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HIV/AIDS

Severely malnourished children with HIV usually respond well to the steps outlined above, although the rate of recovery may be slower. A common opportunistic infection is Gram-negative *Pneumocystis carinii* pneumonia (PCP), especially in infants aged 2–6 months. For severe pneumonia in HIV (rapid breathing + chest indrawing), adequate staphylococcal and Gram-negative cover (e.g., ampicillin and gentamicin) is essential. Respiratory infections, including PCP, can be prevented by prophylaxis with co-trimoxazole, which should be given throughout the inpatient stay and after discharge. Children with profound anorexia in advanced HIV disease may benefit from continuous feeding through a nasogastric tube. Diarrhea may be more protracted in HIV-positive children because gut enteropathy tends to be worse. Preparation of F75 and F100 with lactose-free products may be helpful.

Discharge to Community Care

Establishing community-based care can shorten inpatient treatment for severe malnutrition and also benefit children with moderate malnutrition. An integrated system of prevention, timely referral, correct inpatient treatment, and effective community-based care will improve child survival and development, as well as build health worker capacity and strengthen health systems.

See also: Community-Based Nutrition Programs; Famine; Health Issues of the UN Millennium Development Goals; Pneumonia.

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Relevant Website

http://www.inft.org – International Malnutrition Task Force.

Factors Influencing the Emergence of New (and “Old”) Diseases

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Background

In 1991, the U.S. Institute of Medicine published the report of a multidisciplinary working group to (1) identify significant emerging diseases, (2) determine strategies to deal with them, and (3) recommend actions to confront future threats and to lessen their impact on public health (Lederberg et al., 1992). The group embraced a global rather than U.S.-specific frame of reference and elected to avoid a disease-specific description for an approach based on factors of emergence. Factors of emergence are defined as “…specific forces that shape infectious disease emergence [which] operate on different elements in the process of emergence,” (p. 47, ibid). The original six factors examined were: human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, microbial adaptation and change, and the breakdown of public health measures. The report provided examples of how these factors work and on which emergent infections they apparently operated.
A follow-up report, *Microbial Threats to Health: Emergence Detection and Response* was published in 2003 (Smolinski *et al.*, 2003). Additional factors of emergence were examined in this report: human susceptibility to infection, climate and weather, changing ecosystems, poverty and social inequity, war and famine, the lack of political will, and intent to harm. Thus the original six factors grew to 13. While enriching the discussion and description of emergence, this proliferation of factors also created overlapping domains within factors; for example, climate and weather are an integral physical science aspect of ecosystems, the failure of political will is integral to the neglect of public health systems, and so forth. From an analytic point of view, the need for in-depth study of factors and how they actually work has become critical for scientific insight into public health protection.

### Interplay of Man-Made Factors

This description of factors of emergence will focus on their interplay and how they work where they are most understood: (1) human pressures on the ecosystem and changes in land use, (2) globalization of markets for food animals concurrent with the growth of global trade and commerce, and (3) antimicrobial resistance that leads to microbial change and adaptation. Every factor linked to emergence is essentially created or caused by humans. Some factors are more feasible to correct than others. One is the increasing burden on the Earth’s limited resources. Another is the new ecosystem of sorts that we have created through burgeoning trade and travel – a world of high mobility and porous boundaries. Also, food production practices intensify as global commerce accelerates. Finally, we have a growing array of medical practices with unknown consequences, such as xenotransplantation and widespread antibiotic use (see Figure 1).

#### Exhausting Our Ecospace?

Typically, diseases emerge when a pathogen moves from another vertebrate species to humans. The mechanisms of crossover are largely unknown, but some factors seem to facilitate the process: poor sanitation, encroachment of humans on animal habitats, maintaining food animals in crowded conditions, and extensive use of antimicrobials. The rapid acceleration of poultry agriculture in Southeast Asia has converted avian influenza into a growing number of human cases – 371 at current count. An offshoot, cockfighting, includes behaviors that contribute to further infection, such as humans sucking blood and mucus from the beaks of injured birds. Early in the HIV epidemic, a transmission between monkeys or apes and humans was thought to have occurred. Whether this was through exposure between hunters and their primate prey in the rainforests or through bush meat consumption or another route remains a mystery.

Most new pathogens that have emerged over the last 20 years have done so in response to ecological pressure rather than natural evolutionary change in the microbes. Ecological changes, such as new agricultural practices, urbanization, globalization, and climate change, seem to drive microbes from animals into their new human hosts (Slingenbergh *et al.*, 2004). Again, the drivers are largely the product of human activity. Despite this certainty, little definitive work has been done to determine the threshold of each factor in the emergence of new human pathogens. For example, while most international authorities agree that the intensified poultry industry is related to the emergence of fatal avian influenza outbreaks in Europe and Asia little is known about how, why, or at what point this RNA virus jumps from birds to humans.

#### Influenza: A Recurring Emergence

At the microbial level, recent studies of the highly fatal 1918 influenza virus suggest that the neuraminidase portion of the virus was responsible for its contagiousness in humans. Scientists believe that the 1957 pandemic influenza emerged after the virus moved from ducks to pigs or chickens that were infected at the same time by a human virus. After the viruses exchanged bits of genetic material during their reproduction in the pigs and chickens, the new virus was equipped to infect humans. However, because of the state of science in 1957, this information has always been tentative. In fact, it is now believed that the 1918 influenza virus was avian in origin, did not go through the mixing bowl of a pig or another land-based animal before infecting humans. Intensive study of the virus causing Asian avian influenza is now underway. The virus has already hopped the species barrier in 371 recorded human cases, causing 235 human deaths.
At the macro level, we do not know the threshold number at which a safe density of poultry becomes unsafe. How many birds per square meter can be handled safely? How many are too many? What role do ducks migrating from farm to farm play in disease transmission? The U.S. Department of Agriculture (USDA) stipulates that no more than ten chickens can be housed per square meter. Contemporary practice in the United States is for ten chickens to inhabit a 3-square-foot space for their entire lives, often with their beaks and talons removed to prevent injury. Practices using dense poultry habitat are correlated with the susceptibility of birds to highly pathogenic avian influenza. That susceptibility, thought to be related to stress and crowding, has been demonstrated all over the world (Slingenbergh et al., 2004) (Figure 2).

It appears that Asia has seen relatively little increased productivity in chickens despite a rapidly increasing density of the agricultural population on both small farms and large industrial-scale enterprises. This mixture of large and small enterprises in close proximity has served as a potent combination for the outbreak of avian influenza. The small farms probably served as the first points of illness, but the large commercial farms played a critical role in extending the outbreaks through high-volume traffic of vulnerable fowl populations and products over large geographic areas.

**A New Environment, New Rules?**

Extensive scientific work has been done suggesting that the human community is outstripping the planet’s ability to accommodate it. While not yet as crowded as chickens on factory farms, with 6.2 billion human inhabitants, the Earth’s balance within natural systems is increasingly affected by anthropogenic (man-made) activity. In his landmark 1993 book *Planetary Overload: Global Environmental Change and the Health of the Human Species*, Anthony J. McMichael outlines the human-generated stress on natural systems. He posits that food will become increasingly scarce for the human community. The macro-ecologic effects of human activity on climate, water, food, agriculture, pollution, and human health are well described, but the systematic link between the macro (what we can see) and what is occurring on the micro level remains an important area of research. To address the emergence of new pathogens, we need more precise knowledge about the mechanisms that form the critical pathway to emergence.

While there is a finite amount of space on the surface of Earth, we have, in some sense, created a new dimension of space – the mobile environment. In considering environment, increasing emphasis has been placed on the built environment for humans. For example, the roads and pavement have hardened the land and created challenges for disposing of water and human pollutants. Buildings are studied for their effects on human health, from second-hand smoke to sick-building syndrome.

New man-made spaces also have been created in the pursuit of trade and travel. How they act on the life processes of microbes and affect infection is yet to be described. But we are beginning to see some telltale signs. Human travel, for instance, seems to have
the potential to affect seasonal disease patterns. Many biological aspects of life appear to be seasonal—births, deaths, numerous chronic diseases, and, of course, infectious diseases all peak during certain times of the year. At least this is the case in temperate climates, where the phenomena have been the most extensively studied. Seasonal effect is a well-described aspect of infectious disease, including respiratory infections, such as colds and flu, and more serious infections, such as pneumonia. Interestingly, this seasonality has remained a constant even as humans have modified their natural environment in remarkable ways—building shelters, designing heating and cooling systems, and inventing new protective clothing, for example. This well-described but poorly understood phenomenon has enabled us to plan vaccine development and prevention efforts at certain times of the year in anticipation of upcoming outbreaks. When people travel between hemispheres, where the seasons are reversed, they can introduce viruses off-season, potentially throwing off this historically reliable rhythm of vaccines and prevention.

Another illustration of the influence of human mobility on the microbial world is the transportation, via food products, of a pathogen from one region, where it may be endemic, to another, where it is not. In processing, shipping, packaging, and preparing food, we bring into our homes and our digestive systems food and microbes from thousands of miles away. We experience some of this microbial traffic as illness, when microbes pathogenic to humans infect us. Microbes that we know because they make us ill are an exceedingly small percentage of the microbes moving around. Our new man-made ecological space of mobile microbes impacts the rapidly evolving microbial world, but what that impact is remains a mystery.

### Table 1

| Vector-borne and/or zoonotic | Soil                  | Water               | Human               | Other                |
|-----------------------------|-----------------------|---------------------|---------------------|----------------------|
| Dengue                      | Melioidosis           | Schistosomiasis     | Asthma              | Hemorrhagic fevers   |
| Lyme disease                | Anthrax               | Cholera             | Tuberculosis        |                      |
| Yellow fever                | Hookworm             | Shigellosis         | Influenza           |                      |
| Rift Valley fever           |                      | Rotavirus           |                     |                      |
| Japanese encephalitis       |                      | Salmonellosis       |                     |                      |
| Onchocerciasis              |                      | Leptospirosis       |                     |                      |
| Trypanosomiasis             |                      | Cryptosporidiosis   |                     |                      |
| Plague                      |                      |                     |                     |                      |
| Filariasis                  |                      |                     |                     |                      |
| Meningitis                  |                      |                     |                     |                      |
| Rabies                      |                      |                     |                     |                      |
| Leishmaniasis               |                      |                     |                     |                      |
| Kyasanur forest fever       |                      |                     |                     |                      |
| Hantavirus                  |                      |                     |                     |                      |
| Nipah virus                 |                      |                     |                     |                      |

Adapted from Patz JA, Daszak P, and Tabor GM (2004) Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence. *Environmental Health Perspectives* 112: 1092-1098.
Changes in Land Use

The increased demand for more food, lumber products, and living space are some of the main factors that have dramatically increased the way we change land to fit our daily needs. The question of what land-use changes, if any, have been responsible for the emergence of diseases is summarized in this article. At the same time, looking solely at ecological changes, whether human-induced or not, and the emergence of human diseases would oversimplify the complex relationships between ecological changes, microorganisms, and human and animal diseases.

Humans have made significant changes to the Earth’s landscape. Human history is a record of forests cleared for agriculture, streams redirected for irrigation, cities built, urban dwellings created, roads, dams, and bridges constructed, and other ecological changes. As the population increases, the speed of ecological changes dramatically increases. Humans, sometimes unaware, and at other times fully aware, of the consequences are rapidly altering the basic foundations of the environment that sustains us. According to the World Health Organization’s (WHO) Millennium Ecosystem Assessment report, humans have made more significant ecological changes in the last 50 years than in any other comparable time period. These landscape changes inevitably have increased our access to new ecological niches. Changes in ecology or climate not surprisingly bring about both beneficial and detrimental organisms that cause diseases in humans and animals. Of course, the type and incidence of infectious disease depends on the particular ecosystems affected, type of land-use change, disease-specific transmission dynamics, sociocultural changes, and the susceptibility of human populations.

Ecological Changes

Numerous, simultaneous, and continuous ecological changes make it difficult to characterize its complexity. Ecological changes for agriculture rank highest for impact to public health and are implicated as a major factor in the emergence of diseases. The volume of agricultural impact on public health and spread of disease can only be appreciated by understanding that agriculture occupies about half of the land area of the world’s land and uses more than two-thirds of the world’s fresh water. Changes in land use directly and indirectly linked to agricultural activities include deforestation/reforestation, irrigation, monocropping, construction of roads and dams, macro and micro climate change, and erosion.

Deforestation/Reforestation

The rate of deforestation worldwide is estimated at about 40 million acres per year. In other words, a land area roughly equivalent to the state of Pennsylvania is destroyed each year. Vector-borne diseases are the most sensitive to climate and weather changes, with malaria one of the most climate-sensitive. Deforestation has increased the burden of malaria in some countries by exposing land to sunlight and creating pools of water that are known to favor the breeding of malaria-transmitting mosquitoes, *anopheles gambiae*. An increase in the prevalence of malarial infection in the New Guinea Highlands, an area previously malaria-free, has been linked to a rapid increase of anopheleline populations after forest clearance and other local developments. Similar trends have been documented in several other countries, including Kenya, Madagascar, Uganda, and Rwanda. Of course the increase in malarial infection in the last two decades is not solely due to deforestation but rather is concomitant with increases in anti-malarial drugs, resistance to insecticides, the breakdown of public health services, and the change in demographics. It is very hard to tease out the net increase in the rate of infections as a result of deforestation.

Yellow fever, a viral disease of primates transmitted by the bite of infected mosquitoes, is also classified as an important reemerging disease, with 34 sub-Saharan countries at risk. Like malaria, the increased transmission of yellow fever as well as dengue, another viral pathogen, are influenced by similar ecological changes, including clearing land for agriculture, logging, building roads, and mining. Deforestation creates a suitable environment for mosquito breeding and increases soil erosion. Flooding can increase the transmission of diseases from runoff and from disturbing breeding grounds and habitats. Soil erosion has been linked to an increase in human infection by helminths and pathogenic microbes.

Lyme disease is another vector-borne disease that arose from reforestation and people’s proximity to animal reservoirs. Lyme disease was first recognized in the United States in 1975 in the town of Old Lyme in southeastern Connecticut. It occurred in a new residential development where the deer population had provided the sustenance for the vector *Ixodes dammini*, which were infected by *Borrelia burgdorferi*. Lyme disease illustrates the interrelationship between microorganisms, biodiversity, and change in land use. It also provides us with a timely example of the complexity of the determinants of diseases and how they come to be human pathogens. Once again, as a result of ecological changes, there was a loss of biodiversity and changes in the host communities, increasing the risk of infection by vector-borne diseases.

Irrigation and dams

Some studies have linked the use of irrigation systems to the increase in breeding sites for malaria and other mosquito-borne diseases. A recently published article by Klinkenberg et al. (2005) quantified the incidence of malaria in Accra, Ghana where irrigation is practiced.
They found a higher rate of malarial infection in communities around the urban agricultural sites than in the control group (16.6% vs. 11.4%, respectively). Similarly, building dams causes an increase in the mosquito population. For example, Rift Valley fever is a disease transmitted by mosquito that has surged in Africa as a result of the construction of dams. Dams, by preventing the flushing of snail vectors, increased the prevalence of schistosomiasis in the region. Still bodies of water are particularly well suited for breeding snail vectors. For example, construction of the Aswan Dam in Egypt resulted in a shift from predominantly S. haematobium to S. mansoni.

The Senegal river basin water and environmental management project, which was a joint project of four West African countries (Guinea, Mali, Mauritania, and Senegal), constructed the Manantali and Diama dams. Despite an improvement in water availability and electricity supply, the dams resulted in proliferation of aquatic weeds and higher incidence of schistosomiasis and malaria. These examples illustrate that ecological changes can alleviate the risk of exposure to novel pathogens by creating a suitable environmental niche for mosquito-breeding sites. As a consequence, humans have increased their risk of acquiring new or previously recognized pathogens. The problem is that our understanding of the global microbiological population is less than limited, and we are unable to see the risk to humans and animals as a result of the ecological changes.

Roads

One of the outcomes of deforestation is the construction of roads. Access roads increase the opportunity for animal–human interactions. As a result, hunters, loggers, and others who often frequent the wilderness have a higher risk of contracting a novel pathogen by being in a new environmental niche. The increase in wild meat (bushmeat) trade in parts of central Africa has been attributed to the increase in access roads.

Among the approximately 177 newly emerged human diseases, about 58% are zoonotic. This underscores the influence of human–animal interactions on the emergence of diseases and recognizes that most emerging zoonotic disease outbreaks result from ecological changes. Some known human infections, such as influenza, tuberculosis, and measles, are zoonoses originally introduced to humans from other species. Strong evidence exists indicating that the emergence of HIV-1 and HIV-2 in humans results from transmission of simian immunodeficiency virus (SIV) strains from distinct, naturally infected nonhuman primate hosts. Nipah virus, a newly recognized zoonotic disease found in Malaysia, results from bat–human interactions. Nipah virus demonstrates that infectious diseases do not have boundaries. The infection of people with Nipah virus in Malaysia was traced to disruption of bat habitat in Indonesia that forced bats to migrate to Malaysia. The spread of Nipah virus to humans was aggravated by humans' close vicinity to dense populations of farmed pigs. Other similar examples—the epidemic of Japanese encephalitis in Sri Lanka resulting from pig husbandry; rabies resulting from the spread of raccoons in New York; Lyssaviruses resulting from human–bat interaction in Thailand and Australia—are some examples of emergence and reemergence of diseases caused by human–animal interaction.

Many gaps exist in our understanding of how zoonotic agents are maintained in nature or how they respond to environmental changes exacerbated by overcrowding, living close to animals, and exposure to new microorganisms with potential to become human pathogens. Emergence of zoonoses is likely to persist as long as human–animal interactions increase, particularly interaction caused by destruction of, or encroachment into, wildlife habitat (particularly through logging and road building).

Extending Production Chains

Production of food and biological products has changed dramatically over the last 20 years. In the 1930s, our food came from local farms. Quality and supply of produce and products were often uneven. Good years followed bad years. Not any longer. Production chains extend thousands of miles and often across continents for biological products we eat, such as meat, eggs, and milk, and increasingly for biological products we use as pharmaceuticals.

Globalization and consolidation of agribusiness corporations have changed the playing field. Bovine spongiform encephalopathy demonstrates an aspect of the phenomena. The United Kingdom's beef industry had historically been a relatively stable one when fragmented among many smaller farms across the British Isles. To protect this industry, the government maintained a tariff on the imports of competing products from abroad. With the explosion of global trading in beef after World War II, coincident with refrigerated transport, and the movement toward global free trade, the United Kingdom negotiated a timetable under the General Agreement on Tariffs and Trade to scale down tariffs on beef, which heightened competition in the United Kingdom's beef industry and increased pressure for more efficient and less costly production methods.

Against this backdrop, innovation in rendering was introduced into the slaughterhouses of the United Kingdom. The rendering or processing of carcasses of cows and other animals after the edible and usable bits of flesh and meat have been cut away has been done for centuries. And for decades, United Kingdom farmers used the meat and bone meal (MBM) from rendering as a protein source for beef cattle. Historically, the rendering process
was similar to pressure cooking – applying very high temperatures for very long times so eventually even the bones broke down into powder. It was an expensive, fuel- and time-consuming process. When a new cold vacuum extraction method of rendering was introduced requiring lower temperatures (i.e., less energy) and less time, it seemed a win–win situation considering the increasing pressure on the United Kingdom’s beef industry in the face of global competition. But some time after the new rendering practice was introduced into the United Kingdom, the prion disease known as mad cow disease emerged. The new process, it was discovered, was not effectively disinfecting for prions. Existence of prion disease was unknown prior to its dramatic emergence, first in cows and then in people. The context is important to appreciate. Somehow the streamlining of the rendering process played a role. British scientists tested the new process by deliberately introducing animals with mad cow disease and assaying the resulting MBM product. They found that the newer rendering process does not remove the infection, whereas the older process did. 

**Xenotransplantation: Technology as a Factor in Emergence**

With more than 50,000 Americans waiting for organ transplants in the United States, the demand for new parts is outstripping the supply. Animals seem to many like the logical next source of transplants, and scientific work is underway to access this source. In the United States, the Food and Drug Administration (FDA) has not licensed animal transplants. But other countries have, and they are attracting what the press calls medical tourists.

The truth is that scientists remain largely ignorant of the ecology at the microbial level despite their swagger. Another truth is that there is a nascent industry in xenotransplantation just waiting for the green light from the FDA. When an organ from a pig or baboon is transplanted into a human, four things happen: (1) the human defenses recognize the foreign material and mount a defense, (2) this vigorous immunological battle that would normally cause the rejection of the foreign material is treated with a variety of powerful drugs to stop rejection, and the patient becomes immunosuppressed, (3) any viruses or prions in the animal donor immediately become residents in the human donor, and (4) the new organ slowly begins to pick up the physiological functions of the organ it has been brought in to replace. Clearly, the second and third parts of this scenario introduce potentially dangerous conditions for disease transmission.

Some very strong, compassionate arguments exist for xenotransplantation: There are not enough organs available for transplant, and people with kidney or liver failure or pancreatic crises can wait years for a donor. The wait is difficult and can be life-threatening. Renal dialysis, for example, which replaces the function of a working kidney, makes patients feel increasingly ill as they undergo repeated treatment. According to Matching Donors, a Massachusetts-based nonprofit organization that matches donors with recipients, an estimated 17 people die each day waiting for transplants in the United States alone.

The pig has become the preferred candidate for donating organs to humans. Primates, the other most promising potential candidates, are expensive to acquire and keep, more likely to provoke ethical objections, and are perceived as risky because HIV is a simian (monkey) virus. Pigs can be bred to genetically erase their foreignness to humans by manipulating the genetic coding for the glycoproteins on their cells. Their organs are about the right size to fit the human body. However, pigs also carry new porcine (pig) retroviruses. Recall that HIV is a retrovirus, albeit of a different type. These retroviruses are actually embedded in their genetic material, so although pigs can be bred in sterile surroundings, there is no way to remove retrovirus agents from their makeup. They are, in the language of microbiology, endogenous.

Much work is ongoing to overcome the various obstacles to using pigs as donors for human organs. The problem of the endogenous retroviruses caused the FDA to halt early clinical trials in the United States. But scientists are working hard to study the risks and how to overcome them. In India, caution is not as pronounced, and pig-donated organs are transplanted into humans there. Those humans may return to the United States to recover, and presumably, seek medical care if and when they become ill, potentially exposing other patients. If there are risks from pig retroviruses, eventually they will be known, but the incubation period may be as long as the decade of quiet infection that precedes clinical AIDS in those with HIV. Potential risks lurk on two biological fronts. One concern is that the retroviruses from the pig could infect the human host and, in turn, the infected person’s contacts and community. Another is that the retroviruses might incorporate genes from the human (0.1% of the human genome contains endogenous retrovirus sequences) and the resulting mixed organism would prove infectious to the human and that human’s contacts and community.

A final area of concern, which is general for animal organ donation to humans, is the transfer of antibiotic-resistant infections from the animal. Animals of many types are receiving antibiotics in great volumes in their feed and treatments. While guidelines are very strict for how donor animals for human organ transplantation trials are raised in nations carrying out such experiments (including the United Kingdom and Australia), the guidelines in other countries may not be strict. So medical tourists who travel in search of the cheaper transplant bear close watching, and their close contacts should be made aware of the potential risks of unknown infections.
Factors Influencing the Emergence of New (and “Old”) Diseases

Microbial Change: Antibiotic Selective Pressure

Another type of emergent threat has a clearer path: evolution of resistant microbes in response to exposure to antibiotics. Antibiotics act as a selective pressure for resistance by killing off the susceptible microbes in each generation, leaving only those that have developed a strategy to resist them. Since microbes reproduce so often, this pressure assures the emergence of a fair number of resistant microbes in a relatively short period of time.

The selective power of microbes in response to antibiotics has been well demonstrated, starting with a classic experiment conducted by microbiologist Stuart Levy and his colleagues in the latter half of the 1970s:

In the mid-1970s, we performed a study that involved raising 300 chickens on a small farm outside Boston. We provided 150 newly hatched chicks with oxytetracycline-laced feed and another 150 without. We followed the effect of the antibiotic-laced feed on the animals and people on the farm. As we began the study, the control group had little or no resistant organisms. In the group receiving low levels (200 ppm) of oxytetracycline, tetracycline resistance began to emerge among the fecal Escherichia coli. What was surprising was that, within 12 weeks, we detected as much as 70% of all E. coli with resistance to more than two antibiotics, including ampicillin, sulphonamides, and streptomycin. The resistances were all on transferable plasmids that emerged following use of just oxytetracycline. (Levy, 2002: 27)

While antibiotics were designed to fight off infections in sick people and animals, they were approved for use as growth promoters for animals in the United States in 1949 and in the United Kingdom in 1953. Meanwhile, in the 1960s, scientists began to understand that the presence of antibiotics in the microenvironment of bacteria caused transferable antibiotic resistance. This means that populations of microbes not only become resistant to the antibiotic over time, but also can pass the new, adaptive characteristic resistance to other microbes — their biological extended family, as it were. Antibiotics fed to animals are not deactivated in the animals’ digestion process. In fact, they remain largely biologically active when they are excreted by the animals on fields, into waterways, or elsewhere. Other vertebrates, including humans, begin to colonized with the resistant organisms, if they share an environment with animals in which the resistant strains are developing. In areas where animals and humans are crowded together with poor access to sanitation, this aspect of antibiotic usage in animals becomes even more dangerous.

Campylobacter and Salmonella are the two best known microbes. They have been shown to acquire new resistance while in animals and to transfer that resistance to humans through the consumption or handling of contaminated meat. In the case of Campylobacter, the practice of intensive poultry production plays a role. Most chickens are colonized by Campylobacter — they carry them in their gut. The chickens are not sickened by these microbes; the Campylobacter are part of the normal gut flora. When chickens are raised in very close proximity, with thousands in a single facility, they are more prone to disease, as we have seen with the avian influenza virus. They also are more prone to bacterial disease. Thus, chickens are often treated with antibiotics, including fluoroquinolones, a particular type of antibiotic that is important in treating human infections. According to the U.S. Centers for Disease Control and Prevention, the rate of resistance to this important class of antibiotics in human infections with Campylobacter rose from 13% in 1997 to 19% in 2001. In Minnesota, fluoroquinolone-resistant strains were isolated from 14% of chicken products in retail markets. When molecular-level comparisons were made, these strains exactly matched those isolated from human infections in the surrounding communities.

But the use of antibiotics as growth promoters is not confined to resource-challenged regions. In fact, it has been a long-standing practice in the United States, where a host of microbes have developed resistance, most likely as a result of the drugs in food animals, including Salmonella, Campylobacter jejuni, and Escherichia coli. A number of other industrialized nations have been more diligent about monitoring and curbing the use of antibiotics in animals. The European Union has prohibited lacing the feed of animals with antibiotics that might also be useful in human disease, with the intent of preserving the effectiveness of such antibiotics as long as possible. The scientific evidence for this move is powerful and comes largely from the United Kingdom, Denmark, and Germany, where scientists have carefully monitored feed practices and resistance patterns over the last decade. Research suggests the bans can lead to a corresponding drop in drug-resistant bacteria. One study showed that rate of resistance to the antibiotic avoparcin declined in Germany and Denmark after that drug was prohibited for use as a growth promoter (Witte, 2000). Scientists studied the disease patterns by using molecular genetic techniques to fingerprint specific gene groups that characterize both animal and human resistance to particular bacteria. These characteristic patterns were then tracked in different populations of animals and humans to trace the changes in their frequency of occurrence. Research demonstrated that the decline in resistance was correlated in time with the proscription of the use of avoparcin as a growth promoter and that the decline in the characteristic gene cluster took place in numerous animal and human systems coincidentally.
Antibiotics in Humans: Are Prescriptions Useful?

In many developed countries in Europe and North America, antibiotic prescription authority has been vested in health-care workers since the mid-1900s, and usually is limited to physicians or nurse practitioners. In many other countries, antibiotics are available from pharmacists without a prescription. The U.S. CDC and many state health departments have launched programs to educate the public and physicians about prudent use of antibiotics. Antibiotics are, of course, only useful in infections where bacteria (or mycobacteria, such as tuberculosis) are involved. They have no effect whatsoever on human infections caused by viruses. Viruses cause the majority of infections seen by doctors, including sore throats, cough, fever, and diarrhea. However, when patients come to the doctor, they expect to be treated, not just advised to rest, take fluids and “two aspirin and call me in the morning.” This is even more the case in the current health-care practice milieu in the United States, where visits with health-care providers are difficult to schedule, short, and expensive. Patient demand for antibiotics is a major driver of inappropriate use.

What role does sanitary practice play in the transmission to humans? What are the critical variables in keeping cages clean, providing safe water to poultry, or clean and safe feed? What is the compromise between the most efficient and profitable poultry-raising practices and safety among poultry workers? When the Food and Agriculture Organization of the United Nations (FAO) discusses restructuring the increasingly intense poultry industry in Southeast Asia, the optimal design of that restructuring is not clear—we have no scientific blueprint to follow. The United States’ experience with avian influenza, in fact, suggests that USDA guidelines do not prevent the disease in poultry.

We have quantitative tools we can use to answer some of these important questions. A group of scientists recently analyzed the impact of the livestock revolution on the ecology of infectious diseases. The revolution, or the growing demand for animal protein, has been incited by Earth’s increasing human population and the rising incomes of growing urban populations. This demand is met in Asia primarily with poultry, much of which is raised in crowded conditions just outside urban centers. Slingenberg and his colleagues (2004) outline four major areas of risk in this process that need to be carefully considered in terms of the emergence of new infections:

1. production intensification;
2. the host metapopulation, which means a population that experiences microbial traffic and, therein, experiences the spread of disease (in this case, the poultry);
3. the transmission pathways other than those within the animal population, in other words, the entire food chain from feed to live animals, processing, marketing/distribution, food preparation, and consumption; and
4. the nature of the pathogen, that is, its virulence and the ease with which it spreads.

While crops can only be intensified within the bounds of arable land, the livestock revolution is not so constrained. A key feature is the “severance of the traditional links between the amount of available local land and feed resources” (Slingenbergh et al. 2004: 470). Poultry intensification in Latin America, the Near East, North Africa, East Asia, and South Asia is taking place close to the exploding markets of the urban megacities. It is estimated that by 2015, half of the world’s human population and 35% of the global meat production will be in Asia. Working with data from the FAO on the agricultural population and chicken meat output, the scientists plotted the information on a graph (Figure 2).

Bringing ecological science into the study of how microbes change or adapt within their microscopic world is the study focus of evolutionary biologist Paul Ewald and his colleagues. They have posited that a microbe’s mobility is linked with its virulence (how seriously ill it can make us). The argument is that the basic value of ecological fitness is central for populations of microbes. This is simply the ability to pass their genetic material from one generation of their species to the next through replication. If the microbe can easily move from host to host, that is, if it is highly infectious, it invests more energy moving in mobile hosts and less on developing high virulence. On the other hand, some species, such as anthrax, lie in wait for extended periods of time and then immobilize their hosts by making the host moribund or dead, counting on the immobilized host to serve as a point of infection for other hosts. Ewald has coined the term ‘cultural vectors’ to describe transmission that takes place independent of typical mechanisms such as flagellae, which allow the microbe to swim, or mosquitoes, which transport the microbe to another host (Kimball, 2006). These strategies have developed within the plethora of microbe species over thousands of years of evolution.

The emergence of mad cow disease raises three key points: (1) changes in production and processing of products based on animal or human material can spark the emergence of new human infectious pathogens, (2) production changes can be hastened in a global marketplace in which increased efficiency in production is reward by providing a competitive edge or more profit, and (3) the new agent can be distributed globally before the problem is fully recognized and public health measures are implemented. As these rising resistance rates indicate, one obvious strategy to prevent the emergence of drug-resistant strains is to limit the antibiotic exposure of microbes living in humans.
and food animals. Possible strategies would include limiting or discouraging the use of antibiotics by veterinarians, pharmacists, physicians, and the public through legislation and/or international policy and law. But this is actually not at all straightforward in today’s world. The use of antimicrobials to fight disease in humans and animals and promote growth in animals is a well-entrenched practice.

In the United States alone, an estimated 23,000,000 kg (50,000,000 lbs) of antibiotics are used annually. While surprisingly little information is available about the usage of antibiotics in food animals in most countries, WHO estimates that roughly half of all antimicrobials produced are used to treat humans, and most of the rest are used in animal feed—primarily for pigs and poultry—to either fend off infection or enhance growth (WHO, 2002). The practice has become even more important with the rise of intensive agriculture, in which animals are kept in crowded conditions that make them more vulnerable to infectious diseases.

Subtherapeutic use of antibiotics in these settings not only reduces outbreaks of illness but also has been shown to increase the overall weight of the animal by 4 or 5%, which adds to productivity and eventually to profitability. The tension between ecological caution and business profit is noted in a recent report by the U.S. General Accounting Office:

While antibiotic use in animals poses potential human health risks, it also reduces the cost of producing these animals, which in turn helps reduce the prices consumers pay for food. Antibiotics are an integral part of animal production in the United States and many other countries where large numbers of livestock are raised in confined facilities, which increases likelihood of disease.

(U.S. General Accounting Office, 2004: 1)

The degree to which the drugs are used as growth enhancers (rather than to combat disease in sick animals) is subject to debate. According to the Animal Health Institute, an industry group that represents U.S. antibiotic manufacturers, some 10.2 tons of antibiotics a year are used on the 8 billion food animals produced annually in the United States—87% of which is for “treating, controlling and preventing disease”. In contrast, the Union of Concerned Scientists, an environmental group, in 2001 estimated that U.S. animal producers administer 12300 tons of antibiotics a year for nontherapeutic (i.e., growth-enhancing) purposes.

National legislation and guidelines for antibiotic use in animal husbandry vary among countries, as does the level of surveillance. In the 1990s, amid growing concerns about the emergence of drug-resistant bugs, the WHO identified the issue as one of global public concern. In 2001, WHO, together with the Food and Agriculture Organization of the United Nations and the Office International des Epizooties (World Organization for Animal Health), drafted a set of global principles to address the use and abuse of antimicrobials in animals. Included was a strategy to ban drugs that are important for treating human illnesses for use as growth promoters in animals.

But as the WHO initiative acknowledges, given the world market, any successful effort will have to be global in scope. The strategy that WHO disseminated in 2001 is not a regulation but a series of recommendations “to both persuade governments to take urgent action and then to guide this action with expert technical and practical advice” (WHO, 2001). As a nonbinding recommendation, the strategy may fail to galvanize sufficient international action, particularly in areas that are strapped for public health resources. Indeed, a workshop in 2002 examining the degree to which the recommendations were implemented found significant gaps. The workshop summary concluded:

The extent of implementation of the Global Strategy was very variable, both across and within Regions. Where priority interventions were in place, in many instances these were nominal only, since compliance was not enforced. (WHO, 2002: 1)

Among the obstacles identified were limited resources, unregulated use of antimicrobials in food-producing animals, and “lack of inclination to enforce existing regulations.”

In most developing countries, where agricultural exports are a potential source of critically important foreign currency, few regulatory barriers exist for using antibiotics as growth promoters, and those that do exist are weakly enforced. In many cases, veterinary services have transitioned in recent decades from the government to private hands, and the livelihood of veterinary workers now depends on the ability of farmers to pay for services. If a practice such as subtherapeutic use of antimicrobials is judged potentially profitable, chances are it will continue relatively undisturbed.

As of 2006, all antibiotics were, in principle, banned from use for growth promotion in European Union member countries. Many producers and others have questioned the science behind these bans. Indeed, some have called for a quantitatively based formal risk assessment. But others point out that conducting such an assessment would require waiting until the potential negative health consequences had played out in terms of human therapeutic failures (Witte, 2000). Then, once deaths or other health consequences had begun to occur, we could count them and do calculations to demonstrate risk. Awaiting this outcome when the science from the bench, the lab, and numerous animal systems is clear seems unconscionable. Thus the precautionary principle moved the European Union to implement the ban.

As the recent GAO (the U.S. General Accounting Office) report indicates, the European Union’s impending
implementation of more stringent bans of antibiotics is being watched closely by the United States as a potential source of future trade embargoes (U.S. General Accounting Office, 2004). The United States is beginning to benchmark its own system of monitoring the problem with efforts in other countries, particularly the European Union. But as the report also points out, to date, public authorities in the United States have lacked sufficient access to reliable industry information on the use of antibiotics, making it difficult to assess the current situation and what actions may be appropriate. Here science has no gap in its knowledge. The risks of increasing antibiotic resistance are clear. However, in terms of information needs for policy, the GAO report states flatly that:

Although they have made some progress in monitoring antibiotic resistance, federal agencies do not collect the critical data on antibiotic use in animals that they need to support research on the human health risk.

(U.S. General Accounting Office, 2004: 7)

So at present, the United States, a major meat exporter in the world marketplace – with exports of $2 billion in 2002 – appears to lag behind the global community in this aspect of food safety, running a risk of trade embargoes that eventually could drive it to regulate the practice without key information from industry practice.

Around the world, in developed as well as developing countries, the research base and national policies regarding antibiotic use are uneven. While there is no reason to believe that the biology and ecology are fundamentally different with regards to the use of antibiotics as animal growth-promoting agents in Europe, Asia, or Africa, national policy makers historically have made decisions based only on studies related to their own particular situations. Meanwhile, on a daily basis, additional resistance is being stockpiled through the consumption by humans of resistant strains of pathogenic microbes. As noted earlier, these antibiotics do not disappear from the environment when their use is halted. While information from Europe indicates that resistant strains will become sensitive again when the selective pressure of antibiotic use is removed, that information is not nearly as complete or compelling as it should be to justify the persistence of risky practices in animal husbandry. Antibiotic residues and active compounds are not only found in the food we eat. Increasingly they are found in groundwater and in the soil, begging a serious question: Is there a point where we have accumulated enough active antibiotics in the human environment to permanently alter the equilibrium of nature? Is this prospect a real threat to us?

In other developed countries, antibiotics are often not controlled by prescription. In most Asian, Latin American, and some European countries, they are available from pharmacists over the counter, without a doctor’s prescription. This has become an issue in antibiotic resistance. It might best be apparent in the case of tuberculosis. Tuberculosis is a slow-moving but devastating infection that begins in the lungs. It requires long-term treatment (6 months to a year) with three active antituberculosis drugs. In some countries, such as the Philippines, compounds available in pharmacies to treat cough may contain one active antituberculosis agent mixed with vitamins. This will help with symptoms, but not cure the infection. Instead, as we have seen, resistant organisms will be selected and thrive in the patient. Most of the drug-resistant tuberculosis seen in Seattle and other U.S. West Coast cities occurs in people from countries where this is standard practice.

Creating prescription authority and regulation of antibiotic use internationally is not a simple matter. The majority of pharmaceutical corporations are transnational in their marketing and production. Like their counterparts in the meat industry, they have financial incentives to avoid government regulation of their product sales. While industry has increasingly come to understand that widespread, inappropriate use of antibiotics will shorten the effectiveness of their products, that inevitability is likely to occur well beyond the life of the drugs’ marketing plans, so this consideration may not be as central to decision making as safety would dictate. Misaligned financial incentives also are evident in the Asia Pacific region. Physicians in the region have historically been marketed with financial incentives to prescribe antibiotics. Drug salesmen, known as detailers, call and visit physicians in practice to promote their products. In Asia, some hospital systems actually compensate physicians according to the number of prescriptions they write. This has resulted in profound overuse of antibiotics and, consequently, very effective selection for drug resistance in a number of medical centers.

In developed countries where consumers are able to purchase drugs, incentives exist for drug producers to limit the regulations they work under and to promote the drugs they produce. In the past decade, the United States has seen the emergence of direct marketing to the consumer. This trend includes high investment by pharmaceutical companies in media advertisement campaigns to promote certain brand names of drugs. This trend has not included direct marketing of antibiotics to consumers, rather focusing on the promotion of pain relievers, antidepressants, medications for sexual dysfunction, antihistamines, and cold remedies. This relatively new media approach includes medications available by prescription only, often advising the public to “ask your doctor” for the pill by name.

**Primary Prevention: An Ongoing Challenge**

The actual emergence of new microbes is difficult to prevent. In the case of antibiotic-resistant organisms, the
selective pressure is well known and characterized, and yet it is apparently difficult to remove. The promiscuous use of antimicrobials in humans and animals seems destined to continue in the near term, and thus laws of nature suggest the emergence of new resistant microbes will also continue. Similarly, medical forays into xenotransplantation and other procedures with unknown risks for disease emergence are inevitable. Meanwhile, the human population will continue to grow and increasingly tax the planet’s resources. International travel and trade will continue to expand, all the while tweaking the microbial world in unexpected ways. The challenge of preventing the emergence of new microbes is daunting, and our resources and knowledge for doing so are limited. Factors of emergence provide an outline for additional interdisciplinary research that needs to be done to provide more scientific insight into this phenomenon. As we await such insight, the one clear fact is that emergence is continuous and, if anything, is continuous at a quickening pace.

See also: Emerging Diseases: Overview; Epidemic Investigation; Escherichia Coli; Food Safety; Foundations in Public Health Law; Global Health Initiatives and Public Health Policy; Severe Acute Respiratory Syndrome (SARS); Social and Cultural Perspectives on Eco-Health; Surveillance of Disease: Overview.

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Falls

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Introduction

The incidence of falls for individuals, as well as the burden on the health-care system, shows a U-shaped relationship with age (Figure 1). Across the world, falls rate as a major contributor to injury in children and older adults. Falls during young and middle adulthood are less frequent, although they may impose serious consequences (e.g., occupational falls).

Falls in Children

The World Health Organization has rated falls as one of the leading causes of the global burden of disease for children age 0–14 years. Falls rated in the top 15 leading causes of burden across cultures and high-, middle-, and low-income countries for the year 2000 (Peden et al., 2002).