Supplemental Table 3. Examples* of non-progressive and progressive heteroresistance in different antibiotic classes

Antibiotic Class	Non-progressive HR	Progressive HR	Transition to Resistance	Transition to Susceptbility
Quinolones	*gyrA* mutations (nalidixic acid)	*gyrA* mutations (fluoroquinolones) *gyrA+parC* mutations (fluoroquinolones) *gyrA* and efflux pumps amplifications (nalidixic acid)	Fast	Slow, but fast in amplification
Aminoglycosides	• *rpsL* mutations (streptomycin) • *16S rRNA* A1402G mutation (kanamycin, gentamicin, and spectinomycin)	• *aadB* amplifications • *aac*(3)IId amplifications	Fast	Slow, but fast when either RpsL K43T compensory mutation occurs for streptomycin or in amplification events
Beta-lactams	• Penicillin binding proteins (PBPs) • Outer membrane porin o*prD* (carbapenems)	• Beta-lactamases *bla*TEM-1, TEM-10, and TEM-12 mutations • Beta-lactamase amplication • PBPs mutations • *oprD* mutations in combination with efflux pump mutations (carbapenems)	Fast	Fast or slow, depending on associated fitness cost
Macrolides	• *23S rRNA* mutations • L4, L22 ribosomal mutations	• Overproduction or mutations in efflux pumps • Progressive predominance of L4, L22 mutated ribosomes	Fast with low rRNA copy number	Fast due to high fitness cost
Rifampin	• *rpoB* mutations		Fast	Fast due to *tufA* or *rpoB* Y526H compensatory mutations
Trimethoprim	• *folA* mutations	• Stepwise *folA* mutations	Fast	Slow
Linezolid		• Single nucleotide transversion in *23S rRNA* (typically G2576) leading to recombination with other	Slow	Fast

		copies of the gene (gene conversion)		
Fusidic acid	• *fusA* mutations		Fast	Fast
Lipo and glycopeptides		• Mutations in *mprF*, *yycFG* operon and genes encoding subunits of RNA polymerase • Amplification of *pmrD*, regulating genes encoding proteins that modify lipid A	Slow	Fast due to high fitness cost
Mupirocin	• *ileS* mutations	• Consecutive mutations in *ileS*	Fast	Slow
Fosfomycin	• Mutations in *murA, uhpT,* and *glpT*		Fast (in the absence of glucose-6 phosphate)	Fast
Tigecycline Tetracyclines		• Overproduction of efflux pumps AcrAB–TolC, OqxAB, and MacAB • Sequential mutations in *ramR*, *lon*, and *rpsJ* • Amplification of *tet(A)*	Fast	Fast

* Details and further references about above examples of mentioned resistance mechanisms can be found in: Baquero F, Martínez JL, F Lanza V, Rodríguez-Beltrán J, Galán JC, San Millán A, Cantón R, Coque TM. (2021) Evolutionary Pathways and Trajectories in Antibiotic Resistance. *Rev Clin Microbiol*. 34(4):e0005019, and Pereira, C., Larsson, J., Hjort, K., Elf, J., Andersson, D. I. (2021). The highly dynamic nature of bacterial heteroresistance impairs its clinical detection. *Communications Biology*, *4*(1), 521.