Evolution of mutation rates in bacteria

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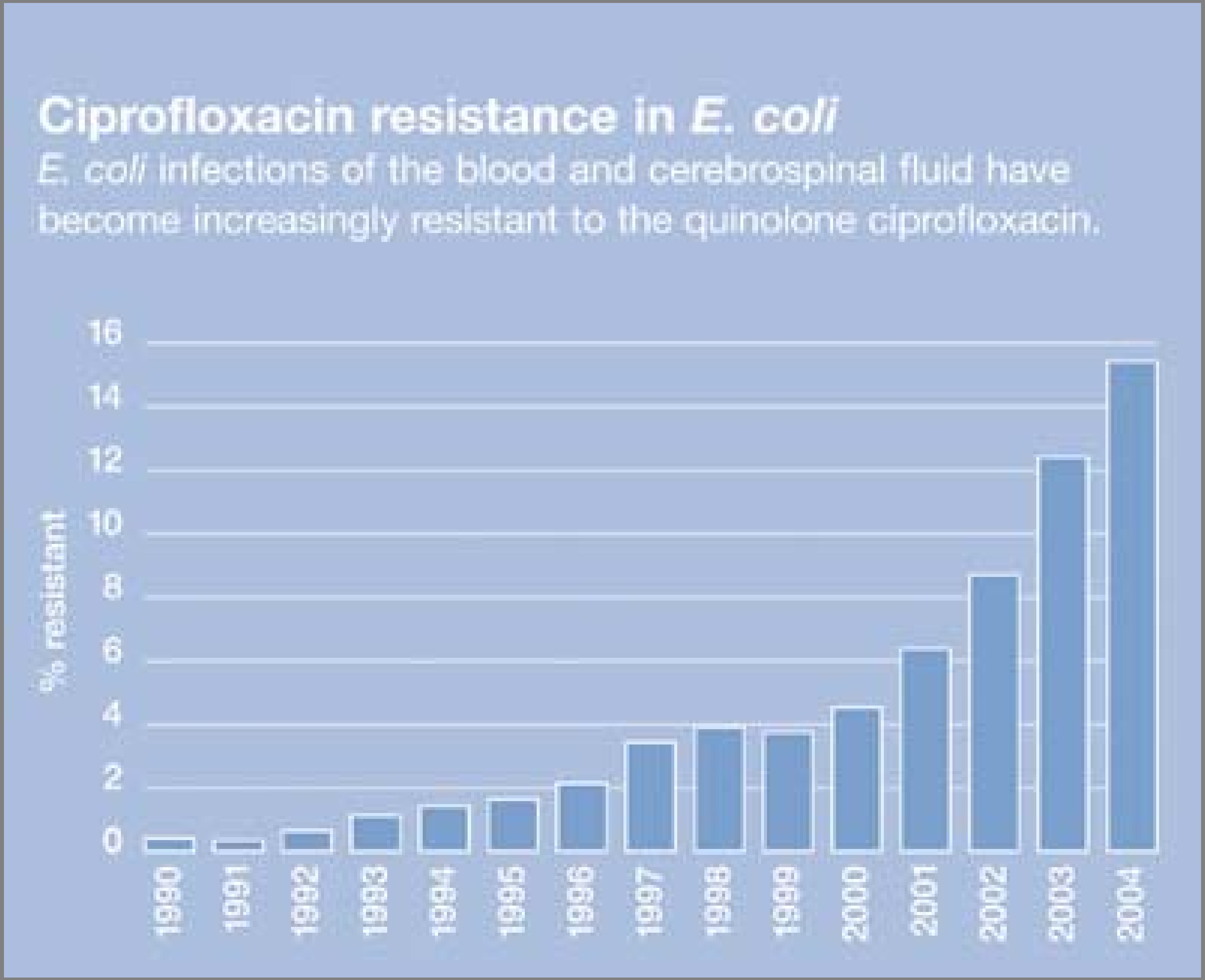
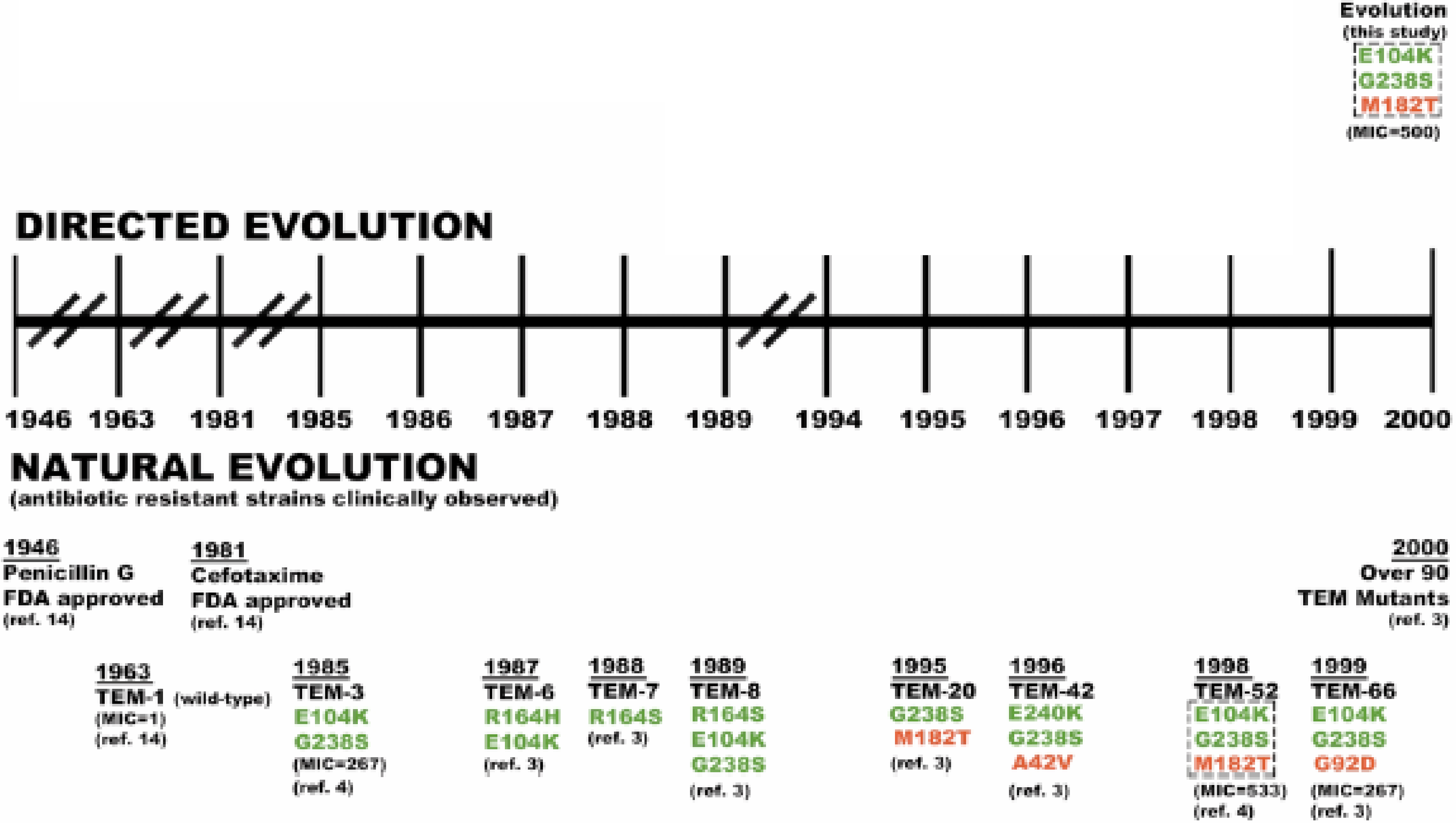
Evolution and human world: antibiotic



Evolution of genes coding for ESBL



Orencia et al Nat Struct Biol. 2001 8:238-242

Classical view

The rate of mutagenesis must be minimal because:

-Mutations are essentially neutral or deleterious

-Cost of anti-mutator systems

Neutral mutations

Some nucleotide changes do not change the amino acid coded for because genetic code is redundant

– 3rd codon position often synonymous
– 2nd position never
– 1st position sometimes

Neutral mutations are:

- neither advantageous nor disadvantageous
- **invisible** to selection

Proteins often have functional constraints

This may involve :

- few amino acids in a critical site

- almost the whole protein

The stronger the functional constraint,
the slower the rate of evolution

Deleterious mutation

- Confers **decrease** in the fitness of the organism
- Selection acts to remove this mutation

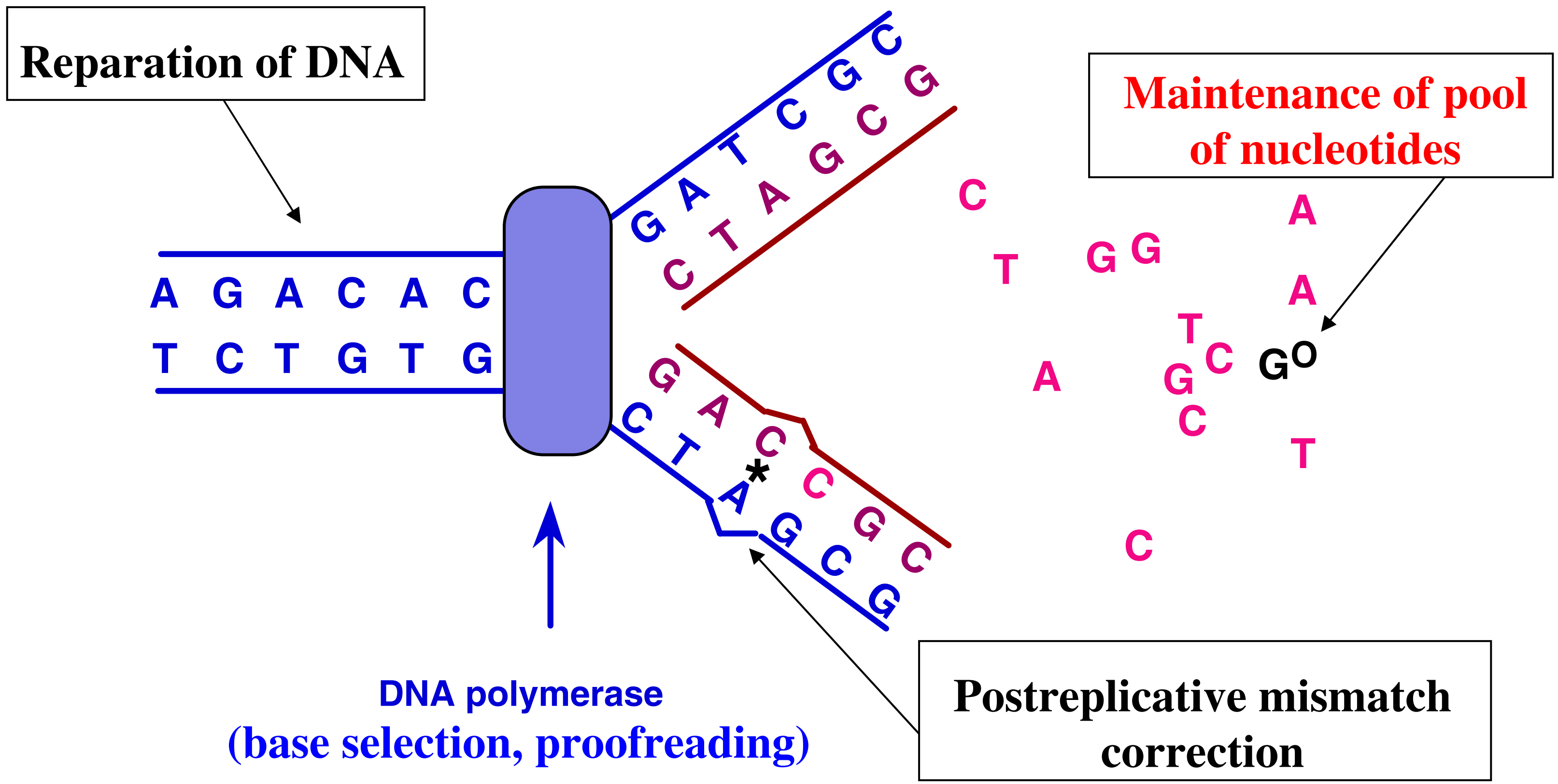
Beneficial mutation

- Confers **increase** in the fitness of the organism
- Selection acts to favour this mutation

Rates of different types of mutations in *Escherichia coli*

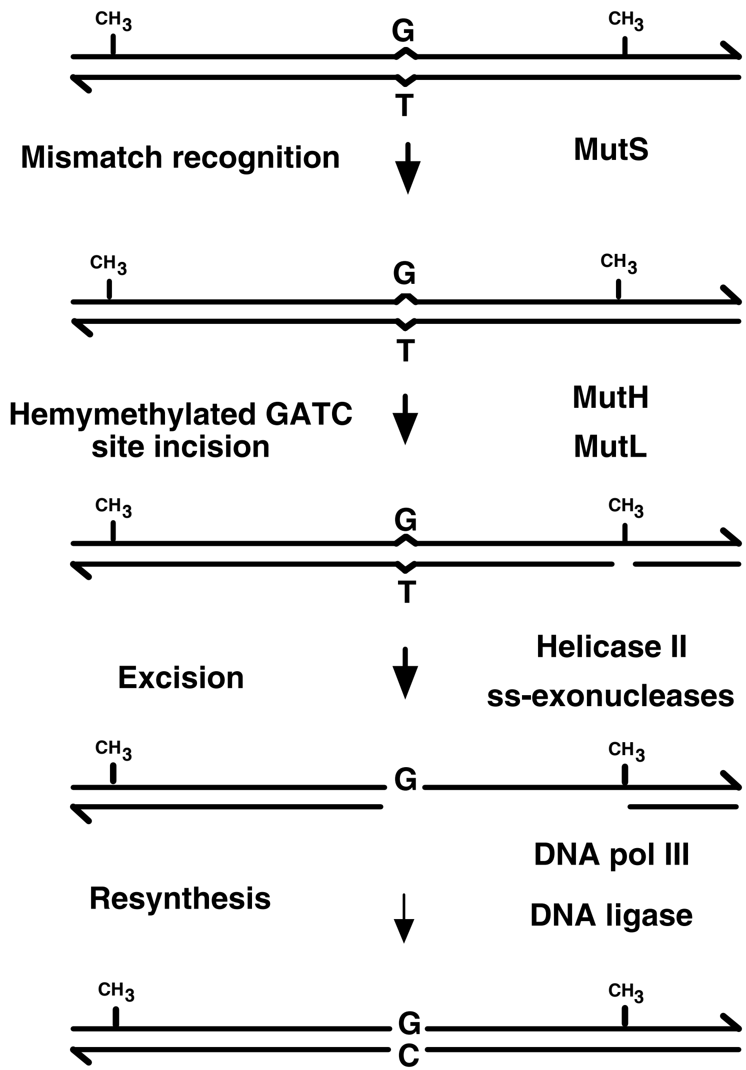
😐	Neutral	10^{-3}
☠	Lethal	10^{-5}
☹	Deleterious	10^{-4}
☺	Beneficial	10^{-8}

Fidelity of DNA replication

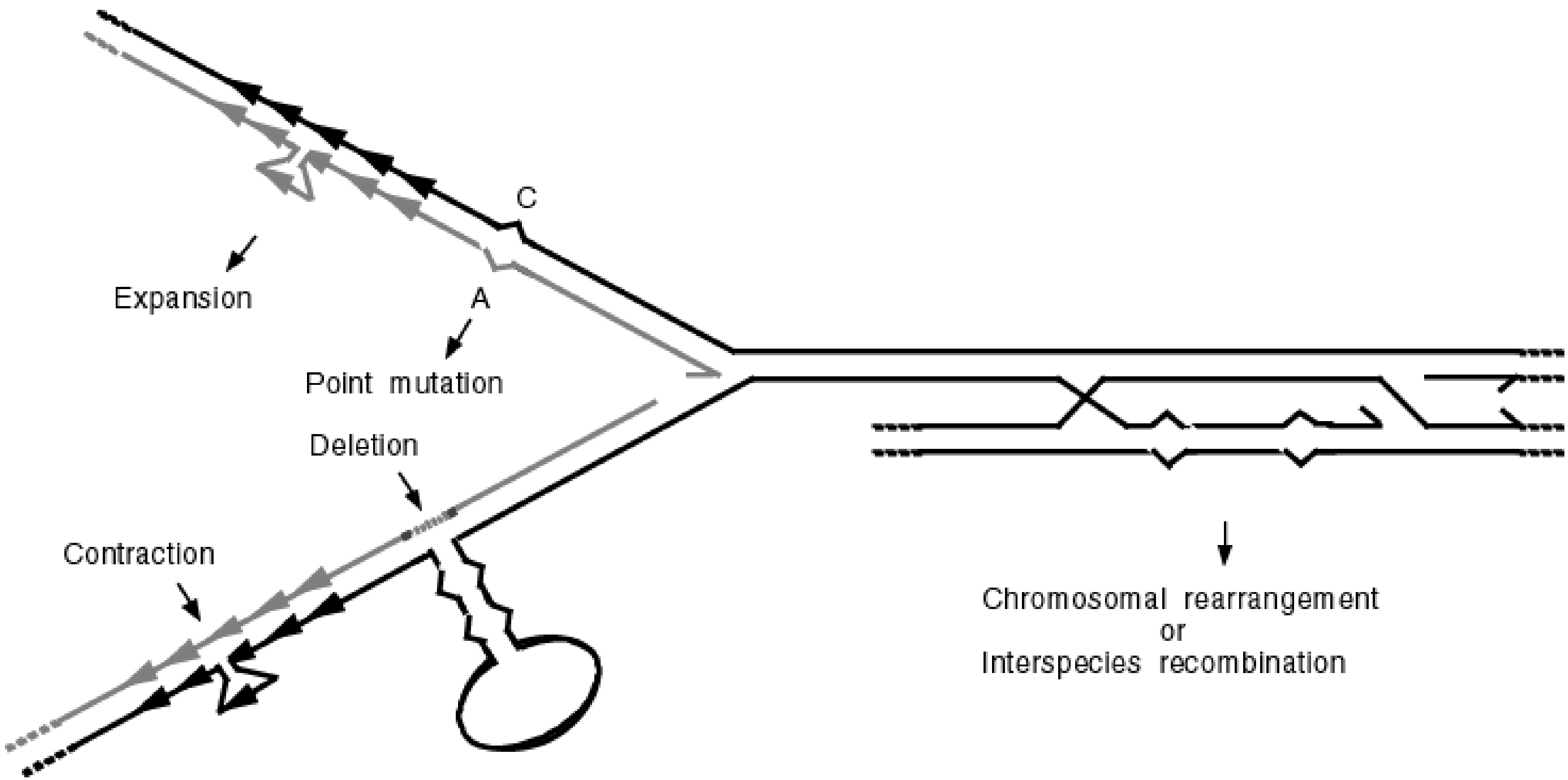


Error rate 10^{-10} / base /replication

Methyl-Directed Mismatch Repair System



Mismatch repair system controls genetic stability



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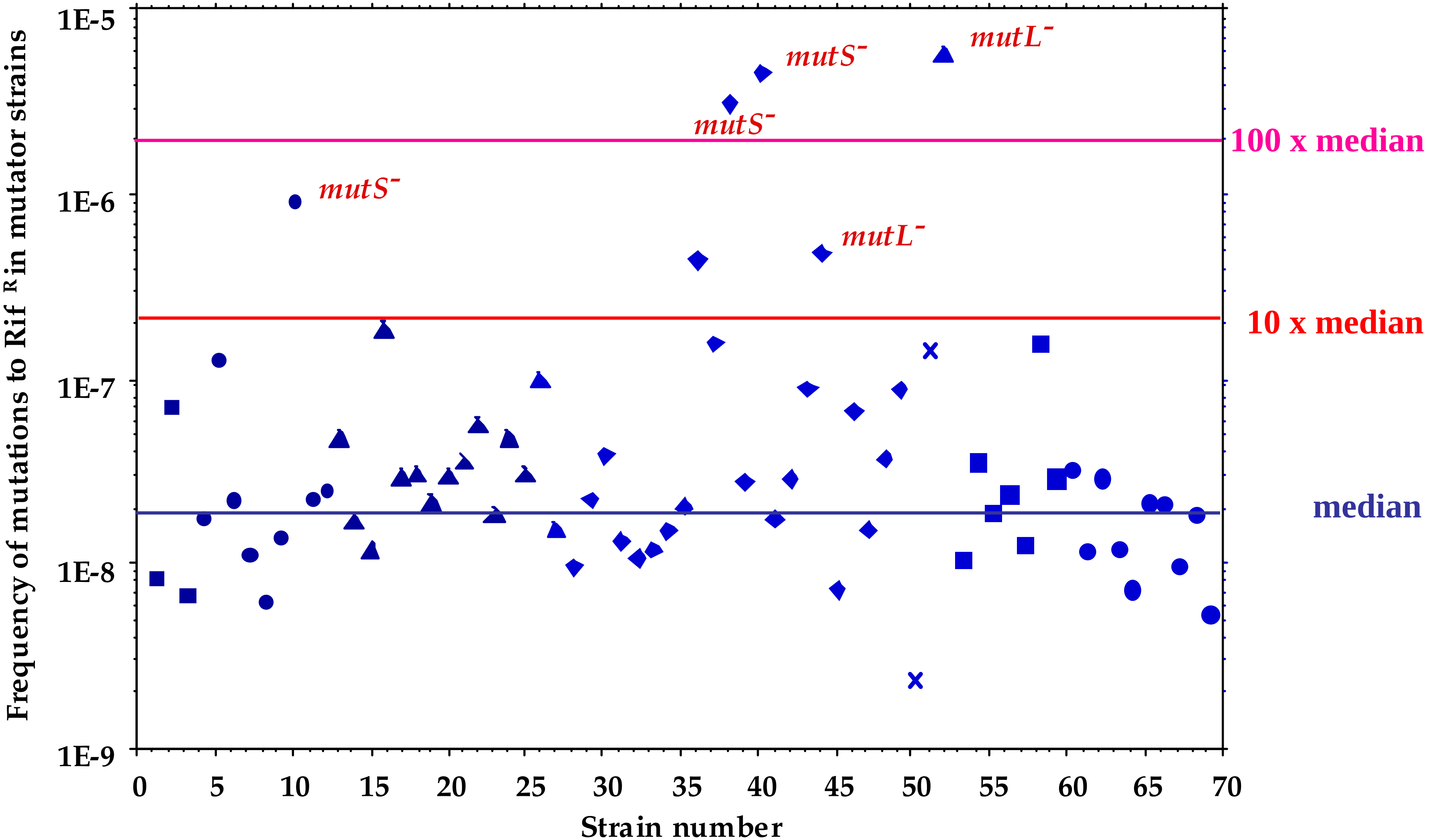
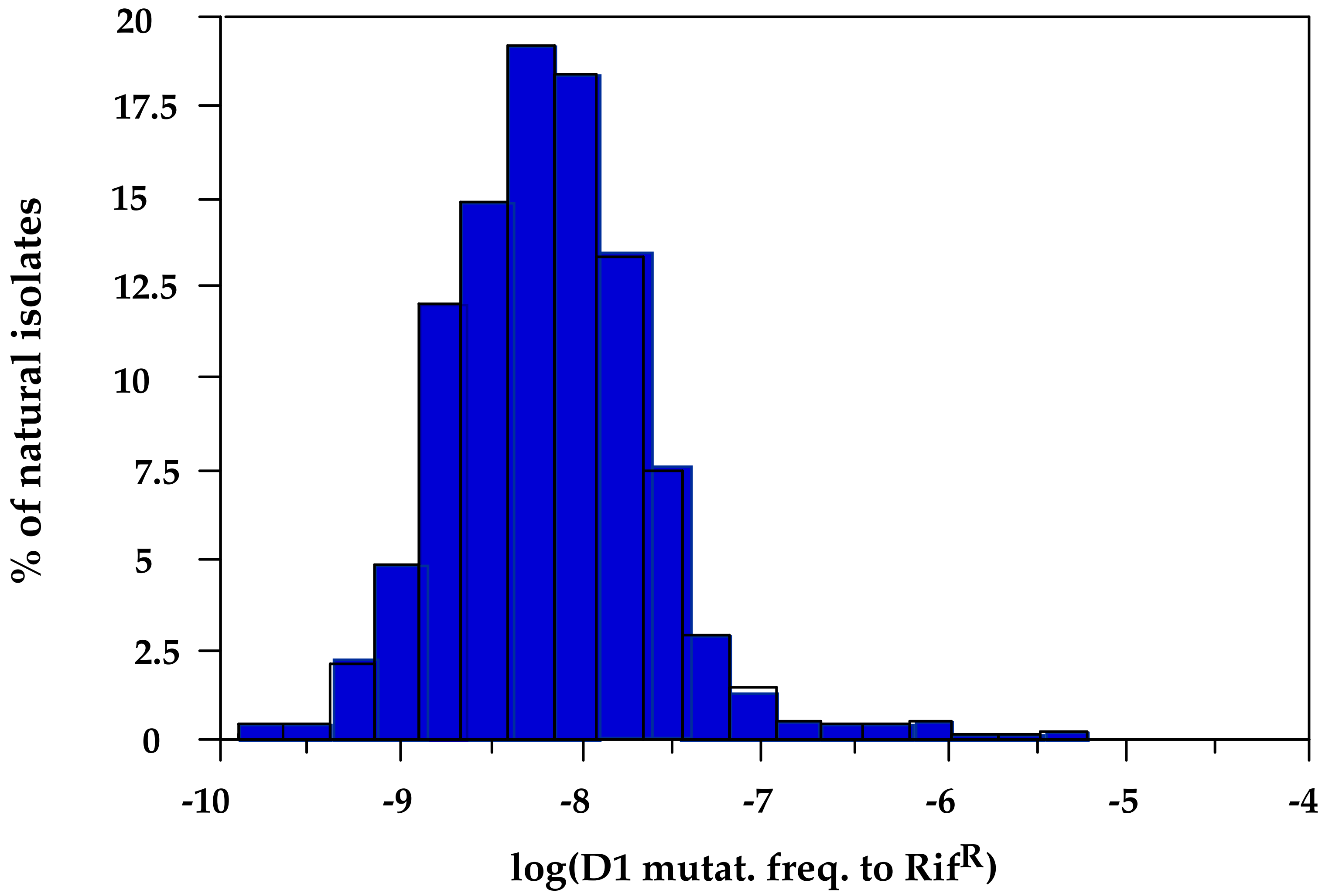
High polymorphism of mutation rates in commensal and pathogenic *Escherichia coli* natural isolates

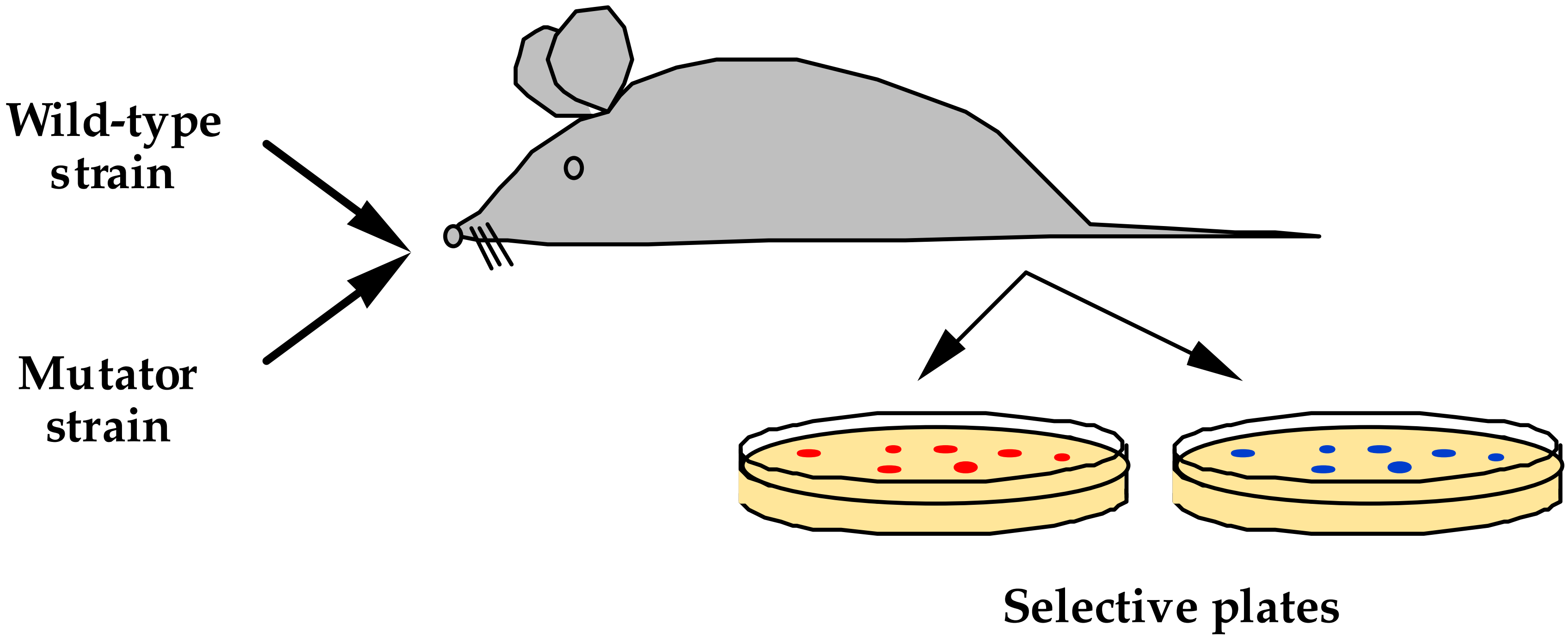


I. Matic, M. Radman, F. Taddei, B. Picard, C. Doit, E. Bingen, E. Denamur and J. Elion
Science (1997) vol. 277 p. 1833

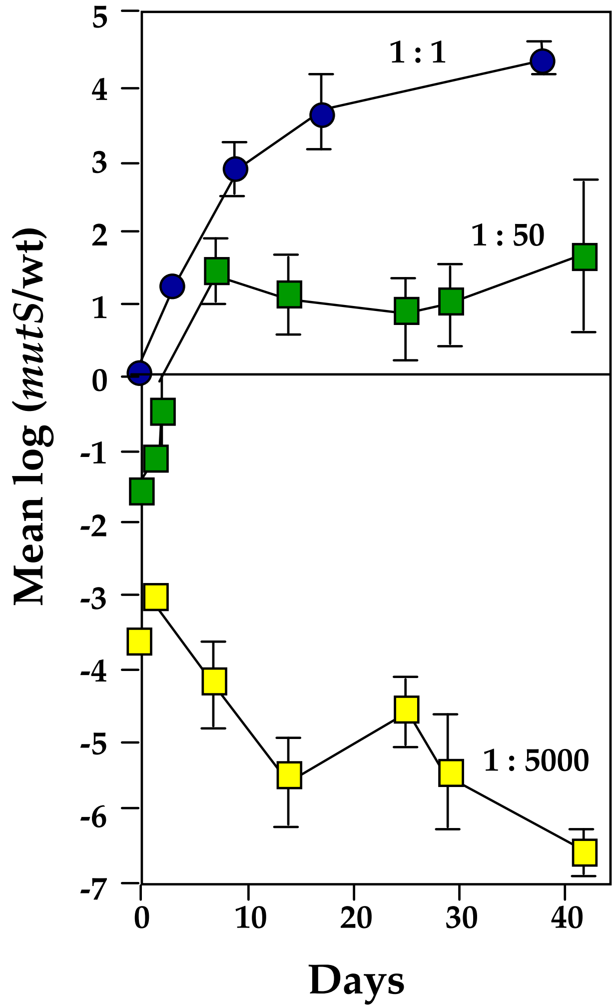
Polymorphism of constitutive mutation rates among *E. coli* natural isolates



Competition in germ-free mice

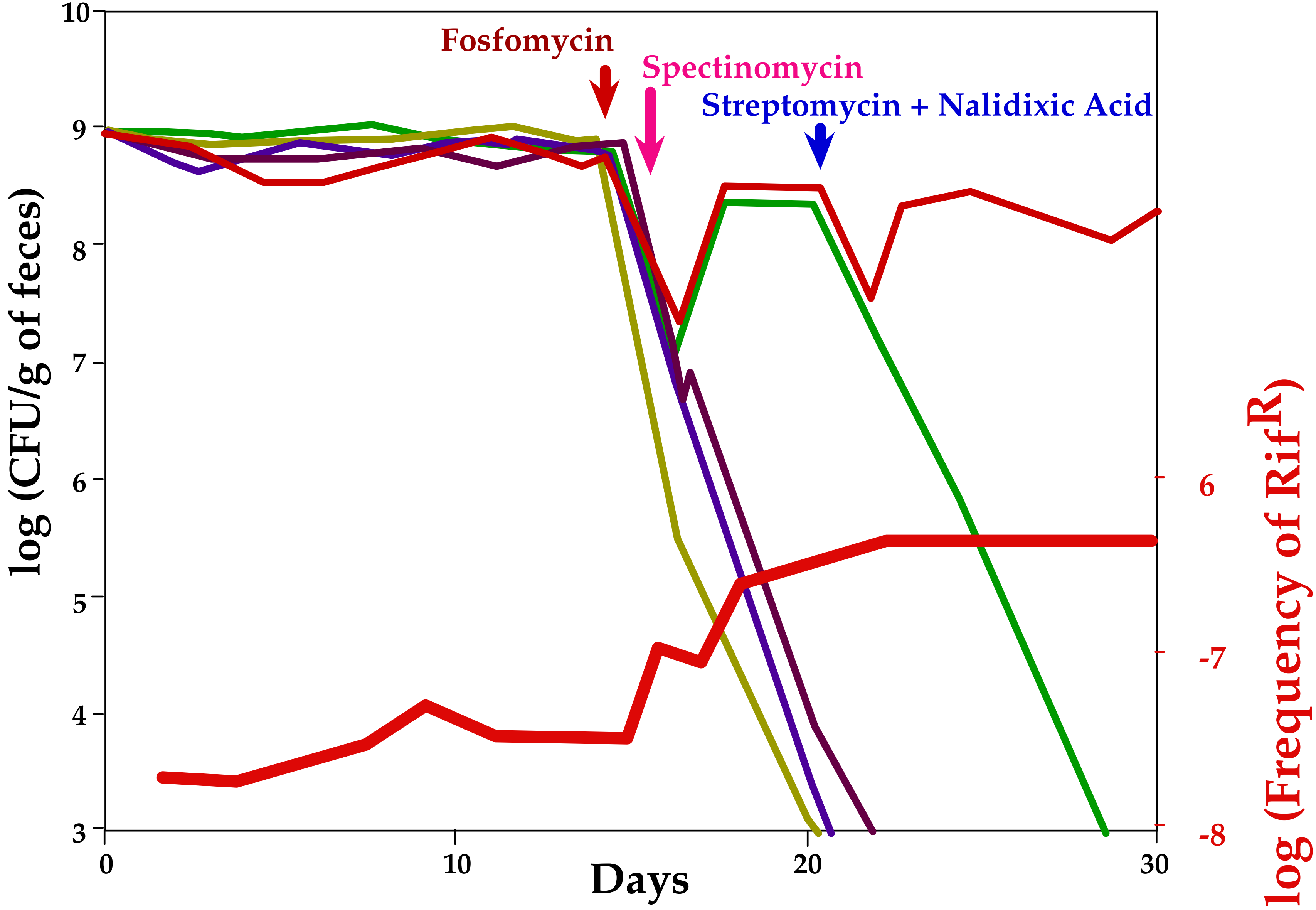


Competitiveness of mutator bacteria:
Role of population size



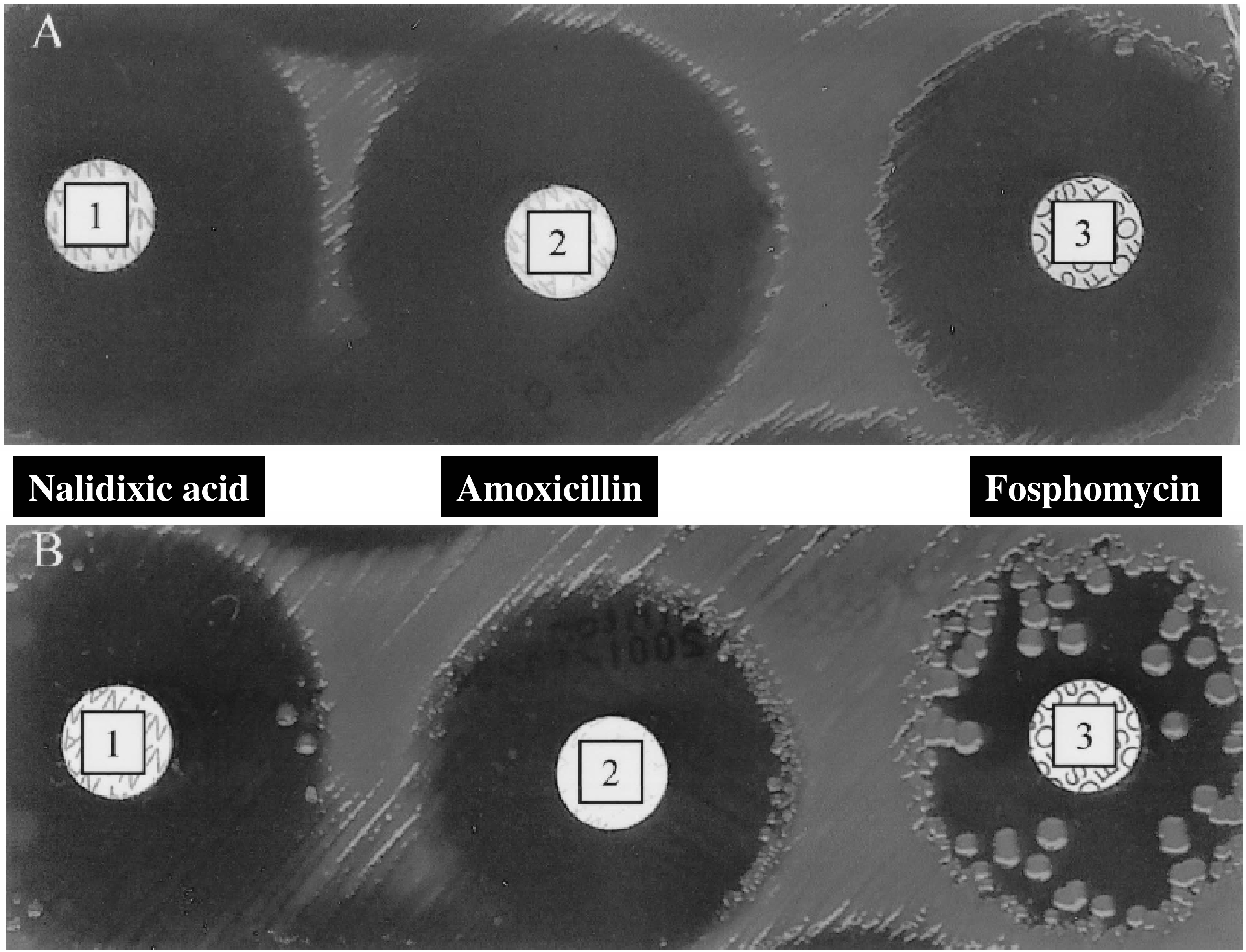
Giraud, A., I. Matic, O. Tenaillon, A. Clara, M. Radman, M. Fons, and F. Taddei. 2001.
Costs and benefits of high mutation rates: adaptive evolution of bacteria in the mouse gut.
Science 291:2606-2608

Selection of mutators by antibiotic treatment in the gut of germ-free mice



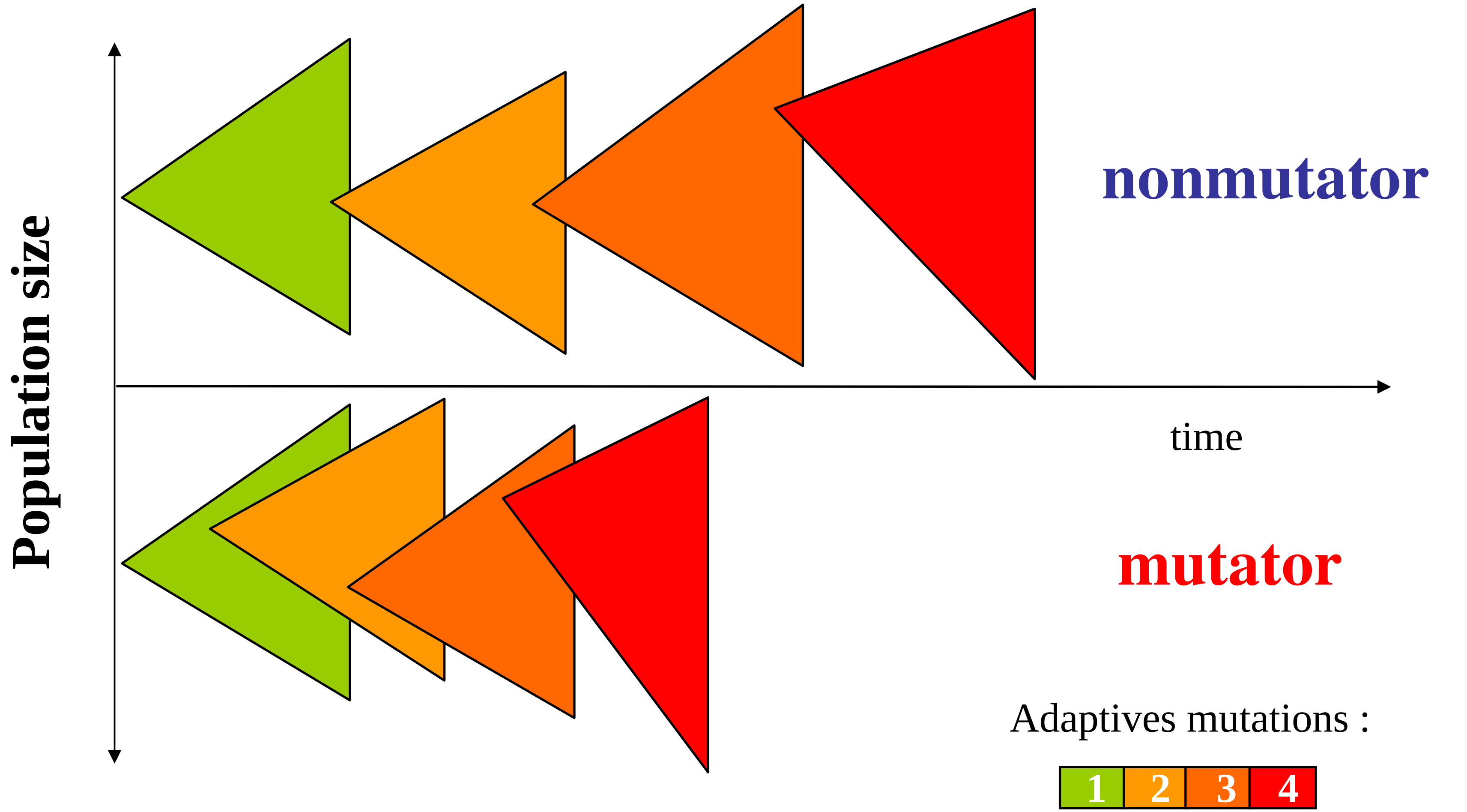
Antibiotic treatment can select mutators that resist treatment with other antibiotics

Non mutator (**A**) and mutator (**B**) phenotypes on antibiograms



Denamur et al J. Bacteriol 2002

Adaptation rate of mutator and nonmutator populations



Selection of mutator alleles depends on:

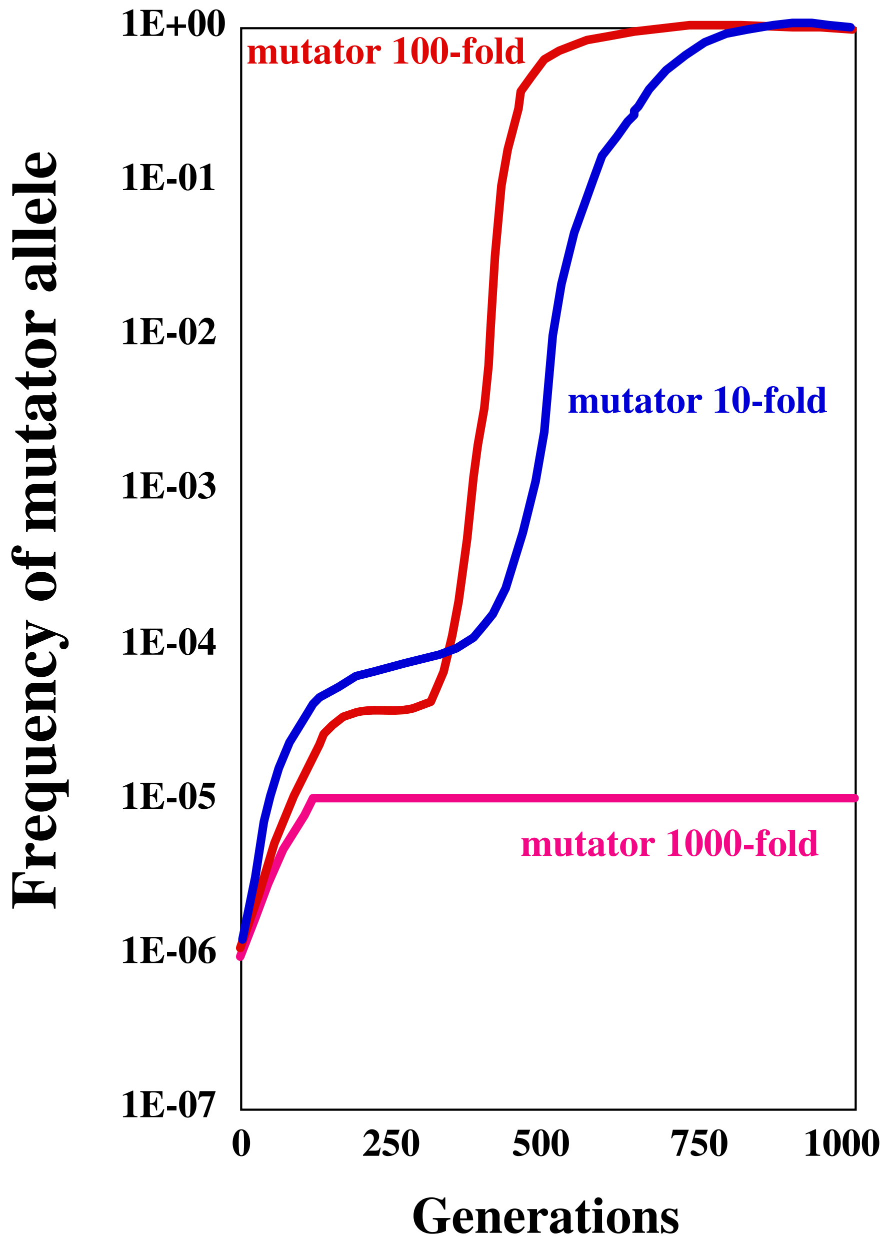
Number of adaptive mutation

Nature of selective pressure

Population size

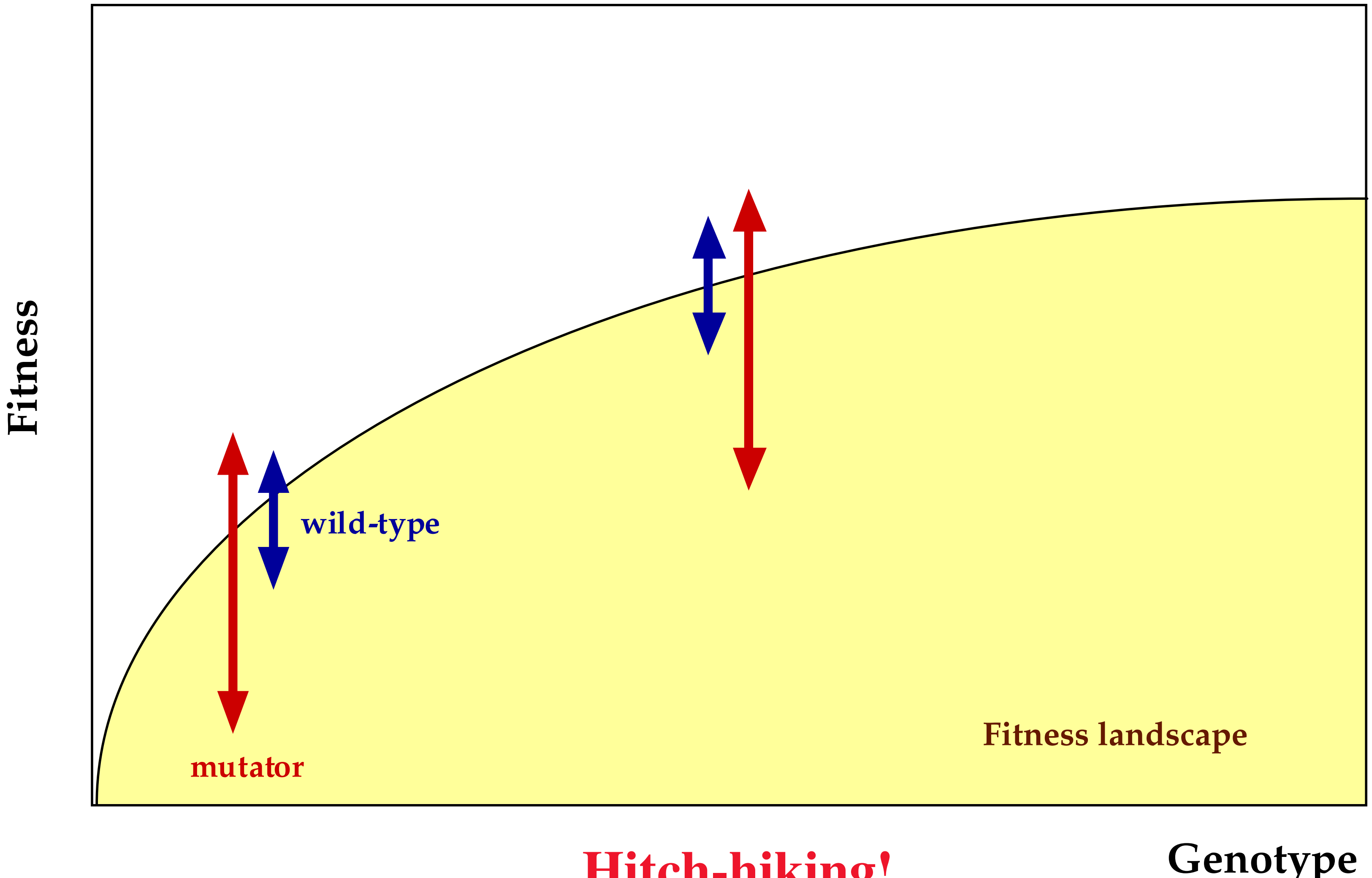
Mutator strength

Selection of a mutator depends on its strength



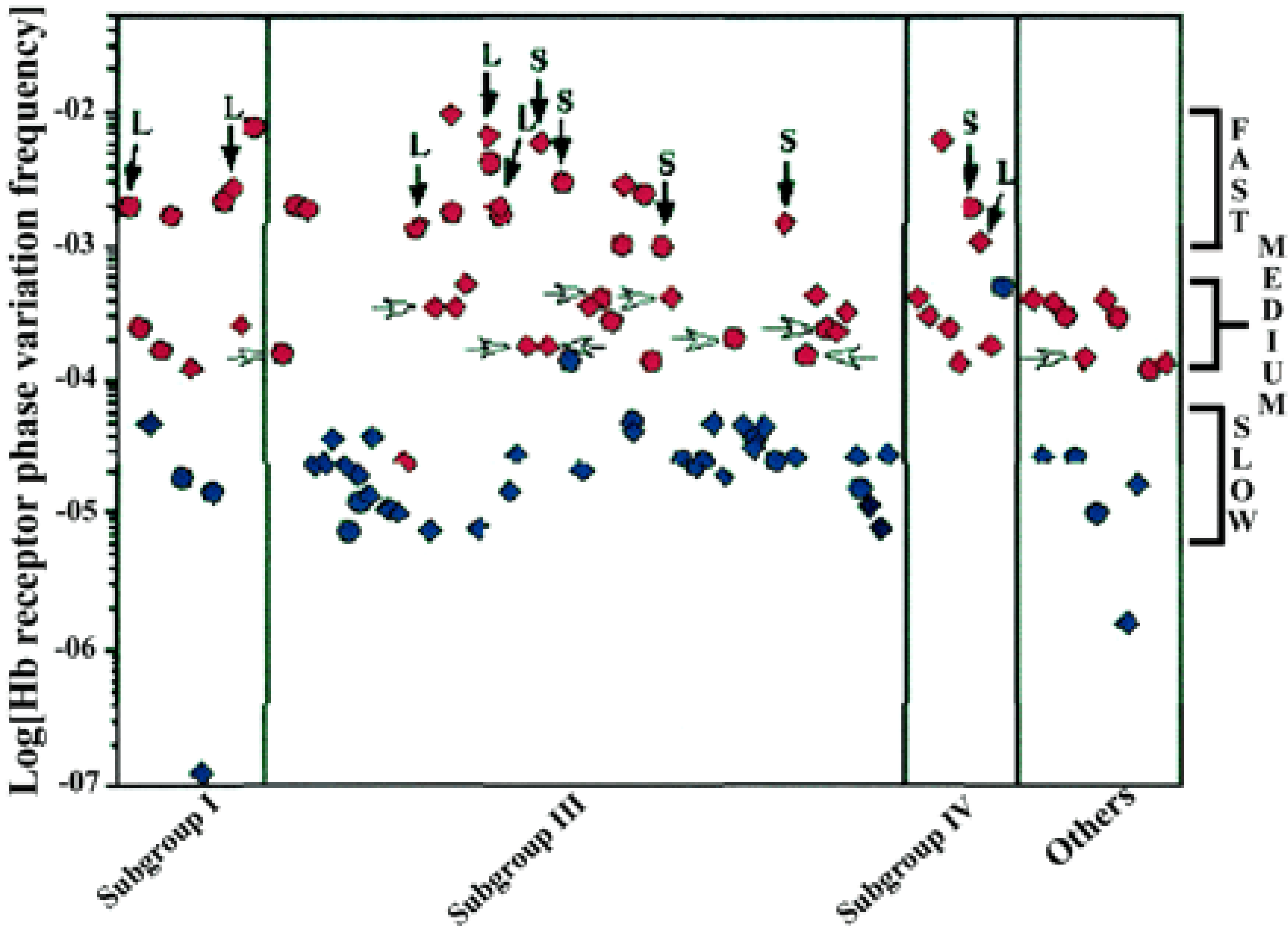
Taddei et al Nature (1997)

Role of mutators in adaptation to a new enviroment



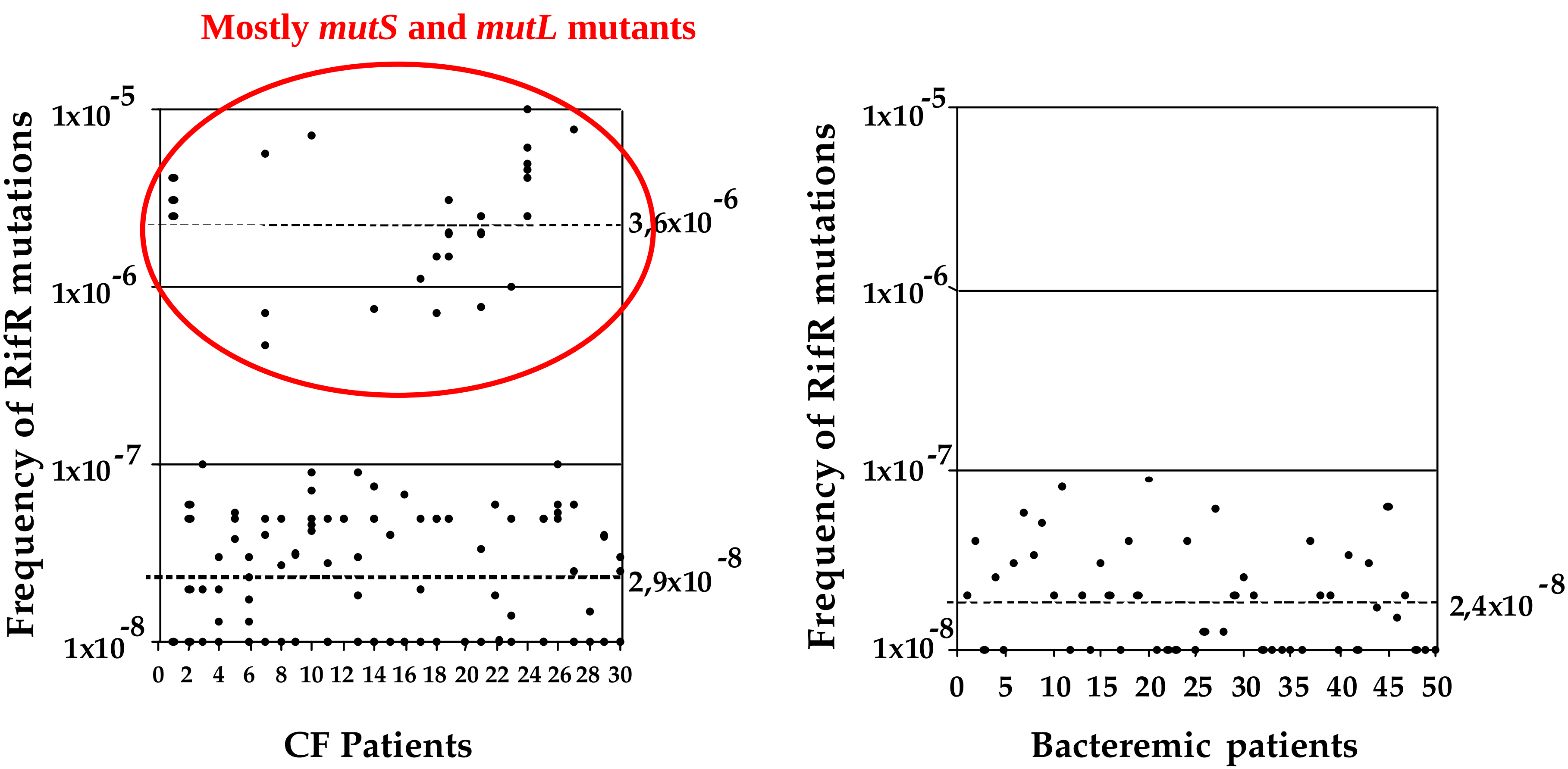
Hitch-hiking!

Hb receptor phase variation frequencies in serogroup A *N. meningitidis*



Richardson & Stojiljkovic PNAS USA, 2002

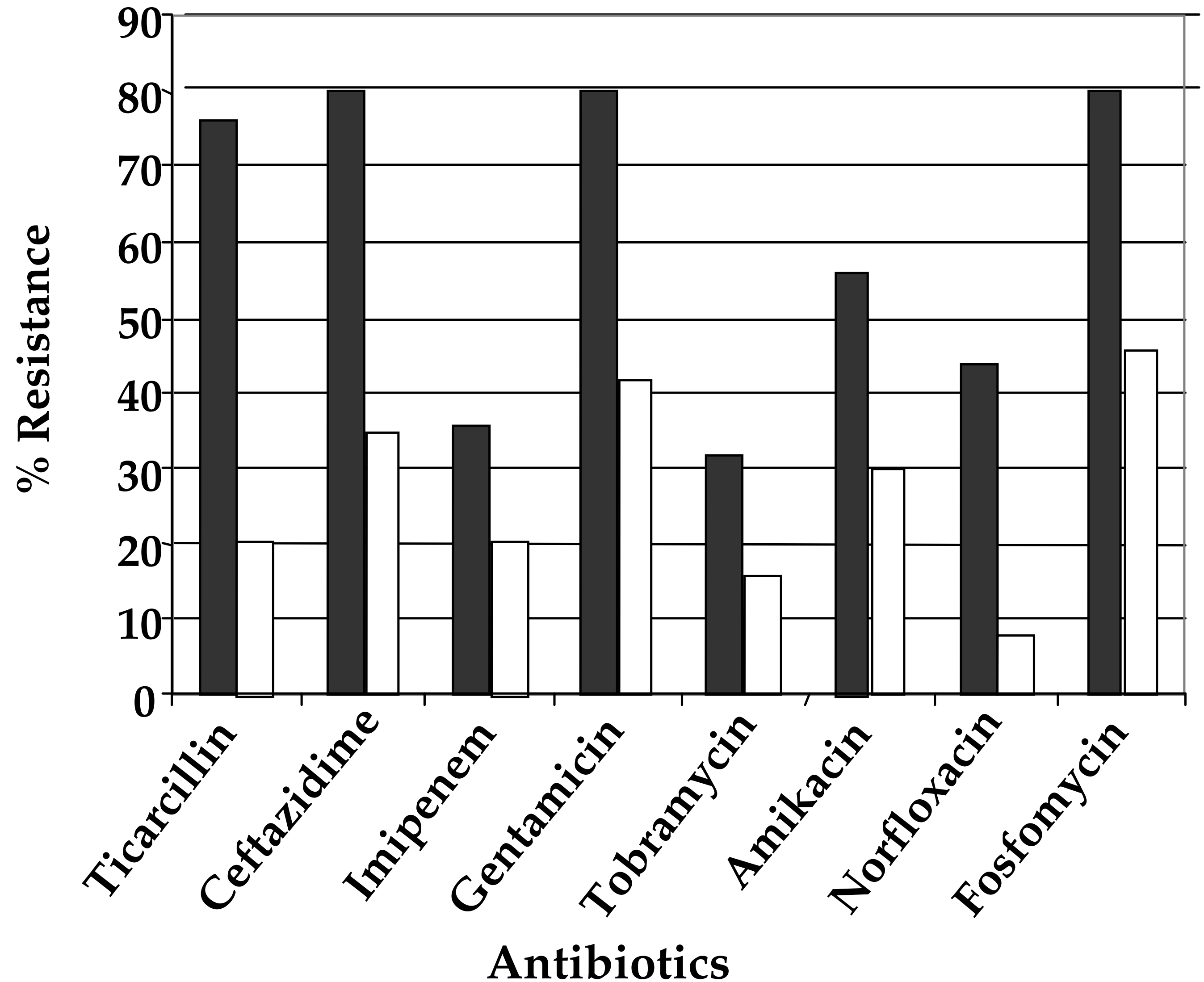
High Frequency of Hypermutable *Pseudomonas aeruginosa* isolates in Cystic Fibrosis Lung Infection



Oliver et al. Science 2000 vol 288:1251-1254

Diferences in antibiotic resistance between mutator (■) and non-mutator (□) *P. aeruginosa* isolates from CF-patients

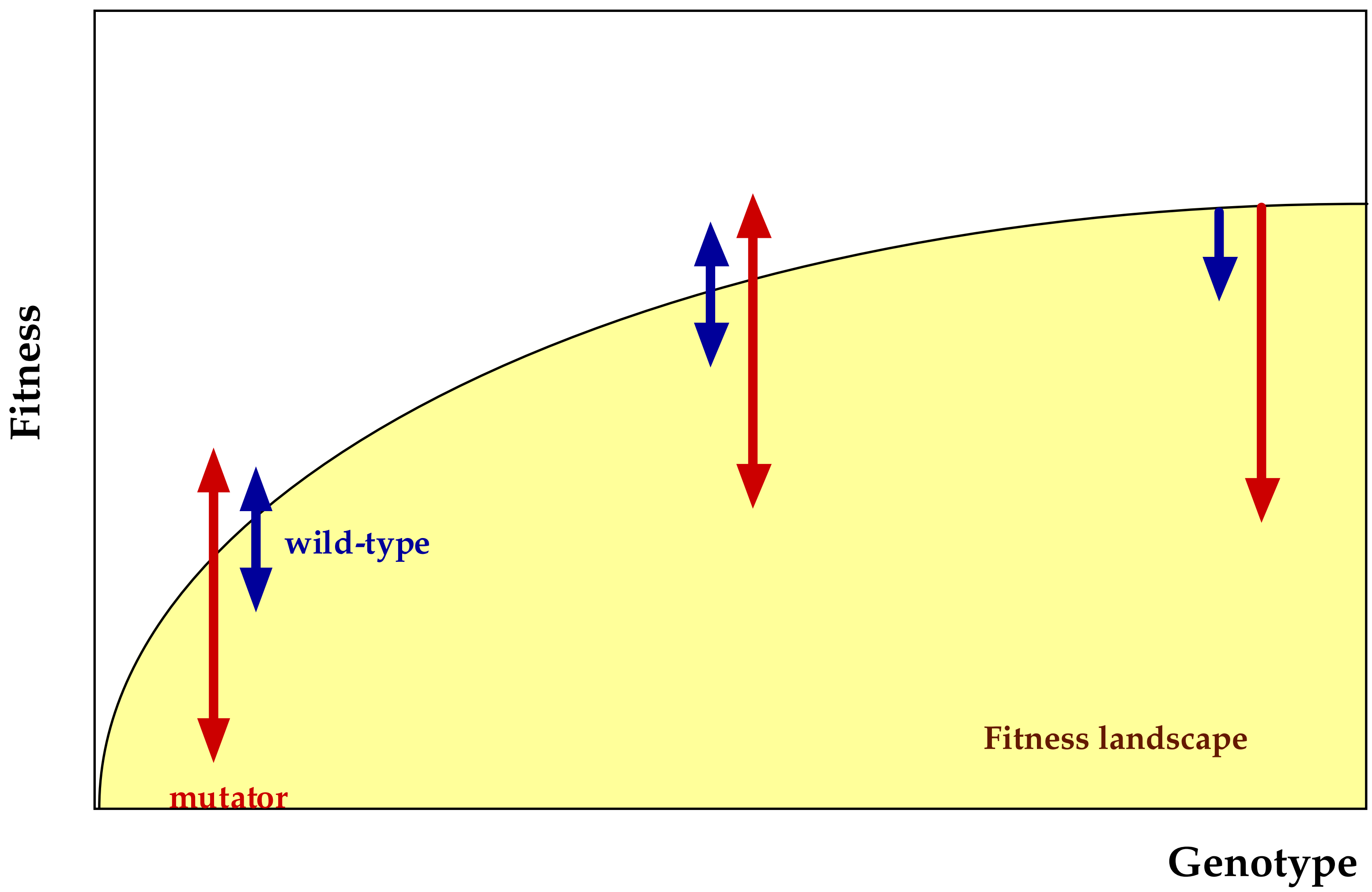
Oliver et al. Science 2000 vol 288:1251-1254



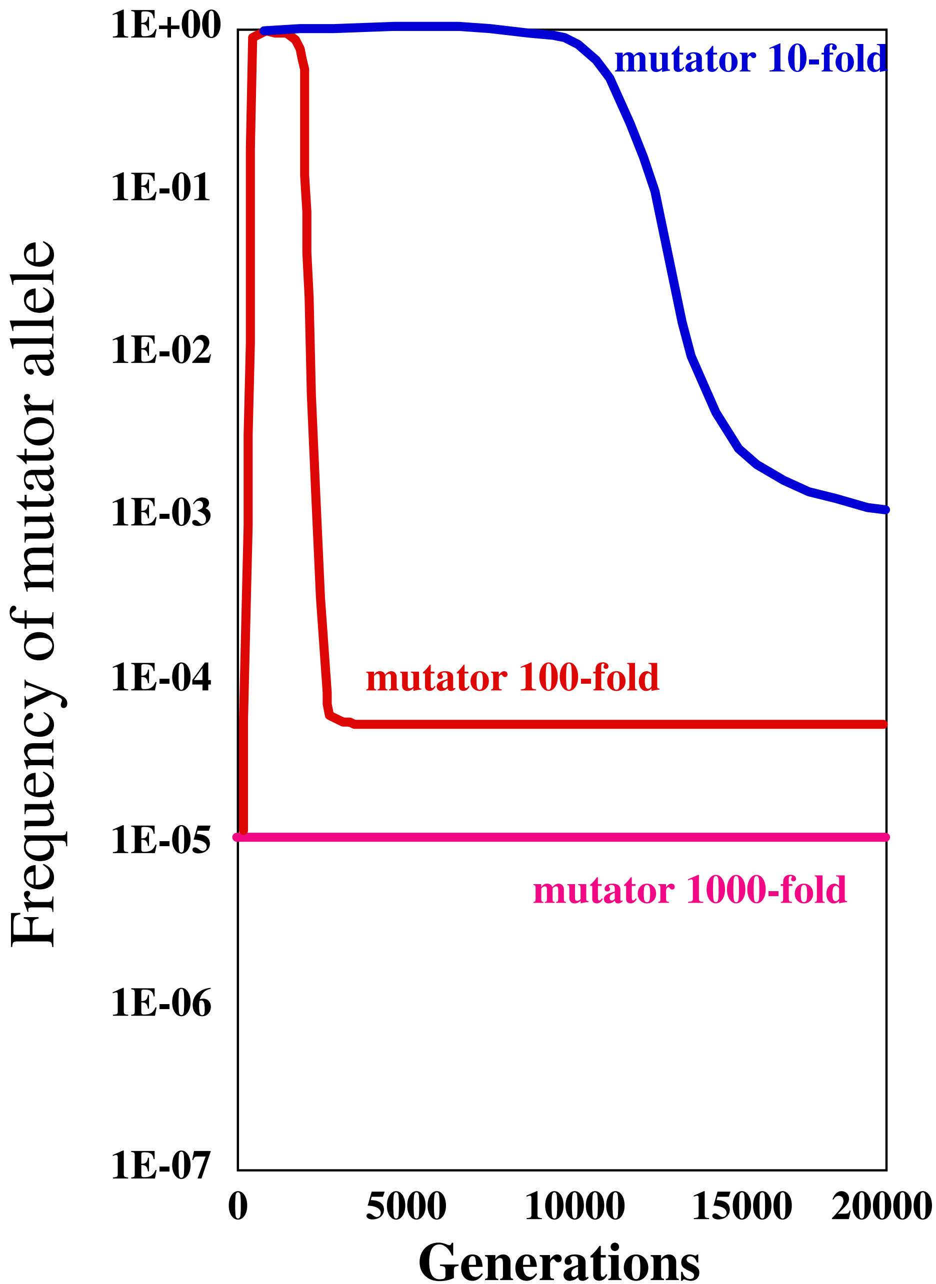
Relationship between age of patients and frequency of mutator strains

	Patients	*P. aeruginosa* strains		
			Mutator strains	
		Strains tested	Number	%
0 Š 5 years	15	15	1	7%
6 Š 10 years	21	23	2	9%
11 Š 15 years	36	39	8	20%
16 Š 20 years	40	49	15	31%
21-25 years	11	14	4	28%
Total	123	140	30	21%

Role of mutators in adaptation to a new enviroment



Decline of a mutator depends on its strength



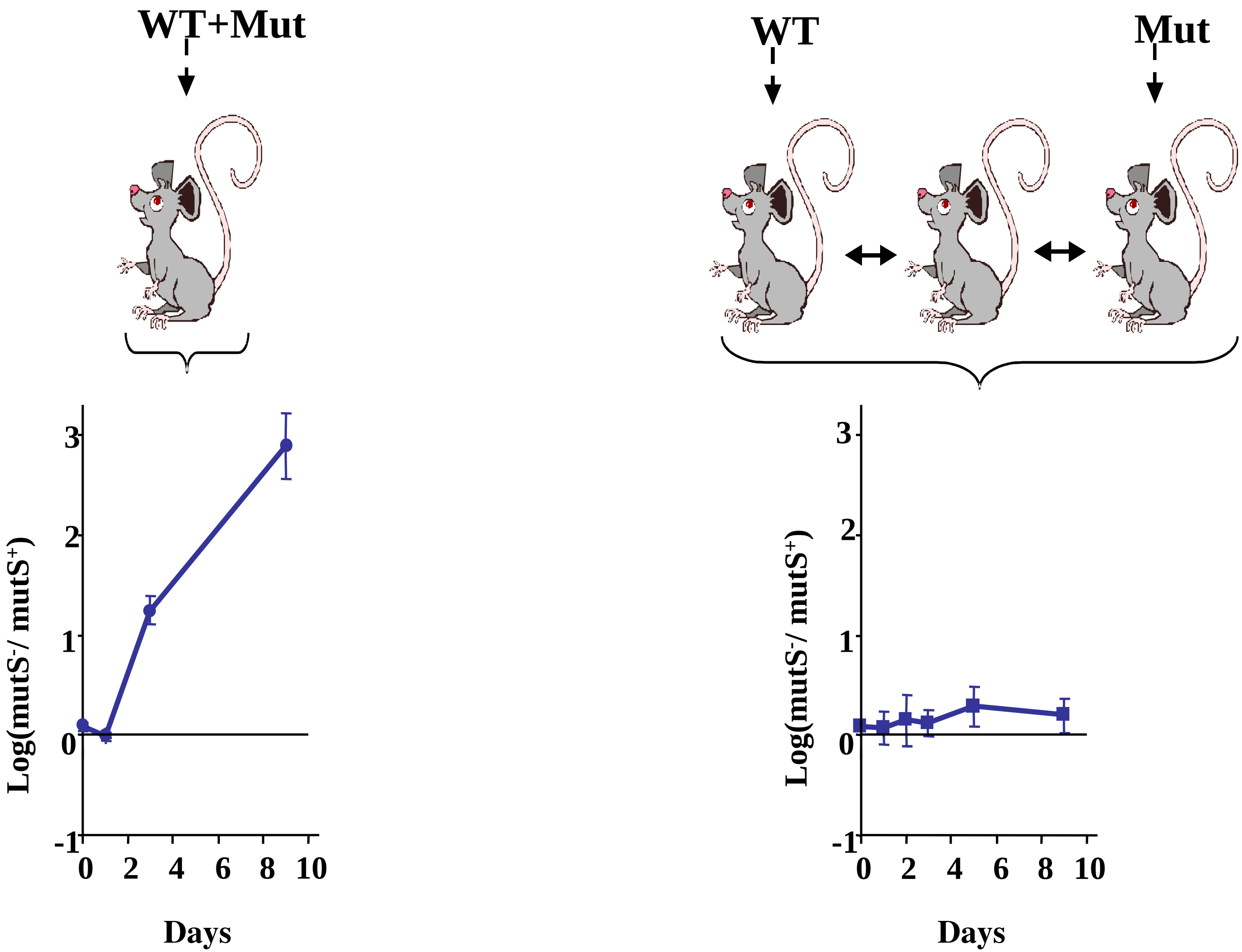
Taddei et al Nature (1997)

Counterselection of mutator alleles results from:

Accumulation of deleterious mutations

Antagonistic pleiotrophy

The advantage of mutators is reduced when migration is possible



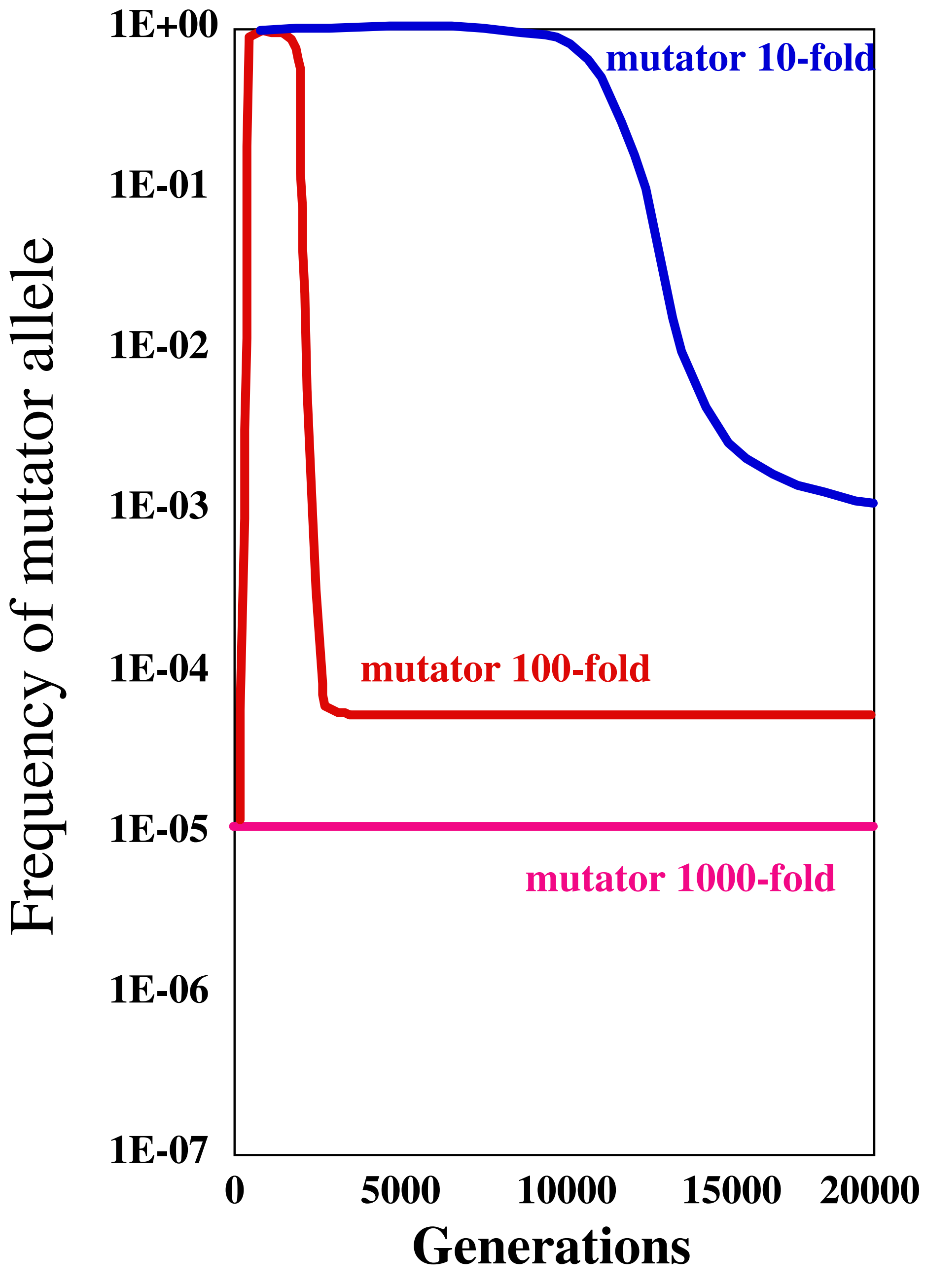
Restoration of low mutation rates

Reversion of mutator mutations

Acquisition of supressor mutations

Horizontal gene transfer

Decline of a mutator depends on its strength



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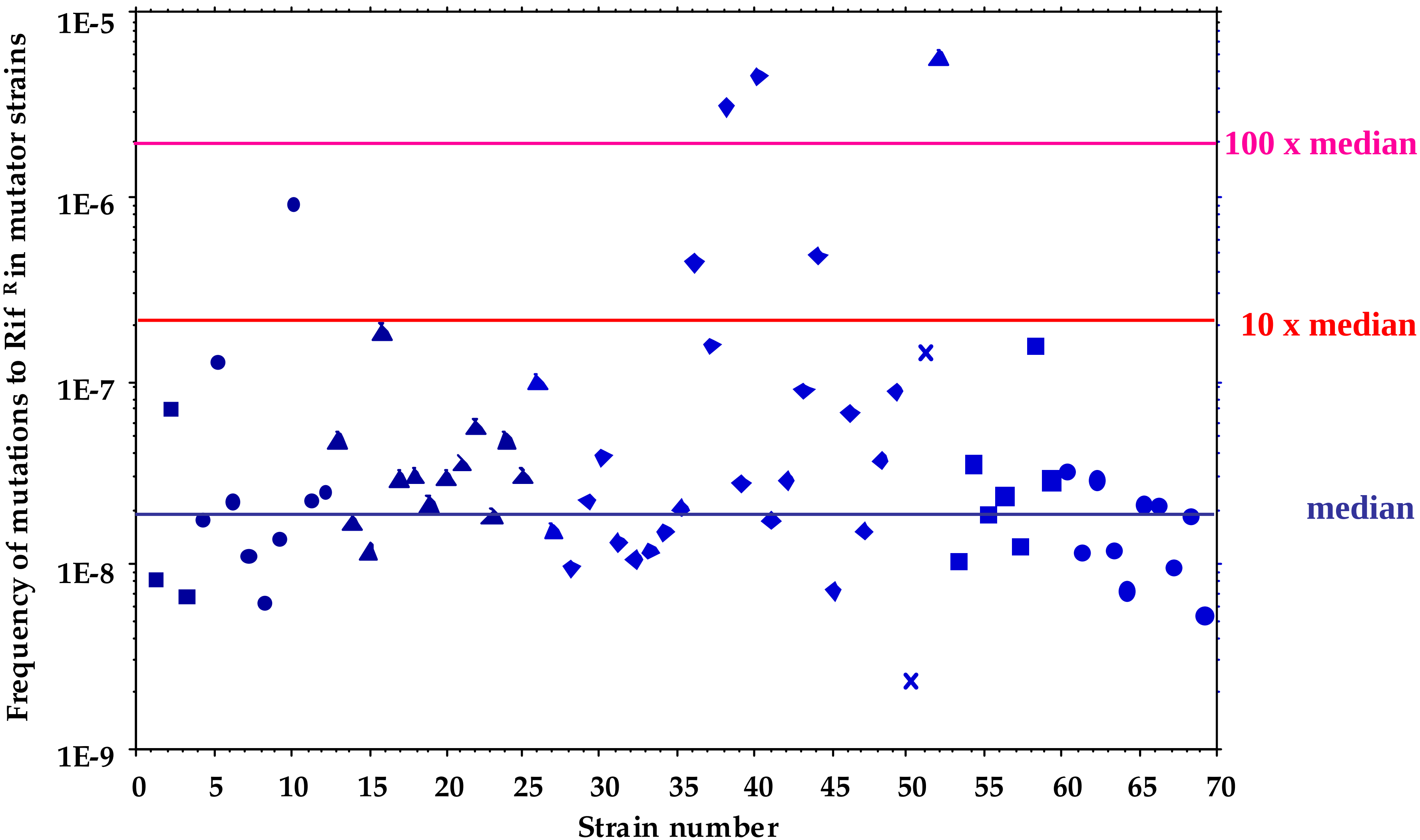

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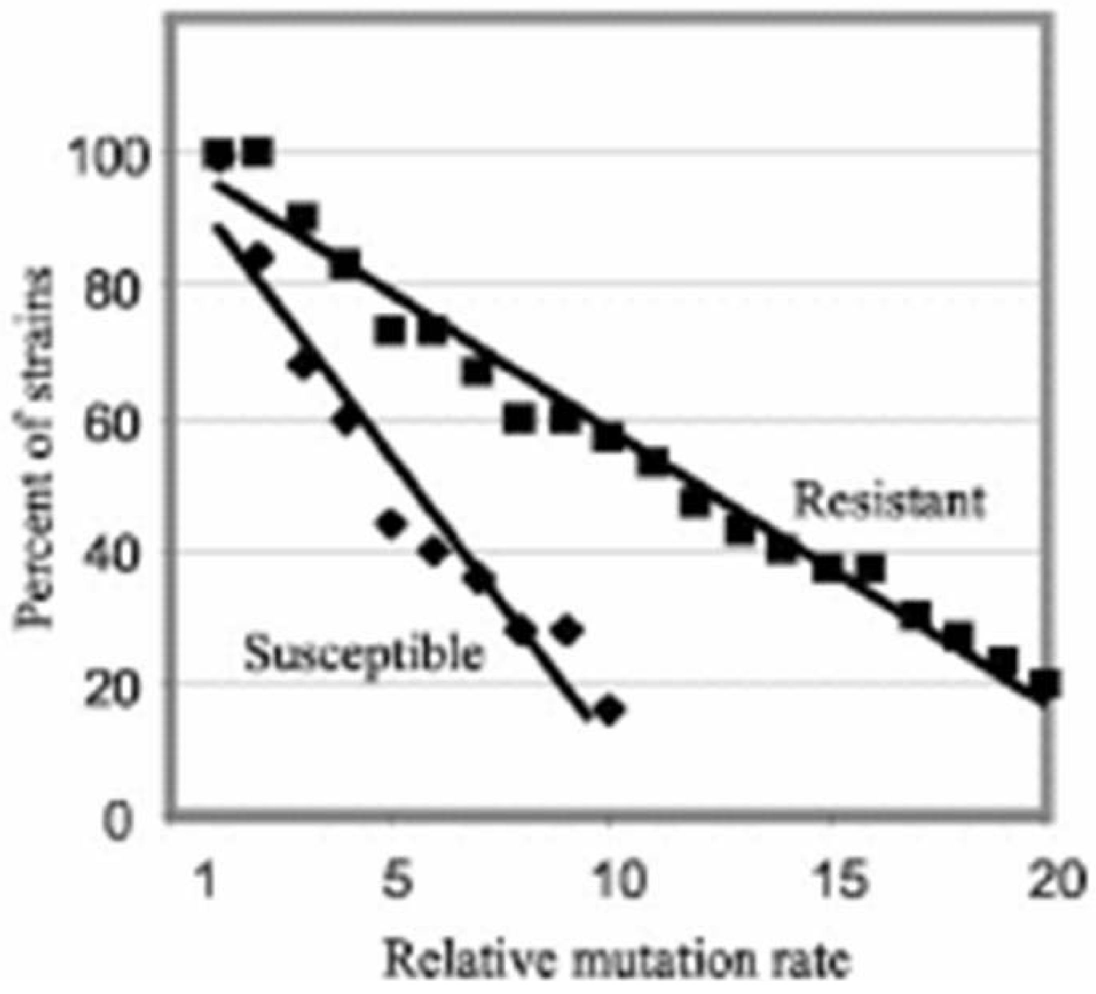

Mutation Rate and Evolution of Fluoroquinolone Resistance in *Escherichia coli* Isolates from Patients with Urinary Tract Infections

Lindgren, et al. (2003) Antimicrob. Agents Chemother.

Among different molecular mechanisms

that control the rate of the generation of genetic variability,

the constant fine-tuning of mutation rates

in function of the strength and the nature of selective pressure

contributes to the formidable evolutionary success of bacteria,

by maximizing their adaptation to constantly changing

environmental conditions

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Miroslav Radman

Mutation rates and antibiotic resistance among natural isolates

Erick Denamur, Ivan Matic

In vivo

Antoine Giraud, Ivan Matic, François Taddei

In silico

Bernard Godelle, Olivier Tenaillon, François Taddei