



health

Department:
Health
PROVINCE OF KWAZULU-NATAL

MDR TB UPDATE

AWACC 2019

Iqbal Master
Clinical Manager
King Dinuzulu Hospital complex

DEPARTMENTAL SUCCESS - SINCE 2006

- ◉ Increased MDR beds in all provinces /Dedicated funding
- ◉ Adopted a model of decentralized care
- ◉ Formed an expert committee
 - Designed country specific guidelines
- ◉ Regular training on MDR for nurses and clinician
 - NIMDR training Support
- ◉ Active support for Research
- ◉ Design program specific tools
 - Electronic DR TB register/MDR Register (paper based)/tools
- ◉ Implemented Rapid Diagnostics
 - GXP/LPA/Reflex testing
- ◉ Intervention for Poor Outcomes/High Mortality/Toxic drugs/Long Regimens
 - Roll out of new drugs BDQ/LZD/DLM (2013) - world leaders
 - Shorter regimens (2017)
 - Substitution for Drug Toxicity
 - Roll out of a Strong ARV program
 - Moved to injection free regimens (2018)

Date	History of SA DR-TB Program
1997-2013	<p>MDR - Standard Treatment 6 Mths/ 18 Mths Kana/Moxi/Ethio/PZA/Teriz -</p> <p>XDR / PReXDR - Individualized treatment</p>
2013-2017	<p>Implementation of new drug program (BCAP) BDQ + LZD for -</p> <ul style="list-style-type: none"> • XDR /Pre-XDRs • MDRs - Drug toxicities + Rx failures • Pregnancy
2017 (June KZN)	<p>Short MDR Regimen & Short BDQ regimen</p>
2017 (Mar 2018)	<p>DCAP - BDQ/LZD/DLM - for XDR / PRe-XDRs</p>
2018 (July)	<p>Injection Free regimen for MDRs - (implemented in RSA as primary Rx option)</p>

WHO RECOMMENDATIONS & NEW SA REGIMENS

- ◉ WHO revised MDR guidelines (preliminary) - 16 July 2018
 - ▣ Compiled a List of medications recommended for long regimens
 - ▣ Not yet enough evidence for a Short Bedaquiline regimen
 - ▣ Amikacin recommended in short regimen but (not Kanamycin)
- ◉ WHO Guidelines review planned(15 Nov 2019)
- ◉ SA MDR Program
 - ▣ **BDQ already used in short regimens**
 - ▣ **Under pressure to implement injection free regimens**
 - ▣ **SA experts confident enough to implement an injection free regimen**



DURATION OF DRUGS ADMINISTRATION

	2 MONTHS	4 MONTHS	6 MONTHS	9 MONTHS
Linezolid				
INH high dose			Extend to 6/12 if smear still pos at 4/12	
Bedaquiline				Continue in some
Levofloxacin				
Clofazamine				
Pyrazinamide				
Ethambutol				



NEW WHO LONG REGIMENS

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin <u>OR</u>	Lfx
	Moxifloxacin	Mfx
	Bedaquiline ^{1,4}	Bdq
	Linezolid ²	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine <u>OR</u>	Cs
	Terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid ^{3,4}	Dlm
	Pyrazinamide ⁵	Z
	Imipenem-cilastatin <u>OR</u>	Ipm-Cln
	Meropenem ⁶	Mpm
	Amikacin (<u>OR</u> Streptomycin) ⁷	Am (S)
	Ethionamide <u>OR</u> Prothionamide	Eto Pto
<i>p</i> -aminosalicylic acid	PAS	

LONG REGIMEN = GROUP A & B DRUGS IN
NEW WHO HIERARCHY OF DRUGS

LONG REGIMEN > 12 YEARS (> 6 YEARS)

- 6 - 8 months (Intensive Phase):

Bdq - Lzd - Lfx - Cfz - Tzd

- 12 months (Continuation Phase):

Lfx - Cfz - Tzd

◦ Indications

- Previous exposure to 2nd line anti-TB agents > 1 month
- MDR TB with Both INH mutation
- Pre-XDR (INJ)
- Where 2nd line resistance is suspected.
 - Close contact of pre/XDR, both INH mutations ,
 - Complicated/severe EPTB (CNS, osteoarticular, ? pericardial)
 - Extensive disease
 - When clinician is unsure if short course ok
- If toxicity to core drugs - discuss with Provincial or National Committee (possible substitution with 2 drugs from category C)

LONG INDIVIDUALIZED REGIMEN - PRE-XDR FLQ/XDR > 12 YEARS (> 6 YEARS)

- 6 - 8 months (Intensive Phase):

Bdq - Lzd - Cfz - Tzd + (DLM or PAS) + (Ethio or hdINH) + Z

- 12 months (Continuation Phase):

Lzd - Cfz - Tzd + (Ethio or hdINH) + Z

Indications

- ◉ XDR / PRe-XDR (FQ)
- ◉ DR Treatment failure

LONG INDIVIDUALIZED REGIMEN: CNS

- **6 - 8 months (Intensive Phase):** Bdq - Lzd - Lfx_(1g) - Cfz - Trd - (hdINH (15mg/kg) or Ethio) - Z

- **12 months (Continuation Phase):** Lfx - Cfz - Trd - (hdINH(15mg /kg) or Ethio) - Z

* Lzd can be extended into continuation phase if no adverse events

- All children with CNS disease should be discussed with experienced paediatric / DR TB clinician
- For TBM & Miliary MDR TB in children ensure adequate appropriate drugs
Should include LFX /LZD / TRD /PZA /HINH

FLQ resistance - contact PCAC / NCAC may need carbapenem/DLM

DR TB + CNS DX - LONGER REGIMEN

- DR TB with CNS Dx will require an individualised regimen with drugs with good CSF penetration:
 - Terizidone
 - High dose isoniazid
 - Linezolid
 - Ethionamide
 - PZA
 - Levofloxacin
- Drugs with poor penetration cannot be relied on
 - Delamanid - penetration is uncertain
 - Some studies were positive
 - BDQ and CFZ - do not penetrate well

Dosages currently advocated in KZN in DR TB – in adults

Medicine	Weight			
	<33kg	33-50kg	50kg to 70kg	> 70
Bedaquiline	½ normal dosage	400mg dailty - 2 weeks – thereafter 200 mg 3 times a week		
Linezolid	300mg (10mg/kg)	600mg	600mg	600mg
Levofloxacin	15-20mg/kg	750mg	1000mg	1000mg
Clofazimine	50mg (2-3mg/kg)	100mg	100mg	100mg
Pyrazinamide	30-40mg/kg	1500mg	1750mg	2000mg
Ethambutol	15-25mg/kg	800mg	1200mg	1200mg
Isoniazid (HD)	10-15mg/kg	~600mg	~600mg	900mg**
Terizidone	15-20mg/kg	500mg	750mg	750mg
Ethionamide	15-20mg/kg	500mg	750mg	750mg
PAS	4g (200-300mg/kg)	8g	8g	12g
Moxifloxacin	400mg (7.5-10mg)	400mg	400mg****	400mg ****
Amikacin	15mg/kg (max 1g) - 6-7 times a week			

PROPOSED CHANGES TO GUIDELINES

- ◉ NCAC meeting held on 31/7/2019 in Cape Town
 - ▢ Not yet for release / needs finalization
- ◉ Significant changes in Paeds Regimen
 - ▢ Adult regimens to be used for children > 6 years
- ◉ Changes in toxicity management
 - ▢ Consideration to not rechallenge LZD after it has caused Anaemia
 - ▢ To cap pyridoxine at 100mg maximum
- ◉ New regimens with regard ARV therapy in MDR patients
 - ▢ Still to be finalized
- ◉ Need for a formal Provincial committee
 - ▢ Greater role for a Clinical Advisory Committee

Revised guidelines are still under discussion and yet to be finalized

PLANNED CHANGES TO PAEDIATRIC REGIMEN

- ◉ New regimens in children < 6
 - No standard short regimen as in adults (Bangladesh)
 - No PZA / EMB unless sensitivity proven
 - DLM recommended (> 3 years)
 - BDQ > 15 kg (or > 6 years)
- ◉ Duration changed
 - no short course - duration dependent on Extent of disease and Type of resistance
 - Non-severe Disease(9-15 mths)
 - Severe disease (12-18 mths)
- ◉ Some recommendation on Prophylaxis
 - Options possible

CRITERIA FOR PROVINCIAL/NATIONAL APPLICATION & APPROVAL

⦿ Provincial

- ❑ XDR /Pre-XDR(FQ)
- ❑ Drug toxicities
- ❑ Pregnancy

⦿ National

- ❑ Pre-XDR or XDR - with limited RX options
- ❑ DR TB Treatment failures
- ❑ Age < 12 years
- ❑ Pregnancy (Inform National so that a register can be kept)

- XDR
- Pre-XDR(FQ)
- Treatment failures
- Children < 12

Being referred to KDHC

BDQ ISSUES - 2013 >>>>

- ◉ Bedaquiline - is used for 24 weeks
 - ▢ Long half life (5 months)
 - ▢ 400 mg (daily) for 2 weeks / 200 mg (3 times a week) for 22 weeks
 - ▢ BDQ can be extended in certain cases (Discussion with NCAC)
- ◉ Levofloxacin preferred to Moxifloxacin (less QTC)
- ◉ Monitoring
 - ▢ ECG - 2 weekly for 1st month & monthly thereafter
- ◉ Drug Interactions
 - ▢ - QT prolongation
 - ▢ - Enzyme Induction
- ◉ ARV switch often required
 - ▢ Need to Switch EFV in FDC (Decreases BDQ levels)
 - ▢ Dolutegravir will be used in more patients (once finalized)
- ◉ BDQ is used for 6 months but can be extended to 12 -18 mths
 - ▢ Discuss with provincial / national expert committee

LINEZOLID (ZYVOXID)

◉ Long term usage is associated with serious A/E

□ Bone marrow suppression

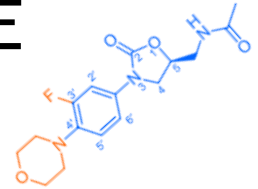
□ Thrombocytopaenia / Anaemia / Neutropaenia

□ Avoid or transfuse if Hb < 8 g/dl / platelets < 50 , neutrophils < 0.75

□ Moderate to Severe peripheral neuropathy (Avoid or Stop)

□ Optic neuritis - reversable if picked up early

□ Lactic acidosis - due to mitochondrial toxicity



◉ Monitoring

□ Regular FBC (monthly) for Ops / weekly for IP

□ Assess vision - Snellen + ? Ishihara tests

□ Assess Neuropathy

□ Check Lactate if ill or if acidotic

DELAMINID

- ◉ DCAP recruitment ended in March 2019 (400)
 - ▢ KZN put 232 patients
- ◉ Delamanid became registered around 29/3/2019
 - ▢ Initial stock will be section 21 stock - apparent price is R 28000
 - ▢ Tender will come out later ? October 2019 (? R14000)
- ◉ National purchased DLM as interim and distributed to the provinces - available from 29/7/2019
 - ▢ Current indication for DLM
 - ▢ Pre-XDR(FQ) / XDR / Treatment Failures / Selected Toxicities
 - ▢ Had more than 70 patients started without DLM since Feb 2019
 - ▢ Reviewing patients to see who is still qualifies for DLM &
 - ▢ What drug combination to start them on DLM alone / DLM + imipenam

BDQ EXTENSION & INTERRUPTION

- ◉ *BDQ is usually given for 6 months but can be extended up to 18 months in the following cases:*
 - Late smear and/or culture conversion
 - Drug Toxicities (Like LZD)
 - No second line DST results *available*
 - *Discuss with PCAC*
 - Extensive TB disease
- ◉ **BDQ interruption -**
 - No reloading if < 30 days default
 - Reload for 1 week if > 30 days default
 - **Reload for 2 weeks after 2 to 4 gap months - NCAC to finalize**

GENE EXPERT ULTRA -TRACE POS RESULT

- If previous TB - GXP may be reflecting Old TB
 - ▢ (up to 5 years ago)
 - ▢ May be false positive for active disease - due to dead bacilli
- If no past TB - more likely to be true positive
- Clinical assessment and Past History must be considered
 - ▢ Culture & LPA should be done in addition and followed up.
- If GXP Pos/ Rif unsuccessful
 - ▢ Treat for sensitive TB
 - ▢ Sensitive TB is far commoner than DR TB - do an LPA

NB - Gene Xpert may remain positive for > 5 years

ISONIAZID MONO-RESISTANT TB (RIF SUSCEPTIBLE) - WHO RECOMMENDATIONS

- ◉ Isoniazid Mono resistant (Rif sensitive)- treat with -
 - Rifampicin
 - Ethambutol
 - Pyrazinamide
 - Levofloxacin
 - with or without Isoniazid for 6 months
- ◉ Practically better give RHZE plus Levofloxacin for 6 months
 - **monthly** TB smear and culture
 - Watch out for Pre-XDR TB

CONGENITAL TB

- Clinical presentation
 - Non specific
 - Lethargy
 - poor feeding
 - low birth weight and poor weight gain
 - Multiple organ involvement / Active TB between week 2-4
 - Respiratory problems
 - Hepatosplenomagaly
 - Lymphadenopathy,
 - Abdominal distension
 - Seizures
 - Jaundice
 - Otitis media
 - paravertebral abscesses
 - Not responsive to antibiotic therapy
- Investigations
 - Complete investigation of mother and neonate
 - CXR/ GA/Tissue for histological diagnosis
 - TST
- BCG should not be given to neonates exposed to TB while screening for active disease

APPROACH TO PREVENTIVE THERAPY

- ◉ Randomized controlled trials required
- ◉ Options for high-risk RR-TB contacts
 - children under 5 years of age
 - older HIV-infected children
- Clinical monitoring, without therapy, and close follow up to detect TB disease early;
- LFX / EMB (although high EMB resistance) /high-dose INH
 - for 6 months (If index case susceptible to the fluoroquinolones).
- INH for 6 months - for confirmed rifampicin mono-resistant TB
 - where confirmed Phenotypic susceptibility to INH (normal dose)
 - MDR-TB with inhA mutation only (high dose)
- Fluoroquinolone alone may be considered but limited evidence

Program must be well Structured & Supported & Good Adherence and adequate supply of Levofloxacin

QUESTION 1

AN ADULT PATIENT PRESENTS WITH A 1ST EPISODE OF TB AND REFLEX RESULT SHOWS RESISTANCE TO INH + RIF + FLUROQUINOLONES + KAT G MUTATION
WHAT REGIMEN WOULD YOU ADVISE?

1. Kanamycin/Moxi//PZA/EMB/Ethio/INH
2. BDQ/LZD/Levo/Clofaz/Pza/EMB/hINH
3. BDQ/LZD/Clofaz/DLM/Terizidone/PZA
4. BDQ/Amikacin/PZA/EMB/Levo/Ethio

QUESTION 2

A PATIENT DIAGNOSED AS GXP RIF SENSITIVE HAS COMPLETED 6 MONTHS RIFAFOUR BUT REMAINS CULTURE POSITIVE. HE ALSO IS NOT VIRALLY SUPPRESSED
WHAT IS A POSSIBLE CAUSE ?

1. Patient is probably defaulting TB treatment
2. Patient is failing due to virological failure
3. Patient may be failing due to extensive cavitary disease
4. Patient has a RPOb 491 mutation (Swaziland Strain)
5. All of the above

QUESTION 3 :

PATIENT IS ON MDR TREATMENT AND REMAINS POSTIVE AFTER 6 MONTHS. WHAT SHOULD WE DO ?

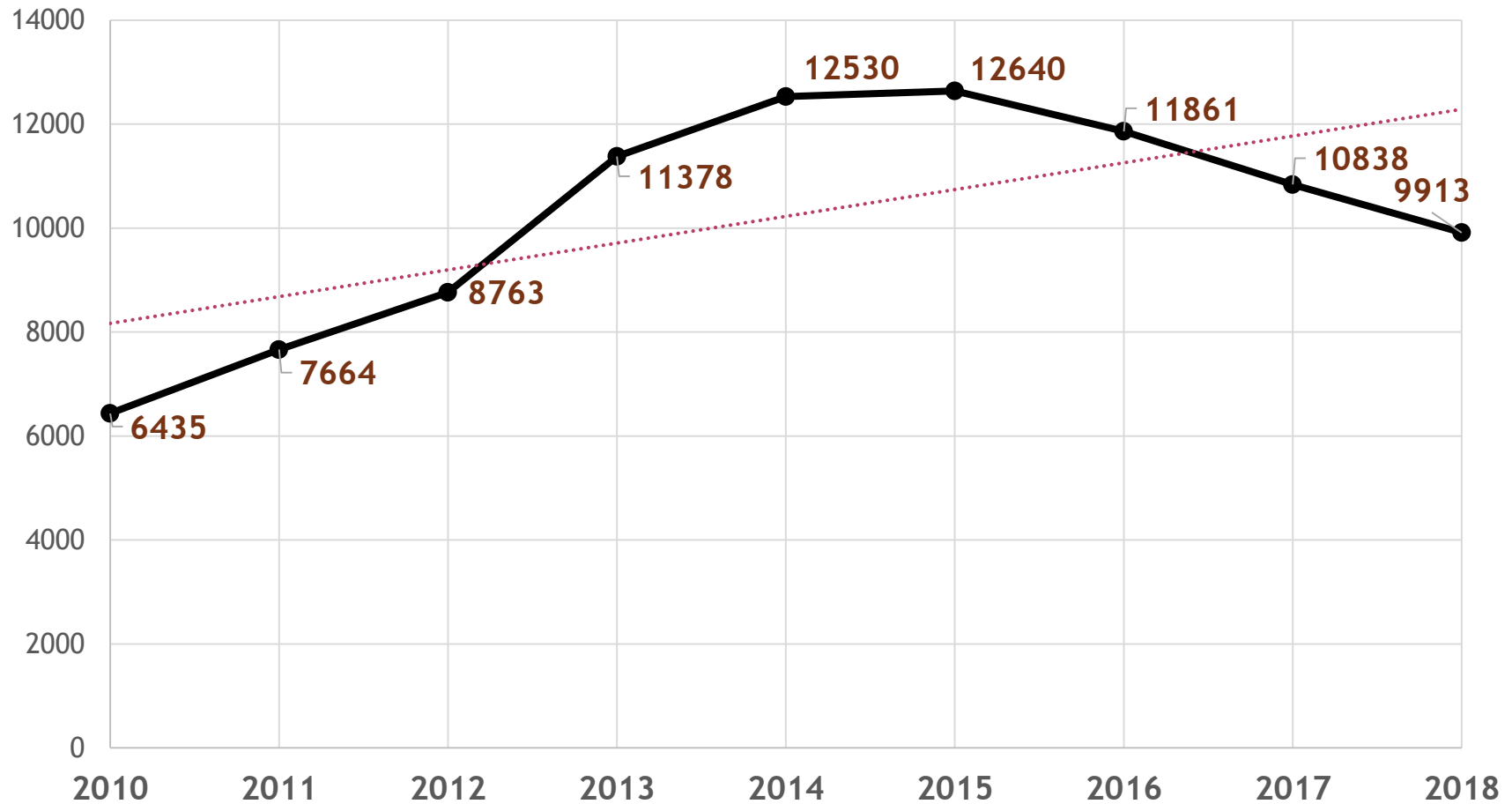
1. Counsel patient & Reinforce adherence to TB Meds. Refer to social worker / bring Family for counselling
2. Optimize ARV therapy / Recheck Viral Load
3. Consider Referring patient for Surgery
4. Repeat a Reflex test and Send a sputum culture for an extended DST
5. ALL of the above

QUESTION 4 :

IS THE SHORT INJECTION FREE REGIMEN GIVING AS GOOD OUTCOMES AS THE OLD LONG REGIMEN

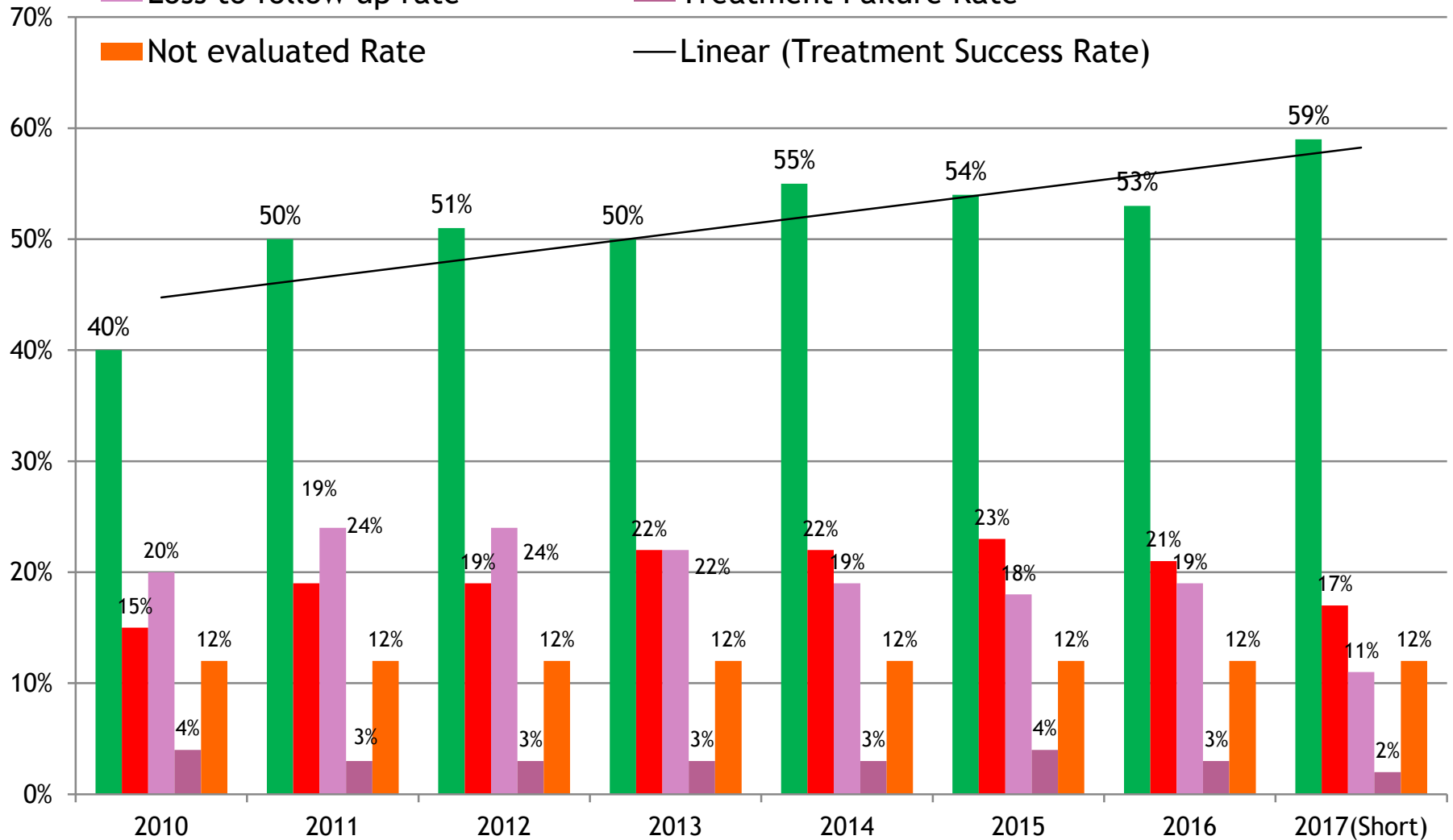
1. No - It is not working , the outcomes are poorer
2. Yes - The outcome are much better than the long regimen
3. Maybe - Initial Data looks good but it is still to early to tell, we need to look at long term relapse rates.

TOTAL NUMBER OF PATIENTS STARTED ON DR-TB TREATMENT

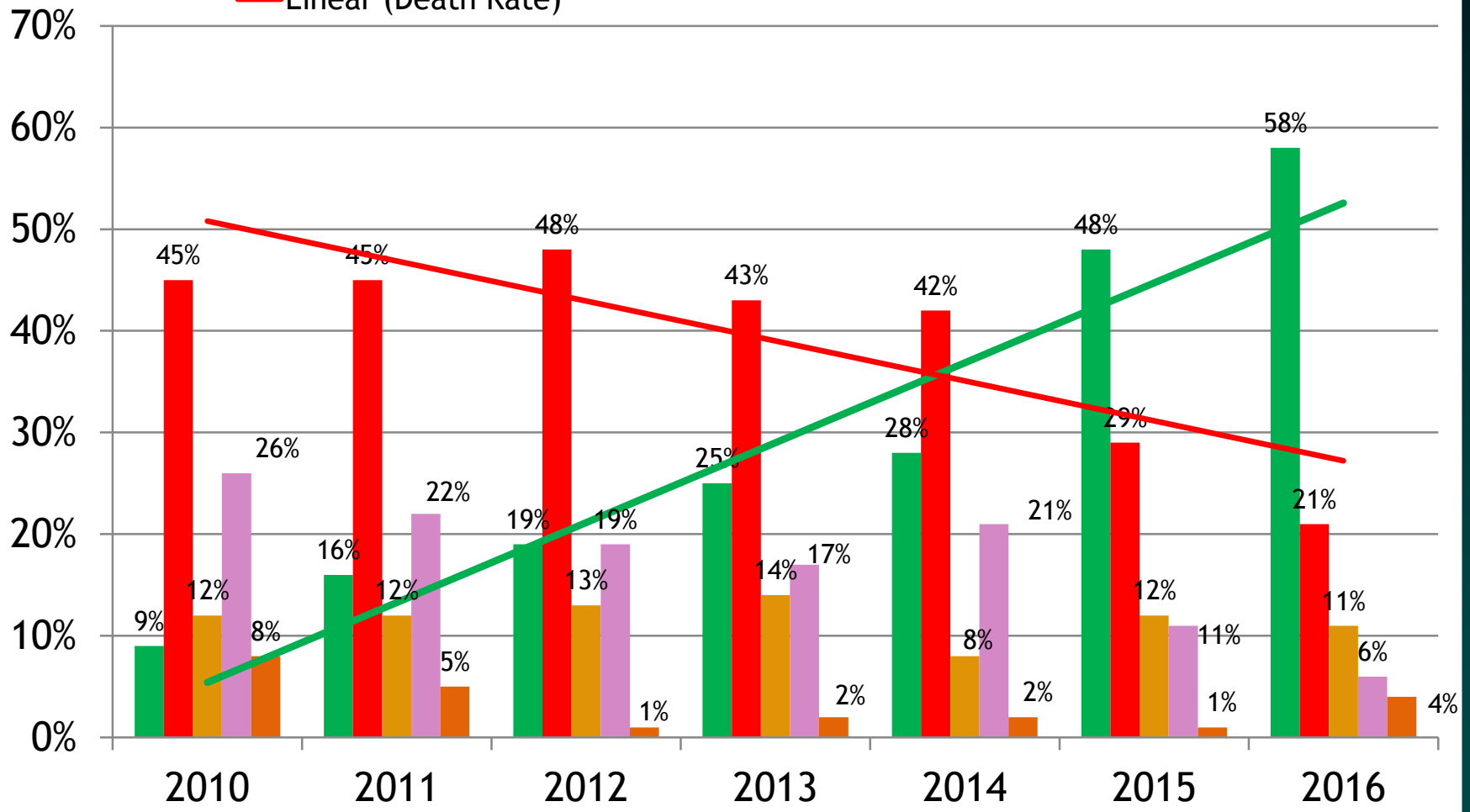


RSA-RR/MDR-TB OUTCOMES

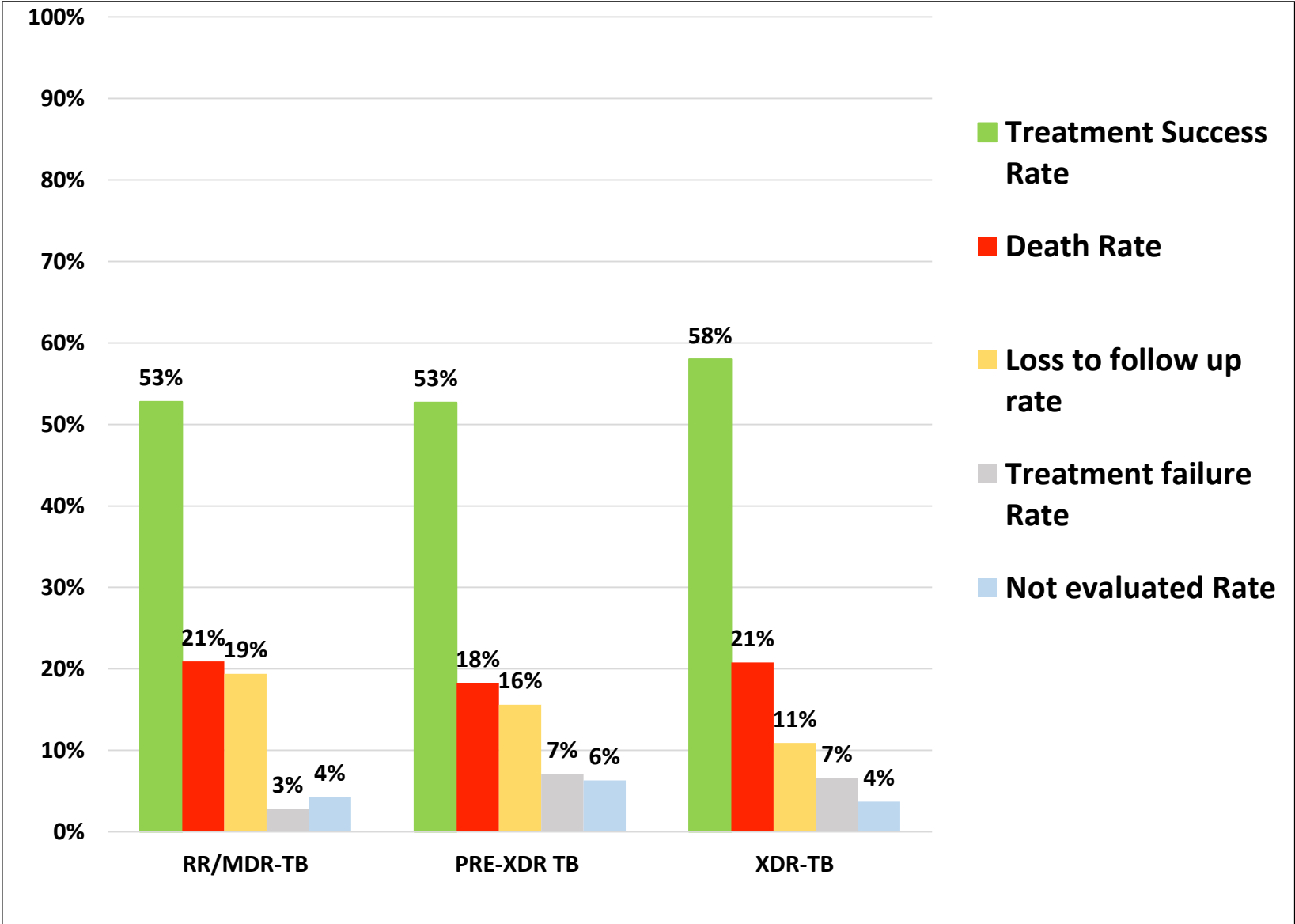
2010-2016 + 2017 SHORT COURSE



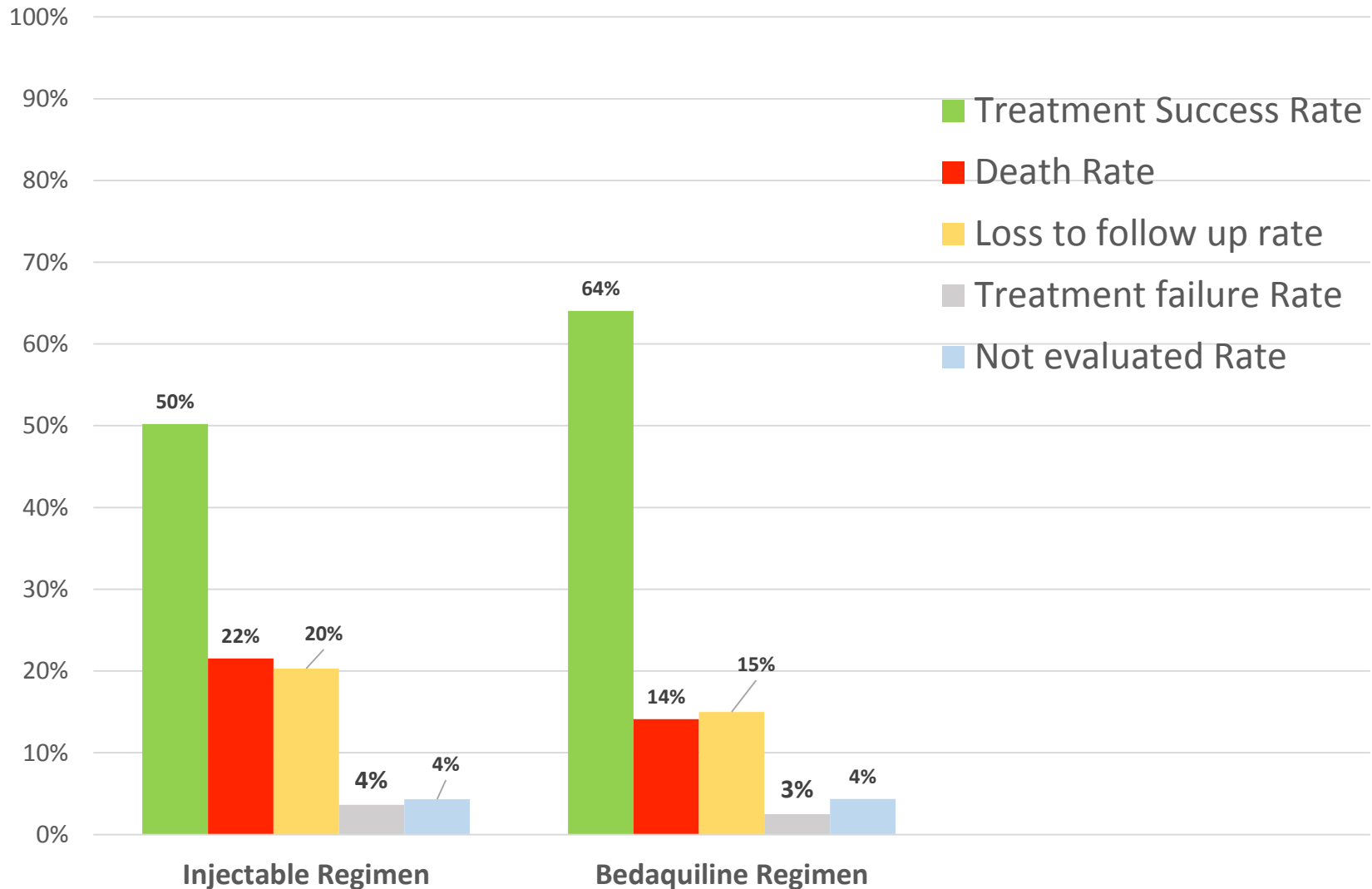
XDR-TB OUTCOMES 2010-2016



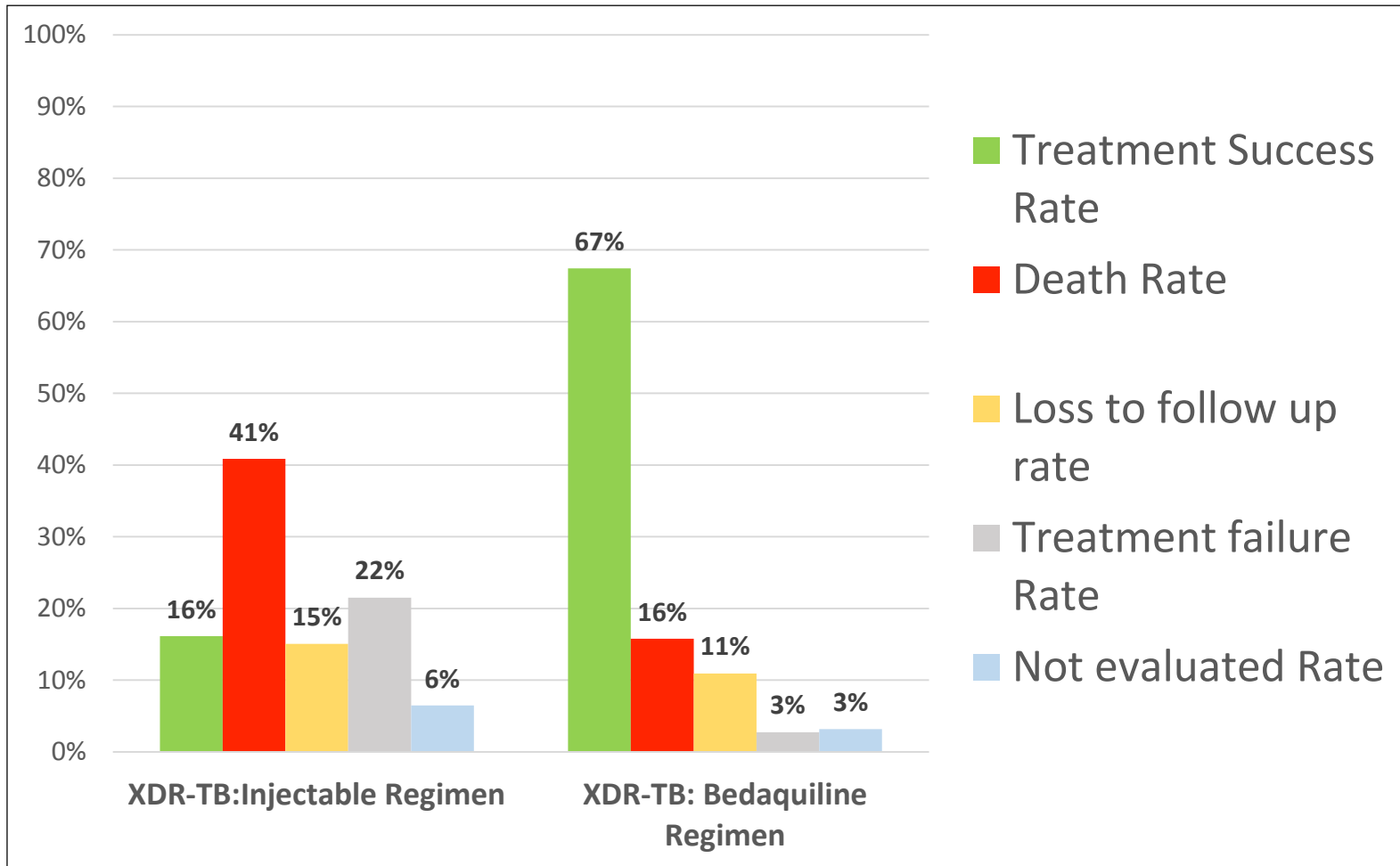
COMPARING OUTCOMES LONG REGIMEN-2016



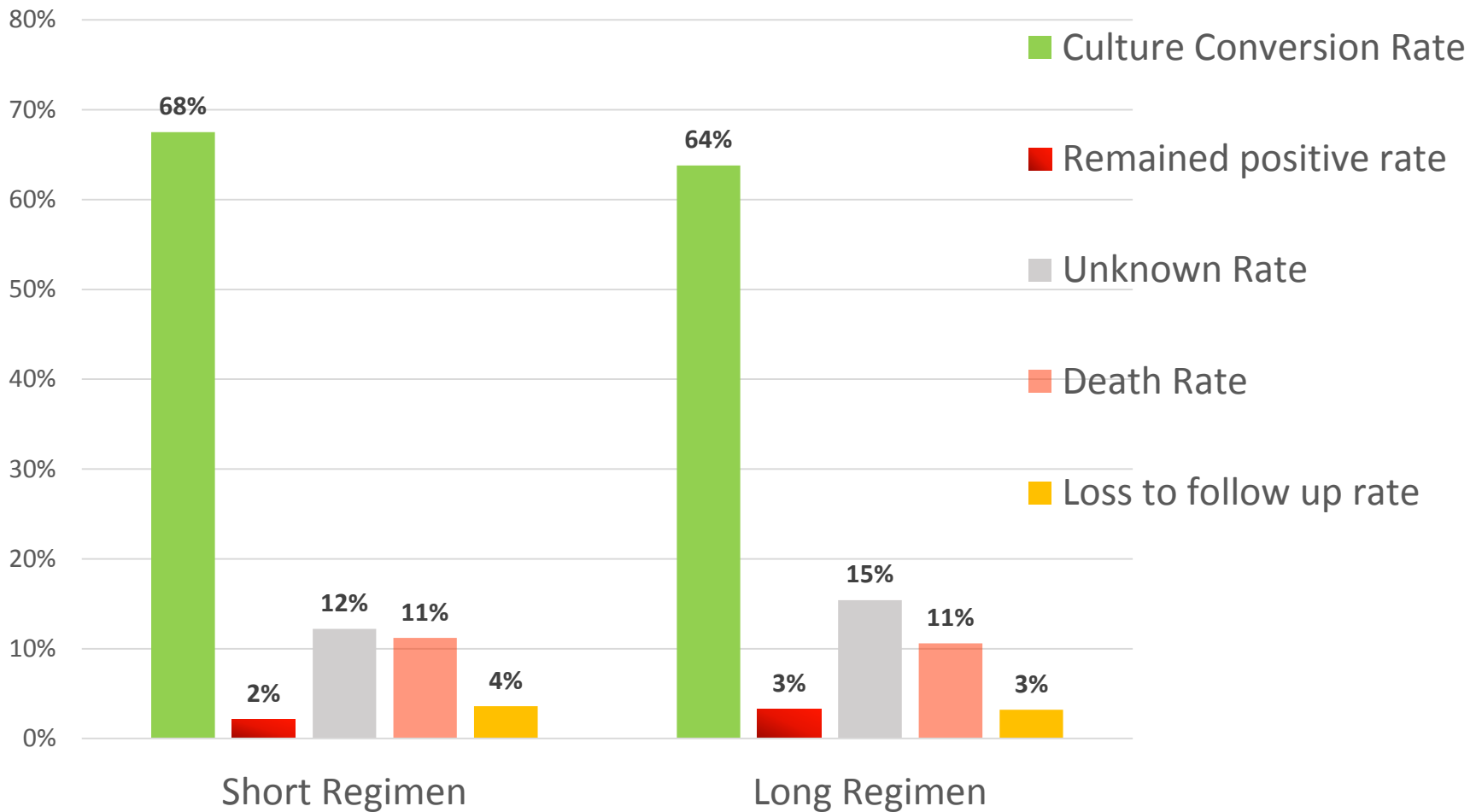
2016 - MDR OUTCOMES : BDQ VS INJ LONG REGIMEN



2016 - XDR OUTCOMES BDQ VS INJ



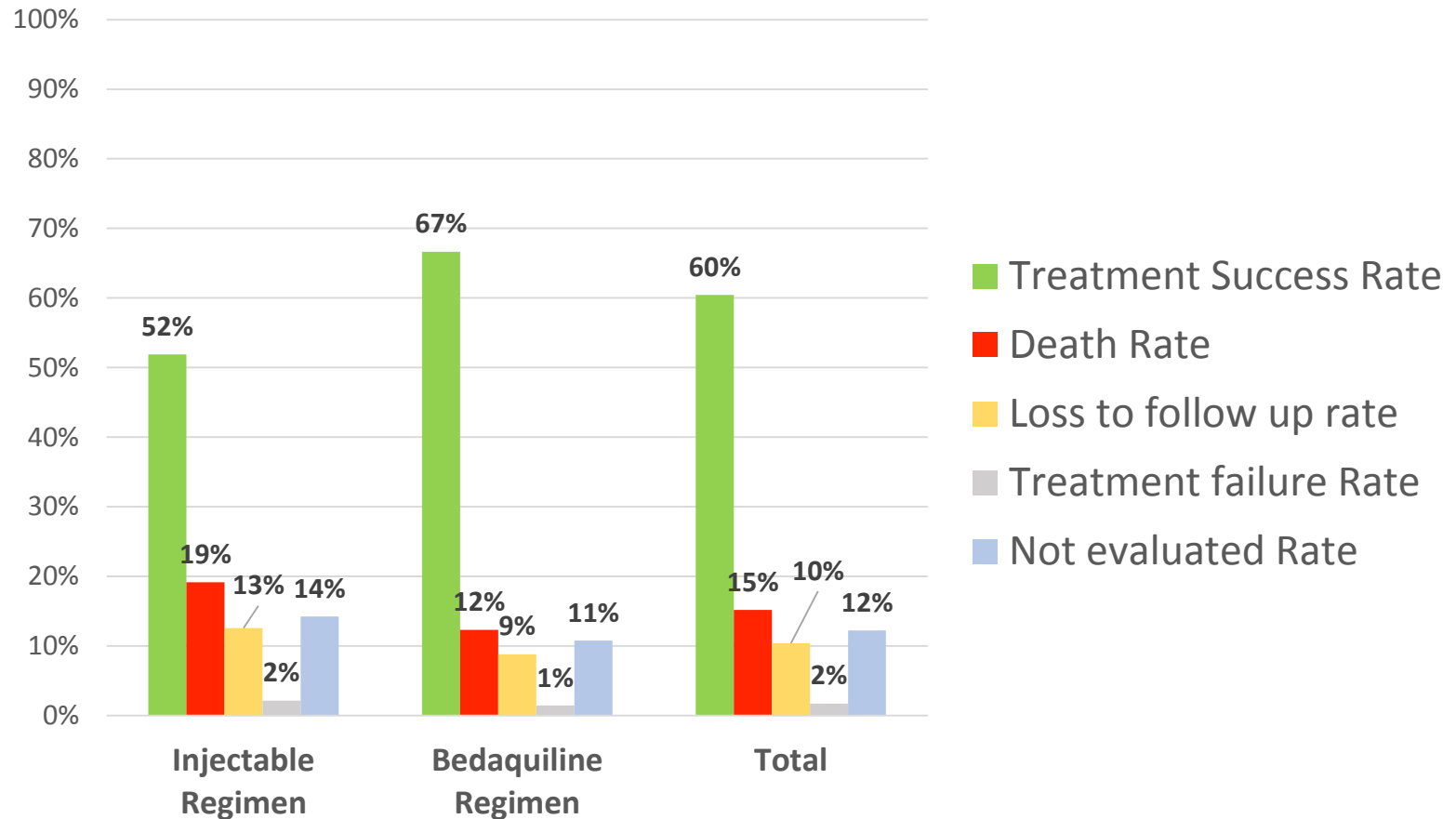
RSA-SIX MONTH INTERIM OUTCOME-2017



	2017	2018
Short Regimen (10838)	34%	64%
Long Regimen (9913)	66%	36%

TREATMENT OUTCOMES SHORT REGIMEN-2017

BDQ VS INJECTABLE



CHALLENGES & SOLUTIONS

◉ Challenges

- ❑ High Defaulters Rates
- ❑ Finding the missing cases
- ❑ Dropping Bed Occupancy Rates
- ❑ Lack of Beds for Ill Sensitive TB patients
- ❑ Issues around Data Capturing

◉ Solutions

- ❑ Beds for Sensitive TB Patients
 - ❑ Reevaluate the distribution of TB Beds
- ❑ Finding the missing cases
 - ❑ Enhance contact tracing
- ❑ Reducing Lost to follow up
 - ❑ Improve defaulter tracing
- ❑ Dropping bed Occupancy
 - ❑ Reviewing criteria for admission / better patient support
 - ❑ Admitting defaulters for supervised treatment
- ❑ Ensure that Data Capturer post is filled

BEDAQUILINE RESISTANCE ??????

- ◉ As more sputa are being sent to NICD for additional resistance testing we are finding more BDQ resistance
 - ▣ Some have baseline resistance
 - ▣ Some develop resistance whilst on treatment
 - ▣ Some are cured despite BDQ resistance
 - ▣ In problem cases - rates may be up to 10 %
- ◉ Issues
 - ▣ We do not understand the drivers of resistance and the implications fully
 - ▣ More work is needed
 - ▣ It is critical to protect the new drugs

NB - Critical to work towards protecting BDQ

THE CHALLENGE

As a country we have made great strides and are leading the world in the rollout of new MDR drugs.

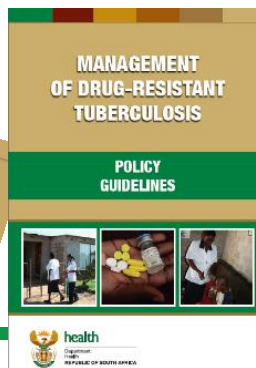
BUT

We need to be vigilant and focus on our high defaulter rates to ensure we do not lose our new drugs.

ACKNOWLEDGEMENTS

- Dr Ndjeka
- Members of National Clinical Access Committee
- Mrs Nirupa Misra
- Management , Doctors & Staff of KDHC
- All Health care Workers

May you be richly rewarded!
Thank you!



Iqbal.master@kznhealth.gov.za