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
<table>
<thead>
<tr>
<th>Time</th>
<th>Duration</th>
<th>Topic</th>
<th>Presented by</th>
</tr>
</thead>
<tbody>
<tr>
<td>09h00 – 09h15</td>
<td>15 min</td>
<td>Welcome, purpose and opening address by the Chair</td>
<td>Rev. Ramphelane Morewane</td>
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<tr>
<td>09h15 – 09h45</td>
<td>30 min</td>
<td>Patients’ dialogue</td>
<td>Cured DR-TB patients</td>
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<tr>
<td>09h45 – 10h15</td>
<td>30 min</td>
<td>The TB Recovery Plan 3.0 and BPaL-L implementation</td>
<td>Prof. Norbert Ndjeka</td>
</tr>
<tr>
<td>10h15 – 11h15</td>
<td>60 min</td>
<td>The emergence of bedaquiline resistance</td>
<td>Prof. Nazir Ismail, Dr Harry Moultrie, Dr Shaheed Vally Omar</td>
</tr>
<tr>
<td>11h15 – 11h45</td>
<td>30 min</td>
<td>Statement by WHO</td>
<td>Dr Owen Kaluwa</td>
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<tr>
<td>11h45 – 12h15</td>
<td>30 min</td>
<td>The plan to address bedaquiline resistance</td>
<td>Prof. Norbert Ndjeka</td>
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<td>12h15 – 12h50</td>
<td>35 min</td>
<td>Q&amp;A</td>
<td>Rev. Ramphelane Morewane</td>
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<tr>
<td>12h50 – 13h00</td>
<td>10 min</td>
<td>Closing remarks</td>
<td>Rev. Ramphelane Morewane</td>
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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.
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.
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
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
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
## Summary: Webinar attendance and engagement

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<td>TB Prevention</td>
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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**

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

Population 2022: 60 million

**Estimates of TB burden*, 2022**

<table>
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<tr>
<th></th>
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<th>(Rate per 100,000 population)</th>
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<tr>
<td>Total TB incidence</td>
<td>280,000 (182,000-398,000)</td>
<td>468 (304-665)</td>
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<tr>
<td>HIV-positive TB incidence</td>
<td>152,000 (99,000-217,000)</td>
<td>255 (166-362)</td>
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<tr>
<td>MDR/RR-TB incidence**</td>
<td>11,000 (6,700-16,000)</td>
<td>19 (11-26)</td>
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<td>HIV-negative TB mortality</td>
<td>23,000 (22,000-24,000)</td>
<td>39 (37-41)</td>
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<td>HIV-positive TB mortality</td>
<td>31,000 (9,900-64,000)</td>
<td>52 (17-107)</td>
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Incidence – Notification Gap Trends in South Africa

Incidence - Notification Gap Trends, South Africa

- WHO Incidence Estimates (2022)
- TB Notifications (DS + DR; new + relapse)

NUMBER OF PEOPLE

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<td>2022</td>
<td>214389</td>
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</table>
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
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.
We are going to prioritise most impactful interventions to support NSP implementation.

- 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 in mines
- Compensation ex-miners

STRENGTHEN TB PROGRAMME IN THE MINES
**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
DR-TB burden
DR-TB Notifications Trends with Proportion PLHIV

Adult RR/MDR-TB Patient Registrations, South Africa

Number of patients

Source: EDRWeb
DR-TB Treatment Outcomes

DR-TB Treatment Outcome Rates, South Africa

Success | LTFU | Died | Fail | NE | Cohort

- 2007: 37, 6, 30, 36, 37
- 2008: 36, 6, 30, 36, 36
- 2009: 18, 7, 18, 18, 18
- 2010: 23, 6, 18, 23, 23
- 2011: 47, 5, 18, 49, 53
- 2012: 49, 4, 18, 49, 53
- 2013: 53, 4, 18, 49, 53
- 2014: 55, 4, 19, 49, 55
- 2015: 60, 3, 19, 49, 55
- 2016: 64, 2, 15, 18, 55
- 2017: 65, 2, 17, 17, 55
- 2018: 61, 2, 17, 17, 55
- 2019: 61, 3, 18, 17, 55
- 2020: 61, 3, 18, 17, 55
- 2021: 61, 3, 18, 17, 55

Source: EDRWeb
Introduction of new TB drugs in SA
# NTP Priorities – Impactful Interventions

<table>
<thead>
<tr>
<th>Pillar I: Communicate &amp; Advocate</th>
<th>Pillar II: Find &amp; Link</th>
<th>Pillar III: Treat &amp; Retain</th>
<th>Pillar IV: Prevent &amp; Prepare</th>
<th>Pillar V: Monitor &amp; Assess</th>
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<tbody>
<tr>
<td>TB is a national priority across sectors</td>
<td>People with TB are linked to care within one week</td>
<td>People with TB have access to high-quality treatment &amp; support</td>
<td>TB prevention is valued as much as treatment</td>
<td>High quality data is used to guide decisions</td>
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<td><strong>Improved DR-TB Diagnostics</strong></td>
<td><strong>Shorter regimens</strong> - increased efficacy - Improved retention in care</td>
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NTP Contribution to Global and local policy

• South Africa's Commitment to TB Control

• Advocacy for TB control and prevention
  o World Health Assembly and Stop TB Partnership
  o 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
  o Xpert rollout
  o 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


Persistent 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, Hanette 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 Schnippel1, Cynthia Firnhaber2,4, Francesca Conradie2, Norbert Ndjeka3, Edina Sinanovic1

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

Norbert Ndjeka5, Kathryn Schnippel2, Iqbal Master3, Graeme Meintjes4,5, Gary Maartens6, Rodolfo Romero7, Xavier Padanilam8, Martin Enwerem9, Sunitha Chotoo9, Nalini Singh3, Jennifer Hughes9,10, Ebrahim Variava11,12,17,18,19, Hannelie Ferreira11, Julian te Riele13, Nazir Ismail14,15,16, Erika Mohr17, Nonkqubela Bantubani18, and Francesca Conradie19

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 Nhungen, Alena Skrahina,¹, Norbert Ndjeka,¹, Dennis Falzon,⁶, Matteo Zignol⁶

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. Conradiæ,⁴ M. Enwerem,⁵ H. Ferreira,⁶ N. Ismail,⁷ Y. Kock,¹ J. Master,⁵ G. Meintjes,⁹ X. Padaniðm,¹⁰ R. Romero,¹¹ H. S. Schaaf,² J. te Riele,¹² G. Maartens⁸

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,¹ Shaheed Vally Omar,² Harry Moultrie,³ Zaheda Bhyat, Francesca Conradiæ, M Enwerem, Hannetjie Ferreira, Jennifer Hughes,⁴ Lavinia Joseph, Yulene Kock, Yen Min Utseago, Cary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okazi, Xavier Padaniðm, Anja Reuter,⁶ Radek Sraïva, Minty van der Meulen, Farzana Ismail,¹ 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,¹ Jonathon R Campbell, Graeme Meintjes, Gary Maartens, H Simon Schaaf, Jennifer Hughes, Xavier Padaniðm, Anja Reuter, Rodolfo Romero, Farzana Ismail, Martin Enwerem, Hannetjie Ferreira, Francesca Conradiæ, Kogieulem Naidoo,⁵ Dick Menzies⁶

DR-TB Treatment Outcomes by Regimen Type

**Treatment Success By Regimen Type**

**LTFU By Regimen Type**

**Mortality By Regimen Type**

Source: EDRWeb
New Regimen – BPaL-L

Old 9-month regimen

BDQ  LZD  LFX  CFZ  INH HD  PZA  EMB

Pretomanid (Pa)

BDQ  LZD  LFX  Pretomanid (Pa)  New 6-month regimen = BPaL-L
TB IS CURABLE

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 + Lepofloxacin

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!
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

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<td><strong>269</strong></td>
<td><strong>241</strong></td>
<td><strong>334</strong></td>
<td><strong>1 176</strong></td>
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</table>

Source: EDRWeb
Conclusion

- SA has 60 million 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 Ndjeka1, Kathryn Schnippel2, Iqbal Master3, Graeme Meintjes4, Gary Maartens4, Rodolfo Romero5, Xavier Padanilam5, Martin Enwerem5, Sunita Chotoo6, Nalini Singh6, Jennifer Hughes6, Ebrahim Varia6,7, Hannelie Ferreira7, Julian Te Raleigh8, Nazir Ismail9,10,11,12, Erika Muhr13, Nonkquebela Bantubani9 and Francesca Conradie9

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: 89 (44.5%) had XDR-TB, 99 (49.3%) were female and the median age was 24 years (interquartile range 22–42). 134 (67.0%) were living with HIV; the median CD4+ count was 281 cells/μL (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. 144 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 to 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 >30 ms from baseline (n=11) and pansystolic 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 Schnippel1, Norbert Ndjeka1, Iqbal Master2, Graeme Meintjes3, Iqbal Master3, Nazir Ismail6, Jennifer Hughes6, Hannelie Ferreira7, Xavier Padanilam5, Rodolfo Romero5, Julian Te Raleigh8, Francesca Conradie9

Figure 4: Kaplan-Meier survival curves, by regimen inclusive of bedaquiline and drug resistance

The shaded area indicates 95% CI.
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

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

Kané Kaniga,* Daniela Maria Cirillo,* Sven Hoffner,* Nazir A. Ismail,*,† Devinder Kaur,‡ Nacer Louissi,* Beverly Ketchum,* Gayle E. Hoffman,* Amnaa Vence‡

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

Nazir A. Ismail †,#, Shabed V. Omar ‡, Lavania Joseph ‡, Netricia Govender ‡, Linsay Blows ‡, Farzana Ismail †,‡, Hendrik Koornhof ‡,‡, Andries W. Dreyer ‡, Koné Kaniga *, Norbert Ndjeka •

* National Institute for Communicable Diseases, Centre for Tuberculosis, Johannesburg, South Africa
‡ Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa
• National Research & Development, Tshwane, GP, United States
# National Department of Health, Tuberculosis Control and Management Unit, Pretoria, South Africa

A Multimethod, Multicountry Evaluation of Breakpoints for Bedaquiline Resistance Determination

© Nazir Ahmed Ismail, Akio Anna, Emanuele Borroni, Daniela Maria Cirillo, Christel Desmaretz, Rumina Hasan, Satoshi Mitani, Sadia Shakoor, Gabriela Torrea, Kané Kaniga, Shaheed V. Omar
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
BDQ Resistance Surveillance 2015 -2019

**BDQ Resistance associated with**

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

- **3.8%** BDQ-Resistance at baseline
- **2.3%** developed BDQ Resistance during treatment
- **Rv0678** sole genetic basis of resistance
Genomic Surveillance of Drug Resistant TB 2019 – 2024 (interim analysis)
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

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)
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
• 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
• 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**

- 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

### Table: Monthly joint BDQ and FLQ susceptibility test results

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

Source: NICD
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

<table>
<thead>
<tr>
<th>Quarter</th>
<th>BDQ-S (n=1,758)</th>
<th>BDQ-R (n=121)</th>
<th>Total (N=1,879)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2023Q2*</td>
<td>674 (93)</td>
<td>48 (7)</td>
<td>865</td>
<td>1</td>
</tr>
<tr>
<td>2023Q3</td>
<td>655 (94)</td>
<td>42 (6)</td>
<td>851</td>
<td>0.98 (0.77-1.25)</td>
</tr>
<tr>
<td>2023Q4</td>
<td>429 (93)</td>
<td>31 (7)</td>
<td>592</td>
<td>1.09 (0.87-1.38)</td>
</tr>
</tbody>
</table>

*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?
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
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 transmission
  • 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

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

• 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

• 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

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

Thank you
ADDRESSING BEDAQUILINE RESISTANCE IN SOUTH AFRICA

Prof. Norbert NDJEKA

23/03/2024
Bedaquiline – mechanism of action
TB Recovery Plan 3.0
Addressing BDQ resistance
Discussion
Adapted from Science 2005, 307, 214
TB Recovery Plan 3.0
<table>
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<tr>
<th>Pillar I: Communicate &amp; Advocate</th>
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<th>Pillar III: Treat &amp; Retain</th>
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<td>TB is a national priority across sectors</td>
<td>People with TB are linked to care within one week</td>
<td>People with TB have access to high quality treatment &amp; support</td>
<td>TB prevention is valued as much as treatment</td>
<td>Provinces use high quality data to guide decisions</td>
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- 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

Support communication and coordination with private sector
- Conduct ULAM implementation assessment
- Increase proportion of children and adolescents notified
- Conduct situational analysis of TB in small to medium sized mines
- Convene programme review meetings with implementation partners
- Support compensation of ex-miners through MBOD

- Advanced clinical care and mortality audits
- Convene programme review meetings with implementation partners
- Support compensation of ex-miners through MBOD
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.
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<td>Create awareness about BDQ resistance</td>
<td>Accelerate diagnosis of BDQ resistance</td>
<td>Strengthen treatment for BDQ-resistant TB</td>
<td>Prevent BDQ resistance</td>
<td>Improve quality of data for decision making</td>
</tr>
<tr>
<td>Involve health leaders and senior managers as allies and advocates for innovation</td>
<td>Urgent introduction of targeted new generation sequencing, starting with most affected areas</td>
<td>Review inclusion criteria for BPaL-L regimen</td>
<td>Implement study to strengthen adherence to BPaL-L</td>
<td>Measure and monitor number of patients with BDQ resistance</td>
</tr>
<tr>
<td>Improve awareness in provinces and ensure routine testing of BDQ resistance</td>
<td>Diversification of TB testing (TB NAAT) to be finalized with introduction of collection of 2 samples upfront</td>
<td>Submit all BDQ-resistant patients to the NCAC for regimen design</td>
<td>Routinely establish previous TB treatment and drug exposure history for all RR-TB patients</td>
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<td>Encourage multisectoral action (research, education, new drug development, etc.)</td>
<td>Ensure all RR-TB patients started on treatment get tested using the XDR-cartridge</td>
<td>NCAC to review BDQ-sparing regimens e.g. 9DLLZ</td>
<td>Measure and monitor treatment outcomes for patients with BDQ resistance</td>
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<td>Flag burden of antimicrobial resistance and importance of treatment adherence</td>
<td>Strengthen the use of extended drug susceptibility testing where necessary</td>
<td>Strengthen adherence to BPaL-L and other individualized BDQ-containing regimens</td>
<td>Collaborate with WHO – data sharing and more extensive analysis</td>
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<td>Disseminate data among healthcare workers in South Africa and globally</td>
<td>Improve SMS notification to individuals who test for TB</td>
<td>Introduce new clinical trials with new anti-TB agents</td>
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• Use the Q&A box to post questions for our panel of experts.
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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