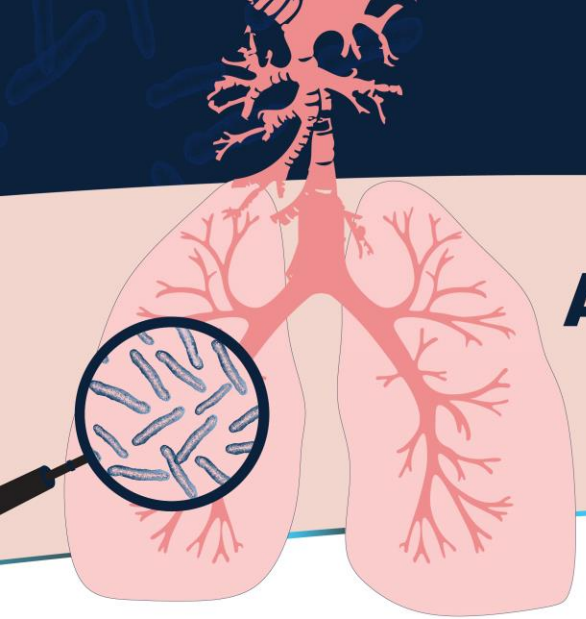


Accelerating progress to end TB

8th SA TB Conference
04 - 07June 2024
Durban ICC

# DESCRIPTION OF MUTATIONS DETECTED IN GENETIC TARGETS ASSOCIATED WITH TUBERCULOSIS RESISTANCE TO "NEW AND REPURPOSED DRUGS" FROM SURVEILLANCE SITES IN SOUTH AFRICA

**Shaheed Vally Omar,** Farzana Ismail, William L. Coggin, Patricia Hall-Eidson, Halima Said, Dumsani Ngcamu, Rhulani Mageza, Adeboye Adelekan & Lavania Joseph

*Centre for Tuberculosis, National TB Reference Laboratory, WHO TB Supranational Reference Laboratory Network, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa*
*US Centers for Disease and Control and Prevention, Division of Global HIV and TB, Atlanta, Georgia, USA*

## BACKGROUND

- Bedaquiline (BDQ), pretomanid (Pa), linezolid (LZD) and delamanid (DLM) are generally referred to as "new and repurposed drugs“ recommended by the WHO for the management of drug-resistant TB
    - BDQ, Pa and DLM are the first novel drugs developed exclusively for TB after 40 years
    - LZD primarily used for the treatment of resistant Gram positive bacteria – has been repurposed for drug resistant as it has been shown to improve DR-TB patient outcomes
- Several genetic targets have been associated with drugs resistance. These include;
    - **BDQ -** *Rv0678*, *atpE*, *pepQ mmpL5*, *mmpS5* and *Rv1979c*
    - **LZD -** *rplC* and *rrl*
    - **DLM and Pa -** *ddn*, *fbiA*, *fbiB*, *fbiC* and *fgd1* (less well characterized)
- To date no commercial rapid molecular assays are available for the detection of resistance to these drugs
- The WHO have recently recommended in 2023 the use of targeted Next Generation Sequencing for this purpose

## INTRODUCTION

- Until recently, interpretation of sequencing data relied on the use of publically available databases or literature review (non-standardised)
- The first edition of the WHO Mutation Catalogue was published in 2021 was the first harmonised guide to classify mutations, however, no resistance gradings published for new and repurposed drugs
- The second edition of the catalogue published in November 2023 and aimed to supplement the existing database with resistance variants for the "new and repurposed drugs“
- Given the expanding use of these drugs, active surveillance to monitor the emergence of resistance is critical for preserving their efficacy and the for the development of novel rapid diagnostics

**AIM** - We describe mutations detected and WHO grading of genetic targets associated with drug resistance to the new and repurposed drugs using whole genome sequencing (WGS).

## METHODS

- As part of a larger study assessing the application of WGS to enhance microbiological and epidemiological surveillance in selected districts of South Africa, DR-TB isolates were prospectively collected between 2020 and 2022.
- WGS was performed using the Illumina sequencing platform (NextSeq 550/1000) (Illumina, USA)
- Bioinformatics analysis for mutation analysis was performed using CLC Genomics Workbench (Qiagen, Venlo, The Netherlands)
- Mutations with a minimum frequency of 90% (fixed) were reported.
- Mutations were graded using the WHO Mutation Catalogues (Version 1 and 2) based on their association with drug susceptibility.

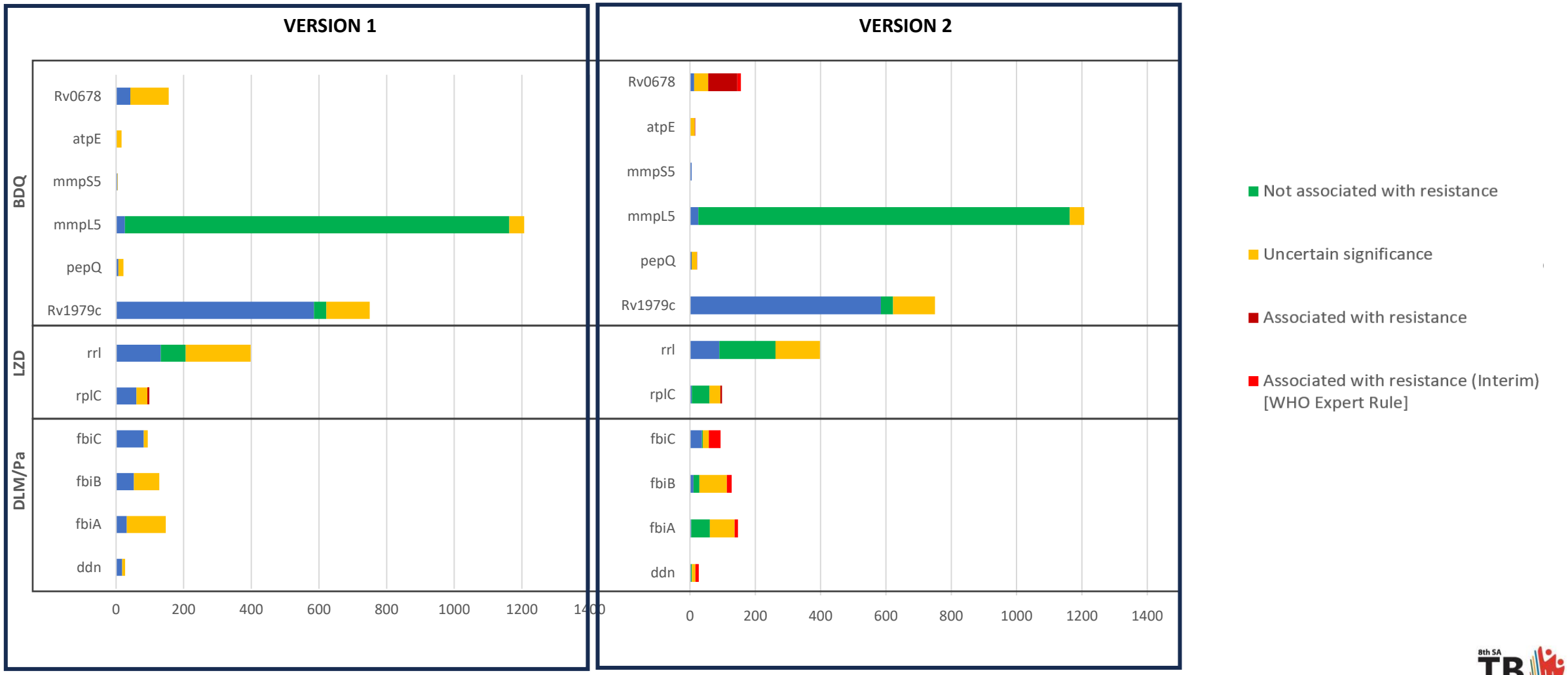
## RESULTS

- A total of **2523** genomes (unique isolate) we included in this study
- Mutation analysis generated **5396** mutations across all genetic targets
- A high level of heterogeneity and frequency of mutations was observed for each genetic target, with the lowest for mmpS5 (n=5) and the highest for fgd1 (n=2361) (Table 1)
- Of the 2523 isolates, 68.5% had 1924 mutations in fgd1 gene only and the remaining isolates harboured 3523 mutations across all the genetic targets investigated.

**Table 1:** Total number of mutations observed in genetic targets associated with the "new and repurposed drugs"

| | Gene | Number of mutations observed |
|---|---|---|
| BDQ | atpE | 16 |
| | mmpL5 | 1207 |
| | mmpS5 | 5 |
| | pepQ | 22 |
| | Rv0678 | 156 |
| | Rv1979c | 789 |
| LZD | rplC | 99 |
| | rrl | 398 |
| DLM/Pa | ddn | 27 |
| | fbiA | 147 |
| | fbiB | 128 |
| | fbiC | 94 |
| | fgd1 | 2361 |

# Mutation gradings for genetic targets associated with the "new and repurposed drugs“ using the WHO Mutation Catalogues (n=2523)



# Percentage of mutations assigned gradings by the WHO Catalogue of mutation

| | n | WHO Version 1 | WHO Version 2 | Grading |
|---|---|---|---|---|
| Rv0678 | 156 | 73.1% | 91.7% | ↑ 18.6% |
| atpE | 16 | 100.0% | 100.0% | – |
| Rv1979c | 789 | 22.0% | 22.0% | – |
| pepQ | 22 | 68.2% | 77.3% | ↑ 9.1% |
| mmpL5 | 1207 | 97.8% | 97.8% | – |
| mmpS5 | 5 | 20.0% | 20.0% | – |
| rplC | 99 | 38.8% | 93.9% | ↑ 55.1% |
| rrl | 398 | 66.8% | 77.4% | ↑ 10.6% |
| ddn | 27 | 33.3% | 88.9% | ↑ 55.6% |
| fbiA | 147 | 78.2% | 97.3% | ↑ 19.0% |
| fbiB | 128 | 58.6% | 91.4% | ↑ 32.8% |
| fbiC | 94 | 12.8% | 60.6% | ↑ 47.9% |
| fgd1 | 2361 | 6.3% | 96.0% | ↑ 89.7% |

## CONCLUSION

- A high level of genetic diversity is observed for targets associated with resistance to the “new and repurposed drugs“
- Using the second edition of the mutation catalogue, gradings could be assigned to 83.7% of mutations, compared to 39.9% using the original catalogue
- Ongoing efforts to improve the mutation catalogue requires strengthening to improve our understanding on the association of mutation with drug resistance to new and repurposed drugs


YES
WE CAN
END TB