## **Evolutionary trajectories of organisms carrying CTX-M enzymes**

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Conventional scientific wisdom dictates that evolution is a process that is sensitive to many unexpected events and influences, and is therefore essentially unpredictable. On the other hand, considering the bulk of recent knowledge about bacterial genetics and genomics, population genetics and population biology of bacterial organisms, and their sub-cellular elements involved in horizontal gene transfer, we could eventually face the possibility of predicting the evolution of bacterial resistance. Such prediction could provide similar clues as weather prediction -higher possibilities of certainty in the closer and more local frames. Indeed there is a local evolutionary biology based on local selective constraints that shapes the possible local trajectories, even though in our global world, some of these locally-originated trends might result in global influences. In the case of CTX-M enzymes, some of the elements whose knowledge is critical for predicting evolutionary trajectories are: i) the origin and function of CTX-M enzymes in the chromosome of environmental bacterial organisms; ii) their ability to be captured (mobilized) by different genetic platforms, and to enter particular in mobile genetic elements; iii) the ability of these mobile genetic elements to be selected and spread among bacterial populations; iv) the probability of recombinatorial events among of these and other mobile elements, with consequences in selectable properties and bacterial host-range, v) the original and resulting fitness of the bacterial clones in which CTX-M enzymes are hosted, including its colonization power and epidemigenicity; vi) the results of interactions of these bacterial hosts with the microbiotic frame in which they are inserted; and vii) the selective events, as the patterns of local antibiotic consumption, that might influence the success of particular CTX-M mutations or complex genetic configurations in which CTX-M genes are hosted. Such a complex frame required for predicting evolutionary trajectories should be analyzed (and integrated) by considering heuristic techniques for the understanding of multi-level selection, covariance, and contextual analysis.

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