



**KWAZULU-NATAL PROVINCE**

HEALTH  
REPUBLIC OF SOUTH AFRICA



# Clinical Update on the Management of Drug Resistant Tuberculosis

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AWAAC

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GROWING KWAZULU-NATAL TOGETHER



# Introduction

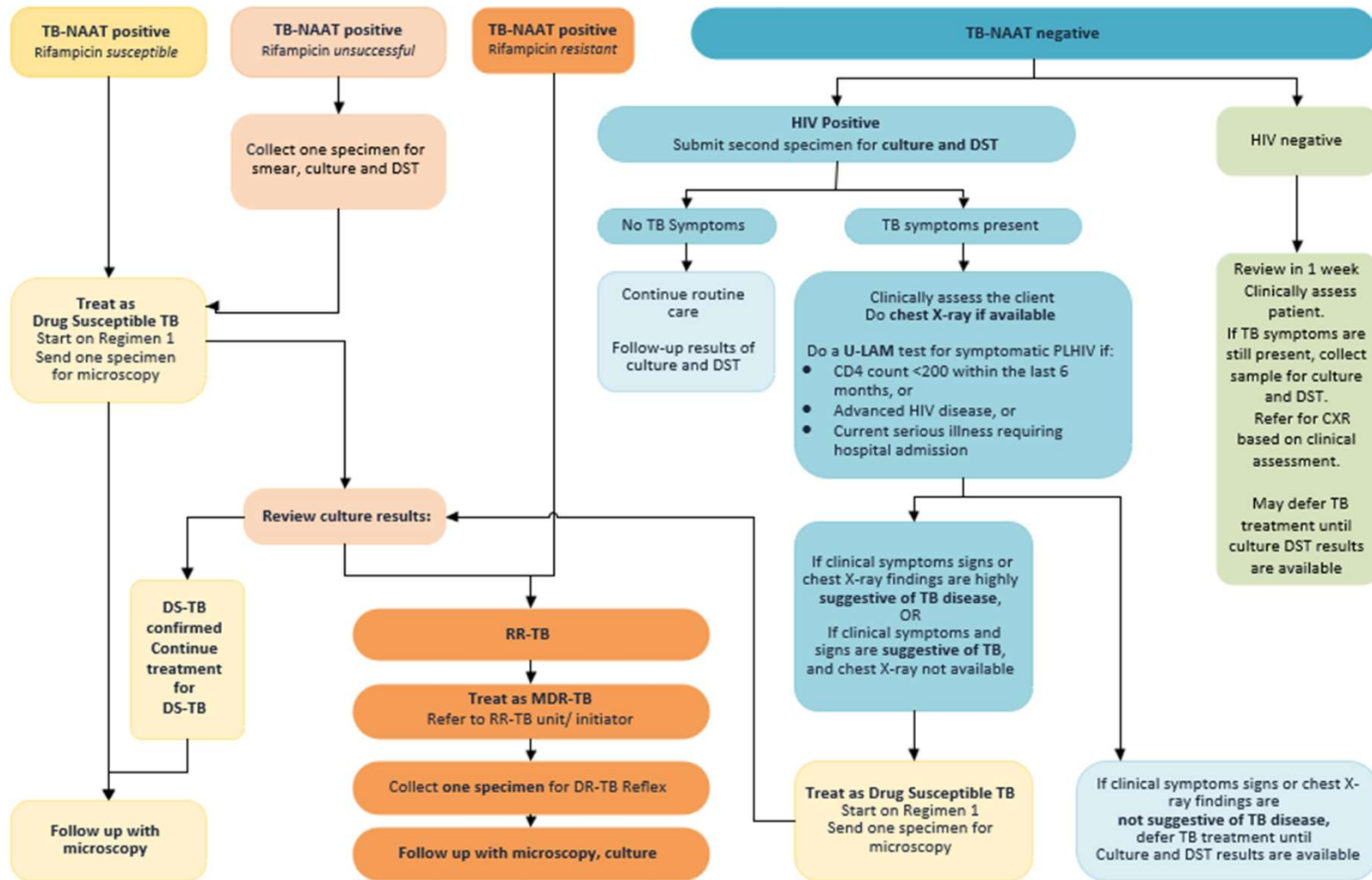
- DR-TB needs no introduction; it remains a threat to global public health and is one of the leading infectious causes of death globally.
- About 410 000 new RR/MDR TB cases were estimated to occur in 2022; only 175 650 enrolments on treatment were reported.
- Until recently, the management of DR TB required complex treatment regimens with long durations. Despite this, the Rx success rate was low and morbidity and mortality high.
- Recent years have seen enhanced diagnostics, the use of new and repurposed medication and a shift away from the injectable-based regimens. This has positively impacted on the treatment success rate.
- Globally, in 2022, the treatment success rate was 63%, an improvement from 50% in 2012.
- This presentation focuses on clinical management, but recognizes the importance of ongoing social, nutritional and psychological support throughout the treatment journey.



# Case Study

- 35 year old male patient Mr N.M
- HIV positive – started ARV's in 2018
- Interrupted Rx 2021
  
- Symptomatic of TB
- Previous DS TB in 2018 – completed 6 months Rx
- No known DR TB contact
  
- No other co-morbidities

**Presumptive TB in clients who have not received TB treatment within the previous two years**  
 TB and DR-TB contacts, non-contact symptomatic individuals, asymptomatic high-risk individuals, and re-treatment after relapse, failure and lost to follow up  
 Collect one sputum specimen at the health facility under supervision







# Definitions

- **Mono-Resistant Tuberculosis**

Resistant to only one anti-TB drug, without resistance to other drugs.

- **Poly-drug Resistant Tuberculosis**

Resistance to more than one anti-TB drug, other than both isoniazid and rifampicin.

- **Multidrug- Resistant Tuberculosis (MDR-TB)**

Resistance to isoniazid and rifampicin with or without resistance to other first line anti-TB drugs.

- **Rifampicin-Resistant Tuberculosis (RR-TB)**

Resistance to at least rifampicin, with or without resistance to other drugs. This category includes MDR-TB, rifampicin mono-resistant TB, pre-XDR TB and XDR TB.

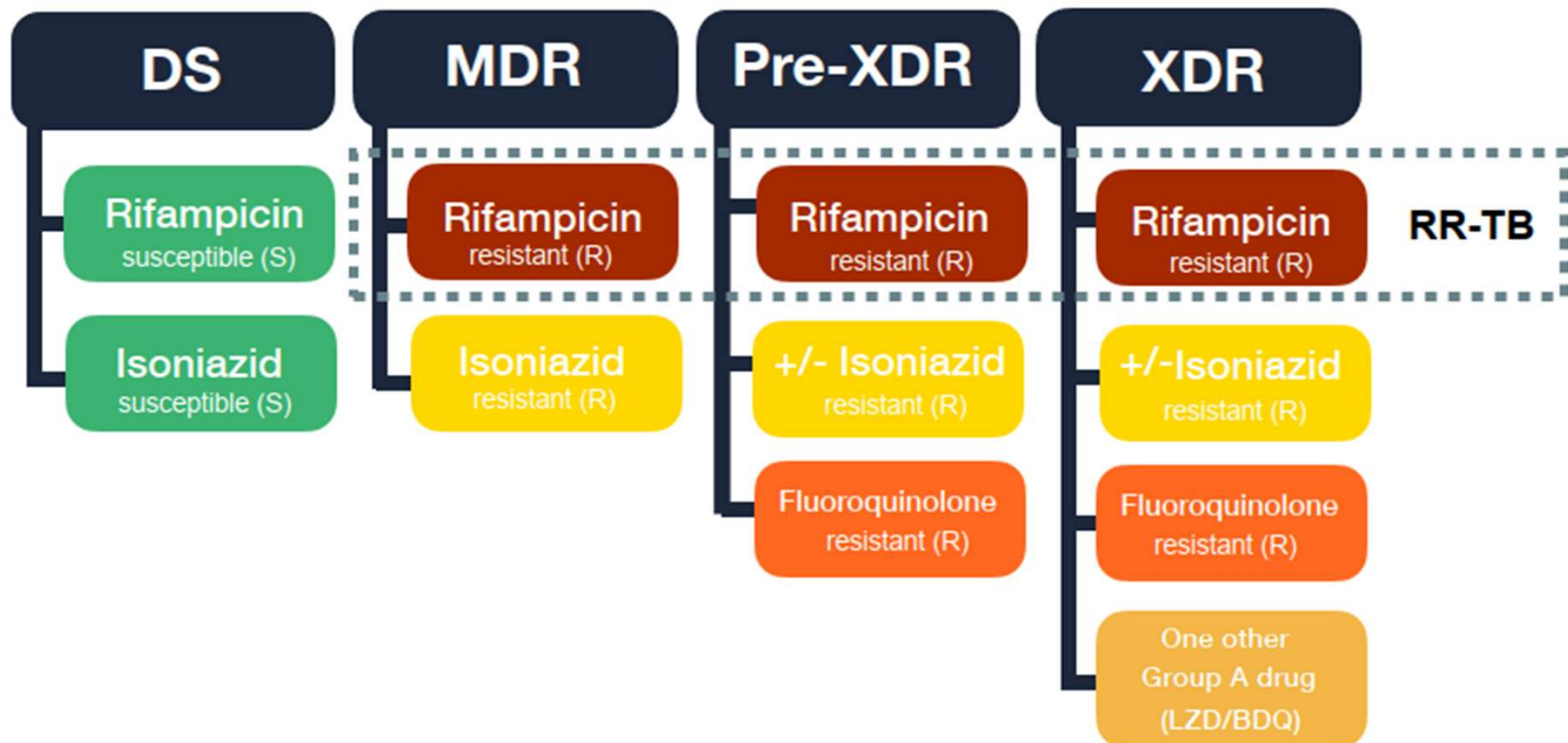
- **Pre-XDR Tuberculosis**

Resistance to rifampicin (and may also be resistant to isoniazid), and that is resistant to fluoroquinolones.

- **Extensively drug Resistant Tuberculosis (XDR-TB)**

Resistance to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levo or moxi), and to at least one additional Group A drug (either bedaquiline or linezolid).

# Drug Susceptible (DS) TB vs. Drug Resistant TB (DR-TB)





# Diagnosis

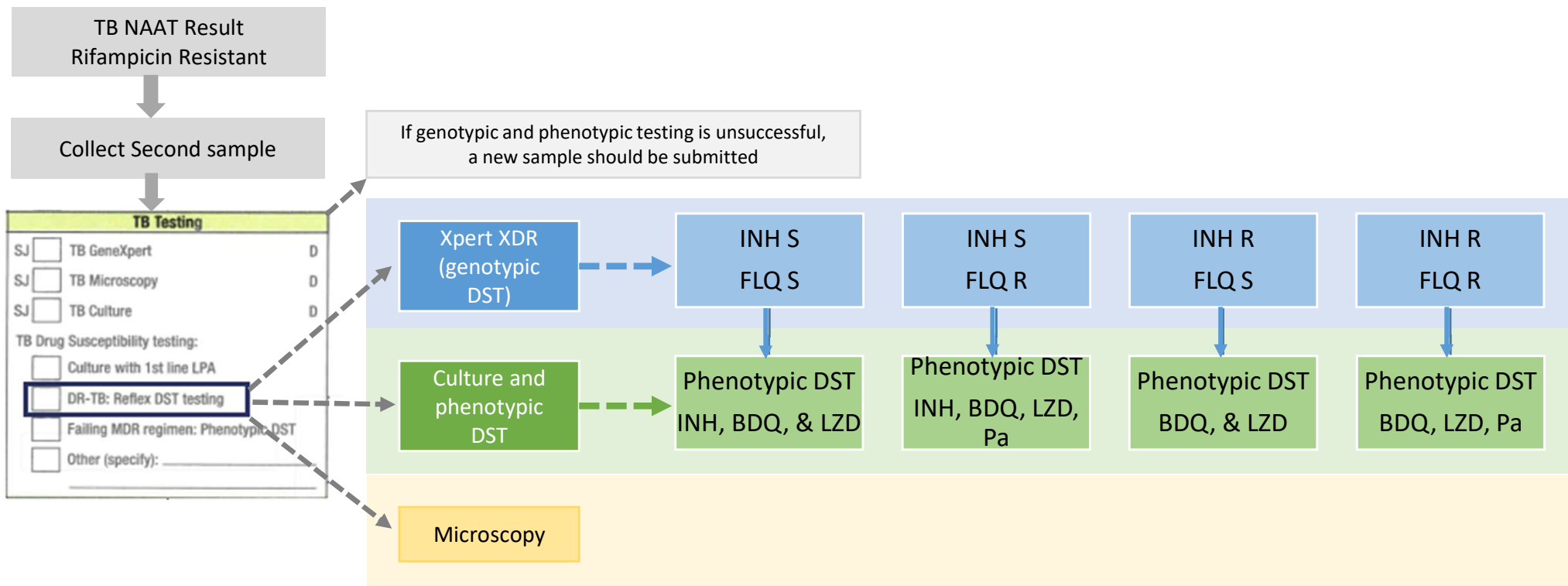
- Clinical presentation
  - Symptoms
  - Contact history
  - Previous TB treatment
- Physical examination
- **Lab diagnosis**
- Radiology
  - CXR
  - Other X-rays
  - Sonography
  - CT scan



# Diagnosis

- TB-NAAT (\*GeneXpert/Roche/BD Max)
- Baseline testing for all RR-TB patients is the DR-TB reflex which includes:
  - smear
  - Culture
  - \*Xpert XDR cartridge (INH, ethionamide, FQ and SLID sensitivity)
  - Phenotypic DST based on Xpert XDR results (BDQ, LZD, INH and Pa)

# DR-TB Reflex Testing Process



# DR TB Reflex – Xpert XDR

**TAT for this sample from sample collection date to Xpert XDR cartridge result – 3 days**

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## MICROBIOLOGY

Tel: 039 687 6013 ext 155, Fax: 039 687 7950

Specimen received: Sputum

Tests requested: TB mic @, TB cult @, Xpert MTB/XDR (sample) @, TB sens 2nd line @  
@ Test referred to another NHLS laboratory

### Auramine O Stain:

Result (concentrated) - IUALTD      Positive 2+ (7-60 AFB in one field)

### TB Culture:

Culture result      Culture positive. AFBs observed.

Incubation time      6      days

### TB-NAAT DR-TB: GeneXpert MTB/XDR (Clinical Sample)

|                                   |   |
|-----------------------------------|---|
| PCR M.tuberculosis result         | Mycobacterium tuberculosis complex detected |
| Isoniazid, INH (molecular)        | Resistant                                   |
| Fluoroquinolones, FLQ (molecular) | Resistant                                   |
| Amikacin, AMK (molecular)         | Sensitive                                   |
| Ethionamide, ETH (molecular)      | Sensitive                                   |

1. Mutations associated with high-level Isoniazid resistance were detected.
2. Mutations associated with Fluoroquinolone resistance were detected.
3. No mutations conferring resistance to amikacin were detected.
4. No mutations conferring resistance to ethionamide were detected.  
Resistance to ethionamide cannot be excluded.

NB. Please correlate with current genotypic Rifampicin result, to determine the drug resistance classification. Phenotypic drug-susceptibility results of additional second-line drugs to follow.



# Case Study

- Mr N.M reviewed with results of baseline investigations
- DR TB reflex result –pending
- CXR – consolidation right upper lobe
- Blood results acceptable:
- Hb = 8,1
- CD4 = 206
- Eye screen and ECG normal

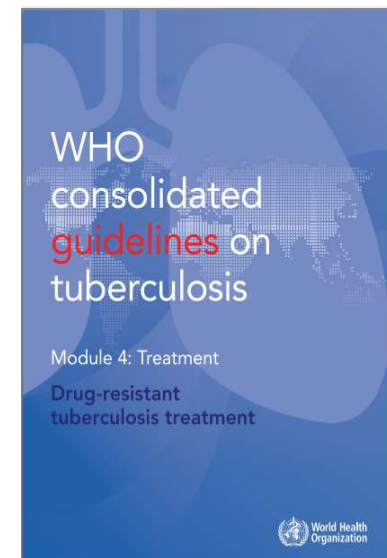


## Case Study

- What treatment do we start?

# Classification of drugs used in DR TB management

| GROUP                 | MEDICINES                     |         |
|-----------------------|-------------------------------|---------|
| Group A               | Levofloxacin <u>OR</u>        | Lfx     |
|                       | Moxifloxacin                  | Mfx     |
|                       | Bedaquiline                   | Bdq     |
|                       | Linezolid                     | Lzd     |
| Group B               | Clofazimine                   | Cfz     |
|                       | Cycloserine <u>OR</u>         | Cs      |
|                       | Terizidone                    | Trd     |
| Group C               | Ethambutol                    | E       |
|                       | Delamanid                     | Dlm     |
|                       | Pyrazinamide                  | Z       |
|                       | Imipenem-cilastatin <u>OR</u> | Ipm-Cln |
|                       | Meropenem                     | Mpm     |
|                       | Amikacin                      | Am      |
|                       | ( <u>OR</u> Streptomycin)     | (S)     |
|                       | Ethionamide <u>OR</u>         | Eto     |
|                       | Prothionamide                 | Pto     |
| p-aminosalicylic acid | PAS                           |         |



- Drugs in red have paediatric friendly formulations



## The BPaL and BPaL-L regimens

- WHO announced the introduction of BPaL-M regimen for RR-TB in May 2022
- The BPaL-M regimen: Bedaquiline (B), pretomanid (Pa), linezolid (L), with or without moxifloxacin (M)
- NEMLC concluded that levofloxacin (L) will be used in replacement of moxifloxacin in SA: BPaL-L



# The BPaL and BPaL-L Regimens

- The BPaL combination (with 600 mg linezolid) retains sufficient efficacy and allows the regimen to be used without levofloxacin in the case of documented resistance to fluoroquinolones (i.e. in patients with pre-XDR-TB).
- In patients receiving the short regimens, where there is a slow response to therapy, an extension of 3 months (bringing the total regimen to 9 months) is possible.
- Individuals who have had more than one month exposure to the second line drugs may be started on BPaL-L, but resistance to BDQ and LZD must be excluded. \*\*\*



- There is NO intensive phase or continuation phase for these regimens.
- All the drugs should be continued throughout treatment, if possible, unless limited by toxicity or intolerance
- Pretomanid is only used in these regimens. It is NOT used outside of the BPaL or BPaL-L regimens.
- Pyridoxine does not need to be prescribed in patients receiving BPaL-L.

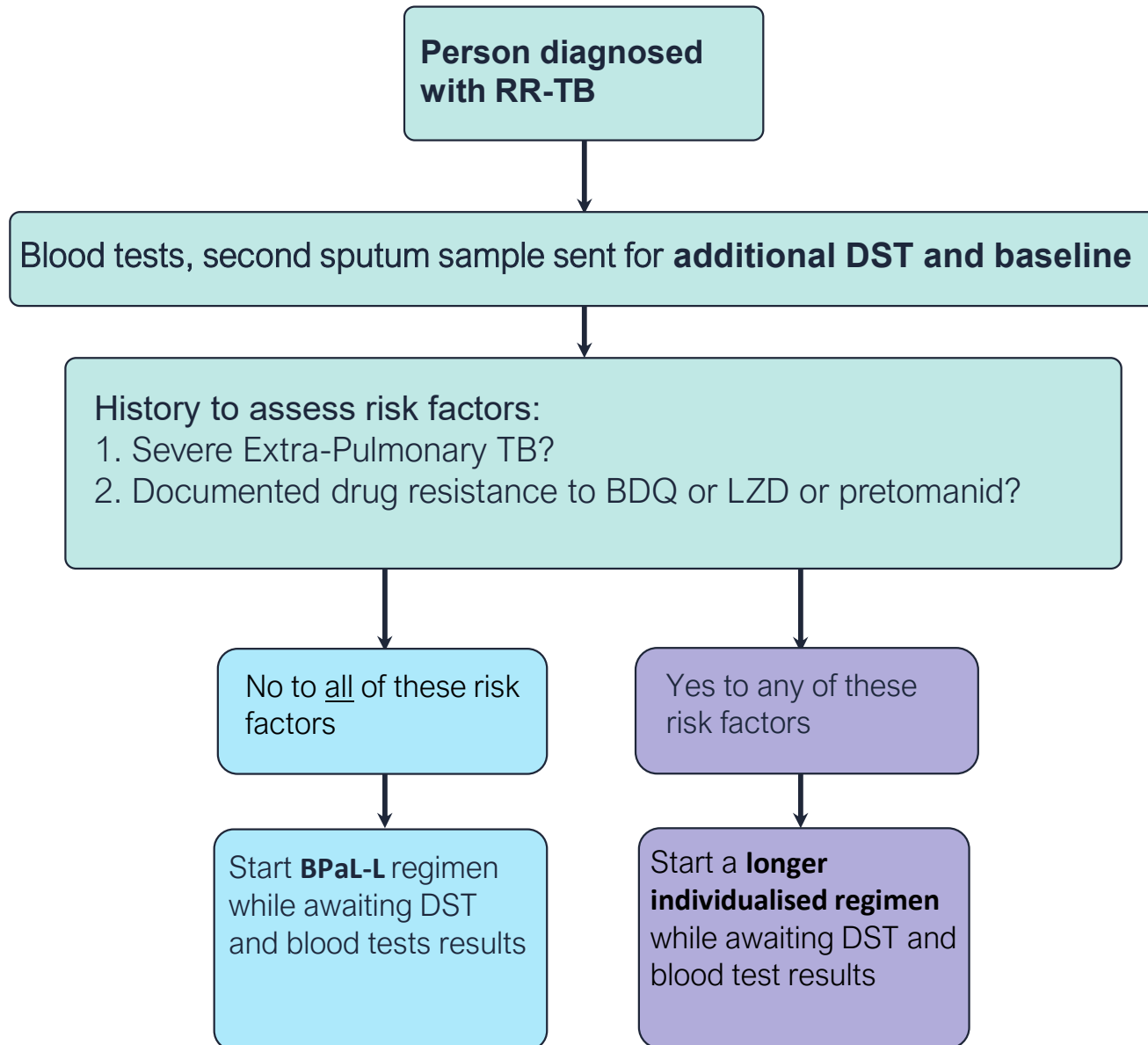


| INCLUSION criteria  | EXCLUSION criteria   |
|---|--|
| <p><b>Individuals with RR-TB</b><br/>Resistance based on initial TB-NAAT result, while awaiting further susceptibility results</p>  | <p>Persons with <b>severe RR-EPTB</b>:<br/>Meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease</p> |
| <p><b>Non-severe RR-EPTB</b><br/>Including lymphadenopathy or (uncomplicated) pleural effusion</p>  | <p>Persons with RR-TB with additional <b>resistance to BDQ, LZD, Pa or DLM</b></p>   |
| <p>Persons with extensive pulmonary disease (i.e. bilateral, cavitory disease with significant fibrosis, scarring or cavities in 3 or more lung zones) should have their treatment extended to 9 months</p> | <p><b>Children under the age of 15 years</b><br/>(<u>Pretomanid</u> safety is not yet confirmed in this population)</p>            |
|   | <p><b>Pregnant women</b><br/>(<u>Pretomanid</u> safety is not yet confirmed in this population)</p>                                |
| <p><b>Low risk of BDQ-resistant RR-TB following prior BDQ-based treatment*</b></p>  | <p><b>High risk of BDQ-resistant RR-TB**</b></p>   |

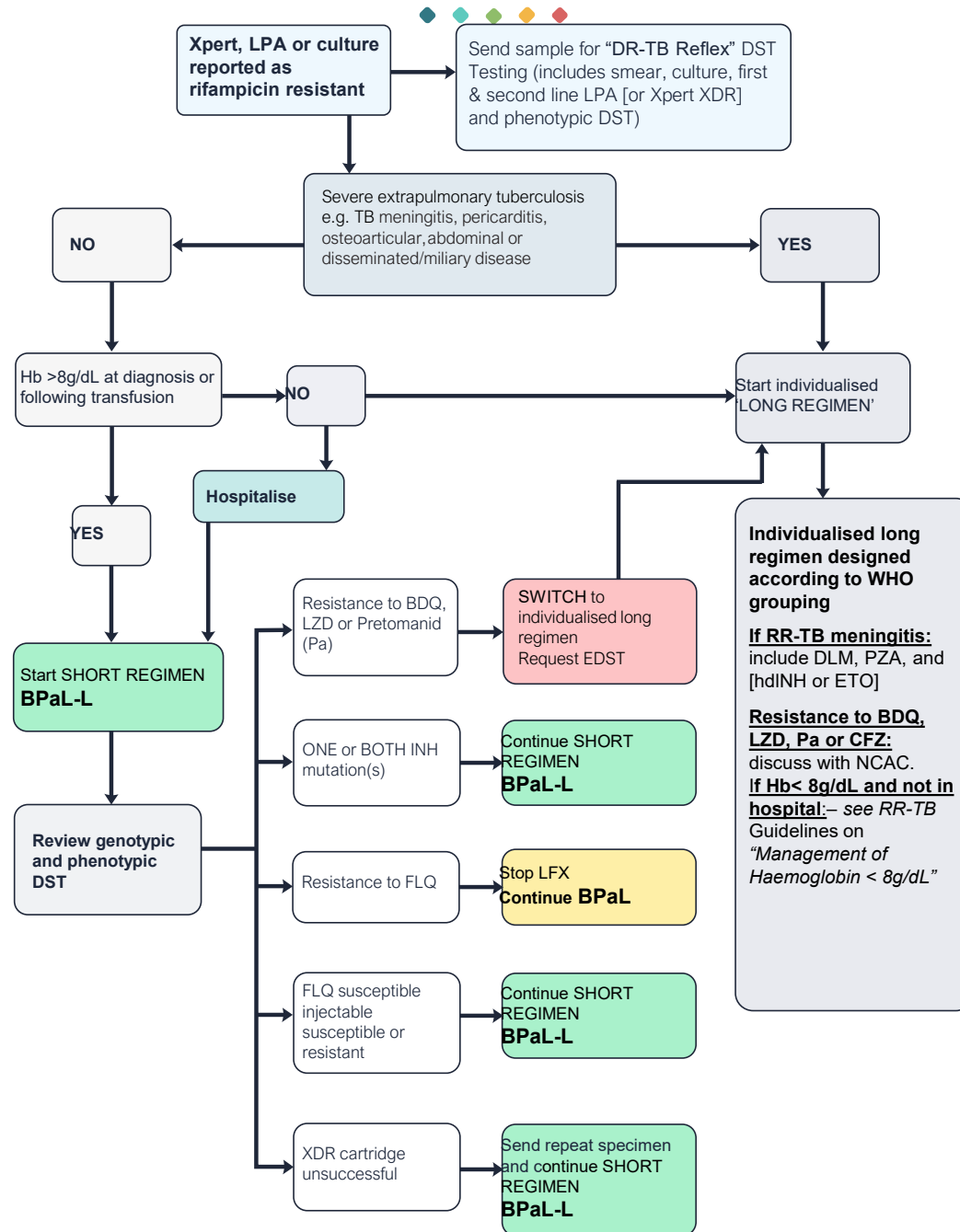
# RR-TB Treatment Regimens in SA



## Initial approach to patients diagnosed with RR-TB



# Overall Flow Diagram for people ≥ 15 years of age



# BPaL-L / BPaL Dosing



| Drug                               | Dose   |
|------------------------------------|--|
| <b>Bedaquiline</b> (100mg tablet)  | 400mg once daily for 2 weeks, then 200mg 3 times per week afterwards |
| <b>Pretomanid</b> (200mg tablet)   | 200mg once daily   |
| <b>Linezolid</b> (600mg tablet)    | 600mg once daily   |
| <b>Levofloxacin</b> (250mg tablet) | 750mg (<46kg) OR 1000mg (≥46kg) once daily                           |



## Case study continued

- Mr N.M seen at his 2 week visit
- Xpert XDR cartridge results were reviewed
- FQ resistant - Regimen changed - **BPaL**
  
- Came back at end of 4 weeks/month 1
- pDST result checked

# DR TB Reflex - pDST

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## Antimycobacterial Drug Sensitivity Testing:<Continued>

### Second Line Drugs - MGIT Culture Based:

|             |           |
|-------------|-----------|
| Bedaquiline | Resistant |
| Linezolid   | Sensitive |

This is a case of extensive (also known as extreme) multi-drug resistant tuberculosis (XDRTB). The patient should be referred for specialist opinion.

@ TB cult, TB mic, TB sens 2nd line, Xpert MTB/XDR (sample) referred to Inkosi Albert Luthuli Central Hospital (Tel 031 240 2758/59)



# The Long Regimens

- The Basic long regimen (BLR) is a 18 to 20 month regimen
- It has an IP and a CP
- Use all 3 Group A drugs and both Group B drugs
  
- Other long regimens include the CNS regimen and the *Rescue regimen* (XDR TB, Rx failures)
- These also have an IP and CP
- These are individualized regimens using Group A,B and C drugs
- Patients requiring a Rescue regimen will need an EDST



## Switching from BPAL-L to a Long Individualised Regimen

- A switch should be strongly considered in the following situations:
  - There is a **positive culture** result at month 4 (delayed culture conversion or reconversion back to positive). Resistance to bedaquiline, pretomanid, delamanid or linezolid must be excluded.
  - **Resistance** to bedaquiline, pretomanid, delamanid or linezolid is detected
  - Bedaquiline, or pretomanid, or linezolid is prematurely and permanently discontinued because of **toxicity**
  - The patient is **clinically deteriorating** or has not clinically improved. Other causes must be excluded in a culture-negative patient
- Extended DST is required

## Example of Extended DST result

### **Mycobacterial Culture Liquid Medium:**

|                 |                                  |
|-----------------|----------------------------------|
| Specimen type   | Sputum                           |
| Growth result   | Culture positive. AFBs observed. |
| Incubation time | 7 days                           |

NO GROWTH ON BLOOD AGAR.

### **Mycobacterial Identification - Antigen:**

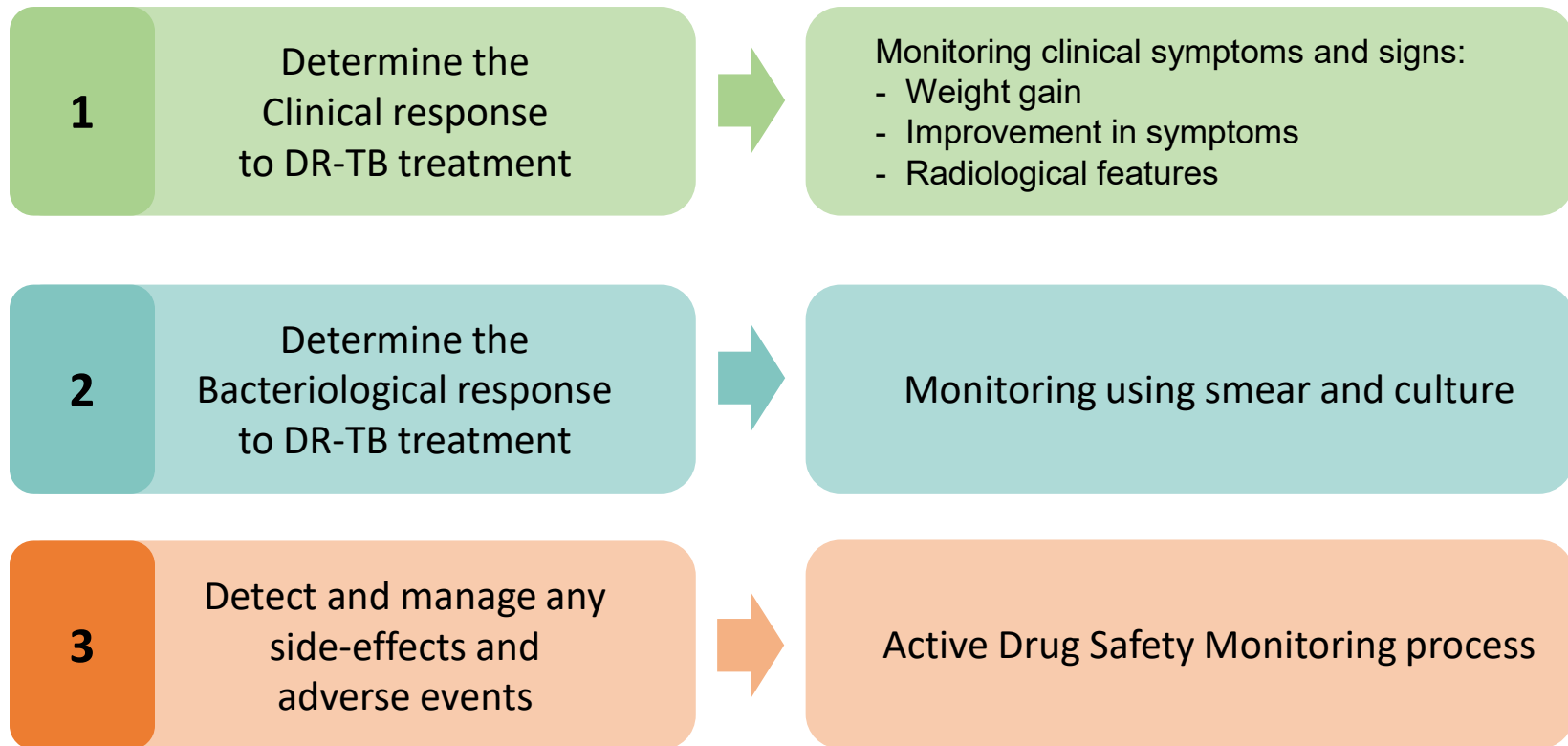
|        |                                    |
|--------|------------------------------------|
| Result | Mycobacterium tuberculosis complex |
|--------|------------------------------------|

### **Antimycobacterial Drug Sensitivity Testing:**

#### **Extended Drug Sensitivity Testing - MGIT Culture Based:**

|                       |           |
|-----------------------|-----------|
| Amikacin              | Sensitive |
| Bedaquiline           | Resistant |
| Clofazimine           | Resistant |
| Ethambutol            | Resistant |
| Isoniazid High        | Resistant |
| Levofloxacin          | Resistant |
| Linezolid             | Sensitive |
| Moxifloxacin Low      | Resistant |
| Moxifloxacin High     | Sensitive |
| p-aminosalicylic acid | Sensitive |
| Pretomanid (II)       | Resistant |
| Rifabutin             | Resistant |

# Monitoring on RR-TB Treatment





# Follow up

- On completion of treatment, patients are seen at six monthly intervals for a year
- At each visit:
  - TB symptoms
  - Clinical examination
  - CXR
  - Sputum



# Linezolid Side Effects

- Myelosuppression: anaemia, neutropenia, thrombocytopenia
- Optic neuritis
- Peripheral neuropathy
- Lactic Acidosis
- **Monitoring is vital**



## Side Effects cont.

- Prolongation of the QtcF
- DILI
- Renal impairment
- **Monitoring is vital**



# Case study continued

- Patient N.M now on a Rescue regimen (XDR TB)
- When should ARV's be started?
- Which ARV's should be used?



## DR TB and HIV

- If ARV-naïve then commence ARV's 2 weeks after DR TB Rx
- If on ARV'S, continue Rx
- TLD is the regimen of choice, provided there is normal renal function
- TBM and CCM require delayed ARV initiation of up to 4- 6 weeks
- Standard guidelines for monitoring
- If renal dosing, TDF will need to be adjusted or changed

# BDQ resistance

- BDQ access has expanded over the past decade
- BDQ is a Group A drug - backbone of DR-TB management
- pDST (as part of the DR TB reflex) routinely checks for BDQ & LZD sensitivity in RR-TB
- BDQ resistance : 6,5% Nationally
- BDQ and CFZ cross resistance around 90% in SA
- XDR = FQ + BDQ & / or LZD resistance
- *RR +/- INH + FQ-Sensitive + BDQ-resistance* ??? Classification  
??? Regimen
- Higher risk of BDQ resistance in patients with prior BDQ exposure



| INCLUSION criteria  | EXCLUSION criteria   |
|---|--|
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| <p><b>Low risk</b> of BDQ-resistant RR-TB following prior BDQ-based treatment*</p>  | <p><b>High risk</b> of BDQ-resistant RR-TB**</p>   |

## BPAL-L Eligibility criteria:

- Prior BDQ exposure: Low risk of Bdq-resistant RR-TB vs High risk of Bdq-resistant RR-TB
- Low risk: previous outcome = cure or Rx complete  
time since previous Rx episode ???
- High risk: Rx failure
  - Close contact
  - Relapse/recurrence – time???
  - LTFU

# Management of INH monoresistant TB

- INH resistance and Rif sensitive
- Must be followed up with a DR TB Reflex (FQ sensitivity)
- Rx is Rifafour and Levoflox for 6 months if FQ sensitive
- Will need monthly smear and culture
- In case of FQ resistance, will need empirical DR TB Rx



# Forthcoming Attraction!!!

- **tNGS**: targeted next generation sequencing
- Molecular/ genotypic test
- Looks for resistance to R,H,Z,E, BDQ,LZD,FQ, Clofazimine, Amikacin
- Picks up the 491 Mutation
- *TAT of 2 to 3 weeks*



# Referrals to KDHC

- XDR TB
- Complicated cases
- Failing Rx – requiring a Rescue Regimen
- Pediatrics
- Pregnant patients
- OP in KDHC drainage area

# Referrals to KDHC

- Hotline number:

0801515155

0760768803

- Email:

[Nontobeko.Zondi2@kznhealth.gov.za](mailto:Nontobeko.Zondi2@kznhealth.gov.za) / [bookingsmdr2@gmail.com](mailto:bookingsmdr2@gmail.com)

- Dr Chotoo - 031 2426122
- Dr Everton - 031 2426154
- Dr Singh - 031 271 1148

**THANK YOU**

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