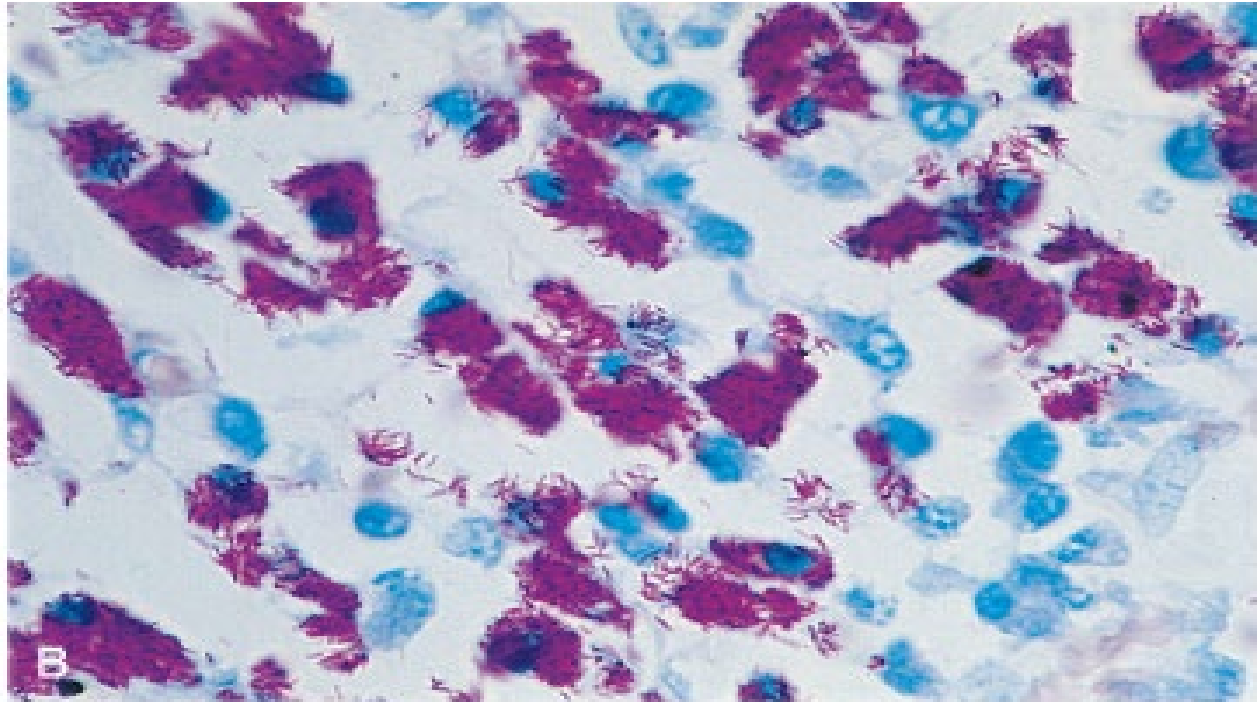
This type mostly affects young children.

- **Swollen lymph nodes**, usually in the neck (cervical lymphadenitis)

***M. avium* complex - treatment, prevention and control**

- Infections treated for prolonged period with **clarithromycin** or **azithromycin** combined with **ethambutol** and **rifabutin**
- **Prophylaxis** in patients with AIDS who have low CD4+ cell count consists of clarithromycin or azithromycin or rifabutin
- **Antibiotic prophylaxis has dramatically reduced the incidence of disease in patients with AIDS**

***M. avium* complex - microscopy**



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Tissue from a patient with AIDS who is infected with *Mycobacterium avium* complex photographed under low (A) and high (B) magnification.

Other Slow-Growing Mycobacteria

* Relatively **low virulence potentials**. Some mycobacteria produce **disease identical to pulmonary tuberculosis** (e.g., *Mycobacterium bovis*, *M. kansasii*), other species commonly cause infections **localized to lymphatic tissue** (*Mycobacterium scrofulaceum*), and others that grow optimally at cool temperatures primarily produce **cutaneous infections** (*Mycobacterium ulcerans*, *Mycobacterium marinum* – contact with water)

With the **exception** of and other mycobacteria closely related *M. bovis* to *M. tuberculosis*, **person-to-person spread of these mycobacteria does not occur.**

Rapidly Growing Mycobacteria

- growth in less than 7 days
- relatively low virulence potential
- most common species associated with disease are *M. fortuitum*, *M. chelonae*, and *M. abscessus*
- associated with disease occurring **after bacteria are introduced into the deep subcutaneous tissues by trauma or iatrogenic infections** (rarely disseminated infection)

M. leprae

- manifestations of leprosy depend on the patient's immune reaction to the bacteria

Diseases

- **Tuberculoid form of leprosy**
- **Lepromatous form of leprosy**

Diagnosis

- **PCR detects specific DNA to confirm a leprosy,** especially when traditional methods are inconclusive.
- **Microscopy** is sensitive for the **lepromatous** form but not the tuberculoid form
- Skin testing is required to confirm tuberculoid leprosy
- Culture is not useful

Tuberculoid (a) and lepromatous lepra (b)



(a)



(b)

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Leprosy - Epidemiology

Leprosy is **spread by person-to-person** contact. Although the most important route of infection is unknown, it is believed that *M. leprae* is spread either **through the inhalation of infectious aerosols or through skin contact with respiratory secretions and wound exudates**. Numerous *M. leprae* are found in the nasal secretions of patients with lepromatous leprosy.

Treatment, Prevention, and Control

- Tuberculoid form is treated with **rifampicin** and dapsone for 6 months; **clofazimine** is added to this regimen for treatment of the lepromatous form, and therapy is extended to a minimum of 12 months
- Disease is controlled through the prompt recognition and treatment of infected people