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A model-guided analysis and perspective on the evolution and epidemiology of antibiotic resistance and its future

Bruce R Levin[1], Fernando Baquero[2] and Pål J Johnsen[3]

A simple epidemiological model is used as a framework to explore the potential efficacy of measures to control antibiotic resistance in community-based self-limiting human infections. The analysis of the properties of this model predict that resistance can be maintained at manageable levels if: first, the rates at which specific antibiotics are used declines with the frequency of resistance to these drugs; second, resistance rarely emerges during therapy; and third, external sources rarely contribute to the entry of resistant bacteria into the community. We discuss the feasibility and limitations of these measures to control the rates of antibiotic resistance and the potential of advances in diagnostic procedures to facilitate this endeavor.

Addresses
[1] Department of Biology Emory University, Atlanta, GA, USA
[2] Ramón y Cajal Institute for Health Research (IRYCIS), Ramón y Cajal University Hospital, Madrid, Spain
[3] Department of Pharmacy, UiT, The Arctic University, Tromsø, Norway

Corresponding author: Levin, Bruce R (blevin@emory.edu)

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Introduction

Although some, not us, may question the contribution of burning fossil fuels to Global Warming, there is no doubt that the human use of antibiotics is responsible for the emergence and spread of pathogenic bacteria with inherited resistance to these drugs. As is the case for Global Warming, what is questionable is whether we can do anything about it. Can we reverse or even slow the rate of ascent and dissemination of antibiotic resistant bacteria by changing the ways we use these drugs, a problem and endeavor of global concern [1–3]. Here we address this question from the perspectives of evolutionary biology and epidemiology.

The evolution of inherited antibiotic resistance was anticipated

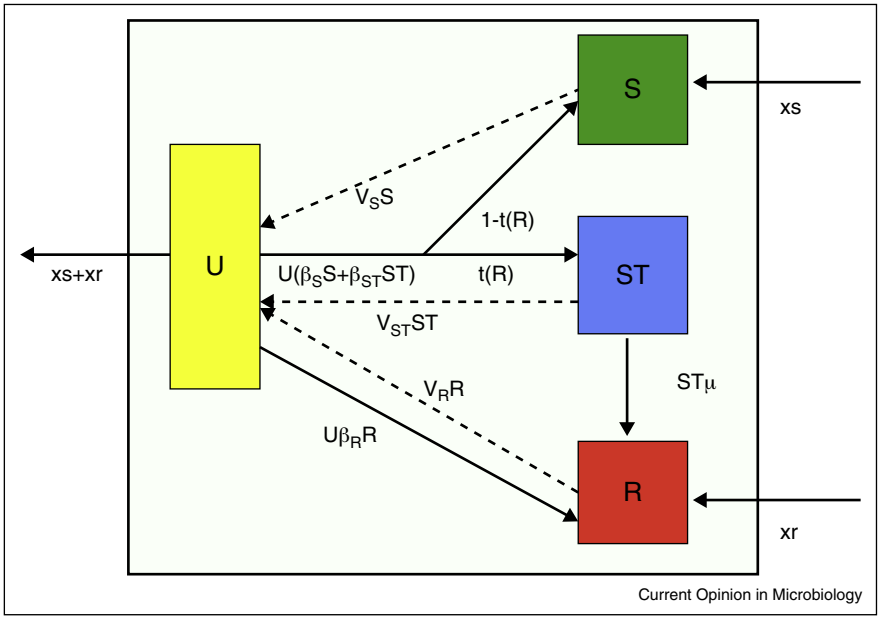
More than 100 years ago Paul Ehrlich already suggested multi-drug (combination) therapy to deal with resistant parasites [4••], and interest in such strategy remains [5–7]. If he were living in Ehrlich's time, Charles Darwin could have predicted the ascent of resistance as well; the elements for its evolution were certainly there, inherited variation in the susceptibility to antibiotics and drug-mediated selection favoring less susceptible variants. Indeed, had Darwin witnessed the emergence and spread of inherited resistance with human use of antibiotics, the first chapter of the 'Origin of the Species' may well have opened with this most compelling example of human-mediated selection.

By mutations in one or two chromosomal genes, bacteria can readily generate resistance to therapeutic concentrations of antibiotics like the aminoglycosides, the rifamycins, the quinolones and fluoroquinolones, and even beta-lactam agents. Many pathogenic bacteria can also acquire heritable resistance to antibiotics by horizontal (infectious) genetic transfer (HGT) of resistance-encoding genes and genetic elements genetic elements from other bacteria of different as well as the same species. The evolution and maintenance of antibiotic resistance is not just a matter of selection for bacteria bearing mutations for resistance. The infectiously transmitted semi-autonomous genetic elements, plasmids, transposons and integrons bearing resistance genes and, arguably the genes themselves, have an evolutionary life of their own [8]. The frequencies of resistant clones of bacteria may wane to extinction, but the infectious genetic elements bearing these resistance genes can live on moving by continually to new clones of the same and different species [9], and pollute wide environments in different ecosystems, if not the entire microbiosphere [10].

Antibiotic use and the evolution and epidemiology of resistance: what mathematical models tell us

Mathematical and computer simulation models have been employed to explore the relationship between antibiotic use and the evolution and epidemiology of resistance in open communities [11–14] and in hospitals [15•,16,17]. To facilitate our consideration of the factors determining the frequencies of resistance and

Figure 1



Model of the epidemiology of a community-acquired directly transmitted, self-limiting infection with antibiotic treatment and resistance. For details, see the text.

consequences of modifying them, we use a minimalist model of the epidemiology of resistance in what may well be the most common use of antibiotics, the treatment of acute, community-acquired, self-limiting bacterial infections (Figure 1).

In this model, which is derived from that in [18], we consider community-acquired directly transmitted bacterial infections. The variables U, S, ST, and R, are respectively the densities and designations of hosts within a defined community that are not colonized, colonized with susceptible bacteria but not treated, colonized with susceptible bacteria and treated, and colonized with resistant bacteria. A fraction $t(R)$ $(0 \leq t(R) \leq 1)$ of hosts colonized with susceptible bacteria are treated. Colonized hosts lose these infections at rates, v_S, v_{ST} and v_R per day and immediately enter the uninfected U state. U hosts become colonized at a rate equal to the product of their densities and that of the colonized hosts and donor-specific transmission rate constant, β_S, β_{ST}, and β_R. With a probability μ per host per day, by mutation or HGT treated hosts acquire resistance and as a consequence of antibiotic-mediated selection are converted into carriers of resistant bacteria, R.

To account for the input of susceptible and resistant bacteria from sources external to the community, like hospitals, nursing homes, daycare centers and some agricultural and veterinary settings, we assume there is a constant input of susceptible and resistant bacteria into the S and R compartments xs and xr and a corresponding reduction in the density of the U subpopulation. To account for the reality that the rate of prescriptions for a given antibiotic (treatment) of the host's will decline with the frequency of resistance to this drug, we assume a hyperbolic function,

$$t(R) = T_{MAX}\left(1 - \frac{p}{(p + k_R)}\right).$$

where p the relative frequency of colonized hosts with resistant bacteria, $p = R/(R + S + ST)$, T_{MAX} the maximum proportion of patients treated with that drug and k_R the frequency of resistance where the rate of treatment is half its maximum.

In this model there is no disease-associated mortality and the population maintains a constant density. As in [18], the transmission rate constants, the βs, are equal to the product of the reproductive number of untreated susceptible bacteria, R_0 [19] and the rates of clearance. The fitness cost of resistance, can be manifest as a higher rate of spontaneous clearance $v_R < v_S$ and/or a lower rate of transmission, $\beta_R = \beta_S(1 - a_r)$ where $(0 \leq a_R \leq 1)$. In addition to reducing the term of infection, $v_{ST} < v_S$, treatment may also reduce the rate of transmission, $\beta_{ST} = \beta_S(1 - a_{ST})$ where $(0 \leq a_{ST} \leq 1)$.

With these definitions and assumptions, the rates of change in U, S, ST and R are expressed as four coupled differential equations in which arrows entering a compartment are positive terms and those leaving negative. Copies of these equations and the Berkeley Madonna^{TM} program used to solve them can be found in the supplementary material or on www.eclf.net.

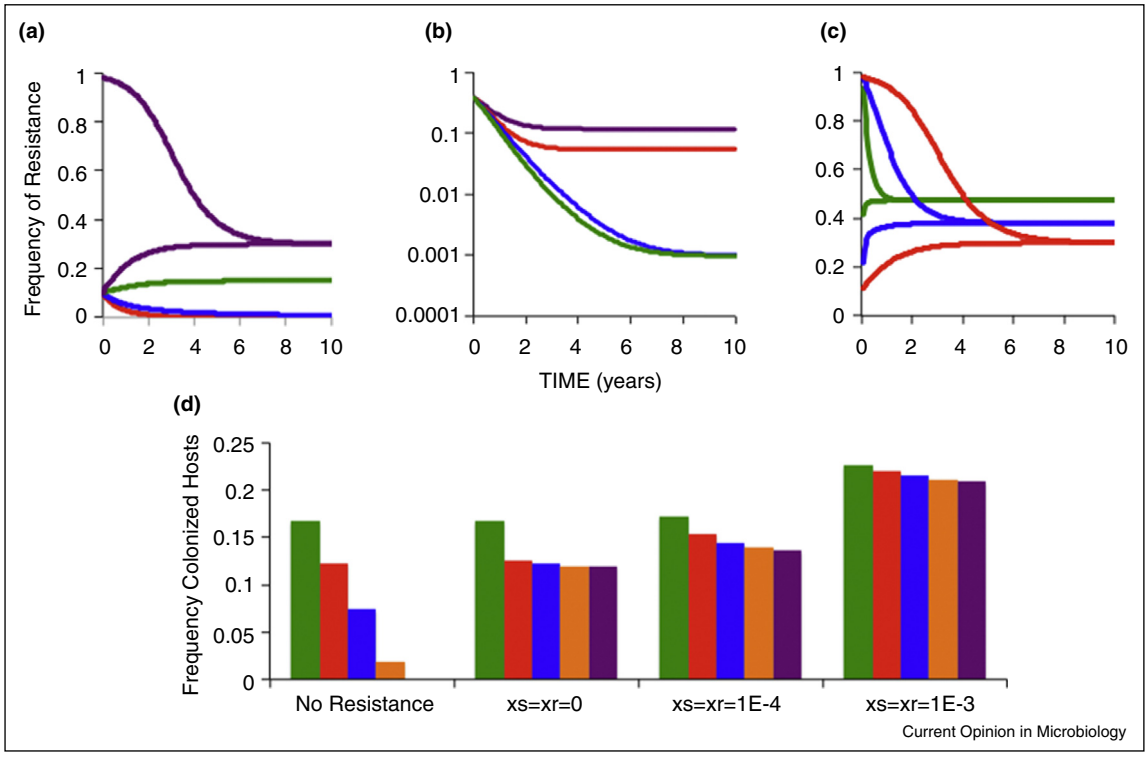
Results, predictions and implications

In Figure 2 we present the results of simulation of this model.

(i) *The classic use-resistance correlation*: As is the case for other models of epidemiology of resistance in open communities [11,13,14], observed empirically [20,21•,22] and anticipated intuitively, this model predicts that the frequency of resistance will be proportional to the rate of antibiotic use (Figure 2a). Because there is a cost of resistance which is manifest by a 5% lower rate of transmission, there is a threshold frequency of antibiotic use, below which resistance will not ascend, $T_{MAX} < 0.1$ with these parameters. Because the treatment is facultative, the rate of treatment with any particular drug declines with the frequency of resistance to that drug, resistance does not continue to increase but rather levels off and is maintained at that level; there is a stable internal equilibrium to use the jargon of mathematical biology. This can be seen by the convergence of lines in Figure 2a,c. When the initial frequency of resistance is high, this frequency declines and when low it increases and in both cases approaches a level (equilibrium) that depends on the rate of antibiotic treatment (T_{MAX} and kr) and the input of bacteria from external sources

(ii) *The contribution of acquired resistance*: Both the rate of increase and/or decrease in the frequency of resistance as well as the sustained level of resistance depends on the rate at which treated hosts, ST, acquire resistance and enter the R state, the parameter μ (Figure 2b). This parameter is rarely measured in the clinical landscape. Its magnitude

Figure 2



Dynamics of the changes in the frequency of resistance and equilibrium frequencies of colonized hosts. Standard parameter values, v_S −0.1 per day, v_{ST} −0.2 per day, v_R −0.1 per day, β −0.12 (R_0 v_S = 1.2 × 0.1) as = 0, a_R = 0.05 (cost of resistance), k_R = 0.15. **(a)** Changes in the frequency of resistance as a function of the maximum frequency of patients treated, T_{MAX} with no external input, xs = xr = 0. Red T_{MAX} = 0.05, Blue T_{MAX} = 0.10, Green T_{MAX} = 0.20, Purple T_{MAX} = 0.30. **(b)** Decline in the frequency of resistance with reductions in antibiotic use and rates of acquired resistance. Lines from the top, Purple (t_{MAX} = 0.10, k_R = 015, μ = 0.01), Red (t_{MAX} = 0.05, k_R = 0.15, μ = 0.01), Blue (t_{MAX} = 0.05, k_R = 0.15, μ = 0.0001) Green (T_{MAX} = 0.05, k_R = 0.05, μ = 0.0001). **(c)** Changes in the frequency of resistance with external input, T_{MAX} = 0.30, Red, xs = xr = 0, Blue xs = xr = 1E−3, Green, xs = xr = 1E−4. **(d)** Equilibrium frequencies of infected hosts for different levels of treatment. Green, T_{MAX} = 0, Red T_{MAX} = 0.10, Blue T_{MAX} = 0.2, Orange T_{MAX} = 0.3, Purple T_{MAX} = 0.4.

obviously depends of the rate at which susceptible bacteria become resistant by mutation and/or HGT, but also on the antibiotic treatment protocol, a subject of some controversy. Could it be, as recently suggested [23,24••], that 'orthodox' high dose therapy more likely lead to acquired resistance than more moderate dosing regimes? Or could it be that high dose therapy is the optimum way to both maximize the rate of cure and minimize the likelihood of resistance emerging during the course therapy [25]?

(iii) *Contribution of external input of bacteria*: If hosts are colonized with susceptible as well as resistant bacteria from environmental sources, the equilibrium frequency of resistance will increase in proportion to the amount of input (Figure 2c).

(iv) *The epidemiological benefit of treatment*: In addition to the virtue of reducing the term of infection of individual host (by a factor of two in these simulations), antibiotic treatment can have an epidemiological benefit. Because it lowers the term of infectiousness and thereby the amount of transmission, treatment can reduce the fraction of the population that is colonized with potential pathogens. Resistance, however, thwarts this epidemiological virtue of antibiotic treatment as does input of bacteria from external sources (Figure 2d).

(v) *The importance of surveillance and awareness*: This model predicts that if the rate of antibiotic use declines with the frequency of resistance, that frequency need not continue to increase and can be maintained at a tolerable levels. Currently to achieve this end, physicians need local, up-to-date information about the frequencies of pathogens resistance to different antibiotics to facilitate their choice of drugs and adjust their doses. There is a caveat, as awareness of high rates of resistance might also provoke higher consumption of broad-spectrum drugs [26•], yet another argument for extensive and ongoing programs to educate the public as well as health care professionals about antibiotic use.

(vi) Modifying rates and patterns of antibiotic use is not the only way to control the incidence of infections and the frequency of resistance [27,28]. This can be seen with this minimalist model. By infection control, better hygiene and other methods, the transmission rates of pathogens, the βs, can be reduced and with that the frequency of resistance. For example if we assume a $T_{MAX} = 0.20$, a 10% reduction in the transmission rate constant, β, results in a 9.1% increase in the frequency of uninfected hosts, U, and respectively a 58.1% and 41.5% decrease in hosts colonized with susceptible and resistant bacteria Vaccination is also a promising strategy to fight against antibiotic resistance [29,30••].

Some inconvenient realities

(i) *The cost of resistance and compensatory evolution*: Central to the control of resistance by changing rates of antibiotic use is that resistant bacteria are less fit than susceptible. When first acquired resistance genes and genetic elements may indeed impose a fitness cost, the magnitude of that cost is likely to be ameliorated by the subsequent evolution of compensatory mutations [31–35,36••,37,38••,39–45,46•].

(ii) *A dearth of alternatives*: Implicit to decisions not to employ an antibiotic because of higher than desired frequencies of resistance, is the availability of alternative drugs for which resistance are less frequent. Not only has the supply of alternative antibiotics with no cross-resistance to existing drugs declined, there is little sign of its being replenished in the near future [47,48•]. Adding to this supply dilemma is an increasing frequency of multi drug resistance; selection for resistance to one antibiotic increases the frequency of other genetically linked resistance genes.

(iii) *Environmental sources of resistance*: In addition to the direct, person to person transmission within the community, in this model antibiotic resistant bacteria as well as genes and genetic elements can be acquired from external sources. For normally self-limiting community acquired infections of the sorts this model considers, like otitis media, sinusitis, conjunctivitis, and many upper respiratory infections, as well as uncomplicated skin infections, the primary external sources of the bacteria responsible, like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*, are likely to be the hospitals, long-term-care facilities, nursing homes and daycare centers, rather than food and water. For enteric infections the external sources of primary concern are reservoirs in the normal microbiota following exposure to food, water (particularly sewage-contaminated water in underdeveloped countries) and other polluted environmental sources [49••,50]. While the mathematical models for infections acquired from these kinds of external sources will be different from that considered above, more like that in [11], we would anticipate an analogous dynamics; environmental sources of resistant bacteria will increase the frequency of resistance in the pathogens colonizing and infecting humans. Unless there is a major effort to address this issue, there is every reason to anticipate that these external to the human community sources of resistant bacteria are going to increase the rate of ascent and frequency of resistant pathogens in human populations. Moreover, even at the subtherapeutic concentrations anticipated in these environmental sources, selection will favor resistance [51–53].

(iv) *The spread of high-risk resistant clones*: In a number of cases, resistance rates might be a consequence of local spread of highly transmissible resistant clones exacerbated by antibiotic exposure [3], but it is also true that the spread of highly transmissible antibiotic-susceptible clones might decrease antibiotic resistance rates.

(v) *The tragedy of the commons*: Antibiotics are perceived to be and largely are to the advantage of individuals, whilst resistance is primarily (but not entirely) a problem for the collective [54]. Presumably motivated by concern for resistance as problem for the collective, Northern European countries tend to use narrow-spectrum antibiotics (narrow-selective antibiotics), but in many other parts of the world the rapid antibiotic effect takes the priority, justifying broad-spectrum (broadly-selective) drugs [55], yet another tragedy of the commons [56,57••,58,59].

The future of antibiotic resistance: we have not crossed the red line

We do not believe 'the post antibiotic era [60]' is upon us. To be sure, we will not return to a time when inherited drug resistance was undetectable in human pathogens. Evolution has taken its course and the tape cannot be played again. On the other hand, even accepting the above listed and doubtless other undesirable realities, there are compelling epidemiological, social and technical reasons to be optimistic about the future of the treatment and prevention of bacterial diseases.

As we attempted to demonstrate in this model/computer-assisted rant, resistance can be controlled; there is no reason to expect that pathogens refractory to all extant antibiotics will universally replace those that are susceptible to one or more effective drug. Despite our excessive use of these drugs and their increasing abundance in our environment, variants that are susceptible to the majority of currently employed antibiotics continue to persist for virtually all bacteria and dominate the majority of pathogenic species. There is no reason to expect the reservoir of susceptible bacteria will be exhausted and it could well be replenished.

From the perspective of social norms, physicians and the population at large are increasingly aware of the resistance problem and its potential deleterious effects on them as practitioners, individuals and even corporations. As suggested by [56,61] the tragedy of the commons that has dominated antibiotic use these past decades can be overcome by social pressure and the reinforcement of responsibility to the collective. Our technology is also working in the right direction. To be sure, even if it were technically and economically feasible, we cannot sustain, much less win the arms race with evolution by developing ever more traditional antibiotics. On the other hand, thanks to the increasing awareness of the resistance problem, impressive advances in molecular biology and tools for that enterprise, and of course economic incentives there is every reason to anticipate the development of methods to deal with the resistance problem. Biomarkers, such as procalcitonin, are useful to guide the initiation and duration of antimicrobial therapy reducing total antibiotic exposure and treatment duration [62,63]. Cost-effective diagnostic procedures are being developed that not only rapidly (within hours) identify the bacteria responsible for symptomatic infections, but also their pattern of resistance. Some of these diagnostic methods are already available for widely distributed strains of community-acquired pathogens, like MRSA [64]. We believe, however, that it is unlikely that these resistance-determining diagnostics will become available for the vast numbers of strains of commensals/pathogens responsible for the majority of community-acquired infections and the plethora of resistance mechanisms involved. It should however be at least possible to develop cheap and rapid diagnostic tests that would enable physicians to determine whether or not the symptoms presented by a patient can be attributed to bacteria and whether antibiotic treatment is appropriate. This would reduce unnecessary prescriptions and thereby the intensity of selection for resistance in our commensal microbiota.

But we need not and should not wait for technological advances to address the resistance problem. The profound decline in infectious disease mortality during the 20th century occurred before the antibiotic era and can be attributed to environmental interventions, deep improvements in sanitation, water supplies, food handling and food preservation, and education about infectious diseases [65]. Coupled with improved antibiotic stewardship [66] the same methods can be used to not only reduce the incidence of infection, but also to control resistance. We certainly have the motivation and technology to achieve this and hopefully the will as well.

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- •• of outstanding interest

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