ANTIBIOTIC RESISTANCE: ORIGINS, EVOLUTION, SELECTION AND SPREAD
Antibiotic resistance: an ecological imbalance

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Abstract. Antibiotic resistance thwarts the treatment of infectious diseases worldwide. Although a number of factors can be identified which contribute to the problem, clearly the antibiotic as a selective agent and the resistance gene as the vehicle of resistance are the two most important, making up a ‘drug resistance equation’. Both are needed in order for a clinical problem to arise. Given sufficient time and quantity of antibiotic, drug resistance will eventually appear. But a public health problem is not inevitable if the two components of the drug resistance equation are kept in check. Enhancing the emergence of resistance is the ease by which resistance determinants and resistant bacteria can spread locally and globally, selected by widespread use of the same antibiotics in people, animal husbandry and agriculture. Antibiotics are societal drugs. Each individual use contributes to the sum total of society's antibiotic exposure. In a broader sense, the resistance problem is ecological. In the framework of natural competition between susceptible and resistant bacteria, antibiotic use has encouraged growth of the resistant strains, leading to an imbalance in prior relationships between susceptible and resistant bacteria. To restore efficacy to earlier antibiotics and to maintain the success of new antibiotics that are introduced, we need to use antibiotics in a way which assures an ecological balance that favours the predominance of susceptible bacterial flora.


In large part, bacteria live in harmony with other inhabitants of the earth. Although some infections are caused by bacteria for which humans are a specific host, in most instances the infections follow entry of bacteria into the body by chance. Over the past 50 years, the classic treatment of bacterial infectious diseases has been antibiotics, the discovery of which vastly changed the relationship between bacteria and people. Today we are witnessing another change, that is, among the bacteria themselves.

While diversity characterizes the microbial flora, antibiotic use has led to a further subgrouping into those bacteria that are susceptible and those that are resistant to antibiotics. Prior to antibiotic introduction, the large majority of commensal and
Antibiotics and the emergence of resistance: the selection density

Antibiotics were initially developed for the treatment of infectious diseases in people. Their miraculous effects led to their being solicited and used for the treatment of animals and eventually plants. The same ones are being used in all three areas. Thus, an enormous worldwide selective pressure has occurred. Antibiotics are used both internally and externally to control bacterial problems for society, maintaining the health of people, animals and agricultural crops. If different antibiotics had been chosen for animals and agriculture than those used in people, we might be witnessing a lower level of resistance today. But, in fact, with each ensuing year, 4-5% more antibiotics have been produced, developed and used. In the USA alone, an estimated 160 million prescriptions for antibiotics were written last year and over 50 million pounds were produced for use in people, animals and agriculture.

There are two major effects of an antibiotic: therapeutically, it treats the invading infectious organism, but it also eliminates other, or non-disease producing, bacteria in its wake. The latter, in fact, contribute to the diversity of the ecosystem and the natural balance between susceptible and resistant strains. The consequence of antibiotic use is, therefore, the disruption of the natural microbial ecology. This alteration may be revealed in the emergence of types of bacteria which are very different from the ones previously found there, or drug resistant variants of the same ones that were already present. The dominance acquired by these new strains in the treated environment is directly linked to the intrinsic or acquired resistance to the antibiotics being used.

To a large extent, the reversibility of the selection process is dependent on repopulation by the original susceptible bacteria. Their residual numbers will be related to the total amount of selective drug used in that environment. This relationship suggests that it is the density of the antibiotic, i.e. the total quantity applied, the number of individuals (people, animals, plants) treated, and the size of the geographic area affected, which quantitatively and qualitatively affects microbial ecology. This concept translates directly into a 'density' selection process which affects that ecology (Fig. 2). The introduction of an antibiotic into an environment has the eventual effect of killing-off most, if not all, of the resident susceptible strains. Any resistant survivors will then have a chance to propagate and take over. But adjacent to that selective environment, and encroaching on it, are untreated, susceptible strains which are still potential competitors for the treated area, if given the opportunity. The size of the area selected for resistance will be related to the total amount of antibiotic used and the geographical extent of its influence. It further relies on the potential for susceptible strains to return after the selective event. One would not expect the same ecological

Antibiotic + Resistance trail \(\rightarrow\) Antibiotic resistance problem

FIG. 1. The drug resistance equation.
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Genetics of drug resistance and spread

The emergence of resistant bacteria raises concern about the bacteria and their progeny and also the extent that they can spread to other environments. The bacterium itself is the focus, if the resistance trait is linked solely to that bacterium and cannot be shared by others. This is, however, not the case with most resistance traits in the majority of bacteria. They have evolved extrachromosomal replicating genes called plasmids and their associated transposons which allow rapid and very broad dissemination of genes (Fig. 3). Gene transfer crosses species and genus barriers (DeFlaun & Levy 1989). Thus, resistant enterococci selected in one environment can pass resistance genes not only to other members of their own genus and species but also to other organisms in other genera. Staphylococci share their plasmids with *Listeria; Escherichia coli* share genes with other members of the *Enterobacteriaceae* as well as the pseudomonads and *Neisseria*, just to mention a few. In fact, the same tetracycline resistance determinants can be found among Gram-positive and Gram-negative bacteria as well as in the mycobacterium (Roberts 1997, this volume). The genetic flexibility and versatility of bacteria have therefore contributed largely to the efficiency by which antibiotic resistance has spread among bacteria and among environments globally. However, it is equally evident that the transfer event has no consequence unless the antibiotic selection is there. Thus, the emergence and maintenance of bacterial resistance relies on the interrelationship between the resistance determinant and the antibiotic.

Reversal of resistance

Data on the reversal of the resistance selection offer further insights into the selection process. The faecal flora of a volunteer, myself, taking tetracycline for five days was examined. Initially tetracycline resistance was present at a low level; it peaked within two days of tetracycline use. After five days, tetracycline was stopped, but the resistance frequency declined very slowly. The rate of loss did not mimic the rate of gain of resistance: it took 15 days to return to the initial pre-antibiotic level (Levy 1986). Antibiotics are so powerful that they provide rapid selection for a new resistant breed, but when you remove the antibiotic, a reversal is slow in coming. The resistant bacteria selected by tetracycline are no less ‘fit’ than the susceptible flora; hence they continue to propagate and persist.

We did similar studies among chickens excreting *E. coli* with multi-resistance plasmids. They did not lose the *E. coli*, despite multiple cleanings of the cage over several months (Levy 1986). However, this was a closed environment, and there was no easy route of entry for susceptible strains. Moreover, the resistant bacteria were clearly not disadvantaged by bearing resistance. When the cages were relocated to different sites around the barn, the surrounding environment was altered and the chickens' flora slowly returned to a more susceptible one (Levy 1986). In another study, we added four chickens excreting a resistant flora to 10 other chickens excreting a susceptible flora. Resistance was lost; the susceptible flora won out. For an immediate change in resistance frequency, the result relies on numbers, not large
differences in bacterial fitness. Moreover, there is no active counter-selective force which propels repopulation with susceptible strains.

In the short term, the resistant bacteria were not less fit than the susceptible ones, so we did not observe a rapid shift from resistance to susceptibility. However, in the long term such changes have been documented in hospitals (Glamare-Hou & Antoniadou 1997, this volume) and on farms (Levy et al 1976) when antibiotics have been removed. But it takes time. In some instances, newly gained plasmid is not stably kept in its new host. Early on, this instability will help in reversing the resistance. However, with time, the plasmid and bacteria may develop a synergistic relationship whereby both are needed for growth, demonstrating a phenomenon to be discussed later in this symposium (Lenksi 1997, this volume). Still, the evidence suggests that, given a ‘ready and willing’ susceptible flora, a resistance predominance can be overturned if antibiotics are removed.

The resistance reservoir

Resistance genes reside not only in disease-causing organisms, but in commensal organisms as well. These normally harmless bacteria, such as E. coli or enterococcus, can cause a fatal illness if the person is immunocompromised. Moreover, these bacteria harbour resistance genes which can spread to the bacterial strains that do cause infection. Unfortunately, these reservoirs are not being examined very much.

People today harbour many multidrug resistant bacteria. In a study of faecal flora from an ambulatory community, we found that 40% of people on antibiotics carried two or more resistances in 10% of their E. coli, 25% had three or more resistances and 10% had four or more (Levy et al 1988). People excrete resistant E. coli at the 50% level, even when not consuming antibiotics (Levy et al 1988). High carriage levels of resistant faecal flora have been reported from Holland (Bonten et al 1992), and elsewhere (Calva et al 1992, Leistevuo et al 1996). Resistant bacteria are plentiful in the environment, providing evidence for an environment in a state of imbalance. While not necessarily inflicting harm, they certainly reflect a significant selection process.

One source of resistant bacteria is food. A large number of drug resistant Gram-negative bacteria are associated with uncooked foods (Levy 1984). In the great majority of instances these bacteria pose no health problem. But they too tell us a lot about the environmental imbalance. A study from France assessed the contribution of food bacteria to the intestinal flora by examining the same volunteers when eating normal or sterilized food (Corpet 1988). Tetracycline resistance in the faecal flora was high when the volunteers were eating normal, non-sterilized food for 21 days, but dropped dramatically when the diet was shifted to sterilized food for 17 days (Table 1).

Beside selecting resistant variants, antibiotics can affect theecology by changing the types of organisms there. New opportunistic infectious disease agents, intrinsically resistant to the antibiotic in use, can emerge and predominate. For instance, the use of second and third generation cephalosporins in hospitals, introduced for Gram-negative bacteria, selected the normally harmless enterococcus, which is intrinsically resistant to these antibiotics. The enterococci, selected by these drugs, have now become prominent members of the hospital acquired flora. Moreover, the organism has emerged with its own multiplicity of resistances, e.g. to aminoglycosides and vancomycin. It is a likely potential donor of vancomycin resistance to the staphylococcus. Replacement of an endogenous flora with a new flora as a consequence of antibiotic use is an important concept that is too often disregarded. It has a significant impact to our health.

If one is thinking about using an antibiotic to target the disease-causing organism, which, of course, is the magic of these drugs, one has to think about the other bacteria as well. If the antibiotic’s sphere of influence is large, then its ecological effect will be large. As we widen antibiotic usage from the individual to the hospital and the community, we see more and more effect on the susceptible strains. Some have talked about spraying hospital rooms with susceptible commensal organisms to replace and compete with the disease agents. It is an approach worth considering.

Overall, let’s focus not just on the antibiotic, but also on the susceptible flora. Susceptible bacteria should be our teammates in confronting and reversing the resistance problem.

Why all the current publicity?

Why has so much recent attention been given to a field that some of us in this room have been working in for decades? Many journalists writing about it are directed by a personal experience. Many of these writers, or their editors, have children who have, or have had, ear infections or other infections that did not respond to antibiotics. The pneumococcus, whether the real culprit or not, has clearly brought the drug resistance issue to public awareness. Not just the kids are suffering, but the parents, as well, because they cannot fulfil their job obligations having to stay home with a sick child. Besides the pneumococcus, there are other resistant bacteria confronting society at large. The tubercle bacillus, which causes tuberculosis, is multidrug resistant and, in some patients, incurable. The gonococcus, the agent of gonorrhoea and a community acquired infection, is now resistant to penicillin, tetracycline, quinolones and some strains show early signs of resistance to cephalosporins. Few if any options remain after these cephalosporins. This is a societal problem. Imagine what’s going to happen when we lose our ability to rapidly treat this organism. The staphylococcus can only reliably be treated with vancomycin. To these can be added Pseudomonasaeruginosa, Acinetobacter.

<table>
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<tr>
<th>TABLE 1 Log number of total and tetracycline-resistant lactose-fermenting enteric bacilli from six volunteers on a sterile diet</th>
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<tr>
<td><strong>Control diet (21 d)</strong></td>
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<tr>
<td><strong>Total</strong></td>
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Data for the control and sterile diets are means + SD for 21 and 17 daily counts, respectively. Tet R denotes tetracycline resistant. Data from Corpet (1988).
and other bacterial disease agents, all thwarting therapy by resistance. The decade of the 1990s is unique. Resistance is no longer confined to hospital environments, but is now common in community populations worldwide. As important, this crisis is heightened by a lack of new antibiotics developed during the decade.

Approaches to the problem

No novel antibiotic is expected to appear soon, and an increasing number of bacterial infectious agents bear resistance to many if not all antibiotics. We must somehow find a means to reverse the ecological imbalance that has occurred in terms of resistant and susceptible strains. One way is to remove or adjust the selection process so as to allow the susceptible strains to regain their former dominance. As demonstrated above, such reversals are possible and provide the necessary optimism. There still are sufficient susceptible bacteria in our environment which, when given a chance, can return and re-establish the susceptible flora. The crux for reversing and curbing the resistance problem lies in restoring the susceptible microbial flora, whether this is in the intestinal tract, the skin, or elsewhere in the environment. To do this, antibiotic use needs to be more rational. The misconceptions and misunderstandings of antibiotics as miracle drugs without adverse consequences have led to their inappropriate use and prescription. Education of the prescriber and the consumer is critical.

In previous decades the pharmaceutical industry has been able to identify and produce newer and more potent antibacterial agents. However, experience in the present decade indicates that this is no longer true. Discovery has diminished, although encouraging signs are appearing once more (Service 1995). There are now renewed efforts in large pharmaceutical houses and smaller biotechnology companies to discover truly novel drugs. These drugs would be those with no structural relationship to prior antibiotics and thus not intrinsically subject to already existing resistances. This offers one approach towards a solution. Another is to define sufficiently the resistance mechanism and use it to identify novel drugs which can poison or inactivate resistance mechanisms and allow the effective antibiotic to work. This is the basis for the success of the combination of β-lactamase blockers and an effective β-lactam drug, initially introduced as clavulanate and amoxicillin by Beecham Pharmaceuticals. It is this same approach which we are using to restore efficacy to the tetracycline family. Here we are using a semi-synthetic tetracycline to block a drug efflux, allowing a classical tetracycline to enter and stop growth (Nelson et al 1993, 1994).

The control of the antibiotic resistance problem lies in a better understanding of how we use antibiotics. Conditions can be envisioned whereby we encourage the re-emergence of susceptible strains following treatments and the maintenance of the normal susceptible microbial flora between treatments. We need to restore the marginal microbial balance between susceptible and resistant bacteria—a balance which has been devastatingly altered by the inappropriate and continued application of antibiotics to our environments.

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DISCUSSION

Lenski: The goal of shifting the ecological balance from resistant to susceptible strains of bacteria is clearly an attractive idea. However, how strong is the evidence that when antibiotic usage is relaxed the resistant flora decline? What kinds of rates
are we talking about? You gave the example that when you treated yourself with tetracycline it took about three times longer for the resistance to be lost than it did to appear. That struck me as a rather fast rate of disappearance: it suggests there may have been a high cost to resistance for the bacteria.

Bush: In the β-lactamase situation, although ceftazidime resistance can be diminished if you take away the drug, resistance plasmids are maintained in colonizing flora. If the use of ceftazidime is reduced, the number of ceftazidime-resistant isolates will diminish and seem to disappear within a hospital. But it has been demonstrated in Chicago nursing home patients that the plasmids continue to survive in the colonizing flora (Wiener et al. 1992).

Levy: Thus, although the resistant bacteria are no longer seen as a nosocomial infection, they're still present in the hospital.

Bush: Yes.

Davies: In the tetracycline ingestion experiment, you only analysed tetracycline-resistant organisms of one particular type. You have no idea of the reservoir of tetracycline resistance in the gut flora. Thus it seems to me that the experiment is incomplete and you should do it again using PCR amplification with tet-specific primers to find out how long the tetracycline-resistance gene stays around in the gut. I believe that the gene for resistance is going to persist longer than you have shown.

Levy: Tetracycline resistance did not go away. The total tetracycline-resistant JE. coli flora went back down to what it was before, but it was clearly detectable.

Levin: I once did a similar experiment to that of Stuart, by sampling my own faeces and plating them on antibiotic-free lactose minimal agar and lactose minimal agar containing antibiotics such as streptomycin, ampicillin, kanamycin and tetracycline. In that way it was possible to monitor the frequency of resistant bacteria, even when they were quite rare, in the order of 10^{-5} or less. Before taking tetracycline, the frequency of resistance to the antibiotic was between 10^{-3} and 10^{-2}. One day after I started taking tetracycline, virtually all the bacteria recovered were tetracycline resistant. Moreover, the frequency of resistance to the other antibiotics also increased. Following the termination of treatment, the frequency of resistance to tetracycline and the other antibiotics waned, but continued to oscillate at levels in excess of 10^{-3} for the month or so I sampled for (B. R. Levin, unpublished results).

Levy: There are clearly many other bacteria entering the intestinal flora from the food we eat. Thus there is a lot of mixing with the external flora. A better way to do that experiment would be for me to go on a sterile diet, so I would just be looking at what was happening within my intestinal flora.

Roberts: If you look at the opposite end — the oral cavity — virtually all of us carry tetracycline-resistant CC-streptococci, regardless of whether we have had tetracycline or not. Many children who routinely never take tetracycline have tetracycline-resistant α-streptococci. One has to go back to the 1960s to find α-streptococci that are susceptible. Many people make the wrong assumption that they are intrinsically resistant, but they have all acquired the tet genes. There are other organisms where you may not get the waxing and waning. We studied bacterial vaginosis in pregnant women, again a group who do not receive tetracycline. Virtually every patient had Tet resistant streptococci and peptostreptococci (Roberts & Hilliet 1990). I’m proposing that in streptococci you actually get less fluctuation from susceptible to resistant than when you do with E. coli in the gut.

Levy: So there’s a resident oral flora that persists?

Roberts: Yes. In some of the dental literature, people mistakenly say that the α-streptococci in the oral cavity are intrinsically resistant which is not true; all of them have acquired tet genes.

Baquero: That is correct, but the real problem is that it may be too late to react, in the sense that our normal flora is now the normal resistant flora. They have adopted the resistance determinants, perhaps taking advantage of these mechanisms for other functions. One of the key points from your discussion is the concept of a ‘resistance gene’. This is a somewhat controversial issue, because many bacteria are normally physiologically susceptible, or intrinsically resistant. I’m worried by the fate of these intrinsically resistant bacteria in the face of antibiotic pressure. Imagine that we are just looking at potentially pathogenic bacteria: the problem with the multiple antibiotics we are taking to control pathogens is that by their use we are altering our normal bacterial environment. For instance, we are eliminating some of our old lactobacilli and these are replaced by other less ‘human adapted’ lactobacilli intrinsically resistant to the antibiotics we are using. Perhaps we are changing our normal gut physiology, replacing the bacteria that have been co-selected with us during evolution. Eventually, we are doing something even worse than modifying the pathogenic bacteria — modifying the normal saprophytic bacteria in alliance with human beings through evolution. Who knows what the implications of such changes are for human health?

 Summers: Has anybody done any prospective studies on hospital admissions in checking the level of resistance on entry to see what level of resistance indeed does involve subsequent clinical compromise?

 Huovinen: We have some results from a study in geriatric units (Leistevuo et al. 1996). When someone is treated with an antimicrobial drug, resistant strains will be enriched in this subject and he or she will then excrete these strains to the surroundings.

 Levy: You come into hospital with a trace of resistant bacteria. You receive an antibiotic, and resistance frequency rises. Anne Summers is asking: if a patient comes into hospital with 10% resistance, does that level of resistance get them into trouble? I don’t know that anyone has done such a prospective study, although many of us have found resistant organisms in the faeces. The frequency probably doesn’t matter, because as soon as you start using the antibiotic the numbers rise.

 Huovinen: In long-term treatment the patients are colonized in the hospital. We can show that although the level of antimicrobial usage in the ward is very low, patients are still colonized with resistant strains. Antimicrobial treatment is not the only factor.

 Cohen: This is a reflection of the underlying problem, which is that we look at only a subset of the microbial flora. Within the greater ecosystem, we’re examining just a small part: often just a single pathogen. We often don’t know what other species are out there. It is difficult to look at this small microcosm and understand everything that’s occurring.
If we look at the Chicago experience with $\beta$-lactamases, the first ceftazidime-resistant $\beta$-lactamases appeared in two Klebsiella isolates in January 1988. They were not identified again until November 1990 when nursing home patients were then admitted to Chicago hospitals. Resistant Klebsiella strains in the hospital were apparently taken back to nursing homes where patients were eventually colonized with E. coli with the same plasmids. Species to species transmission was occurring (Wiener et al 1992).

It's my understanding that we cannot culture all of the organisms in the gastrointestinal tract. The whole point about resistance transfer is that we really don't know where resistance genes are going within the bacterial population. In many cases we don't know what the reservoir is. While we are looking at the bugs that we can grow, we are missing a lot of the microbial ecology of drug resistance.

Some years ago we showed there are differences between what skin patients have in their nose and what they have on their skin (Noble 1977). What they have on their skin tends to be much more antibiotic resistant even if it's apparently the same strain. There are other factors. For example, many of the penicillinase-producing strains are somewhat more resistant to lipid. We thought this was a rather tidy way of looking at it. It may be that it is actually the skin lipid that is selecting for penicillinase-producing strains, and not the penicillin. We're talking about a resistance determinant as though there's no other DNA on that plasmid or transposon.

It's going to be slightly naive to look just at one genus, because within a genus you can get quite diverse results. In patients with peritoneal dialysis, the coagulase-negative staphylococci are quite often resistant to three or four antibiotics. In contrast, the coagulase-positive staphylococci are usually sensitive to everything except perhaps penicillin and tetracycline. It may be the case that what is normal on the skin is able to cope with lots of resistant determinants, but what is abnormal on skin can't, unless it's under antibiotic pressure.

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Another point that concerns me is that although in Greece people in the community use tons of $\beta$-lactams, we have a low rate of $\text{Streptococcus pneumoniae}$ resistance: only 8% of the intermediate type with a fairly low MIC of 0.25 to 0.5 $\mu$g/ml. I cannot explain it.

Witte: Is there real evidence that MRSA has already become part of the colonizing flora in the community? It was my impression that whenever this has been reported there has always been some link back to the hospital. In Germany, the frequency of MRSA doubled from 1990 to 1995. We now have 5% in nosocomial infections. Our community studies have shown that MRSA is still rare among carriers outside hospitals and that we cannot always exclude previous hospital stays.

Roberts: We are currently working with the native population in Alaska, where there is some evidence to suggest that antibiotic resistance has developed in situ primarily because they are small communities. For the first 10-12 years there was multidrug resistant $\text{Streptococcus pneumoniae}$ 6B only in one region of Alaska; now it has been spread all over the state. You will occasionally get another serotype with the same pattern, but this does not seem to spread. There are some factors in the 6B which allow it to be maintained in the community and other factors where it perhaps isn’t as good a pathogen, and therefore it may have a little cluster effect but you don’t see it maintained for long periods.

Levy: Antibiotics not only select the resistant form of the organism you are trying to treat, but also wreak havoc in the environment. We don’t know how large that domino effect is. You cause the resistant organisms to emerge, but they are now in an environment which has also changed. Thus a bacterium that might have been a minor participant in the previous environment, now finds an environment so changed that it can become a major participant.

The antibiotic certainly is a player in the resistance imbalance, but so are the non-target organisms in the environment, many of which we do not know about. We can only look at those things we know. One of the recommendations that I propose should come out of this Symposium is that greater attention should be given to the other organisms being affected by antibiotic use, as well as the factors which cause a change in the levels of resistance which are not linked to antibiotic usage.

References

