

WGS To Quantify MDR-TB Transmission

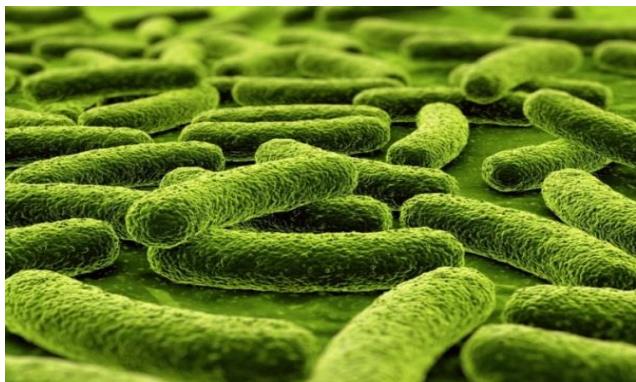
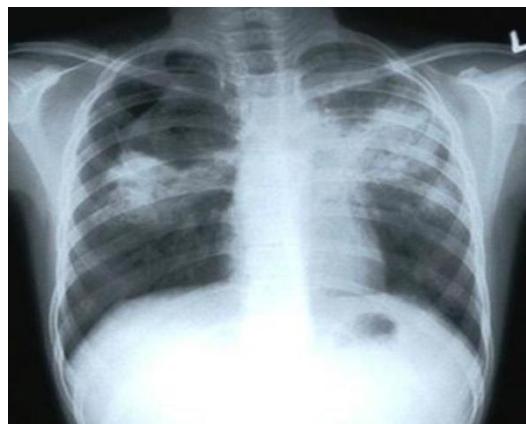
Sébastien Gagneux, PhD

ICCMg3

Geneva, 18th – 19th October 2018

Tuberculosis (TB)

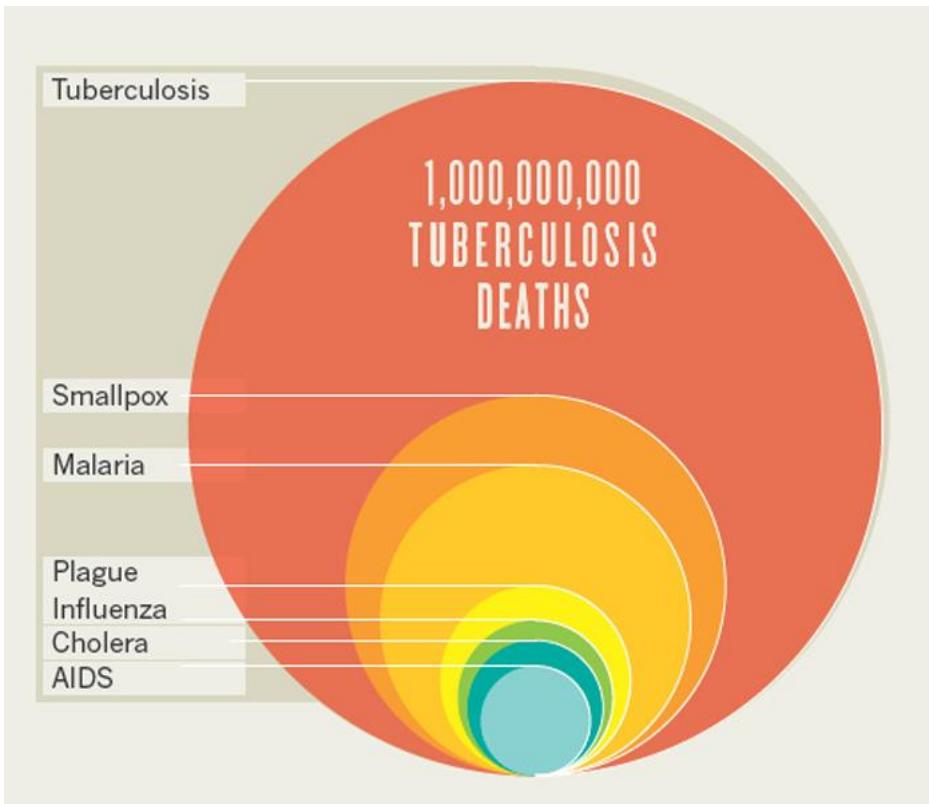
- *Phthisis* (gr.)
- Consumption
- White plague



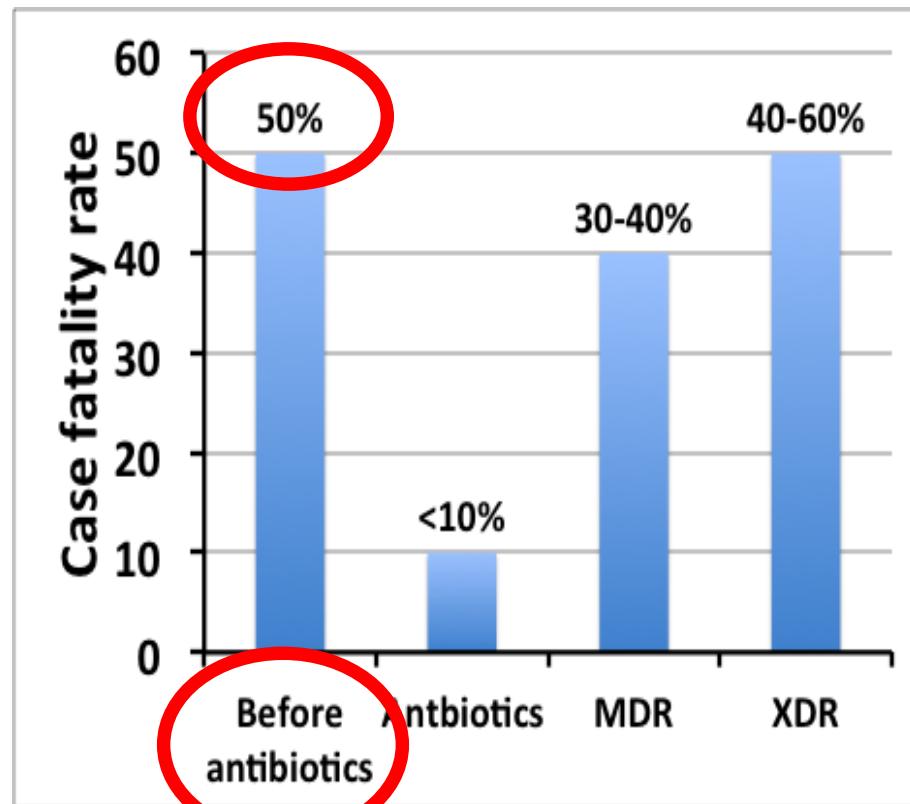
*Mycobacterium
tuberculosis*



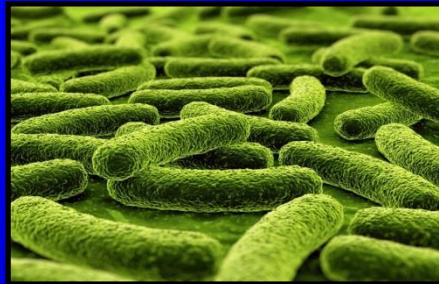
TB is a deadly disease...



Deaths during the last 200 years



Global TB Estimates (2018)



	Number of cases	Number of deaths
All forms of TB	10.0 million	1.3 million
MDR-TB	560,000	230,000
XDR-TB	~ 50,000	~ 25,000

**>50% Case-fatality:
→ Entering Post-Antibiotic Era !**

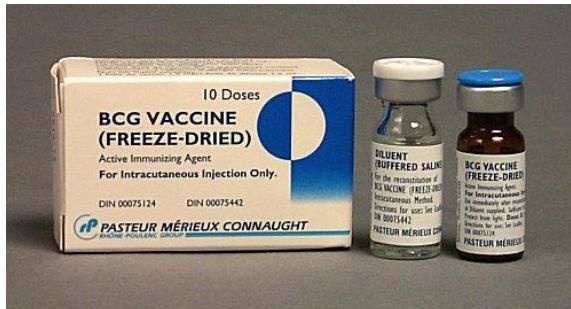
The Problems



- **Diagnostics**
~120 years old

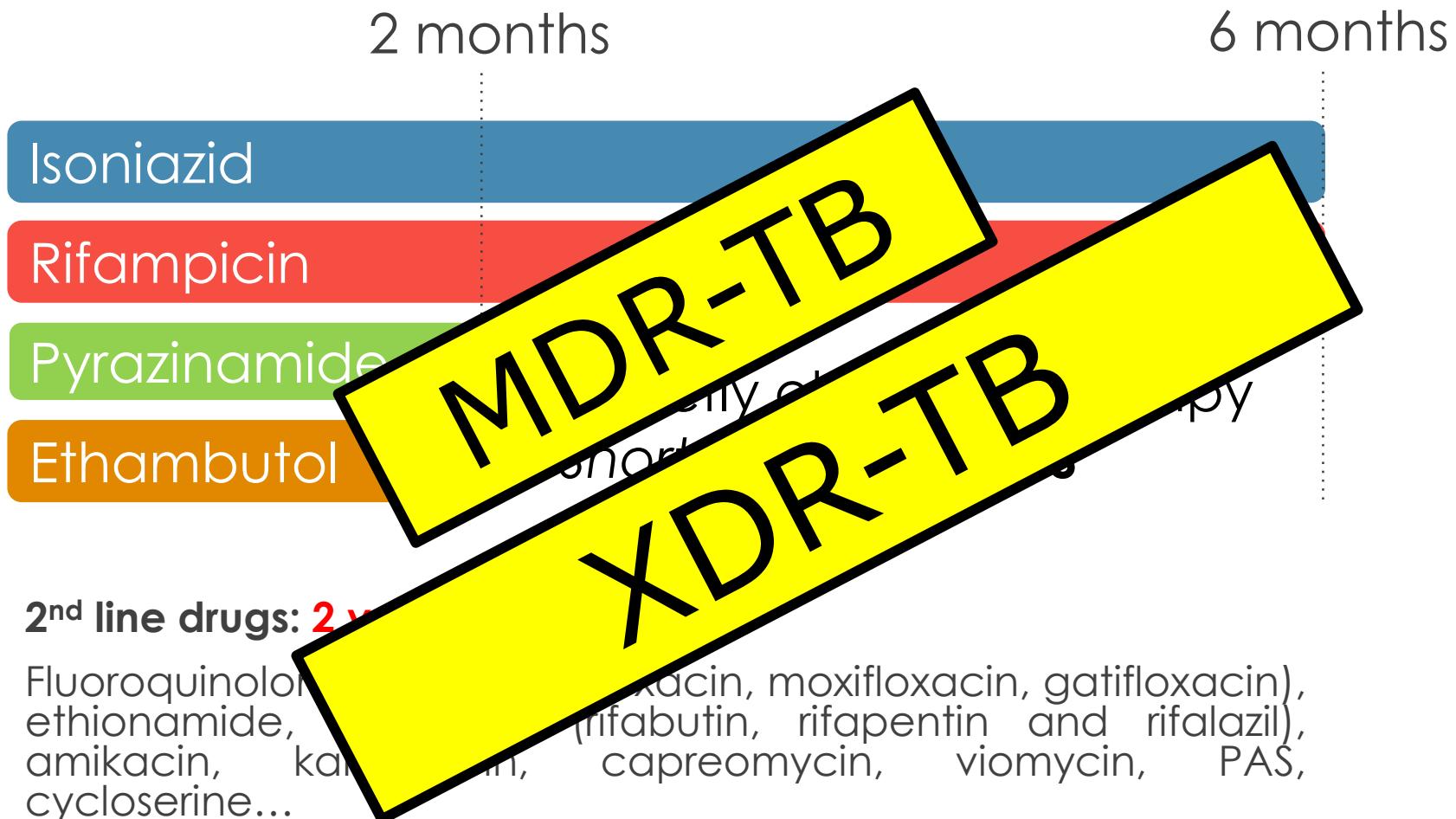


- **Drugs**
~50 years old

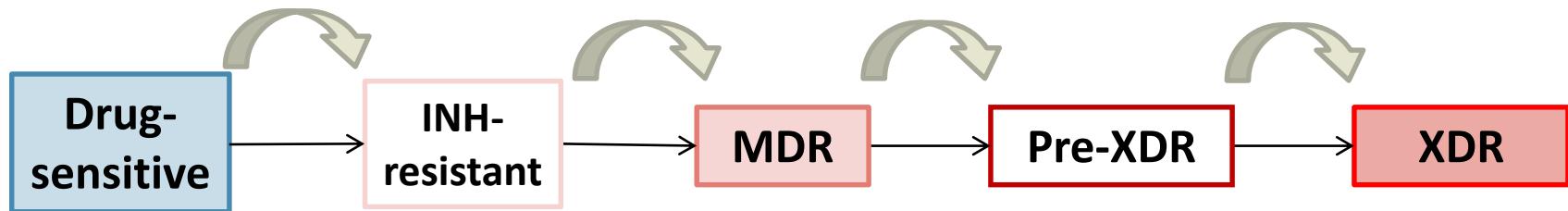


- **Vaccine**
~100 years old

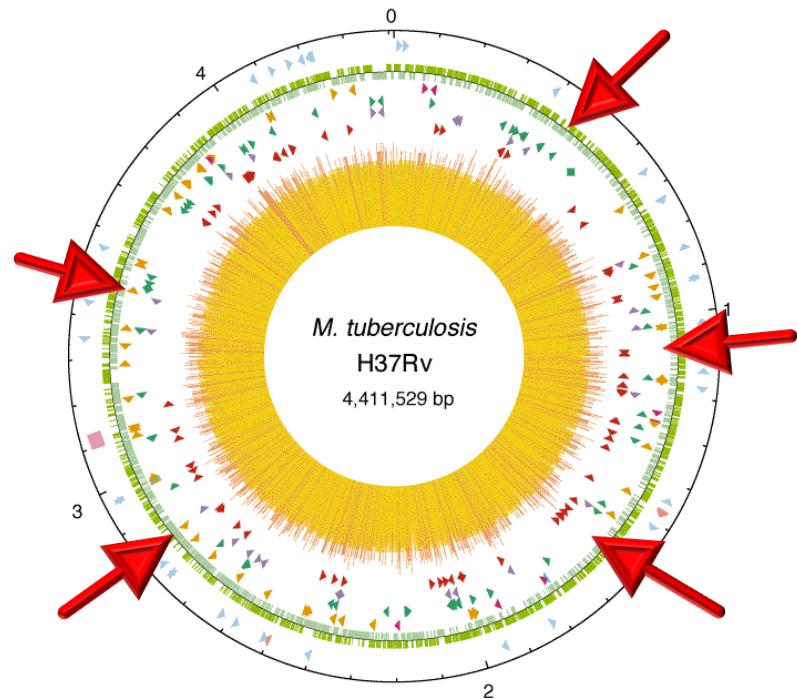
Tuberculosis Treatment



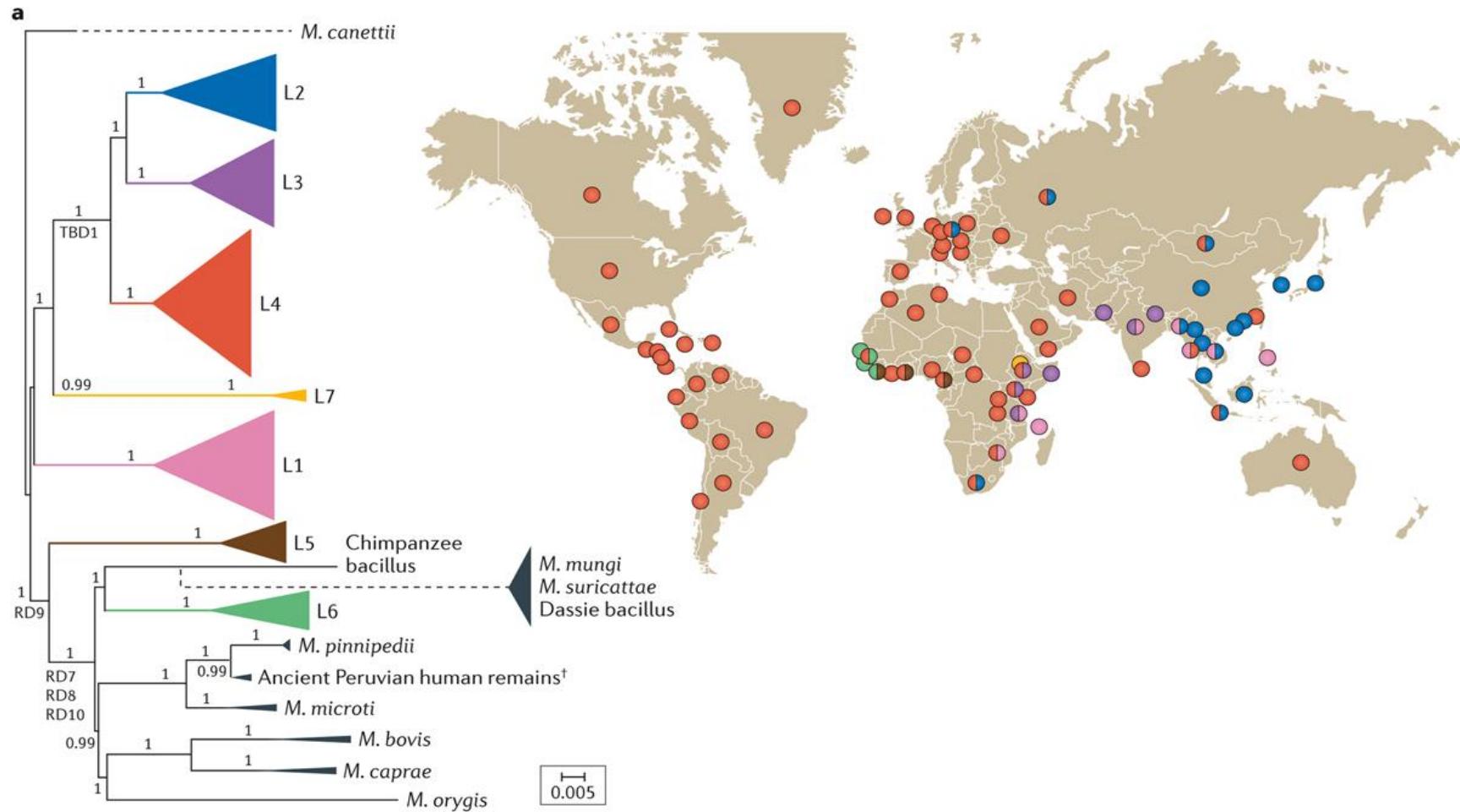
From Drug-sensitive to XDR-TB



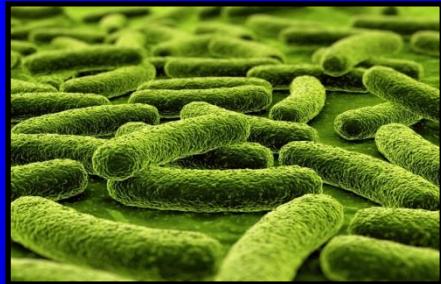
- No resistance plasmids
- No horizontal gene transfer



Global Phylogeography of *M. tuberculosis*



Global TB Estimates (2018)



Number of
cases

Number of
deaths

All forms of TB

10.0 million

1.3 million

MDR-TB

560,000

230,000

XDR-TB

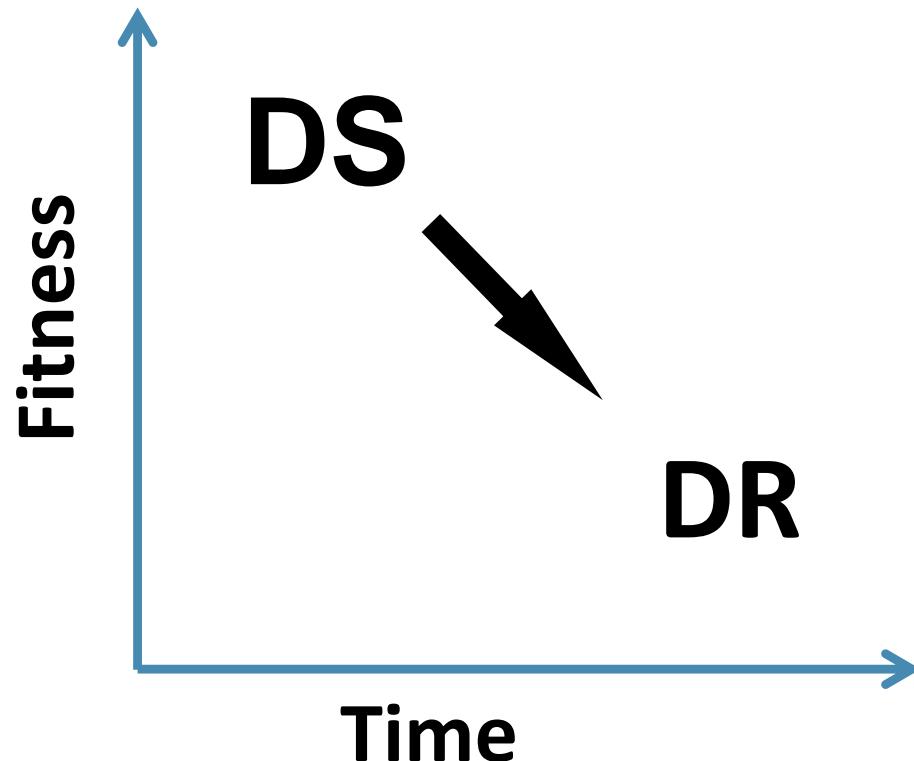
~ 50,000

~ 25,000

“Only” ~ 5% MDR / XDR

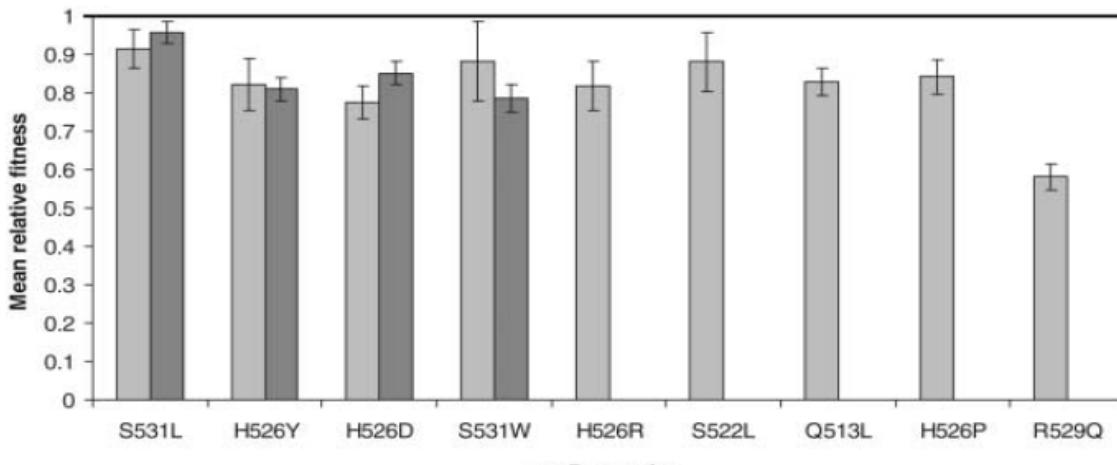
DOGMA:

“Drug-Resistant Bacteria Are Less Fit”

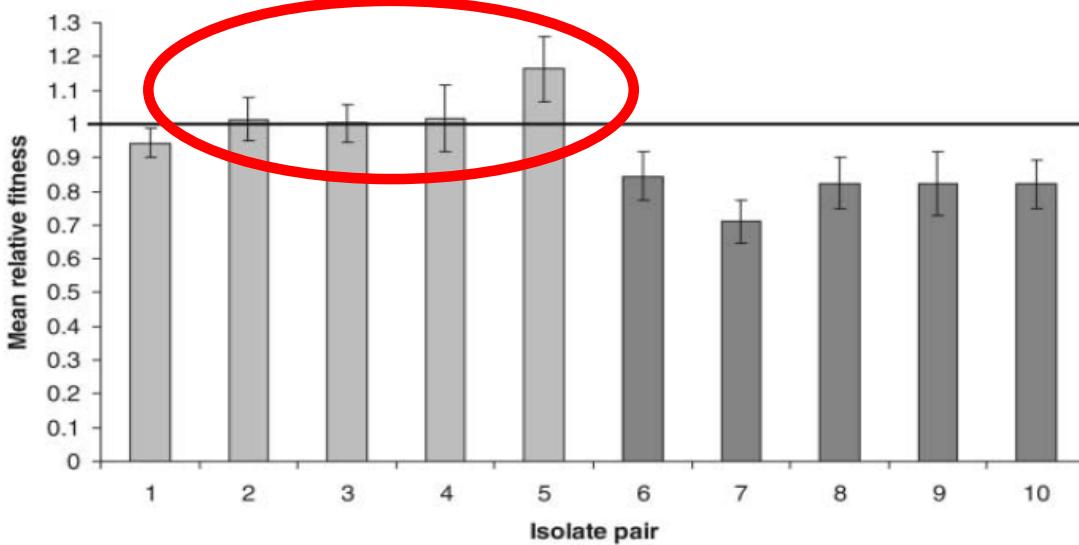




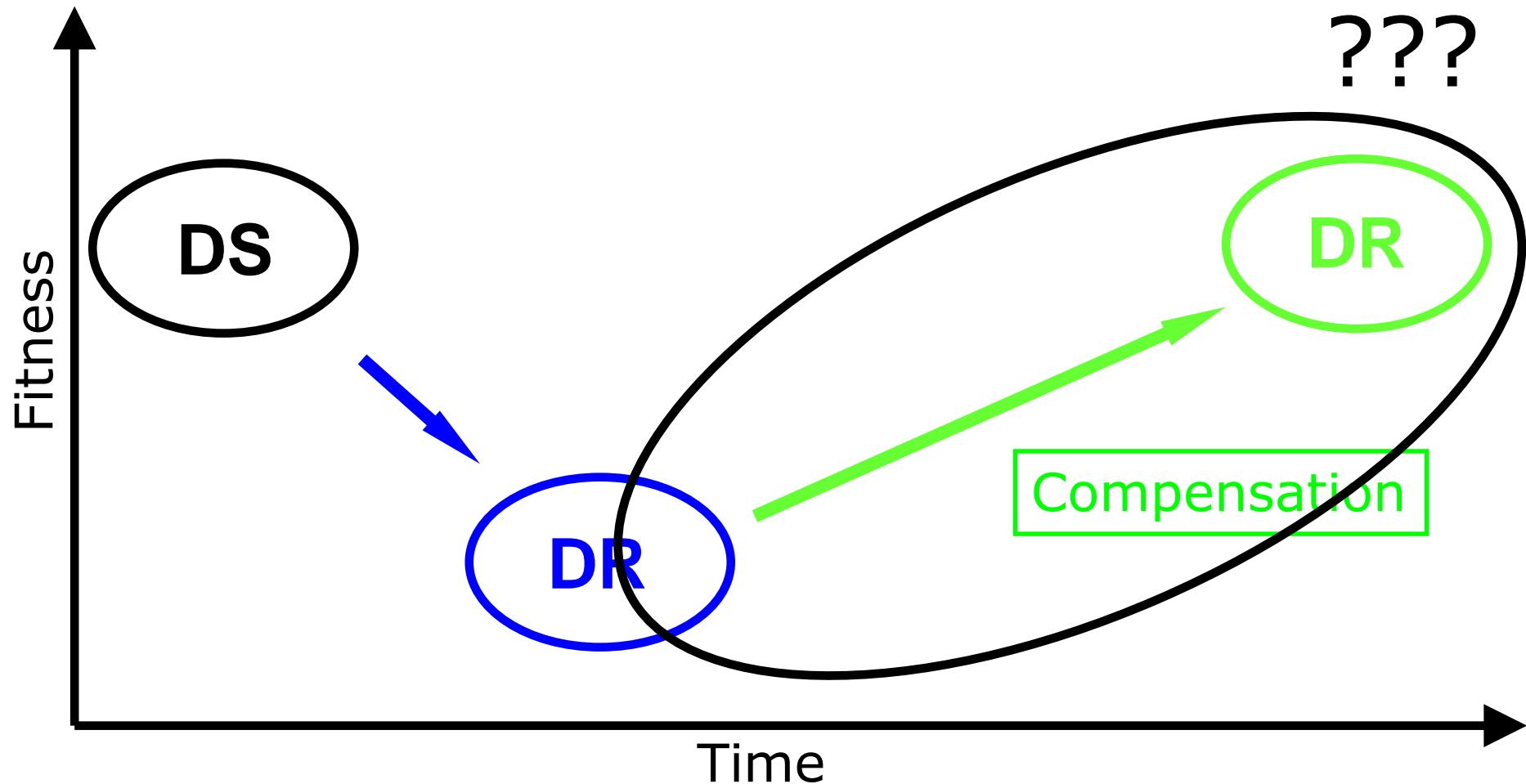
Lab strains



Clinical strains

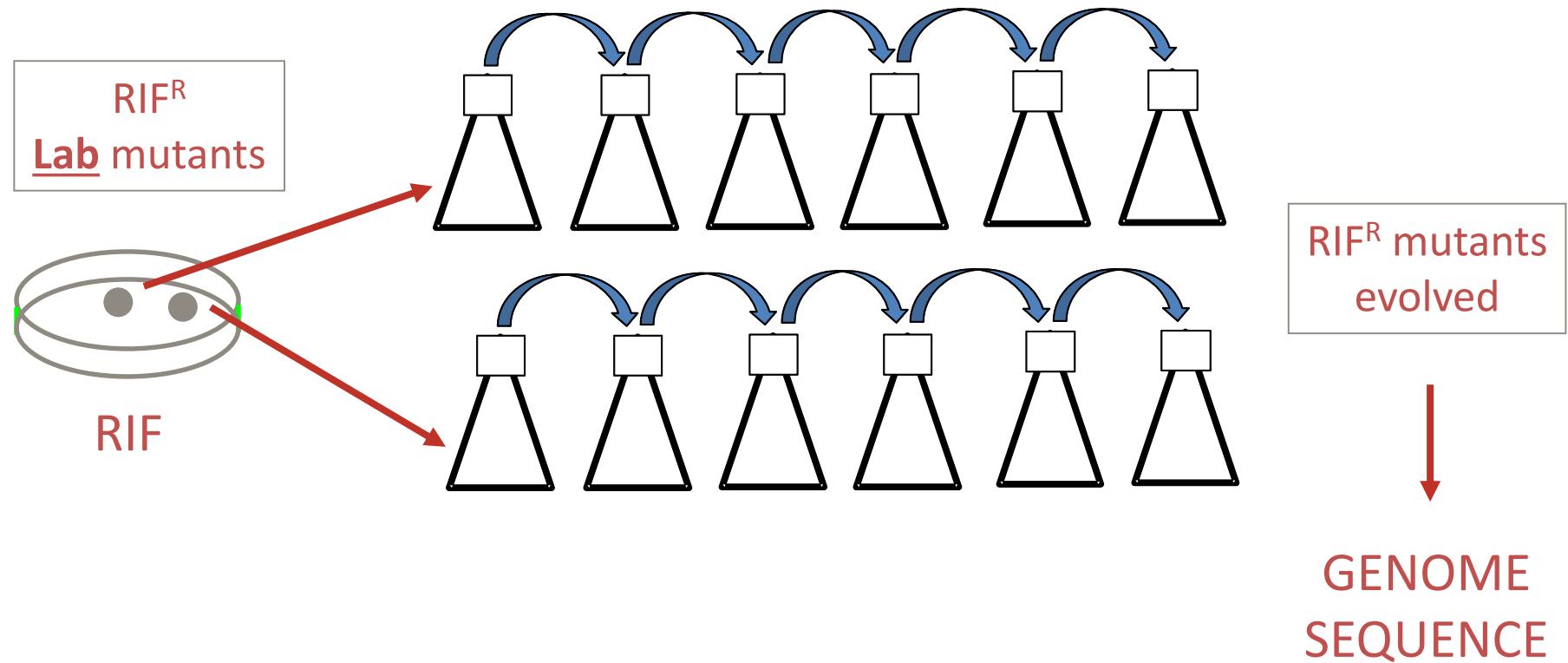


Evolution of Drug Resistance

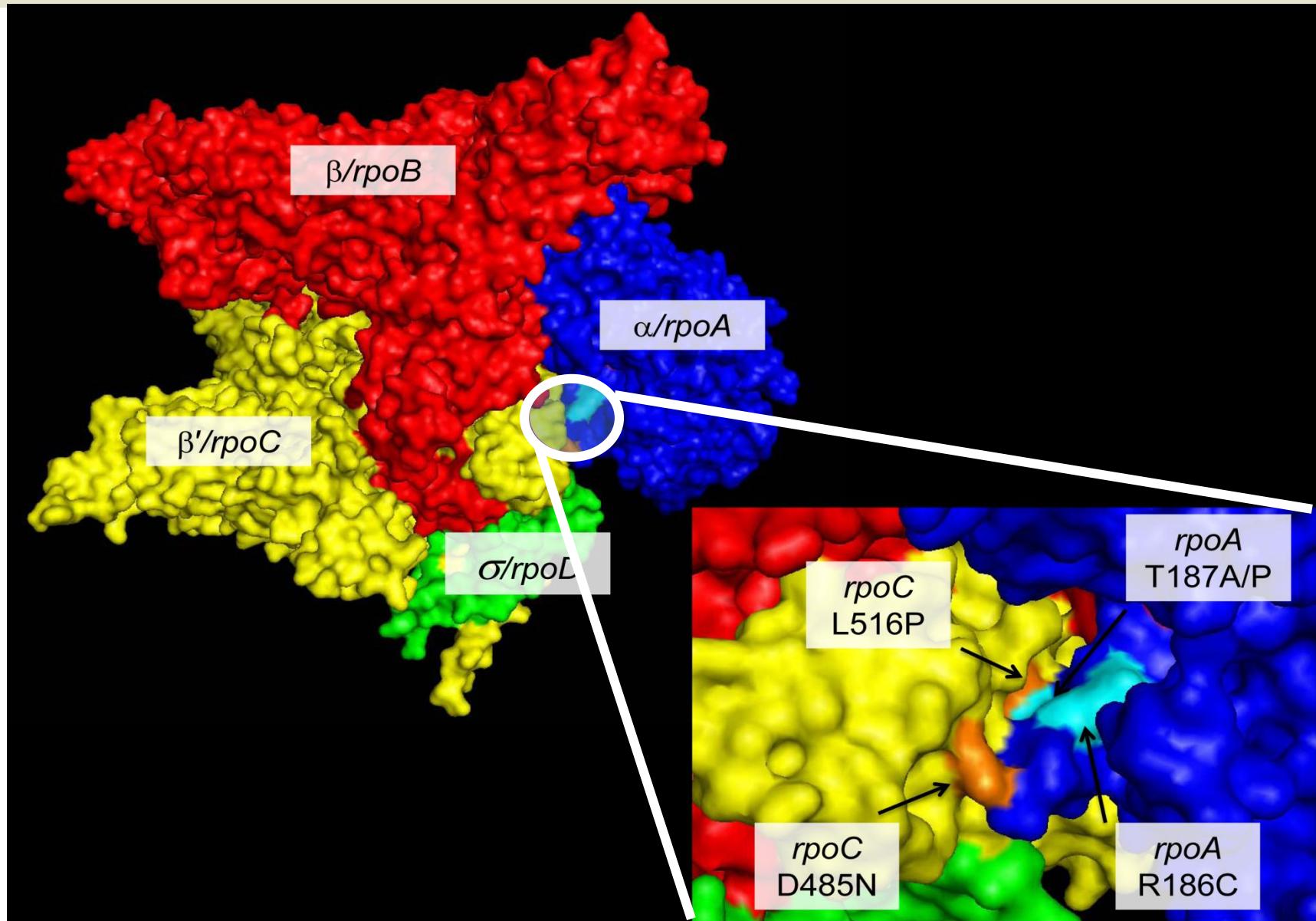


Experimental Evolution

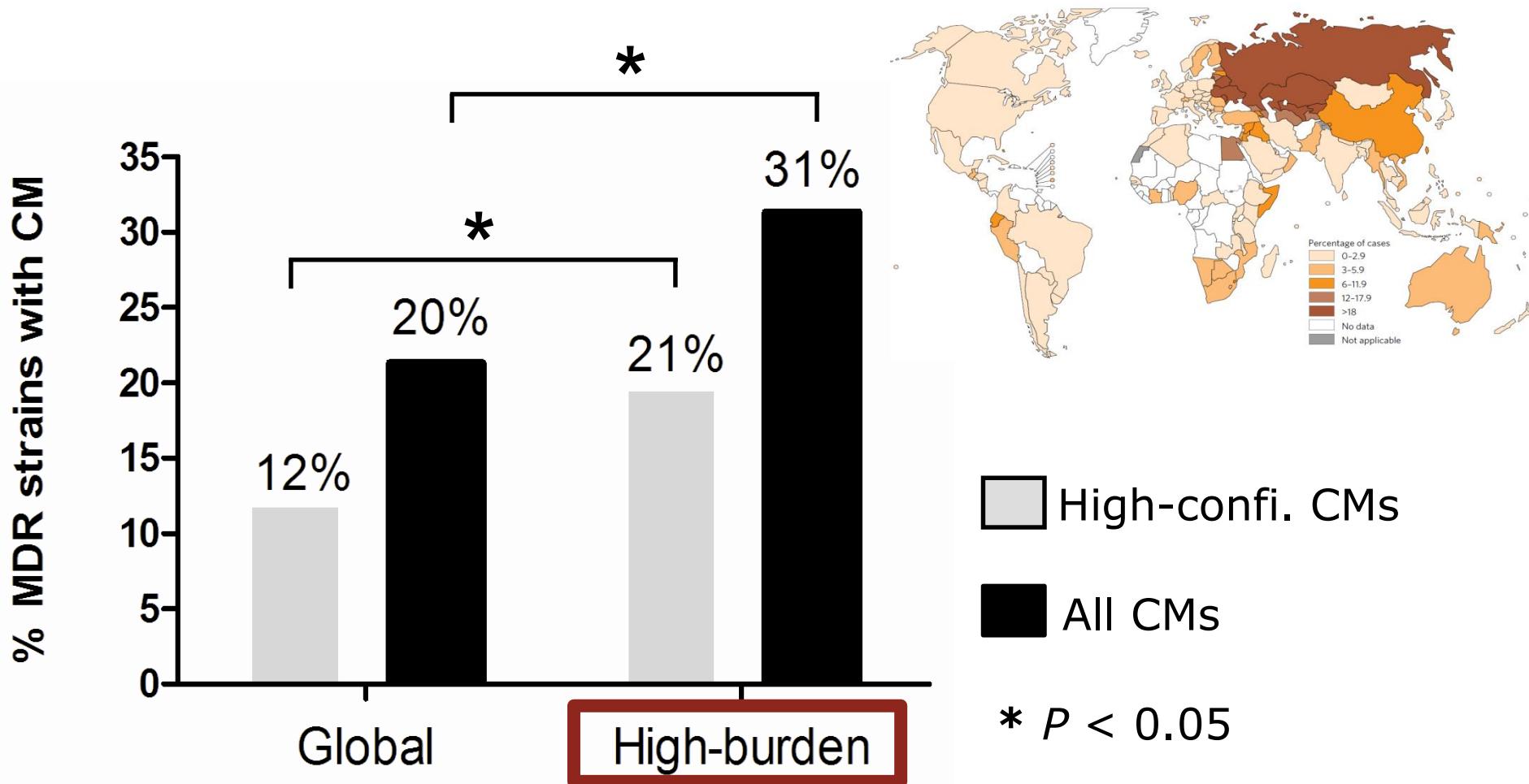
15 x (every 3 weeks)



Compensatory Mutations in *rpoA/C*



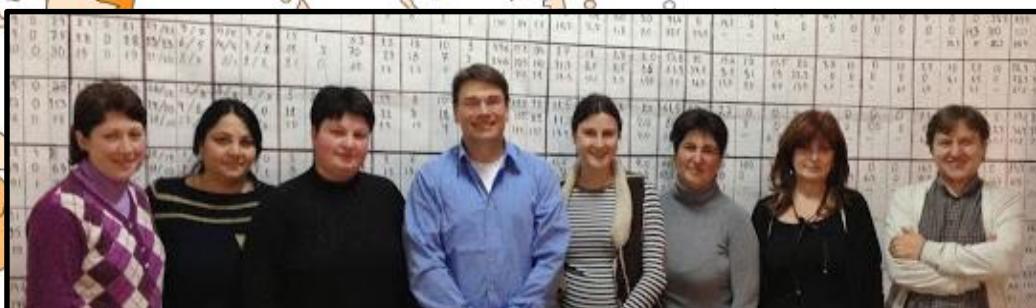
In clinico Fitness of *rpoA/C* Mutations



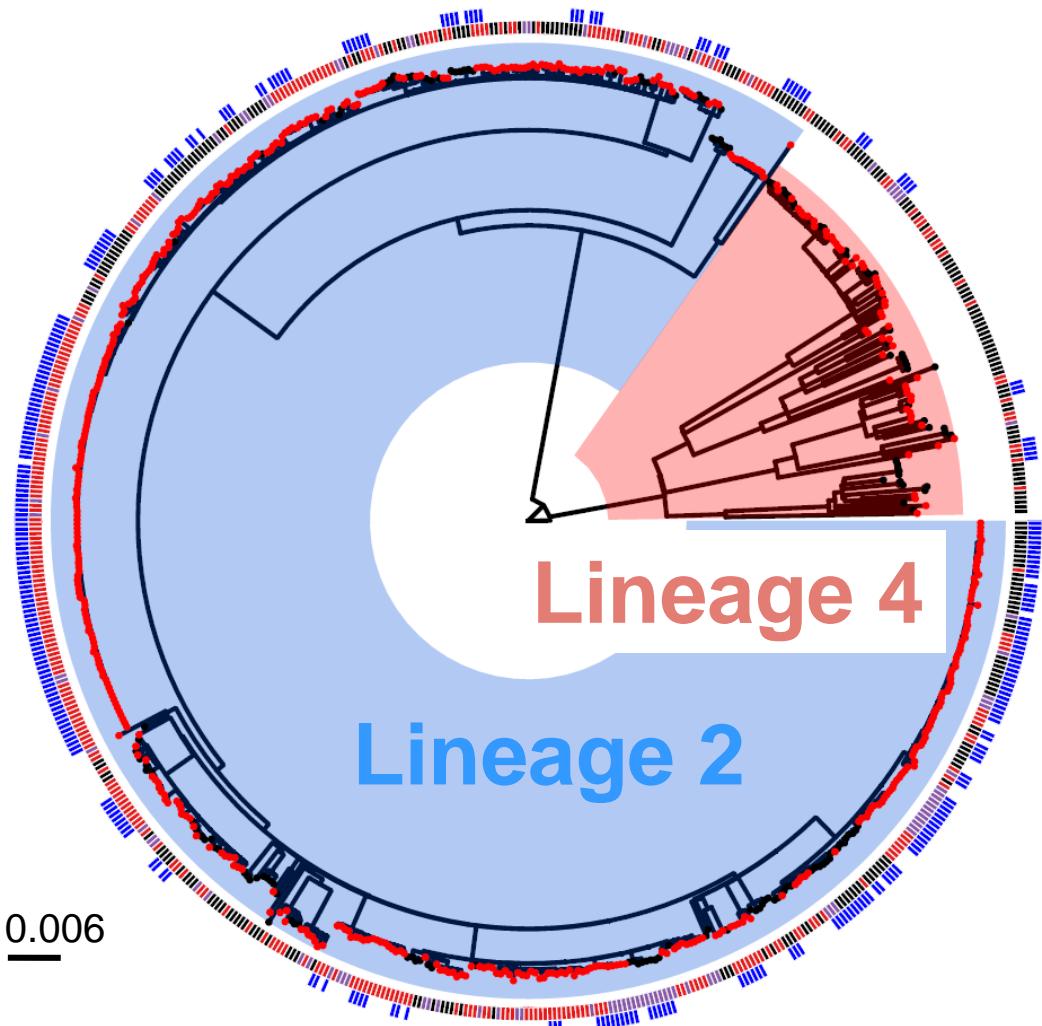
Population-based Study in Georgia



**Sebastian
Gygli**



Georgian MDR(+) *Mtb* Dataset 2011-2013



- **659 MDR(+) strains**
- **53% of all MDR(+)**

Secondary *rpoA/B/C* mutation:

- Present (77%)
- Absent

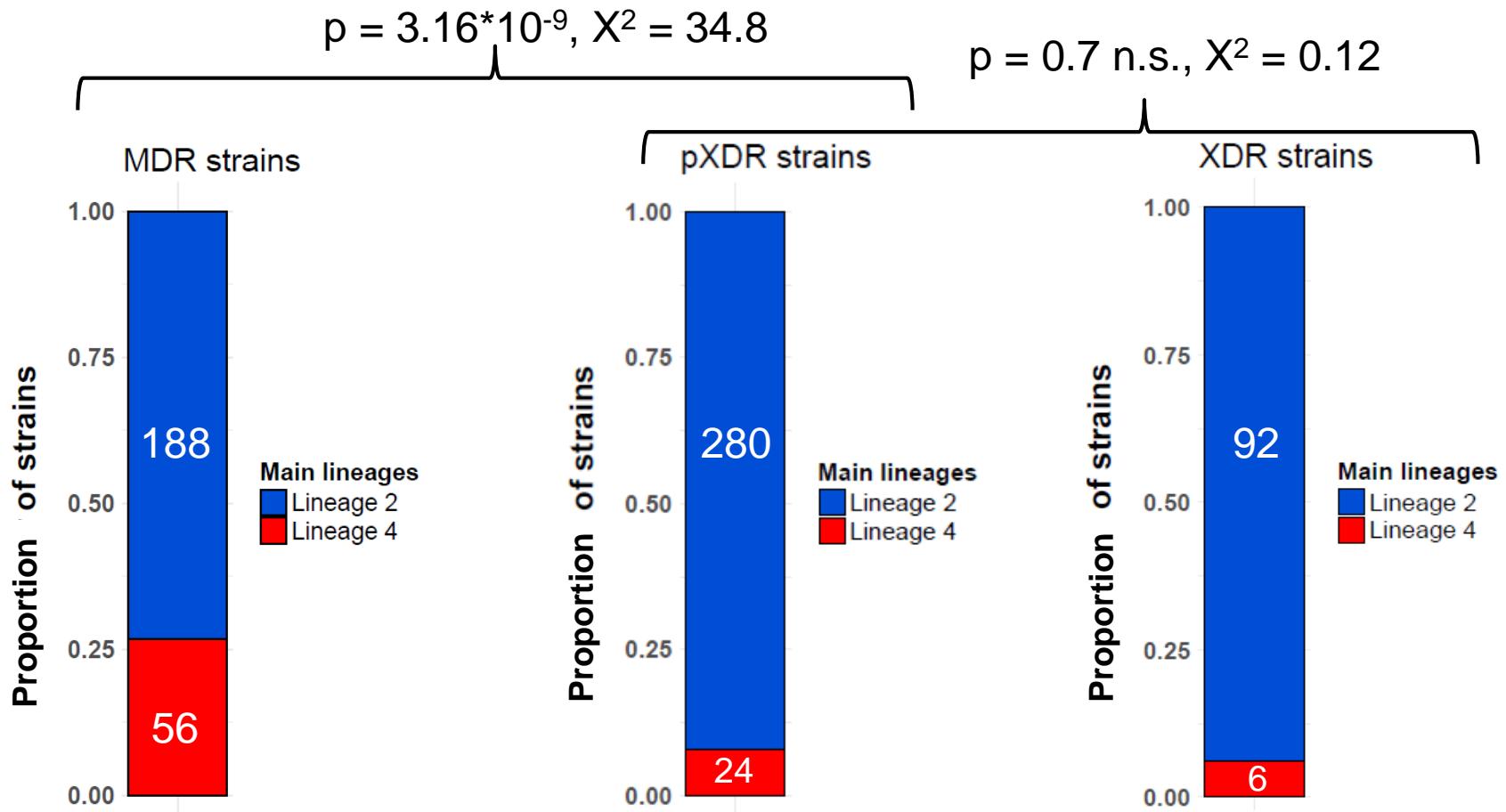
DR-profile:

- MDR (39%)
- Pre-XDR (46%)
- XDR (15%)

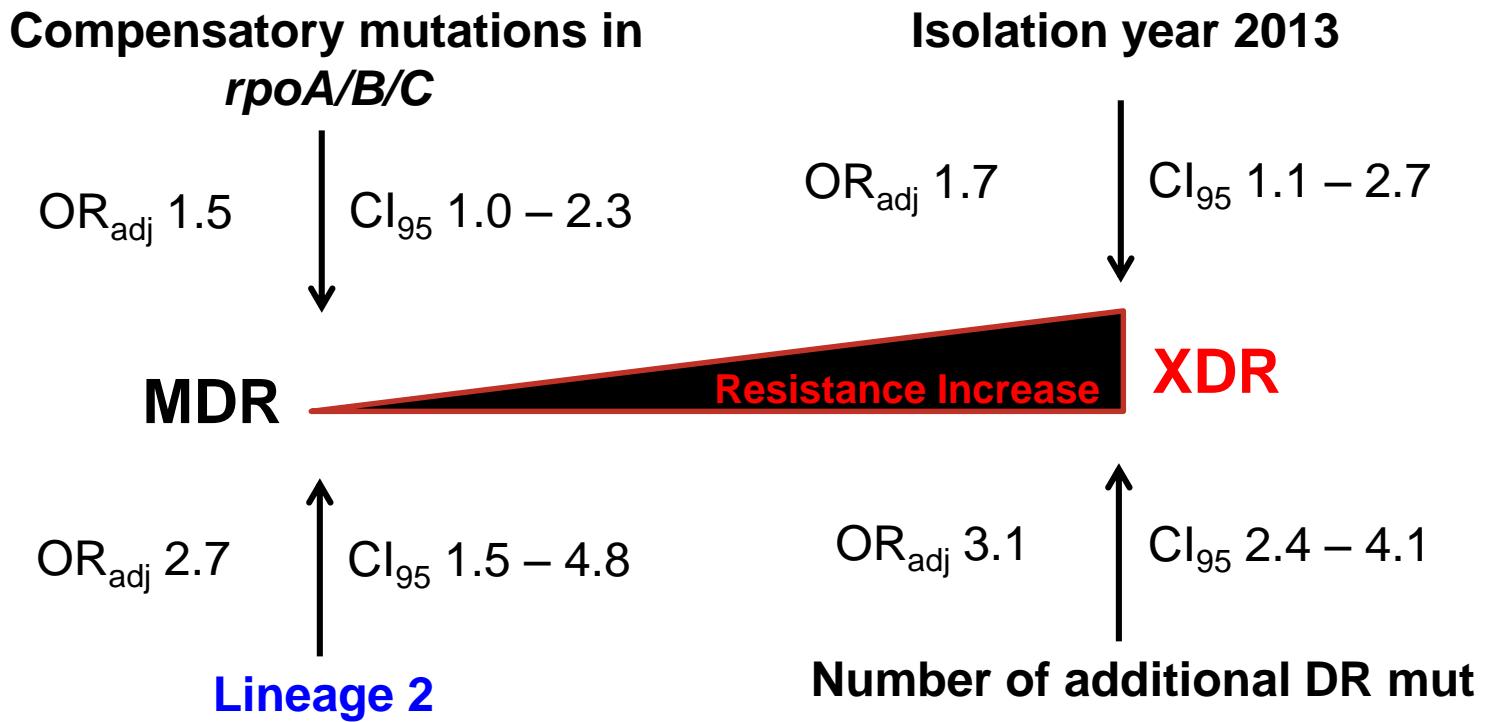
Clustering:

- Clustered (43%)

Bias Towards Lineage 2 (Univariate Analysis)

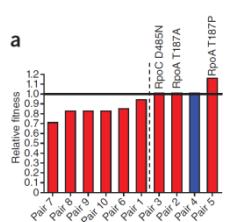


Factors Associated with Increased Drug Resistance



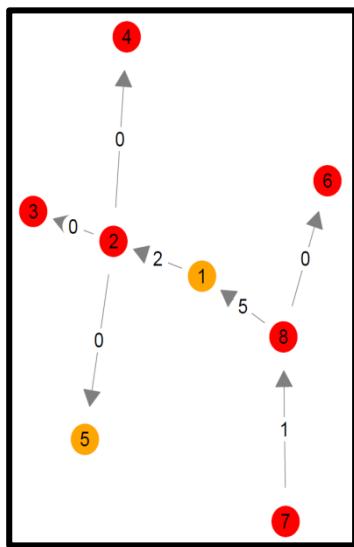
Factors Associated with Clustering of MDR/XDR-TB

Compensatory mutations

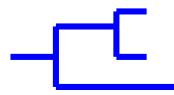


OR_{adj} 2.53
 CI_{95} 1.54 – 4.24

Clustering

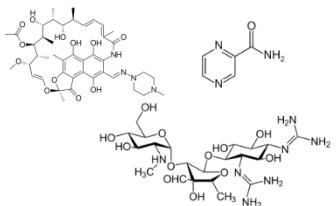


Lineage 2



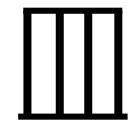
OR_{adj} 5.26
 CI_{95} 2.65 – 11.23

No. DR mut



OR_{adj} 0.72
 CI_{95} 0.56 – 0.97

Prisons



OR_{adj} 6.18
 CI_{95} 3.74 – 10.49

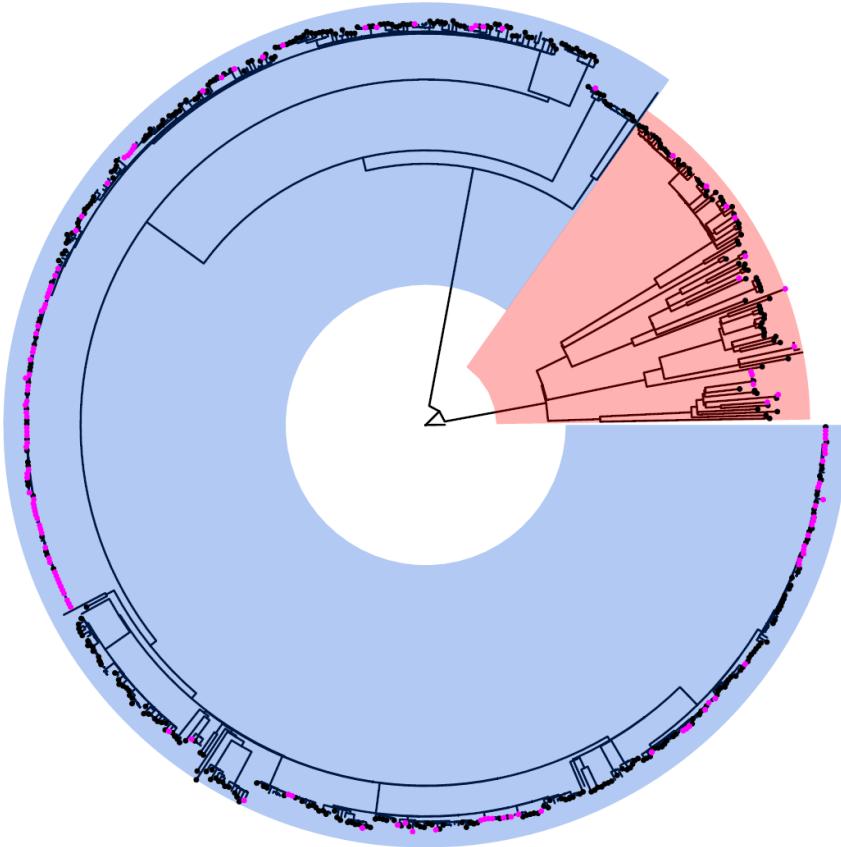
Age



OR_{adj} 0.98
 CI_{95} 0.97 – 1.0

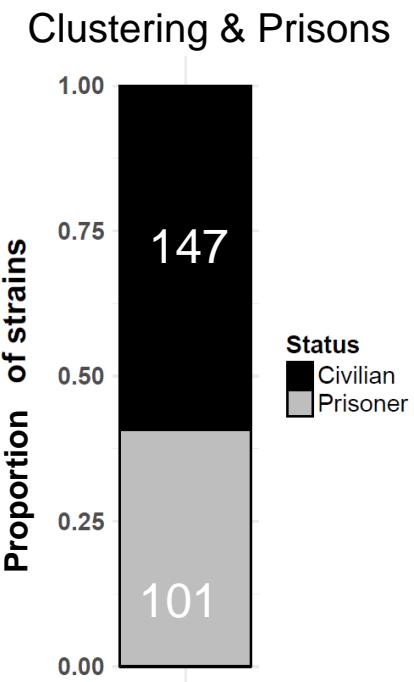
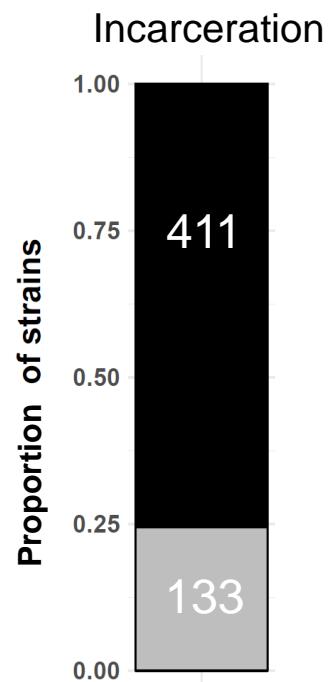


MDR/XDR-TB in Prisons & Clustering

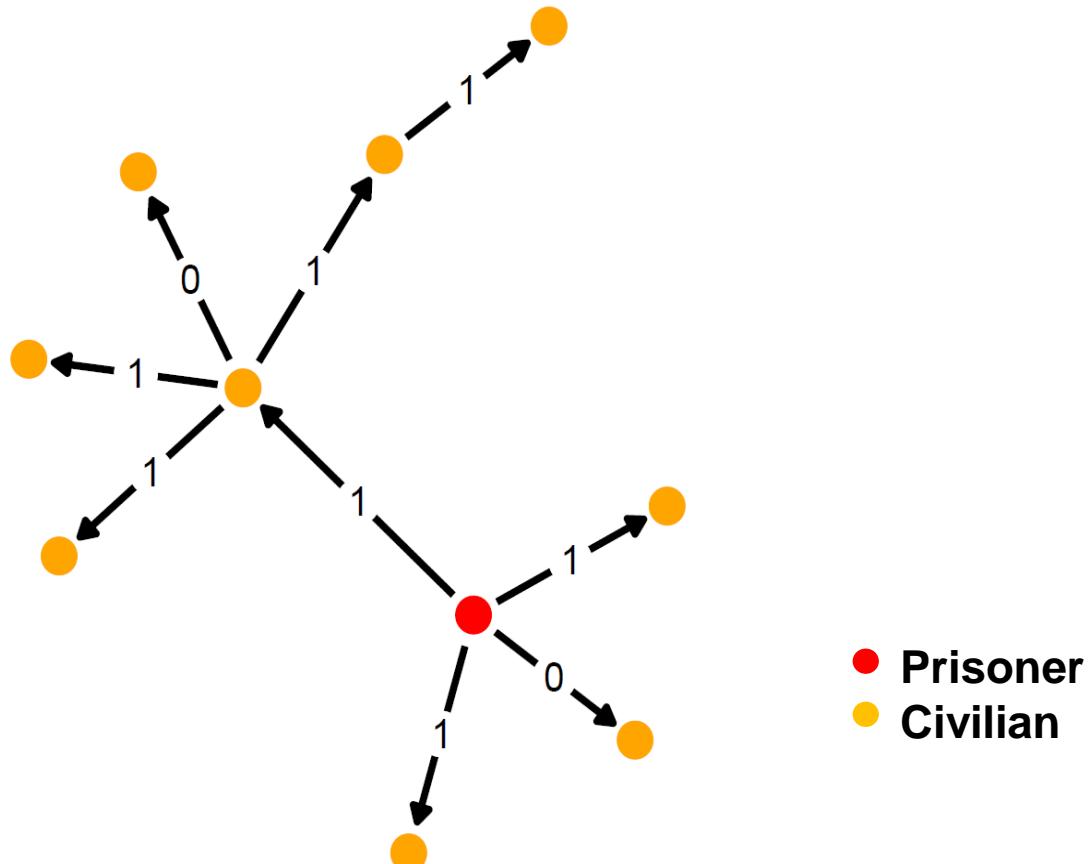


Isolate origin

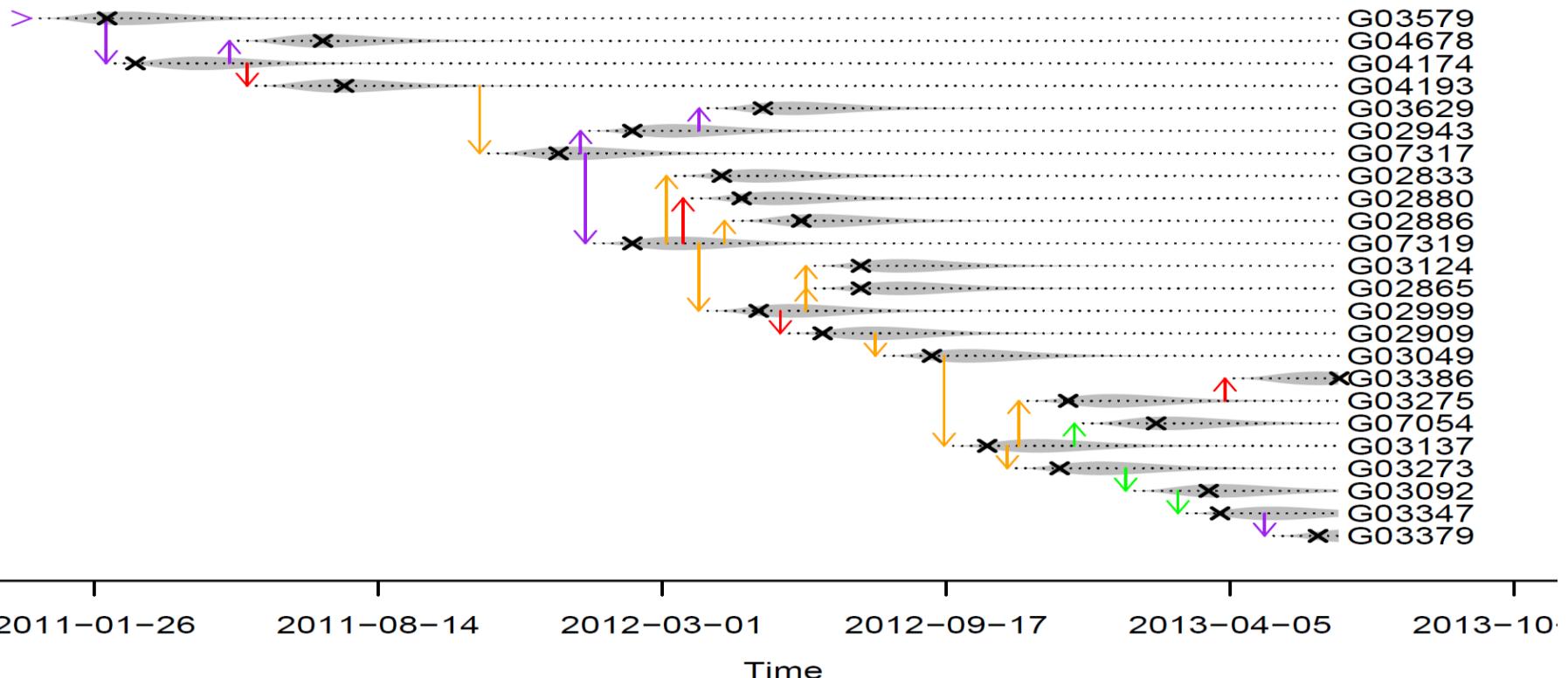
- Prisoner
- Civilian



Reconstructing Transmission Trees

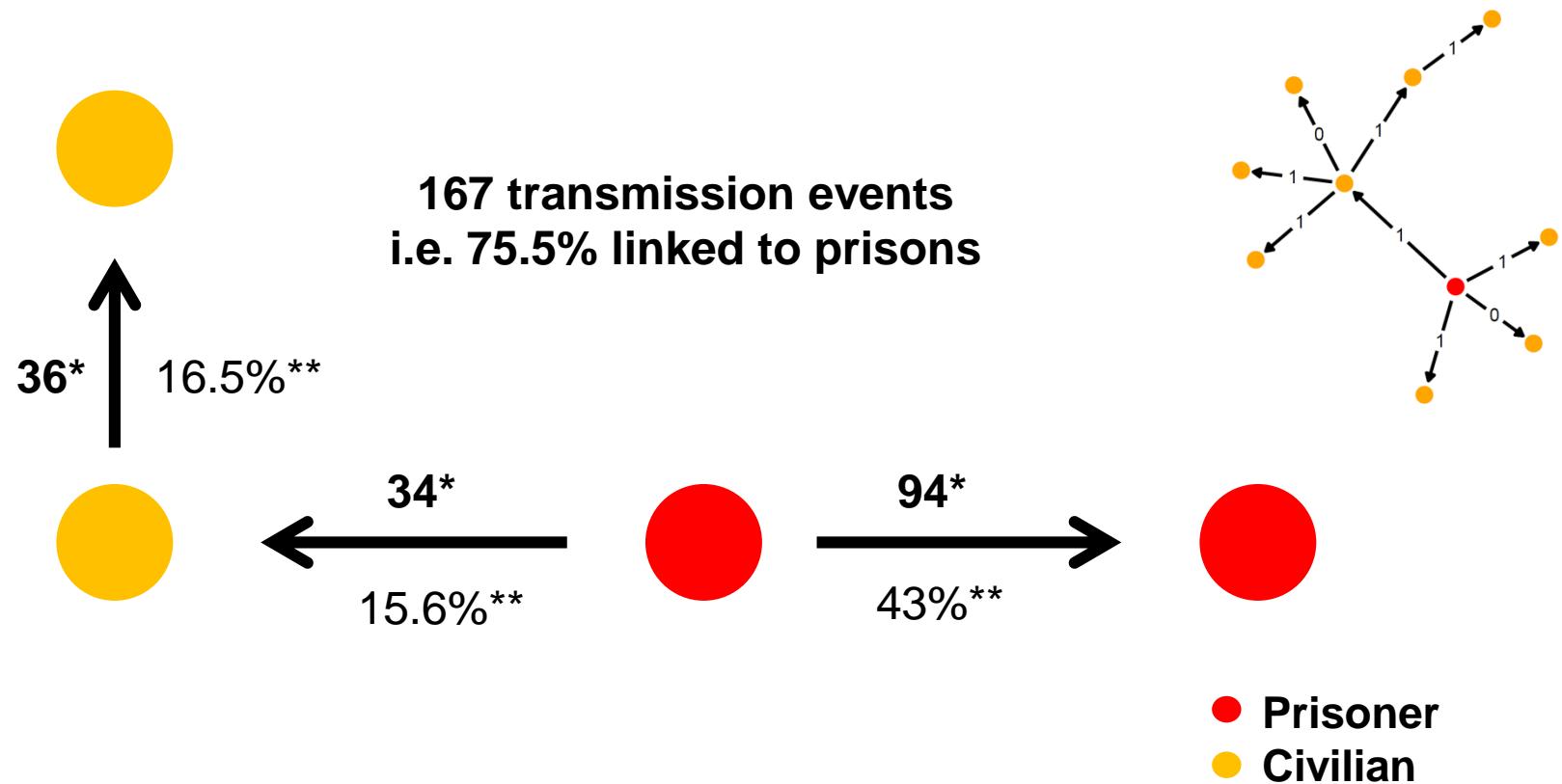


Reconstructing Transmission Trees - Phybreak

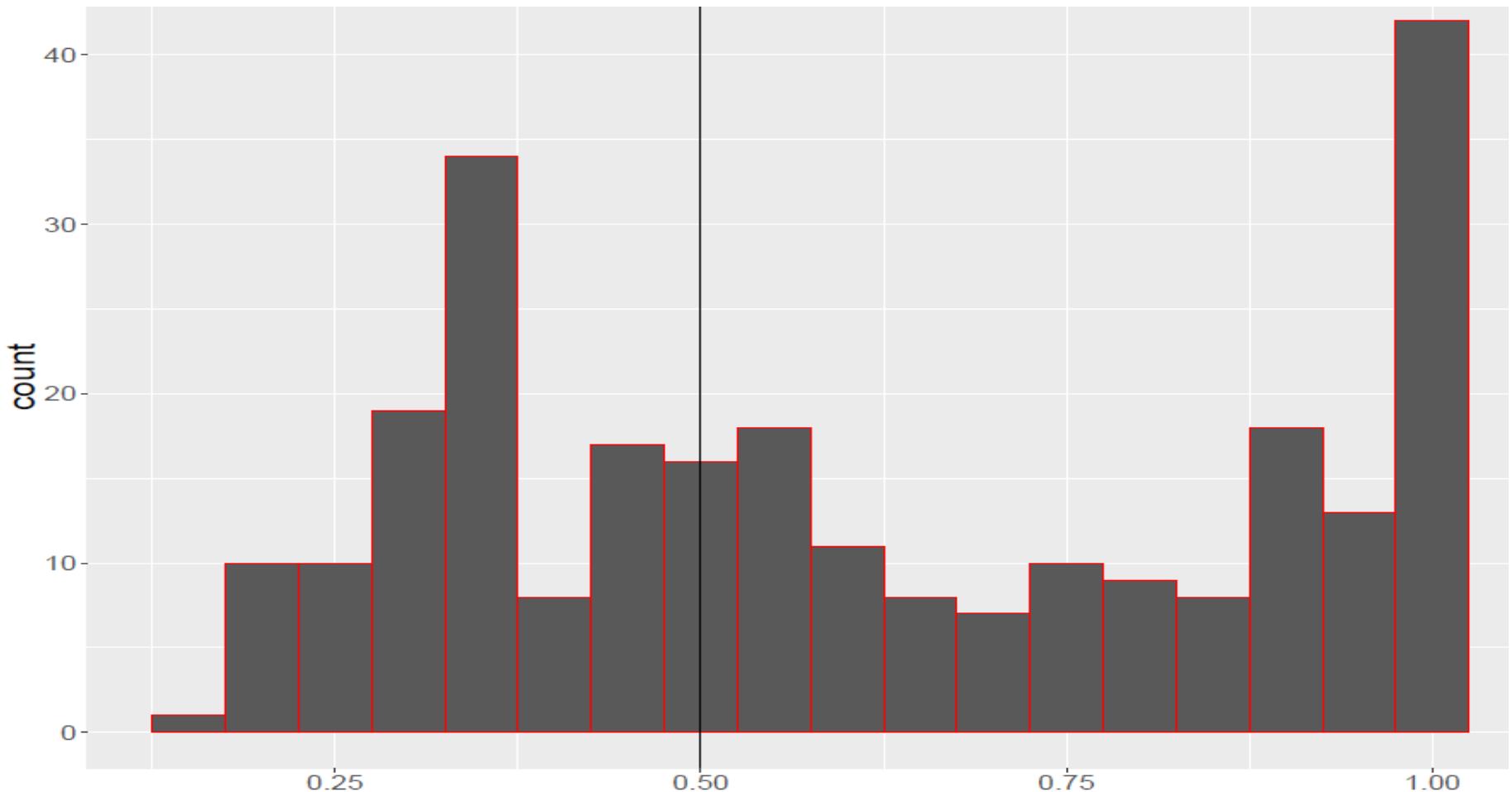


Posterior probability (%)				
Blue	Green	Orange	Red	Purple
0-20	20-40	40-60	60-80	80-100

Contribution of Prisons to the MDR-TB Epidemic in Georgia

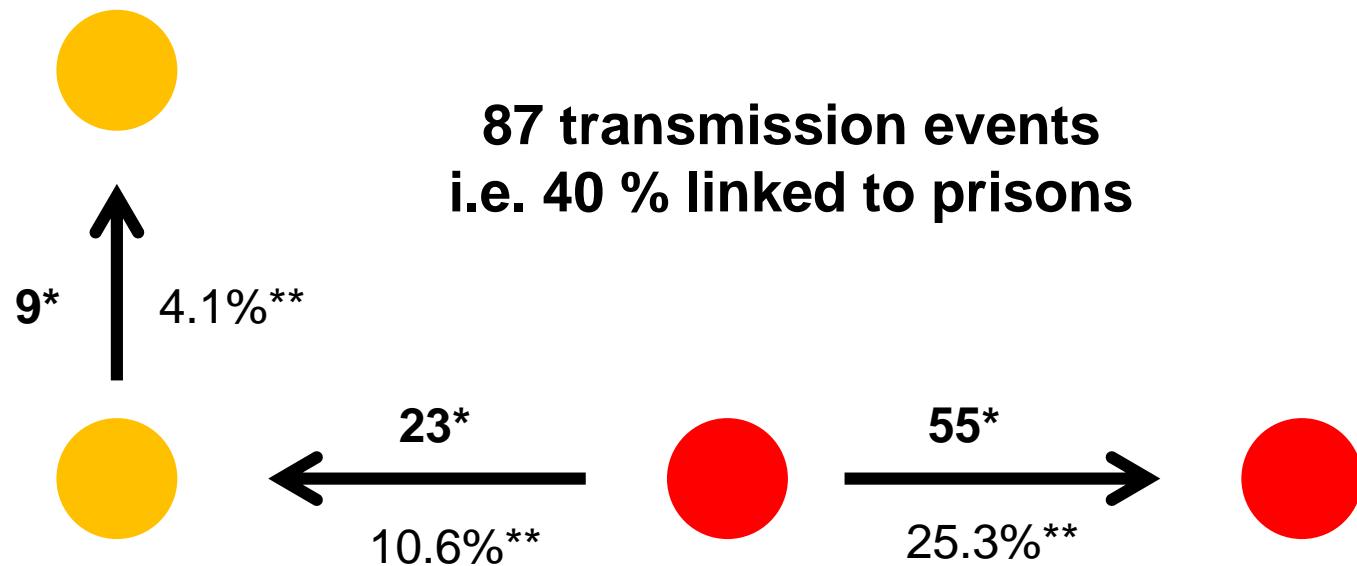


Posterior Probabilities of Transmission Events



Contribution of Prisons to the MDR-TB Epidemic in Georgia

Transmission events with >0.5 posterior probability



*Transmission events

**Of the total 217 high confidence transmission events

- Prisoner
- Civilian

Conclusions

- Compensatory mutations in RNAP of RIF^R *Mtb*
- High frequency in MDR/XDR 'hotspots'
- Associated with progression MDR to XDR
- Associated with ongoing transmission of MDR/XDR
- High spill-over from prisoners to civilians

→ **Compensatory evolution contributes
to the spread of MDR/XDR-TB**

→ **Prisons as breeding grounds for fit MDR-TB**

Thanks to...

IBV, Valencia
Iñaki Comas
University of Valencia
Mireia Coscollá
University of Cape Town
Helen Cox
Stellenbosch University
Rob Warren
University of Bern
Matthias Egger
University of Ghana
Dorothy Yeboah-Manu
ITM, Antwerp
Bouke de Jong
University of Basel
Richard Neher
ETH Zurich
Ruedi Aebersold/Ben Collins
Uwe Sauer
Tanja Stadler
Jörg Stelling
Christian Beisel
FZ Borstel
Stefan Niemann



- Sonia Borrell
- Daniela Brites
- Andrej Trauner
- Miriam Reinhard
- Levan Jugheli
- Sebastian Gygli
- Liliana Rutaihwa
- Rhastin Castro
- Chloé Loiseau
- Monica Ticlla
- Peter Major
- Fabrizio Menardo
- Nino Maghradze
- Jerry Hella



European Research Council
Established by the European Commission



SystemsX.ch
The Swiss Initiative in Systems Biology

