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The resistance ratchet: theoretical implications of cyclic selection pressure

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Objectives: To investigate the effects of cyclic antibiotic selection pressure on resistance in a simple mathematical model.

Methods: The model assumed that resistance in microbial ecologies changes slowly with changing selection pressure, at a rate proportional to the difference between the current resistance level and the resistance level that would be in equilibrium with current selection pressure. The maximum rate of increase in resistance during periods of increasing selection was assumed to be greater than the maximum rate of decrease during decreased selection.

Results: Under a simulated annual cyclic selection pressure variation of 40%, with maximum resistance rise and fall rates of 10 and 0.5%, respectively, resistance rose above the level expected from the mean selection pressure by small ratchet-like increments. Over 50 simulated years, resistance increased to 62%, rather than the 50% expected from the mean level of selection. Welsh community prescribing for a selection of antibiotics showed a seasonal cyclic variation of 13–45%.

Conclusions: The intuitive assumption that cyclic selective pressure would produce resistance levels commensurate with the mean selection pressure was contradicted; rather resistance drifted towards a level commensurate with maximum selection pressure. If the ratchet effect exists in reality, it may produce unexpected excess resistance, particularly in the community for antibiotics used in respiratory infection, where cycling is pronounced, or in ITU antibiotic rotation. It should be most pronounced for resistance systems with strong asymmetry between rates of adaptation under rising and falling selection pressure. Non-linear dynamic systems in physics and ecology are notorious for producing counter-intuitive effects; resistance epidemiology may be similar.

Keywords: cyclic selection pressure, seasonal antibiotic prescribing, antibiotic resistance, ratchet effect

Introduction

Periodic variation in antibiotic usage is probably a common phenomenon. It would be reasonable to expect that community prescribing of oral antibiotics would change with the seasonal variation in respiratory infection rates that occurs in the UK, for example. Equally, cyclic antibiotic rotation has been suggested as a possible approach to controlling resistance in intensive care units,[1] although its efficacy remains unproven.[2,3] Superficially, in these situations one might expect resistance levels in the microbial ecology to equilibrate at a level commensurate with the mean annual selection pressure. However, selection is a complex dynamic process, and subtle interactions may intervene. Observations (see below, Methods) indicate that, for some species and antibiotics, the rate of increase in resistance under high selection pressure is greater than the rate of decrease under low selection pressure.

This asymmetry may interact with cyclic variation in selection pressure in unexpected ways. The paper considers this interaction, outlining a hypothetical mechanism that may yield unexpected excess resistance.

Methods

Antibiotic prescribing rates (prescriptions per 1000 registered patients per quarter) were obtained from the Welsh Prescription Pricing Unit, for all Welsh community practices during April 1996–March 2003 inclusive.

The model

A simple model (available as an Excel spreadsheet as Supplementary data at www.jac.oupjournals.org) was constructed based upon the following assumptions.

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Table 1. Annual variation in community prescribing of oral antibiotics in Wales for the period April 1996–March 2003, contributed by Health Solutions Wales. Data for April 1999–March 2000 was omitted, as figures for the last two quarters of this year were not available for analysis

	Difference from mean quarterly prescribing (%) in financial quarter				Span of seasonal
Antibiotic	Jan–Mar	Apr–Jun	Jul–Sep	Oct–Dec	differences (%)
Amoxicillin/ampicillin	19.0	−12.9	−25.1	19.0	44.2
Erythromycin	14.2	−8.9	−16.9	11.6	31.1
Cephalexin	10.5	−7.2	−11.1	7.8	21.6
Tetracycline	10.0	−3.2	−11.4	4.5	21.3
Penicillin V	7.9	−2.3	−10.8	5.2	18.6
Co-amoxiclav	6.6	−3.0	−7.7	4.1	14.2
Ciprofloxacin	5.5	−6.5	−4.7	5.7	12.2
Trimethoprim	1.7	−3.8	−1.2	3.3	7.1
Flucloxacillin	−5.7	−5.2	11.9	−1.0	17.6

Significant cyclic variation in antibiotic selection pressure occurs. Table 1 illustrates the seasonal variation in community oral antibiotic prescribing. Prescribing in the January–March financial quarter was 2–19% higher than mean quarterly prescribing and 1–25% lower in the July–September quarter. Flucloxacillin was a notable exception where this pattern was reversed, with highest prescribing in the July–September quarter.

Resistance levels are affected by antibiotic prescribing. Increasing statistically based evidence has accumulated over the past decade, suggesting associations between usage of antibiotics and resistance levels in the microbial population.[4,5]

Resistance levels increase rapidly when selection pressure rises, but decrease slowly when selection pressure decreases. This is logical, as different processes are involved, which are likely to operate at different rates. Increased selection pressure has a double-hit mechanism; first, the greater selection removes susceptible organisms by direct bactericidal action, or by preventing reproduction; second, inhibition or death of susceptible organisms leaves nutritional resources and instances of the ecological niche available for growth of resistant variants. Conversely, falling selection pressure leaves a non-equilibrium level of resistant variants, and these are selected against by a single-hit mechanism; their only postulated disadvantage is that they may (or may not[6]) carry a metabolic overhead that reduces their competitive ability.

Evidence for a rapid rise in resistance under increased antibiotic selection is largely anecdotal, but rates of 5–15% per annum have been observed.[7] The slow fall in resistance under decreased selection pressure is less well documented, but decreases at 0.5% per annum or less have been observed.[8] Resistance genes can become 'fixed' during prolonged *in vitro* selection, yielding strains that compete as well or better than the ancestral antibiotic-susceptible strain, and show low loss rates for resistance markers.[6] It has been suggested that changes in the genetic background re-optimize metabolism and associate resistance genes with genes coding for essential products.[6]

The model assumes that equilibration with changing selective pressure proceeds with a rate of change that decreases as the system approaches equilibrium. Maximum rise and fall rates for resistance (rates attained when current resistance levels differ from selection equilibrium levels by 100%) were taken conservatively as 10 and 0.5% per annum, respectively. Other values yielded similarly shaped response curves to that illustrated (Figure 1, line A), provided that the rise rate was greater than the fall rate.

The cyclic changes in selection pressure occur with a period less than that required for the species population to attain an equilibrium level of resistance. Evidence for this derives from the Welsh community antibiotic resistance survey. Seasonal variation in resistance was only marginally significant for a few of a range of appropriate antibiotics and five common community pathogens, despite a seasonal approximately twofold variation in antibiotic prescribing (unpublished data). In contrast, significant inter-practice correlation between resistance and annual prescribing rates was found for urinary coliforms, and other common community pathogens with a range of mean annual prescribing rates only a little greater than the seasonal variation described above.[4]

Results and discussion

The model yielded a stepwise increase in resistance during each seasonal prescribing cycle (Figure 1, line A). The initial bacterial ecology had a resistance level of 50%, in equilibrium with a constant selection pressure corresponding to the mean annual selection pressure of subsequent annual cycles. The selection pressure was then cycled annually from a maximum level that would, if maintained, yield an equilibrium resistance of 70%, to a minimum level that would, if maintained, yield an equilibrium resistance of 30%. In the initial 6 months of elevated selection pressure, resistance increased by 0.62%, and then decreased by 0.03% during the subsequent 6 months of decreased selection, yielding a net increase in resistance of 0.59% in this first cycle. The excess resistance gained during the rise phase was largely retained, because the maximum rate of rise in resistance (set to 10% per annum) was greater than the rate of fall (0.5% per annum), and the slower adaptation rate under low selection pressure could not eradicate the gain during high selection, producing a ratchet-like effect. The next annual cycle increased the resistance level by a further 0.56%, and so on, to a long-term pseudo-equilibrium level of about 62% resistance. With the conservative parameters chosen, an excess resistance of 12.1% over that expected from the mean annual selection pressure was attained in 50 years. Although the annual increments were small, the cumulative effect was large over periods corresponding roughly to the useful life-span of an antibiotic.

Changes in the maximum rate of fall in resistance over the range 2–0% per annum yielded closely similar results. Other assumptions on kinetics increased the rise. If the rate of equilibration was assumed to be proportional to the square root of the disequilibrium difference
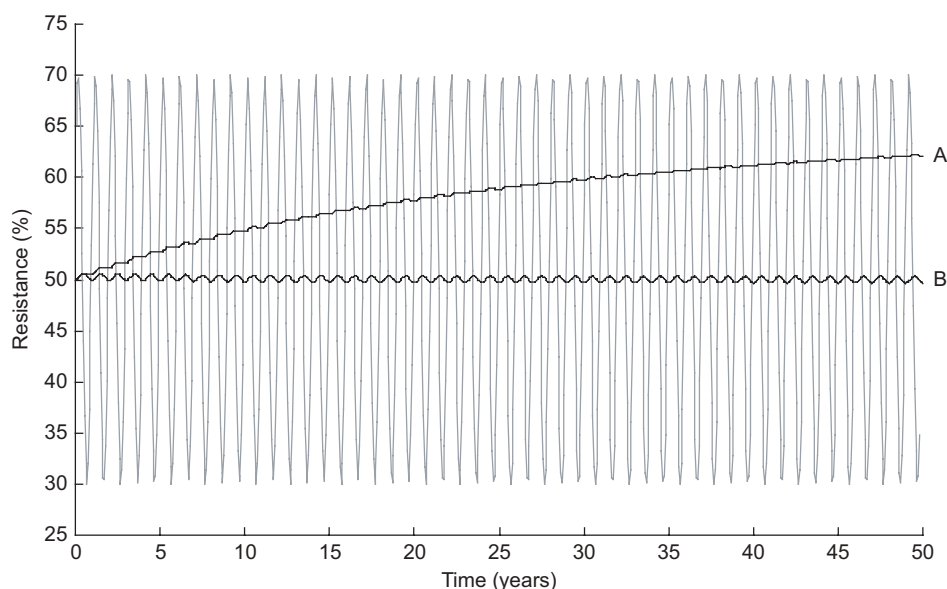
The resistance ratchet

Figure 1. The annual stepwise drift of resistance from that expected from the mean selection pressure under cyclic selection pressure conditions. Line A assumes strong asymmetry in the rate at which resistance rises under elevated selection pressure, and the rate at which it falls with decreased selection. Line B assumes these rates are equal. The grey line indicates the cyclic changes in selection pressure. Model parameters: maximum resistance rise rate = 10% pa; maximum resistance fall rate = 0.5% pa (line A) or 10% pa (line B); actual rates of change in resistance were calculated as proportional to the difference between current resistance and the resistance level that would be in equilibrium with current selection pressure, with a difference of 100% yielding the appropriate maximum rate; iteration interval 1 day; selection pressure cycled as a sine curve from minimum to maximum levels that would be in equilibrium with 30 and 70% resistance, respectively, with a mean yielding 50% equilibrium resistance.

(difference between current resistance and the level that would be in equilibrium with current selection pressure), the rise over 50 years was 67.4%, and if the rate of change was assumed to be independent of the disequilibrium difference, resistance rose to 70% in 11 years. Discontinuous stepped cyclic changes in selection, such as might occur in ITU antibiotic rotation, produced ratchet-type changes similar to those illustrated for smooth sinusoidal variation in selection, unless the ratio between the durations of low and high selection approached the ratio of the rise to fall rates (set to 20:1).

The model makes predictions that could be tested. The ratchet phenomenon should be most marked for species/antibiotics that combine a particularly rapid rise with a particularly slow fall in response to, respectively, increasing or decreasing selection pressure. These characteristics are most likely to be found in highly evolved resistance systems, where resistant strains have a minimal competitive disadvantage, and ready, rapid inter-strain genetic transfer has been achieved, i.e. for antibiotics where long-standing, intense selection pressure has been applied and resistance is common. Wide cyclic variation in prescribing with a short cycle period is a prerequisite, and significantly increasing mean annual prescribing is desirable to avoid misinterpretation of a late pseudo-equilibrium state as a negative result. During periods when mean annual selection pressure is increasing, resistance levels should correlate slightly better with the maximum seasonal selection pressure than with mean selection pressure.

Conversely, where resistance is poorly evolved, unstable or has not evolved an effective transmission mechanism, and there is a large competitive disadvantage to carriage of resistance genes, the ratchet effect should be negligible. Figure 1, line B illustrates this case, with rise and fall adaptation rates set equal in the model. This may be the situation where the rates of forward and reverse mutation to resistance are similar, and there is little or no inter-strain transmission. A possible example is current fusidic acid resistance in methicillin-susceptible *Staphylococcus aureus*.[9]

It should be remembered that selection pressure may cycle widely and rapidly between doses in antibiotic treatment of individual patients. It seems unlikely that the ratchet mechanism might have a significant role in selection of resistant commensal or infecting flora in individual patients over average treatment periods of a few weeks, but some conditions require prolonged treatment. It may be interesting to explore this, and the possible longer-term broad ecological effects discussed here, in more sophisticated models.

Non-linear dynamic systems are notorious sources of unanticipated effects in physics, engineering and ecology. At the extreme, apparently simple systems can produce chaotic behaviour, leaving no possibility of definitive prediction of their state. It is well to remember that the epidemiology of resistance is essentially a problem in microbial ecology, and that early ventures into chaos theory included May's work on ecological models.[10]

The potential behaviour outlined here is not so extreme, yielding predictable consequences analogous to well-characterized 'hysteresis' phenomena in electromagnetism and mechanics. The predictions that the model makes could be tested. However, whether or not the model is correct, in the sense that it predicts a real phenomenon, is not the main issue. What is important is that a plausible model has yielded predictions that are counter-intuitive, indicating complex behaviour that would not be anticipated by the average medical microbiologist. The resistance problem might well benefit from the attention of those who are trained in ecology or mathematics and familiar with the problems of prediction in dynamic systems.

Equally, the contrast between the behaviour in the two hypothetical examples given here illustrates the point that resistance may not be a single epidemiologically uniform phenomenon. There are considerable potential differences between the ecological behaviour of a resistance that is acquired readily by genetic transfer, and a resistance that results from high-frequency reversible mutation. It would not be surprising to find distinctive patterns of epidemiological behaviour amongst the wide range of species, resistance mechanisms, and prescribing patterns that exist. Despite nearly a century of antibiotic use, we are still struggling to define methods for gathering, validating and analysing resistance data. There may be many surprises to come from the infant science of resistance epidemiology.

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Transparency declaration

The author has no affiliations with the pharmaceutical industry or any related commercial concerns.

Supplementary data

The mathematical model discussed is available as Supplementary data (in Excel format) at www.jac.oupjournals.org

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