Resistance ratchet effect: author’s response

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Sir,

The ratchet model\textsuperscript{1} predicts a small, unexpected additional effect to straightforward Darwinian selection for antibiotic resistance—a hill on top of a mountain—that may be encountered in circumstances where the assumptions stated in the paper comply with reality. It is important in two ways. As a counter-intuitive scientific curiosity, it emphasizes that we must think long and hard to understand the ramifications of Nature’s laws; and, as a prediction, it offers an opportunity to test some basic assumptions on the epidemiology of resistance. Huovinen\textsuperscript{2} goes to the heart of these assumptions with his examples of variation of resistance epidemiology. Resistance epidemiology is clearly not a simple single uniform effect; the rise in resistance is not the same in every species, or for every antibiotic. The observed differences may hold clues to a deeper understanding of the mechanisms involved, and lead to rational, effective intervention. To achieve this, we need bulk longitudinal validated data on resistance, prescribing and the host of other factors that may affect resistance, to test our assumptions and discover which are correct in general, which are correct—but only for special cases—and which are incorrect.\textsuperscript{3} This is the prime objective of models in biology; models that reliably predict the future are only attainable in well understood, tightly defined areas such as the physics of aeroplanes and bridges.

The one area where I must disagree with Huovinen is the comment that the ratchet model predicts a continuous increase in resistance. The key here is the asymmetry between the rates of selection for resistance or susceptibility in disequilibrium conditions. If the rate of rise under excessive selective pressure is greater than the rate of loss of resistance under a deficit of selection pressures, then the ecology ratchets to unexpectedly high resistance than the rate of loss of resistance under a deficit of selection pressures. If the rate of rise under excess selective pressure is greater than the rate of gain in resistance for resistance or susceptibility in disequilibrium conditions. An example might be in early development of resistance to an antibiotic with a new antibacterial mechanism, where incomplete evolution may result in a large metabolic overhead for resistance, low inter-strain transmission and poor competitive capability. Models generalize; the behaviour for specific pathogens and antibiotics lies in setting the model parameters to values that realistically mirror their individual properties.

As Huovinen indicates, the rates of gain and rate of loss under disequilibrium conditions are likely to depend upon a host of factors. Some are inaccessible to intervention; metabolic overheads, ease of inter-strain transmission and the epidemiology of the disease are coded in the genetics of the pathogen. Others provide for natural changes in these rates; in clonal pathogens where the surface antigens of the resistant clone lead to host immunity, and inter-strain transmission is rare, the clone—and the proportion of resistance it contributes—will wane as increasing herd immunity erodes its competitive ability. Yet others may allow intervention; good hygiene and isolation of patients with resistant infection from the ecology are likely to reduce the rate of gain in resistance; we assume that the main effect is straightforward Darwinian selection, and strive for a reduction in usage that may alleviate the problem. The ratchet mechanism, if confirmed, suggests that gross seasonal cycling in community use for some antibiotics—particularly ampicillin/amoxicillin—may be another possible target for intervention, particularly as clinical work suggests that much of the winter use for minor upper respiratory infection does not affect the course of disease.\textsuperscript{4}

The key areas of agreement are on the likely complexity of resistance epidemiology, the need for progress in this field, and the need for validated bulk data on all aspects of resistance.\textsuperscript{1,2} Ultimately, success in stemming the rise of resistance will depend upon adequate research funding. At present this derives largely from governmental sources. I suggest again\textsuperscript{5} that changes in the regulatory and economic environment which provide incentives to the pharmaceutical industry to prolong the effective life of current antibiotics may offer some solutions.

References


