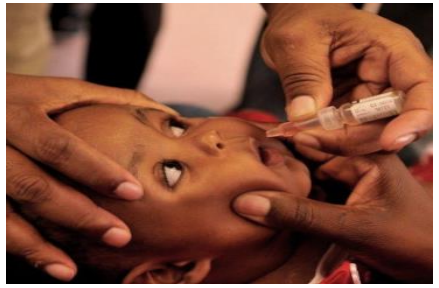
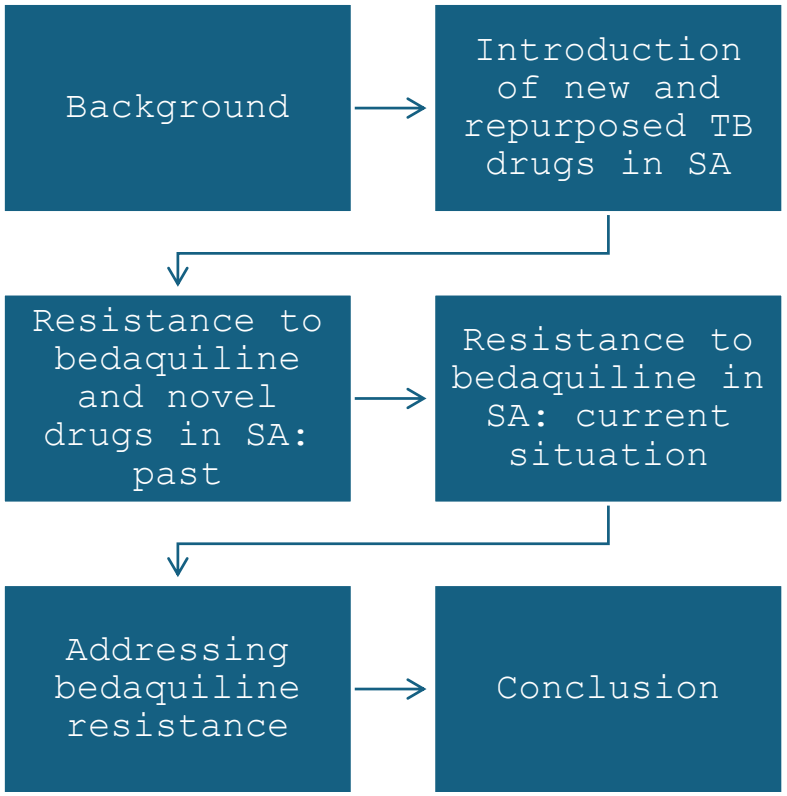


New drugs for drug-resistant TB in a high TB burden setting: Leadership, opportunities and the challenges of emerging drug resistance in South Africa

Prof. Norbert Ndjeka
National Department of Health, South Africa
TB Control and Management Cluster

20 March 2024

Outline of the presentation



Background

Overview of TB Services in South Africa

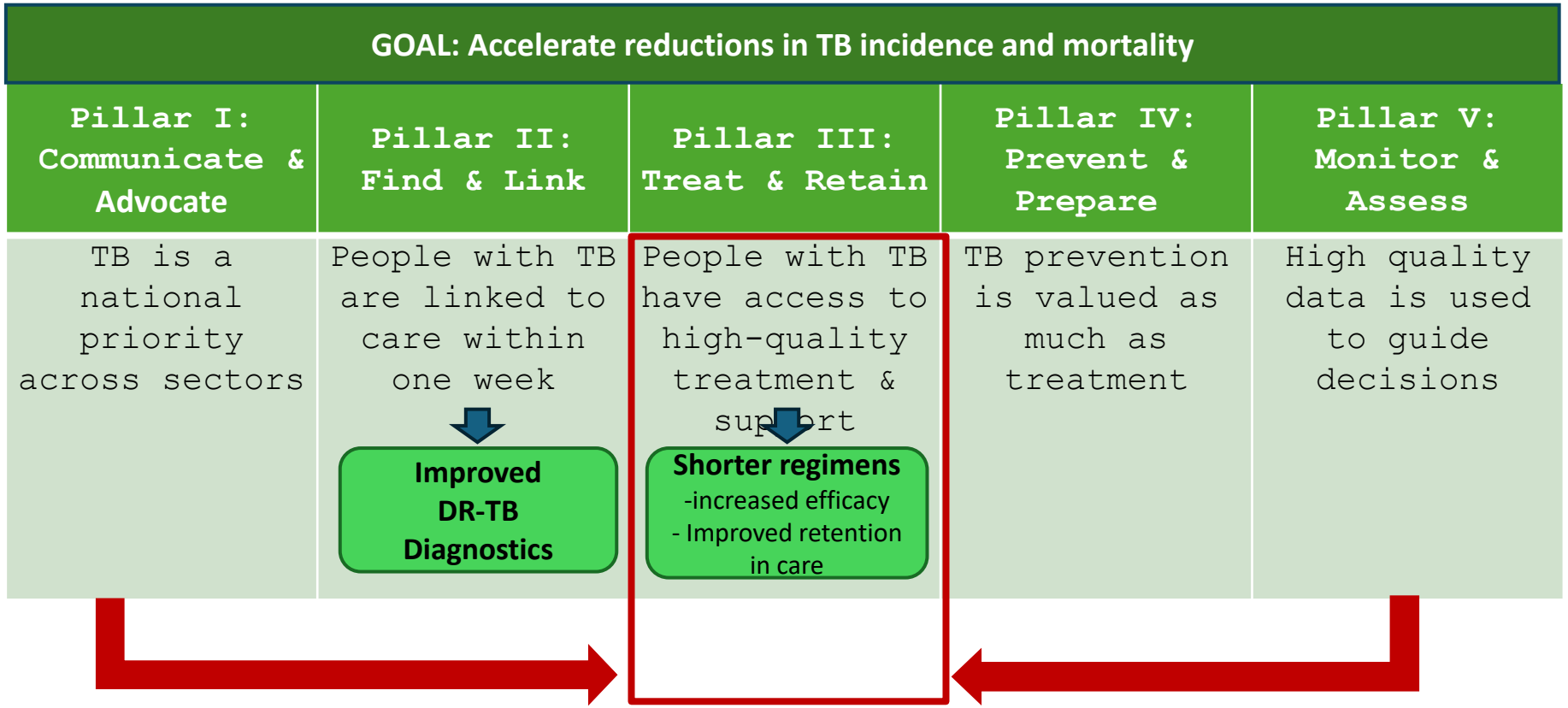
- Country population: 60 million
- Provinces: 9
- Districts: 52
- Sub-districts: 232
- DS-TB diagnosed and treated at 3,700 health facilities
- DR-TB services provided at 758 sites distributed in 95% of Sub-districts
- All TB presumptive individuals are tested using TB-NAAT


National Strategic Plan
For HIV, TB and STIs
2023-2028
REPUBLIC OF SOUTH AFRICA
2030 NDP

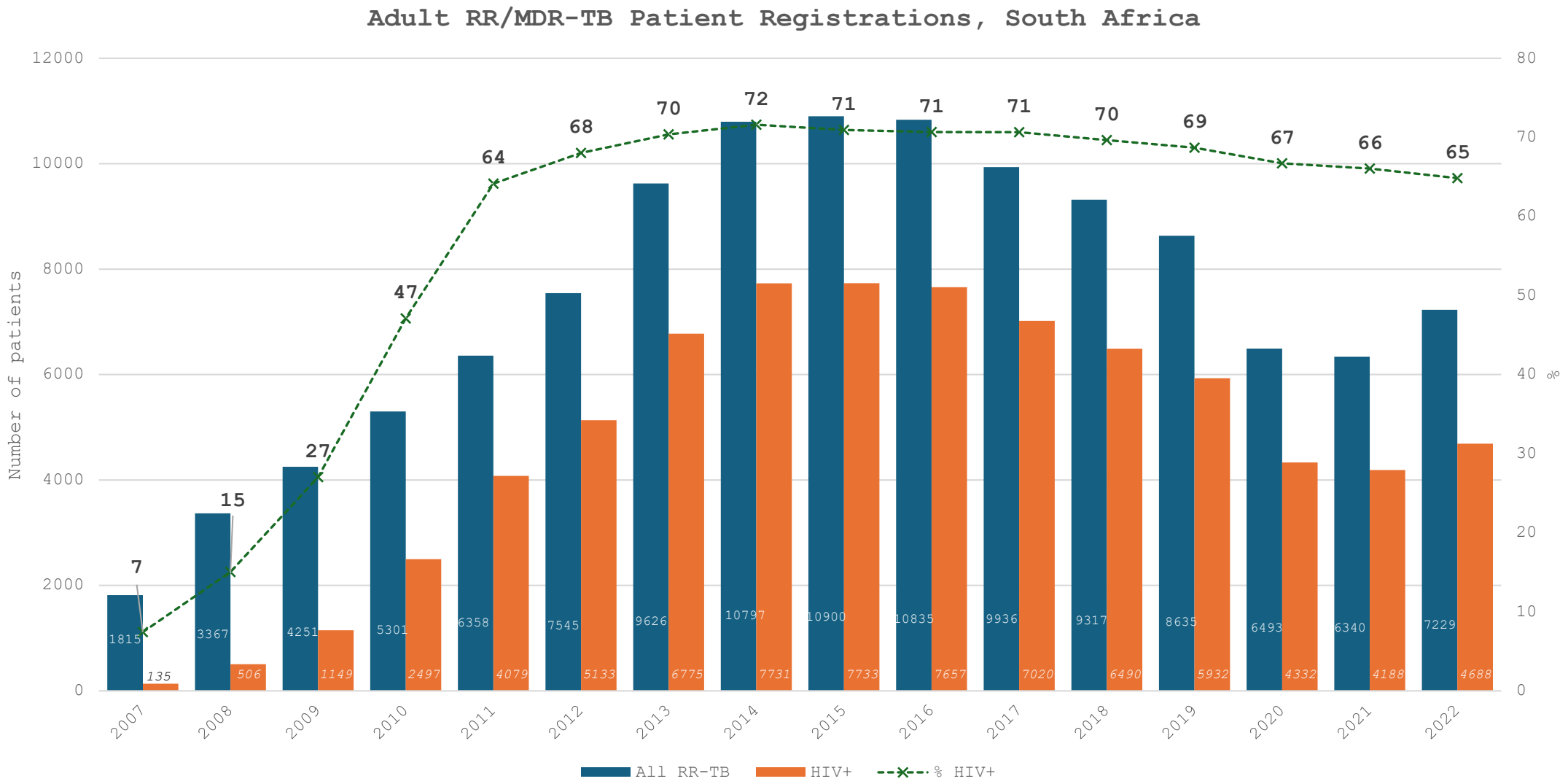

VISION
2028
health
Department:
Health
REPUBLIC OF SOUTH AFRICA
TB STRATEGIC PLAN:
2023-2028
SOUTH AFRICAN NATIONAL
TB PROGRAMME


NATIONAL TB RECOVERY PLAN
2.0
APRIL 2023 – MARCH 2024
health
Department:
Health
REPUBLIC OF SOUTH AFRICA
Version 2.0 | 05 June 2023
1

NTP Priorities – Impactful Interventions

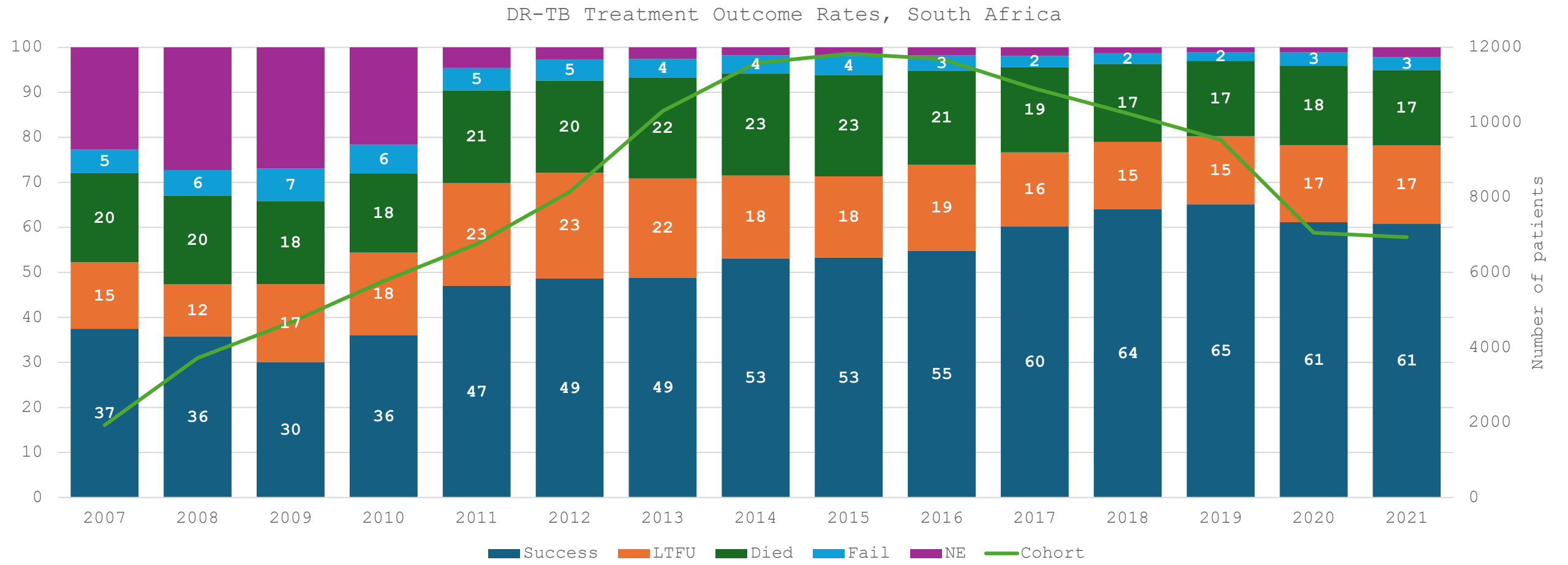


DR-TB Notifications Trends with Proportion PLHIV



Source: EDRWeb

DR-TB Treatment Outcomes



Source: EDRWeb

Introduction of new TB drugs in SA

NTP Contribution to Global and local policy

- South Africa's Commitment to TB Control
- Advocacy for TB control and prevention
  - World Health Assembly and Stop TB Partnership
  - Advocated for increased funding, improved diagnostics, and better access to TB treatment for all
- Experience in managing a high TB burden allowed SA to offer valuable insights and best practices
  - Xpert rollout
  - New drugs and shorter regimens
    - Bedaquilline
    - BPAL
- Collaboration with Global Initiatives
- Achievements and Milestones

Introduction of new and repurposed TB drugs in South Africa

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

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

N. Ndjeka,* F. Conradie,†‡ K. Schnippel,†‡ J. Hughes,§ N. Bantubani,¶ H. Ferreira,# G. Maartens,**†† D. Mametja,* G. Meintjes,**†† X. Padanilam,‡‡ E. Variava,†# A. Pym,§§ Y. Pillay*

Persistently high early mortality despite rapid diagnostics for drug-resistant tuberculosis cases in South Africa

K. Schnippel,*† C. Firnhaber,†‡ N. Ndjeka,§ F. Conradie,† L. Page-Shipp,¶ R. Berhanu,#** E. Sinanovic*

Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study

Kathryn Schnippel, Norbert Ndjeka*, Gary Maartens, Graeme Meintjes, Iqbal Master, Nazir Ismail, Jennifer Hughes, Hannetjie Ferreira, Xavier Padanilam, Rodolfo Romero, Julian te Riele, Francesca Conradie*

Incremental Cost Effectiveness of Bedaquiline for the Treatment of Rifampicin-Resistant Tuberculosis in South Africa: Model-Based Analysis

Kathryn Schnippel[1] · Cynthia Firnhaber[2,4] · Francesca Conradie[2] · Norbert Ndjeka[3] · Edina Sinanovic[1]

High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen

Norbert Ndjeka[1], Kathryn Schnippel[2], Iqbal Master[3], Graeme Meintjes[4,5], Gary Maartens[6], Rodolfo Romero[7], Xavier Padanilam[8], Martin Enwerem[9], Sunitha Chotoo[3], Nalini Singh[3], Jennifer Hughes[10], Ebrahim Variava[11,12], Hannetjie Ferreira[11], Julian te Riele[13], Nazir Ismail[14,15,16], Erika Mohr[17], Nonkqubela Bantubani[18] and Francesca Conradie[19]

(1) Conradie F et al, SAMJ 2014; (2) Ndjeka N et al, Int J Tuberc Lung Dis 2015; (3) Schnippel K et al, Int J Tuber Lung Dis 2017; (4) Schnippel K et al, Lancet Respir Med 2018; (5) Schnippel K et al, Appl Health Econ Health Policy 2018; (6) Ndjeka N et al, Eur Resp J 2018;

Defining Bedaquiline Susceptibility, Resistance, Cross-Resistance and Associated Genetic Determinants: A Retrospective Cohort Study

Nazir A. Ismail [a,b,*], Shaheed V. Omar [a], Lavania Joseph [a], Netricia Govender [a], Linsay Blows [a], Farzana Ismail [a,b], Hendrik Koornhof [a], Andries W. Dreyer [a], Koné Kaniga [c], Norbert Ndjeka [d]

Advances in clinical trial design for development of new TB treatments—Translating international tuberculosis treatment guidelines into national strategic plans: Experiences from Belarus, South Africa and Vietnam

Grania Brigden [1]*, Nguyen Viet Nhung [2], Alena Skrahina [3], Norbert Ndjeka [4], Dennis Falzon [5], Matteo Zignol [5]

Implementing novel regimens for drug-resistant TB in South Africa: what can the world learn?

N. Ndjeka,[1] J. Hughes,[2] A. Reuter,[3] F. Conradie,[4] M. Enwerem,[5] H. Ferreira,[6] N. Ismail,[7] Y. Kock,[1] I. Master,[8] G. Meintjes,[9] X. Padanilam,[10] R. Romero,[11] H. S. Schaaf,[2] J. te Riele,[12] G. Maartens[8]

Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study

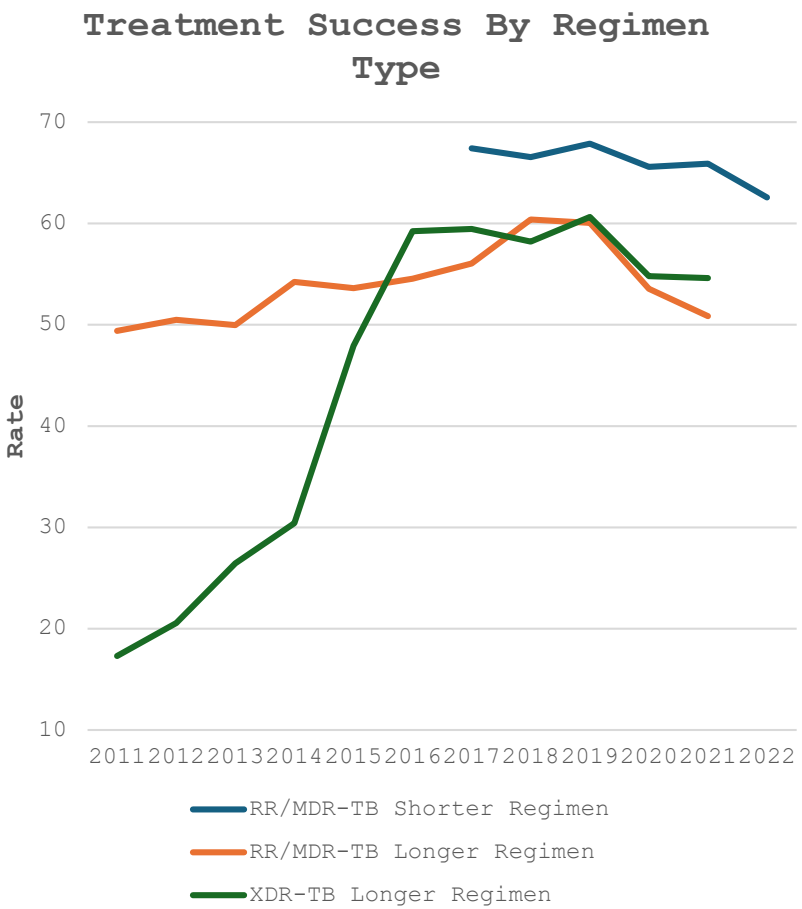
Nazir Ahmed Ismail, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsoalo, Gary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okozi, Xavier Padanilam, Anja Reuter, ...iava, Minty van der Meulen, Farzana Ismail†, Norbert Ndjeka†*

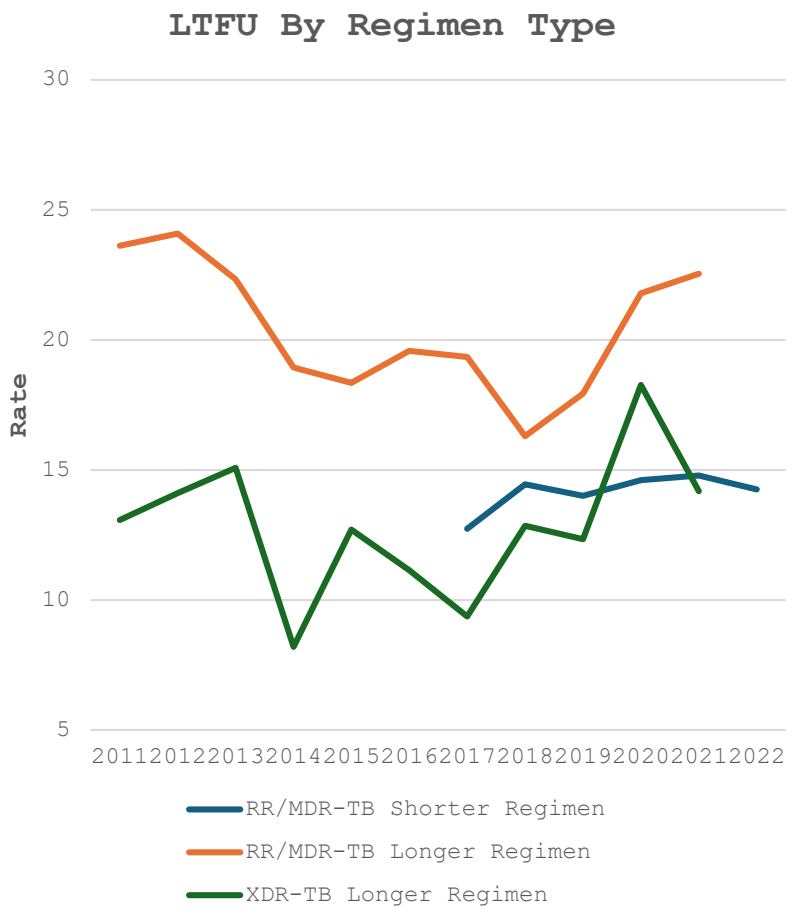
Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study

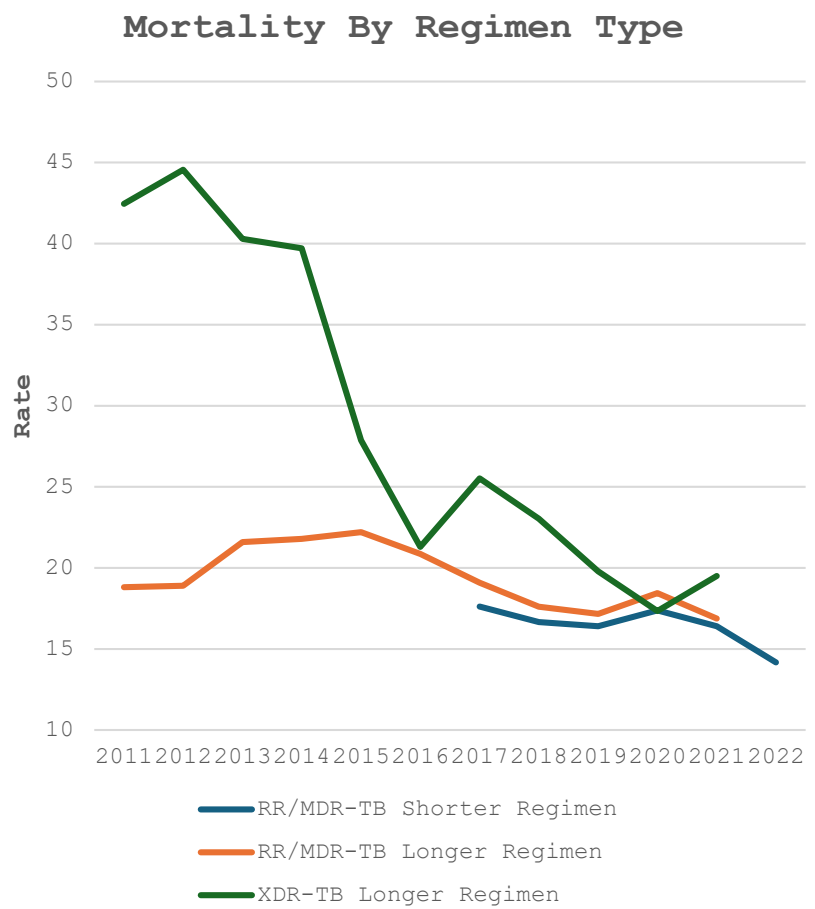
Norbert Ndjeka, Jonathon R Campbell, Graeme Meintjes, Gary Maartens, H Simon Schaaf, Jennifer Hughes, Xavier Padanilam, Anja Reuter, Rodolfo Romero, Farzana Ismail, Martin Enwerem, Hannetjie Ferreira, Francesca Conradie, Kogieleum Naidoo*, Dick Menzies**

(7) Ismail N et al, EBioMedicine 2018; (8) Brigden G et al, PLoS Med. 2019; (9) Ndjeka N et al, Int J Tuber Lung Dis 2020; (10) Ismail N et al, Lancet Infect Dis 2021; (11) Ndjeka N et al, Lancet Infect Dis 2022

DR-TB Treatment Outcomes by Regimen Type







Source: EDRWeb

Reviews/ research conducted: BPAL-L

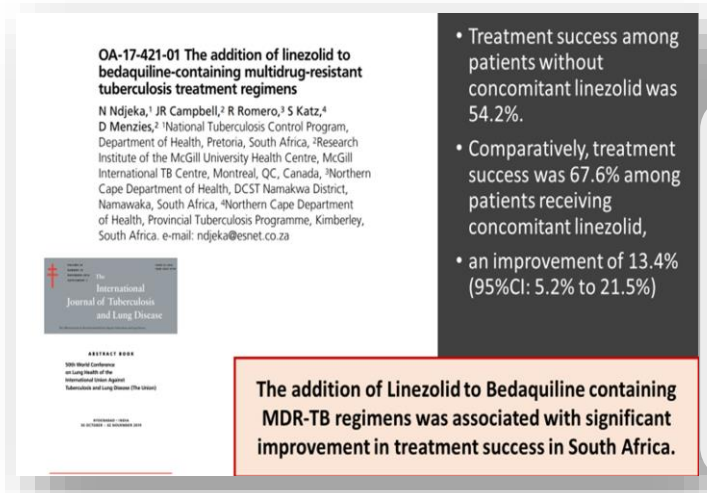
South African NEMLC

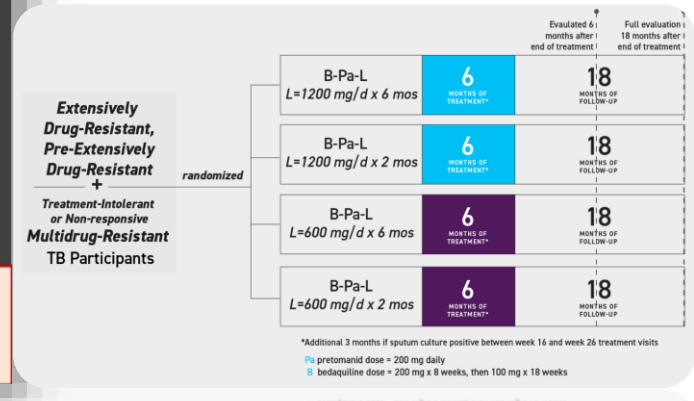
MEDICINE REVIEW Guideline Question:

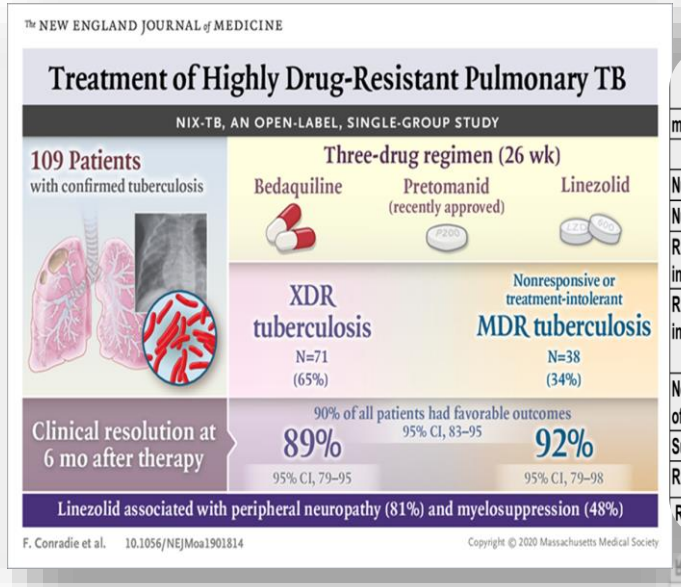
In adults diagnosed with RR-TB, should a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone be used rather than 9-month or longer (18-month) regimen? (Considering the WHO consolidated guidelines on TB: Drug-resistant TB treatment)

NEMLC RECOMMENDATIONS:

The PHC/Adult hospital ERC suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Although WHO recommend moxifloxacin for inclusion in their updated regimen (BPaLM), the PHC/Adult hospital level committee suggest that levofloxacin to be used as fluoroquinolone of choice.

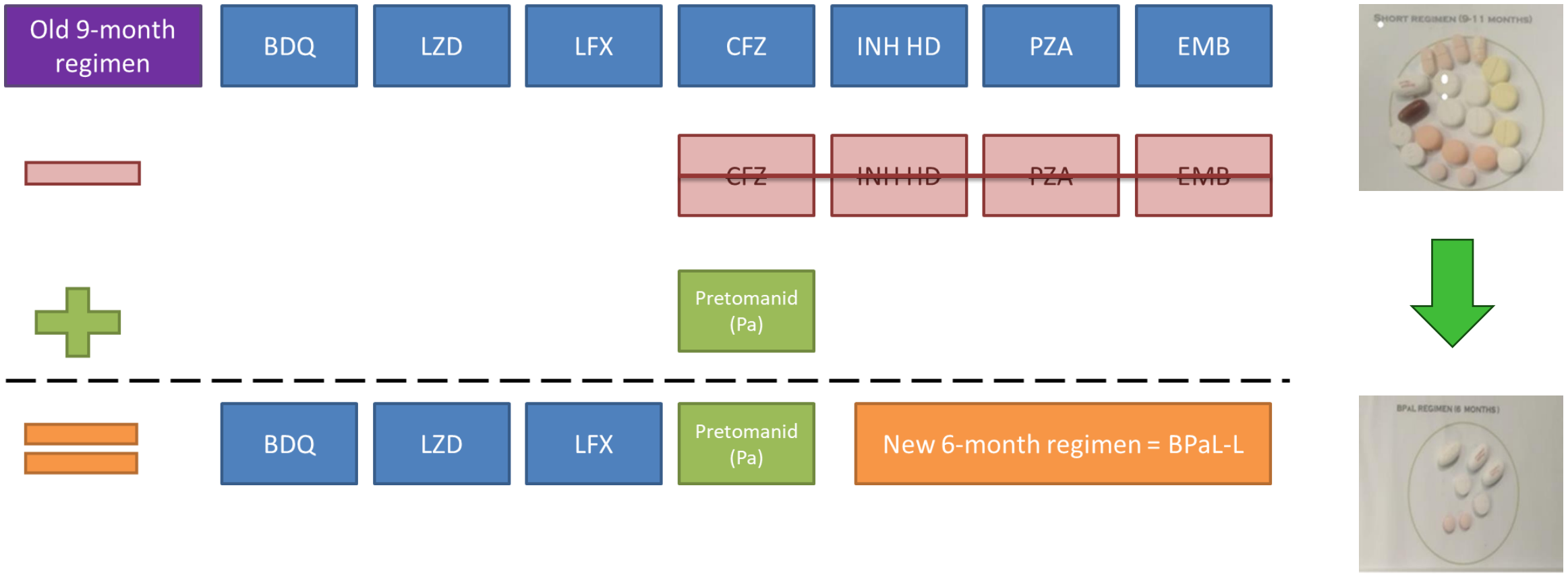






	Control	PRACTECAL arm 1 (BPaLM)	PRACTECAL arm 2 (BPaLC)	PRACTECAL arm 3 (BPaL)
mITT population 72 weeks	66	62	64	60
Number with no unfavourable outcome	34 (51.5%)	55 (88.7%)	52 (81.3%)	46 (76.7%)
Number with an unfavourable outcome	32 (48.5%)	7 (11.3%)	12 (18.8%)	14 (23.3%)
Risk difference (one-sided 98.3% confidence interval)		-37.2% (-∞ to -21.6%)		
Risk difference (one-sided 97.5% confidence interval)			-29.7% (-∞ to -14.3%)	-25.2% (-∞ to -9%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001		
Superiority p-value		p<0.0001		
Risk ratio (one-sided 98.3% CI)		0.23 (-∞ to 0.52)		
Risk ratio (one-sided 97.5% CI)			0.39 (-∞ to 0.68)	0.48 (-∞ to 0.81)

New Regimen – BPaL-L



NEW REGIMEN for MDR-TB

BPaL – L is better for you!

ONLY 6 months of treatment	3 to 4 medicines	90% cure rate	Simplified regimen

BPaL-L = Bedaquiline + Pretomanid + Linezolid + Levofloxacin

The new regimen for **MDR-TB patients** has many advantages, including:

- Fewer pills required – only 23 pills per week
- Shorter treatment – only 6 months
- Fewer facility visits, which means a lower costs for you to get treated

Speak to your healthcare worker today to find out if you are eligible!

health Department Health REPUBLIC OF SOUTH AFRICA | Cheka Impilo | NDP | www.health.gov.za | @HealthZA | YouTube

BPaL-L launched on 1 Sept @ Jose Pearson

Resistance to novel drugs including BDQ

Bedaquiline resistance –key issues (1)

- WHO warned that the improper use of BDQ could accelerate the emergence of resistance **(WHO)**
- BDQ resistance first described in 2015, followed by multiple case reports and series, emphasizing the crucial need for the systematic surveillance of resistance.
- Resistance is primarily driven by **non-target efflux pumps through mutations in *Rv0678* (***mmpL5-mmpS5*** efflux pump repressor) and less commonly through **target-based atpE**.
- Mutations in Rv0678 are the dominant mechanism found across the entire gene length and are associated with clofazimine cross-resistance **(Nguyen).**
- Consequence of other genetic targets such as Rv1979 and pepQ is less well characterized**.**
- It is postulated that this is driven by the complex ongoing evolution patterns of Mtb as the concentration of BDQ decreases in the patient after completion of BDQ-based treatment (long half-life).
- An alternative explanation is the emergence of existing BDQ-resistant Mtb from lesions which rupture following continuation of treatment without BDQ and after stopping all TB treatment **(Vos)**.
- isolated mutants in vitro, non-target based resistance to BDQ, and cross-resistance to CFZ, is due to mutations in Rv0678, rate of mutations associated with high-level BDQ resistance reduces with increase in drug concentration **(Andries)**
- Cape Town in patients with sustained culture positivity, 2016-2017: 3/38 (8%) had primary resistance, 18 (47%) gained resistance (acquired or reinfection), and 17 (45%) were susceptible at both baseline and follow-up. Patients with baseline fluoroquinolone resistance, clofazimine exposure, and four or less effective drugs were more likely to have BDQ-resistant gain **(Derendinger**).

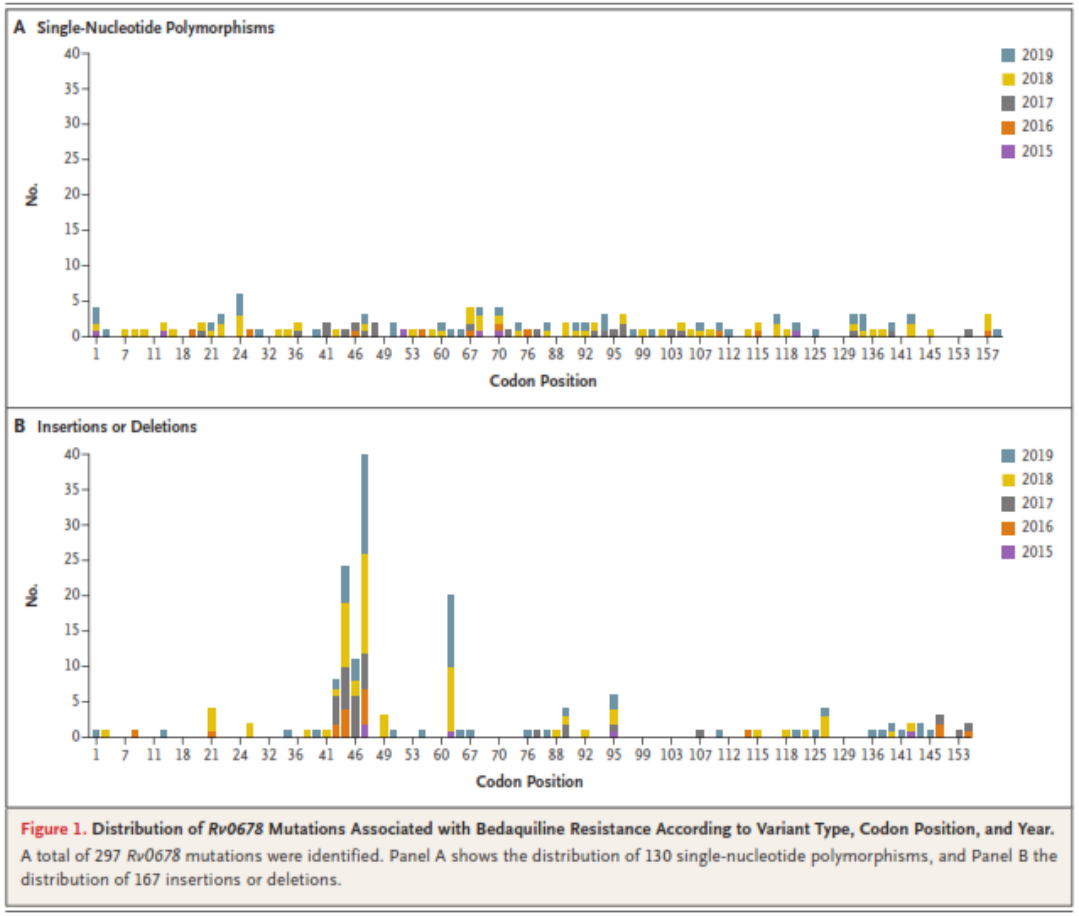


Figure 1. Distribution of *Rv0678* Mutations Associated with Bedaquiline Resistance According to Variant Type, Codon Position, and Year.
A total of 297 *Rv0678* mutations were identified. Panel A shows the distribution of 130 single-nucleotide polymorphisms, and Panel B the distribution of 167 insertions or deletions.

Omar SV, Ismail F, Ndjeka N, Kaniga K, Ismail NA. Bedaquiline-Resistant Tuberculosis Associated with Rv0678 Mutations. N Engl J Med. 2022 Jan 6;386(1):93-94. doi: 10.1056/NEJMc2103049. PMID: 34986292.

Bedaquiline resistance – key issues (2)

- EDR Web analysis of 14 SA sites, 2015-2017: 3.5% of BDQ-susceptible isolates at baseline acquired phenotypic resistance **(Pai)**
- South African Surveillance - linked analysis EDRWeb NICD National TB Ref Lab, 2015-2019:
  - 3.8% baseline BDQ resistance, associated with previous exposure to BDQ or clofazimine, RR/MDR/pre-XDR/XDR-TB.
  - Rv0678 mutations were the sole genetic basis of phenotypic resistance.
  - Baseline resistance could be attributed to previous BDQ or clofazimine exposure in 4/76 (5·3%) patients and to primary transmission in 6 (7·9%).
  - Odds of successful treatment outcomes were lower in patients with baseline BDQ resistance (0·5, 0·3–1).
  - Resistance during treatment developed in 16 (2·3%) of 695 patients, at a median of 90 days (IQR 62–195), with 12 of these 16 having pre-XDR or XDR

- KZN genotypic/phenotypic analysis, 2013-2019: identified 30 isolates with Rv0678 mutations from 16 (4%) of 391 patients.(Nimmo)

- Systematic review, 13 studies included, 2022:The median (IQR) frequency of phenotypic acquired BDR resistance (ABR) was 2.2% (1.1%–4.6%) and 4.4% (1.8%–5.8%) for genotypic ABR. (Mallick)

Linezolid resistance

- Resistance primarily driven by mutations in rplC and rrl
  - In SA resistance remains low with an estimated prevalence of less than 2% nationally (Routine Lab Surveillance – NICD)
- Systematic review, 25 studies included, 2000-2021: 4,956 MDR Mtb strains were isolated from TB patients. Poled frequency of LNZ resistance among the clinical isolates of MDR TB was 4.2%. (Azimi)
- Cohort SA, 2019: 13/39 (33%) with LNZ-based treatment failure, had phenotypic or genotypic LNZ resistance. Resistance occurred late - median duration of 22months (range"7–32) of LNZ therapy; and was predicted by a limited number of mutations in rrl and rplC. (Wasserman)
- Cohort India, 2020: 23/343 (6.7%) had LNZ-resistant MDRTB. Prior LNZ and percent lung involvement associated with LNZ resistance (Tornheim)

References:

- Azimi T, Khoshnood S, Asadi A, Heidary M, Mahmoudi H, Kaviar VH, Hallajzadeh M, Nasiri MJ. Linezolid resistance in multidrug-resistant mycobacterium tuberculosis: A systematic review and meta-analysis. Frontiers in pharmacology. 2022 Aug 30;13:955050
- Wasserman S, Louw G, Ramangoaela L, Barber G, Hayes C, Omar SV, Maartens G, Barry III C, Song T, Meintjes G. Linezolid resistance in patients with drug-resistant TB and treatment failure in South Africa. Journal of Antimicrobial Chemotherapy. 2019 Aug 1;74(8):2377-84.
- Tornheim JA, Intini E, Gupta A, Udwadia ZF. Clinical features associated with linezolid resistance among multidrug resistant tuberculosis patients at a tertiary care hospital in Mumbai, India. Journal of clinical tuberculosis and other mycobacterial diseases. 2020 Aug 1;20:100175.

Nitroimidazole resistance

- Loss-of-function mutations in the ddn, fbiA, fbiB, fbiC, fbiD, and fgd1 genes, the products of which are responsible for the activation of the nitroimidazoles pretomanid and delamanid, typically result in large MIC and probably clinical resistance

- Despite the introduction of Pretomanid into treatment regimens interpretive criteria has not been recommend as yet for susceptibility testing.

- Ongoing Surveillance – Pretomanid Resistance Surveillance Programme 2021-2022 (TB Alliance) – no shift in MIC being observed in DR-TB patient isolates (interim report)

References:

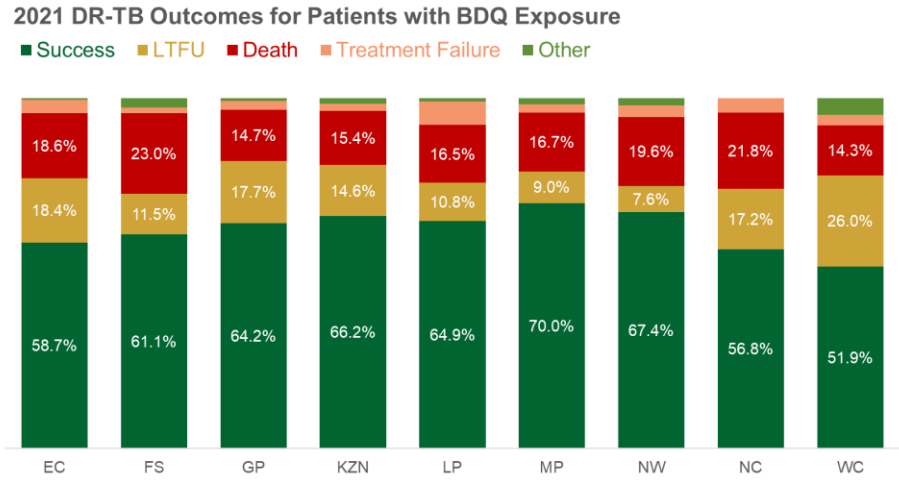
- Kadura S, King N, Nakhoul M et al. Systematic review of mutations associated with resistance to the new and repurposed Mycobacterium tuberculosis drugs bedaquiline, clofazimine, linezolid, delamanid and pretomanid. J Antimicrob Chemother 2020; 75: 2031-43. 348
- Rifat D, Li SY, Ioerger T et al. Mutations in fbiD (Rv2983) as a novel determinant of resistance to pretomanid and delamanid in

BDQ Resistance in South Africa

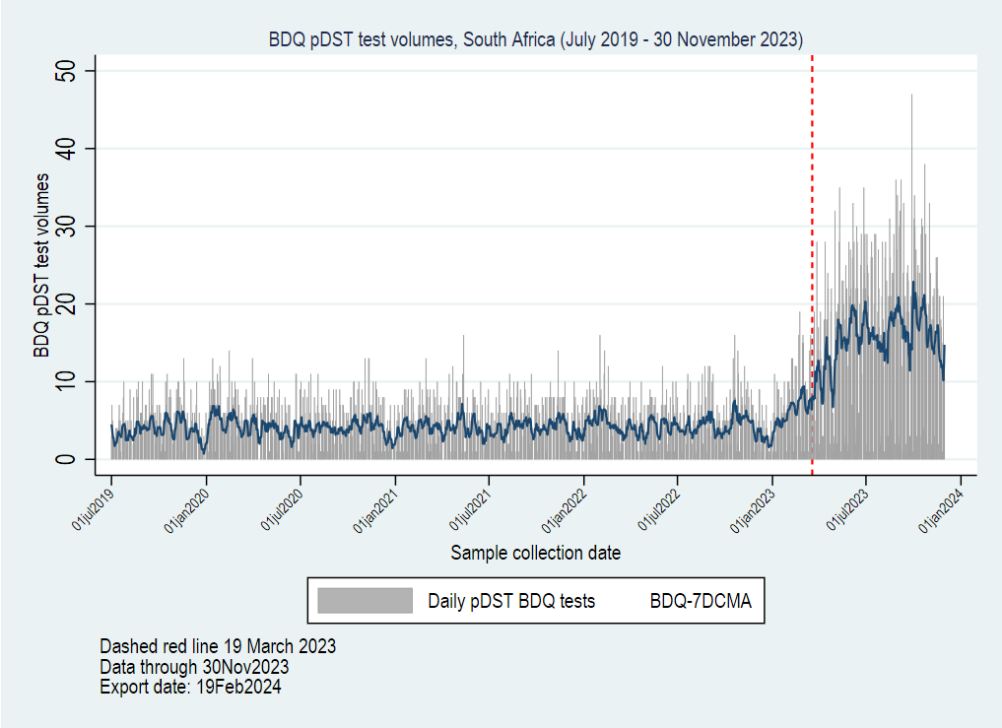
Background

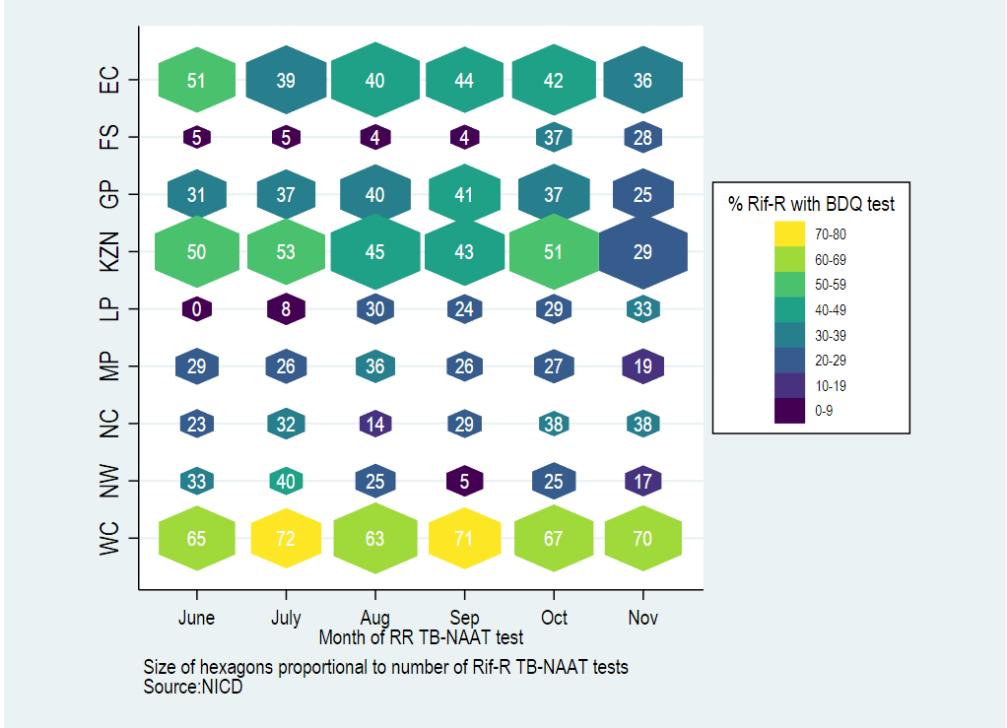
- In 2021, 96% of people with DR-TB received BDQ
- While bedaquiline has improved treatment outcomes, loss to follow-up and TB mortality remain high
- In March 2023 DR-TB reflex testing guidelines updated indicating that all people with rifampicin resistant (RR-TB) TB should have bedaquiline (BDQ) and linezolid (LZD) susceptibility tests (pDST)
- Prior to this BDQ pDST was only indicated for those with SLI, FLQ, or dual INH drug resistance.
- Prevalence of BDQ resistance in South Africa was 3.8% in 2015-2019 (**Ismail N, Lancet. 2021.)**

RSA Totals			
	2019	2020	2021
Total DR-TB Cohort	9 242	7 151	6 973
DR-TB Cohort with BDQ Exposure	8 764	6 876	6 713
% with BDQ Exposure	**94.8%**	**96.2%**	**96.3%**



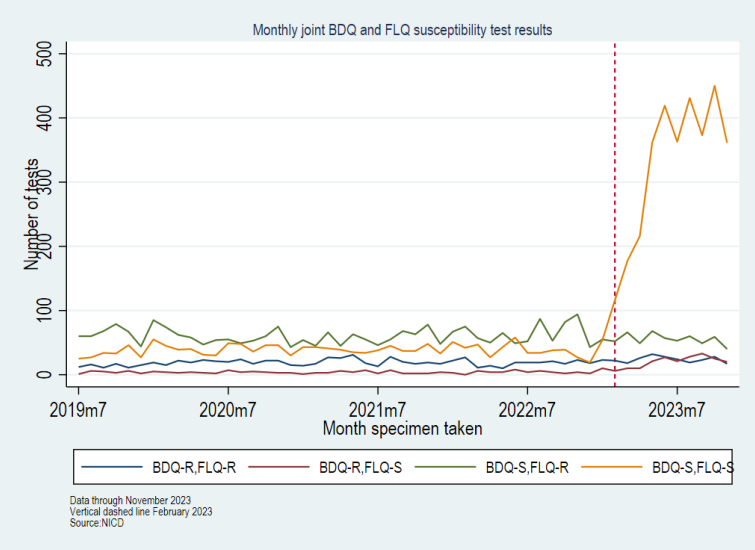
Trends in BDQ pDST volumes, July 2019 – November 2023





- BDQ pDST volumes started increasing in February 2023, reaching a peak in October 2023.
- Nationally, 43% of individuals with RR-TB between June and November 2023 had a BDQ pDST test conducted
- Provincial variation in implementation with higher coverage in EC, KZN and WC
- Despite improvement laboratory turn around times remain long at 57 (IQR 40 – 75 days)

National trends in BDQ-FLQ joint susceptibility



Month	BDQ-S FLQ-S	BDQ-S FLQ-R (Pre-XDR TB)	BDQ-R FLQ-S (not classified)	BDQ-R FLQ-R (XDR-TB)	All BDQ-R	Total tests
2023m3	177 (65.3%)	66 (24.4%)	10 (3.7%)	18 (6.6%)	28 (10.3%)	271
2023m4	216 (71.8%)	49 (16.3%)	10 (3.3%)	26 (8.6%)	36 (12.0%)	301
2023m5	362 (74.9%)	68 (14.1%)	21 (4.3%)	32 (6.6%)	53 (11.0%)	483
2023m6	419 (78.9%)	57 (10.7%)	27 (5.1%)	28 (5.3%)	55 (10.4%)	531
2023m7	363 (78.7%)	53 (11.5%)	21 (4.6%)	24 (5.2%)	45 (9.8%)	461
2023m8	431 (80.1%)	60 (11.2%)	28 (5.2%)	19 (3.5%)	47 (8.7%)	538
2023m9	373 (78.0%)	49 (10.3%)	33 (6.9%)	23 (4.8%)	56 (11.7%)	478
2023m10	450 (80.1%)	59 (10.5%)	25 (4.4%)	28 (5.0%)	53 (9.4%)	562
2023m11	361 (82.4%)	40 (9.1%)	20 (4.6%)	17 (3.9%)	37 (8.4%)	438
Total	**3152 (77.6%)**	**501 (12.3%)**	**195 (4.8%)**	**215 (5.3%)**	**410 (10.1%)**	**4063**

- Change in DR-TB reflex testing guidelines enabled identification of bedaquiline (BDQ) resistance amongst people with fluoroquinolone (FLQ) susceptible TB
- In August, September and November 2023, the absolute number of BDQ-R/FLQ-S tests was greater than BDQ-R FLQ-R tests
- Prevalence of BDQ resistance in tests conducted between March and November 2023 was 10.1%. The test-level is however biased upwards because of repeat tests in individuals not responding to treatment and inclusion of provinces with lower coverage
- Therefore cross-sectional study conducted in 3 provinces

Cross-sectional study of BDQ resistance

Methods

- Restricted to 3 provinces (EC,KZN and WC) which attained BDQ pDST coverage of >50% in at least one month in the period March to November 2023
- Excluded patients who had a BDQ pDST prior to March 2023
- 1,895/2,308 (82%) of patients with BDQ pDST laboratory tests were linked to EDRWeb using deterministic and probabilistic linkages with manual review in order to assess prior exposure to BDQ

Results

- 2,308 patients included
- Combined prevalence of BDQ resistance in the 3 provinces: 149/2,308 (6.5%)
  - Eastern Cape: 3.6%
  - KwaZulu-Natal: 4.8%
  - Western Cape: 10.2%
- Nearly two thirds (96/148, 65%) of patients with BDQ-R had FLQ-S TB
- 42% of patients with BDQ-R had no documented previous exposure to BDQ, with 22% unknown exposure history
- Prevalence of linezolid (LZD) resistance very low in this population (5/

	BDQ-S (n=2,159)	BDQ-R (n=149)	Total (N=2,308)	Unadjusted OR (95% CI)
Sex				
Female	851 (94)	59 (6)	910	1
Male	1300 (94)	90 (5)	1390	0.99(0.71-1.40)
Age category				
<15	49 (96)	2 (4)	51	0.54 (0.13-2.25)
15-24	277 (91)	26 (9)	303	1.24(0.79 -1.95)
25-44	1230 (93)	93 (7)	1323	1
45-64	521 (96)	22 (4)	543	0.56 (0.35-0.90)
65+	68 (96)	3 (4)	71	0.58 (0.18-1.89)
Province				
EC	666 (96)	25 (4)	691	1
KZN	726 (95)	37 (5)	763	1.36 (0.81-2.28)
WC	767 (90)	87 (10)	854	3.02 (1.91-4.77)
Quarter				
2023Q2*	807 (93)	58 (7)	865	1
2023Q3	800 (94)	51 (6)	851	0.89 (0.60 - 1.31)
2023Q4#	552 (93)	40 (7)	592	1.01 (0.66 - 1.53)
FLQ resistance				
S	1902 (95)	96 (5)	1998	1
R	237 (82)	52 (18)	289	4.35 (3.02-6.25)
I or miss	20 (95)	1 (5)	21	0.99 (0.13-7.46)
SLI resistance				
S	1888 (94)	124 (6)	2012	1
R	139 (89)	17 (11)	156	1.86 (1.09 - 3.18)
I or unk	132 (94)	8 (6)	140	0.92 (0.44 - 1.93)
LZD resistance				
S	2141 (94)	145 (6)	2286	1
R	3 (60)	2 (40)	5	9.84 (1.63 - 59.38)
Unk	15 (88)	2 (12)	17	0.92 (0.44 - 1.93)
Previous BDQ exposure				
No	1479(96)	64 (4)	1543	1
Yes	208 (80)	51 (20)	259	5.66 (3.18 - 8.41)
Unknown	472 (93)	34 (7)	506	1.66 (1.08-2.56)
Previous CFZ exposure				
No	1275 (96)	55 (4)	1330	1
Yes	193 (80)	48 (20)	241	5.76 (3.8-8.74)
Unknown	691 (94)	46 (6)	737	1.54 (1.03-2.31)

*includes 81 samples from March 2023
No data from December 2023

Addressing BDQ and novel drug Resistance

Pillar I: **Communicate & Advocate**	Pillar II: **Find & Link**	Pillar III: **Treat & Retain**	Pillar IV: **Prevent & Prepare**	Pillar V: **Monitor & Assess**
TB is a national priority across sectors	People with TB are linked to care within one week	People with TB have access to high quality treatment & support	TB prevention is valued as much as treatment	Provinces use high quality data to guide decisions
Create awareness about BDQ resistance	Accelerate diagnosis of BDQ resistance	Strengthen treatment for BDQ-resistant TB	Prevent BDQ resistance	Improve quality of data for decision making
Involve health leaders and senior managers as allies and advocates for innovation	Urgent introduction of targeted new generation sequencing, starting with most affected areas	Review inclusion criteria for BPaL-L regimen	Implement study to strengthen adherence to BPaL-L	Measure and monitor number of patients with BDQ resistance
Improve awareness in provinces and ensure routine testing of BDQ resistance	Diversification of TB testing (TB NAAT) to be finalized with introduction of collection of 2 samples upfront	Submit all BDQ-resistant patients to the NCAC for regimen design		Routinely establish previous TB treatment and drug exposure history for all RR-TB patients
Encourage multisectoral action (research, education, new drug development, etc.)	Ensure all RR-TB patients started on treatment get tested using the XDR-cartridge	NCAC to review BDQ-sparing regimens e.g. 9DLLZ		Measure and monitor treatment outcomes for patients with BDQ resistance
Flag burden of antimicrobial resistance and importance of treatment adherence	Strengthen the use of extended drug susceptibility testing where necessary	Strengthen adherence to BPaL-L and other individualized BDQ-containing regimens		Collaborate with WHO – data sharing and more extensive analysis
Disseminate data among healthcare workers in South Africa and globally	Improve SMS notification to individuals who test for TB	Introduce new clinical trials with new anti-TB agents		

Bedaquiline, Pretomanid, and linezolid Resistance Emergence in Drug-resistant TB treatment in South Africa (B-Prepared study)

- Collaborative project between South Africa, Columbia University (B Mathema) and Emory University (N Gandhi)

- **Objectives**:
-
- **To characterize changes in *resistance-conferring mutations* for Bdq, Pa and Lzd.** We hypothesize that the selective pressure from widespread implementation of these new drugs will lead to a more focused set of resistance-conferring polymorphisms. Characterizing common resistance-conferring mutations will be invaluable for new molecular tests of Bdq, Pa, and Lzd susceptibility (e.g., Xpert, line probe assays).

- **To characterize changes in *phenotypic resistance* to Bdq, Pa and Lzd.** We hypothesize that resistance to Bdq, Pa and Lzd will be associated with higher MICs over time. Understanding changes in phenotypic resistance will inform clinical decisions on whether to add additional drugs to the BPaL regimen (*e.g.*, moxifloxacin) or increase the dose of specific drugs (*i.e.*, similar to high-dose isoniazid in DR TB).

- **To identify increased clonality and geographic spread of Bdq-, Pa- and Lzd-resistant TB strains and to characterize molecular changes associated with increased transmissibility.** We hypothesize clonal spread of Bdq-, Pa- and Lzd-resistant strains will begin during the study period (2023- 2027). Identification of specific early warning signs such as clustered genotypes and geographic spread can alert TB control programs to the shift towards transmitted Bdq, Pa and Lzd resistance

Conclusion

Concluding remarks (1)

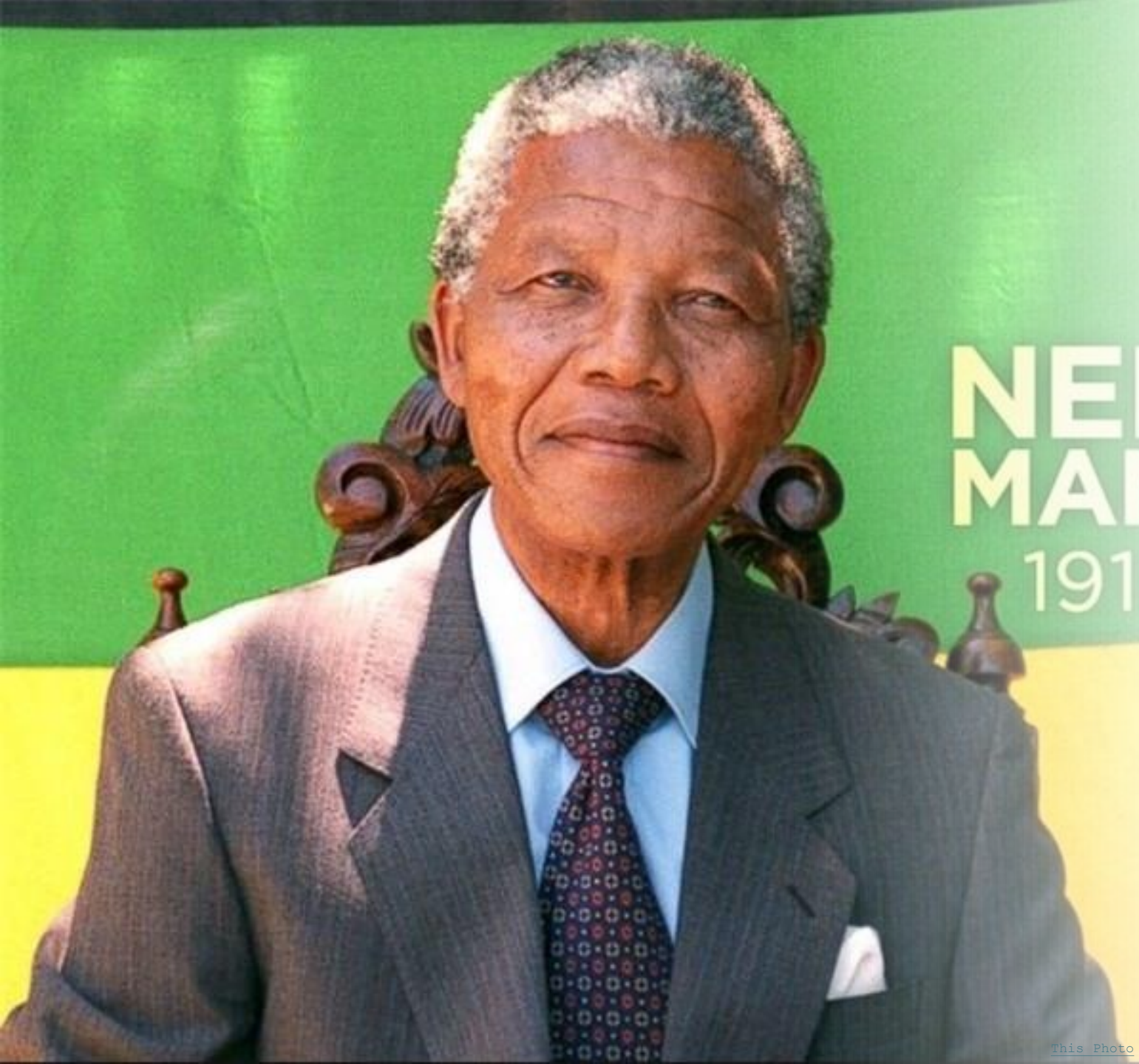
- Through effective TB Programme Leadership and political commitment, SA has successfully introduced new diagnostic and treatment tools for TB
- New tools enhanced diagnostic tests and favorable treatment outcomes
- The introduction of bedaquiline and other new and repurposed TB drugs from 2013 has remarkably increased the proportion of DR-TB patients successfully treated
- However, high TB mortality and loss to follow up remain our major challenges
- 49 out of 52 districts have introduced BPaL-L regimen

Concluding remarks (2)

Resistance to bedaquiline has increased from 3.8 % to 6.5% (10 % in the Western Cape province)

64% of individuals with BDQ-resistant are fluoroquinolone susceptible

A proposed plan is aligned with the pillars of our TB Recovery Plan: Advocacy & Communication, case finding and linkage to care, appropriate treatment and retention in care, further prevention and use of data for evidence-based decision making



After Climbing a great hill. One only finds that there are many more hills to climb.

Nelson Mandela

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Thank you