

Swiss TPH



Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Dept. of Medical Parasitology & Infection Biology
Tuberculosis Research Unit

24th **ECCMID** Barcelona, Spain
10-13 May 2014



ESCMID EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES

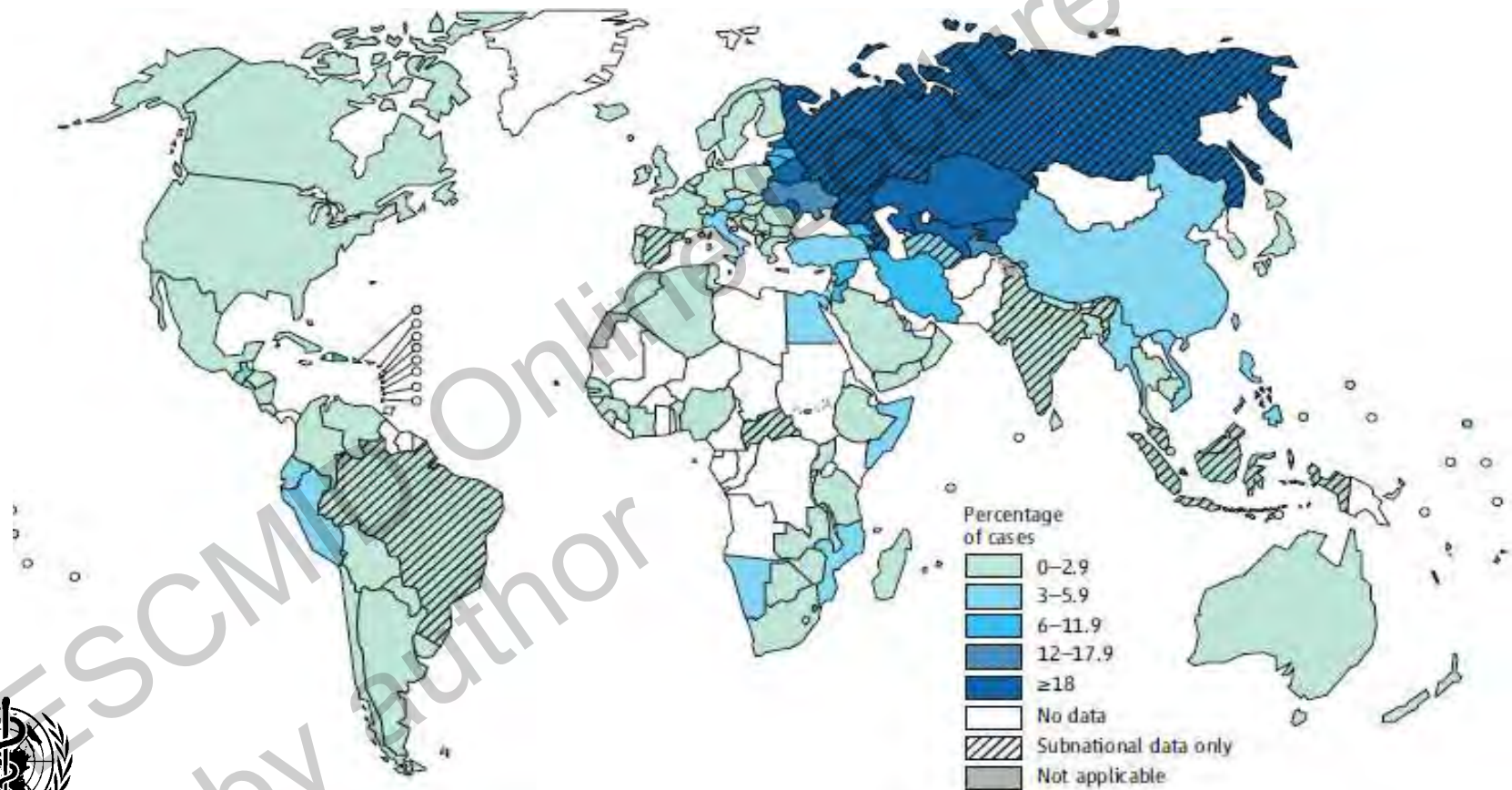


Resistance of Beijing tuberculosis

SONIA BORRELL, PhD
BCN, 13th of May

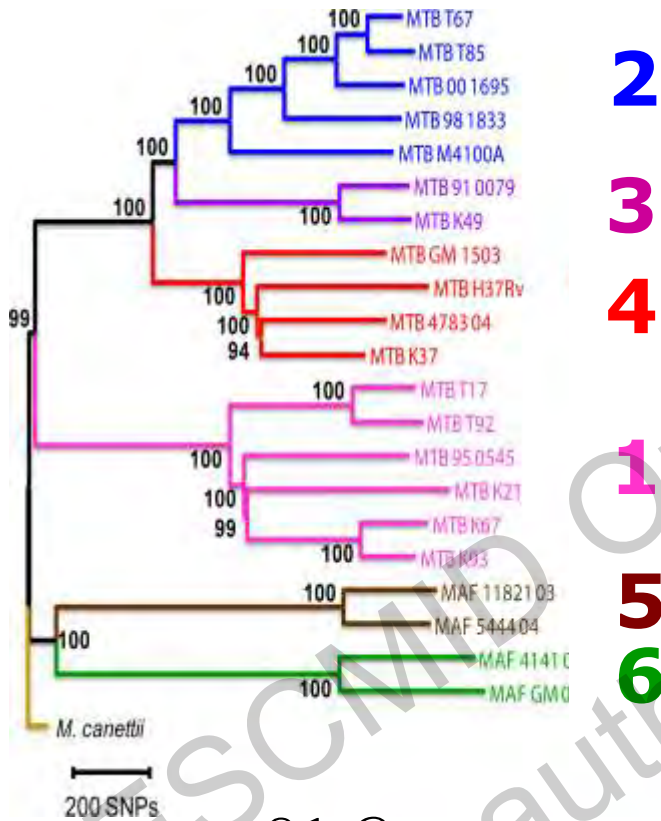


Proportion MDR among new TB (2012)

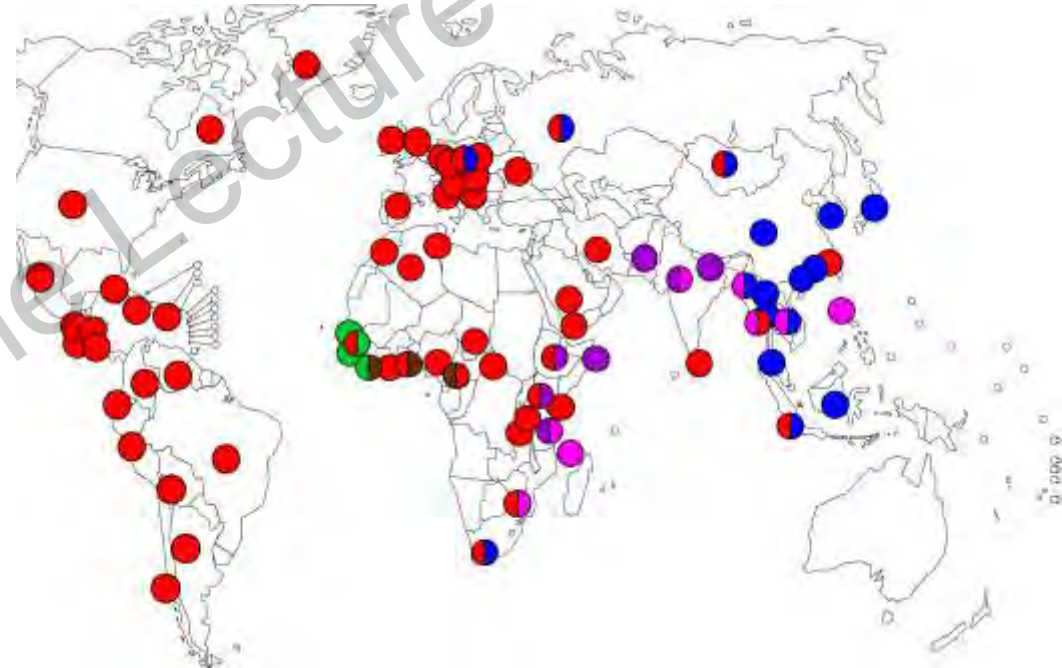




Global Phylogeography of *Mtb*

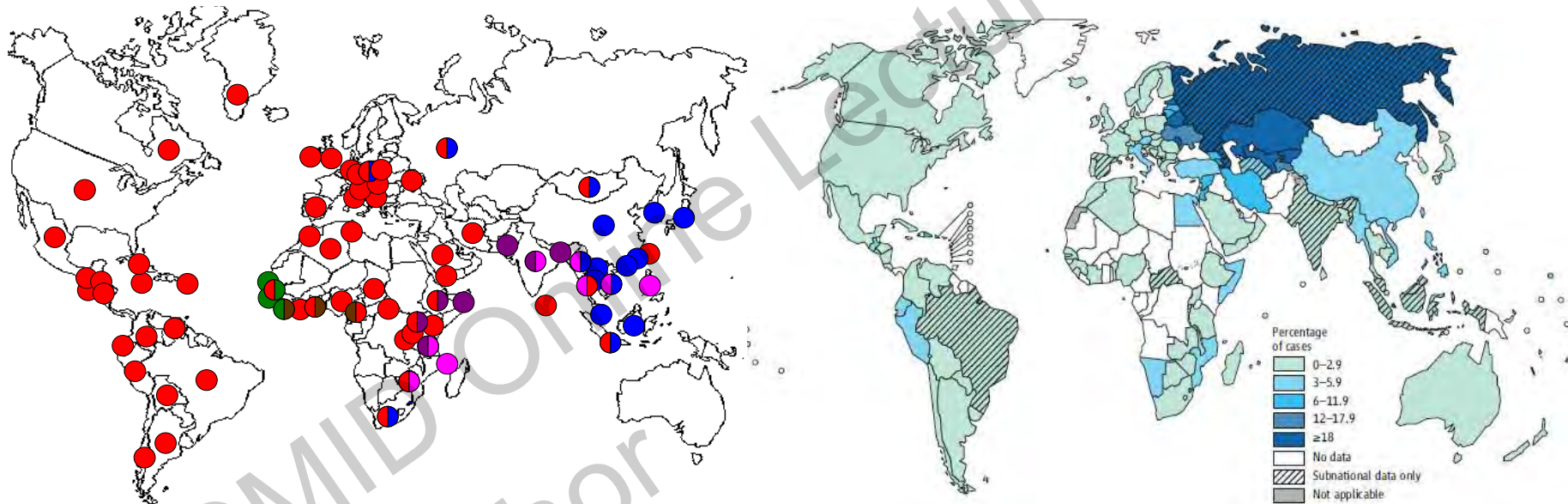


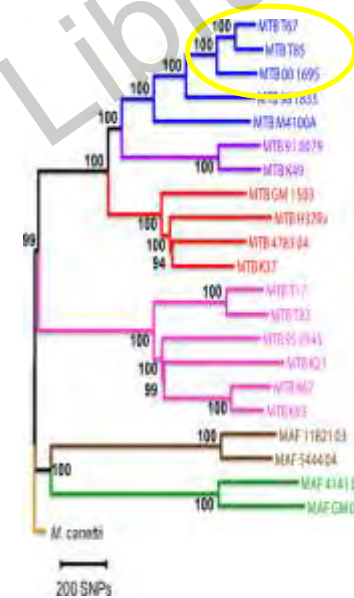
2
3
4
1
5
6





BACTERIAL FACTORS ???

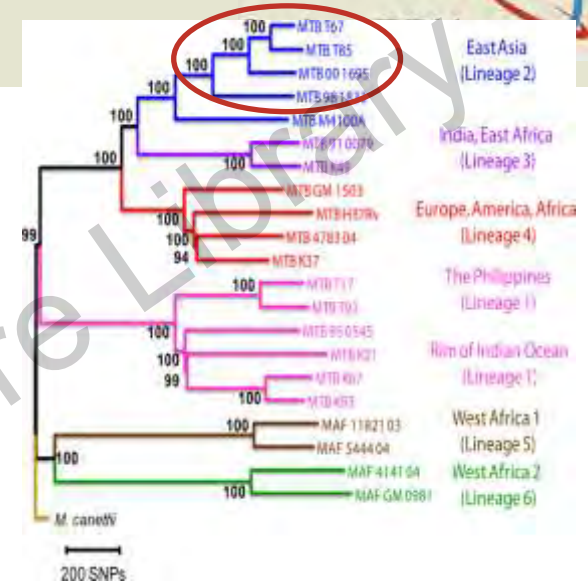




WHO IS BEIJING??

Beijing genotype

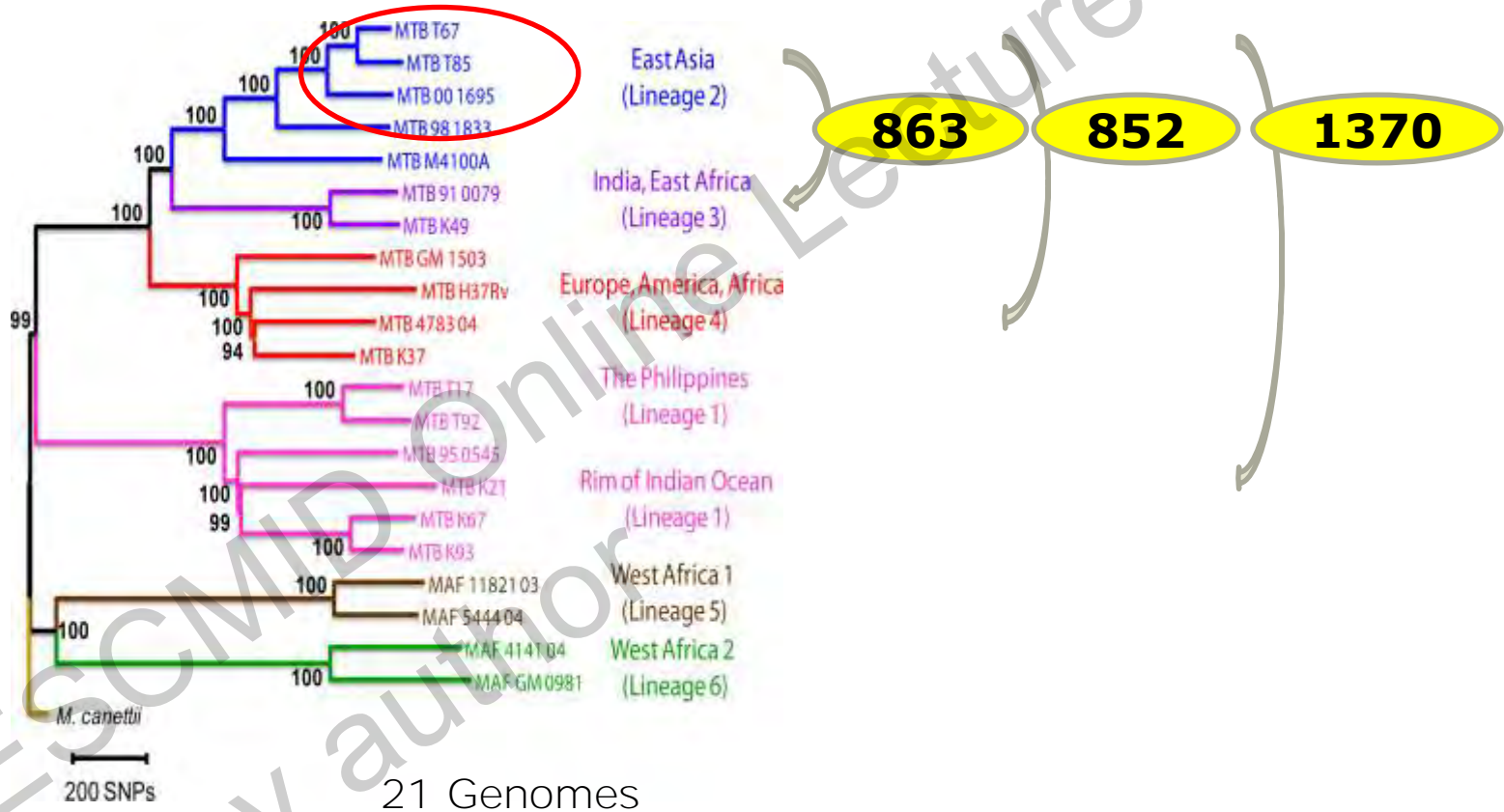
- Identified first time in 1995, Beijing (China).
- Nowadays, in all continents.
- Highly related genetically.
- Largest population increase in the past 180 years.
- 50% of strains in East Asia and 13% of strains worldwide.
- More virulent (transmission, progression from latent to active tuberculosis, linked to escape from BCG vaccination and to relapse).
- Linked to acquisition of drug resistance and to MDR.



Beijing genotype



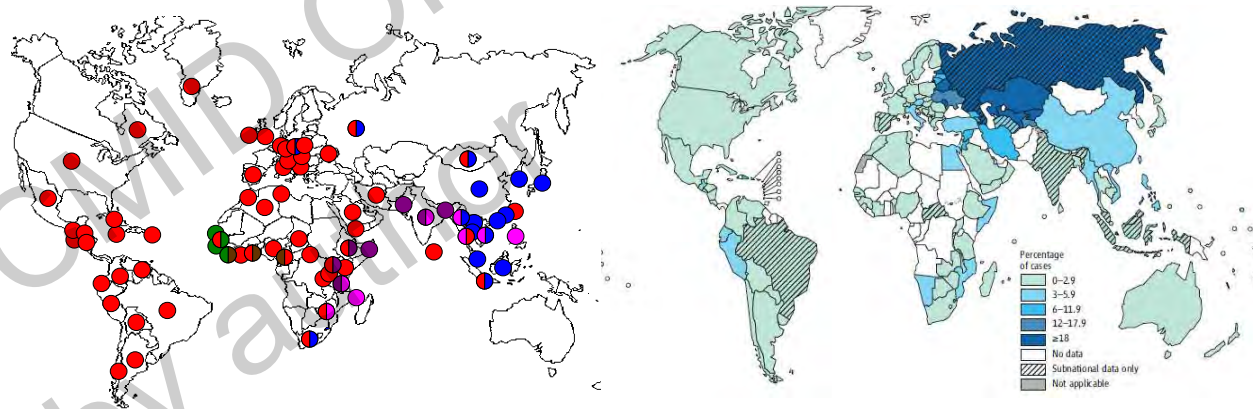
Genetic distance (N°SNPs)



Beijing genotype and DR



- ❖ Beijing genotype is dominant in areas where the burden of MDR-TB is high.
- ❖ Associated with DR outbreaks.
- ❖ **Beijing genotype have repeatedly been associated with DR-TB (some areas)**





WHAT MAKES A DR MTB GENOTYPE SUCCESSFUL?

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PREVALENCE OF A DR GENOTYPE



- **Rate of Acquisition of DR mutation
(acquired resistance)**
- **Rate of Transmission of DR strains
(primary resistance)**

FITNESS

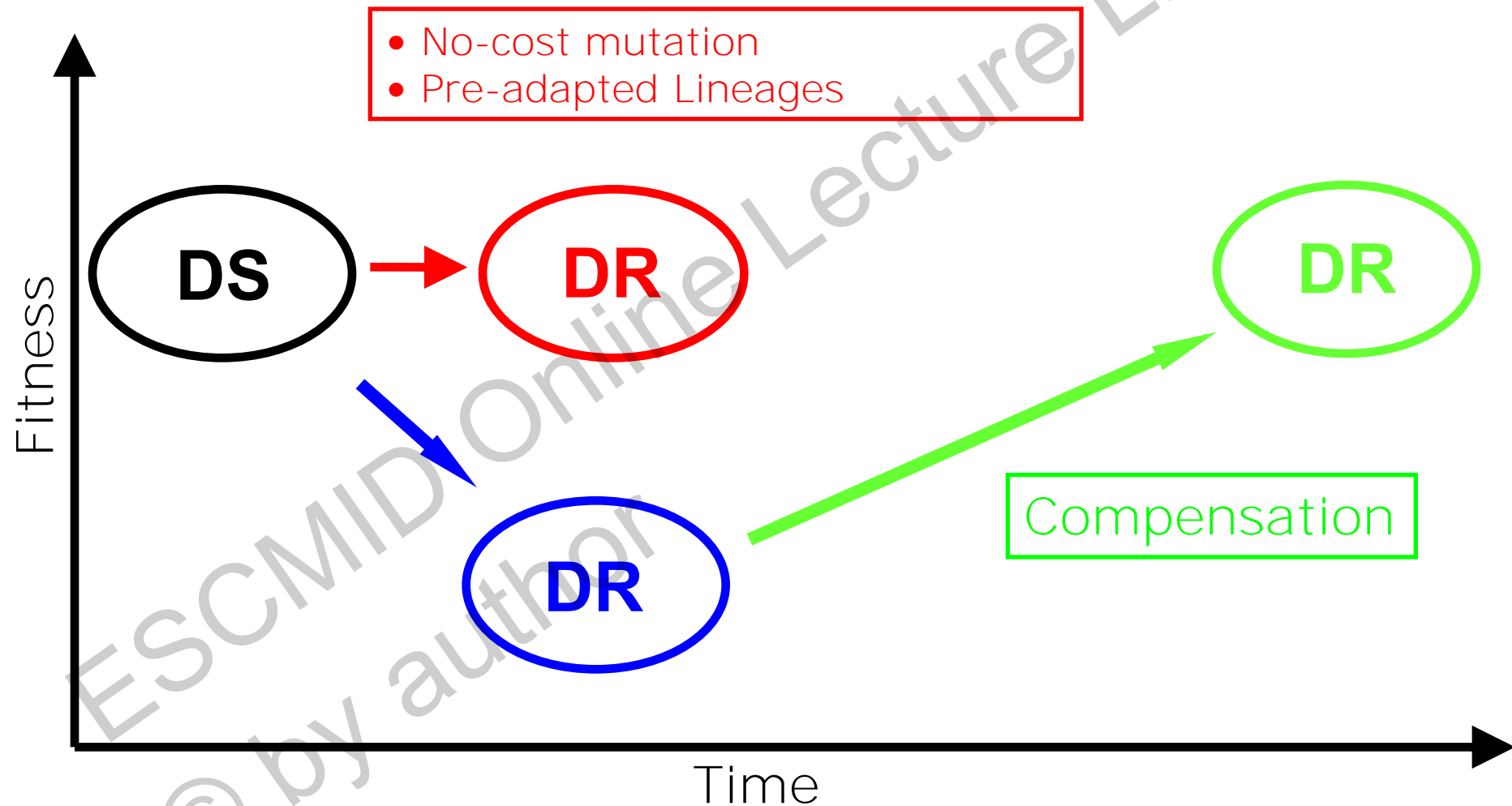


**“Organism’s ability to survive, reproduce
and to be transmitted”**





Evolution of Drug Resistance



TRANSMISSION ??



**Drug-resistance
mutation(s)**

genotype



**Relative Fitness
of DR *Mtb***

**Compensatory
mutations**

Lineage

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Why is DR Beijing more successful?

- ❖ Higher rate of acquisition of mutations???
- ❖ Higher Baseline DR???
- ❖ Better able to adjust to the physiological costs associated to DR mutations????
- ❖ Transmits better????



Acquisition of mutations

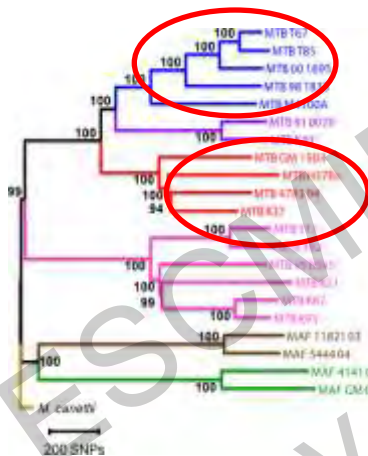
BEIJING-INH MUTATION RATE

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Mycobacterium tuberculosis mutation rate estimates from different lineages predict substantial differences in the emergence of drug-resistant tuberculosis

Christopher B Ford¹, Rupal R Shah¹, Midori Kato Maeda², Sebastien Gagneux^{3,4}, Megan B Murray⁵, Ted Cohen⁵⁻⁷, James C Johnston⁸, Jennifer Gardy^{8,9}, Marc Lipsitch^{1,7} & Sarah M Fortune^{1,10,11}



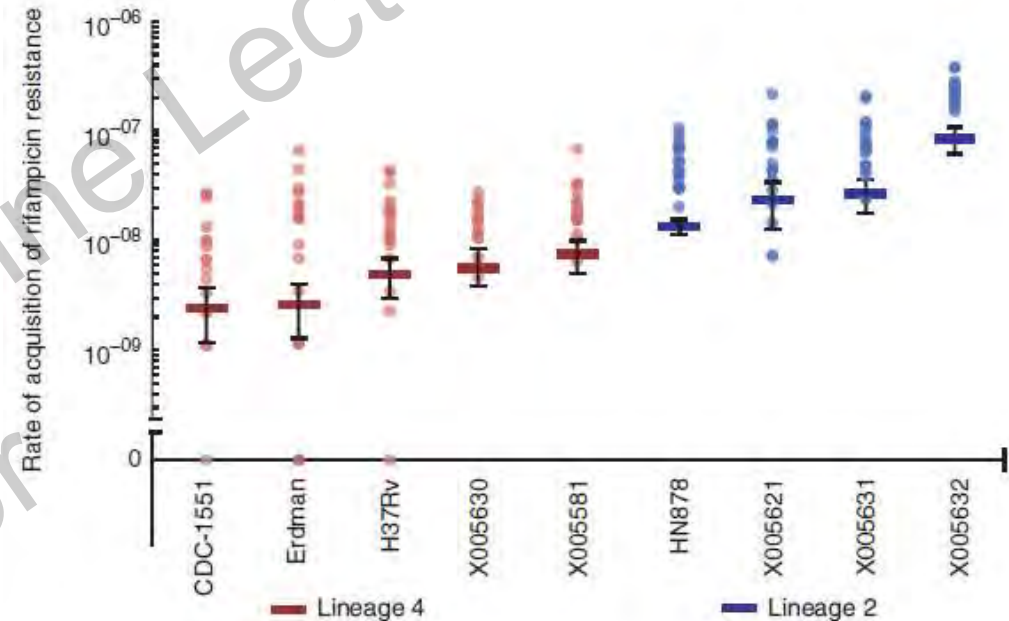
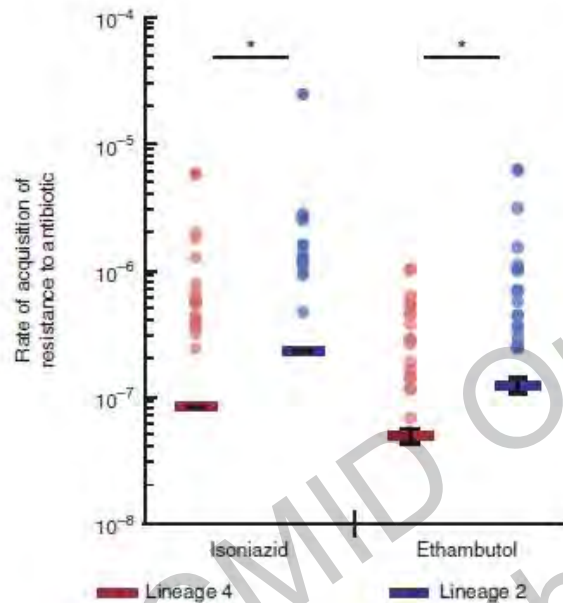
- ❖ Calculate the rate of acquisition of mutations on a panel of isolates from both **lineage 2** and **lineage 4**.
- ❖ Rate of acquisition of resistance to INH, RIF and ETH.

Rate of acquisition of resistance to antibiotic

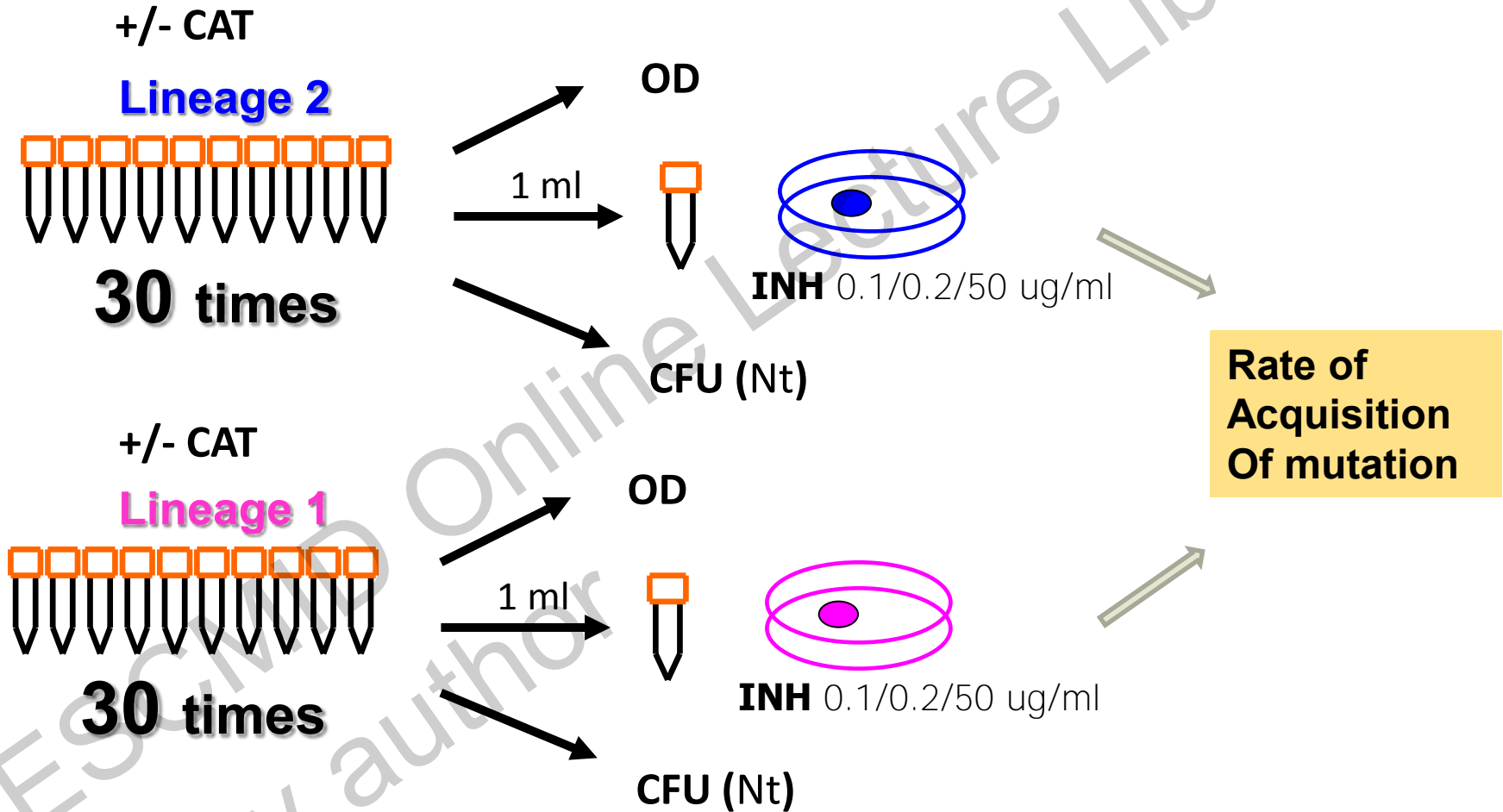
INH

ETH

RIFAMPICINE



Luria-Delbrück fluctuation assay

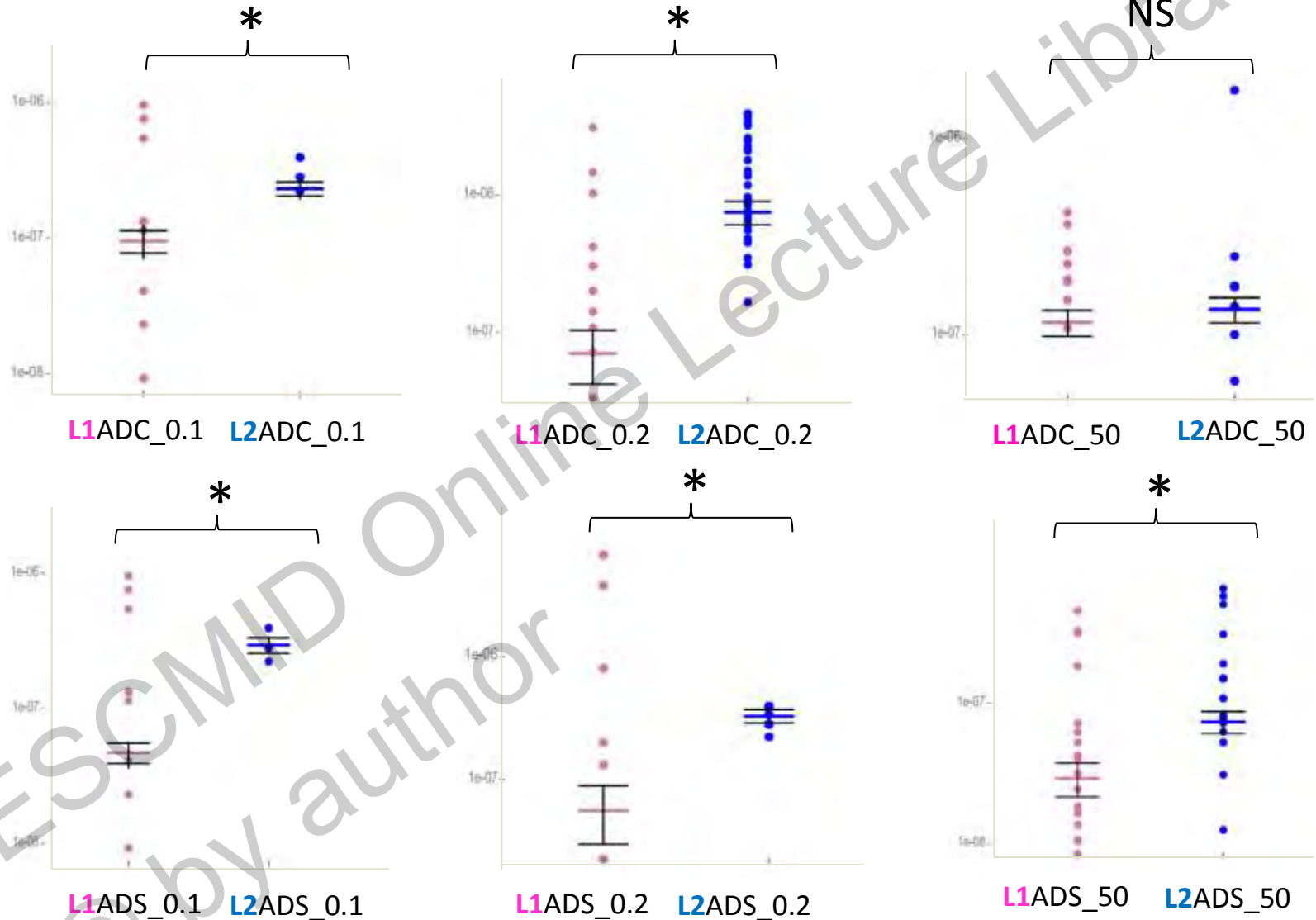


INH Mutation Rate/Lineage

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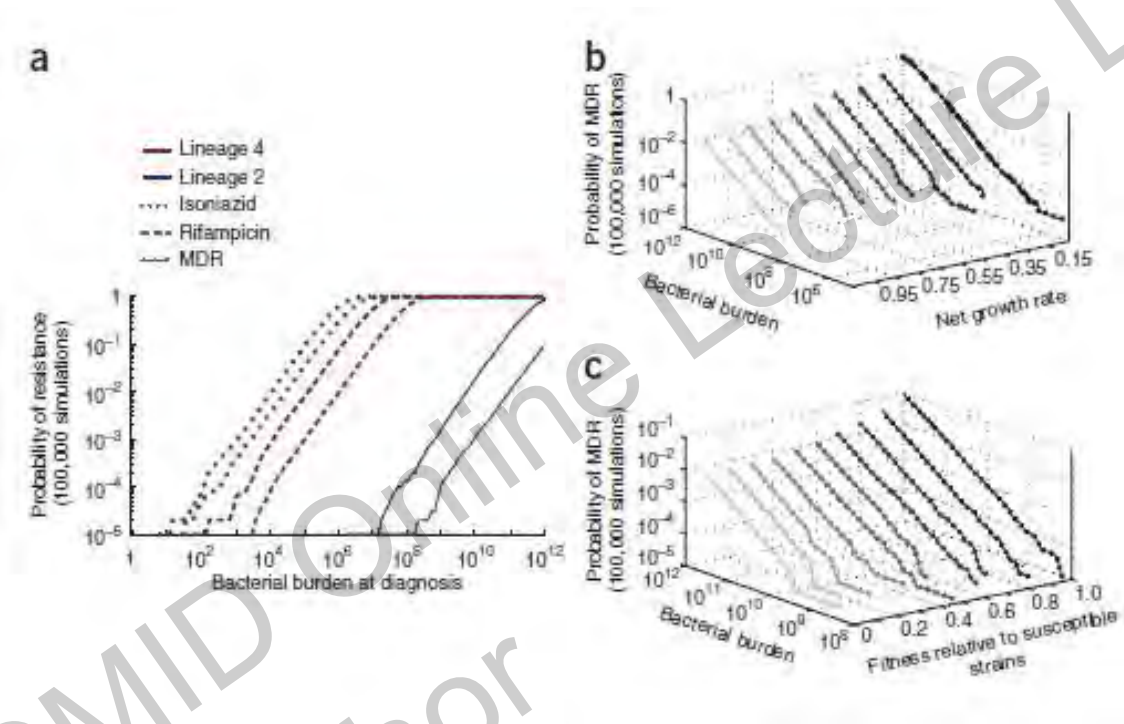
rate of acquisition of INH resistance



Lineage *in vitro* INH-DR acquisition rate



Different lineages have different propensity for the acquisition of MDR



Lineage 2 shows **22x** higher rate of acquired RIF and INH (MDR-TB) resistance compared to **Lineage 4**.



Phenotypic resistance

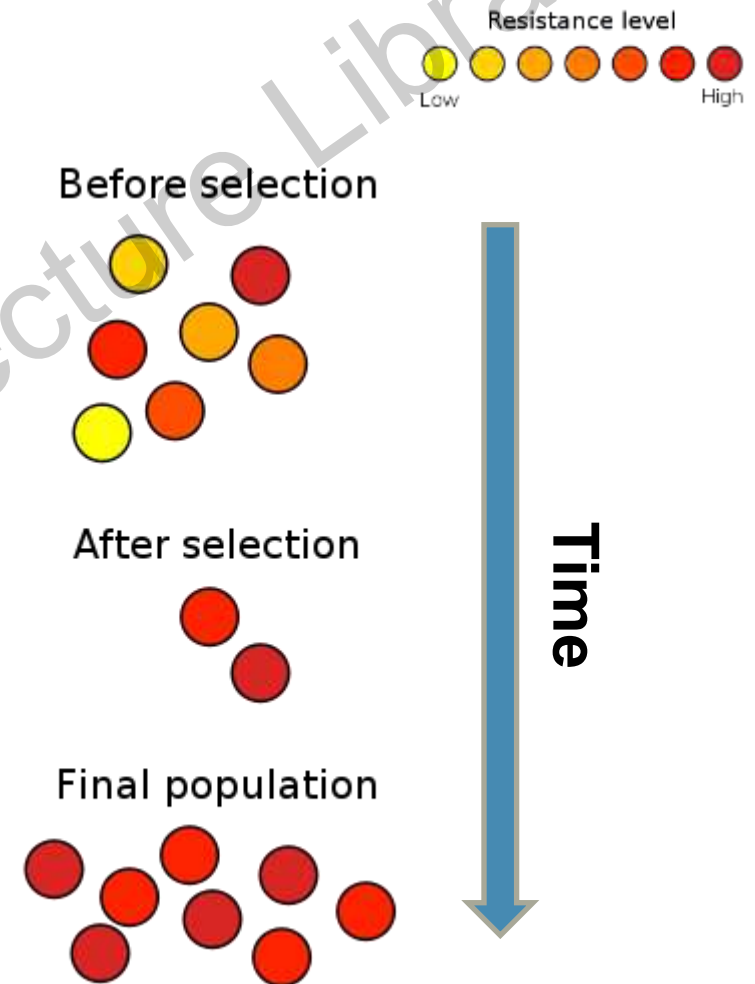
BEIJING-MIC

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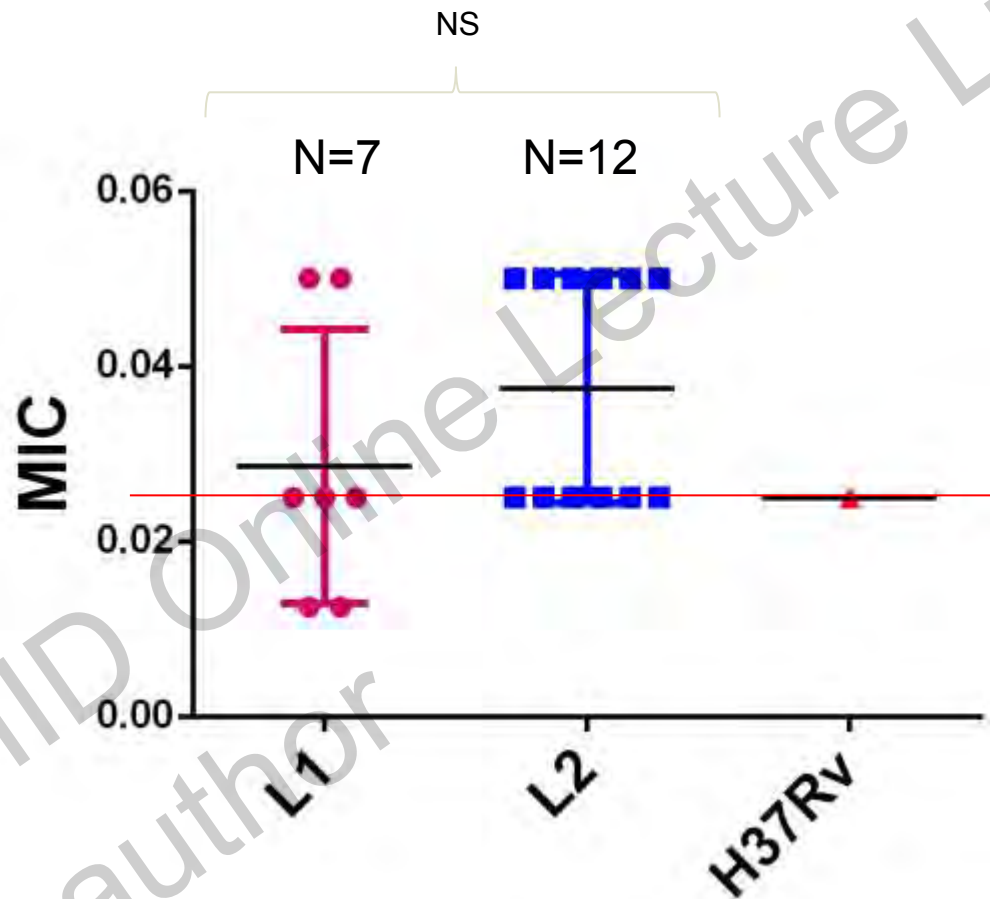


Lineage vs MIC

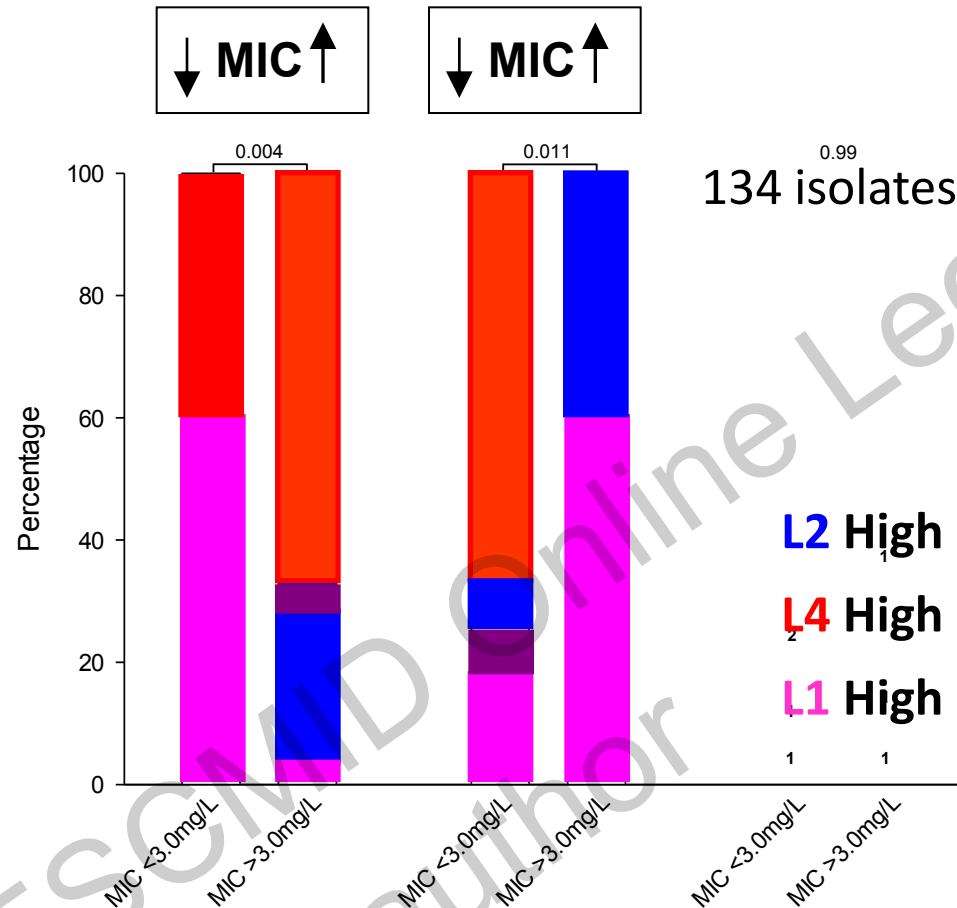
- ❖ Hypothesis: Having a higher baseline DR might give some advantage for the acquisition of further associated resistant mutations.
- ❖ Objective: Evaluate the influence of the Lineage genetic background on the baseline resistant level.



Baseline INH resistance



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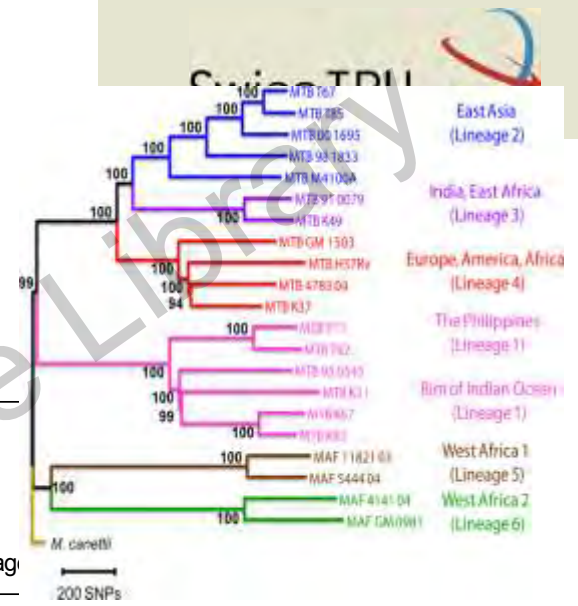
KatG 315 mutations

InhA pro -15 mutations

Other or no mutation detected

0.99
134 isolates

- Lineage 1
- Lineage 2
- Lineage 3
- Lineage 4
- Other lineage



L2 High MIC both mutations

L4 High MIC *KatG* mut, Low MIC *inhApro*

L1 High MIC *inhApro*, low MIC *KatG*



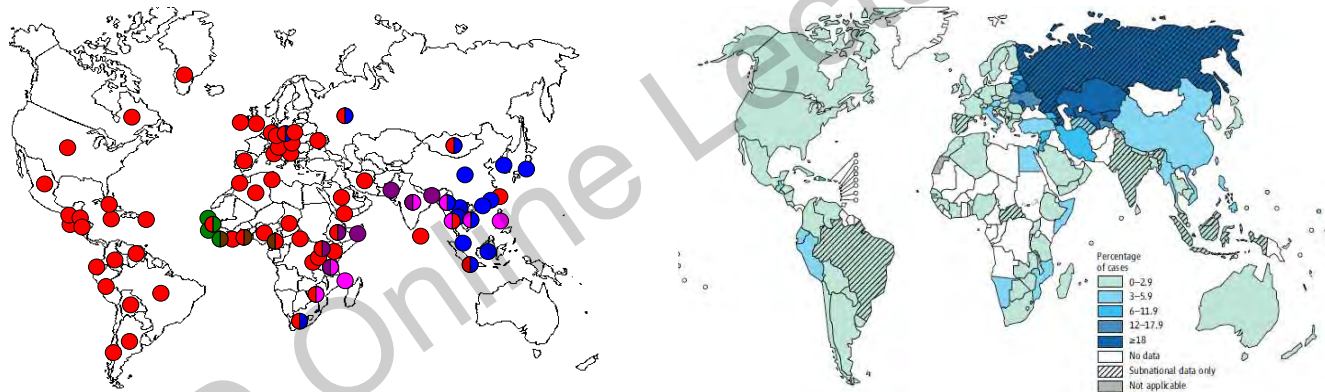
Transmission

DOES DR-BEIJING GENOTYPE TRANSMIT BETTER?

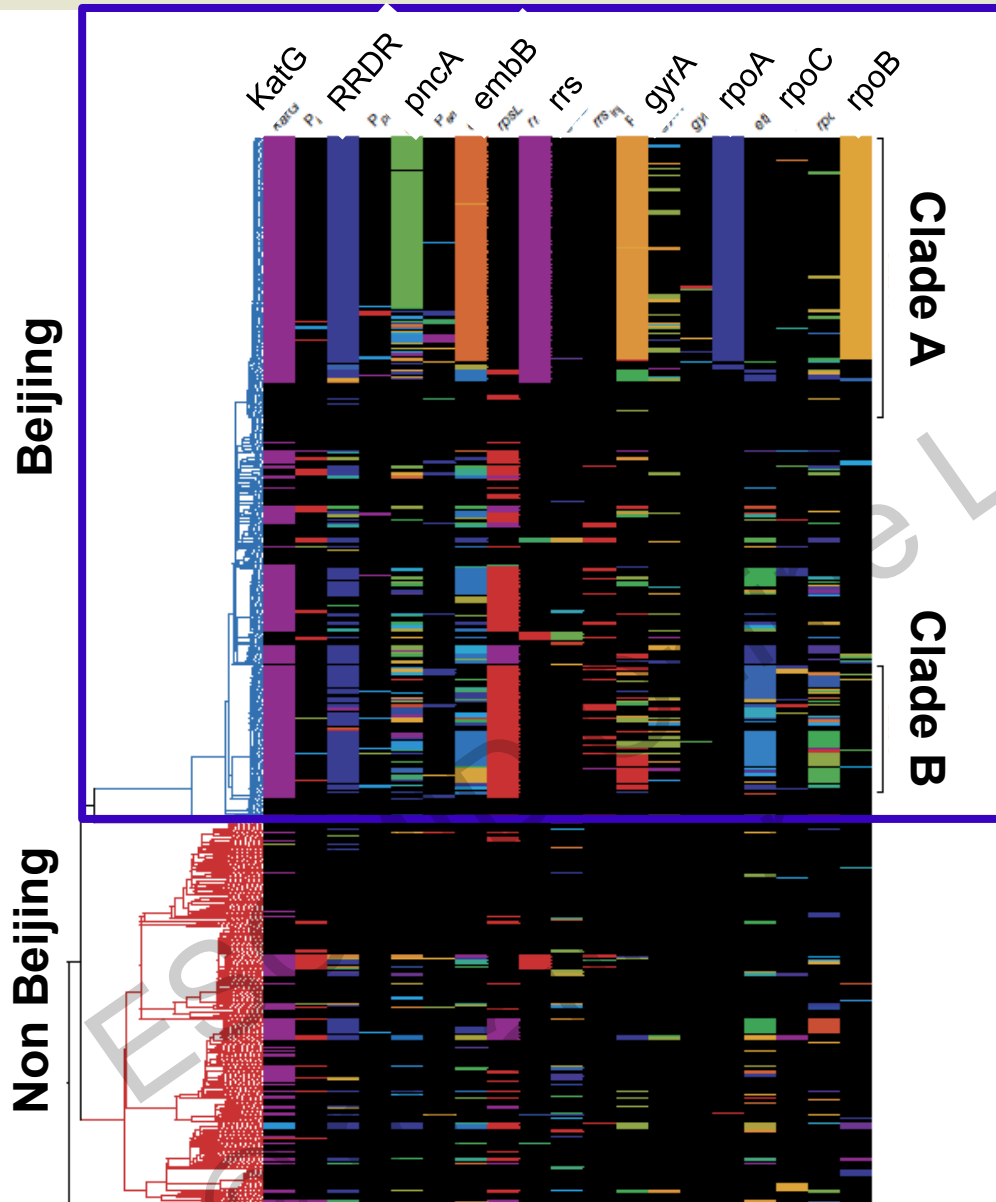


Evolution and transmission of drug-resistant tuberculosis in a Russian population

Nicola Casali¹, Vladyslav Nikolayevskyy¹, Yanina Balabanova¹, Simon R Harris², Olga Ignatyeva¹, Irina Kontsevaya¹, Jukka Corander⁴, Josephine Bryant², Julian Parkhill², Sergey Nejentsev², Rolf D Horstmann⁶, Timothy Brown¹ & Francis Drobniewski^{1,7}



- ❖ 1000 Whole Genome Sequences of patients isolates from Samara, Russia
- ❖ 48% isolates MDR and 16% XDR
- ❖ Representative sample of all the population and of the whole region.
- ❖ **64% Beijing**



- + Recent transmission
- + MDR phenotype
 - 66% Beijing
- + Compensatory mutations



Is DR Beijing a more successful genotype?

- ❖ Beijing acquires **INH-DR** at a higher rate.
- ❖ INH-DR Beijing **show a Higher** Clinical M...
- ❖ More transmissi... clinical setting.

YES

Thanks to...

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