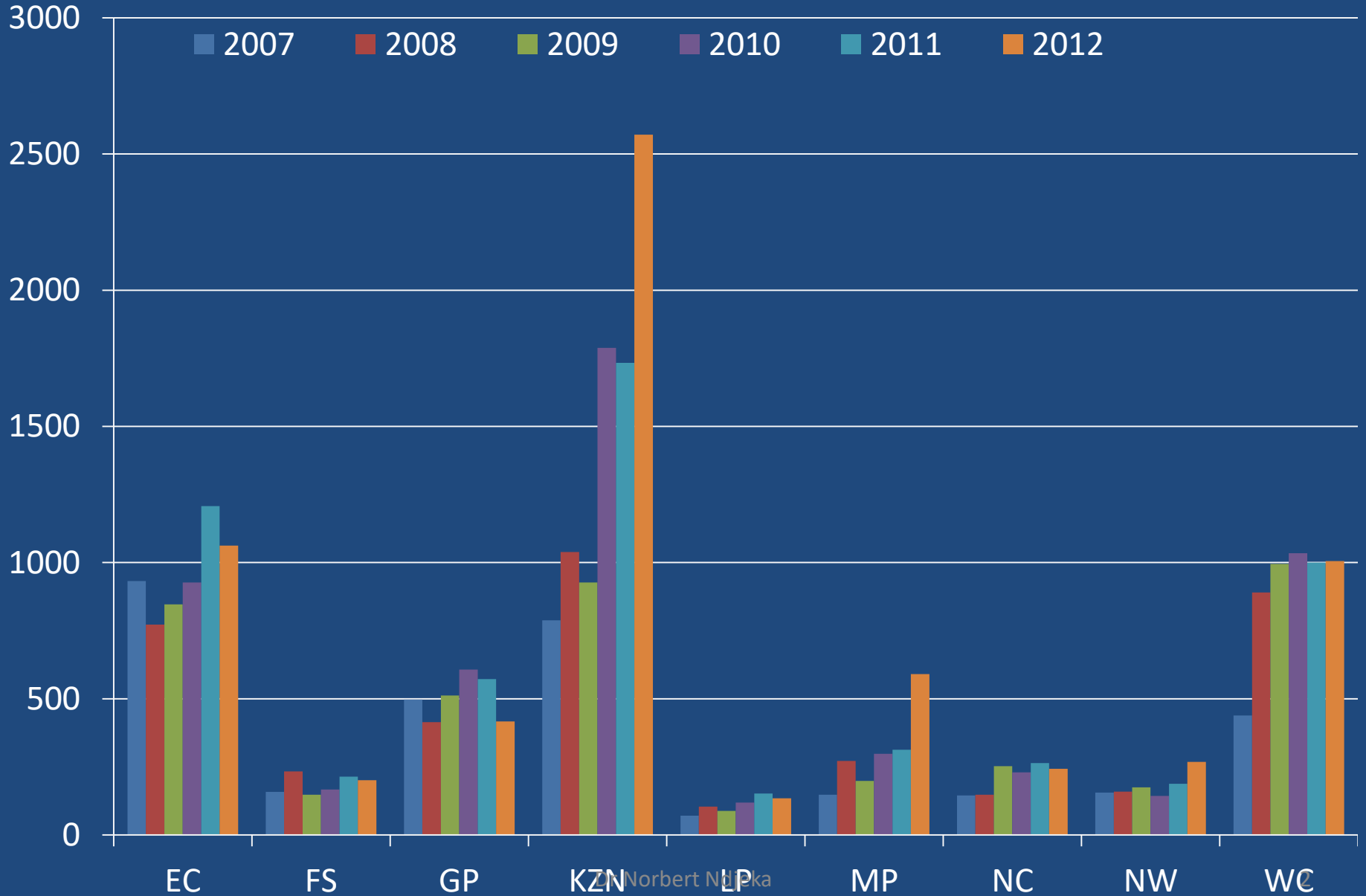


# Management of Drug resistant TB

Dr Francesca Conradie  
Clinical HIV research Unit  
University of Witwatersrand

# MDR-TB Cases Started on Treatment

## Extent of the problem in South Africa

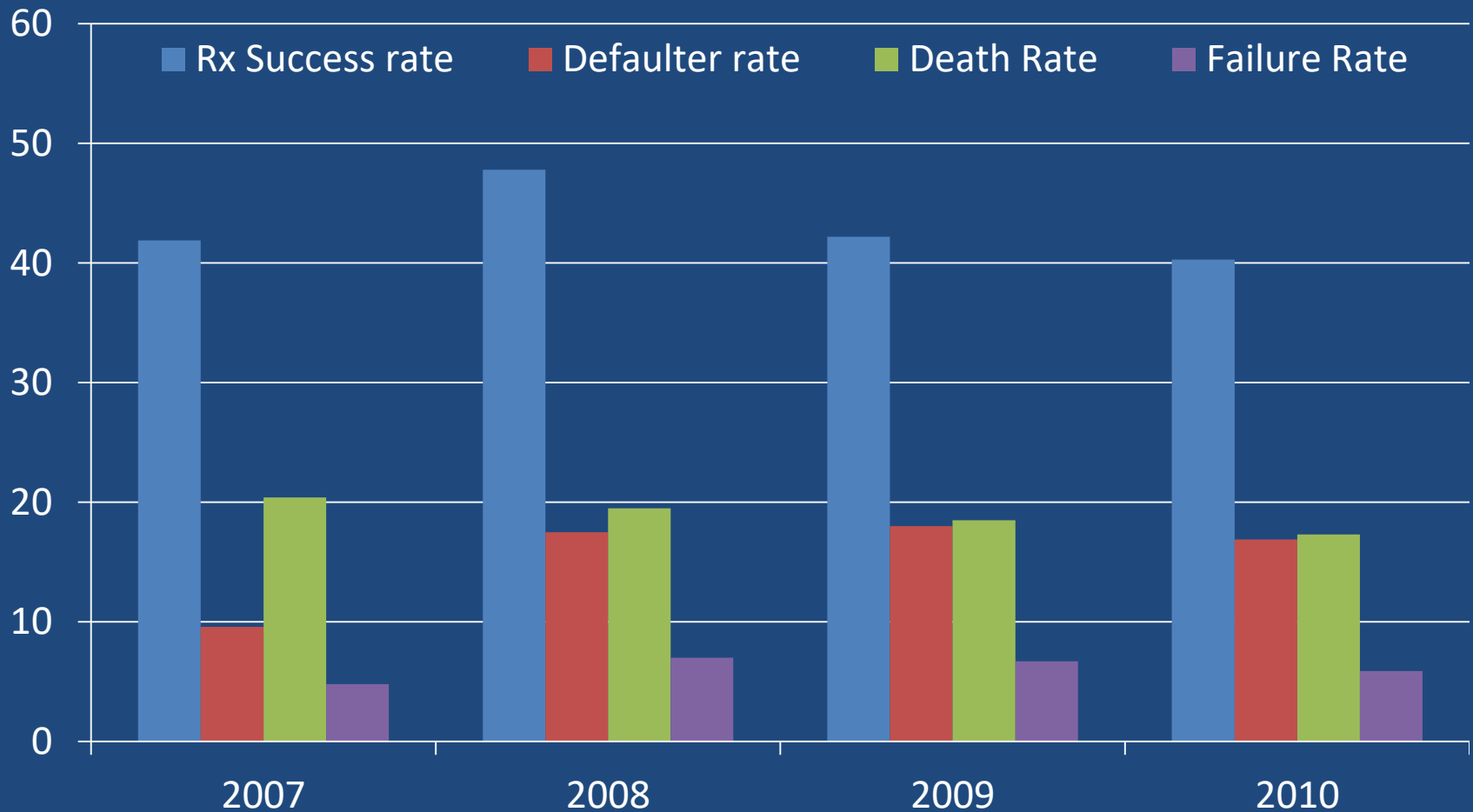


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# Topics to be covered

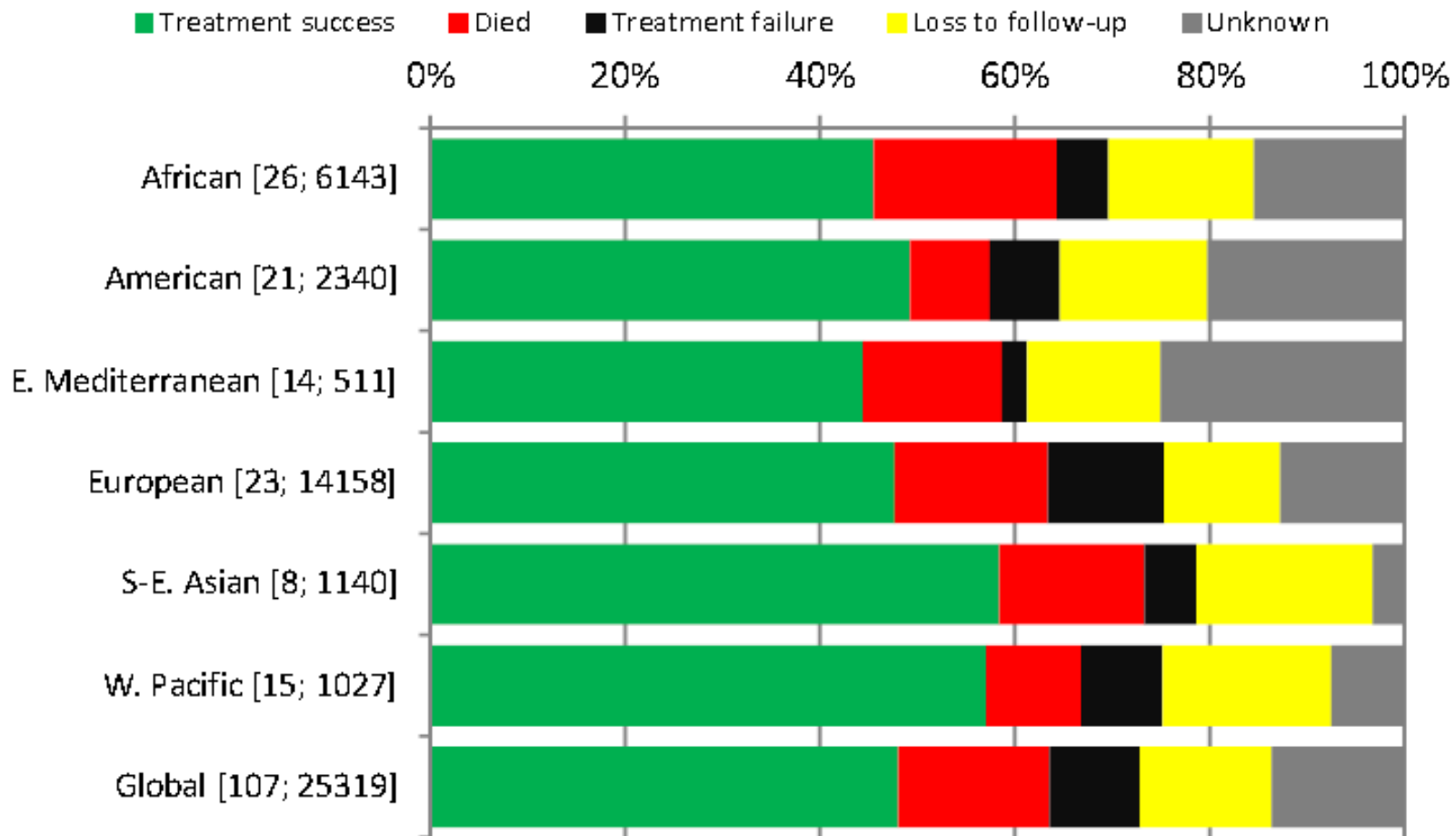
- Epidemiology
- Current treatment
- Rationale for short course
- AOB

# MDR-TB Treatment Outcomes (24 months)



# Relatively ineffective

Treatment outcomes for MDR-TB patients started on treatment in 2009, by WHO Region and Global



# The Conventional treatment for RR TB

## Standardised approach

- Intensive phase
  - Kanamycin
  - Moxifloxacin
  - PZA
  - Terizidone
  - Ethionamide
- Continuation phase
  - Moxifloxacin
  - PZA
  - Terizidone
  - Ethionamide

# Duration and outcomes of treatment

- Intensive phase
  - Add 4 months after culture conversion/ minimum of 6 months
- Continuation phase
  - 18 months
- Successful Outcomes
  - Cure
  - Treatment complete

# Significant and debilitating side effects

## Short term and usually reversible

- Painful injections
- Nausea and vomiting
- Hepatitis

## • Medium term

- Kidney failure
- Psychiatric side effects (depression, paranoia)
- Peripheral neuropathy (tingling, numbness, pain)

## • Long term and usually irreversible

- Hearing loss due to the injectable drugs (~30% of patients in some settings)

# What would the ideal MDR TB regimen be?

- Shorter- less than a year
- At least one new agent
- Standardised- perhaps even for drug sensitive TB
- NO INJECTIONS
- Can be prescribed with antiretrovirals





# STREAM

## The Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB

ISRCTN 78372190

- Standard of Care vs. the Bangladesh regimen
  - Moxifloxacin
  - Clofazamine
  - Ethambutol
  - PZA
  - INH
  - Prothionamide
  - Kanamycin



## **STREAM**

**The Evaluation of a Standardised Treatment  
Regimen of Anti-Tuberculosis Drugs for  
Patients with MDR-TB**

ISRCTN 78372190

- Currently enrolling
- Results out in 2018

# Short Course vs Conventional Treatment

Control regimen of 24 months (taken twice daily) →



← Study regimen of 9 months (taken once daily)



# THE SHORTER MDR-TB REGIMEN

## WHO treatment guidelines for drug- resistant tuberculosis

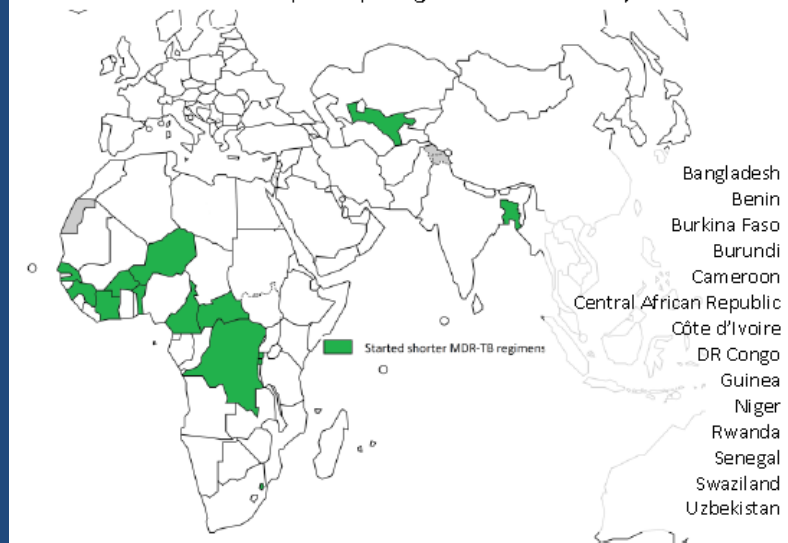
2016 update

THE  
**END TB**  
STRATEGY



### Countries using the shorter MDR-TB regimen

(in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)



# Results of the 9-month regimen in Bangladesh

## *Published cohort (206 pts)*

Cure	82.5%
Completion	5.3%
Default	5.8%
Death	5.3%
Failure	0.5%
Relapse	0.5%

Overall success rate:

87.9% (95% CI 82.7, 92.6)

## *Cohort update (515 pts)*

81.2%
3.3%
7.8%
5.6%
1.4%
0.8%

Overall success rate:

84.5% (95% CI 0.81, 0.88)

Am J Respir Crit Care Med Vol 182. 684–692, 2010

**Introduction**

**Objectif**

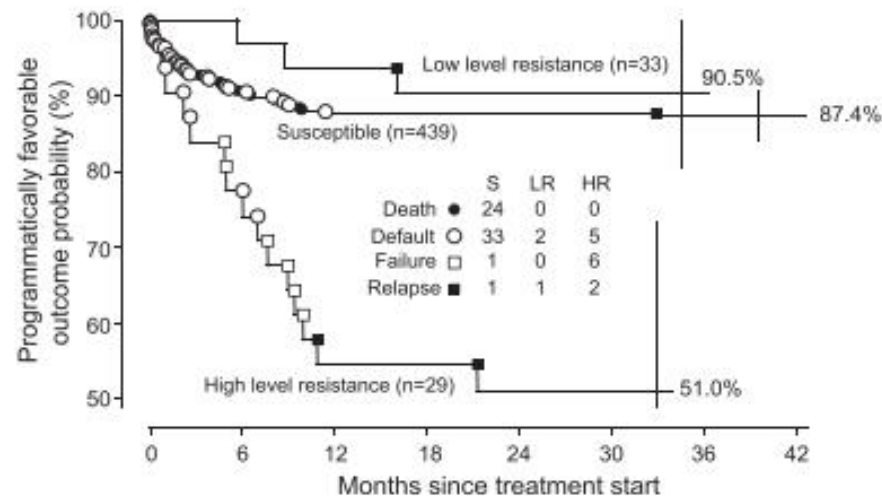
Aung et al, IJTL 18(10):1180–1187, 2014

**Méthodes**

**Conclusion**

# Are these results generalizable?

*Low HIV prevalence*



**Figure 3** Programmatically favorable treatment outcome probability derived from a Cox's proportional hazard model among 501 patients, stratified by initial fluoroquinolone susceptibility test result, adjusted for age and sex. S = susceptible to ofloxacin and/or GFX at the standard critical concentration; LR = low-level resistance (GFX MIC 0.5–1.0 mg/l); HR = high-level resistance (GFX MIC  $\geq 2$  mg/l); GFX = gatifloxacin; MIC = minimum inhibitory concentration.

# The Shorter Regimen

## Intensive phase

- Kanamycin
- Levofloxacin
- Prothionamide
- Clofazamine
- PZA
- High Dose INH
- Ethambutol

## Continuation Phase

- Levofloxacin
- Clofazamine
- PZA
- Ethambutol

# Rationale (1)

- Kanamycin:
  - 4-6 months
  - Duration determined by smear conversion.
  - If still smear positive at months 3, repeat DST
  - Should be given at least 6 times a week.

# Rationale (2)

- Levofloxacin
  - Chosen due to decreased increase in QT interval
  - 750mg to 1g
  - Amenable to addition of BDQ

# Rationale (3)

- Prothionamide and High Dose INH
  - To cover InhA and katG mutations
  - If InhA- drop ethionamide
  - If katG- drop INH
  - If both- for individualised regimen usually with BDQ and LNZ
  - If neither- drop one

# Rationale (4)

- Clofazamine
  - Anti leprosy drug
  - Anti-inflammatory and immunomodulatory agent
  - Cost effective
  - QT prolonger
  - Hyper pigmentation (100%)
  - NO currently registered or on tender.

## CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

### CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to  $\geq 1$  second-line medicines in the shorter MDR-TB regimen for  $>1$  month
- ✓ Intolerance to  $\geq 1$  medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

#### Intensive phase

Duration: 4-6 months

Composition: 4 second-line drugs

FAILING REGIMEN, DRUG INTOLERANCE,  
RETURN AFTER INTERRUPTION  $>2$  MONTHS,  
EMERGENCE OF ANY EXCLUSION CRITERION

YES

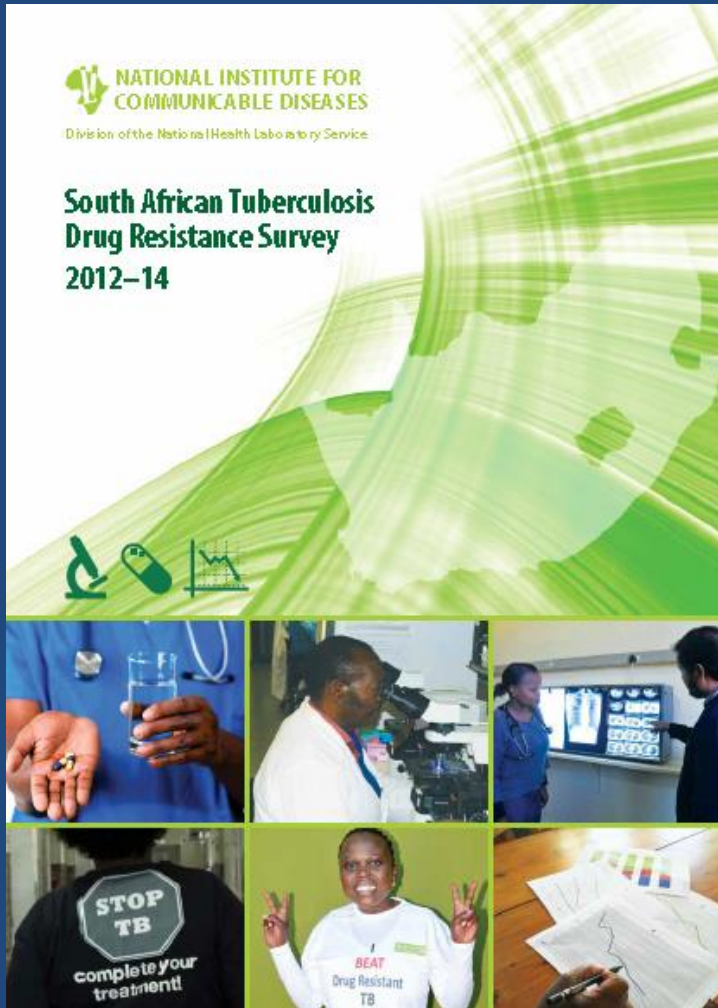
Individualised  
("conventional")  
MDR/RR-TB regimens

#### Intensive phase

Duration: Up to 8 months

Composition: 4 or more second-line drugs

# Potential pit falls



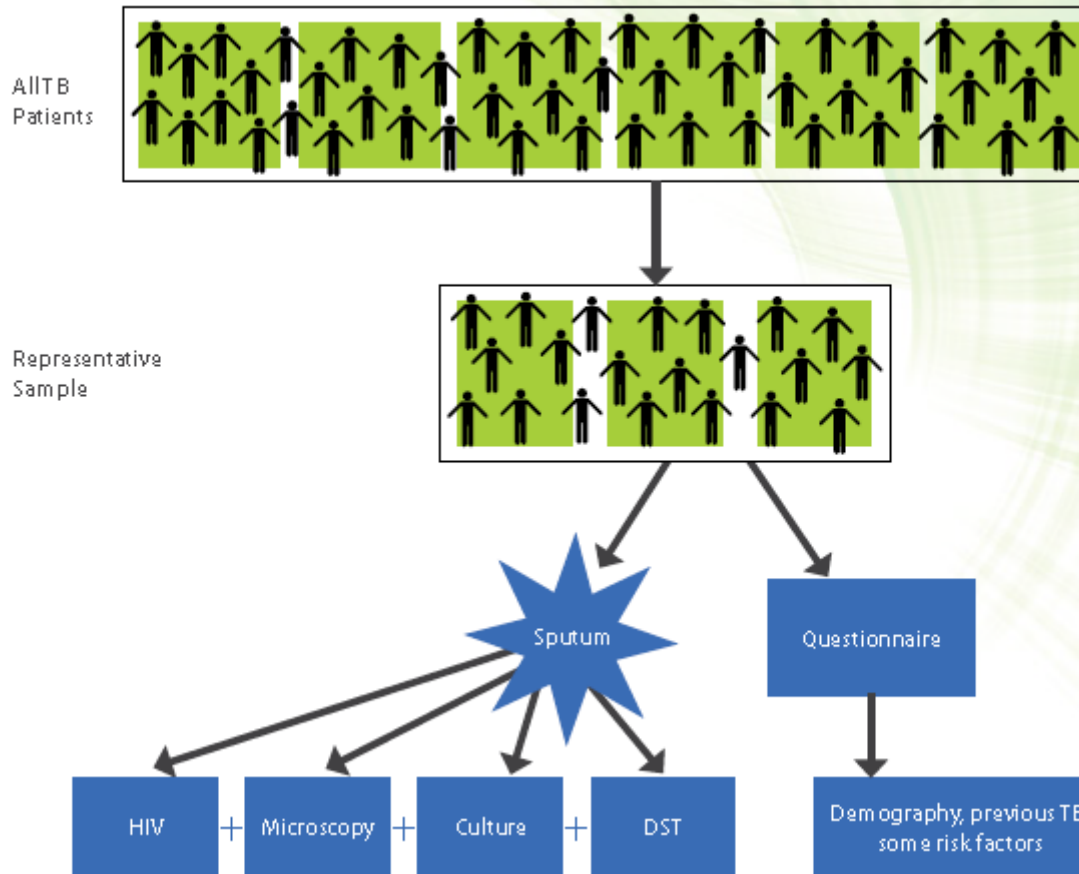


Table 21: National second-line drug resistance among MDR cases

Drug	Overall (%; 95%CI)
Pyrazinamide	59.1 (49.0-69.1)
Ethambutol	44.1 (30.2-58.0)
Streptomycin	63.0 (52.8-73.2)
Ethionamide	44.7 (25.9-63.6)
P-aminosalicylic acid	5.3 (2.2-8.3)
Second-line injectable	13.0 (5.0-20.9)
Ofloxacin	13.0 (5.0-21.0)
XDR-TB	4.9 (1.0-8.8)

# The addition of new drugs

- Additional resistance
  - XDR
  - “preXDR”
- Treatment limiting toxicity e.g. ototoxicity

# Conclusions

- For the first time in years, there are changes to the regimen
- Combination of the short course and BDQ with other new drug is likely to improve outcomes

# Save the Date

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# SAVE THE DATE

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