Tuberculosis treatment. Extrapulmonary tuberculosis. Non-tuberculous mycobacteriosis.

General Medicine

English Learning Programme

Phthisiology, Lecture #3

Pharmacological treatment basic principles and terms

- combination treatment
- long-term treatment (short-course=6 months)
- intensive/continuation phase
- almost all administered once a day
- first/second/third line drugs
- MDR-TB = multi drug-resistant TB (resistance to izoniazid and rifampicin)
- XDR-TB = extensively drug-resistant TB (MDR-TB + resistance to any fluoroquinolone and any of the second-line anti-TB injectable drugs: amikacin, kanamycin or capreomycin)

First line drugs

- H - izoniazid
- R - rifampicin
- Z - pyrazinamide
- E - ethambutol
- S - streptomycin
- $2HRZE/4(HR)_3$

Second line drugs

- aminoglycosides (amikacin)
- polypeptides (capreomycin, viomycin, enviomycin)
- fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)
- thioamides (ethionamide, prothionamide)
- cycloserine
- terizidone

Third line drugs

- rifabutin, rifapentin
- macrolides
- linezolid
- thioacetazone
- thioridazine
- arginine
- vitamin D
- bedaquiline

Standard treatment regimens

	New patients presumed or known to have drug-susceptible TB	Previously treated patients
S	2HRZE/4HR	DST or 2HRZES/1HRZE/5HRE
A	2HRZE/4$(HR)_3$	
HIV-	2$(HRZE)_3$/4$(HR)_3$	

S - standard regimen
A - alternative regimen
HIV- - alternative for patients NOT living with HIV or living in an HIV-prevalent setting
DST - drug susceptibility testing

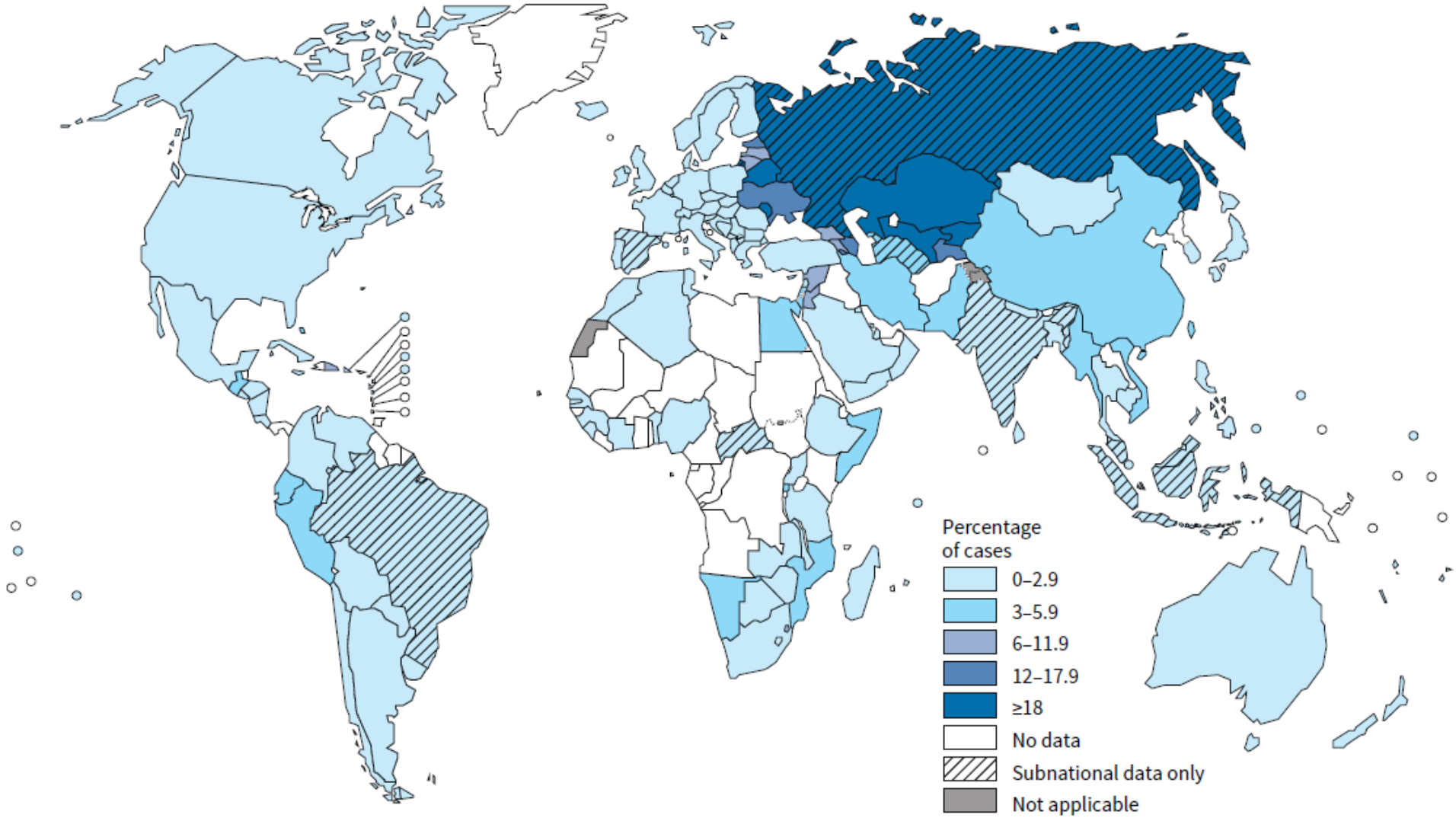
90% sterilization after 2 months,
95% effectiveness after 6 months

Drug susceptibility testing (DST)

- Standard DST (6-9 weeks)
- Rapid DST - molecular-amplification assays e.g. line probe test (2-7 days)

- If MDR prevalence > 3% then DST in all new cases

MDR-TB among new TB cases



Treatment effectiveness in MDR-TB 52%

Standard regimen for MDR-TB treatment 2018

- levofloxacine/moxifloxacine + bedaquiline + linezolide
- + clofazimine + cycloserine
- ? + ethambutol , delamanide, pyrazinamide, imipenem-cilastatine/meropenem, amikacine/streptomycine, ethionamide, prothionamide, PAS
- 20 months after debacilization

Izoniazid

- synthetic, bactericidal/bacteriostatic, intracelullar
- inhibits synthesis of mycolic a.
- clinically available since 1952
- well resorbed from GIT, usually orally admin., i.v. available
- 4-6 mg/kg (up to 900 mg/day)
- AE:
  - GIT intollerance
  - hepatotoxicity
  - CNS effects (precipitation of seizures, mental disorders, peripheral neuropathy)
  - anaemia
  - drug-induced SLE
  - allergy

Rifampicin

- semisynthetic bactericidal antibiotic
- inhibition of RNA-polymerase
- clinically available since 1967
- well resorbed from GIT, i.v. available
- 8-12 mg/kg (up to 600 mg/day)
- AE:
  - GIT intollerance
  - hepatotoxicity
  - flu-like sy.
  - allergy (shock, purpura)
  - renal failure
  - adrenal dysfunction
  - orange-red colour of the body fluids

Pyrazinamide

- bacteriostatic, cross haematoencephalic barrier
- effective in acid environment
- fast development of acquired resistance
- inhibition of fatty acid syntetase
- well resorbed from GIT
- 20-30 mg/kg (up to 2000 mg/day)
- AE:
  - GIT intolerance
  - hepatotoxicity
  - hyperuricaemia
  - allergy, photosensitivity
  - anaemia

Ethambutol

- bacteriostatic, synthetic
- obstructs the formation of cell wall
- well resorbed from GIT
- 15-20 mg/kg (up to 1600 mg/day)
- AE:
  - optic neuritis
  - hyperurikaemia

Streptomycin

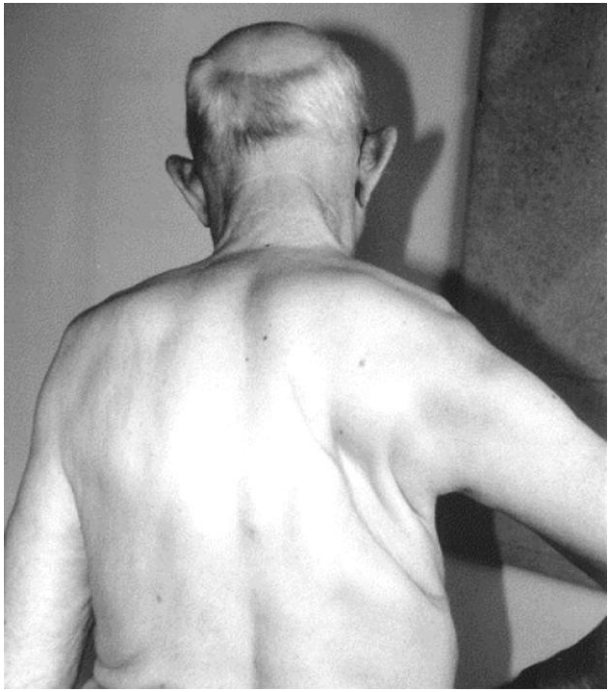
- bacteriostatic, in neutral- alcaline environment working aminoglycoside antibiotic
- protein synthesis inhibitor
- clinically available since 1947 (first antituberculotic)
- not resorbed from GIT – exclusivelly i.m.
- 1000 mg/day (500-750 mg/day in elderly)
- AE:
  - vestibulocochlear nerve toxicity (deafness, tinnitus, vertigo, ataxia)
  - nephrotoxicity

Corticosteroids

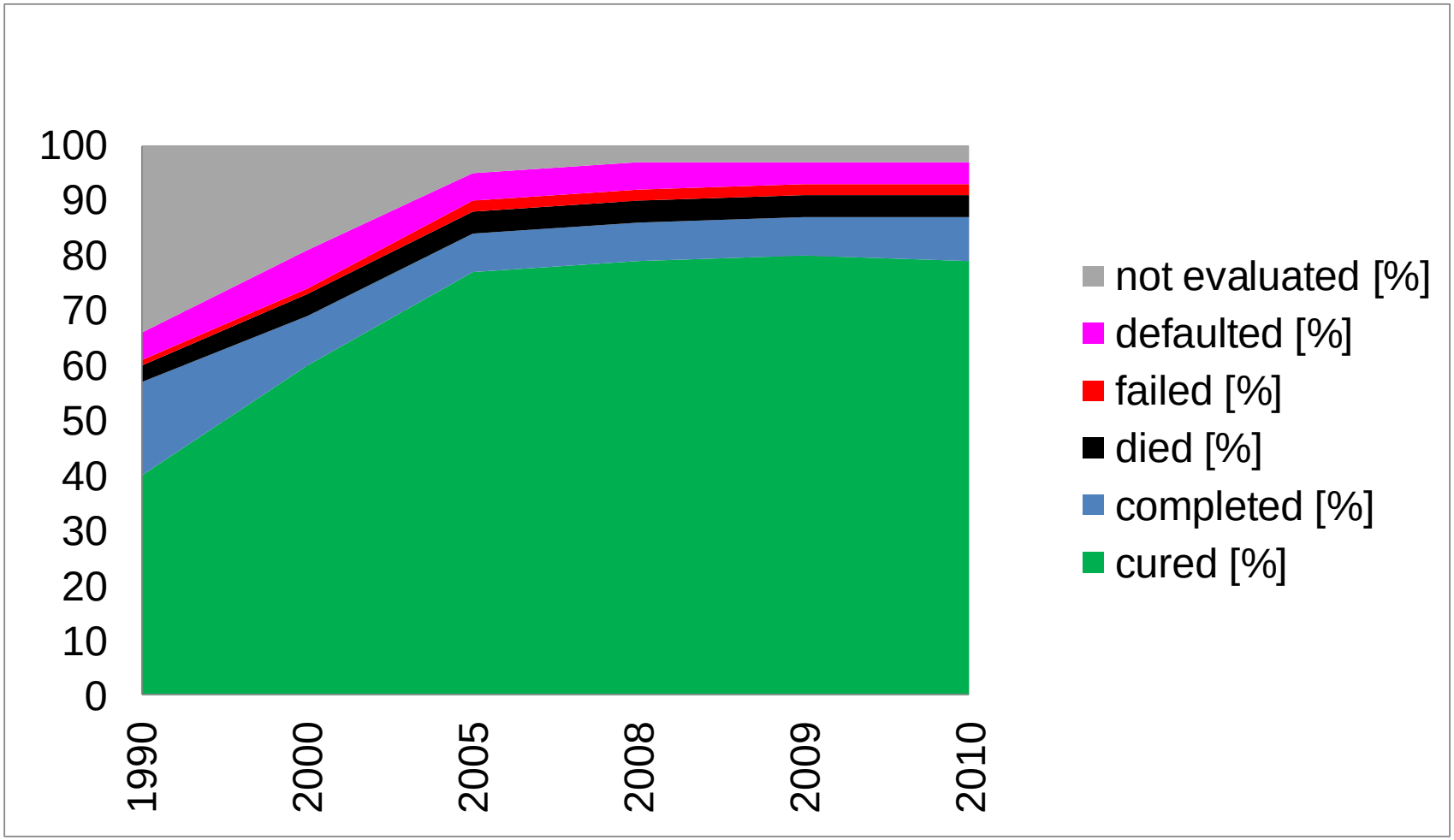
- meningitis, pericarditis, pleurisy, extremely advanced TB - prednisolone 20-60 mg/day tapered off over 4-8 weeks.
- peritonitis, miliary disease, osteomyelitis, laryngeal TB, lymphadenitis and genitourinary disease?

Surgical treatment

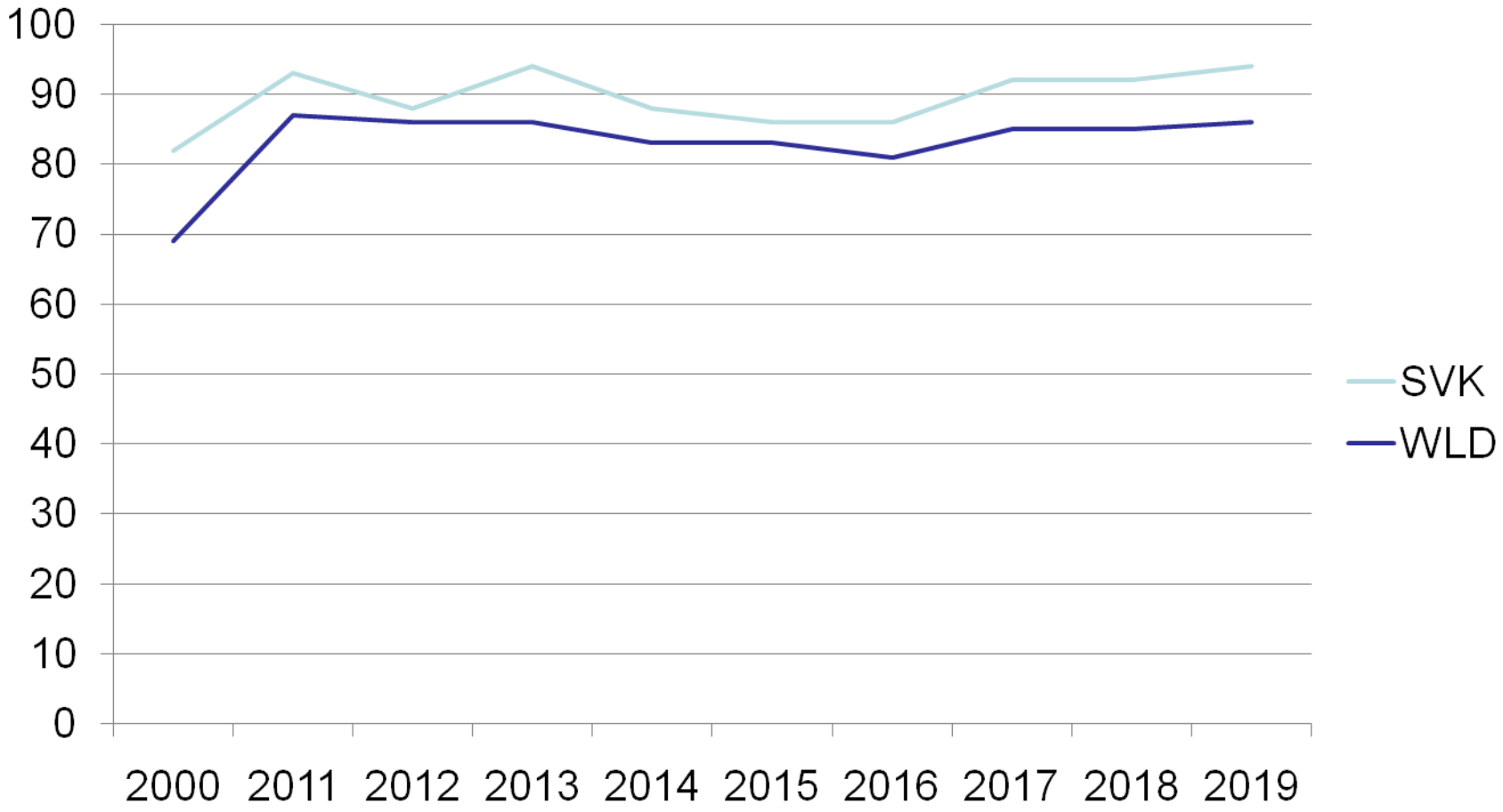
- pneumothorax
- plombage of pleural cavity (porcelain balls)
- thoracoplasty
- phrenic nerve crushing
- resection



Global treatment outcomes (new smear-positive cases)



The effectiveness of tuberculosis treatment



Global objectives of TB control

- To cure 85% of smear-positive cases
- To diagnose > 70% of cases

Treatment using short-course chemotherapy

- standardized treatment
- protection of rifampicin
- DOTS
- fixed-dose combination
- at least 3 other drug in smear +
- prohibition of sale

Directly Observed Therapy (DOT)

- watch patient swallow each dose of medication
- consider DOT for all patients
- DOT should be used with all intermittent regimens
- DOT can lead to reductions in relapse and acquired drug resistance
- Use DOT with other measures to promote adherence

Indications for hospitalization

- severe deterioration of the patient's general state
- complications of TB (haemoptysis, pneumothorax)
- complications of treatment (severe liver impairment, purpura, allergic skin reaction)
- severe concomitant disease (diabetes, kidney failure, stomach ulcer)

Conditions That Increase Risk of Progression to TB Disease

- HIV infection
- Substance abuse
- Recent infection
- Diabetes mellitus
- Silicosis
- Prolonged corticosteroid therapy and other immunosuppressive therapy
- Cancer of the head and neck
- Hematologic and reticuloendothelial diseases
- End-stage renal disease
- Intestinal bypass or gastrectomy
- Chronic malabsorption syndromes
- Low body weight (10% or more below the ideal)

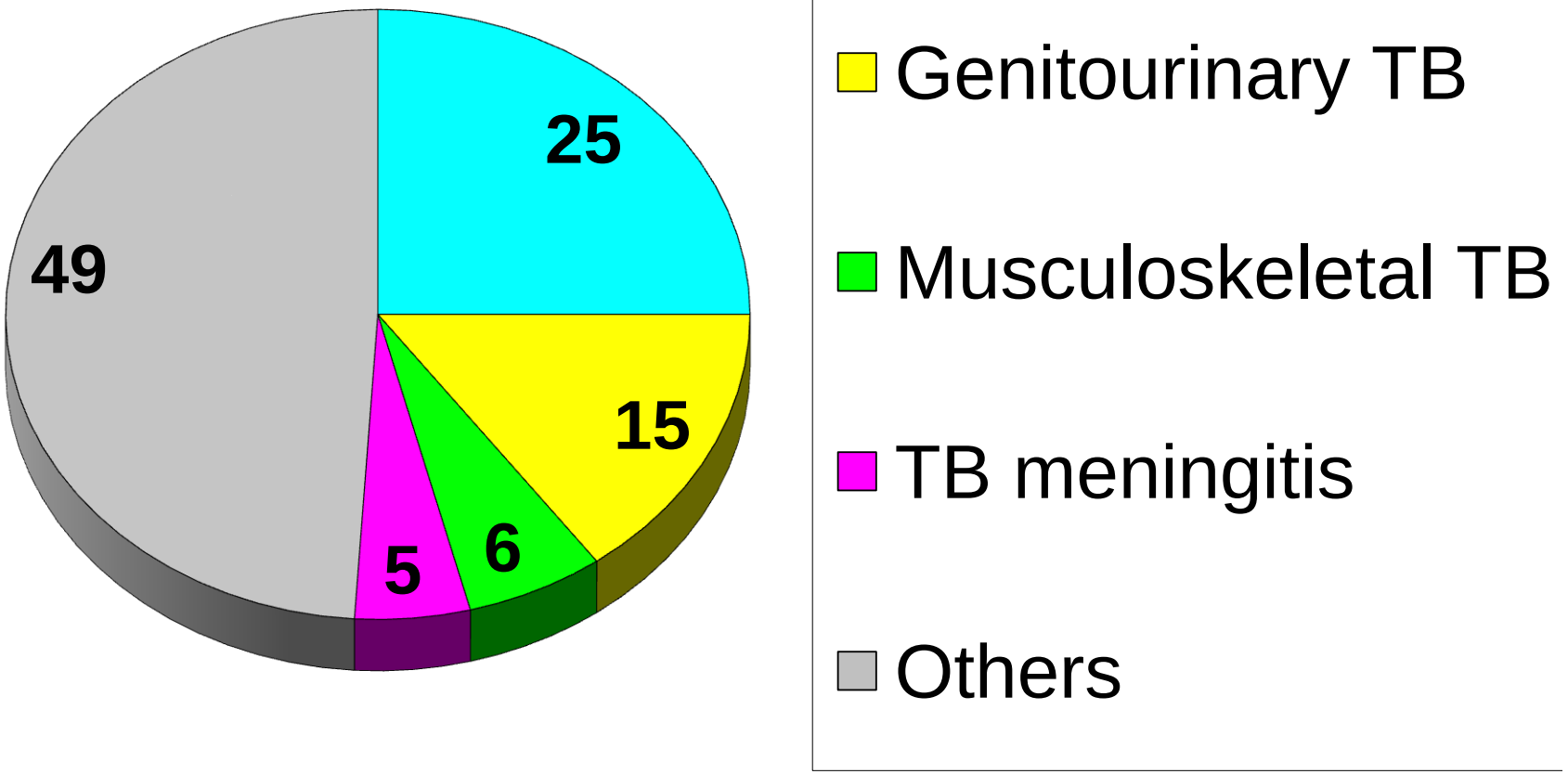
HIV infection

	Early (CD4+>200/mm^3)	Late (CD4+<200/mm^3)
Chest XR	upper-lobe infiltrates, cavities	lymphadenomegaly, effusions, miliary, diffuse, normal
Smear+	frequently	less commonly
PPD+	frequently	less commonly
Extrapulmonary	less commonly	frequently

Extrapulmonary Tuberculosis

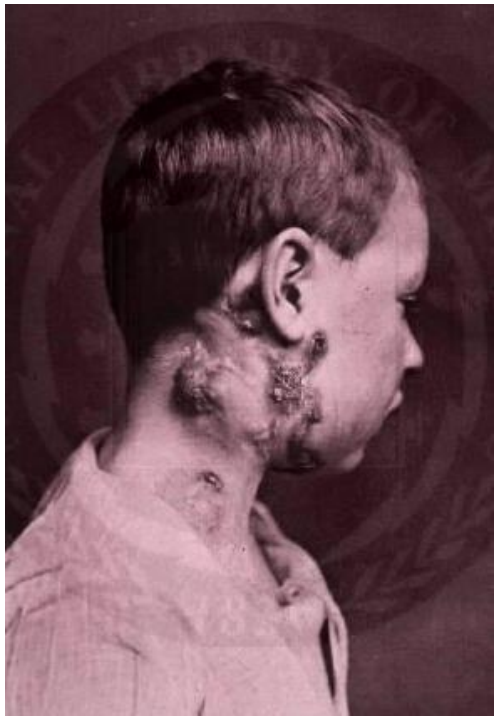
- 15% of active tuberculosis
- likelihood increased in immunocompromised host

Extrapulmonary Tuberculosis



Tuberculous lymphadenitis

- M. tuberculosis, M. scrofulaceum
- anterior cervical chain nodes
- painless swelling
- initially firm, discrete, later large, fistulous
- biopsy, smear (50% positive) culture (80% positive)
- drugs + surgical intervention
- scarring



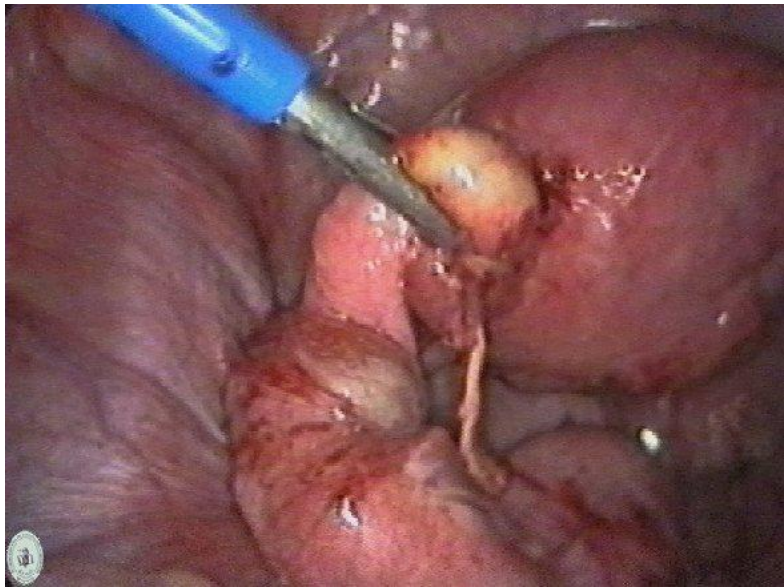
Urinary tuberculosis

- dysuria, hematuria, pollakiuria, flank discomfort
- clinically unilateral, histologically bilateral
- sterile pyuria
- morning urine specimen 3 times = 90% sensitivity
- good prognosis

Genital Tuberculosis

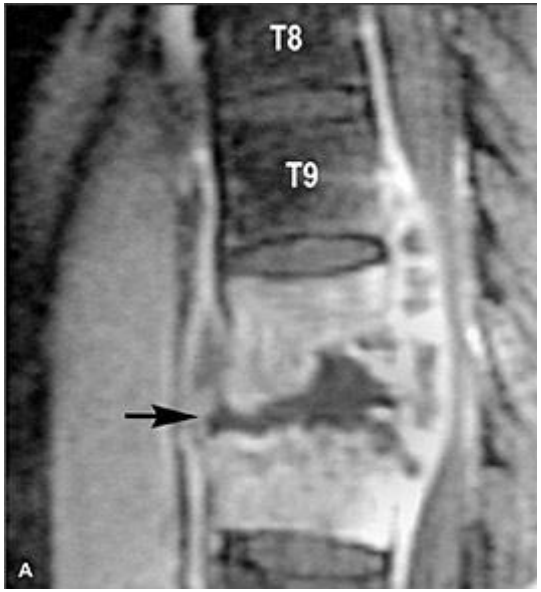
- slowly progressive mass in seminal vesicles, prostate, or epididymis

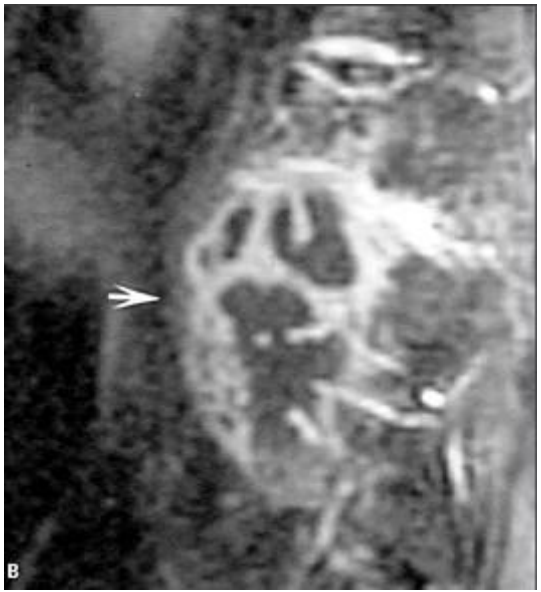
- pelvic pain, abnormal uterine bleeding, irregular menses, amenorhea, infertility



Musculoskeletal tuberculosis

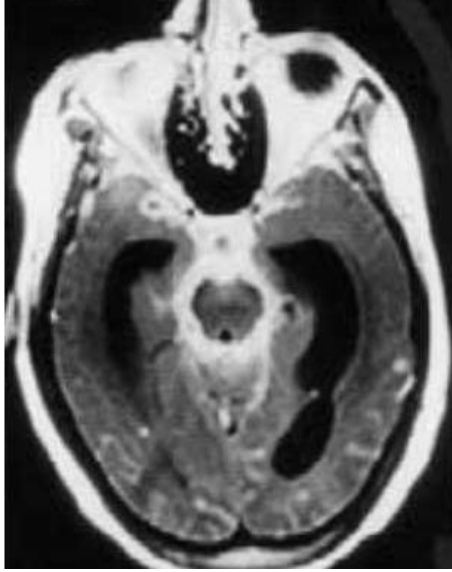
- midle-aged HIV-infected patients
- lower spine and weight-bearing joints
- „cold abscess“
- spinal cord compression
- surgical intervention





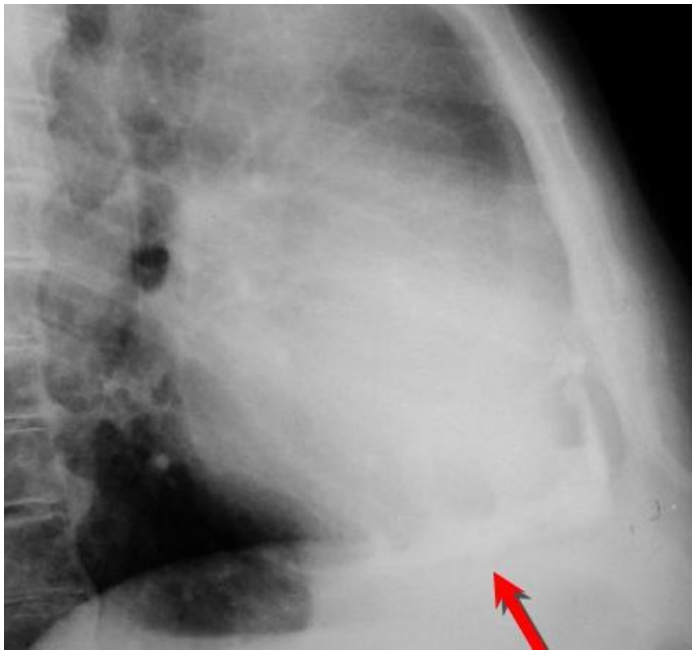
Tuberculous meningitis

- elderly and HIV-infected patients
- confusion, abnormal behavior, headache, fever, cranial nerve abnormalities, seizures
- cerebrospinal fluid:
  - ↑ protein
  - ↓ glucose
  - white blood cell 100-1000/cm^3
  - lymphocytes
  - smear: 25% sensitivity, culture: 75% sensitivity
- mortality 20%
- cortisosteroids



Tuberculous pericarditis

- fever, dyspnea, orthopnea, cough, edema
- pericardial rub absent in 50%
- fluid hemoragic, similar to pleural fluid
- smear and culture sensitivity 50%
- biopsy
- corticosteroids
- surgery
- thickening, calcification



Tuberculous gastrointestinal involvement

- Ileocecal
  - symptoms of appendicitis, Crohn's disease, diarhea
  - fistula
- Peritonitis
  - pain, ascites, "doughy abdomen"
  - smear -, culture sensitivity 80%
  - biopsy

Non-tuberculous mycobacterial infections

endemic occurrence:

- MAC – public water resources
- fast growing M – pools
- M. malmoense - water resources, Finland
- M. simiae - southwestern USA, Cuba, Israel
- M. xenopi - hot water, hospitals, Western Europe
- M. kansasii – USA, Ostrava region

NTM – clinical picture

- symptoms similar to tuberculosis
- pulmonary form
- non-tuberculous lymphadenitis
- skin and soft tissue involvement
- disseminated form

NTM - imaging

- infiltrates with or without nodules
- cavities
- micronodulation
- multifocal bronchiectasis

NTM - treatment

- MAC, M. fortuitum, M. chelonae – macrolides, EMB, rifabutin, aminoglycosides
- M. kansasii – AT except for PZA
- M. xenopi, M. malmoense – clarithromycin + RMP + EMB + STM
- often quinolones