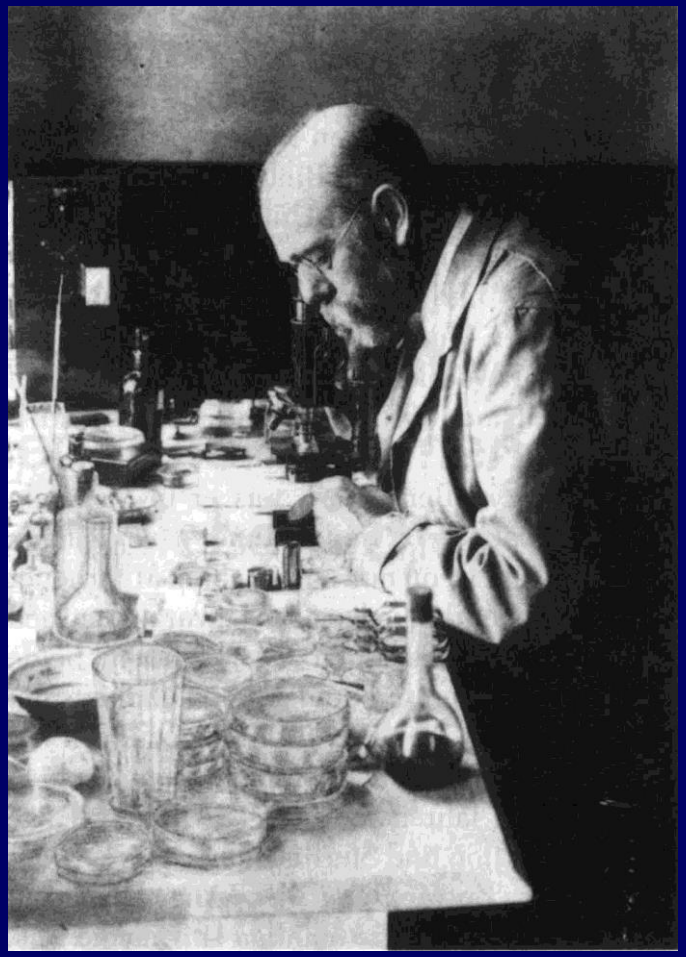
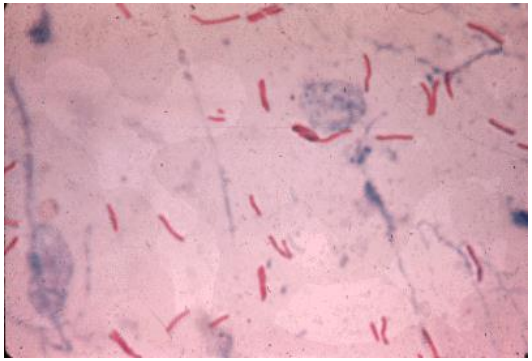
Tuberculosis





Robert
Koch

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- سل یک مشکل بهداشتی جدی اغلب کشورهای دنیا
- حدود یک سوم مردم جهان آلوده به باکتری مایکو باکتریوم توبر کلوزیس می باشند.
- در ایالات متحده آمریکا انسیدانس سالانه کمتر از 5 مورد در 100000 نفر است در حالیکه در آفریقای زیر صحرا و در آسیا به صدها مورد در 100000 نفر میرسد.

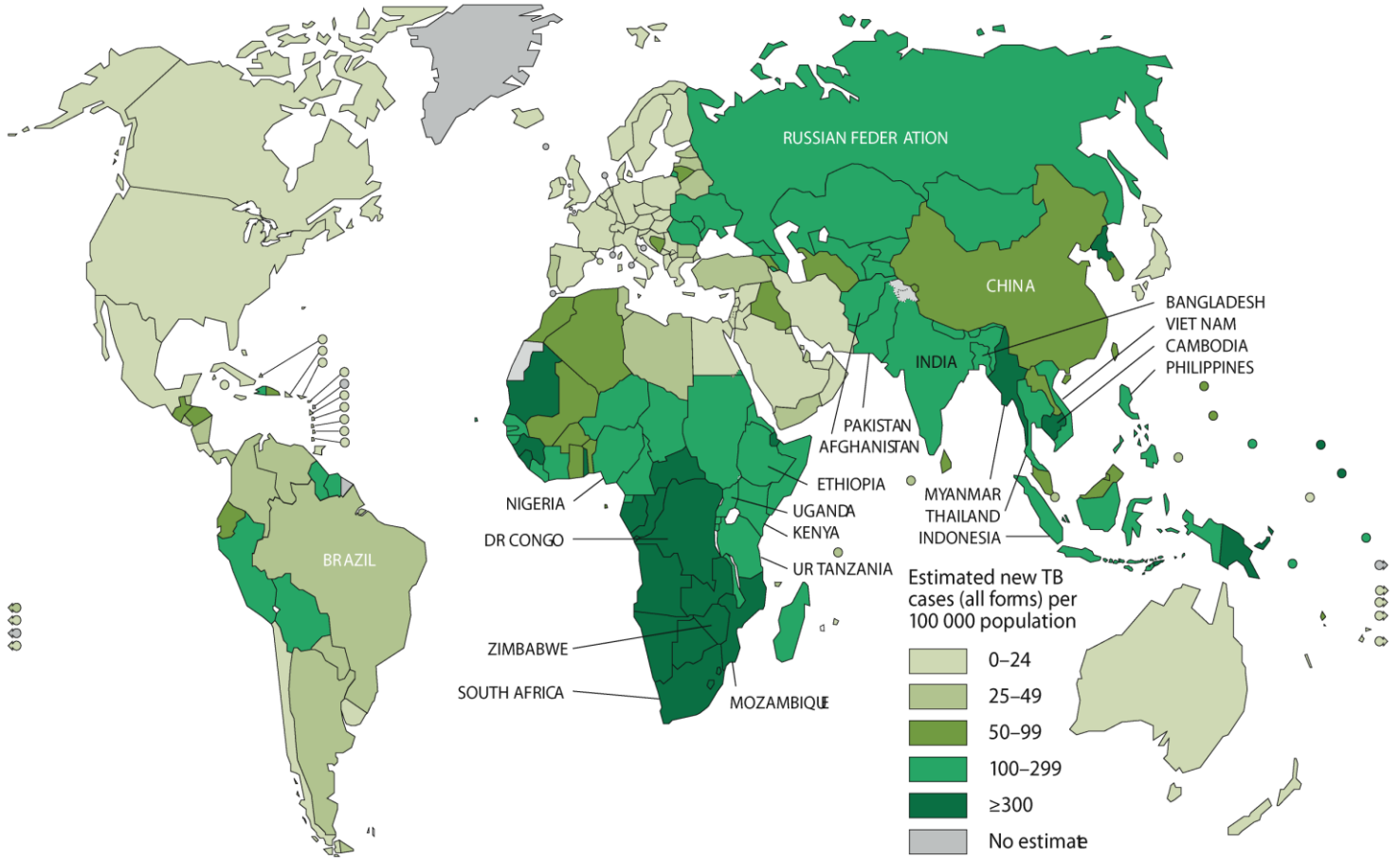
14/5میلیون نفر در دنیا مبتلا به بیماری سل هستند که بیش از 80 درصد این موارد مربوط به 22 کشور در حال توسعه دنیا است.

- آلودگی همزمان به ویروس ایدز خطر ابتلا به بیماری سل را بطور معناداری افزایش میدهد.

- سالیانه 9 میلیون نفر مورد جدید بیماری سل در دنیا گزارش می شودکه تقریبا دو میلیون نفر در اثر بیماری جان خود را از دست میدهند.
- بیش از 90% مورتالیته سل مربوط به کشورهای در حال توسعه

بالاترین میزان بروز سل اسمیر مثبت درکشور مربوط به استان سیستان و بلوچستان (28.8) میباشد.

Estimated TB incidence rates, 2010



Source: *Global Tuberculosis Control 2011*. WHO, 2011.

World Health Organization

❖ علل شکست در کنترل بیماری سل وپیدای‌ش (MDR-TB):

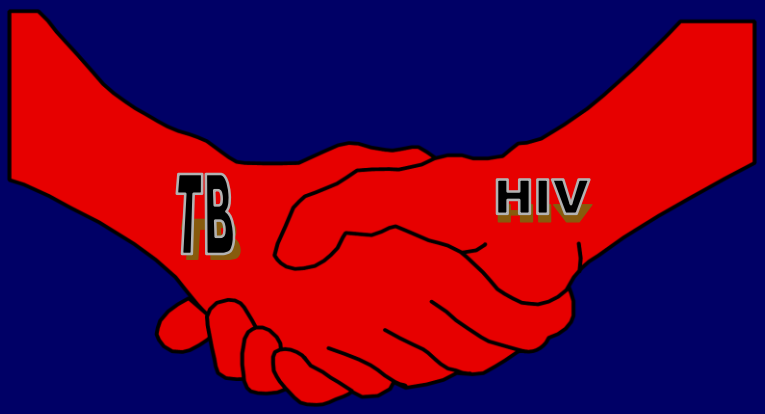
1. در بسیاری از موارد تاخیردر تشخیص
2. رژیم های درمانی اشتباه
3. دوزهای دارویی اشتباه و/یا مدت درمان ناکافی
4. نقص در پایش بیماران در طی درمان
5. نقص در بررسی افراد در تماس با بیماران شناسایی شده

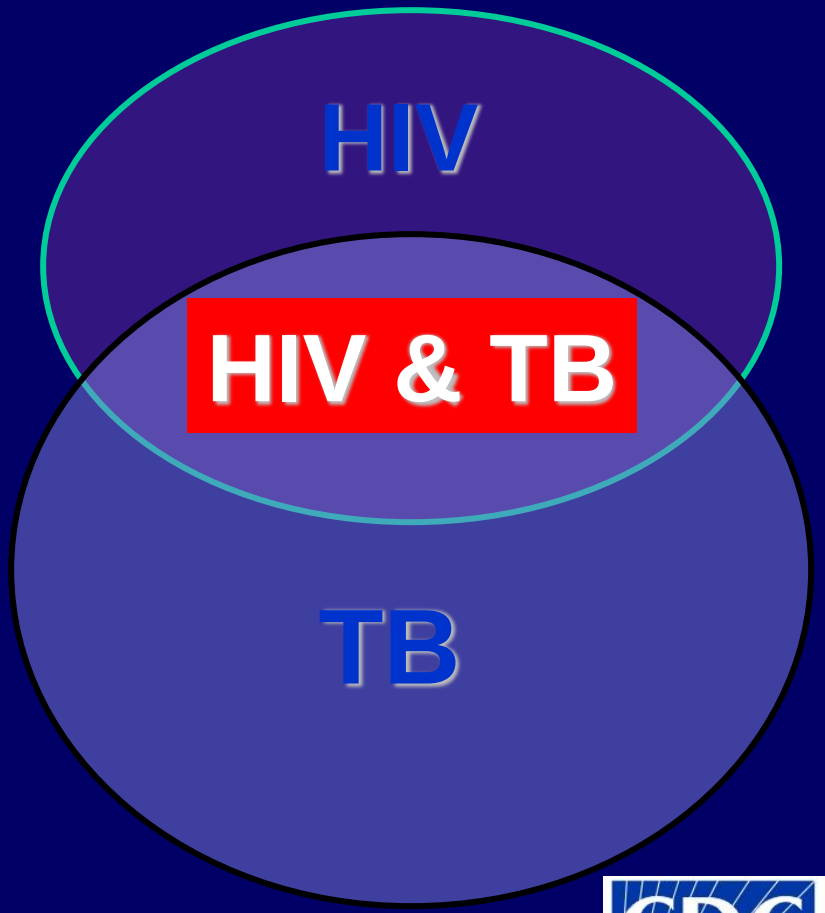
❖ علل افزایش باربیماری در جهان:

1. فقر
2. غفلت در تشخیص و درمان موارد بیماری
3. تغییرات جمعیتی،بویژه مهاجرت
4. بحران های شدید اقتصادی و نا آرامی های داخلی
5. پاندمی ایدز

TB/HIV

One patient Two Diseases





- TB is one of the leading causes of death in people with HIV, particularly in low-income countries

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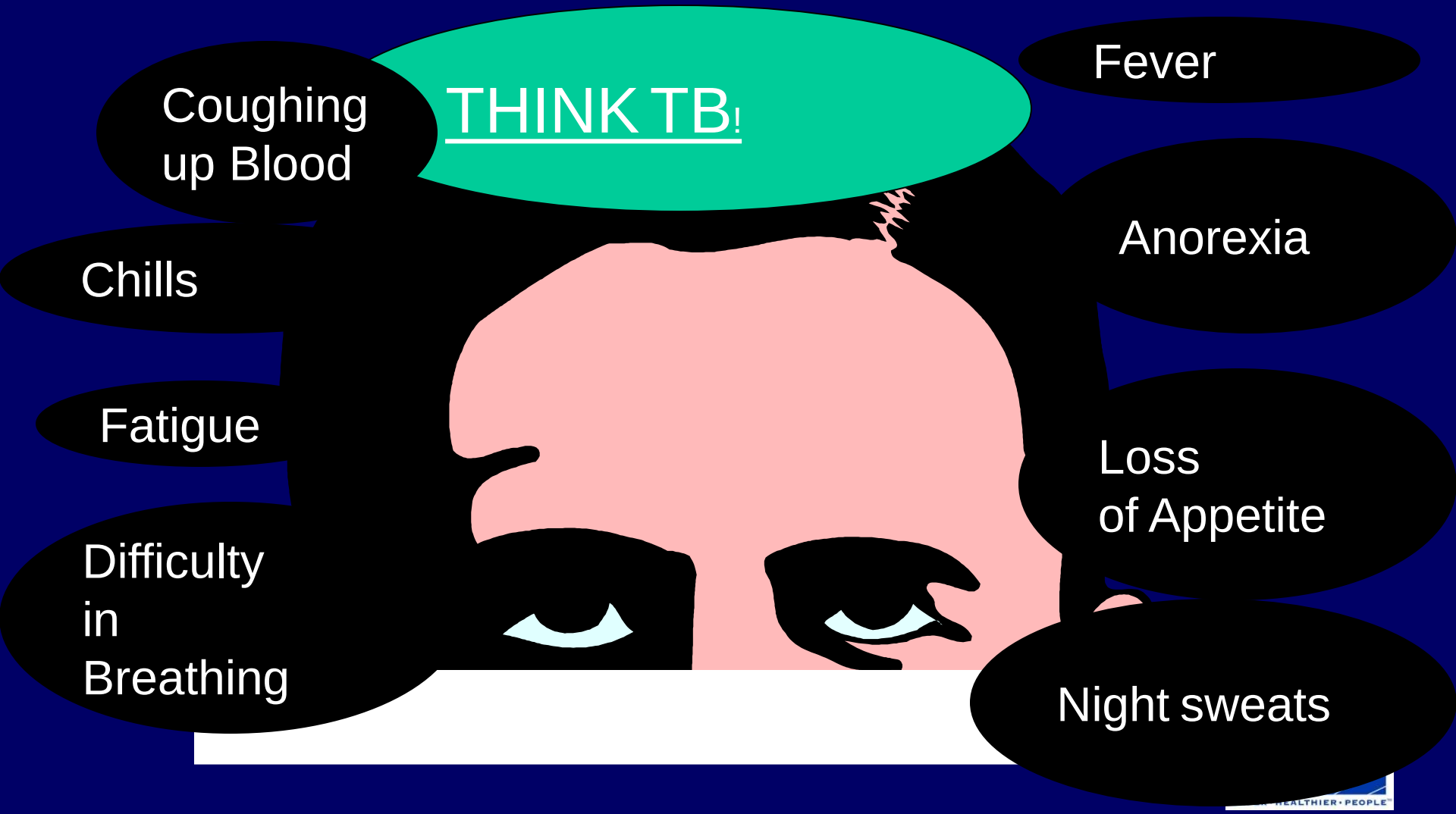
TB Screening

TB Screening Questionnaire

1. Has the patient had a cough for ≥2-3weeks?
2. Has the patient had night sweats for ≥3 weeks
3. Has the patient lost ≥3 kg in the past four months?
4. Has the patient had fever for ≥3 weeks?
5. Has the patient had recent contact with another person with active TB?

Even if a Skin Test is Negative…..



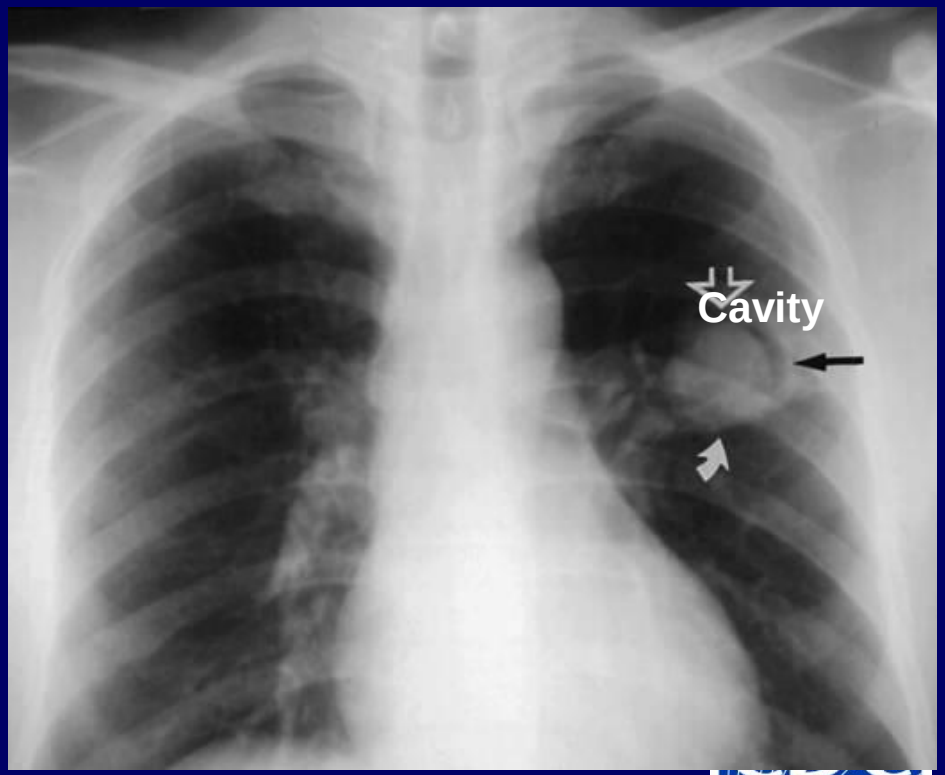
TB Screening

- All patients suspected or known to be HIV-seropositive and those who have AIDS should be examined for TB, particularly when there is a cough

TB Disease

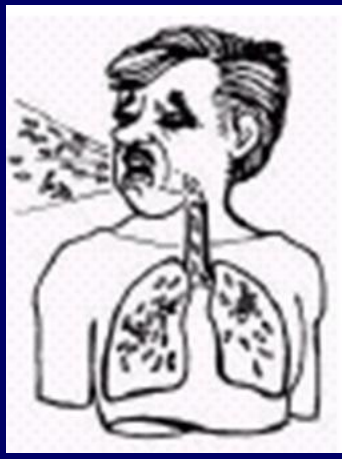
- More likely to get TB disease when a persons body is weakened from:

  - HIV
  - Diabetes
  - Poor Nutrition
  - Cancer medications
  - Steroids
  - Drug use
  - Smoking
  - Old Age



What happens during active TB disease?

- Active TB disease may occur in the lungs (pulmonary TB) and/or in other parts of the body (extrapulmonary TB).



- Pulmonary TB is the most common form of TB disease and is the infectious form

- Extrapulmonary TB is normally rare but occurs in up to 40% of TB cases among people living with HIV

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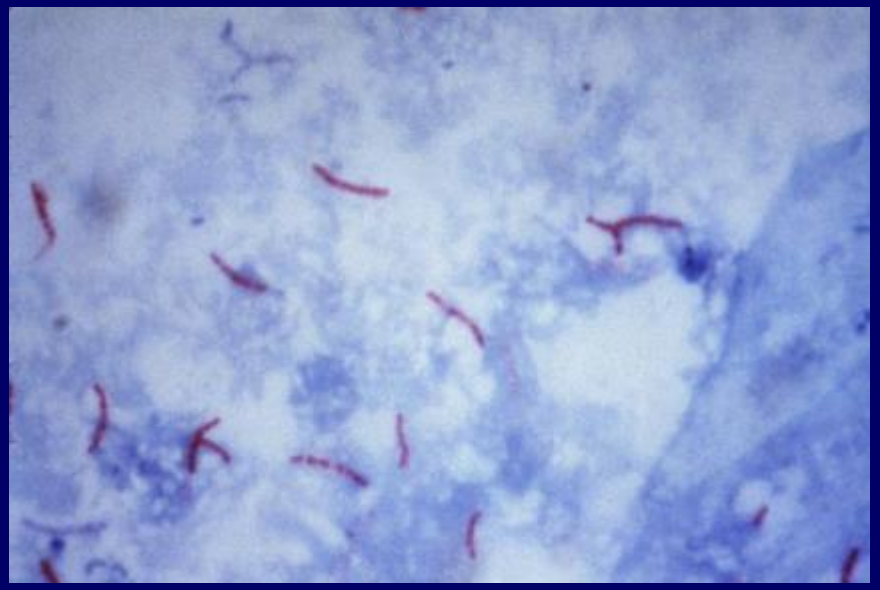
TB Transmission

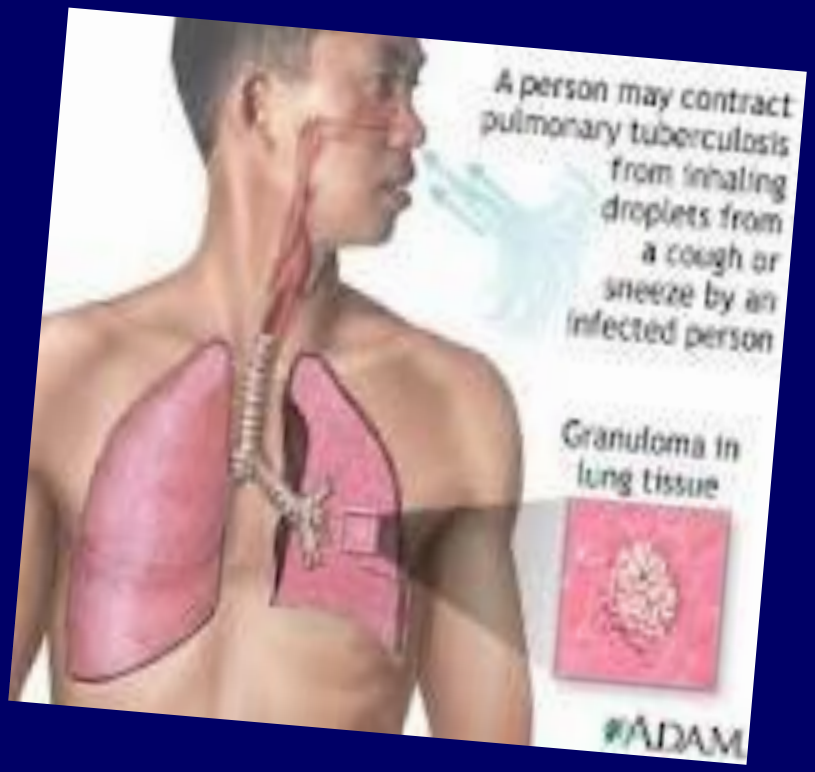
- *M. tuberculosis* causes most TB cases in U.S.

- Mycobacteria that cause TB:
  - *M. tuberculosis*
  - *M. bovis*
  - *M. africanum*
  - *M. microti*
  - *M. canetti*

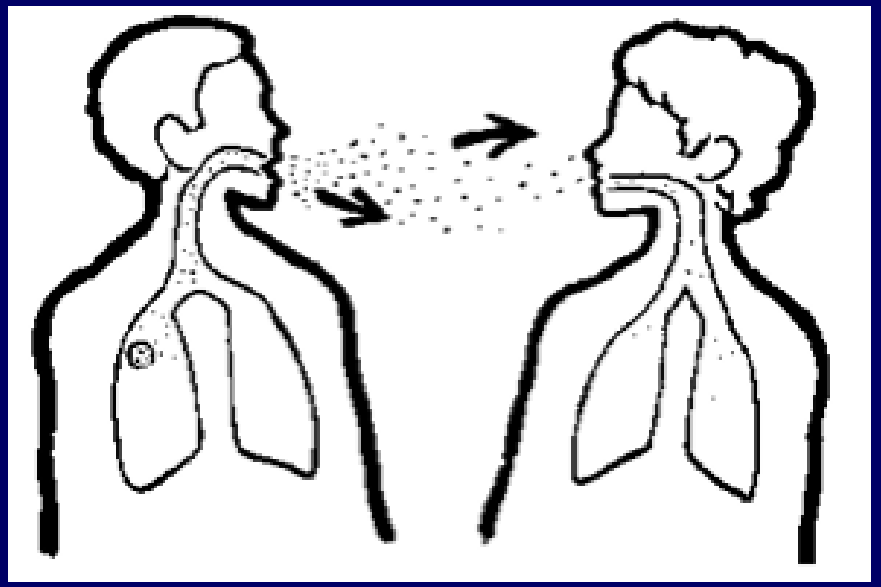


M. tuberculosis

- It also caused by breathing in air droplets from a cough or sneeze of an infected person this is called Primary TB.
- **Risk factors of tuberculosis is;**
  - Elderly
  - Infants
  - Low socioeconomic status
  - Crowded living conditions
  - Disease that weakens immune system like HIV
  - Alcoholism
  - Recent Tubercular infection (within last 2 years) and ect.



- TB spread from person to person by airborne transmission. Infected person release droplet nuclei (1-5 micro meter in diameter) through,
  - Talking
  - Coughing
  - Sneezing
  - Laughing
  - Singing



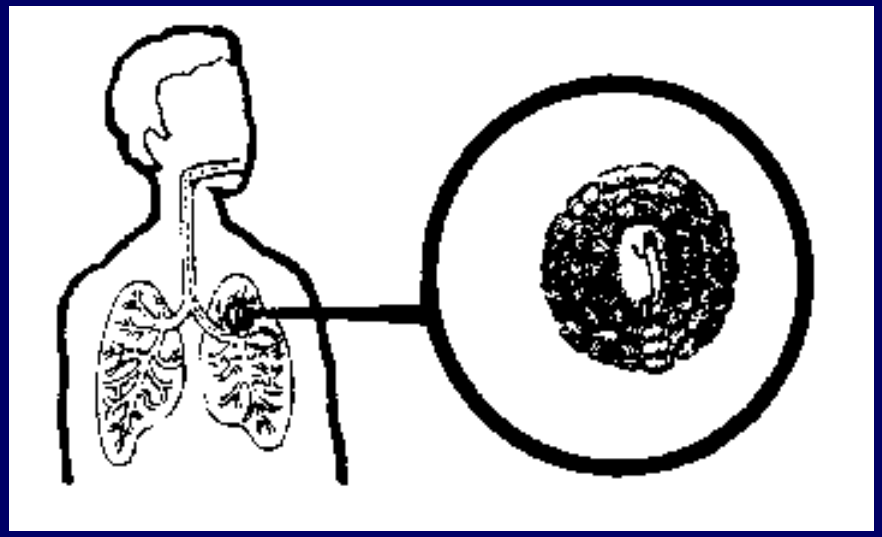
- If not treated properly, TB can be fatal.

TB Transmission

- **Probability that TB will be transmitted depends on:**
  - Infectiousness of person with TB disease
  - Environment in which exposure occurred
  - Length of exposure
  - Virulence (strength) of the tubercle bacilli

- **The best way to stop transmission is to:**
  - Isolate infectious persons
  - Provide effective treatment to infectious persons as soon as possible

TB Invades/Infects the Lung

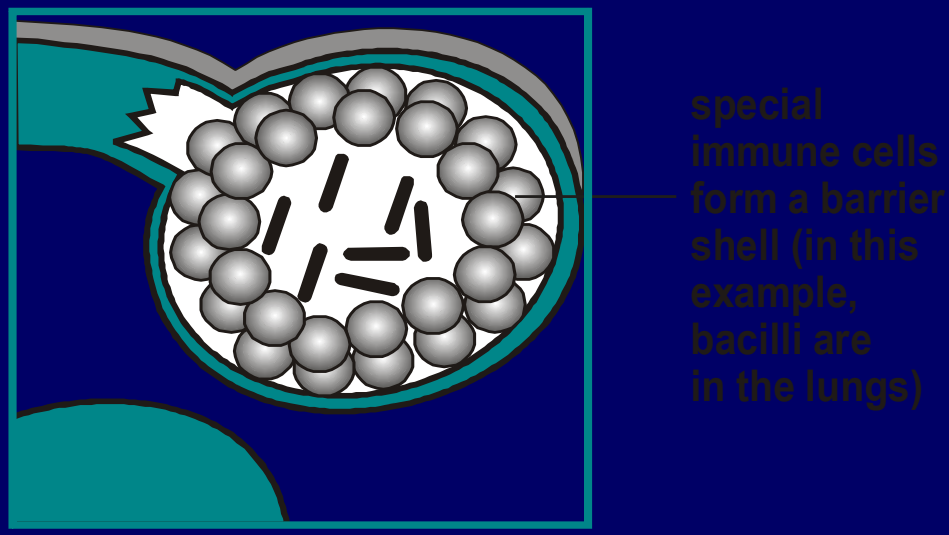


Effective immune response

Infection limited to small area of lung

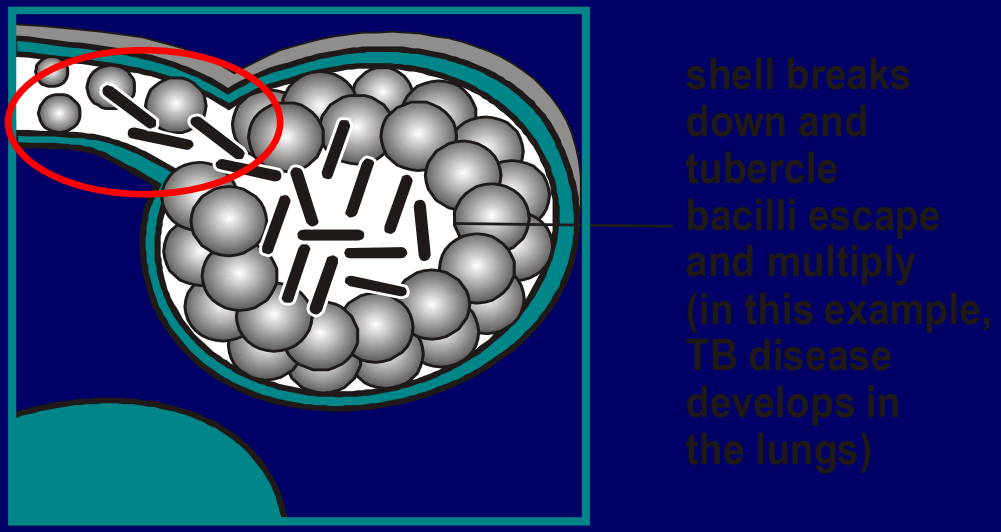
Immune response insufficient

TB Pathogenesis
LTBI



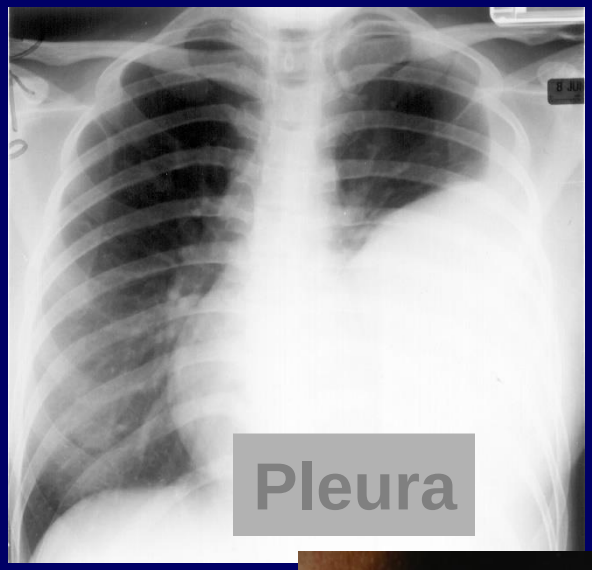
- Within 2 to 8 weeks the immune system produces special immune cells called macrophages that surround the tubercle bacilli
- These cells form a barrier shell that keeps the bacilli contained and under control (LTBI)

TB Pathogenesis
TB Disease

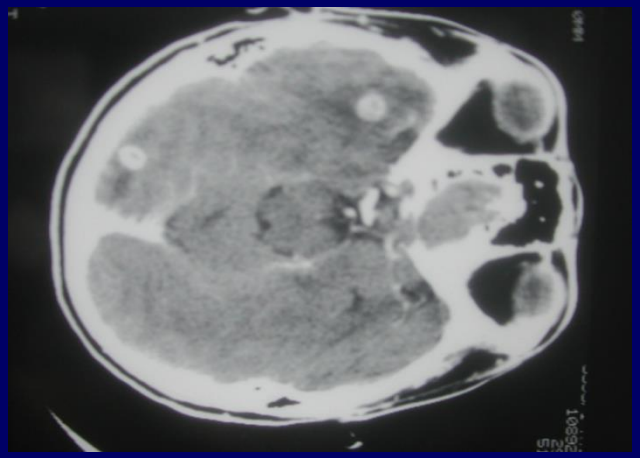


- If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease
- This process can occur in different places in the body

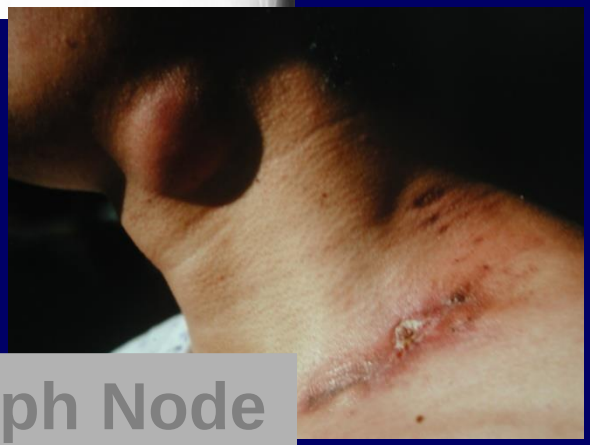
TB Can Affect Any Part of Your Body: Extrapulmonary TB



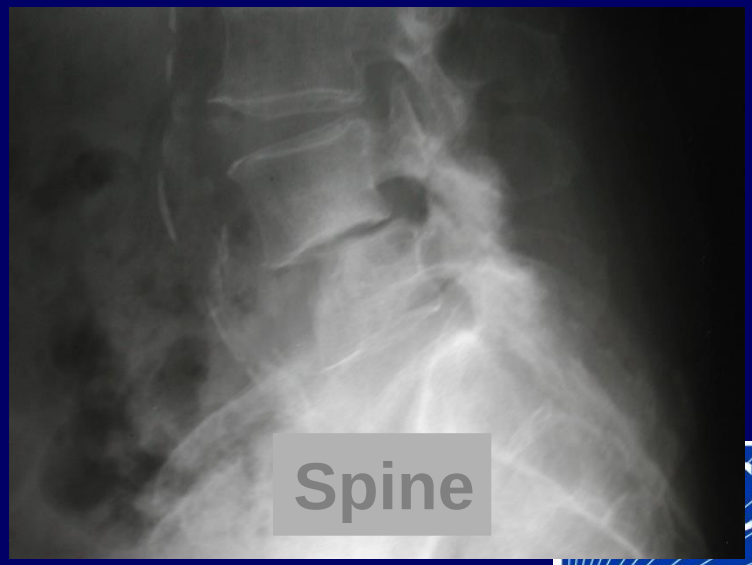
Pleura



Brain



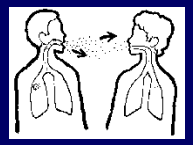
Lymph Node



Spine

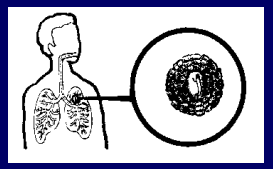
Natural History of TB Infection

Exposure to TB

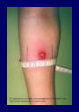


No infection
(70-90%)

Infection
(10-30%)

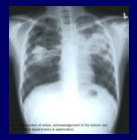


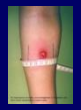
Latent TB
(90%)



Never develop
Active disease

Active TB
(10%)





Untreated

Treated

Die within 2 years

Survive

Die

Cured

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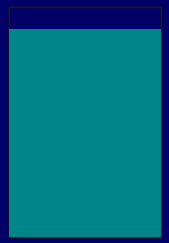
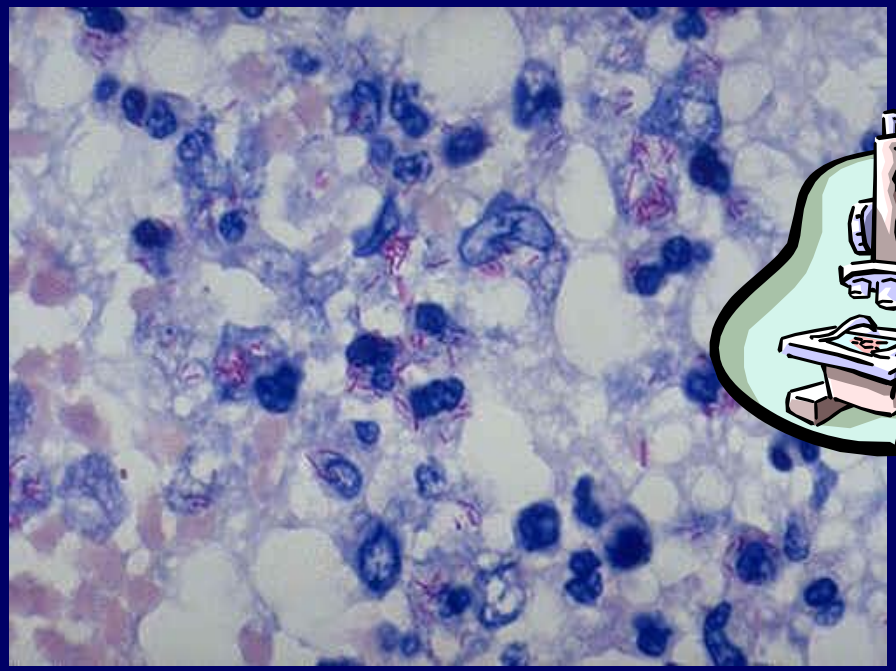
Progression to TB Disease
TB and HIV

People who are infected with both *M. tuberculosis* and HIV are much more likely to develop TB disease

TB infection and NO risk factors	TB infection and HIV infection (pre-Highly Active Antiretroviral Treatment [HAART])
	
Risk is about 5% in the first 2 years after infection and about 10% over a lifetime	**Risk is about 7% to 10% PER YEAR, a very high risk over a lifetime**

Diagnosis



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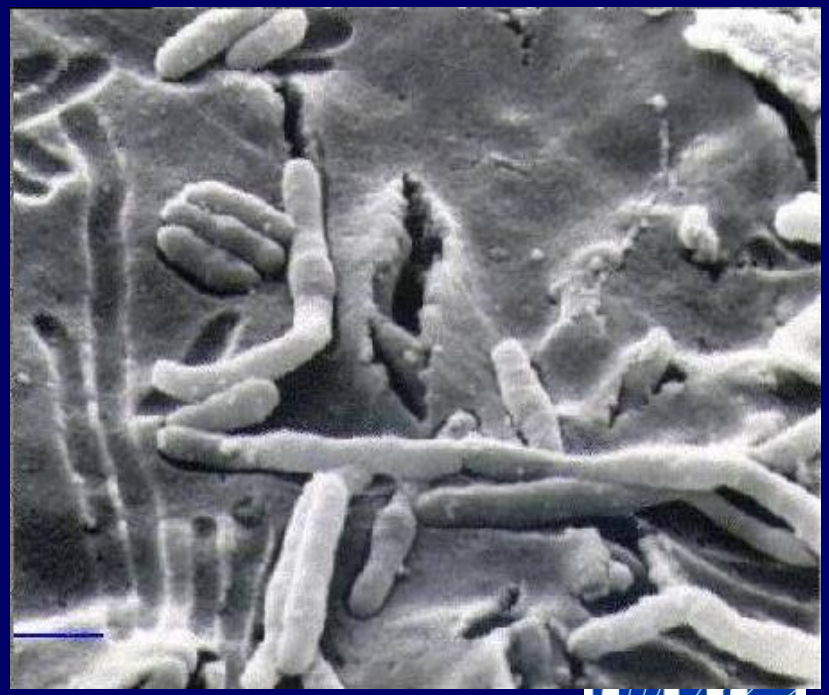
Mycobacterium tuberculosis

long, slender, straight or curved, acid fast bacilli

- **slow grow,**
- **obligate aerobes,**
- **intracellular bacterium**



Direct Microscopy identification

M. tuberculosis is a acid–fast bacterium, so They appear as bright red rods against a contrasting background.

The Ziehl-Neelsen stain is used to demonstrate the presence of the bacilli in a smear.

The technique is simple, inexpensive.

M. tuberculosis **appearing as bright red bacilli (rods) in a sputum smear stained with the Ziehl-Neelsen stain**

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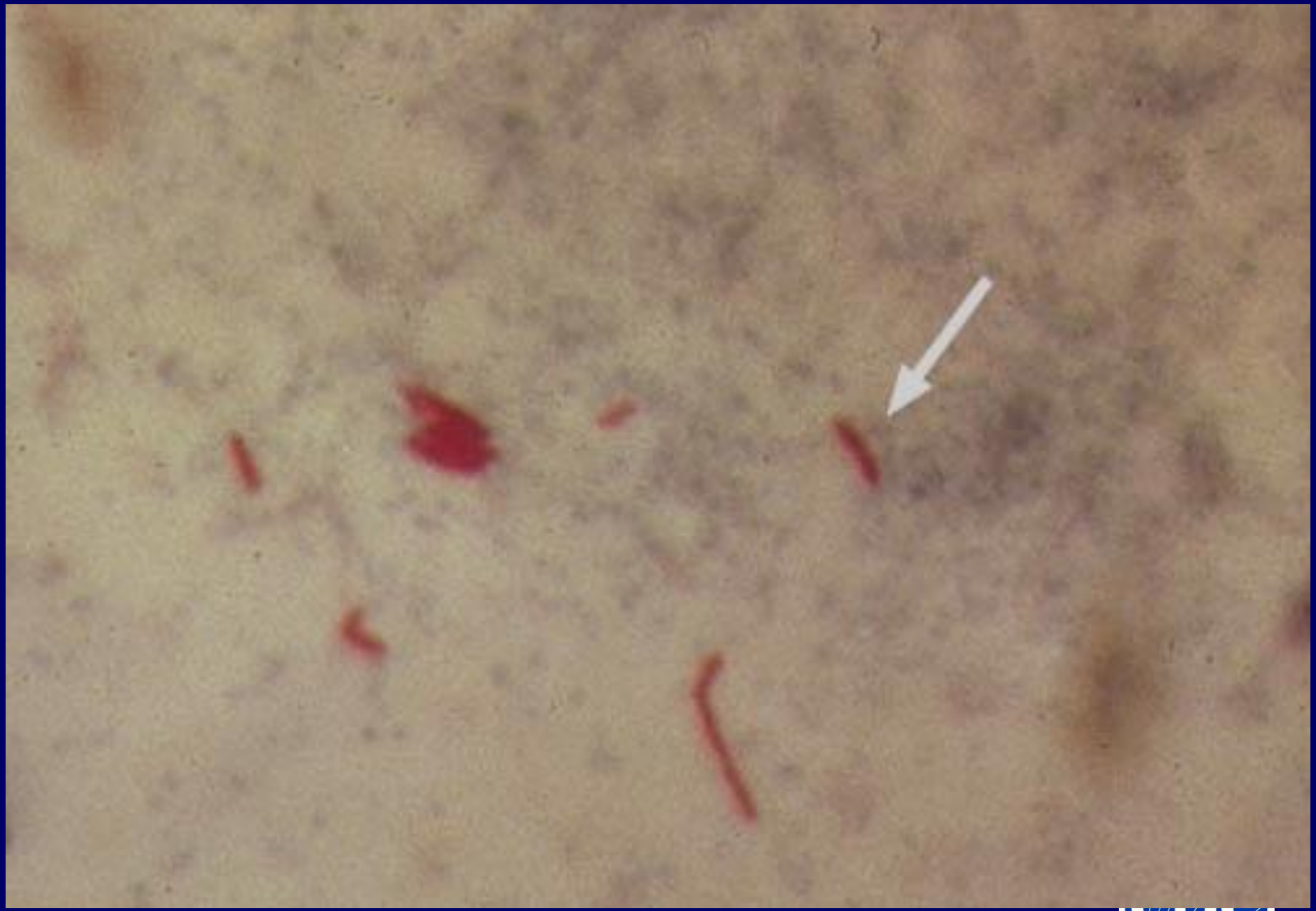
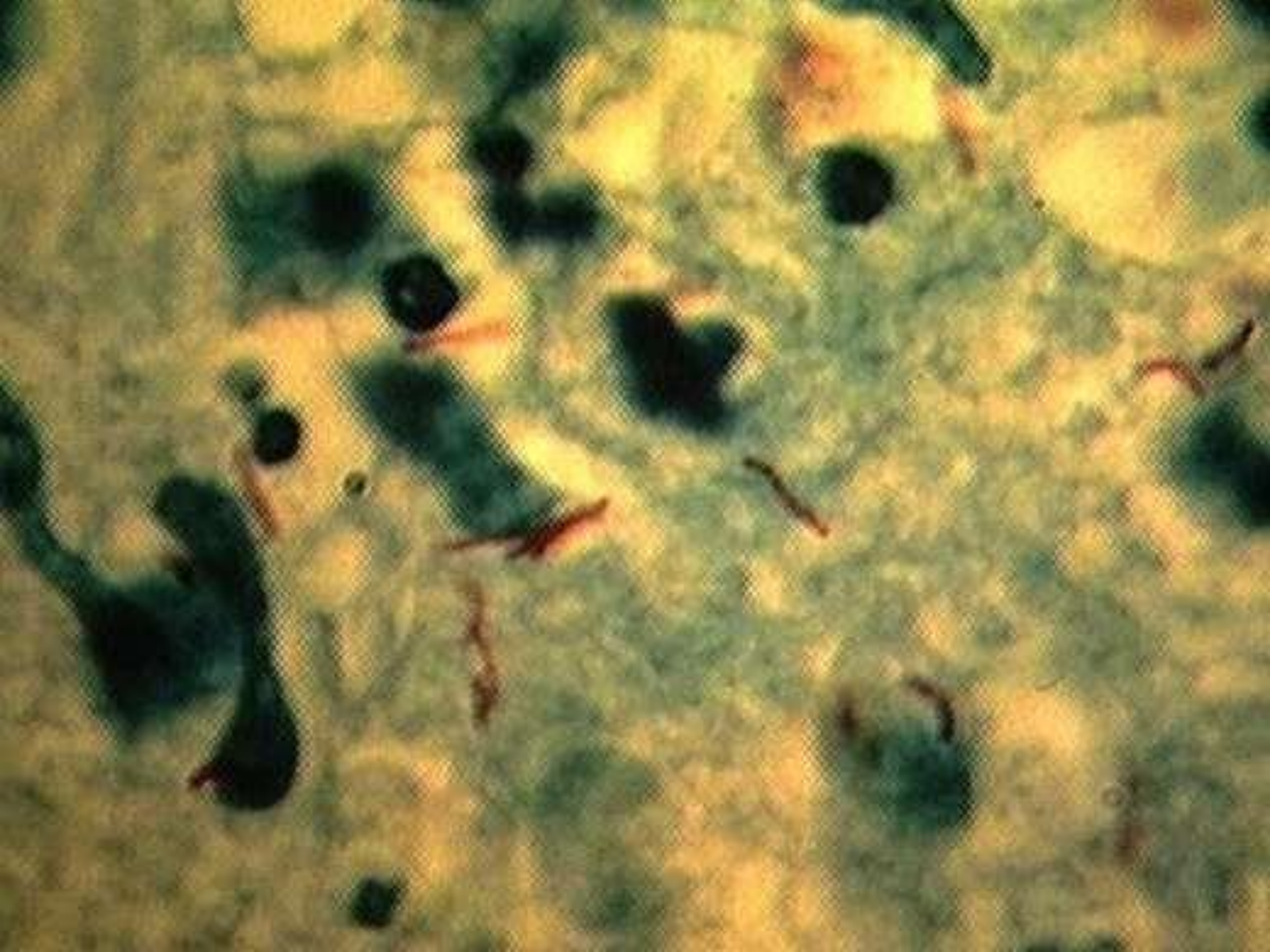
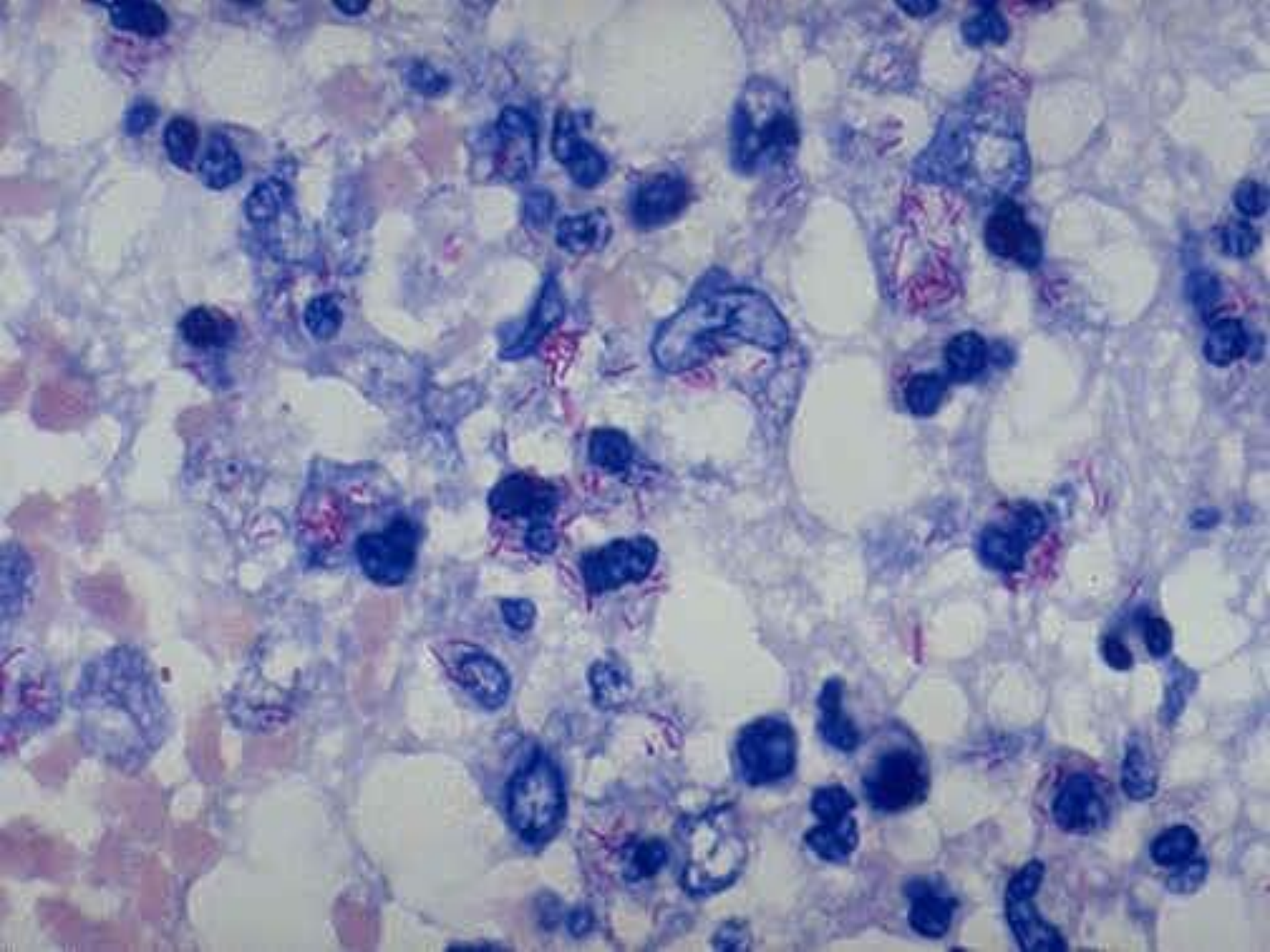
➢آزمایش میکروب شناسی خلط، مهم ترین، دردسترس ترین و ارزان ترین وسیله تشخیص سل ریوی بویژه در بالغین میباشد.

برای مثبت شدن این آزمایش نیاز به وجود حداقل 5000 تا 10000 باسیل در یک میلی لیتر از نمونه خلط است.







Reporting on AFB Microscopy

Number of bacilli seen	Result reported
None per 100 oil immersion fields	Negative
1-9 per 100 oil immersion fields	Scanty, report exact number
10-99 per 100 oil immersion fields	1+
1-10 per oil immersion field	2+
> 10 per oil immersion field	3+

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AFB MICROSCOPY

Advantages

-Rapid

- High specificity (AFB in sputum = TB)

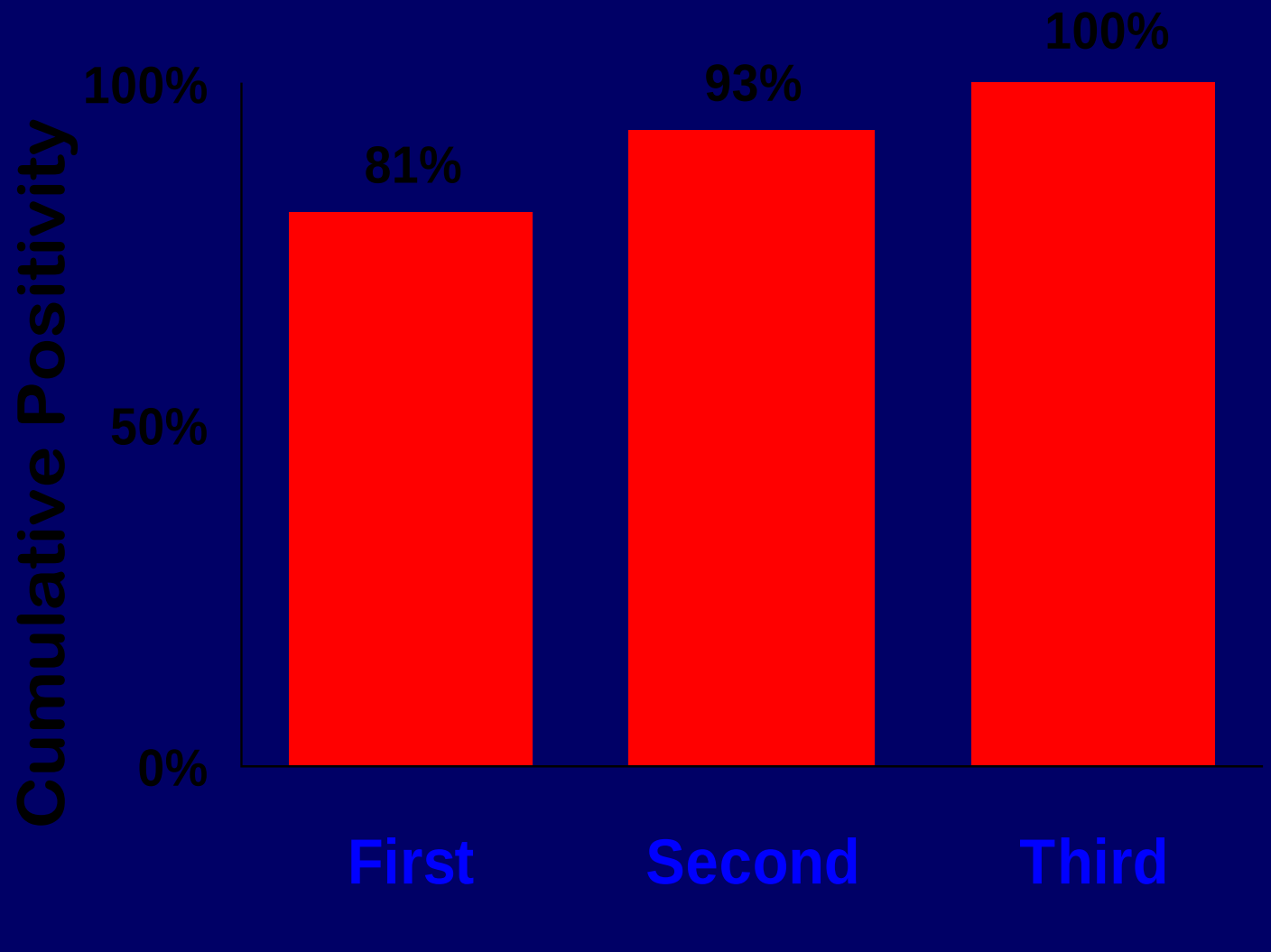
- All mycobacterium are acid fast, no exception ;

Disadvantage

Low sensitivity; Reported sensitivity ranging 25 to 65% when compared to culture

Species differentiation impossible. False positive; Saprophytic mycobacteria.

Three sputum smears are optimal



AFB MICROSCOPY: SENSITIVITY

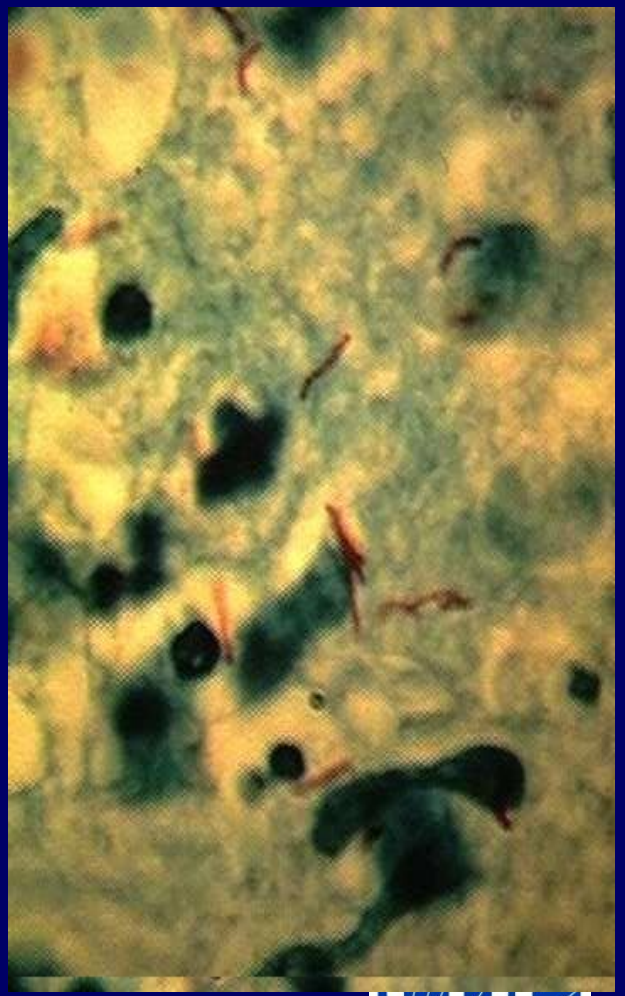
3 smears = sensitivity of 1 culture

About 95% of infectious cases

- Smear-positive patients are 4-20 times more infectious

- **Untreated, a smear-positive patient may infect 10-15 persons/year**

- Smear-positive patients are much more likely to die if untreated



منظور از سل ریوی فعال بیمارانی است که علاوه بر داشتن علائم بالینی ناشی از درگیری ریوی،دارای یکی از سه معیار زیر باشند:

الف- مثبت بودن حداقل دو نمونه خلط صبحگاهی بیمار

ب- وجود یک نمونه خلط مثبت از نظر باسیل سل همراه با یک نمونه کشت خلط مثبت

ج- وجود یک نمونه اسمیر خلط مثبت به همراه شواهد مثبت رادیوگرافی از نظر درگیری سل ریوی.

این سه گروه به عنوان بیماری سل ریوی فعال مورد بررسی قرار می گیرند

سل خارج ریه : درگیری سایر ارگانها و اثبات با میکروبیولوژی و یا پاتولوژی

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❖بهتر است نمونه ها در محلی با تهویه مناسب **ترجیحا در هوای باز** جمع آوری گردد. در صورتی که بیمار بستری باشد بهتر است هر سه نمونه از خلط صبحگاهی تهیه شود.

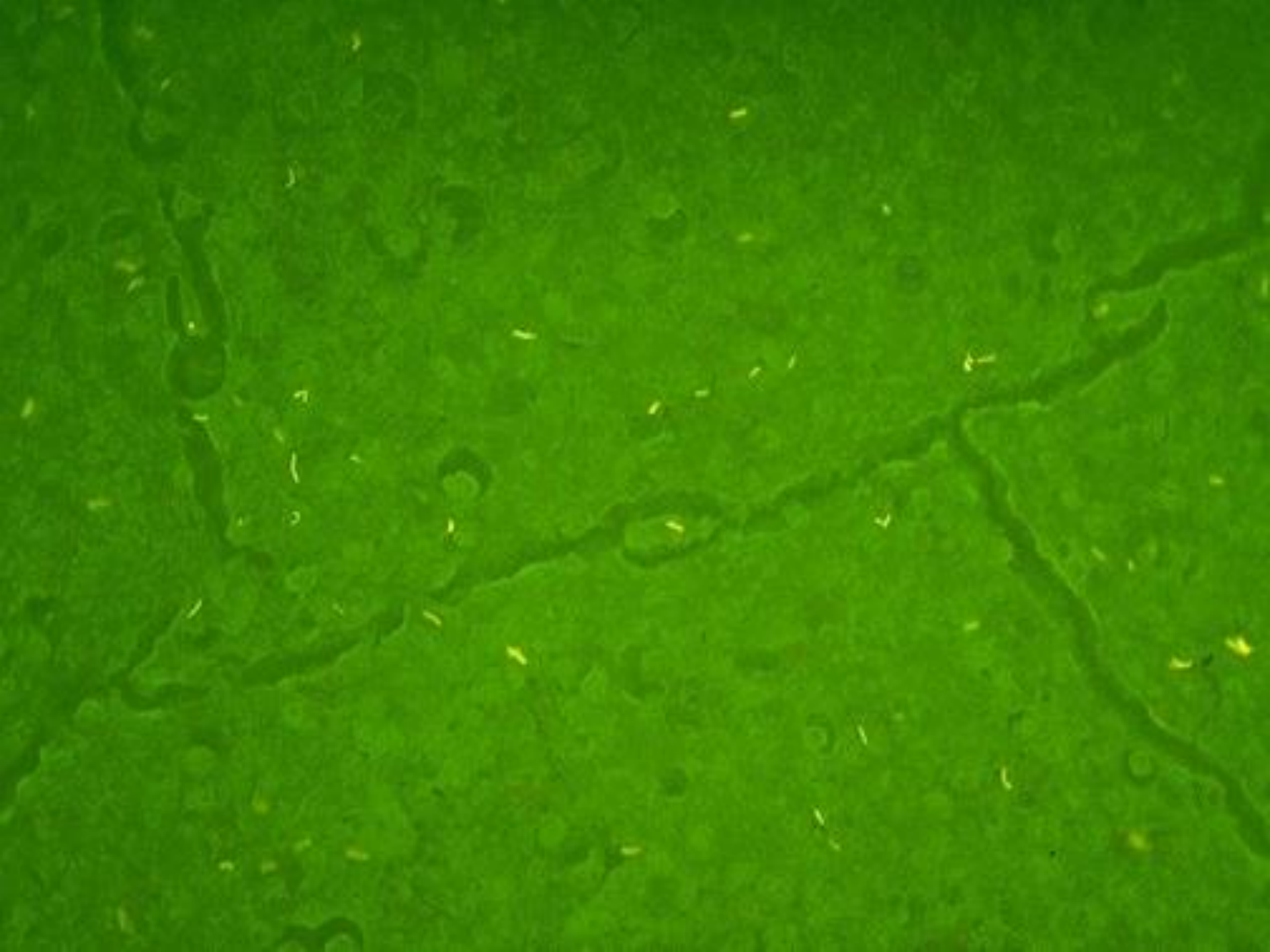
❖حجم مطلوب برای هر نمونه خلط3-5 سی سی است.

❖نمونه ها باید در اسرع وقت به آزمایشگاه ارسال گردد. ایده آل آنست که این کار درکمتر از **72 ساعت** صورت پذیرد و نباید بیشتر از یک هفته بطول انجامد.

❖آزمایشگاه ظرف مدت 24 ساعت از زمان دریافت نمونه باید نتیجه آن را تعیین و
گزارش کند و نتیجه آزمایش اسمیر بیمار می بایست **حداکثر ظرف مدت 4 روز** از زمان تحویل نمونه به آزمایشگاه در اختیار محل بیماریابی (مرکزی که نمونه بیمار را ارسال نموده است) قرار بگیرد.

Direct Microscopy identification

- **Fluorescent dye (Auramine O and Rhodamine B)**
  - Good for labs with high workload.
  - Auramine O- Bright yellow
  - Auramine O-Rhodamine B- Yellow orange.



Appropriate collection techniques

–Time

- Sputum -3 consecutive samples.
  - Early morning complete sputum.
- Urine -3 or more consecutive samples

–Volume

- Pleural, peritoneal fluids
- Cerebrospinal fluid

Culture

M. tuberculosis grows in Lowenstein Jensen medium, which contains inhibitors to keep contaminants from outgrowing the organism.

Because of its slow growth, it takes 4-6 weeks before small buff-coloured colonies are visible on the medium.

Typical small, buff coloured colonies of *M. tuberculosis* on Lowenstein Jensen medium

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Culture

- more sensitive
- main problem: DELAYS
  - on classical media (Lowenstein-Jensen....)
  - newer commercial media (BACTEC..)
    - faster (about 10 days)
    - but expensive++, technical demands
- first step for susceptibility testing

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Radiology

- Not confirm,Not refuse

No characteristic view

Tests based on Immune responce

- **PPD test**
- **Gama interferone response**
- **Invitro Blood Test (ELISPOT)**
- **Serodiagnostic Test (ELISA)**

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Adenosine deaminase (ADA)

- Adenosine deaminase (ADA) and interferon gamma studied for dx of extrapulmonary TB
- Both are markers of immune response to TB
- Not that specific

PCR polymerase chain amplification

1) Diagnose tuberculosis rapidly by identifying DNA .

2) Determine rapidly whether acid-fast organisms identified by microscopic examination in clinical specimens are M.tuberculosis

3) Identify the presence of genetic modifications known to be associated with resistance to some anti mycobacterial agents.

4) Determine whether or not isolates of M.tuberculosis from different patients have a common origin in the context of epidemiological studies.

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Sensitivity and Specificity of PCR

- Incase of smear and culture positive the sensitivity is ranging 80% to 90% with specificity of 97%-99%.
- Incase of smear negative and culture positive the sensitivity is ranging 60% to 80% with specificity of 97%-99%.

Disadvantages:

- Identification of the target sequence of DNA doesn't imply organism viability.
- Contamination of samples by product from previous PCR experiments

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NAAT Summary

- NAA is useful to distinguish TB from NTM in smear + specimens
- Less sensitive in smear – specimens
- Clinical judgement must always take priority
- Relatively expensive tests; need data to support cost-effectiveness

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Real time PCR

- **Rapid analysis** (typically under 90 min)
- **No post-amplification processing** (no gels or autoradiographs)
- **Automated** (data collection and analysis)
- **Objective** (controls & standards can be built-in)
- **Precise, sensitive and reproducible**

Drugs and Adverse Effect

Isoniazid (INH)

- Acts only on mycobacteria
- Interferes with mycolic acid synthesis (unique to mycobacterial cell wall)
- Bacteriostatic – to resting organism
- Bactericidal – to multiplying organism
- CSF penetration: 20% of plasma concentration with non-inflamed meninges

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Rifampin

- Inhibits bacterial DNA-dependent RNA polymerase
- bactericidal
- Gram positive and negative
- kill intracellular organism
- Well absorbed from GIT
- CSF penetration: 10-40% of plasma concentration with non-inflamed meninges

Ethambutol

- Inhibits arabinosyl transferases involved in cell wall biosynthesis

- Bacteriostatic to *M.tuberculosis*
- CSF penetration poor
- Resistance develops rapidly if used alone

Pyrazinamide

- Interferes with mycobacterial fatty acid synthesis

- Inactivate mycobateria at acidic PH
- Poor bactericidal
- Effective against intracellular organism in machrophages
- CSF penetration: equal to plasma concentration

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Streptomycin

- Aminoglycoside - Inhibits protein synthesis

- Bactericidal
- Poorly absorbed from GIT - given IM.
- CSF penetration: poor if meningitis good.
- Renal elimination

Common Adverse Reactions to Drug Treatment (1)

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	Allergy	Skin rash
Ethambutol	Eye damage Optic neuritis	Blurred or changed vision Changed color vision
Isoniazid, Pyrazinamide, or Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Fatigue Lack of appetite Nausea Vomiting Yellowish skin or eyes Dark urine

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Common Adverse Reactions to Drug Treatment (2)

Caused by	Adverse Reaction	Signs and Symptoms
Isoniazid	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Gastrointestinal intolerance	Upset stomach, vomiting, lack of appetite
	Arthralgia	Joint aches
	Arthritis	Gout (rare)
	Blood suger ↓↑	
Streptomycin	Ear damage	Balance problems
		Hearing loss
		Ringing in the ears
	Kidney damage	Abnormal kidney function test results

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Common Adverse Reactions to Drug Treatment (3)

Caused by	Adverse Reaction	Signs and Symptoms
Rifamycins • Rifabutin • Rifapentine • Rifampin	Thrombocytopenia	Easy bruising Slow blood clotting
	Gastrointestinal intolerance	Upset stomach
	Drug interactions	Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment

رژیم استاندارد سل

- رژیم استاندارد درمان سل ریوی
- ایزونیازید+ریفامپین+اتامبوتول+پیرازینامید 2ماه(مرحله حمله ای)
- ایزونیازید+ ریفامپین 4ماه(مرحله نگهدارنده)

انواع سل که مدت درمان بیش از 6ماه نیاز دارند:

سل ستون مهره، مننژیت و درگیری عصبی ،سل ارزنی یا میلیری 3مورد دیگر

Thanks for attention