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Health
REPUBLIC OF SOUTH AFRICA

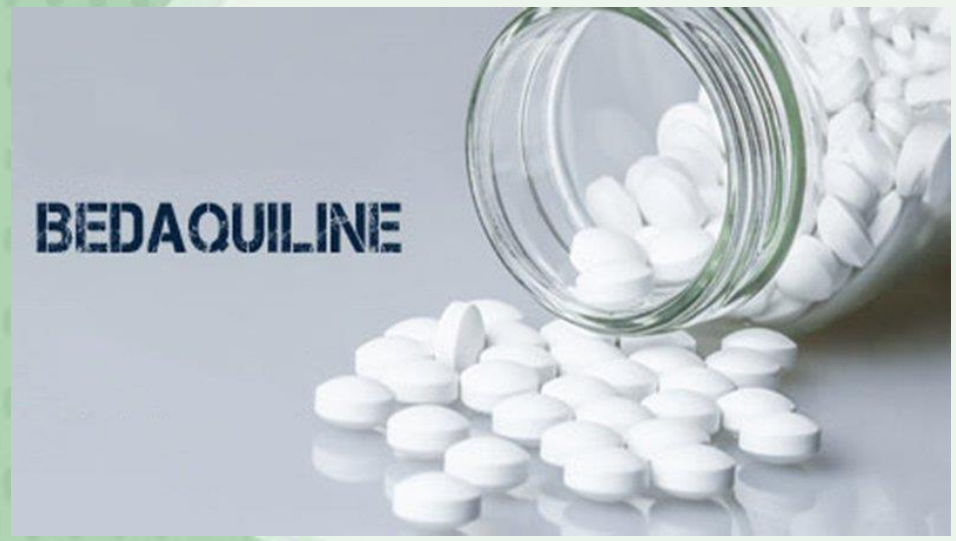
KnowledgeHub

2030 NDP

END TB

BPaL-L and the emergence of bedaquiline resistance

This webinar will discuss the implementation of BPAL-L and development of Bedaquiline resistance in South Africa



DATE **23 March 2024**

09:00 – 13:00 | 4 Hours

Rev. Ramphelane Morewane leads the national efforts towards the attainment of the UN Targets of 95-95-95 in HIV and AIDS. He has led the conceptualisation and implementation of the 100-health facilities project; implementation of the TB Recovery plan to trace and link the patients back to care; and implementation of the Maternal Clinical Guidance, Neonatal Health Guidelines, New guidelines for HIV Testing and Screening etc.

He has presided over several national and regional forums such as: Incident Management Team for Covid-19 pandemic; SADC Malaria E8 Technical Committee, the departmental lead in the United Nations Convention on Climate Change.

He was the co-author of several policies and strategic documents. He was the leader of the work stream on health system strengthening in the development of the National Health Insurance Bill.

Rev. Morewane has been the champion of District Health System for the past 15 years and has developed national district health planning tools.

Qualifications
Masters Development Policy and Practice
Post Graduate Diploma in Health Management
B Tech Business Management

Programme Director: Prof. Norbert Ndjeka

Time	Duration	Topic	Presented by
09h00 – 09h15	15 min	Welcome, purpose and opening address by the Chair	Rev. Ramphelane Morewane
09h15 – 09h45	30 min	Patients' dialogue	Cured DR-TB patients
09h45 – 10h15	30 min	The TB Recovery Plan 3.0 and BPaL-L implementation	Prof. Norbert Ndjeka
10h15 – 11h15	60 min	The emergence of bedaquiline resistance	Prof. Nazir Ismail Dr Harry Moultrie Dr Shaheed Vally Omar
11h15 – 11h45	30 min	Statement by WHO	Dr Owen Kaluwa
11h45 – 12h15	30 min	The plan to address bedaquiline resistance	Prof. Norbert Ndjeka
12h15 – 12h50	35 min	Q&A	Rev. Ramphelane Morewane
12h50 – 13h00	10 min	Closing remarks	Rev. Ramphelane Morewane

Prof Norbert Ndjeka serves as the Chief Director TB Control and Management, under the National Department of Health in South Africa. He previously served as the Director, Drug-Resistant TB, TB & HIV. Under his leadership, there has been a decline in the number of cases of DR -TB in South Africa and a remarkable improvement in proportion of patients successfully treated for DR- TB.

He is a Specialist Family Physician with interest in TB and HIV. He has authored a numerous paper in peer-reviewed journals.

He is currently the Chairperson of the Afro-GLC (African Green Light Committee), a committee that advises WHO on how to manage drug-resistant tuberculosis. He recently (July 2021) received an Honorary Doctorate from UCT in recognition of his outstanding contribution to the fight against DR-TB locally and globally. He was recently (January 2022) nominated as Honorary Associate Professor of Medicine, University of Cape Town.

Qualifications
MD, DHSM (Wits), MMed (Fam Med) (MED), Dip HIV Man (CMSA), DSc (h.c.)

Dr Shaheed Vally Omar is a Medical Scientist, with a research focus on Mycobacterium tuberculosis with over 15 years' experience. Currently serving as the Head of the Centre for Tuberculosis at the National Institute for Communicable Diseases, a division of the National Health Laboratory Service in South Africa. Further he oversees operations encompassing the National & WHO Supranational TB Reference Laboratories. He has been instrumental in advancing diagnostic evaluations and laboratory interpretative criteria for drug resistance determination. His current research focus is directed to improving national surveillance methodologies through the adept application of next-generation sequencing techniques. His contributions transcend laboratory confines, as he actively shapes national and global policy guidance pertaining to tuberculosis management. His direction has facilitated the seamless implementation of cutting-edge TB diagnostics into the routine laboratory, thereby strengthening standard practices and augmenting the efficacy of tuberculosis control measures.

Qualifications
PhD (Medical Microbiology)

Dr Harry Moultrie is the senior medical epidemiologist at the Centre for Tuberculosis, National Institute for Communicable Diseases. His current research focuses on COVID-19, TB surveillance and the geospatial distribution of TB in South Africa. He convened the South African Covid-19 Modelling Consortium (SACMC) and was a member of the South African Ministerial Advisory Committee on COVID-19. He is a member of the South African National TB Think Tank. Dr Moultrie has served on a number of local, national and international committees and has published more than 60 peer-reviewed publications.

Qualifications
MBBCh, MSc

Prof Nazir Ismail is the Head of the Department for Clinical Microbiology and Infectious Diseases at Wits University and NHLS' Charlotte Maxeke Academic Complex in Johannesburg, South Africa. He formerly led the diagnostics team at the WHO's Global Tuberculosis (TB) Programme in Geneva, Switzerland, where he was responsible for developing global policies, norms and standards for TB diagnosis and laboratory strengthening. He is a medical doctor by training and specialized in microbiological pathology. His experience covers diagnostics, epidemiology, public health responses, and transmission.

Qualifications
MBChB
FC Path (Microbiology)
MMed (Microbiology)
DTM&H
PDIC

Dr. Owen Laws Kaluwa is specialized in Epidemiology and Preventive Medicine from the Free University of Berlin in Germany. Prior to his appointment as WHO Representative for South Africa, he was WHO Representative for Ghana, WHO Representative for Swaziland, and Regional Adviser for HIV/AIDS for the Africa Region. Before joining WHO, Dr Kaluwa worked in his home country of Malawi as the Head of Research, Monitoring, and Evaluation of HIV/AIDS Programmes at the Ministry of Health, National Coordinator of HIV/AIDS Strategic Planning, and as Programme Director of the National AIDS Commission.

Qualifications
MD, MS

Main Objectives:

- Disseminate Updates on TB Recovery Plan 2.0
- Enhance implementation of the 6-month regimen (BPaL-L) to achieve the last mile
- Discuss a plan required to achieve the last mile of BPaL-L introduction
- Provide data on the current status of bedaquiline resistance
- Discuss a plan to mitigate bedaquiline resistance

Key issues to be covered:

- Brief overview of NSP HIV, TB & STIs
- Brief overview of TB Strategic Plan pillars
- Overview of TB Recovery Plan 2.0 and progress to date including BPaL-L
- Emerging bedaquiline resistance

World TB Day: Symposium

TB Recovery Plan and BPAL Introduction

Prof Norbert Ndjeka

Chief Director: TB Control & Management

23 March 2024

Outline

- Build up to World TB Day
- TB Burden
- TB Recovery Plan 2.0 (2023/24)
- Progress against TB Recovery Plan 2.0
- Introduction of BPAL-L
- Conclusion

Activities in the build up to World TB Day

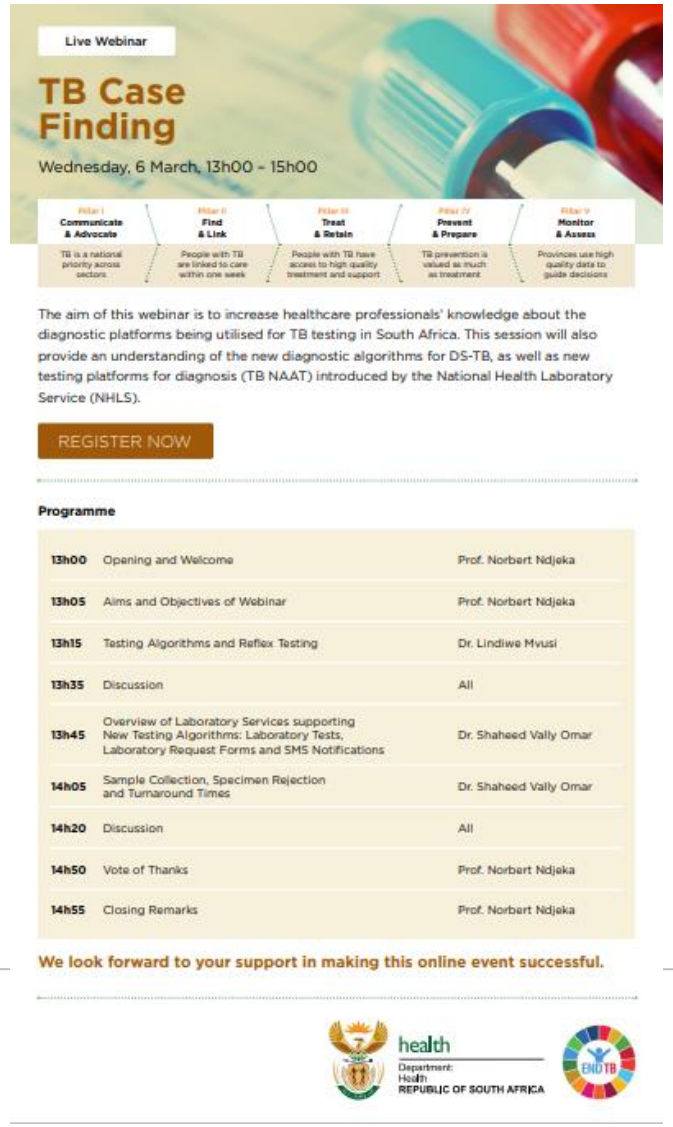
National TB Programme: Webinar Series

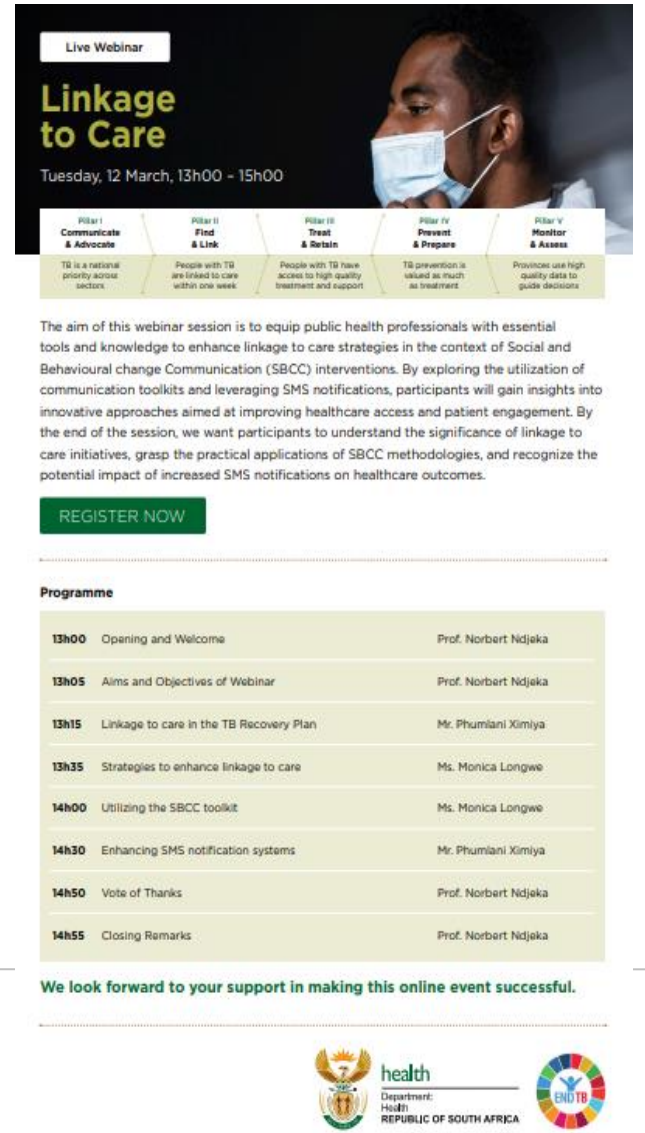
The NTP programme is hosting a 6-part webinar series:

- As a build-up to the World TB Day 2024 event in Evaton, Gauteng.
- To raise the profile of the National TB Programme in the country.
- Increased programme visibility and awareness via the Knowledge Hub Platform.

Target Audience

- National, Provincial and District TB Programme and management staff
- Public healthcare workers
- Doctors
- Nurses
- Pharmacists
- Public health practitioners
- Epidemiologists
- Community Health Workers
- Private Health workers and GPs
- TB Programme partners and implementing partners.
- Health policy specialists
- Medical supply-chain
- Researchers





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Summary: Webinar attendance and engagement

Webinar	Topic	Total Registered	Total Attendance	%	# of Questions
1	TB Recovery Plan	3581	1708	48	143
2	BPAL-L Implementation	2467	1400	57	86
3	TB Case Finding	5389	2373	44	274
4	TB Linkage to Care	2888	1504	52	98
5	TB Prevention	2980	1280	43	59

TB Burden in SA

TB Situation – Global vs. Local

WHO Global TB Report 2023

Tuberculosis profile: Global

Population 2022: 7 946 million

Estimates of TB burden*, 2022

	Number	(Rate per 100 000 population)
Total TB incidence	10 600 000 (9 870 000-11 400 000)	133 (124-143)
HIV-positive TB incidence	671 000 (600 000-746 000)	8.4 (7.5-9.4)
MDR/RR-TB incidence**	410 000 (370 000-450 000)	5.2 (4.7-5.7)
HIV-negative TB mortality	1 130 000 (1 020 000-1 260 000)	14 (13-16)
HIV-positive TB mortality	167 000 (139 000-198 000)	2.1 (1.7-2.5)

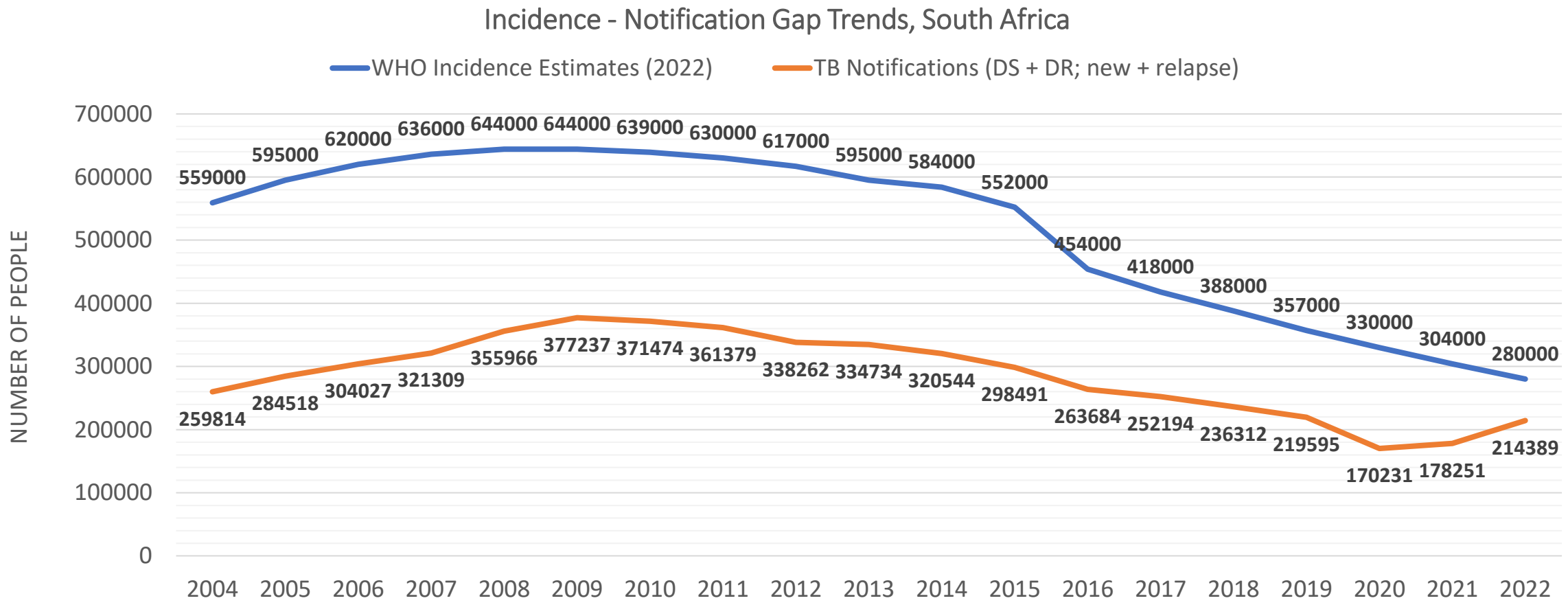
Tuberculosis profile: South Africa

Population 2022: 60 million

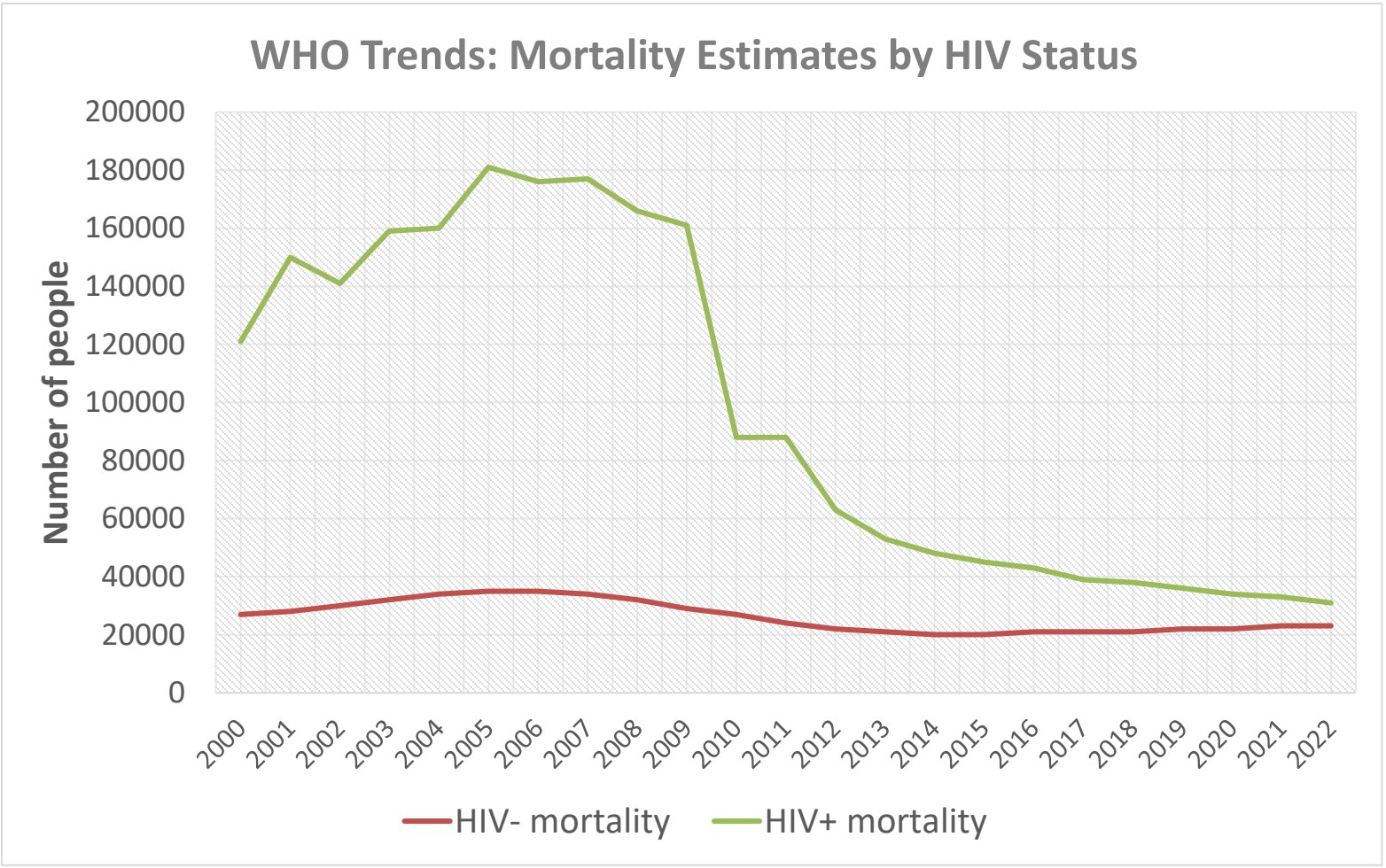
Estimates of TB burden*, 2022

	Number	(Rate per 100 000 population)
Total TB incidence	280 000 (182 000-398 000)	468 (304-665)
HIV-positive TB incidence	152 000 (99 000-217 000)	255 (166-362)
MDR/RR-TB incidence**	11 000 (6 700-16 000)	19 (11-26)
HIV-negative TB mortality	23 000 (22 000-24 000)	39 (37-41)
HIV-positive TB mortality	31 000 (9 900-64 000)	52 (17-107)

Incidence – Notification Gap Trends in South Africa



TB Mortality Estimates



- Failed to achieve mortality reduction targets for END TB milestones **(only 17% reduction)**
- Major reductions in mortality over time for PLHIV
- Mortality in HIV-negative people is estimated to be on the rise since 2015

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Critical issues across the TB programme

Important drivers

- **Patient factors**: advanced HIV, late presentation, delayed diagnosis, use of alternative medicine, mobility, stigma, catastrophic costs (56%), misunderstanding of TB, conflicting health beliefs, alcohol and substance use, mental illness,
- **Health system factors**: access barriers, gaps between levels of the health system, lack of system integration, limited ability of programme staff to track clients moving between facilities, lack of person-centred adherence approach, clinic congestion, health worker uncertainty, difficulty getting samples from young children.

TB Recovery Plan


National Strategic Plan
For HIV, TB and STIs
2023-2028
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VISION
2028
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REPUBLIC OF SOUTH AFRICA
TB STRATEGIC PLAN:
2023-2028
SOUTH AFRICAN NATIONAL
TB PROGRAMME


NATIONAL TB RECOVERY PLAN
2.0
APRIL 2023 – MARCH 2024
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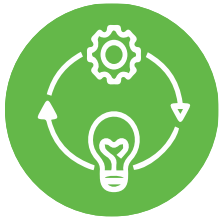
Version 2.0 | 05 June 2023
1

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 DEMAND FOR TB TESTING THROUGH ADVOCACY & COMMUNICATION	ACCELERATE IMPLEMENTATION OF TUTT	ESTABLISH RELIABLE LINKAGE PATHWAYS	IMPROVE RETENTION IN CARE	STRENGTHEN TB PREVENTION	IMPROVE GOVERNANCE AND ACCOUNTABILITY
Costed SBBC plan	3 million GXP tests	TB result SMS notification system	Shorter regimens (Paeds and DR-TB)	Scale up treatment of latent TB infection	Streamline and integrate TB data systems
Communication toolkit	Scale up DCXR		Strengthen adherence counselling	UVGI guidelines	100 Facilities Nerve Centre Approach Project
	Scale up ULAM				Partner coordination

STRENGTHEN TB PROGRAMME IN THE MINES

Strengthen TB in mines
Compensation ex-miners

We are going to prioritise most impactful interventions to support NSP implementation

Performance Highlights

- January – December 2023
  - TB NAATs done (Dr H Moultrie, NICD)
  - SMS notifications (Dr H Moultrie, NICD)
  - Notifications* (DHIS, EDRWeb, TIER.Net)
  - PTB linkage to care* (NICD, TIER.Net, EDRWeb)
- January – December 2022
  - DS-TB treatment success* (DHIS, TIER.Net)
- January – December 2021
  - DR-TB treatment success (EDRWeb)

*Includes preliminary data

TB Recovery Plan - Key Indicators, National

National

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Xpert Tests Done - National
Target: 3 085 166
2 843 976 Xpert 92%
Tests done

SMS Notification Coverage - National
Target: 60%
1 129 259 SMS 40%
Delivered

TB Patients Notified - National
Target: 224 776
204 767 Patients 91%
Started treatment

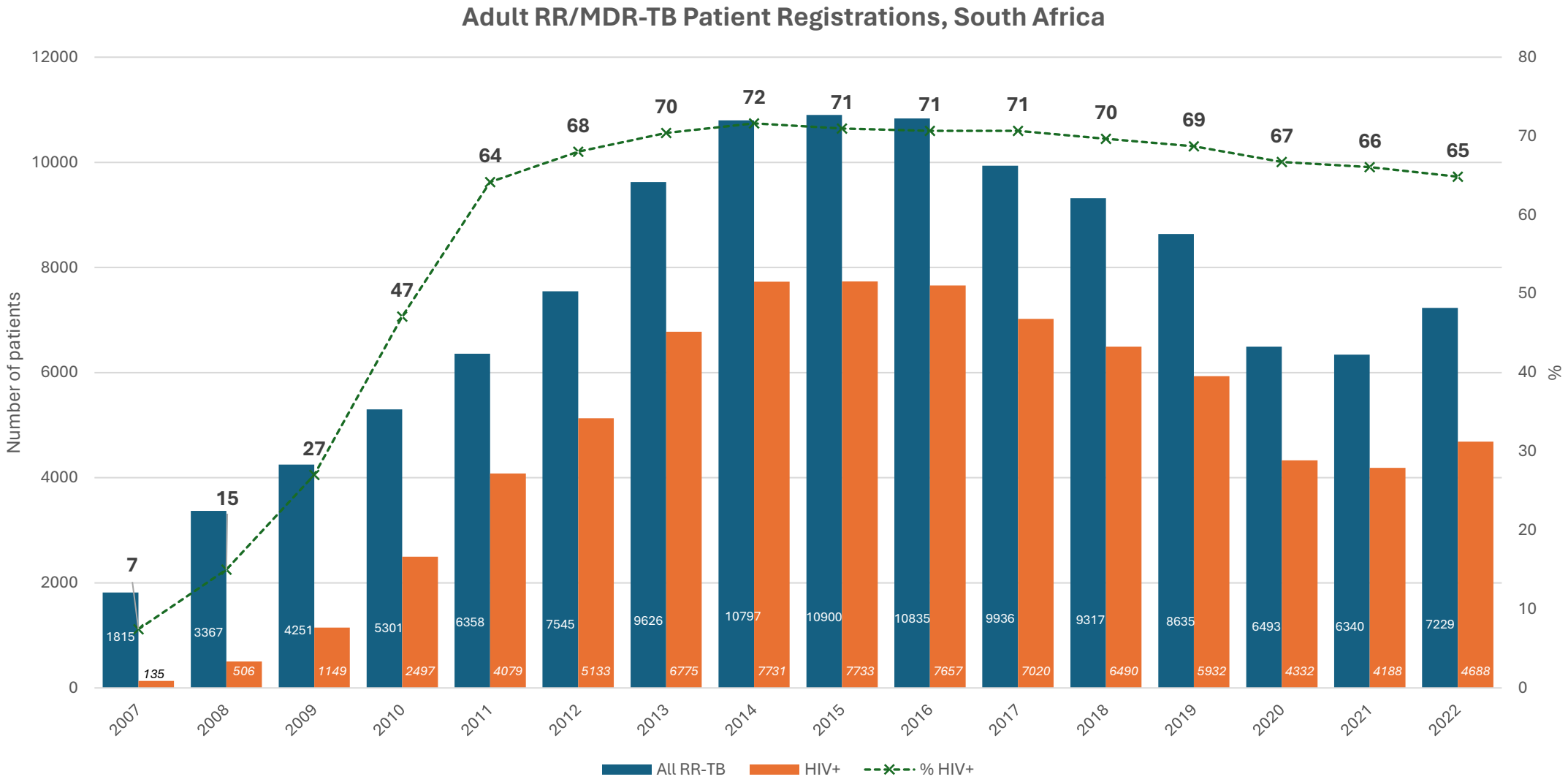
Linkage to Care (PTB) - National
Target: 85%
128 639 Patients 67%
Linked to care

DS-TB Treatment Success - National
Target: 80%
163 486 Patients 75%
Successfully treated

DR-TB Treatment Success - National
Target: 68%
4 220 Patients 61%
Successfully treated

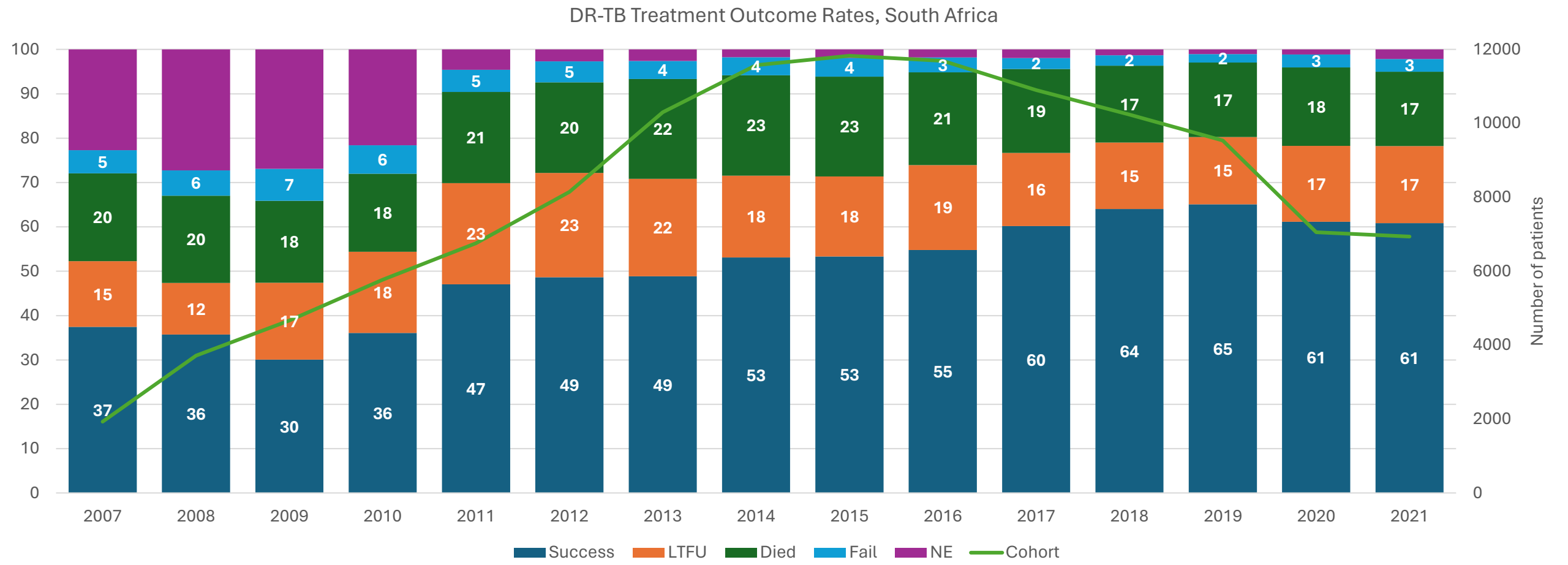
DR-TB burden

DR-TB Notifications Trends with Proportion PLHIV



Source: EDRWeb

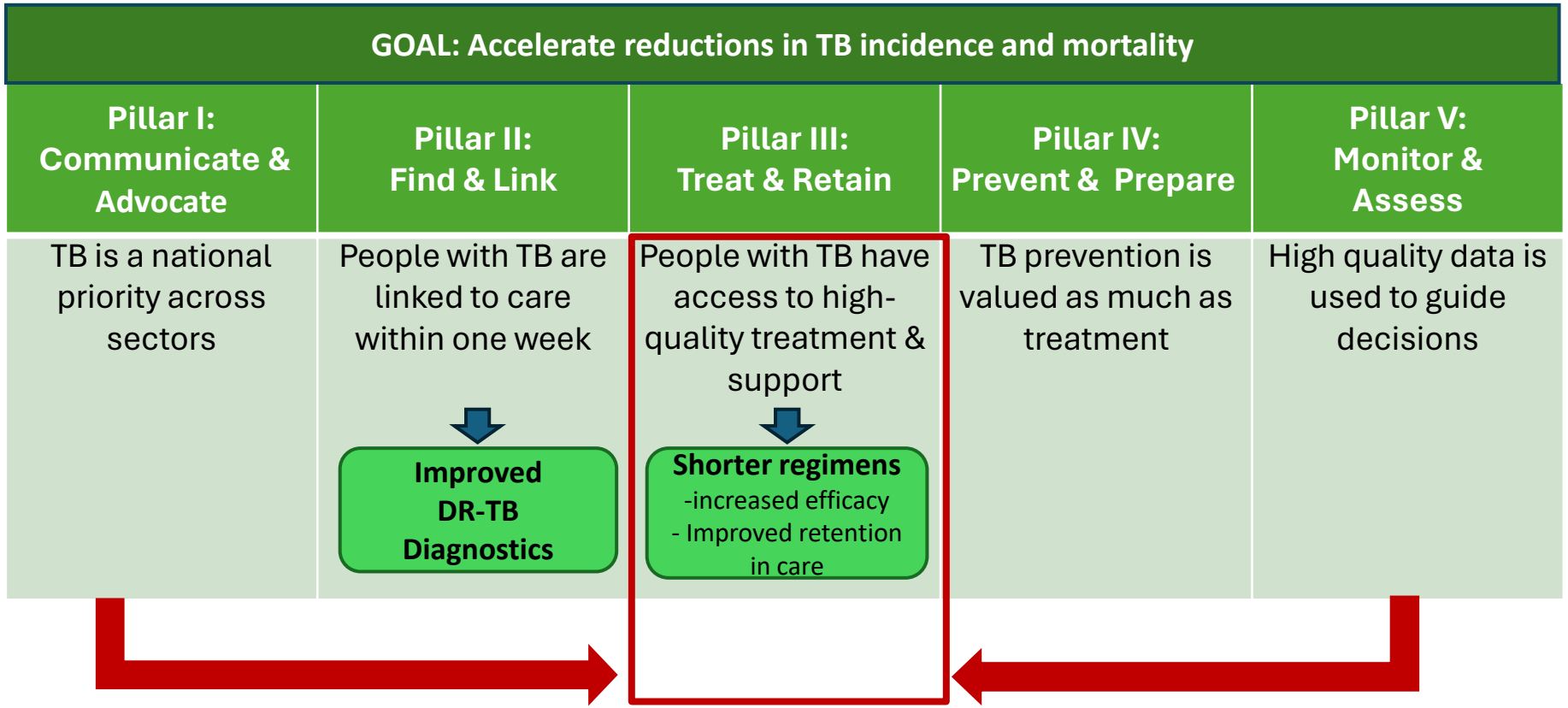
DR-TB Treatment Outcomes



Source: EDRWeb

Introduction of new TB drugs in SA

NTP Priorities – Impactful Interventions



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

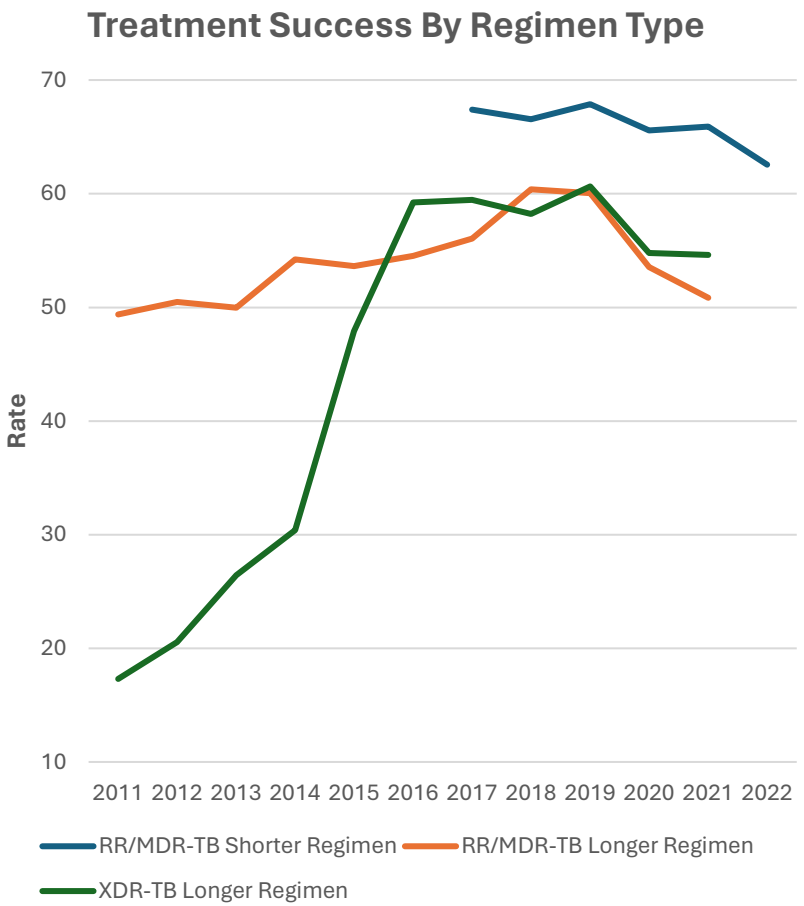
Nazir Ahmed Ismail*, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsoalo, Gary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okozi, Xavier Padanilam, Anja Reuter, ...iava, Minty van der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

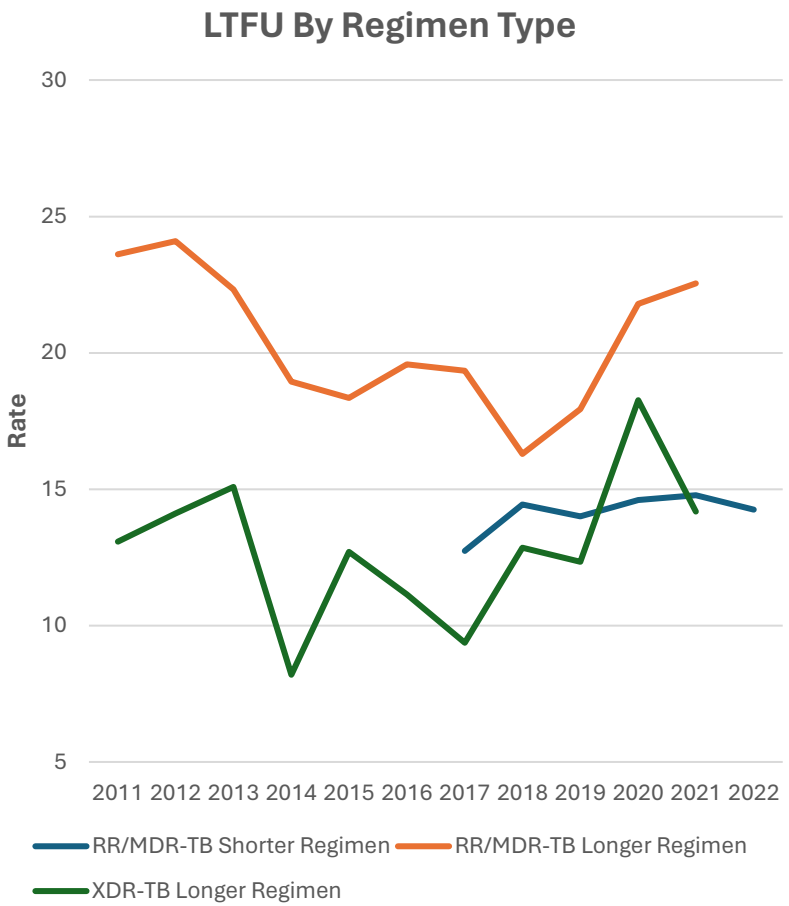
Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study

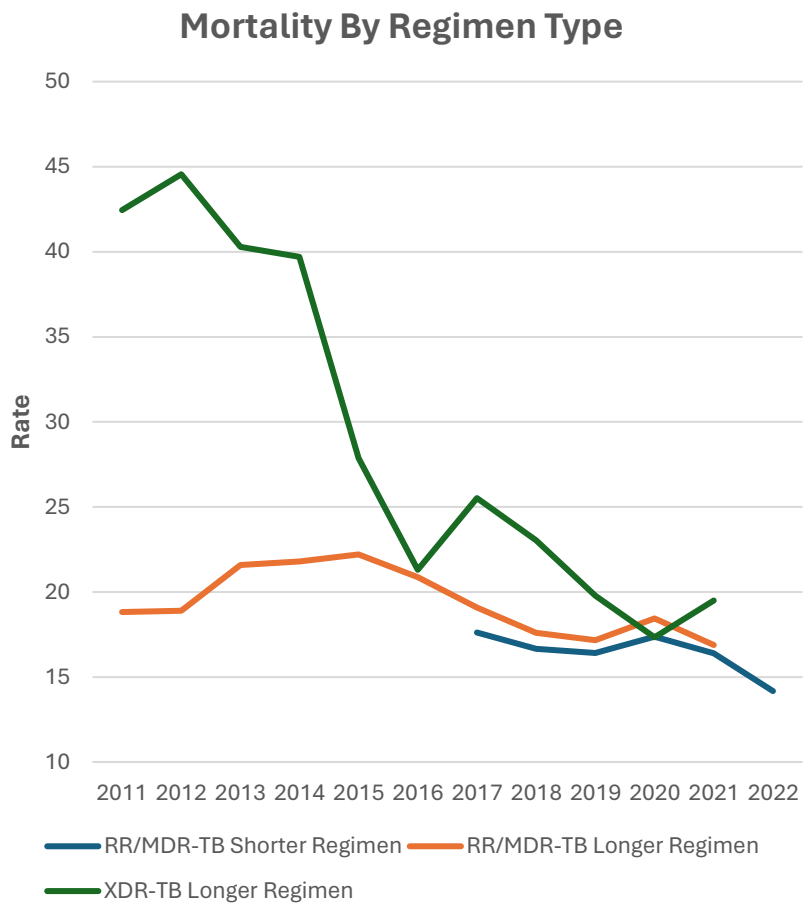
Norbert Ndjeka, Jonathon R Campbell, Graeme Meintjes, Gary Maartens, H Simon Schaaf, Jennifer Hughes, Xavier Padanilam, Anja Reuter, Rodolfo Romero, Farzana Ismail, Martin Enwerem, Hannetjie Ferreira, Francesca Conradie*, Kogieleum Naidoo*, Dick Menzies*

(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

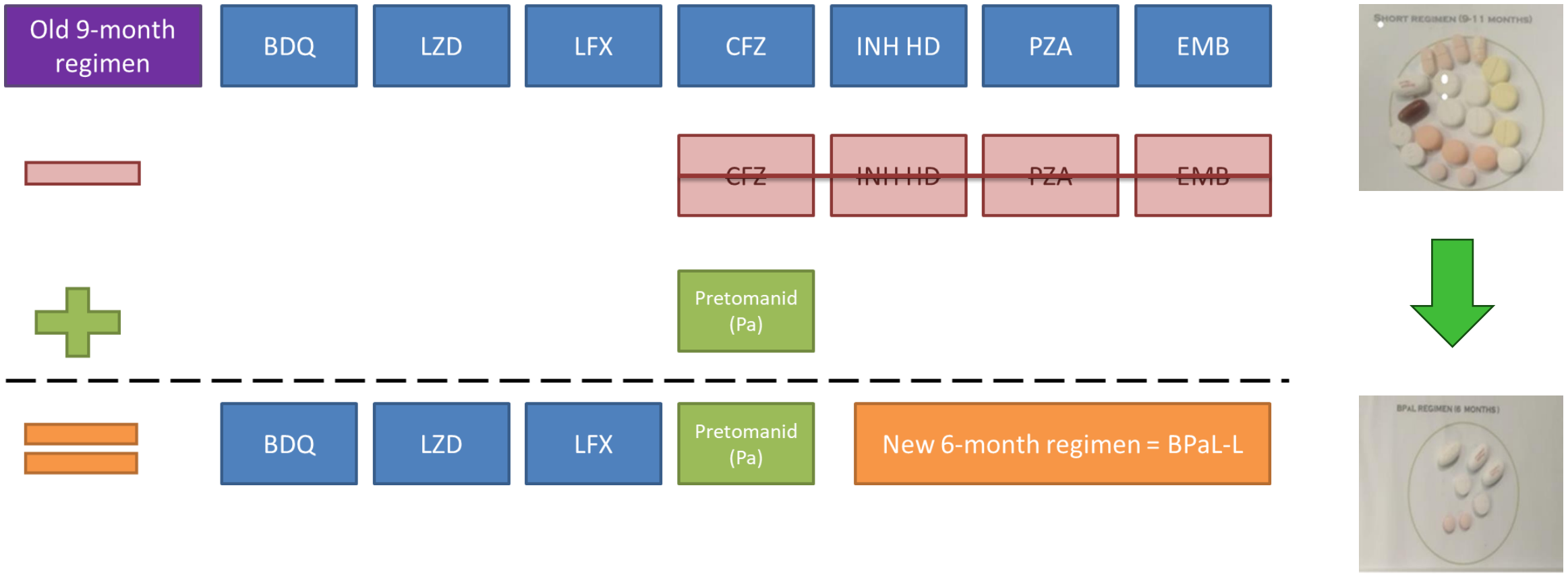






Source: EDRWeb

New Regimen – BPaL-L



BPaL-L launched on 1 Sept @ Jose Pearson

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!

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BPAL-L Implementation Progress

- 49 out of 52 districts enrolling patients on BPaL-L
- 397 facilities initiating patients on BPaL-L
- Total number of patients enrolled from 1st September 2023 to 23 February 2024

Patients on BPaL-L by Province						
Province	**Sep-2023**	**Oct-2023**	**Nov-2023**	**Dec-2023**	**Jan-2024**	**Total**
EC	69	70	72	57	76	344
FS			6	6	8	20
GP	18	45	62	39	43	207
KZN	11	38	65	71	94	279
LP	1	16	15	9	9	50
MP	1	9	13	15	16	54
NC	21	17	21	16	18	93
NW	5	10	11	6	9	41
WC		1	4	22	61	88
Total	**126**	**206**	**269**	**241**	**334**	**1 176**

Source: EDRWeb

Conclusion

- SA has 60million people distributed in 9 provinces, 52 districts, 232 sub-districts
- DS-TB is diagnosed and treated in all 3700 facilities although DR-TB treatment is initiated from 758 sites in at least 90% of sub-districts

- Progress of TB Recovery Plan
  - TB incidence has decreased by 53% between 2015 and 2022
  - TB treatment coverage has attained 77% by end of 2022
  - High TB mortality and loss to follow up remain our major challenges

- Introduction of BPAL-L
  - 49 out of 52 districts have introduced BPaL-L regimen
  - Over 1700 patients initiated since September 2023
  - First patients completing the regimen March 2024

Thank you

Emerging Bedaquiline Resistance in South Africa

Shaheed V Omar

Centre Head |Centre for Tuberculosis

National TB Reference Laboratory |WHO TB Supranational Reference Laboratory Network

National Institute for Communicable Diseases | Division of the National Health Laboratory Service

Bedaquiline (BDQ) use in South Africa

First new TB drug in 40 years (28 December 2012) – receiving accelerated FDA approval for use to treat drug resistant TB

South Africa initiated the BDQ compassionate use Access Program in end 2012

In October 2014 BDQ was registered for use in South Africa – pre-XDR/XDR TB

December 2017 - BDQ containing “Bangladesh Regimen” was introduced

July 2018 - all-oral regimen containing BDQ

Over a decade of use in South Africa

Bedaquiline (BDQ) use in South Africa

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]

ABSTRACT South African patients with rifampicin-resistant tuberculosis (TB) and resistance to fluoroquinolones and/or injectable drugs (extensively drug-resistant (XDR) and preXDR-TB) were granted access to bedaquiline through a clinical access programme with strict inclusion and exclusion criteria.

PreXDR-TB and XDR-TB patients were treated with 24 weeks of bedaquiline within an optimised, individualised background regimen that could include levofloxacin, linezolid and clofazimine as needed. 200 patients were enrolled: 87 (43.9%) had XDR-TB, 99 (49.3%) were female and the median age was 34 years (interquartile range (IQR) 27–42). 134 (67.0%) were living with HIV; the median CD4$^+$ count was 281 cells·μL^{-1} (IQR 130–467) and all were on antiretroviral therapy.

16 out of 200 patients (8.0%) did not complete 6 months of bedaquiline: eight were lost to follow-up, six died, one stopped owing to side effects and one was diagnosed with drug-sensitive TB. 146 out of 200 patients (73.0%) had favourable outcomes: 139 (69.5%) were cured and seven (3.5%) completed treatment. 25 patients (12.5%) died, 20 (10.0%) were lost from treatment and nine (4.5%) had treatment failure. 22 adverse events were attributed to bedaquiline, including a QT interval corrected using the Fridericia formula (QTcF) >500 ms (n=5), QTcF increase >50 ms from baseline (n=11) and paroxysmal atrial flutter (n=1).

Bedaquiline added to an optimised background regimen was associated with a high rate of successful treatment outcomes for this preXDR-TB and XDR-TB cohort.

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*

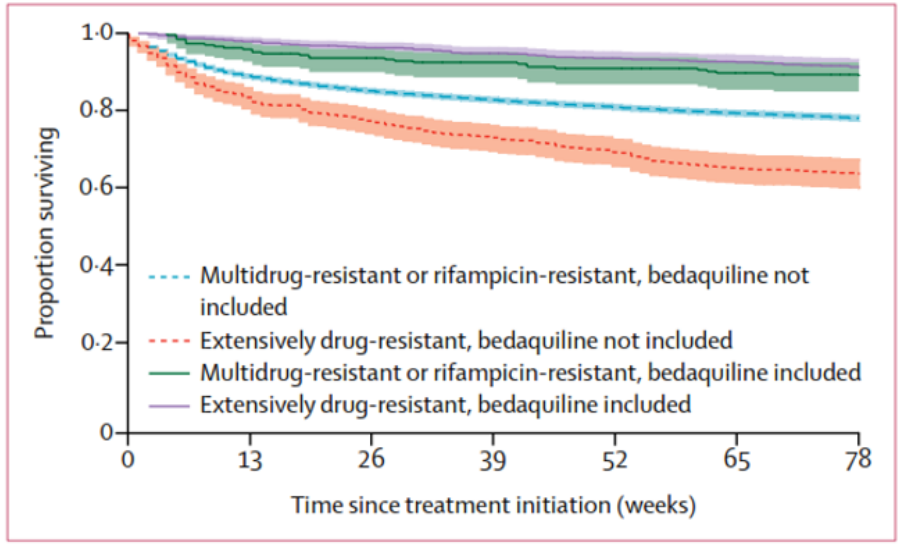
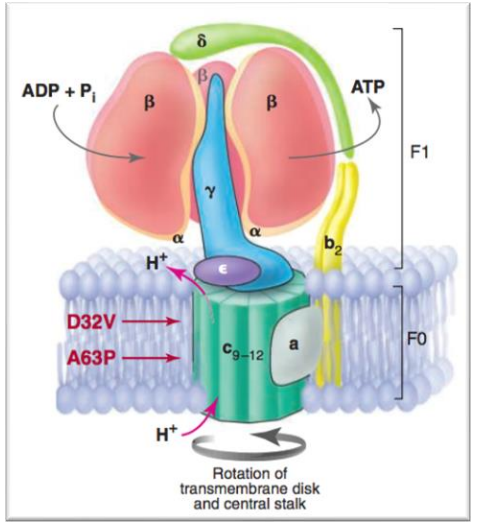


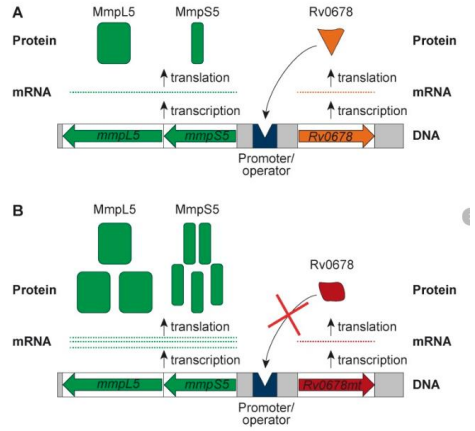
Figure 4: **Kaplan-Meier survival curves, by regimen inclusive of bedaquiline and drug resistance**
The shaded area indicates 95% CI.

http://dx.doi.org/10.1016/S2213-2600(18)30280-7

BDQ Resistance

- BDQ resistance first described in 2015, emphasizing the crucial need for the systematic surveillance of resistance.
- Genetic basis of resistance has been associated with;
  - ***atpE* (target-based)**
    - ATP synthase enzyme a crucial enzyme involved in the production of ATP
  - ***Rv0678* or *mmpR* (non-target based) efflux pump repressor**
    - mutations results in the overexpression of the efflux pumps which actively pumps the drug out of the cell
  - **Other targets pepQ & Rv1979c**
    - Consequences less well characterized
- Mutations in ***Rv0678*** are the dominant mechanism for resistance and are associated with clofazimine cross-resistance.





BDQ Lab testing

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A Multilaboratory, Multicountry Study To Determine MIC Quality Control Ranges for Phenotypic Drug Susceptibility Testing of Selected First-Line Antituberculosis Drugs, Second-Line Injectables, Fluoroquinolones, Clofazimine, and Linezolid

Koné Kaniga,[a] Daniela M. Cirillo,[b] Sven Hoffner,[c] Nazir A. Ismail,[d,e] Devinder Kaur,[f] Nacer Lounis,[g] Beverly Metchock,[h] Gaby E. Pfyffer,[i] Amour Venter[j]

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]

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[b] Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa
[c] Janssen Research & Development, Titusville, NJ, United States
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A Multimethod, Multicountry Evaluation of Breakpoints for Bedaquiline Resistance Determination

Nazir Ahmed Ismail,[a] Akio Aono,[b] Emanuele Borroni,[c] Daniela Maria Cirillo,[c] Christel Desmaretz,[d] Rumina Hasan,[e,f] Satoshi Mitarai,[b] Sadia Shakoor,[e] Gabriela Torrea,[d] Koné Kaniga,[g] Shaheed V. Omar[a]

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Validation of Bedaquiline Phenotypic Drug Susceptibility Testing Methods and Breakpoints: a Multilaboratory, Multicountry Study

Koné Kaniga,[a] Akio Aono,[b] Emanuele Borroni,[c] Daniela Maria Cirillo,[c] Christel Desmaretz,[d] Rumina Hasan,[e,f] Lavania Joseph,[g] Satoshi Mitarai,[b] Sadia Shakoor,[e] Gabriela Torrea,[d] Nazir Ahmed Ismail,[g,h,i] Shaheed V. Omar[g]

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Bedaquiline-Resistant Tuberculosis Associated with *Rv0678* Mutations

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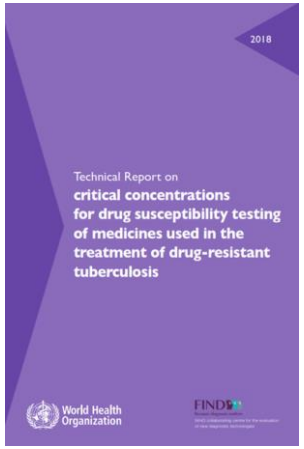
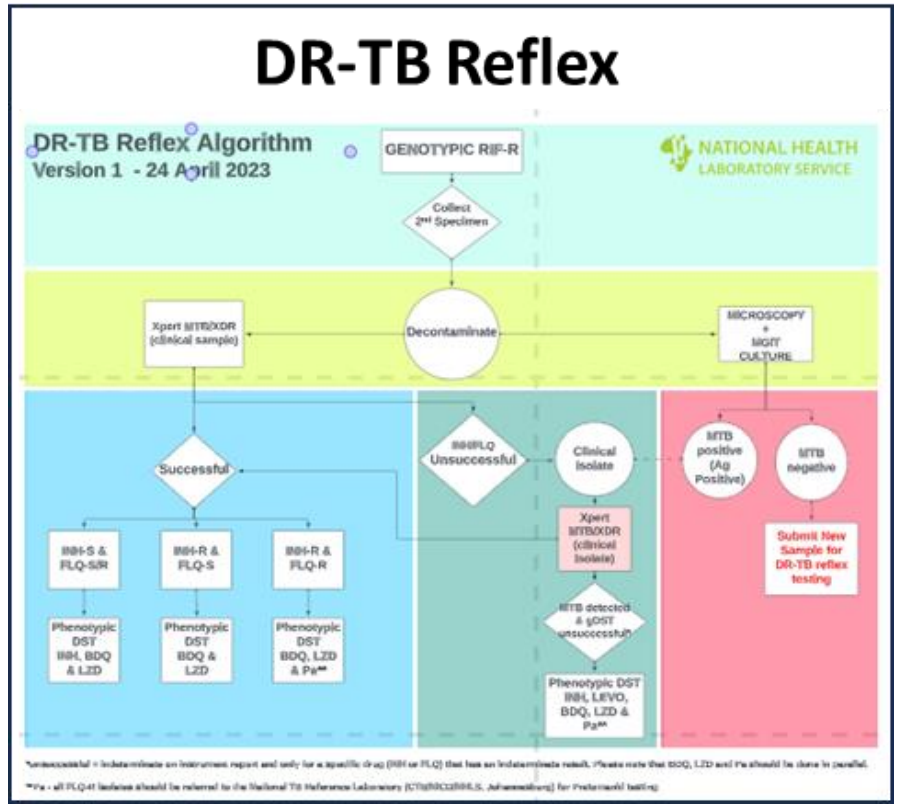


BDQ Lab testing

- June 2018 introduced as part of DR-TB Reflex testing for FLQ-Resistant and/or INH double mutations
  - All testing performed at the NTBRL/NICD
  - Confirmatory sequencing performed on resistant isolates

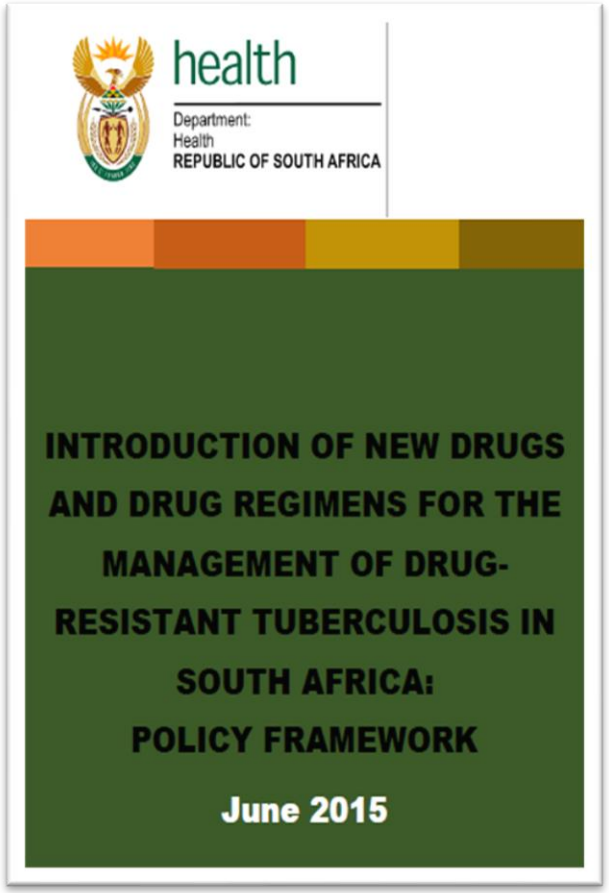
- May 2019 decentralized testing initiated
  - PTS panel distributed to the 6 regional referral laboratories
  - No commercial product available in South Africa to date
  - Preparation and distribution of BDQ by NTBRL for routine laboratory use & EQA programme in place

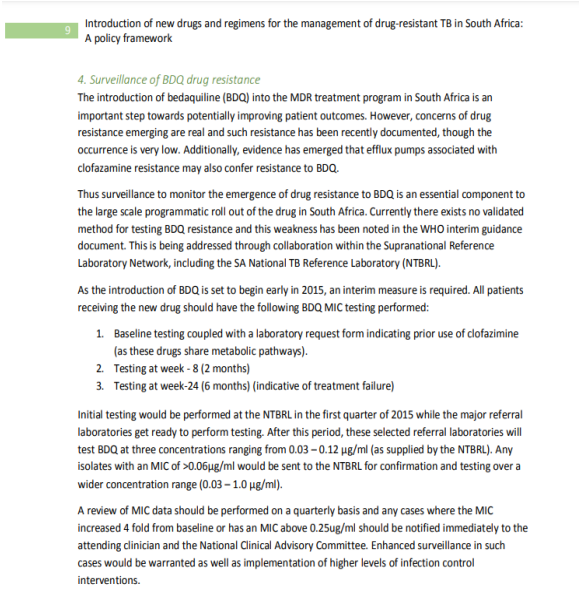
- March 2023 testing expanded to all Rif-R samples as part of the DR-TB Reflex testing algorithm



BDQ Resistance Surveillance

- As part of the National Policy Framework for the implementation of new drugs - Surveillance was initiated in 2015
- All Patients initiated on a BDQ containing regimen submitted samples to the NTBRL/NICD at M0, M2 & M6
- To detect and analyze baseline BDQ resistance & associated risk factors
- To detect and analyze the emergence of resistance on treatment





9 Introduction of new drugs and regimens for the management of drug-resistant TB in South Africa: A policy framework

4. Surveillance of BDQ drug resistance

The introduction of bedaquiline (BDQ) into the MDR treatment program in South Africa is an important step towards potentially improving patient outcomes. However, concerns of drug resistance emerging are real and such resistance has been recently documented, though the occurrence is very low. Additionally, evidence has emerged that efflux pumps associated with clofazamine resistance may also confer resistance to BDQ.

Thus surveillance to monitor the emergence of drug resistance to BDQ is an essential component to the large scale programmatic roll out of the drug in South Africa. Currently there exists no validated method for testing BDQ resistance and this weakness has been noted in the WHO interim guidance document. This is being addressed through collaboration within the Supranational Reference Laboratory Network, including the SA National TB Reference Laboratory (NTBRL).

As the introduction of BDQ is set to begin early in 2015, an interim measure is required. All patients receiving the new drug should have the following BDQ MIC testing performed:

1. Baseline testing coupled with a laboratory request form indicating prior use of clofazimine (as these drugs share metabolic pathways).
2. Testing at week - 8 (2 months)
3. Testing at week-24 (6 months) (indicative of treatment failure)

Initial testing would be performed at the NTBRL in the first quarter of 2015 while the major referral laboratories get ready to perform testing. After this period, these selected referral laboratories will test BDQ at three concentrations ranging from 0.03 – 0.12 µg/ml (as supplied by the NTBRL). Any isolates with an MIC of >0.06µg/ml would be sent to the NTBRL for confirmation and testing over a wider concentration range (0.03 – 1.0 µg/ml).

A review of MIC data should be performed on a quarterly basis and any cases where the MIC increased 4 fold from baseline or has an MIC above 0.25ug/ml should be notified immediately to the attending clinician and the National Clinical Advisory Committee. Enhanced surveillance in such cases would be warranted as well as implementation of higher levels of infection control interventions.

BDQ Resistance Surveillance **2015 -2019**

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

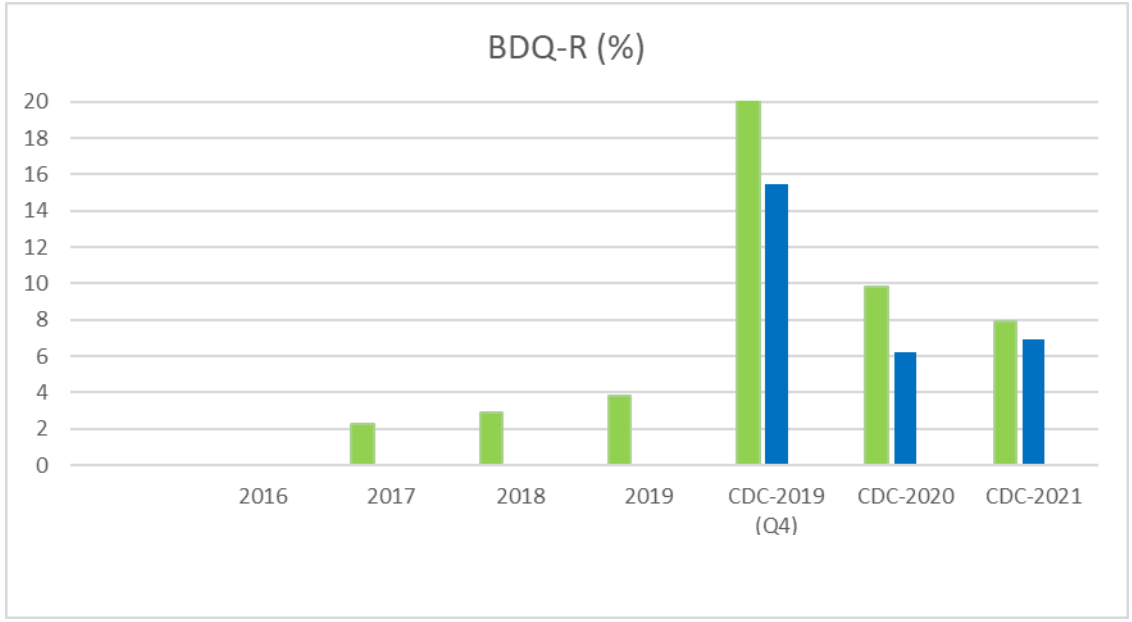
Nazir Ahmed Ismail, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsaolo, Gary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okozi, Xavier Padanilam, Anja Reuter, Rodolf Romero, Simon Schaaf, Julian te Riele, Ebrahim Variava, Minty van der Meulen, Farzana Ismail†, Norbert Ndjeka†*

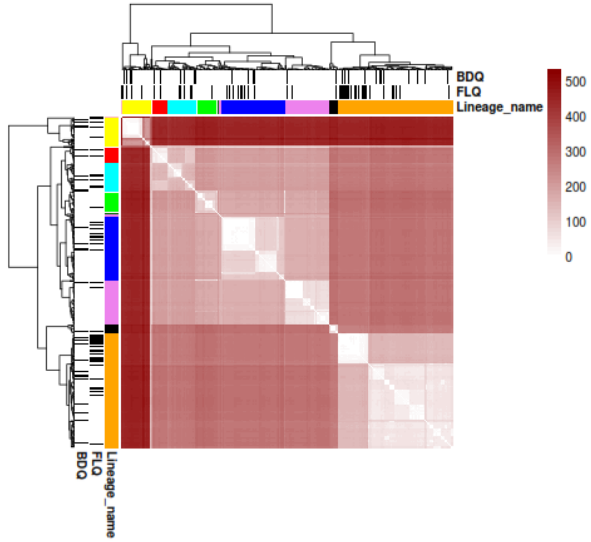
- **3.8%** BDQ-Resistance at baseline
- **2.3%** developed BDQ Resistance during treatment
- ***Rv0678*** sole genetic basis of resistance

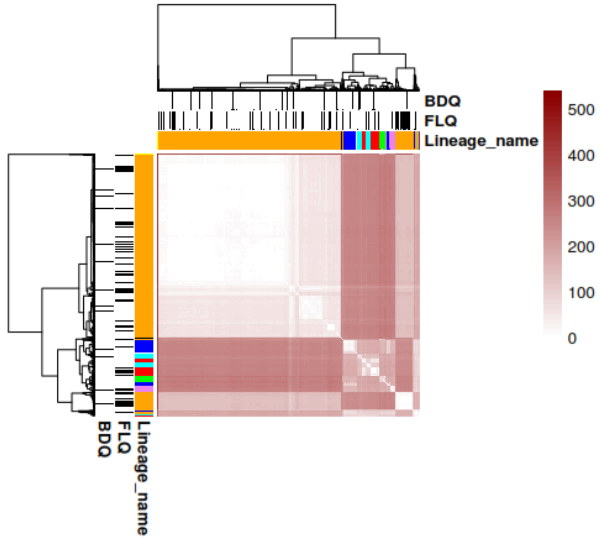
BDQ Resistance associated with

- Previous BDQ or CFZ exposure (OR 7.1)
- Pre-XDR or XDR TB (OR 4.2 – 4.8)
- Fluroquinolone resistance (OR 4.8)

Genomic Surveillance of Drug Resistant TB 2019 – 2024 (interim analysis)








YES
WE CAN
END TB

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

YES WE CAN END TB

Bedaquiline susceptibility surveillance using routine laboratory data, South Africa (July 2019 – November 2023)

Dr Harry Moultrie, Elizabeth Kachingwe, Dr Farzana Ismail, and Dr Shaheed Vally Omar
Centre for Tuberculosis incorporating the National TB Reference Laboratory
National Institute for Communicable Diseases,
Division of the National Health Laboratory Services

World TB Day 2024

Overview

1. Acquired and primary bedaquiline (BDQ) resistance
2. Implementation of bedaquiline, and bedaquiline phenotypic drug susceptibility testing (pDST) in South Africa
3. Trends in bedaquiline and joint bedaquiline-fluoroquinolone (FLQ) resistance
4. A cross-sectional analysis of the prevalence of bedaquiline resistance and associated factors between March and November 2023

Acquired and primary bedaquiline resistance

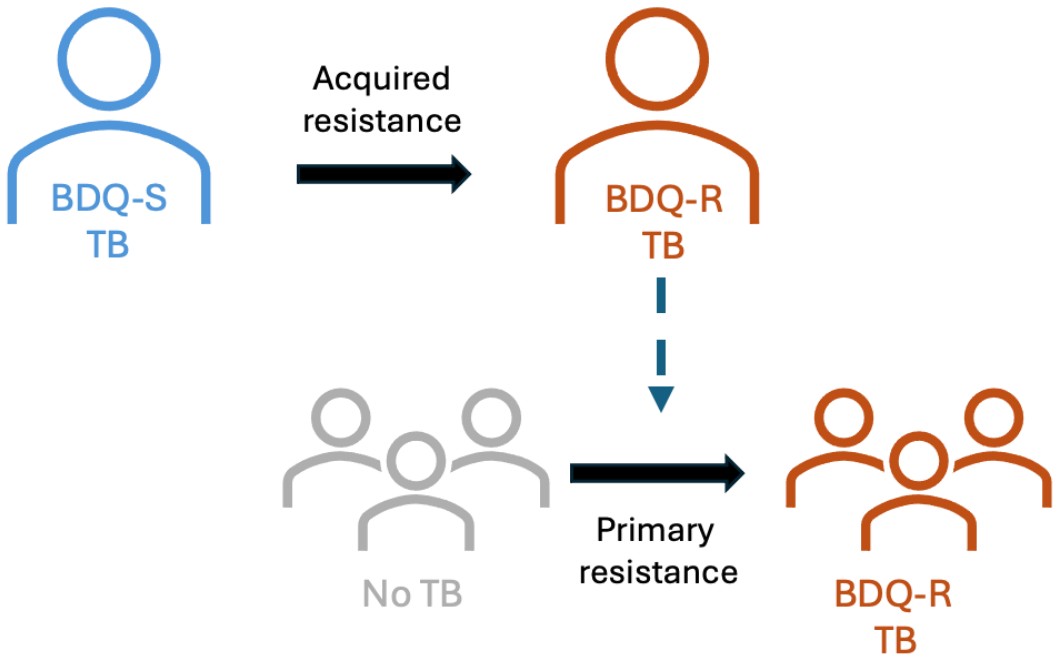
Acquired resistance:

- BDQ has a very long half-life of 5 months
- Treatment interruptions result in a long tail of sub-optimal BDQ exposure unsupported by other drugs increasing the risk of acquisition of resistance
- Similarly, inadequate optimised background regimens can increase risk of BDQ resistance

Primary resistance:

- With widespread use of bedaquiline, the infectious circulating pool of resistant strains expands
- Once established, antibiotic resistance is more often due to primary than acquired
- Transmission model for MDR-TB suggests that the vast majority of MDR-TB is from primary resistance

(Kendall et al. *Lancet Respir Med*, 2015)



Emergence of bedaquiline resistance

Selected studies

1. Retrospective study in Cape Town (2016-2017) amongst 40 patients who were culture positive after >4 months on BDQ, 12 (31%) acquired BDQ resistance and 3 (8%) had primary BDQ resistance.

   (Derendinger et al. *Lancet Microbe*, 2023)

2. Prevalence of BDQ resistance in South Africa in 2015-2019 was 3.8%. (Ismail et al. *Lancet*, 2021)

3. In a systematic review 2.2% (IQR: 1.1% - 4.6%) acquired BDQ resistance.

   (Mallick et al. *JAC Antimicrob Resist*, 2022)

4. Model to assess tradeoffs between mortality, resistance and transmission estimated that 5.9% (95%CI: 2.2% - 9.5%) would acquire BDQ resistance if BDQ was part of MDR-TB regimens. However, this would also decrease XDR-TB (*old definition*) by protecting other drugs.

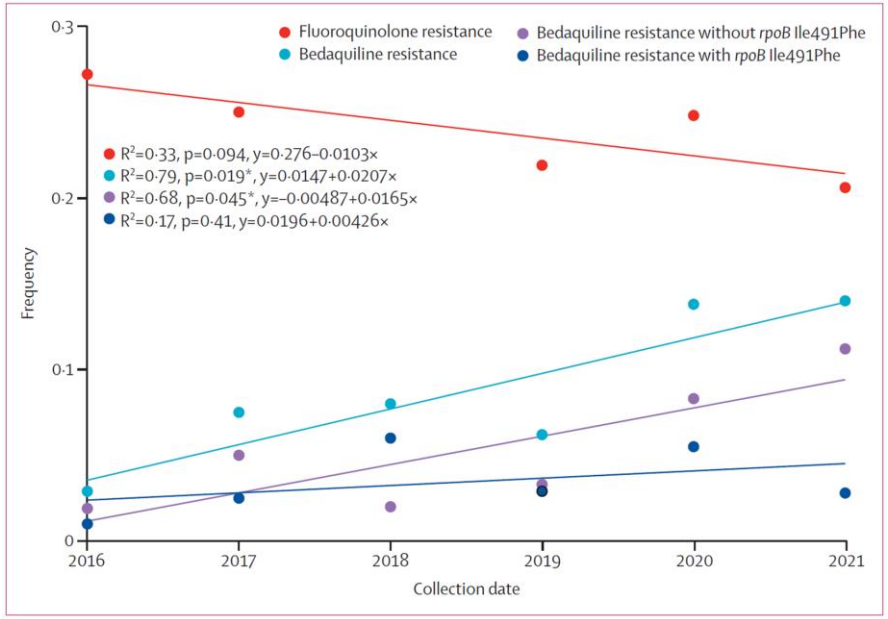
   (Kunkel et al. *Plos Med*, 2016)

5. Prevalence of BDQ genotypic resistance in Mozambique increased from 3% to 14% between 2016 and 2021. 37/61 (61%) of those BDQ-R had FLQ-S TB. But representativeness of samples (n=809) unclear.

   (Barilar et al. *Lancet Inf Dis*, 2023)

Policy	Outcome of Interest					
BDQ Available for	Maximize Health	Minimize Acquired Resistance			Minimize Secondary Cases	
	Life Expectancy	XDR	BDQR	XDR+BDQR	Total Number	Life Years Lost To
XDR Only	20.8%	0.0%	100.0%	10.8%	0.0%	*0.0%
PreXDR+XDR	1.1%	0.0%	0.0%	85.6%	0.0%	0.0%
All MDR	78.1%	100.0%	0.0%	3.6%	100.0%	100.0%

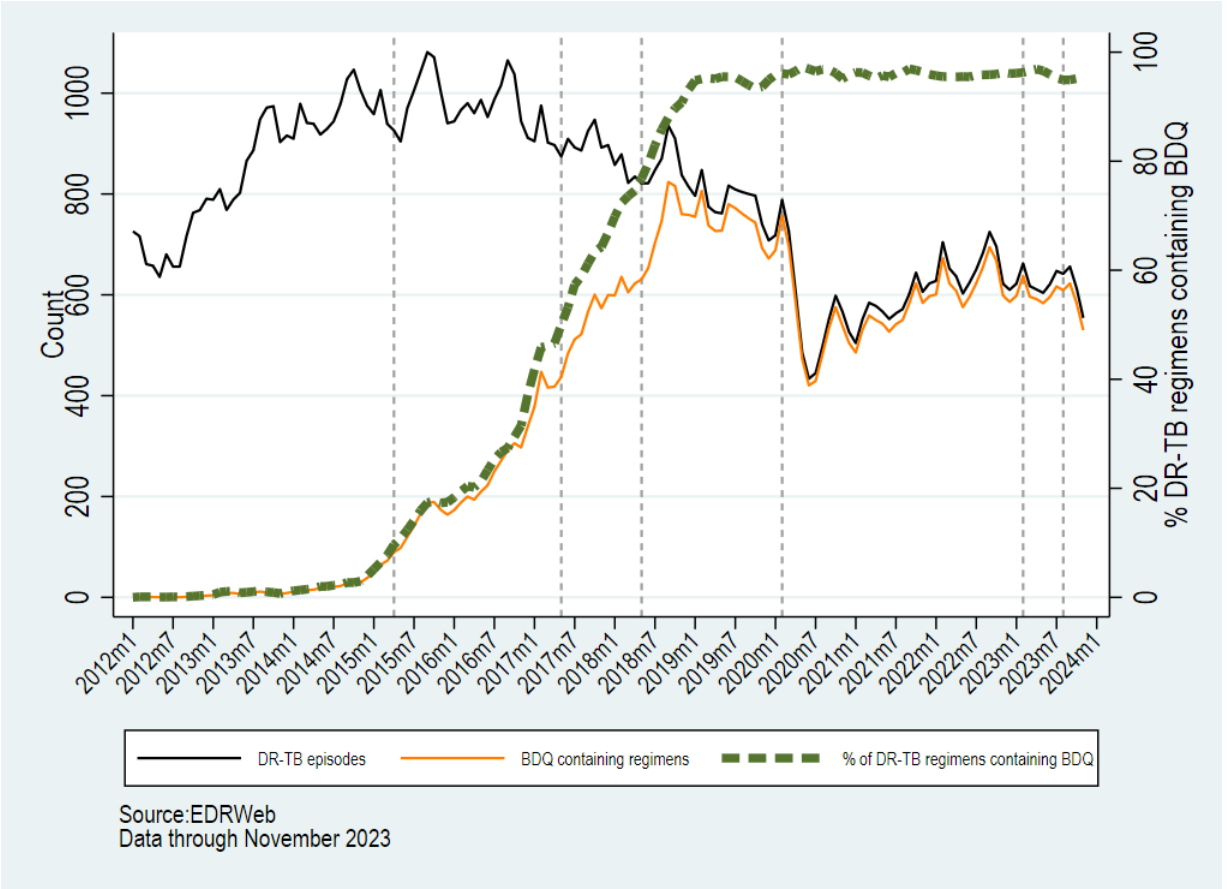
(Kunkel et al. *Plos Med*, 2016)



(Barilar al. *Lancet Inf Dis*, 2023)

Bedaquiline and pDST implementation in South Africa

- **Late 2012:** BDQ Clinical Access Programme commenced
- **May 2015:**
  - Pre-XDR and XDR-TB at specialised sites
  - BDQ pDST surveillance program commenced
- **June 2017:** Decentralisation
- **June 2018:** BDQ containing all oral regimen for all RR-TB
- **2019:** BDQ pDST for FLQ-R, SLI-R and/or dual INH mutations
- **July 2021**: BPaL CAP
- **March 2023**: BDQ and linezolid (LZD) pDST for all RR-TB
- **Sep 2023:** BPaL and BPaL-L introduced



Source: EDRWeb

Objectives

Test-level:

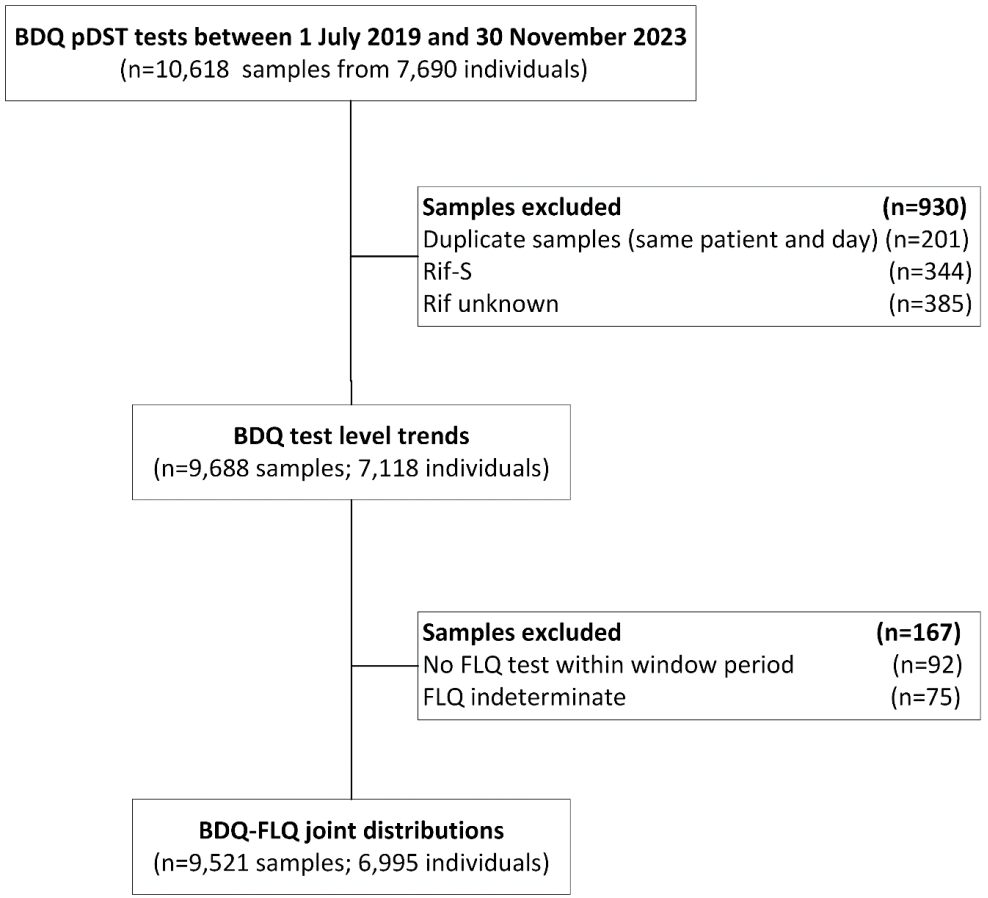
1. To describe the long-term trends in BDQ pDST volumes amongst patients with RR-TB
2. To assess the implementation of the updated BDQ pDST guidelines since March 2023
3. To assess trends in BDQ drug susceptibility, and joint BDQ-FLQ resistance patterns amongst patients with RR-TB

Patient-level:

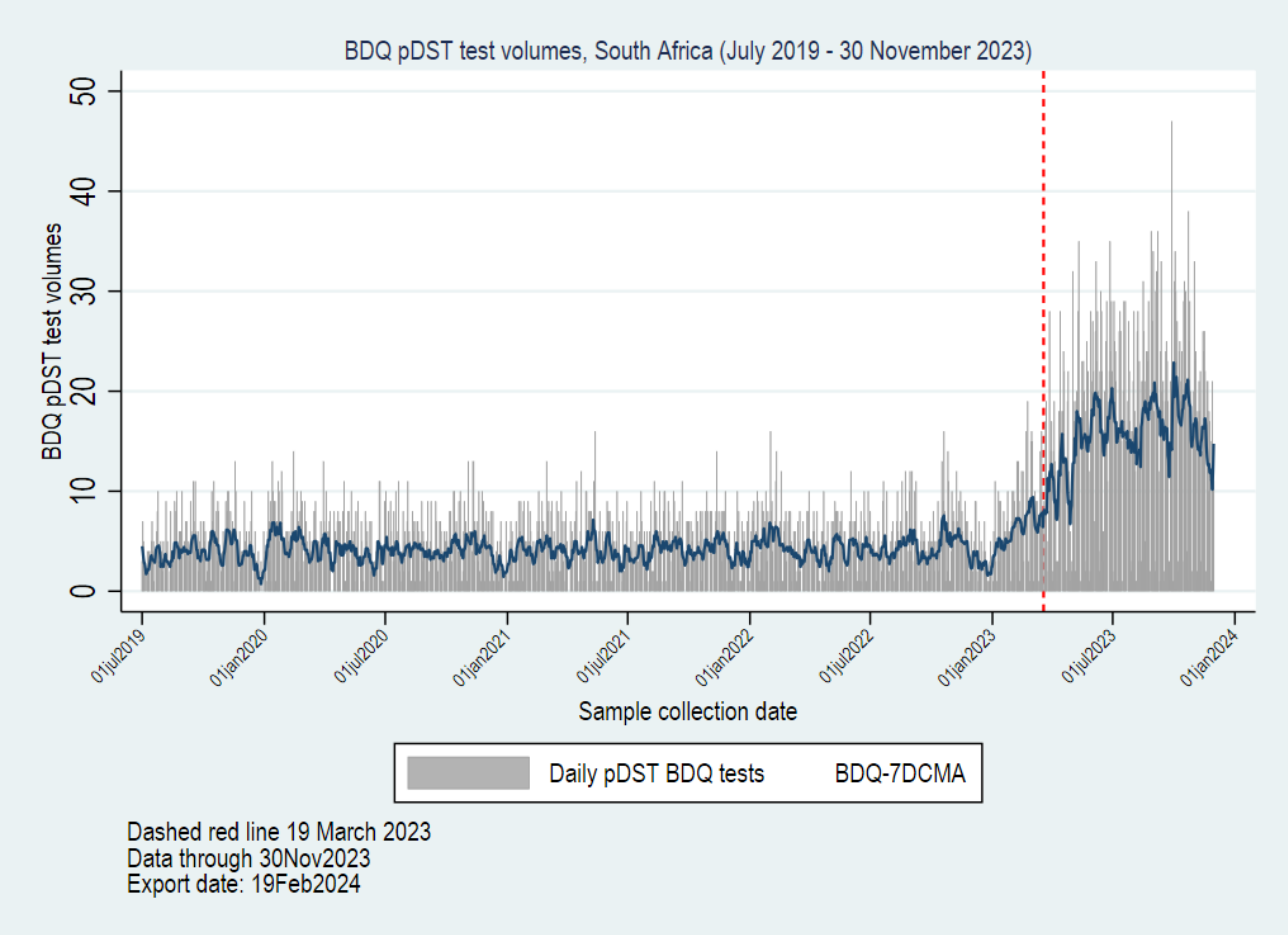
4. To describe the prevalence of BDQ-R TB amongst patients who had their first BDQ pDST conducted during the period March – November 2023 in provinces which achieved >50% coverage of BDQ pDST amongst RR-TB patients

Methods in brief (Objectives 1-3)

- BDQ pDST results exported from NICD SDW (19 Feb 2024). Data were right censored to 30 November 2023 (81 days from date of export).
- Where more than one BDQ pDST was conducted on the **same sample**, the result from the National TB Reference Laboratory (NTBRL) was held. In the event of discrepant BDQ pDST results from two non-NTBRL labs the BDQ-R result was used.
- RIF, INH, FLQ, SLI and LZD drug susceptibility was determined for each patient using a window period of 182 days prior to 28 days after date of BDQ pDST.
  - 91% of FLQ results obtained from the same sample
- Laboratory turnaround times (TAT) from time of sample collection until result reviewed were assessed
- Implementation of BDQ pDST reflex testing for all RR-TB assessed by province and month using patient level data

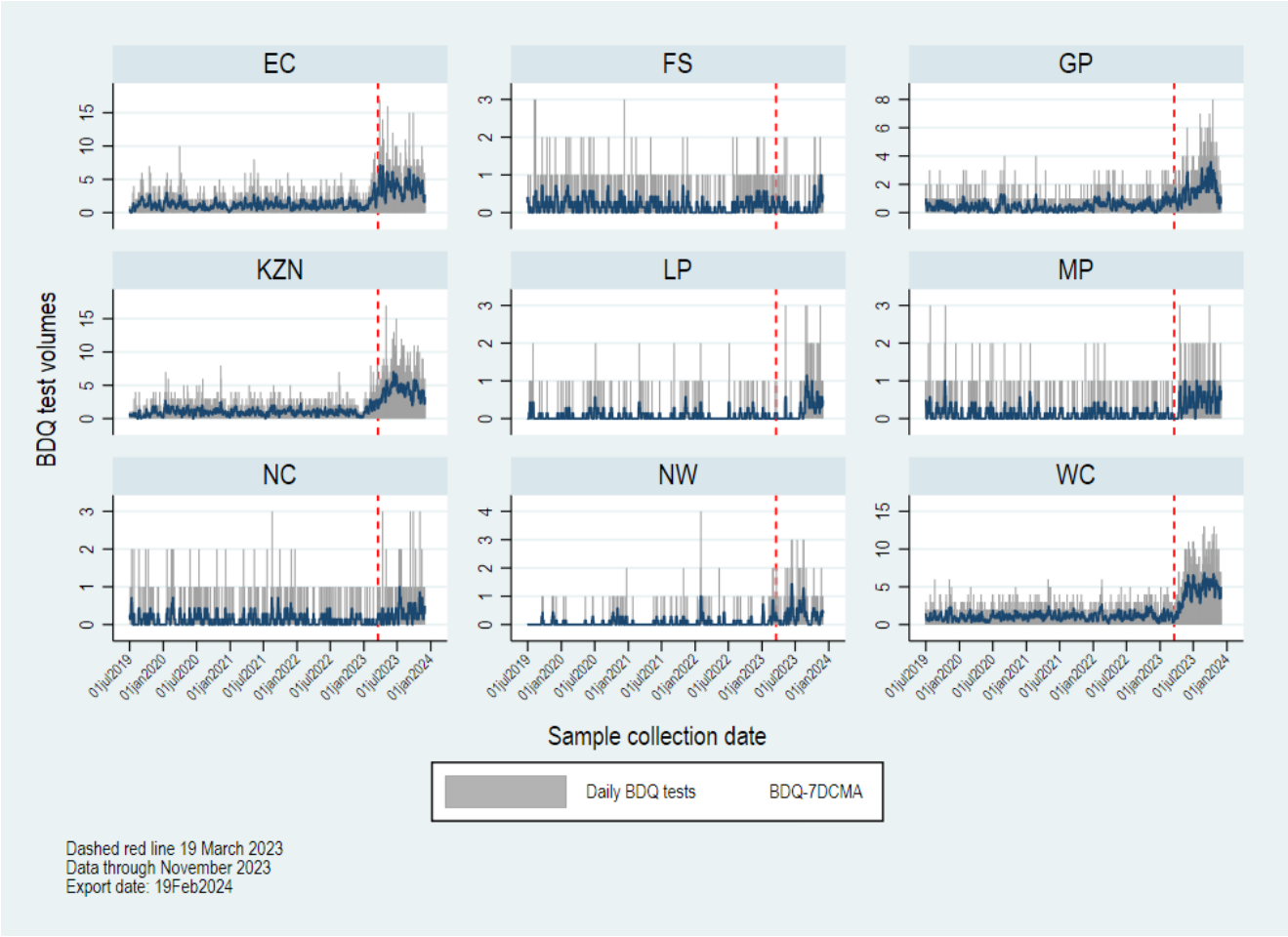


Long-term national trends in BDQ pDST volumes (June 2019 – November 2023)



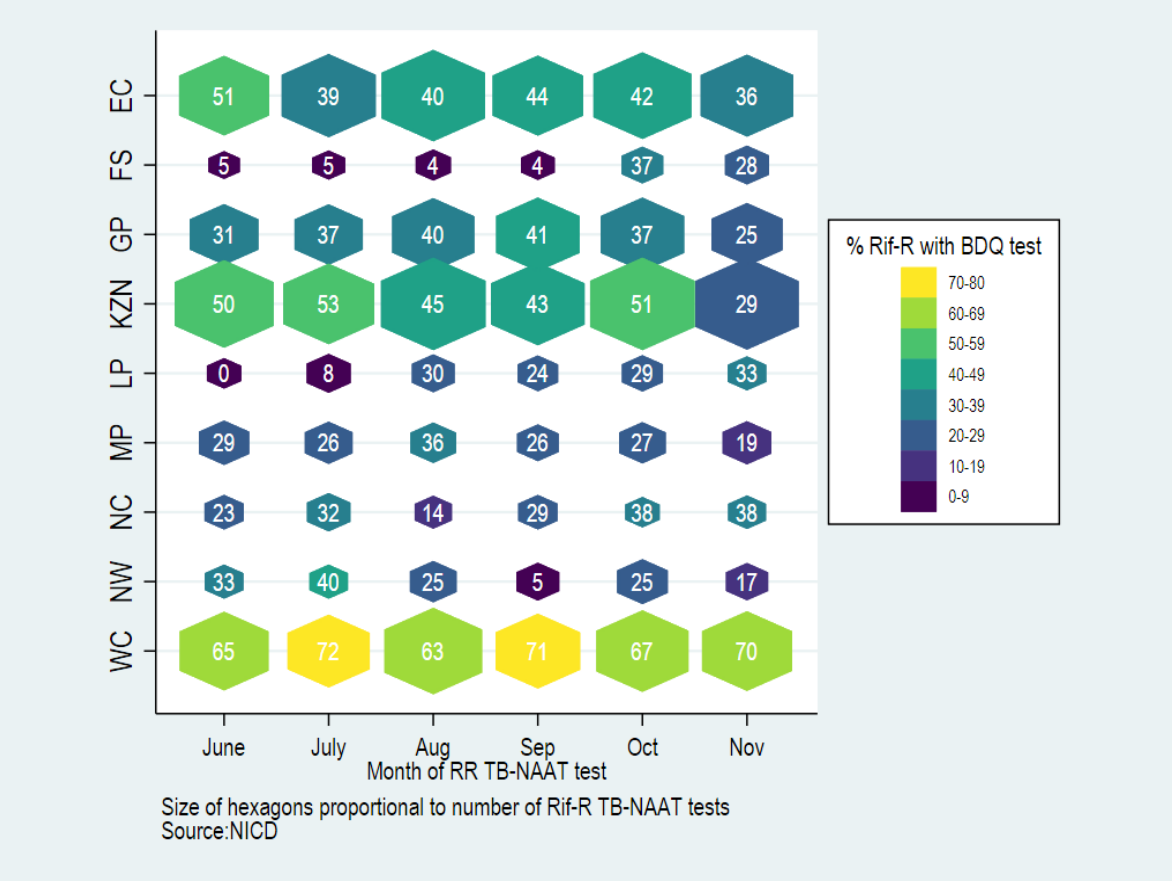
7-day centred moving average BDQ pDST volumes increased from February 2023, reaching a peak in October 2023

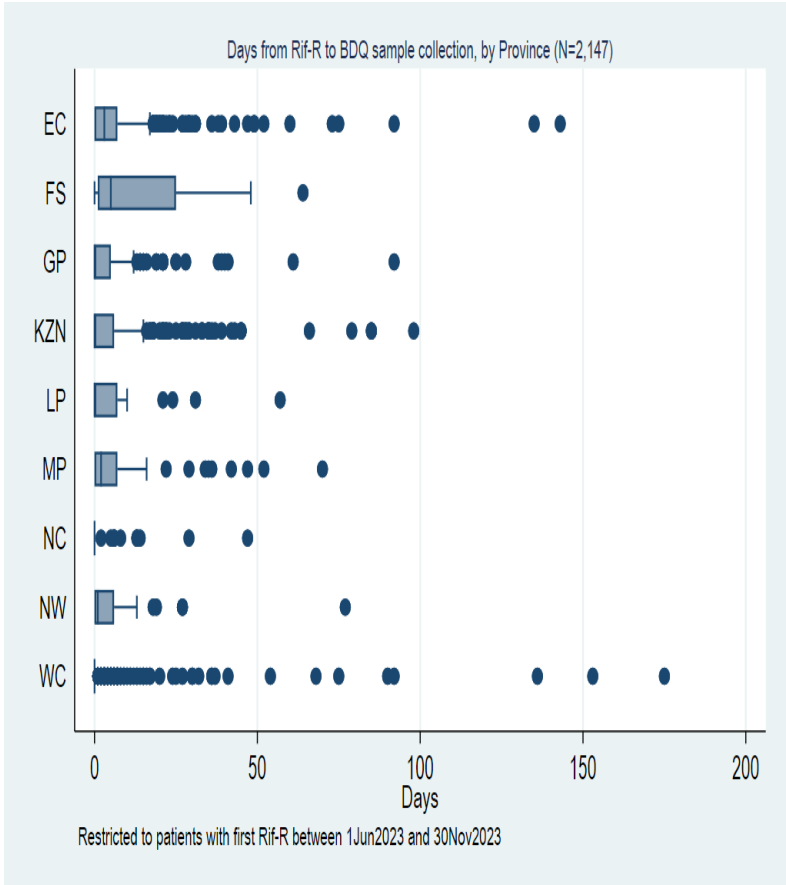
Long-term provincial trends in BDQ pDST volumes (June 2019 – November 2023)



- Substantial provincial heterogeneity in timing and scale of implementation, but this does not account for differences in provincial burden of RR-TB
- Note: the y-scales differ to improve legibility

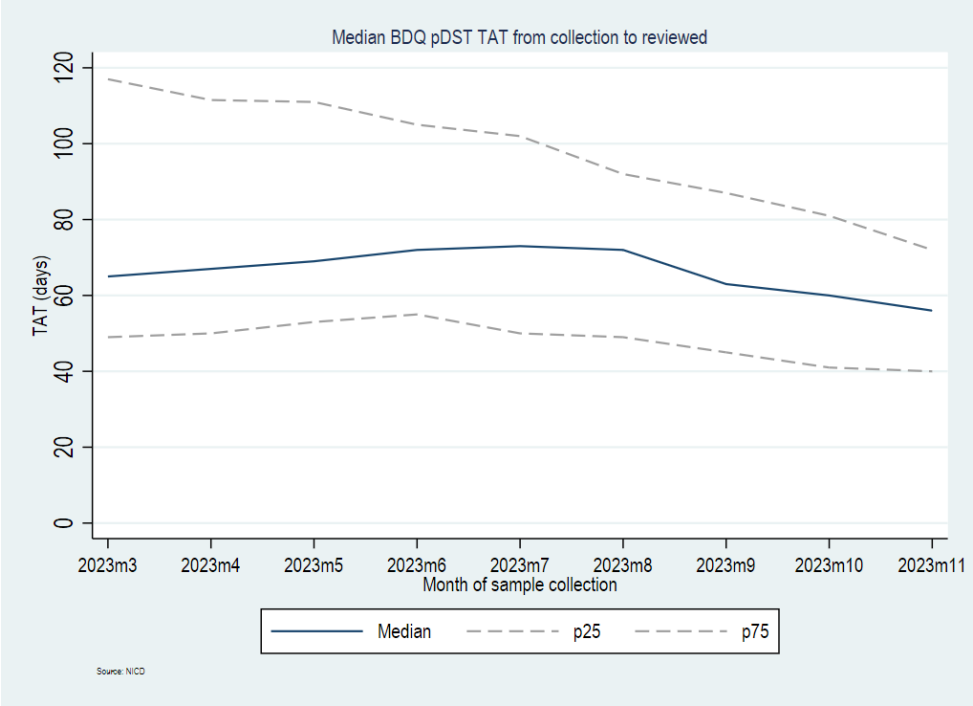
Coverage of BDQ pDST tests amongst patients with first RR TB-NAAT test (June to November 2023)

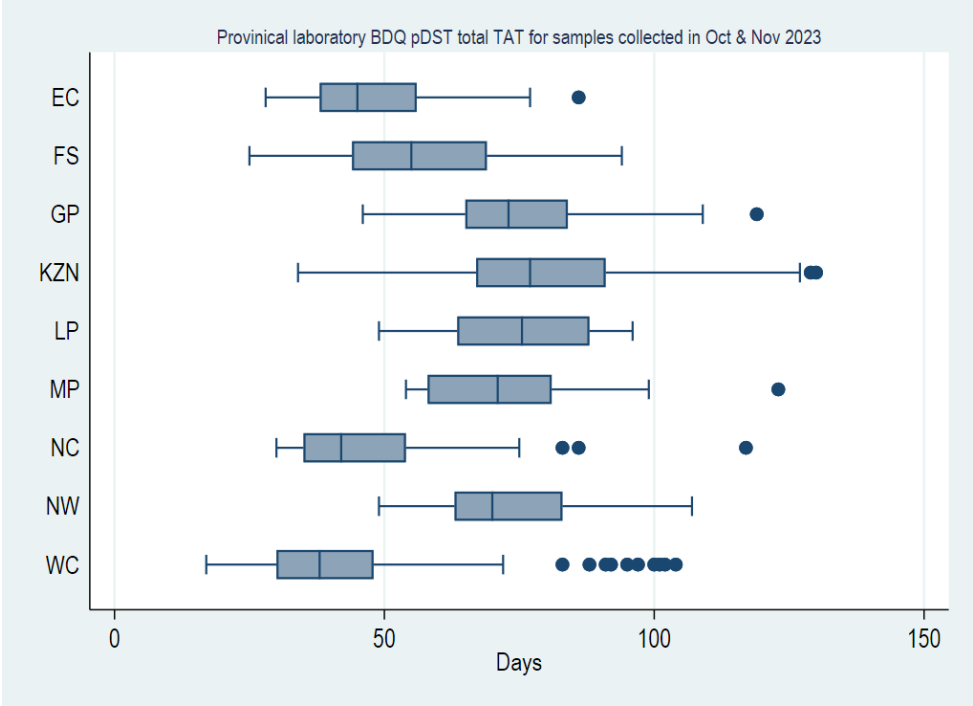




- Restricted to individuals who had **their first** (since 2019) RR TB-NAAT test in the period June to November 2023
- Nationally, 2,147/4,991 (43%) of individuals had a BDQ pDST test conducted
- Higher coverage in the Western Cape the result of collection of two initial samples for DR-TB reflex testing

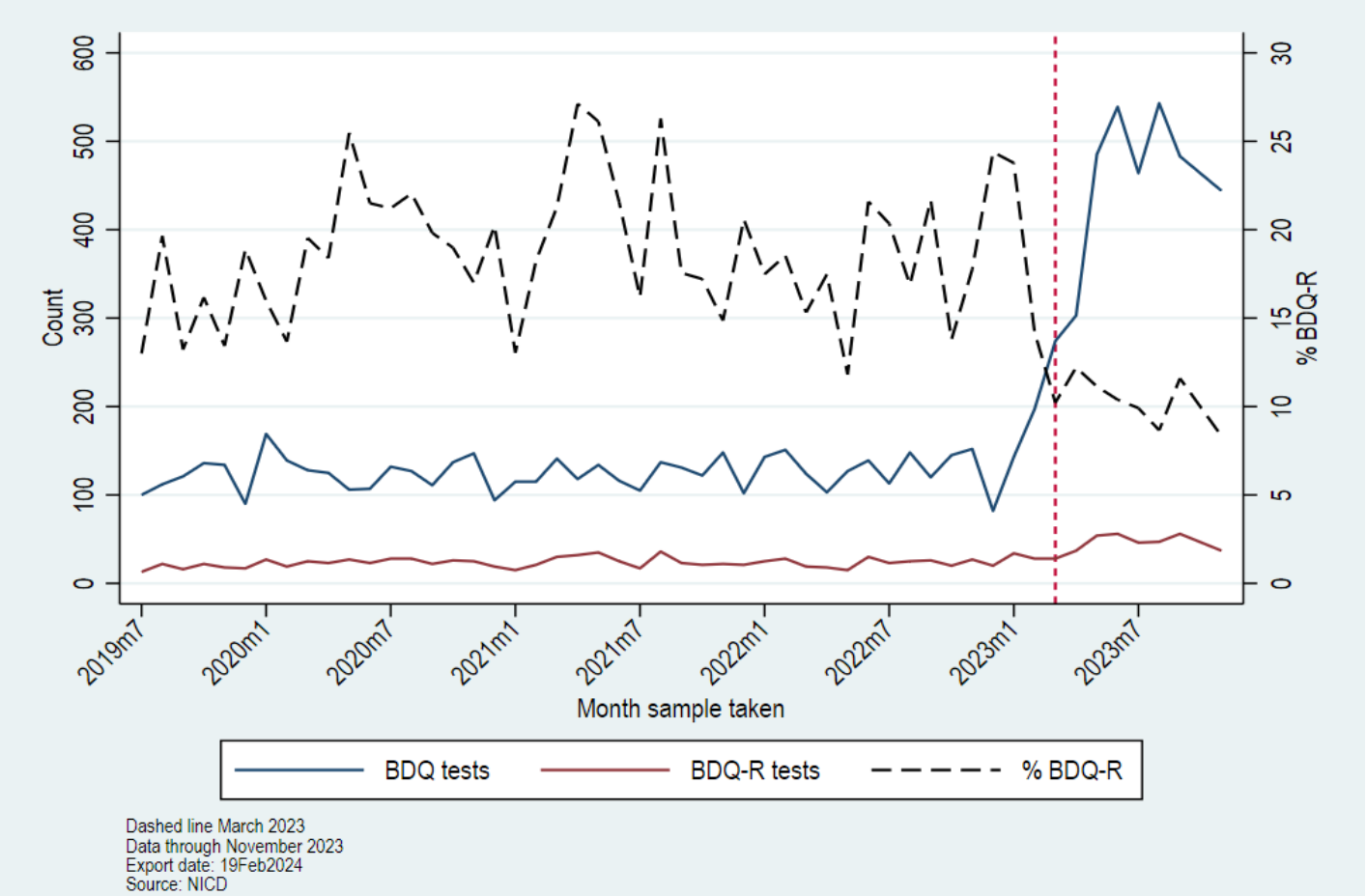
BDQ pDST Laboratory turn around times





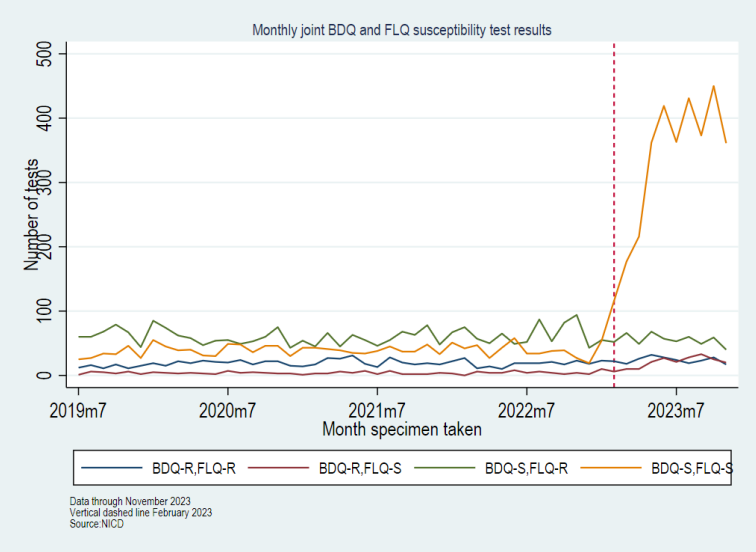
- While median laboratory BDQ pDST turnaround times (TAT) have decreased in recent months, TAT remains long and unlikely to decrease much further
- November 2023: median 56 days (IQR: 40 – 72 days)
- Provincial variation in laboratory TATs the result of both transport and laboratory capacity

Monthly BDQ tests, BDQ-R tests and % BDQ-R



- Change in DR-TB reflex testing guidelines resulted in an increase in BDQ-R tests and a decline in the percentage of tests which were BDQ-R

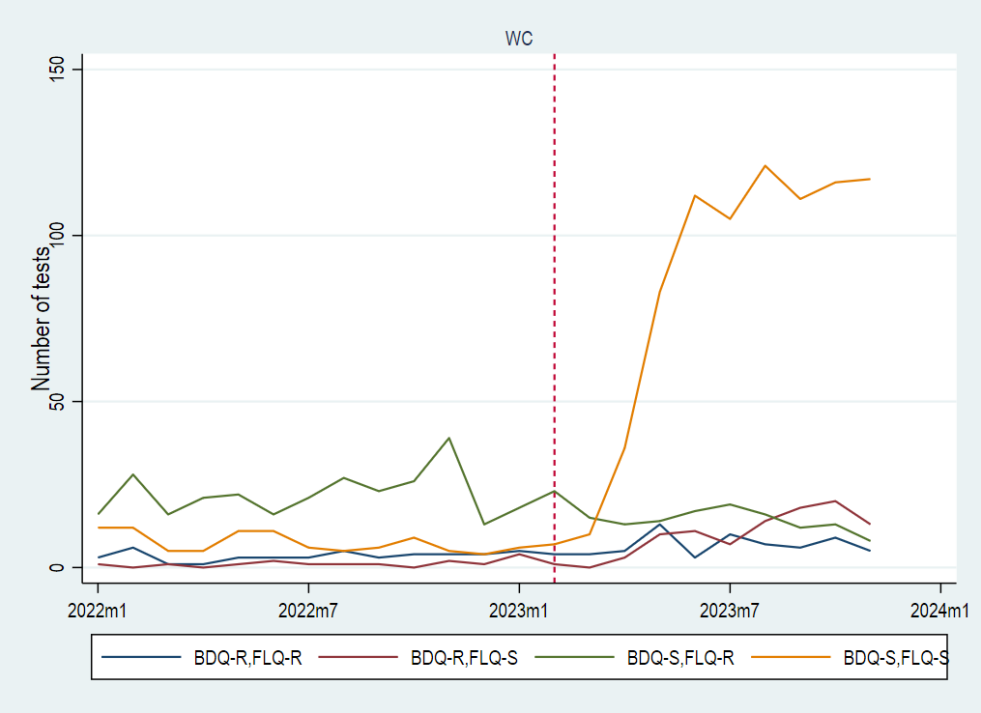
National trends in BDQ-FLQ joint susceptibility

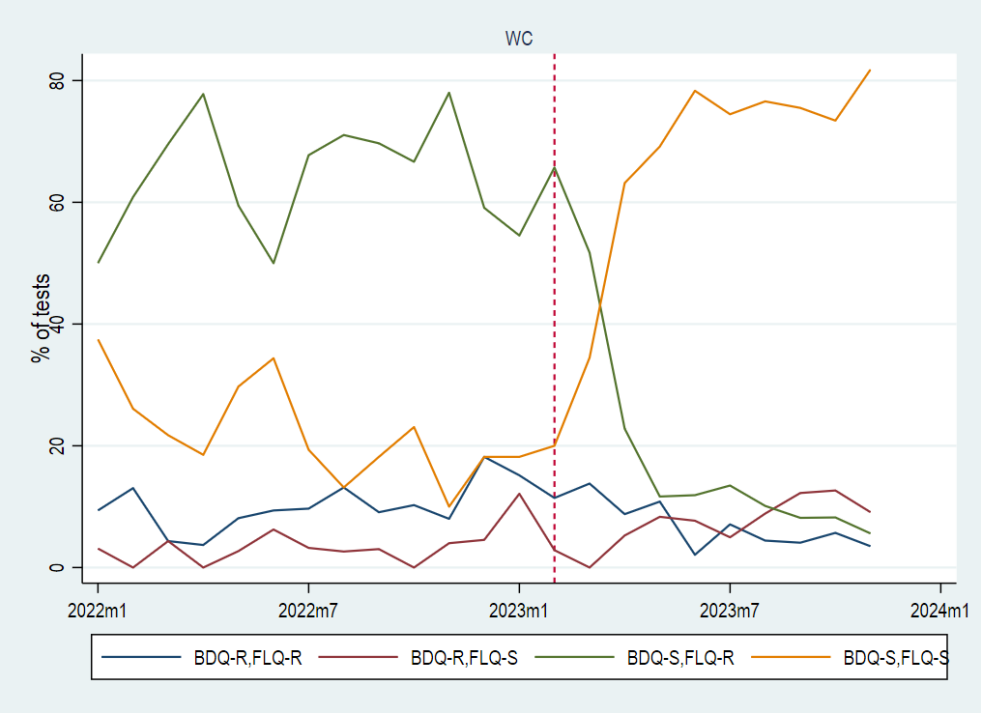


Month	BDQ-S FLQ-S	BDQ-S FLQ-R (Pre-XDR TB)	BDQ-R FLQ-S (not classified)	BDQ-R FLQ-R (XDR-TB)	All BDQ-R	Total tests
2023m3	177 (65.3%)	66 (24.4%)	10 (3.7%)	18 (6.6%)	28 (10.3%)	271
2023m4	216 (71.8%)	49 (16.3%)	10 (3.3%)	26 (8.6%)	36 (12.0%)	301
2023m5	362 (74.9%)	68 (14.1%)	21 (4.3%)	32 (6.6%)	53 (11.0%)	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 guidelines enabled identification of BDQ resistance amongst people with FLQ-S TB
- Prevalence of BDQ resistance between March and November 2023 was 10.1%
- In more recent months, the number of BDQ-R/FLQ-S tests exceeded BDQ-R/FLQ-R tests
- Test-level BDQ-R prevalence is, however, biased upwards because of repeat tests in those not responding to treatment and inclusion of provinces with lower coverage of BDQ reflex tests

WC trends in BDQ-FLQ joint susceptibility (January 2022 – November 2023





Cross-sectional study

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 (N=2,308)

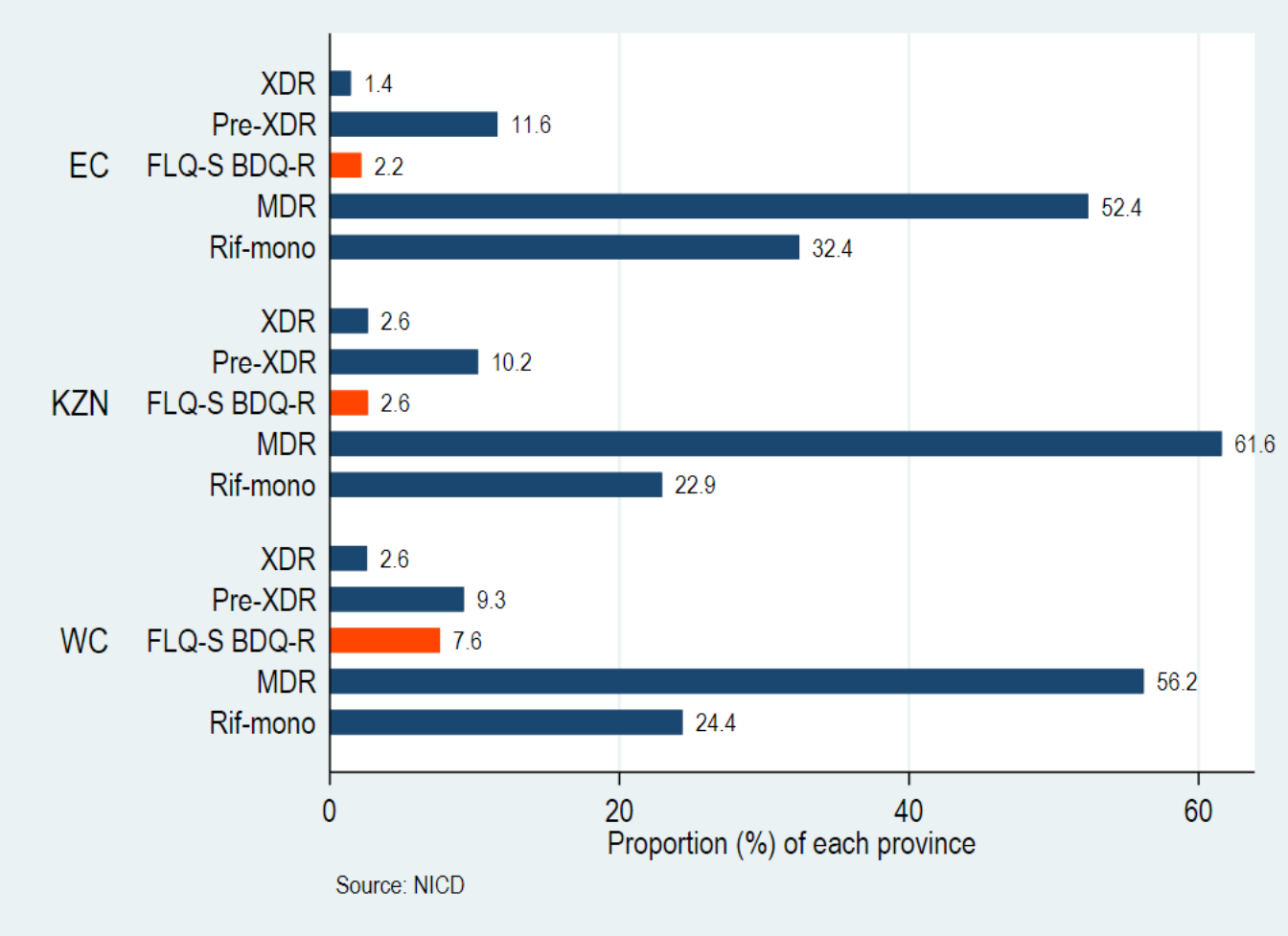
- Combined prevalence of BDQ resistance in the 3 provinces: 149/2,308 (6.5%)
  - Eastern Cape: 3.6%
  - KwaZulu-Natal: 4.8%
  - Western Cape: 10.2%
- Nearly two thirds (96/148, 65%) with BDQ-R had FLQ-S TB
- 64/115 (56%) of patients with BDQ-R had no documented previous exposure to BDQ indicating transmission of BDQ-R TB
- Prevalence of linezolid (LZD) resistance very low: 5/2291 (0.2%)
- Adjusted OR for BDQ-R in the Western Cape:
  - AOR = 3.0 (95%CI: 1.8 – 4.9)
  - Adjusted for age, sex, previous BDQ and CFZ exposure, and calendar month

	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

DR-TB classification in cross-sectional study

- RR FLQ-S BDQ-R TB does not meet the WHO criteria for either Pre-XDR or XDR TB.
- Previously reported by NICD in quarterly reports as either RR-TB or MDR-TB depending on INH susceptibility



Effect of calendar time on BDQ resistance in cross-sectional study

Multivariable logistic regression model to assess whether risk of BDQ resistance had changed with time

Model included:

- province
- previous BDQ/CFZ exposure
- previous DR-TB treatment
- FLQ susceptibility

Quarter	BDQ-S (n=1,758)	BDQ-R (n=121)	Total (N=1,879)	Adjusted OR (95% CI)
2023Q2*	674 (93)	48 (7)	865	1
2023Q3	655 (94)	42 (6)	851	0.98 (0.77- 125)
2023Q4	429 (93)	31 (7)	592	1.09 (0.87 - 1.38)

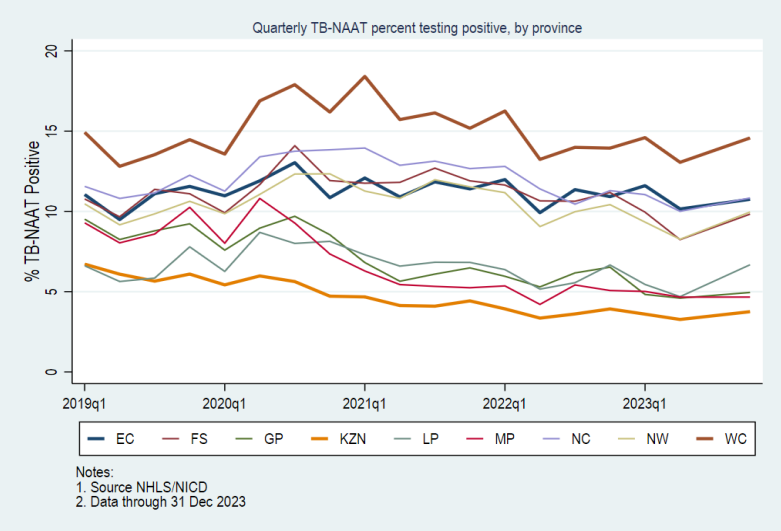
*includes 81 samples from March 2023

No indication yet of increasing risk of BDQ-R with time

Why the substantial increase in BDQ-R in the Western Cape?

- Both the higher coverage of BDQ pDST amongst patients with RR-TB and better linkages as a result of PHDC file numbers expected to result in a lower estimate of BDQ resistance compared to EC and KZN
- No substantial differences in timing or use of bedaquiline and/or clofazimine in the Western Cape compared to other provinces (data not shown).
- Higher force of infection with clonal expansion of BDQ-R strains?
  - Analysis of whole genome sequencing is underway
- Higher rates of LTFU on BDQ containing regimens in the Western Cape?
- Targeted contact tracing of BDQ-R contacts in the WC?

TB-NAAT Percent testing positive



% of patients LTFU with BDQ exposure	2019	2020	2021
EASTERN CAPE	16.0%	18.0%	18.4%
FREE STATE	10.7%	12.8%	11.5%
GAUTENG	15.6%	17.6%	17.7%
KWAZULU-NATAL	13.0%	14.2%	14.6%
LIMPOPO	8.7%	13.9%	10.8%
MPUMALANGA	6.8%	10.5%	9.0%
NORTH WEST	9.2%	8.9%	7.6%
NORTHERN CAPE	22.4%	17.0%	17.2%
WESTERN CAPE	22.6%	28.3%	26.0%
Grand Total	**15.0%**	**17.7%**	**17.3%**

Source: Prof Ndjeka from EDRWeb

Limitations and strengths

Limitations

- Routine data sources
  - Coverage of pDST BDQ amongst people with new RR-TB episodes remains <80% in all provinces
  - Residual linkage errors arising from probabilistic linkages within and between data sources despite manual review
  - Late arriving data, data quality and data completeness of routine data sources
- Too early to assess the culture conversion rates and treatment outcomes amongst those with bedaquiline resistance on BPaL or BPaL-L regimens

Strengths

- Trend analysis included a total of 9,666 BDQ pDST tests collected between 1 July 2019 and November 2023
- The cross-sectional analysis included pDST results from 2,308 individuals in three provinces with high coverage of DR-TB reflex guidelines

Conclusions

Test-level surveillance

- Substantial provincial differences in implementation of DR-TB reflex testing guidelines
  - Western Cape achieved higher coverage because of collection of two initial samples
  - Need to increase adherence to DR-TB reflex testing algorithm
- The median turnaround time of 56 days (IQR 40 – 72 days) remains too long to inform targeted contact tracing or patient management
- BDQ-R FLQ-S tests exceeded BDQ-R FLQ-R tests in more recent months

Cross-sectional analysis (EC, KZN, WC)

- Prevalence of BDQ resistance in the Western Cape (10.2%) substantially higher than EC (3.6%) and KZN (4.8%).
  - Analysis of whole genome sequencing data is underway
- Prior bedaquiline and clofazimine exposure is strongly associated with increased risk of bedaquiline resistance in keeping with prior studies
- More than half of those with BDQ resistance had no previous BDQ or CFZ exposure suggesting primary BDQ resistance
- Nearly two thirds of patients with BDQ resistance had FLQ sensitive TB
- Prevalence of linezolid resistance was very low (0.2%). Likely that pretomanid resistance is similarly low
- No evidence of increase in risk of BDQ resistance with calendar time yet
- Analysis of culture conversion and treatment outcomes will be conducted once sufficient data have accrued

Acknowledgements

- Patients and health care workers
- NHLS Laboratory staff
- NICD Surveillance Data Warehouse team:
  - Dr Trevor Bell, Dr Stanford Kwenda, and Morgan Mashinini
- Ayanda Shabalala, NICD CTB data manager

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Division of the National Health Laboratory Service

Tackling bedaquiline resistance emergence

Prof Nazir Ahmed Ismail

Head of Department: Clinical Microbiology and Infectious Diseases,
Wits University & National Health Laboratory Service

World TB Day 2024

The basics

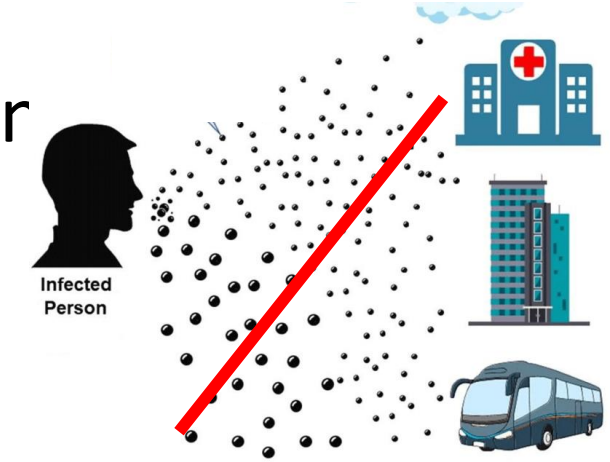
- *One cannot manage what one cannot measure*
- Bedaquiline is the backbone of all current MDR/RR-TB regimens
- Measuring the frequency of bedaquiline resistance and tracking changes over time is critical
- The surveillance system in SA is invaluable and usually lacking in many parts of the world
- The extension to include all RR-TB patients is positive however, improving coverage of the second specimen is needed

Tackling resistance – three prongs

1. Early identification
2. Early detection
3. Early and effective treatment

Tackling resistance emergence: Identify (1)

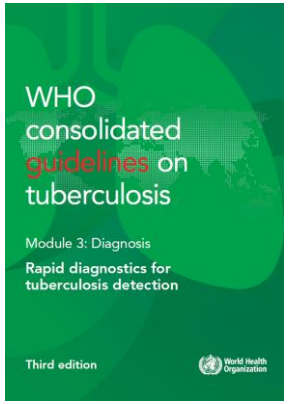
- Early identification of individuals on BDQ-based regimens who are lost to follow-up
  - Tracing such individuals and providing treatment adherence support
  - Understand and deal with underlying issues for LTFU
- Early identification of individuals at risk of BDQ resistance, i.e. cut person-to-person transmissior
  - Contact tracing of close contacts with BDQ-R
  - Granular interrogation of data to identify geographic areas of concern
  - Improve infection control efforts



Tackling resistance emergence: Detect (2)

- Early detection: adoption of new technologies such as **targeted Next Generation Sequencing**

Recently released by WHO



2. In people with bacteriologically confirmed rifampicin-resistant pulmonary TB disease, targeted NGS technologies may be used on respiratory samples to diagnose resistance to isoniazid, fluoroquinolones, bedaquiline, linezolid, clofazimine, pyrazinamide, ethambutol, amikacin and streptomycin rather than culture-based phenotypic drug susceptibility testing.
(Conditional recommendation, certainty of evidence high [isoniazid, fluoroquinolones and pyrazinamide], moderate [ethambutol], low [bedaquiline, linezolid, clofazimine and streptomycin], very low [amikacin])

https://www.who.int/publications/i/item/9789240089488

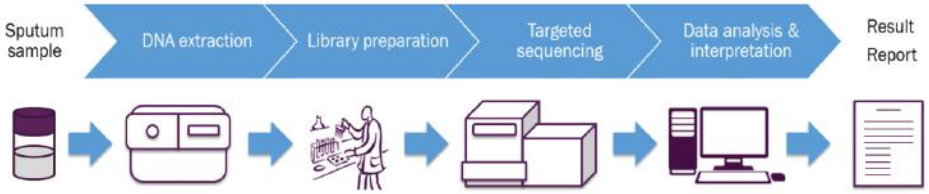


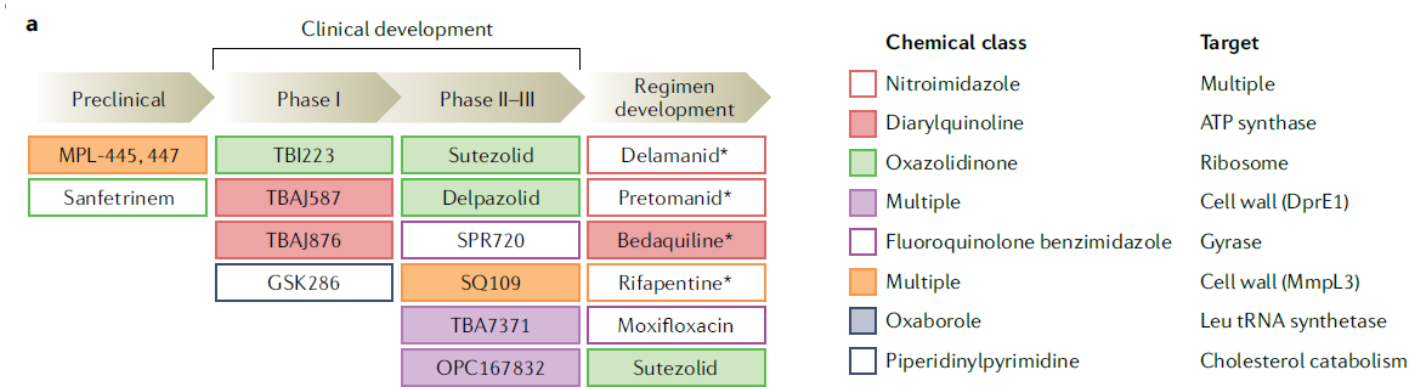
Table 2.3.6. The accuracy and certainty of evidence of targeted NGS for the detection of resistance to anti-TB drugs among bacteriologically confirmed rifampicin-resistant pulmonary TB

Drug	Reference standard	Accuracy % (95% CI)	Studies (persons)	Certainty in evidence
Isoniazid	Phenotypic DST	Se: 96.5 (93.8–99.2)	12 (1440)	High
	Phenotypic DST	Sp: 95.8 (91.8–99.8)	12 (517)	High
Levofloxacin	Phenotypic DST	Se: 95.8 (90.4–100)	6 (654)	Moderate
	Phenotypic DST	Sp: 96.0 (93.1–98.9)	7 (913)	High
Moxifloxacin	Phenotypic DST	Se: 96.5 (93.6–99.5)	6 (652)	High
	Phenotypic DST	Sp: 95.2 (91.0–99.4)	8 (921)	High
Pyrazinamide	Phenotypic DST+WGS	Se: 90.0 (86.8–93.2)	3 (346)	High
	Phenotypic DST+WGS	Sp: 98.6 (96.8–100)	3 (269)	High
Bedaquiline	Phenotypic DST	Se: 67.9 (42.6–93.2)	3 (31)	Low
	Phenotypic DST	Sp: 97.0 (94.3–99.7)	4 (519)	High
Linezolid	Phenotypic DST	Se: 68.9 (38.7–99.1)	4 (31)	Low
	Phenotypic DST	Sp: 99.8 (99.6–100)	6 (1093)	High
Clofazimine	Phenotypic DST	Se: 70.4 (34.6–100)	4 (36)	Low
	Phenotypic DST	Sp: 96.3 (93.2–99.3)	6 (789)	High

- Early detection: Regular **reporting of routine surveillance** data to program implementers for action

Tackling resistance emergence: Treat (3)

- Early and effective treatment:
  - NCAC to determine optimum regimen for such cases (tNGS will help)
  - R&D for new drug development



progress

https://doi.org/10.1038/s41579-022-00731-y

  - Clinical research on bedaquiline-free regimens
    - New studies are being developed: promote research in this area.
    - Encourage local studies to evaluate their utility for BDQ-R patients

Bedaquiline resistance in context

- New tests for rapid detection of resistance and drug regimens have changed the landscape over the last decade
  - The burden of laboratory-confirmed MDR/RR-TB was twice as high over a decade ago (2013:>15000 to 2023:<7000)
  - Successful treatment outcomes for XDR-TB used to be 20% a decade ago (2012 cohort), and now 53% (2020 cohort). Expected outcomes for BPaL are estimated at >80%
- Even with 10% bedaquiline resistance prevalence, 90% are still susceptible. Continued use of the all-oral short regimens is justified and important but needs to be managed based on risk factors and results
- Quick action is needed to address the bedaquiline resistance emergence before transmission is the primary mode
  - Early identification, detection and treatment
  - LTFU is a concern and needs specific attention

https://www.who.int/teams/global-tuberculosis-programme/data https://tbksp.org/en/node/568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WITWATERSRAND,
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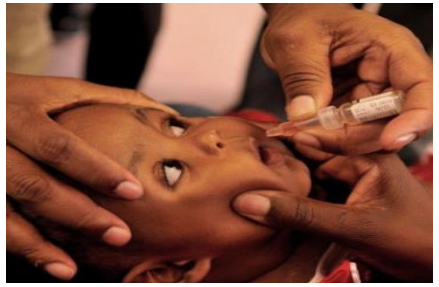
Thank you

TB SYMPOSIUM – MARCH 2024



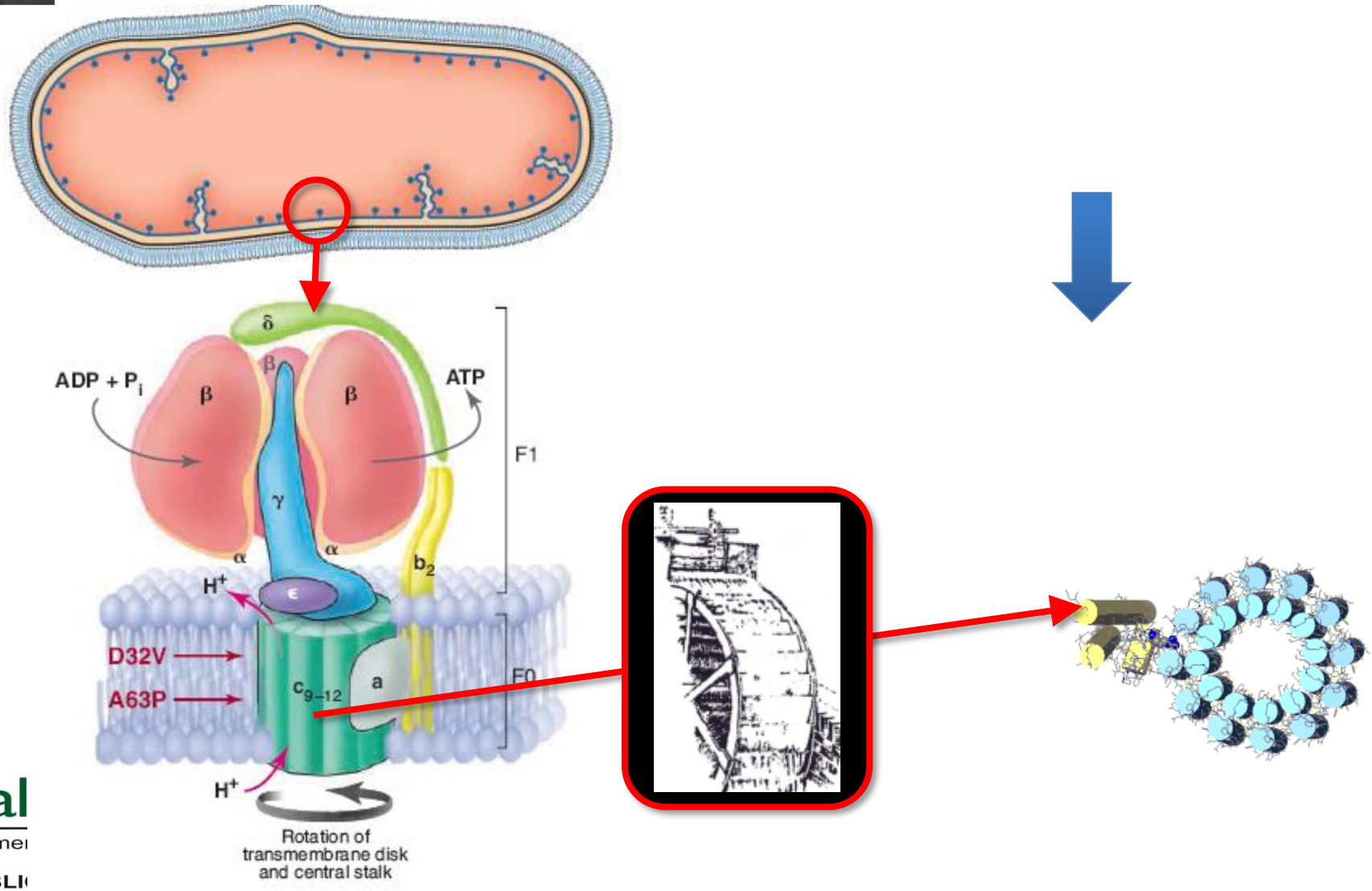
ADDRESSING BEDAQUILINE RESISTANCE IN SOUTH AFRICA

Prof. Norbert NDJEKA

23/03/2024

Outline

- Bedaquiline – mechanism of action
- TB Recovery Plan 3.0
- Addressing BDQ resistance
- Discussion



Adapted from Science 2005, 307, 214

TB Recovery Plan 3.0

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 demand for TB testing and treatment services through advocacy and communication	Increase the number of people identified with TB	Establish reliable linkage pathways	Improve retention in care	Strengthen TB prevention	Increase the use of data for monitoring and decision making
Implement costed SBCC plan	Conduct 3 million TB NAATs	Increase TB SMS notification coverage	Introduce shorter paediatric DS-TB regimen	Scale up treatment of latent TB infection	Streamline and integrate TB data systems
Implement advocacy and communication toolkit	Accelerate implementation of TUTT	Strengthen hospital – PHC TB patient referrals	Strengthen adherence counselling (including risk assessments for PWTB)	TB Vaccine – evidence review (NAGI)	Develop and share TB data platforms and products/ reports as appropriate
Support National and Provincial TB Caucuses	Scale up DCXR	Notify 221,941 TB patients	Support implementation of differentiated models of care	Address bedaquiline resistance	Develop national standards and metrics for TB care and data quality
Strengthen communication and coordination with private sector	Conduct ULAM implementation assessment	Increase proportion of children and adolescents notified	Advanced clinical care and mortality audits		Convene programme review meetings with implementation partners
			Conduct situational analysis of TB in small to medium sized mines		
			Support compensation of ex-miners through MBOD		

STRENGTHEN TB PROGRAMME IN THE MINES

Addressing BDQ and novel drug Resistance

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

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		

- Use the Q&A box to post questions for our panel of experts.

Acknowledgements:

- All Speakers
- The Knowledge Hub Unit (NDoH)
- The TB Control and Management Cluster (NDoH)
- The National Institute for Communicable Diseases (NICD)
- TB Technical Support Unit (Genesis Analytics)
- TB funding partners (Global Fund, USAID, PEPFAR, CDC, BMGF)

- Thank you for attending this webinar.
- For any enquiries regarding the webinar, please email: SAEDP@health.go.za
- The session recording and all the presentations will be shared on the Knowledge Hub – www.knowledgehub.health.gov.za

THANK YOU