Individualised Approach In Management Of Drug Resistant TB

DM SEMINAR

Dr Srikant

Topics To Be Discussed

1. Burden Of DR-TB – World and Indian Scenario

2. PMDT/NSP/WHO DR-TB Guidelines- What's new

3. Current Treatment Regimens For DR-TB

4. Management Of DR-TB in special situations

5. Algorithm

6. Way Forward

Burden Of Tuberculosis : GLOBAL TB REPORT 2019

END TB

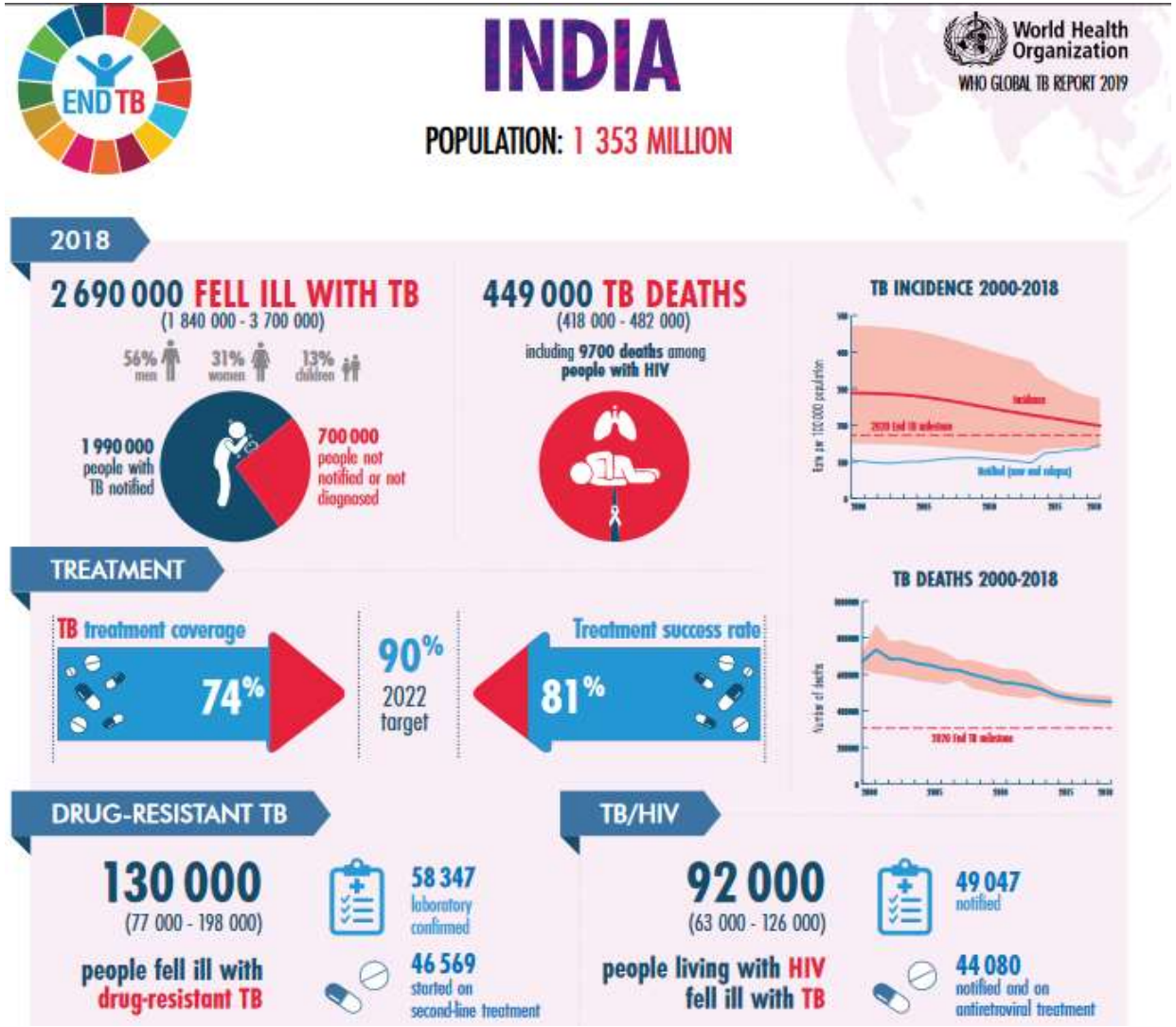
World Health Organization

NO. OF NEW CASES	1,00,00,000 (6.3% decline)
NO. OF DEATHS	15,00,000 (11% decline)
NO. OF RR-TB CASES	4,84,000(78% - MDR)

Still par below milestones needed for END TB STRATEGY

WHO Global TB Report 2019

Indian Scenario



Estimated New Cases	26,90,000
Estimated DR-TB cases	1,30,000
No. Of Lab confirmed DR-TB	58,347(44%)

INDIA SHARES 27% OF GLOBAL TB AND DR-TB BURDEN

WHO Global TB Report 2019

Scenario Of DR-TB Burden In India - Gaps In Diagnosis and Treatment

DRUG-RESISTANT TB CARE, 2018

% of bacteriologically confirmed TB cases tested for rifampicin resistance[c]		
– New cases		46%
– Previously treated cases		91%
Laboratory-confirmed cases[d]	MDR/RR-TB: 58 347,	XDR-TB: 3 400
Patients started on treatment[d,e]	MDR/RR-TB: 46 569,	XDR-TB: 2 724
MDR/RR-TB cases tested for resistance to second-line drugs		38 236

THE PUBLIC HEALTH CRISIS OF DRUG-RESISTANT TB

IN 2018

ONLY
ONE IN THREE OF THE
PEOPLE WHO DEVELOPED
DRUG-RESISTANT TB
ACCESSED TREATMENT

~56 % OF MDR-TB DID NOT RECEIVE DST

~64% OF ESTIMATED MDR-TB DID NOT RECEIVE TREATMENT

WHO Global TB Report 2019

Obstacles On The Path To END TB STRATEGY

1. Gaps in TB diagnosis and Treatment
2. Growing crisis of DR-TB
3. Deficits in TB prevention services
4. Funding gaps in TB research, diagnosis and treatment

Executive Summary WHO Global TB Report 2019

Factors Promoting Resistance

4 Ps:
- **Patient**
- **Physician**
- **Prescription**
- **Program**

Delayed diagnosis

Inappropriate drug regimen

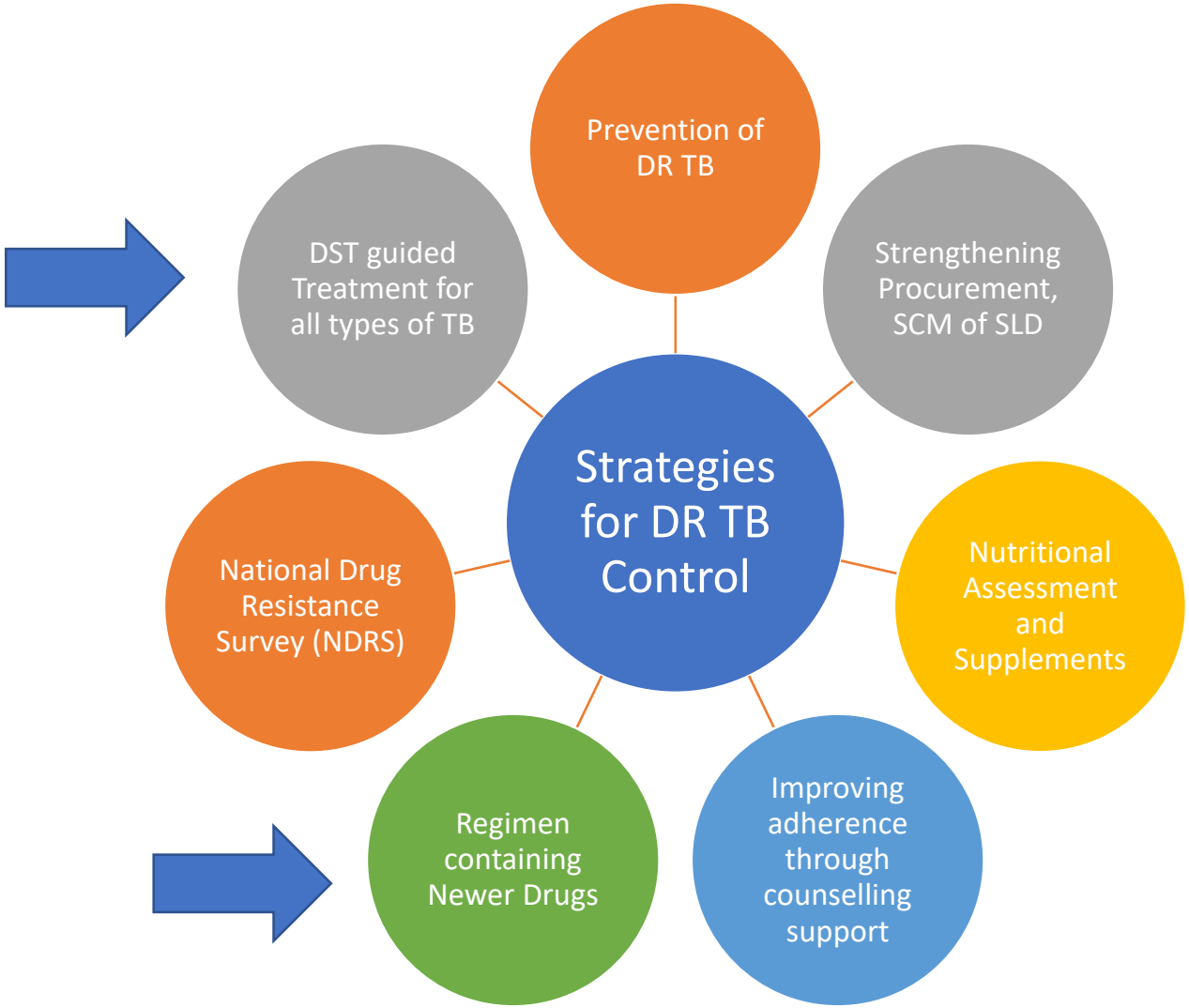
Inadequate initial therapy

Poor adherence and follow up

Inappropriate treatment modification

Deficiencies in program

Tackling DR-TB - PMDT



INDIA TB Report (PMDT Achievements)

Total Notified Cases 21,55,894

UDST(%) 6,18,729(29%)

Estimated MDR/RRTB 1,30,000

Shorter Rx 16,488

Patient eligible for DST guided Rx 11,209

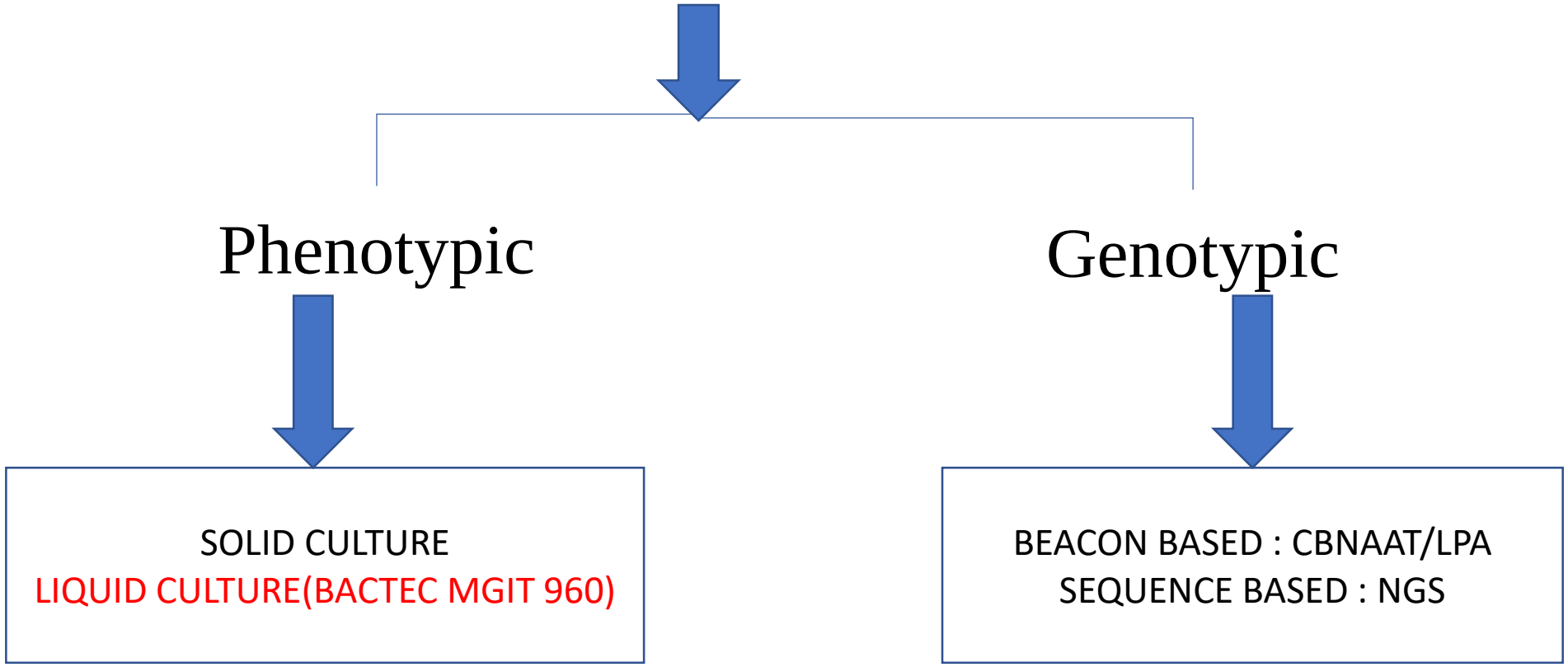
TOTAL NOTIFIED CASES DR-TB 3Q15-2Q16	30,183
SUCCESSFUL TREATMENT	14,195(47%)
DEATH	5934(20%)
LOST TO FOLLOW UP	5761(19%)
FAILED TREATMENT	595(2%)
CONV. TO XDR/SEV ADR	3698(12%)

INDIA TB REPORT 2019 CENTRAL TB DIVISION

National Strategic Plan(2017-2025)

DETECT	PREVENT	TREAT	BUILD
UNIVERSAL DST	INFECTION/DR-TB	DST GUIDED RX	SCALE UP PMDT

Drug Susceptibility Tests

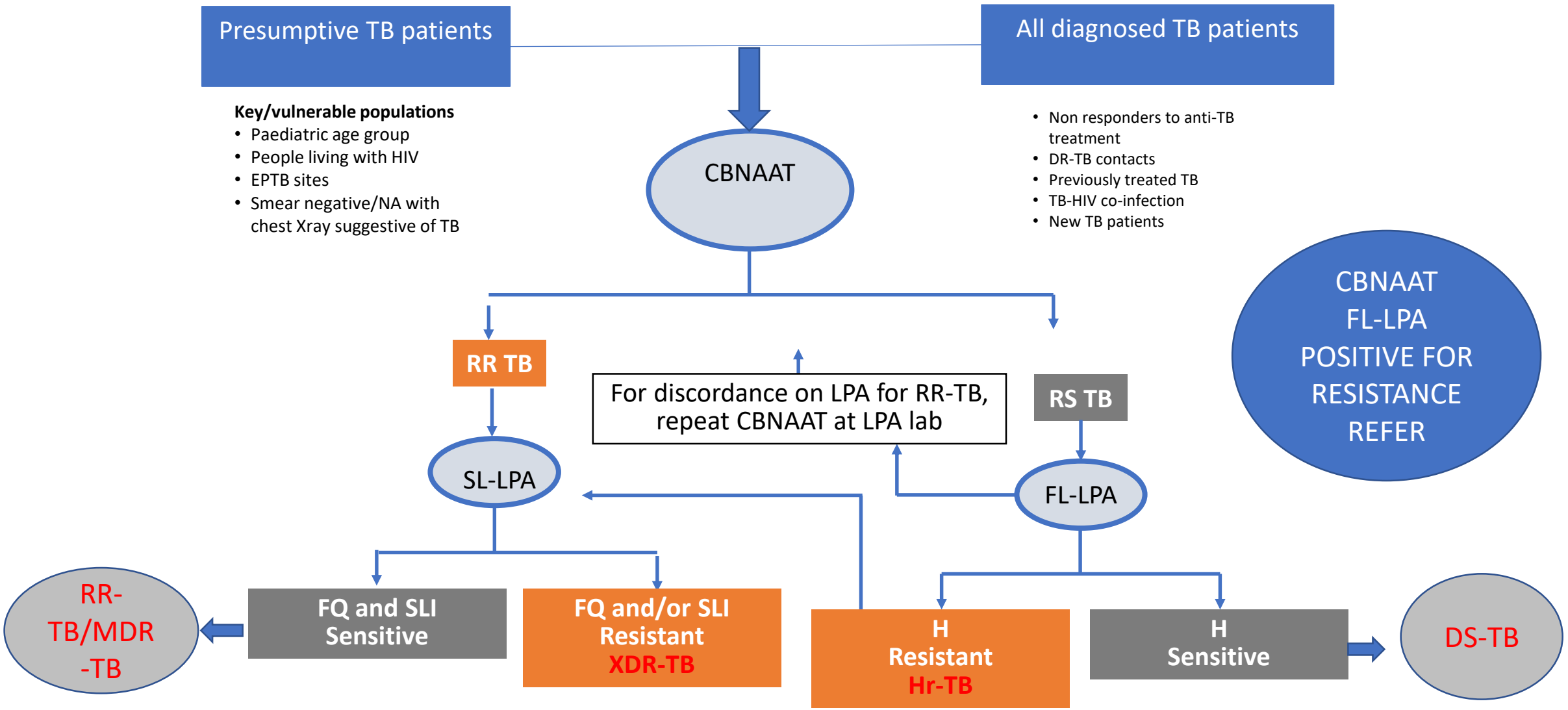


CBNAAT – RIFAMPICIN
FL-LPA – RIFAMPICIN and INH
SL-LPA – FQ and SLI

Available DSTs

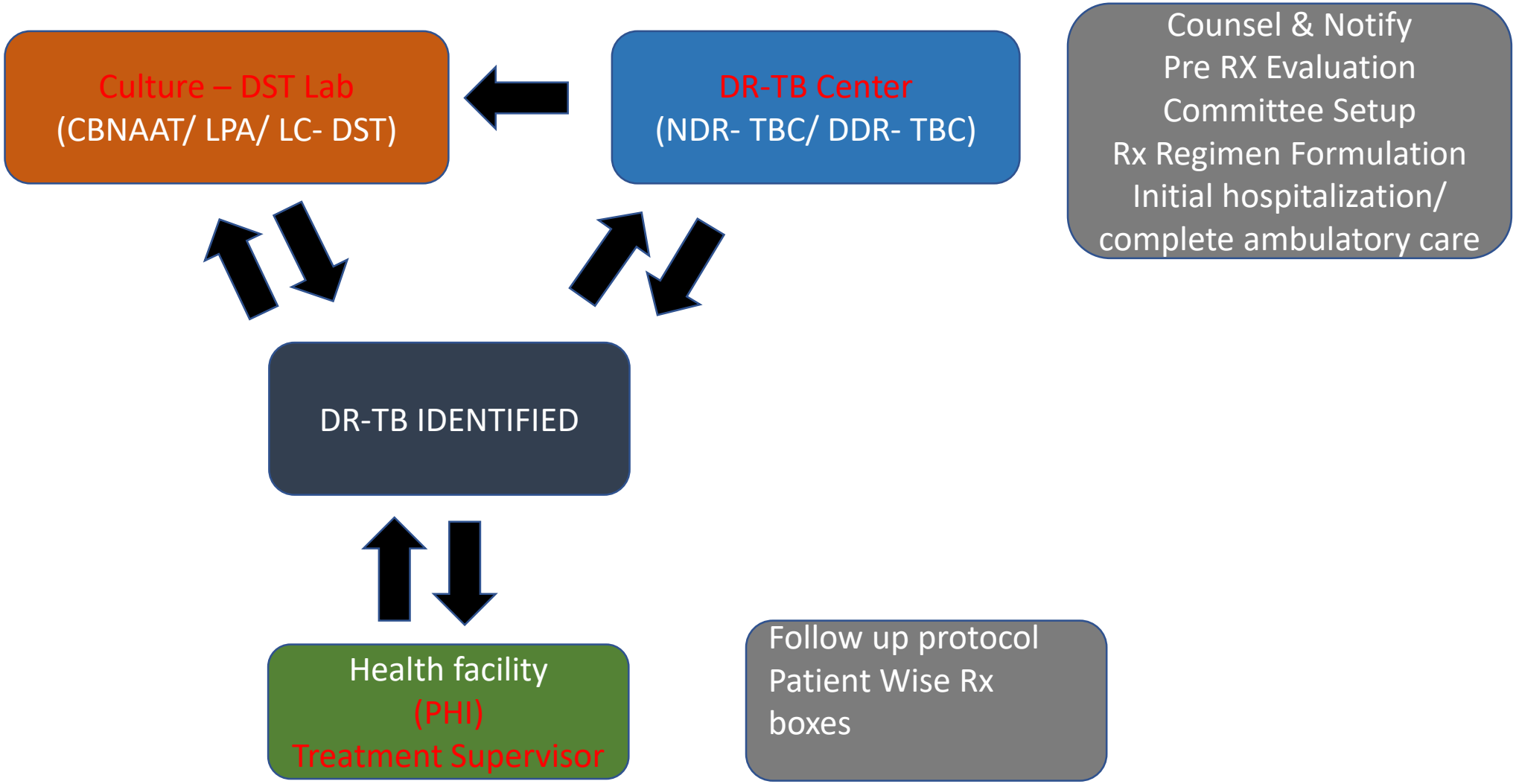
DST	Sample Processed	Turn over Time	Detects Resistance To
CBNAAT(XPERT MTB/RIF) (XPERT MTB/RIF Ultra)	Pulmonary + Extrapulmonary(except blood/stool)	2 hours	Rifampicin(rpoB)
LPA FL-LPA(MTb DR Plus) SL-LPA(MTb DR sl)	Sputum +/Culture +	 48-72 hours 7-10 days	 Rifampicin(rpoB) INH(inhA & katG) FQ(gyrA & gyrB) AG(rrs & eis)
LC-DST(MGIT 960)	Pulmonary + Extrapulmonary	42-56 Days	INH, Rifampicin, Z,Mfx, Lfx, Lzd, Am, Km, Cm, Bdq, Dlm, Cfz

Diagnosis-DR-TB Diagnostic Algorithm



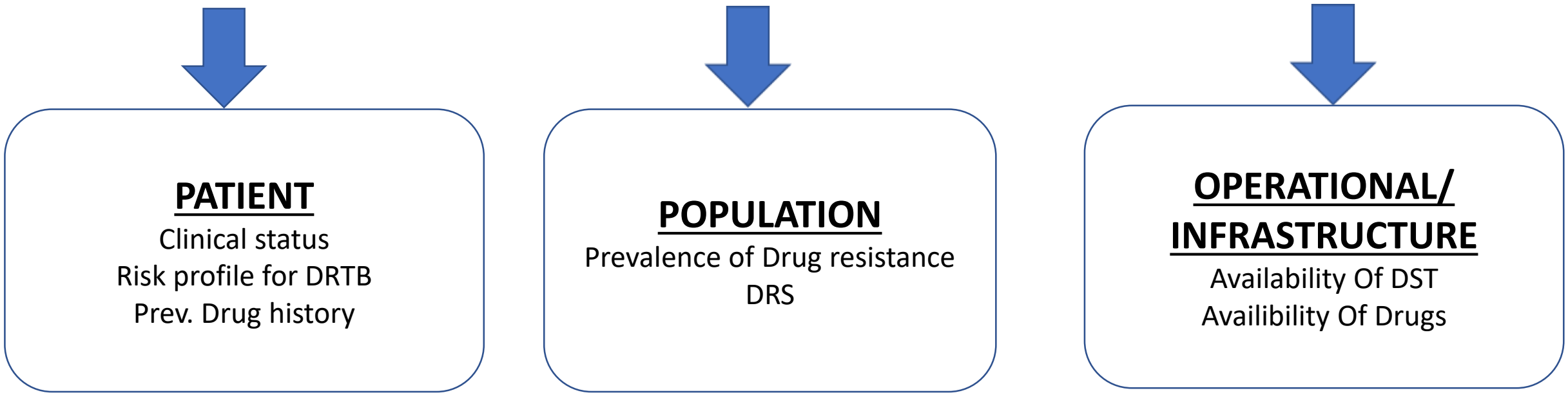
Guidelines On PMDT In India 2017

Care Of DR-TB Patient -



Guidelines On PMDT In India 2017

Factors To Consider Prior To designing DR-TB Regimen



Patient Factors

Variable
Age
Pregnancy/Lactation
Diabetes/CVD/Psychiatric Illness/Seizure disorder/Liver disease
Extent Of Disease(Extensive) PTB/EPTB
Past History
Drug History
HIV Status
Addiction

Baseline Investigations
Weight and Height
CBC
BSL
SERFT,LFT
ECG (Mfx,Bdq,Cfz,Dlm)
Urine R/ME
UPT
HIV
S. TSH
Audiogram
S. protein, Amylase, Lipase
Ophthalmologist evaluation
CxR

Guidelines On PMDT In India 2017

Prevalence Of Drug Resistance

	NEW TB PATIENT	PREVIOUSLY TREATED	ALL
DST RESULT	3065	1893	4958
SUSCEPTIBLE	77.46%(2346)	63.18%(1196)	72.01%(3570)
ANY RESISTANCE	22.54%(691)	36.82%(697)	28.02%(1388)
MDR	2.84%(87)	11.62%(220)	6.19%(307)
XDR	2.3%(2)	0.91%(2)	1.3%(4)

Most common drug to which resistance documented- INH
Negligible Rifampicin monoresistance

WHO- RGLC MISSION REPORT INDIA 2019

Regimen for H mono/Poly DRTB

Previous regimen

IP: 3-6 months- Km, Lfx, R, Z, E
CP: 6 months - Lfx, R, Z, E

Approved regimen (WHO recommended)

Duration: 6 months- Lfx, R, Z, E

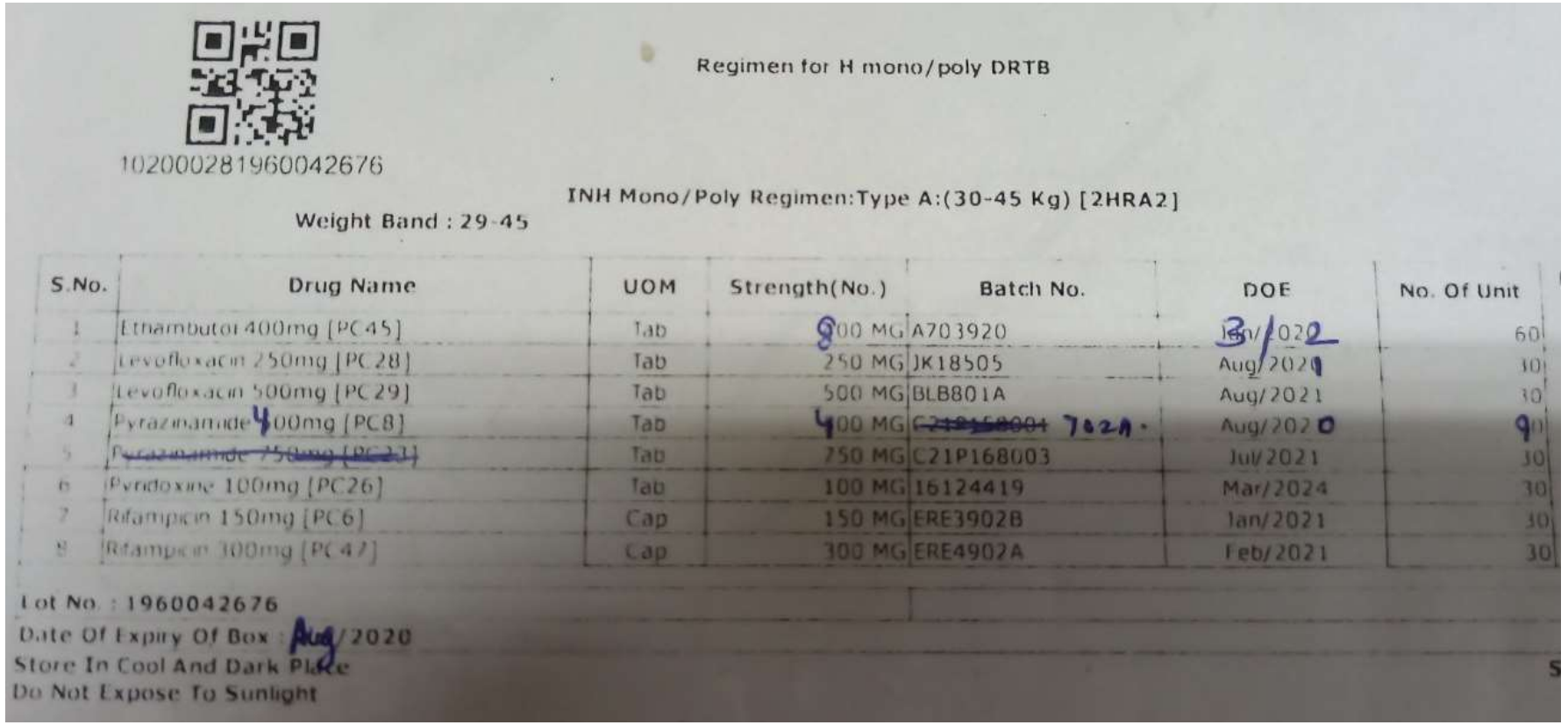
- No separate IP and CP
- Treatment can be extended up to 9 months

WHO after reviewing observational studies and Individual Patient Data (IPD) came up with these specific guidelines for resistance to Isoniazid in the absence of R resistance – 33 database, n- 5418 h mono resistant cases

WHO consolidated guidelines on drug-resistant tuberculosis treatment 2019

INH Mono/Poly Resistant TB

Drugs Dispensed In Patient Wise Boxes (weight band based)



Regimen for H mono/poly DRTB

10200028196O042676

INH Mono/Poly Regimen:Type A:(30-45 Kg) [2HRA2]

Weight Band : 29-45

S.No.	Drug Name	UOM	Strength(No.)	Batch No.	DOE	No. Of Unit
1	Ethambutol 400mg [PC45]	Tab	800 MG	A703920	Jan/2022	60
2	Levofloxacin 250mg [PC28]	Tab	250 MG	JK18505	Aug/2021	30
3	Levofloxacin 500mg [PC29]	Tab	500 MG	BLB801A	Aug/2021	30
4	Pyrazinamide 400mg [PC8]	Tab	400 MG	~~C21P158001~~ 7021	Aug/2020	90
5	~~Pyrazinamide 750mg [PC23]~~	Tab	750 MG	C21P168003	Jul/2021	30
6	Pyridoxine 100mg [PC26]	Tab	100 MG	16124419	Mar/2024	30
7	Rifampicin 150mg [PC6]	Cap	150 MG	ERE3902B	Jan/2021	30
8	Rifampicin 300mg [PC47]	Cap	300 MG	ERE4902A	Feb/2021	30

Lot No. : 1960042676

Date Of Expiry Of Box : Aug/2020

Store In Cool And Dark Place

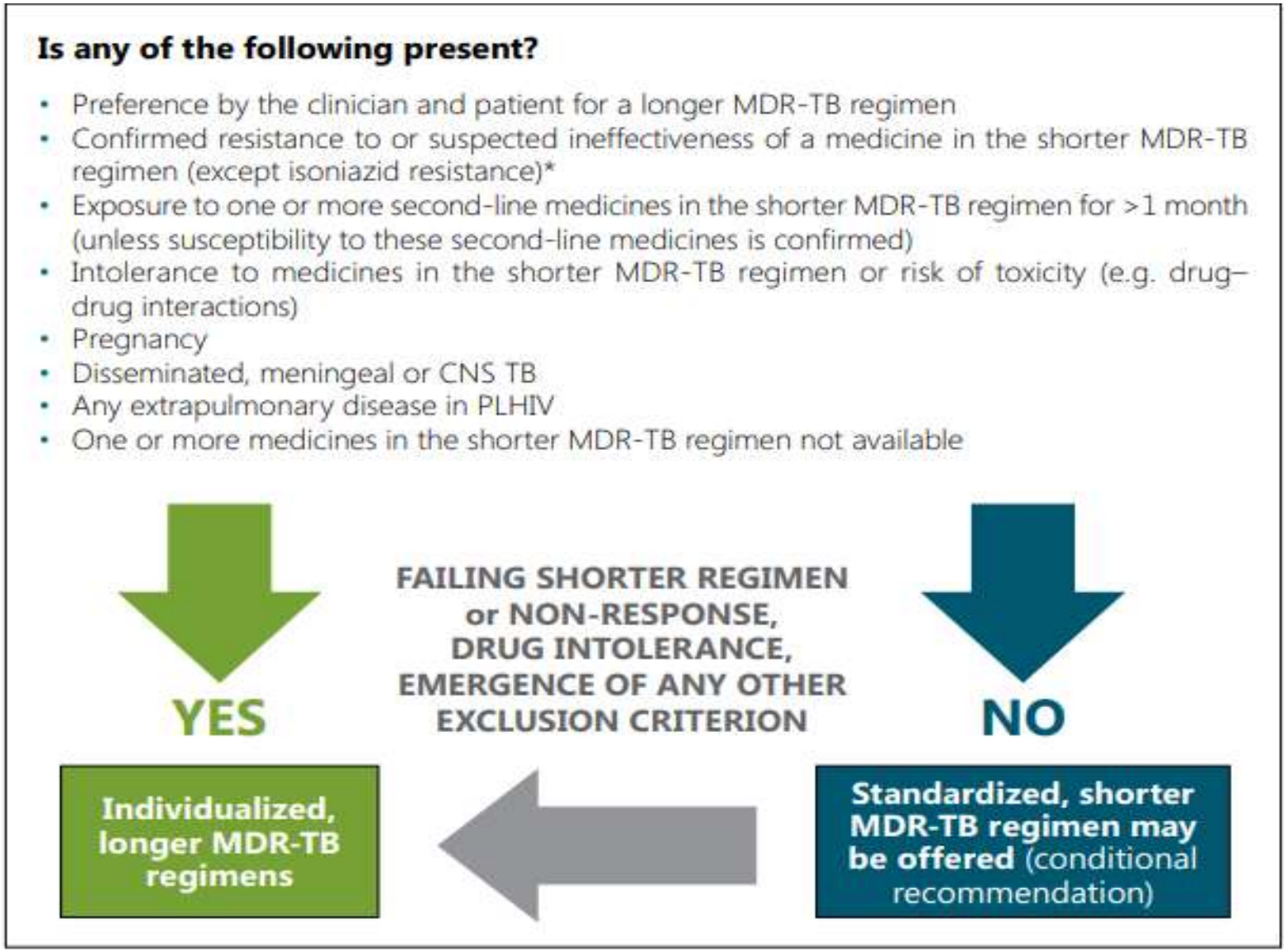
Do Not Expose To Sunlight

MDR-TB Treatment :

Cut down/simplified from 11 different regimen → 2

REGIMENS	LONGER	SHORTER
DURATION	≥ 18 Months	9-12 Months
Composition	~~Conventional~~ → All Oral – 4 drugs	Inj. Plus Oral – 7 drugs
Type	Individualised	Standardised
	(6-8m)4 Drugs 3A + 1B (From WHO Table) (12m)3 Drugs	(4-6m) Z $H_{(hd)}$ E Km Eto Cfz Mfx (5 m) Mfx Cfz Z E
Applicable	All	Selected patients

Which Regimen To Offer ?



Shorter MDR Regimen effective but in a selected population

WHO consolidated guidelines on drug-resistant tuberculosis treatment 2019

Need For Shorter Regimen

- Therapy for DRTB usually needed 24-30 months treatment
- Use of toxic drugs
- Poor outcomes <50% success
- Interventions with social support and counseling had a marginal success

Bangladesh regimen

- Six Different treatment regimens tested in 427 MDR-TB Patients[1]
- Sixth Gatifloxacin containing regimen yielded 89.2% success rate
- 9-month, seven-drug containing potent fluoroquinolone, high-dose isoniazid, and clofazimine in addition to the injectable aminoglycoside kanamycin
- Same regimen used in 515 MDRTB patients by Aung et al., yielded cure rate of 83%[2]

1. Van deun et al. Am J Respir Crit Care Med Vol 182. 2010
2. K.J.M.Aung et al. The International Journal of Tuberculosis and Lung Disease 2014

Evidence For Shorter Regimen : IPDMA from Observational Studies

Likelihood Of Treatment Success Of Shorter Regimen v/s Longer Regimen

Resistance pattern	Shorter MDR-TB regimen		Conventional MDR-TB regimen	
	N	% (95% CI)	N	% (95% CI)
All patients regardless of pyrazinamide and fluoroquinolone susceptibility	1008/1116	*90.3% (87.8%- 92.4%)*	4033/5850	*78.3% (71.2%- 84%)*
Pyrazinamide resistant; fluoroquinolone resistant	19/28	67.9% (47.6%-84.1%)	81/137	59.1% (50.6%-67.1%)
Pyrazinamide resistant; fluoroquinolone susceptible	90/100	88.8% (47.3%-98.6%)	840/1075	81.4% (71.6%-88.4%)
Pyrazinamide susceptible; fluoroquinolone resistant	12/15	80.0% (50.0%-94.1%)	72/120	64.4% (49.6%-76.9%)
Pyrazinamide susceptible; fluoroquinolone susceptible	121/125	96.8% (77.3%-99.6%)	890/1119	83.5% (75.7%-89.2%)

Evidence For Shorter Regimen : STREAM TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 28, 2019 VOL. 380 NO. 13

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

A.J Nunn et al., NEJM 2019

STREAM TRIAL

Study	Population	Intervention	Outcome
Randomized Multicentre Phase 3 Non inferiority Trial	N= 424 RR-TB	Shorter Regimen – 282 (9-11 months) Longer Regimen -142 (20 months)	Favourable Status at 132 wk.(i.e. culture negative) Incidence Of side effects

Exclusion Criteria

1. Resistance to FQ and/or SLI
2. Pregnant/Lactating
3. CNS TB/ Bone TB
4. AST/ALT > 5XULN
5. QTc >500ms

A.J Nunn et al., NEJM 2019

Primary End Point : Shorter Regimen Non Inferior To Longer

Variable	Modified Intention-to-Treat Population			Per-Protocol Population		
	Long Regimen	Short Regimen	Total	Long Regimen	Short Regimen	Total
Disposition of the participants						
Underwent randomization — no.	142	282	424	142	282	424
Were included in the population — no.	130	253	383	87	234	321
Were considered not able to be assessed — no.						
Had reinfection with a different strain	1	7	8	1	6	7
Had a negative culture at 76 weeks but lost to follow-up thereafter	5	1	6	3	1	4
Were included in primary outcome analysis — no.	124	245	369	83	227	310
Outcome						
Attained favorable status — no. (%)†	99 (79.8)	193 (78.8)	292 (79.1)	67 (80.7)	186 (81.9)	253 (81.
Had an unfavorable outcome — no. (%)	25 (20.2)	52 (21.2)	77 (20.9)	16 (19.3)	41 (18.1)	57 (18.4
Determined on the basis of bacteriologic findings‡						
Had no negative cultures§	1	5	6	1	5	6
Had bacteriologic reversion during treatment period¶	4	13	17	4	11	15
Had bacteriologic relapse after treatment period and started ≥2 additional drug therapies‖	0	7	7	0	7	7
Had positive culture at last assessment**	2	1	3	2	1	3
Determined on the basis of criteria other than bacteriologic findings						
Had negative culture at last assessment but died during the treatment or follow-up period	5	9	14	5	9	14
Had treatment extended or changed after adverse event	3	4	7	2	3	5
Started ≥2 additional drug therapies owing to decision by the investigator††	3	2	5	2	0	2
Withdrew consent for treatment, was given a different regimen, or was lost to follow-up before 76 weeks	4	8	12	0	3	3
Had treatment extended or changed after poor adherence or loss to follow-up	0	2	2	0	1	1
Had negative culture at last assessment but was lost to follow-up before 76 weeks	3	1	4	0	1	1

Culture -ve
79.8 v/s 78.8%

A.J Nunn et al., NEJM 2019

Secondary End Point : Incidence Of Side Effects- similar

Table 3. Summary of Safety Outcomes.*

Outcome	Long Regimen (N=141)	Short Regimen (N=282)	Total (N=423)
Grade 3 to 5 adverse event — no. (%)	64 (45.4)	136 (48.2)	200 (47.3)
Serious adverse event — no. (%)	53 (37.6)	91 (32.3)	144 (34.0)
Death — no. (%)	9 (6.4)	24 (8.5)	33 (7.8)
Related to tuberculosis	2	7	9
Related to tuberculosis treatment	1	1	2
Related to HIV or HIV treatment	3	6	9
Other or uncertain	3	10	13

A.J Nunn et al., NEJM 2019

Is shorter Regimen Good enough?

Advantages	Issues
Greater adherence, Less loss to follow up	Side effect profile similar
Standardized	Ototoxic and Nephrotoxicity issues
Easier to practice in Programmatic condition	Audiometric evaluation
Less expensive	

Churchyard GJ. N Engl J Med 2019; 380:1279-1280

Is All Oral Shorter Regimen A Possibility ? – STREAM 2 Study

Treat TB Org. Stream Trial Overview

STREAM 2 TRIAL – Longer v/s Short Regimen v/s Oral 10 m v/s 7 m Regimen

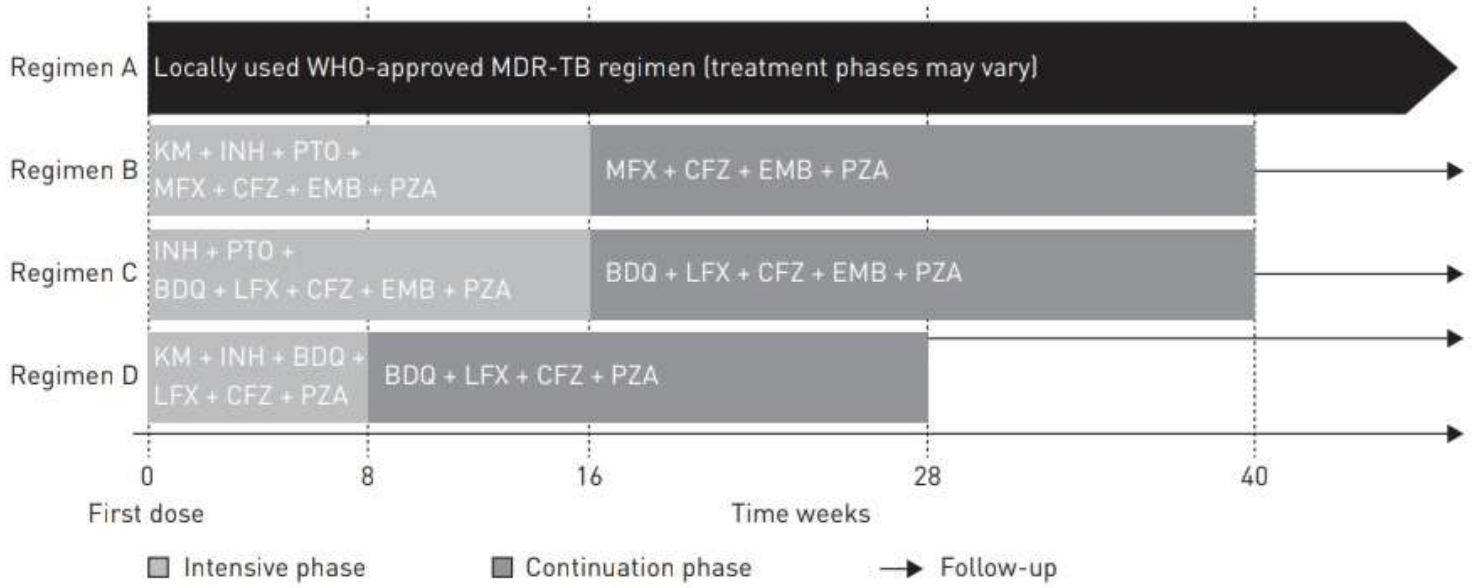


FIGURE 1 STREAM (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis) treatment regimens. WHO: World Health Organization; MDR-TB: multidrug-resistant tuberculosis; KM: kanamycin; INH: isoniazid; PTO: prothionamide; MFX: moxifloxacin; CFZ: clofazimine; EMB: ethambutol; PZA: pyrazinamide; BDQ: bedaquiline; LFX: levofloxacin.

R. Moodley et al., Short Course Treatment For MDR-TB, Eur Respir Rev 2015

Indian Setup : NTEG Recommendations for the Shorter Regimen

DST based Criteria	Non DST based Criteria
FQ/SLI Resistance +	Pregnancy
FL-LPA – Inh A mutation(Eto cant be used)	Any EPTB in PLHIV
Z resistance +	Disseminated, Meningeal and CNS TB
H/o use of Mfx/Lfx/Km/Eto/Cfz > 1 month	Intolerance h/o or risk of toxicity +

Indian Setup : NTEG Recommendations for the Shorter Regimen

- Signs of failure or ADR observed switch to longer regimen
- Strengthen counselling and aDSM to avert permanent loss of hearing, eye-sight, neuropathy and cardiotoxicity etc(ECG & Audiometry)
- Inj Km to be continued to all patients on shorter regimen
- Some selected sites to replace Km with Am and document lessons learnt to guide further expansion

Follow Up In Shorter Regimen

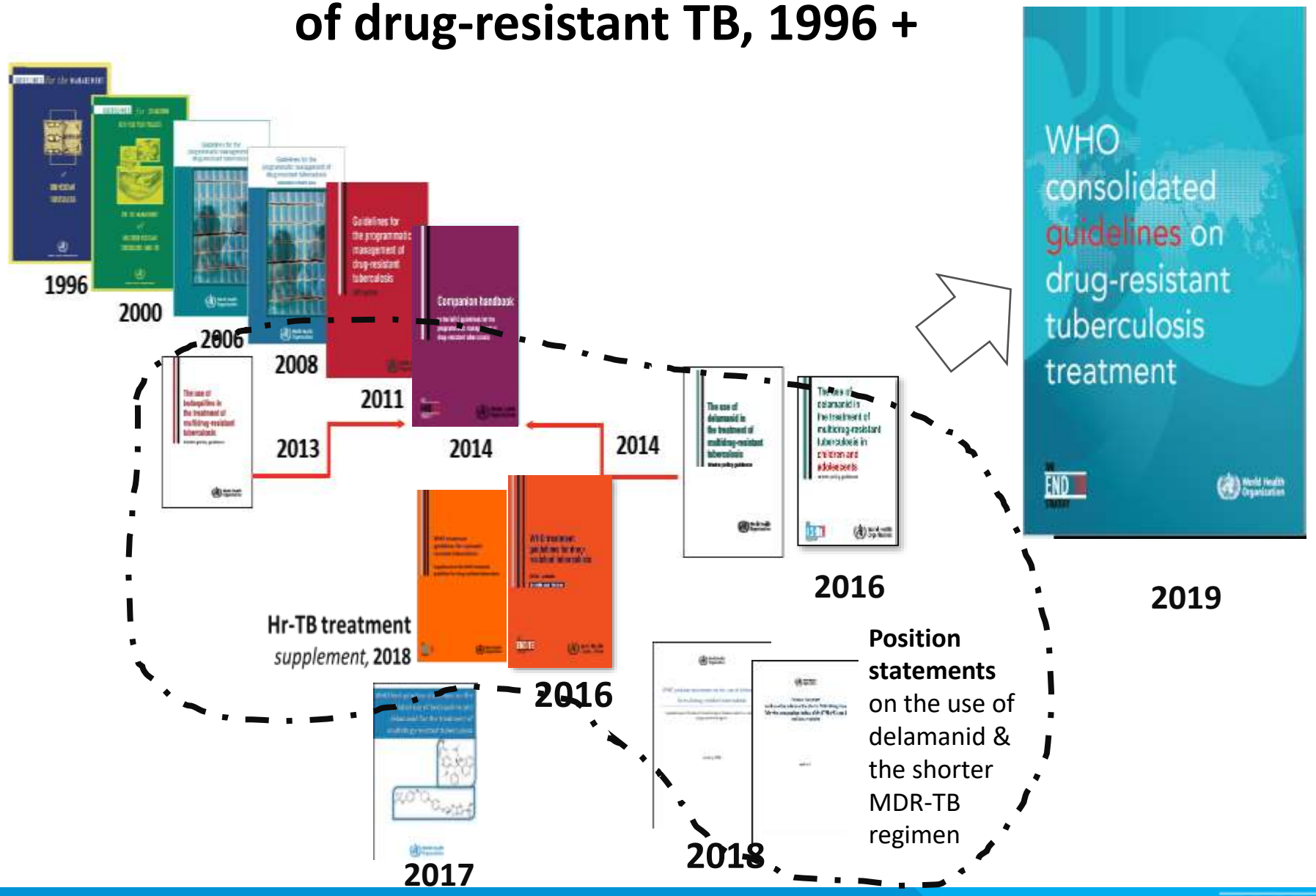
Ix/Time	B/L	15d	1M	2M	3M	4M	5M	6M	9M	12M
Wt/Ht/ GPE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sp. Smear and C/S	✓ ✓				✓	✓	✓	✓ ✓		✓
SERFT	✓		✓	✓	✓			✓		
CXR	✓		✓							
ECG	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Others	✓									

VISIT DR-TB CENTRE

VISIT DR-TB CENTRE

Guidelines On PMDT In India 2017

WHO guidance on treatment & management of drug-resistant TB, 1996 +



WHO DR-TB 2019 -Drug Grouping For Framing Longer MDR-TB Regimen

WHO 2016 TB drugs classification		
Group A **Fluoroquinolones**	Levofloxacin Moxifloxacin Gatifloxacin	
Group B **Second-line injectable agents**	Amikacin Capreomycin Kanamycin (Streptomycin)	
Group C **Other core second-line agents**	Ethionamide/ Prothionamide Cycloserine/terizidone Linezolid Clofazimine	
Group D **Add-on agents** **(not core MDR-TB regimen components)**	D1	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	Para-aminosalicylic acid Imipenem-cilastatin Meropenem Co-amoxiclav (Thioacetazone)

GROUP	MEDICINE
Group A: **Include all three medicines (unless they cannot be used)** **Group B:** **Add both medicines (unless they cannot be used)**	Levofloxacin OR Moxifloxacin Bedaquiline[1,4] Linezolid[2] Clofazimine Cycloserine OR Terizidone
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	Ethambutol Delamanid[3,4] Pyrazinamide[5] Imipenem-cilastatin OR Meropenem[6] Amikacin (OR Streptomycin)[7] Ethionamide OR Prothionamide *p*-aminosalicylic acid

WHO consolidated guidelines on drug-resistant tuberculosis treatment 2019

Reclassification Of Second Line Drugs : IPDMA and Trial 213(Dlm)

	Medicine	Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% confidence limits)	Number treated	Adjusted odds ratio (95% confidence limits)
A	Levofloxacin *OR* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *OR* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)*	290	1.2 (0.5–3.0)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

Individual contribution of Second Line drugs , Z and E to patient outcomes w.r.t treatment failure, relapse and death were assessed

Analyse Optimal number of medicines to be included for favourable outcome

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Reclassification Of Second Line Drugs - Serious adverse events

Table 2.3. Serious adverse events (SAEs) in patients on longer MDR-TB regimens*

Medicine	Absolute risk of SAE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine/terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide/prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
p-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

Relative Harms and Benefits Of Individual Drugs were assesed

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Evidence In Favour Of Bedaquiline

	India BDQ-CAP	Meta-analysis
	N = 620	N = 391
Number Converted	**513 (83%)**	312 (79.7%)
Death	**73 (11.8%)**	37 (10.6%)
Lost to Follow-up	**30 (4.8%)**	46 (12.8%)
Reversion after conversion	---	9 / 66 (13.6%)**

SUMMARY OF EFFECTIVENESS AND TREATMENT OUTCOME DATA

The use of bedaquiline led to a 79.7 % culture conversion rate at 6 months. At the end of follow-up (18-24 months) the cure rate was 63.8%. The death rate was 10.6%. Overall treatment success rate was 69.3%.

Diacon AH et al. N Engl J Med 2014

Initial experience of Bedaquiline implementation - NITRD, Delhi, India

- Study of 290 DR-TB patients concluded that regimens containing Bedaquiline lead to early smear and culture conversion(97.9% at 6 months).
- Adverse reactions though common are manageable
- Significant QTc prolongation in 13 patients (Permanently discontinued in 4 patients)
- ECG and electrolyte testing must

Sarin R et al. Indian J Tuberculosis Jan 2019

Principles of designing a WHO recommended **All Oral** longer MDR TB regimen

1. All three Group A agents and one Group B agent should be included

2. At least three agents for the rest of the treatment after Bdq is stopped

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

4. If the regimen cannot be composed with agents from Groups A and B alone,add Group C agents

5. As the likelihood of stopping Lzd due to toxicity is greater, the **all oral longer regimen in INDIA will include five drugs**

Recommendations for Longer all oral regimen

6-8 Bdq(6) Lfx Lzd Cfz Cs

12 Lfx Lzd (l) Cfz Cs

Replacement drugs in sequence of preference(Initial 6 months)

I. if Lfx cannot be used → Mfx(h) based on SL-LPA

II. if Mfx(h) cannot be used → Dlm;

III. If Mfx(h) & Dlm cannot be used → 2 drugs from replacement sequence

IV. If Bdq cannot be used → Dlm;

V. If Bdq & Dlm cannot be used → 2 drugs from replacement sequence

Replacement drugs in sequence of preference(Initial 6 months)

VI. If one of Lzd, Cfz or Cs cannot be used no replacement required

VII. If 2 or all 3 of Lzd, Cfz or Cs cannot be used ⟶ 2/3 drugs from replacement sequence

VIII. If FQ and Bdq both cant be given/ any 3/5 drugs from A & B group cant be used ⟶ 3 drugs from replacement sequence

Replacement sequence: Z*, Am*, Eto*, PAS, E, Imp/Cln or Mpm +Amx/Clv in given order.

Replacement drugs in sequence of preference(After 6 months)

- If one drug (Lfx, Lzd, Cfz, Cs) cannot be used, no replacement

- If two drugs cannot be used, replace with 2 drugs from Z*, Eto*, PAS, E in given order to complete the 4 drugs regimen

Recommendations for Longer all oral regimen

- DST for Lzd, Cfz, Bdq, Dlm will be done
- Monthly follow up culture to be done from 3rd month
- Extension of treatment will depend on culture report at 4th and 5th month
- Lzd to be given at 300 mg after 6-8 months of treatment based on C/S
- Total duration of regimen 18-20 months
- Ensure adherence

All Oral regimen for MDR RR TB - Advantages

- Injection Free regimen
- Duration of treatment reduced from 24 months to 18-20 months
- No ototoxic and nephrotoxic effects
- Estimated to improve outcomes

ATS/CDC/ERS/IDSA DR-TB Guideline

Differences From WHO Guideline

Initial longer regimen composed of 5 drugs
(Reason : Lesser BDQ related studies in IPDMA/Anticipated side effects)

No recommendation FOR/AGAINST shorter regimen
(Reason : Use of kanamycin/INH/Z/E)

American Journal of Respiratory and Critical Care Medicine
2019

Oral Regimens For Other DR-TB

All regimen under RNTCP of longer duration **(MDR/MDR+FQ/SLI/XDR-TB) to be replaced with this longer oral regimen** in adults.

Follow Up In Longer Regimen

Ix/Time	B/L	15d	1M	2M	3M	4M	5M	6M	9M	12M	15M	18M	20M
Wt/Ht/ GPE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sp. Smear C/S	✓ ✓				✓ ✓	✓ ✓	✓ ✓	✓ ✓					
SE RFT	✓				✓			✓					
CXR	✓		✓					✓					✓
ECG	✓	✓	✓	✓	✓	✓	✓	✓					
Others Amy/Lip ase	✓				✓			✓					
CBC	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Newer Regimens- NIX- TB Trial - All Oral Regimen

The NEW ENGLAND JOURNAL of MEDICINE

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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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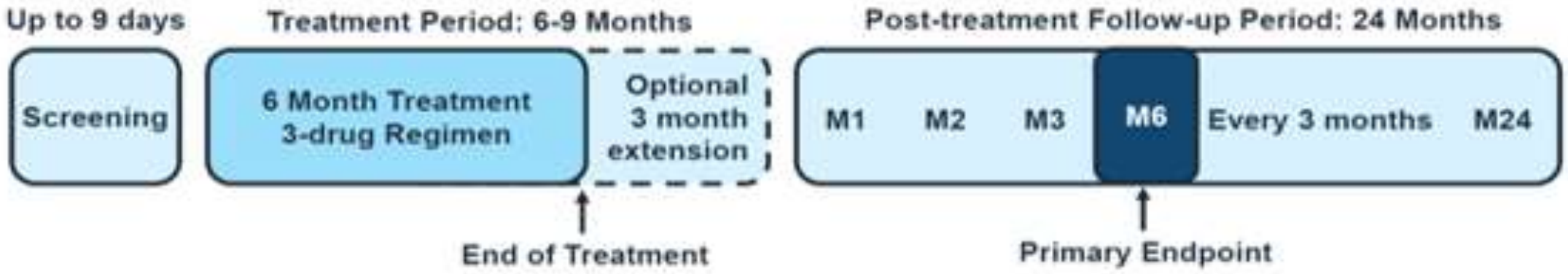
Conradie F et al. N Engl J Med 2020

NIX-TB Trial

Study	Population	Intervention	Outcome
Open label Single group South Africa	N= 109 Pulmonary XDR(71) + MDR patients(38) Not responsive to treatment(6m) Discontinued treatment d/t drug related side effects	Oral BPaL regimen daily for 26 weeks F/U of 6 months post treatment	Incidence of Treatment failure and Relapse Time to unfavourable outcome Time to sputum culture conversion Adverse effects



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Primary Outcome - Favourable Outcome

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡
Per-protocol population			
No. of patients	68	37	105
Favorable outcome			
No. of patients	62	35	97
Percent of patients (95% CI)	91 (82–97)	95 (82–99)	92 (86–97)
Unfavorable outcome — no. (%)	6 (9)	2 (5)	8 (8)
Deaths — no.	5	1	6
Relapse — no.	1	1	2‡

90% Patients at 6 months had resolution of clinical disease and culture -ve

Conradie F et al. N Engl J Med 2020

NIX-TB Trial – Adverse Events

Event*	HIV Status		Linezolid Regimen		Overall (N=109)
	Negative (N=53)	Positive (N=56)	600 mg Twice Daily (N=44)	1200 mg Daily (N=65)	
			number (percent)		
Adverse event	53 (100)	56 (100)	44 (100)	65 (100)	109 (100)
Adverse event leading to death	3 (6)	3 (5)	4 (9)	2 (3)	6 (6)
Serious adverse event	10 (19)	9 (16)	13 (30)	6 (9)	19 (17)
Grade 3 or 4 adverse event	27 (51)	35 (62)	27 (61)	35 (54)	62 (57)

<u>Adverse Events</u>

Peripheral neuropathy	81
Myelosuppression	52
Hepatic	17
QTc > 480ms	Nil

Conradie F et al. N Engl J Med 2020

Ray Of Hope In -Difficult To Treat DR-TB

Treatment Challenges	Opportunities with BPaL
Too long: 18+ months	6-month regimen
Too complicated: ≥ 5 drugs, some IM / IV, no defined regimen	3 drug, all oral, set regimen
Highly toxic, leading to discontinuations	Manageable tolerability, few discontinuations
Poor efficacy: ~20% cure rate pre-bedaquiline era in South Africa	90% cure rate

Role Of Surgery In DR-TB

As a adjunct to medical therapy in patient with good pulmonary reserve and localized disease

Indications:

1.Absence of response despite 6-9 months of effective treatment

2.Complications – haemoptysis, BPF and Empyema

3.Presence of extensive drug resistance unlikely to respond to chemotherapy

Role Of Surgery In DR-TB

Based on IPDMA of 6000 patients*

1. Treatment success i.e, was higher with partial lung resection compared to no surgery/pneumonectomy

2. Success was higher when surgery performed after culture conversion

Fox G et al. Clin Infect Dis 2016;62:887

EPTB ?

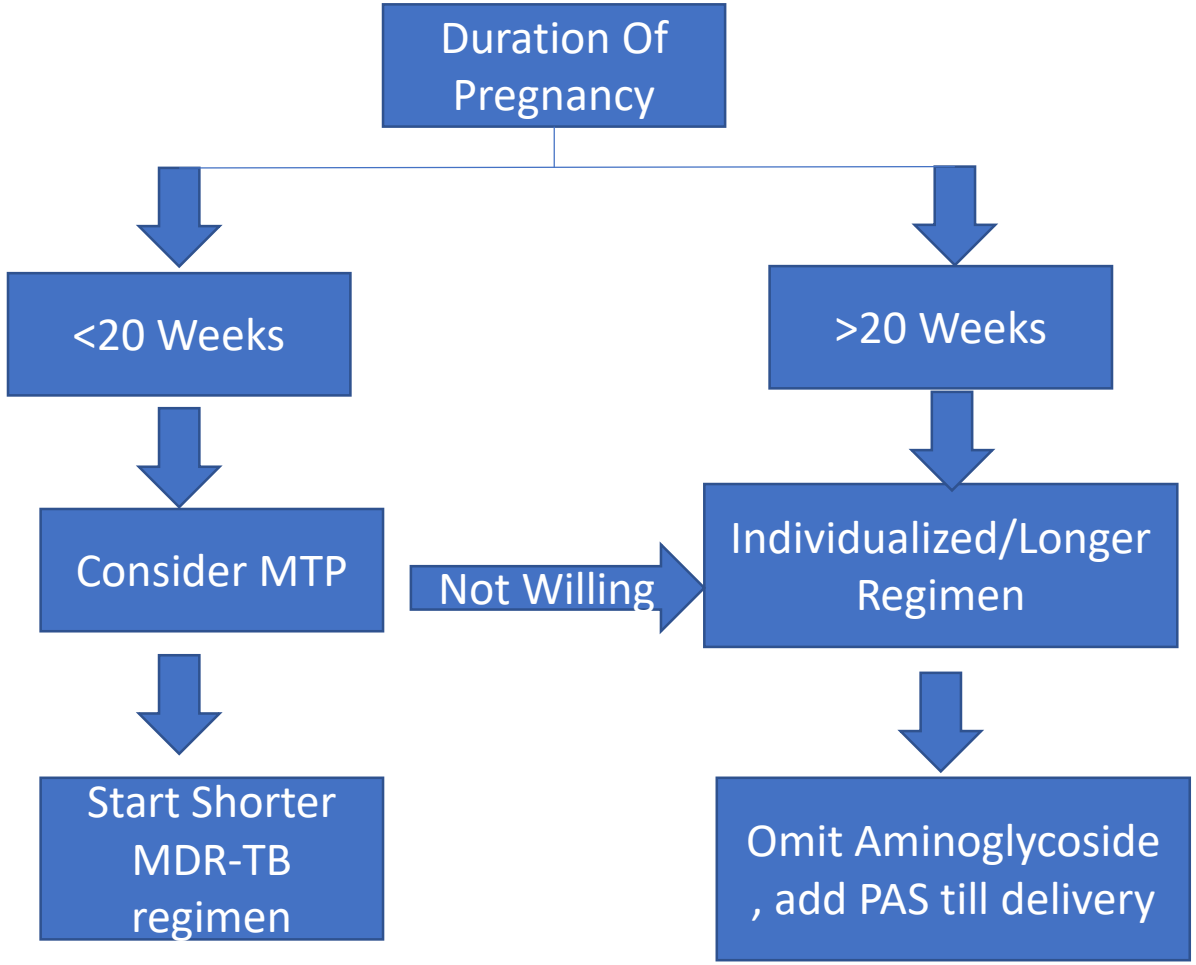
1. HIV + use longer regimen

2. All EPTB except(Lymph node and Pleural) prefer longer

3. Composition guided by DST

4. TBM – prefer FQ/Eto/Pto/Lzd/Imp-cls/H/Z
   Avoid E/PAS
   ?Cfz/Dlm/Bdq

DR-TB In Special Situations - Pregnancy



<u>Avoid</u>
Aminoglycosides
Prothionamide/Ethionamide
Delamanid

Bedaquiline ?

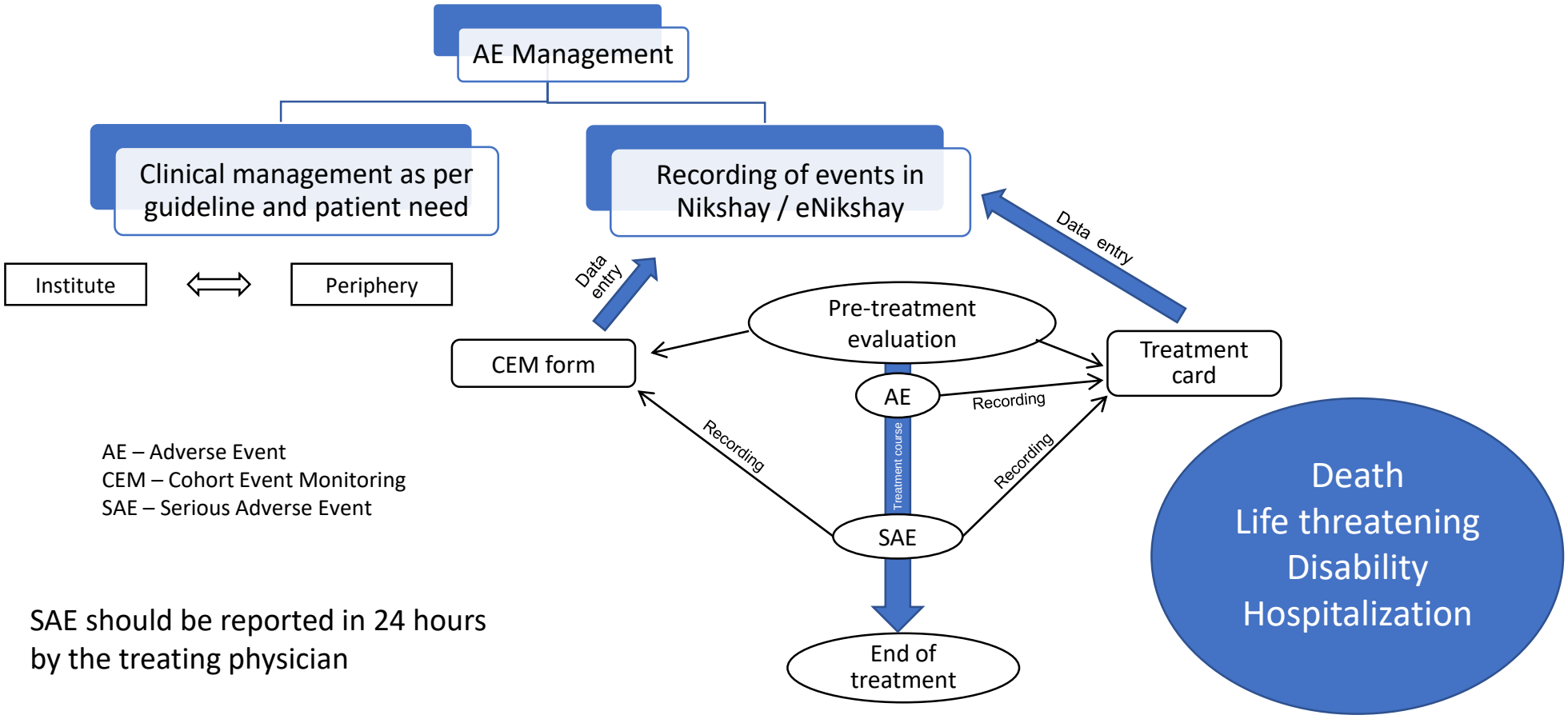
Condition	Drug Implication
HIV Co-infection	Shorter regimen not to be used in EPTB Efavirenz decreases BDQ/Pretomanid level (substitute with nevirapine) Tenofovir- AG (additive nephrotoxicity)
Children	Avoid Aminoglycosides BDQ >6yr Dlm >3yr
Renal Impairment	Z & E AG &FQ Cs PAS → Dosage adjustment and Monitoring
Cardiac illness	QTc monitoring with FQ/Cfz/Bdq/Dlm
Pre existing liver disease	Avoid Z / Caution with use of PAS/Eto
Seizure disorder	Cs avoided in active seizure d/s Pyridoxine prophylaxis
Psychiatric Illness	Caution with use of Cs/FQ/Eto

Common Adverse Effects With DR-TB Regimen

Adverse Effect-	Causative Drug	Management	Implication
Rash/Allergy	Any	Antihistamine/Hct cream	
Gastro Intestinal N & V Pancreatitis	 PAS/Eto/Pto Bdq/Lzd	 Antiemetic >3xULN/Symp. –Stop	Avoid anatacid
Hepatotoxicity	Z/Bdq/PAS/H/Eto/Pto	>5xULN- Switch to FQ/Cs/Injectables	R/o alternate causes
Myelosuppression	Lzd	Stop- start at lower dose	
Peripheral Neuropathy	Lzd(70%)/Cs/H HIV/DM/Alcoholic	100mg Pyridoxine/TCA/Dose⬇	Irreversible
Nephrotoxicity	AG	Frequency and dose⬇	D/C If progressive
Ototoxicity	AG	Frequency and dose⬇	D/C If progressive
Psychiatric	Cs/H/FQ	Dose⬇ /Haloperidol/200mg pyridoxine	Suicidal tendency- D/C
Optic Neuritis	Lz/E	D/C	
Cardiotoxicity	Bdq/Dlm/FQ/Cfz/Cm	QTc>500ms- D/C	

Guidelines On PMDT In India 2017

Active Drug Safety Monitoring(aDSM)



AE – Adverse Event
CEM – Cohort Event Monitoring
SAE – Serious Adverse Event

SAE should be reported in 24 hours by the treating physician

Guidelines On PMDT In India 2017

Standardised v/s Individualised Regimen

	STANDARDISED REGIMEN	INDIVIDUALISED REGIMEN
RISK	1. Increased risk of resistance amplification d/t suboptimal regimen 2. Usage of ineffective plus toxic drugs	1.Greater complexity in regimen formulation 2.Increased delay in initiation of treatment
BENEFIT	1.Simplified approach, lesser requirement of specialised knowledge 2.Easier to practice/apply at population level	1.Lesser risk of resistance amplification 2.Lesser risk of toxicity

H cox et al. Precision medicine in DR-TB Lancet Infect Dis 2018

Other Aspects Of PMDT

1. Drug and Vaccine distribution system – e Aushadhi

2. Patient Support

3. Project ECHO(Extension Of Community Health Care Outcomes)
   Use of video conferencing to link specialist with primary care providers

4. Infection control measures

5. Co-ordination with Private sector

Guidelines On PMDT In India 2017

Nikshay (Monitoring Of TB patients data by all concerened)

Register patients, record details, monitor treatment adherence and to transfer cases b/w providers

Pivotal role in DR-TB surveillance

Collecting information at source and its dissemination

Evaluate epidemiological characteristics of TB for better management

Monitor performance of TB management activities

Guidelines On PMDT In India 2017

Individualized Longer Regimen V/S Shorter Standardized Regimen

IPDMA of ~5000 patients from 9 studies on shorter regimen v/s 53 studies on longer regimen (Significant heterogeneity)

Treatment success was higher with shorter regimen

Less loss to f/u in shorter regimen

	Success	Failure or relapse	Death during first 12 months of treatment	Loss to follow-up
Shorter, 9 studies	2164/2625 80% (72.1-86.1%)	118/2625 3.6% (1.3-9.6%)	201/2625 7.6% (4.2-13.1%)	142/2625 4.2% (2.3-7.5%)
Heterogeneity estimates	*I^2= 92%, τ^2=0.35*	*I^2= 95%, τ^2=2.04*	*I^2=91%, τ^2=0.6*	*I^2=85 %, τ^2=0.51.0*
Longer, 39 studies	1814/2717 75.3% (69.8-80.0%)	112/2717 2.7% (1.5-4.7%)	265/2717 4.6% (2.9-7.2%)	526/2717 14.6% (11.0-19.0%)
Heterogeneity estimates	*I^2=79%, τ^2=0.42*	*I^2=60%, τ^2=0.8*	*I^2=69%, τ^2=0.74*	*I^2=76 %, τ2=0.5*

Abidi S et al. Eur Respir J 2019

New Trials

INDEX STUDY (Individualized management of DR-TB based on WGS)

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	448 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Patients randomized to the intervention receive a individualized tuberculosis treatment based on whole genome sequencing and the patients randomized to the control receive the standard of care tuberculosis treatment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	The Individualized M(X) Drug-resistant TB Treatment Strategy Study A Strategy to Improve Treatment Outcomes in Patients With Drug-resistant TB
Actual Study Start Date :	June 14, 2017
Estimated Primary Completion Date :	June 2021
Estimated Study Completion Date :	December 2021

Clinicaltrials.gov/ NCT03237182

UNMET NEEDS

Increase availability and manpower for UDST

Use of NGS to further narrow down treatment regimen

Newer drugs and treatment regimen

Decentralisation - Patient centred approach

WHO- RGLC MISSION REPORT INDIA 2019

PGI Data

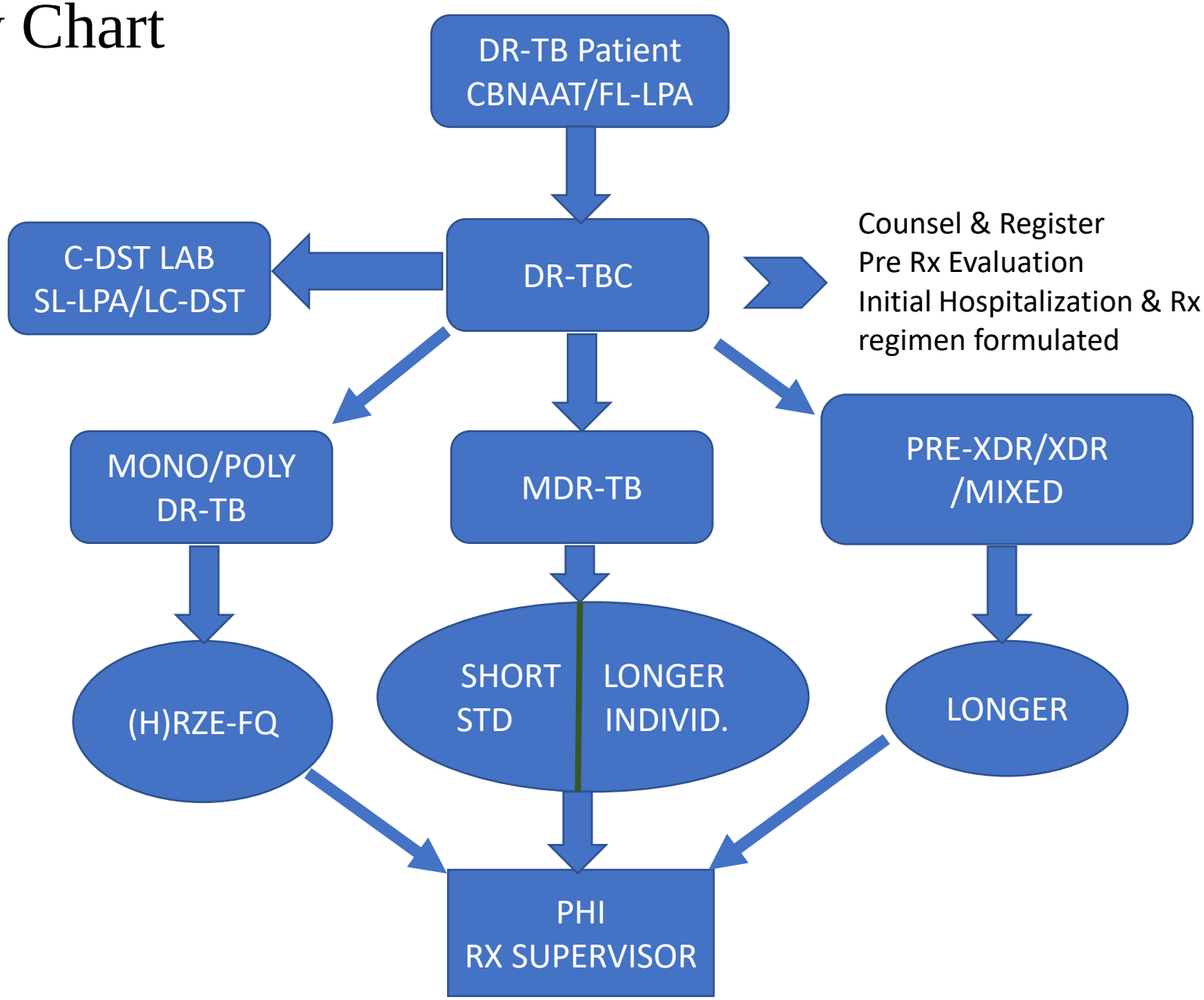
MONTHLY PERFORMANCE CHART DMC PGI TU-IV 2019

MONTHS	NEW NSP	NEW NSN	NEW NEP	PREVIOUSLY TREATED Relapse	PREVIOUSLY TREATED TAD	PREVIOUSLY TREATED Failure	PREVIOUSLY TREATED other	MDR MDR	MDR MONO DR	MONTHLY TOTAL	OUTCOME DURING THE MONTH cur.	OUTCOME DURING THE MONTH TC	OUTCOME DURING THE MONTH	OUTCOME DURING THE MONTH	OUTCOME DURING THE MONTH	TRA. OUT	SHIFT CAT IV	TB/ HIV CO. Inf.	INSIDE CHD.	OUT SIDE CHD.	NIRSHAY ID
JAN.	11	3	8	-	-	-	1	-	-	23	10	13							13	98	134
FEB.	6	4	10	-	1	-	2		1	22	5	5							23	117	162
MARCH	3	3	5	-	1	-	1			13	3	10							31	90	134
IST QUT.	20	10	23	-	1	-	4		1	58	18	28							67	305	430
APRIL.	11	2	7	1	1	-	-	-		22	7	15							17	123	162
MAY.	6	5	12	-	1	-	1	2		25	3	8							30	143	198
JON.	4	1	6	1	-	-	-	-	-	12	9	6	-	1					17	98	127
IInd QUT.	21	8	25	2	2	-	1	2		59	19	29		1					64	364	487
JULY.	12	1	9	-	1	-	-	-	-	24	5	12							31	151	206
AUG.	10	2	8	-	-	-	-	-	-	20	5	17							37	97	154
SEP.	7	1	8	1	-	-	-	-	-	17	8	8		1					35	137	189
IIIrd QUT.	29	4	25	1	1	-	-	-	-	61	18	37		1					103	385	549
OCT.	3	2	-	-	-	-	-	-	-	5	6	6							22	76	103
NOV.	5	1	5	2	-	-	1	-	-	14	7	17		1					17	100	129
DEC.	10	-	8	NIL	1			2		20	4	7		1					25	84	117
IVth QUT.	18	3	13	2	1	-	1	2	-	39	17	30		2					64	246	349
TOTAL	88	25	86	5	5	-	6	4	1	217	72	124		5					298	1300	1815

MDR-TB – 4(All On shorter regimen)

Hr-TB - 1

Flow Chart


DR-TB Patient
CBNAAT/FL-LPA
C-DST LAB
SL-LPA/LC-DST
DR-TBC
Counsel & Register
Pre Rx Evaluation
Initial Hospitalization & Rx
regimen formulated
MONO/POLY
DR-TB
MDR-TB
PRE-XDR/XDR
/MIXED
(H)RZE-FQ
SHORT
STD
LONGER
INDIVID.
LONGER
PHI
RX SUPERVISOR

Conclusion

Management of TB has changed by leaps and bounds

Focus has shifted towards eliminating TB from controlling it(RNTCP-NTEP)

Significant gaps in diagnosis and management exist especially w.r.t DR-TB still remain

New tests(molecular DST) and new effective drugs are need of the hour

THANK YOU