TITLE: How is coexistence between drug-susceptible and -resistant bacteria maintained? Joint work with Carl Bergstrom, William Hanage, Ron Dagan, Christophe Fraser, Alethea McCormick, Sarah Deeny, Ted Cohen, Caroline Colijn.

ABSTRACT: A classic concept in population biology, economics and other fields is the competitive exclusion principle, which roughly translates in the infectious-disease population-biological context into the prediction that only one species or strain of microbe will remain viable in competition with others, absent some selective force that favors rare strains. In the context of antimicrobial resistance, this principle and associated mathematical models suggest that in a closed population, either drug-resistant or drug-susceptible bacteria will "win" at equilibrium by depriving their competitors of enough susceptible hosts to continue spreading; the winner in this competition, according to mathematical models, will be determined by the balance between selection by antimicrobial use (favoring the R strain) and a fitness cost of resistance (favoring the S strain) (1,2). The bacteria, however, appear not to have read the papers on competitive exclusion, and coexistence over a long period between R and S strains in a population is the norm. In some cases, we have a reasonable theory of how this works. For example, hospital-acquired resistant bacteria may have greater fitness in the hospital, under strong antimicrobial selection, but they are prevented from reaching a prevalence of 100% by the continued import of susceptible bacteria with incoming patients (3). In other words, the population is not closed but is open to importation of S bacteria. In other cases, the phenomenon is clear but the explanation is less so. For example, resistance of Streptococcus pneumoniae to major antimicrobials, such as penicillin and erythromycin, is persistent in many countries but has not reached 100%. The population is closed (more or less), so the explanation from hospital-acquired pathogens does not apply here. One possible explanation is that the prevalence of resistance will reach 100% but is moving there slowly. While this explanation has seemed credible in the past, it seems less so following data from Israel on seasonal fluctuations in the prevalence of resistance in S. pneumoniae, which demonstrate that prevalence of resistance can change by a factor of two in a matter of months as antimicrobial pressure changes (4). Another possibility is that each pneumococcal serotype behaves independently, and resistance is increasing or remaining at 0 for each serotype, so coexistence is merely an artifact of combining serotypes. We argue that this is not the case based on published data (including (5)). Another possibility is that our models are too simple, and more realistic models would predict coexistence. We have evaluated a number of more complex and possibly more realistic models, and found that coexistence of S and R strains is not a generic prediction of any, though it can occur (6). We conclude that the coexistence of S and R strains in community-acquired infections is an ongoing puzzle, and that quantitative predictions from models that cannot explain this puzzle should be viewed with suspicion. All is not lost, however. Despite being poorly suited to explain coexistence as a generic outcome, a range of models suggest that coexistence should be observed only in those pneumococcal strains which have a relatively long duration of infectiousness, because these are the strains in which resistance might be beneficial enough to offset a fitness cost. Data are consistent with this prediction, as low-duration serotypes tend to have 0% resistance while longer-duration serotypes tend to have higher (but not 100%) prevalence of resistance. These unpublished results will be described as a conclusion.

Refs

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