



Swiss TPH



Ecology and Evolution of MDR
M. tuberculosis

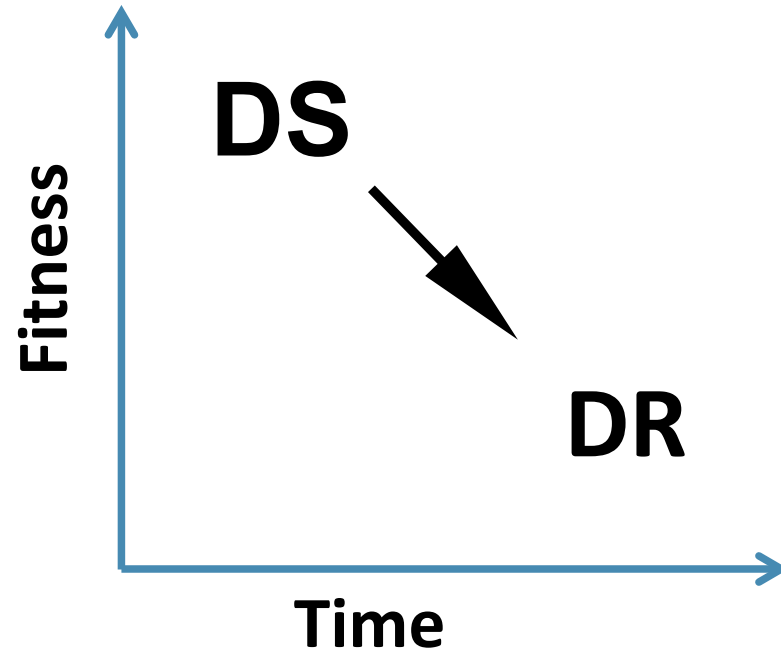
Swiss TPH TB Symposium

Sébastien Gagneux, PhD 21st – 22nd March 2023

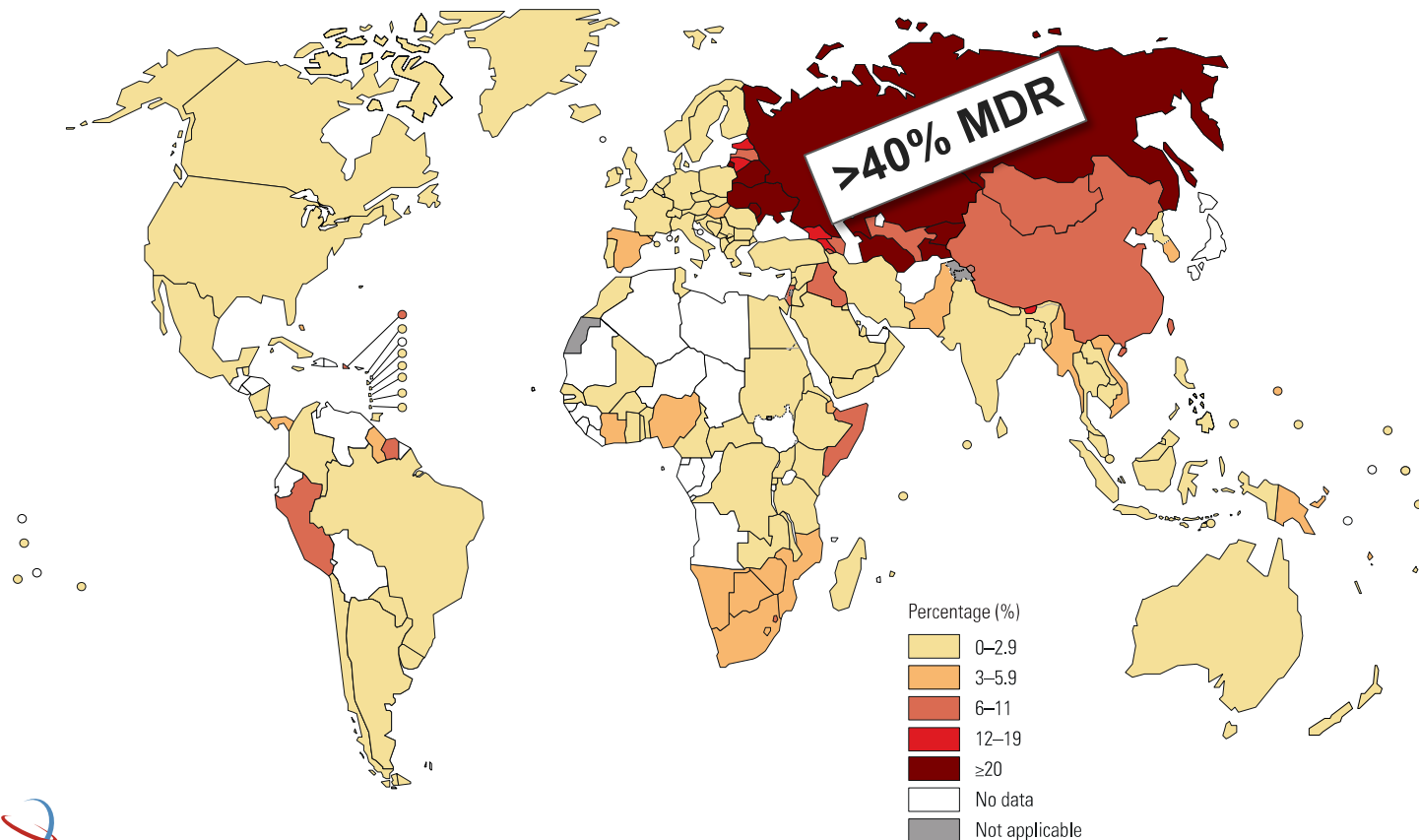
WHO TB Report 2022:

- 10.6 million new TB cases
- “Only” **3%** of global TB is MDR/XDR-TB

DOGMA: “Drug-Resistant Bacteria are Less Fit”

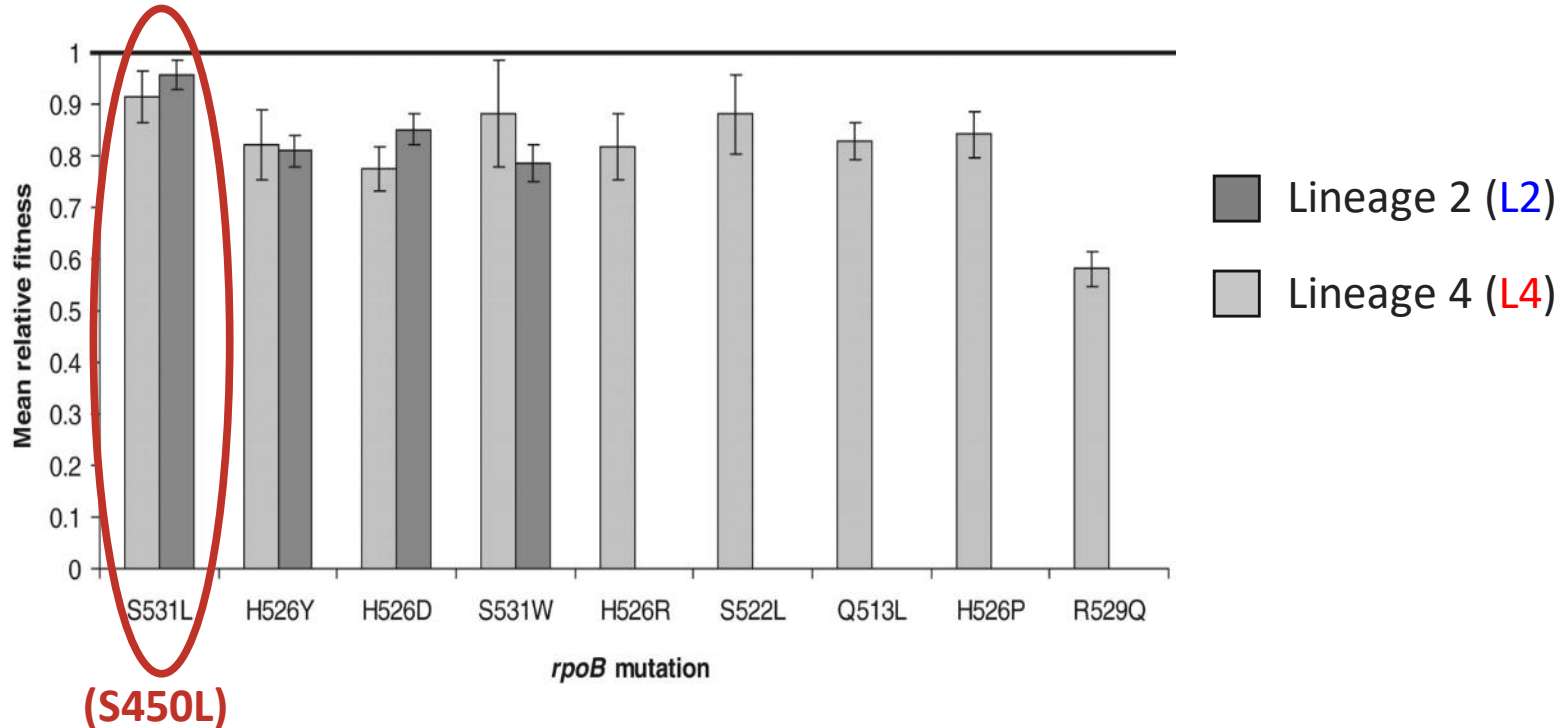


“Hot-spots” of MDR-TB (WHO TB Report 2020)



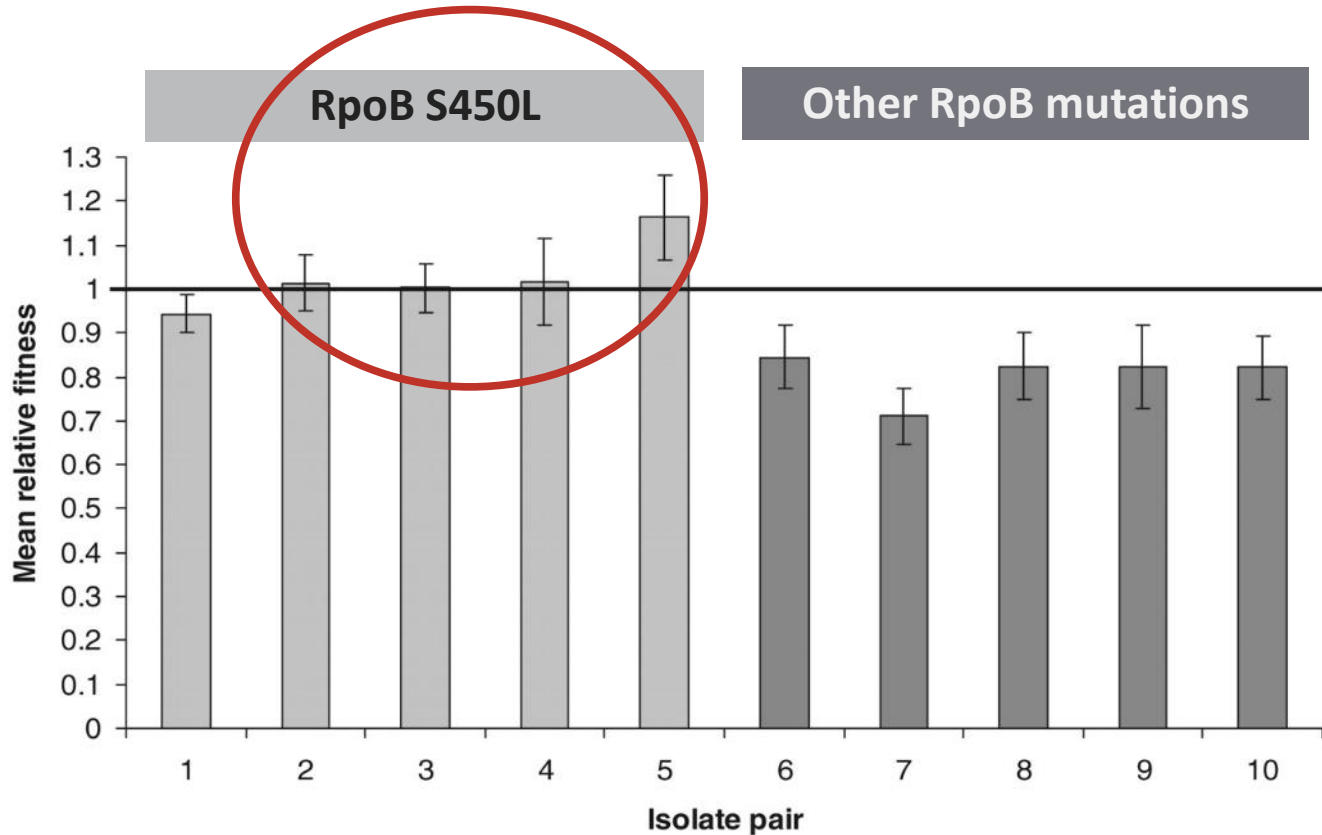
All Lab-derived RIF^R Strains Have a Fitness Cost *in vitro*

**Lab
strains**

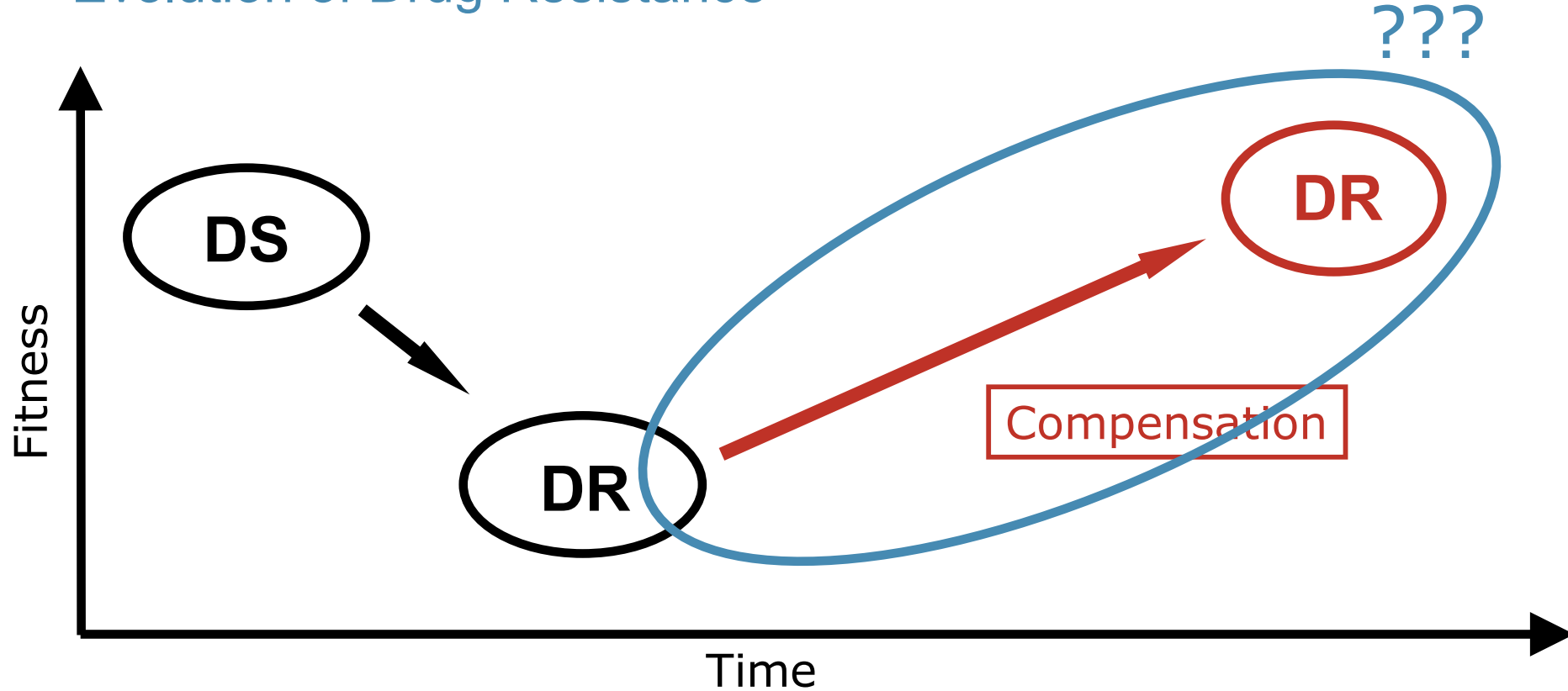


Some Clinical Strains with RpoB S450L Have No Fitness Cost

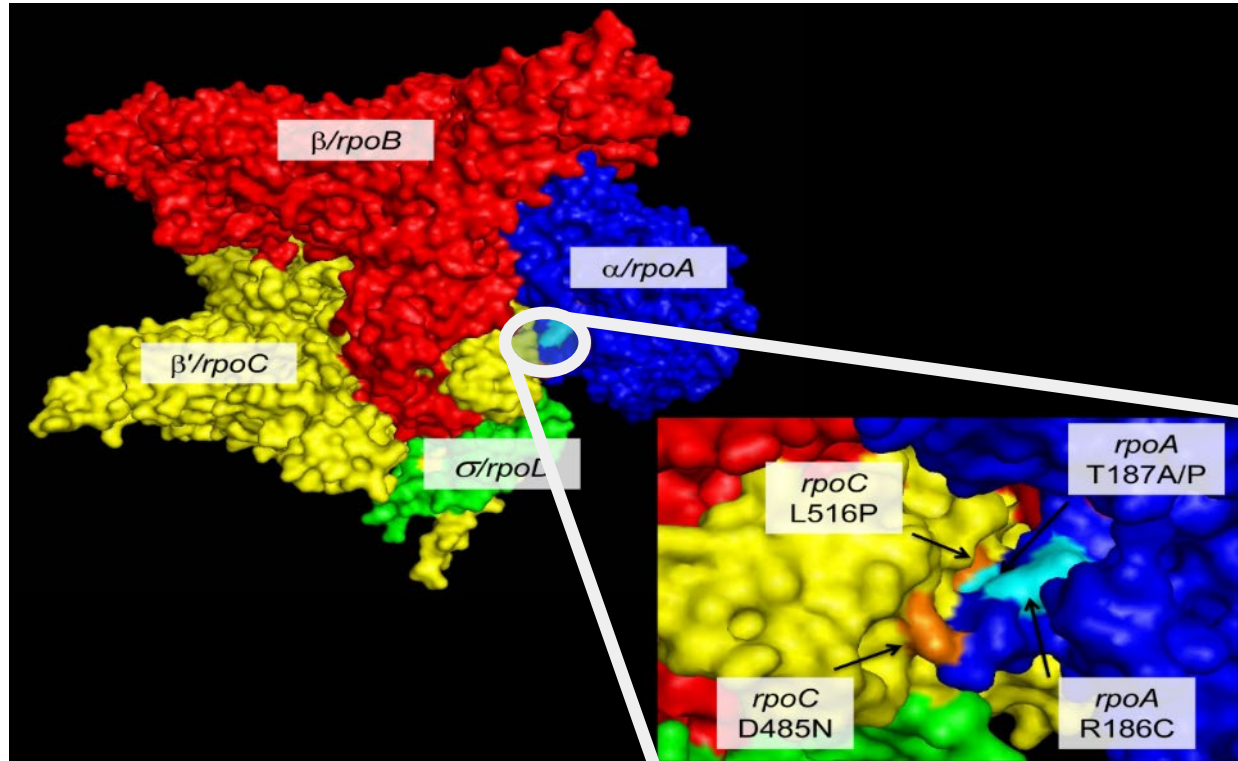
**Clinical
strains**



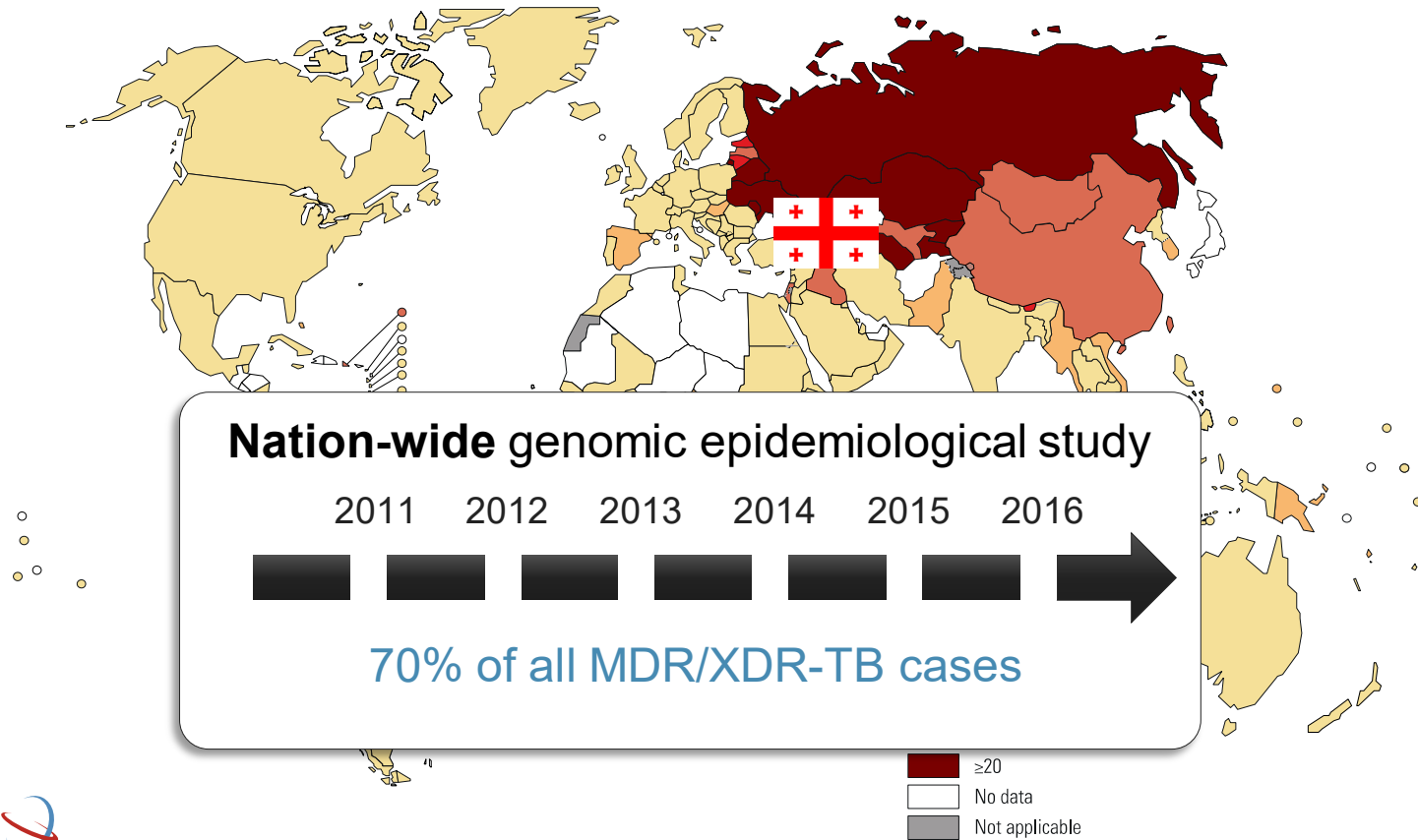
Evolution of Drug Resistance



Compensatory Mutations in the RNA Polymerase of RIF^R *Mtb*



Nationwide Study in Georgia



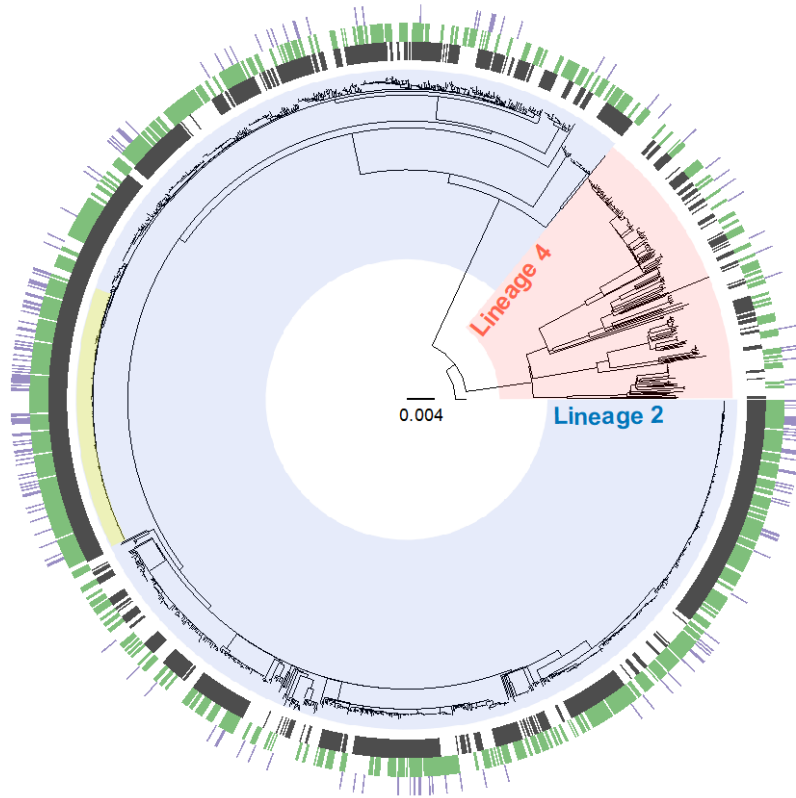


Sebastian
Gygli



Chloé
Loiseau

Phylogenetic tree of 1,613 MDR genomes



■ Compensated (69%)

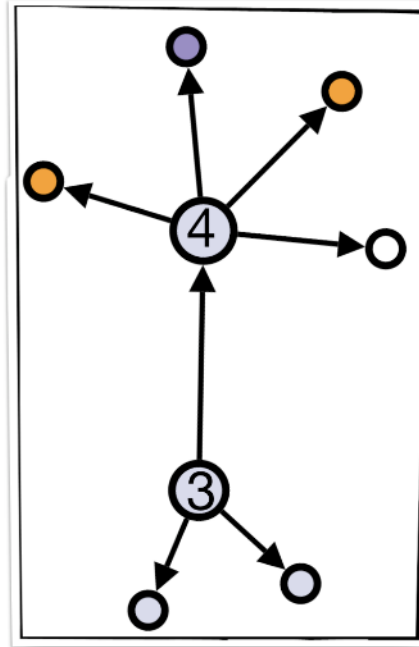
Factors Associated with Transmission of MDR Strains

Compensatory mutations



$$\text{IRR}_{\text{adj}} \ 1.34$$
$$\text{CI}_{95} = 1.05 - 1.71$$

Number of secondary cases



Lineage 2



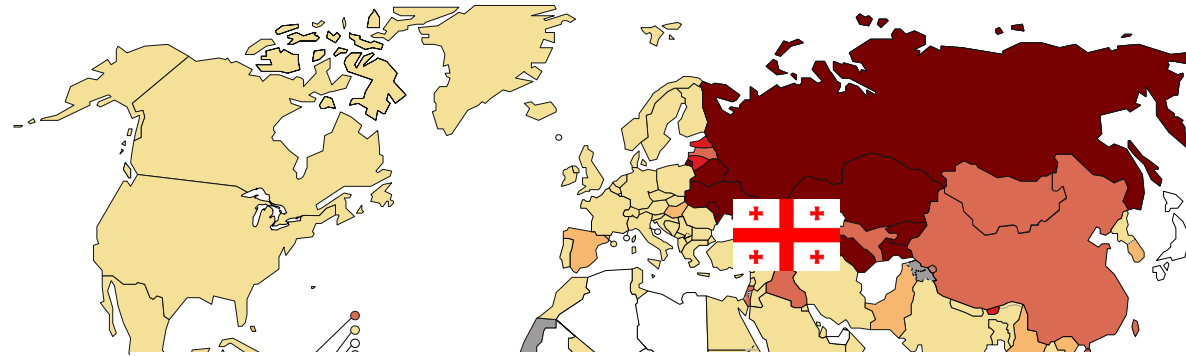
$$\text{IRR}_{\text{adj}} \ 2.24$$
$$\text{CI}_{95} = 1.48 - 3.53$$

Incarcerated individual

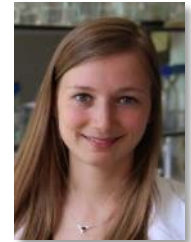
$$\text{IRR}_{\text{adj}} \ 1.42$$
$$\text{CI}_{95} = 1.11 - 1.81$$



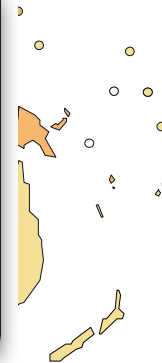
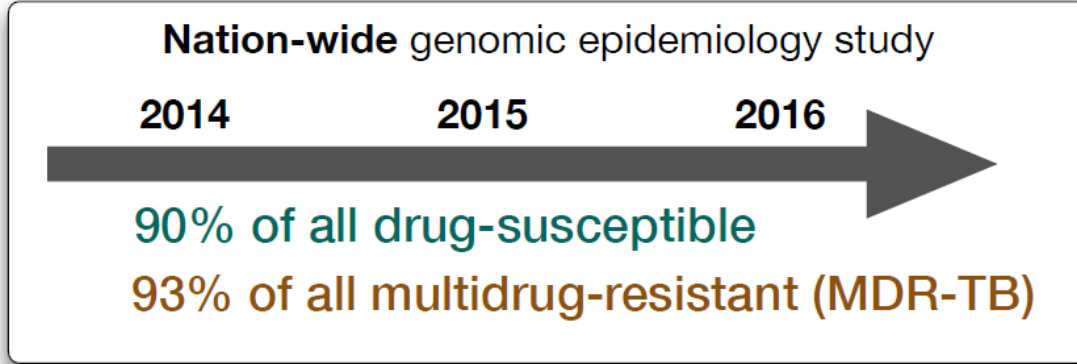
Adding the Drug-Susceptible Strains



Tanja Stadler



Ethel Windels



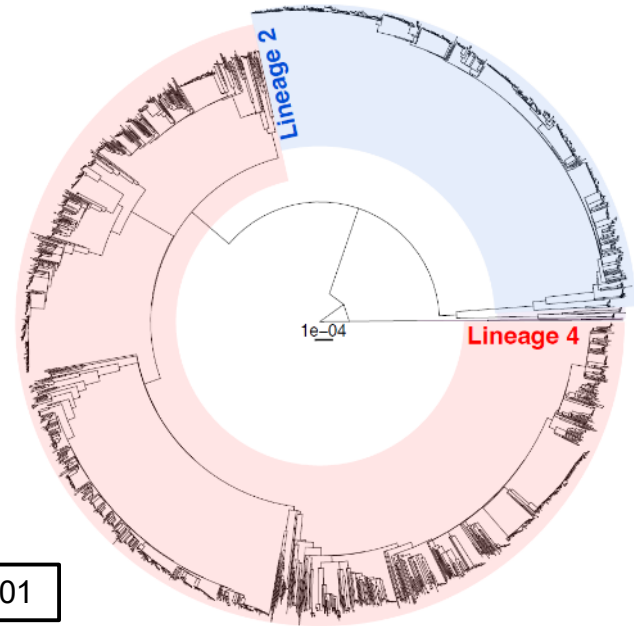
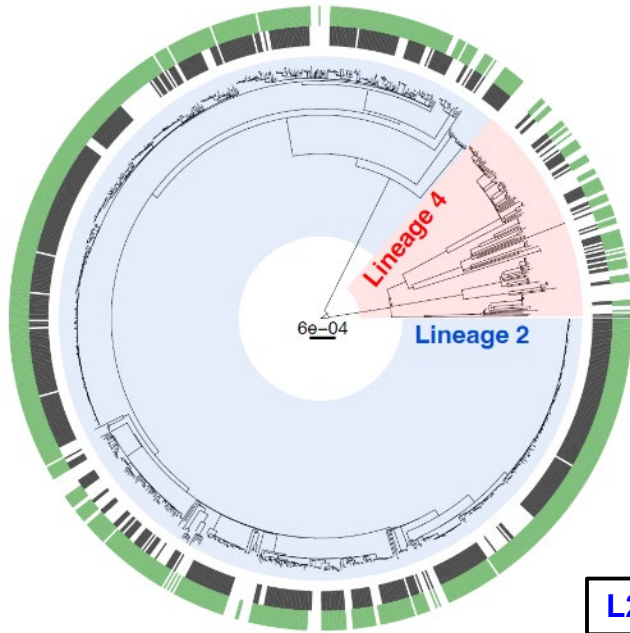
Chloé Loiseau



MDR-TB is Associated with Lineage 2

983 MDR genomes

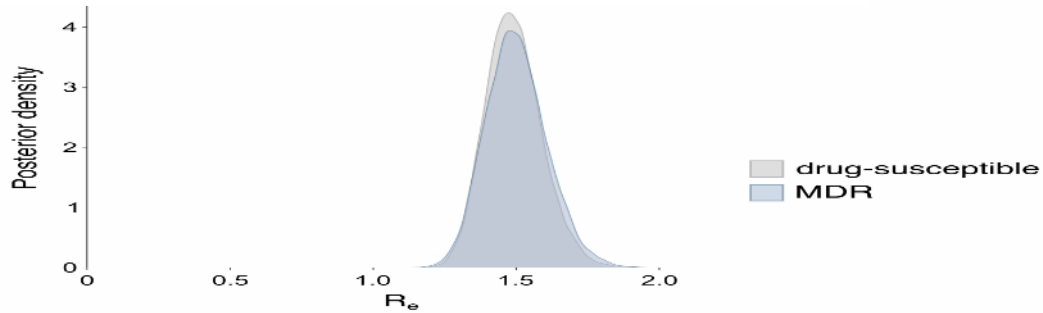
2,982 pan-susceptible genomes



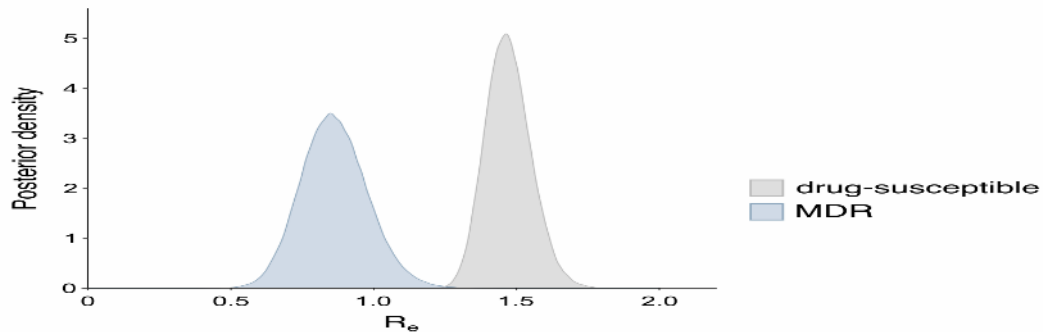
L2 versus L4: χ^2 , $p < 0.001$

MDR-TB in **L2** carries No Cost in Transmission Fitness

Lineage 2

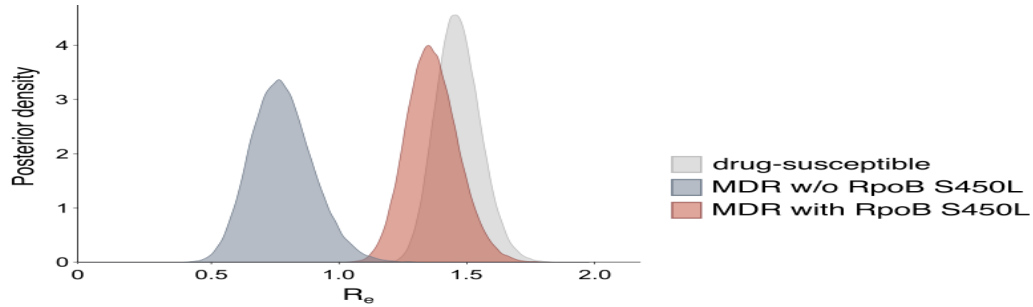


Lineage 4

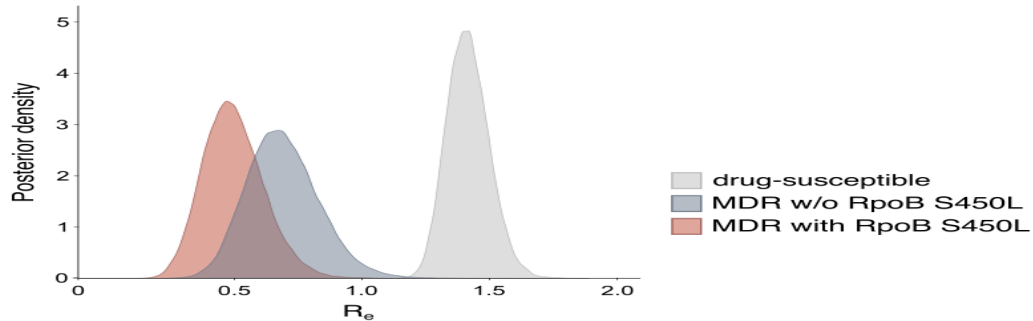


Effect of Lineage and RpoB Mutation

Lineage 2

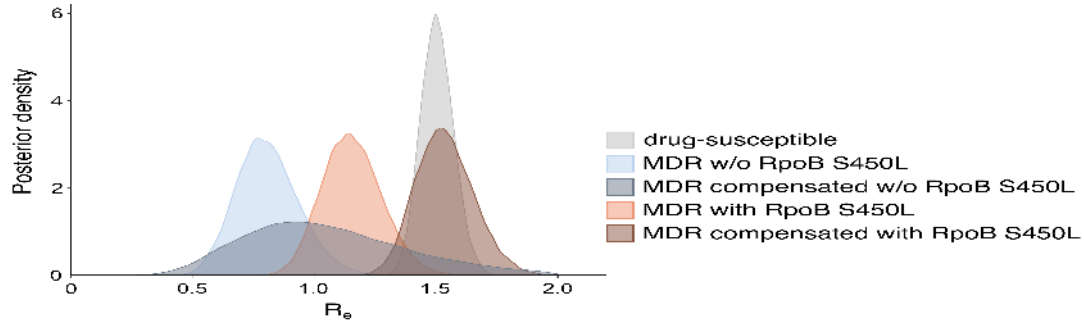


Lineage 4

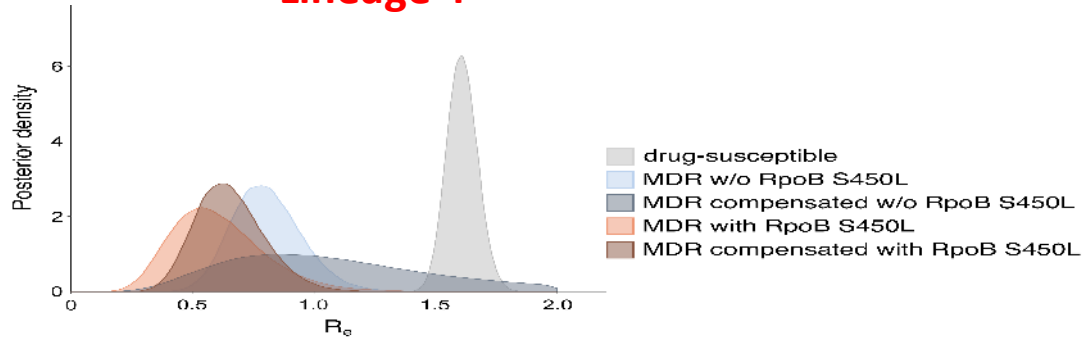


Effect of Lineage, RpoB Mutation and Compensation

Lineage 2



Lineage 4



Validation Study in Kayalitsha, South Africa



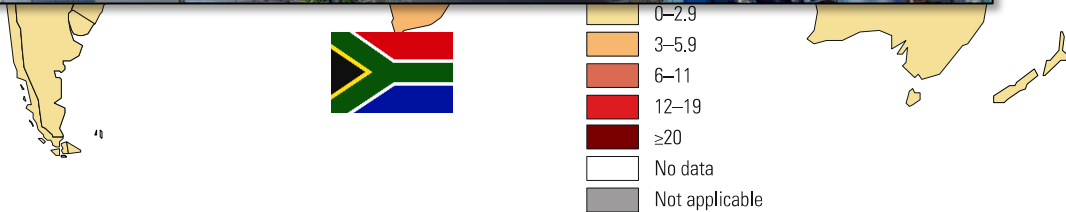
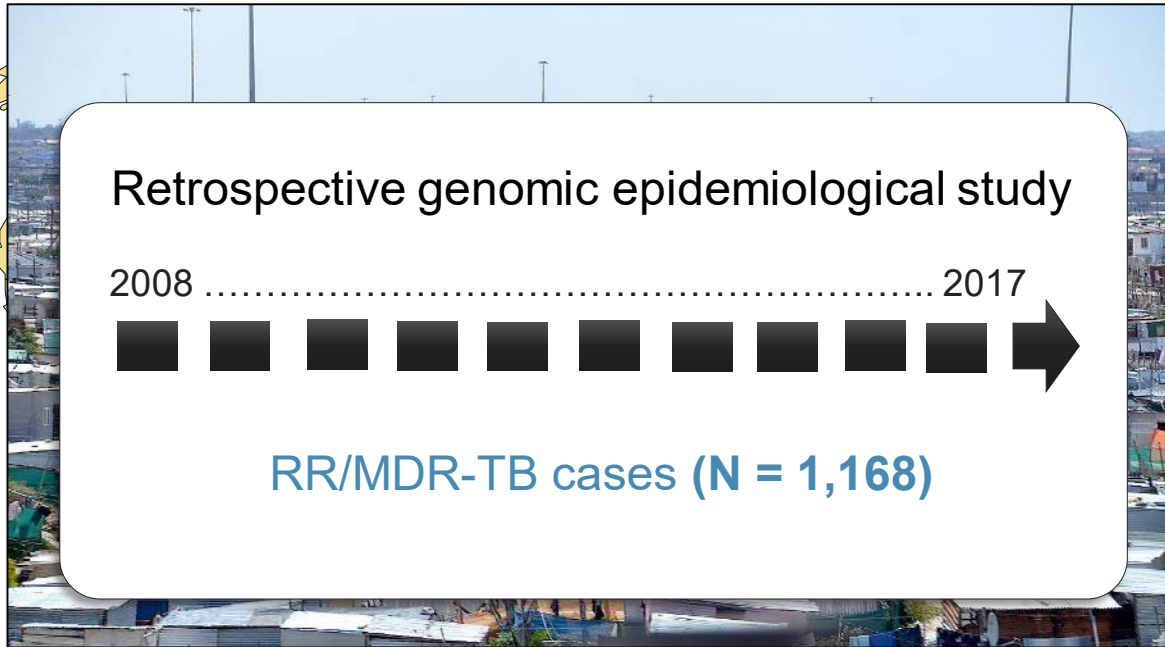
Helen Cox



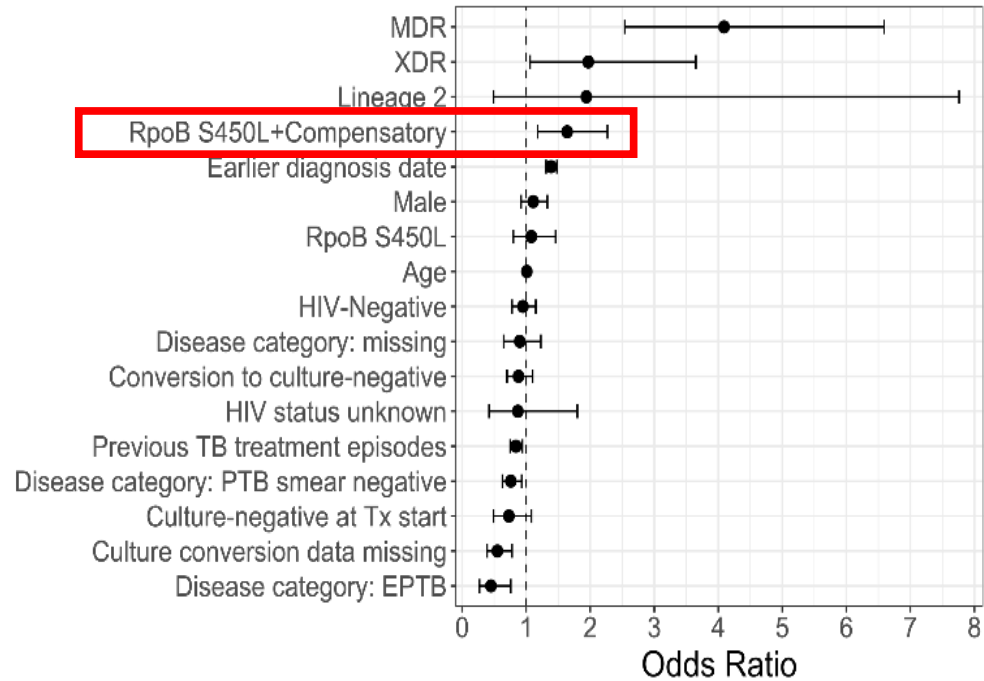
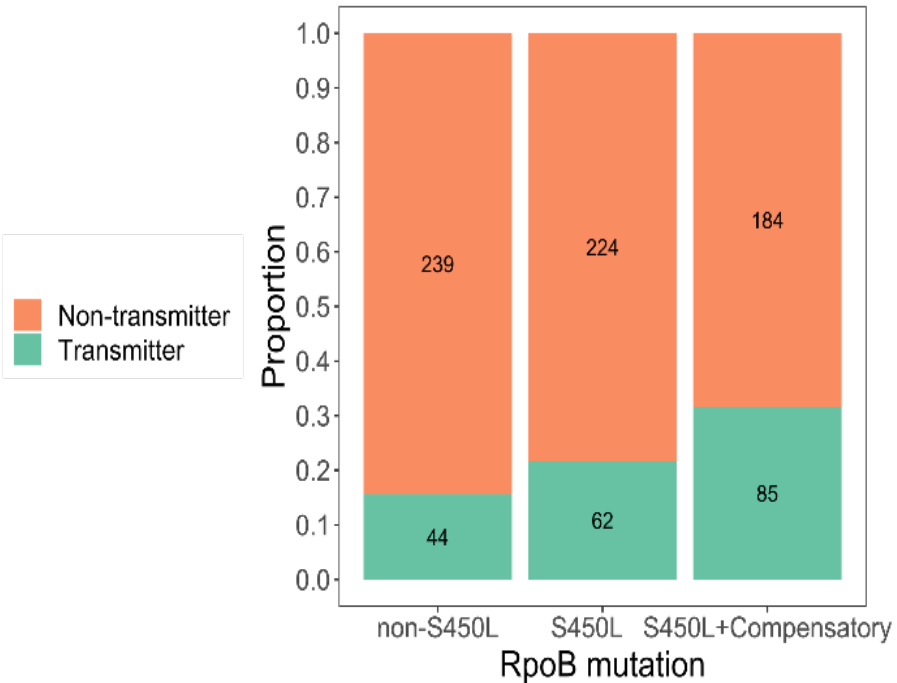
Rob Warren



Galo Goig

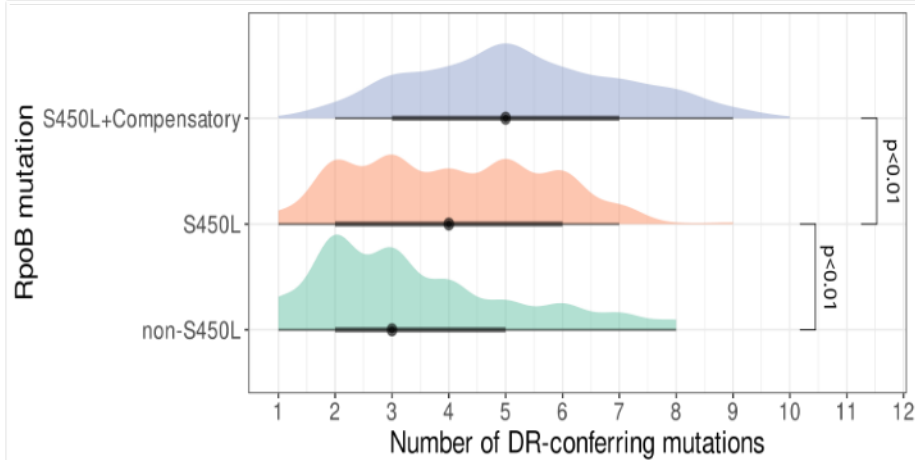


Factors Associated with Being a Transmitter of RR *Mtb*

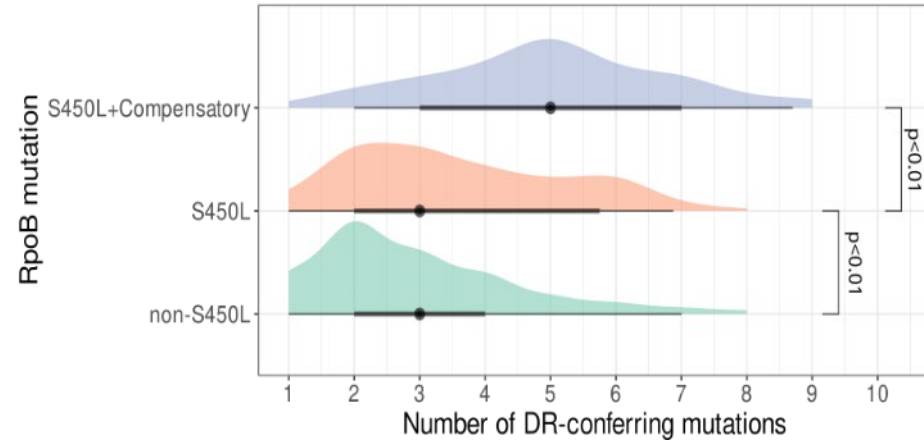


Compensation is Associated with Drug Resistance Amplification

All isolates (n=1,134)



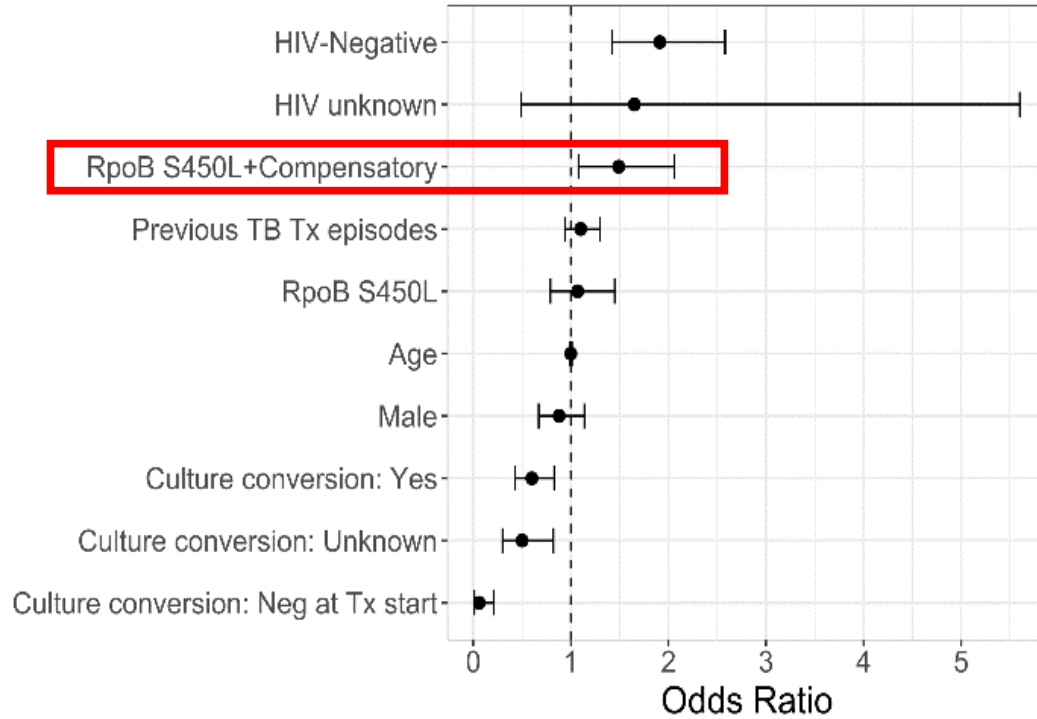
One isolate per cluster and all unclustered isolates (n=355)



RpoB mutation

- non-S450L
- S450L
- S450L+Compensatory

Factors Associated with Sputum Smear Positivity



Conclusions

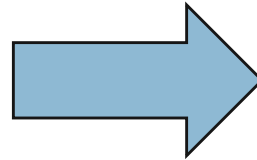
Compensatory evolution affects both:

- Between-patient fitness (transmission fitness)
- Within-patient fitness (replication fitness → DR amplification)

3-Way Epistasis

Strain Background
(e.g. L2)

Epistasis!



**Transmission Fitness
of MDR *M. tuberculosis***

DR Mutations
(e.g. RpoB S450L)

Compensatory Mutations
(e.g. RpoA/B/C)

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