Current Topics

Airborne Viruses Migrate on Vapors among Yellowstone Hot Springs

Viruses in acidic hot springs at Yellowstone National Park appear to migrate on steam droplets, sometimes traveling up to 20 miles between pools. The unexpected finding helps to explain how such viruses spread far and wide, according to molecular microbiologist Frank Roberto of the Idaho National Laboratory (INL), Idaho Falls, virologist Mark Young at Montana State University (MSU), Bozeman, and their collaborators. These findings emerged during a two-year survey of microbial diversity in those hot springs, part of the National Science Foundation Microbial Observatories Program.

The researchers were investigating how changes in water geochemistry and host populations affect viral populations. “We thought viruses would be a quick sensor of the environment,” says Young. Members of the research team collected samples of water about every 30 days for two years from the Crater Hills, Ragged Hills, and Rabbit Creek hot springs, each of which is situated in distinct geological regions within Yellowstone.

“There’s a lack of awareness that viruses exist in Yellowstone thermal pools,” says Roberto of INL. Members of his laboratory sequenced the genomes of various Sulfolobus spindle-shaped viruses (SSV) and Sulfolobus islandicus rod-shaped viruses (SIRV). These DNA-containing viruses infect Sulfolobus, one of the best characterized of the archaea microbial species discovered in Yellowstone 35 years ago. From 2,165 independent SIRV clones, the researchers identified 722 unique sequences representing 12 distinct clades, five of which were common to all three hot springs. Meanwhile, 300 unique sequences of SSV formed six distinct clades, with three of them common to all three hot springs.

In surveys of viral abundance at the three hot springs, some clades proved to be in rapid flux. Thus, seemingly dominant SIRV and SSV clades seemed to disappear and then reappear within days. These viral fluctuations did not correlate with any visible changes in geochemistry, and were too extreme and rapid to attribute to mutations. “We didn’t know what to make of the surprising data,” Young says.

However, when ecological models were applied to those data sets, the patterns suggested that viruses were migrating from one hot spring to another, according to their collaborator Matthew Lavin, a botanist who studies biodiversity at MSU. Although Yellowstone has plenty of underground waterways, the researchers ruled them out as potential conduits for viruses because the temperatures in the waterways can exceed 400°C, which would be lethal even for the hardiest thermophiles. That left steam as the likely means for transporting viral particles between hot springs. Indeed, the researchers detected viruses in air columns above hot springs. Additional details are described the November 19, 2007 Proceedings of the National Academy of Sciences.

“Few virologists have combined phylogeny with ecological models,” Young says, and virologists would be more inclined to attribute fluctuating
sequence changes to mutations, rather than to migrations. “This is a new way for virologists to think,” he notes. Moreover, environmental microbiologists should take multiple samples from particular environments at different times to develop fuller profiles of viral communities and avoid developing a “distorted view,” he says. Additionally, airborne migrations might explain how viruses that thrive in Russian, Japanese, or Icelandic hot springs also are sometimes found in Yellowstone.

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Forecasting Climate Change Effects on Infectious Diseases—Not Simple

Many experts expect global climate change to have a substantial impact on infectious diseases. However, predicting the direction or extent of those anticipated changes is not so clear-cut, according to the participants of a two-day forum on microbial threats, convened last December in Washington, D.C., by the Institute of Medicine Board on Global Health.

Part of that difficulty stems from the uncertainties that are inherent to climate change. Once called “global warming,” this phenomenon now sometimes is referred to as “global ‘weirding,’” an amusing but apt reference to the irregularities of climate change. Yes, temperatures are on the rise in some parts of the globe, and ice caps are melting rapidly. However, elsewhere, the ferocity of storms—and other “extreme weather events”—are what worry officials, including those charged with protecting public health.

Why such uncertainty about the shifting climate and its impact on infectious diseases? These are “dynamic, non-linear processes,” says forum participant Donald Burke of the University of Pittsburgh in Pittsburgh, Pa. Indeed, even without accounting for seasonal effects or more substantial climate effects, epidemics “tend to oscillate...spontaneously and inherently,” he says. For example, outbreaks of dengue fever in Thailand not only follow a seasonal pattern but also show a three-year periodicity. Further, outbreaks tend to launch in Bangkok and then travel in waves to outlying areas, following patterns that “had not been recognized before,” he points out. Poorly understood, if at all, such patterns complicate any effort to account for the effects of climate change on dengue.

Similar uncertainties attend other infectious diseases, with occasional exceptions where changes in disease pattern seem instead to coincide neatly with changes in weather patterns, according to Andrew Haines of the London School of Hygiene and Tropical Medicine in London, England. For instance, the incidence of diarrheal diseases among young children increases in parallel with decreases in rainfall—possibly because reduced rainfall in underdeveloped countries leads to less-frequent hand washing, he says. Meanwhile, sporadic cases of salmonellosis in industrialized countries rise in parallel with temperature increases, while rising meningitis case numbers in West Africa “match with the dry winds of winter.”

Italy experienced an outbreak of mosquito-borne Chikungunya virus infections affecting more than 200 people during 2007 that was likely of African origin, according to Jean-Paul Chretien of the U.S. Department of Defense Global Emerging Infections Surveillance and Response System in Silver Spring, Md. A Chikungunya virus outbreak earlier reached epidemic levels along the east coast of Africa and on several nearby islands in the western Indian Ocean. However, at least for the limited outbreak in Italy, the question remains open whether “climate played a role,” he says. “The summer was drier and warmer than
usual, but rapid international travel was also a factor.”

In other cases, changes in vector-borne infectious disease patterns appear to depend on habitat changes but, here again, observations range widely. Tickborne encephalitis in Sweden seems to be marching steadily northward, following increases in average temperatures, Haines says. However, details about changes in malaria patterns in Africa and in parts of South America are “controversial” despite general agreement that climate change is affecting the range of this disease while exposing different human populations to the mosquitoes that carry malarial parasites. While it is safe to expect changes, sometimes they may lead to decreases instead of increases in this disease—for instance, when storms or other changes “wash out vector-breeding areas,” he points out.

Despite such “uncertainty,” Haines says, “we [need to] look at economic impacts because the cost of inactivity is far greater in the long run. We can [try to] meet the emerging needs of the poor, and help them to reduce the impact of and adapt to climate change, [and] we may get health co-benefits.”

Even while lacking the “firm evidence” that would be needed to settle many of the scientific uncertainties underlying questions about the impact of climate change on infectious diseases, a separate strategy is taking shape to address some attendant policy issues, according to Diarmid Campbell-Lendrum of the World Health Organization (WHO) in Geneva, Switzerland. Climate change is adding pressure to already “intolerable burdens” from global infectious diseases, he says. “WHO has to be careful not to redirect attentions away from these. . . issues just to those that are new and interesting. Even boring, everyday killers are sensitive to climate variation, [while] many other disease determinants are climate-independent.”

Nonetheless, WHO is no longer treating climate change as merely a matter of risk assessment and now considers it an “operational interest” in terms of its effects on health, according to Campbell-Lendrum. That shift entails recognizing that climate change threatens “health security,” he says. “Health is a topic moving to the center of the climate change debate,” and recognizing how it can threaten “health security has a great deal of traction among the general public.”

**Jeffrey L. Fox**
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**CO Gas Treatments of Meat and Fish Prompt Partisan Parley**

Treating fish and meat with carbon monoxide (CO) gas, which binds to hemoglobin and myoglobin molecules, is safe and helps to enhance the appearance of such stored food products, according to advocates of this widely used adjunct to food packaging. However, critics say, treating meat and fish with CO, which is called “tasteless smoke” and turns those foods bright red, makes them look fresher than they are, deceiving consumers and putting them at risk for illnesses from handling and eating spoiled foods.

That debate, joined last November during a partisan congressional hearing whose atmosphere verged on courtroom melodrama, remains unresolved. During that hearing, officials from the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), who have overlapping food safety responsibilities, defended the practice of treating meats and fish with CO, noting that this practice has “generally recognized as safe” (GRAS) status. However, following sometimes tense exchanges with several Democratic members of the subcommittee on oversight and investigations of the House of Representatives Committee on Energy and Commerce, those agency officials agreed to reexamine data that were used to uphold GRAS status and “to think further about it.”

The November hearing, “Deception in Labeling,” was one in a series examining the safety of drugs and foods, particularly imports. It was convened by Representative Bart Stupak (D-MI), who chairs the subcommittee. Stupak, Rep. John Dingell (D-MI), who chairs the overall committee, and Rep. Jan Schakowsky

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**iGEM 2007 Jamboree Top Award to Peking Team for On-Off Microbial Switch**

A team of 12 undergraduates from Peking, China, won the grand prize during the 2007 Jamboree, part of the International Genetically Engineered Machine Competition (iGEM) that was held at the Massachusetts Institute of Technology last November. They belonged to one among 59 teams with more than 750 participants working on synthetic biology projects, most of which depend on microbiology in one way or another. In this award-winning case, the Peking team used molecular genetics to construct elaborate plasmids to reprogram *Escherichia coli* cells with a “bistable, push on-push off switch that responds to ultraviolet light, providing control over two separate metabolic pathways.” More information about the Jamboree is available at http://parts.mit.edu/igem07/index.php/Main_Page.
(D-IL) joined one side of what proved a partisan debate to criticize CO use for treating packaged meats and fish. Other members of the subcommittee, including Rep. Ed Whitfield (R-KY), Rep. Marsha Blackburn (R-TN), and Rep. Michael Burgess (R-TX), staunchly defended this CO use.

For example, Whitfield argued that the benefits of using CO outweigh any risks, and cited several prominent food microbiologists to back his arguments. He also suggested that a Michigan-based company called Kalsec that markets spice extracts as treatments for meat and fish stands to benefit if current CO practices were to be further restricted. His Republican colleague Blackburn said that this use of CO “has nothing to do with foodborne illness” and that their Democratic colleagues on the subcommittee were “misleading the public with [their move toward] overzealous regulation of [CO].”

Meanwhile, in forcefully questioning FDA and USDA officials, Stupak called the use of CO on packaged food products “highly deceptive,” saying that it makes “meat and fish appear fresh even though [they are] spoiled,” that it “does nothing to make food safer,” and “its sole purpose is to fool consumers.” He also urged officials to suspend use of CO on foods while reconsidering its GRAS status. In a similar vein, Schakowsky, who calls herself a “strong consumer advocate,” criticized FDA and USDA officials for being “tone deaf” to consumers and for not requiring labeling that notifies them whether CO was used to treat packaged food products. She and other consumers “want to buy fresh fish—not fresh-appearing fish,” she says.

Producers now are required to label foods indicating specific “use or freeze-by dates” to assure freshness, which serves as a critical safeguard when CO is used to treat those foods, according to Daniel Englejohn of the USDA Food Safety and Inspection Service. Any additional labeling, such as notices explicitly claiming that particular products had not been CO-treated, would be subject to agency review to determine whether such information is “truthful and not misleading,” he says.

Food producers raised several other issues regarding CO use on fish and meats. For example, there is “industry uneasiness” about the 360 million pounds of frozen tilapia being imported per year because some of it is being treated with CO and falsely sold as fresh, thus competing with a smaller output of this same fish being produced domestically, according to Mike Picchietti, president of Regal Springs Trading in Bradenton, Fla. “This deceptive practice has been going on for 10 years...because there is no enforcement,” he says, making domestic producers “compete on an uneven playing field.”

Meanwhile, some representatives of the meat industry say that, although they consider CO use safe, they are considering changing labels on packaged meat products. Noting that there are “no documented illnesses associated with CO treatment” on packaged meats treated with 0.4% CO, Jeffrey Ettinger, who is president of Hormel in Austin, Minn., said that the company would “add additional language to our label to address the color issue and expressly inform consumers that ‘Color is not an accurate indicator of freshness. Refer to use or freeze-by date.’”

Jeffrey L. Fox

New Detection Systems, Unusual Vaccine Aim at MRSA

Two new early warning microbial detection technologies could help in dealing with the rise in methicillin-resistant Staphylococcus aureus (MRSA) by improving the means for monitoring this pathogen. On a separate track, investigators are reporting that an experimental vaccine, one which aims at interfering with quorum sensing by this pathogen and proves effective in rodents, someday could provide a means for blocking harmful MRSA infections.

In terms of monitoring for MRSA, Universal Detection Technology (UDT) in Beverly Hills, Calif., has de-
Several Host Enzymes Tied into Infectious Disease Processes

Researchers recently reported disparate examples of host enzymes playing key roles in several infectious disease processes, including:

- High protease levels in the lungs of patients with cystic fibrosis disable immune cells, helping to explain why such patients fail to clear lung infections, according to Dominik Hartl of Children’s Hospital in Munich, Germany, and collaborators, whose findings were published online in *Nature Medicine* on 2 December 2007.

- The enzyme prostatic acidic phosphatase in human semen produces amyloid fibrils that boost the ability of HIV-1 to infect cells, according to Frank Kirchoff at the University Clinic of Ulm, Germany, and his collaborators, whose findings were published in *Cell* on December 14, 2007.

- An intestinal enzyme of zebrafish, alkaline phosphatase (iap), serves as a detoxifying agent, reducing levels of endotoxin, or lipopolysaccharide, in the gut and thus preventing these animals from developing septic shock-like symptoms, according to Karen Guillemin of the University of Oregon in Eugene and her collaborators, whose findings are published in the December issue of *Cell Host & Microbe*.

Developed a system for monitoring airborne spores, the presence of which indicates that local hygiene is compromised and provides an indirect sign that MRSA could be present, according to Amir Ettehadieh, who directs Research and Development at UDT.

Separately, a team at Cepheid of Sunnyvale, Calif., is developing a means for quickly detecting MRSA in individuals. The need for such tests is substantial. Thus, for example, more than 19,000 people in the United States die each year from MRSA, while another 94,000 become seriously infected with this pathogen, according to officials at the Centers for Disease Control and Prevention in Atlanta, Ga. Not only can infections spread through contact with contaminated surfaces, but MRSA can also become airborne.

UDT is adapting its Microbial Event Monitor (MEM) system for use in alerting personnel to the possibility of MRSA by monitoring airborne spores. Initially developed with collaborators at the Jet Propulsion Laboratory in Pasadena, Calif., for monitoring spacecraft assembly clean rooms, this system analyzes dipicolinic acid from spores and correlates such levels with total biomass “to let a hospital know that hygiene has been compromised,” Ettehadieh says.

“Monitors should be placed in locations where patients might come into contact with MRSA. We are currently in negotiations to test the device at a hospital in the Detroit area that has had a persistent MRSA problem.”

Cepheid is developing a PCR-based MRSA system to deliver results in about two hours, compared to the two days that traditional culture methods may take. Its primers probe for a drug-resistance “cassette” in the *S. aureus* chromosome. The rapid turnaround times would allow health care professionals to identify MRSA carriers and to implement infection control measures more rapidly than is now possible. That system is aimed for use in hospitals and other health care set-

ings. Other tests for detecting staph in blood cultures and from skin or soft tissue infections that now are for research use are being developed for eventual use in detecting community-acquired MRSA, according to a company official.

Meanwhile, in a separate vaccine development effort, microbiologists from the Scripps Research Institute in La Jolla, Calif., are following an unusual approach for preventing MRSA infections. Their strategy is to disrupt quorum sensing in *S. aureus* with an experimental vaccine consisting of a low-molecular-weight hapten, whose structure is based on a quorum-sensing autoinducer, that is chemically linked to proteins that help to induce host antibodies. When administered to mice that were exposed to *S. aureus*, those antibodies were “highly effective at binding with and sequestering the targeted autoinducer,” and thus “efficiently blocked quorum sensing and infection in the mice,” the Scripps researchers report.

“These experiments with the mice were conducted over a period of a week but [the experimental vaccine] started working as soon as it was injected,” says Kim Janda of Scripps. He says that equivalent antibodies could one day be given to humans as a passive vaccine to block infections as they do when given to mice. Alternatively, the hapten might be introduced into humans directly to induce antibodies to block quorum sensing. Additional details appear in the 29 October issue of *Chemistry & Biology*.

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New Details Help To Explain How Rabies Virus Does Deadly Damage

The rabies virus can produce marked anatomical abnormalities in dendrites
and axons in mice, according to Alan C. Jackson of the University of Manitoba, Winnipeg, Canada, and his collaborators. Despite searching for years, researchers failed to detect rabies-elicited anatomical abnormalities beyond characteristic inflammation of the brain and spinal cord in humans or animals infected with this virus. Now, however, detecting these several localized abnormalities helps to fill in crucial gaps in understanding rabies pathogenesis, and also could help in developing novel therapies. Details of their study appear in the January *Journal of Virology* (82:513–521).

Earlier, several lines of evidence, including the recovery of a young woman with rabies who was treated with a specific blocking compound, pointed to excitotoxicity as an important pathological mechanism in rabies, according to Jackson. That mechanism, which depends on small molecules damaging or killing nerve cells, plays an important role in other neurological diseases. Separately, Zhen F. Fu of the University of Georgia, Athens, and his collaborators described abnormalities in neuronal processes in rodents that were infected intracerebrally with rabies. Their research appeared in 2005 in the *Journal of Virology* (79:12554–12565).

In his experiments with rabies virus, Jackson used transgenic mice that express yellow fluorescent protein (YFP) in neuronal cells. Once expressed, YFP provides a sensitive means for illuminating axons and dendrites under yellow fluorescence microscopy. Jackson and his collaborators inoculated mice with rabies virus through their footpads, closely modeling natural transmission of this virus.

“We observed ‘beading’ in dendrites and axons in different brain areas,” Jackson says. Moreover, mitochondria in infected neurons were swollen, while neuronal processes, including presynaptic nerve terminals, displayed degenerative changes. However, these experiments uncovered no evidence of the rabies virus causing excitotoxicity, Jackson says. Instead, the pathology resembles that which results from ouabain toxicity, in that the cell membrane sodium pump is damaged. That damage boosts the intracellular sodium concentration, thus suggesting a mechanism for the disease, says Mary Warrell of Oxford University in Oxford, United Kingdom, who was not involved in the research. “This hypothesis remains to be proved,” she says. “Although the laboratory strain of ‘fixed’ virus is pathogenic in the mice studied, variations in virus type and host species may affect the outcome of infection. It would be of great interest to know if the same changes are seen in infected human neurons.”

“Pathogenetic mechanisms of viruses are complex, and as for rabies, still poorly understood,” says Charles Rupprecht, chief of the rabies program at the Centers for Disease Control and Prevention in Atlanta, Ga., who notes that there is a “need for novel, and more relevant models, to provide broader insights to pathogenesis.” The disease is complex and diverse, he points out, noting that it is “predicated in part on viral variant, dose, route, severity, and species of origin, sex, life stage, and genetic background.”

The need for progress in understanding rabies pathogenesis remains pressing, Warrell adds. “Bat rabies, the cause of most human rabies deaths in North America, cannot be controlled. Understanding the pathogenesis of the infection may lead eventually to an effective treatment after the onset of clinical signs and symptoms.”

**David Holzman**

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