Drug Resistance Mutations and Tuberculosis Mortality in High-burden Countries

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Veronika W. Skrivankova[1], Sebastien Gagneux[2,3], Erik C. Boettger[4] and **Matthias Egger**[1,5] for the IeDEA TB Genomics Group ‡
[1]University of Bern, Bern, Switzerland; [2]University of Basel, Basel, Switzerland; [3]Swiss Tropical and Public Health Institute, Basel, Switzerland;
[4]Swiss National Center for Mycobacteria, Zurich, Switzerland; [5]University of Cape Town, Cape Town, South Africa

BACKGROUND

- Global emergence of **drug resistance (DR)** in *Mycobacterium tuberculosis (MTB)* threatens the WHO target to end the tuberculosis (TB) epidemics by 2030[1].
- **Inaccurate DR testing** often leads to inadequate TB treatment, and is hence associated with increased mortality among TB patients[2].

The future of DR testing in *MTB* relies on **rapid molecular tests** to guide the prescription of adequate treatment regimens, and thereby maximise treatment success.

METHODS

We assessed the **impact of drug resistance mutations (DRM) on mortality** in HIV+ and HIV- patients with TB.

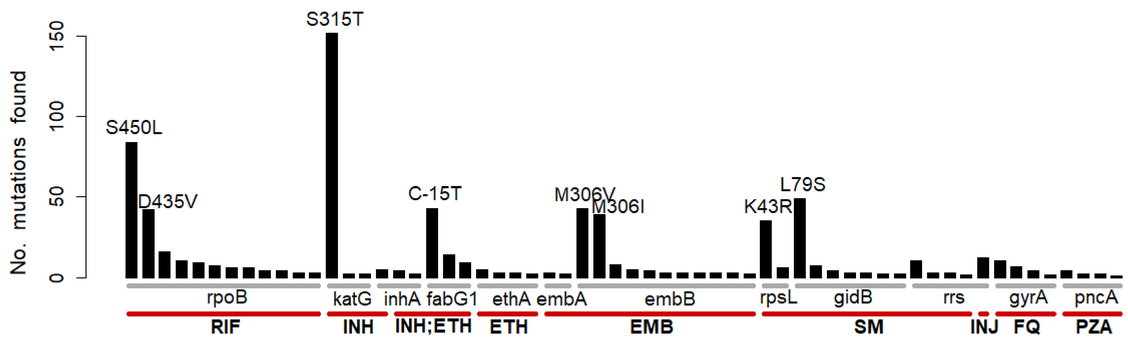
- Design: Prospective recruitment of adult TB patients (2013 – 2016) in seven high TB burden countries: Kenya, South Africa, Democratic Republic of the Congo, Nigeria, Ivory Coast, Peru and Thailand. Sampling was stratified by HIV and local DR status.
- Data: *MTB* isolates, patient-level characteristics and mortality during TB treatment, local DR test results.
- Mutations: We used whole genome sequencing (WGS) to identify the most common DRM and the DR missed by local testing.
- Mortality: We estimated odds ratios for mortality during TB treatment associated with DRM. A separate logistic regression model compared each group of DRM (grouped by conferred DR) to the pan-susceptible *MTB*. All models were adjusted for age, sex and HIV status.

RESULTS

We included *n* = 582 adult patients diagnosed with TB (247 HIV+ and 335 HIV-); 60 patients died during treatment. Local DR testing was based on Xpert, Line-probe assays and/or culture. Whole genome sequences of *MTB* isolates were scanned for high-confidence DRM.

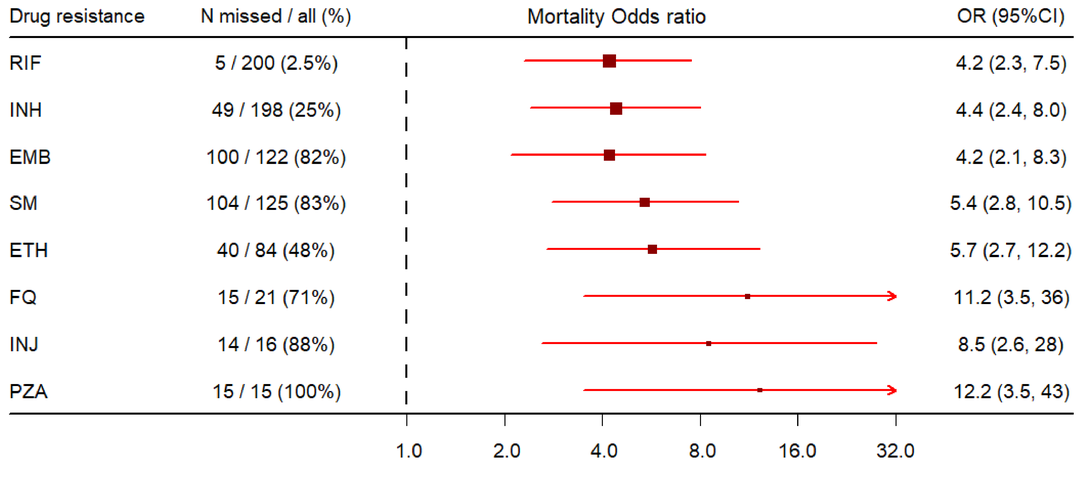
In high TB burden countries, TB drug resistance is often missed, potentially leading to increased mortality.

- **DR mutations found in our sample (n > 1) – ordered by *MTB* genes and conferred DR**



RIF Rifampicin; INH Isoniazid; EMB Ethambutol; SM Streptomycin; ETH Ethionamide; FQ Fluoroquinolones; INJ Injectable drugs; PZA Pyrazinamide

- **Mortality during TB treatment associated with DRM (grouped by DR)**



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- Proportion of DR missed by the local DR tests varied across TB drugs from 2.5% (RIF) to 100% (PZA).
- Mortality during TB treatment in patients with pan-susceptible *MTB* was 6%.
- Odds ratios for mortality associated with DR genetically conferred by DRM ranged from 4.2 to 12.2.

CONCLUSIONS

- We identified several DRM associated with increased mortality in TB patients from 7 high-burden countries.
- Many of the conferred DR were missed by local DR tests, potentially leading to inadequate treatment.

Our results highlight the critical need for **more detailed molecular point-of-care DR tests** for *MTB* that cover a broader range of DRM and thus could contribute to more effective treatment and reduced mortality among patients with DR TB.

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ADDITIONAL INFORMATION

Contact: Veronika Skrivankova, veronika.skrivankova@ispm.unibe.ch; www.iedea-sa.org

‡ **IeDEA TB Genomincs Group (alphabetically):** Alashle Abimiku[1], Anchalee Avihingsanon[2], Marie Ballif[3], Erik C Boettger[4], E Jane Carter[5], Jimena Collantes Loo[6], Helen Cox[7], Matthias Egger[3,7], Lukas Fenner[3], Sebastien Gagneux[8,9], Chloe Loiseau[8,9], Olivier Marcy[10], Neesha Rockwood[11], Veronika W Skrivankova[3], Robert J Wilkinson[7,11], Marcel Yotebieng[12], Kathrin Zürcher[3]

[1]Institute of Human Virology, Abuja, Nigeria; [2]HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]University of Bern, Bern, Switzerland; [4]Swiss National Center for Mycobacteria, Zurich, Switzerland; [5]Moi University School of Medicine, Eldoret, Kenya; [6]Universidad Peruana Cayetano Heredia, Lima, Peru; [7]University of Cape Town, Cape Town, South Africa; [8]Swiss Tropical and Public Health Institute, Basel, Switzerland; [9]University of Basel, Basel, Switzerland; [10]Bordeaux Population Health Research Center, Bordeaux, France; [11]Imperial College London, UK; [12]Ohio State University, College of Public Health, Columbus, OH, USA

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