



## REVIEW: EVOLUTION

# Humans as the World's Greatest Evolutionary Force

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In addition to altering global ecology, technology and human population growth also affect evolutionary trajectories, dramatically accelerating evolutionary change in other species, especially in commercially important, pest, and disease organisms. Such changes are apparent in antibiotic and human immunodeficiency virus (HIV) resistance to drugs, plant and insect resistance to pesticides, rapid changes in invasive species, life-history change in commercial fisheries, and pest adaptation to biological engineering products. This accelerated evolution costs at least \$33 billion to \$50 billion a year in the United States. Slowing and controlling arms races in disease and pest management have been successful in diverse ecological and economic systems, illustrating how applied evolutionary principles can help reduce the impact of human-kind on evolution.

**H**uman impact on the global biosphere now controls many major facets of ecosystem function. Currently, a large fraction of the world's available fresh water, arable land, fisheries production, nitrogen budget, CO<sub>2</sub> balance, and biotic turnover are dominated by human effects (1). Human ecological impact has enormous evolutionary consequences as well and can greatly accelerate evolutionary change in the species around us, especially disease organisms, agricultural pests, commensals, and species hunted commercially. For example, some forms of bacterial infection are insensitive to all but the most powerful antibiotics, yet these infections are increasingly common in hospitals (2). Some insects are tolerant of so many different insecticides that chemical control is useless (3). Such examples illustrate the pervasive intersection of biological evolution with human life, effects that generate substantial daily impacts and produce increasing economic burden.

Accelerated evolutionary changes are easy to understand—they derive from strong natural selection exerted by human technology. However, technological impact has increased so markedly over the past few decades that humans may be the world's dominant evolutionary force. The importance of human-induced evolutionary change can be measured economically, in some cases, and is frequently seen in the exposure of societies to uncontrollable disease or pest outbreaks. Attempts to slow these evolutionary changes are widespread but uncoordinated. How well do they work to slow evolution? Can successes from one field be generalized to others?

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## The Pace of Human-Induced Evolution

Paul Müller's 1939 discovery that DDT killed insects won him the 1948 Nobel Prize, but before the Nobel ceremony occurred, evolution of resistance had already been reported in house flies (3, 4). By the 1960s, mosquitoes resistant to DDT effectively prevented the worldwide eradication of malaria (5), and by 1990, over 500 species had evolved resistance to at least one insecticide (6). Insects often evolve resistance within about a decade after introduction of a new pesticide (7), and many species are resistant to so many pesticides that they are difficult or impossible to control (3). Similar trajectories are known for resistant weeds (8), which typically evolve resistance within 10 to 25 years of deployment of an herbicide (Table 1).

Bacterial diseases have evolved strong and devastating resistance to many antibiotics. This occurs at low levels in natural populations (9) but can become common within a few years of the commercial adoption of a new drug (Table 1). For example, virtually all Gram-positive infections were susceptible to penicillin in the 1940s (2, 10) but in hospitals today, the vast majority of infections caused by important bacterial

agents like *Staphylococcus aureus* are penicillin-resistant, and up to 50% are resistant to stronger drugs like methicillin (11). Treatments that used to require small antibiotic doses now require huge concentrations or demand powerful new drugs (10). But such solutions are short-lived. For example, vancomycin, one of the only treatments for methicillin-resistant infections, has been overcome by some of the most frequent infectious agents in hospitals (2, 12). Antibiotics also generate evolution outside hospitals. Resistant strains are common on farms that use antibiotics in livestock production (13) and have been found in soils and groundwater affected by farm effluents (14).

Retroviruses with RNA genomes evolve even more quickly than bacteria (15). Every year, vaccinations against influenza must be reformulated, making prediction of next year's viral fashion one of preventative medicine's chief challenges (16). The virus that causes AIDS, human immunodeficiency virus-1, evolves so quickly that the infection within a single person becomes a quasi-species consisting of thousands of evolutionary variants (15). Over the course of months or years after HIV infection, the virus continually evolves away from immune system sup-

**Table 1.** Dates of deployment of representative antibiotics and herbicides, and the evolution of resistance. [Source (75)].

### EVOLUTION OF RESISTANCE TO ANTIBIOTICS AND HERBICIDES

Antibiotic or herbicide	Year deployed	Resistance observed
<i>Antibiotics</i>		
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s
<i>Herbicides</i>		
2,4-D	1945	1954
Dalapon	1953	1962
Atrazine	1958	1968
Picloram	1963	1988
Trifluralin	1963	1988
Triallate	1964	1987
Diclofop	1980	1987

pression (17, 18). Evolution in the face of antiviral drugs is just as rapid. For example, the drug nevirapine reduces viral RNA levels for only about 2 weeks (19). Thereafter, mutations in the HIV reverse transcriptase gene quickly arise that confer drug resistance, and the HIV mutants have a doubling time of 2 to 6 days (19). This rapid evolution is repeated with virtually all other antiretroviral drugs when given singly, including the inexpensive antiviral drugs zidovudine (azidothymine, AZT), lamivudine (3TC), didanosine (ddI) and protease inhibitors like indinavir (20–24).

Rapid evolution caused by humans is not restricted to disease or pest species. Under heavy fishing pressure, fish evolve slower growth rates and thinner bodies, allowing them to slip through gill nets (25, 26). In hatchery populations of salmon, there is strong selection for dwarf males that return from sea early, increasing their survival (25). Invading species, transported by humans, have been known to rapidly change to match local selection pressures (27). For instance, house sparrows, introduced to North America in 1850, are now discernibly different in body size and color throughout the United States (28). In some cases, species introduced by humans induce evolution in species around them. For example, after the subtidal snail *Littorina littorea* invaded coastal New England in the late 1800s, native hermit crabs [*Pagurus longicarpus* (Say)] quickly evolved behavioral preference for their shells. The crabs also evolved body and claw changes that fit them more securely in these new,

larger shells (29). Even more quickly, introduced predatory fish have caused rapid evolution of life-history traits and color pattern in their prey species (30, 31). Rates of human-mediated evolutionary change sometimes exceed rates of natural evolution by orders of magnitude (30).

### Causes of Evolution

These examples demonstrate pervasive and rapid evolution as a result of human activity. In most cases, the causes of this evolutionary pattern are clear: if a species is variable for a trait, and that trait confers a difference in survival or production of offspring, and the trait difference is heritable by offspring, then all three requirements of evolution by natural selection are present. In such cases, the evolutionary engine can turn, although evolutionary directions and speed can be influenced by factors such as drift, conflicting selection pressure, and correlated characters (31).

The overwhelming impact of humans on evolution stems from the ecological role we now play in the world, and the industrialization of our agriculture, medicine, and landscape. Successful pesticides or antibiotics are often produced in massive quantities. DDT, for example, was first used by the Allied Army in Naples in 1943, but by the end of World War II, DDT production was proceeding on an industrial scale. Currently, we use about 700 million pounds of pesticide a year in the United States (7). Antibiotic production is also high, with 25 to 50% going into prophylactic use in livestock feed (13).

Inefficient use of antibiotics has been cited as a major cause of antibiotic resistance. Partial treatment of infections with suboptimal doses leads to partial control of the infecting cell population and creates a superb environment for the evolution of resistant bacteria. Up to one-third of U.S. pediatricians report overprescribing antibiotics to assuage patient concerns, particularly in cases of viral childhood congestions that cannot respond to the drug (32). Failing to complete a course of antibiotics is associated with increased emergence of resistant tuberculosis and HIV infections (33, 34), and differences in antibiotic use may partly explain differences among nations in antibiotic resistance rates (2).

Spread of antibiotic resistance has been accelerated by transmission of genes between bacterial species (13). Recently, biotechnology has applied this acceleration to other species as well, and a new human-mediated mechanism for generating evolutionary novelty has emerged—insertion of exogenous genes into domesticated plants and animals. Taken from bacteria, plants, animals, or fungi, these genes convey valuable commercial traits, and they are placed

into new host genomes along with genes that control expression and in some cases allow cell lineage selection (35, 36). Examples include the insertion of genes for insecticidal proteins (37), herbicide tolerance (38, 39) or novel vitamins (40) into crop plants; growth hormone genes into farmed salmon (41); and hormone production genes into livestock “bioreactors” (42). These efforts effectively increase the rate of generation of new traits—akin to increasing the rate of macromutation. When these traits cross from domesticated into wild species, they can add to the fuel of evolution and allow rapid spread of the traits in natural populations (43). Genetic exchange from crops has already enhanced the weediness of wild relatives of 7 of the world’s 13 most important crop plants (44), although no widespread escape of an engineered gene into the wild has been reported yet.

### The Economics of Human-Induced Evolution

Evolution is responsible for large costs when pests or disease organisms escape from chemical control. Farmers spend an estimated \$12 billion on pesticides per year in the United States (7). Extra costs due to pest resistance, such as respraying fields, may account for about 10% of these direct expenditures (45, 46). Despite the heavy use of chemical pesticides, 10 to 35% of U.S. farm production is lost to pest damage (45). If even 10% of this loss is due to activities of resistant insects (and the figure may be far higher), this represents a \$2 billion to \$7 billion yearly loss for the \$200 billion U.S. food industry. The development of resistance in diamondback moths to *Bacillus thuringiensis* (Bt) toxin in 1989 (47) foreshadows the decline in use of the world’s largest selling biopesticide and the need for new approaches (Fig. 1). The price of developing a single new pesticide, about \$80 million in 1999 (7), is an ongoing cost of agricultural business. Even higher development costs (about \$150 million per product) are incurred by pharmaceutical companies [p. 157 in (7)]. In both sectors, evolution sparks an arms race between human chemical control and pest or disease agent, dramatically increasing costs that are eventually paid by consumers (7, 11). For example, the new drugs linezolid and quinupristin-dalfopristin were recently approved by the U.S. Food and Drug Administration (FDA) for use on vancomycin-resistant infections (48). Previously, vancomycin had been used to overcome methicillin resistance (10), and methicillin was itself a response to the failure of penicillin treatment (13). This development cascade (Fig. 2) has been ongoing since the birth of



**Fig. 1.** In this field of water cress, the world’s biggest selling biopesticide, *Bacillus thuringiensis* (Bt) toxin, was overcome by the evolution of resistance in diamondback moths. This pesticide is engineered into millions of acres of crop plants, and so the ability of insects to evolve resistance has created anxiety in the biotechnology industry.

the chemical-control era and represents a poorly quantified cost of evolution.

More direct expenses stem from the increase in drug payments and hospitalization necessary to treat resistant diseases. There are approximately 2 million hospital-acquired infections in the United States each year [data from 1995 (11, 49)], a quarter of which are caused by antibiotic-resistant *S. aureus* (2). Half of these are penicillin-resistant strains that require treatment with methicillin at a cost of \$2 billion to \$7 billion (11, 49). The other half are methicillin-resistant infections, and they cost hospitals an estimated \$8 billion per year to cure (11). Community-acquired, antibiotic-resistant staph infections more than double these costs (49, 50). These figures are for a single type of infection and do not include other well-known drug-resistant bacteria. For example, in the United States up to 22% of hospital-acquired infections of *Enterococcus faecium* are resistant to vancomycin, and combating such infections drives the price of evolution even higher.

Similar conservative tabulations can be made for the cost of HIV treatment. The current standard of care in the United States is to treat HIV with massive doses of at least

three drugs (51). Because treatment with the inexpensive antiretroviral drug AZT would successfully halt HIV if it did not evolve resistance, the need for more powerful drugs is due to HIV evolution. Drug and treatment prices vary but have recently been estimated at \$18,300 per year per patient in the United States (52). If half the 700,000 HIV patients (53) in the United States receive this level of care, these costs amount to \$6.3 billion per year (52). Costs of lost labor, disruption of health services, development of new drugs, and medical research are not included in this figure, and so the actual cost of HIV evolution is far higher.

The annual evolution bill in the United States approaches \$50 billion for these examples (Table 2), and probably exceeds \$100 billion overall. However, the social price of evolution is far higher. Skyrocketing costs of treating resistant diseases create a situation where effective medical treatment may be economically unattainable for many people. Thus, evolution expands the class of diseases that are medically manageable but economically incurable.

### Ways of Slowing Evolution

Responding to the pervasive reach of evolution in medicine and agriculture, health specialists and agricultural engineers have developed an impressive series of innovative methods to slow the pace of evolution. A large body of theory guides deployment of some of these attempts (54–59). Other methods, circulated as guidelines for clinical practices or farming strategies, often appear to be developed through a combination of trial and error and common sense. Independent of their theoretical underpinnings, the following examples show that successful methods often slow evolution for clear evolutionary reasons and that these approaches may be generalizable to

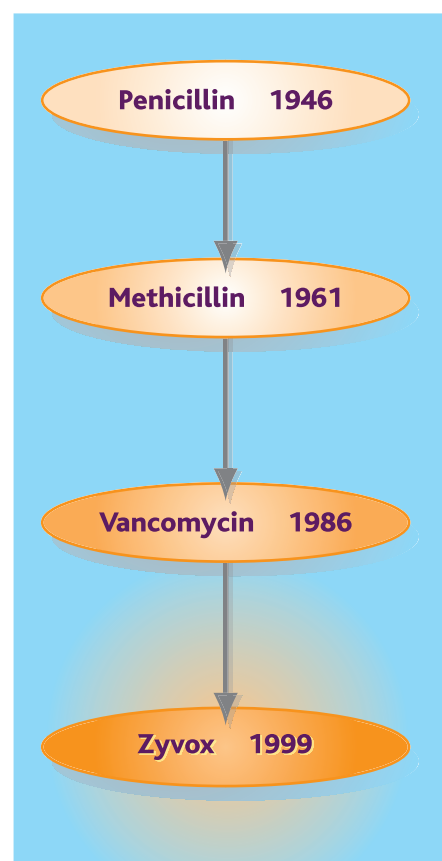
other systems.

**Drug overkill and HIV triple-drug therapy.** Overkill strategies, the combination of treatments to kill all infectious or invading pests, are common. For example, treatment with a drug cocktail that includes a protease inhibitor and two different reverse transcriptase inhibitors is the Cadillac of AIDS treatment strategies (51). This approach has been successful longer than any other, because it not only reduces viral levels but also slows the evolution of resistance. The evolutionary biology hidden in this strategy is simple: a strong, multiple-drug dose leaves no virus able to reproduce, and so there is no genetically based variation in fitness among the infecting viruses in this overwhelming drug environment. Without fitness variation, there is no evolutionary fuel, and evolution halts. Lack of HIV variation for growth in this regime is responsible for reduced evolutionary rate and probably drives the current success of triple-drug treatment. However, sequential treatment with single drugs or voluntary drug cessation can foster the evolution of drug resistance (33), which appears to be increasing (60, 61). This suggests that the triple-drug overkill strategy will not halt HIV evolution forever but may provide only a brief window for the development of more permanent solutions, such as HIV vaccines.

Overkill strategies have been echoed in pesticide management programs, where they are often termed “pyramiding” (62), and in treatment of bacterial infections (11). However, their use is limited by drug toxicity: extreme doses can have physiological or ecosystem side effects.

**Direct observation therapy.** Tuberculosis infects one-third of the world’s population (10, 34), and is difficult to treat because it requires 6 months of medication to cure. Partial treatment has resulted in evolution of multidrug resistance (34). To combat this, drug doses are brought individually to patients, who are observed while they take the drugs. This direct-observation therapy has been used to improve patient compliance during the whole treatment regimen, reducing evolution of resistance by ensuring a drug dose long enough and severe enough to completely eradicate the infection from each person. Direct-observation therapy has been credited with snuffing out emerging tuberculosis epidemics and dramatically reducing costs of medical treatment (10).

**Withholding the most powerful drugs.** The antibiotic vancomycin has been called the “drug of last resort,” because it is used only when other, less powerful antibiotics fail (10). Withholding the most powerful drugs lengthens their effective life-span (11), because overall selection pressure exerted by the drug is reduced, slowing the pace of evolution. Although successful in reducing



**Fig. 2.** Developmental cascade of antibiotics used to treat dangerous *Staphylococcus* infections. Dates reflect evolution of resistance to each drug, requiring search for more powerful alternatives.

**Table 2.** Examples of the costs of human-induced evolution in insect pests and several disease organisms in the United States.

Factor	\$U.S. billions per year
Additional pesticides	1.2
Loss of crops	2 to 7
<i>S. aureus</i>	
Penicillin-resistant	2 to 7
Methicillin-resistant	8
Community-acquired resistant	14 to 21
HIV drug resistance	6.3
Total for these factors	33 to 50



the evolution of resistance to vancomycin by some bacteria, the strategy depends on low use rates in all sectors of the antibiotic industry, including livestock and prophylactic use (13). Failure to include these sectors in the strategy will engineer its failure.

**Screening for resistance before treatment.** Screening infections for sensitivity to particular antibiotics before treatment allows a narrow-range antibiotic to be used instead of a broad-spectrum antibiotic. Reduced use of broad-spectrum antibiotics slows evolution of resistance as in the mechanism above. Genotyping of viruses in an HIV infection and prediction of the antiviral drugs to which they are already resistant improves drug usefulness (63). Similarly, farmers are advised to check their fields after pesticide treatment and then to change the chemical used in the next spraying if many resistant individuals are discovered. Screening for pest susceptibility reduces use of chemicals for which resistance has begun to evolve.

**Cyclic selection due to changing chemical regimes.** Farmers are encouraged to follow several simple rules to reduce herbicide resistance: (i) do not use the same herbicide 2 years in a row on the same field, and (ii) when switching herbicides, use a new one that has a different mechanism of action (64). These guidelines slow evolution through a rapid alteration of selection pressure that sequentially changes the selective landscape. Mutants favored in one generation are not favored in the next, because one mutation is not likely to provide resistance to two herbicides with different mechanisms. Similar cyclic selection regimes have been proposed to limit resistance in intensive-care units (11, 59) and agricultural fields (62). Mosaic selection, in which different chemicals are used in different places at the same time (65) is a spatial version of this tactic.

**Integrated pest management.** Integrated pest management (IPM) may include chemical control of pests, but does not rely on it exclusively, and is credited with better pest control and with slower evolution of resistance (62). Slow evolution can come from two sources. First, the multiple control measures used in IPM reduce reliance on chemical treatments, thereby reducing selection for chemical resistance. Second, physical control of populations (e.g. through baiting, trapping, washing, or weeding) reduces the size of the population that is exposed to chemical control. Smaller populations have a reduced chance of harboring a mutation, thereby slowing the evolution of resistance. The term IPM is common only in insect management, but the strategy has appeared independently in hospitals where hand-washing, instead of prophylactic antibiotic use, is encouraged and in weed management, where resistant weeds are pulled by hand.

**Refuge planting.** Biotechnology has introduced insecticidal toxin genes into numerous crop species, but resistance to toxins produced by these genes has already evolved in pests, threatening the commercial use of this technology (66–68). To reduce the potential for evolution, crop engineers have instituted a program of refuge planting to slow the success of resistant insects (69). If farmers plant a fraction of a field with non-toxin-producing crop varieties, and allow these to be consumed by insects, a large number of non-resistant pests are produced. These can then mate with the smaller number of resistant individuals emerging from fields of plants producing insecticidal proteins, greatly reducing the number of offspring homozygous for the resistance alleles. In cases where resistance is recessive, refuges slow the spread of resistant alleles (69), although they require high crop losses in the refuge plantings. This mechanism functions by reducing the inheritance of resistance through increases in the proportion of breeding individuals without resistance alleles.

**Engineering evolution.** Using evolution to our advantage may also be possible, although this is seldom attempted [p. 215 in (70)]. One illustrative exception is the use of the drug 3TC to slow the mutation rate of HIV and thereby, perhaps, to limit its ability to rapidly evolve resistance to other drugs (24). An ongoing use of evolutionary theory is the prediction of which influenza strains to use for future vaccines (15). Another is the use of chemical control where resistance includes a severe metabolic cost, making resistant individuals less fit when the chemicals are removed (71). In such cases, the potential of evolution to lower pest fitness in the absence of a pesticide may be a method of using the

power of evolution to our advantage. An unintended evolutionary outcome may be the escape of antibiotic, herbicide, or pesticide resistance genes to natural populations, possibly making them less susceptible to pesticides in the environment. In some agricultural settings, artificial selection for pesticide resistance has been used to protect populations of beneficial insects (72).

This summary shows that successful control of evolution has followed many different strategies, and that the methods currently used impact all three factors driving evolutionary change (Table 3). However, seldom have all three evolutionary prerequisites been manipulated in the same system, and seldom has the engineering of the evolutionary process been attempted in a systematic way. Instead, in every new case, human-mediated evolution tends to catch us by surprise, and strategies to reduce or stop it are invented from scratch. For example, cyclic selection has been invented at least three times (for control of insects, bacteria, and HIV), IPM at least three times (insects, weeds, and bacteria), and drug overkill at least twice (HIV and tuberculosis).

Overall, three ways to adjust selective pressures are widely used in pest and health management: application of multiple simultaneous chemicals or “pyramiding,” cyclic application of different chemicals, and using different chemicals in different places or “mosaic application.” Although the principles are exactly the same in all fields, seldom has the literature from one field been used to inform the other (73). Some strategies that are very successful in one arena have not been tried in others (e.g., no direct-observation therapy has been tried on farms). Yet, the commonality of successful methods (Table

**Table 3.** The success of evolutionary engineering: mechanisms that reduce evolution can and do work on all three parts of the evolutionary engine.

MECHANISMS THAT WORK TO SLOW EVOLUTION	
Method of slowing evolution	Example
<i>Reduce variation in a fitness-related trait</i>	
Drug overkill with multiple drugs	Triple-drug therapy for AIDS Pesticide pyramiding
Ensure full dosage	Direct observation therapy of tuberculosis
Reduce appearance of resistance mutations	Engineer RT gene of HIV-1
Reduce pest population size	Integrated pest management of resistant mutants Nondrug sanitary practices
<i>Reduce directional selection</i>	
Vary selection over time	Herbicide rotation Vary choice of antibiotics, pesticides or antiretrovirals
Use nonchemical means of control	Integrated pest management
Limit exposure of pests to selection	Withhold powerful drugs, e.g., restricted vancomycin use
Avoid broad-spectrum antibiotics	Test for drug or pesticide susceptibility before treatment of infections or fields
<i>Reduce heritability of a fitness-related trait</i>	
Dilute resistance alleles	Refuge planting

3) suggests that lessons in evolutionary engineering from one system may be useful in others and that it may be possible to control evolution far more successfully than is currently practiced. Mathematical models of evolutionary engineering provide some guidance about practical field methods (54, 62), but this exchange between prediction and practice has only been common in pest management (65) and antibiotic resistance (59). A critical need is the inclusion of evolutionary predictions in the current debate on global HIV policy. Most important, it is seldom realized that a pivotal goal is slowing the evolution of resistance and that, without this, all successful pest and disease control strategies are temporary (62, 70, 74).

### Conclusions and Prospects

Rapid evolution occurs so commonly that it is, in fact, the expected outcome for many species living in human-dominated systems (62). Evolution in the wake of human ecological change should be the default prediction and should be part of every analysis of the impact of new drugs, health policies, pesticides, or biotechnology products. By admitting the speed and pervasiveness of evolution, predicting evolutionary trajectories where possible, and planning mechanisms in advance to slow evolutionary change, we can greatly reduce our evolutionary impact on species around us and ameliorate the economic and social costs of evolution (70). Ignoring the speed of evolution requires us to play an expensive catch-up game when chemical control agents and medications fail. Because our impact on the biosphere is not likely to decline, we must use our knowledge about the process of evolution to mitigate the evolutionary changes we impose on species around us.

*Note added in proof:* In two recent papers (76, 77), the genetic basis of resistance to BT toxins has been discovered in nematodes and lepidopterans. In both cases, mutations at single genes appear to confer substantial resistance, and might also provide cross resistance to different BT toxins. Without efforts to mediate this evolutionary potential, strong selection in diverse plant pests at a single locus may generate field resistance to transgenic Bt-producing crops or to commercially used sprays of Bt toxin.

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