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TUBERCULOSIS
PROJECT
SOUTH AFRICA



health

Department:
Health
REPUBLIC OF SOUTH AFRICA

Treatment of Tuberculosis

URC

Taking TB Treatment



Learning outcomes

- Describe the use of TB case definitions & the management of TB patients
- Successfully treat TB using the appropriate regimen for the appropriate category of TB patient
- Know the different actions of TB drugs
- Manage the adverse effects of TB drugs
- Treat TB in special situations

TB case definitions (WHO)

Used for easy classification according to the :

- ***Site of the disease:*** PTB or extra- PTB
- ***Severity of the disease:*** According to the smear and culture results (+, ++, +++)
- ***History of previous exposure to TB treatment***
Determines regimen and risk of drug resistance

Case definitions

- Pulmonary TB
 - New (treated for less than one month)
 - AFB positive
 - AFB negative
- Extra-pulmonary
 - Pleural TB
 - TB Spine
 - TB Kidneys

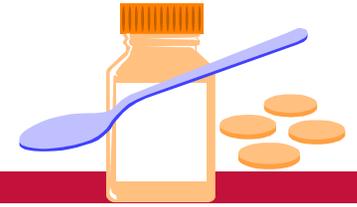
TB Re-treatment categories

<i>Abbreviation</i>	<i>Category</i>	<i>Explanation</i>
RC	Relapse	Cured & becomes sputum+ again
RF	Retreatment - failure	Remained sputum + on/after treatment
RD	Retreatment – default	Interruption 2 months or more
Other	Retreatment – all other not mentioned above	After completion with no proof of cure, smear negatives, E-PTB Retreatment

Case management

- Classification of cases
- Choice of treatment regimen
- Communication, education of patient
- Support to the patient throughout treatment
- Correct registration and follow up

TB treatment: Aims



- To cure at least 85% of smear positive PTB cases
- To prevent death in very ill patients
- To prevent lung damage
- To prevent relapse
- To prevent the development of acquired drug resistance
- To reduce transmission and the spread of the TB epidemic

TB treatment: Principles

- Use multiple drugs in combination tablets
- Patients must be DOT supported
- Use standardised treatment regimens
- Cure patients the first time round
- Give the correct drugs, at the correct dosages and for the correct period of time (6 months short course)
- No trials of therapy should be given

Anti-Tuberculosis Drugs



Fixed Dose Combination (FDC) Background

4 combination drugs introduced in 2000

Reasons for introduction:

- fewer drugs
- prevention of resistance
- better ordering system
- one expiry date
- easier administration (DOT)

Essential TB drugs

- **Isoniazid (H)**
- **Rifampicin (R)**
- **Pyrazinamide (Z)**
- **Streptomycin (S)**
- **Ethambutol (E)**

Dosage formulations :

RH - (300R + 150 H)

RHZ adults – (150R+75H+400Z)

RHZ pediatrics – (60R+30H+ 150Z)

RHZE - (150R+75H+400Z+275E)

Essential TB drugs cont...

- 3 main properties of TB drugs
 - bacteriocidal
 - bacteriostatic
 - ability to prevent resistance
- Different drugs act against different populations of bacilli in a tuberculous lesion
- Bacilli may occur either in the intracellular or extracellular spaces

Justification for dosage formulations

Different populations of TB bacilli

- metabolically active
- intermediately active
- semi-dormant bacilli (persisters)
- dormant bacilli

TB Drugs: Action

<i>Meta-bolic activity</i>	<i>Early bactericidal</i>	<i>Bacteriostatic (sterilizing)</i>	<i>Preventing drug resistance</i>
High	Isoniazid	Rifampicin Pyrazinamide	Isoniazid Rifampicin
Inter- mediate	Rifampicin Ethambutol	Isoniazid	Streptomycin Ethambutol
Low	Streptomycin Pyrazinamide	Streptomycin Ethambutol	Pyrazinamide

TB drugs: Action cont...

<i>Drug</i>	<i>Bacterio- static</i>	<i>Bacterio- cidal</i>	<i>Intra- cellular</i>	<i>Extra- cellular</i>
Rif		X	X	X
INH		X	X	X
PZA		X	X	
Eth	X			
Strep		X		

Effective treatment to cure TB

1. Ensure **correct dosage for correct time** period:
 - 6 months Regimen 1
 - 8 months Regimen 2
2. Ensure that patient is on **DOT**
3. Treat with **combination tablets** to ensure that all organisms are inactivated:
 - active and dormant bacilli
 - acid/alkaline medium
4. **Manage side effects**
5. **Educate** patient, family and treatment **supporter**

Advantages of Fixed Drug Combinations (FDC)

- **Reduction of TB drug costs**
- **Reduction in number of tablets (promotes adherence)**
- **Standardized regimen world wide**
 - Less prescription errors
 - Easy to adjust dosage according to weight
 - Fewer number of tablets
- **Prevention of DR-TB**
 - Prevent single drug therapy

Isoniazid (INH)

- Bactericidal both intra- and extra-cellular, MA inhibition – Mycolic Acid inhibition
- Rapidly absorbed, acts within 1-2 hours
- First line agent in treating both pulmonary and extra-pulmonary TB
- Prescribed in **Initial and Continuation phase**
- Used as solo prophylaxis in HIV-infection to prevent TB
- **Main side effects:** peripheral neuropathy, hepatitis, skin rash, joint pains

Rifampicin

- Bactericidal with a wide spectrum of activity
 - mRNA polymerase
- Acts both intra/extra-cellular
- Main sterilising anti-TB drug, acts on all populations of growth

Main side effects

- Headache, dizziness, nausea and vomiting, abdominal cramps, hepatitis, skin rash and flu-like symptoms, hematologic effects.

Pyrazinamide

- Acts only in an acid environment, intra-cellular)
 - Used in **Initial Phase only**
 - In combination with other drugs

Main side effects

- gout, arthritis, hepatitis

Contraindications

- hepatic damage

Ethambutol

- Acts both intra/extracellular
- Inhibits biosynthesis of arabinoglycan/LAM
- Low potency
- Used in **Initial and Continuation** phase for :
 - Retreatment patients
 - DR patients

Main side effects

- Retro-bulbar neuritis, loss of colour vision if on treatment >2 months
- Do not use in children under 8 years

Streptomycin

- Broad spectrum of activity (G+/G-)
- Inhibits protein synthesis
- Active against extracellular group of bacilli
- Intramuscular injections/not absorbed
- Aminoglycosides – glomerular filtration
- Ototoxicity increased by diuretics
- Neuromuscular blocking effect

Standard Treatment Regimen for Adults (>8yrs)

- A standard code is used to describe TB treatment regimens
- This describes the drug combinations, treatment phase, and the number of doses per week

New adult TB patients

- A patient who **has never been treated for TB** before
- A patient who has been **treated for less than 4 weeks** on a previous occasion

Remember

- Treatment regimen consists of two phases
- **Intensive Phase** - 2 months = 2(RHZE)
- **Continuation Phase** 4 months = 4(HR)

Drug dosages calculated according to patient's weight before treatment is started

Regimen 1 for New TB cases

<i>Pre treatment body weight</i>	<i>Initial phase 2 months 7 x a week</i>	<i>Continuation phase 4 months</i>			
		7 times a week		* 3 times a week	
	RHZE 150/75/400/25	RH 150/75	RH 300/150	RH 150/150	RH 300/150
30-37 kg	2 tablets	2 tablets		2 tablets	
38-54 kg	3 tablets	3 tablets		3 tablets	
55-70 kg	4 tablets		2 tablets		3 tablets
≥ 71kg	5 tablets		2 tablets		3 tablets

* NB Not used un²⁶ SA

Re-treatment adult patients

Patients who have been treated for TB before:

- Smear negative *ie* cured at the end of treatment (RC)
- Treatment failed as the patient was still sputum positive at end of treatment (RF)
- Treatment interrupted by more than 2 months (RD) in total
- Other Re-treatment – all other re-treatment categories not mentioned above

Re-treatment regimen phases

Re-treatment regimen consists of 2 phases

Intensive phase 3 months, but has 2 parts:

- 2 months = 2(RHZE)S
- 1 month = 1(RHZE)

Continuation phase 5 months = 5(RH) (E)

- The Re-treatment regimen is written as:
2(RHZE)S/1(RHZE)/5(RH) E

Regimen 2: Re-treatment

<i>Pretreatment body weight</i>	<i>Initial phase 2 months 7 times a week</i>		<i>Initial phase at month 3 7 times a week</i>	<i>Continuation phase 7 times a week</i>			
	RHZE 150/75/400/ 275	Streptomycin (g)	RHZE 150/75/400/ 275	RH 150/75	E 400	RH 300/150	E 400
30-37 kg	2 tabs	0.5	2tabs	2 tabs	2 tabs		
38-54 kg	3 tabs	0.75	3 tabs	3 tabs	2 tabs		
55-70 kg	4 tabs	1.0	4 tabs			2 tabs	3 tabs
71 kg	5 tabs	1.0	5 tabs			2 tabs	3 tabs

Drug interactions

- Few drugs substantially change concentrations of TB drugs
- TB drugs can change concentrations of other drugs
- Isoniazid increases phenytoin concentration to toxic levels
- Rifampicin may reduce effect of oral diabetic drugs, contraceptives, digoxin, oral anticoagulants, phenobarbitones, ARVs
- Always refer patients for clinical evaluation and dosage adjustments

Common adverse reactions

<i>Caused by</i>	<i>Adverse reaction</i>	<i>Signs and symptoms</i>
Isoniazid	Peripheral Neuro-pathy Allergy	Tingling sensation in hands and feet Itchy skin, rash
Pyrazina- mide	Gastro- intestinal Intolerance Arthralgia Arthritis	Upset stomach, Vomiting Joint aches Gout (rare)

Common adverse reactions cont...

<i>Caused by</i>	<i>Adverse reaction</i>	<i>Signs and symptoms</i>
Ethambutol	Eye damage	Blurred or changed vision Altered color vision
Streptomycin	Vestibular toxicity Allergy	Balance problems Hearing loss Ringing in the ears Itchy skin

Common adverse reactions cont...

<i>Caused by</i>	<i>Adverse reaction</i>	<i>Signs and symptoms</i>
Rifampicin	Gastro-intestinal intolerance	Anorexia, nausea, abdominal pain
Isoniazid, PZA, Rifampicin	Hepatitis	Abdominal pain, anorexia, nausea, vomiting, abnormal LFTs

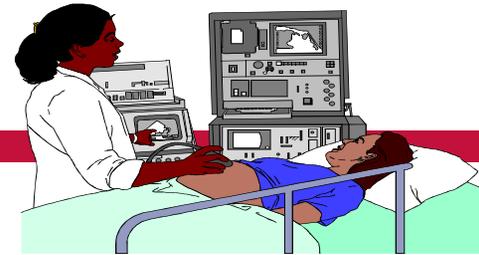
Minor side effects

Adverse event	Probable responsible drug(s)	Management
Minor		Continue anti-TB drugs
Anorexia, nausea, abdominal pain	Rifampicin	Give tablets at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in feet	Isoniazid	Pyridoxine 25mg daily
Orange / red urine	Rifampicin	Reassurance

Major side effects

Adverse event	Probable responsible drug(s)	Management
Major		Stop drugs responsible
Skin itching or rash (anaphylactic reaction)	Streptomycin	Stop drug, treat as for hypersensitivity reaction
Deafness (no wax on auroscopy)	Streptomycin	Stop drug
Dizziness (vertigo and nystamus)	Streptomycin	Stop drug if severe
Jaundice (other causes excluded)	Most anti-TB drugs	Stop drugs until jaundice resolves, then re-introduce one by one
Vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	Most anti-TB drugs	Stop drugs, urgent liver function tests
Visual impairment	Ethambutol	Stop drug
Generalised reaction, including shock and purpura	Rifampicin	Stop drug

TB and Pregnancy



- PMTCT for all pregnant women
- All drugs in standard Regimen are safe
- **Do NOT** give Streptomycin
- **Do NOT** give MDR drugs: (Ethionamide, Ofloxacin, Kanamycin)
- **BCG** vaccination to newborn – after completion of INH prophylaxis (wait 48hrs)
- Do not give BCG at birth if mother is HIV+

When and who to refer to hospital?

- **PTB Complications**
 - haemoptysis, extreme weight loss
 - pneumothorax, lung abscess
- **Retreatment patients for the Streptomycin injections**
- **Extra-Pulmonary TB: eg TBM, Pericardial TB**
- **Multi-drug resistant TB**
- **Severe co-morbid disease**
 - HIV, diabetes, CCF, asthma, hypertension
- **Severe adverse drug reactions**
- **Adherence/social problems- rare cases**

When and who to discharge

- **Discharge planning: priority is to ensure continuity of care**
- The **clinical condition** will determine when a patient can be discharged (weight gain, no dyspnoea at rest)
 - counsel patient again
 - **ensure DOT/ health education**
 - contact **clinic/treatment supporter**
 - **complete all necessary documentation (referral form)**

Case management

Follow-up during treatment

- Patients general condition (side effects etc..)
- Body weight
- Sputum examinations to monitor response to treatment, identify resistance early
- Specimens examined at ('treatment months?*)
 - 2 months (7 weeks, to start continuation phase)
 - 5 months (to detect failures for changing the treatment)
 - End of treatment (7-8 months) to detect failures

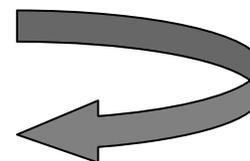
* *Not 'calendar months'*

How to manage irregular attendance

INTENSIVE PHASE

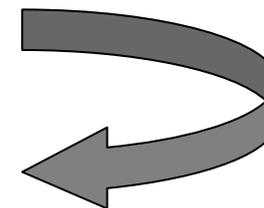
If 10 doses missed in total

Continue with intensive phase,
add doses to end of this phase



If more than 1 month missed

Do culture, drug susceptibility,
continue with intensive phase until
result is available



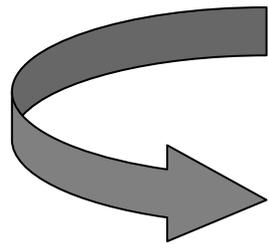
* If smear positive start re-treatment
regimen

How to manage irregular attendance cont...

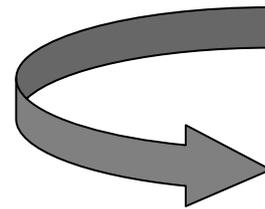
CONTINUATION PHASE

If missed 2 months in total

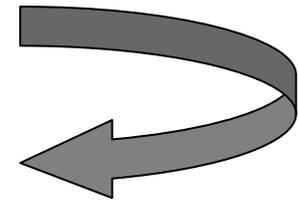
Request sputum microscopy



If smear-negative,
complete
continuation phase



If smear positive,
start retreatment
regimen again



We can stop TB



TB case detection and diagnosis



Learning Outcomes

- How to identify TB suspects among clients attending Health Facility
- Discuss the role of the laboratory in the diagnosis of TB
- Explain the requirements, the successful collection and submission of specimens
- Discuss other tests used in TB diagnosis
- Complete the necessary documentation to monitor TB suspects activities in the facility

Who can spread TB

- Patients with ***cough for more than two weeks(undiagnosed)***
- Patients with ***sputum positive for AFB***
- Patients not on treatment
- Patients just started on treatment
- Patients with a poor response/ adherence to treatment
- Close contact of DR TB cases

How to organise TB case detection activities

- Sensitise all health care workers on the importance of early TB case detection
- Sensitise communities on the importance of TB case detection (information leaflets, social mobilisation)
- Train health care workers in the correct operational procedures for TB case detection
- Organise activities for TB case detection – flowcharts (algorithms), posters, triage
- Implement the monitoring and evaluation system for TB case detection (Suspect Register, lab forms, reporting forms)

Key questions for all patients attending PHC/OPD

The goal is to adequately identify and examine 100% of all adults and children >5 years of age who present with a cough and cold symptoms for more than 2 weeks

- *Do you have a cough?*
- *For how long have been coughing?*
- *Do you expectorate/have a phlegm?*

Medical history of the patient

Important questions to ask

- Is there a history of previous TB treatment.
When and for how long
- Are there family members, co-workers, friends with TB or TB symptoms
- What do you know about TB

History of other medical conditions

- e.g. diabetes, steroid dependent medication

Physical examination: Signs & symptoms of PTB

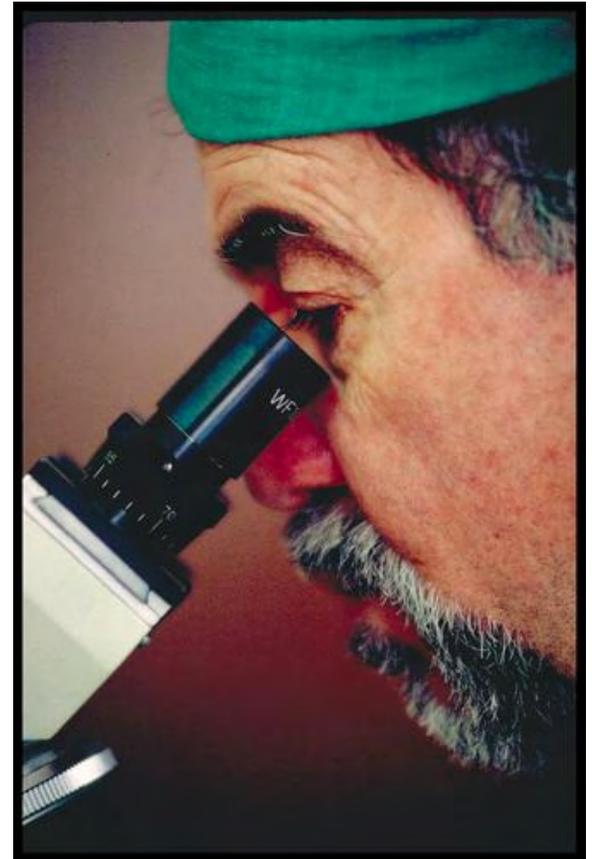
- Cough – Chronic or more than 2 weeks
- Weight loss and anorexia
- Chills and night sweats
- Pyrexia of unknown origin
- Chest pain
- Dyspnea
- Haemoptysis
- Malaise and unusual tiredness

Sputum collection

- All TB suspects collect sputum for smear microscopy to confirm diagnosis of Pulmonary TB
- It is important to carry out smear microscopy because it correctly and efficiently identifies the cases that are infectious and therefore have the highest priority for care.

Why sputum smear microscopy

- Cornerstone of the **TB Control Program**
- Most specific and cost-effective proof of PTB
- Identifies those patients that are smear positive, therefore most infective
- Relatively easy to obtain a specimen
- Test results reliable and mostly back within 24 - 48 hours



Sputum smear microscopy

- **Spot-morning**
 - Why spot?
 - The patient is registered and if positive can be traced
 - Specimen collection can be ‘observed’
 - Quality of specimen collected – not saliva
- Two smears
 - If the services can truly not handle two consecutive specimens per patient then it may be better to compromise and take two smears on the same day rather than risking non-compliance with a non-feasible strategy

Sputum collection: When and why

Pretreatment

- to confirm diagnosis

After 7 weeks of the intensive treatment phase of New PTB cases

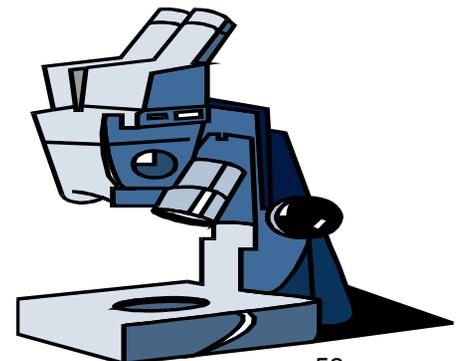
- to monitor clinical progress; and
- to monitor smear conversion

After 11 weeks of the intensive treatment of Re treatment TB cases

- to monitor clinical progress; and
- to monitor smear conversion

At end of treatment

- to prove cure
- identify treatment failure



How to collect the sputum

- This procedure should occur in a well ventilated area or outside, but in private.
- Supervise the collection , stand behind the patient.
- The patient must rinse out the mouth with water.
- Demonstrate a deep cough from the bottom of the chest, beginning with deep breathing.
- Give the patient the container labeled, but without a lid.

Sputum collection: Instructions to the patient (2)

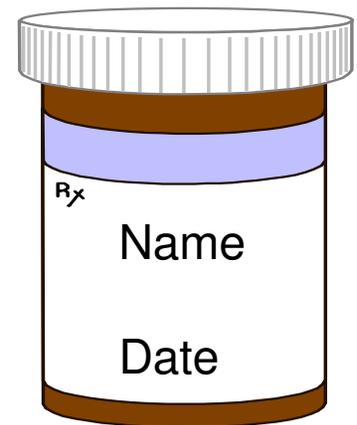
- Take in a lot of air (inhale deeply)
- Retain the air in the lungs
- Make an effort to cough in order to loosen the phlegm
- Repeat the action at least three times for each sample – to ensure adequate amount
- Close the sputum container
- Give sputum container to the nurse

SAFETY AT SPUTUM COLLECTION



Safety at sputum collection

- All HCW's must protect themselves when supervising sputum collection
- Outdoors or in a well ventilated area is best
- Use surgically clean rigid containers, properly closed, apply standard precautions
- Accurate labeling and prompt transportation necessary
- Don't forget to wear gloves!!



Sputum sample labeling

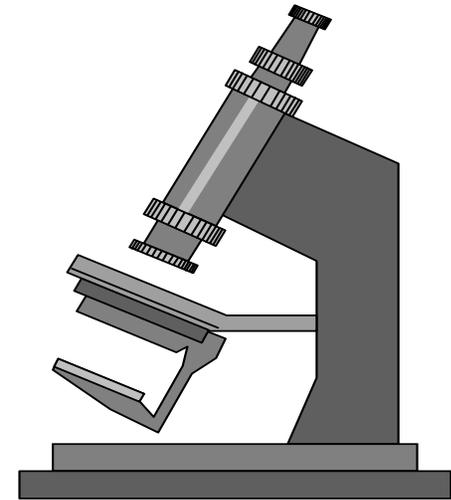
- All patient personal information: the file number, the name, age and sex of the patient
- Clear instruction on investigations requested (smear micro, pre or phase specimen)
- Name and address of the clinic
- Store in a fridge (bottom) for not 24 hrs

Always label the container as the lids may get mixed up!!!

Laboratory errors can occur

Causes of False Positive

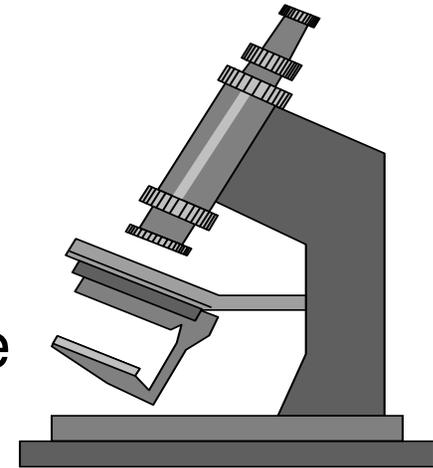
- Scratches
- Food particles
- Administrative errors
- Mix up of specimens
- Accidental transfer of bacilli from one slide to the next

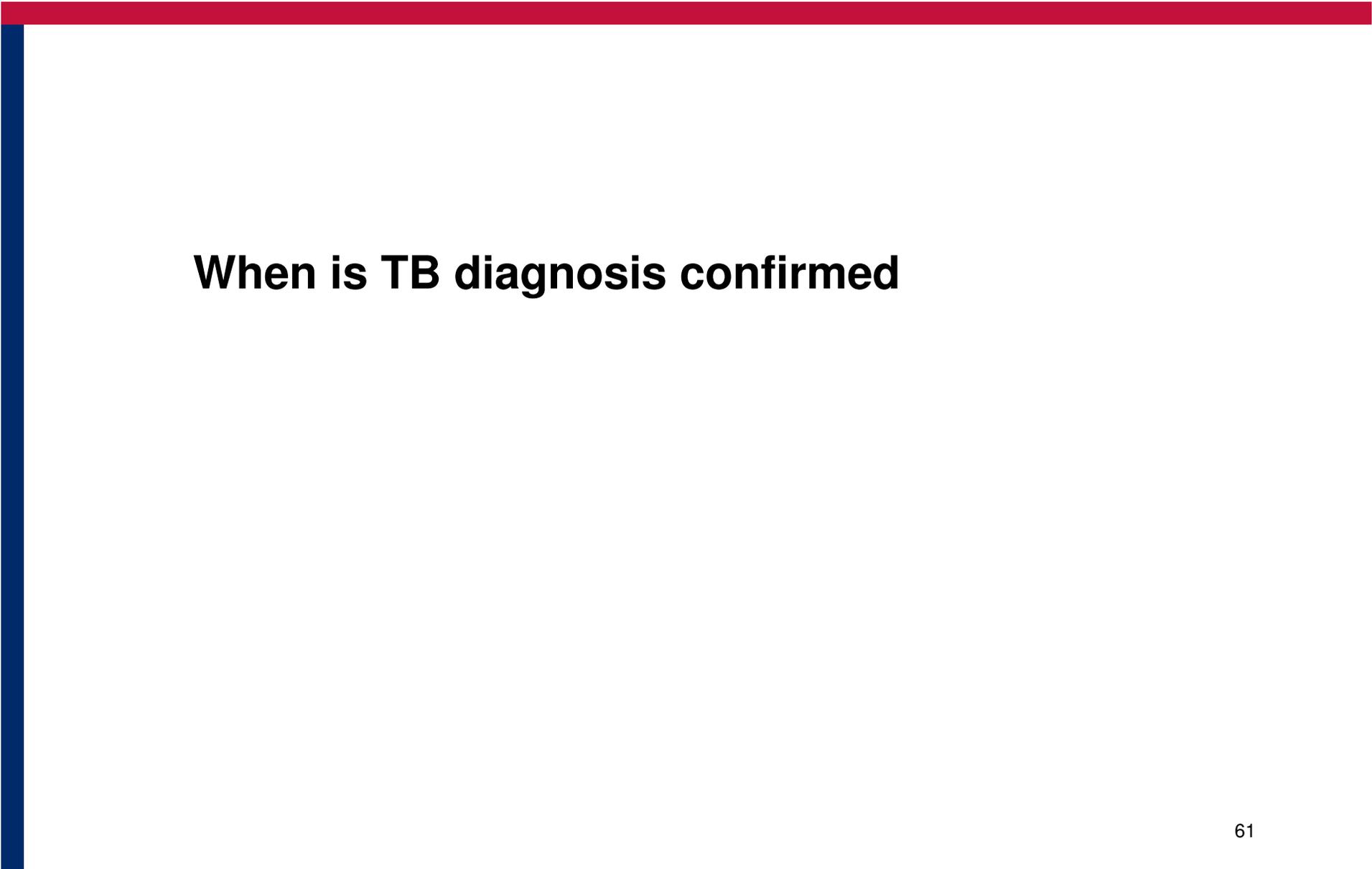


Laboratory errors can occur cont...

False Negative

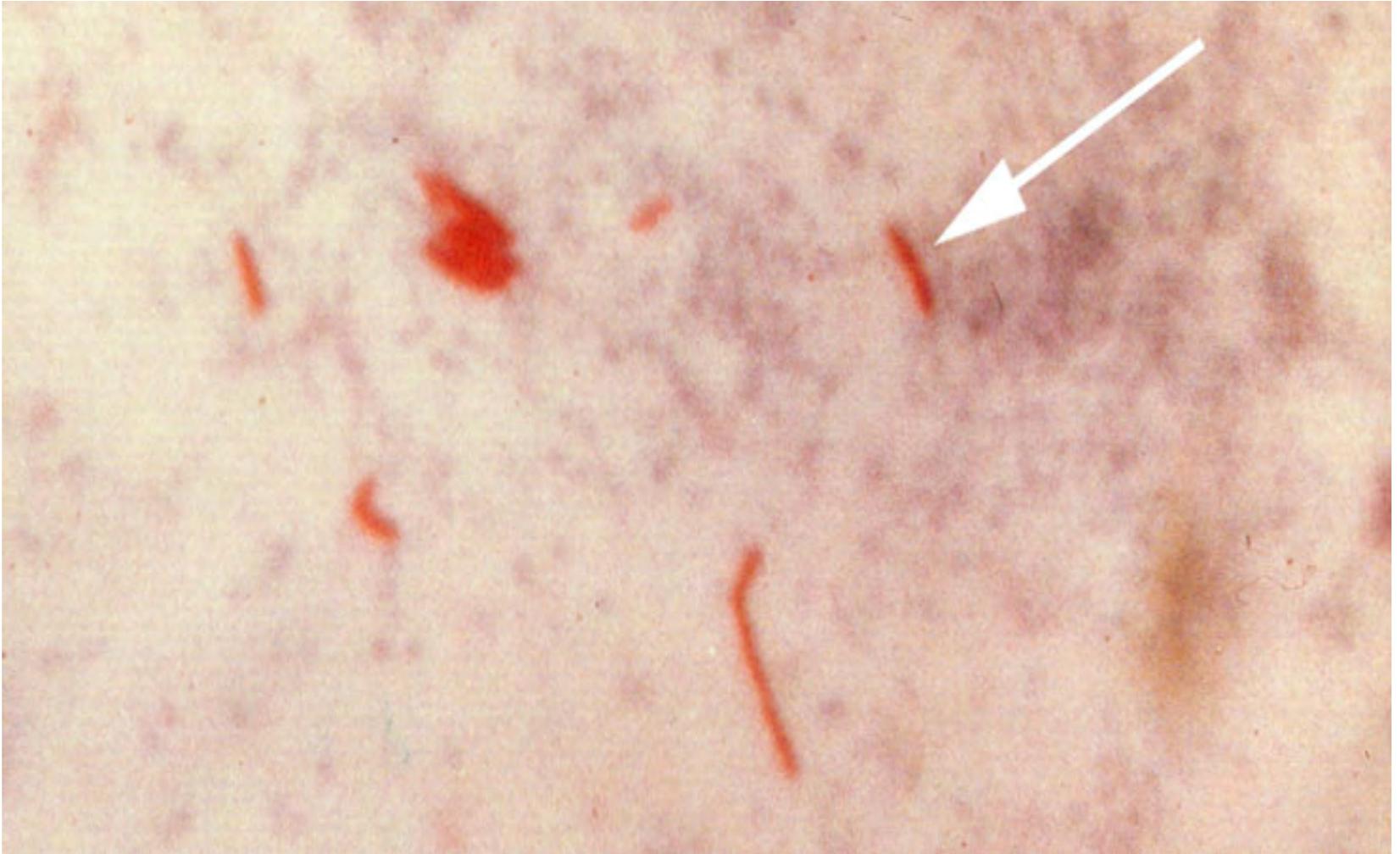
- Poor sample
- Laboratory error
- Inadequate time spent on slide
- Poor quality control
- Administrative error



A decorative L-shaped bar is located in the top-left corner of the slide. It consists of a thick red horizontal line extending across the top, and a thick dark blue vertical line extending down the left side.

When is TB diagnosis confirmed

AFB seen



Laboratory results: what do they mean?

Number of bacilli seen on a smear		Results Reported
No. of AFB	Per 100 oil immersion field	Negative/ no AFB seen
1-9 AFB	Per 100 oil immersion field	Scanty pos (1 – 9)
10-99 AFB	Per 100 oil immersion field	1+
1-10 AFB	Per 1 oil immersion field	2++
>10 AFB	Per 1 oil immersion field	3+++

M Tuberculosis Characteristics

- Microscopic thin and *rod like (G + bacilli)*
- Occur singly or in clusters
- Complex thick waxy cell wall (Mycolic acids)
 - ✓ need special antibiotics
 - ✓ special staining methods needed [ZN] or Auramine stain (acid and alcohol fast)
 - ✓ Can survive for long periods in the dark, cool places
- Destroyed by heat, UV light, pasteurisation

Bacilli growth & invasive properties

Various populations of bacilli in a TB lesion:

- Active,
- Intermediately active,
- Semi-dormant, slow growing
- Dormant, may become active at any time

They grow both Intra- and Extra-cellularly

TB Culture and Drug Susceptibility Testing (DST)

- The growth of live TB bacilli on culture media
 - Lowenstein Jensen - takes 6 weeks
 - Bactec - expensive, takes 2-3 weeks
- Not done routinely
- More sensitive than sputum smear microscopy,
- Much more expensive & done on selected cases only



Culture and drug susceptibility testing

- Drug susceptibility tests are used to determine the susceptibility or resistance of a patient anti-tuberculosis drugs
- Culture results should not delay the initiation of therapy, the decision to treat can be based on the history, clinical findings and chest x-ray, where smear is negative or one negative one positive

When to request culture and sensitivity

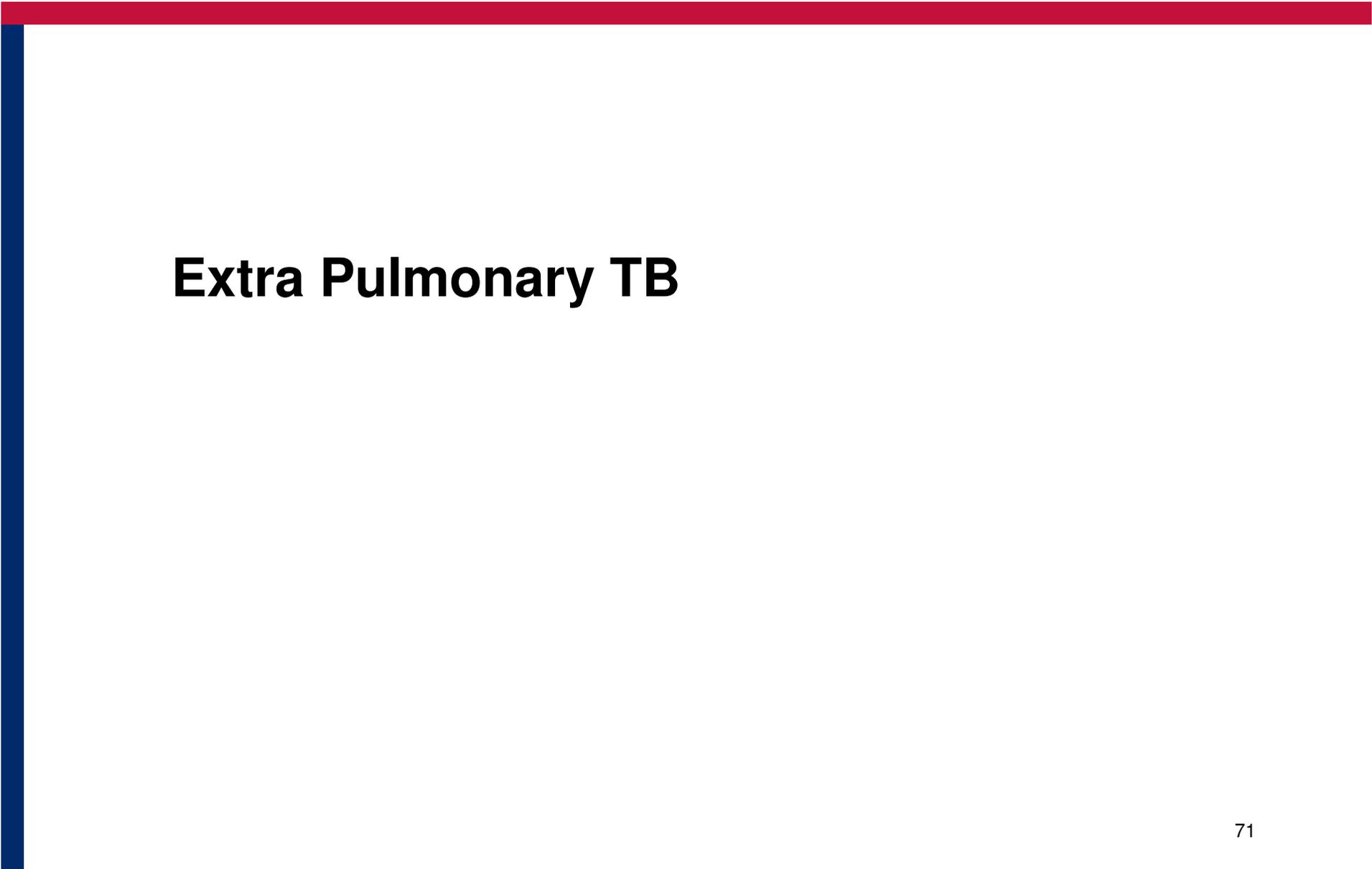
- All re-treatment cases
- All symptomatic contacts of DR TB cases
- For diagnosis when only one smear is positive
- For diagnosis if two smears are negative in a TB suspect case e.g. HIV +
- Cases who remain positive at end of initial phase OR end of treatment
- If drug susceptibility is required

Criteria for starting TB treatment

- Two positive smears
- One positive smear and abnormal CXR
- One positive smear and positive culture
- One positive culture and abnormal CXR
- Very ill patient with one positive smear *or* one positive culture
- Smear negative with suggestive clinical picture and an abnormal CXR

Complete the case identification register using 10 scenarios

- Exercise



Extra Pulmonary TB

Extra-pulmonary TB

- Symptoms depend on the site affected
- Difficult to diagnose – symptoms are
- Vague or non-specific until advanced
- May cause permanent damage (TBM)
- Now, more common in HIV +

Extra-pulmonary TB cont...

- Lymphadenopathy
- Miliary TB
- Pleural and pericardial effusion
- Ascites
- TB Meningitis
- TB spine/bone
- Hepatic/Renal/Adrenal
- Male/female genital tract
- Upper respiratory ie larynx

How to diagnose Extra-pulmonary TB

- Clinical symptoms
- Depend on the site affected
- Taps, biopsies, x-rays
- Always check sputum for AFBs as well

Principles of treatment for Extra-Pulmonary TB

- Treatment same as PTB
- Regimen 1 for new cases and Regimen 2 for re-treatment but excluding Streptomycin
- Severe forms may be treated for a longer period, depending on the site e.g. TBM
- Decision to extend treatment should only be done by a specialist after individual clinical assessment
- Close monitoring of patients important – may also get resistant strains of TB

We can stop TB

