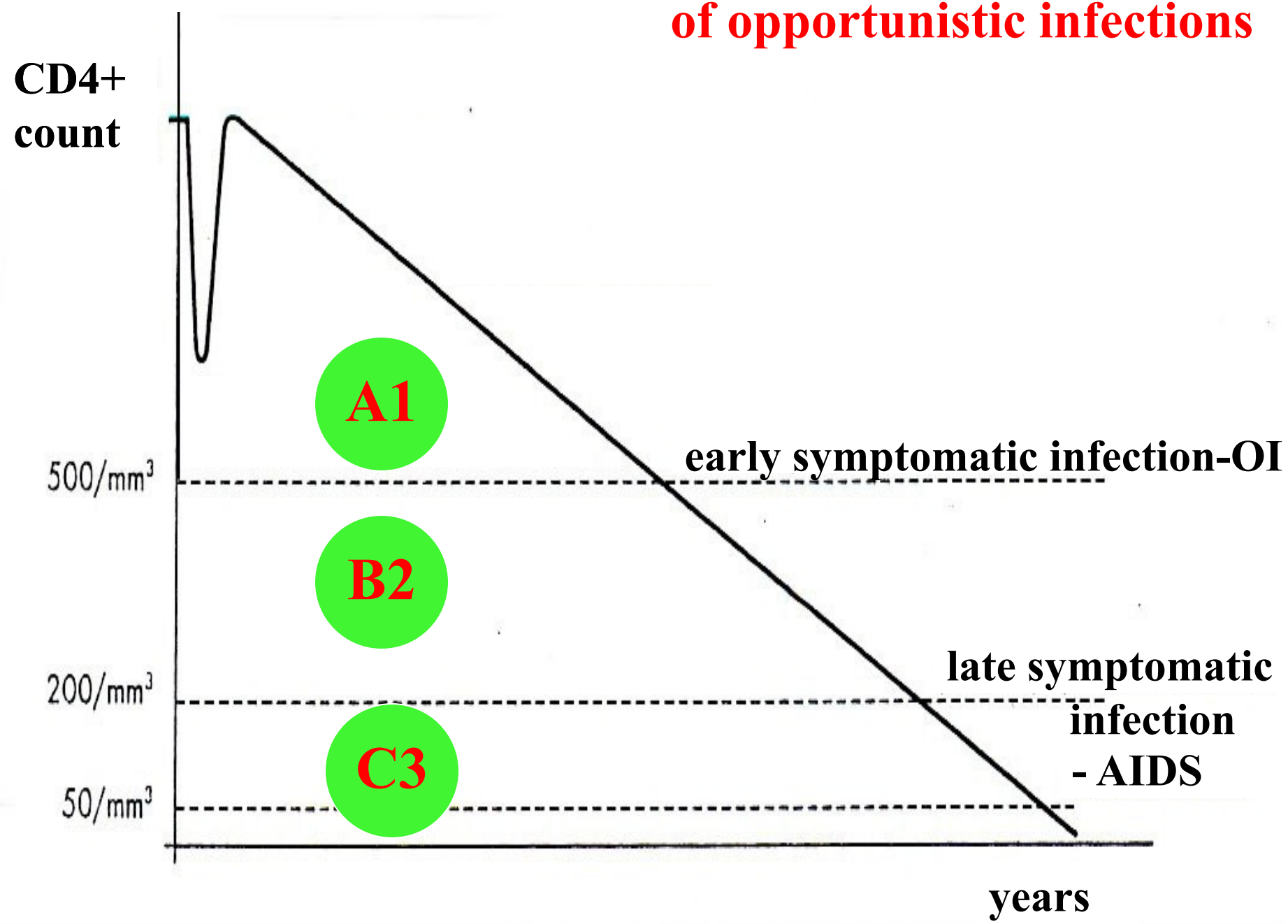
2nd part

- **Opportunistic infections**
  - **Tuberculosis**
  - **PCP**
  - **Cryptococcosis**
  - **MAC**

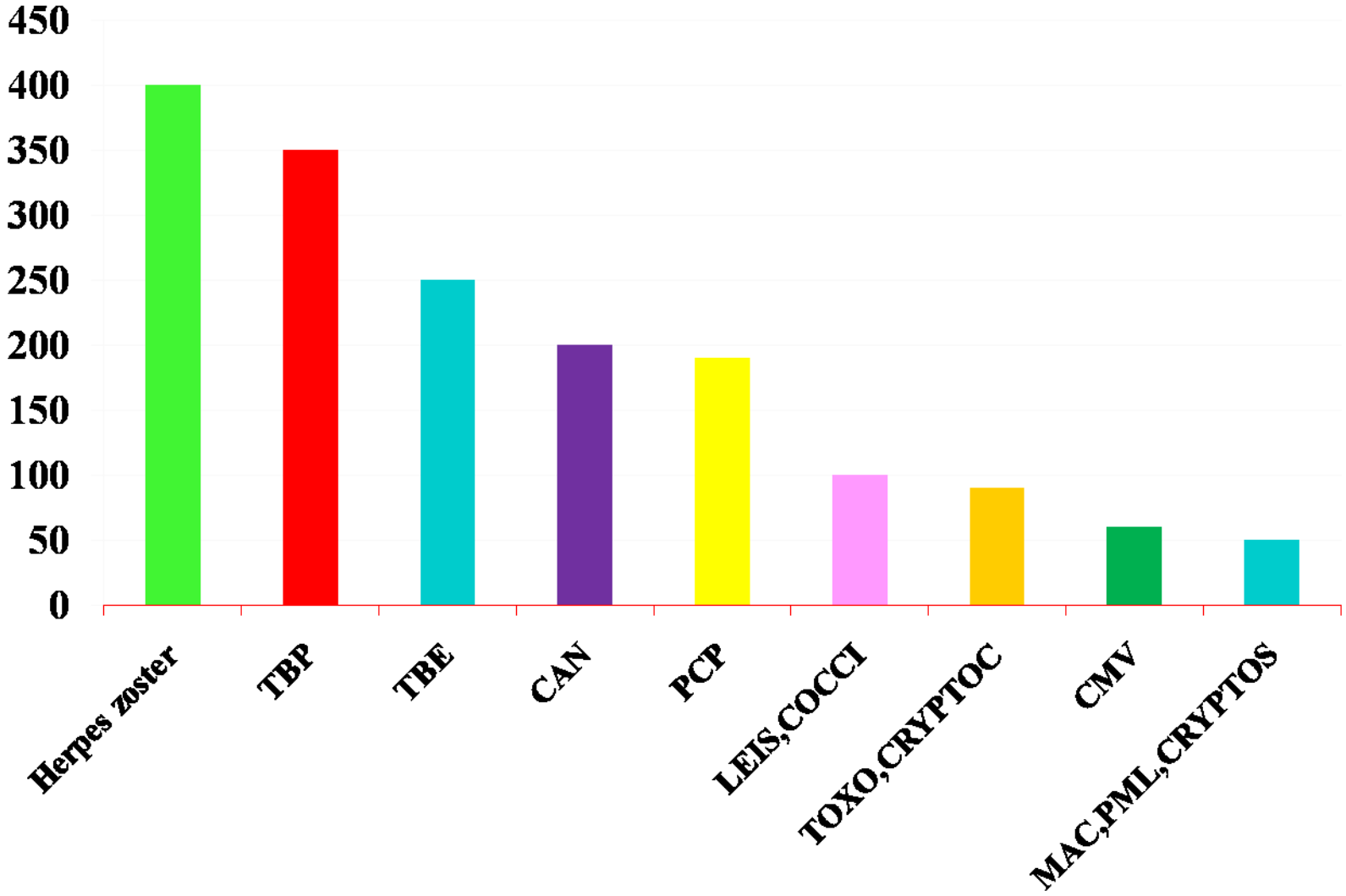
Opportunistic infections

- **Decrease in number of CD4 lymphocytes** is condition for development of opportunistic infections
- Risk is started, when number of CD4 lymphocytes drops to number **500 of CD4 lymphocytes/mm^3**

D4+ lymphocytes depletion = condition for development of opportunistic infections



CD4 count and opportunistic infection



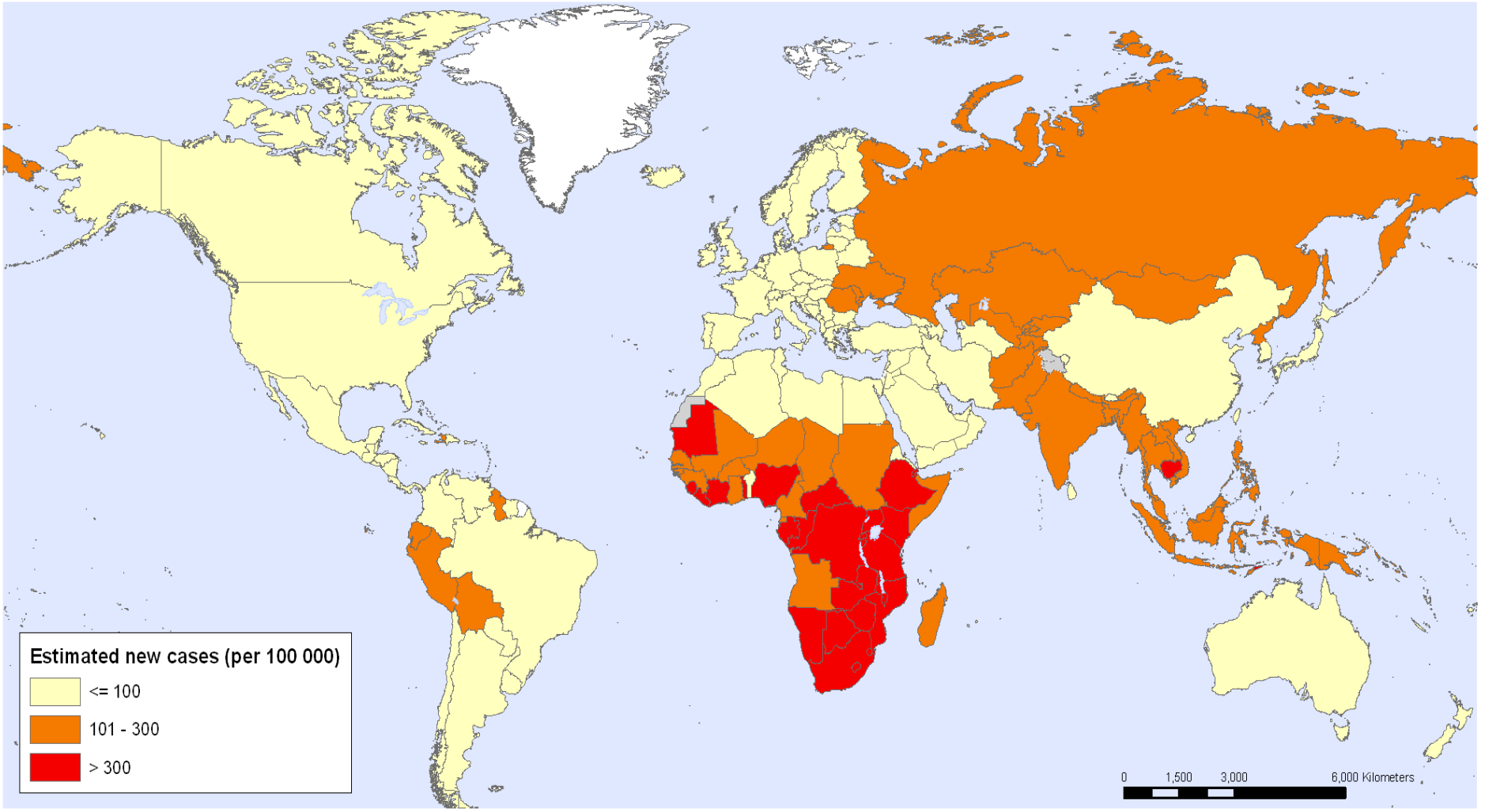
TUBERCULOSIS

- the most important
- the most common OI

Epidemiology

- **One-third** of the world´s population is infected with TB
- **HIV infection** has had **a big impact** in increasing the numbers of patients affected with disease caused by TB
- TB is **the most important** severe **opportunistic infection** among patients with HIV in developing countries

TB – estimated new cases (per 100 000)



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Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Tuberculosis

- Is **a leading cause of HIV-related deaths** worldwide
- In some countries with higher HIV preavalence, up to **80% of people with TB test positive for HIV**
- Globally approximately **30% of HIV** infected persons are estimated to have **latent TB infection**

Tuberculosis

- In last years, there were an estimated

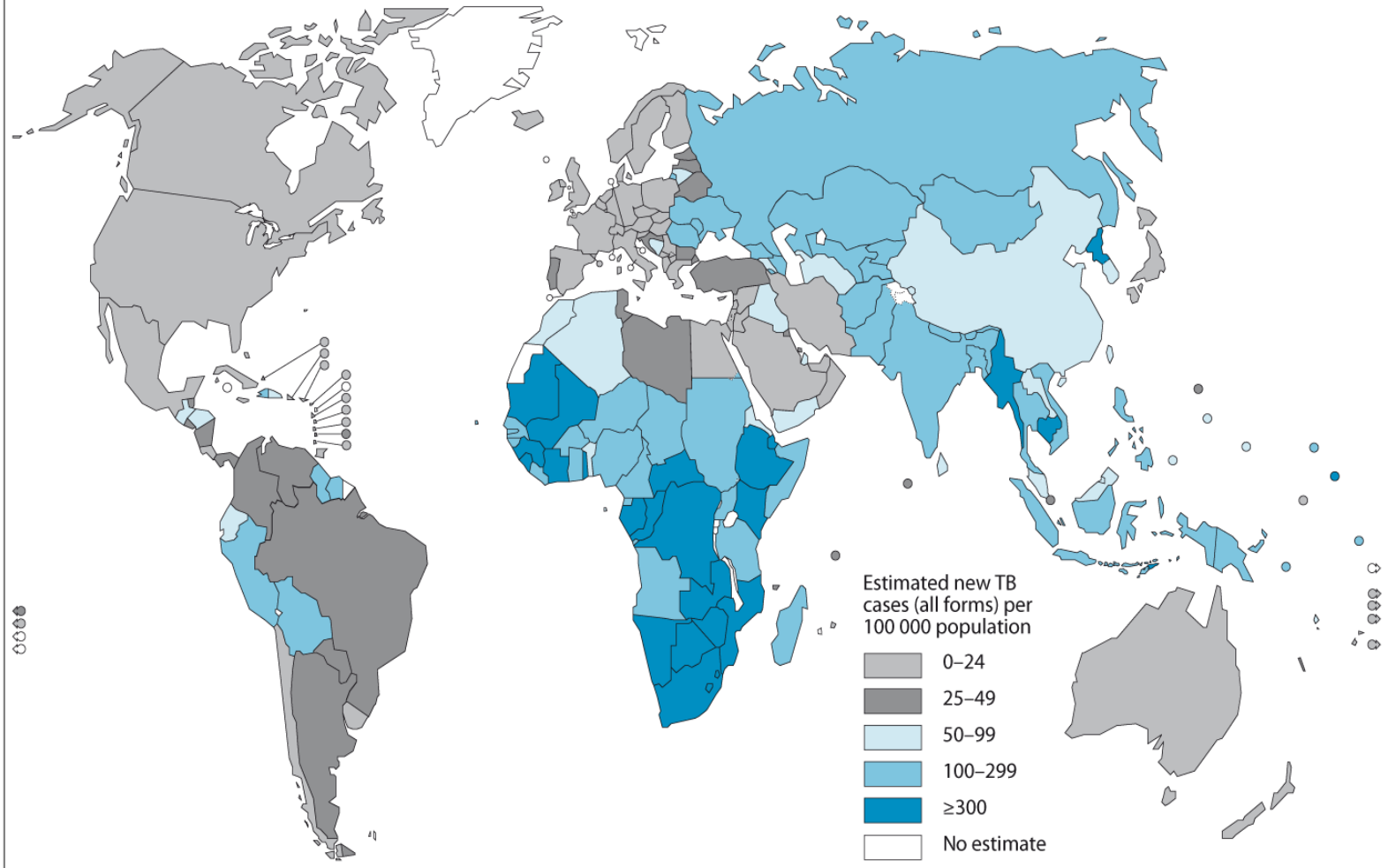
  1,4 million new cases of TB

  among persons **with HIV** infection

- TB accounted for

  23% of AIDS-related deaths

Estimated TB incidence rates, by country,



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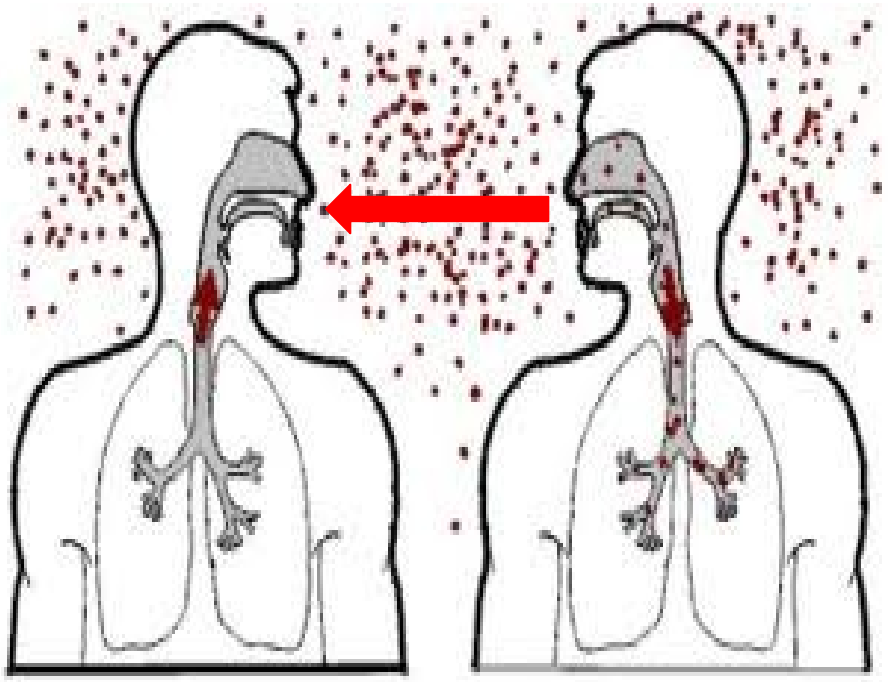
Source: *Global Tuberculosis Control 2010.* WHO, 2010.

World Health Organization

TB – droplet infection

- TB is transmissible to both people
  - with HIV infection
  - uninfected persons

  can be treated and can be prevented

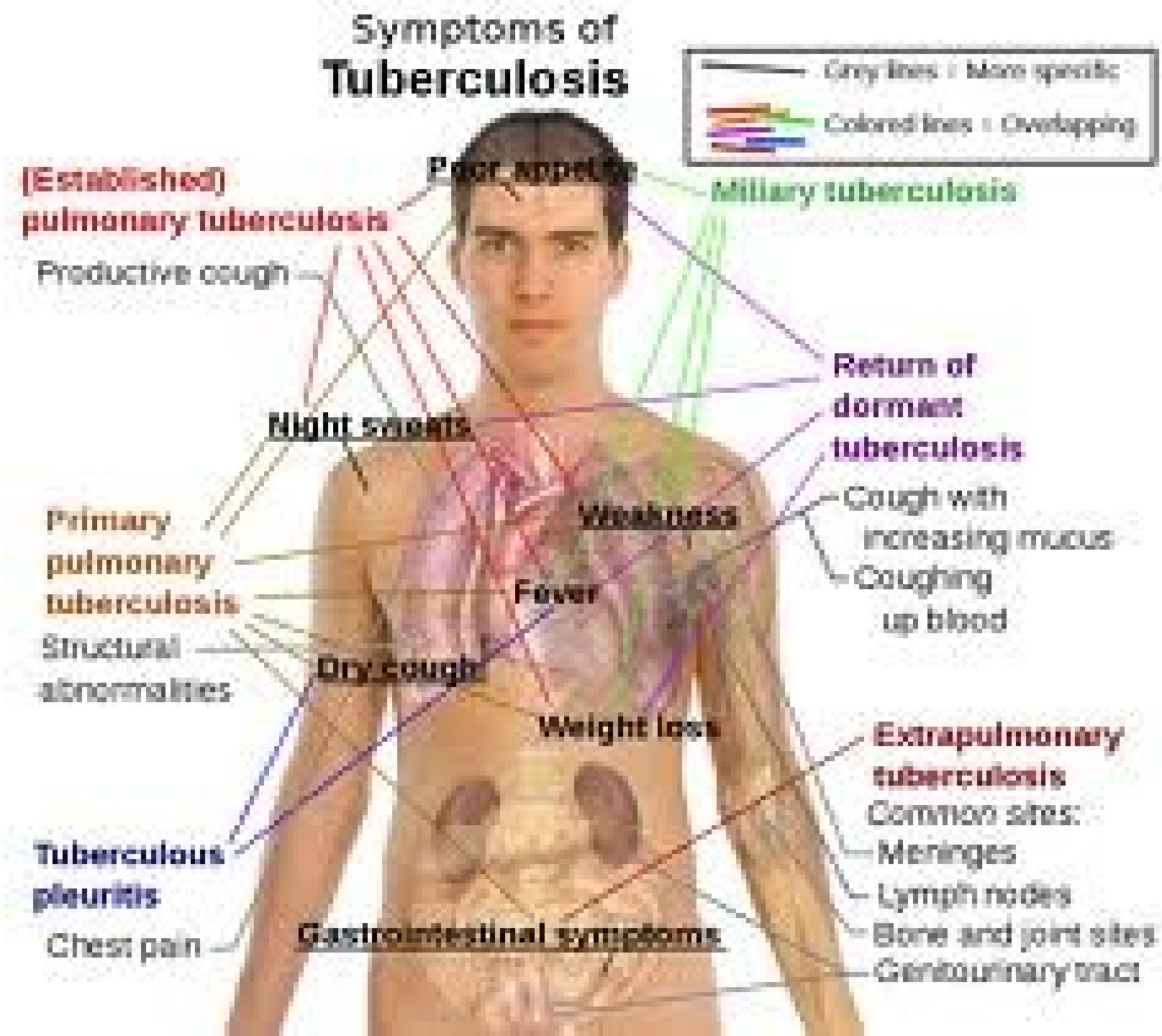


Clinical Manifestations

Myco TB

- **Is highly contagious**
- **Leads to a number of serious medical syndromes affecting, at time,**

  most of the organ systems

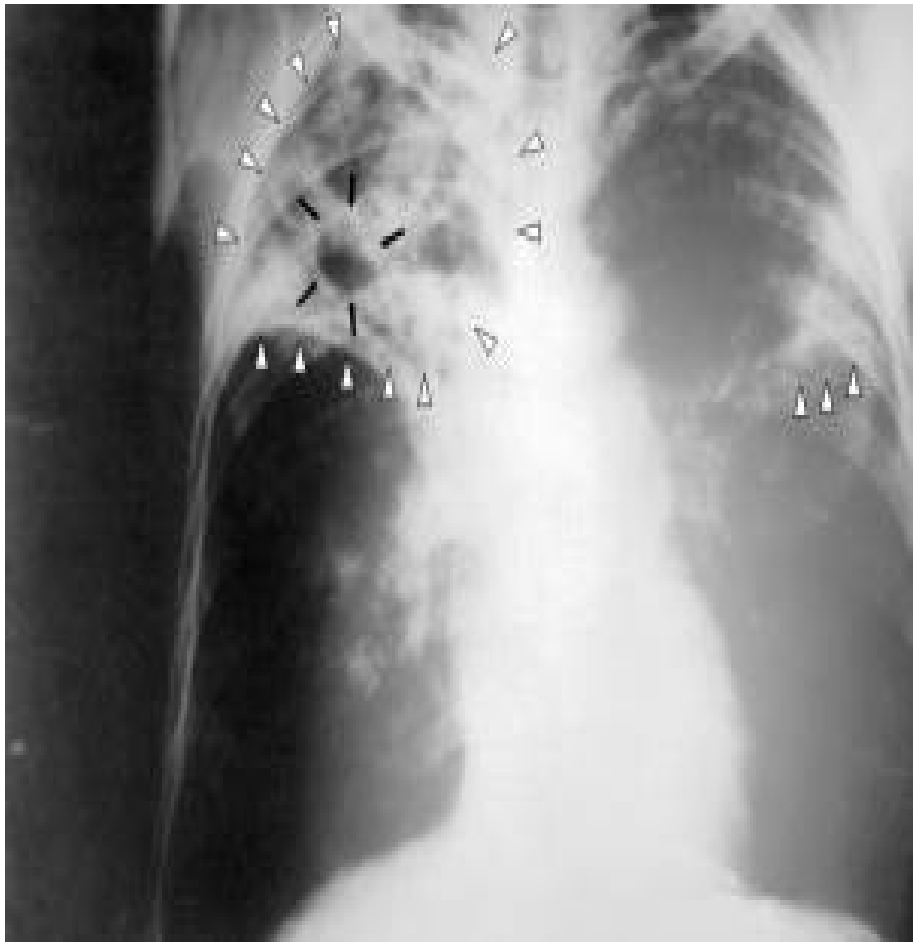

Symptoms of
Tuberculosis
Grey lines = More specific
Colored lines = Overlapping
(Established)
pulmonary tuberculosis
Productive cough
Poor appetite
Military tuberculosis
Return of
dormant
tuberculosis
Night sweats
Weakness
Cough with
increasing mucus
Coughing
up blood
Primary
pulmonary
tuberculosis
Fever
Structural
abnormalities
Dry cough
Weight loss
Extrapulmonary
tuberculosis
Common sites:
Meninges
Lymph nodes
Bone and joint sites
Genitourinary tract
Tuberculous
pleuritis
Chest pain
Gastrointestinal symptoms

Myco TB can causes:

1. Pulmonary disease
    - ♦ Pneumonia
    - ♦ Cavitary disease
2. Extrapulmonary disease
    - ▪ Adenitis („scrofula“)
    - ▪ Otitis media
    - ▪ Laryngitis
    - ▪ Miliary TB
    - ▪ Meningitis
    - ▪ Skeletal TB
    - ▪ Gastrointestinal TB
    - ▪ Renal TB…

Pulmonary TB

Cavities in the lungs (X-ray of thorax)



Miliary TB

Tb adenitis („scrofula“)

TB absces in brain

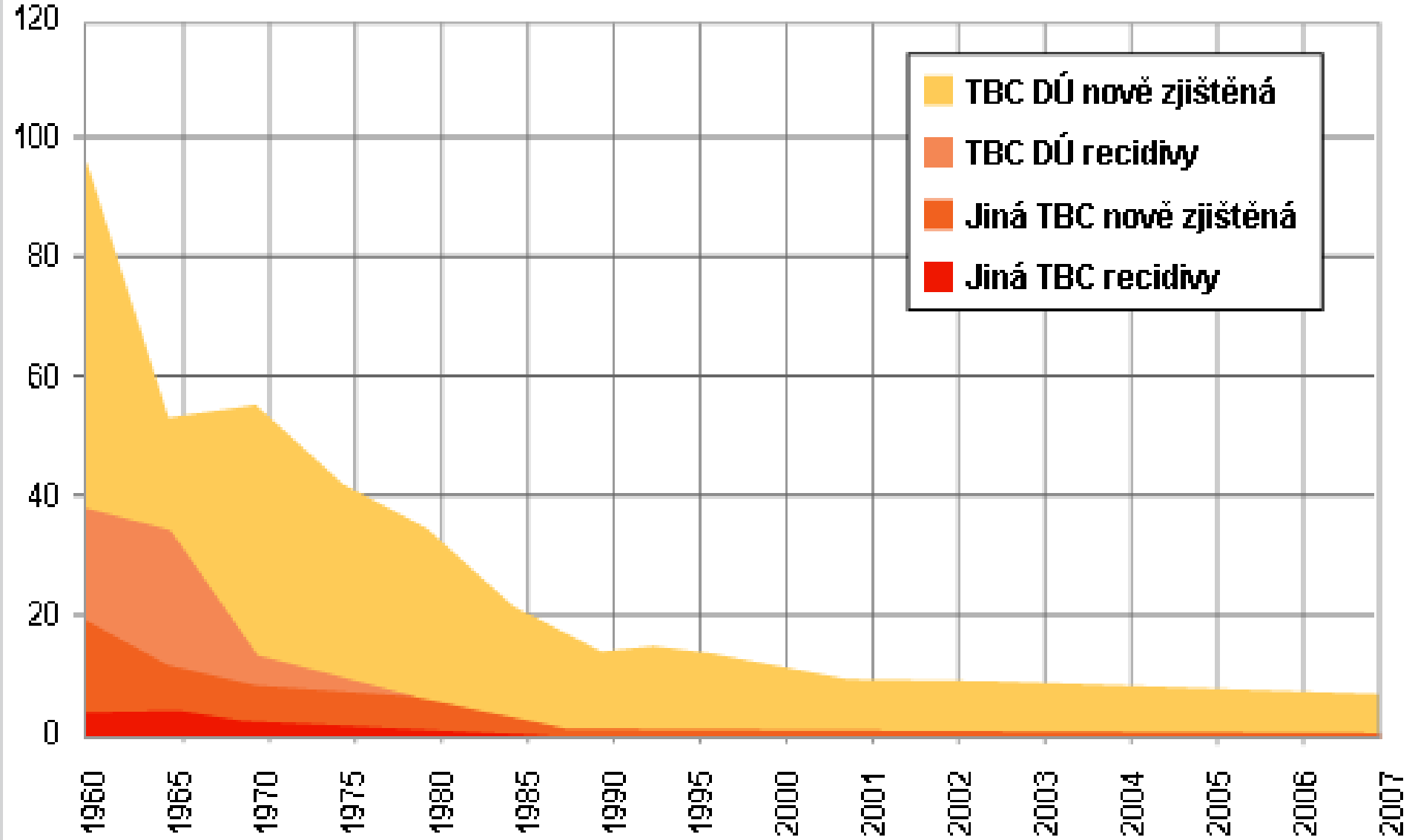
Skeletal TB

- destruction of the lumbar vertebrae
- skeleton of the Great Moravian Empire

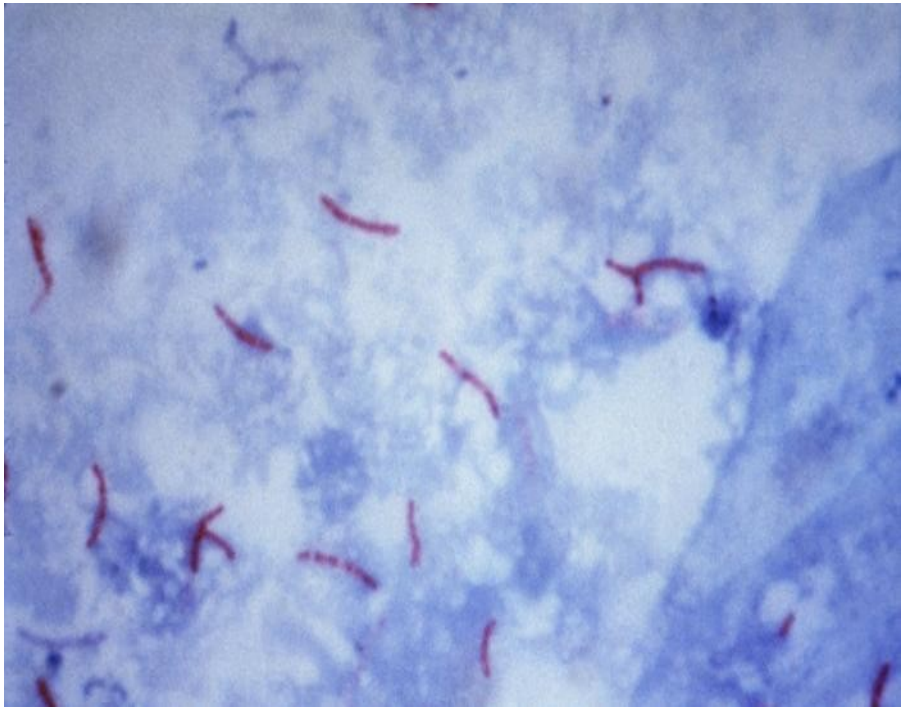
Soška Metriho ze Sakkáry.
Páteř je silně zakřivena
v hrudním úseku a hrudník
deformován nejpravděpodobněji
v důsledku TBC páteře.
Foto: Eugen Strouhal

Destruction of the thoracic vertebrae (skeleton of the Old Egypt Empire)

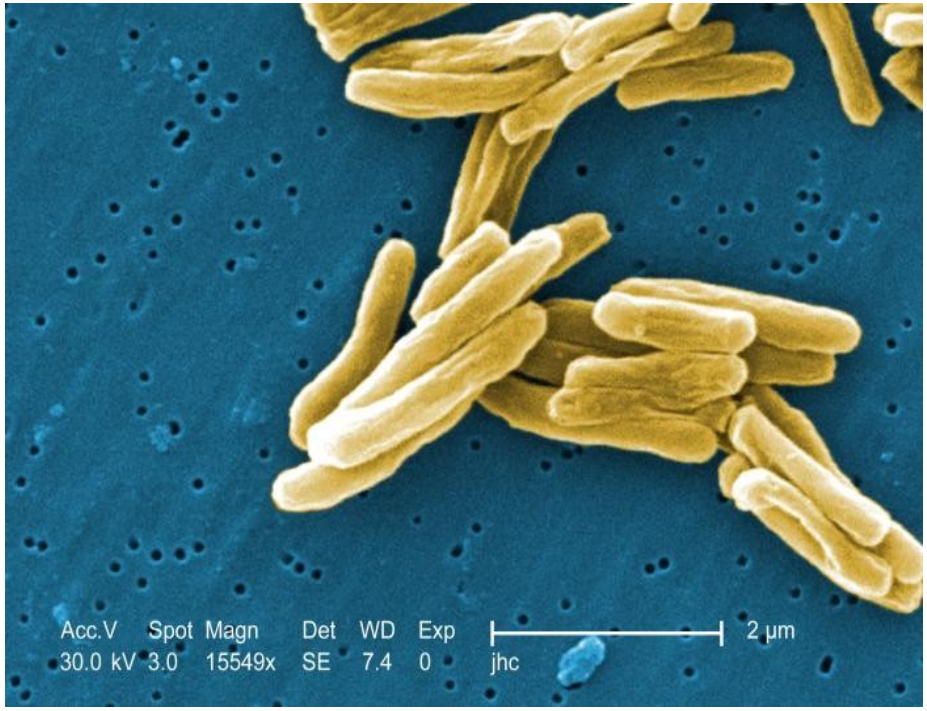
Number of TB in Czech Republic



Mycobacterium tuberculosis bacteria (G+) is acid-fast, appearing red on a Ziehl-Neelsen stain



M. tuberculosis bacteria (G+) – ultrastructural details (electron micrograph)



Primary prophylaxis

conditions	pathogen	drug
CD4+ any + TB exposure (when HIV+ individual is in exposure of TB we must start primary prophylaxis)	***M. tuberculosis***	**isoniazid (+pyridoxin), rifampicin, pyrazinamid, ethambutol**

Myco TB is highly contagious !!!

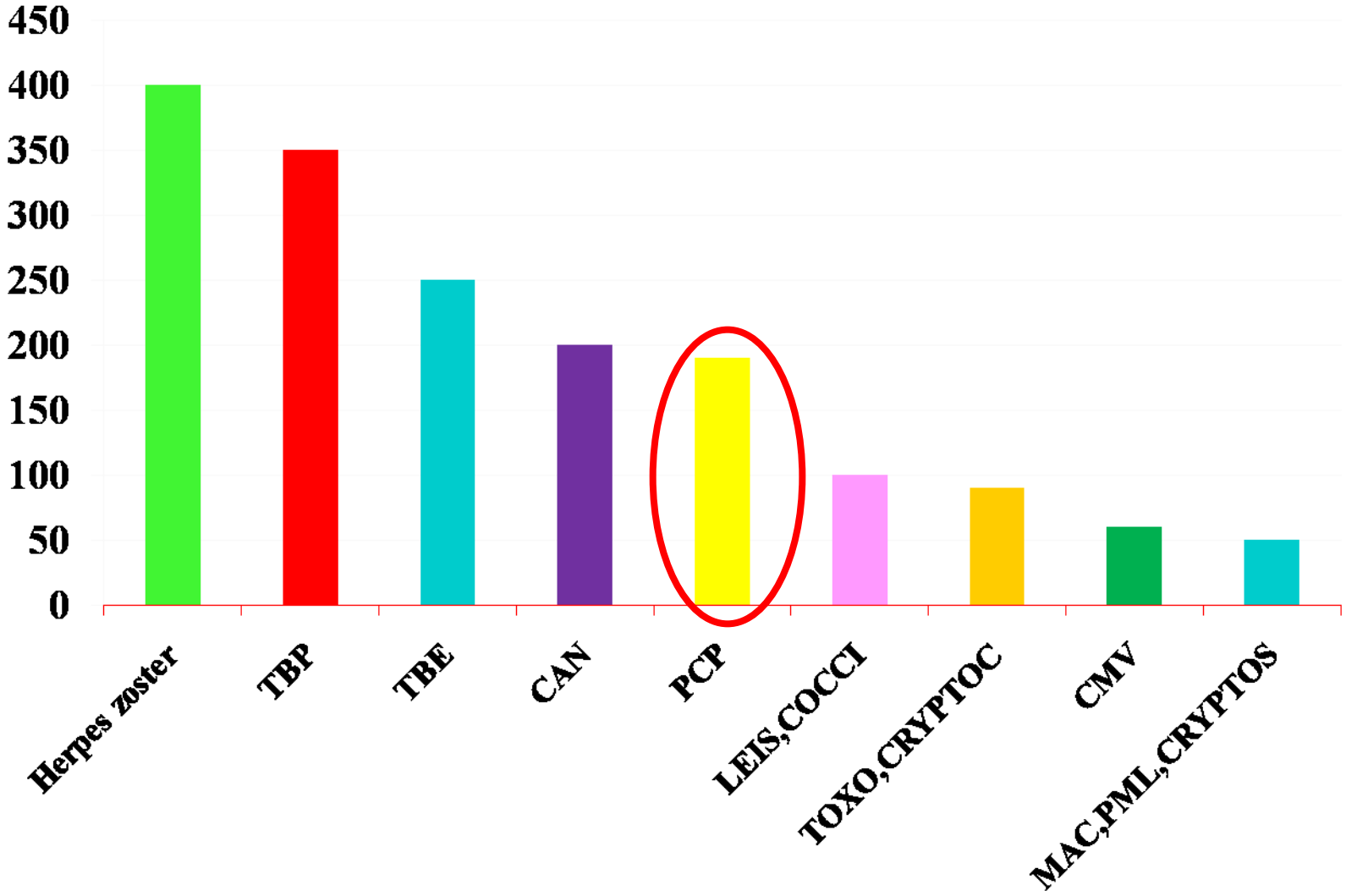
Pneumocystis jiroveci

pneumonia

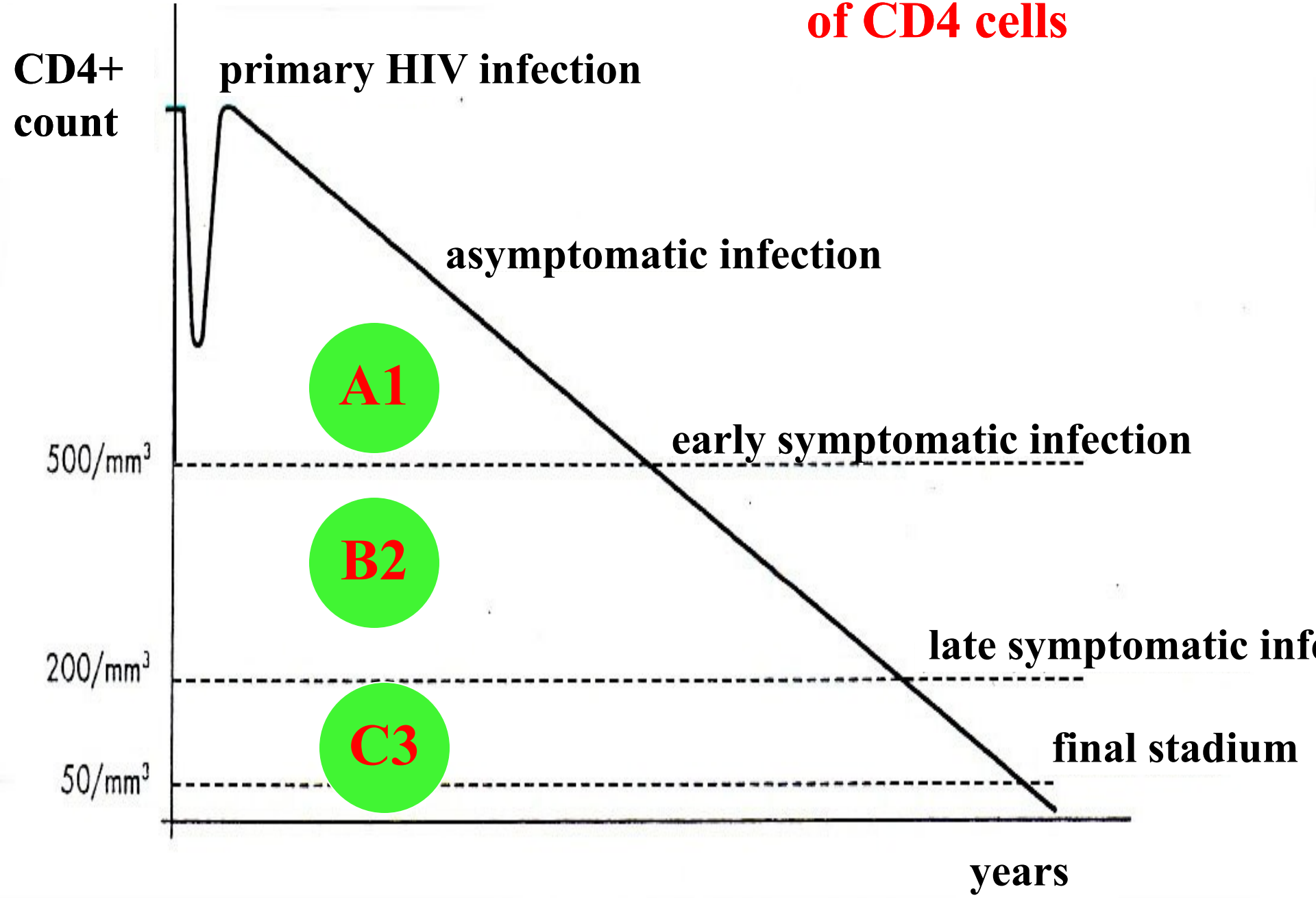
Pneumocystis jiroveci

- **Is an opportunistic pathogen, the natural habitant of which is the lung**
- **The organism is an important cause of pneumonia in the compromised host**
- **The organism can be found in other organs and tissues**

CD4 count and opportunistic infection



CD4+ lymphocytes depletion – gradual loss of number of CD4 cells



Pneumocystis jiroveci

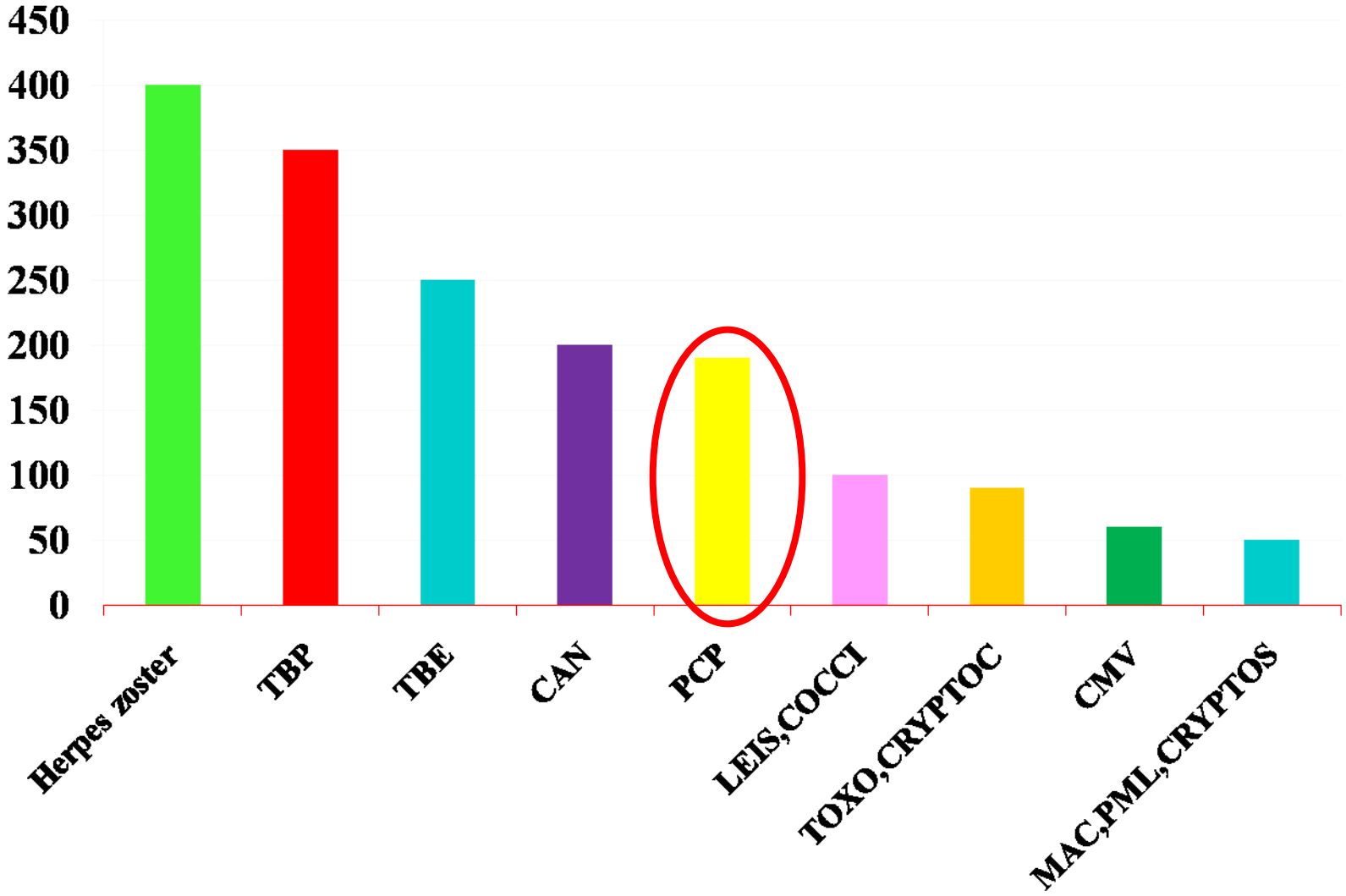
- **Has a worldwide distribution**
- **Serologic serveys indicate that already most healthy children have been esposed to the organism**
- **It means that we meet with this organism in early childhood**
- **Taxonomy – the fungal kingdom**

Risk Factors

Pn. carinii jiroveci **occurs in the following hosts:**

- **premature, malnourished infants**
- **children with primary immunodeficiency disease**
- **patients receiving corticosteroids**
  or other immunosuppressive therapy
- **patiens with autoimmune diseases with disorder of immune system**
- **severely immunosuppressed patients with hematologic or other malignancies, organ transplantation, and so forth**
- **HIV-infected individuals**

CD4 count and opportunistic infection



Incidence

- **PCP accounted for 42% of all AIDS-indicator diseases before ART**
- **Incidence of PCP in this population is declining (with ART and prophylaxis)**
- **But incidence of extrapulmonary *Pn. carinii jiroveci* is increasing**

Extrapulmonary *Pn.carinii jiroveci* infection

involves in fewer than 3% of cases.

- **Lymph nodes** (in up to 50% of cases)
- **Spleen**
- **Liver**
- **Bone marrow**
- **GI and genitourinary tracts**
- **Adrenal and thyroid glands**
- **Heart, pancreas, eyes, ears, skin…**

Incubation Period

- **On the basis of animal studies, the incubation period is thought to be**

from 4 to 8 weeks

Symptoms

- The clinical picture is quite variable
- HIV-infected patients are usually ill

  for several weeks or longer

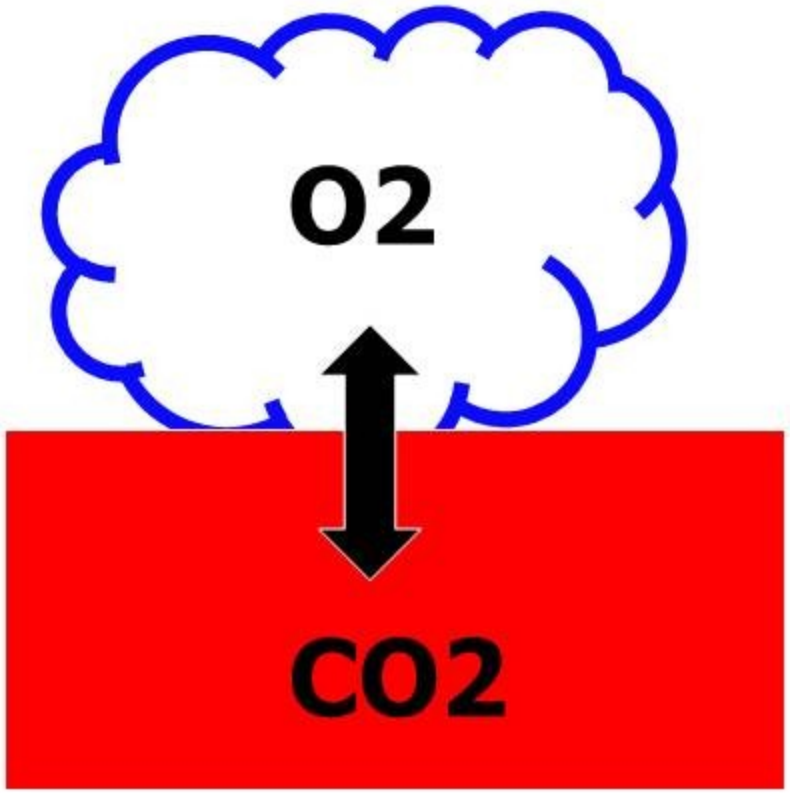
  and have relatively subtle and light manifestations
- Can mimic influenza-like illness
  - Over a few weeks or months

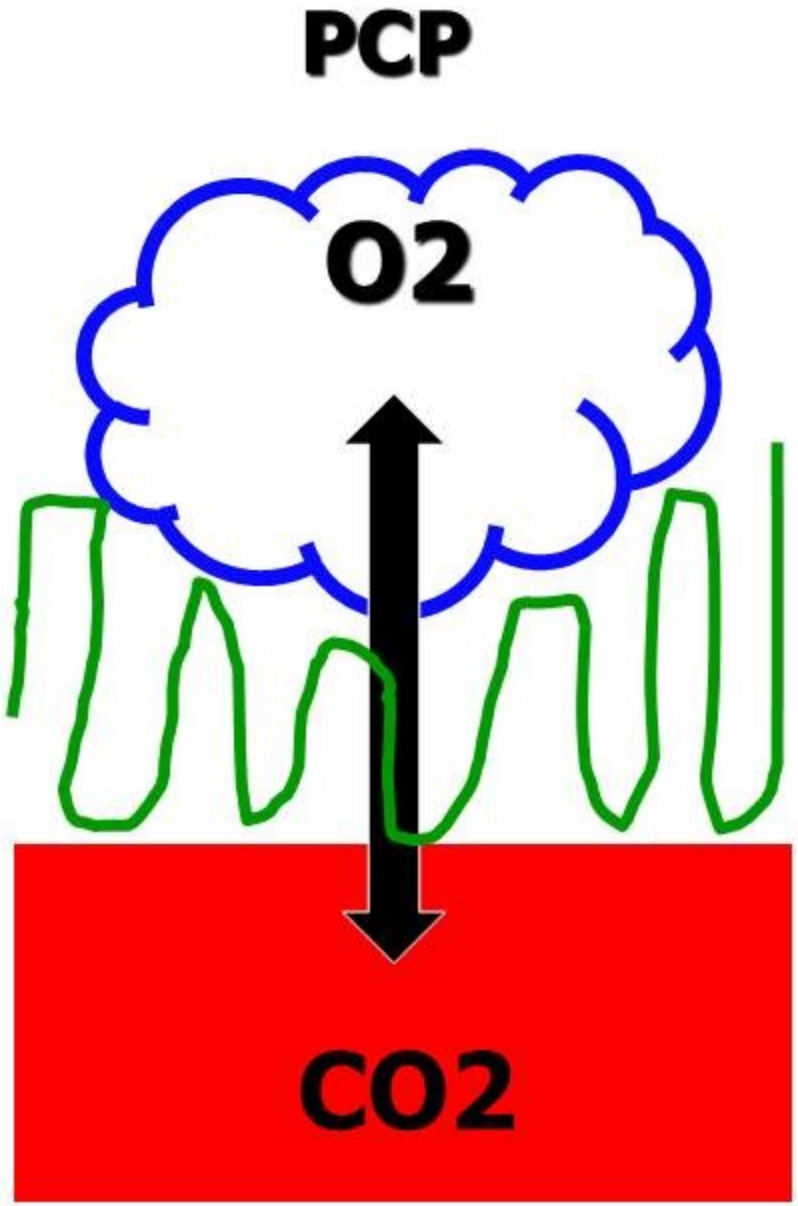
Typical Symptoms

- Patients with PCP usually develop the following:
  - Dyspnea
  - Mild fever
  - Nonproductive cough
- Physical findings of PCP include the following:
  - Tachypnea
  - Tachycardia
  - Cyanosis
- Lung auscultation is usually unremarkable

Alveolocapillary membrane

- characteristic exudate
  is in the inter alveolar space





Differential Diagnosis

The differential diagnosis of PCP is very broad and includes

- infectious diseases
  - Atypical pneumonia (due to *Mycoplasma* or *Chlamydia* spp, etc.)
  - Atypical presentation of pneumococcal or fungal pneumonia
  - Legionnaires´ disease
  - Tuberculosis
  - Viral pneumonia

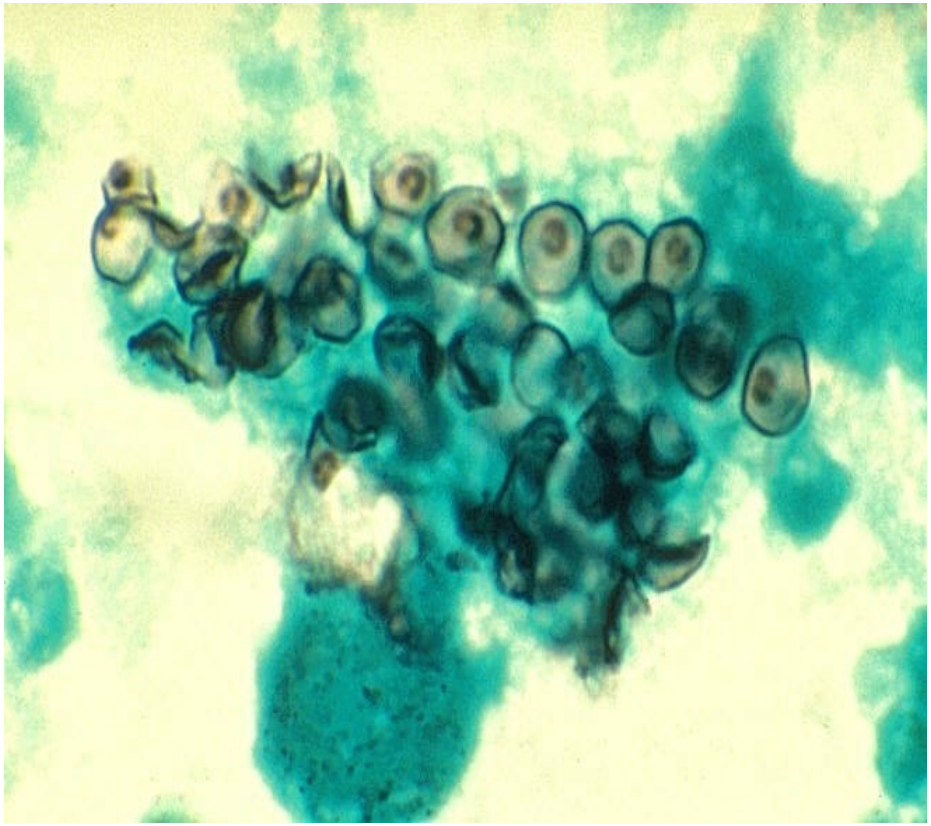
and also can mimic

- noninfectious diseases
  - Congestive heart disease
  - Kaposi´s sarcoma
  - Lymphoma involving the lungs
  - Pulmonary embolism
  - …

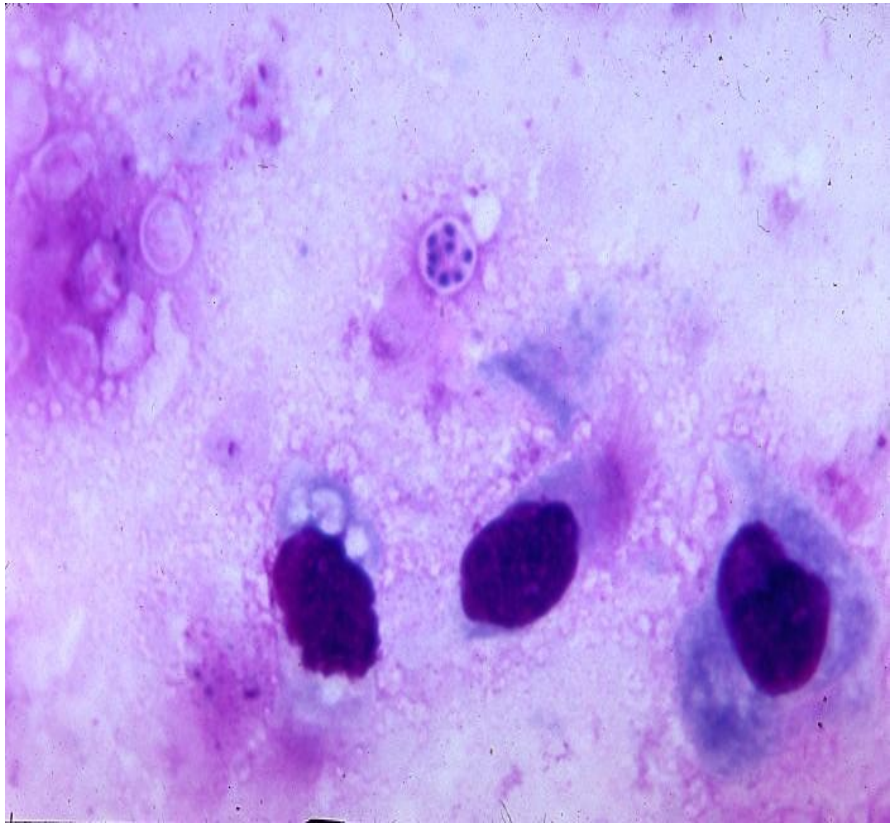
Laboratory

- There is no reliable way to cultivate the organism *in vitro*
- A definitive is made by histopathologic staining, which selectively stain the wall of *Pn. carinii jiroveci,* cysts or nuclei
- PCR technique which demonstrate nuclei acid

Cysts of *Pn. Jir*oveci - Methenamine silver stain.
In smear from bronchoalveolar lavage.
Characteristic cysts with cup forms and cyst wall thickenings

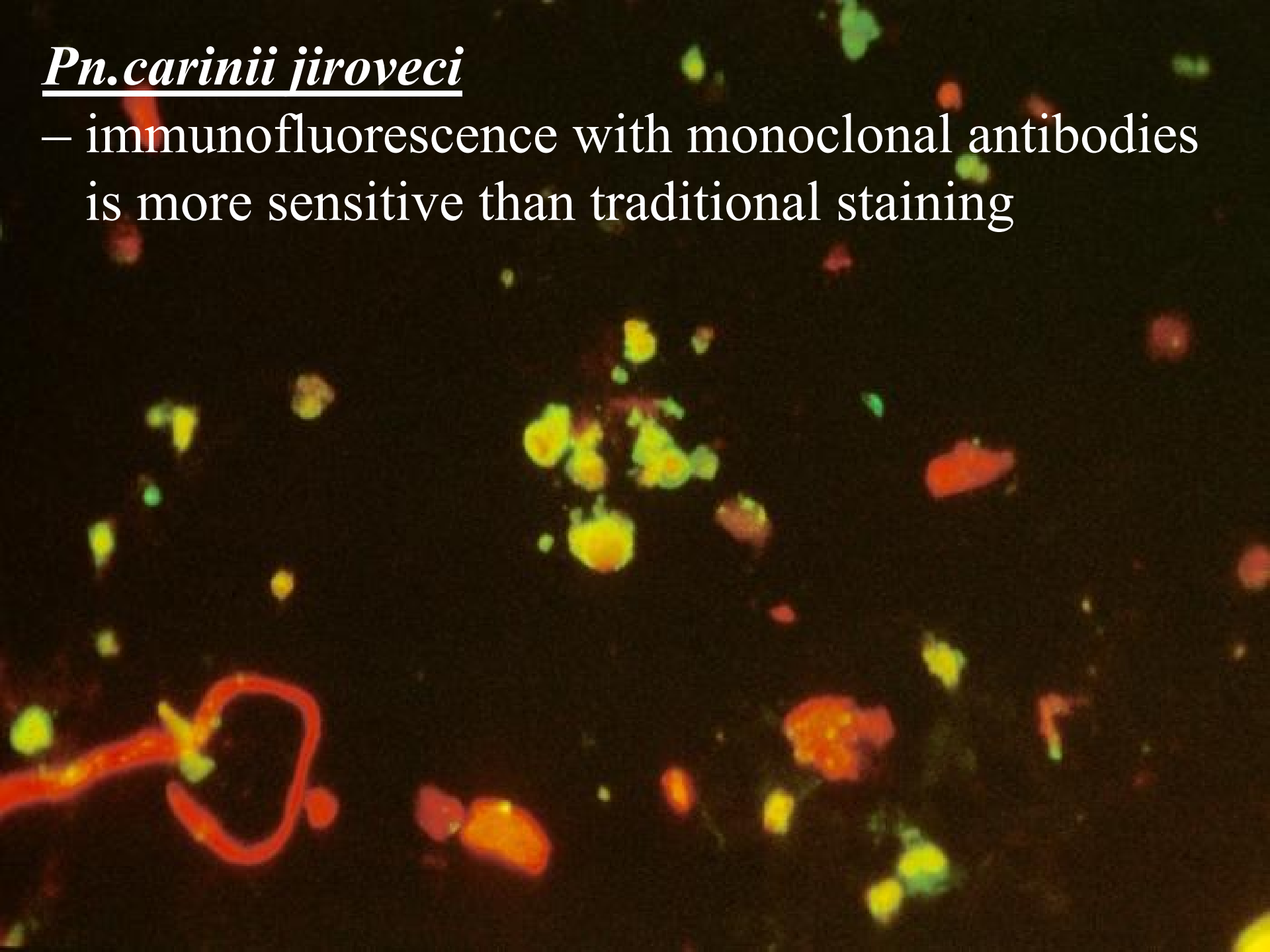


Pn. jiroveci – trophozoites (growth stage), Giemsa-stained, large nuclei



Pn.carinii jiroveci

– immunofluorescence with monoclonal antibodies is more sensitive than traditional staining



Laboratory

LDH

- **Elevated serum concentrations of lactate dehydrogenase have been reported but are not specific to *Pn. Carinii* infection**

Leucocytes

- **The white blood cell count is low**

Oxygen saturation is very low

- **Is probably the most sensitive noninvasive test for dg. PCP**

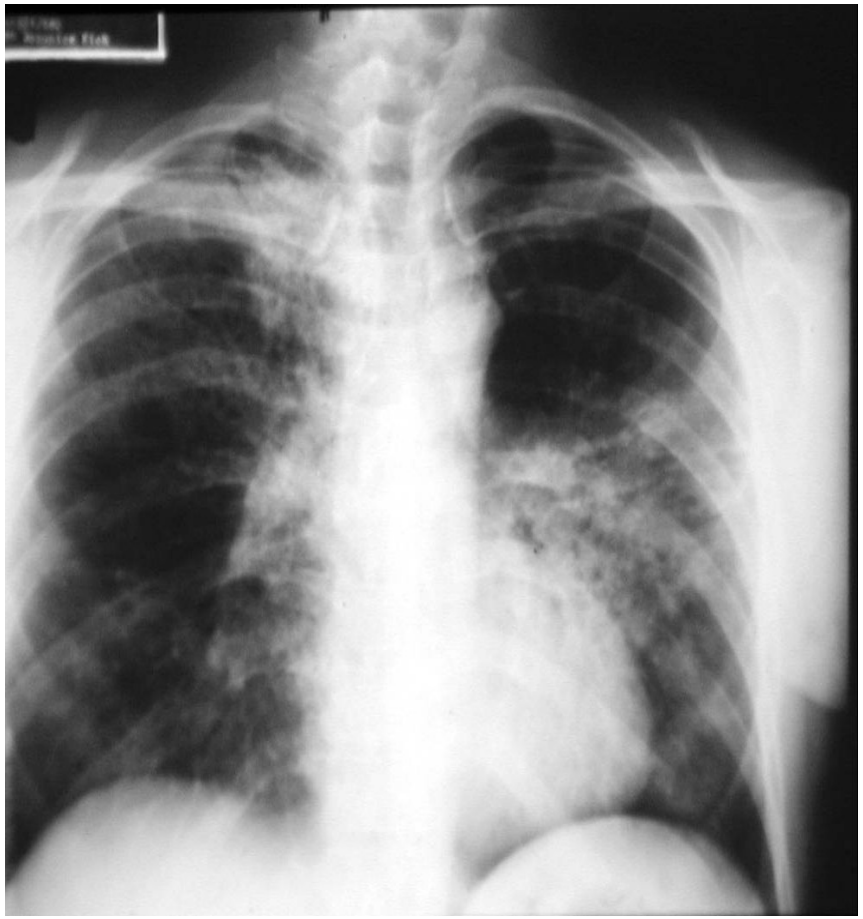
Arterial blood gases demonstrated

  - **Hypoxia**
  - **An increased alveolar-arterial oxygen gradient**

Imaging

- The classic findings on chest radiography consist of bilateral diffuse infiltrates involving the perihilar regions.
- Atypical manifestations also have been reported.
- Early in the course of pneumocystosis, the chest radiograph may be normal.

Pneumocystis jiroveci pneumonia (PCP)



HR CT imaging

– the most important imaging method shows white glass picture

Diagnostic/testing procedures

Fiberoptic bronchoscopy

- With bronchoalveolar lavage (and investigation of bronchoalveolar fluid by PCR) remains the mainstay of PCP diagnosis

Sputum

- is a simple, noninvasive technique, but its sensitivity has extremely low

Transbronchial biopsy and open lung biopsy

- are the most invasive, are reserved for situations in which a diagnosis cannot be made by lavage

Complications

- In the typical case of untreated PCP, progressive respiratory compromise leads to death.

- Therapy is most effective when instituted early in the course of the disease, before there is extensive alveolar damage.

Main treatment

Trimethoprim-sulfamethoxazol

- **Is the drug of the first choice for all forms of *Pn. Carinii* infection**
- **It is administered intravenously (orally) at a dosage 120 mg of TSX/kg/d in four divide doses**

Glucocorticoids

- Administration of glucocorticoids to HIV-infected patients with moderate to severe pneumocystosis can improve the rate of survival
- The recommended regimen:

  40 mg prednisone PO twice daily, with tapering to a dose of 20 mg/d over a 3-week period

Duration of treatment

non-HIV-infected patients

- Treatment of pneumocystosis should be continued for 21 days

HIV-infected patients

- Treatment of pneumocystosis should be continued for 21 days

Alternative treatment

- **Pentamidine**

  4 mg/kg/d by slow intravenous infusion
- **Clindamycin**
- **Primaquine**

  avoided in patients with glucose-6-phosphate dehydrogenase deficiency
- **Trimethoprim + dapson**
- **Atovaquone**

Primary prophylaxis

- Is indicated for HIV-infected patients at high risk of developing pneumocystosis

  CD4+ lymphocyte count < 200/mm^3

- Is indicated for other immunocompromised hosts in known risk groups:
  - Bone marrow transplant recipients
  - With acute lymphoblastic leukemia…

Secondary prophylaxis

Is indicated for all patients who have recovered from PCP

Prophylactic regimen

- Trimethoprim-sulfamethoxazol
  (160mg of trimethoprim) per day

Alternative regimens

- Dapsone (50mg daily), pyrimethamine (50mg once per week), and folinic acid (24mg once per week)
- Dapsone (100mg daily)
- Nebulized pentamidine
  (300mg once per month via nebulizer)

Primary prophylaxis

conditions	pathogen	drug
CD4+ any + TB exposure	*M. tuberculosis*	isoniazid (+pyridoxin), rifampicin, pyrazinamid, ethambutol
CD4+ < 200/mm3	*Pn. carinii jiroveci*	co-trimoxazol, pentamidine (aerosol), dapson

CRYPTOCOCCOSIS

- **Is a systemic infection caused by the yeastlike fungus**

  Cryptococcus neoformans

Cryptococcus neoformans

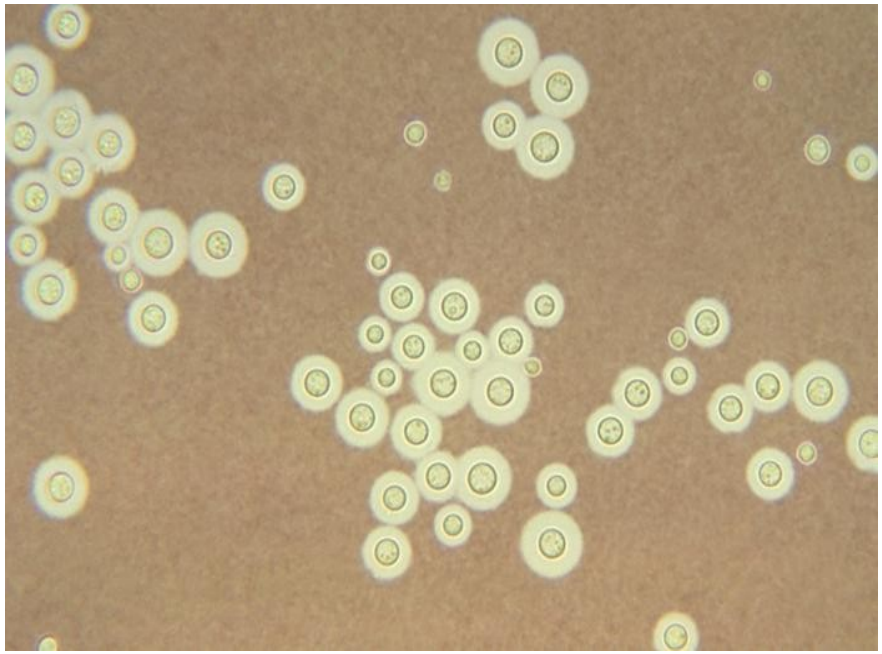
- An encapsulated, yeastlike fungus that reproduces by budding
- A saprobe in nature, with a worldwide distribution
- Soil may also contain the fungus, especially if the soil is contaminated with bird droppings
- The portal of entry is the lung

Epidemiology

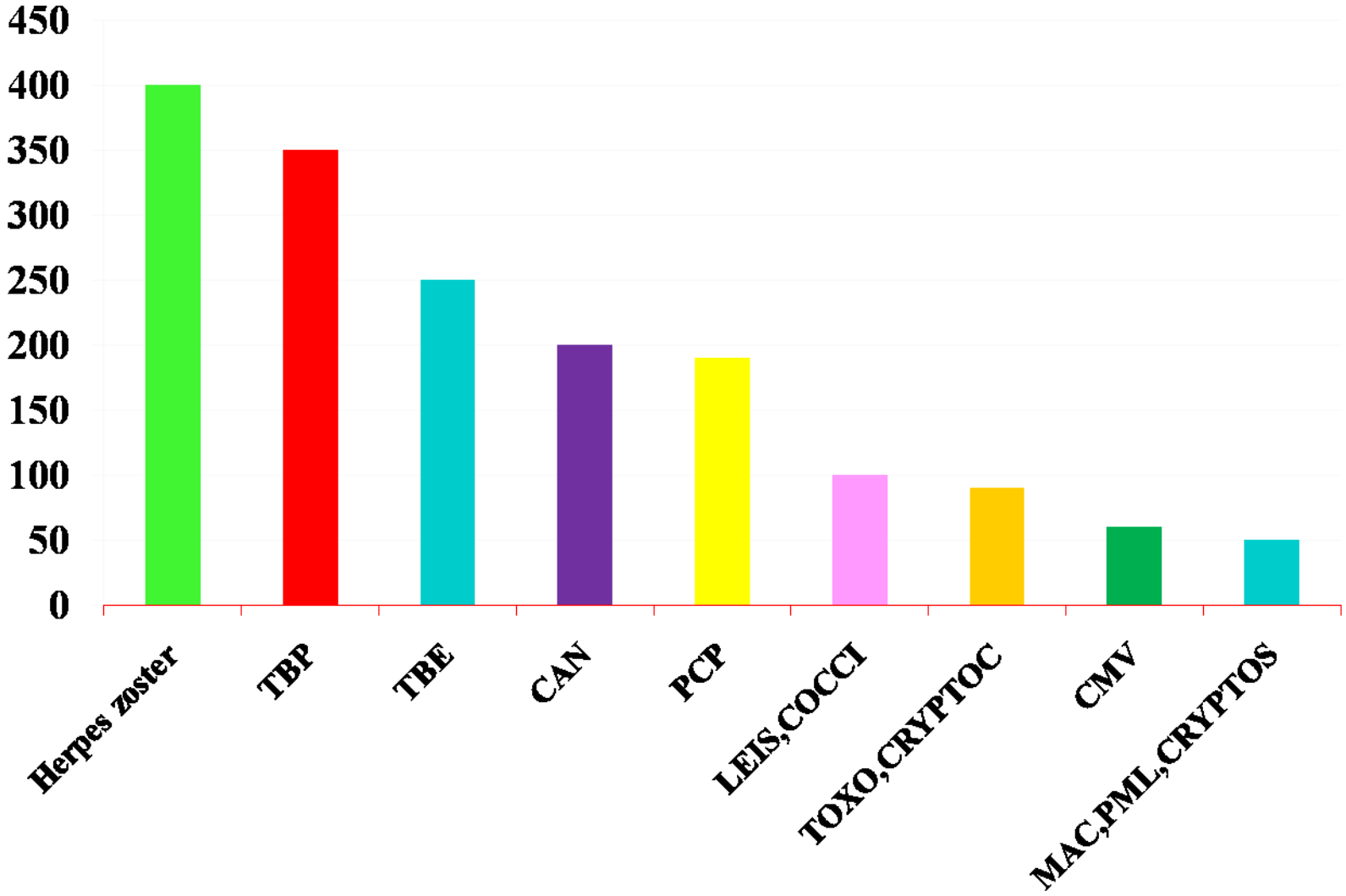
- AIDS is the major predisposing factor
- AIDS-associated cases usually occur when CD4+ T-lymphocyte counts fall below 200 cells/mm3

  usually bellow 100 cells/mm3

Cryptococcus neoformans
– a light India ink staining preparation



CD4 count and opportunistic infection



Risk factors

- Numbet of CD4+ lymphocyte
- Organ transplantation (the second most frequent risk factor), largely attributable to the use of corticosteroids and immunosippresive drugs.
- Lymphoreticular malignancies (especially Hodgkin´s disease)
- High-dose corticosteroids or other immunosuppresive agents
- Sarcoidosis or diaetes mellitus
- About half of patients with cryptococcosis lack apparent predisposing factors

Clinical manifestations of CNS cryptococosis

- The onset of CNS cryptococcosis may be acute or insidious
- Those who have a more chronic course have waxing and waning manifestations over weeks or months, often with completely asymptomatic periods

Symptoms include:

- Confusion, dizziness, headache, irritability
- Nausea, obtundation
- Seizures, somnolence, visual loss

- Some HIV+ patients have minimal or no symptoms at the time of presentation
- Patients are often afebrile or have a mildly elevated temperature
- Most patients have minimal or no nuchal rigidity
- Papilledema is noted in up to one-third of the cases

CNS cryptococcosis

Abnormmalities in cerebrospinal fluid

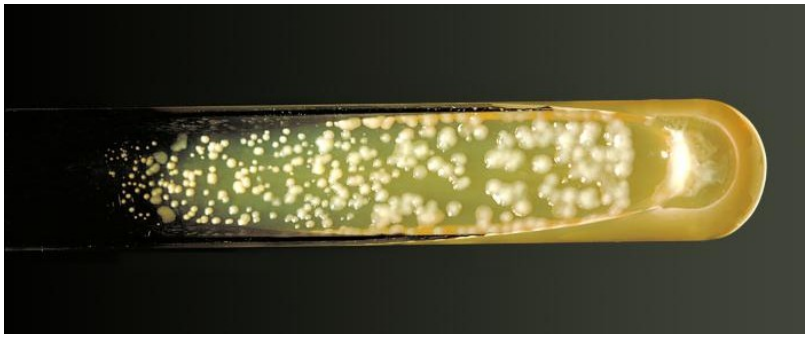
- ↑ opening pressure
- ↓ glucose
- ↑ protein concentration
- ↑ leukocyte counts

Cryptococci grow in culture

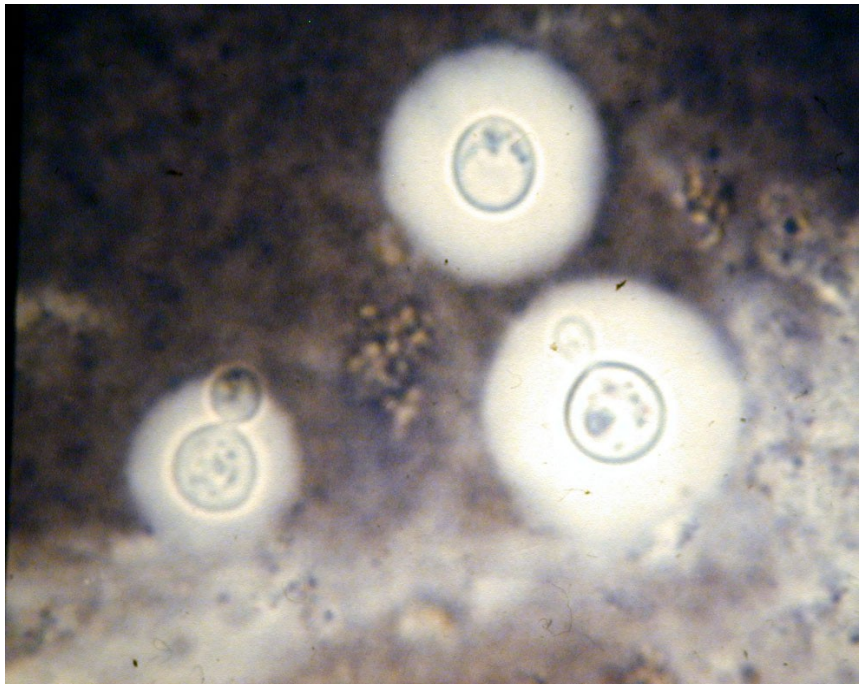
Latex agglutination

- detects antigen in CSF or serum (or both) from 90% or more of the HIV-infected patients with cryptococcal meningitis

This SABHI agar slant culture is growing *Cr. Neoformans* grown at 37°C.



Cr. neoformans in CSF



Pulmonary cryptococcosis

- Asymptomatic
- Symptomatic
  - – with production of only scant, sometimes blood-streaked sputum
    - Fever
    - Cough and dyspnea
    - Pleuritic chest pain (often)
    - Roentgenographic findings of lymphadenopathy or pleural effusions, with diffuse mixed interstitial and intraalveolar infiltrates

Laboratory

Pulmonary cryptococcosis

The isolation of *C. neoformans* from respiratory specimens

- **It can represent a pulmonary infection**
- **It can represent an asymptomatic carriage**

Other organs

Besides the respiratory system and the CNS, cryptococcosis may involve a number of other organs:

- Bone (causing lesions that can be mistaken for neoplasms)
- Eye
- Heart (leading to pericarditis, myocarditis, endocarditis)
- Sinus
- Skin (causing nonspecific lesions that could be the first signs of infection)
- Urinary tract (as an unusual cause of pyelonephritis)

Extrapulmonary cryptoccocosis - skin

Fig. 1 - Left forearm with an extensive ulceration with erythematous borders and irregular infiltrates.

Primary prophylaxis

conditions	pathogen	drug
CD4+ any + TB exposure	*M. tuberculosis*	isoniazid (+pyridoxin), rifampicin, pyrazinamid, ethambutol
CD4+ < 200/mm3	*Pn. jiroveci*	co-trimoxazol, pentamidine (aerosol), dapson
CD4+ < 150/mm3 + antibody to *Toxoplasma* positive	*Toxoplasma gondii*	co-trimoxazol, dapson, pyrimethamin(+folinat)
CD4+ < 75/mm3	*M. avium-intracellulare*	clarithromycin, azitromycin, rifabutin

conditions	pathogen	drug
CD4+ < 50/mm3	Cytomegalovirus	Ganciclovir (PO)
	Candida sp.	fluconazol, itraconazol
	Cryptococcus neoformans	fluconazol, itraconazol
CD4+ < 50/mm3 + endemic area of *Histoplasma*	*Histoplasma capsulatum*	itraconazol, fluconazol
CD4+ < 50/mm3 + endemic area of *Coccidioides*	*Coccidioides immitis*	fluconazol, itraconazol

Disseminated *Mycobacterium avium* complex

Mycobacterium avium complex (MAC)

Comprises two closely related organisms:

- *Mycobacterim avium*
- *Mycobacterium intracellulare*

MAC organisms are common in many environmental sites:

- Natural water sources
- Indoor water systems, pools, hot tubes…
- Soil
- Animals

Disseminated *Mycobacterium avium* complex

MAC is acquired by

- Inhalation
- Ingestion
- 80 – 90% of infections are acquired by **ingestion** (water, soil, animals – food…)

Risk

- Severe depression of the CD4 lymph.
- Rarely in patients with greater than 100 CD4/mm3
- **Median** CD4+ lymf. count among patients with AIDS is **10 cells/µl**

Mycobacterium avium complex

- Is relatively avirulent in the normal host
- They cause od disseminate disease in AIDS patients
- The organisms grow slowly
- The organisms penetrate the gut wall,
- subsequently are phagocytized by macrophages and other RES cells
- →mesenteric adenopathy
- →**hematologic dissemination** occurs (after 6-12 months)

Disseminated *Mycobacterium avium* complex

Clinical presentation

- Fever, night sweats
- Cachexia
- Pain of abdomen
- Severe anemia, elevation of serum alkaline phosphatase
- Disease leads to death by inanition
  - Decreased caloric intake
  - Increased metabolic demand
  - Median survival after diagnosis was only 134 days

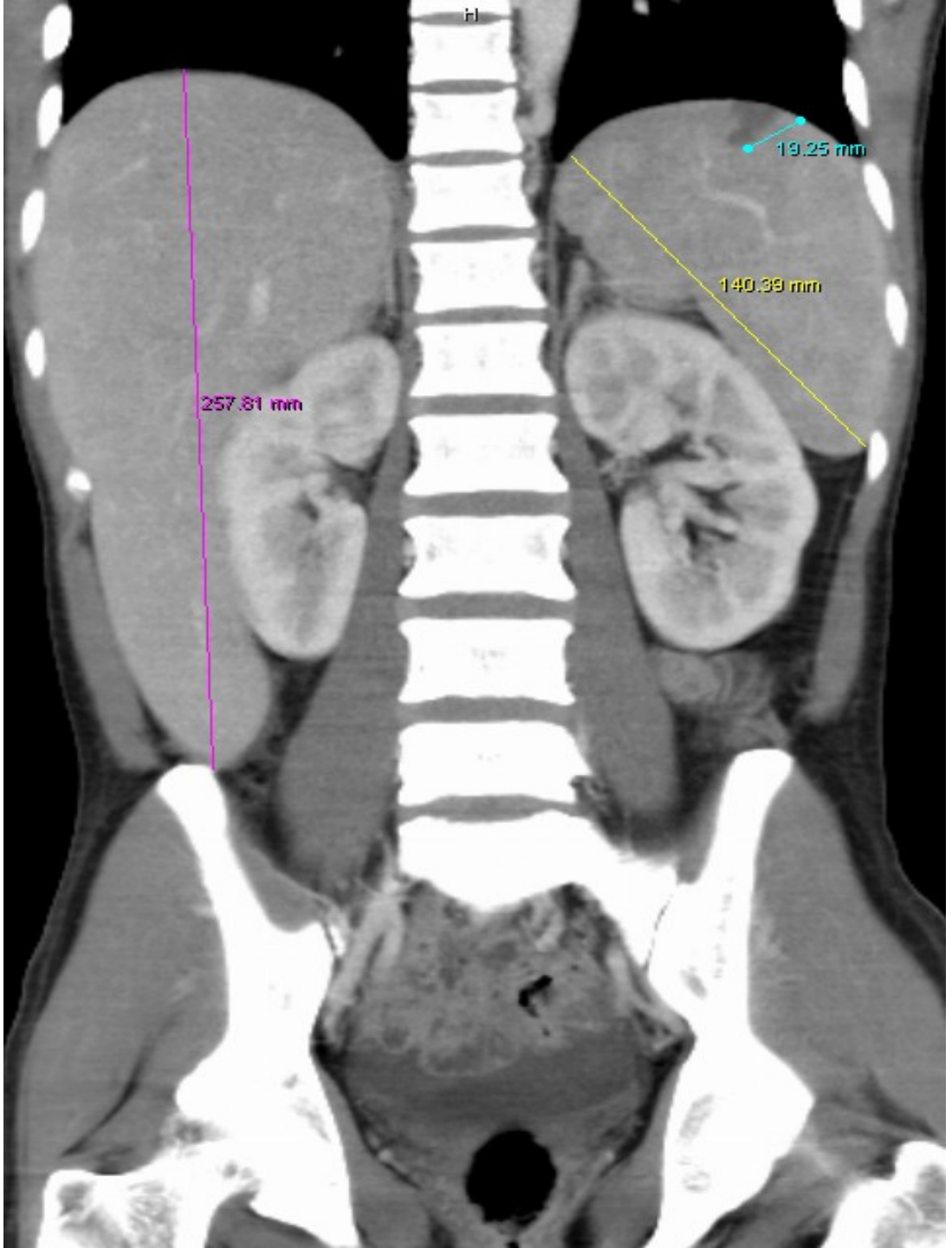
Disseminated *Mycobacterium avium* complex

Common organs involved:

- **Liver, spleen** (hepatosplenomegali)
  - Little elevation of bili, AST, ALT
  - High elevation of (20-40x) ALP, GGT
- **Hepatic biopsy**
  - Histologic picture inthe liver does not show marked abnormality, suggesting interference with enzyme metabolism rather than hepatic tissue destruction

CT of abdomen

- Hepatomegaly
- Splenomegaly
- Retroperitoneal and mesenterial lymfadenopathy
- Increase portobilium



CT of abdomen transversally

Multiple small focuses in hepar (small abscesses?) and dilatation of intrahepat. ductus biliares. Increase of hepar. Increase of lien. Retroperitoneal and mesenterial lymphadenopathy.

CT of abdomen

Multiple small focuses in hepar (small abscesses?) and dilatation of intrahepat. ductus biliares

- Increase of hepar
- Increase of lien
- Retroperitoneal and mesenterial lymphadenopathy
- Susp. thickness of caecum and c.ascendens

Disseminated *Mycobacterium avium* complex

- **Lymphnodes**
- **Bowel wall** with severe pain of abdomen, but histologically, epithelial cells show only mild inflammatory changes, and ulceration is unmommon
- **Bone marrow**
  - The mechanism of the severe anemia seen is not well understood
  - Bone marrow involvement can be minimal
  - Clinical response to exogenous erythropoietin is unpredictable

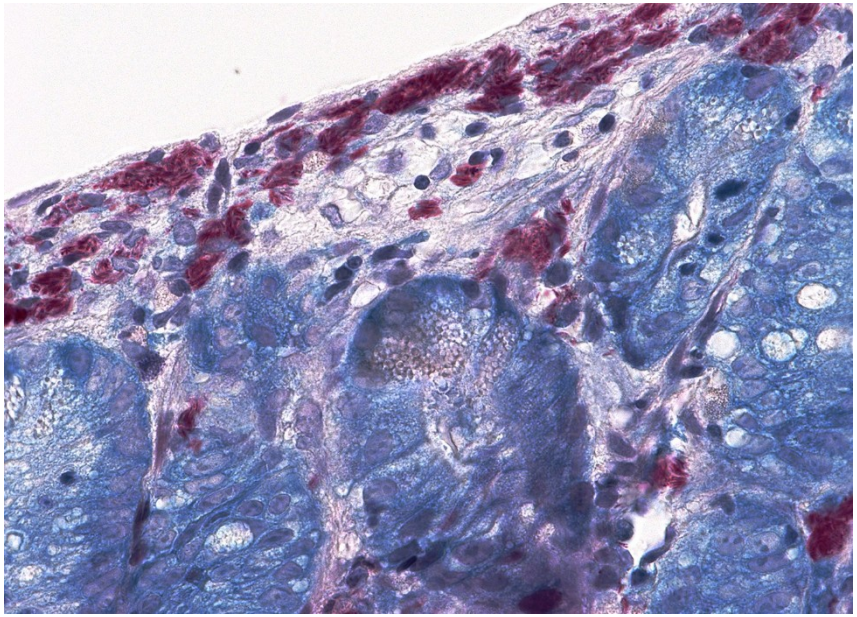
Disseminated *Mycobacterium avium* complex

Less commonly organs involved:

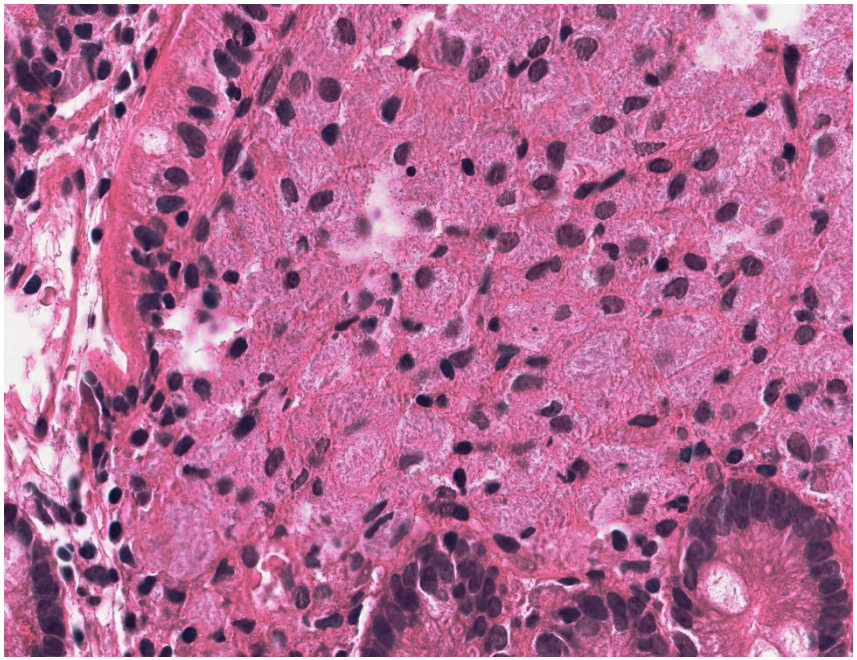
- **Lungs**
- **Adrenals**
- **Stomach**
- **Central nervous system**

(not typical environmental for mycobacterium)

Duodenum – detail – surface – bk. Numerous of acidoresistant sticks in cytoplasma of macrofages (staining Ziehl-Nielsen).



Duodenum – detail. Mucosa of duodenum, accumulation of macrofages, inflammatory infiltration by lymfoplasmocytes.



Post mortem

Hepar

- weight 3130 g (normal 1500g)

Lien

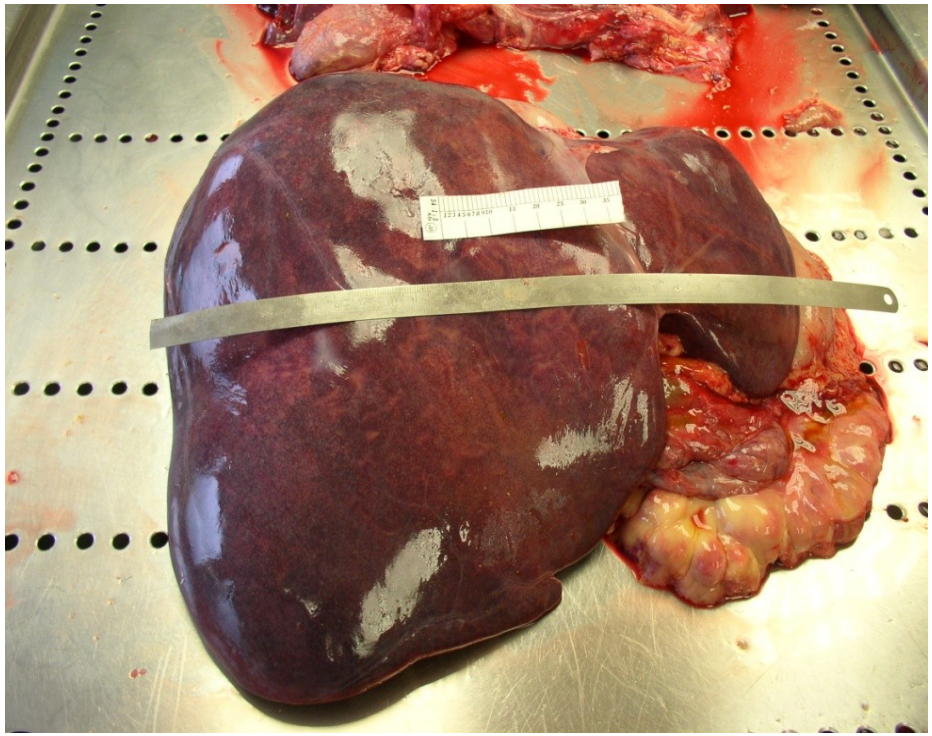
- weight 530 g (normal max 250 g)

Cerebrum

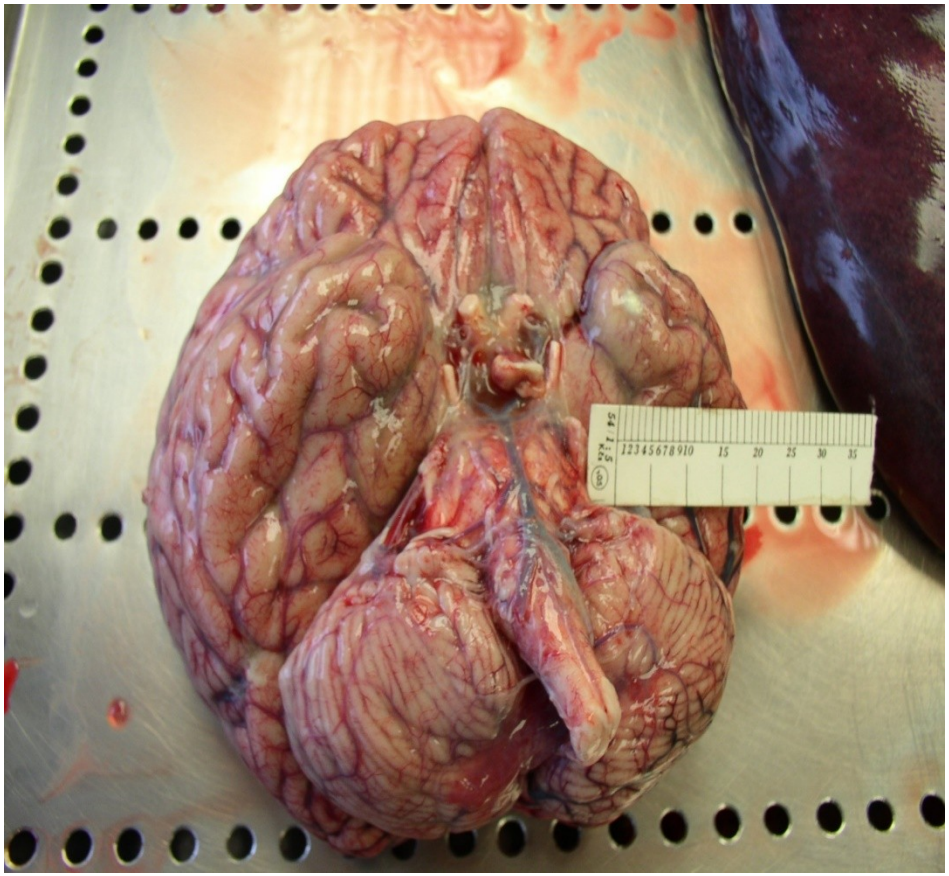
- weight 1302 g (normal 1500 g)

Disseminated *Mycobacterium avium* complex

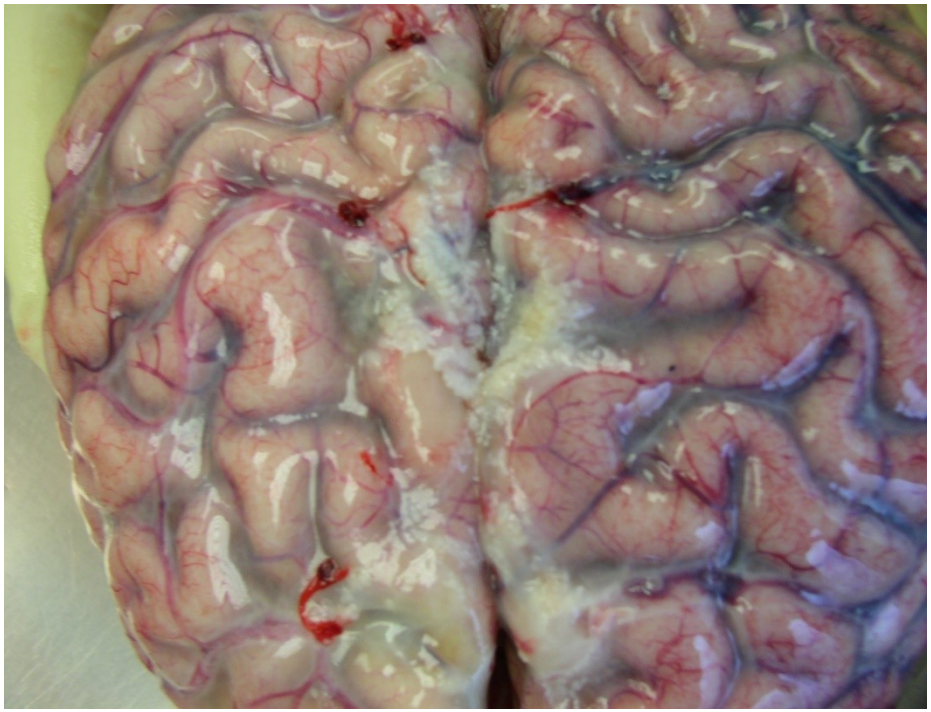
Necrosis of intrahepatic biliary ducts



Slight wet brain, well-kept structure of cortex. Slightly defibering of neuropil.



Multiple capillaries, subarachnoideal inflamatory celluolus infiltration. Mycobacteria negative – special staining.



Treatment

- Combination therapy is essential
- Failure rates and mortality remained very high
- Clarithromycin, rifabutin, ethambutol
- Greater than 17% of strains of MAC had baseline resistance to macrolides

Thank you for your attention….