The rise and fall of antimicrobial resistance

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Antimicrobial resistance is a growing problem in nearly every infectious disease, but the extent and rate of increase of the problem varies widely with different pathogen–drug combinations. The rate of increase of resistance depends primarily on the availability of resistant variants and the intensity of selection imposed by antimicrobial treatment (appropriately measured). Declines in resistance following antimicrobial control measures are typically faster in hospital-acquired infections than in community-acquired ones, probably owing to the dependence in the latter case on the fitness cost of resistance. Open questions and approaches for testing the hypotheses proposed here are outlined.

The rise of antimicrobial resistance in human pathogens poses a growing challenge to medicine and public health. Increasing resistance to preferred therapies has limited the options for treating such diverse infections as HIV infection and malaria, as well as a variety of hospital- and community-acquired bacterial infections[1,2]. Preserving the effectiveness of existing therapies is an increasingly urgent consideration in the choice of treatment for these infections. However, apart from avoiding unnecessary use of antimicrobial agents, the best way to extend the life of these drugs at the population level is not well understood. Resistance not only makes treatment of individual patients more complicated and more expensive; it also compromises the effectiveness of disease control programs for those infections where effective case detection and treatment are central to the prevention of disease transmission [notably tuberculosis (TB) and some sexually transmitted infections][3].

Although the problem of antimicrobial resistance is almost ubiquitous in infectious diseases, the scale of the problem, and the rate at which resistance becomes a problem, is highly variable, depending on the antimicrobial agent, the pathogen and the setting in which transmission occurs. For example, resistance to single anti-infective agents used for treatment of both TB and HIV infection was documented almost immediately after these agents became available, and the development of effective combination therapy regimens has provided only a partial solution to these problems[2,3]. The result has been not only treatment failures in individual patients, but also the transmission of resistant infections to others. At the other extreme is the use of penicillin to treat infections with group A streptococci; despite >50 years of use, no case of penicillin resistance has been documented in this organism[4]. Most pathogen–drug combinations fall between these two extremes[5].

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Just as the rate of increase in resistance is highly variable, the rate at which resistance declines in response to interventions also differs considerably in different pathogen–drug combinations, ranging from dramatic reductions in a few months to equivocal results or small declines after several years of control measures. In designing and evaluating efforts to control antimicrobial resistance, it is crucial to understand the factors that determine whether resistance spreads rapidly or slowly in a population, and whether measures to reduce resistance are likely to show results over a span of months, years, or longer. In this review, I will describe some of what is known on this topic from both empirical and theoretical studies, and also attempt to highlight key areas of present ignorance. The discussion will concentrate on human uses of antimicrobial agents; this omission is for the sake of space and is not intended to minimize the importance of agricultural and veterinary uses of antibiotics.

The rise of resistance

The appearance and growth of antimicrobial resistance as a clinical problem requires several distinct steps. Any one of these steps can be 'rate-limiting'; the span of time between the first use of a particular drug and the appearance of resistance to that drug as a clinical problem for a given pathogen depends on the rates at which these steps are accomplished.

First, resistance must be genetically and physiologically possible for the infectious agent. In some infections, such as TB, creation of a resistant organism requires only a single point mutation; these mutations occur so frequently that at least one bacterium with a mutation is present in nearly every host with active disease. In other cases, the appearance of the first viable resistant organism can take much longer, for any of several reasons. Resistance can be genetically and biochemically complex, requiring the assembly of several genes that work together to create the resistant phenotype, as in the case of vancomycin resistance in *Enterococcus*[6]. A related phenomenon is the requirement for multiple mutations in the same or different genes to confer high-level resistance to certain drugs; in this case, resistance can be delayed because bacteria containing only one mutation are not sufficiently resistant to gain an advantage in the face of clinically achievable drug concentrations, and double mutants are

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Box 1. Resistance to antiviral agents in influenza A virus and herpes simplex viruses: case studies in differential rates of increase

Recent mathematical modeling studies have assessed the likely rate of increase in resistance of influenza A virus and HSV-1 and -2 to antiviral agents if these agents were used widely in human populations. A model of the use of amantadine and rimantadine during an epidemic of influenza A predicted that substantial levels of resistance would be observed within weeks of the onset of widespread antiviral use[a]. By contrast, three studies of resistance to nucleoside analogs in HSV-1 (Ref. b) and -2 (Refs c,d) infections predicted that it would take decades or longer for resistance to these drugs in viruses infecting immunocompetent hosts to increase to a few percent, even if antiviral use were significantly increased. These divergent predictions can be explained by several important differences between the viruses.

- If resistance to an antimicrobial agent is initially rare, then early increases in the prevalence of resistance will be driven by the probability that resistance emerges in treated hosts; this probability can be as high as 30% in amantadine- or rimantadine-treated influenza patients[e], whereas it appears to be between zero and 0.2% in immunocompetent HSV-infected patients treated with nucleoside analogues[b]. One reason for the low rate of emergence in HSV could be the limited viral replication that takes place during HSV-1 recurrence, making it likely that many fewer viruses are exposed to selection for resistance than is the case in treatment of influenza. Once resistance has emerged in treated hosts, its spread to other hosts depends on the generation time of the infection, the transmissibility of resistant viruses, and the selection imposed by treatment in reducing transmission of the susceptible virus.
- Although resistant influenza A viruses appear to be highly transmissible[e], most resistant HSV are severely reduced in infectiousness, at least in animal models[f].
- The time from infection to transmission in influenza can be measured in days, whereas for HSV-1, at least, it is measured in decades[b].
- Amantadine and rimantadine appear to have substantial efficacy in preventing influenza infection or shortening its duration; these reductions in infectiousness directly translate into selective pressure in favor of resistance[e]. By contrast, some formulations of nucleoside analogs have relatively modest effects in reducing the duration of viral shedding, translating into reduced selection pressure in favor of resistance[b].

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extremely unlikely in any given patient. Examples of this phenomenon include Gram-negative resistance to third-generation cephalosporins encoded by plasmid-borne, extended-spectrum β-lactamases, which often require multiple mutations to confer resistance to a novel agent[7,8], and high-level fluoroquinolone resistance in many bacterial species, which occurs only after mutations in two genes, *parC* and *gyrA* (Ref. 9). In other cases, resistance requires changes in structural components of the pathogen (e.g. components of the cell wall) that are physiologically too damaging for the bacterium to survive; this might explain the continuing absence of penicillin resistance in group A streptococci[4].

A second step required for many clinically important resistance mechanisms in bacterial pathogens is the transfer of resistance genes from another bacterial species. Again, this process can be relatively common, as in the interspecific transfer of multi-resistance plasmids among Gram-negative Enterobacteriaceae[10], or can be an extremely rare event, perhaps happening only one or a few times. The relatively limited number of molecular mechanisms for vancomycin resistance in *Enterococcus* spp.[11] suggests a few introductions into the genus, followed by rapid dissemination and diversification within the genus.

For the prevalence of resistance to spread in the host population (to create 'primary resistance' in patients who have not yet been treated), resistant pathogens must colonize or infect new hosts. The rate at which this occurs has an important role in determining the timescale on which resistance increases at the level of the host population. For bacteria that colonize and infect hospitalized patients, this can occur in a matter of days, or even less, via transmission by health-care workers or environmental contamination, resulting in the potential for rapid outbreaks of resistant organisms[12]. At the other extreme, a long-lived infection, such as infections with herpes simplex viruses (HSV), can have a 'generation time' – the average time from infection of one host to transmission of that infection to another host – on the order of perhaps a decade or more[13]. All else being equal, the rate of spread of resistance is faster in infections with shorter generation times.

Finally, antimicrobial resistance substantially impairs the growth rate or infectiousness of some pathogens, thereby limiting the ability of resistant infections to spread. However, it has repeatedly been found in laboratory-based studies that this 'fitness cost' can be reduced by subsequent evolution, in which further mutations are selected that attenuate the deleterious effects of resistance[14]. Although this evolution occurs quickly in laboratory experiments, it is possible that evolution of sufficient compensation for the cost of antimicrobial resistance could be a limiting

Box 2. Antimicrobial use and changes in resistance

Mathematical models of the transmission dynamics of resistant and susceptible organisms support the intuition, described in the text, that antimicrobial use should correlate with changes in the prevalence of resistance, rather than with present levels of resistance. Perhaps the simplest model of transmission of resistant and susceptible strains of a pathogen (modified from Ref. a) assumes that individuals can be infected only with one strain or the other and, upon recovery, become immune to both strains (whether or not there is immunity plays little role in the behavior of resistance in the model). The effect of treatment (at rate τ) is to shorten the duration of infectiousness of the drug-susceptible strain (but not of the resistant strain); hence, higher levels of antibiotic use translate to a shorter duration of infectiousness of the susceptible strain, thereby favoring the transmission of the resistant strains. In standard notation[b] the relevant part of the model is:

$$\frac{dX}{dt} = b - uX - \beta_s XY_s - \beta_R XY_R \quad (1)$$

$$\frac{dY_s}{dt} = \beta_S XY_S - v_S Y_S - \tau Y_S - uY_S \quad (2)$$

$$\frac{dY_R}{dt} = \beta_R XY_R - v_R Y_R - uY_R \quad (3)$$

where X, Y_S and Y_R are the fractions of the population not carrying the bacterial species of interest, carrying the susceptible strains and carrying the resistant strains, respectively. The subscripts refer to susceptible and resistant strains, and the β_i are the transmission rate constants for the strains, $1/v_i$ are the average duration of carriage of strain i, τ is the rate at which hosts receive treatment, $1/u$ is the average time a host remains in the population of transmitters, and b is the rate of recruitment of new hosts.

If we define $p(t) = \dfrac{Y_R(t)}{Y_S(t) + Y_R(t)}$ (4)

as the proportion of all infections that are resistant at time t, and we let $L = \text{logit}(p) = \ln(p/1\text{-}p)$, then L changes according to the following simple equation:

$$\frac{dL}{dt} = (\beta_R - \beta_S)X - (v_R - v_S) + \tau \quad (5)$$

The first two terms reflect any differences in fitness (either transmissibility or duration of infectiousness) between susceptible and resistant strains; in general, these will tend to make the proportion of resistant strains decrease. The last term (treatment) of course reflects selection by the antibiotic to increase the proportion of resistance.

An implication of this (obviously oversimplified) model is that if the fitness differences between resistant and susceptible pathogens stay approximately constant, and if the proportion of susceptible hosts stays nearly constant, then the change in L (the natural logarithm of the ratio of resistant strains to susceptible strains) in any given time period should be linearly related to the amount of antibiotic used (if this is measured appropriately). The ratio of resistant to susceptible strains is a convenient measure because it does not depend on knowing the absolute number of either in a particular community.

This formulation is also convenient because cumulative antimicrobial use and time then fit naturally as independent variables in the framework of logistic regression, a standard technique in infectious disease epidemiology. Under the approximation that X remains approximately constant over time, equation (5) corresponds to:

$$Logit(p(t)) = Logit(p(0)) + [(\beta_R - \beta_S)X - (v_R - v_S)]t + C(t) \quad (6)$$

where the term in square brackets reflects the fitness cost of resistance (if any) in the absence of treatment and

$$C(t) = \int_0^t \tau(u)du \quad (7)$$

is the cumulative antibiotic use up to time t.

Similar results can be obtained for more complicated models. For example, with models of transmission in a hospital[c], the basic form of the equation is preserved, but additional terms are present to account for admission and discharge of patients from the hospital.

Given this theoretical basis to expect antimicrobial use to correlate with rates of change of resistance, it is not unreasonable to expect in some circumstances that use will indeed correlate with present levels of resistance[d]. In particular, if levels of antimicrobial use in particular places are correlated across time (e.g. localities with more use than others in one year are likely to have more use the next), then current use will reflect the history of use, which should in turn be reflected in resistance levels. More generally, if patterns of antimicrobial use change much more slowly than levels of resistance, then the prevalence of resistance at a given time should indeed show a relationship to current levels of use.

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process in the spread of some resistant organisms. The number of organisms present in a given host, and the changes in the size of the pathogen population during transmission from host to host, can have important effects on the direction of compensatory evolution[15].

Several factors determine how fast a particular pathogen resistant to a given antimicrobial agent will 'accomplish' these steps (contrasting case studies are described in Box 1). The first of these is the availability of resistant variants in treated hosts, arising either by mutation or by acquisition of resistance genes from other organisms. If mutations for resistance are readily acquired and selected during treatment of patients with drug-susceptible infections, such as HIV and TB, with suboptimal therapy, there will be a ready source of resistant cases that can then transmit to other, uninfected individuals[2,3]. If the appearance of resistance in a treated host is a very rare event because of the complexity of the genetic basis of resistance, then it will take longer before large numbers of resistant strains are available for transmission[5].

The second factor is the intensity of the selective pressure imposed by the use of antimicrobial agents. The intensity of selection is a complex quantity, which can be measured in different ways, depending on the mechanism by which treatment selects for resistance in a particular infection. One might expect the volume of antimicrobial use to be positively related to the prevalence of resistance. This is a reasonable expectation for pathogen–drug combinations in which antibiotic use selects for resistance primarily by curing drug-susceptible infections (or carriage), thereby increasing the relative opportunities for transmission of resistant infections (e.g. penicillin-resistant *S. pneumoniae*[16]). It might also be an appropriate expectation for infections – such as many nosocomial bacterial infections – where treatment adds to the risk of resistance by altering the normal flora to permit colonization by resistant strains or to permit increases in the density of resistant strains[17,18].

However, the relationship between volume of use and resistance has often been difficult to establish[19]. There are several reasons why volume of use might not directly correlate with resistance. First, the spread of resistance is a dynamic process, and one would expect that in many cases antimicrobial use should be related to the rate of change in the prevalence of resistance, rather than to its current prevalence (Box 2). For example, if antimicrobial use remains at a high but constant level, we would expect continuing increases in the prevalence of resistance, and if all antimicrobial use ended suddenly, we would expect resistance to decline but not to reach zero immediately. Analyses linking antimicrobial use to rates of change in resistance have only rarely been carried out[20]. Second, in infections for which emergence of resistance during treatment is a concern, low-dosing (or non-compliance) is often a risk factor[21–24]. In such cases, increased dosing of the same number of individuals would presumably reduce resistance; thus, in these cases, we might even expect a negative relationship between total use and resistance (Box 3). Finally, differences in pharmacokinetics and pharmacodynamics could make it difficult to compare and aggregate consumption of different antibiotics within the same class; for example, small quantities of a topical or long-acting systemic antibiotic could exert the same selective effect in favor of resistance as could larger quantities of a rapidly eliminated, systemic drug. The use of units such as per-capita prescriptions or defined daily doses, rather than total weights of antibiotics used, will help to reduce this last complication. There are several other factors that could play important roles in the spread of antimicrobial resistance in bacterial populations, but whose contributions have been difficult to quantify. Open questions concerning these factors include:

- What role do 'incubators' of antimicrobial resistance play in the spread of resistance in the population at large? Institutions such as nursing homes, hospitals, day-care centers and some prisons house populations that combine high levels of antimicrobial use, heightened susceptibility to infection owing to age or medical condition, and frequent opportunities for transmission of infectious agents. Residence in each of these types of institutions has been implicated as an individual risk factor for antibiotic-resistant infections; it is less clear to what extent such institutions act as 'core groups'[25] from which resistant infections spread to the general population.
- How important is the transmissibility of plasmid-borne resistance (as measured by the frequency of conjugation of the plasmids encoding resistance) in determining the rate of increase in the prevalence of resistance? The occurrence of plasmid-borne resistance in the plague bacillus[26,27] is surprising because plague transmission is primarily zoonotic and should not be subject to selection pressure by antibiotic use. One hypothesis for the spread of plasmid-borne resistance in this organism is that it is promoted by extremely high rates of plasmid transfer[26,27].
- How important is the genetic background of pathogen strains containing resistance determinants to the success of those resistance determinants? The international success of a few multiply resistant clones of *S. pneumoniae*[28] suggests the hypothesis that some features of these clones other than their resistance genes can contribute significantly to their success and to the resulting increases in the prevalence of resistance in certain countries.
- In what ways does resistance of some bacteria to multiple antibiotics affect the changes in prevalence of resistance to some antimicrobial agents? For example, given the high frequency with which resistance to penicillin and trimethoprim-sulfamethoxazole co-occur in strains of *S. pneumoniae*[29], to what degree does use of each of these agents contribute to the spread of resistance to the other?

The fall of resistance

Several efforts have been made to control and ultimately reduce antimicrobial resistance. The success of these efforts has varied considerably. Thanks to the considerable logistical difficulties in implementation and evaluation, there have been only a few studies of the effectiveness of measures to control resistance in community-acquired pathogens. Perhaps the best known of these studies is the reduction in the use of macrolides (such as erythromycin) in Finland in the 1990s, which was cited as the cause of a 50% reduction in the proportion of group A streptococci in that country that were resistant to macrolides (Fig. 1)[30]. The temporal sequence of changes in macrolide use and resistance raises some questions about the cause–effect

Box 3. Controlling drug resistance in TB

Strategies to control resistance in TB differ considerably from those contemplated for other community-acquired infections. There are several reasons for these differences: the high case-fatality rate of untreated disease, the importance of treatment in preventing transmission, and the need for sustained multidrug therapy to prevent emergence of resistance in treated patients. Indeed, the directly observed therapy (short course), or DOTS strategy recommended for TB control programs worldwide, emphasizes use of sufficient doses of an adequate number of drugs to prevent resistance from emerging during treatment[a]. The need for additional case-finding, treatment and infection-control measures to prevent the spread of multiply resistant TB became apparent in the United States in the early 1990s (Ref. b) and is now receiving increasing attention worldwide[c,d]. Thus, in contrast to other infections, where efforts to control resistance often involve reducing antimicrobial use, efforts to control resistance in TB require increased access to and assurance of adherence to appropriate antimicrobial treatment, in addition to other measures to prevent transmission.

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relationship in this study, but if one attributes the observed decline in resistance to the intervention, then the approximate timescale of that decline (estimated as the time required for the proportion of isolates resistant to the drug to decline by 50%) is on the order of five years. A similar attempt was made in Iceland to control the spread of a highly successful penicillin-resistant clone of *Streptococcus pneumoniae* by curtailing the use of β-lactam antibiotics. In this case, penicillin resistance declined by ~25% over four years[31]. The dynamics of highly successful clones, which can be driven by factors other than antibiotic use, could also complicate interpretation of changes in resistance, particularly in the latter case[32]. Perhaps most pessimistic is the recent finding that the almost complete cessation of sulfonamide use in the UK during the 1990s was accompanied by a small increase in the prevalence of resistance to this class of drugs in *Escherichia coli*. A likely explanation is that plasmids containing sulfa-resistance determinants also contained genes encoding resistance to other antibiotics, whose continuing use during the study-period maintained selection for the multi-resistance plasmids[33].

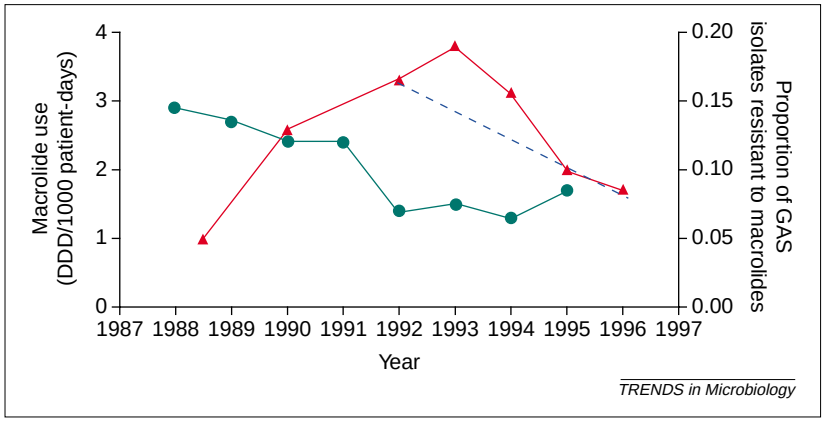

Fig. 1. Changes in macrolide use (circles) and resistance to macrolides (triangles) in group A streptococci (GAS) in Finland, 1988–1996. The dashed line shows the reported halving of the proportion resistant from 1992–1996. Modified from Ref. 30.

Taken together, these limited data suggest that interventions to control antimicrobial use could, in certain cases, result in declines in resistance in community-acquired pathogens, but expectations for their success should be moderate. In the most successful cases, at least five years, and perhaps more, are required to observe a substantial decline in resistance, even following large-scale interventions to control antimicrobial use. Such knowledge is vital in planning and evaluating the success of such interventions; if these examples are typical, then long-term interventions (and evaluations) will be required if one wishes to observe their effects.

What determines the rate at which a bacterial population responds to reductions in the use of antimicrobials? Mathematical models suggest that a key parameter determining this rate for community-acquired infections is the 'fitness cost' of antimicrobial resistance, defined as the difference in transmissibility between a drug-susceptible and a drug-resistant pathogen, in the absence of antibiotic treatment[34–36]. On the one hand, if drug resistance imposes a substantial cost on the transmissibility of an organism, then we would expect that once selection (i.e. antibiotic treatment) is reduced, susceptible organisms would rapidly replace resistant ones in the population. On the other hand, if resistance has no such cost, then even the complete cessation of antibiotic treatment would leave no net selective force favoring a return of susceptibility. In the worst case, it is possible that resistance genes could find their way into bacterial clones that are highly successful (transmissible) for reasons other than resistance; in this case, one might expect continued increases in resistance even in the absence of antimicrobial treatment.

The magnitude of this fitness cost is the subject of considerable experimental investigation at present[14].

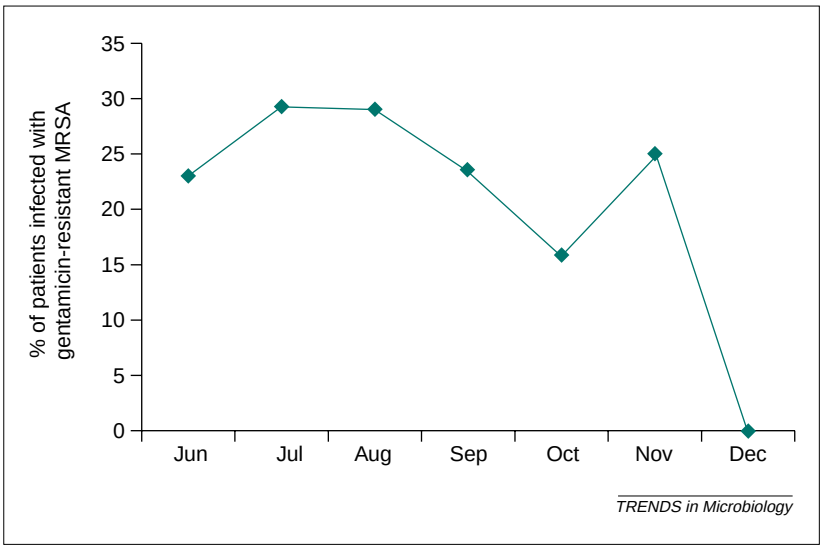

Fig. 2. Changes in the proportion of patients in an intensive care nursery infected with gentamicin- and methicillin-resistant *Staphylococcus aureus* (MRSA) in 1979, by month of discharge. Antibiotic prescribing controls, cohorting of infants colonized with the resistant strain, and infection-control measures were instigated on August 16. This figure shows the proportion of all patients infected with the resistant strain, a different measurement scale from Fig. 1, which shows the proportion of all isolates that were resistant. Modified from Ref. 42.

Only a few studies have addressed the fitness cost of resistance to clinically important drugs in major pathogenic bacteria (or a related question, the effects of resistance on virulence)[37,38], but several general principles have been gleaned from studies of model organisms. Many, but not all, chromosomal mutations conferring antimicrobial resistance have some fitness cost, which can be measured as a reduction in growth rate or competitive ability *in vitro* or in animal models. In those cases where there is a cost, it is often possible to obtain, after a relatively short period of growth in the lab, compensatory mutants that maintain their resistance while showing growth rates and competitive abilities comparable to those of the wild-type, susceptible organisms. Studies of plasmid-borne resistance, although less widespread, have come to similar conclusions[14]. One could speculate, then, that the relatively long time required to see changes in the prevalence of resistance following interventions could be related to a small or negligible fitness cost of resistance in natural isolates. It would thus be very useful to know to what degree naturally occurring resistant isolates have compensated for any fitness costs they do suffer[37].

Questions for future research

- What role does multiple resistance play in frustrating efforts to reduce resistance to individual drugs?
- How do patterns of antibiotic use contribute to (or help to slow) the appearance of such strains?
- How useful will vaccines be in combating resistance, and for how long?
- To what degree are resistant organisms actually circulating in human populations suffering from a fitness cost of resistance, compared with their susceptible counterparts?
- What role does infection control play in the prevention of drug-resistant infections in particular?

Interventions to control resistance in hospital-acquired infections have been studied much more frequently and provide an illuminating contrast to interventions directed against resistant community-acquired infections. In several cases, the prevalence of resistance in hospital-acquired infections has declined substantially (by more than half) within weeks or months following the implementation of control measures, which often include both changes in antibiotic use policies and interventions to reduce transmission of bacteria within hospitals (Fig. 2)[39,40]. Several factors could be responsible for this difference. Most such reports concern 'outbreaks' of resistant infections in a particular hospital. On the one hand, the urgency and limited scope of such outbreaks permits more comprehensive, immediate and coordinated interventions than are usually possible in whole communities. On the other, as most interventions to stem outbreaks of resistant organisms are not compared against controls, it is difficult to know how many of these outbreaks would have waned even without intervention.

A dynamical explanation for the rapid response to interventions in hospitals was proposed in a recent mathematical model[40]. Unlike most communities, hospitals and intensive care units are extremely 'open' populations, where the average resident can stay less than a week. Furthermore, most hospital-acquired pathogens are members of the normal flora that enter the hospital with each admitted patient. These factors combine to produce a constant influx of new bacterial populations to the hospital. To the extent that resistant organisms are maintained by transmission and selection within the hospital, the effect of the entry of new patients with their normal flora will be to 'dilute' the prevalence of resistant organisms, tending to reduce it from the prevalence it would reach if the hospital were a closed system, toward the (lower) prevalence of resistance in the community. Even if there is no difference in fitness (transmissibility) between resistant and susceptible organisms, this hypothesis predicts that when antibiotic selection is relaxed in a hospital, the prevalence of resistance will decline rapidly, owing to the 'dilution' effect of the flora that enters with admitted patients.

Testing these hypotheses

The foregoing is an attempt to account for what we know about the population dynamics of antimicrobial resistance in populations using a few general principles. Although largely consistent with existing data, many of these principles (hypotheses) have not been subjected to prospective testing. With respect to the rise of resistance, ethical and logistical considerations limit the range of population-level experimental studies that can be done, and we must

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rely on adequate surveillance and historical data to assess the effects of changes in antimicrobial use on the rate of increase in resistance.

With efforts to reduce resistance, there is more scope for formal, prospective evaluation of various interventions, including reductions in antibiotic use, restrictions on the types of antibiotics prescribed for particular infections, and infection-control measures. Ongoing reports of efforts to control outbreaks of resistant infections in individual hospitals, nursing homes or day-care centers will provide valuable data. However, as for other measures to control infectious diseases in populations (e.g. insecticide-impregnated bednets for malaria), the 'gold standard' test of an intervention should be a randomized, controlled trial, in which the population (community or institution) is the unit of randomization[41]. Although financially and logistically challenging, such studies are necessary if we hope to obtain a sound, scientific understanding of the effectiveness of resistance-control measures.

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Note added in press

A recent study in Finland showed a strong geographical correlation between macrolide resistance and the use of various antimicrobial agents[43]. This confirms a series of studies showing such correlations, although interestingly, such studies in several cases find stronger correlations between the use of one class of antibiotics and resistance to another class, than between use of and resistance to the same class, indicating the importance of multiple resistance for selective dynamics[44].