Biological Diversity and Public Health

Aaron S. Bernstein

Center for Health and the Global Environment, School of Public Health, Harvard University, Boston, Massachusetts 02115

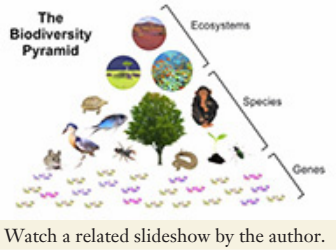
Division of General Medicine, Boston Children's Hospital, Boston, Massachusetts 02115; email: aaron.bernstein@childrens.harvard.edu

Annu. Rev. Public Health 2014. 35:153–67

First published online as a Review in Advance on January 2, 2014

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

This article's doi: 10.1146/annurev-publhealth-032013-182348



Watch a related slideshow by the author.

Keywords

climate change, emerging infectious diseases, natural products, undernourishment, pollinators

Abstract

In the wake of a species extinction event unprecedented in human history, how the variety, distribution, and abundance of life on earth may influence health has gained credence as a worthy subject for research and study at schools of public health and for consideration among policy makers. This article reviews a few of the principal ways in which health depends on biodiversity, including the discovery of new medicines, biomedical research, the provision of food, and the distribution and spread of infections. It also examines how changes in biological diversity underlie much of the global burden of disease and how a more thorough understanding of life on earth and its relationships has the potential to greatly alleviate and prevent human suffering.

INTRODUCTION

Eukaryote: a single-celled or multicellular organism that possesses membrane-bound nucleus/nuclei and membrane-bound organelles

The discipline of public health, in its quest to jointly prevent disease and promote health, has over time increasingly confronted the relevance of species other than *Homo sapiens* to its work, and for good reason. Biological diversity, or biodiversity for short, a term that refers to the variety of life, including species, the genes they contain, and ecosystems they form, underlies much of what keeps people healthy, from adequate and clean water, to food, medicines, and freedom from infectious diseases.

Attention to biodiversity as it pertains to human health has grown as present rates of species extinction, a key indicator of the status of the biosphere, are 100 times, and in some cases 1,000 times or more, faster than those observed in the fossil record (57). The rapid pruning of the tree of life has raised sober consideration about whether the earth's sixth mass extinction event has commenced (4). To put this prospect in perspective, the earth's most recent mass extinction transpired 65 mya when an asteroid struck the earth and wiped out the dinosaurs as well as more than half of all species with them. As humans have evolved as part of the web of life, this loss of biodiversity raises major questions about how humanity will fare as the rest of the living world is thrown into tumult.

This article presents an overview of biodiversity and how it is assessed and then turns to several key interfaces between biodiversity and health, including the discovery of new medicines from natural products, advances in biomedical technology made possible through harnessing unique evolutionary adaptions, the provision of food and food security, and the prevalence and spread of certain infectious diseases.

BIODIVERSITY UPSIDE DOWN

Assessment of earth's biodiversity has most often been performed by counting species. To date, about 2 million species have been identified, but the total number may be four or more times as many (14, 49). Little more than their names, however, may be known about many of these creatures. Just over 65,000 species, for example, roughly 4% of those known, have received any scrutiny on their conservation status (31). Astonishingly, far more is known about the details of molecules within individual organisms, such as genomes, than is known about the variety of organisms that inhabit the planet, and this despite the latter having been studied for centuries more.

Biological diversity consists of more than just the diversity of species. Advances in molecular biology in the late twentieth and early twenty-first centuries have enabled the assessment of biodiversity at a genetic level and have begun to change the way in which biodiversity is understood. In a seminal paper published in 1977, Carl Woese and George Fox presented a model of life that sorts organisms into three domains, instead of the traditional five kingdoms, on the basis of their ribosomal RNA composition (85). Their analyses revealed that two-thirds of all the genetic diversity on earth resides in single-celled organisms that comprise the prokaryotic and archaeal domains (see **Figure 1**). The rest of life, including all plants, animals, and fungi, are subsumed into the third domain, the eukaryotes. The three domain model turns the traditional five kingdom view of life, which posits that life's diversity is mostly eukaryotic, on its head (see **Figure 2**).

Genetic diversity matters to health in many ways, some of which are presented below, and the recognition that most of it derives from microbial organisms has brought about a sea change in understanding about how the diversity of life influences health (see also Appendix 1: Microbial Diversity, the Human Microbiome, and Health). Another emerging area of research that pertains to biodiversity and human health involves understanding the ramifications of human transformation of earth's ecosystems. Lesser biodiversity within and among ecosystems reverberates in agricultural productivity and in the transmission of infectious diseases, topics that are also considered below.

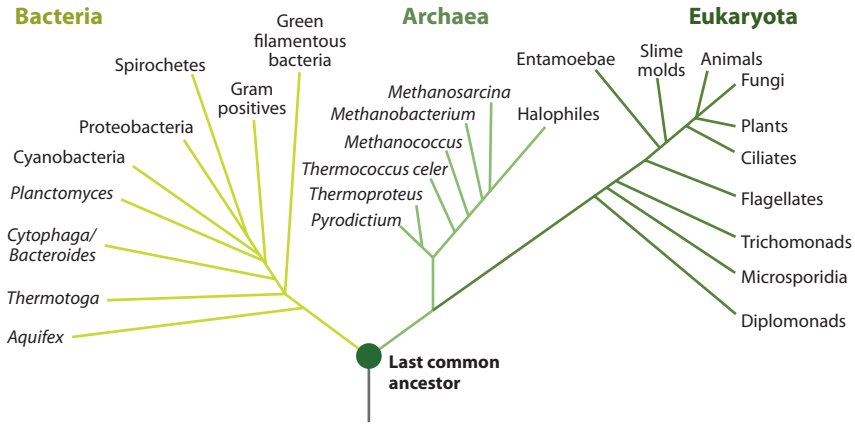


Figure 1

The three-domain model of life.

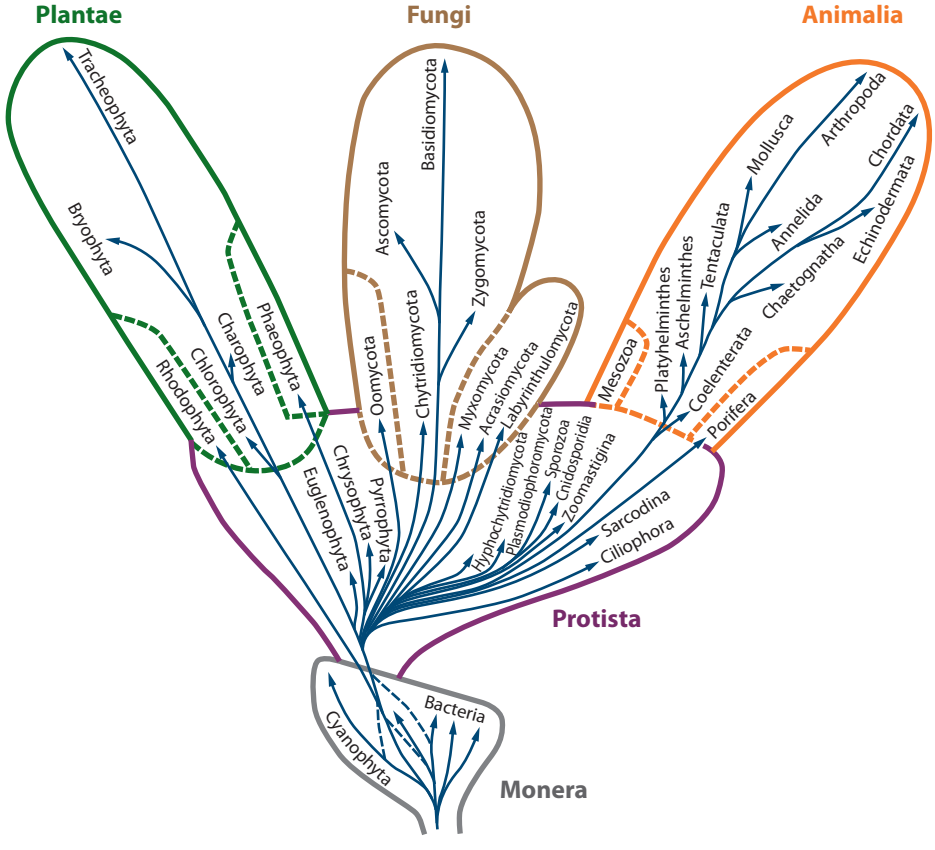


Figure 2

The five kingdom model as described by Whittaker in 1969 (modified from 84). Colors have been added to clarify. Reprinted with permission from AAAS.

NATURAL PRODUCTS AND DRUG DISCOVERY

Evolutionary processes may not be the perfect tool for designing biologically active compounds, but they may be the best ever realized. Through eons of trial and error, natural selection has crafted a panoply of molecules that exert influence on living things. Human use of natural products as medicines has occurred for thousands of years and continues today. More than half of the 1,355 newly approved drugs by the US Food and Drug Administration (USFDA) between 1981 and 2010 relied on nature in their creation (54). The heavy and long-standing dependence of drug development on natural products manifests the common molecular currency of life on earth, a fact evident in molecules from species as diverse as *Conus geographus*, *Penicillium citrinum*, and *Taxus brevifolia*—a meat-eating marine snail, fungus found growing on rice, and boreal conifer—serving in humans to relieve pain, reduce cholesterol synthesis, and treat breast, ovarian, lung, and other cancers, respectively.

Nearly every domain of medicine relies on natural products, but dependence on natural products has been particularly heavy for antibiotics and anticancer drugs. Of 14 major classes of antibacterials, 10 derive from natural products.[1] Between 1981 and 2010, 75% (78 of 104) of antibacterials newly approved by the USFDA can be traced back to natural product origins (54). Percentages of antivirals and antiparasitics derived from natural products approved during that same period are similar or higher. More than 80% (103 of 123) of new anticancer agents licensed during the same time interval have natural product origins.

Although a treasure trove of medicines has already been produced from mining biodiversity, most of the potential has yet to be tapped. Plants have been the most prolific contributor to natural product drug discovery to date, and although an estimated 400,000 plant species populate the earth, only a fraction of these have been studied for pharmacologic potential. One of the largest plant specimen banks, the natural products repository at the National Cancer Institute, contains ~60,000 specimens, for instance. Other realms of the living world, especially the microbial and marine, are almost entirely unknown and hold immense potential for drug discovery given the extraordinary diversity of molecules that have already been discovered from them (16).

BIODIVERSITY AND BIOMEDICAL BREAKTHROUGHS

In much the same way as medicinal discovery has used the diversity of life to alleviate human disease, so too has the broader field of biomedicine. Model organisms have been used to understand how human organs, for example, may function in health and disease states at least since the time of Aristotle. The idea that biodiversity provides a resource for the investigation of questions of medical relevance has been articulated many times by eminent physiologists, notably by Claude Bernard in 1865 (5, p. 27) ("Dans l'investigation scientifique, les moindres procédés sont de la plus haute importance. Le choix heureux d'un animal, un instrument construit d'une certaine façon, l'emploi d'un réactif au lieu d'un autre, suffisent souvent pour résoudre les questions générales les plus élevées"/"In scientific inquiry, even the smallest processes are of utmost importance. The proper choice of an animal, an instrument built in a certain way, the use of one reagent instead of another, may suffice to resolve the most significant questions") and August Krogh in 1929 (37) ("For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied"). Today, animals, plants, and microbes all are widely used to answer fundamental questions of biology.

[1]The fourteen classes are penicillins, cephalosporins, macrolides, aminoglycosides, carbapenems, glycopeptides, lincosamides, lipopeptides, monobactams, nitrofurans, sulfonamides, oxazolidinones, quinolones, and tetracyclines. Nitrofurans, sulfonamides, oxazolidinones, and quinolones are synthetic.

Most species have been chosen for use in biomedical research because they are common and because they can reproduce quickly and be easily manipulated (e.g., *Drosophila melanogaster*, the fruit fly, or *Saccharomyces cerevisiae*, a yeast), but in many cases adaptations to peculiar circumstances serve as the basis for their utility to biomedical research. Take the example of the heat-stable DNA polymerase from *Thermus aquaticus*, which acts as the central cog in the polymerase chain reaction (PCR) and has transformed the discipline of molecular biology. *T. aquaticus*, though now known to be widespread, was first discovered in the 69°C Mushroom Spring in Yellowstone National Park by Thomas Brock and Hudson Freeze in 1967. *Taq* polymerase thrives at temperatures that would cook its human counterpart and makes it well suited to work in the high temperatures required to separate paired DNA strands and make PCR possible. In 2012, more than 27,000 articles in the PubMed database made reference to PCR. PCR serves as the basis for diagnostic tests for infectious diseases, such as HIV, and detects the presence of genes in cancers and cancer patients to predict response to chemotherapies.

Disability-adjusted life year (DALY): one lost year of "healthy" life. In aggregate, DALYs define a burden of disease in a population

Taking the full measure of biodiversity's value to discoveries that benefit human medicine is a daunting task. Scarcely a breakthrough in biomedicine has been attained without it. Nearly all the Nobel Prizes in Medicine awarded since Emil von Behring in 1901, who did research with guinea pigs to develop serum therapy for diphtheria, have relied on model organisms. The 2013 prize was awarded to James Rothman, Randy Schekman, and Thomas Südhof for discoveries related to vesicle trafficking in the cell, which relied on organisms as disparate as the bacterium *Escherichia coli*, the Chinese hamster *Cricetulus griseus*, and the roundworm *Caenorhabditis elegans*. Although new model organisms may not have been introduced in recent years as often as they have in years past, ample evidence indicates that studying the diversity of life may yield insights into presently incurable diseases.

BIODIVERSITY AND HUNGER

Human civilization has been built on the success of agriculture and the ability of relatively few people to grow the food needed for all. Agriculture is by evolutionary time standards still a new invention, having appeared in the past 12,000 years or so, the first time in which fully modern humans have lived in a climate suitable to grow crops over much of the earth's land surface. In this century alone, anthropogenic climate change threatens to push the planet's climate outside the envelope in which agriculture has been established. It is likely to increase the number of heat waves, droughts, and floods, as well as the salinity of groundwater used for irrigation in coastal areas owing to sea level rise. These changes disrupt the foundations of agriculture, and recent estimates suggest that climate change may curtail yields by 40% or more from major staple crops such as corn and soybeans by 2100 (61). Climate change spells uncertainty for the future of global food security in general, and the developing world and children in particular. Nearly 1 billion of the world's undernourished people live in developing countries, and ~20 million children already suffer from severe malnutrition (7). Childhood underweight is the single largest risk factor for disability-adjusted life years (DALYs) in the world and is the leading cause of mortality in children from low-income countries (87).

Biodiversity offers opportunities to protect the global food supply as climate change unfolds. Breeding crops to be resistant to drought, salt, and heat, which makes use of their endogenous genetic diversity, has become a cornerstone of climate adaptation. Research has only recently characterized some of the molecular mechanisms that confer these abilities to plants. In rice, soy, corn and wheat, and other staple crops, researchers have identified candidate genes and hybridization strategies to endow them with resilience (15, 44, 47, 65, 88), and all crops in widespread use have been bred to be resilient to biotic and abiotic stressors.

Resiliency in agroecosystems to environmental change depends on the innate attributes of crop varieties, which makes preserving crop biodiversity a vital part of food security. Vast seed banks have been established to warehouse crop seeds in Svalbard, Norway (**http://www.regjeringen.no/en/dep/lmd/campain/svalbard-global-seed-vault.html?id=462220**), and in West Sussex, United Kingdom, among other locations, as part of the Millennium Seed Bank Partnership, where seeds from ~10% of the world's plants have already been stored (**http://www.kew.org/science-conservation/save-seed-prosper/millennium-seed-bank/index.htm**).

The prospective value of seed banking is readily apparent from experiments that have repeatedly shown greater pathogen resistance among hybrid varieties or when multiple crop varieties are planted in the same plot (41). One such experiment from China examined vulnerability to rice blast, a major rice pathogen, in fields where several varieties of rice were grown together as compared with monocultures. Over several years, rice blast was 94% less prevalent and rice yields were 89% greater when disease-susceptible rice varieties were planted in mixtures with resistant hybrid strains (89).

Intercropping, or growing several crops in the same field, may also directly benefit crop yields. In a four-year study, Li et al. (40) found that corn grown with fava beans in low-phosphorous, high-nitrogen soil had 43% higher yields than did corn grown on its own. In those same plots, fava bean yield also increased 25%. They determined that the fava plants released acidic substances into the soil, which mobilized phosphorous for use by the corn. Although modern science has begun to uncover the biological basis for the success of intercropping, indigenous peoples around the world have used such practices for centuries (see, for example, 51).

Successfully raising any single crop requires more than its seeds; a multitude of species are necessary, from microbes, insects, worms, and small vertebrates in the soil to a host of species above ground that control pests, fertilize soils, and pollinate flowers. Marked population declines have been observed in organisms vital to agriculture in recent years, and these losses bear directly on food security. The fungus *Geomyces destructans*, for example, has well earned its moniker, having killed more than 5.5 million bats in 22 states and 5 Canadian provinces since it was first recognized in a New York cave in 2006 (78, 80). The fungus causes white-nose syndrome and was likely introduced to North America from Europe (82). Bats can eat immense volumes of insects, including crop pests. Whitaker et al. (83) estimated that an average-sized colony of big brown bats (*Eptesicus fuscus*), capable of eating 600,000 cucumber beetles annually, prevents the production of 33,000,000 cucumber beetle larvae (also known in their larval stage as corn rootworms, which infest corn roots). In North America, bats provide ~$3.7 billion in pest control services each year (10). For comparison, ~$4.3 billion were spent on insecticides in the United States in 2007 (27).

Agricultural biodiversity has in recent years also sustained a dramatic loss of pollinators, especially honeybees, *Apis mellifera*. Each winter since 2006, widespread losses, ranging most often between 30% and 60%, of honeybee hives have been observed in North America, a phenomenon that has come to be known as colony collapse disorder (CCD) (77). Although abrupt population declines are not unknown to beekeeping, the extent and duration of these losses have raised concern, given that 3–8% of crop production worldwide depends on pollinators, and since the 1960s, the proportion of food production that depends on pollinators has increased in both the developing and the developed world by 50% and 62%, respectively (1). In addition, ~$15 billion of crops depend on insect pollination in the United States each year (12), and worldwide, pollination services, mostly from bees, had an estimated value of 153 billion Euros in 2005 (23).

CCD may very well be a final common pathway, with multiple insults—infections, toxins, or other environmental stresses—resulting in the same outcome. Among other putative causes of CCD, several pathogens, including the *Varroa* mite and Israeli paralytic virus (58), and toxic exposures, especially to the neonicotinoid class of pesticides, have been implicated (64). As of

April 2013, neonicotinoid pesticides have been banned for two years in the European Union out of concern for their effects on honeybees. Beyond losses of domesticated bees are widespread die-offs of wild pollinators (11), and flower for flower, wild pollinators appear to be more effective than their domesticated counterparts (24).

Still other alterations to biodiversity matter to the future of agriculture and global hunger. The rhizosphere, a scarcely explored realm just beneath the soil's surface, houses a bounty of organisms, many too small to be seen with the naked eye but some, such as the mycorrhizae, fungi that shepherd nutrients to plant roots and stabilize the soil, create vast filamentous networks that may stretch meters in length and connect multiple plant root systems together. The relationship between plant roots and mycorrhizal fungi may be the most widespread in nature and dates back to the first land plants more than 400 mya (3). Mycorrhizal species may improve tolerance to drought (e.g., 2) and salt (e.g., 22) and, in certain circumstances, improve crop yields (69). In conventional agriculture, tilled soils and those treated with certain fungicides may have decreased integrity and abundance of mycorrhizal networks (13, 33, 46, 52). Although some mycorrhizal services may be replaced with, for example, phosphorous-containing fertilizers, other services, such as soil integrity promotion, enhanced nutrient uptake, and even heavy metal remediation, have fewer readily available substitutes.

As with biodiversity on a global scale, a large share of biodiversity relevant to food production remains unknown. What is known indicates that this diversity provides resilience against vulnerabilities in crop yields, which carries an increasingly high premium as the earth's climate changes.

BIODIVERSITY AND INFECTIOUS DISEASES

Some 60% of the more than 1,400 human pathogens spend a part of their life living in at least one, and often several, species other than *Homo sapiens* (70). How these other host species may curtail or augment risk of human infection has become a matter of great interest to all those concerned with preventing infectious epidemics.

For some vector-borne pathogens, the aggregate diversity of host species in which they may live may influence the risk of infection. In the case of Lyme disease in New England, vertebrate host diversity appears to alter the prevalence of infected black-legged ticks, *Ixodes scapularis*, the disease vector. Black-legged ticks feed on a wide assortment of vertebrates. However, not all these vertebrates are equally able to transmit the bacteria to ticks that feed on them if they themselves are infected. Among the vertebrates that may provide a tick's blood meal, white-footed mice are among the most capable of transmitting the Lyme bacteria to an uninfected tick (43). As a consequence, bloodthirsty ticks questing for a meal in forests with a higher diversity of vertebrates are more likely to feed on an animal other than a white-footed mouse and are less likely to get infected with Lyme bacteria. The dilution effect refers to a scenario, exemplified by Lyme disease, in which high diversity of pathogen hosts may dilute a pathogen in a reservoir pool and decrease the odds that the disease vector will become infected (63). Evidence has indicated that the dilution effect may influence West Nile virus and hantavirus transmission as well (55).

Zoonotic host species may influence disease spread in other ways. The joining of three previously unacquainted influenza viral strains in the novel 2009 H1N1 influenza resulted in a pandemic that, after its first year, killed an estimated 280,000 people and sickened about 1 in 5 people worldwide (19, 81). This mutt of a virus contained genes from swine influenza on two continents, as well as genes from strains of human and avian influenza viruses. Swapping of genetic segments among influenza viruses, which may produce pandemic influenza virus strains, is not a new occurrence. However, some evidence has raised concern about whether human activities that have dramatically

reshaped populations of species that participate in the influenza ecosystem may be enhancing the likelihood of influenza viruses to do so.

CAFO: concentrated animal feeding operation

Emerging infectious disease: an infectious disease that has (*a*) newly evolved resistance or virulence, (*b*) recently entered humans for the first time, or (*c*) recently substantially increased incidence

The influenza ecological landscape has changed substantially over the past century. The influenza virus ecosystem includes pigs, water fowl, migratory birds, domesticated fowl (mostly chickens), and humans, and the distribution and population density of each of these groups may affect influenza epidemiology. Concentrated animal feeding operations (CAFOs), of pigs, for instance, which have grown substantially more common since 1950, may foster genetic reassortment among influenza viruses (25, 62). Pig husbandry has intensified rapidly in recent decades around the world. In the United States in 1992, 240,000 pig farms raised an average of 945 pigs per farm. By 2004, the number of farms dropped to less than one quarter as many—roughly 70,000—but each farm raised nearly 5 times as many pigs (4,646 per farm) (36). Crowding pigs, especially when they are genetically homogenous, may increase the potential for influenza viruses to infect them, just as plant monocultures may be more vulnerable to crop pests and pathogens. Once pigs in a CAFO become infected, influenza viruses may swap strands of genetic material (26).

Pandemics such as the 2009 H1N1 influenza, in which pathogens move from animals into humans, often referred to as pathogen "spillover" (56), have become increasingly more common in recent decades. Of 335 emerging infectious disease events Jones et al. (32) examined between 1940 and 2004, 60% were zoonoses, and of these, just over 70% entered humans from wildlife. Such data beg the question of whether biodiversity loss may predispose to disease emergence given the rapid rate of species extinctions in the latter half of the twentieth century. A review by Keesing et al. (34) found that given available evidence, biodiversity loss tends to favor disease transmission.

Spillover also contributes to the spread of antibiotic-resistant pathogens. Fluoroquinolone-resistant *Campylobacter jejuni* and methicillin-resistant *Staphylococcus aureus*, as examples, have been transmitted to humans from chickens and pigs, respectively, that have been given antibiotics as part of husbandry (28, 45). In the United States, an estimated 80% of antibiotics are given to livestock each year, with the remainder given mostly to humans (79).

Most of the antibiotic resistance present in human pathogens, however, derives from human use of antimicrobials, and antibiotic resistance in bacteria and other pathogens exacts a large share of the global annual total of DALYs. Rates of antibiotic resistance in *Streptococcus pneumoniae* and *Haemophilus influenza*, for instance, two of the most common causes of the lower respiratory tract infections that exact the second highest number of DALYs annually (53), have increased under antibiotic pressure (21) as have those of *Mycobacterium tuberculosis* (18). Of ~12 million new cases of tuberculosis each year, roughly 4% are multidrug resistant (MDR). For those who contract tuberculosis and have received treatment in the past, the statistic jumps to 20% (86). Some organisms, such as Gram-negative bacteria that possess the New Delhi metallo-beta-lactamase-1 (NDM-1), or extensively drug-resistant (XDR) tuberculosis, have become so resistant that they thwart nearly all available medical remedies (42, 48).

Although the genes that code for microbial resistance to antibiotics have been around at least since the last ice age, and perhaps for millions if not billions of years (17), their prevalence has changed substantially since human production of antibiotics began. Rather than a problem related to an absolute loss of biodiversity—and specifically genetic diversity—antibiotic resistance reflects a diminution of genetic evenness, or a skewing of the relative abundance of genes in a population. The example of antibiotic resistance serves to illustrate the point that an absolute loss in biodiversity is not necessary to realize harms to human health.

In light of the evidence that alterations to, and in some instances outright reductions of, biodiversity have been driving pathogen spillover and an overall increase in emerging infectious diseases, research has begun to look at where such events are most likely to occur. Zoonotic pathogens occur most often in the tropics, with distributions largely confined to their animal

TREATING MICROBES WITH MICROBES

Microorganisms used alone or in combination have become a compelling new approach for both treatment and prevention of certain infections. Fecal transplantation for treatment of refractory cases of *Clostridium difficile* colitis (akin to transfaunation in veterinary medicine, which has been performed for decades) and ulcerative colitis reveals how previously untreatable diseases may have microbial cures (9, 35).

Another intriguing example of the power of harnessing life's diversity to combat disease comes from the use of *Wolbachia*, a genus of rickettsial bacteria. *Wolbachia* species inhabit the reproductive gametes of perhaps as many as 70% of arthropods, as well as those of many nematodes, in some cases fully integrating their DNA into the host genome (20, 29). The relationships these bacteria have established with their hosts over their 50-million-year history, which range from parasitic to symbiotic, have been seized on as vehicles to limit the spread of and damages from certain infectious diseases.

More than 200 million people are infected with parasitic roundworms that cause lymphatic filiriasis and river blindness. *Wolbachia* infect these roundworms and contribute to the disease process. In the case of onchocerciasis, the worm appears to be the vehicle for *Wolbachia* to enter the body and cause blindness (59). Treatment of patients with lymphatic filiriasis and onchocerciasis with tetracyclines has shown to reduce lymphatic swelling and the chances of blindness, respectively, presumably through decreasing populations of *Wolbachia* (71).

Targeting *Wolbachia's* arthropod connections has also been a promising therapeutic strategy. *Wolbachia* infect *Anopholes* and *Aedes* mosquitos that transmit malaria and dengue fever, respectively. *Wolbachia* infection in *Aedes* inhibits mosquitos' ability to transmit the pathogen (8). For malaria, which ranks seventh among causes of DALYs worldwide, *Wolbachia* infection of *A. stephensii* conferred resistance to the malarial parasite *Plasmodium falciparum* (6).

hosts' ranges. [In contrast, nonzoonotic infectious diseases tend to occur wherever humans live (67).] Even if zoonotic diseases may most often be found in the tropics, outbreaks are most often discovered in temperate regions, particularly in developed countries, likely because of reporting bias, trade routes, and travel hubs (32, 66).

The Emerging Pandemic Threats program, funded through the US Agency for International Development, is a new and promising initiative that has the ambitious goal of preempting zoonotic disease emergence. Thus far, more than 200,000 samples have been obtained from 20,000 animals from 20 developing countries, and 150 novel viruses have been identified from viral families known to cause disease (50). Data obtained from this research is being analyzed to further clarify the circumstances in which disease emergence is most likely to occur.

Combing through the excreta and sera of animals around the world in search of the next great pandemic—an exercise in trying to find the proverbial needle in the haystack—has become a legitimate response to the increased frequency of pathogen spillover. However, as the examples of H1N1 influenza, severe acute respiratory syndrome (SARS), HIV, and other infections that have recently spread from wildlife into humans attest, pathogen identification alone will not forestall disease emergence. A nuanced appreciation for the relationships among pathogens, the many life forms they encounter, and the places they inhabit—in short, understanding the biodiversity relevant to infectious disease spread and how changes to the built environment may affect that biodiversity—is likewise essential to the prevention of zoonotic disease outbreaks.

BIODIVERSITY AND HEALTH IN THE TWENTY-FIRST CENTURY

The rapid and ongoing simplification of the biosphere in the past 100 years has occurred primarily because of the degradation or outright destruction of habitats, be it from deforestation, the draining

of wetlands, pollution, or other causes. In the next 100 years, climate change, in the absence of substantial mitigation of greenhouse gas emissions, may surpass habitat loss as the leading cause of biodiversity loss. Predictions of species extinctions due to climate change alone vary but may be more than 30% by 2100 for species on land (72). As the biosphere has been depleted, and along with it many of its health-giving services, technological fixes have patched the gaps.

Prokaryote: a single-celled organism characterized by the absence of a distinct, membrane-bound nucleus or membrane-bound organelles, and by DNA that is not organized into chromosomes

Gnotobiotic mice: mice reared with just a few strains of bacteria and other microorganisms present

Innovation, however, is sporadic and the calculus of investing in it versus protecting the biodiversity it replaces is as complex as humanity has ever faced. From the perspective of recent history, technological advancement has more than outpaced biological decline, and the human species is doing far better today even if the rest of nature is not. All those concerned with the health of people must then ask, will our species be able to engineer itself a secure place in the fraying tapestry of life? Bearing on this question is the reality that whereas human ideas may come and go, be tinkered with, improved on if inadequate, or recanted if found to be false, once biodiversity is lost, it is gone forever. The paucity of knowledge about the relationships among organisms, let alone their identities, and that our species has evolved as part of the earth's singular web of life, upon which, for better or worse, health utterly depends, are reasons for all people, and especially those directly concerned with ensuring human health, to take heed of nature's upheaval and act judiciously to conserve the biodiversity necessary for human welfare.

APPENDIX 1: MICROBIAL DIVERSITY, THE HUMAN MICROBIOME, AND HEALTH

Single-celled prokaryotes intimately colonize all multicellular life on earth, and humans are no exception. Only recently has the veil been pulled back on the human microbiome, the consortium of microorganisms that cohabit the human body, to reveal its diversity. An estimated 10,000 species with 8 million protein-coding genes (that is roughly 360 times the number of protein-coding genes in the "human" genome) can be found in the average human's microbiome (30). In this new frontier of exploration into human life, much has already been learned about how alterations to the diversity of the microbiome can affect human health.

In the twenty-first century, noncommunicable diseases exact the greatest share of DALYs in the global burden of disease studies (53), and for many of these diseases, changes to the diversity of the microbiome have contributed. Kwashiorkor, a pernicious form of severe malnutrition characterized by edema, hepatic steatosis, and anorexia, had long and mistakenly been thought to result from inadequate protein intake. Smith et al. (68) recently reported on research they had conducted with Malawian twins who suffered from kwashiorkor. They discovered that those affected with kwashiorkor had different intestinal flora than did their healthy twin siblings and that the intestinal microbiome of affected children had an atypical maturation pattern with age.

In further experiments, Smith et al. gave gnotobiotic mice fecal transplants from children with kwashiorkor. These mice lost weight when fed a typical Malawian diet, whereas those given a gut flora from healthy Malawians did not. Remarkably, although mice transplanted with the kwashiorkor flora and then fed ready-to-use therapeutic food (the standard nutritional therapy most often used in such settings) gained weight, they failed to maintain it once a Malawian diet was resumed (68). Further investigation into the cause of persistent weight loss in the face of seemingly adequate nutrition uncovered that the gut flora in children with kwashiorkor may interfere with the tricarboxylic acid cycle, which occurs in the mitochondrial matrix [the mitochondria itself is a descendent of alphaproteobacteria (73)], a finding that if validated, suggests a fascinating new dimension of metabolic symbiosis between humans and our microbial symbionts.

This discovery has prompted broad, new thinking about remedying undernourishment. As one example, severely malnourished Malawian children were administered the relatively

narrow-spectrum antibiotics amoxicillin and cefdinir. As a result, they were more likely to recover weight (their z-scores went above −2) and were less likely to die than were those who received a placebo (74).

As much as undernourishment has beset human health in the past, and as much as has been discovered about how changes to human microbial diversity may influence it, overnourishment, having already become an immense public health burden in the developed world, is well on its way to becoming a leading cause of morbidity and mortality globally. Just as with undernourishment, alterations to the microbiome have likely been affecting the prevalence of overweight and obesity as well. Starting with seminal papers by Ruth Ley, Peter Turnbaugh, and colleagues in 2006 (39, 76) that found obese mice had categorically different assemblages of microbes in their intestines as compared with lean mice, and that these microbes had increased capacity for energy harvest from their diets, a bevy of research has ensued on the contributions of the intestinal microbiome to obesity. Overweight people tend to have distinctive intestinal microbial ecosystems as well. Their intestinal bacteria are overall less diverse than in people of normal body weight, and those bacteria that are present have a relative oversupply of genes involved in carbohydrate and fat metabolism (75), which may contribute to intestinal inflammation and insulin resistance (38).

Given these and other observed differences between the intestinal microbiomes of lean and overweight people, further studies have asked how an obesity-associated microbiome may affect weight loss. Santacruz et al. (60), for example, put a group of 36 obese adolescents on a strict diet and exercise regimen. All subjects lost weight, but those who lost the most weight were more likely to have *Bacteroides fragilis* and *Lactobacillus* spp, present in their feces and less likely to have constituents from the *Clostridium coccoides* group.

Rates of obesity have nearly doubled since 1980 and more than half a billion people alive today are obese. Obesity claims 3 million lives worldwide each year. Tackling this immense public health problem will require attention to diet and exercise, and, evidence is suggesting, greater attention to the intestinal microbiome.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Aizen MA, Garibaldi LA, Cunningham SA, Klein AM. 2009. How much does agriculture depend on pollinators? Lessons from long-term trends in crop production. *Ann. Bot.* 103(9):1579–88
2. Allen MF, Boosalis MG. 1983. Effects of two species of VA mycorrhizal fungi on drought tolerance of winter wheat. *New Phytol.* 93(1):67–76
3. Andreas B, Martin P. 2006. The most widespread symbiosis on Earth. *PLoS Biol.* 4(7):e239
4. Barnosky AD, Matzke N, Tomiya S, Wogan GOU, Swartz B, et al. 2011. Has the Earth's sixth mass extinction already arrived? *Nature* 471(7336):51–57
5. Bernard C. 1865. *Introduction a l'étude de la médecine expérimentale*. Paris: J-B Baillière Fils
6. Bian G, Joshi D, Dong Y, Lu P, Zhou G, et al. 2013. *Wolbachia* invades *Anopheles stephensi* populations and induces refractoriness to *Plasmodium* infection. *Science* 340(6133):748–51
7. Black R, Cousens S, Johnson H, Lawn J, Rudan I, et al. 2010. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 375(9730):1969–87
8. Blagrove MSC, Arias-Goeta C, Failloux A-B, Sinkins SP. 2012. *Wolbachia* strain *w*Mel induces cytoplasmic incompatibility and blocks dengue transmission in *Aedes albopictus*. *Proc. Natl. Acad. Sci. USA* 109(1):255–60

9. Borody TJ, Warren EF, Leis S, Surace R, Ashman O. 2003. Treatment of ulcerative colitis using fecal bacteriotherapy. *J. Clin. Gastroenterol.* 37(1):42–47
10. Boyles JG, Cryan PM, McCracken GF, Kunz TH. 2011. Conservation. Economic importance of bats in agriculture. *Science* 332(6025):41–42
11. Burkle LA, Marlin JC, Knight TM. 2013. Plant-pollinator interactions over 120 years: loss of species, co-occurrence, and function. *Science* 339(6127):1611–15
12. Calderone NW. 2012. Insect pollinated crops, insect pollinators and US agriculture: trend analysis of aggregate data for the period 1992–2009. *PLoS One* 7(5):e37235
13. Campagnac E, Fontaine J, Lounès-Hadj Sahraoui A, Laruelle F, Durand R, Grandmougin-Ferjani A. 2009. Fenpropimorph slows down the sterol pathway and the development of the arbuscular mycorrhizal fungus *Glomus intraradices*. *Mycorrhiza* 19(6):365–74
14. Chapman AD. 2009. *Numbers of Living Species in Australia and the World*. Canberra: Rep. Aust. Biol. Resourc. Study Canberra, Aust., Sept.
15. Cossani CM, Reynolds MP. 2012. Physiological traits for improving heat tolerance in wheat. *Plant Physiol.* 160(4):1710–18
16. Cragg GM, Newman DJ. 2013. Natural products: a continuing source of novel drug leads. *Biochim. Biophys. Acta* 1830(6):3670–95
17. D'Costa VM, King CE, Kalan L, Morar M, Sung WWL, et al. 2011. Antibiotic resistance is ancient. *Nature* 477(7365):457–61
18. Dalton T, Cegielski P, Akksilp S, Asencios L, Campos Caoili J, et al. 2012. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet* 380(9851):1406–17
19. Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, et al. 2012. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect. Dis.* 12(9):687–95
20. Dunning Hotopp JC, Clark ME, Oliveira DCSG, Foster JM, Fischer P, et al. 2007. Widespread lateral gene transfer from intracellular bacteria to multicellular eukaryotes. *Science* 317(5845):1753–56
21. Felmingham D, White AR, Jacobs MR, Appelbaum PC, Poupard J, et al. 2005. The Alexander Project: the benefits from a decade of surveillance. *J. Antimicrob. Chemother.* 56(Suppl. 2):3–21
22. Feng G, Zhang FS, Li XL, Tian CY, Tang C, Rengel Z. 2002. Improved tolerance of maize plants to salt stress by arbuscular mycorrhiza is related to higher accumulation of soluble sugars in roots. *Mycorrhiza* 12(4):185–90
23. Gallai N, Salles J-M, Settele J, Vaissière BE. 2009. Economic valuation of the vulnerability of world agriculture confronted with pollinator decline. *Ecol. Econ.* 68(3):810–21
24. Garibaldi LA, Steffan-Dewenter I, Winfree R, Aizen MA, Bommarco R, et al. 2013. Wild pollinators enhance fruit set of crops regardless of honey bee abundance. *Science* 339(6127):1608–11
25. Gilchrist MJ, Greko C, Wallinga DB, Beran GW, Riley DG, Thorne PS. 2007. The potential role of concentrated animal feeding operations in infectious disease epidemics and antibiotic resistance. *Environ. Health Perspect.* 115(2):313–16
26. Gray GC, Baker WS. 2011. The problem with pigs: It's not about bacon. *Clin. Infect. Dis.* 52(1):19–22
27. Grube A, Donaldson D, Kiely T, Wu L. 2011. *Pesticide Industry Sales and Usage: 2006–2007 Market Estimates.* Washington, DC: US Environ. Prot. Agency. **http://www.epa.gov/opp00001/pestsales/07pestsales/market_estimates2007.pdf**
28. Harrison EM, Paterson GK, Holden MTG, Larsen J, Stegger M, et al. 2013. Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel mecA homologue mecC. *EMBO Mol. Med.* 5(4):509–15
29. Hilgenboecker K, Hammerstein P, Schlattmann P, Telschow A, Werren JH. 2008. How many species are infected with *Wolbachia*? A statistical analysis of current data. *FEMS Microbiol. Lett.* 281(2):215–20
30. Hum. Microbiome Proj. Consort. 2012. Structure, function and diversity of the healthy human microbiome. *Nature* 486(7402):207–14
31. Int. Union Conserv. Nat. 2012. *Numbers of threatened species by major groups of organisms* (*1996–2012*). IUCN Red List v. 2012:2. **http://www.iucnredlist.org/documents/summarystatistics/2012_2_RL_Stats_Table_1.pdf**

32. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, et al. 2008. Global trends in emerging infectious diseases. *Nature* 451(7181):990–93
33. Kabir Z. 2005. Tillage or no-tillage: impact on mycorrhizae. *Can. J. Plant Sci.* 85(1):23–29
34. Keesing F, Belden LK, Daszak P, Dobson A, Harvell CD, et al. 2010. Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature* 468(7324):647–52
35. Kelly CR, de Leon L, Jasutkar N. 2012. Fecal microbiota transplantation for relapsing *Clostridium difficile* infection in 26 patients: methodology and results. *J. Clin. Gastroenterol.* 46(2):145–49
36. Key N, McBride W. 2007. The changing economics of U.S. hog production. *Econ. Res. Rep. No. ERR-52.* Econ. Res. Serv., U.S. Dep. Agric.
37. Krogh A. 1929. The progress of physiology. *Am. J. Physiol.* 90(2):243–51
38. Ley RE. 2010. Obesity and the human microbiome. *Curr. Opin. Gastroenterol.* 26(1):5–11
39. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. 2006. Microbial ecology: human gut microbes associated with obesity. *Nature* 444(7122):1022–23
40. Li L, Li S-M, Sun J-H, Zhou L-L, Bao X-G, et al. 2007. Diversity enhances agricultural productivity via rhizosphere phosphorus facilitation on phosphorus-deficient soils. *Proc. Natl. Acad. Sci. USA* 104(27):11192–96
41. Lin BB. 2011. Resilience in agriculture through crop diversification: adaptive management for environmental change. *BioScience* 61(3):183–93
42. LoBue P, Sizemore C, Castro KG. 2009. Plan to combat extensively drug-resistant tuberculosis: recommendations of the Federal Tuberculosis Task Force. *MMWR. Recomm. Rep.* 58(RR-3):1–43
43. LoGiudice K, Ostfeld RS, Schmidt KA, Keesing F. 2003. The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk. *Proc. Natl. Acad. Sci. USA* 100(2):567–71
44. Manavalan LP, Guttikonda SK, Tran L-S, Nguyen HT. 2009. Physiological and molecular approaches to improve drought resistance in soybean. *Plant Cell Physiol.* 50(7):1260–76
45. Marshall BM, Levy SB. 2011. Food animals and antimicrobials: impacts on human health. *Clin. Microbiol. Rev.* 24(4):718–33
46. Mathew RP, Feng Y, Githinji L, Ankumah R, Balkcom KS. 2012. Impact of no-tillage and conventional tillage systems on soil microbial communities. *Appl. Environ. Soil Sci.* 2012:1–10
47. Mishra KK, Vikram P, Yadaw RB, Swamy BPM, Dixit S, et al. 2013. qDTY12.1: a locus with a consistent effect on grain yield under drought in rice. *BMC Genet.* 14:12
48. Moellering RC Jr. 2010. NDM-1—a cause for worldwide concern. *N. Engl. J. Med.* 363(25):2377–79
49. Mora C, Tittensor DP, Adl S, Simpson AGB, Worm B. 2011. How many species are there on Earth and in the ocean? *PLoS Biol.* 9(8):e1001127
50. Morse SS, Mazet JAK, Woolhouse M, Parrish CR, Carroll D, et al. 2012. Prediction and prevention of the next pandemic zoonosis. *Lancet* 380(9857):1956–65
51. Mt. Pleasant J, Burt RF. 2010. Estimating productivity of traditional Iroquoian cropping systems from field experiments and historical literature. *J. Ethnobiol.* 30(1):52–79
52. Murillo-Williams A, Pedersen P. 2008. Arbuscular mycorrhizal colonization response to three seed-applied fungicides. *Agronomy J.* 100(3):795–800
53. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, et al. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380(9859):2197–223
54. Newman DJ, Cragg GM. 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J. Nat. Prod.* 75(3):311–35
55. Ostfeld RS, Keesing F. 2012. Effects of host diversity on infectious disease. *Annu. Rev. Ecol. Evol. Syst.* 43(1):157–82
56. Parrish CR, Holmes EC, Morens DM, Park E-C, Burke DS, et al. 2008. Cross-species virus transmission and the emergence of new epidemic diseases. *Microbiol. Mol. Biol. Rev.* 72(3):457–70
57. Pimm SL, Russell GJ, Gittleman JL, Brooks TM. 1995. The future of biodiversity. *Science* 269(5222):347–50
58. Ratnieks FLW, Carreck NL. 2010. Ecology. Clarity on honey bee collapse? *Science* 327(5962):152–53
59. Saint André A, von Blackwell NM, Hall LR, Hoerauf A, Brattig NW, et al. 2002. The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. *Science* 295(5561):1892–95

60. Santacruz A, Marcos A, Wärnberg J, Martí A, Martin-Matillas M, et al. 2009. Interplay between weight loss and gut microbiota composition in overweight adolescents. *Obesity* 17(10):1906–15
61. Schlenker W, Roberts MJ. 2009. Nonlinear temperature effects indicate severe damages to U.S. crop yields under climate change. *Proc. Natl. Acad. Sci. USA* 106(37):15594–98
62. Schmidt CW. 2009. Swine CAFOs and novel H1N1 flu: separating facts from fears. *Environ. Health Perspect.* 117(9):A394–401
63. Schmidt KA, Ostfeld RS. 2001. Biodiversity and the dilution effect in disease ecology. *Ecology* 82(3):609–19
64. Schneider CW, Tautz J, Grünewald B, Fuchs S. 2012. RFID tracking of sublethal effects of two neonicotinoid insecticides on the foraging behavior of *Apis mellifera*. *PLoS One* 7(1):e30023
65. Schubert S, Neubert A, Schierholt A, Sümer A, Zörb C. 2009. Development of salt-resistant maize hybrids: the combination of physiological strategies using conventional breeding methods. *Plant Sci.* 177(3):196–202
66. Smith KF, Guégan J-FJ. 2010. Changing geographic distributions of human pathogens. *Annu. Rev. Ecol. Evol. Syst.* 41(1):231–50
67. Smith KF, Sax DF, Gaines SD, Guernier V, Guégan J-F. 2007. Globalization of human infectious disease. *Ecology* 88(8):1903–10
68. Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, et al. 2013. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science* 339(6119):548–54
69. Smith SE, Smith FA. 2011. Roles of arbuscular mycorrhizas in plant nutrition and growth: new paradigms from cellular to ecosystem scales. *Annu. Rev. Plant Biol.* 62:227–50
70. Taylor LH, Latham SM, Woolhouse ME. 2001. Risk factors for human disease emergence. *Philos. Trans. R. Soc. B* 356(1411):983–89
71. Taylor MJ, Hoerauf A, Bockarie M. 2010. Lymphatic filariasis and onchocerciasis. *Lancet* 376(9747):1175–85
72. Thomas C, Cameron A, Green R. 2004. Extinction risk from climate change. *Nature* 427(6970):145–48
73. Thrash JC, Boyd A, Huggett MJ, Grote J, Carini P, et al. 2011. Phylogenomic evidence for a common ancestor of mitochondria and the SAR11 clade. *Sci. Rep.* 1:13
74. Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, et al. 2013. Antibiotics as part of the management of severe acute malnutrition. *N. Engl. J. Med.* 368(5):425–35
75. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, et al. 2009. A core gut microbiome in obese and lean twins. *Nature* 457(7228):480–84
76. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444(7122):1027–31
77. US Dep. Agric. 2013. *Honey bees and colony collapse disorder*. Agric. Res. Serv., Washington, DC. **http://www.ars.usda.gov/News/docs.htm?docid=15572**
78. US Fish Wildl. Serv. 2013. *North American bat death toll exceeds 5.5 million from white-nose syndrome*. News release, Jan. 17, US Fish Wildl. Serv., Washington, DC. **http://www.fws.gov/northeast/feature_archive/Feature.cfm?id=794592078**
79. US Food Drug Adm. Cent. Vet. Med. 2013. *2011 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*. Silver Spring, MD: US FDA
80. US Geol. Surv. 2013. *White-nose syndrome* (*WNS*). Natl. Wildl. Health Cent., Madison, Wis. **http://www.nwhc.usgs.gov/disease_information/white-nose_syndrome/**
81. Van Kerkhove MD, Hirve S, Koukounari A, Mounts AW. 2013. Estimating age-specific cumulative incidence for the 2009 influenza pandemic: a meta-analysis of A(H1N1)pdm09 serological studies from 19 countries. *Influenza Other Respir. Viruses* 7(5):872–95
82. Warnecke L, Turner JM, Bollinger TK, Lorch JM, Misra V, et al. 2012. Inoculation of bats with European *Geomyces destructans* supports the novel pathogen hypothesis for the origin of white-nose syndrome. *Proc. Natl. Acad. Sci. USA* 109(18):6999–7003
83. Whitaker JO. 1995. Food of the big brown bat *Eptesicus fuscus* from maternity colonies in Indiana and Illinois. *Am. Midl. Nat.* 134(2):346–60
84. Whittaker RH. 1969. New concepts of kingdoms or organisms. Evolutionary relations are better represented by new classifications than by the traditional two kingdoms. *Science* 163:150–60

85. Woese CR, Fox GE. 1977. Phylogenetic structure of the prokaryotic domain: the primary kingdoms. *Proc. Natl. Acad. Sci. USA* 74(11):5088–90
86. World Health Organ. (WHO). 2012. *Global Tuberculosis Report 2012*. Geneva: WHO
87. World Health Organ. (WHO). 2009. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks*. Geneva: WHO
88. Yu S, Liao F, Wang F, Wen W, Li J, et al. 2012. Identification of rice transcription factors associated with drought tolerance using the ecotilling method. *PLoS One* 7(2):e30765
89. Zhu Y, Chen H, Fan J, Wang Y, Li Y, et al. 2000. Genetic diversity and disease control in rice. *Nature* 406(6797):718–22