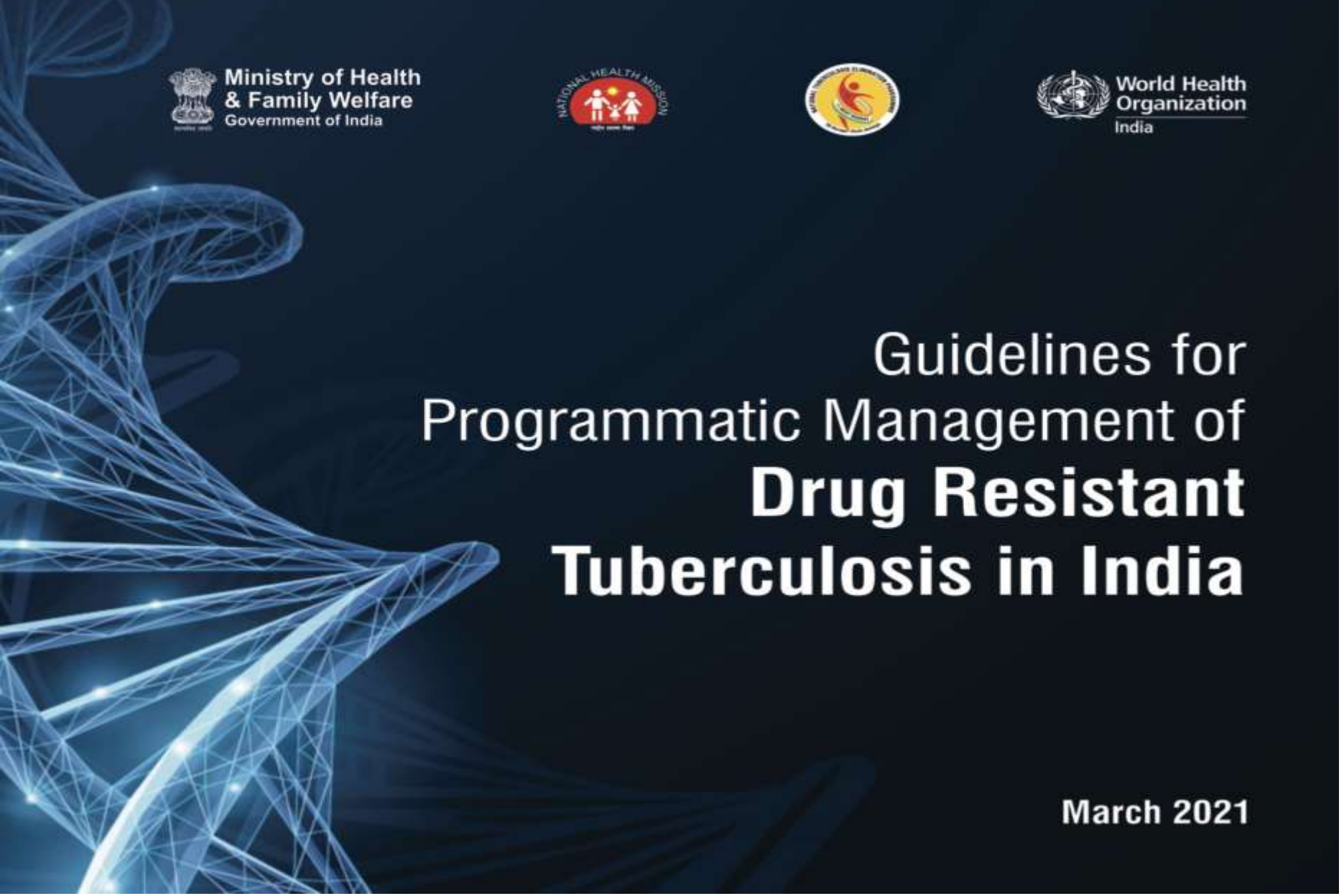


DR AYUSH SAHU
JUNIOR RESIDENT
INTERNAL MEDICINE

Introduction

- Half million new cases of Rifampicin resistant TB occurred in 2019.
- 78% of them were confirmed MDR-TB
- Incidence of MDR/RR-TB cases in India is 124000[9.1/lakh population]
- PMDT services started in 2007 and complete coverage achieved by 2013

Introduction

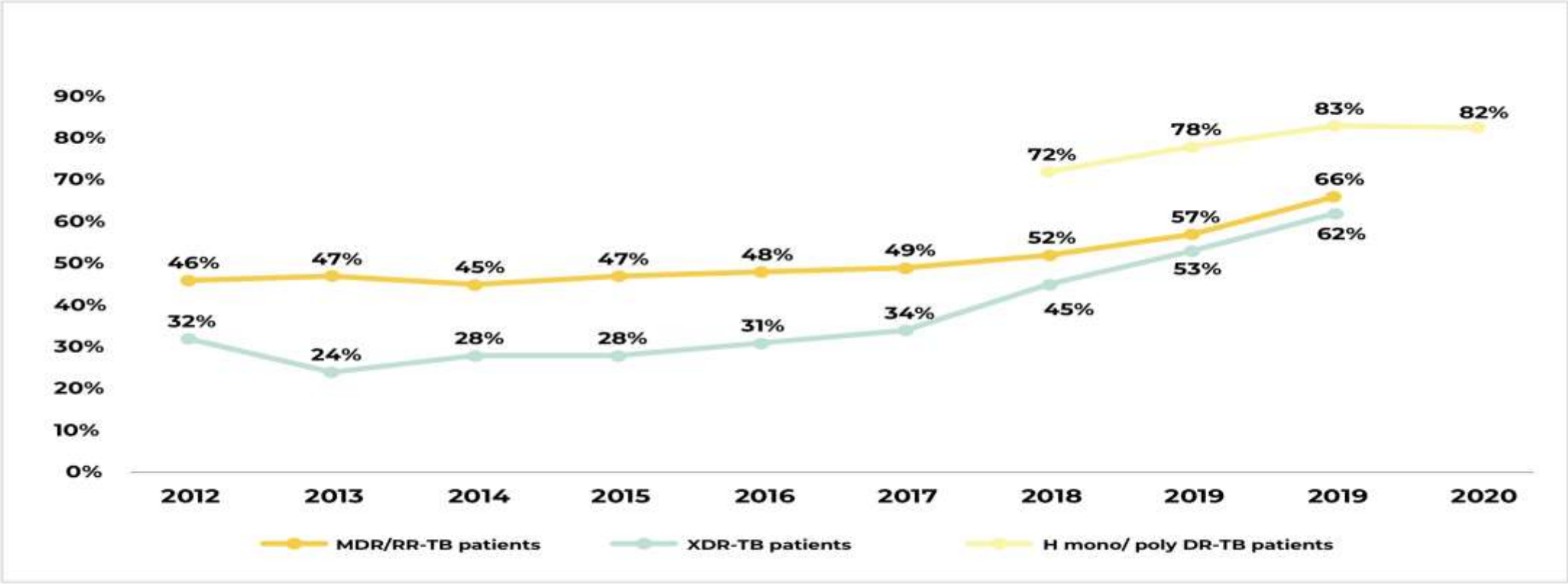
First NDRS conducted in India revealed that

- 28% of TB patients were resistant to any drugs (22% among new and 36.82% among previously treated)
- 6.19% had MDR-TB (2.84% among new and 11.62% among previously treated)
- Isoniazid (H) resistance (16% in all with 11.6% in new and 25% in PT)

INDIA TB REPORT 2023

DR-TB CASES	TOTAL CASES

TREATMENT SUCCESS RATE IN DR TB



DEFINITIONS

1. **INH resistant TB**

   Resistant to INH and Sensitivity to R - confirmed.

2. **Mono-resistant TB (MR TB)**

   Resistant to one first- line anti-TB drug only.

3. **Multidrug-resistant TB (MDR-TB)**

   Resistant to both INH and R , +/- Resistance to other first-line anti-TB drugs

4. **Rifampicin resistant TB (RR-TB)**

   Resistant to R+/- Resistance to other anti-TB drugs

DEFINITIONS

5

Poly-drug resistant TB (PDR-TB)

Resistant to more than one first-line anti-TB drug, other than both H and R.

6

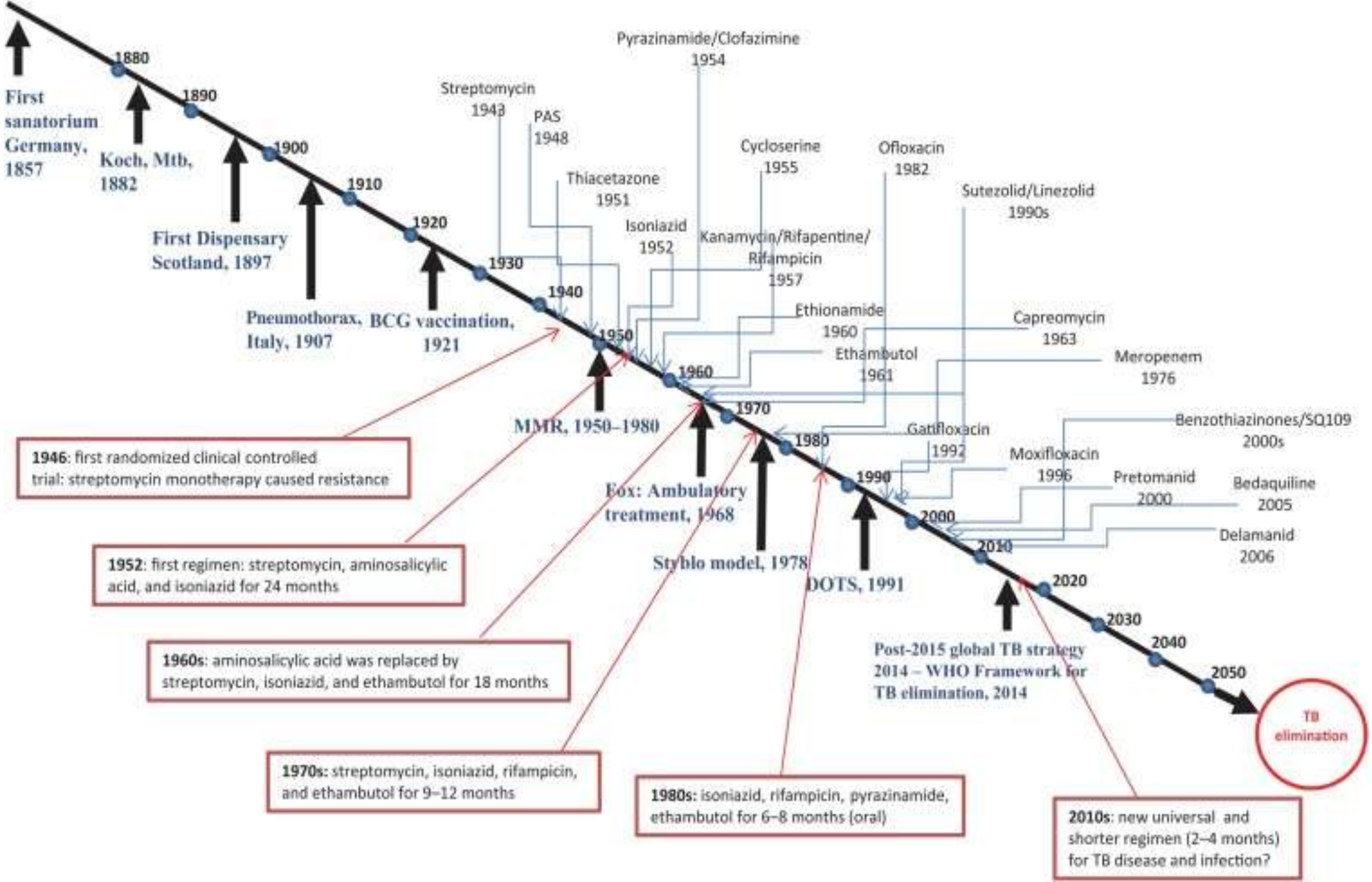
Pre-extensively drug resistant TB (Pre-XDR-TB)

MDR/RR-TB + Resistant to any Fluoroquinolone

7

Extensively drug resistant TB (XDR-TB)

MDR/RR-TB + Resistant to any Fluoroquinolone (levofloxacin or moxifloxacin) + at least one Group A drug (either Bedaquiline or Linezolid [or both])


First sanatorium Germany, 1857
Koch, Mtb, 1882
First Dispensary Scotland, 1897
Pneumothorax, Italy, 1907
BCG vaccination, 1921
MMR, 1950–1980
Fox: Ambulatory treatment, 1968
Styblo model, 1978
DOTS, 1991
Post-2015 global TB strategy 2014 – WHO Framework for TB elimination, 2014
1880
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
2030
2040
2050
Streptomycin 1943
PAS 1948
Thiacetazone 1951
Isoniazid 1952
Pyrazinamide/Clofazimine 1954
Cycloserine 1955
Kanamycin/Rifapentine/ Rifampicin 1957
Ethionamide 1960
Ethambutol 1961
Ofloxacin 1982
Sutezolid/Linezolid 1990s
Capreomycin 1963
Meropenem 1976
Gatifloxacin 1992
Moxifloxacin 1996
Benzothiazinones/SQ109 2000s
Pretomanid 2000
Bedaquiline 2005
Delamanid 2006
1946: first randomized clinical controlled trial: streptomycin monotherapy caused resistance
1952: first regimen: streptomycin, aminosalicylic acid, and isoniazid for 24 months
1960s: aminosalicylic acid was replaced by streptomycin, isoniazid, and ethambutol for 18 months
1970s: streptomycin, isoniazid, rifampicin, and ethambutol for 9–12 months
1980s: isoniazid, rifampicin, pyrazinamide, ethambutol for 6–8 months (oral)
2010s: new universal and shorter regimen (2–4 months) for TB disease and infection?
TB elimination

Evolution of PMDT

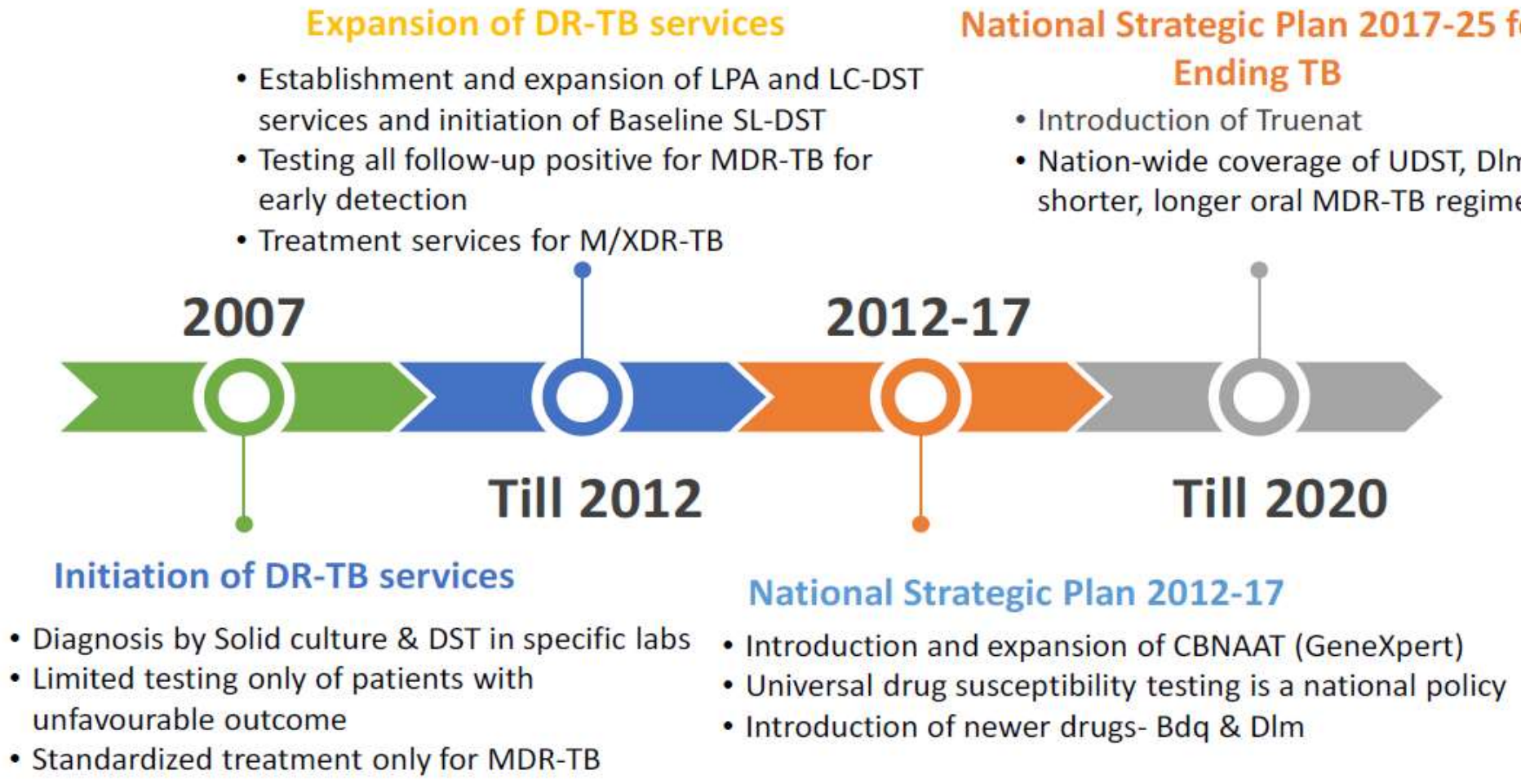


Figure 1.2 Milestones in evolution of PMDT in India

DR TB CASE FINDING

SPECIMEN COLLECTION

Number of Sputum Specimen-

- One spot and one early morning, or 2 spot specimens collected with a gap of at least one hour.

Good quality Sputum specimen-

- 2-5 ml, preferably mucopurulent and not heavily blood stained or contaminated on visual appearance.
- Collect the specimen in a sterile container (50ml screw capped conical tube; after thorough rinsing of the mouth with clean water)
- Triple layer packaging procedure

Extra-pulmonary specimen

- Collected in sterile saline with no other added preservatives (Formalin).
- Transported to the laboratory as soon as it is collected, not exceeding 4 hours.

DR-TB CASE FINDING

DRUG RESISTANCE TESTING [DRT]	DRUG SUSCEPTIBILITY TESTING [DST]
1. Genotypic test	1. Phenotypic test
2. Detects specific genetic mutations associated with drug resistance	2. TB bacilli are grown and subsequently tested for drug susceptibility
3. Respiratory specimen , Non-respiratory specimen & Culture isolates	3. Only on culture isolates

Rapid Molecular Drug Resistance Testing

i. The Xpert MTB /RIF

ii. The Xpert MTB/XDR

iii. Truenaat real-time quantitative micro PCR system

iv. Line Probe Assay [LPA]

RAPID MOLECULAR METHODS

The Xpert MTB/RIF

- **CB-NAAT**
- Detects **MTB specific DNA** sequences and mutations in the RNA polymerase beta (**rpob**) gene – **simultaneously.**
- Unprocessed sputum sample result in **90 minutes**
- Ambient room temperature of **below 30 degrees**
- Designed for **larger volumes of sample**

Truenat

- **NAAT based**
- **Truenat MTB** -*M. tb* bacilli in sputum after DNA extraction- **1 hour.**
- **Truenat MTB -Rif Dx** -used sequentially for RIF resistance detection- **1 hour.**
- Does not need air conditioning, it is portable and battery operated, needs trained technician.
- **Single sample** at one time

The Xpert MDR/XDR

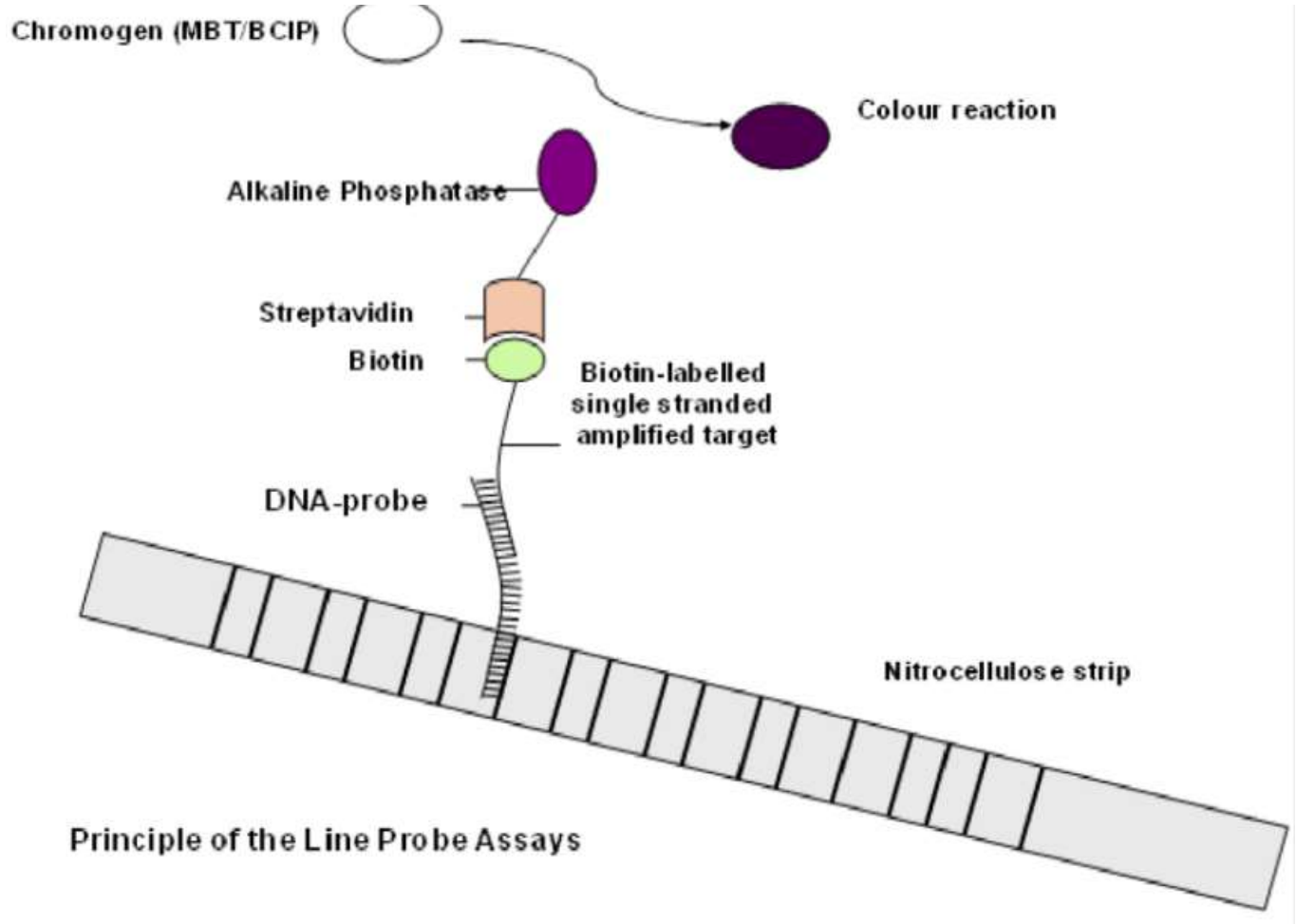
Mutations associated with resistance towards **INH, FQ, SLI and Eto in a single test.**

- Results in **90 min**

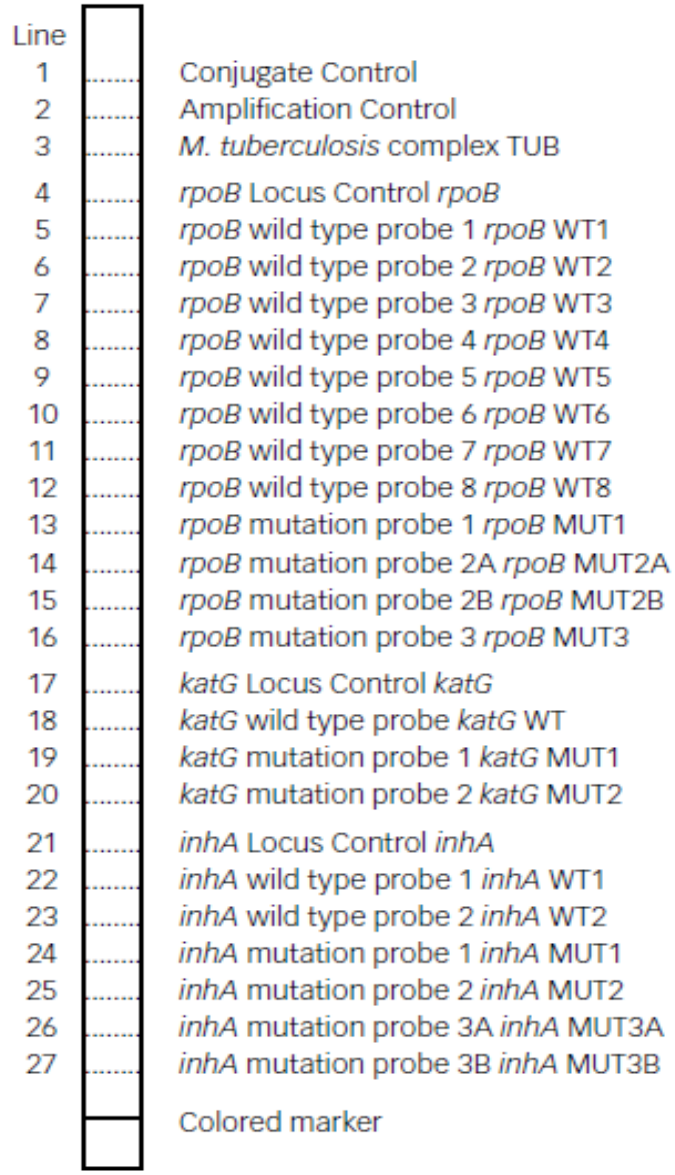
LPA

- **PCR and reverse hybridization methods**
- **FL LPA** - mutations in the ***rpo*B, *Kat*G and *Inh*A gene.**
- **SL LPA** - mutations in **gyrA, gyr B, rrs and eis gene.**

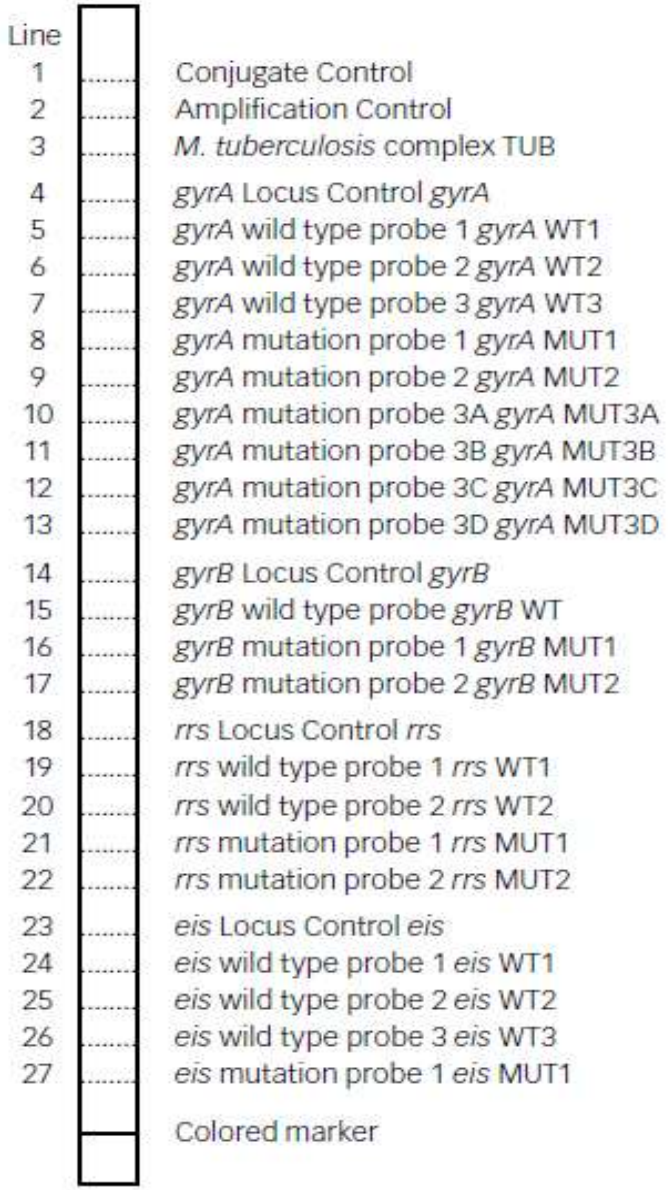
Principle of Line Probe assay



Principle of the Line Probe Assays



Genotype MTBDR plus



Genotype MTBDRsl

Interpretation of Line Probe Assays [LPA]

- Results of LPA are interpreted based on development/absence of Wild Type[WT] and Mutant Type bands [MUT]

LPA FINDINGS	INTERPRETATION
All WT probes developed and none of MUT probes	“Resistance not Detected”
One or more WT probes are not developed and none of the MUT probes developed	“Resistance Inferred”
One or more MUT probes are developed Regardless of WT probe status	“Resistance Detected”

Case Scenario 1

- What is the interpretation ?

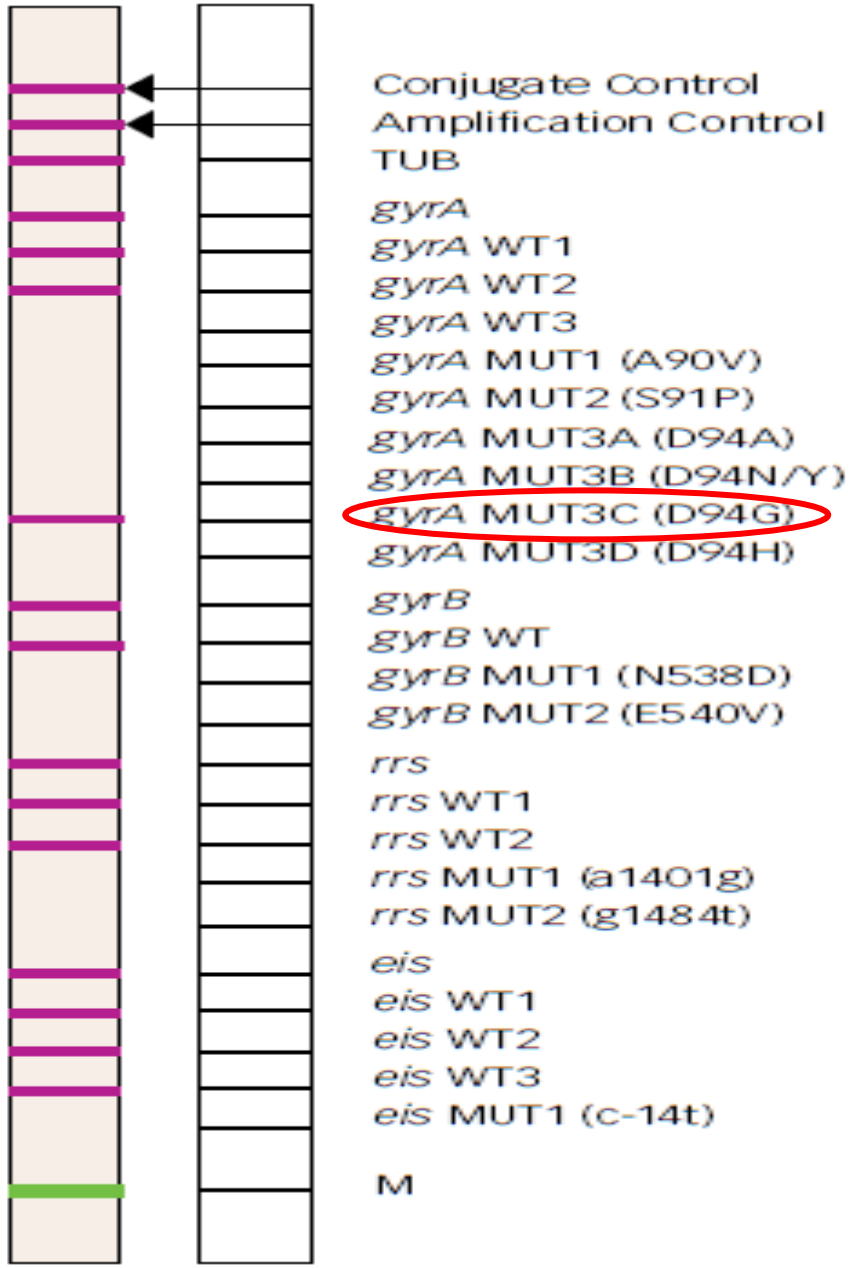
  -All WT probes developed &

  gyrA MUT3C[D94G] developed

- Final Report :

  Levofloxacin-Resistance detected

  Moxifloxacin-Mutations associated with high level increase in MIC for Mx detected



Case Scenario 2

- What is the interpretation

  -gyrA WT1 probe not developed &

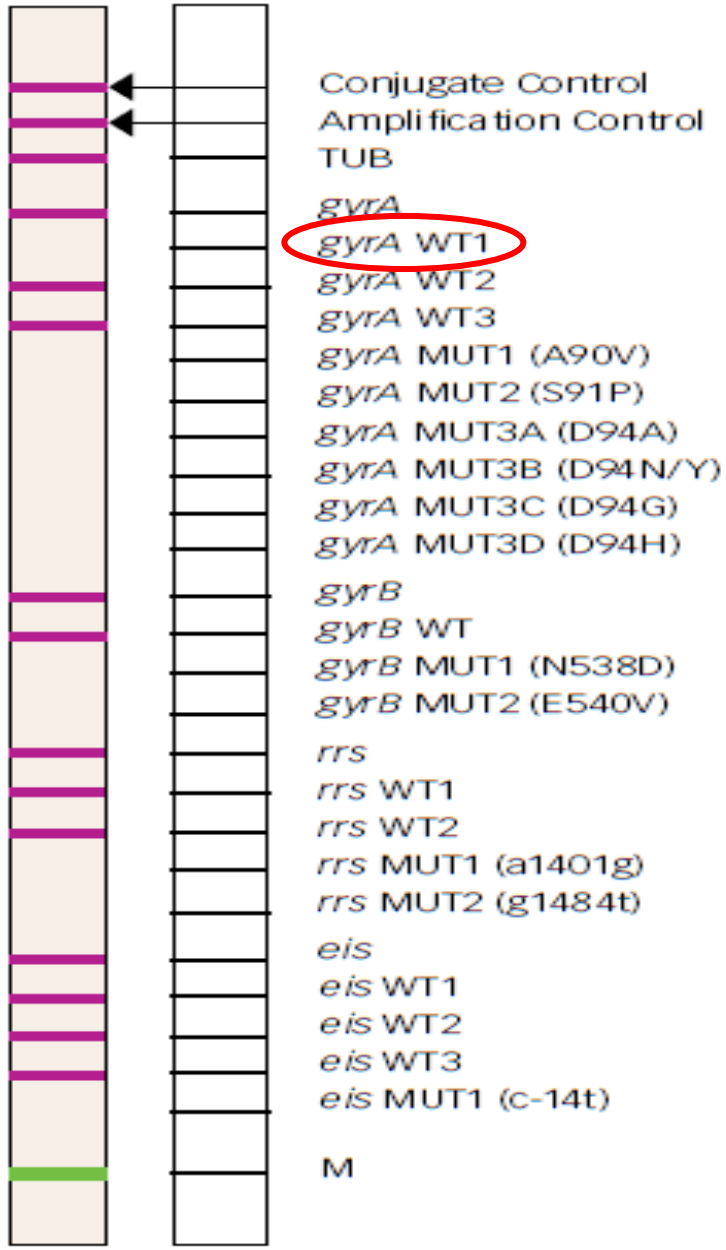
  none of the mutant probes developed

- Final Report:

  -Levofloxacin- Resistance Inferred

  Moxifloxacin-Mutations associated with atleast

  low level increase in MIC detected for Mx



Interpretation of Line Probe Assays [LPA]

Drug	Gene	Test results	Clinical Interpretation
Rifampicin	rpoB	Resistance inferred or detected	R –not effective
Isoniazid	katG	Resistance to high level H inferred or detected	H is unlikely to be effective even at high dose
	InhA	Resistance to low level H inferred or detected	H at high dose is likely effective Eto/Pto are not effective
Second line injectable drugs	rrs	Resistance inferred or detected	Am,Km and Cm- not effective
	eis	Resistance inferred or detected	Am,Cm-likely effective Km-not effective

Interpretation of Line Probe Assays [LPA]

Drug	Gene	Test results	Clinical interpretation
Fluoroquinolones	gyrA	Resistance to Lfx and low level Mfx inferred/detected	Lfx –not effective Mfx could be used at higher dose
		Resistance Lfx and high level Mfx detected (MUT 3B,MUT 3C,MUT 3D)	Lfx/Mfx- not effective
	gyrB	Resistance to Lfx and low level Mfx inferred/detected	Lfx- not effective Mfx- could be at higher dose

LPA

DRUG	SENSITIVITY	SPECIFICITY
Rifampicin	96.7%	98.8%
Isoniazid	90.2%	99.2%
Fluroquinolone	86.2%	98.6%
Second Line Injectables	87.0%	99.5%

LPA

Limitations

- Performed only on positive cultures or smear positive clinical specimens
- Some mutations that confer resistance are outside the regions covered by these tests and therefore resistance cannot be completely excluded
- Has high Biosafety requirements [Level 2 or 3]
- Requires well trained staff in professional laboratory
- Not fully automated – so Error in interpretation possible

GROWTH BASED DST

BACTEC MGIT 960 – LIQUID CULTURE	LOWENSTEIN JENSEN – SOLID CULTURE
AUTOMATED LIQUID CULTURE SYSTEM PREFERRED METHOD FOR DST - Higher rate of MTB detection - Shorter turnaround time - Uses oxygen quencher for fluorescence detection as growth index - Can be used for both pulmonary and EP specimens - Used to monitor response to treatment and follow up of patients on drug resistant TB treatment.	LONGER TURNAROUND TIME Not preferred anymore.

The Xpert MTB/XDR

- Introduced as an follow-on test to Xpert MTB/RIF
- Detects mutations associated with resistance to INH,FQ, SLI and Ethionamide
- Uses a semi quantitative nested PCR followed by high resolution melt technology
- Results are obtained in less than 90 minutes
- Especially important for ruling out FQ resistance , before starting shorter Oral Bedaquiline-containing MDR/RR-TB regimen

The Xpert MTB/XDR

Drug Resistance	Target Region
Isoniazid	inhA promoter ,katG ,**fabG1 & oxyR-ahpC intergenic region**
Ethionamide	InhA promotor region
Fluoroquinolones	gyrA and gyrB
Amikacin, Kanamycin Capreomycin	rrs , eis promotor

ARTICLES | VOLUME 22, ISSUE 2, P242-249, FEBRUARY 01, 2022

Detection of isoniazid, fluoroquinolone, ethionamide, amikacin, kanamycin, and capreomycin resistance by the Xpert MTB/XDR assay: a cross-sectional multicentre diagnostic accuracy study

Adam Penn-Nicholson, PhD * • Sophia B Georghiou, PhD * • Nelly Ciobanu, MD • Mubin Kazi, PhD • Manpreet Bhalla, MD • Anura David, MSc • et al. Show all authors • Show footnotes

Published: October 07, 2021 • DOI: https://doi.org/10.1016/S1473-3099(21)00452-7 • Check for updates

	Number*	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Isoniazid resistance							
MTBDR*plus*	575	461	0	36	78	93% (90 to 95)	100% (94 to 100)
Xpert MTB/XDR	575	469	0	28	78	94% (92 to 96)	100% (94 to 100)
Difference	575	..	..	..	..	1·6% (0·2 to 3·4)	0 (−4·7 to 4·7)
Fluoroquinolone resistance							
MTBDR*sl*	532	222	2	13	295	95% (91 to 97)	99% (97 to 100)
Xpert MTB/XDR	532	222	2	13	295	95% (91 to 97)	99% (97 to 100)
Difference	532	..	..	..	..	0 (−1·6 to 1·6)	0 (−1·3 to 1·3)
Amikacin resistance							
MTBDR*sl*	511	60	2	22	427	73% (62 to 82)	100% (98 to 100)
Xpert MTB/XDR	511	60	2	22	427	73% (62 to 82)	100% (98 to 100)
Difference	511	..	..	..	..	0 (−4·5 to 4·5)	0 (−0·9 to 0·9)
Kanamycin resistance							
MTBDR*sl*	515	181	5	29	300	86% (81 to 90)	98% (96 to 99)
Xpert MTB/XDR	515	181	5	29	300	86% (81 to 90)	98% (96 to 99)
Difference	515	..	..	..	..	0 (−1·8 to 1·8)	0 (−1·2 to 1·2)
Capreomycin resistance							
MTBDR*sl*	513	53	1	34	425	61% (50 to 71)	100% (99 to 100)
Xpert MTB/XDR	513	53	1	34	425	61% (50 to 71)	100% (99 to 100)
Difference	513	..	..	..	..	0 (−4·2 to 4·2)	0 (−0·9 to 0·9)

TREATMENT

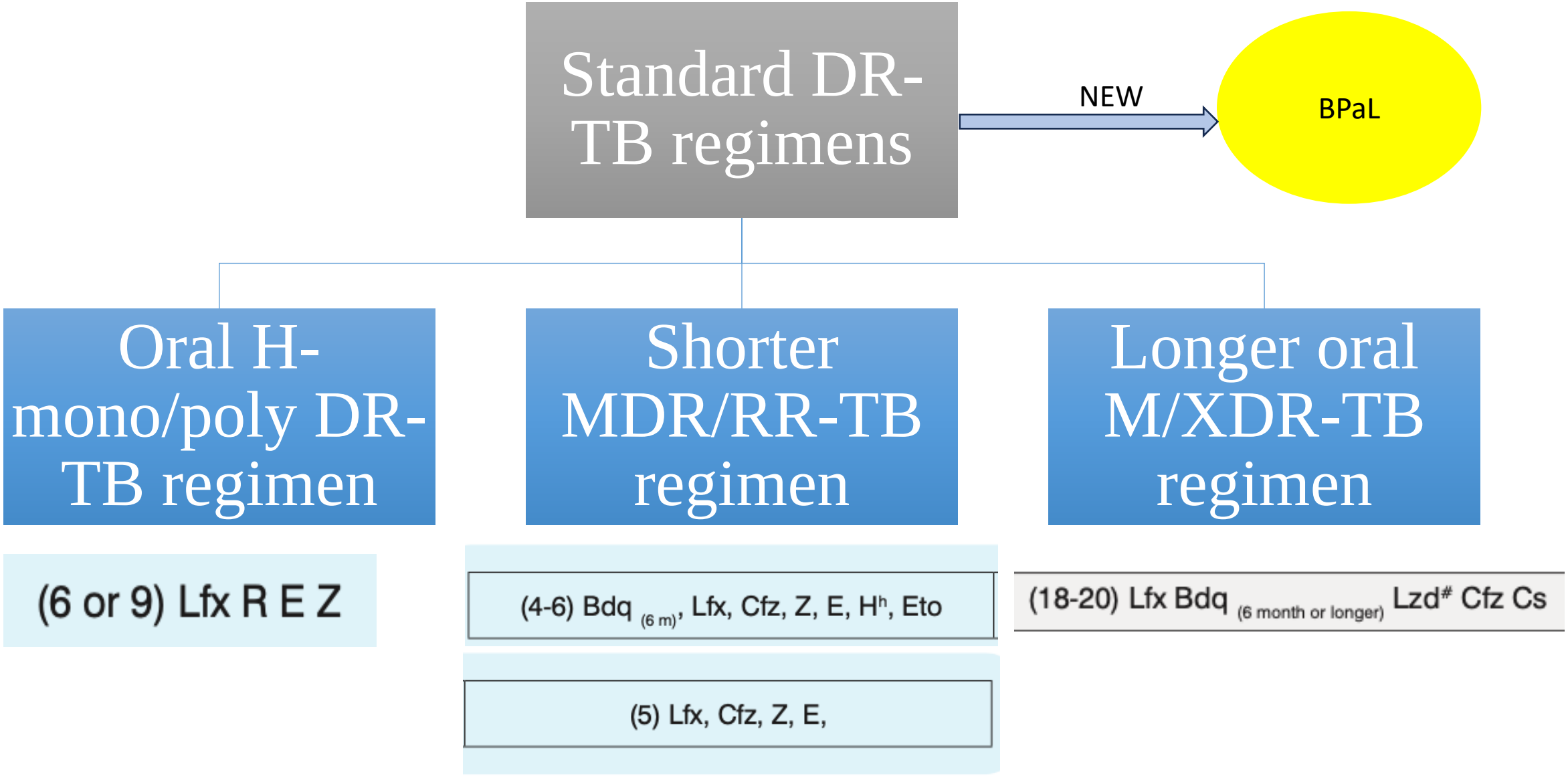
GOALS OF TREATMENT

- Render the patient non-infectious
- Break the chain of transmission
- Decrease the pool of infection
- Decrease TB deaths and related comorbidity by ensuring relapse-free cure
- Minimize & prevent the development and amplification of drug resistance

OVERVIEW

GROUPS & STEPS	MEDICINE	ABBREVIATION
Group A **Include all three medicines**	Levofloxacin or	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine or	Cs
	Terizidone	Trd
Group C **Add to complete the regimen and when medicines from Group A and B cannot be used**	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or	Ipm-Cln
	Meropenem	Mpm
	Amikacin	Am
	(OR Streptomycin)	(S)
	Ethionamide or	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS

STANDARD DR-TB REGIMEN UNDER PMDT



OVERVIEW

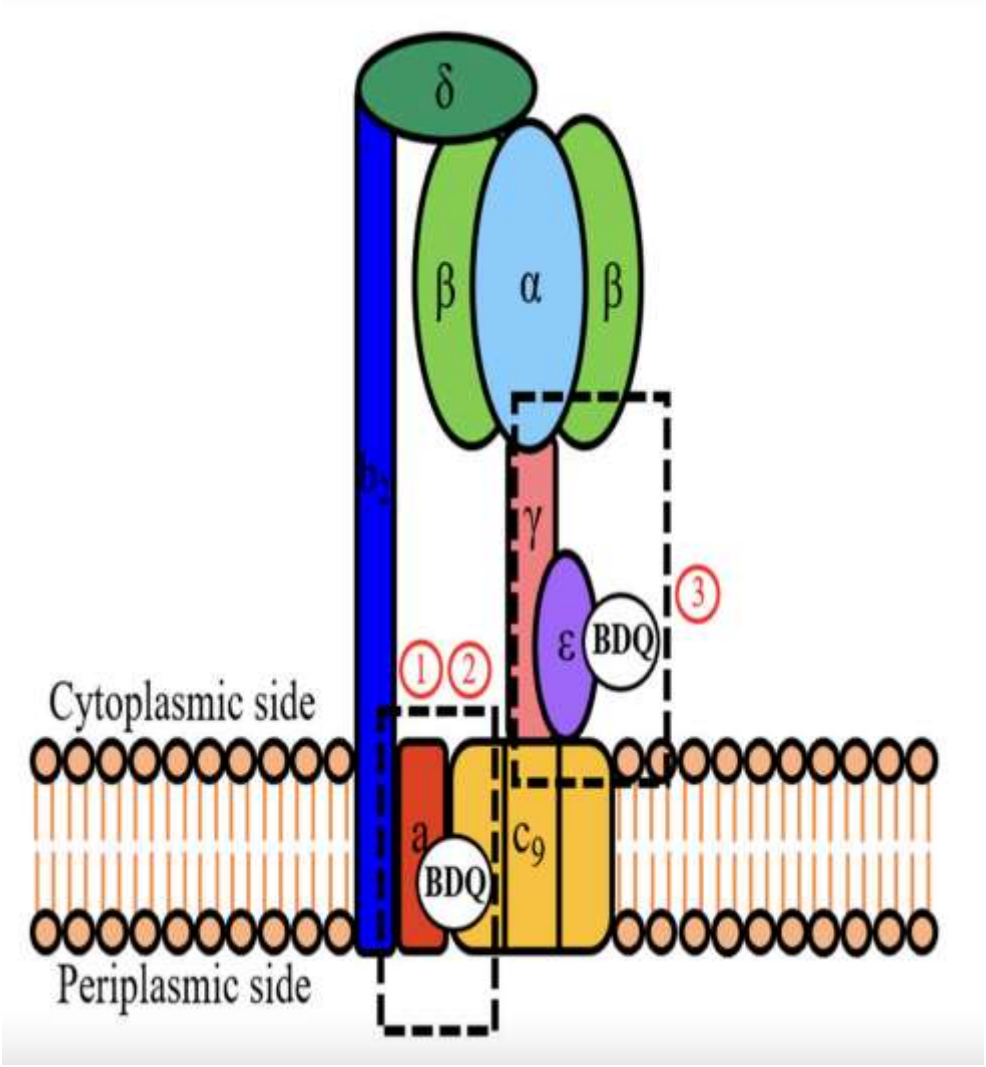
BEDAQUILINE (Bdq)

Targets mycobacterial ATP synthase.

High volume of distribution, extensive tissue distribution, highly bound to plasma proteins, hepatically metabolized.

Extended half-life, present in the plasma up to 5.5 months post stopping Bdq.

Improves the time to culture conversion in MDR-TB patients.



OVERVIEW

DELAMANID (Dlm)

Class of nitro-dihydro-imidazo-oxazoles

Bactericidal drug

36 hours of half-life

Two different mechanism of action

Blocks the synthesis of mycolic acids

Drugs release Nitric Oxide when metabolized

Dlm - approved for use and available under NTEP for >/= 6 years

Use of Dlm - 3-6 years approved by WHO, the regulatory approval in India is awaited.

OVERVIEW

PRETOMANID (Pa)

Class of Nitroimidazoles

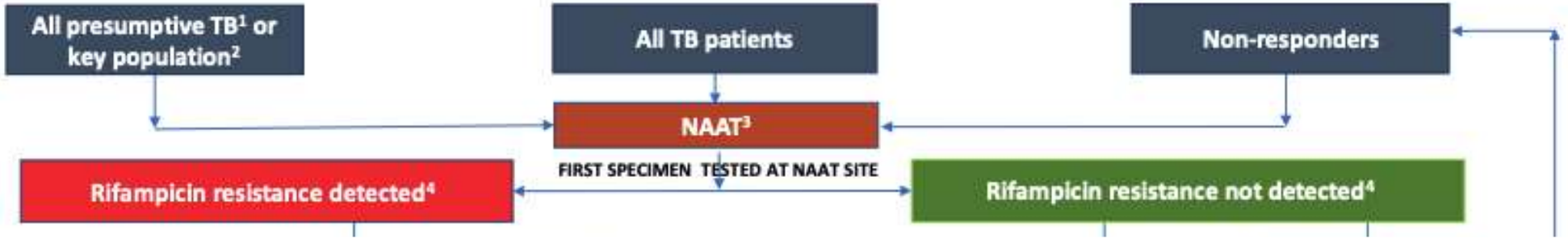
First identified in 2000

Orphan drug

Activity against static M.tuberculosis isolates that survive under anaerobic conditions.

FDA – approval of Pa only with Bdq and Lzd for treatment of a limited and specific population of DR-TB patients.

Diagnostic and treatment algorithm



Key population:

PLHIV

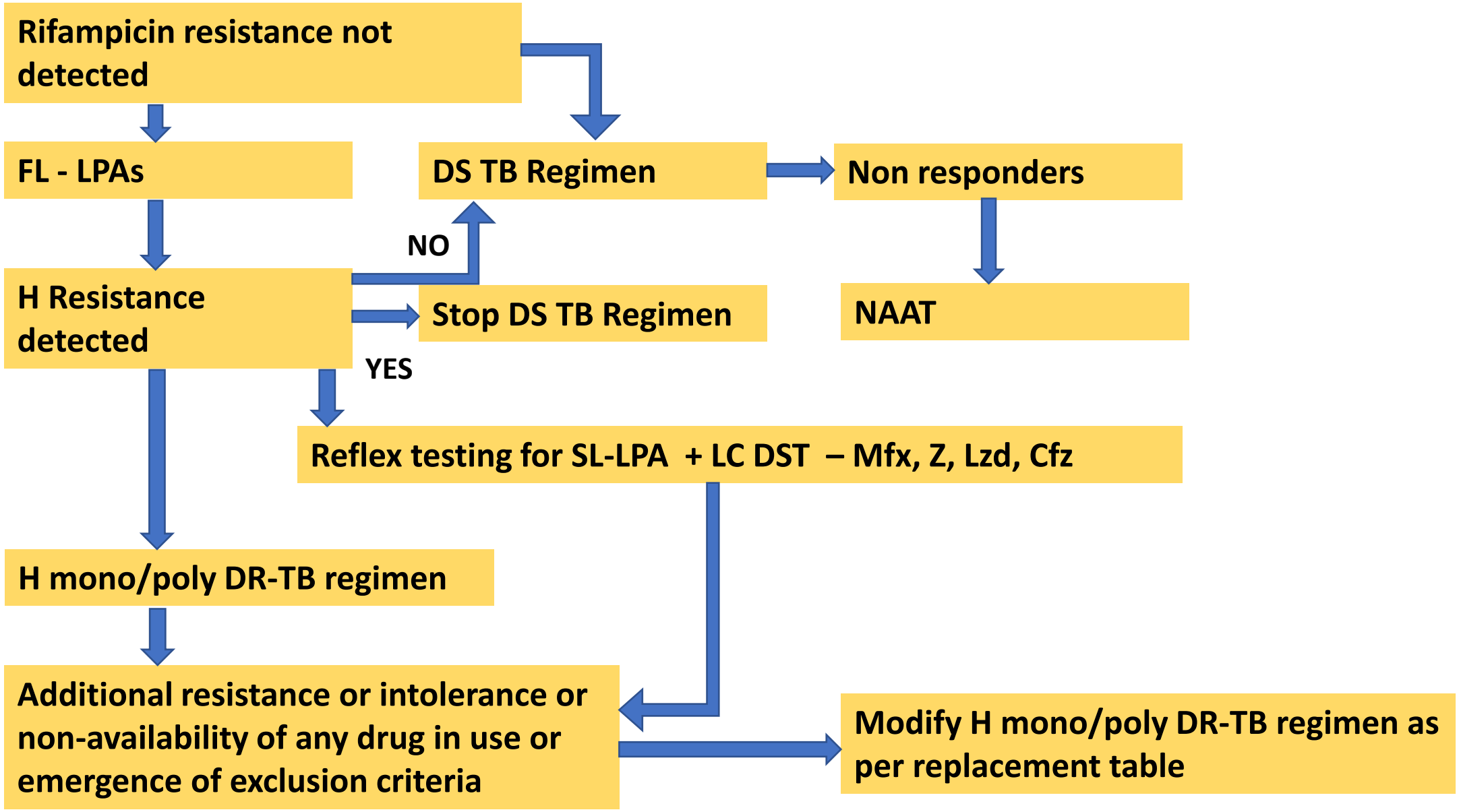
Children

EP TB

Smear negative/ NA with CXR s/o TB

Contacts of DR-TB

H MONO/POLY DR-TB REGIMEN



H MONO/POLY DR-TB REGIMEN

PRE-TREATMENT EVALUATION

thorough clinical evaluation by a doctor with

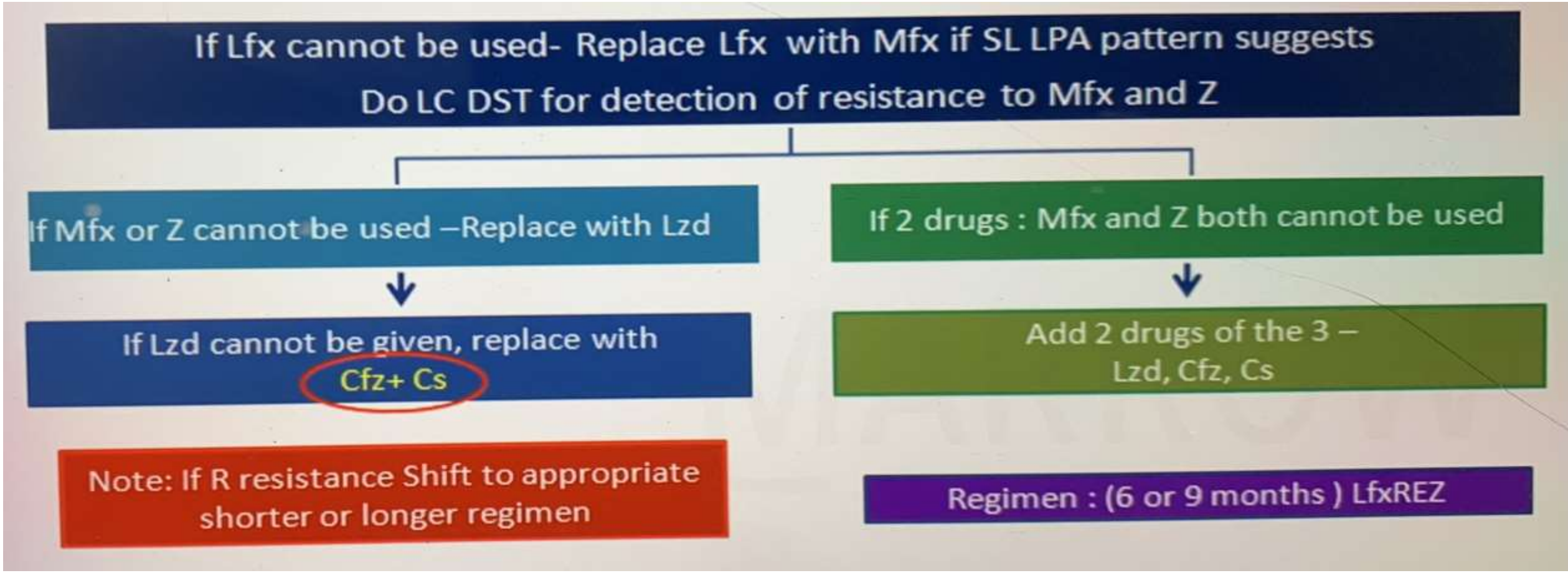
- History and physical examination , Height/weight
- Random blood sugar (RBS)
- Chest X-ray ,HIV testing

REGIMEN, DURATION AND DOSAGE

(6 or 9) Lfx R E Z

6 or 9 months
No separate IP/ CP

Replacement sequence



H MONO/POLY DR-TB REGIMEN

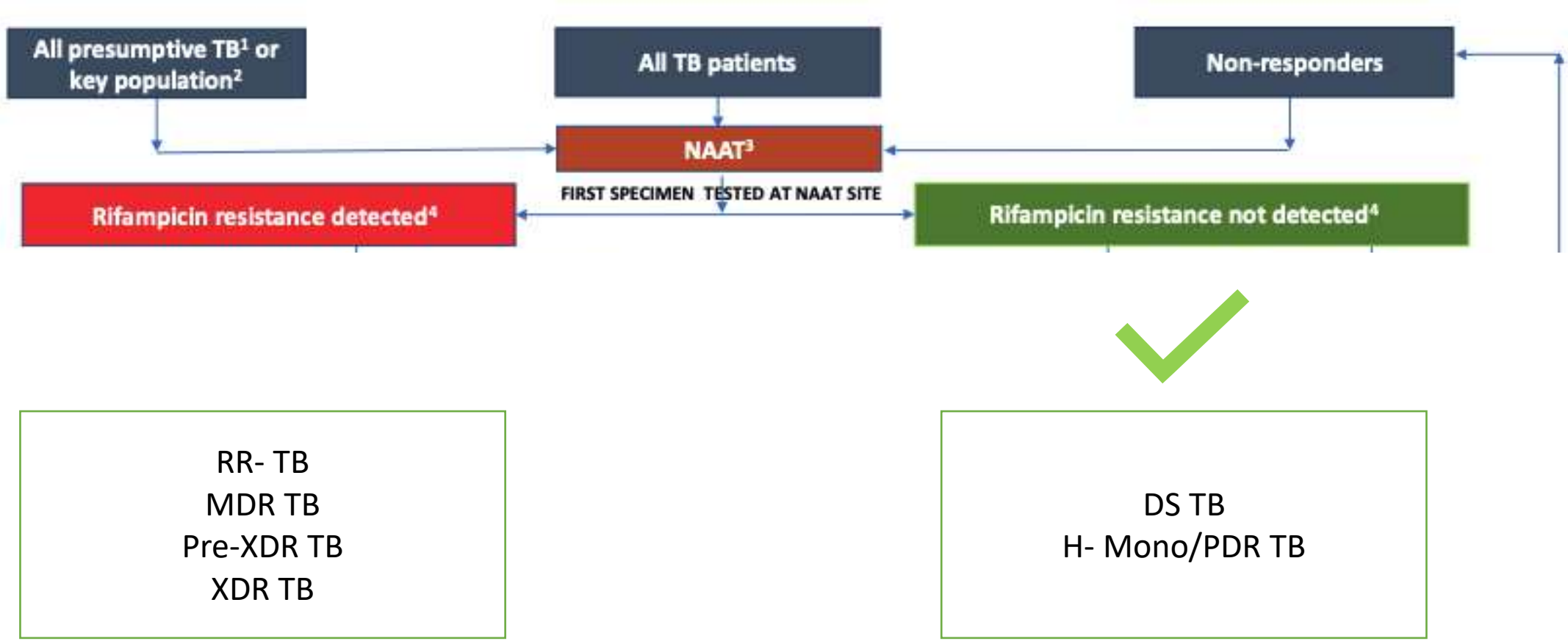
TREATMENT EXTENSION - Extended directly to 9 months in

- Patients with extensive disease
- Uncontrolled comorbidity
- Extra- pulmonary TB
- If smear at the end of month 4 is found positive and
- When regimen is modified

No monthly extensions in this regimen

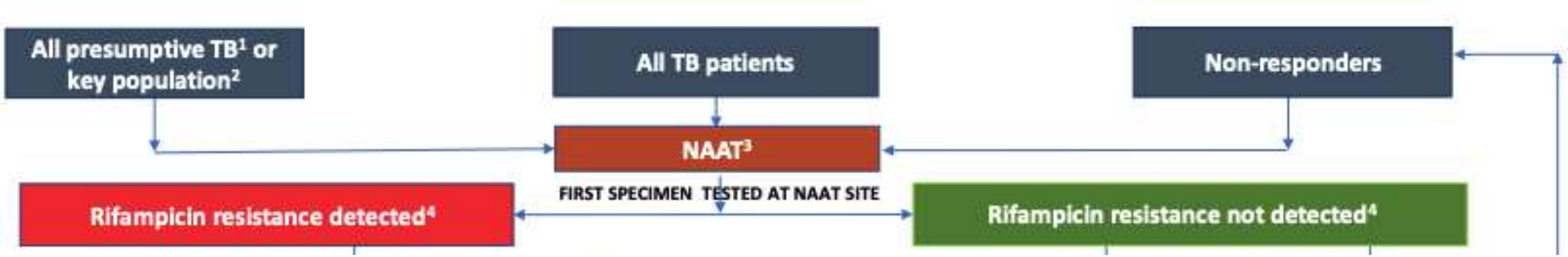
Sputum smear positive at the end of month 5 or later - Treatment outcome declared as **'treatment failed'**

Patient will be re-evaluated as per the diagnostic algorithm as a non-responder.



AIM :

1) Which regimen – Shorter ? Longer ?
2) How to modify the regimen if needed? (replacements)



RR- TB
MDR TB
Pre-XDR TB
XDR TB

→ Not candidates for shorter Bdq regimen

AIM :

1) Which regimen – Shorter ? Longer ?
2) How to modify the regimen if needed? (replacements)

Inclusion Criteria (shorter regimen)

1. DST Based
- Rifampicin resistance
- MDR/RR-TB with H resistance based on either InhA mutation or KatG mutation (not both)
- MDR/RR-TB with FQ resistance not detected

2. Other Criteria
- Children, aged 5 years onwards and weighing at least 15 kg
- No history of exposure to previous treatment with second-lin x, Eto or Cfz) for more than 1 month (unless susceptibility to these med
- No extensive TB disease or severe EP TB
- Women who are not pregnant or lactating

(4-6) Bdq (6 m) Lfx, Cfz, Z, E, H^h, Eto

(5) Lfx, Cfz, Z, E,

Extensive disease :
B/L cavitary disease or extensive parenchymal damage on chest radiogaphy

Severe EPTB –
Miliary TB/ TBM/ CNS TB

Exclusion Criteria

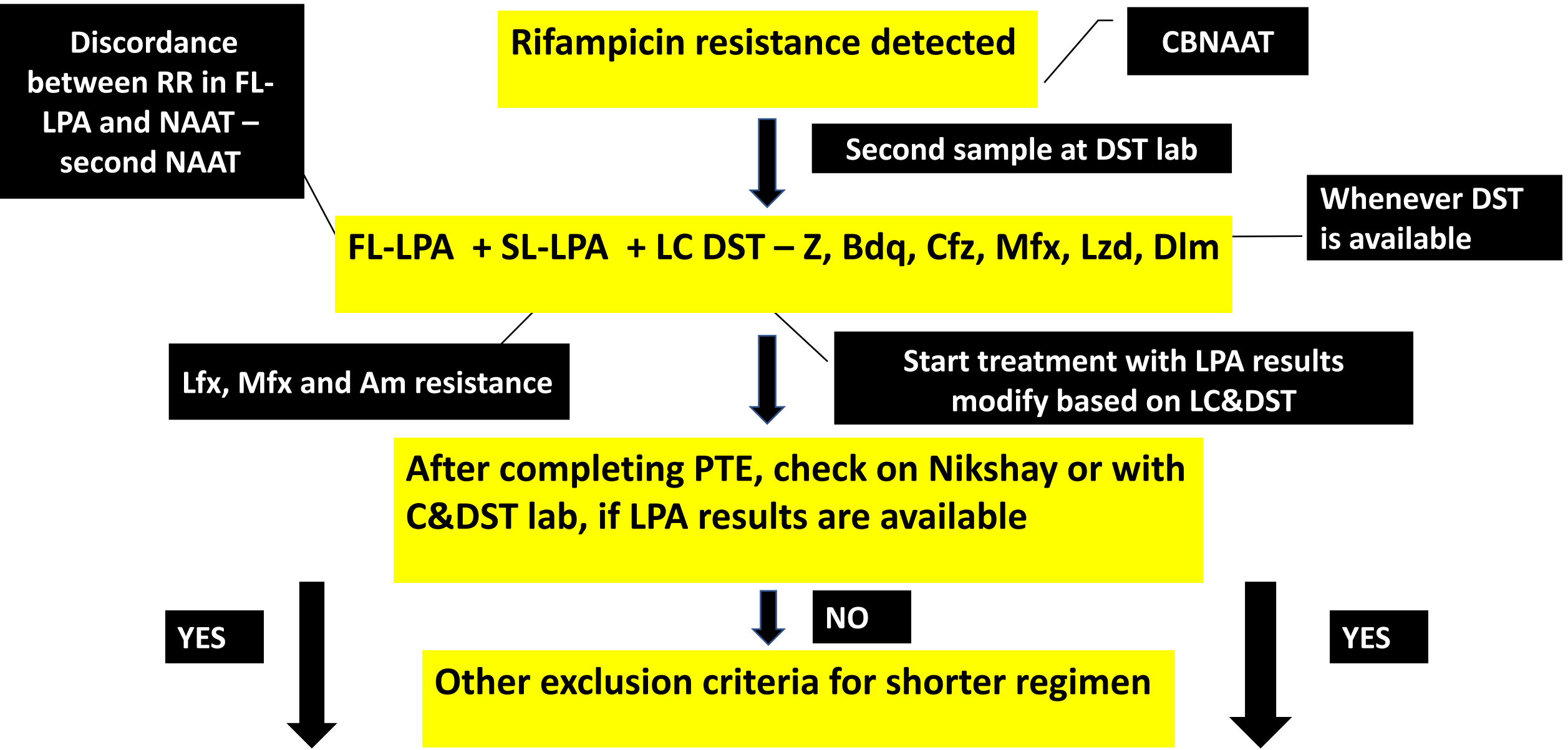
1. DST Based

- MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation
- MDR/RR-TB patients with FQ resistance detected.

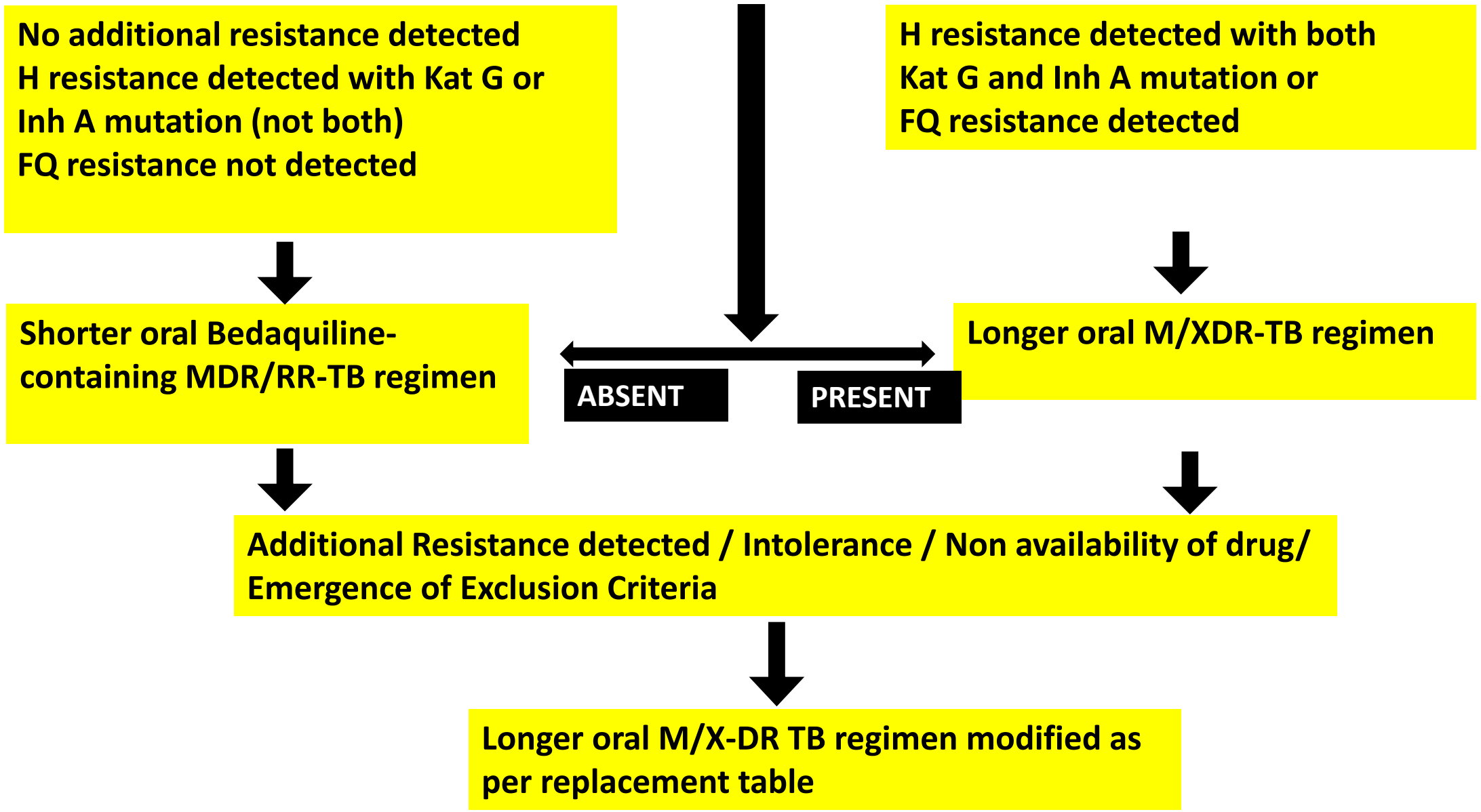
2. Other Criteria

- History of exposure for > 1 month to Bdq, Lfx, Eto or Cfz, if result for DST (Bdq, FQ, Inh A mutation, Cfz & Z) is not available;
- Intolerance to any drug or risk of toxicity (eg: drug drug interactions)
- Extensive TB disease
- Severe EP-TB disease
- Pregnant and lactating women (with conditional exceptions)
- Children below 5 years

SHORTER MDR / RR-TB REGIMEN



SHORTER MDR / RR-TB REGIMEN



PRE-TREATMENT EVALUATION

Clinical evaluation	Laboratory based evaluation
History and physical examination	Random blood sugar (RBS)
Height	HIV testing following counselling
Weight	Complete blood count (Hb, TLC, DLC, platelet count)
Psychiatric evaluation if required	Liver function tests (including serum proteins)
	TSH levels
	Urine examination – routine and microscopic
	Serum electrolytes (Na, K, Mg, Ca)
	Urine pregnancy test (in women of reproductive age group)
	Chest X-ray
	ECG

SHORTER MDR / RR-TB REGIMEN

WHERE IS THE EVIDENCE FROM

Based on the programmatic data from South Africa - reviewed by WHO

Shorter regimen - Injectable agent was replaced by Bdq, in combination with Lfx (or Mfx), Cfz, Hh, E, Z and Eto.

Preliminary analysis –

13% higher treatment success rates among the shorter oral Bedaquiline-containing MDR/ RR-TB regimen group as compared to the Shorter injectable containing regimen and

Similar treatment success rates compared to Longer oral M/XDR-TB regimen.

SHORTER MDR / RR-TB REGIMEN

REGIMEN AND DURATION

(4-6) Bdq $_{(6\ m)}$, Lfx, Cfz, Z, E, H^{h}, Eto	(5) Lfx, Cfz, Z, E,

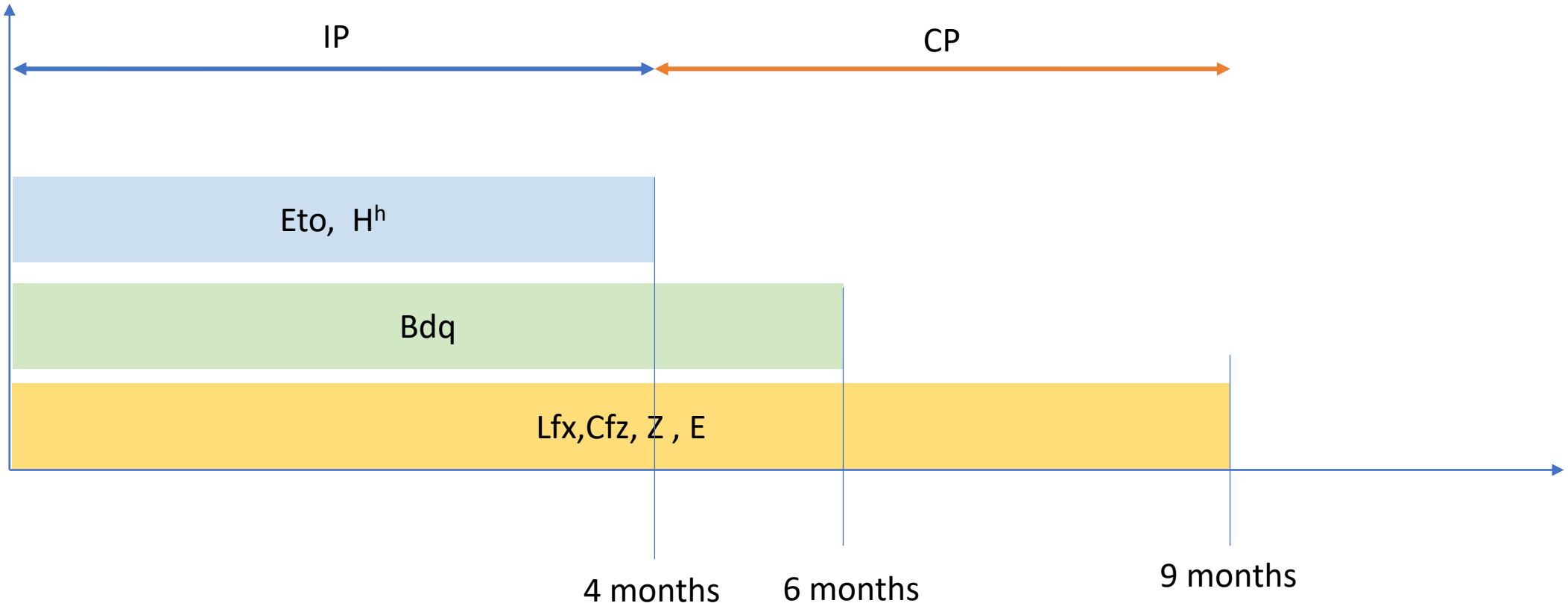
Initial phase - 4 months, may be extended up to 6 months

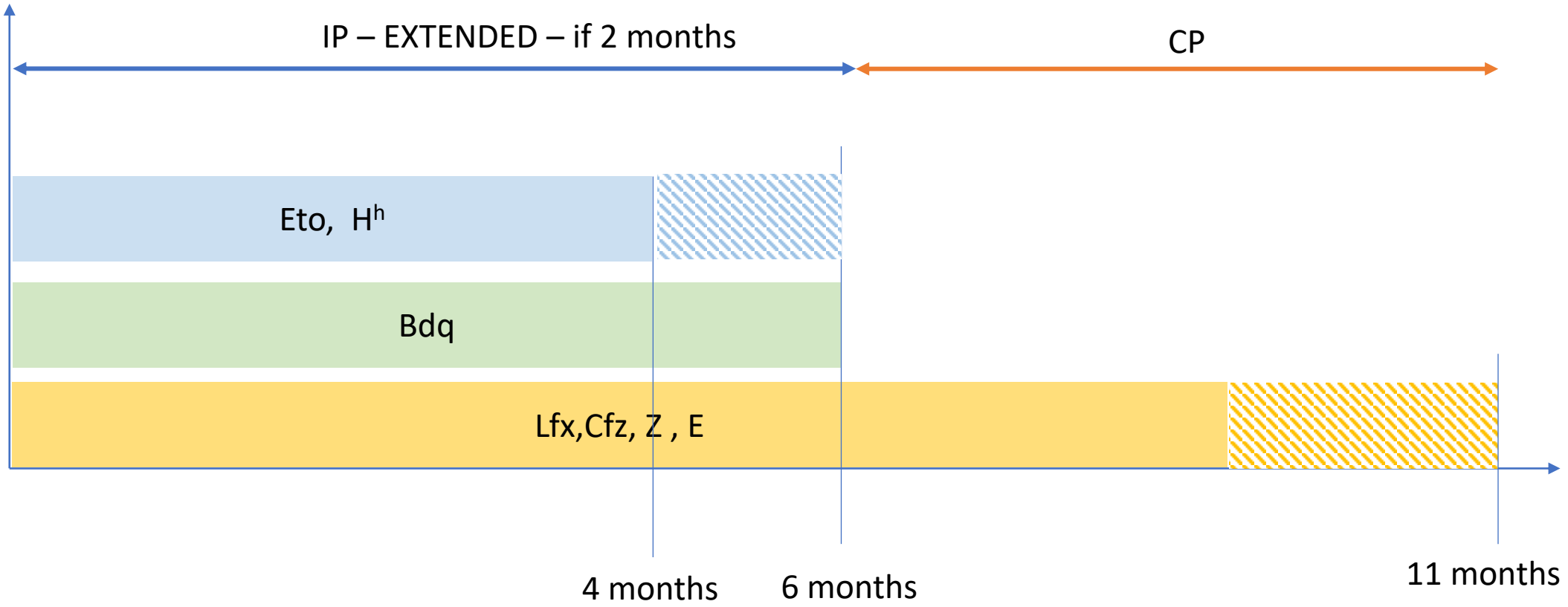
Continuation - 5 months

Total duration - 9–11 months

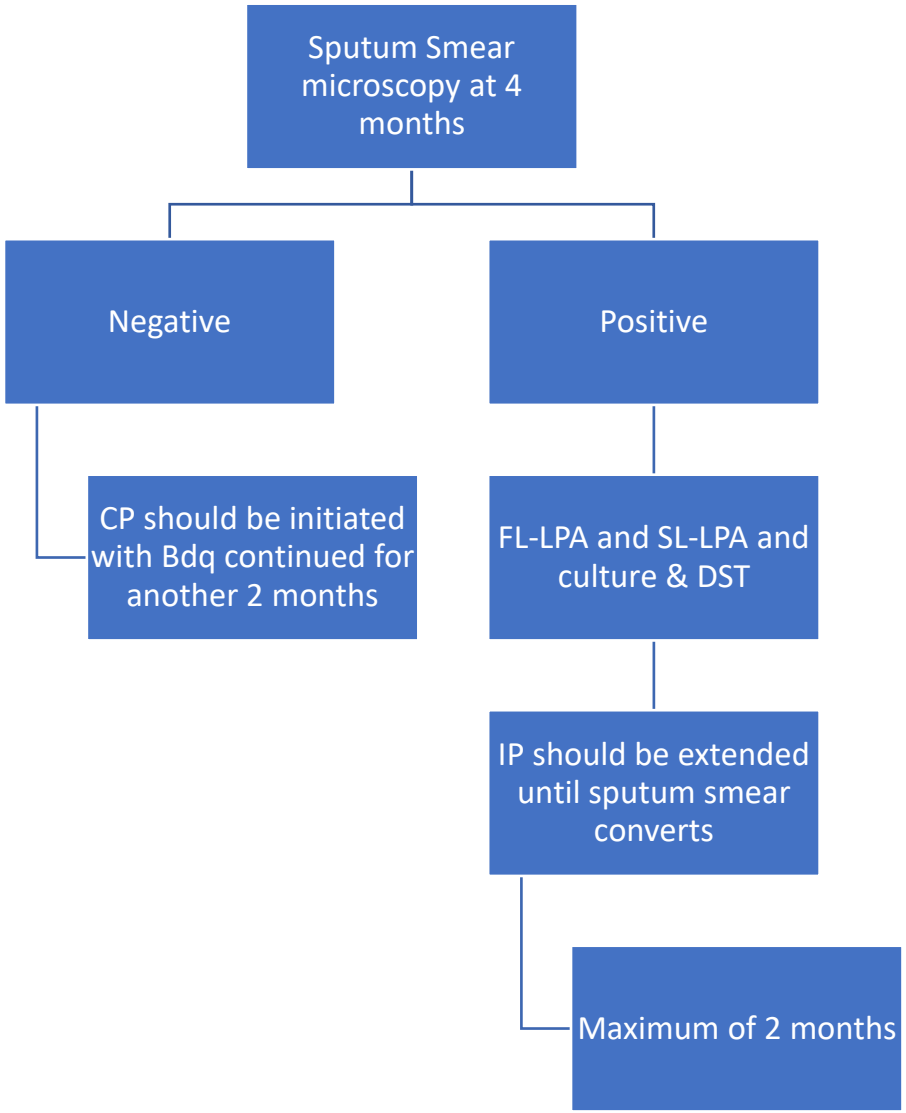
Bdq is used for a duration of 6 months

Composition/ Duration of the IP or CP cannot be changed


IP
CP
Eto, H^h
Bdq
Lfx,Cfz, Z , E
4 months
6 months
9 months


IP – EXTENDED – if 2 months
CP
Eto, H^h
Bdq
Lfx,Cfz, Z , E
4 months
6 months
11 months

Treatment Extension



If found to be smear/culture positive at the end of 6 months or later, the patient will be declared as **'treatment failed'**

- Needs evaluation for longer oral M/XDR-TB regimen

SHORTER MDR / RR-TB REGIMEN

CONSIDERATIONS FOR Bdq

Inclusion criteria

- Age > 5 years , and weight at least 15 kg, in consultation with pediatrician.
- Controlled stable arrhythmia - after cardiac consultation.
- Pregnant & lactating women

Exclusion criteria

- Currently having uncontrolled cardiac arrhythmia that requires medication.
- QTcF > 500 at baseline & normal electrolytes,

ECG to be repeated after 6 hours - if both ECGs show Q
challenged with cardiotoxic drugs; and

- History of additional risk factors for Torsade de Point
  family history of long QT syndrome.

Hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to treatment initiation

Drug Dosage- Shorter Bdq Regimen

Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
High dose H (H_h) (15 to 20mg/kg)	300 mg	600 mg	900 mg	900 mg
Ethambutol(E)	400 mg	800 mg	1200 mg	1600 mg
Pyrazinamide(Z)	750 mg	1250 mg	1750 mg	2000 mg
Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
Ethionamide (Eto)	375 mg	500 mg	750 mg	1000 mg
Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

- If weight increases or decreases by 5 kg or more & crosses the current weight band, then **weight band must be changed** at the time of issuing **next month** box.

- **Don't consume milk containing products at the same time**, as the calcium in these can decrease the absorption of FQs.

- **Large fatty meals should be avoided**, as these can impair absorption of some of the other anti-TB drugs (Cs, H etc.).

FOLLOW UP

Regimen Class	Shorter oral Bedaquiline-containing MDR/RR-TB regimen
Clinical + Wt.	• Monthly in IP, Quarterly in CP
Smear Microscopy	• Monthly from 3rd month onwards
Culture	• At the end of month 3, end of month 6 and/or end of treatment
DST	• FL & SL LPA and LC&DST if any- 1. culture +ve (end of month 3 or later and end of treatment) or 2. smear +ve at end of IP, end of extended IP and end of treatment
TSH & LFT	• At end of IP, then as and when clinically indicated
CXR	• At end of IP, then as and when clinically indicated, end of treatment
ECG$^{\$}$	• At 2 weeks, then monthly in first 6 months, then as and when clinically indicated

Extend IP if previous smear + (max 6 months)

Long-term follow-up will be done with 6 monthly cultures **among symptomatic patients** till two years after completion of any DR-TB regimen i.e. months 6, 12, 18 and 24 post treatment.

SPECIAL SITUATION

RENAL IMPAIREMENT

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving hemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Ethionamide	No adjustment necessary
Bedaquiline	No dosage adjustments required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Clofazimine	No adjustment necessary

SHORTER MDR / RR-TB REGIMEN

Hepatic Impairment

- Hepatotoxic drugs - H, Z, Eto and Bdq. Rarely - FQ.

- The potential for hepatotoxicity – more in

elderly, alcoholics, malnourished and in patients with pre-existing liver disease.

- Other etiologies should be excluded.

In patients with pre-existing liver disease with persistently abnormal liver function test, a shorter oral MDR/RR-TB regimen will be avoided due to presence of H(h), Eto and Z.

SHORTER MDR / RR-TB REGIMEN

People Living With HIV

- The shorter or longer oral MDR-TB regimen can be used
- Toxicities or drug-drug interactions between anti-TB and ART medicines

Efavirenz and Bdq,

Ritonavir and Bdq - increase the risk of Bdq related adverse events – avoid combined use / use with caution.

- Patients co-infected with HIV and TB - start on ART as soon as possible after initiating TB treatment, irrespective of CD4 cell counts.

(Generally, within the first two weeks of initiating DR-TB treatment)

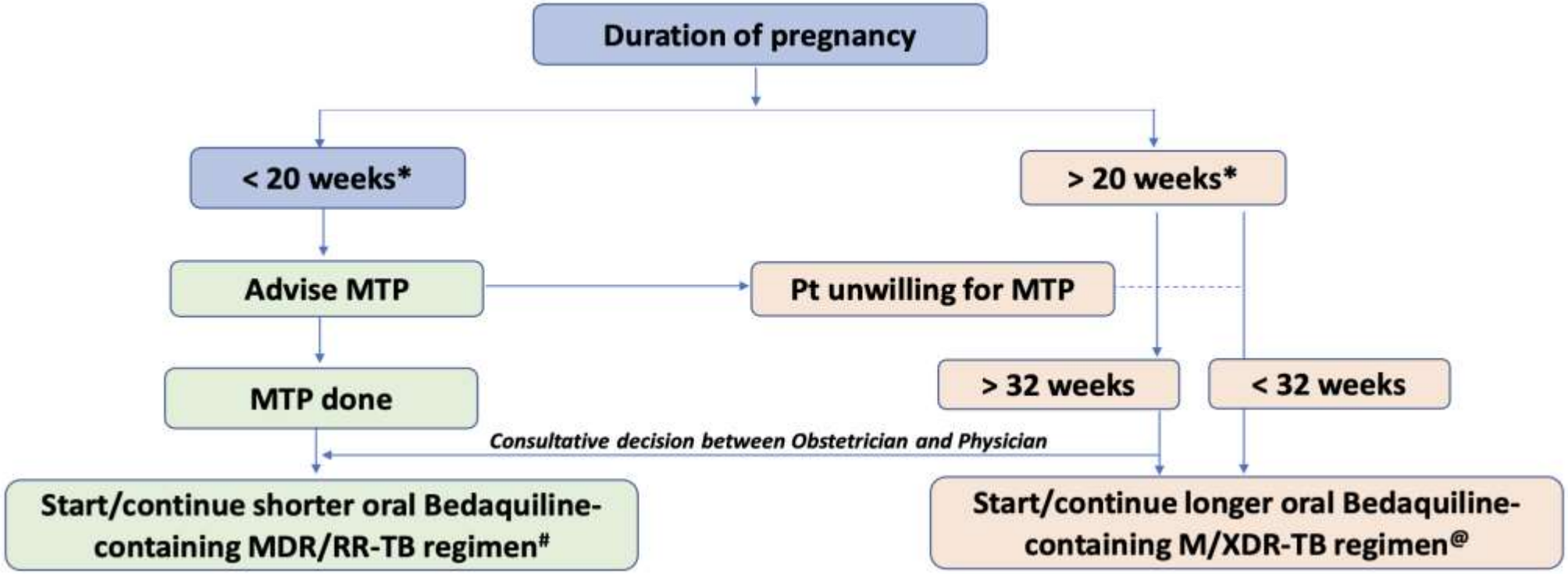
SHORTER MDR / RR-TB REGIMEN

SPECIAL SITUATIONS

Pregnancy and lactation

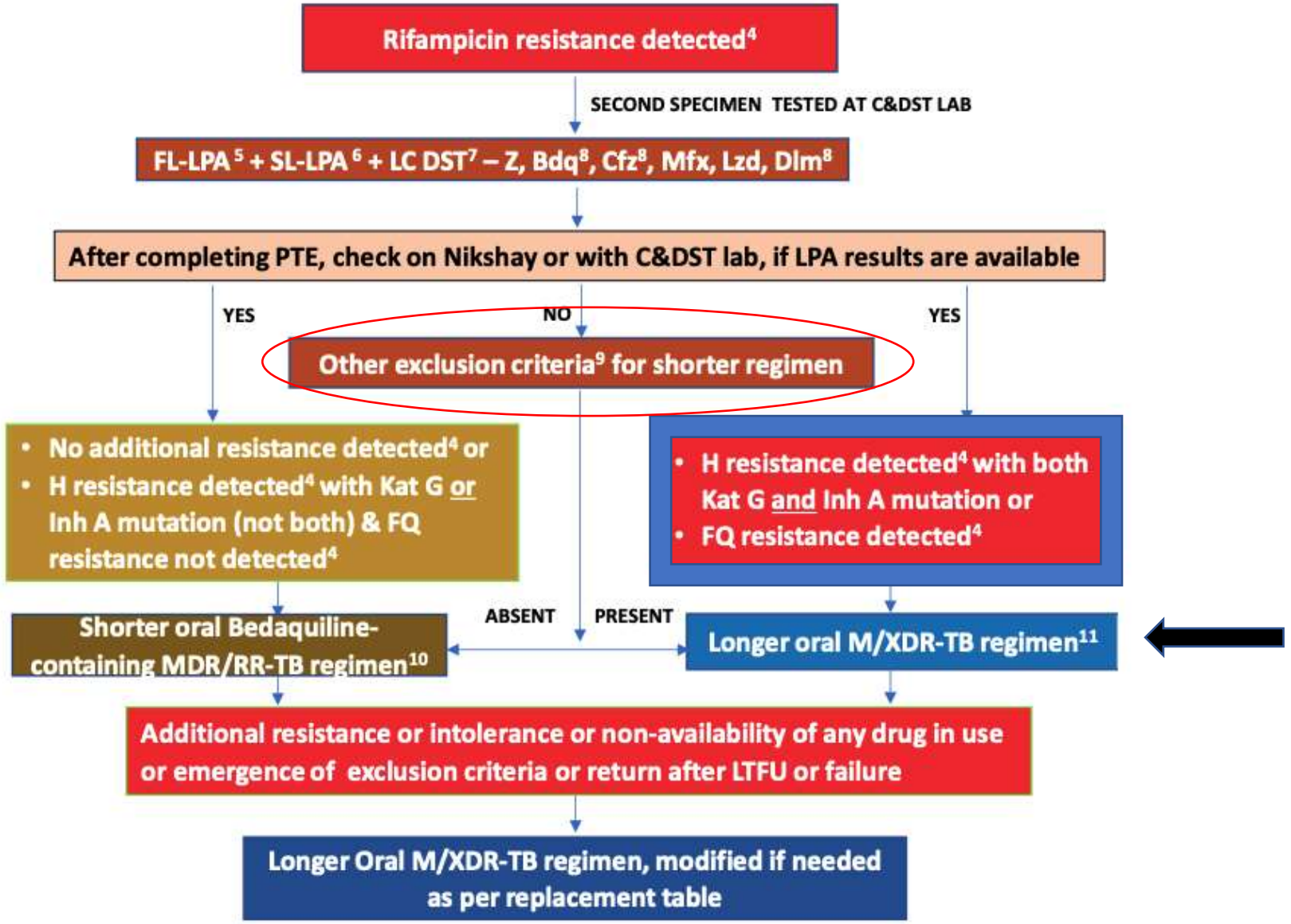
Ethionamide - contraindicated during the first 32 weeks of pregnancy –

animal reproduction studies - adverse effect on the foetus, no adequate studies in humans.



24 WEEKS*

Longer MDR/XDR Regimen



LONGER MDR / RR-TB REGIMEN

LONGER ORAL M/XDR-TB REGIMEN

Eligibility criteria

- MDR/RR-TB patients - excluded from shorter oral Bedaquiline-containing MDR/RR-TB regimen
- PRE/XDR- TB patients
- Additional resistance / Intolerance / Non-availability of any drug in use
- Emergence of exclusion criteria to shorter oral Bedaquiline-containing regimen -

the patient re-evaluated and initiated on longer oral M/XDR-TB regimen.

LONGER MDR / RR-TB REGIMEN

Regimen and duration

In MDR/RR-TB patients on longer oral M/XDR-TB regimen,

- All three Group A agents
- At least one Group B agent should be included

Treatment starts with at least four effective TB agents and

At least three agents are included for rest of the treatment if Bdq is stopped.

If only one or two Group A agents are used, both Group B agents are to be included.

If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it as recommended by WHO.

LONGER MDR / RR-TB REGIMEN

In India –

Start with all 5 drugs of Group A and B and

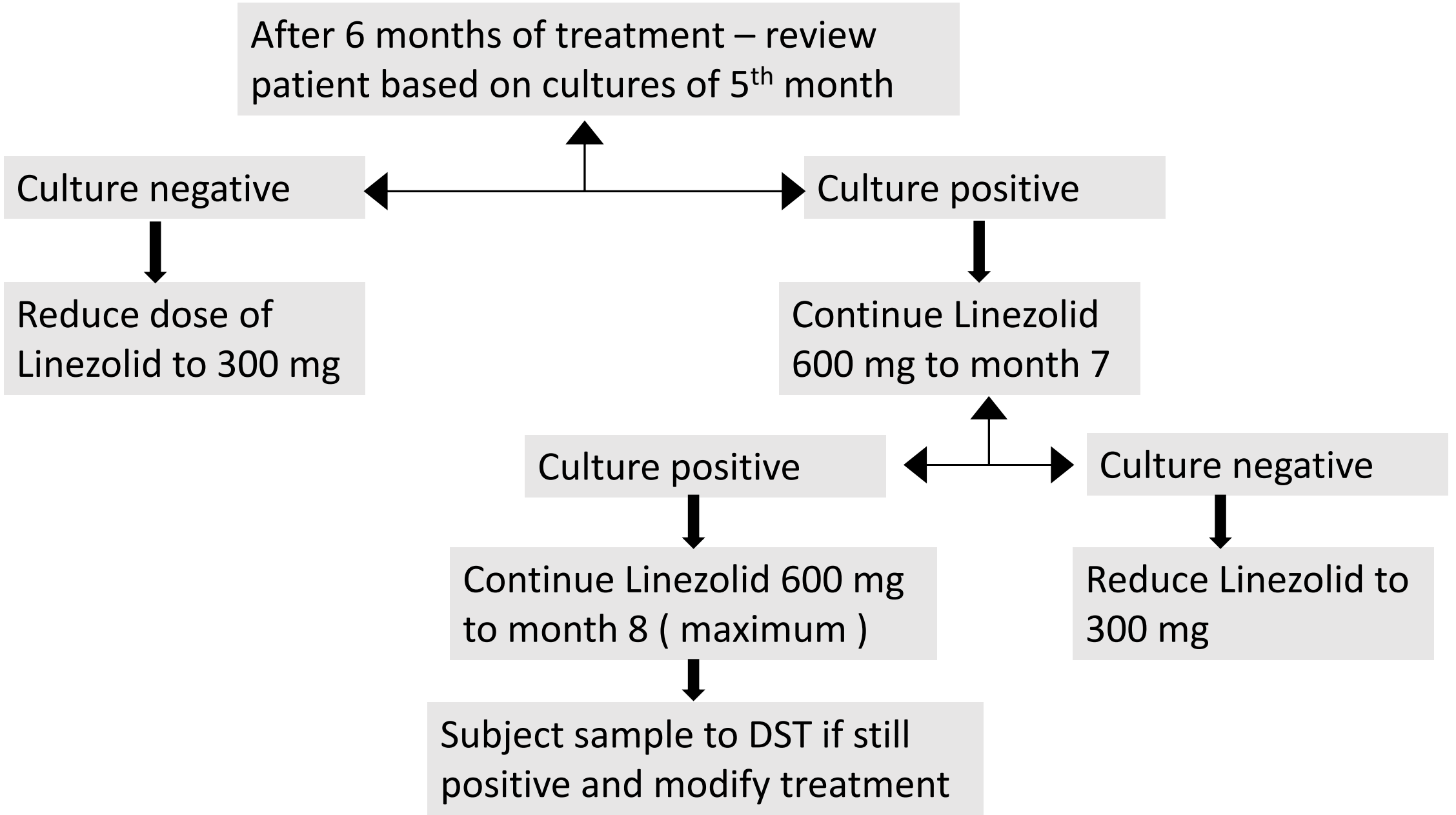
Continue with 4 drugs in the latter part of the regimen (beyond 6-8 months)

18-20 months, no separate IP or CP

Once patient is placed on a longer regimen for at least 4 weeks - can no longer be switched to the shorter regimen

(18-20) Lfx Bdq $_{(6\ month\ or\ longer)}$ Lzd# Cfz Cs
#dose of Lzd will be tapered to 300 mg after the initial 6–8 months of treatment
Bdq will be given for 6 months & extended beyond 6 months as an exception
Pyridoxine to be given to all DR-TB patients as per weight band
For Pre-XDR-TB and XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months with appropriate modifications

LONGER MDR / RR-TB REGIMEN



Replacement Sequence- Rules

1. Replaced according to their **efficacy, no demonstrable resistance, prior use, side-effects profile and background resistance.**

2. Preferably be fully **oral.**

3. Replacement sequence of Group C drugs is in the order of - **delamanid, amikacin, pyrazinamide, ethionamide, PAS, ethambutol, carbapenems , DA(PE)2**

4. Combined use of Bdq and Dlm is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all 5 drugs from Group A and B.

5. In final 12 months of treatment, atleast 3-4 drugs from group A and B to be used. (group C may be used if needed as per replacement seq)

6. Dlm and Am will not be started in final 12 months of treatment.

Replacement Sequence- Outcome

Sr. No	Drugs to be replaced	No. of drugs to include from			Final Regimen after replacement
		Group A (3 drugs)	Group B (2 drugs)	Group C (7 drugs)	
1	None	3	2	-	6-8 Lfx, Bdq, Lzd, Cfz, Cs / 12 Lfx, Lzd, Cfz, Cs
2	1 group A drug	2	2	1	**No FQ,** then 6-8 Bdq, Lzd, Cfz, Cs, Dlm / 12 Lzd, Cfz, Cs **No Bdq,** then 6-8 Lfx*, Lzd, Cfz, Cs, Dlm / 12 Lfx*, Lzd, Cfz,Cs **No Lzd,** then 6-8 Lfx*, Bdq, Cfz, Cs, Dlm / 12 Lfx* Cfz, Cs
3	1 group B drug	3	1	1	**No Cfz,** then 6-8 Lfx* Bdq, Lzd, Cs Dlm / 12 Lfx* Lzd, Cs **No Cs,** then 6-8 Lfx* Bdq, Lzd, Cfz Dlm / 12 Lfx* Lzd, Cfz
4	1 group A drug& 1 group B drug	2	1	2	**No FQ & Cfz** then 6-8 Bdq, Lzd, Cs, Dlm, Am# / 12 Lzd, Cs, Z#, Eto# **No FQ & Cs** then 6-8 Bdq, Lzd, Cfz, Dlm, Am# / 12 Lzd, Cfz, Z#, Eto# **No Bdq & Cfz** then 6-8 Lfx* Lzd, Cs, Dlm, Am# / 12 Lfx* Lzd, Cs **No Bdq & Cs** then 6-8 Lfx* Lzd, Cfz, Dlm, Am# / 12 Lfx* Lzd, Cfz **No Lzd & Cfz** then 6-8 Lfx* Bdq, Cs, Dlm, Am# / 12 Lfx*, Cs, Z#, Eto# **No Lzd & Cs** then 6-8 Lfx* Bdq, Cfz, Dlm, Am# / 12 Lfx*, Cfz, Z#, Eto#

Replacement Sequence- Outcome

Sr. No	Drugs to be replaced	No. of drugs to include from			Final Regimen after replacement
		Group A (3 drugs)	Group B (2 drugs)	Group C (7 drugs)	
5	2 group A drugs	1	2	2	**No FQ & Bdq** then 6-8 Lzd, Cfz, Cs, Dlm, Am# / 12 Lzd, Cfz, Cs, Z# **No FQ & Lzd** then 6-8 Bdq, Cfz, Cs, Dlm, Am# / 12 Cfz, Cs, Z#, Eto# **No Bdq & Lzd** then 6-8 Lfx*, Cfz, Cs, Dlm, Am# / 12 Lfx*, Cfz, Cs, Z#
6	2 group B drugs	3	0	2	**No Cfz & Cs** then 6-8 Lfx* Bdq, Lzd, Dlm, Am# / 12 Lfx*, Lzd, Z#, Eto#
7	3 or more from group A drugs& group B drugs	Use the remaining drugs		3 or more	Remaining drugs from Group A and B plus 3-5 drugs from Group C using the sequence explained to make a regime with at least 5-6 drugs known to be effective. If Bdq and Dlm can be used, their combined use in the regimen with at least 4 -5 drugs or its extended use beyond 6 months till clinical and bacteriological conversion is achieved. **If Bdq and Lzd can be used, explore the possibility of using BPaL regimen under prevailing ethical conditions.**

FOLLOW UP

Regimen Class	Longer Oral M/XDR-TB Regimen
Clinical + Wt.	Monthly up to month 6 or 7 or 8 if previous month S+ve , Quarterly in from month 7 or 9 onwards
Smear microscopy	With culture at C&DST lab
Culture	Monthly from month 3 onwards to end of 6 months or 7 or 8 if the previous month's culture is +ve Quarterly from month 6 or 7 or 8 onwards based on previous month's culture results
DST	FL & SL-LPA (Lfx, Mfx, Am, Eto) and LC&DST (Mfx, Lzd, Cfz*, Bdq*, Dlm*, Z) if any time culture +ve at the end of 6 months or beyond
CBC^	Day 15, monthly in first 6 months or 7 or 8 if previous month S+ve
TSH & LFT	LFT quarterly, TSH every 6 months
CXR	At the end of month 6, end of treatment
ECG	At 2 weeks, monthly in first 6 months and till Bdq/Mfx/Cfz/Dlm is extended
S. electrolytes (K, Mg, Ca)	In case of any QTc prolongation

^ If Lzd is part of the regimen to rule out bone marrow suppression

If found to be smear/culture positive at the end of 8 months or later, the patient will be declared as **'treatment failed'**

Long-term follow-up will be done with 6 monthly cultures **among symptomatic patients** till two years after completion of any DR-TB regimen i.e. months 6, 12, 18 and 24 post treatment.

BPaL REGIMEN

Bedaquiline, Pretomanid, Linezolid (BPaL) regimen

May be used under operational research conditions –

MDR-TB patients with no previous exposure to Bedaquiline and Linezolid or

Exposure < 2 weeks

To be used under operational research conditions - does not apply to routine programmatic use

90% favourable outcomes among XDR, MDR with FQ resistance, treatment intolerant /non responders.

BPaL REGIMEN

Dosage & duration

Pretomanid

200 mg once daily for 26 weeks

Bedaquiline

400 mg once daily for the first 2 weeks of treatment (days 1–14)

200 mg three times a week for 24 weeks

Linezolid

1200 mg once daily for 24 weeks

with an option to extend treatment to 39 weeks if they were culture-positive at week 16.

Last resort by NTEP under prevailing ethical standards in patients for whom the design of an effective regimen is not possible as per WHO recommendations.

Table B. Evidence available for the guidelines update

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
TB-PRACTECAL trial (South Africa, Belarus, Uzbekistan)	Microbiologically confirmed *M. tuberculosis* in sputum and resistance to rifampicin *The primary analysis population is followed up at 72 weeks.* The number of people reaching 24, 72 and 108 weeks differs because the study was terminated early	Stage 2 (phase 3 trial) 24 weeks BPaLM (B-Pa-$Lzd_{600->300}$-Mfx) Stage 1 (phase 2 trial) 24 weeks BPaLC (B-Pa-$Lzd_{600->300}$-Cfz) 24 weeks BPaL (B-Pa-$Lzd_{600->300}$)	Multiple – local standard of care, including: 9–12-month injectable-containing regimen 18–24-month WHO-recommended regimen (pre-2019) 9–12-month all-oral regimen 18–20-month all-oral regimen
Nix-TB (South Africa)	14 years and older XDR-TB (pre-2021 definition) or treatment intolerant nonresponsive MDR-TB	6–9 month $BPaL_{1200–26}$ Including linezolid 1 200 mg daily for 6 months (option of 9 months for subjects who remain culture positive at month 4)[10]	No standard of care control group
ZeNix (South Africa, Georgia, Moldova and the Russian Federation) *(22)*	14 years and older XDR-TB, pre-XDR-TB (pre-2021 definition) or intolerant/ nonresponsive MDR/RR-TB Stratified by HIV status and type of TB Phase 3 partially blinded	6–9 month BPaL 4 arms with varying linezolid dosing $BPaL_{1200–26\ weeks}$ $BPaL_{1200–9\ weeks}$ $BPaL_{600–26\ weeks}$ $BPaL_{600–9\ weeks}$ Treatment extended if culture positive in weeks 16–26	No standard of care control group

WHO CONSOLIDATED GUIDELIONES ON TB – 2022 UPDATE

STUDY	Regimens	Duration	N	Favorable outcomes	ADVERSE EFFECTS
Nix	BPaL	26 wks	105	90 % favorable	neuropathy 81% , myelosuppression 45 %
ZeNix	BPaL (L 1200 & 600 mg for 26 /9 wks)	26 wks	181	Linezolid 1200 mg 26/9 wks- 93 /84 % & **600 mg 26**/9 wks- **91** /84 %	Neuropathy – 1200mg 26 /9 wks- 38 /24 % 600mg – 26/9 wks- 24/13 % Myelosupression 1200 mg 26/9 wk- 22/15 % % 600mg 26/9 wk- 2/7 %
TB PRACTICAL	WHO standard BPaL BPaLM BPaLC	24 wks	522	WHO- 52 % BPaL- 77 % **BPaLM- 89 %** BPaLC- 81 %	BPaLM vs WHO regimen toxicity -20 VS 59 %

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.
2. This recommendation applies to the following:
   a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
   b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.[11]
   c. Adults and adolescents aged 14 years and older.
   d. All people regardless of HIV status.
   e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.[12]
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[13]

Section 1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)

1.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

WHO CONSOLIDATED GUIDELIONES ON TB – 2022 UPDATE

Preventive treatment for contacts of DR-TB

- **Tuberculosis (TB)-** Is the disease that occurs in someone infected with M. tuberculosis having signs or symptoms of TB disease. AKA "active" TB or TB "disease" to distinguish it from TB infection.

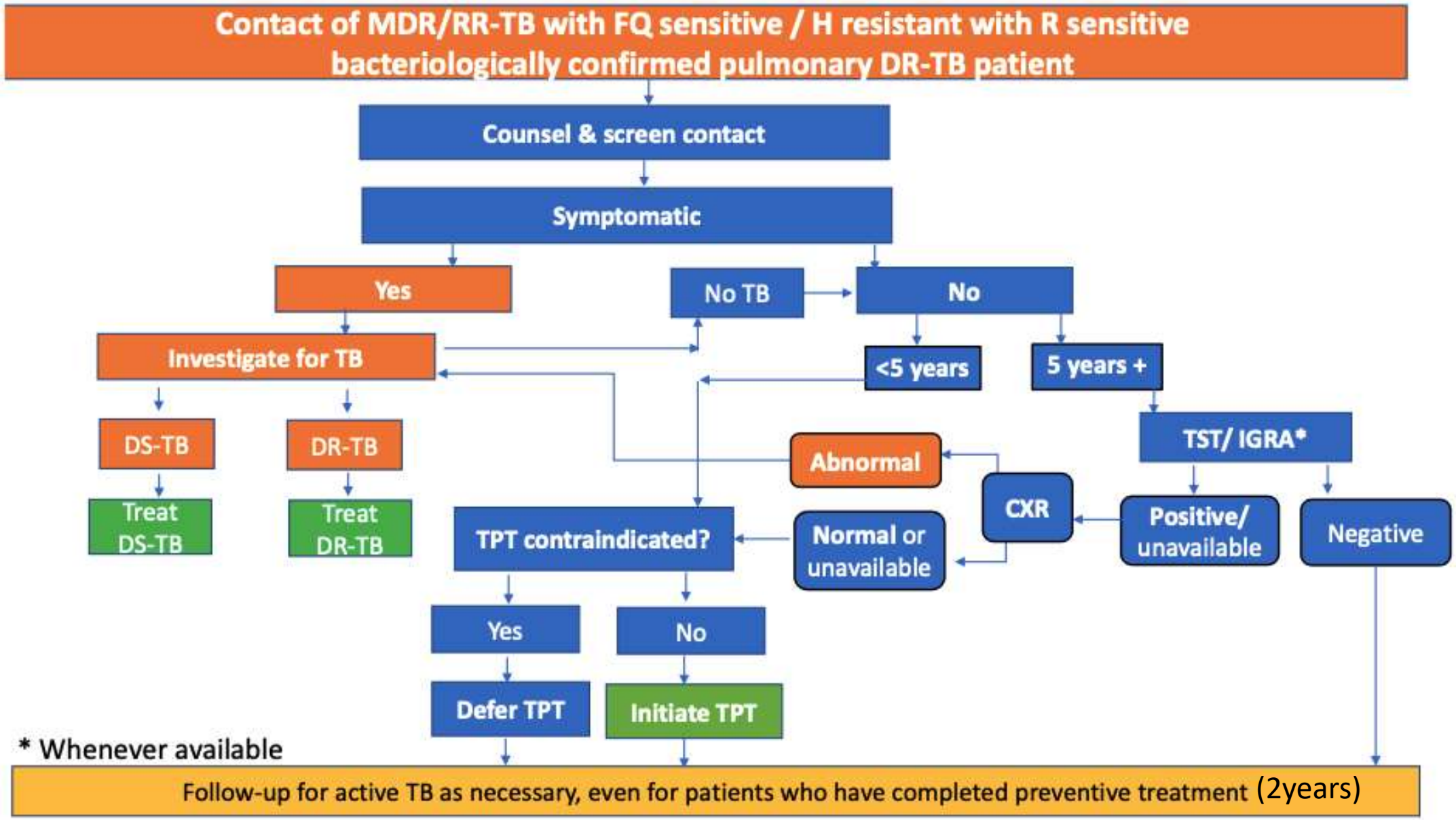
- **Tuberculosis infection (TBI)-** Is a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of clinically manifest TB disease. They have no signs or symptoms of TB but are at risk for developing TB disease. AKA "latent TB infection" (LTBI)

- **Tuberculosis preventive treatment (TPT)-** Treatment offered to individuals who are considered to be at risk of developing TB disease, in order to reduce that risk. [AKA treatment of TBI.]

WHO IS A CONTACT ?

HOUSEHOLD CONTACT	CLOSE CONTACT
Shares the same enclosed living space as index TB patient for **one or more nights** or for frequent or extended daytime periods **during the 3 months** before the start of current TB treatment.	Not a HHC but shares an enclosed space, such as at a social gathering, workplace, or facility, for extended periods during the day with the index TB patient during the **3 months before** the the start of current TB treatment. THIS GROUP WILL BE INCLUDED FOR ALL INTERVENTIONS AS APPLICABLE FOR HHC.

Integrated Algorithm



Regimen, Dosage & Duration

Regimen	Dose by age and weight band
Six months of daily levofloxacin (6Lfx) for contacts of MDR/RR FQ sensitive patients#	**Age > 14 years, by body weight: < 45 kg, 750 mg/day; ≥ 45 kg, 1g/day** Age < 15 years (range approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day 10–15 kg: 200–300mg/day 16–23 kg: 300–400mg/day 24–34 kg: 500–750mg/day
Four months of rifampicin daily (4R) for contacts of H resistant R sensitive patients*	**Age 10 years & older: 10 mg/kg/day (Max-600mg/d)** Age <10 years: 15 mg/kg/day (range, 10–20 mg)

	Total duration in months	Expected no. of doses	**80% of recommended doses (days)**
6Lfx (daily)	6	180	144
4R (daily)	4	120	96

Contraindications for TPT

TPT is contraindicated in the following situations:

- Active TB disease
- Acute or chronic hepatitis
- Concurrent use of other hepatotoxic medications (such as nevirapine)
- Regular and heavy alcohol consumption
- Signs and symptoms of peripheral neuropathy like persistent tingling, numbness and burning sensation in the limbs
- Allergy or known hypersensitivity to any drugs being considered for TPT

Note

- Pregnancy or a previous history of TB are not contraindications for TPT

Thank you