

# Diseases Gone Global: What causes epidemics?



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6:00 – 7:30 p.m.**

The Joseph B. Martin Conference Center  
The New Research Building  
Harvard Medical School  
77 Avenue Louis Pasteur  
Boston, MA 02115



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# Diseases Gone Global: What causes epidemics?

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## Moderator



### **Don Goldman, MD**

- Clinical Professor of Pediatrics at Harvard Medical School
- Professor of Immunology and Infectious Diseases, and Epidemiology at Harvard School of Public Health
- Chief Medical and Scientific Officer at the Institute for Healthcare Improvement

## Speakers



### **Paul Farmer, MD, PhD**

- Kolokotronis University Professor of Global Health and Social Medicine at Harvard University
- Head of the Department of Global Health and Social Medicine at Harvard Medical School
- Chief of the Division of Global Health Equity at Brigham and Women's Hospital
- Cofounder and Chief Strategist of Partners In Health



### **Megan Murray MD, PhD, ScD**

- Professor of Global Health and Social Medicine at Harvard Medical School
- Professor of Epidemiology at the Harvard School of Public Health
- Professor of Medicine and the Director of Research at the Brigham and Women's Hospital Division of Global Health Equity

## **About the Speakers:**

### **Paul Farmer, MD, PhD**

Paul Farmer is the Kolokotronis University Professor at Harvard University and head of the Department of Global Health and Social Medicine at Harvard Medical School. Farmer is a medical anthropologist, physician and chief of the Division of Global Health Equity at Brigham and Women's Hospital. He is cofounder and chief strategist of Partners In Health, an international non-profit organization that provides direct health care services and has undertaken research and advocacy activities on behalf of those who are sick and living in poverty. Additionally, Farmer serves as special adviser to the United Nations Secretary-General on community-based medicine and lessons from Haiti. Farmer and his colleagues in the United States, Haiti, Peru, Russia, Rwanda, Lesotho, and Malawi have pioneered novel community-based treatment strategies that demonstrate the delivery of high-quality health care in resource-poor settings.

### **Don Goldman, MD**

Don Goldman is a Harvard Medical School professor of pediatrics at Boston Children's Hospital, and professor of immunology and infectious diseases, and epidemiology at the Harvard T.H. Chan School of Public Health. Goldman is the chief medical and scientific officer at the Institute for Healthcare Improvement (IHI). He also serves as senior lead for the IHI Fellowship Program, and he trains and mentors emerging investigators at Harvard Medical School, Boston Children's Hospital, and the Harvard School of Public Health. He has more than 220 peer-reviewed publications and numerous commentary papers. Goldman currently serves on the boards of the National Public Health and Hospital Institute and AcademyHealth. He is also a member of the National Association of Public Hospitals' and Health Systems' Strategic Planning Committee and AcademyHealth's Translation and Dissemination Institute Planning Committee.

### **Megan Murray, MD, PhD, ScD**

Megan Murray is a professor of global health and social medicine at Harvard Medical School and a professor of medicine and the director of research at Brigham and Women's Hospital in the Division of Global Health Equity and its sister organization, Partners In Health. She is also a professor of epidemiology at the Harvard T.H. Chan School of Public Health. Murray is an epidemiologist and an infectious disease physician, whose work focuses on the management of tuberculosis programs and tuberculosis (TB) epidemiology. After graduating from Dartmouth College, Murray worked with the intergovernmental committee for migration in Thailand managing a TB screening program for refugees being resettled in other countries. She then attended Harvard Medical School and completed a residency in internal medicine at Massachusetts General Hospital. She has conducted field studies in South Africa, Russia, Peru, the United States, and Rwanda. She has previously worked in Kenya, Niger and Pakistan.



Dr. Anthony Komaroff, Harvard Medical School | In Association with Harvard Health Publications

## Should I get vaccinated against whooping cough?

Posted November 17, 2012

### DEAR DOCTOR K:

My daughter wants me to get a booster shot for pertussis. She says it will help protect her young kids against whooping cough. Is this true?

### DEAR READER:

Your daughter is right. Pertussis, also known as whooping cough, is a highly contagious bacterial infection that causes violent coughing. The coughing makes it hard to breathe and produces a deep “whooping” sound. Pertussis can occur at any age, but infants and young children are most likely to become seriously ill from the infection.

When I went to medical school, a vaccine for pertussis was radically reducing the number of cases. It was another example of how infectious diseases were going away because of vaccines. The vaccine has, indeed, made a huge difference. But vaccines only work if people take them, and not every vaccine offers lifetime protection.

Unfortunately, many people resist getting vaccines, and the protective effects of the pertussis vaccine tend to decline over time. As a result, the number of pertussis cases in the United States has increased in recent years. There were about 17,000 reported cases in 2009; this year, more than 23,000 cases of pertussis had already been reported by August.



To keep kids healthy, adults need to get immunized, too. That’s because of something called “herd immunity.” When enough people are immunized against a disease, it becomes uncommon—simply because the immunized people can’t catch it, and therefore can’t spread it.

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Herd immunity helps to protect

- small children, especially infants, who either are too young to be immunized or haven't had enough doses to be fully protected.
- people who have problems with their immune systems, many of whom can't get vaccines, and all of whom are more susceptible to infections.

Herd immunity works when enough people are immunized. The Centers for Disease Control and Prevention (CDC) recommends that adults get a Tdap vaccine (which protects against pertussis, along with tetanus and diphtheria) in place of one of their regular tetanus boosters (the Td shot that is recommended for adults every 10 years).

You can get the Tdap vaccine no matter when you last received a Td shot. Getting vaccinated with Tdap at least two weeks before coming into close contact with an infant is especially important.

By getting a Tdap vaccine, you'll be helping to keep your grandkids healthy. Even though that's the main message of this column, it is worth remembering that we adults also need protection against the germs spread by little kids.

Several months ago a family with young children visited us, and one of the kids had what we in New England call a "wicked cough." About two weeks later I developed a bad cough, and when I took in a deep breath I let out a loud "whoop!" Like everyone, I've had plenty of coughing illnesses in my life. But I've never (not even as a kid) "whooped."

I got better, but I wonder if I caught pertussis from our young visitor. Fortunately, I stopped coughing the next day, and so I never tested myself and never will know if I had it.

### To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our *Ask Dr. K* column, available at [askdoctork.com](http://askdoctork.com).

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## Is there a treatment or vaccine being created for Ebola?

Posted November 10, 2014

### DEAR DOCTOR K:

Like everyone, I'm afraid that the Ebola virus could spread in the United States. There must be research underway to find treatments and vaccines to prevent it in the first place. Please tell me there is.

### DEAR READER:

Infection with the Ebola virus is indeed frightening. In West Africa, the site of the latest outbreak of Ebola, more than half the people who have become infected with it have died. I doubt there will be an epidemic of Ebola in the U.S. and other developed nations, but there have been cases, and there will be more.

There is some encouraging news to report. Last month, an international research team developed a "cocktail" of several antibodies to the Ebola virus, called ZMapp. (Antibodies attach themselves to the virus. This signals other immune system cells to kill it.) This treatment was given to monkeys several days after they became infected with the virus. Most of the monkeys already were having symptoms



from the infection when the treatment started. All of the animals treated with ZMapp survived. Animals that did not receive the treatment died.

But keep in mind that treatments that work in animals don't always work in humans. Even though monkeys are more like humans than they are like other animals such as mice and rats, treatments that work in monkeys don't always work in humans.

Another note of encouragement about ZMapp is that two U.S. health care workers who became infected with the virus while working in Africa were treated with the medicine. Each recovered, but that does not prove that the ZMapp treatment caused the recovery.

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A second international team recently reported that it had created a vaccine that protected monkeys against becoming sick with the Ebola virus. As with ZMapp, this encouraging result in monkeys does not guarantee that the vaccine will work in humans and be free of complications.

The first reported outbreak of Ebola virus infection in Africa occurred about 40 years ago. There have been other outbreaks since, each producing terrible casualties. Why didn't we already have a proven treatment, and a proven vaccine, to use when this new Ebola outbreak began? The techniques for making ZMapp, and for making the vaccine, have been around for some time.

I believe the answer is that neither the government nor the pharmaceutical and biotechnology industries invested enough in medical research. The government's ability to support research is dependent on tax dollars, and no one likes to pay taxes. The private sector invests when it sees a big problem affecting lots of people — people who can pay for the treatments and vaccines. Until the current outbreak, that didn't seem likely with Ebola.

Every time I close a column saying we need to invest more in biomedical research, I get letters from some readers who say, "Money doesn't grow on trees — we just don't have the money to support more research." I believe that, as a society, we do have the money, and we are asking for trouble by not investing it to protect ourselves.

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## The SARS story

The world witnessed the shocking speed of viral transmission by way of people traveling on airplanes when, in February 2003, a previously unknown virus originating in bats in rural China spread to Hong Kong, and two days later appeared in Toronto, Canada. The virus eventually killed 33 people there and spread to cause epidemics in 29 other countries around the world.

Quickly dubbed SARS, for severe acute respiratory syndrome, the deadly virus caused worldwide alarm and a media frenzy as the World Health Organization issued a global alert. Over the next five months, the virus spread by way of tiny particles of saliva and mucus, usually made airborne by coughing. Close to 10% of the more than 8,000 infected persons died, including many healthy young adults. Hospital staffers were infected, and hospitals shut down. Thousands of people were quarantined in their homes until the WHO declared the epidemic to have ended five months later on July 5. Because of the public health measures, a worldwide pandemic was averted.

How did this come about? Scientists determined that a doctor who had been treating patients in the Guangdong province of China checked into a hotel in Hong Kong on February 21. Investigation led scientists to believe he was a “superspreader,” coughing frequently and transmitting infectious droplets into the air around him at the hotel. Hong Kong became ground zero, the place where a variety of travelers contracted the disease. They boarded airplanes and spread the virus to their fellow travelers and to people in their destination countries even before they knew they were infected.

Following the trail backward from the doctor in Hong Kong, investigators found that he had treated some people in Guangdong province who had the virus. There, in food markets, food sellers kept a variety of small animals in cages prior to being sold and killed. Investigators concluded that one small animal, called a palm civet, had picked up the virus from bats. Palm civets from the market were also kept alive in cages in a specific restaurant before being cooked. A waitress working in that restaurant had contracted the virus from the palm civet and passed it to some customers she served there. The doctor treated some of these people, contracted the virus himself, and then traveled to the hotel in Hong Kong. From there, the virus spread across the globe—all in a few days.



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The SARS tale demonstrates the ability of such diseases to jump from one species to another. A virus that normally lives in bats in southern China mutated and became “humanized.” That is, it changed sufficiently to be able to infect humans and jump from human to human even though its normal reservoir is bats.

These kinds of changes in viruses and other microbes have always happened. Microbes have been mutating effectively for millions of years. What’s new in the SARS story is the speed at which it circumnavigated the globe. In earlier times, the virus might have entered the human population in southern China and infected and killed people there, but likely would not have made it beyond China because infected people, traveling by slower methods like boats, would have died in transit. Therefore, the infection would never have made it to so many faraway places.



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## Viruses and Disease

*Protecting yourself from the invisible enemy*



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Are you immune?  
Evading common viruses  
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## How infectious diseases are transmitted

How a virus spreads from one host to the next is called transmission. The way a microbe spreads tells us many things about it. When you get sick, among the first few things you want to know are, "How did I get this?" and "Is it contagious?" Knowing how the infection is transmitted helps answer these questions.

Viruses and other microbes are known to travel from site to site. That means the viruses expelled from your nose when you sneeze can cause illness when they reach the nose of the person who breathes in your airborne particles. These viruses travel from nose to nose, sometimes directly through the air, sometimes landing on surfaces where they are picked up by the hands of unsuspecting victims who unwittingly infect themselves the next time they touch their nose or eyes or mouth. The virus that caused your intestinal distress will end up in another person's intestines if you fail to wash your hands after using the restroom and then prepare a meal for others to eat. In this way, a virus travels from digestive tract to digestive tract. Sexually transmitted diseases follow the same rule, passing from one person's genitals to another's during sexual contact.

For scientists and public health officials, understanding transmission is the key to determining a disease's progress in the world, how widely it is likely to spread, how difficult it will be to stop, and whether measures like quarantine will be useful in halting its progression. Transmission also tells them a lot about what kind of microbe may be causing the disease.

### **Infection definitions**

**endemic:** when a disease is continually present among people in a region.

**epidemic:** a disease outbreak in a community or region.

**pandemic:** a disease outbreak affecting large populations or a whole region, country, or continent.

### ***Methods of transmission***

It wasn't all that long ago that no one understood that infectious diseases were caused by tiny organisms that moved from person to person. People had many creative explanations for illness, ranging from evil spirits to poison in the bedding, air, or food. Even as late as the 1850s, immigrant ships were greeted in the United States and Canada by doctors who thought the rampant and deadly typhus

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infection existed in the "miasma"—the fetid air in the holds of overcrowded ships—rather than among the lice that thrived in those unsanitary conditions and transmitted infection from person to person.

### **The reservoir**

The confusion is understandable. Even now, although we know that microscopic living microbes cause disease, the method of transmission is not always obvious. The solution to the transmission puzzle is often found in what is known as the reservoir. A reservoir, in biological terms, is an animal in which a microbe lives and reproduces itself. In some cases, humans are the only reservoir for a particular infection. Poliovirus is a good example. In areas where every human is vaccinated against polio, the disease no longer exists because humans are its only reservoir. If every human is immunized, the virus has no place to live and cannot survive.

But many other microbes have reservoirs in the animal world and can infect humans who are bitten by an infected animal or who come in contact with infected animal feces, saliva, or blood. Reservoirs for diseases that can infect humans include rodents, birds, and many other animals. What about insects? Biting insects such as mosquitoes, ticks, and lice often serve merely as a vector—that is, a shuttle bus transferring a disease from human to human or from animal to human.

The reservoir often determines how the infection spreads. For example, just about any mammal can be the reservoir for rabies, a potentially deadly viral disease. A bite from an infected animal or human will transmit rabies. Humans are the reservoir for many other diseases.

Transmission can be described as horizontal or vertical. Horizontal transmission is the most common way germs spread from one person to another. Vertical transmission occurs when they spread from parent to child and usually refers to the transfer of infection from a mother to child during pregnancy or childbirth.

### **Horizontal transmission**

There are four methods of horizontal transmission.

**Inhalation.** The most easily spread diseases are those, like influenza and the common cold viruses, that travel by way of droplets of saliva or mucus coughed into the air or spread by other means to another person's respiratory tract. Viruses that travel this way cause the respiratory infections we call colds and the flu. They can also cause more serious and dangerous infections. A droplet of saliva can teem with tens of millions of tiny viruses. Once a virus finds its way into the respiratory tract of another person, the process of reproducing within the new host begins over the next two to three days.

**Fecal-oral.** Some microbes are transmitted from one person's gastrointestinal tract to another's. This most often happens when an infected person defecates, gets feces on his or her hands, and then doesn't wash his or her hands. Similarly, in areas of poor sanitation, water may be polluted by infected feces. Many different types of germs can be transmitted this way, causing diarrhea and other intestinal

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ailments. This method can also transmit some of the most dangerous viruses, including poliovirus, which paralyzed many children in previous centuries.

**Direct contact.** This method of transmission requires direct human-to-human contact with infected tissues, blood, or body fluids. Germs transmitted this way are unlikely to spread by casual contact or in food or water. Instead, sexual contact or direct contact with blood, such as in blood transfusions or via previously used hypodermic needles, is the most likely way these germs spread. Human papillomavirus (HPV) and other sexually transmitted diseases are typically transmitted by way of direct contact—genital-to-genital, genital-to-anal, or genital-to-oral—with another person. HIV (the virus that causes AIDS) and hepatitis C are among the viruses that can be transmitted by way of direct contact with the blood or body fluids of another person.

**Via animals.** Transmission of infectious disease from animals to people can occur by way of zoonotic transmission (for example, when someone gets rabies from an animal bite), or by way of an insect vector, such as a mosquito.

Some major world diseases such as dengue and yellow fever are spread by mosquitoes, the most common vector. These are called arboviruses. Ticks, lice, and other biting insects can also transmit disease in this way. The vector serves as a small transport vehicle, ferrying the virus from animal to human, or human to human, but does not itself become infected. West Nile virus, which first appeared in the United States in 1999, spreads in this way. Mosquitoes become infected when they feed on infected birds or other infected animals. The mosquitoes transmit West Nile virus to humans or other animals when biting. The virus is located in the mosquito's salivary glands, and during each feeding, it is injected into the animal or human, where it multiplies and possibly causes illness. West Nile virus is responsible for the largest epidemic of arboviral illness in the Western hemisphere. Since 1999, it has infected about 3 million people and appeared in almost every state (except Hawaii and Alaska).

Some animal viruses do not require a bite from an insect or animal to infect humans. Rodents, for example, can spread disease to humans who come into contact with their feces or body fluids.

### **Vertical transmission**

A few viruses can be transmitted vertically—that is, they pass from parent to child, sometimes during pregnancy or childbirth. HIV can be transmitted to a baby during childbirth as it passes through the birth canal; more rarely, it can spread to the baby through the placenta late in pregnancy. HIV can also be transmitted from mother to child through breastfeeding. Vertical transmission of herpes simplex virus is also possible. Antiviral drugs are often effective in preventing transmission from mother to child during pregnancy, birth, and early life.

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## Infectious disease in the 21st century

If you are like most people, you probably got your vaccinations as a child and, since then, you've had tetanus boosters, maybe some flu shots, and some antibiotics when you needed them. When you catch a pathogen, you usually recover quickly. Most people in the United States and other developed countries have good reason to feel smug. They are well protected against infectious disease by vaccination, antibiotics, good hygiene, and general good health.

But for people whose immune systems are weakened by age or disease, it's a different story. There are plenty of infectious microbes looking for a place to multiply and cause illness or sometimes death. In addition, diseases that just a few years ago seemed to be nearly extinct have made worrisome comebacks. Resistant strains of infections frequently appear. Still more alarming are the "new and emerging" diseases, like severe acute respiratory syndrome (SARS) or bird flu, for which we have little or no immunity. And sexually transmitted diseases continue to pose a major health threat, with HIV at the top of the list, but also human papillomavirus, herpes simplex, chlamydia, gonorrhea, and syphilis continuing to spread.

What is the status of infectious disease in the 21st century? Wasn't modern medicine supposed to have this under control by now with vaccines, antibiotics, and antiviral drugs? Are the news reports and alarming headlines about the threat of new and emerging diseases to be believed? Will resistant strains of disease overpower our ability to develop new drugs and vaccines? Is the landscape of infectious disease changing in the 21st century, and if so, how can medical science meet the new challenges?

To some degree, the tables have turned. But there's always been a tug of war between humans and microbes. It is the nature of infectious microbes to damage and kill their hosts. As Cedric Mims described it in his book *Pathogenesis of Disease*, "If none of the microorganisms associated with man did any damage and none was notably beneficial, they would be interesting but relatively unimportant objects. In fact, they have been responsible for the great pestilences of history, [and] have at times determined the course of history."

Infectious diseases in general, and those caused by viruses in particular, have shaped history. Take, for example, the settlement of North America by Europeans. Smallpox and other diseases carried by Europeans played at least as great a role in wiping out indigenous American populations as did war and weapons. The conquest of Aztecs in Mexico by Hernán Cortés in 1520 was accomplished less by the use of weapons than by the inadvertent introduction of the smallpox virus. It was common in Europe but completely new to the Aztec people—who had no immunity to it and fell ill and died at a staggering rate. Two years after Cortés arrived, 3.5 million native Americans were dead of smallpox.

The battle of human versus microbe is far from over and is never likely to be so, writes Mims: "Because of their rapid rate of evolution and the constantly changing circumstances of human life, they continue to present threats of future pestilences."

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The age-old story does, however, take some twists in the 21st century. Several conditions of the modern world combine to influence the threat of infectious disease today.

### ***Speed of global transport***

The massive increase in the speed and volume of global travel has accelerated the potential spread of infectious disease. An infection like SARS, which in the past might have circulated only within a single region, now can spread swiftly across the globe as infected people board airplanes to all parts of the world. Like a businessman with a deal to close, a microbe can now travel from Singapore to Los Angeles in a matter of hours, packing a briefcase of infection.

And it's not just airplanes. Transport ships, plying the global waters in ever-greater numbers, are bringing along mosquitoes and other disease-carrying insects in pools of water on board. Exotic reptiles and other animals captured in the tropics and transported to pet shops and homes in temperate zones bring their infectious microbes with them. Fresh produce from around the world, sometimes with unseen insects, fungi, bacteria, viruses, or parasites on board, disembarks cargo ships daily. As far as infectious disease is concerned, it is a small world.

On the other hand, the speed of today's information technology also means that public health officials and scientists can track the spread of disease more accurately than ever before, taking steps to block epidemics and pandemics before they happen. They can know almost immediately where and when a disease is spotted, issue public health alerts and quarantine orders, monitor the advance of an epidemic, and communicate instantly with scientists and public health officials around the globe to control the spread of disease.

#### **Fast fact**

What is a germ? Although scientists don't generally use the word, it is accepted in English language and medical dictionaries as interchangeable with the word "micro-organism," especially one causing disease.

### ***Resistance to drugs and vaccines***

The ability of microbes to mutate has set science back on its heels. It's been hard to swallow, but we now know that, with occasional exceptions, permanent eradication of infectious disease is unrealistic. Microbes constantly mutate. That's a big problem, because our drugs and vaccines can actually make matters worse by promoting mutant strains.

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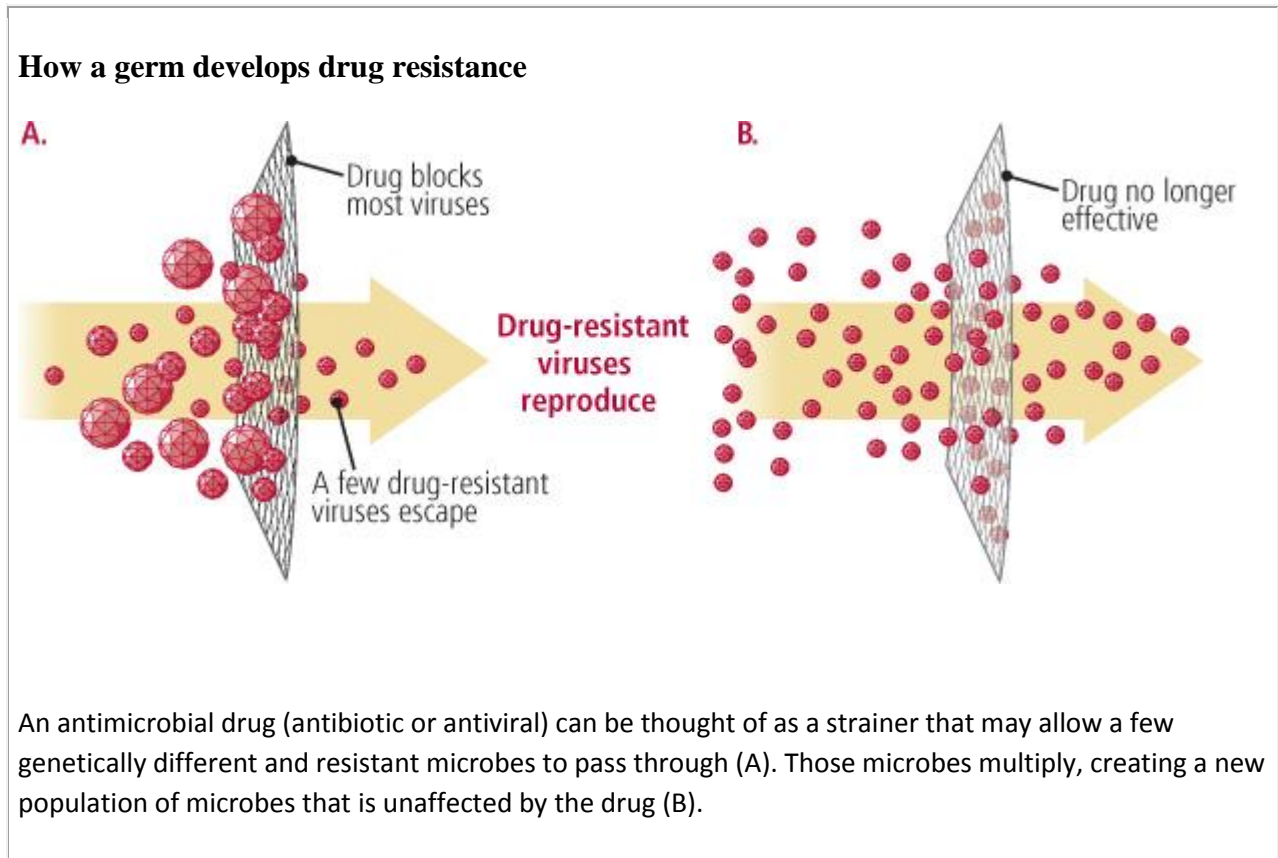
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Here's how it works: You take an antibiotic or an antiviral drug. It kills most of the germs it was intended to kill, except for a few genetic mutants that survive. The survivors multiply, creating a new population that is resistant to the drug (see the figure).



An antimicrobial drug (antibiotic or antiviral) can be thought of as a strainer that may allow a few genetically different and resistant microbes to pass through (A). Those microbes multiply, creating a new population of microbes that is unaffected by the drug (B).

Infectious diseases that were under control for decades are making comebacks in this way. Resistant strains, sometimes referred to as "superbugs," are now infecting up to 2 million people a year in the United States, with an accompanying death toll of more than 20,000. And drug-resistant microbes formerly found only in hospitals are now appearing in the community.

HIV, the virus that causes AIDS, is an important example of the power of a virus to stay one step ahead of the development of antiviral drugs. Drug-resistant strains of HIV frequently develop in the very people who are taking antiviral drugs to keep their infection under control. These people can then pass the new resistant strains to others.

The World Health Organization considers drug-resistant disease to be among the top threats to global health. Many of the world's top killers, including influenza, HIV/AIDS, diarrheal diseases, tuberculosis, and malaria, are mutating into resistant strains. Resistance to first-line drugs has been observed in all

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these diseases. In some cases, the level of resistance has forced a change to more expensive second- or third-line drugs. When resistance against these drugs also emerges, the world may run out of treatment options.

According to the World Health Organization, "the spread of antimicrobial resistance recognizes no national boundaries, and has reached proportions that require urgent action at national, regional, and global levels, especially in view of the decreasing development of new antimicrobial agents."

### ***Genetics***

With this dark cloud rumbling, advances in genetics may provide a silver lining. Our growing understanding of microbes at the molecular level may help tip the balance of power between microbes and humans in our favor. Back when vaccines and antibiotics first emerged, scientists were only beginning to develop the science of molecular biology and genetics that has given us the codes used by cells to control their functions. Since then, researchers have decoded all human genes and are now busily decoding the genes of infectious microbes in hopes of identifying and comparing different strains, developing diagnostic tests, and learning which strains are most dangerous and why.

Compared with humans, viruses have far fewer genes. Sequencing these genes allows scientists to study the functions of the proteins encoded by each gene. Their goal is to develop new vaccines and antiviral drugs. When the respiratory virus dubbed severe acute respiratory syndrome, or SARS, threatened to sweep the globe in 2003, health officials quickly released the "SARS chip." This was a quartz chip containing a sample of each gene that makes up the SARS virus. The chip was widely distributed to scientists around the world to help them study how the virus works and develop countermeasures. In another example, scientists developed a diagnostic chip for influenza containing 55 different variations of the influenza virus to help researchers identify which strain a person contracted and identify the more dangerous mutant strains.

Researchers are also looking at the vastly more complex human genome to uncover clues to why some people are more susceptible to particular infections or resistant to them. For example, if scientists can determine that the ability to absorb a certain vitamin or generate a certain enzyme is what makes one person more resistant to infection than another, they could use that information to boost levels of that enzyme or vitamin to ward off disease.

Scientists are already mining the human genome to determine why some people with HIV survive longer without getting sick than others do. An international research effort is analyzing the genetic characteristics of 2,000 people, known as viral controllers, who have low "viral loads" despite longstanding disease. Viral load is what dictates, to a large extent, whether you get sick or transmit the disease without getting sick. If a treatment could be developed to keep people's viral loads low, then the disease might be contained.

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### ***Climate change***

Some experts are concerned that changing climate patterns, including global warming, affect the spread of infectious diseases worldwide. The largest threat appears to be from insects that carry disease. If a mosquito species that transmits a particular infection is able, because of global warming, to live in a wider range, it will spread the infection as it expands its range. For example, the tropical virus chikungunya made a surprise appearance in northern Italy in 2007 as its vector, the tiger mosquito, began increasing its range. European health officials are expecting to see outbreaks in more northern regions as the mosquito continues to advance.

Other effects of climate change are also worrisome. As global warming melts glaciers and polar icecaps, some experts predict that flooding will increase in populous areas of the world. Mosquitoes breed in standing water, so flooding could boost the transmission of mosquito-borne illnesses. Climate change could also lead to increasing desert dust storms in Asia and Africa. These storms put dust into the atmosphere that could spread microbes around the globe.



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This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *Viruses and Disease*, available at [hvr.d.me/KcJyY](http://hvr.d.me/KcJyY).

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# Epidemic Proportions

The fight against infectious diseases increasingly links discovery with care

By Jake Miller



**A WAR WITH LITTLE PEACE:** The incidence of extensively drug-resistant tuberculosis continues to grow in Russia. This young man is a patient in a tuberculosis ward in a psychiatric hospital in the North Caucasus region of that nation.

Photo: Thomas Dworzak/Magnum Photos

When *Mycobacterium tuberculosis* invades a person's body, it doesn't just settle into the lungs and look for a spot from which to eke out a living. It hijacks that person's macrophages—cells that attack invading bacteria—and uses the mechanisms of inflammation to manipulate the environment around it, remodeling its new home to suit its needs.

Salmaan Keshavjee knew about *Mycobacterium*'s penchant for makeovers, and thought that this knowledge might be useful in the fight against tuberculosis. So he was intrigued when he learned of an unusual approach that researchers at Sweden's Karolinska Institutet were taking to control these bacteria-orchestrated renovations.

To understand this twist in the body's normal path of self-defense, and to find ways to get the immune response back on track, the Sweden-based team, led by Markus Maeurer, a professor of clinical immunology at the institute, had cultured the mesenchymal stem cells from patients with extensively drug-resistant tuberculosis (XDR TB), then reinfused the patients with those cultured stem cells. Because mesenchymal stem cells help suppress inflammation, the researchers wanted to see if they could safely dampen and refocus the inflammatory response without compromising immune function.

"Their preliminary data suggested that the stem cells didn't suppress immunity in an adverse way, and surprisingly, the patients who received the transplanted cells did much better on their XDR TB treatment than typical patients in their condition," says Keshavjee, an HMS associate professor in the Department of Global Health and Social Medicine and a physician in the Division of Global Health Equity at Brigham and Women's Hospital. With the treatments now in use, fewer than a third of

patients with XDR TB recover, but in this small initial study, all the participants appeared to recover.

Keshavjee is developing a partnership with the institute's team, laying a foundation for more-extensive trials of the treatment in Russia and Peru. "Saving lives from a disease that's killing people—that's always good," Keshavjee says. "But this work also opens the door to thinking about tuberculosis differently. If the mycobacterium is manipulating its environment by modulating T cells and other immune cells, we need to ask, 'What if we unmodulate that environment?'"

"Inside our bodies, the bugs are living in an ecosystem," he adds. "As humans, we also have our own ecology, which plays out in society. Recognizing the complex biosocial nature of infectious diseases moves you toward some crucial insights about how these diseases work and how to fight them."

To fight infectious diseases worldwide, biomedical researchers and clinicians are joining efforts to apply laboratory-based discoveries to the challenge of saving the lives of people with tuberculosis, cholera, and other age-old ravages. These international collaborations are increasingly considering such diseases in context, as integrated parts of complex interconnected systems that involve humans.

"We now have genomic and proteomic platforms that are beginning to have immediate relevance to the challenges of diagnosing and treating infectious disease in poor communities," says Paul Farmer '90, the Kolokotronis University Professor at Harvard, head of the Department of Global Health and Social Medicine at HMS, and a cofounder of Partners In Health, an international nonprofit that brings health care to the poor. "Many of these new technologies are more portable, scalable, and affordable than ever before."

## **In Black and White**

Tuberculosis is a global public health issue that is unevenly distributed: the burden of the disease is highest in Asia and Africa, with India and China accounting for almost 40 percent of cases. Africa has 24 percent of the world's cases and the highest rates of disease and death per capita. In the Russian Federation, XDR TB is a particular concern: it has rapidly spread through prison populations. In Peru, while the incidence of tuberculosis is decreasing, the incidence of multidrug-resistant tuberculosis is on the rise. Overall, according to a 2012 report from the World Health Organization, there were an estimated 8.7 million new cases of tuberculosis and 1.4 million deaths worldwide from the disease in 2011.

Similar sobering statistics can be found for cholera. Although up to 80 percent of cholera cases can be successfully treated with low-cost oral rehydration salts, the WHO estimates that annually more than 100,000 people succumb to the disease. The impact of cholera is most acute in regions with poor sanitation and unsafe supplies of drinking water, conditions that annually spawn three to five million cases

worldwide. The entire country of Bangladesh is considered at high risk for this disease, the only country with this designation from the WHO.

## **Delete Buttons**

Like tuberculosis, cholera elicits a complex immune response. The infection takes place in the mucosal membrane of the small intestine, where billions of beneficial bacteria live. Our gut microbiota perform welcome chores such as fermenting carbohydrates to release their useful energy. Although our gut mucosa is always on the alert for foreign bacteria, killing every newcomer would be imprudent, as some may be useful in maintaining the health of their human host. Yet when a pathogen is identified, the mucosal cells mount a vigorous immune response.

Unfortunately, the basic mechanisms of that response are still poorly understood. This knowledge gap has hindered the development of effective, durable vaccines for diseases such as cholera. In fact, current vaccines offer only partial protection that lasts for just a few years.

To extend this protection, or perhaps even block the disease permanently, researchers, including John Mekalanos, the Adele H. Lehman Professor of Microbiology and Molecular Genetics and head of the Department of Microbiology and Immunobiology at HMS, are tweaking the genetic makeup of *Vibrio cholerae*. The trick has been determining how to eliminate the genes that turn off the disease without disturbing the ones that elicit an immune reaction. Mekalanos, along with Mike Levine at the University of Maryland, has pioneered the use of a live oral cholera vaccine. This vaccine uses a genetically altered version of the organism that is unable to cause disease.

In addition to learning which genes halt the cholera bacterium, it is necessary to understand which ones are activated during its transmission and infection. Stephen Calderwood '75, the Morton N. Swartz, M.D. Academy Professor of Medicine (Microbiology and Immunobiology) at HMS and Massachusetts General Hospital, is looking at gene expression at different points in *V. cholerae*'s life cycle to determine which genes are expressed by the pathogen during infection, as well as which trigger immune responses in the human host.

For this research, Calderwood is collaborating with clinicians and researchers at the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh. Calderwood's team has collected thousands of samples from patients who have been hospitalized with severe cholera.

## **The Sniff Test**

The insights from such molecular biology studies can also lead to some surprising diagnostic tools for infectious disease. The tubercle bacterium, for example, can be insidious; it can lurk in the lungs of a mildly infected patient for years. Active infections of the bacterium, however, release a detectable signature of volatile

organic compounds. This airborne fingerprint may be useful in diagnosing the disease, particularly in children; not only is it difficult for them to produce sufficient sputum for analysis, their sputum contains relatively few of the organisms.

“A baby’s exhalation could be captured,” says Ed Nardell, an HMS associate professor of medicine at Brigham and Women’s, “so she wouldn’t need to produce a sputum sample.”

Nardell is part of a team that’s investigating the effectiveness of a new gas chromatography technology that can detect the chemical signature of *M. tuberculosis* in a few puffs of human breath. In some parts of the world, giant Gambian rats, trained to sniff out the bacterium’s signature compounds, are already being used to detect *M. tuberculosis* in sputum samples. Unlike humans using microscopes, these trained rats accurately examine specimen after specimen without fatigue—and all for the fee of a sweet treat.

## **Phase Shifts**

Another complicating factor in the fight against these diseases is that the causal agents change throughout their life cycles. The tubercle bacterium modifies its environment to suit its needs. By contrast, the cholera bacterium acclimates itself to the environment it inhabits. Many cholera microbes spend their lives in water, feeding on plankton to derive energy. During this aquatic phase, the adaptations that help them survive in water make them much less infectious in humans. Calderwood and his team, however, have discovered that the cholera microbes found in the fecal matter of infected humans—before the microbes adapt to the aquatic environment—are hyperinfectious for a brief period following their evacuation from the host.

Because this human ecology is important to the transmission of the disease, Calderwood’s collaborators in Bangladesh dispatch research teams to patients’ homes. To study disease transmission in a household, the team invites all family members, sick or well, to participate. While visiting, the team can survey a patient’s living conditions and, if needed, provide medical care to other family members.

“These diseases are perfect examples of how knowing the social context of an infection can be crucial,” says Mercedes Becerra, an HMS associate professor of global health and social medicine. “It’s not some vague notion of social context; it’s actually seeing the physical setting where people live and testing the strains that have infected different members of a family or community. The household is a really important unit for analysis and for medical interaction.”

Just as it is crucial to see how the bacteria operate—at the chemical and genetic levels—in human hosts, it is important to understand how the illness plays out in the context of specific human populations, according to Becerra.



## **Knit One, World View**

These diseases also interact in another key ecosystem: the community of HMS researchers working on global health and infectious disease. Some may be community health workers with knowledge of the lives of their neighbors. Some are social scientists measuring the clinical effectiveness of different approaches to preventing and treating these diseases, or mapping the social, political, and historical aspects of health. Geneticists, immunologists, engineers, and architects—each play a role in teasing out the intricacies of these diseases and the pathogens that cause them.

“To beat these diseases, somebody has to understand the immune system and the bugs at different levels,” Becerra says, “while others have to work on understanding the impact on patients and families. That’s why it’s so important to work together from multiple angles, linking discovery with care delivery—and then turn around to look for new discoveries.”

*Jake Miller is a science writer in the HMS Office of Communications and External Relations.*

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<http://hms.harvard.edu/news/harvard-medicine/harvard-medicine/how-bugs-are-built/epidemic-proportions>

# Investing in health systems may stem Ebola outbreak

A broad humanitarian response that includes investments in health care staff, medical resources, and health systems is more likely to be effective in halting the current Ebola outbreak in West Africa and creating sustainable models for responding to future infectious disease outbreaks than “a surge of stopgap solutions,” according to a Viewpoint article published October 6, 2014 in the Journal of the American Medical Association (JAMA).

The article was written by Ashish Jha, K.T. Li Professor of International Health and Health Policy at Harvard School of Public Health and director, Harvard Global Health Institute; Andrew Boozary, SM '14 visiting scientist in the Department of Health Policy and Management; and Paul Farmer, MD '90, PhD '90, Kolokotronis University Professor of Global Health and Social Medicine at Harvard Medical School and co-founder of Partners in Health.

The Ebola epidemic—which the authors described as one of the most devastating health crises of the 21st century—has exposed “the pathology of chronic neglect amid broad global inequalities.” Before the outbreak, Liberia’s 4.3 million people had only 51 physicians—less than many U.S. teaching hospital clinical units. If the outbreak occurred in cities like Boston or Toronto, the health systems would better control the disease and there would be far fewer deaths, the authors wrote.

The lack of protective equipment, IV fluids, and clear treatment guidelines has dissuaded health workers from risking their lives to care for Ebola patients and has contributed to patients’ mounting distrust in health systems. “When people receive care that is unsafe or ineffective, or they are not treated with respect, it is little surprise they avoid further care,” the authors wrote. “Preventing such ‘betrayals of trust’ through a systematic focus on quality is crucial, for both the current epidemic and the next.”

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<http://www.hsph.harvard.edu/news/hsph-in-the-news/investing-in-health-systems-may-stem-ebola-outbreak/>

# Ebola: A long way from over

Though this epidemic is waning, the conditions that fostered it remain, so it can strike again

March 5, 2015 |

By Alvin Powell, Harvard Staff Writer



“The majority of people who die of Ebola won’t die of Ebola, they die because they don’t have a health care system,” said Paul Farmer, who, through the nonprofit he heads, Partners In Health, is working to improve such systems in two of the afflicted nations, Liberia and Sierra Leone.

The worst days of the Ebola epidemic appear to be past, but authorities speaking at Harvard warned Thursday against any sense of “triumphalism” until the last patient is healed and health system improvements are in place to prevent recurrences.

The experts on the disease and the campaign to fight it, both in West Africa and in the United States, reflected on lessons that were hard-won over the past year, during which 23,000 people were infected, mostly in three West African nations, and nearly 10,000 died.

A key lesson, according to Marshall Lyon, a physician at Emory University Hospital, where four U.S. Ebola patients were treated, is that defeating the disease is medically straightforward: provide supportive care as the patient’s body fights off the virus.

While that prescription is pretty simple, Lyon said that doesn’t mean it is easy. The disease wracks patients with horrific bouts of vomiting and diarrhea — one patient lost 10 kilograms (about 22 pounds) of body weight in one night — that require oral rehydration, if they can keep fluids down, or intravenous rehydration, if they cannot.

Even with rehydration, patients aren’t out of the woods. The fluid loss upsets their bodies’ normal balance of electrolytes, so hospitals have to check those balances and ensure they’re restored properly. One patient had diluted potassium levels, which created cardiac arrhythmia. In addition, the disease also can cause organ failure, and some patients spent time on dialysis machines or ventilators while their kidneys or lungs recovered.

“There is nothing magic about taking care of these patients. It’s supportive care,” Lyon said. “It’s not rocket science ... but it is demanding and took a lot of effort.”

The access to modern medical facilities in the United States means that the fatality rate for the few cases here has been far lower than in West Africa, leading some observers to question just how inherently deadly the disease is — or ought to be. Paul Farmer, Harvard’s Kolokotronis University Professor of Global Health and Social Medicine, pinned the epidemic’s deaths not so much on the disease as on the region’s failed health care systems.

“The majority of people who die of Ebola won’t die of Ebola, they die because they don’t have a health care system,” said Farmer, who, through the nonprofit he heads, Partners In Health, is working to improve such systems in two of the afflicted nations, Liberia and Sierra Leone.

Lyon and Farmer made their comments at an all-day conference on the Ebola epidemic and the responses to it at Harvard Medical School’s (HMS) New Research Building. The conference, organized by the HMS Department of Microbiology and Immunobiology, attracted an audience of several hundred to the Joseph B. Martin Conference Center.

The event took place as positive signs in treating the epidemic continued to emerge. Liberia reported no new cases during the week of March 1 for the first time since May 2014, though 132 new cases were reported that week in Sierra Leone and Guinea.

The session was introduced by HMS Dean Jeffrey Flier and John Mekalanos, the Adele Lehman Professor of Microbiology and Molecular Genetics and chair of the HMS Department of Microbiology and Immunobiology. Mekalanos said although the event was focused on Ebola, the issues it addressed were applicable in other medical settings.

“The issues here are really quite broad,” Mekalanos said, adding that old threats from ailments such as HIV, tuberculosis, pertussis, and measles haven’t gone away, even as threats like MERS (Middle East Respiratory Syndrome), multidrug-resistant superbugs, and deadly strains of influenza emerge. In addition, the speed and ease of global travel means that an ailment in a region that seems remote one day can be on your doorstep the next.

“It really reminds us how we don’t know where the evolutionary race between microbes and our immune system will lead us,” Mekalanos said.

Mekalanos and Jens Kuhn, lead virologist at the National Institute of Allergy and Infectious Diseases and an expert on filoviruses, the family of viruses to which Ebola belongs, called for more basic research, saying that too much remains unknown about Ebola.

Kuhn said that though much has been written during the recent outbreak, most of the information is not useful scientifically, since it's heavy on anecdote and light on scientific rigor. For example, he said, though fruit bats have been fingered as a likely animal reservoir for the disease, that contention is based on the fact that some bats had antibodies for it, which could simply mean that they had been exposed to it, not that they serve as a natural reservoir.

"I would say we can say bats are most likely exposed, but whether they're the host is unclear," Kuhn said, adding that other animals are also possible hosts, including the bush pig, the blue duiker, the central chimpanzee, and the lowland gorilla. "There are many gaps that need to be filled. ... We don't know anything about the ecology of this virus."

Another concern, he said, is that most of the scientific work that has been done has been limited to a single strain — there are five species of Ebola — and the assumption that the results can be generalized to the others could turn out to be untrue.

"I would strongly encourage more basic research," Kuhn said.

Kuhn questioned whether public campaigns against eating bushmeat — wild animals caught for food — are warranted, since the evidence that infection comes from bushmeat is weak, and the meat provides an important source of protein.

Farmer, whose Partners In Health organization has rapidly expanded since arriving in the region several months ago, agreed, saying that nutrition continues to be an important factor in the health of people there. That factor, he said, along with basic medical care, are important keys to fighting Ebola.

Farmer said the difference in death rates between those who get Ebola treatment in the West and those treated in West Africa shows what is really going on in fighting the disease: People who can get the proper supportive care have a much greater chance of living, meaning that the core issue really is one of ensuring that high-quality care is available everywhere.

"The majority of people who have received early aggressive care have survived. That means most people never receive aggressive care," Farmer said. "Ebola triumphalism is just not true."

Farmer said the most "fatal strain" in Ebola is the "low aspirations that we have for medical care for people living in poverty." He called those "the poison that we have to work against."

Anthony Fauci, director of the National Institute of Allergy and Infectious Disease, who participated in the discussion by video connection, pointed out that with

properly functioning health care systems, the number of patients to be treated would be far less, because early detection, contact tracing, isolation, and other steps could help stop an epidemic early.

When asked what the medical community can do to further the fight against Ebola, Fauci said it's important to emphasize that health is not local any longer.

"We have a moral responsibility to address global health," Fauci said.

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<http://news.harvard.edu/gazette/story/2015/03/ebola-a-long-way-from-over/>

# Public Enemies

Scientists get pathogens to spill their secrets

By Elizabeth Cooney

Invisible invaders have long lived among us. Bacteria, viruses, and parasites have had an upper hand as agents of sickness and death for much of our joint existence.

In sickrooms and on battlefields, antibiotics vanquished bacteria only in the past century. The victory seemed sweeping and miraculous. It was, however, short-lived: Bacteria are resilient pathogens that mutate to survive challenges to their well-being. Replicating every 20 minutes, these microbes have proven to be quick-change artists adept at thwarting drugs that target their weak points.

Viruses are equally mutable, although it is their genetic infidelity that makes them so slippery. A person infected with the human immunodeficiency virus (HIV) may carry multiple versions of the original virus, copies whose genetic makeups differ so markedly that no single drug can recognize them all.

Parasites, including the insidious *Plasmodium falciparum*, which causes malaria, evolved with humans in order to survive. We know this because they've left their fingerprints on our genome.

All told, antimicrobial drug resistance strains budgets and threatens some of the greatest successes in global health. In the United States, for example, treating antibiotic-resistant infections costs \$20 billion per year.

Worldwide, up to one in five people diagnosed with HIV infection harbor a strain that is resistant to antiretroviral therapy, now the standard of care. Even antiviral drugs aimed at seasonal influenza are losing their punch, unable to topple influenza A.

Progress against malaria, which causes nearly one million deaths each year—90 percent of those among children in Africa—is hampered by emerging resistance to the only available antimalarial drug. The story is similar for tuberculosis: more than 50 countries have reported cases of extensively drug-resistant tuberculosis.

A new breed of researchers has emerged to counterattack the resistance efforts of these changeable microbes. Scientists are finding ways to reanimate so-called wonder drugs and to develop new technologies that reveal genetic vulnerabilities. These investigators peer back into evolutionary history and trace forward the microorganisms' escape routes to discover ways to eradicate the pathogens and the infectious diseases they cause. But that's not all. These investigators also seek to apply the lessons learned from a given pathogen to other microbial foes that evade our immune defenses.



## **In the Pink**

For Bruce Walker, the challenge is HIV and the unusual patients called “elite controllers,” untreated patients who live with only trace levels of the virus that causes AIDS. He looks beyond the global pandemic.

“I think HIV is giving us a window into the immune system,” says Walker, an HMS professor of medicine at Massachusetts General Hospital and director of the Ragon Institute. “If we’re talking about the future of medical interventions, I think the next decade is going to show incredible progress in terms of harnessing the immune system to prevent and cure human diseases.”

Research has produced drug cocktails that keep HIV infections in check. Scientists generally agree that combination therapies will likely be necessary to fend off other pathogens, too. As an example, Suzanne Walker, an HMS professor of microbiology and immunobiology, points to a once-successful group of antibiotics known as beta-lactams, which have been disarmed by a bacterial stratagem. Beta-lactams act by targeting the bacterial cell wall, disrupting how a cell divides, and disabling the way it grows and establishes an infection. To foil such attacks, bacteria that were once sensitive to beta-lactams changed; they became able to produce an enzyme that chews up the antibiotic before it reaches its target. How to reestablish beta-lactam’s effectiveness? One approach: create a drug that blocks the drug-eating enzyme. Once the enzyme is rendered ineffective, the first-line antibiotic works again. This, says Walker, is the strategy behind the composition of Augmentin, the pink liquid known to any parent with a child prone to ear infections. It combines beta-lactam with a defense against the aggressive enzyme.

## **Envelope, Please**

Although rebooting beta-lactam by disabling the disruptive enzyme is effective against mild infections such as sinusitis, pneumonia, and bronchitis, it doesn’t faze tougher ones, such as MRSA.

Methicillin-resistant *Staphylococcus aureus*, named MRSA after the antibiotic it deflects, is one of the most virulent pathogens to plague hospitalized patients. Its facility in developing resistance has allowed it to evade all major classes of antibiotics. Suzanne Walker studies the cell envelope of *S. aureus*, the first line of defense for the organism, but also a point of vulnerability.

In their search for a way to target MRSA, Walker’s research team screened genes and proteins in *S. aureus* cells to understand steps along the resistance pathway—and to then find compounds that might work against another target. Together with scientists at the HMS Institute of Chemistry and Cell Biology–Longwood Screening Facility, Walker’s team singled out an effective chemical compound. A pharmaceutical company is now testing that compound along with other drug candidates that hit the same target.

“If you combine any one of these compounds—including ours—with beta-lactams, they overcome methicillin-resistant infections in animals,” Suzanne Walker says. “That’s pretty good.”

Walker is cautious when she talks about her lab’s discovery, pointing to the long history of short-lived successes in our battles against infectious diseases. A footnote to that history, in fact, proved pivotal to her decision to become a chemist. When Walker was nine years old, she heard it was possible to die from a hangnail that had become infected.

“I realized that little things used to kill people,” she says. “That was when I learned that antibiotics had not always existed.”

That revelation propelled Walker to study biological pathways and to pursue new ways to target infectious disease pathogens.

## **Particle Field**

For Tim Lu ’10, the eye-opening career moment hit when he was a medical student on rotation at a VA hospital. He was struck by the number of chronic wound infections he was seeing and by the fact that patients returned again and again, never cured.

Lu, an assistant professor of biological engineering and electrical engineering at MIT, looked backward for innovation and found it in an area of biology and infectious disease study that had been shelved for nearly 80 years. He became fascinated by bacteriophages, viruses that were first identified in the early twentieth century. Capable of targeting bacteria in highly specific ways, phages have evolved in step with the bacteria they infect and consume. Yet they do not harm human cells.

More than a century ago, scientists sought to capitalize on this benevolence in studies that attempted to marshal the phages’ antimicrobial activity to halt bacterial infections in people. Sometimes the phages worked as the researchers hoped; other times they didn’t. This perceived unreliability caused bacteriophages to fall from favor as potential antimicrobials, a loss of interest hastened by the expanded use of the more broadly effective, and lifesaving, penicillin.

Those early hit-or-miss results, however, stemmed from a trait that now makes the phages relevant, Lu says. Bacteriophages naturally target certain species of bacteria, some narrowly and some broadly.

Bacteriophages have already proven their worth in molecular biology as tools for overproducing targeted genes or for picking out peptides, short chains of amino acids that have specific properties. Lu and others in the field see a wider potential for these small workhorses.

“Phages are a form of personalized therapy,” says Lu. “You can tune the bacteria that the phage likes to feed on.”

## **Tuning Fork**

Bruce Walker also seeks to fine-tune systems, specifically the human immune system so that it will fight off HIV. He has witnessed how drug cocktails have changed the face of HIV infection since the early days of the epidemic, when he first saw AIDS patients while a resident at Mass General. After more than 30 years as a researcher in the field, Walker says, “HIV is gradually revealing its secrets.”

Among those secrets are the rare individuals who become infected but whose immune systems do not become overwhelmed by a high viral load. Some such people have been infected for more than 30 years and remain healthy without treatment. Scientists have learned that these elite controllers possess a genetic variation that keeps HIV at bay, holding it harmless in reservoirs within their bodies.

The same variation is also associated with a heightened risk for autoimmune diseases, kicking immune systems into high gear and making individuals vulnerable to disorders that cause the body to consider its own tissues to be foreign invaders, marked for destruction.

“The same thing that helps elite controllers potentially fight HIV makes one more susceptible to the cells of one’s own body,” Walker says. “To understand how it’s happening gives us the hope that we might be able to augment immune control of HIV in people who are not controlling it spontaneously.”

Drawing on analytic skills more typically applied to stock market movements, computational biologists working with Walker have discovered regions of striking rigidity in the virus—genetic material that has stayed stable in a sea of dynamic mutations. These stable regions might be good therapeutic targets. Other HMS researchers, in collaboration with scientists at Rockefeller University, have isolated potent HIV-neutralizing antibodies from elite controllers.

Knowing how the immune system functions in such powerful ways in some individuals may have broad implications for understanding how the immune system hides disease, Walker speculates.

“We don’t yet know how to induce those antibodies, but we do know that the body, under the right circumstances, can make them,” he says. “We just have to figure out how to initiate that response with a vaccine.”

## **Fitness Regimen**

As with the genetic mutation that confers both HIV control and autoimmune disease risk, changes in genetic character also affect another infectious disease: malaria.

For more than a century, scientists have known that the mutation that causes sickle-cell disease, a red blood cell disorder, also protects people from malaria. This was the first elucidated example of natural selection in humans.

Pardis Sabeti '06, an associate professor of organismic and evolutionary biology at Harvard University, studies genetic variation in the malaria parasite as it occurs through the forces of evolutionary pressure. Like other microbes, the malaria parasite has developed the ability to resist drugs. A program to eradicate the disease, launched in the 1950s, began to fail by the 1970s as the parasite developed resistance not only to chloroquine, the first-line treatment, but also to the insecticide DDT, an agent aimed at mosquitoes that carry the parasite. As each new mutation arose, the parasite evolved; newly mutated forms then spread worldwide. Sabeti calls this “evolution in action”—a demonstration of natural selection occurring in observable time.

“There’s a good percentage of the country that doesn’t believe in natural selection or evolution, but everybody understands the emergence of drug resistance,” Sabeti says. “These microbes are evolving, they’re changing, they’re developing resistance, and they’re spreading. And it’s happening all the time.”

Malaria is deeply challenging for another reason: the parasite needs humans as part of its life cycle. “Anytime you become a critical part of a microbe’s life cycle, it’s going to be a far bigger challenge to get it to give you up,” Sabeti adds.

Better knowledge of the malaria parasite’s changing genome can contribute to vaccine development and to better diagnostics. This knowledge can also be used to track which mutations lead to drug resistance to help inform which treatments to offer which patients.

“We have not exhausted our ability to get more information from understanding our defenses against malaria,” Sabeti says. “The more we understand how these microbes use their own diversity to their advantage, the better off we will be in our development of treatments, vaccines, and surveillance capacity.”

Suzanne Walker hedges when asked if she is hopeful about taming antibiotic resistance.

“I’m not unoptimistic, so long as people think differently about the problem. We need to take a variety of approaches and explore novel ideas,” she says.

The microbes—in all their diversity and novelty—won’t wait.

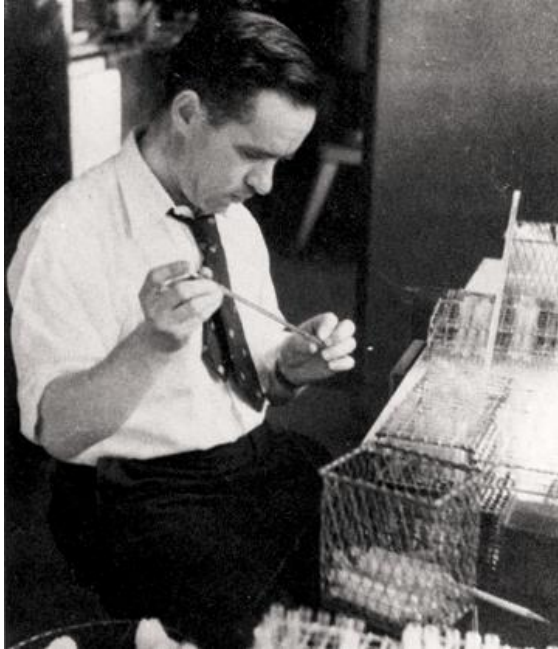
*Elizabeth Cooney is a science writer in the HMS Office of Communications and External Relations.*

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## To Finland and Back

The field of infectious disease research at HMS is filled with luminaries and rich in legacy  
by Scott H. Podolsky



For more than two centuries—from the pre-germ theory era, through the antibiotic age, and into recent decades marked by emerging infections and fears of a postantibiotic period—researchers at Harvard Medical School have confronted infectious disease. HMS faculty such as Benjamin Waterhouse; Oliver Wendell Holmes, Class of 1836; and Maxwell Finland '26 have figured prominently in this work, as have Harvard researchers Theobald Smith, Edward Kass, and Nobelists John Enders and Thomas Weller '40. The work by these scientists and others has spanned the spectrum from vaccination and infection control to the rational application of antimicrobial therapy itself.

The roots of this interest in infectious disease might be traced to Waterhouse, the School's first Hersey Professor of the Theory and Practice of Physic. Waterhouse trained in London and Edinburgh at the time of the American Revolutionary War. This did not help his application to the Hersey Professorship—both John Hancock and Samuel Adams opposed his appointment—but it did lead to important London connections. Edward Jenner, an English physician, performed his classic smallpox vaccination experiments in 1796, and Waterhouse himself received the vaccine from friends in England in July 1800. His enthusiasm for vaccination, which earned him the nickname “Jenner of America,” began at home: Waterhouse performed his first vaccination on his five-year-old son, then on three more of his children and two servants, and later confirmed the vaccine's efficacy by inoculating all of them with smallpox. Waterhouse also supplied vaccine to Thomas Jefferson, who vaccinated his own family members and arranged for the vaccination of members of a Native American delegation to Washington, DC, in December 1801. But Waterhouse later fell from favor at HMS. After antagonizing the Warrens, the Boston family instrumental in the founding and development of HMS as a center for medicine and medical education, he was ousted from the School in 1812 and replaced by Boston physician James Jackson.

Jackson's son pursued medicine in Paris and, sadly, died there of typhoid fever. But before his untimely death, he studied with the young Holmes, of whom the elder Jackson wrote: “Do not mind his apparent frivolity.”

When Holmes returned home, he set up shop in Boston under a sign stating, “Small fevers gratefully received.” But for all his wit, Holmes was deadly serious when necessary. He was never more so than during his investigations of the contagiousness of puerperal (childbed) fever, conducted and written “in a great heat and with passionate indignation” in 1843. After collecting cases from across New England, Holmes reported his findings to the Boston Society for Medical Improvement, demanding that physicians take care not to spread the pestilence. He advised that those physicians who were linked to two cases of puerperal fever “within a short period” withdraw from the practice of obstetrics for at least a month. Applying his full literary talents to the cause, Holmes angrily concluded: “The woman about to become a mother, or with her new-born infant upon her bosom, should be the object of trembling care and sympathy wherever she bears her tender burden, or stretches her aching limbs.... God forbid that any member of the profession to which she trusts her life, doubly precious at that eventful period, should hazard it negligently, unadvisedly, or selfishly!” Holmes delivered his cautionary statements a full 4 years before Hungarian physician Ignaz Semmelweis conducted prospective studies of the contagiousness of puerperal fever, and 36 years before Louis Pasteur identified the streptococcal bacterium as the agent that causes puerperal fever and erysipelas.

### **Infectious Personality**

Another six decades would pass before sulfa drugs would be used to successfully treat puerperal fever and erysipelas. At HMS, sulfa drugs, and then antibiotics, would be evaluated by Finland, arguably the foremost antibiotic researcher in the world at the time.

Finland had started at Boston City Hospital in the mid-1920s, conducting controlled clinical trials of antipneumococcal antiserum for the treatment of pneumonia. Throughout the next five decades, nearly every successful antimicrobial agent, from sulfa drugs to penicillin and broad-spectrum antibiotics, seemed to require what Robert Petersdorf—himself a renowned infectious disease expert and, at one time, the president of Brigham and Women’s Hospital—called the “Finland stamp of approval.” In the process, Finland worked to instill caution and rigor in the emerging post-World War II field of clinical pharmacology by demanding objectivity and rigor from investigators.

By any measure, Finland’s impact was enormous. He trained more than 100 fellows in infectious diseases, including seven future presidents of the Infectious Diseases Society of America (he served as its first president) and numerous others who would go on to chair infectious disease departments and lead training programs of their own. As his Harvard colleagues remembered: “There were relatively few places in which to train in infectious diseases in the years immediately following the cessation of World War II, and expansion of training programs basically had to wait until his former fellows had risen to prominence.”

Finland left other important legacies. He drew early attention to emerging staphylococcal antibiotic resistance, writing in 1951: “No honest or self-respecting physician or surgeon, whether his practice be limited to pediatrics, geriatrics, or any other special field of medicine or surgery, can help but feel a bit conscience stricken each time he prescribes or administers a sulfa drug or antibiotic after a hurried visit to the bedside of a patient or after a brief interview and examination in his office.... Are we in medicine, like our counterparts in industry, exhausting our most valuable resources at too rapid a rate?... Only time will tell.”

Fundamentally, Finland attempted to inculcate “rational” therapeutics—the right drug for the right patient at the right time at the right cost—more generally. In the 1950s, the U.S. Food and Drug Administration was still assessing only drug safety, not efficacy. Infuriated by combination antibiotic products promoted on the basis of what were largely testimonials, Finland argued for the importance of the controlled clinical study to underpin rational therapy. By 1959, his protestations were picked up by the popular press, just as Senator Estes Kefauver was about to begin his landmark investigations into the pharmaceutical industry. The Kefauver–Harris Amendment to rules governing the approval of new drugs had passed by 1962, mandating proof of drug efficacy via “adequate and well-controlled” studies by qualified investigators.

Today, the legacies of Waterhouse, Holmes, and Finland continue to shape the many approaches to infectious disease investigation at HMS. Whether devising and testing new vaccines, discovering novel targets for antimicrobials, monitoring or attempting to prevent antimicrobial resistance, or taking measures to ensure the rational worldwide delivery of antimicrobials to those who need them, HMS researchers continue to confront infectious disease at the intersection of patients and clinicians, bugs and drugs, and science and society.

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<http://hms.harvard.edu/news/harvard-medicine/harvard-medicine/how-bugs-are-built/finland-and-back>



# Under the Radar

A vast network monitors the veiled movements of virulent pathogens  
by Shraddha Chakradhar

In the late summer of 1999, physicians in Queens, New York, confronted something out of the ordinary: patients with encephalitis and muscle weakness—and addresses notably near one another. Doctors were perplexed; there seemed to be no recognizable pathogen associated with the outbreak. Nearly a week after the first cases, and the first fatalities, the New York City Department of Health and the Centers for Disease Control and Prevention (CDC) identified what turned out to be West Nile virus. The news unnerved the infectious disease community: This was the first recorded appearance of West Nile virus in the United States.

“I canceled my trip to San Francisco,” says Alfred DeMaria ’74, state epidemiologist and medical director for the Bureau of Infectious Disease in Massachusetts. “I knew all hell was about to break loose even if the virus wasn’t in Massachusetts.”

And sure enough, the presence of West Nile virus shook, and continues to shake, the nation, with widespread spraying of insecticides aimed at killing virus-bearing mosquitoes and annual warnings urging people to protect themselves from insects carrying the virus.

In 1999 there were 62 cases and 7 deaths reported. In the years since the initial outbreak, incidence has varied, with 2003 representing a peak; the CDC registered nearly 10,000 cases and more than 260 deaths that year. In 2012, the CDC recorded 5,674 cases of West Nile virus disease, of which 51 percent were neuroinvasive, precipitating conditions such as meningitis or encephalitis. Although the incidence continues to dip, the annual number of deaths has seesawed: in 2012, 286 people succumbed to the disease, more than in the peak infection year of 2003.

In the nearly 14 years since West Nile came ashore, disease surveillance teams in the United States have had to address the appearance of other previously unknown pathogens, from the severe acute respiratory syndrome (SARS) virus of a decade ago to the new strains of influenza viruses that develop annually. While threats of fast-adapting and hard-to-stop bugs are common, what keeps the nation’s public health infrastructure from being overwhelmed is the information exchanged through an intricate and efficient network of physicians, infectious disease researchers, epidemiologists, and public health officials who survey, identify, and, when necessary, respond to emergent threats.

## Who Are You?

The CDC and global health agencies such as the World Health Organization (WHO), as well as state and local public health units, have developed tools to monitor the spread of infectious disease. The WHO, for instance, supports the use of WHONET, a software project begun by Thomas O’Brien ’54, an HMS associate professor of

medicine at Brigham and Women's Hospital, and developed and distributed by John Stelling '91, an HMS instructor in medicine at the hospital. The two researchers codirect the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance.

WHONET changed the face of public health and disease surveillance by leveraging existing routine information resources available in microbiology laboratories worldwide.

"Doctors used to send samples to microbiology labs, which would then send the test results to public health departments," says Stelling. "So public health officials would often know about a disease before doctors would."

With WHONET, authorized users in more than 100 nations contribute to local, regional, and international databases for tracking microbial populations, including information on bacterial, fungal, and parasitic pathogens isolated in hospitalized and community-dwelling patients. This level of monitoring allows clinicians and epidemiologists to stay abreast of trends, point occurrences, and broad outbreaks.

WHONET has, for example, been useful for tracking in real time the global spread of carbapenem-resistant Enterobacteriaceae. The Enterobacteriaceae are a family of bacteria that include *Escherichia coli* and the *Klebsiella* species, normal inhabitants of the human gut. Resistance to the carbapenem family of antibiotics, last-line agents in the treatment of patients infected with multi-drug resistant, illness-causing gram-negative bacteria, is troubling—and often fatal. Of particular concern is that many of these infections are health care associated and attributable to the use of medical devices that raise the risk of infection, such as ventilators or intravenous and urinary catheters.

## **National Guard**

A tool that has long been a touchstone for U.S. physicians and researchers is the CDC's Morbidity and Mortality Weekly Report, which highlights disease trends, occurrences, and fatalities based on information collected from state departments of public health. In addition, the CDC houses departments responsible for infectious disease surveillance. Within its Office of Infectious Diseases, for instance, is the National Center for Emerging and Zoonotic Infectious Diseases, which tracks diseases that are passed to humans from animal sources.

The CDC has networks that connect state and regional public health organizations. And it has formed partnerships with the National Association of County and City Health Officials and the Association of State and Territorial Health Officials in order to share near real-time data. Overall, the goal is to maintain effective communication and preparedness at all levels of the public sector.

State departments of public health, in turn, have their own systems that allow clinicians, laboratory personnel, public health workers, and epidemiologists to

report and share data. The Massachusetts Virtual Epidemiologic Network (MAVEN) has been the Commonwealth's system since 2006.

"MAVEN allows public health officials to identify infectious diseases quickly," says DeMaria. "Once the disease has been identified, a public health worker investigates to help prevent its spread."

The system has been instrumental in improving the timeliness of the reporting of hepatitis A infections and, subsequently, the ability of public health officials to identify infected individuals who may be at risk for infecting others. Although MAVEN was developed to meet the specific needs of Massachusetts, other jurisdictions, including Connecticut, North Carolina, and New York City, have adopted the software.

### **Continental Drift**

Although surveillance tools can help identify disease trends, what happens when a patient comes to a hospital with an unidentified illness?

"The first step in evaluation is to consider the history of the patient," says David Hooper, an HMS professor of medicine and chief of the Infection Control Unit at Massachusetts General Hospital. "And in such cases, the person's travel and exposure history and other medical conditions become important. The sicker the patient, the broader the range of things to consider, so a thorough history helps ensure we don't miss something that could help with the diagnosis."

"We also look closely at data from the microbiology lab to help identify the specific pathogens involved," he adds. To illustrate, Hooper tells of a patient who was infected by a strain of bacteria that produces NDM-1, or New Delhi metallo-beta-lactamase-1, an enzyme that renders the bacteria resistant to many antibiotics, including those effective against gram-negative microbes. Many bacterial isolates with this resistance have arisen within populations in India.

A history revealed that the Mass General patient had in fact been hospitalized in India before returning to the United States. In addition, microbiologic analyses quickly identified the strain as one resistant to carbapenem antibiotics and, later, showed it was the NDM-1 "superbug."

Once a resistant pathogen is identified and a treatment regimen initiated, Hooper's focus shifts to containment. "We're worried not only about the spread of a particular resistant bacteria between patients," he says, "but also about the potential for patients to develop a hospital-acquired infection."

It is estimated that hospital-acquired infections affect 1 of every 20 people admitted to hospitals nationwide. These infections include those associated with the use of medical devices. The bacteria that cause them can include methicillin-resistant

Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and pathogens linked with respiratory infections such as pneumonia. Combating these infections can cost hospitals between \$5 billion and \$7 billion per year.

### **In a Lather**

“There is a real public health crisis in this country,” says Erika D’Agata, an HMS associate professor of medicine at Beth Israel Deaconess Medical Center, “because since the 1970s, only three completely new antimicrobials have been introduced to market.”

D’Agata develops computational models that devise scenarios for controlling the rate of hospital-acquired infections. “We ask questions like, ‘What would happen if we decreased the use of antibiotics?’ or ‘What if everyone complied with handwashing guidelines?’ ”

One study by D’Agata found that compliance with handwashing guidelines among health care workers in a particular dialysis unit was approximately 40 percent. The corresponding rate of VRE in that unit hovered near 12 percent. A simulation by D’Agata, however, showed that 100 percent compliance would reduce that prevalence to 2.5 percent.

In order to focus on ways to judiciously use antibiotics, hospitals have begun to participate in antibiotic stewardship programs that monitor the use of the drugs. Driven by data provided by microbiology labs within the hospitals, the programs allow hospitals to monitor, analyze, and improve the ways antibiotics are used. Says Hooper, “We start collecting samples from the patient before anything is administered so we can ensure that the best treatment is chosen and so we can follow the trajectory of the disease and the patient’s response to treatment.”

### **Outside the Box**

A concrete building in Jamaica Plain, Massachusetts, houses a welter of micro-biology labs, each with technicians who monitor, identify, and record the movement of pathogens into and out of the Commonwealth.

“It’s the reports from these lab workers,” says DeMaria, “that help public health officials identify and investigate outbreaks and respond to them.”

The expertise of the laboratory personnel strengthens the surveillance system, more so because they communicate daily with epidemiologists. This type of exchange among clinicians and other relevant parties, says DeMaria, is also what makes the West Nile outbreak such a good example of the public health system at work.

“When we are doing our jobs well, you won’t even know we exist,” he says. “Pandemics and epidemics are inevitable. But how quickly we get to the bottom of

them depends on how well we maintain this network of medical and public health professionals.”

*Shraddha Chakradhar is a science writer based in Boston.*

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# Behind the measles outbreak

Study finds vaccination rate far below what's needed to keep virus in check

By Tom Ulrich, Harvard Medical School Communications

March 20, 2015 |

*It's estimated that an infected individual in a population fully susceptible to measles will spread the virus to between 11 and 18 additional people. "The fundamental reason why we're seeing the number of cases we are is inadequate vaccine coverage among the exposed," said John Brownstein, an HMS associate professor.*

Inadequate vaccine coverage is likely a driving force behind the ongoing Disneyland measles outbreak, according to calculations by a research team at Harvard Medical School (HMS) and Boston Children's Hospital, a Harvard affiliate.

Their report, based on epidemiological data and published online by JAMA Pediatrics, indicates that vaccine coverage among the exposed populations is far below that necessary to keep the virus in check, and is the first to positively link measles vaccination rates and the ongoing outbreak.

The researchers — led by Maimuna Majumder, a research fellow at HealthMap, and John Brownstein, HMS associate professor of pediatrics at Boston Children's — examined case numbers reported by the California Department of Public Health and current and historical case data captured by the HealthMap disease surveillance system.

They estimate that the measles vaccination rate among the case clusters in California, Arizona, and Illinois is between 50 and 86 percent, far below the 96 to 99 percent necessary to create a herd immunity effect.

Measles is highly contagious. It's estimated that an infected individual in a population fully susceptible to measles will spread the virus to between 11 and 18 additional people. This number is called the virus' basic reproduction rate, or  $R_0$ . In a population where at least some individuals are immune to measles, the virus spreads from person to person more slowly. The rate of spread in an immune population is called the virus' effective reproduction rate, or  $R_E$ .

Using case data,  $R_0$ , and measles' serial interval (the length of time for each successive wave of transmission to follow the one before), Majumder and Brownstein calculated that the virus'  $R_E$  in the Disneyland outbreak is between 3.2 and 5.8. From there, they calculated the vaccination estimate.

The researchers are quick to note that their estimate does not reflect vaccination across the United States, in the state of California, or even among the population of Disneyland visitors at the outbreak's start. Rather, it reflects the vaccination rate

among the exposed populations in each cluster of cases linked to the outbreak so far.

“It’s as though you took everyone exposed to measles in the areas with case clusters, put them in a room, and measured the level of vaccine coverage in that aggregate population,” said Majumder.

Using the same data sources, the HealthMap team has separately released an interactive model illustrating how differing rates of vaccine coverage could affect the growth of a measles outbreak over time.

The model, available at [healthmap.org/measlesoutbreak](http://healthmap.org/measlesoutbreak), puts the effects of vaccination into stark relief. If a population is fully vaccinated against the virus, the model predicts that one case of measles will give rise to only two additional cases over 70 days. By contrast, if only 60 percent of a population is vaccinated, more than 2,800 cases will occur over the same time period.

“Our data tell us a very straightforward story — that the way to stop this and future measles outbreaks is through vaccination,” said Brownstein, a digital epidemiologist and co-founder of HealthMap and VaccineFinder, an online service that allows users to search for locations offering a variety of vaccinations, including the MMR vaccine that protects against measles.

“The fundamental reason why we’re seeing the number of cases we are is inadequate vaccine coverage among the exposed,” he said.

“We hope these data encourage families to ensure they and their loved ones are vaccinated, and help local public health officials in their efforts to control this outbreak.”

*This work was supported by the National Library of Medicine.  
Adapted from a Boston Children’s news release.*

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<http://news.harvard.edu/gazette/story/2015/03/behind-the-measles-outbreak/>

# Translating Success

Three centers launched to battle infectious pathogens

By Elizabeth Cooney

March 11, 2014

In order to better combat infectious disease, Harvard Medical School is creating three Centers of Excellence for Translational Research: one in tuberculosis, one in bacteriology and one in virology.



Three five-year grants totaling up to \$15 million per year from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, will allow HMS researchers to move discoveries about TB and emerging infections closer to applications in diagnosis, treatment and prevention.

## Improving diagnosis, fighting drug resistance

The TB center will focus on improving diagnostics, especially in children, and on combatting drug resistance. Megan Murray, HMS professor of global health and social medicine, will lead the center.

“The TB epidemic is still fueled by the fact that people are diagnosed relatively late in the course of their disease and a lot of transmission happens before diagnosis,” said Murray, who is also HMS associate professor of medicine at Brigham and Women’s Hospital and director of research at Partners in Health. “There’s no single therapy for TB, so there’s a big need to know which drugs people are resistant to.”

The TB center will build on previous work that used whole-genome sequencing to identify genetic mutations associated with drug resistance. Using bioinformatics and evolutionary techniques, they will study some 1,500 TB strains collected from an ongoing clinical research study in Peru to characterize resistance mechanisms. The scientists will correlate what they find with a measure called quantitative drug resistance, or the specific amount of a drug to which a strain becomes resistant.

Another project in the center, to be led by Eric Rubin, professor of immunology and infectious disease at the Harvard School of Public Health, will apply functional genomics to the mutations found by sequencing to see if the mutations confer drug resistance.

The TB center will work with an industry partner, Akonni Biosystems, to develop a diagnostic tool to be used in the field. Led by Chief Scientific Officer Darrell Chandler



and Director of Engineering Christopher Cooney, the molecular diagnostics company will optimize a microarray for TB to test mutations associated with drug resistance.

The TB center's fourth of four projects may be its most ambitious, Murray said. Inspired in part by techniques used to interpret archeological DNA in Neanderthal samples, the scientists hope to capture fragments of TB's genetic material from children. The standard TB test looks at sputum, but children can rarely cough up a useful sample. What if clinicians could examine bits of DNA in blood or urine and do other diagnostic tests as well?

"In the Neanderthal project, the challenge has been to take very degraded mammalian DNA mixed with bacterial DNA," she said. "In our case, we've got the other problem: We try to pull microbial DNA mixed with human DNA in urine. Can we sequence that?"

### **Searching for new defenses**

The two new centers in bacteriology and virology will build on the success of the New England Regional Center for Excellence, a regional research hub established at HMS after anthrax attacks in 2001 heightened national concerns about biological threats. Dennis Kasper, the HMS William Ellery Channing Professor of Medicine at Brigham and Women's Hospital and professor of microbiology and immunobiology at HMS, is the principal investigator on the NERCE grant.

HMS researchers will continue to focus on pathogens and diseases for which no vaccines or therapies exist—and microbes that resist current drugs. These include the bacterium *Francisella tularensis*, considered a potential agent of bioterrorism, as well as dengue fever, a significant disease in much of the world, which is now creeping into Florida.

"In NERCE, there was a lot of basic research on biodefense pathogens and later on emerging infectious disease pathogens," added Kasper. "These new centers are now here to take those discoveries to the next step: translation." Kasper will head the bacteriology CETR, a program that will focus on tackling the cell envelope that surrounds bacteria in such microbes as *Burkholderia*, *Brucella*, *Vibrio cholerae* and methicillin-resistant *Staphylococcus aureus*.

The virology CETR will be led by Sean Whelan, professor of microbiology and immunobiology and associate head of the Harvard Program in Virology. "This really is an opportunity to make a significant impact in understanding the entry mechanisms of emerging viral pathogens," Whelan said. "We're going to learn new biology and understand how some small molecules block viral entry."

Viral entry is a target of our natural antibody response to viral infection, a step in the viral replication cycle that has not been well exploited by synthetic inhibitors.

One virology project involves small molecules that inhibit dengue virus replication and another concerns small molecules that block the Ebola virus from getting into cells. A third effort will search for cellular molecules that many viruses use to reach and enter cells. A fourth project will explore how viruses move from one cellular compartment to another before infecting cells with their genes.

New science for emerging threats

“We are looking at a very broad spectrum of emerging viruses that are threats to human health and potential biodefense agents, asking what molecules and cellular factors are needed to get into cells,” Whelan said. “We’re hoping that we will identify both pathogen-specific host factors as well as those that are shared among different viruses.”

In a similar vein, scientists in the bacteriology CETR hope to find common weaknesses to exploit.

“A lot of antibiotic research addresses enzymes or proteins that are involved in the synthesis of the cell wall of bacteria. There are key proteins that are very similar between different bacteria that could potentially serve as targets,” Kasper said. “Vaccines tend to be organism-specific, but we’re developing platforms that can be applied to any organism for which you want to develop a vaccine.”

“For many years it was sufficient for people to talk about their basic research as perhaps leading to a drug or to a vaccine someday,” said Gerald Beltz, administrative director for the two centers in the Department of Microbiology and Immunobiology. “Now it has to be much more direct, and I think these centers are part of that.”

HMS investigators within the bacteriology CETR are John Mekalanos, the Adele Lehman Professor of Microbiology and Molecular Genetics and head of the department of microbiology and immunobiology; Suzanne Walker and Stephen Lory, both professors of microbiology and immunobiology; Thomas Bernhardt and David Rudner, associate professors of microbiology and immunobiology; and Daniel Kahne, professor of biological chemistry and molecular pharmacology.

Virology CETR investigators at HMS include James Cunningham, associate professor of medicine (microbiology and immunobiology) at Brigham and Women’s Hospital; Stephen Harrison, the Giovanni Armenise-Harvard Professor of Basic Biomedical Science; Tomas Kirchhausen, professor of cell biology; Priscilla Yang, associate professor of microbiology and immunobiology; and Nathanael Gray, professor of biological chemistry and molecular pharmacology.

Other researchers involved in the TB center include Max Salfinger, lab director of mycobacteriology and pharmacokinetics at National Jewish Health in Denver, who will lead quantitative genomics project. In the later years of the TB grant, scientists will work with Ann Goldfeld, HMS professor of medicine at Boston Children’s

Hospital, who heads a clinical research site in Cambodia. Louise Ivers, HMS associate professor of Global Health and Social Medicine and associate professor of medicine at Brigham and Women's Hospital, will lead similar clinical research in children in Haiti.

James Sacchettini, professor of biochemistry and biophysics and of chemistry at Texas A&M University, and Thomas Ioerger, associate professor of computer science at Texas A&M, will lead gene sequencing.

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Atul Gawande - OCTOBER 3, 2014

<http://www.newyorker.com/news/daily-comment/ebola-epidemic-stoppable>

### **Ebola Update - Responding to a global crisis**

October 3, 2014

<http://hms.harvard.edu/news/ebola-update>

### **AIDS Symposium Plots Epidemic's End**

Alvin Powell - December 9, 2011

<http://hms.harvard.edu/news/aids-symposium-plots-epidemics-end-12-9-11>

### **Ebola, a year after the epidemic began**

WBUR - December 29, 2014

*Interview with Raj Panjabi of Brigham and Women's Hospital*

<http://hms.harvard.edu/news/ebola-year-after-epidemic-began>

### **Measles Cases and Outbreaks**

Measles cases in 2015

<http://www.cdc.gov/measles/cases-outbreaks.html>

### **Measles outbreak: How bad is it?**

Mariano Castillo - February 2, 2015

<http://www.cnn.com/2015/02/02/health/measles-how-bad-can-it-be/>

### **Facts about the Measles Outbreak**

Jonathan Corum, Josh Keller, Haeyoun Park and Archie Tse

February 6, 2015

[http://www.nytimes.com/interactive/2015/02/02/us/measles-facts.html?\\_r=0](http://www.nytimes.com/interactive/2015/02/02/us/measles-facts.html?_r=0)

### **Infection Control and Hospital Epidemiology**

Cambridge University Press

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