FROM OUTSIDE to INSIDE:
Environmental Microorganisms as Human Pathogens

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The American Academy of Microbiology convened a colloquium February 6-8, 2004, in Portland, Oregon, to discuss environmental pathogens and the current state of research on these organisms. Scientists with expertise in infectious diseases, food microbiology, bacteriology, molecular biology, microbial ecology, pathogenic mycology, and other areas in the microbiological sciences participated. Participants considered the knowledge gaps related to the incidence and epidemiology of environmental infectious diseases, dynamics of human pathogens in our surroundings, ways to alleviate environmental infectious diseases, research needs in the field, and education and communication issues. Recommendations were made for how to proceed on these fronts.

Environmental pathogens are defined as microorganisms that normally spend a substantial part of their lifecycle outside human hosts, but when introduced to humans cause disease with measurable frequency. They are borne in the water, soil, air, food, and other elements of our surroundings, and they affect almost every individual on the planet. Their adverse effects on human health and productivity cannot be controlled without first obtaining a thorough understanding of their environmental niches, their incidence, and the epidemiology of the diseases they cause. To achieve this understanding, surveillance of the environment to determine the numbers and distribution of environmental pathogens is needed, as is research into the microbial virulence and host factors that enable microbes to invade and damage human hosts.

The key difference between environmental pathogens and other human pathogens is their ability to survive and thrive outside the host. Their widespread occurrence in the environment makes them difficult to monitor and control. Inroads have been made to understand the persistence of these organisms in the environment, the reservoirs they inhabit, the ways they exchange virulence factors, and their diversity, but a great deal more research is needed. By grouping together phylogenetically diverse organisms under the umbrella of “environmental pathogens,” it is hoped that the topic can gain the critical mass needed for sustained progress.

Colloquium participants examined other research needs for the field, including the diagnostic and environmental technologies that will be necessary for taking the next steps. It was agreed that because of the complex nature of studying organisms that can exist in the environment and in human hosts, work in this area is best carried out in an interdisciplinary fashion with coordinated input from medical, molecular, and environmental microbiologists, specialists in host responses, epidemiologists, ecologists, environmental engineers, and public health experts. The development of improved diagnostic techniques is critical for accurate assessment of health risks and potential human or animal population impact associated with environmental pathogens.
Introduction

In July 1976, over 4,000 World War II veterans from all over the United States converged on the Bellevue Stratford Hotel in Philadelphia for the bicentennial convention of the American Legion. A week after they arrived, several Legionnaires, as they are known, began to develop the same symptoms: chest pain, fever, lung congestion, and pneumonia. Influenza was ruled out. Public health officials, faced with mounting public anxiety, were forced to admit that the cause of the disease could not be identified. After months of investigation, the causative agent of the disease was found to be a common bacterium, later named Legionella pneumophila, often found in natural aquatic systems. Somehow, L. pneumophila had found its way into the air conditioning cooling towers at the Bellevue Stratford, enabling it to be spread as an aerosol throughout the hotel. A total of 221 hotel visitors eventually developed the disease, which was named for its first recognized victims. Today, Legionnaires’ disease continues to strike between 8,000 and 18,000 people in the United States every year, usually in the summer and fall months. Also known as Legionellosis, the disease kills 5%-30% of those afflicted.

In the summer of 1999, a new disease arrived in United States. Victims suffered symptoms that ranged from mild flu-like symptoms to encephalitis, or swelling of the brain, a condition that is often fatal. The causative agent was identified as the West Nile Virus, a mosquito-borne pathogen endemic to Africa, the Middle East, and central and southern Europe. Just five years after the first U.S. cases were identified, West Nile Virus infections have been reported in all continental United States, except Oregon and Washington. In the 2003 mosquito season alone, 9,862 West Nile cases were reported to the Centers for Disease Control and Prevention. Over 260 of these individuals died as a result of their infections.

Every year, thousands of Americans develop a parasitic infection that can bring on diarrhea, stomach cramps, vomiting, and fever. The organism responsible, Cryptosporidium parvum, is a common parasite that resides in food, drinking water, and recreational waters. Chlorine-resistant strains of Cryptosporidium have been isolated from swimming pools with increasing frequency in recent years. Cryptosporidiosis is now considered one of the most common waterborne diseases in the U.S. and abroad.

These organisms have something in common. They are all environmental pathogens—organisms that normally spend a substantial part of their lifecycle outside human hosts, but when introduced to susceptible humans cause disease with measurable frequency. The world around us has a complex and dense content of microbes, including parasites, fungi, bacteria and viruses, and only a tiny fraction have been cataloged. Most cannot be grown in the laboratory today. The vast majority of these microbes are not capable of causing human disease, but the few microorganisms referred to as “environmental pathogens” pose significant threats to human health.

Virulence is the result of an evolved strategy for replication within a host that unavoidably causes pathology, e.g., because the preferred site for persistence or replication within the host is a “privileged” site, or because the evolved mechanisms for subverting or avoiding host defenses result in host damage. These replication strategies are rare among organisms that have not evolved in close contact with humans or closely-related hosts. However, a number of known human primary pathogens (those that commonly cause disease in normal hosts) and opportunistic pathogens (those that only cause disease in impaired hosts) exist primarily in the external environment, and there are reasons to believe that there are also currently-recognized pathogens that reside primarily in the external environment. These environmental pathogens cause disease in normal or immunocompromised humans when acquired from food, air, water, soil, living reservoirs, and vectors.

These threats to human health can only be assessed in a comprehensive multidisciplinary context in which ecology, epidemiology, and emerging areas in environmental engineering and microbiology are integrated. This combined approach can yield immediate and long-term health benefits by mitigating established environmental risks, identifying risky situations for disease emergence, and finding the causes of diseases of unknown etiology.

Environmental pathogens can be found in almost all the microbial phylogenetic groups, including bacteria, protozoa, and viruses (See Table 1).

Where Environmental Pathogens Are Found

Microbes surround us. They exist on almost every surface and in almost every liquid, and we interact with them continually. Environmental pathogens occur in a range of environments that, for practical purposes, can be divided into seven habitat types: water, food, soil, air, vectors, living reservoirs, and products of human activity.

• Aquatic Environments: Many environmental pathogens, including Legionella pneumophila, Mycobacterium avium complex (MAC), and Vibrio cholerae thrive in aquatic environments. Environmental pathogens can exist in human drinking water supplies, recreational water (including fresh water, sea water, and even chlorinated systems), wastewater, air conditioning cooling towers, recirculating hot water systems, and other water systems.

• Food: Food can also serve as a habitat for environmental pathogens. Today, the picture of environmental pathogens in food is complicated by the global network of food supply and transportation. Changes in food harvesting, processing, handling, and livestock feeding practices can introduce new routes of infection and new pathogens to the food supply. Foodborne pathogens include Listeria monocytogenes, Escherichia coli O157:H7, and Campylobacter jejuni.

• Soil: A number of human pathogens, including the common fungal pathogens Histoplasma, Coccidioides,
and Aspergillus fumigatus, can spend part of their lifecycle in soil. Soil-borne pathogens can be affected by soil saturation, local geography, and by climatic and other environmental disturbances.

- **Air:** Pathogens in soil or other environments may also become airborne and can be found in indoor or outdoor air. Climatic events, like dust storms, can distribute airborne pathogens on a global scale.

- **Vectors:** Pathogen vectors are defined as organisms that play an active role in transmitting a pathogen. For human diseases, vectors are usually biting insects, including mosquitoes, fleas, and ticks, which can transmit West Nile Virus, plague, and Lyme disease, respectively. Vectors may also serve as reservoirs (see below). Various arthropod vectors (e.g., mites, sand flies, and mosquitoes) can transovarially transmit pathogens from one generation to the next so that the next generation is able to transmit at their initial blood feedings.

- **Living Reservoirs:** Living reservoirs are organisms in which a pathogen lives and multiplies without damaging the host. Reservoirs may include vectors, or may include organisms that do not actively participate in transmission of the disease to humans. Beavers, for example, can harbor the parasite Giardia lamblia without exhibiting signs of illness. Life in nonhuman reservoirs may help some pathogens to maintain their abilities to infect humans.

- **Products of Human Activity:** Products of human activity, including dwellings and fomites (objects on which pathogens are deposited and transmitted to

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
<th>Clinical Signs*</th>
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<tbody>
<tr>
<td><em>Bacteria</em></td>
<td></td>
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<tr>
<td>Vibrio cholerae</td>
<td>Cholera</td>
<td>Diarrhea</td>
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<tr>
<td>Vibrio parahaemolyticus</td>
<td>Gastroenteritis; wound infection; septicemia</td>
<td>Diarrhea, abdominal pain, nausea, vomiting, headache, fever</td>
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<tr>
<td>Campylobacter species</td>
<td>Gastroenteritis</td>
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<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td>Pulmonary, localized, or disseminated MAC</td>
<td>Lymphadenitis and tuberculosis-like diseases</td>
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<td>Coxiella burnetti</td>
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<td>Pneumonia</td>
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<tr>
<td>Legionella species</td>
<td>Legionnaire's disease</td>
<td>Pneumonia</td>
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<tr>
<td>Rickettsia typhi</td>
<td>Endemic typhus</td>
<td>Fever</td>
</tr>
<tr>
<td>Bartonella hensleii</td>
<td>Cat scratch disease</td>
<td>Swollen lymph nodes, fever</td>
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<tr>
<td>Borrelia burgdorferi</td>
<td>Lyme disease</td>
<td>Fever, rash, arthritis</td>
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<td>Listeria monocytogenes</td>
<td>Listeriosis</td>
<td>Gastroenteritis, meningitis, spontaneous abortions, neonatal sepsis</td>
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<tr>
<td>Bacillus anthracis</td>
<td>Anthrax</td>
<td>Fever, respiratory illness</td>
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<td>Burkholderia cepacia</td>
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<td>Pneumonia</td>
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<tr>
<td><em>Viruses</em></td>
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<td>SARS virus</td>
<td>Severe Acute Respiratory Syndrome</td>
<td>Pneumonia</td>
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<td>Influenza viruses</td>
<td>Flu</td>
<td>Fever, cough, headache</td>
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<td>West Nile virus</td>
<td>West Nile fever, encephalitis</td>
<td>Fever, headache, altered mental status</td>
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<tr>
<td>Hantavirus</td>
<td>Hantavirus pulmonary syndrome or Hemorrhagic fever</td>
<td>Cardiopulmonary or renal malfunction</td>
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<tr>
<td><em>Eukaryotes</em></td>
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<tr>
<td>Histoplasma capsulatum</td>
<td>Histoplasmosis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Coccidioides immitis/posadasii</td>
<td>Valley fever</td>
<td>Pneumonia, chest pain, fever, cough, malaise</td>
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<tr>
<td>Cryptosporidium parvum</td>
<td>Cryptosporidiosis</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Cryptococcosis</td>
<td>Meningitis, fever, headache</td>
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</table>
humans) can also be home to environmental pathogens.

In addition to the familiar suite of microbes with which we are confronted on a daily basis, altered human interactions with the environment can lead to exposure to new pathogens. For example, the organism responsible for Lyme disease, *Borrelia burgdorferi*, has come into close proximity with human populations in recent decades as suburbanization of wild lands and increased deer populations has forced a closer-than-comfortable relationship between humans and deer. As a result, the deer ticks that spread Lyme disease are now familiar, even in city parks and backyards. The incidence of Lyme disease has now reached epidemic proportions in some regions. Other changes that have brought new microbes to our doorstep include advances in transportation, which have allowed the movement of people, products, foods, and microbes at an unprecedented pace. Global climate change also can be expected to change the landscape of environmental pathogens by altering surface water temperatures and destabilizing weather patterns.

In studying diseases caused by environmental pathogens, scientists are sometimes forced to battle the notion that "what we don't know can't hurt us." Environmental pathogens, which strike many millions of people every year, certainly can hurt us, especially if we remain ignorant about their numbers and patterns of infection. Research into the incidence and epidemiology of environmental diseases is needed to understand the organisms and mechanisms that perpetuate disease and to better gauge the scope of the threat posed by environmental pathogens. These data, in turn, can be applied in risk assessments to develop appropriate responses for combating pathogens in the environment.

**Surveillance**

Surveillance is the key to understanding the incidence and epidemiology of environmental diseases. Accurate counts of the abundance of pathogens in natural environments and the number of cases of environmental disease are needed to enable researchers and public health officials to assess the true scope of the threat posed by these organisms. Surveillance must, therefore, include epidemiological surveillance (systematic collection of the number of cases of human or animal disease) and microbiological surveillance (determining the number of a given organism in the environment). A great deal of useful information can be assembled about a given environmental pathogen or disease from a combined approach of active and passive surveillance and point prevalence studies.

Microbiological surveillance for environmental pathogens should be targeted to specific environments at specific times. Targeting surveillance efforts appropriately requires knowledge of pathogen ecology and of the likely locations of human exposure. Environmental surveillance is needed not only for the known pathogens, but for the ranks of environmental pathogens we have yet to name and characterize. New tools may be required and existing tools improved to detect these organisms. Today, many of the methods available for detection are modifications of clinical procedures developed for other diseases and are not effective in detecting the low densities of pathogens found under most environmental conditions. Moreover, detection methods are needed that can deliver information about the virulence of targeted pathogens.

Methods for reporting and tracking of environmental infectious diseases (e.g., epidemiological surveillance) are in need of improvement. Disease reporting mechanisms in hospitals need to be enhanced to allow scientists and public health officials to track disease trends in real time. Many nations, including the United States, lack a single computerized system for tracking and collecting information on emerging outbreaks of environmental diseases. Such a system would enable the detection of spikes in the incidence of infectious disease and the detection of the emergence of particularly virulent strains. In the absence of a centralized tracking database, better use should be made of existing tools, such as PulseNet, Promed, and the Emerging...
Infections Network. In addition, regional centers are needed on the state level to serve as repositories of the records of all cases of infectious disease. These centers could report to the state or to the Centers for Disease Control and Prevention.

Other important points in surveillance of environmental diseases include monitoring spikes in infections abroad and tracking trends in the environmental diseases of animals, particularly livestock. Also, the emergence of new syndromes that lack an identifiable cause should be investigated thoroughly to determine whether a new infectious environmental agent may be involved.

Surveillance and Virulence Factors
The natural environment is rife with microorganisms, the vast majority of which pose no threat to human health. When conducting surveillance to determine the numbers and types of pathogens present in the environment, it is of paramount importance to distinguish harmless microbes from those that can make us sick. The fundamental difference between them is the expression of virulence factors—cellular products that enable a microbe to colonize or harm its host. Pathogens possess virulence factors; non-pathogens either do not possess them or they possess forms that are not active against humans. The types of virulence factors and their levels of expression can vary greatly between strains. Hence, with the right information in hand, virulence factors can be used to discriminate between human pathogens and non-pathogens and, in some cases, can identify the degree of virulence of pathogenic strains. This predictive strategy has been termed "Virulence Factor-Activity Relationships" (VFAR), similar to the Structure-Activity Relationships (SAR) used to predict the effects of chemical compounds in the environment.

The key virulence genes of environmental pathogens are rarely known. This information is vital to ensuring that the correct organism is targeted in environmental surveillance efforts and in efforts to quantify the risk associated with surveillance results. The dual use of genotyping and phenotyping tools is a feasible goal and could help to identify virulence factors. For example, if the virulence factors associated with a given disease were identified, cutting-edge tools like quantitative genomics could be used to determine the magnitude of the hazard in a specific environment. This approach, measuring the amount of a virulence-associated gene or gene product in the environment, offers an advantage over measuring the numbers of a given pathogen, since not all strains of an organism are equally virulent and a "false positive" identification would conclude that a weakly pathogenic strain poses a high level hazard.

The ability to measure virulence factors can be a powerful resource, since an understanding of the dynamics of the movement of virulence factors in the environment can provide insights into environmental disease in general. However, this tool must be applied with great caution. Many virulence factors are multi-functional, e.g., adhesion factors that may function in the colonization of living as well as non-living surfaces. Moreover, many virulence factors are present and expressed in animal pathogens that do not pose threats to humans. In the absence of information about specific virulence factors that are highly predictive of adverse effects on human health, strain genotyping methods could be applied to identify particular genotypes associated with disease.

Overall, better real-time methods are needed for enumerating the pathogens associated with key diseases. Also, tools are needed that can distinguish between the environmental species responsible for disease (for example, pathogens within fecal contaminants of water and food) from non-pathogenic microbes and can quantify pathogen numbers.

Bioterrorism
The question of intentional release occasionally arises when discussing environmental pathogens because of the relative ease with which some microbes could be employed to create a potential or real threat or even result in disease or death. Environmental pathogens can infect scores of individuals from a single source. They do not necessarily rely on infection by person-to-person contact or on engineered dispersal as is the case with other pathogens. Better information on environmental pathogens is needed to rapidly determine whether a given outbreak is the result of a natural occurrence or an intentional release and to allow public health and emergency officials to respond appropriately.

The fundamental information needed to investigate cases involving suspicious spikes in the incidence of an environmental disease is the baseline rate of infection. This information is not always available, and this limits the ability to investigate seemingly unusual numbers of illness.

The possibility of intentional introduction also makes it necessary to have a grasp of the genetic variability of natural populations of environmental pathogens. When infection rates rise, clinical isolates can be compared against known strains to determine whether the strain responsible for the outbreak can be matched with an environmental source. Such analysis can also identify unusual combinations of genes that might be the hallmark of a biologically engineered pathogen.

Culture Collections
Efforts to monitor the incidence and epidemiology of environmental diseases are greatly facilitated by the availability of strain collections. Among other advantages, the investigation of possible acts of bioterrorism involving environmental pathogens and the identification and tracking of new virulent isolates are facilitated by the comparison of new isolates with previously isolated strains.

Unfortunately, maintenance of strain collections is an expensive proposition. Some of the operating costs can be defrayed by streamlining the process of strain trans-
Climate Change and Environmental Diseases

Climate affects environmental pathogens and diseases in a number of known and, probably, unknown ways. It is anticipated that global climate change will have an impact on these pathogens, creating new problems and diminishing old ones. In uncovering the effects of climate change, it will be necessary to continue to collect accurate disease surveillance data so that weather events can be linked to changes in incidence. Climatological data (precipitation, airborne particulates, surface water temperature, water pH and dissolved oxygen) and microbiological data (disease incidence and microbiological counts in environmental samples) will need to be assessed together to identify correlations.

Improving communication among researchers concerned with environmental pathogens and professionals in other fields will be helpful in uncovering the effects of climate change on environmental disease. The technologies used in remote biosensing, for example, could be adapted to tracking climate and diseases. This will require that the communication gap between biological scientists and engineers be bridged.

Predicting Outbreaks

Predicting outbreaks of environmental disease poses a major challenge to scientists and health workers. Retrospective analyses of data from recent outbreaks can be used to determine the conditions that preceded spikes in incidence, offering hints as to what might trigger the next outbreak. Such modeling efforts may make it possible to prevent outbreaks or at least to allow officials to prepare an appropriate public health response. Also, monitoring trends in human health across the globe can lend insights into the global dissemination of diseases and can allow public health officials to prepare for diseases that may be on the way.

Many recently identified human diseases (for example, Lyme disease) have been linked to animal reservoirs. Therefore, more aggressive tracking of zoonotic diseases may help to predict outbreaks of new diseases of humans.

Reservoirs

Locating the environmental reservoir of a pathogen can be a difficult endeavor. However, identifying the source of a pathogen is the key to controlling infection rates. Identification of reservoirs requires multidisciplinary efforts involving epidemiologists, ecologists, Geographic Information Systems (GIS) specialists, microbiologists, and others.

Persistence

Unlike pathogens that are passed by person-to-person contact or by animal-to-person contact, environmental pathogens must find ways to survive, and possibly to reproduce, in the soil, water, air, and other materials that surround us. They accomplish this through dormancy and the formation of spores, cysts, biofilms, or alternative morphotypes. In some cases, they are part of the normal microbiota in soils and waters, where they grow and divide like any other predominantly environmental organism. Many techniques for survival serve a second purpose, in addition to the ability to cause disease in the host. For example, Legionella pneumophila replicates in the environment by colonizing the cells of aquatic amoebae, an ability that may allow the parasite to infiltrate the cells of human tissues. The mechanisms of environmental persistence are understudied and deserve more research attention.

Antibiotic Resistance

It has been said that the world is a dilute solution of antimicrobial agents. Many such compounds in the environment are produced naturally, most commonly by environmental microbes. All living things make substances to protect themselves from harmful microbes, and these substances exert constant selective pressure on microorganisms within their influence. Other antimicrobial agents in the environment originate from human sources, such as the agricultural use of antibiotics and the discharge of byproducts of antibiotic production. It is not surprising, therefore, that antibiotic resistance has been noted in a number of environmental pathogens that are unlikely to have developed this resistance through clinical exposure.

Some of the ways microbes have found to circumvent the effects of antibiotics in the environment may also confer resistance to antibiotics used in treating human infections. For example, in order to eliminate toxic agents inflicted on them by other organisms, microbes in the
vents attack by immune defenses.

Antibiotic resistance could also be acquired through development of resistance to other substances, like metals, or by horizontal gene transfer between organisms. Horizontal transfer is especially troubling in cases where new resistances can be introduced to environmental pathogens from organisms that acquired resistance from human use of antibiotics. More work is needed to determine the extent of antibiotic resistance in environmental pathogen populations and to distinguish between intrinsic drug resistance acquired in natural environments and human-induced resistances acquired in clinical settings. New drug development is needed to control the human health effects of some intrinsically drug resistant environmental pathogens.

**Virulence factors**

Virulence factors, the abilities that pathogens use to invade or damage a host, are found in all pathogens, but how did they evolve in organisms that spend large parts of their lifecycles in the environment? As with the acquisition of antibiotic resistance, it is unlikely that a single answer to this question exists, but a number of hypotheses and relevant findings can be put forward for consideration.

Parallel selective pressures on pathogens in the environment and in human hosts may have facilitated the crossover of these organisms from the environment to the human body. The formation of biofilms by certain microbes, for example, is an ecological strategy that improves their persistence in certain habitats. This adaptation could help endow environmental microbes with virulence, since biofilm formation in the human lung and other tissues causes illness and often prevents attack by immune defenses.

Adaptations to living within a non-human host or vector may also confer virulence. Legionella pneumophila, for example, lives within the cells of microbial eukaryotes, an adaptation that may have enabled this organism to adapt to life within human macrophages. Vibrio cholerae colonize the surface of zooplankton copepods using bacterial factors that also contribute to colonization of the human intestine. Possible mechanisms leading to adaptations that promote virulence include gene reassortment, lateral transfer, and mutational drift. There is grave concern, for example, that co-infection of swine with strains of human and avian influenza will lead to viral gene reassortments that could result in new epidemic strains. A recent example of this is the emergence of avian influenza in many parts of the world.

Environmental microbes could also acquire virulence factors via horizontal transfer from pathogens in the environment. For example, type III secretion factors and certain bacterial toxins, like Shiga toxins are readily exchanged by horizontal transfer and may be changing hands among environmental microbes. Transfer of virulence factors can be mediated by phages and plasmids.

Characterizing the distribution and flow of the genetic material that enables virulence should be a research priority. Investigators should seek to evaluate the roles of environmental influences and human activities (including specific activities like animal husbandry) that may enhance the exchange of genetic material (and hence potential virulence determinants) within microbial populations. Other work should be aimed toward uncovering whether distinctions exist between environmental reservoirs of pathogens (where high densities of pathogens can be found) and reservoirs of virulence (where high densities of the genes that enable microbes to become pathogenic are found). Transmissible genetic material may be the key to making certain environmental organisms pathogenic. Understanding the movement of these genes in the environment may help in predicting the areas of greatest risk to human health.

**Intraspecific Diversity**

The designation “species” is difficult to apply to predominantly asexually-reproducing organisms like microbes; microbial strains identified as belonging to the same species can differ greatly from one another. In environmental pathogens, these differences can have critical consequences for virulence, transmissibility, environmental persistence, and patterns of environmental distribution. Research on environmental pathogens needs to address intraspecific diversity in order to understand the ecology of these diseases and to design and implement strategies for their control. Microbial surveys, databases, and sequence analysis are valuable tools in this effort. Currently, there is a need for targeted inventories of known pathogenic bacteria and their close relatives and for a renewed effort to survey viruses, fungi, and parasites in the environment.

Surveillance data should be appropriately housed in databases, including background information on the organisms present in specific habitats. This information can be analyzed to identify subpopulations of microbes associated with virulence. Sequence data from surveillance efforts can be used to determine whether increases in virulence are genetic or whether they are the result of environmental influences, such as an altered route of exposure. Once differences between more virulent and less virulent strains of the same species have been identified, efforts should be made to develop simplified laboratory methods for predicting the degree of virulence of unidentified strains.

**Biofilms**

In the environment, microbes, including environmental pathogens, often form assemblages known as biofilms. Biofilms likely play roles in ensuring the persistence of environmental pathogens, but little is currently known about the specific ways they benefit from these associations. Research is needed to uncover these details.

Biofilm formation can be modeled, albeit imperfectly, in the laboratory using microcosms. Naturally-occurring biofilms such as those in water pipes, on shower curtains, and on mechanical devices, can be analyzed by
using a handful of available techniques. These include PCR-dependent methods, fluorescent in situ hybridization, and confocal microscopy. The role of biofilms in the antibiotic resistance of certain fungal pathogens, for example, could be studied in situ using biofilms on catheters or shower walls. Legionella biofilms are another suitable source of biofilms for study.

One difficulty in working with biofilms is the problem of collecting intact biofilm samples from the environment, as sampling often destroys the delicate structure of these films. More refined methods of biofilm collection are needed, as are methods for defining the microbial composition of biofilms.

Model Systems
Although it is wise to take a cautious approach in extrapolating findings from a model system to the wider world of pathogens in the environment, model systems have often illuminated key features of microbe physiology, adaptability, and virulence. Although no single system could represent the complexity of environmental pathogens, models can be useful for answering specific questions and for exploring potentially pathogenic mechanisms. Extensive study of selected systems has provided insights into other diseases of the same category. Studies of Salmonella, for example, have shed light on other zoonoses, while V. cholerae has served as a model for the ecology and epidemiology of other waterborne diseases.

Ideally, an infection is modeled in its natural host (defined as a host in which the pathogen can complete its development) as well as in the human host. Legionella species, for example, should be modeled in both amoebae and in human cells. There are advantages, however, in using host models that are amenable to genetic manipulation, such as the fruit fly Drosophila melanogaster or the nematode Caenorhabditis elegans, as these models facilitate the identification of host responses that may be important towards limiting infection. Where possible, model systems should represent the natural route of infection for that organism, as this can be an important determinant of virulence. The conditions under which virulence genes are expressed should be modeled as well. Highly virulent human isolates or strains that have caused large pandemics could be appropriate models for identifying the most dangerous genes and combinations of genes and identifying and studying virulence factors that may be common to other environmental pathogens.

Once an appropriate model system is developed and standardized for a given type of environmental pathogen, researchers and interested agencies should arrange for its use as a regional or national core resource. Such an arrangement would enable study of the system by many different researchers in a standardized way and would conserve money and resources.

Mitigating Environmental Diseases
Although environmental pathogens have proven difficult to understand and prevent, science and public health have had some degree of success in combating the diseases these organisms cause. More and better interventions are needed, however, as are new methods to control exposure.

Strategies for Interventions
Interventions to reduce infections from environmental pathogens can tackle the problem from a number of different angles. Simple hygiene and cleanliness measures are often the first line of defense. Such basic practices as wearing protective clothing, improving sanitation and waste disposal, and proper food hygiene are essential for preventing infections. Even makeshift practices like filtering drinking water through cloth or fabric have been shown to be effective in resource-limited settings. This was illustrated by the recent demonstration that filtering drinking water through sari cloth effectively removed copepod-borne Vibrio cholerae, resulting in a measurable decrease in cholera in rural Bangladesh settings.

More complex interventions can take on other strategies. One approach is to target the vectors of disease, for example, the insects that transmit pathogen to humans. Other interventions seek to destroy the specific habitats where infectious agents or their vectors flourish. Draining standing water to reduce mosquito populations is an example of this type of method. Avoiding exposure to the sources of infection, like reservoir species and suspected habitats, can also be extremely effective in reducing infections. However, the monetary and environmental costs of such measures must be weighed against the benefits, especially when considering relatively rare opportunistic infections.

Developing Interventions
The design and implementation of new interventions to combat environmental pathogens should be based on a careful assessment of risk. The foundation of such an assessment requires a hazard evaluation and exposure assessment of environmental pathogens. Dose-response analysis and risk characterization should also be determined in order to properly address risk, however it is not currently possible to address these two points for environmental pathogens. A risk assessment framework for most environmental pathogens has yet to be designed, but would prove highly valuable for the field.

In the absence of a framework with which to establish risk-based priorities for interventions, other criteria must be implemented. The first line of defense should be composed of relatively simple and inexpensive interventions that reduce the exposure of susceptible humans to environmental pathogens. These interventions should be consistent with the ecology of the organisms. Uncomplicated, proactive approaches are often much more effective than interventions that involve monitoring and response. For example, the prevalence of L. pneumo...
could be effectively reduced in many water systems by initiating a heating routine, a much simpler approach than water sampling, analysis, and treatment. If such straightforward methods fail to sufficiently protect human health, then the next set of interventions should be aimed toward reducing existing practices that encourage the proliferation of pathogens or encourage contact with the pathogens. For example, in certain cases agricultural practices could be altered to prevent the growth or spread of pathogens to nearby residents or consumers. Alternatively, susceptible people could be encouraged to modify their behaviors and daily routines during times in which these agricultural practices are going on.

Once an intervention is devised and ready for implementation, surveillance needs to be carried out to determine the burden of disease before and after execution of the new measures.

Controlling Exposure
Controlling exposure to environmental pathogens can reduce infections under some conditions, and it may be the only line of defense available against pathogens such as viruses that do not lend themselves to antimicrobial therapy. However, the full consequences of exposure controls are not currently known and are impossible to predict. For example, natural exposure to environmental mycobacteria, some of which cause disease in susceptible people, is thought to impact the immune systems of susceptible and non-susceptible people alike. It is possible that such exposure confers some level of resistance to infection by the related professional human pathogen, Mycobacterium tuberculosis. Thus, wholesale exclusion of such organisms from human exposure could have favorable or unfavorable consequences on human health. More study is needed to adequately describe human responses to environmental microorganisms and their products, like endotoxins. Human responses such as immunity development and tolerance, the acquisition of specific and heterologous immunity, and the development of hypersensitivity and autoimmunity all need to be more fully characterized.

Efforts to control exposure can also have adverse effects on the environment. The use of ozone in disinfecting municipal effluent, for example, can break down dissolved organic materials into compounds that feed microbial blooms in receiving waters. In light of the unknowns about the effects of reducing exposure to environmental microbes, indiscriminate application of non-scientifically based control procedures is not acceptable.

New Drugs for Combating Environmental Pathogens
For many environmental infections, control at the level of exposure is not practical or cost effective, and antimicrobial therapy is the most feasible line of defense. Unfortunately, many existing antibiotics that are effective against well-known pathogens are less so against their environmental cousins. For example, drugs used to treat tuberculosis are not effective against environmental mycobacteria. New antibiotics targeted at treatment-refractory environmental pathogens are badly needed. In many cases, this will require new information about the basic biology of these organisms. Such information can be used to aim antibiotics at individual environmental microbes based on their unique properties.

Vaccines
There is considerable expense involved in developing vaccines; studies of efficacy and safety must be carried out in large populations of volunteers, requiring tremendous commitment of time and resources. Because of these costs, other routes of prevention, including exposure prevention and disease treatment, should be thoroughly explored first to lower the incidence of disease. However, certain criteria favor vaccine development as an effective strategy. These include:

- When risk analysis concludes that the incidence and severity of the disease are sufficiently taxing on human life and productivity to justify the investment, or
- When few or no treatment options are available for the disease, or
- When special subpopulations are at high risk from the disease and would benefit significantly from a vaccine.

If recovery from the disease confers immunity to an individual then vaccine success is likely. However, not all infections confer immunity. Those that do not may be difficult to control with vaccines unless improvements can be made.

Research opportunities exist in examining the role of innate immune responses to environmental pathogens. Understanding these phenomena could enable manipulation of innate immunity in an effort to combat infection without the aid of antibiotics or vaccines.

In light of the fact that many environmental pathogens appear to target individuals with weakened immune systems, a need exists for environmental disease vaccine strategies for immunocompromised populations. Lessons for this effort may be learned from experience in vaccinating HIV patients.

Problems in Developing Drugs and Vaccines for Environmental Pathogens
The current model for drug and vaccine development seeks to address the impacts of common diseases efficiently. In this system, diseases are recognized and defined by physicians, and the public health community defines their impact and the market to which drugs would be appropriate. In the United States the National Institutes of Health (NIH) as well as private industry funds needed research for discovering the drugs or vaccines to address these diseases, and industry follows up with drug and vaccine development, marketing, and distribution.
This arrangement breaks down in the case of diseases that affect only a small number of people, as is true of many environmental diseases. Such diseases, which can occur at consistent, low rates in the population or in punctuated bursts, present a lower opportunity for profit than more common diseases, and this profit margin may not be sufficient to overcome the costs of seeing these products through safety testing and other required stages. Although modern research can and does provide meaningful drug candidates for environmental diseases, drug development does not proceed at a corresponding pace because of the costs involved. Moreover, the current form of the "orphan drug law", which offers financial incentives to companies that develop drugs for rare diseases, does not always bring needed drugs to market. As a result, environmental diseases often fall through the cracks in the system and may not be addressed with drug or vaccine development.

Solutions to the problem of getting drugs and vaccines for environmental diseases to market must be sought outside the usual routes of development. It may be desirable to involve smaller pharmaceutical and vaccine companies in developing remedies for environmental diseases, as these firms may have more rapid development paths and, in some cases, stronger motivation to carve out "niche" markets.

Although the technologies and research available to date have brought us no small measure of success in understanding and combating environmental pathogens, new techniques and innovative research are needed to answer the challenges of the future.

Diagnostic and Environmental Technologies and Sensors

There are common needs inherent in detecting pathogens in clinical and environmental samples. Both endeavors require sensitive, specific, rapid, and simple tools for detecting pathogens and differentiating them from closely related species. Often, quantitative tools are also necessary to evaluate the threat posed by a given organism.

A number of polymerase chain reaction (PCR) based techniques have been developed to meet these needs in recent years, but difficulties can arise in their application and in the interpretation of results. For example, most PCR-based methods cannot provide an understanding of the viability of the organisms under scrutiny in environmental or clinical samples, and contamination by impurities or non-target nucleic acids can muddle testing results. Also, in dealing with environmental samples, it can be difficult to design specific probes for the target organism without complete knowledge of the background microbial population. In the absence of complete information, the probe and the PCR-based analysis may accidentally target avirulent strains of the organism. For this reason, detection of environmental pathogens should never rely on a single probe, and rarely on a single method. Hence, the current selection of PCR-based methods is not enough; more refined methods for detecting environmental pathogens are needed.

New technologies that should be developed or enhanced for exploring environmental pathogens and diseases include:

- Nucleic acid characterization, either by direct sequencing of DNA isolated from environmental sources or larger scale genomic analyses of cloned molecules
- High throughput flow cytometry
- Techniques for measuring the characteristics of single cells, including metabolic activity measurements,
- Real-time techniques to measure the viability, infectivity, and metabolic activity of environmental pathogens, and
- Technologies that employ microbial sentinels as biosensors of pathogen activity.

In addition to these technologies, there is a need to develop species-specific sensors to monitor known pathogens in the environment. Ideally, these sensors could be placed permanently in the environment of inter-
environment are identified and described, requires the input of experts in multiple disciplines. Consequently, all areas of investigation into environmental pathogens, the need to cultivate some organisms must not be overlooked. Cultivation-dependent methods of study represent an important complement to non-cultural techniques as the availability of a living, growing pathogen is a prerequisite for answering many questions about virulence. The sophistication of cultivation techniques has increased considerably in recent years, but unfortunately many of these new approaches have yet to be introduced or accepted in routine clinical laboratories or reference labs. The continued improvement and dissemination of cultivation methods remains a critical need.

Getting Technologies to Market
In developing new technologies for the study of environmental pathogens, it will help to encourage feedback between developers and end-users. Such an effort would serve to inform continued development and adaptation of appropriate technologies. This will also require communication and collaboration between microbiologists and industrial technologists.

Interdisciplinary Research
Research on environmental pathogens and diseases requires the input of experts in multiple disciplines, including microbial ecology, genomics and bioinformatics, environmental sensor technologies, epidemiology, medicine, and other fields. Effectively addressing almost any single issue related to environmental pathogens requires the input of experts in multiple disciplines. These investigations also frequently require the assistance of theorists, database specialists, and data mining specialists. Consequently, all areas of investigation into environmental pathogens would benefit from using a multidisciplinary approach. Reservoir analysis, for example, in which the sources of pathogens in the environment are identified and described, requires the input of environmental and clinical microbiologists, ecologists, epidemiologists, engineers, and (depending on the reservoir) industrial hygienists. Similarly, investigations of outbreaks of environmental infections would benefit from the contributions of clinical and molecular microbiologists, physical chemists, water systems technicians, food purity technicians, air conditioning experts, epidemiologists, and analytical chemists.

Communications bridges are particularly needed to bring together two seemingly independent spheres of microbiology: pathogenesis specialists and environmental microbiologists. Fostering more meaningful interactions between these groups would do more than anything else to expand the state of knowledge of environmental pathogens. To further the goal of improved interactions, it may be advisable to arrange a meeting of 100 to 150 professionals to explore the ways environmental microbiology can be used to provide insights into environmental pathogens. Participants could include investigators interested in pathogenesis and environmental microbiology, investigators working with environmental pathogens, clinical microbiologists, and investigators with expertise in pathogen-rich environments. In the interest of garnering the contributions of many different types of investigators, the participants should represent a mix of senior investigators, post-doctoral researchers, and graduate students.

Long-term Effects of Environmental Diseases
The long-range impacts of environmental diseases on human health merit further investigation. The effects of infection may be shown to include impacts on mental health, immune function, and other parameters. The economic and social impacts of environmental disease should be researched as well.

Ecology of Environmental Pathogens
Although the human disease aspects of environmental pathogens are becoming better defined every year, the lives these organisms lead outside the human host remain much less clear. Research is needed to uncover how environmental pathogens survive, multiply, and evolve in the environment and how they are introduced to human hosts. These types of investigations can eventually shed light on the differences between pathogen gene expression, physiology, structure, morphology, and other activities in the environment and in the diseased host. This information has the potential to reshape our understanding of the spread of these pathogens, their evolutionary derivation, and the mechanisms by which they cause disease.

Targeted Environmental Inventories
A number of habitats where environmental pathogens are thought to thrive have yet to be thoroughly characterized with respect to the composition of their microbial communities. Targeted inventories of many environments are needed to understand the distribution and population dynamics of environmental pathogens. Particularly critical is the generation of viral inventories...
and determining the stability of different viral types in different habitats. Some locales where environmental inventories are needed include:

- Indoor habitats
- Drinking water (both optimized, ideal systems and real-world systems)
- Public buildings and construction materials
- Animals, and
- Biofilms with which humans come in contact.

Inventories are also needed of the endogenous microflora of human skin and mucosal surfaces, including the nose, mouth, and gastrointestinal tract. A two-pronged approach of broad surveys combined with targeted tracking of specific organisms would answer outstanding questions about how and when humans acquire new strains of commensals and potential pathogens and when pathogens cause disease and when they assimilate with the normal flora.

Diversity Surveillance
Questions of diversity are important to our understanding of endemicity, environmental monitoring results, and pathogen evolution. The natural diversity of many environmental pathogens is, at best, little understood. Surveillance to better describe the diversity of environmental pathogens should be carried out to bridge these gaps in our knowledge. Such efforts could uncover the environmental determinants of endemicity, helping to identify the reasons why certain diseases and pathogens are localized to specific geographic areas and aiding in the public health battle against these illnesses. Appropriately sensitive methods for differentiating strains and methods that can resolve microbes at the sub-strain level should be applied in this effort.

Surveillance is also critically needed to identify the baseline or background incidence of environmental pathogens so that perceived perturbations and spikes in pathogen populations can be put into the context of their usual patterns of occurrence. Such surveillance can tackle targeted inventories of microbes or targeted habitats relevant to public health, such as watercourses.

Database Integration and Consolidation
Currently, most databases of information on microorganisms specialize in organisms from one habitat type: either the environment or the clinical setting. Moreover, these databases curate diverse types of information, ranging from molecular information to host and habitat figures. Because environmental pathogens bridge these two habitats, both the environment and human tissues, and because different types of key information for these organisms are only found in different databases, it has been difficult to successfully integrate the full information on a given environmental pathogen. It is recommended that clinical and environmental databases be integrated and that the information technology related to environmental pathogens be better coordinated. In the U.S., a national database should be established in which all these disparate pieces of information are consolidated to full advantage for research and for public health. These databases should include information on the emergence of diseases in the interest of developing predictive capabilities for the appearance of new environmental diseases. Smaller, organism-specific models for this type of enhanced database exist; the NSF and NIH are currently coordinating efforts to compile a database on the West Nile Virus, for example. Such database development would enable the development of new models for predicting the occurrence of known pathogens and the emergence of new threats to public health.

The Human Component of Environmental Disease
Research efforts are needed to better understand the interplay of human population dynamics and environmental pathogens. For example, what are the effects of increased population on disease incidence? What are the effects of movement to population centers? By answering these and other questions, scientists can empower public health officials with a better knowledge of how population density issues impact environmental disease.
Environment pathogens affect the lives of almost every member of the public. From consumers of municipal drinking water to hikers in tick country to anyone outdoors during mosquito season, the vast majority of people face exposure or even infection by environmental pathogens many times in their lives. Steps need to be taken to convey the results of research on environmental pathogens and the diseases they cause to the public and to students. Professional societies can play a powerful role in this effort.

Communicating Research Results
Environmental diseases are pervasive while understanding of microbiological topics among nonscientists remains limited. There is a great need to educate the public and policy makers in the basics about pathogens in our environment. Communicating with the lay public is most easily carried out through print media and television. The public affairs boards of interested scientific societies may be most suited to promoting these messages in the media. In order to assure that this information is conveyed accurately and the risk of infection by opportunistic pathogens in the environment is not overstated, it is important to work with journalists with specialized training in microbiology

One captivating way to convey the results of research on environmental pathogens would be a series of announcements of "success stories" summarizing the achievement of milestones in research. These stories could be communicated via a website or possibly through a television program. Campaigns like this are not only an effective way to educate the public; they also serve to capture the imaginations of children and future researchers.

Since environmental pathogens have two homes, namely, the environment and human tissues, research into these organisms must bridge two traditional schools of learning in microbiology. The schools of environmental microbiology and clinical microbiology do not often find common ground, but in order to make progress and save lives, communication among professionals in these areas and others, including engineering, hydrology, soil science, etc., must be swift and complete. More interdisciplinary contact must be encouraged, possibly by including interdisciplinary sessions centered on environmental pathogen-related topics at national scientific meetings. It is expected that interest and participation in this research will grow, and will eventually warrant convening a specialized annual meeting. By considering these diverse organisms under the "environmental pathogens" umbrella, it should be possible to gain the critical mass needed to discuss and make progress on an appreciable list of shared issues.

Integrating Research and Education
Exposure to exciting research stimulates young people’s desire to pursue training in that discipline. Students are drawn to fields that are perceived as pertinent, stimulating, and revolutionary. By exposing students to the results of cutting-edge work on environmental disease, researchers can encourage the next generation of scientists to focus their energies on this important public health issue. Some exposure at the primary and secondary levels of education may be warranted. Increased attention to environmental pathogens and disease in college courses and in clinical microbiology curricula in particular is strongly advised. Education regarding environmental pathogens is best conveyed in conjunction with a component on risk and cost-benefit analysis. It should also be connected with timely issues of environment and climate change, biodefense, human population growth, and refugee movement.

Professional Societies
Professional societies play many roles in education and outreach for science. In educating schoolchildren and the general public about environmental pathogens and disease, it is best to start with fundamental messages about microbial life in order to promote the public’s understanding of microbiology. By sponsoring programs to educate high school teachers in microbiology and by providing opportunities for high school students to interact with microbiologists and to do basic microbiological work, professional societies can foster public awareness of microbes and of the risks posed by pathogens in the environment.

In advancing the cause of research, interdisciplinary meetings are one highly effective way of spurring a field forward. Professional societies can sponsor meetings to encourage interactions between scientists with expertise in microbiology and professionals in other fields, to develop common ground from which to tackle the interdisciplinary challenge of environmental pathogens.

In the interest of curbing outbreaks of environmental disease, societies can also sponsor training programs to tutor primary care physicians in the recognition of environmental infectious diseases and in the reporting of unusual occurrences of disease.
Recommendations

1. The most critical factor limiting our understanding of environmental pathogens is information on the incidence of infections by these organisms, and on their occurrence in environmental samples. Therefore, the development and improvement of surveillance and reporting strategies should be a top priority. Effective monitoring of pathogens in the environment would allow researchers to understand the baseline incidence and persistence of pathogens in areas that are considered to be at risk for harboring these organisms. Existing tools, including the BioWatch infectious agent monitoring network and various infectious disease databases, could be leveraged to fill many of these needs in a cost effective fashion.

2. Multidisciplinary research is needed to predict the effects that changes in our environment, e.g. climate change, urbanization, and new agricultural practices, may have on the frequency of diseases caused by environmental pathogens.

3. The fields of medical and environmental microbiology need to be better integrated to stimulate the type of work that is required to combat environmental pathogens effectively. Positive measures to bring these fields together could include the establishment of interdisciplinary meetings and research funding opportunities. Professional societies and funding agencies that focus on individual aspects of the problem these organisms pose should collaborate to bring medical and environmental microbiologists together. New technologies for monitoring and cultivation of environmental pathogens are sorely needed. It is critical that, as these tools are developed, they be implemented in clinical as well as environmental settings, on the front lines of disease emergence.

4. Genetic and phenotypic virulence factors can be helpful in predicting the pathogenic capabilities of new organisms detected in the environment. However, this virulence factor-activity relationship (VFAR) approach must be used with considerable caution, because many microbial virulence factors are in fact multi-functional, and therefore not entirely predictive of risk to humans.

5. The adverse effects of environmental pathogens can be mitigated by reducing the frequency of exposure, or alternatively by reducing the effects of exposure through new vaccine and drug development. Control of exposure may be the most practical option for especially widespread and/or difficult-to-treat agents such as viruses and Borrelia, the causative agent of Lyme disease. Environmental infections that are relatively rare may best be combated at the level of antimicrobial therapy. New drugs may be needed for many environmental pathogens that are intrinsically resistant to existing antibiotics.

6. Catalogued culture collections of pathogen isolates greatly enhance efforts to identify, monitor, and characterize microbial pathogens. The development and maintenance of a multi-species environmental pathogen culture collection would be an expensive undertaking. However, it should be feasible to develop and maintain a general database of information that informs users of existing environmental pathogen collections that are available to the broad community of scientists and health care professionals. An integrated database of culture collections would not only help scientists locate strains of interest for research, but would also serve as a resource for the comparison of existing strains with new or emerging pathogens.