Distinguishing drug-sensitive from drug-resistant tuberculosis

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12 Sep 2020

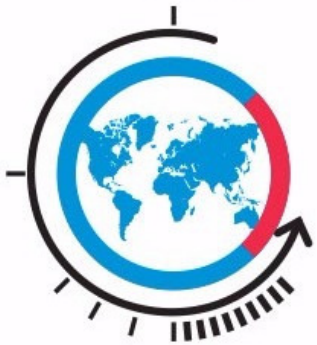
CHRU Themba Lethu
CLINICAL HIV RESEARCH UNIT
A Division of the Wits Health Consortium (Pty) Ltd

TB IS THE TOP INFECTIOUS DISEASE KILLER IN THE WORLD

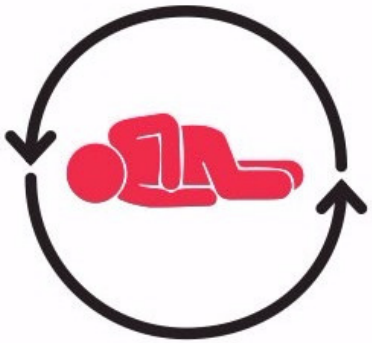
IN 2016

1.7 MILLION PEOPLE DIED FROM TB

INCLUDING NEARLY 400 000 PEOPLE WITH HIV-ASSOCIATED TB



10.4 MILLION PEOPLE FELL ILL FROM TB



TB IS THE MAIN CAUSE OF DEATHS RELATED TO ANTIMICROBIAL RESISTANCE AND THE LEADING KILLER OF PEOPLE WITH HIV

XDR-TB in Tugela Ferry, KwaZulu-Natal

- This was an outbreak of XDR-TB in Tugela Ferry, KwaZulu-Natal Province, South Africa.
- From January 2005 to March 2006, 221 MDR-TB cases were identified in Tugela Ferry, of whom 53 (23%) were also resistant to kanamycin and ciprofloxacin.
- Half of the patients had never previously received anti-TB treatment.
- Of the 53 patients, 44 were tested for HIV and all were found to be HIV-positive.
- Mortality was extremely high: 52 (98%) of the patients died within a median range of 16 days of initial sputum collection,
- 15 (28%) were receiving treatment with antiretroviral drugs (ARVs).

Lancet 2006; 368:1575-80

Whirlwind tour of DR-TB

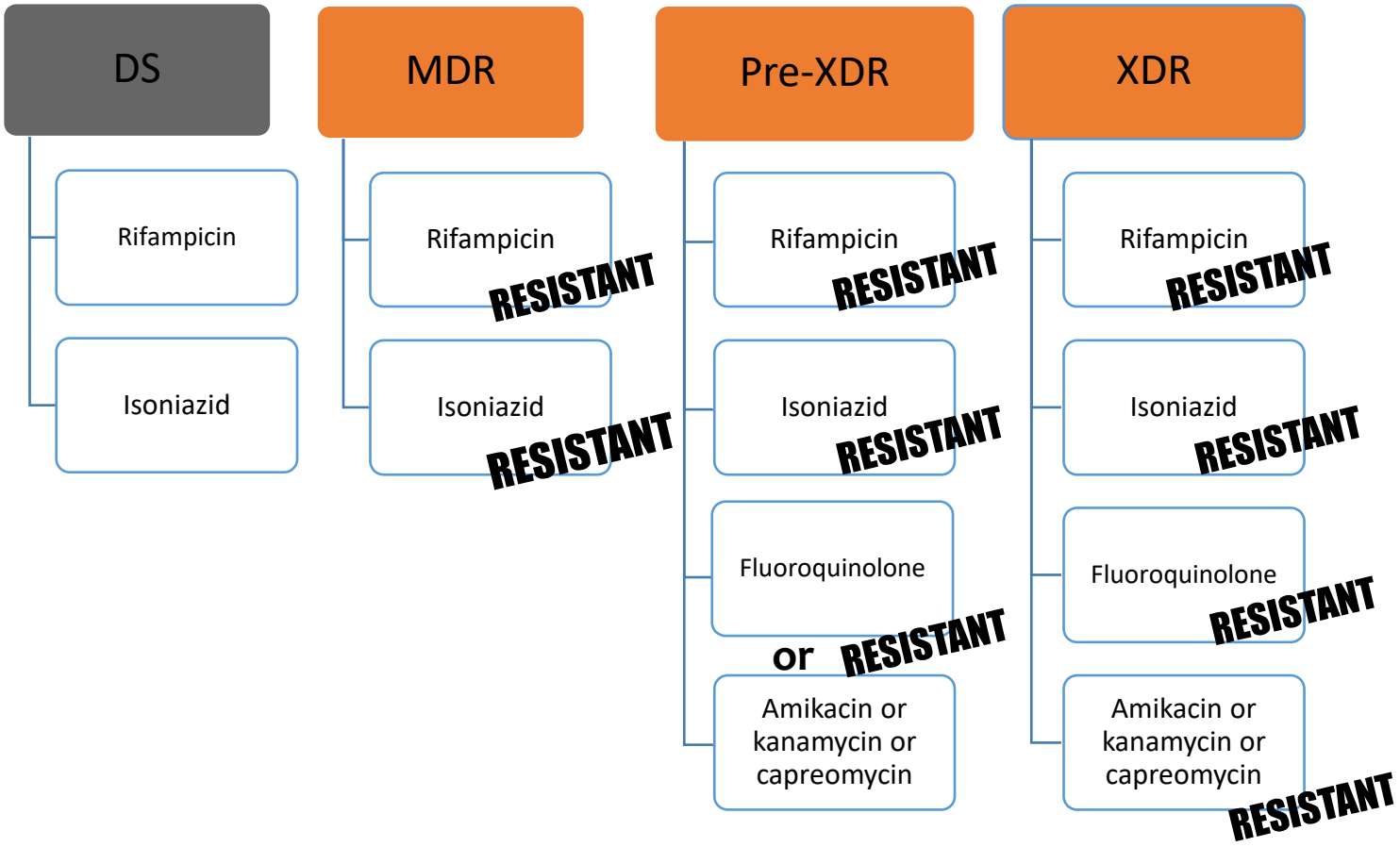
1. What is drug resistant TB?
2. What is the current situation?
3. How do you get DR-TB?
4. Tuberculosis infection and disease
5. History of drug-resistant tuberculosis
6. Current DR-TB treatment
7. What's coming?

1. What is drug resistant TB?

Very Simplified

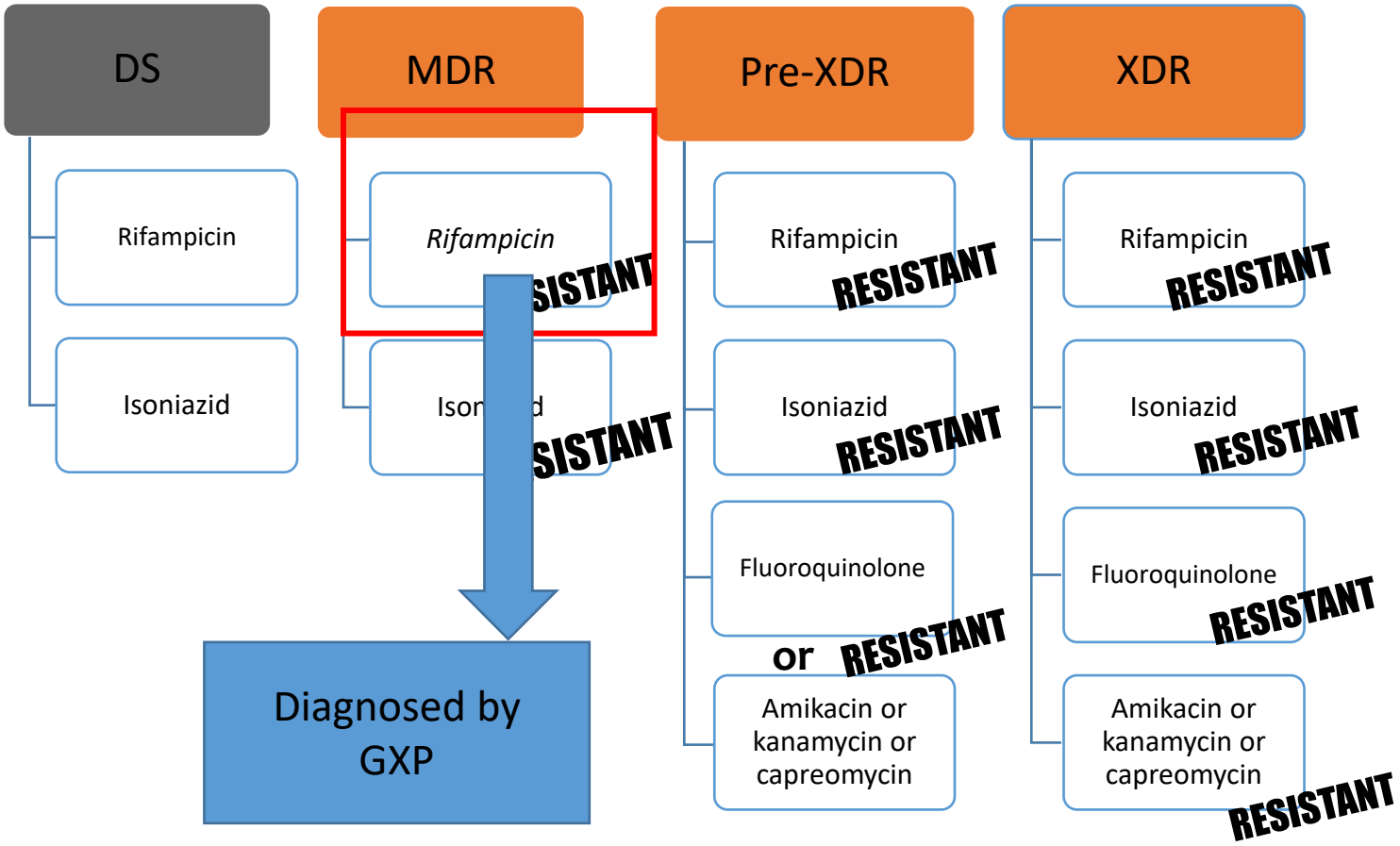
- There are “killer drugs” (bacteriocidal)
  - Rifampicin
  - INH
  - Fluoroquinolones
  - Second line injectable drugs (SLID)
- There are “supportive drugs” (~bacteriostatic)
  - PZA/Eto/Pto/TZD/EMB/PAS/etc
- **Resistance to a killer drug changes the TB “name”**
- Traditionally: 2 killers + number of supporters (depending on type of TB) with intensive phase for at least 6 months, and continuation phase afterwards for up to an additional 18 months.

TB Resistance

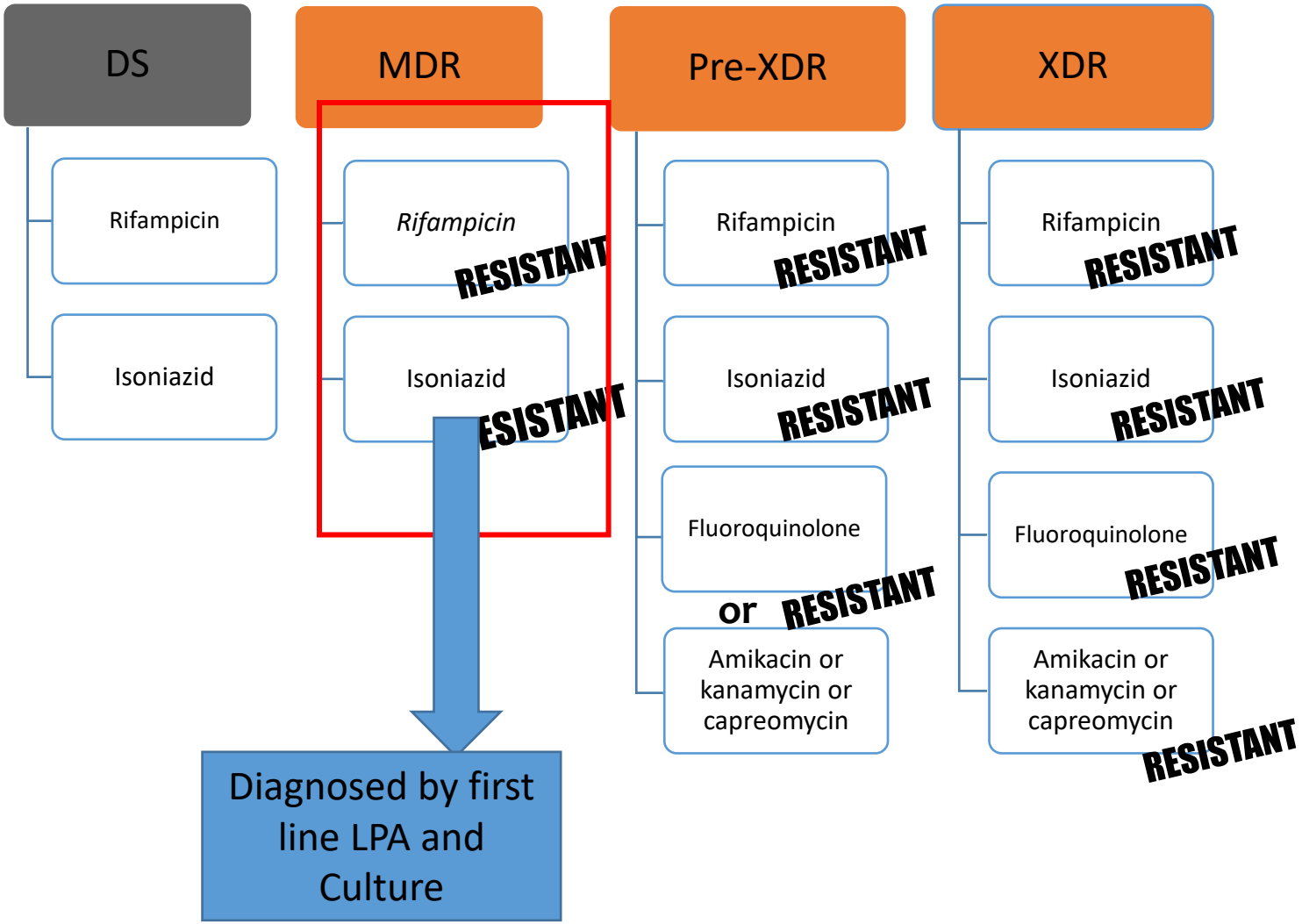


*If only Rifampicin resistant: RMR-TB

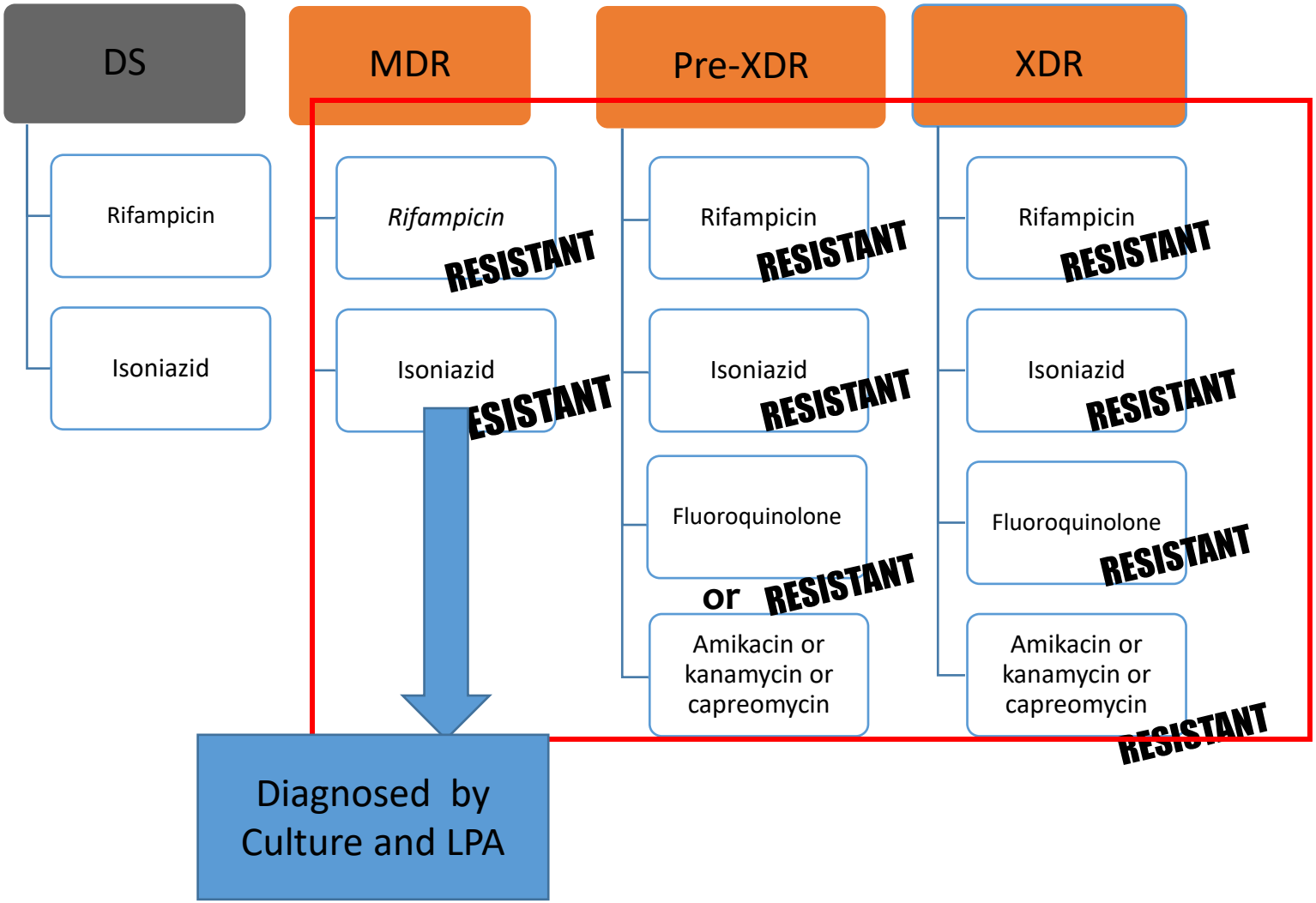
TB Resistance



TB Resistance



TB Resistance



NHLS result

MICROBIOLOGY

Tel: 011 489 8421, Fax: 011 489 8457

Specimen received: Sputum
Tests requested: TB mic @, TB cult @, MTBDRplus @, MTBDRsl @, TB sens 2nd line @
@ Test referred to another NHLS laboratory

Auramine O Stain:

Result (concentrated)	Positive +++ (>10 AFB/immersion field)

Specimen appears to consist mainly of saliva. Please treat results with reserve.

TB Culture:

Culture result	Culture contaminated, but AFBs observed.
Incubation time	7 days

Molecular resistance testing for first line agents for TB:

Test performed on	Clinical sample
PCR/Line Probe Assay Result	Mycobacterium tuberculosis complex
Isoniazid (INH)	Resistant
Rifampicin	Resistant

This patient has multi-drug resistant tuberculosis. Please ensure that this patient has been referred to an appropriate treatment facility. 2nd line susceptibility testing will follow.

This isolate has a mutation in the inhA gene, which has been shown to correlate with ethionamide resistance. There is also a mutation in the katG gene which may represent high level INH resistance.

Molecular resistance testing for second line agents for TB:

Test performed on	Clinical sample
MTBDRsl PCR Result	Mycobacterium tuberculosis complex

NHLS result

Fluoroquinolones	Mutation detected (resistant)
Second Line Injectables	Mutation detected (resistant)

Comment:

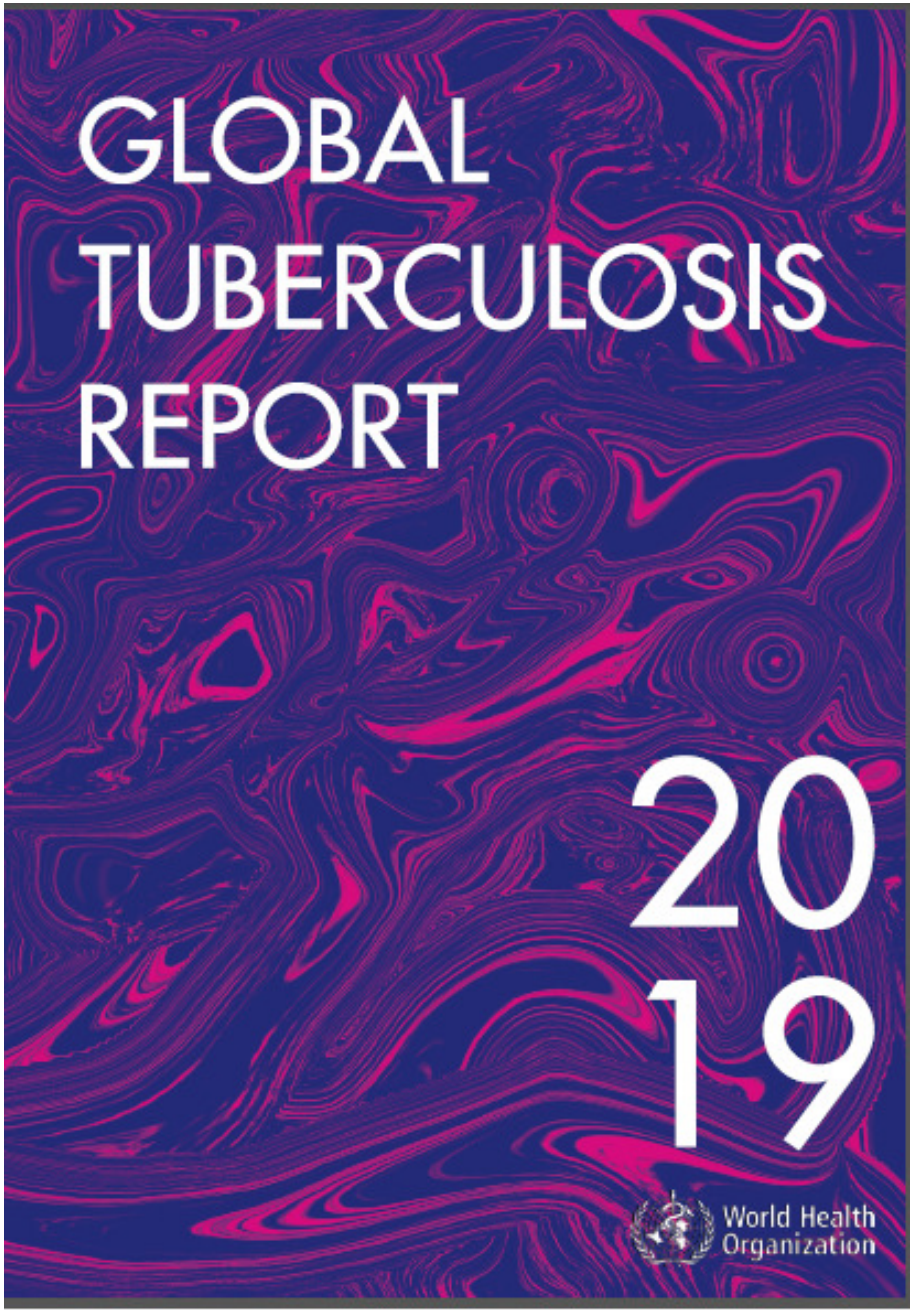
Mutations with a high likelihood of resistance to both fluoroquinolones and second-line injectable agents have been detected. This patient may have XDR-TB. Please refer to an appropriate treatment facility for further management. Additional second-line drug-susceptibility testing to follow.

@ MTBDRplus, MTBDRsl, TB cult, TB mic, TB sens 2nd line referred to Braamfontein Central Laboratory (Tel 011 489 9433)

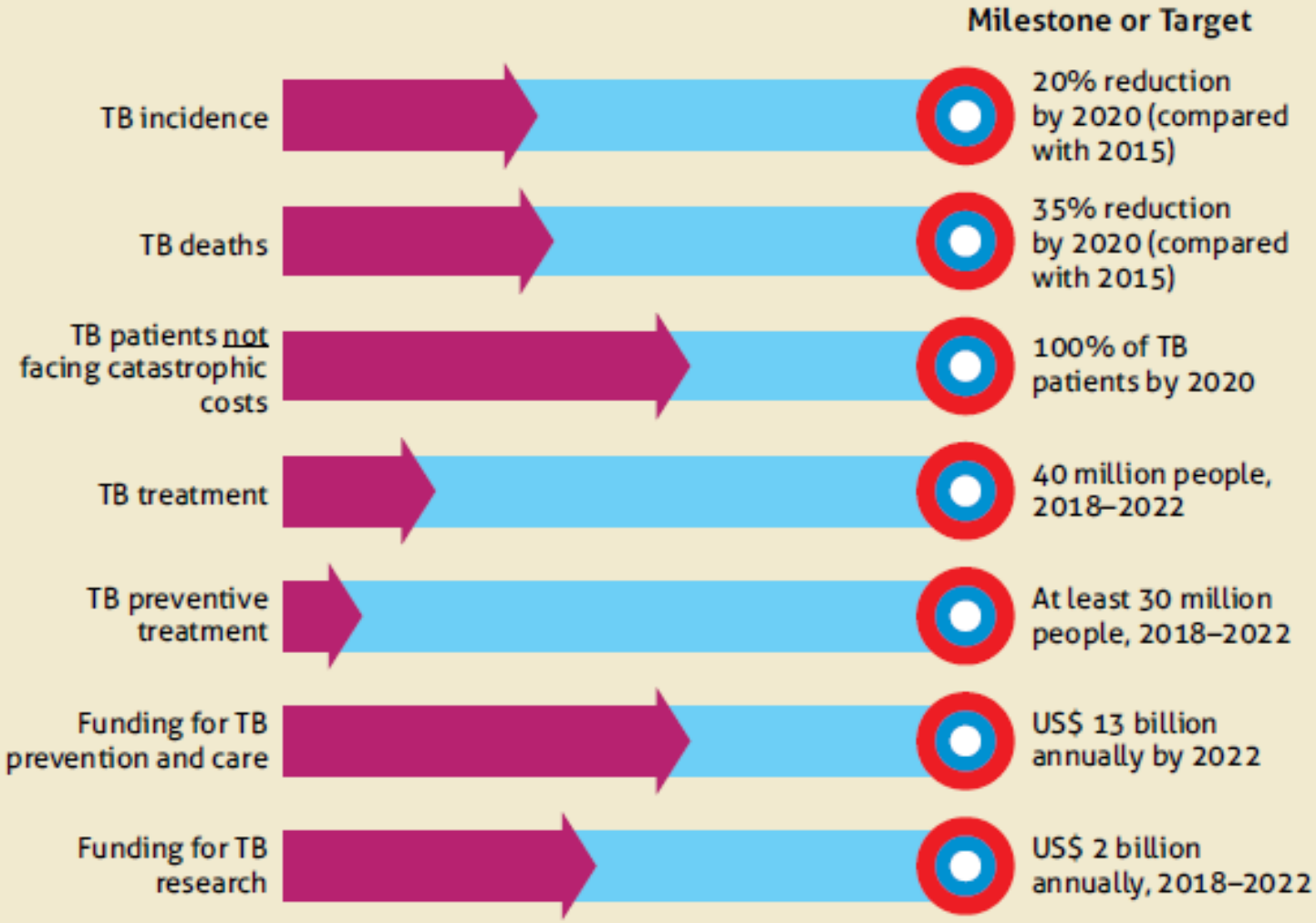
Authorised by: Dr B Masango (Registrar) MTBDRplus
KA Moloi (Medical Technologist) TB cult
Dr M Le Grange (Registrar) MTBDRsl
NP Kotsi (Medical Technologist) TB mic

-- End of Laboratory Report --

2. What is the current situation?


GLOBAL
TUBERCULOSIS
REPORT
2019
World Health
Organization

Progress towards End TB Strategy milestones for 2020 and the four global targets set in the political declaration at the UN high-level meeting on TB: latest status[a]



[a] End of 2018 except for funding for TB prevention and care (2019) and funding for TB research (2017).

:: FIG. 3.20

Estimated incidence of MDR/RR-TB in 2015, for countries with at least 1000 incident cases. Areas that are not applicable are in grey.

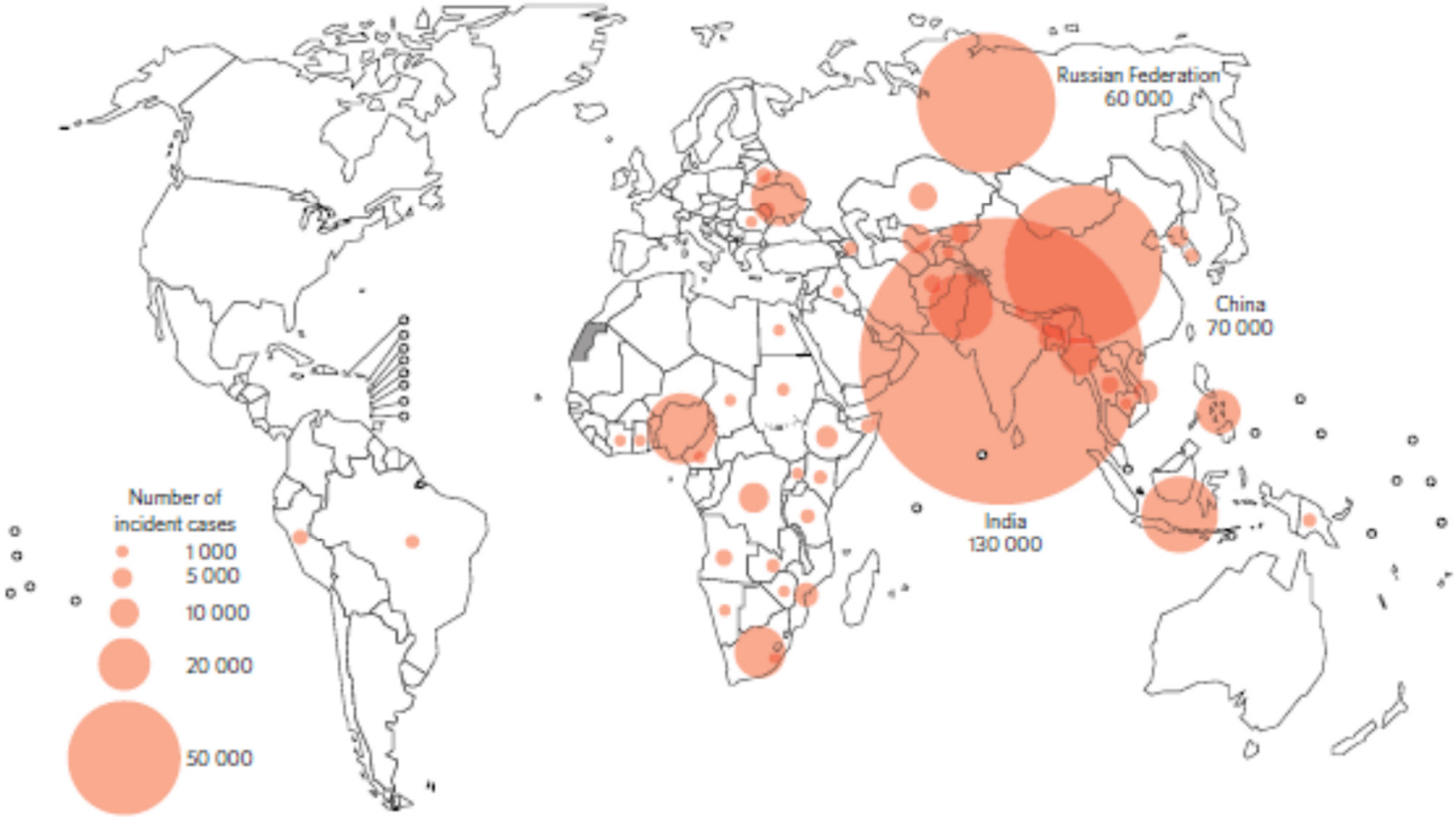
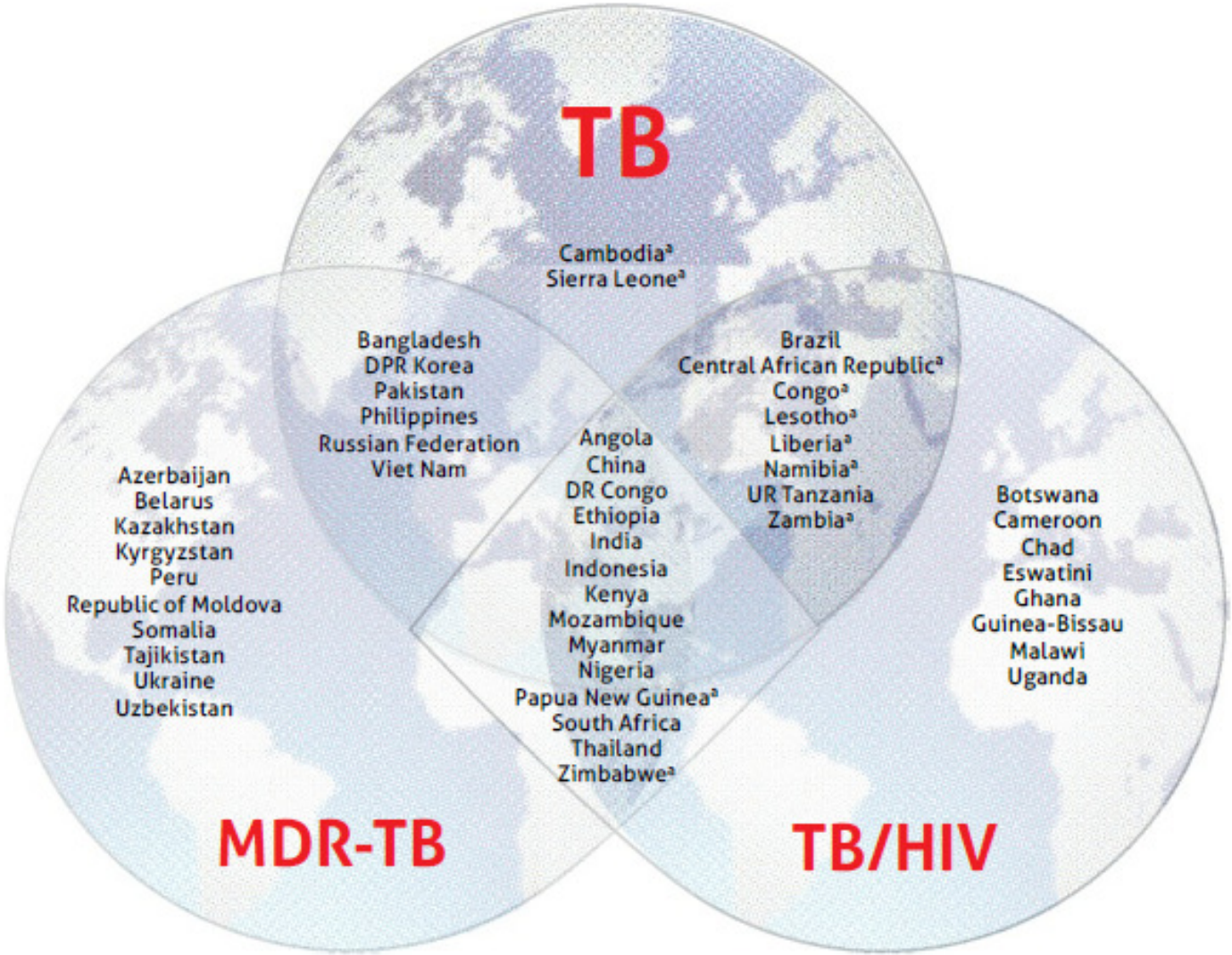


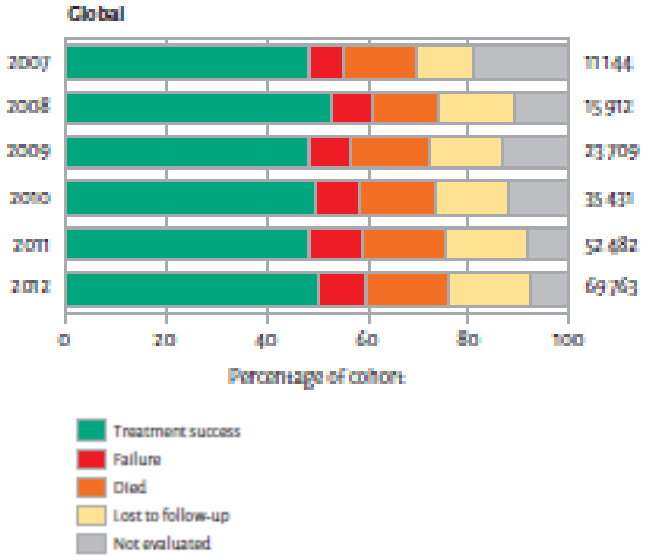
FIG. 2.5

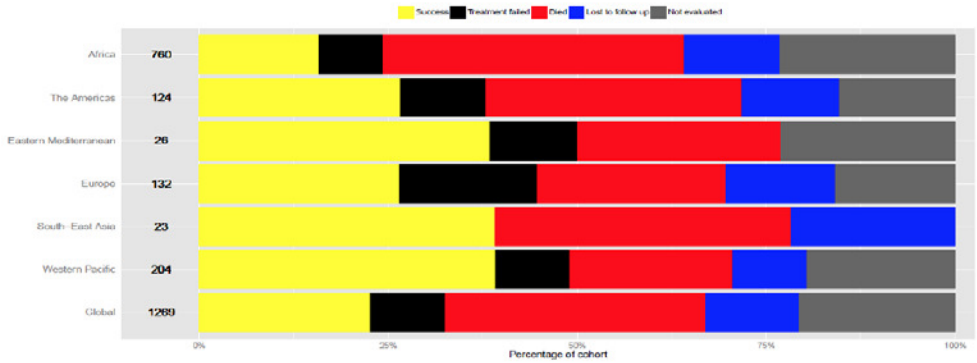
The three high-burden country lists for TB, TB/HIV and MDR-TB defined by WHO for the period 2016–2020, and their areas of overlap



[a] Indicates countries that are included in the list of 30 high TB burden countries on the basis of the severity of their TB burden (i.e. TB incident cases per 100 000 population per year), as opposed to the top 20, which are included on the basis of their absolute number of incident cases per year. Also see Table 2.4.

Low Treatment Success and High Mortality





*number of cases observed shown over the bars

MDR TB: 50% treatment success, 16% death

XDR TB: 24% treatment success, 30% death

WHO Global TB Report 2015

Big difference DS/DR tuberculosis

Epidemiology

- Rifampicin-resistant tuberculosis is a major cause of M&M worldwide, with estimated 580 000 new cases/year
- Until recently, success in only 50% of pt's STARTED on Rx
- WHO released 6 guidelines since 2018 – rapidly changing field!
- South Africa has the 5th highest incidence of RR-TB in the world, with 19 000 cases detected in 2016.
- 65% of diagnosed cases initiate treatment, but only 50% have successful outcomes

Big difference DS/DR tuberculosis

South African Situation - 2017

FIG. 4.28

Treatment outcomes for new and relapse HIV-positive TB cases in 2017, 30 high TB/HIV burden countries, WHO regions and globally

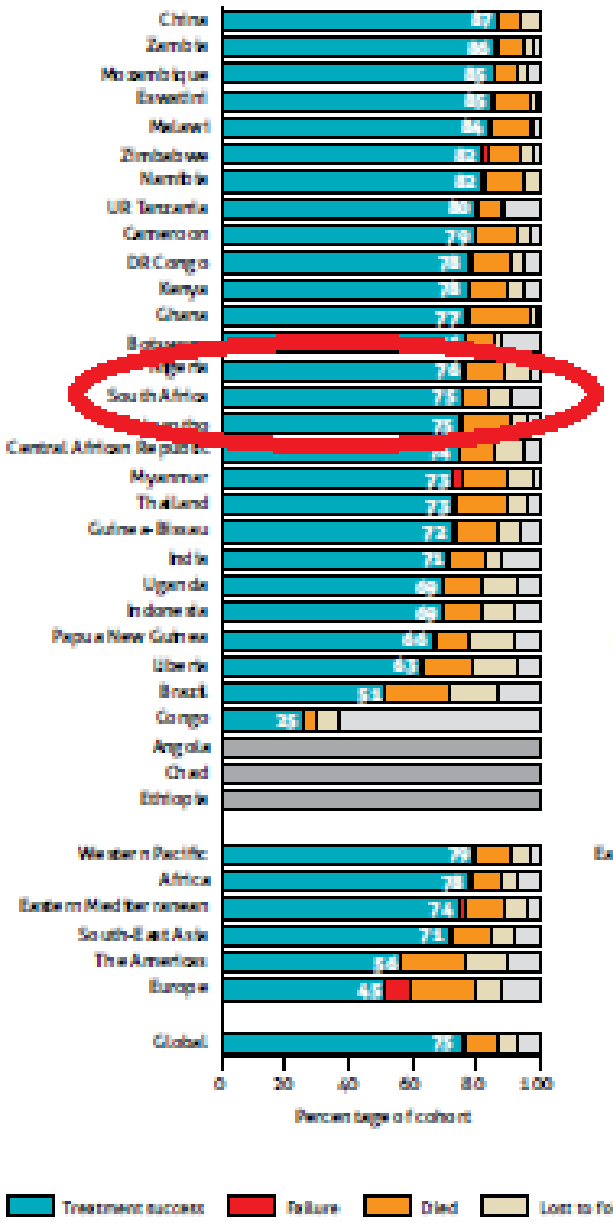
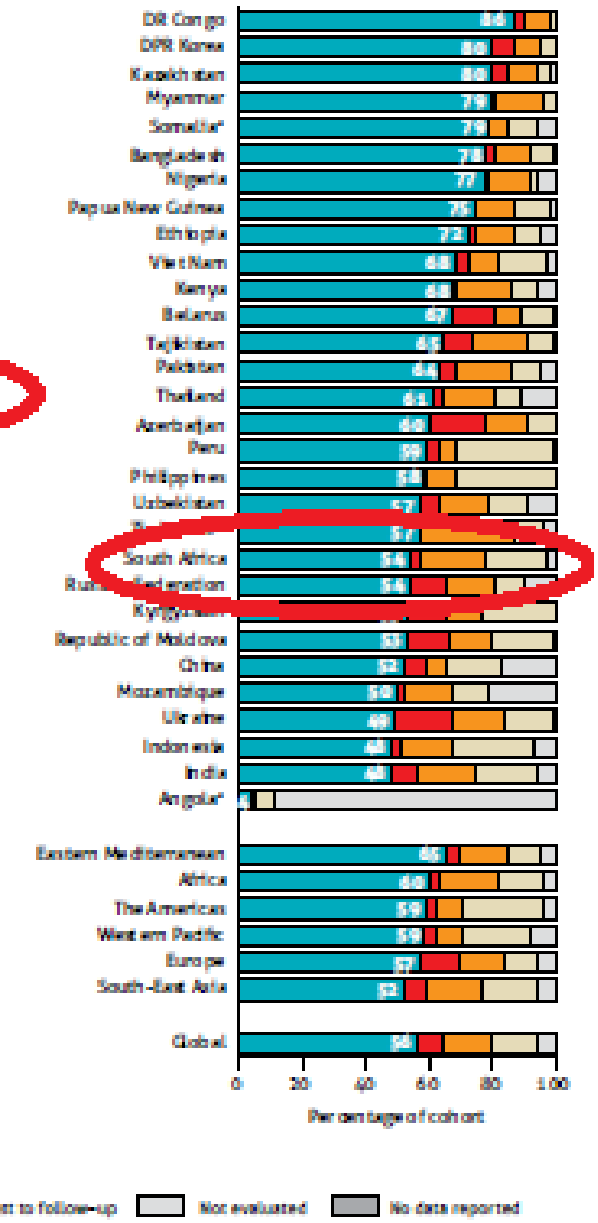


FIG. 4.29

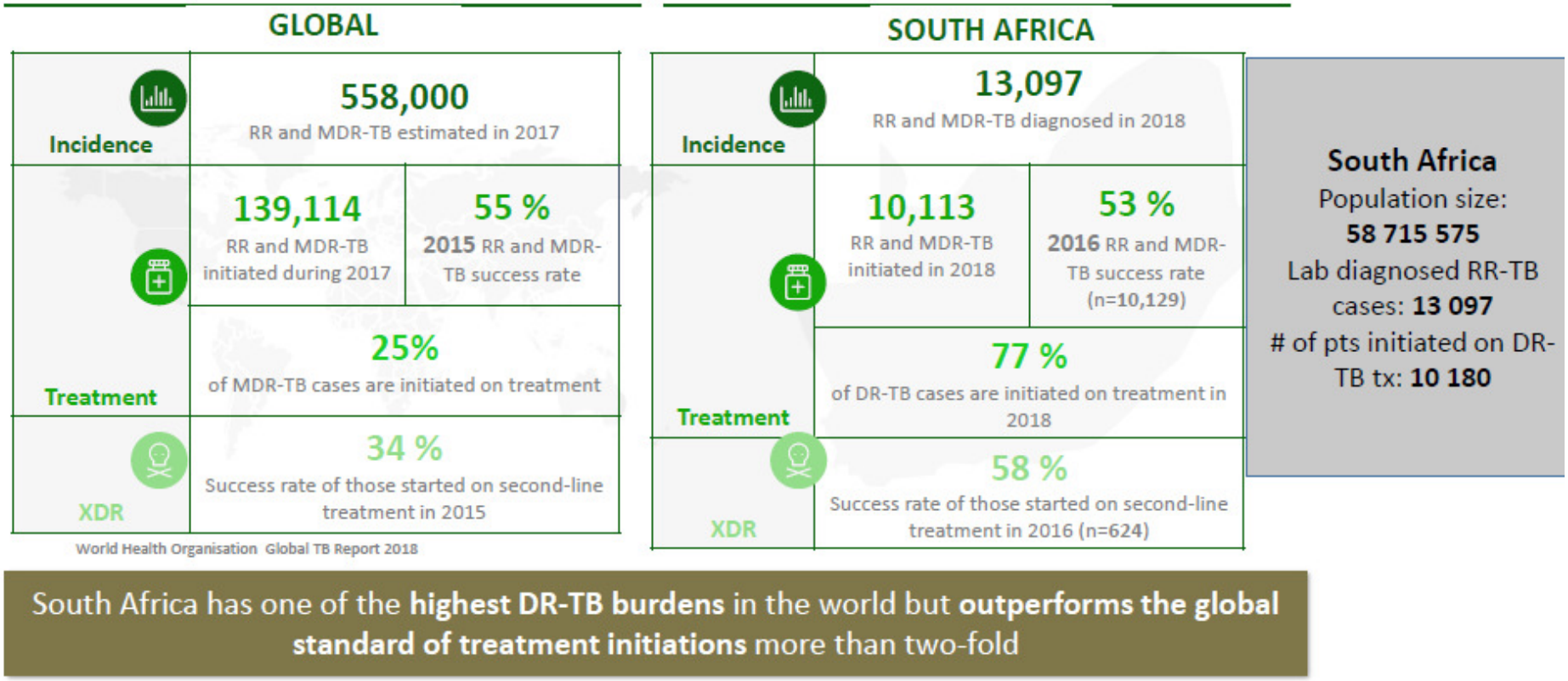
Treatment outcomes for MDR/RR-TB cases started on treatment in 2016, 30 high MDR-TB burden countries, WHO regions and globally



Treatment success | Failure | Died | Lost to follow-up | Not evaluated | No data reported

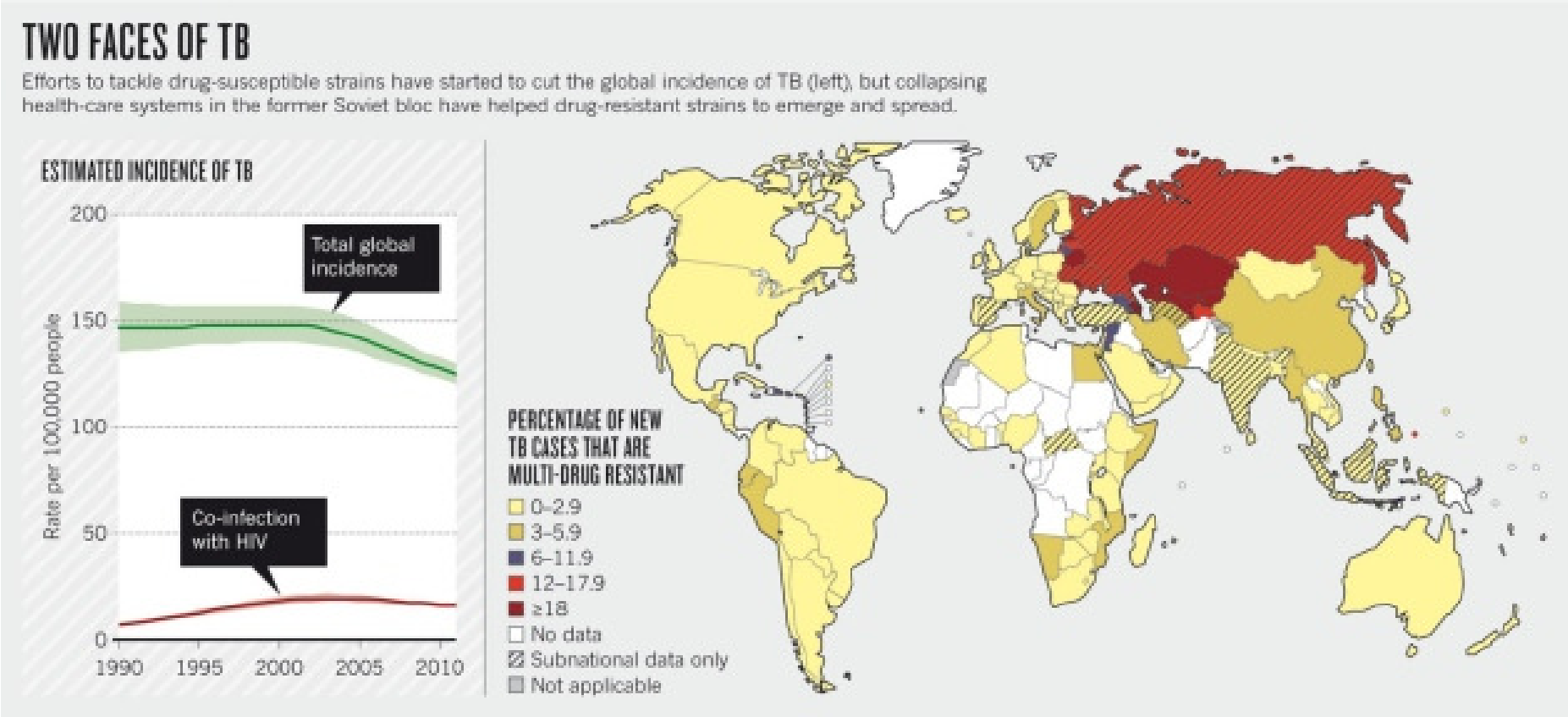
* These countries reported cohorts of less than 100 MDR/RR-TB cases in 2016.

How does SA compare?



South Africa has one of the **highest DR-TB burdens** in the world but **outperforms the global standard of treatment initiations** more than two-fold

With thanks to Dr Norbert Ndjeka



Difference DS/DR tuberculosis

3. How do you get DR-TB?

How does resistance to TB medicines happen?

- **Acquired resistance (secondary resistance)**
  - Patients with drug sensitive TB can't or don't take medications as required
  - Resistant mutants are selected for during treatment
- **Transmitted resistance (primary resistance)**
  - Infecting organisms are already resistant

Contributing factors to the development of DR-TB

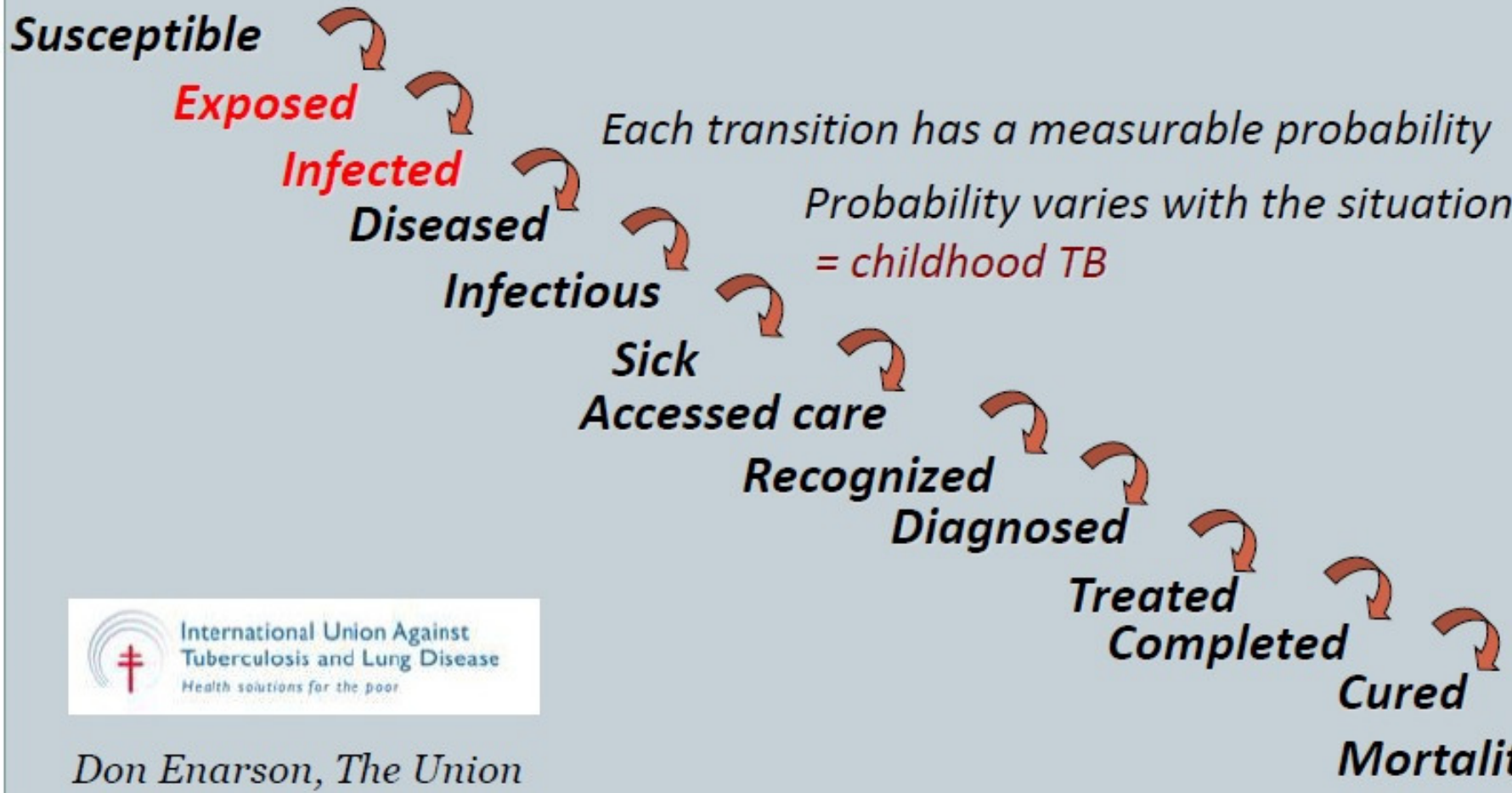
HEALTH-CARE PROVIDERS: INAPPROPRIATE TREATMENT	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE OR TREATMENT RESPONSE
Inappropriate guidelines	Poor quality medicines	Lack of information
Non-compliance with guidelines	Unavailability of certain medicines (stock-outs or delivery disruptions)	Lack of means to adhere to treatment (transportation, food, etc.)
Absence of guidelines	Poor storage conditions	Adverse effects
Poor training	Wrong dose or combination	Social barriers
Financial disincentives	Poor regulation of medicines	HIV
Poor patient education		Diabetes mellitus
No monitoring of treatment		Undernutrition
Poor management of adverse drug reactions		Malabsorption
Poor treatment support		Substance abuse/dependency
Poorly organized or funded TB control programmes		Psychiatric condition

WHO 2014

TB RUNS IN FAMILIES

4. Tuberculosis infection and disease

Key transitions in TB transmission



International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Don Enarson, The Union

PLOS | MEDICINE

RESEARCH ARTICLE

Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study

Louis Grandjean[1,2,3]*, Robert H. Gilman[2,4], Laura Martin[2], Esther Soto[2], Beatriz Castro[2], Sonia Lopez[2], Jorge Coronel[2], Edith Castillo[5], Valentina Alarcon[6], Virginia Lopez[7], Angela San Miguel[7], Neyda Quispe[8], Luis Asencios[8], Christopher Dye[9], David A. J. Moore[2,3]

1 Wellcome Centre for Clinical Tropical Medicine, Imperial College London, London, United Kingdom, **2** Universidad Peruana Cayetano Heredia, Lima, Peru, **3** TB Centre, London School of Hygiene & Tropical Medicine, London, United Kingdom, **4** Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **5** Laboratorio de Mycobacteriologia, Dirección Regional de Salud–Región Callao, Lima, Peru, **6** Unidad Técnica de TB-MDR, Ministerio de Salud, Lima, Peru, **7** Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis and Laboratorio de Mycobacteriologia, Dirección de Salud II–Lima Sur, Lima, Peru, **8** Instituto Nacional de Salud, Lima, Peru, **9** Office for HIV/AIDS, Malaria, Tuberculosis and Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

CrossMark
click for updates

- Prospective cohort (2010 – 2013) in Peru
- A total of 35/1,055 (3.3%) household contacts of 213 MDRTB index cases developed tuberculosis disease, while 114/2,362 (4.8%) household contacts of 487 drug-susceptible index patients developed tuberculosis disease
- After adjustment for potential confounding variables, the risk for developing active TB was nearly 50% lower among contacts of MDR-TB patients than among contacts of DS-TB patients (hazard ratio, 0.56; 95% confidence interval, 0.34–0.90).

Transmissibility and potential for disease progression of drug resistant *Mycobacterium tuberculosis*: prospective cohort study

Mercedes C Becerra,[1] Chuan-Chin Huang,[2] Leonid Lecca,[3] Jaime Bayona,[4] Carmen Contreras,[3] Roger Calderon,[3] Rosa Yataco,[3] Jerome Galea,[5] Zibiao Zhang,[2] Sidney Atwood,[2] Ted Cohen,[6] Carole D Mitnick,[1] Paul Farmer,[1,2] Megan Murray[1,2]

BMJ: first publishe

- Prospective cohort study in Peru over 3 years (Sep 2009 – Sep 2012)
- To measure the association between phenotypic drug resistance and the risk of tuberculosis infection and disease among HHCs of patients with PTB.
- 10 160 household contacts of 3339 index patients with TB were classified on the basis of the DSTof the patient:
  - 6189 were exposed to DS-TB
  - 1659 to strains resistant to isoniazid or rifampicin
  - 1541 to strains that were MDR-TB
- Positive TST and incidence of active disease (smear pos/CXR) after 12/12
- Results: HHC exposed to MDR had an 8% (95% CI 4% to 13%) higher risk of infection by end of 12/12 vs HHC exposed to DS-TB (Hazards ratio didn't differ)
- Conclusion: HHC of MDR-TB increased risk of infection. Risk of TB disease did not differ.
- NB: early detection and effective treatment of infection and disease.

Possible difference DS/DR tuberculosis

TB Disease

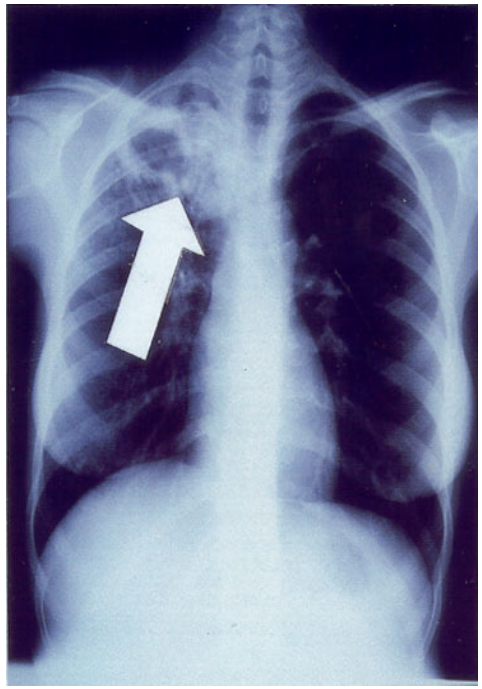
Signs and Symptoms:

- Cough of any duration
- Constant fatigue
- Fever
- Night sweats (drenching)
- Chest pain
- Haemoptysis
- Loss of appetite
- Weight loss

No difference DS/DR tuberculosis

Chest X-ray

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB



Arrow points to cavity in patient's right upper lobe.

No difference DS/DR tuberculosis

Diagnosis of TB

- Medical history and physical exam
- Chest X-ray
- Microbiological
  - Sputum smear microscopy
  - Molecular
  - Sputum culture
- Drug susceptibility testing
- (Genome sequencing)

Some differences DS/DR tuberculosis

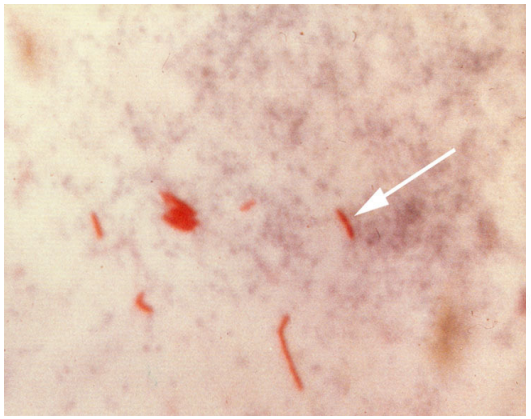
Microscopy

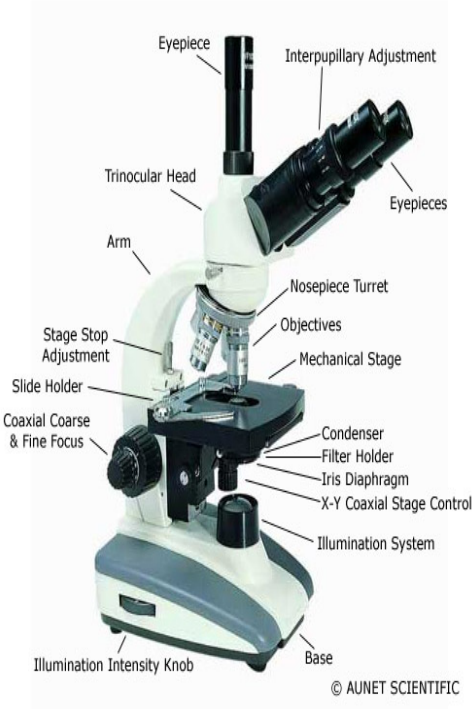
- Acid fast bacilli visualized on a slide may represent Mtb or NTM
- High bacterial load **5,000-10,000 AFB /mL** is required for detection
- Often referred to as ‘smear’/’direct’
- Results should be available within 24 hours of specimen collection
- Labour intensive – manually count all the bacilli in a field.
- Presumptive diagnosis of TB

The IUATLD scale proposes five groups for reporting the results of reading smears for acid fast bacilli. They should be recorded as follows:

FINDING	RECORDING
No acid-fast bacilli found in at least 100 fields	negative
1 to 9 acid-fast bacilli per 100 fields	exact figure/100/scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

Reference: The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network. Minimum Requirements, Role and Operation in a Low-Income Country. International Union Against Tuberculosis and Lung Disease 1998.





Culture

- Gold standard
- Can detect as few as **6-10 (liquid) to 100 (solid) AFB / mL**
- Drug susceptibility testing ('phenotypic testing')
- Species identification.
- There are three types of traditional culture media:
    - Egg based (Lowenstein-Jensen),
    - Agar based (Middlebrook 7H10 or 7H11), and
    - Liquid (Middlebrook 7H12 and other commercially available broths).
- Growth in liquid media is faster (one to three weeks) than growth on solid media (three to eight weeks)

GeneXpert MTB/RIF

- **Detects ~130 AFB/ml; GXP Ultra ~36 AFB/ml**
- Originally developed by Cepheid to detect anthrax after attacks in 2001 and were installed in post offices throughout the US.
- Automated real-time nucleic acid amplification technology (PCR) for rapid and simultaneous detection of tuberculosis
- Rifampicin resistance only (currently!)
- **GXP Ultra:** sensitivity was up to 17% higher than Xpert MTB/RIF (↑sensitivity seen in smear-negative, culture-positive, and HIV-positive TB patients); ↑ false positives due to detection of non-viable TB bacteria.

Laboratory Diagnosis & Interpretation of Test Results

- Patient with signs and symptoms of TB: Send specimen for GXP (1 to several days)
- If **MTb pos + Rifampicin resistance** --> reflex testing
- Reflex testing (7-21 days) **SEND SECOND SPECIMEN**:
  - **If smear pos**: 1st line LPA + 2nd line LPA + culture
  - **If smear neg:** 1st line LPA + culture. If culture pos: 2nd line LPA
  - (Based on results of 1st and 2nd line LPAs – additional phenotypic testing)
- Ongoing surveillance will determine need for upfront phenotypic testing for BDQ/DLM/LZD and/or CFZ (4-12 weeks)
- Individualized Extended Phenotypic DST can be requested when failing DR-TB regimen with previous exposure to second line drugs.

First Line: Rifampicin Isoniazid	Second Line: FLQ Injectables

Molecular tests

- ‘Line Probe Assay’ (LPA) - Based on reverse hybridization of DNA on the strip
- **LPA ~170 bacilli/ml**
- The assay MTBDRplus is a molecular probe capable of speciating (M.tb) and detecting resistance to:
  - Rifampin (rpoB)
  - Isoniazid (katG and inhA)
- Second line LPA
  - Fluoroquinolones
  - Second line injectable drugs (SLID)
- Advocated for use in smear positive samples
  - Smear positive sample – sensitivity 98%
  - Smear negative sample – sensitivity 72-77%

Treatment: Bactericidal vs. Bacteriostatic

- Sensitive TB treated with:
    1. Rifampicin (R)
    2. Isoniazid (H) or (INH)
    3. Pyrazinamide (Z) or (PZA)
    4. Ethambutol (E) also (EMB)
- RHZE for 2/12 (Rifafour)
- RH for 4/12 (Rifinah)

- If no DST available, treat as DS-TB, but suspect resistance if poor response to treatment with good adherence.

Difference DS/DR tuberculosis

Defer ART when have TB

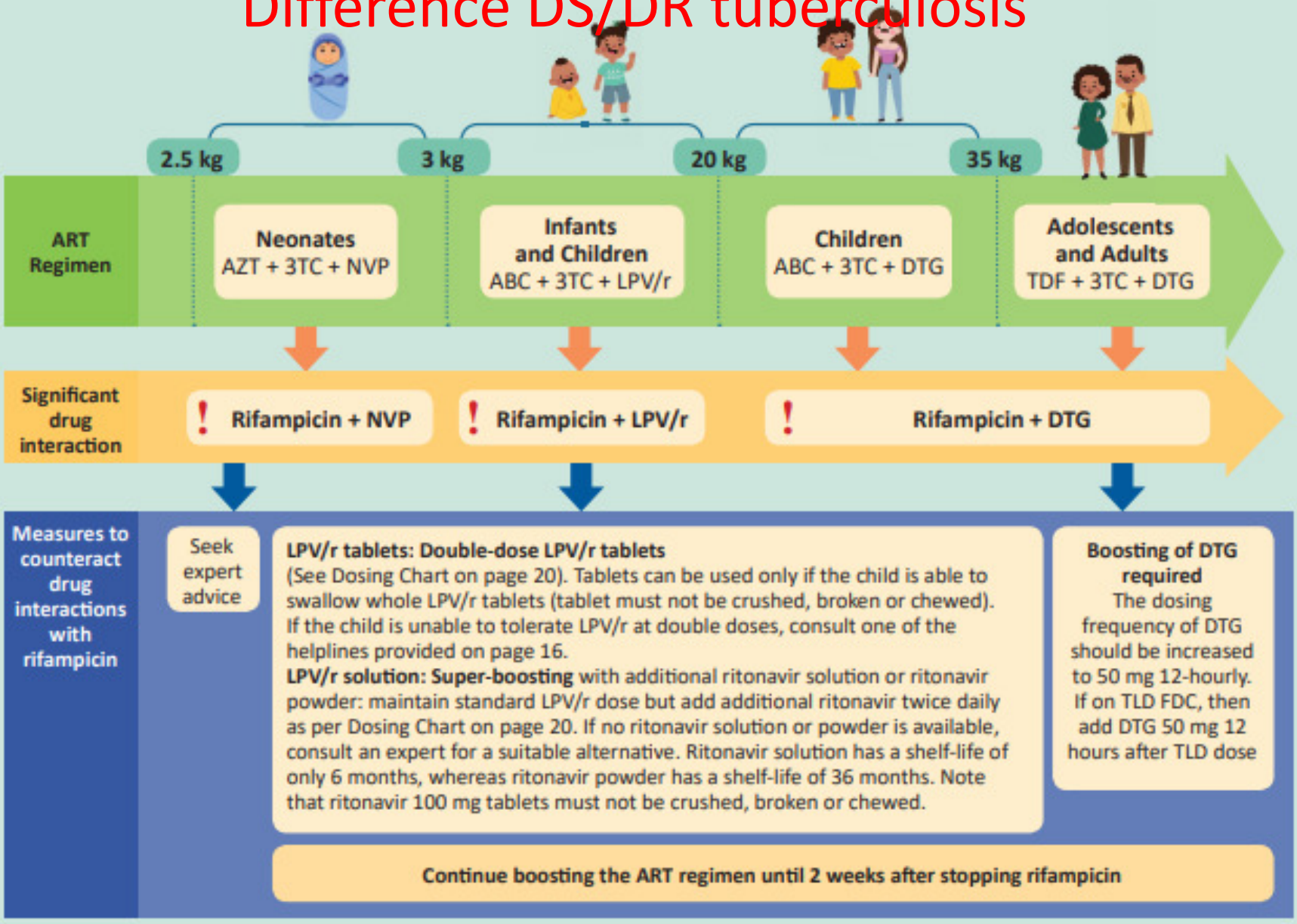
Medical Indications to Defer ART	
Indication	**Action**
TB symptoms (cough, night sweats, fever, recent weight loss)	Investigate for TB before initiating ART. If TB is excluded, proceed with ART initiation and TB preventive therapy (after excluding contra-indications to TPT). If TB is diagnosed, initiate TB treatment and defer ART. The timing of ART initiation will be determined by the site of TB infection and the client's CD4 cell count
Diagnosis of drug-sensitive (DS) TB at a non-neurological site (e.g. pulmonary TB, abdominal TB, or TB lymphadenitis)	Defer ART initiation as follows: • If CD4 < 50 cells/µL – initiate ART within 2 weeks of starting TB treatment, when the client's symptoms are improving, and TB treatment is tolerated • If CD4 ≥ 50 cells/µL – initiate ART 8 weeks after starting TB treatment
Diagnosis of drug-resistant (DR) TB at a non-neurological site (e.g. pulmonary TB, abdominal TB, or TB lymphadenitis)	Initiate ART after 2 weeks of TB treatment, when the client's symptoms are improving, and TB treatment is tolerated
Diagnosis of DS-TB or DR-TB at a neurological site (e.g. TB meningitis or tuberculoma)	Defer ART until 4-8 weeks after start of TB treatment

No difference DS/DR tuberculosis

Drug Interactions

Rifampicin-containing TB treatment has significant drug interactions with all paediatric ART regimens, as well as with adult/adolescent regimens containing DTG:

Difference DS/DR tuberculosis



Cost of Diagnosis and Treatment of DR-TB

- Assuming adherence to national drug resistant TB management guidelines, the per patient cost of XDR TB in South Africa has been estimated to be $26,392 (R387000), four times greater than MDR TB ($6,772 ~R99200) and 103 times greater than drug sensitive TB ($257 ~R3800).

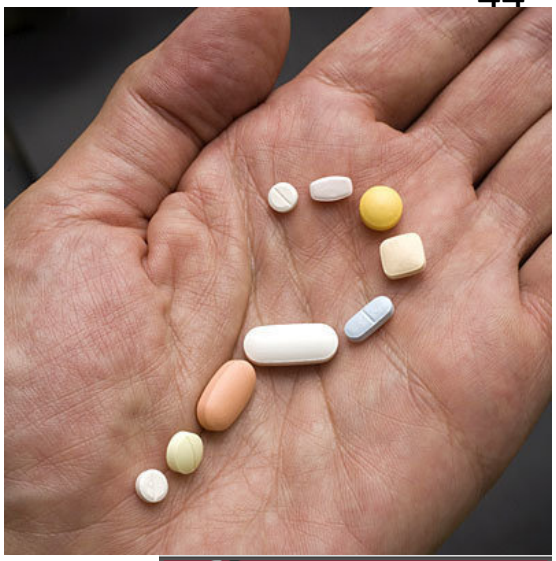
- Despite drug resistant TB comprising only 2.2% of the case burden, it is estimated to have consumed approximately 32% of the total estimated 2011 national TB budget of US$218 million. But it is still said to be underfunded.

“It is grossly underfunded. Not enough money is put into research, innovation, implementation. The fight against TB is struggling.” Dr Sanni Babutunde, WHO head of TB programme

5. History of drug-resistant tuberculosis

Historically…?

(Where are we coming from)

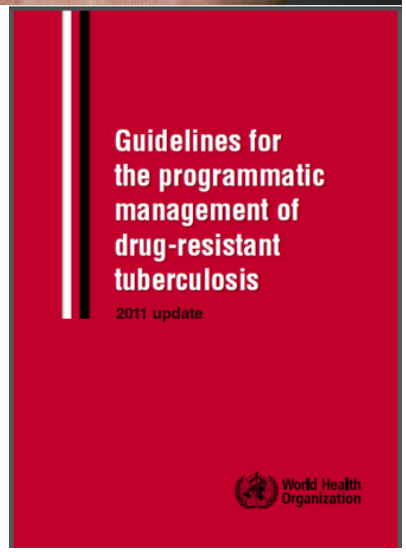


4. Duration of second-line anti-tuberculosis regimens

Recommendations

4.1 In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, ⊕◯◯◯/ very low quality evidence).

4.2 In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕◯◯◯/very low quality evidence).

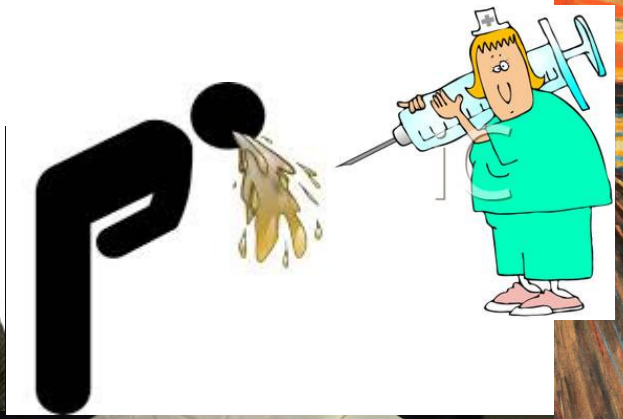


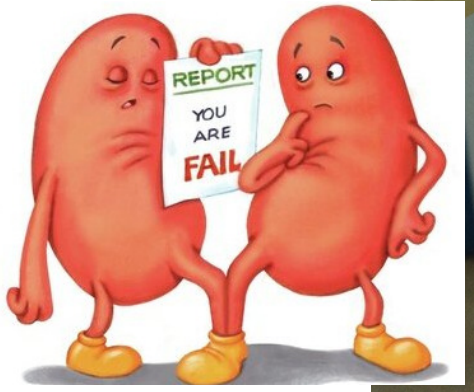
Conventional/longer regimens for MDR-TB

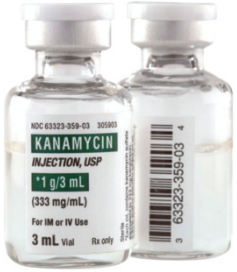
- Usually between 20-24 months, with 2 phases
- Intensive phase (4mo after culture conversion ~ 6mo)
  - Fluoroquinolone (Moxifloxacin)
  - Injectable agent (Amikacin, Kanamycin or Capreomycin)
  - PZA
  - Ethionamide
  - Terizidone/Cycloserine
  - Ethambutol (depends on local prevalence of resistance)
- Continuation phase
  - Fluoroquinolone (moxifloxacin)
  - PZA
  - Ethionamide
  - Terizidone/Cycloserine
  - Ethambutol (depends on local prevalence of resistance)


MEDECINS SANS FRONTIERES
IT CAN TAKE
DAY 1
20 pills swallowed + 1 painful injection
START
DAY 240
4,800 pills swallowed
240 painful injections received
DAY 365
7,300 pills swallowed
DAY 730
14,600 pills swallowed
FINISH
2 YEARS
TO TREAT DRUG-RESISTANT TB

Problems/challenges with DR-TB treatment?

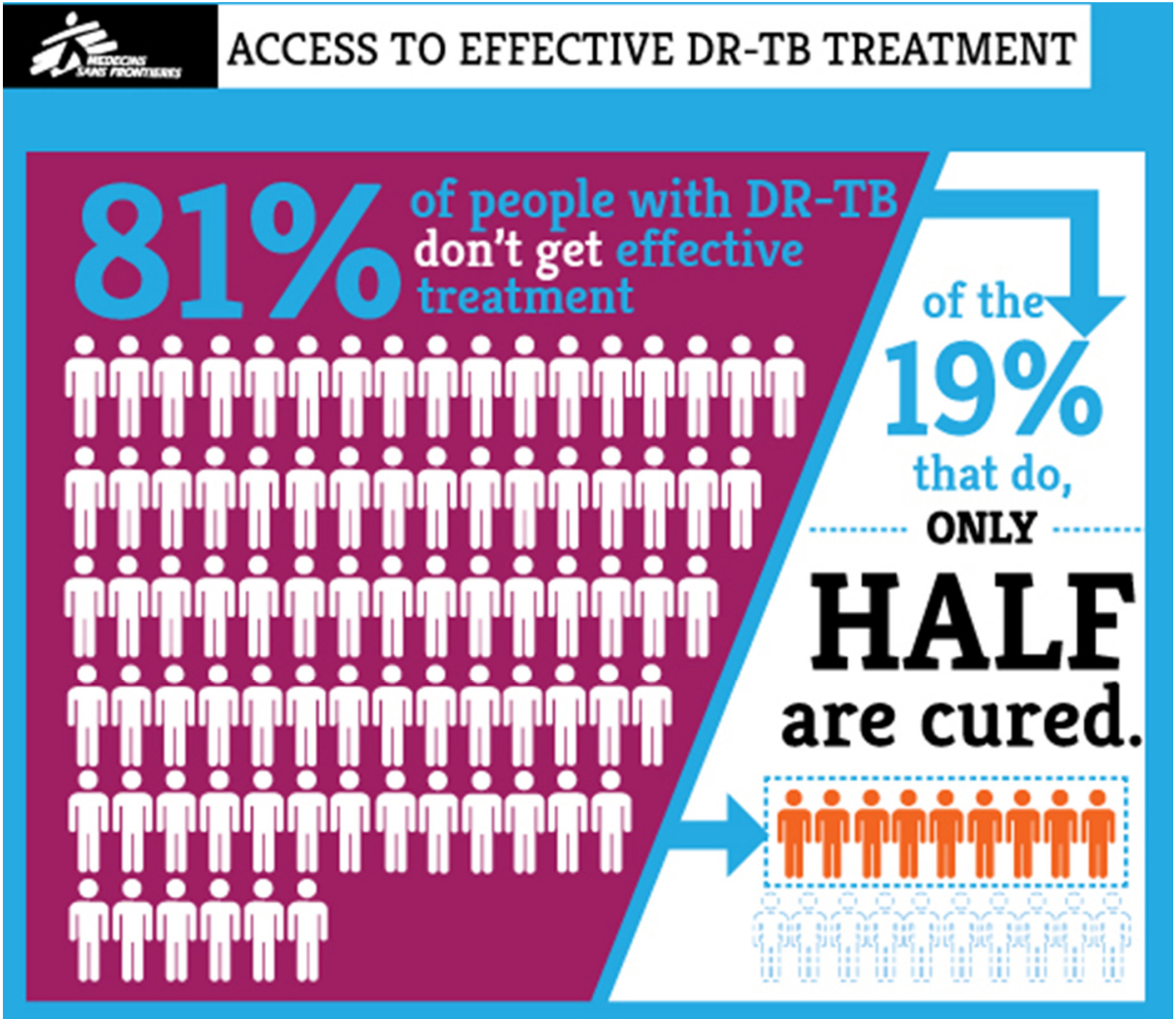






ADR	Drugs	ADR	Drugs
Skin reactions	CFZ	Nausea & Vomiting	Eto/Pto/CM/PAS/E/Z
Seizures	CS/TZD/FQs	Gastric	PAS/Eto/Pto/E/Z
Peripheral Neuropathy	CS/TZD/injectables/Eto/Pto/INH/FQs	Hepatitis	Z/FQs/PAS/EMB/Eto/Pto
Hypothyroidism	PAS/Eto/Pto	Renal failure/nephrotoxicity	Injectables
Ototoxicity	Injectables	Optic Neuritis	E
Psychosis	CS/TZD/FQs/Eto/Pto	Arthralgia/arthritis	FQs/Z
Depression	CS/TZD/FQs/CM/Eto/Pto	Electrolyte disturbances (hypokalaemia/hypomagnesaemia)	Injectables

ACCESS TO EFFECTIVE DR-TB TREATMENT



So…

- We agree that this DR-TB treatment is too long, too toxic and only works about half the time with perfect adherence…
- STREAM – 1st RCT in DR-TB started in 2012
- Based on Bangladesh regimen: A prospective observational study conducted in Bangladesh reported a cure or treatment completion rate of 84.5% in 515 patients

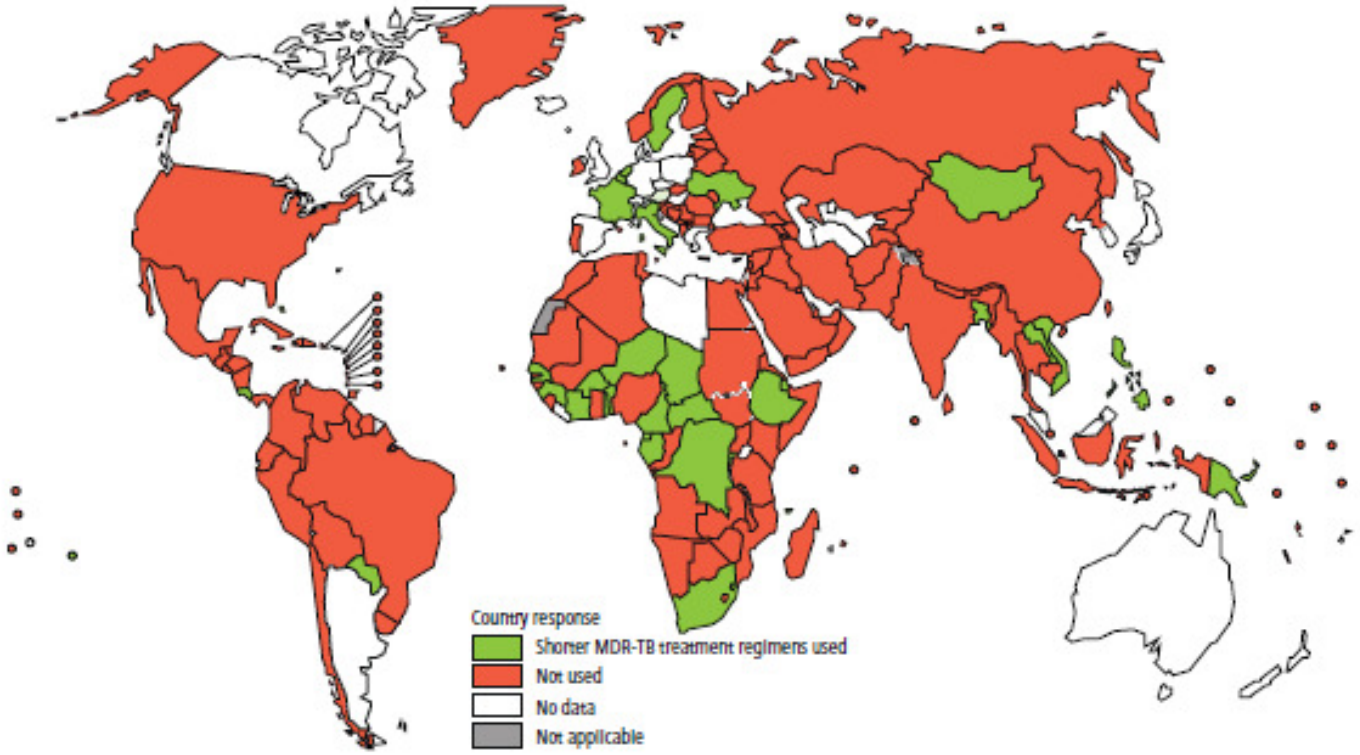
Bangladesh regimen–Intensive Phase

- High dose fluoroquinolone (Moxifloxacin/ Gatifloxacin)
- Injectable agent (Amikacin, Kanamycin or Capreomycin)
- PZA
- Ethionamide/Prothionamide
- High dose INH
- Clofazimine
- Ethambutol

Bangladesh regimen–Continuation Phase

- High dose fluoroquinolone (Moxifloxacin/Gatifloxacin)
- PZA
- Clofazimine
- Ethambutol
- No injectable

FIG. 4.27
Countries that had used shorter MDR-TB treatment regimens by the end of 2016



STREAM

Release of Preliminary Stage 1 Results

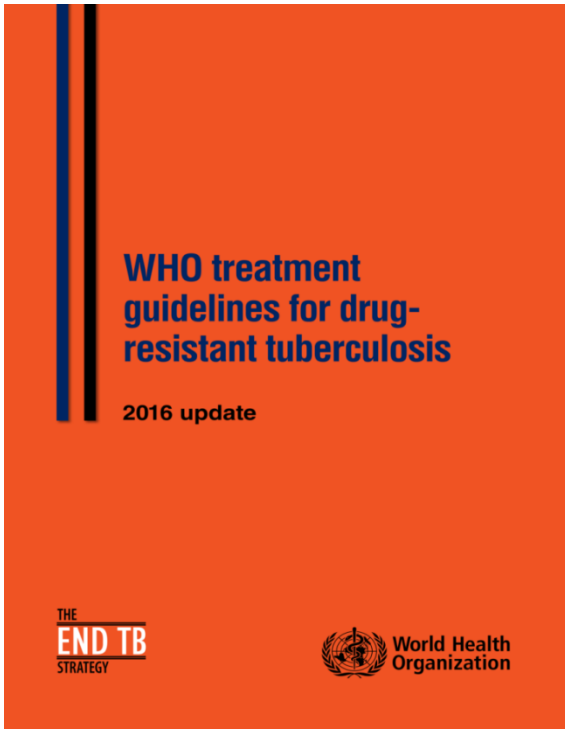
STREAM is the world's first multi-country randomized clinical trial to test the efficacy, safety, and economic impact of shortened multidrug-resistant tuberculosis (MDR-TB) treatment regimens. Preliminary results for Stage 1 of the STREAM trial were released at The Union Conference at a symposium attended by more than 150 people. The preliminary results

STREAM 1 Results

- The ***9–11-month regimen was statistically non-inferior to the 20-month regimen in terms of efficacy.***
  - **79.8%** of patients on the 20-month regimen had a favorable outcome
  - **78.8%** of patients on the 9-11 month regimen had a favorable outcome
- There was no evidence that efficacy results were worse in HIV-infected participants than the results for HIV-negative participants.
- The STREAM 9–11-month regimen presents substantial advantages, despite the ECG monitoring required. ***The 9–11-month regimen reduces treatment times, may improve retention under programmatic conditions, and reduces the overall pill burden for patients.***
- There were very similar rates of severe adverse events between the short and long regimens: 48.2% of participants on the 9-11 month regimen vs. 45.4% on the 20 month regimen.
- Research is ongoing into ways of improving the nine-month regimen in STREAM Stage 2.

New WHO recommendation for shorter regimens - 2016

- For most patients with MDR-TB, a shorter regimen (9-12 months) can be used instead of a longer, conventional regimen



But: WHO's recommendation acknowledges that additional evidence is required

CLINICAL PRACTICE

Clinical Access to Bedaquiline Programme for the treatment of drug-resistant tuberculosis

F Conradie, G Meintjes, J Hughes, G Maartens, H Ferreira, S Siwendu, I Master, N Ndjeka

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While clinical disease caused by drug-sensitive *Mycobacterium tuberculosis* (MTB) can usually be treated successfully, clinical disease caused by drug-insensitive MTB is associated with a poorer prognosis. In December 2012, a new drug, bedaquiline, was approved by the US Food and Drug Administration. This article documents the process whereby the National Department of Health, Right to Care and Médecins Sans Frontières obtained access to this medication for South Africans who might benefit from subsequent implementation of the Clinical Access to Bedaquiline Programme.

S Afr Med J 2014;104(3):164-166. DOI:10.7196/SAMJ.7263

INT J TUBERC LUNG DIS 19(8):000–000

http://dx.doi.org/10.5588/ijtld.14.0944

Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis

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SUMMARY

BACKGROUND: South Africa has a large burden of extensively drug-resistant tuberculosis (XDR-TB); only 15% of XDR-TB patients have successful outcomes.

OBJECTIVE: To describe the safety and effectiveness of bedaquiline (BDQ) in the South African BDQ Clinical Access Programme.

DESIGN: An interim cohort analysis.

RESULTS: Of the first 91 patients enrolled between March 2013 and July 2014 (with follow-up until August 2014), 54 (59%) were human immunodeficiency virus (HIV) infected. The median CD4 count was 239 cells/μl, and all patients were on antiretroviral therapy (ART) at initiation of BDQ; 33 had XDR-TB, 41 were pre-XDR-TB with fluoroquinolone resistance and 17 were pre-XDR-TB with resistance to an injectable. Of the 91 patients, 58 (64%) had completed 24 weeks of BDQ, 28 were still on BDQ, 3 were lost to follow-up, 1 had died and 1 had BDQ withdrawn following atrial fibrillation. Of the 63 patients with 6 months follow-up, 48 (76%) had either culture-converted or remained culture-negative after initiation of BDQ. QTcF was monitored monthly and exceeded 500 ms in three participants; this resolved in all three.

CONCLUSION: Interim safety and culture conversion outcomes for patients accessing BDQ in South Africa, including HIV-infected patients on ART and patients with pre-XDR- and XDR-TB, suggest that BDQ may be both efficacious and safe.

KEY WORDS: extensively drug-resistant tuberculosis; South Africa; compassionate access; adverse events

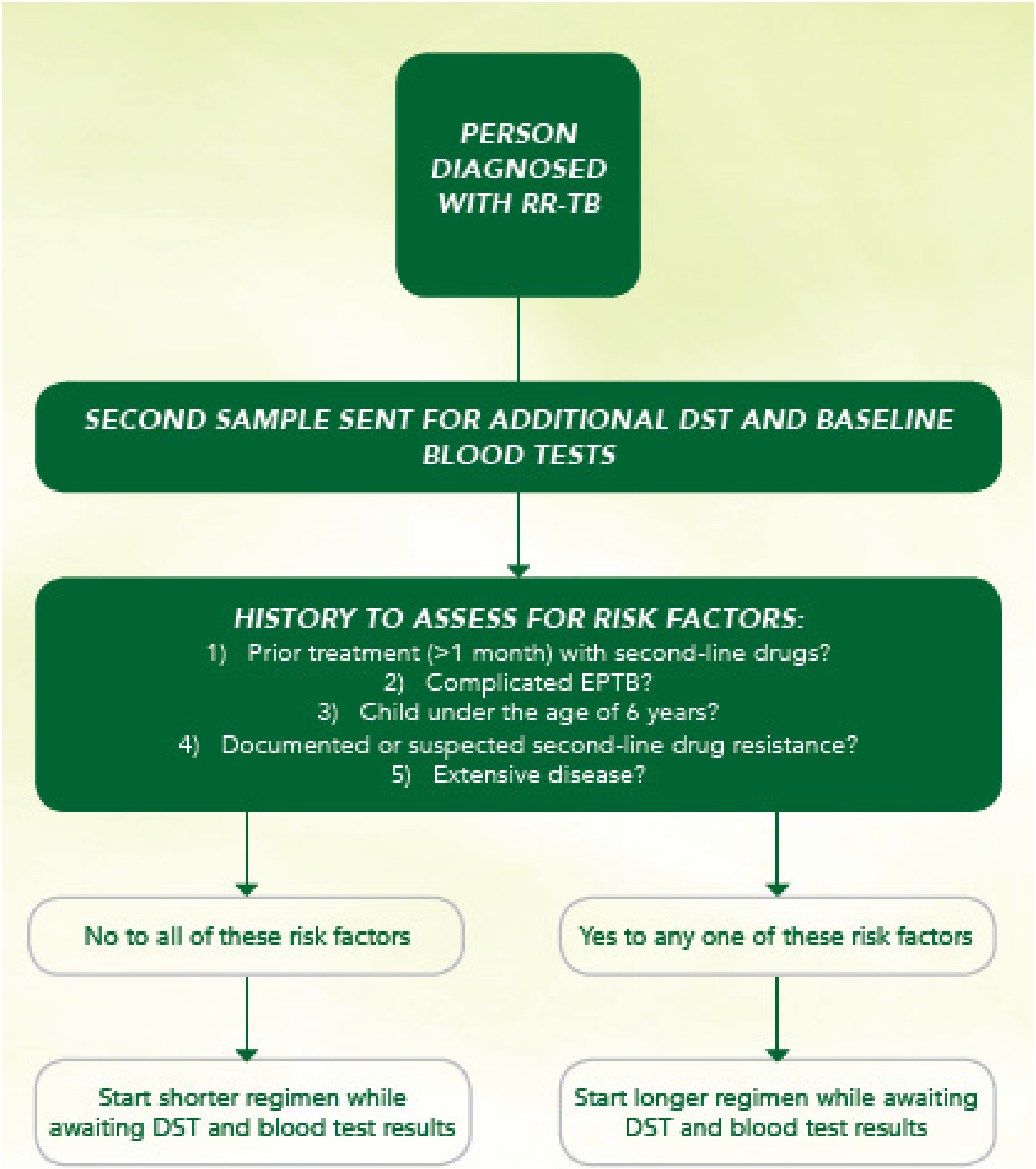
Ideal DR-TB Rx Regimen?

6. Current DR-TB treatment

So where are we now?

- BCAP in 2013 --> DoH guidelines in 2015 to substitute injectables with Bedaquiline (BDQ)
- Retrospective analysis of impact of access to BDQ on RR-TB and XDR-TB outcomes with SA demonstrated 4x reduction in mortality
- Therefore June 2018 NDoH decided to replace SLID with BDQ to make injection free regimens for all patients presenting with RR-TB
- As of Jan 2019, ~15000 patients have received BDQ under programmatic conditions
- SA DoH – Management of Rifampicin-resistant tuberculosis guidelines updated again in April 2019, and handbook for Nov 2019
  - Modified short regimen for RR-TB
  - New longer regimens for RR-TB on core backbones individualized based on
    - Age (<6 yrs)
    - FQ resistance
    - Site (i.e. CNS disease)

Short vs Long?



Short Course

4-6 months (Intensive Phase):

LZD (2 months only)–BDQ (total 6 months)*
–hdINH (4-6 months)–LFX–CFZ–PZA–EMB

5 months (Continuation Phase):

LFX–CFZ–PZA–EMB

	2 MONTHS	4 MONTHS	6 MONTHS	9 MONTHS
Linezolid		Give for 2 months even if second-line LPA shows injectable and fluoroquinolone susceptibility		
High-dose isoniazid			Extend for another 2 months if smear positive at month 4*	
Bedaquiline				Continue to 9 months in some patients
Levofloxacin				
Clofazimine				
Pyrazinamide				
Ethambutol				

*If smears remain positive at month 4, begin extended workup for treatment failure while isoniazid is continued.

Medicines recommended for the treatment of multidrug-resistant TB

Group A: **Include all three medicines (unless they cannot be used)**	Levofloxacin/Moxifloxacin Bedaquiline Linezolid
Group B: **Add both medicines (unless they cannot be used)**	Cycloserine / Terizidone Clofazimine
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	Ethionamide / Prothionamide Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin / Meropenem Amikacin *p*-aminosalicylic acid (PAS)

Designing a longer regimen:

GROUPS AND STEPS	MEDICINE	COMMENTS
Group A: include all three medicines, where possible	Levofloxacin or moxifloxacin	Include for CNS disease. Omit in fluoroquinolone-resistant RR-TB.
	Bedaquiline	No dosing data currently available in age<6 years.
	Linezolid	Include for CNS disease. Avoid if LZD resistance demonstrated. In patients with Hb <8 g/dL, neutrophils <0.75 x 109/L and/or platelets <50 x 109/L, only consider reintroducing or initiating in hospital under close monitoring; otherwise substitute with other Group C drugs including delamanid.
Group B: add one or both medicines, if possible	Clofazimine	
	Terizidone	Include for CNS disease.
Group C: add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	Only use as a reliably effective drug if susceptibility demonstrated on DST.
	Delamanid	Include for CNS disease. Dosing data not currently available in age <3 years.
	Pyrazinamide	Include for CNS disease. Only use as a reliably effective drug if susceptibility demonstrated on DST.

Designing a longer regimen:

GROUPS AND STEPS	MEDICINE	COMMENTS
Group C: add to complete the regimen and when medicines from Groups A and B cannot be used	Imipenem-cilastatin, or meropenem, or ertapenem	Adequate CNS penetration. Must be given in combination with amoxicillin/clavulanic acid.
	Amikacin	Only administer in rescue regimens, if there is documented susceptibility, if formal hearing tests can be done, and if the patient consents to its use after the risks and benefits of the drug have been explained.
	Ethionamide	Consider for CNS disease. Should only be given if *inhA* mutation is not present.
	para-aminosalicylic acid	

Longer regimen >6 years

EXAMPLE	INTENSIVE PHASE	CONTINUATION PHASE	COMMENTS
"Basic" longer regimen	6 months of: BDQ–LZD–LFX–CFZ–TRD	12 months of three drugs: LFX–CFZ–TRD (if one of these three drugs are not tolerated, extend either LZD or BDQ instead)	If TRD contra-indicated or not tolerated in intensive phase, then no need to substitute TRD (unless there was previous treatment with second-line drugs, or extensive disease)
Fluoroquinolone-resistant RR-TB longer regimen	6 months of: BDQ–LZD–DLM–CFZ–TRD	12 months of three to four drugs: CFZ–TRD– [LZD, BDQ and/or DLM, depending on tolerance]	Use four drugs in continuation phase if extensive disease, co-morbidities
CNS RR-TB longer regimen	12 months of: BDQ–LZD–DLM-LFX–CFZ–TRD–PZA– [high-dose INH 15 mg/kg, or ETO, depending on INH mutation]	6 months of four to five drugs: LFX– CFZ–TRD–PZA– [LZD or high-dose INH 15 mg/kg or ETO depending on INH mutation]	High-dose INH is higher than usual (15 mg/kg) for CNS disease in adults

*Treatment duration is 18 months but could be extended to 20 months per clinician discretion

LZD = linezolid; BDQ = bedaquiline; LFX = levofloxacin;
CFZ = clofazimine; TRD = terizidone; DLM = delamanid;
PZA = pyrazinamide; INH = isoniazid; ETO = ethionamide

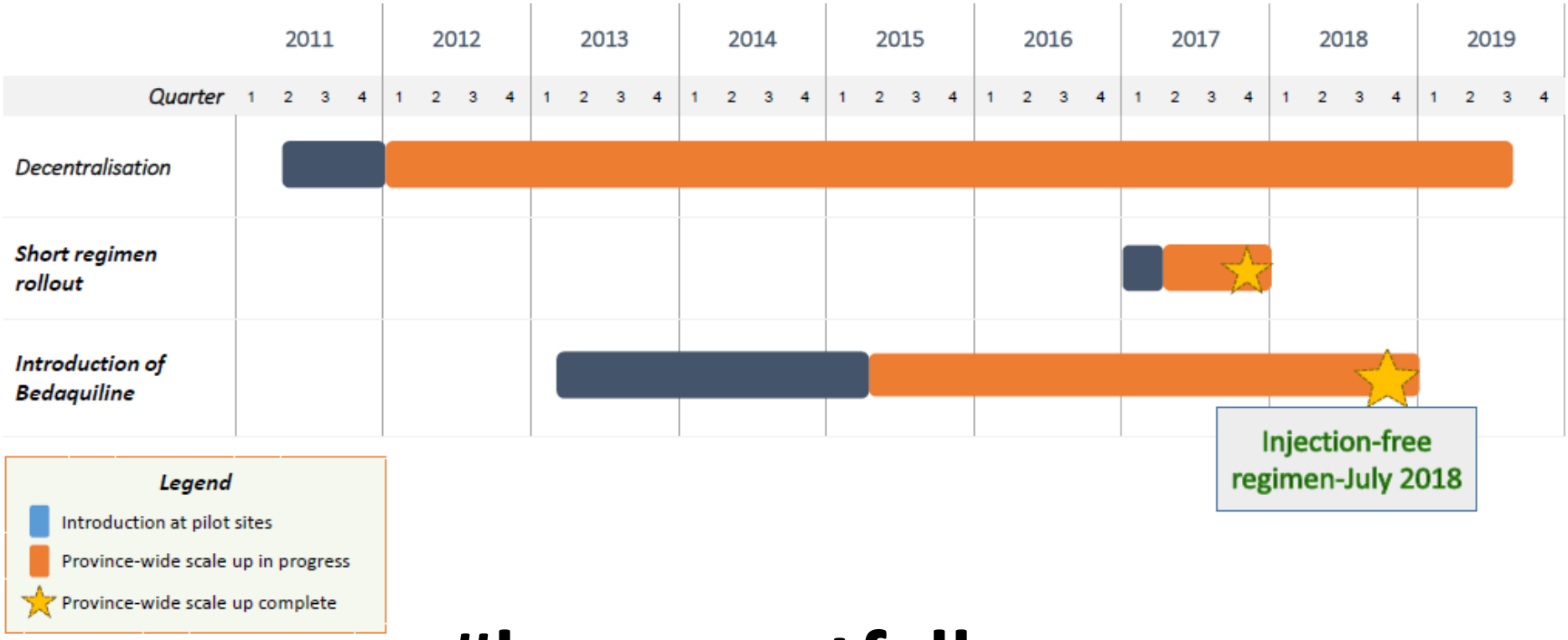
Longer regimen <6 years

DRUG SUSCEPTIBILITY PATTERN	AGE GROUP	SUGGESTED REGIMEN
RR-TB that is NOT fluoroquinolone resistant or central nervous system disease	3-6 years	LFX–LZD–CFZ– TRD–[DLM or PAS]
	0-3 years	LFX–LZD–CFZ–TRD – [PAS or ETO/high-dose INH]
RR-TB that is resistant to fluoroquinolones	3-6 years	LZD–CFZ–TRD–DLM–[PAS or ETO]
	0-3 years	LZD–CFZ–TRD–DLM* –[PAS and/or ETO/high-dose INH]
RR-TB central nervous system disease	<6 years	LFX–LZD–TRD–DLM* – [ETO/high-dose INH]–[PZA]

*Benefit of delamanid use likely outweighs risks in these populations and should be strongly considered for use.

LZD = linezolid; LFX = levofloxacin; CFZ = clofazimine;
TRD = terizidone; DLM = delamanid; PZA = pyrazinamide;
INH = isoniazid; ETO = ethionamide; PAS = para-aminosalicylic acid

Implementation of short course in SA



#kanamustfall

With thanks to Dr Norbert Ndjeka

Injectable vs BDQ in MDR and XDR-TB (2016)

RR/MDR-TB-2016	Number started on treatment	Treatment Success	Treatment Success Rate	Died	Death Rate	Loss to follow up	Loss to follow up rate	Treatment failure	Treatment failure Rate	Not evaluated	Not evaluated Rate
Injectable Regimen	7166	3724	**52%**	1547	**22%**	1510	**21%**	218	**3%**	167	**2%**
Bedaquiline Regimen	1777	1161	**65%**	**242**	**14%**	297	**17%**	45	**3%**	32	**2%**

XDR-TB-2016	Number started on treatment	Treatment Success	Treatment Success Rate	Died	Death Rate	Loss to follow up	Loss to follow up rate	Treatment failure	Treatment failure Rate	Not evaluated	Not evaluated Rate
Injectable Regimen	98	20	**20%**	37	**38%**	14	**14%**	24	**24%**	3	**3%**
Bedaquiline Regimen	467	321	**69%**	74	**16%**	53	**11%**	15	**3%**	4	**1%**

With thanks to Dr Norbert Ndjeka

Short Regimen Outcomes: Injectable vs BDQ

Treatment Outcome Short Regimen: 2017	Number started on treatment	Treatment Success	Treatment Success Rate	Died	Death Rate	Loss to follow up	Loss to follow up rate	Treatment failure	Treatment failure Rate	Not evaluated	Not evaluated Rate
RR/MDR-TB	3695	2479	**67%**	645	**18%**	446	**12%**	62	**2%**	63	**2%**

Short Regimen: 2017 (RR/MDR-TB)	Number started on treatment	Treatment Success	Treatment Success Rate	Died	Death Rate	Loss to follow up	Loss to follow up rate	Treatment failure	Treatment failure Rate	Not evaluated	Not evaluated Rate
Injectable Regimen	1372	830	**60%**	273	**20%**	205	**15%**	30	**2%**	34	**2%**
Bedaquiline Regimen	1936	1436	**74%**	256	**13%**	190	**10%**	26	**1%**	28	**1%**

With thanks to Dr Norbert Ndjeka

XDR outcomes: Injectable vs BDQ

Treatment Outcome: Q3 2017	Number started on treatment	Treatment Success	Treatment Success Rate	Died	Death Rate	Loss to follow up	Loss to follow up rate	Treatment failure	Treatment failure Rate	Not evaluated	Not evaluated Rate
XDR-TB	139	92	**66%**	26	**19%**	13	**9%**	5	**4%**	3	**2%**

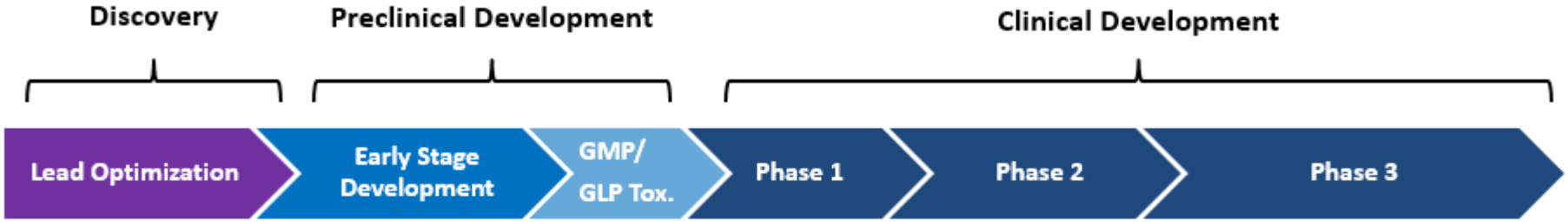
Treatment Outcome: Q3 2017 (XDR-TB)	Number started on treatment	Treatment Success	Treatment Success Rate	Died	Death Rate	Loss to follow up	Loss to follow up rate	Treatment failure	Treatment failure Rate	Not evaluated	Not evaluated Rate
Injectable Regimen	7 (5%)	1	**14%**	6	**86%**	0	**0%**	0	**0%**	0	**0%**
Bedaquiline Regimen	119 (86%)	87	**73%**	17	**14%**	8	**7%**	5	**4%**	2	**2%**

13(9%) patient records do not have an indication of whether they received an injectable or Bedaquiline containing regimen.

With thanks to Dr Norbert Ndjeka

7. What’s coming?

2017 Global New TB Drug Pipeline [1]



Lead Optimization

- Diarylthiazoles
- DprE1 Inhibitors
- InhA Inhibitor
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, Clp, PKS13
- Oxazolidinones
- Pyrimidines
- Squaramides

Early Stage Development

- CPZEN-45*
- SATB082*
- Spectinamide - 1810*
- SPR-720 (pVXc-486)*
- TB-47*
- DC-159a

GMP/ GLP Tox.

- BTZ-043*
- TBAJ-587
- TBI-166*
- TBI-223
- GSK-286*

Phase 1

- OPC-167832*
- Q203*
- GSK-656 (070)*
- Contezolid MRX-4/ MRX-1
- TBA-7371*

Phase 2

- Delpazolid (LCB01-0371)
- SQ-109*
- Sutezolid (PNU-100480)
- PBTZ169*

Phase 3

- Bedaquiline* (TMC-207)
- Delamanid* (OPC-67683)
- Pretomanid* (PA-824)

Underline = new to Phase

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

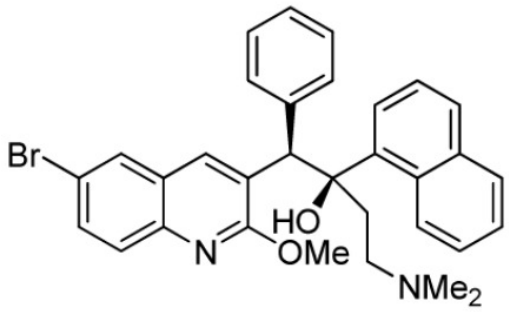
Updated: October 2017

Promising drugs

- New Drugs
  - Bedaquiline
  - Sutezolid (Oxazolidenone)
  - TBI-223 (Oxazolidenone)
  - Pretomanid
  - Delaminid
- Re-purposed:
  - Linezolid
  - Clofazimine

Bedaquiline (TMC-207)

- BDQ is diarylquinoline compound with a new mechanism of antituberculosis action by specifically inhibiting mycobacterial ATP synthase
- First new TB drug registered in 50 years! (SA – 2015)
- Approved as an add-on to SOC in many countries, starting 2012



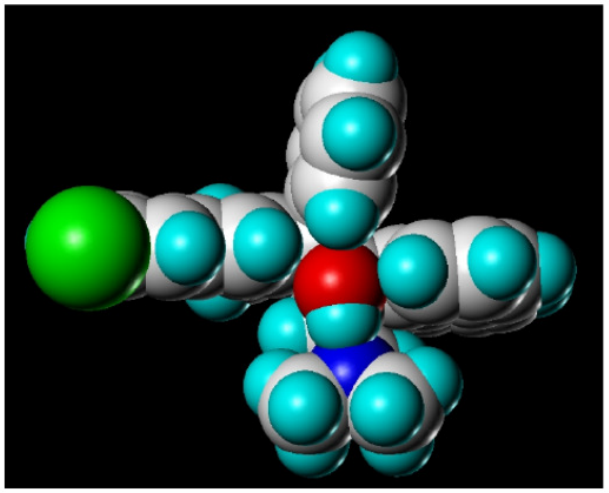
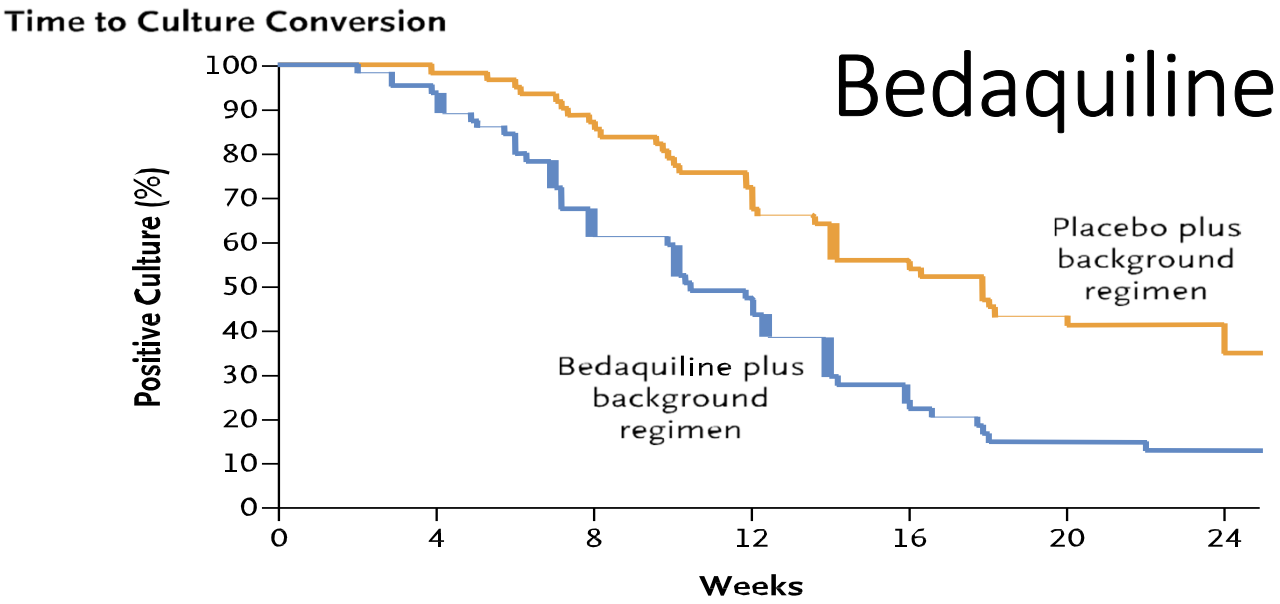


Figure 8 **Chemical Structure of Bedaquiline (TMC207)**



Bedaquiline

Conditional approval: FDA
MCC: 2014
India
Black box warning

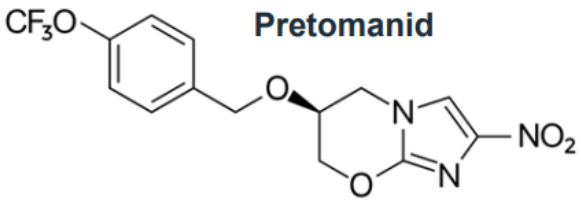
Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.*

Variable	Bedaquiline (N=79)	Placebo (N=81)
Median duration of overall treatment phase (range) — wk	91.7 (2.0–120.0)	94.1 (2.0–137.3)
Adverse event — no. (%)		
Any	78 (99)	79 (98)
Related to treatment	55 (70)	56 (69)
Grade 3 or 4†	34 (43)	29 (36)
Leading to discontinuation of treatment	4 (5)	5 (6)
Serious adverse events — no. (%)‡	18 (23)	15 (19)
Adverse event occurring in ≥20% of patients — no. (%)		
Nausea	32 (41)	30 (37)
Arthralgia	29 (37)	22 (27)
Vomiting	23 (29)	22 (27)
Headache	23 (29)	18 (22)
Hyperuricemia	20 (25)	27 (33)
Hemoptysis	16 (20)	14 (17)

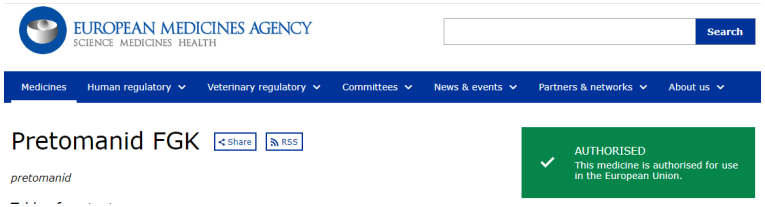
Diacon, NEJM, 2015

Pretomanid

Pretomanid: New Chemical Entity Developed Specifically to Treat TB



- Nitroimidazooxazine with novel mechanisms of action
- Nonclinical and clinical studies showed anti-TB activity against drug-susceptible and drug-resistant *M. tuberculosis*
- Possesses bactericidal and curative activities
- Studied in 1168 individuals, 19 clinical studies
- FDA granted Priority Review, Qualified Infectious Disease Product, and Orphan Drug status



DR-TB Drug interactions with ART

- Bedaquiline – cannot give with EFV. Can use NVP/Aluvia/DTG (normal doses)
- Linezolid – can cause significant bone marrow suppression. Don't give with AZT
- SLID – can cause renal dysfunction. Ideally not with TDF
- No significant interactions: DLM/Pretomanid/Fluoroquinolones/CFZ

Global TB Drug and Regimen Clinical Research [1]

Ongoing Clinical Development Research: Strategy/Optimization/Regimen Development

Phase 2

Bedaquiline-Delamanid (ACTG 5343)

Bedaquiline - Pretomanid - Pyrazinamide (BPaZ) (NC-005)

Bedaquiline - Pretomanid – Moxifloxacin - Pyrazinamide (BPaMZ) (NC-005)

Levofloxacin with OBR for MDR-TB (OPTI-Q)

Linezolid Dose-Ranging

Nitazoxanide

Beta-Lactams

High Dose Rifampicin (PANACEA)

TB PRACTECAL - regimens with Bedaquiline-Pretomanid-Linezolid

Phase 3 Regimens

Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)

Bedaquiline-Pretomanid-Linezolid (NiX-TB)

Delamanid with OBR for MDR-TB

High Dose Rifampicin for DS-TB (RIFASHORT)

Rifapentine - Moxifloxacin for DS-TB (CDC TBTC 31)

Pretomanid-Moxifloxacin-Pyrazinamide (STAND)

Optimization/Post Market

Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

endTB 5-Regimen Trial for MDR TB

PredictTB – PET/CT, biomarkers DS-TB, 4 mo

Clofazimine - formulation development

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: October 2017

Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

[1] **Strategy trials, regimen development, open label, repurposed drug studies. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical**

[2] **OBR = Optimized Background Regimen**

TB-PRACTECAL regimens rationale

Principles for designing future regimens for multidrug-resistant tuberculosis

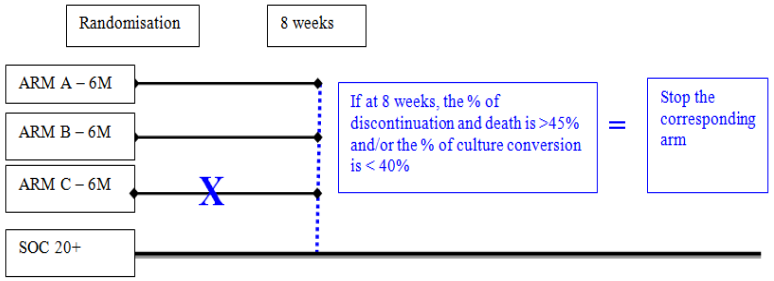
Grania Brigden,[a] Bern-Thomas Nyang'wa,[b] Philipp du Cros,[b] Francis Varaine,[c] Jennifer Hughes,[d] Michael Rich,[e] C Robert Horsburgh Jr,[f] Carole D Mitnick,[g] Eric Nuermberger,[h] Helen McIlleron,[i] Patrick P J Phillips[j] & Manica Balasegaram[a]

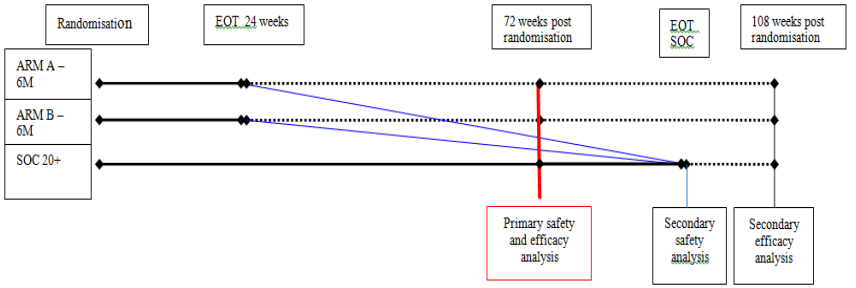
- At least one new class
- At least 3 and max 5 effective drugs
- Effective against MDR and XDR strains
- 6 - 9 months
- Oral
- Simple dosing schedule
- Good side effect profile, limited monitoring
- Minimal interaction with antiretrovirals

3 Investigational Arms:

- Bedaquiline + pretomanid + linezolid
- Bedaquiline + pretomanid + linezolid + moxifloxacin
- Bedaquiline + pretomanid + linezolid + clofazimine

Control arm: Locally accepted standard of care which is consistent with the WHO recommendations for the treatment of M/XDR-TB





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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Nix-TB Pilot Phase 3 Trial in XDR-TB

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB Treatment

XDR-TB

- **Pretomanid 200 mg qd**
- **Bedaquiline 200 mg tiw after 2 week load**
- **Linezolid 1200 mg qd***

6 months of treatment

Follow up for relapse-free cure over 24 months

Additional 3 months if sputum culture positive at 4 months

*Amended from 600 mg bid strategy

Sites

Sizwe Hospital, Johannesburg, South Africa

Brooklyn Chest Hospital, Cape Town, South Africa

King Dinuzulu Hospital, Durban, South Africa

Nix Results

Pretomanid with Bedaquiline and Linezolid Cured ~90% of Patients with Highly-Resistant TB

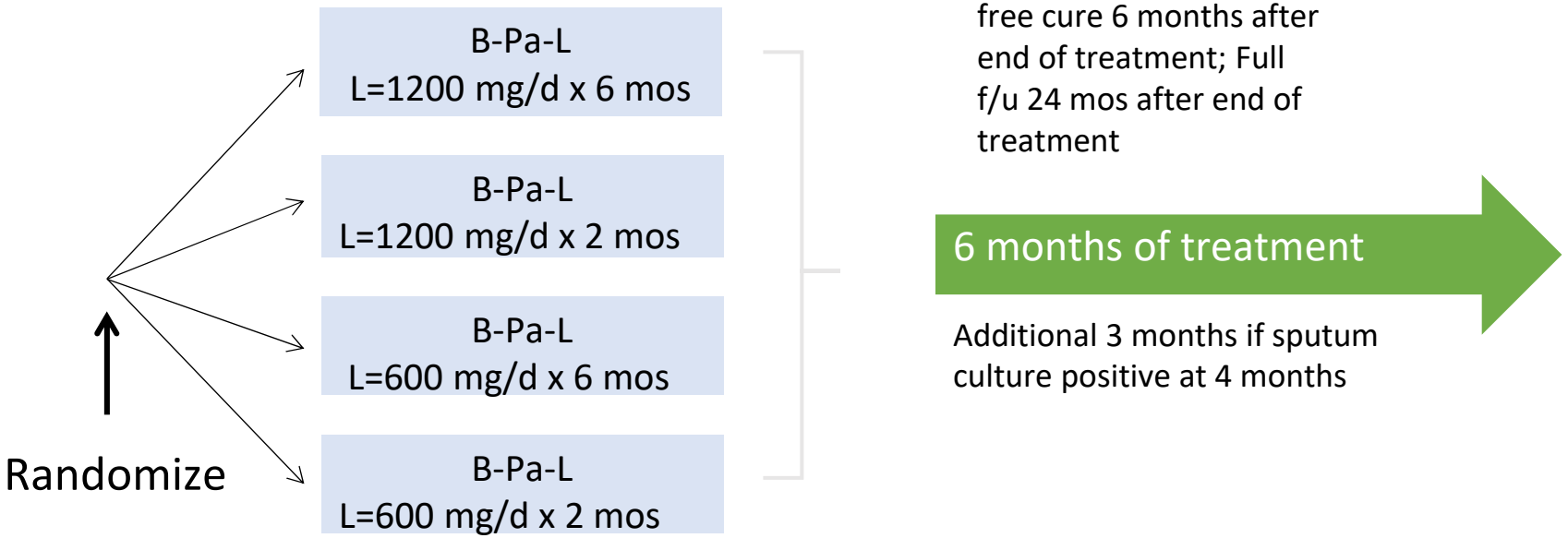
- 3-drug, all-oral, 6-month regimen
- Patients converted to culture negative status very quickly
  - Median time of < 6 weeks
- Patients improved clinically
  - Reduction of TB symptoms
  - Overall improvement in patient-reported health status

Experience with Linezolid Toxicity

- Linezolid likely responsible for most adverse events and all dose modifications
- 50 patients interrupted and resumed treatment at same or lower dose
- 33 patients permanently discontinued linezolid, with all surviving patients (27) completing treatment
  - Peripheral neuropathy most common reason for discontinuing linezolid
- 34 patients had no linezolid dose interruptions
- Myelosuppression requiring interruption or reduction generally in the first 2-3 months
- Neuropathy requiring interruption or reduction generally in months 4-6

ZeNix: Linezolid Optimization Trial

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment



N=30 XDR-TB per group AND
up to 15 pre-XDR or intolerant/non-responsive MDR-TB per group

Pa dose = 200 mg daily; B Dose = 200 mg daily x 8 weeks, 100 mg x 18 weeks


thank
you

inhA and katG mutation info

- In-vitro evidence seems to suggest that when specific inhA mutations are detected (and in the absence of any katG mutations), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid to a maximum dose of up to 15 mg/kg per day could be considered. In the case of katG mutations, which more commonly confer higher-level resistance, the use of isoniazid even at a higher dose is less likely to be effective
- An isolated katG or inhA mutation can correspond to variable minimum inhibitory concentration (MIC) levels. This implies that inhA mutations do not always indicate low-level isoniazid resistance or that katG mutations are necessarily correlated with high-level isoniazid resistance. The presence of both mutations is usually an indication of high-level resistance.
- The MTBDRplus rapid assay can determine whether both the inhA and katG mutations are present, in which case both isoniazid and ethionamide are likely to be ineffective and therefore the shorter regimen is not indicated
- The presence of both inhA and katG mutations is a contraindication for the use of the shorter regimen.