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PUBLICATION OF THE AMERICAN SOCIETY FOR MICROBIOLOGY

(RE)EMERGENCE OF INFECTIOUS DISEASES

AMERICAN SOCIETY FOR MICROBIOLOGY

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In this issue of Microcosm, we explore the intersections between the spread of disease, climate change and human health. Check out the fall issue for articles about virus hunting, infection prevention, public health communication and more.

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From the Editor

BY STANLEY MALOY, PH.D.,
EDITOR-IN-CHIEF

I recently attended a symposium in honor of Dr. Abigail Salyers, a former ASM President who pioneered the development of a genetic system for Bacteroides. Work from her lab led to many important discoveries, including elucidation of bacterial carbohydrate metabolism in the gut and characterization of conjugation transposons that facilitate promiscuous transfer of antibiotic resistance. Although she was not the first to use germ-free mice to study microbes in the gut, she proselytized their use for studies on the gut microbiome.

Salyer's journey nicely exemplifies an exciting era for microbiology as the field shifted from a focus on studying microbial physiology of cultured microbes to the elucidation and implementation of molecular biology techniques, the subsequent integration of computational methods (driven largely by DNA sequence analysis) and development of new approaches to understand complex communities and microbial ecology. Microbiology became a more integrative science that provided a robust understanding of the microorganisms and microcosms that make up our world.

This issue of *Microcosm* reflects the power produced by the fusion of these different disciplines. Articles in this issue describe how molecular tools have facilitated our ability to track the evolution of pathogens during a pandemic; predict where the next emerging diseases will arise; identify optimal vaccine targets; and reveal correlations between climate change, population biology and evolution. The articles emphasize that these issues are not restricted to human pathogens—we know that human health also depends upon animal health and environmental health ("One Health"). Studies on microbiomes of humans, animals, plants and the environment have demonstrated that microbes play important roles in keeping each of these ecological niches healthy.

Despite the many things we've learned over the last half century of microbiology, there is still so much to learn—our discipline has an exciting future. Our better understanding of the role of microbes in the health and disease of organisms and natural environments has prompted many exciting questions that were previously intractable. How can we rapidly develop novel therapeutics to thwart infectious diseases? How can we accurately predict outbreaks before they happen, and build upstream interventions? How can we enlist microbes to engineer a healthier natural environment?

These are only a few of the exciting questions that build on what we've learned to address important, complex issues. Whether dissecting details of basic science or developing new applications based upon the lessons learned, one thing is clear—innovative solutions to these big, sticky questions will require diverse teams that bring together different experiences, complementary approaches and global perspectives. Like the diversity of microbes, the wonderful diversity of ASM members will catalyze the innovations in scientific discovery, education and entrepreneurship needed to overcome these grand challenges.

Stanley Maloy, Ph.D.
Microcosm Editor-in-Chief

Hunting for the Next Pandemic Virus

BY MADELINE BARRON, PH.D.

What if researchers could find the next pandemic virus before it finds humans? This is the basis of virus discovery initiatives, which involve searching for and cataloguing viruses in animal populations to uncover potential zoonotic threats. But where should researchers look for zoonotic pathogens they don't know exist? More importantly, how can they use the knowledge gained from virus hunting endeavors to prevent pandemics? It's complicated.

On the one hand, computational tools have boosted the utility of discovery data by identifying novel animal viruses (and their hosts) that pose the greatest zoonotic risk. On the other hand, preventing the next pandemic, which, like every viral pandemic since the start of the 20th century, will likely stem from a virus with animal origins, is an enormous task. According to Dr. Gregory Albery, a disease ecologist at Georgetown University and co-founder of the Viral Emergence Research Initiative (Verena), discovering viruses is only a single gear in a complex system of zoonotic risk mitigation procedures and behaviors.

THE ROLE OF VIRUS DISCOVERY IN ZOONOTIC PANDEMIC PREVENTION

According to Dr. Neil Vora, a former epidemic intelligence service officer with the U.S. Centers for Disease Control and Prevention (CDC) and a physician with Conservation International, there are 2 branches of pandemic prevention: primary and secondary. The latter is largely reactionary; surveillance for diseases of concern and associated efforts to contain the spread of that disease take place after a spillover event has occurred.

Conversely, primary prevention centers on preventing spillover from animal to human hosts from happening in the first place. Viral discovery aligns with this strategy. Ideally, by profiling viruses circulating among animals, researchers hope to learn which viruses exist in close proximity to humans and how those viruses may evolve or acquire the ability to infect people. Such insights could help scientists develop strategies to prevent spillover down the road. They could also inform secondary prevention tactics, including the development of vaccines and diagnostics for emerging zoonotic threats.

This branched view of virus discovery as a steppingstone for pandemic preparedness has informed several initiatives over the past decade. One prominent example is PREDICT, a project through the U.S. Agency for International Development (USAID) in partnership with the University of California (UC) Davis One Health Institute. PREDICT, which ran from 2009 to 2020, enabled global surveillance of pathogens that can spillover from animals hosts into people. Researchers identified 958 novel viruses, including a novel ebolavirus and over 100 novel coronaviruses from more than 160,000 animals and people at high-risk animal-human interfaces in over 30 countries. The discoveries shed light on the distribution of viruses with zoonotic potential and provided a foundation to study their virology, pathogenesis and evolution.

New initiatives are also in the works. In October 2021, USAID announced a 5-year, $125 million project (Discovery & Exploration of Emerging Pathogens—Viral Zoonoses, or DEEP VZN) geared toward bolstering global capacity to detect and understand the risks of viral spillover from wildlife to humans that could cause another pandemic. The U.S. National Institute of Allergy and Infectious Disease (NIAID) also recently initiated the Centers for Research in Emerging Infectious Diseases (CREID), which unites multidisciplinary teams of investigators across the globe to study emerging and re-emerging infectious diseases. Although CREID does not specifically focus on virus discovery, the network's projects include sampling wildlife for viruses with high zoonotic potential in Malaysia and Thailand, and surveilling animal populations in various regions for known and unknown viruses.

When scientists go on a virus hunt, they generally collect samples from animals (e.g., blood and feces) and use molecular biology methods (e.g., PCR and/or high-throughput sequencing) to detect which viruses are present in the sample. But where should researchers look for viruses with zoonotic potential, and what types of viruses should they look for? The spillover risk of a virus depends on factors related to the virus itself, its animal host(s) and the environment, all of which shape discovery strategies.

Target Animal-Human Interfaces in Spillover Hotspots

Spillover is intricately linked with human-associated impacts on, and changes to, the environment. Deforestation, for instance, increases the chances of humans encountering previously isolated animals—and their viruses. It also contributes to climate change, which (along with its myriad other negative effects) promotes spillover by forcing animals out of increasing inhospitable environments into regions populated by people. As such, spillover hot spots are centered in biodiverse tropical regions undergoing land-use changes (e.g., deforestation), particularly in Southeast Asia, West and Central Africa and the Amazon Basin, where climate change has, and will continue to have, pronounced effects.

Within these hotspots, virus discovery efforts focus on animal-human interfaces. Researchers collect samples from livestock and domesticated animals that may serve as reservoirs for viruses to jump into humans. They also target wild animals in the wildlife trade (1 of several key routes of animal-human viral transmission) and those that live with or near people. For instance, Bombali virus, a novel ebolavirus discovered via the PREDICT project, was isolated from free-tailed bats roosting in people's homes in Sierra Leone. Dr. Christine Johnson, director of the EpiCenter for Disease Dynamics at the UC Davis One Health Institute highlighted that the virus has since been detected in other countries, and researchers are currently studying whether it could infect humans (or already has).

Greater proximity between wild animals and humans, via land-use changes and the wildlife trade, among others, creates opportunities for spillover. Seen here: monkeys in Bali, Indonesia. Source: Iker Martiarena/iStock.

Sample from Animals Likely to Harbor Zoonotic Viruses

The proximity of humans to animals is only 1 driver of a virus's spillover risk; the physiology, behavior and geographical distribution of its host(s) also play a role. For example, the genetic relatedness between a virus's animal host and humans may influence whether people possess the cellular machinery to facilitate viral entry and replication. This is 1 of several reasons why zoonotic diseases often emerge from wild mammals. To that end, Johnson and her colleagues recently found that 3 mammalian orders—rodents, bats and primates—hosted nearly 76% of known zoonotic viruses. Bats and rodents are particularly notable for harboring zoonotic pathogens, though the reasons why aren't entirely clear. It may be tied, in part, to the sheer number of bat and rodent species spread across the globe (roughly 1,400 and 2,500, respectively).

Indeed, animals with high species diversity and broad geographic ranges have a greater chance of cross-species viral transmission. As climate change forces animals into new habitats, viral sharing among diverse mammal species (including humans) is expected to increase. Thus, focusing virus discovery initiatives on select animal (i.e., mammalian) groups is useful for uncovering zoonotic threats. While this is no small task (it is estimated that scientists only know about 1% of mammal viruses), it does allow for more targeted hunting.

Focus on Viruses with High Spillover Potential

Not all viruses are equal in their potential to spread to, and among, humans. For example, the genetic variability, adaptability and broad host range of RNA viruses, like coronaviruses and influenza viruses, make them prime spillover candidates. DNA viruses have an evolutionary rate of <1% that of RNA viruses, making successful infection of, and adaptation to, new hosts (e.g., humans) less likely. Indeed, RNA viruses are the culprits behind recent pandemics, from the H1N1 flu pandemic to COVID-19. Given that it is likely the next pandemic virus will bear similarities to those already known to infect humans, experts believe that looking for viruses with demonstrated spillover potential is an advantageous approach. For this reason, PREDICT mainly used consensus PCR (cPCR) for the targeted discovery of coronaviruses, filoviruses, paramyxoviruses and influenza viruses; each group includes viruses of "known zoonotic concern" with a "high-risk for causing future outbreaks or pandemics." An emphasis on studying select high priority 'prototype' pathogens to mitigate future threats has also gained traction in the NIAID's Pandemic Preparedness Plan, announced earlier this year.

MAKING SENSE OF DISCOVERY DATA WITH ZOONOTIC RISK TECHNOLOGIES

Still, even with a targeted virus hunting strategy, "identifying the viruses is only the first step," Albery said. "After that point, you have to assess their risk, which is a whole other kettle of fish." In other words, finding a virus is great, but knowing the risk it poses to humans is key.

This need has led to the development of computational tools, or zoonotic risk technologies, that use what is known about viruses that do infect humans to predict which animal pathogens may pose a spillover threat. For example, researchers developed an open-source, interactive web tool, called SpillOver, which uses data from PREDICT to perform a comparative risk assessment between known zoonotic viruses and those with uncharacterized spillover potential. In their initial analyses, the team found that the top-ranking viruses were known pathogens, including Lassa virus and Ebola virus, although the list also contained newly detected viruses, specifically coronaviruses. Johnson and her colleagues have also developed a new method that uses machine learning to determine the host range of known zoonotic viruses to predict the host species of novel animal viruses—and where humans fit into the mix.

These tools offer several benefits. Albery noted that viral discovery and identification must be followed up with laboratory experiments to understand the infection dynamics of viruses of interest (e.g., human cell entry receptor and usage, viral replication and pathogenesis, among other characteristics). Zoonotic risk technologies can help researchers narrow their experimental focus (and resources) to high-risk viruses.

Bats are key reservoirs of zoonotic viruses. These Commerson's leaf-nosed bats belong to the Hipposideridae family, which is known to harbor many betacoronaviruses. Source: Charles J. Sharp/Wikimedia.

With that in mind, zoonotic risk technology can also shape virus hunting pipelines from the get-go. Albery and his colleagues recently used machine learning models to identify bat species likely to harbor undiscovered betacoronaviruses (a family of viruses with high spillover risk that includes MERS-CoV, SARS-CoV-1 and SARS-CoV-2), based on characteristics of known carriers. The team identified 400 bat species worldwide that could be undetected hosts of betacoronaviruses.

"What our tools allow us to do is narrow down the bats that might be hosting betacoronaviruses, target our sampling to those species and pull out the viruses that we think might actually, someday, be a real risk to human health," said Dr. Colin Carlson, senior author of the study and an assistant research professor at the Center for Global Health Science and Security at Georgetown University, during the Verena Forum on Zoonotic Risk Technology digital workshop in January 2021. Carlson, who co-founded Verena with Albery, noted that this subset of viruses can then be pegged for downstream analyses—perhaps allowing for the targeted development of diagnostics and vaccines for problematic viruses before they infect humans.

HUNTING FOR VIRUSES IS NOT ENOUGH TO PREVENT ZOONOTIC PANDEMICS

Nevertheless, Carlson cautioned that "knowing about a virus does not inherently make us more prepared." Indeed, MERS-CoV and SARS-CoV-1 hinted at the potential threat of SARS-like coronaviruses, yet knowing about the threat did not stop COVID-19. Moreover, just because one looks for the next pandemic pathogen doesn't mean they will find it. It is virtually impossible to detect every single virus in the animal world. Some will inevitably slip through the cracks. Vora highlighted that, with our current knowledge and technologies, it is difficult to determine which newly discovered animal viruses could cause human illness, or a pandemic for that matter. A complex mix of factors rooted in immunology, ecology and epidemiology determines whether a virus successfully infects a human host and spreads. Albery agreed: discovery, even when bolstered by emerging computational tools, "is not really going to cut it" for driving coordinated, effective action toward curbing zoonotic pandemics.

"We have to be clear what is for today—actions here and now to save lives—versus what is for generating knowledge," Vora said. He pointed to actions that minimize the chances of spillover, regardless of the specific viral threat. These include reducing deforestation, regulating commercial wildlife markets and trade, improving infection control when raising farm animals and enhancing the health of communities living in emerging disease hotspots.

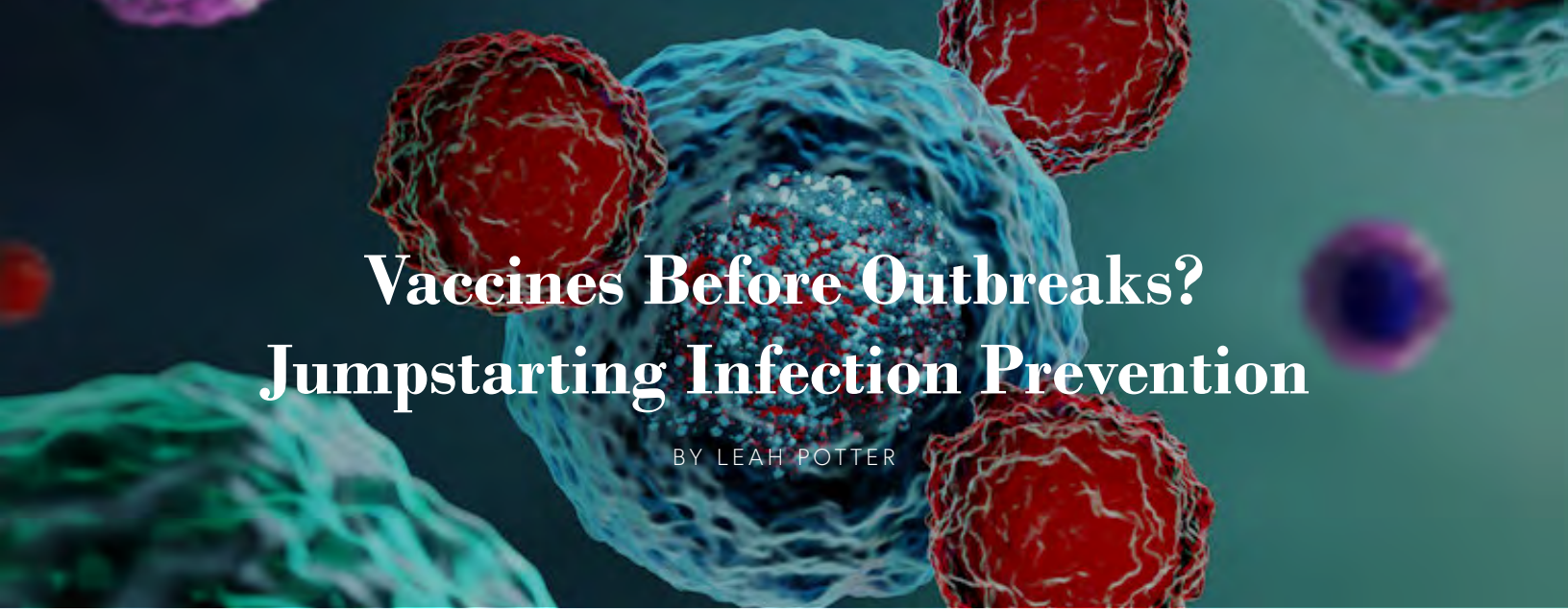
Deforestation in the Amazon rainforest. Less forest creates more opportunities for animal-human interactions. Source: Paralaxis/iStock.

For Johnson, there is no question that virus discovery is important, but the framework in which it is implemented is critical. She used PREDICT as an example, stating that the project wasn't only about discovering novel viruses, it also "sought to unify virus surveillance across the animal and human health sectors and identify wildlife-human interfaces, especially in areas with landscape change, deforestation and other aspects of the environment that could drive some of the connectivity between animals and people and increase the level of risk." PREDICT aimed to strengthen detection and surveillance capacities in countries where, historically, such capabilities were limited. The project also combined viral discovery efforts "with an approach that also detected known viruses in those virus families that were already of concern."

Accordingly, all experts stressed that, in addition to primary prevention efforts that reduce spillover risk, there is a need to support secondary prevention strategies that deal with spillover when it (inevitably) happens. This includes surveilling animals and people to keep tabs on known and unknown zoonotic pathogens as they appear in a population and bolstering health care infrastructure to respond to them when they do. "If [we] choose not to invest in any 1 of these items, we are going to have a weak link, and we are going to remain susceptible," Vora warned. "None of them are perfect in and of themselves."

Learn more about how researchers use computer modeling to predict spillover events:

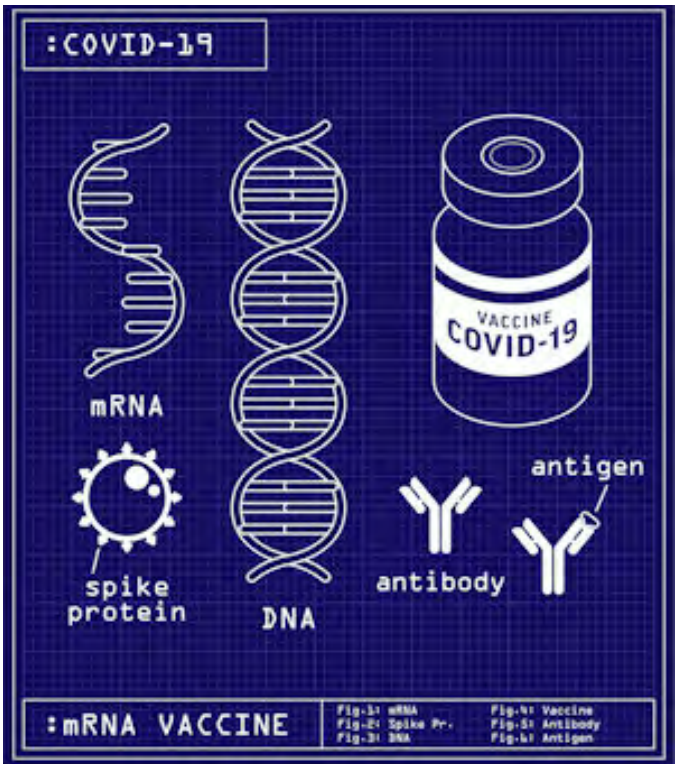
MEET THE MICROBIOLOGIST
103: Predicting Spillover Events with Barbara Han



Vaccines Before Outbreaks? Jumpstarting Infection Prevention

BY LEAH POTTER

When a new pathogen that infects humans is discovered, what's the next step? The initial response may include a rush to develop vaccines and therapeutics, but even conducting this clinical research at an expedited rate can take months. With the omnipresent threat of undiscovered pathogens, scientists have been investigating methods to jumpstart vaccine and monoclonal antibody development before an outbreak occurs, shifting containment efforts from preventive to compulsory. But how does one arm themselves against a pathogen that has yet to be identified? Lessons learned during the COVID-19 pandemic may offer clues.



COVID-19 mRNA (messenger ribonucleic acid) vaccines use a lipid nanoparticle to deliver mRNA encoding SARS-CoV-2 spike proteins to the cytoplasm of the cell. Source: iStock

LESSONS LEARNED FROM BUILDING COVID-19 VACCINES

Is it possible to start building a vaccine without the complete genomic sequencing data for a pathogen? Stuart Ray, M.D., Vice Chair of Medicine for Data Integrity and Analytics at Johns Hopkins School of Medicine, said a vaccine template is realistic within certain boundaries. Over the last few years, scientists have put this idea in motion.

Ray noted the collaboration between Kizzmekia Corbett, Ph.D., an assistant professor of immunology and infectious diseases at Harvard T.H. Chan School of Public Health and a National Institutes of Health (NIH) investigator, and Barney Graham, Ph.D., a professor in the Departments of Medicine and Microbiology, Biochemistry and Immunology at Morehouse School of Medicine and a former investigator for the National Institute of Allergy and Infectious Diseases (NIAID) and NIH. In studying the Middle East Respiratory Syndrome (MERS) coronavirus spike protein, Corbett, Graham and their colleagues ascertained—based on their knowledge of the way the spike proteins of coronaviruses bind and fuse—that a pre-fusion conformation might expose more neutralizing determinants than the native spike protein. The team endeavored to mutate 2 of the proteinogenic amino acids (prolines) that assist spike proteins in a pre-fusion conformation, exposing the binding surface for these 2 proteins. The result: better neutralizing titers in model systems.

When researchers in China first shared the COVID-19 source code genome in January 2020, Corbett, Graham and their team were able to design a spike antigen with the 2 previously mutated prolines within 48 hours. "Based on their knowledge of beta coronaviruses, they were pretty confident that this would improve immunogenicity for protection," Ray said. "That work was built before they had all the tools you would want to develop a vaccine antigen because they couldn't empirically test this at the time they were designing it." Pharmaceutical companies dedicated to rolling out a COVID-19 mRNA vaccine all committed to using the same spike protein sequence (all including the 2 proline changes) when developing the shot.

In studying the Middle East Respiratory Syndrome (MERS) coronavirus spike protein, researchers accelerated the process for designing COVID-19 mRNA vaccines. Source: Wikimedia Commons.

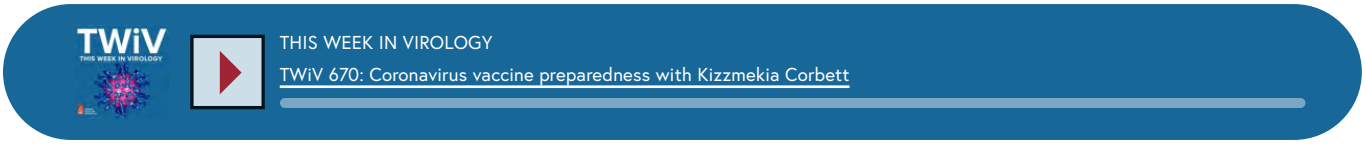
mRNA Vaccine Technology at Work

COVID-19 mRNA (messenger ribonucleic acid) vaccines use a lipid nanoparticle to deliver mRNA encoding SARS-CoV-2 spike proteins to the cytoplasm of the cell. "This was groundbreaking because there was a lot of hesitation about if the vaccine affects [the human host cell's] DNA, when, in fact, it never enters the nucleus," said Shalin Shah, M.D., senior medical affairs manager at T2 Biosystems. Once the mRNA is released inside the cytoplasm, host ribosomes translate the encoded message to produce, package and express copies of SARS-CoV-2 spike protein. This, in turn, elicits an immune response and facilitates production of antibodies and T cells against the virus. "mRNA vaccines are the future," Shah added. "For the most part, you're going to have an immune response that is robust and can ward off potential disease."

Beyond COVID-19, there is particular interest in mRNA technology for treating patients with human immunodeficiency virus (HIV) and mitigating the spread of other infectious diseases, like Zika virus, Ebola virus and tuberculosis.

The Future of mRNA Vaccines

Corbett and Graham's team developed a model pathogen vaccine design years before the COVID-19 pandemic began. Could researchers do it again? Ray thinks it's a possibility. "What Dr. Corbett and Dr. Graham have advocated for is a pandemic pathogen model antigen system, where they learn the biology of a type of pathogen—what it requires for entry or completion of its initial infection of a cell—and [then] design vaccine approaches around the critical steps in the entry program," Ray said. "That's a powerful approach when you know that there's a good chance that a filovirus, coronavirus or other pathogen type will come out and be a problem."



Could scientists make a vaccine without the protein sequence or structure? According to Ray, that may be less realistic, as this might entail binding to a host receptor rather than the pathogen. Here, there's the risk of causing off-target effects because the vaccine's contents would bind to every cell that has the selected feature, not just the cells that are being attacked by a pathogen.

STARTING VACCINE DEVELOPMENT BEFORE A PATHOGEN SPREADS

Before a zoonotic virus begins to spread to humans, researchers can sequence viruses from animals and start to design pre-pandemic vaccine candidates. "You can look and say, 'we know this type of virus family, and we can design proteins from those viruses and start testing them,'" said Jarrod Mousa, Ph.D., an associate professor in the Department of Infectious Diseases at the University of Georgia. "It might not necessarily be plug-and-play, but we're not starting from square 1." He added that mRNA vaccine technology makes it possible to test multiple protein candidates at once, further accelerating the process of developing a vaccine.

In short, there are steps a researcher can take to develop a vaccine before a pathogen makes its way to human hosts. These include, but are not limited to:

1. **Go Virus Hunting:** Look for and sequence novel viruses in animal populations (e.g., coronaviruses and paramyxoviruses, which have a high risk of crossing over to humans).
2. **Consider Feasibility:** Investigate whether it's possible to develop a vaccine candidate based on the genomic sequencing data.
3. **Test Vaccine Candidates:** With the sequence, test mRNA vaccines and see whether they elicit an immune response in an animal model.
4. **Build a Database:** Develop a bank of vaccine candidates. If a new virus emerges, determine whether a previously tested vaccine candidate (e.g., in mice) has a protein similar to the novel pathogen.
5. **Make It Work:** Begin modifying the vaccine candidate based on the genomic data from the new pathogen.

SHARING DATA CATALYZES VACCINE DEVELOPMENT

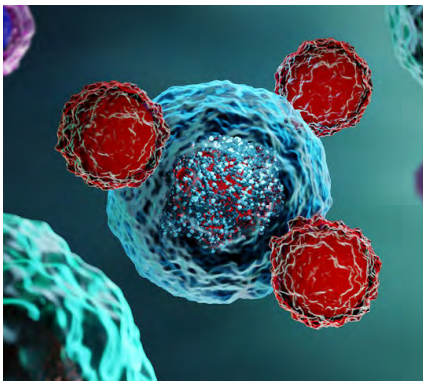
Data sharing can significantly increase the speed at which vaccines are developed and deployed. Source: istock.com.

COVID-19 vaccine development and rollout were directly dependent upon the speed at which genomic data from the pathogen was shared. However, sharing the sequence of a newly discovered pathogen before the data are published has not historically been the norm. "It is remarkable that the data were shared so freely, and we had a bunch of examples of people making these data visible to the world very rapidly," Ray said. "If we try to imagine 2020, where researchers in China did not share genomic data so early, we would have seen bigger lags [in vaccine development]. I think we can argue that in the pace of a pandemic, a delay of 1 or 2 or 3 months would have [cost] many more lives."

Ray added that there should be consideration for finding a way to continue this type of data-sharing to address other emerging and re-emerging pathogens, while, at the same time, honoring the individuals who share the data and recognizing the impact of their contributions. One suggestion is that the scientific community begin building a model pathogen library to store information for researchers around the world to tap into once a new virus makes an appearance.

IMMUNOTHERAPY AND VACCINES: THE DYNAMIC DUO OF INFECTION PREVENTION

Currently, Mousa's lab investigates monoclonal antibodies and their applications for immunotherapies to combat infectious diseases. This involves extracting cells from an individual infected with a pathogen, determining the sequence of the antibody that the B cell creates, then mass-producing it in the lab.



Immunotherapies are developed by extracting cells from an individual infected with a pathogen, ascertaining the sequence of the antibody that the b cell creates and mass-producing it. Source: istock.com.

Immunotherapy can be an excellent alternative to vaccines for patients who are immunocompromised and do not respond well to immunization (i.e., they might be given a prophylactic monoclonal antibody intravenously that will last a few months and can subsequently be delivered to the patient again), or for patients who are allergic to certain vital ingredients in a vaccine.

Additionally, immunotherapy can be coupled with vaccines for patients who may only be immunocompromised during a certain window of time. For example, Mousa said that patients who have cancer and are undergoing chemotherapy may use immunotherapy throughout the course of their treatment. Once the patient's treatment is complete and their immune system is back to baseline, they could benefit from receiving a vaccine (i.e., they would then be able to generate an effective immune response). With this in mind, Mousa emphasized the importance of both immunotherapy and vaccines to keep patients safe and mitigate the spread of disease—one doesn't necessarily replace the other.

"There's lots of labs working to develop antibodies to viruses that do exist, but aren't necessarily widespread," Mousa explained. "Researchers are working to find patients [who have been infected], get blood samples and then generate antibodies against that virus. You could think about stockpiling those, so that if a particular virus does emerge [or re-emerge] at a larger scale, you'd already have an antibody stockpile and the capacity to generate it much faster."

IMPROVING ACCESS TO VACCINES THROUGH POLICY

Even if proactive steps are taken to ensure rapid vaccine development, public health officials must also consider how vaccines are distributed in order for them to effectively protect as many individuals as possible on a global scale. Prior to the identification of a pathogen, Gizachew Taddesse Akalu, M.Sc., Ph.D. Fellow, Lecturer in the Department of Microbiology, Immunology and Parasitology at St. Paul's Hospital Millennium Medical College, said public health officials can create infrastructure that will ensure that vaccines are accessible.

Almost 70% of the global population has received at least 1 COVID-19 vaccine dose. However, data on the disruption of COVID-19 vaccines shows that under-resourced countries have limited access to vaccines. "Equitable distribution is particularly important in the area of vaccines, which, if used correctly and equitably, could help to stop the acute phase of a pandemic and allow the rebuilding of our societies and economies," Akalu said, noting the spike in funding for COVID-19 mitigation efforts and a recent desire to be proactive about preventing future pandemics.

To ensure that vaccines against emerging and re-emerging pathogens are accessible and equitably distributed, Akalu recommends focusing on 3 key areas when developing policies:

1. **Support Production:** An increase in vaccine production for infectious diseases will require consistent government support on a global scale to help countries expand their vaccine development and deployment capacities.
2. **Bolster Trade:** When scaling up vaccine production, streamlined vaccine supply chains will be critical.
3. **Address Inequities:** Akalu emphasized that market forces by themselves will not be enough to ensure successful vaccine deployment. He noted the World Bank's investment of $6 billion toward the Guyana COVID-19 Emergency Response Project, which not only supports equitable vaccine access, but also provides an example of the type of investment required in many under-resourced countries to facilitate better vaccine distribution. "Market forces alone will not suffice to ensure accessibility in vaccine deployment; we must also support policies that establish production equity," Akalu emphasized.

ASM's Global Public Health Programs (GPHP) equip countries to surveil and respond to infectious diseases. Learn more about Global Public Health.

MEET THE MICROBIOLOGIST:

Outbreak Detection with Wun-Ju Sheih

BY ASHLEY HAGEN, M.S.

EPISODE SUMMARY

Dr. Wun-Ju Sheih worked as a pathologist and infectious diseases expert with the CDC from 1995-2020. He recounts his experiences conducting high risk autopsies on the frontlines of outbreaks, including Ebola, H1N1 influenza, monkeypox and SARS-CoV-1 and 2. He also addresses key questions about factors contributing to the (re)emergence and spread of pathogens and discusses whether outbreaks are becoming more frequent or simply more widely publicized.

ASHLEY'S BIGGEST TAKEAWAYS

- Pathologists are a group of medical doctors serving behind the line of the daily hospital activities.
- Pathology service can be divided into atomic pathology and clinical pathology. The field covers all the laboratory diagnostic work in the hospital, and clinical microbiology or medical microbiology is actually a subdivision within the clinical pathology service.
- Usually, a pathologist working in a hospital will examine and dissect tissue specimens from surgery or biopsy.
- The pathologist also performs autopsies as requested to determine or confirm the cause of death.
- Serving as first a clinician in Taiwan, and then a pathologist in the U.S., has provided Sheih with the unique experience of evaluating patients from both the outside-in and the inside-out!
- Even when a major outbreak of a known etiologic agent is taking place, confirmatory diagnosis is necessary for subsequent quarantine, control and prevention of the outbreak.
- During major disease outbreaks, other pathogens do not go away, and we must simultaneously facilitate their timely diagnosis to ensure effective patient treatment and care.
- SARS-CoV-2 appears to be transmitted more easily than SARS-CoV-1. One possible explanation for this is that the amount of viral load appears to be the highest in the upper respiratory tract of those with COVID-19, shortly after the symptoms develop. This indicates that people with COVID-19 may be transmitting the virus early in infection, just as their symptoms are developing … or even before they appear or without symptoms.
- SARS-CoV-1 viral loads peak much later in the illness.

- Asymptomatic transmission is rarely seen with SARS-CoV-1 infection.
- Almost 99% of SARS-CoV-1 patients developed prominent fever when they started to carry infectivity. Temperature monitoring was therefore, very effective at detecting sick patients and facilitating prompt quarantining procedures, which effectively contained/minimized transmission of the virus.
- This was not as effective for SARS-CoV-2, despite early attempts at temperature monitoring.
- SARS-CoV-2 was much harder to contain both because of the milder display of host symptoms and the demonstration of higher viral transmissibility.

DEFINITIONS:

- Outbreak: An outbreak is defined as a sudden rise in the numbers of cases of a disease more than normally expected in a given community or geographic area.
- Epidemic: An outbreak is declared an epidemic when the disease spreads rapidly to many people locally.
- Pandemic: A pandemic is an outbreak of disease across several countries or continents across the globe.
- Endemic: An endemic is a disease outbreak that is consistently present, but only limited to a certain geopolitical area.

FEATURED QUOTES:

"I was working at CDC, Centers for Disease Control, which is a public health institute, and not a hospital. So my duty and daily activities are somewhat different from the hospital pathologist."

"In conjunction with the clinical and epidemiologic information, I will interpret all these test results, including molecular testing and electromicroscopy—if they're performed—to generate a report with final diagnosis."

"In a nutshell, I was utilizing pathologic, microbiologic, immunologic and molecular techniques to help investigate major outbreaks and difficult cases with unknown etiology of infection."

"A pathologist is like a ninja, or a shadow warrior—highly skilled but usually working in the dark, behind the frontlines. We don't get as much credit or visibility for what we do, but our work is essential for patient care in the hospital and for public health as well."

"I used to be a hospital clinician, so I certainly saw a lot of patients. And like many of my colleagues, I did have severe cases or fatal cases—patients who died of certain infections. But back then, I couldn't find the etiologic pathogens using the available laboratory methods. In Taiwan and many other Asian countries, the autopsy rating is, in general, very low because people don't usually accept that type of procedure because of the culture or religious reasons."

"If my patient unfortunately passed away, and if I could not find the etiologic agent, that case would bother me because I couldn't help the patient."

"When I was a clinician, I looked at the disease from outside-in. Later, I became a pathologist with my training in the U.S., and it was the reverse. When performing an autopsy, I was looking at things from the inside-out. Meaning, I was examining their tissue samples from histology and all those pathologic methods, and then trying to correlate with their clinical course."

"It's very rewarding for me and such a good learning experience for my professional career to see things from both sides."

"I got a chance to perform a partial autopsy in Vietnam on an anesthesiologist who contracted an infection from the index case [of SARS-CoV-1] at the emergency room when he was intubating the patient, and unfortunately died of the infection later."

"The knowledge and experience from studying SARS-CoV-1, I think, paved a faster and concrete way to the identification of SARS-CoV-2."

"Back in 2003, after the SARS-CoV-1 outbreak, we performed many subsequent studies on animal models. We collaborated with NIH and other academic institutes, and we learned a lot in terms of the pathogenesis and pathology of SARS-CoV-1. And again, some of that information was very useful."

"There are multiple reasons why we are seeing more pandemics caused by emerging and reemerging pathogens over the past 40 years or so. Evidence suggests that the risk of pandemics has increased because of many factors, such as increased global travel and integration, urbanization, change in land use, deforestation, global warming, greater exploitation of natural environments. And all these play some roles in terms of the so-called emerging outbreaks."

"When [pathogens] spread from a local area to a larger area geopolitical area or even globally, they become pandemic."

Let us know what you thought about this episode by tweeting at us @ASMicrobiology or leaving a comment on facebook.com/asmfan.

The Rise and Fall of Infectious Diseases

BY STEPHEN ORNES

To figure out where new diseases come from—and how old diseases return—it's tempting to first investigate the pathogens. Viruses, after all, can quickly evolve into new versions of themselves, and human antibodies that pevent an infection one year may be ineffective the next. Immunity to past variants of a virus may not guarantee protection against future ones. Similarly, pathogenic bacteria, parasites and fungi can develop resistance to existing treatments, blunting their efficacy.

Mutations and other biological factors play a role in disease emergence and reemergence, but they're not the only culprits behind the waxing of infectious agents. They may not even be the principal drivers. "People assume that the emergence of infectious diseases is a natural phenomenon, but it's not," said Wubshet Mamo, Ph.D., a public health expert and clinical professor at the University of Washington in Seattle and the International Training and Education Center on Health in Ethiopia. He pointed out that viruses tend to remain stable when they're left undisturbed in nature, and it's only when under threat or otherwise disturbed that they develop new mutations. "The emergence of infectious disease is not merely associated with viral or bacterial evolution," he said.

HOW HUMAN ACTIVITY DRIVES THE SPREAD OF DISEASE

Mamo is among a growing chorus of researchers and public health experts who believe that factors related to human activity and behaviors are more powerful forces driving the persistence and emergence of disease. These factors include climate change, which can worsen extreme weather events like droughts and floods linked to higher risks of disease. Recent floods in Pakistan, for example, have displaced large numbers of people and increased case counts of diseases like dengue, malaria, measles and COVID-19. Human activity also includes disruptive events, like wars and political struggles, that can destabilize large populations of people; increased interactions with animals that can boost the transmission of zoonotic pathogens; and the shipping of foods and animals from country to country, running the risk of expanding the reach of parasites.

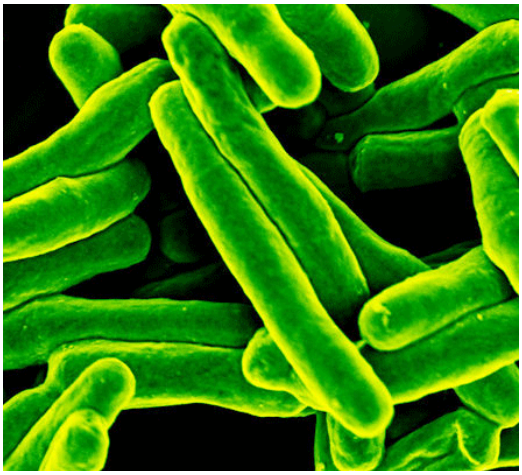
A view of deforestation in progress with a logging crane. Source: iStock.

"My concern is that our increasingly unbalanced interactions with nature, such as deforestation, increased urbanization, drought and wars, could further increase the risk factors and provoke new disease emergences or re-emergence of the old infections," Mamo said. "A large human population size favors the spread and perpetuation of diseases."

These risk factors have been exacerbated by the global response to the ongoing COVID-19 pandemic, which has critically reshaped incidence and mortality rates for infectious diseases in locations around the world, especially in under-resourced countries. In those places, limited public health resources and infrastructure—which themselves are immediate consequences of the larger issue of global health inequities—can make the problem worse.

Tuberculosis, a disease that kills more people than any other infectious disease except COVID-19, offers a compelling case study of how infectious diseases thrive in the shadow of the pandemic.

TUBERCULOSIS LOOMS UNDER THE SHADOW OF COVID-19



Mycobacterium tuberculosis. Source: Flickr.

Tuberculosis, or TB, is a stubborn adversary. It spreads quickly in crowded and unventilated living situations, and it disproportionately affects individuals who are malnourished and live at or below the international poverty line. TB has always been a menace: DNA tests on bones found in a now-submerged city in the eastern Mediterranean, dating back 9,000 years, show that *Mycobacterium tuberculosis*, the pathogenic bacterium that causes most cases of the disease, was causing trouble even then. Now, *M. tuberculosis* is believed to infect 2 billion people—a quarter of the world's population—and kill about 10 million yearly. TB remains the 13th leading cause of death worldwide, according to the World Health Organization (WHO), and in 2014, the organization set a goal of eradicating the disease by 2035.

For microbiologists, infectious disease researchers, epidemiologists and other experts, this persistence is particularly vexing because TB is both preventable, by vaccine, and curable (in its active form), by a 6-month course of antibiotics.

Between 2015 and 2020, WHO reported that global incidence of the disease fell by about 2% per year. This was encouraging, if not quite on track with the 2035 goal. However, the COVID-19 pandemic threw a wrench into that trajectory in many parts of the world. "There were an additional 500 million deaths in 2020, which meant we were set back by almost 10 years," said Jamie Tonsing, M.B.B.S., D.F.M., M.Sc., senior advisor for TB at the Global Fund, which financially supports global efforts to prevent and treat TB, HIV/AIDS and malaria.

Many factors contributed to that setback. In biosafety labs in some resource-limited countries—and the 30 countries with the highest burdens of TB are all resource-limited—reagents used for TB diagnostic tests were repurposed for COVID-19. Skilled health care workers prioritized COVID-19 care, and "people focused more on testing for COVID-19 than for TB," said microbiologist Shirematee Baboolal, Ph.D., who is based in Trinidad and Tobago and works with low- and middle-income countries to develop microbiology-based strategies for tackling TB. Surveillance, which is the cornerstone of public health strategies to respond to emerging and re-emerging diseases, took a backseat to the growing pandemic crisis.

SHIFTS IN TUBERCULOSIS SURVEILLANCE AND TREATMENT IN SIERRA LEONE

Sierra Leone, an under-resourced country in West Africa, was hit particularly hard by the convergence of COVID-19 and TB. Over the last 2 decades, TB incidence in the country peaked in 2009 but then began to fall, largely in response to global efforts to improve diagnoses and treatment in the country.

As the COVID-19 pandemic took hold, the country responded quickly with lockdowns and emergency orders. "It's understandable, that was the fire in the house," said Tonsing. TB resources were repurposed for the new pathogen. TB diagnostic tests that often use GeneXpert assays, for example, were now being used for COVID-19 testing instead of TB.

Perhaps because of those early measures, or for reasons that aren't yet clear, the COVID-19 death toll in Sierra Leone and other sub-Saharan African countries remained lower than in other parts of the world. At the same time, TB incidence in Sierra Leone rose and the treatment success rate fell. From 2019 to 2020—just a 1-year change—the case-detection rate fell from 77% to 66%, which means that 1/3 of all new cases went undiagnosed and, therefore, untreated.

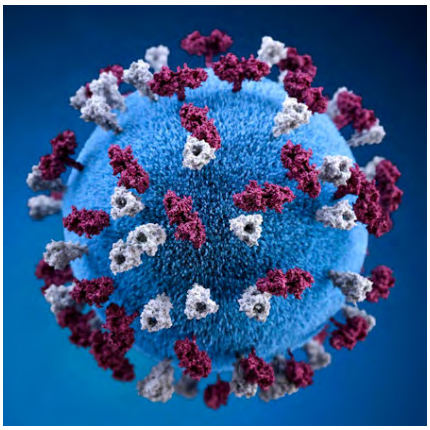
That shift revealed a major weakness in surveillance programs. "A surveillance system is so important in a country for TB, for COVID-19, for all infectious diseases," said Baboolal. "If you don't have an active surveillance system working in your country, then what happens? You will not pick up the first case, so you will end up picking up many cases."

Baboolal noted that it's simplistic to blame the pandemic alone. India accounts for an estimated one-quarter of all TB deaths worldwide, and early in the pandemic it experienced a similar drop in confirmed cases. The country's public health agency had implemented a testing program that combined TB and COVID-19 screening and obtained hundreds more diagnostic machines. As a result, case-detection rates in India have nearly returned to pre-pandemic levels.

Going into the pandemic, Sierra Leone already had an understaffed and underfunded public health system. Another factor was poor living conditions. "Many people still live in very poorly ventilated homes," said Baboolal. *M. tuberculosis* spreads in the air and can rapidly infect an entire family, especially if they live in close quarters. People who lack access to nutritious food and basic health resources face additional risks, as the 24-week treatment and its side effects can be grueling. As a result, many people abandon treatment, promoting the spread of drug-resistant TB, which is even more difficult to treat.

MEASLES, MALARIA AND MORE

Other diseases also surged during the pandemic. In the first 2 months of 2022, the number of measles cases reported worldwide jumped by nearly 80% compared to the same time period in 2021. A major drop in vaccinations is likely to blame: According to UNICEF, 23 million children missed out on routine immunizations in 2020. Most of those children live in areas that lack reliable access to routine health care or in places affected by conflict.

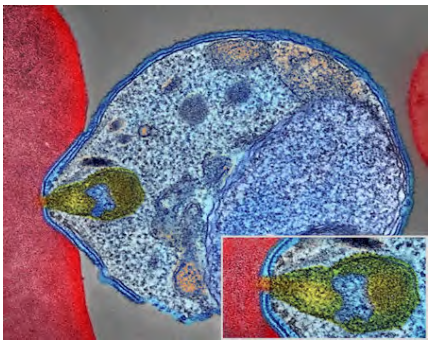


A 3D graphic representation of a spherical-shaped measles virus. Source: Rawpixel.

Because measles is so contagious, WHO researchers worry that the early 2022 data portend a disastrous comeback for the disease. Experts similarly worry about polio, which is caused by a virus and preventable by a vaccine. Nearly 30 countries suspended polio vaccination campaigns in the early months of the pandemic in 2020, and despite attempts to maintain surveillance, many cases have likely gone uncounted.

Malaria, too, has been affected by COVID-19. Scott Filler, M.D., is based in Geneva, Switzerland, and leads the Global Fund's efforts against malaria, which is caused by a plasmodium parasite transmitted by infected mosquitoes. Early in the pandemic, he and his group could see the potential for a dangerous re-emergence of malaria—again, not because of the parasite, but because of a weakened response.

"We were worried that more people would actually suffer from and potentially die from malaria than COVID-19 itself due to the concerns about health seeking related to COVID-19," he said. "Malaria has this incredible rebound capability if you take your foot off the gas."



A human red blood cell and malaria parasite connect. Source: Wikipedia Commons.

According to the World Malaria Report from WHO, COVID-19 did make malaria worse. There were about 14 million more cases of malaria in 2020 than in 2019, and roughly 69,000 additional deaths. For comparison, the total number in 2020 was 241 million cases and 627,000 deaths, and WHO linked most of those additional deaths to disrupted systems for preventing, diagnosing and treating the disease.

But Filler said that wasn't the worst-case scenario. "Of course, we saw perturbations due to COVID-19, but the early organization of the community—at all levels—made sure a more disastrous spread didn't happen."

PARASITIC INFECTIONS AND OUTBREAKS

Malaria didn't follow the same pattern around the world, though. "No one got malaria in the U.S. because no one was traveling," said Bobbi Pritt, M.D., who runs the Clinical Parasitology Laboratory at the Mayo Clinic in Rochester, Minn. But they did get infectious diseases connected to parasites: People who spent more time outdoors, Pritt said, were more likely to acquire a tick-borne illness like Lyme disease, which is caused by a bacterium carried by the black-legged (deer) tick.

She sees the emergence of parasitic infections as having "multifactorial" causes, but says human behaviors are likely behind most of them. For example, "there have been outbreaks of parasitic infections related to eating things," like raw fish, she said.

Pritt suspects the rise of tickborne diseases is connected to another human activity: an increasing encroachment on natural habitats. Researchers who study zoonotic diseases, which can jump from animals to humans, worry about future outbreaks due to increasingly frequent interactions between people and animals, as on big farms or places where new construction erases wildlife habitat.

"Vigilance should be a guiding principle in watching for the emergence of zoonotic diseases," said Tara Smith, Ph.D., an epidemiologist at Kent State University in Ohio. An estimated three-quarters of infectious diseases that infect people originated in animals, including SARS, MERS, dengue, Ebola, Zika, influenza and COVID-19. Many viruses likely lie in wait. In 2013, researchers hypothesized that animals harbor hundreds of thousands of unknown viruses. In a paper published in Cell in 2019, microbiologists used metagenomic analyses to identify nearly 200,000 types of viruses that live in the world's oceans.

LOOKING TO THE FUTURE

Smith does, however, see signs of progress—if not in public opinion, then in science. She credits the rapid global response to COVID-19 to decades of research—going back at least to the SARS outbreak of 2003—for enabling the rapid development of a vaccine for SARS-CoV-2. "We already had so much information about what species could be infectious," she said. Years of work on surveillance, she added, enabled researchers to quickly pivot their work and focus on SARS-CoV-2. And COVID-19, in turn, has highlighted the crucial need to better anticipate the next crisis. "We have learned so much about zoonotic coronaviruses because of it," she said.

She and other experts can point out ways to prepare for the future. Managing multiple, human-driven factors to tamp down infectious diseases will be a Herculean undertaking, especially if another catastrophe comes along. "There are so many things to deal with, whatever is the priority," said Tonsing. "We start working on something like that, like COVID-19, then forget that we still have TB. Or malaria. Or something else."

Mamo, in Seattle, said next steps must include focused strategic plans—at the national and international levels—that support better surveillance systems. "The goals need to focus on intensified science; sustainable investments in research, development and innovation; strengthening laboratory capacity and surveillance; improvement in health care delivery; and equity, access and public policy issues," he said. "There is a collective responsibility associated with emerging diseases, and we need coordinated responses, especially in [under-resourced] countries."

How Pathogens Survive and Thrive in a Changing Climate

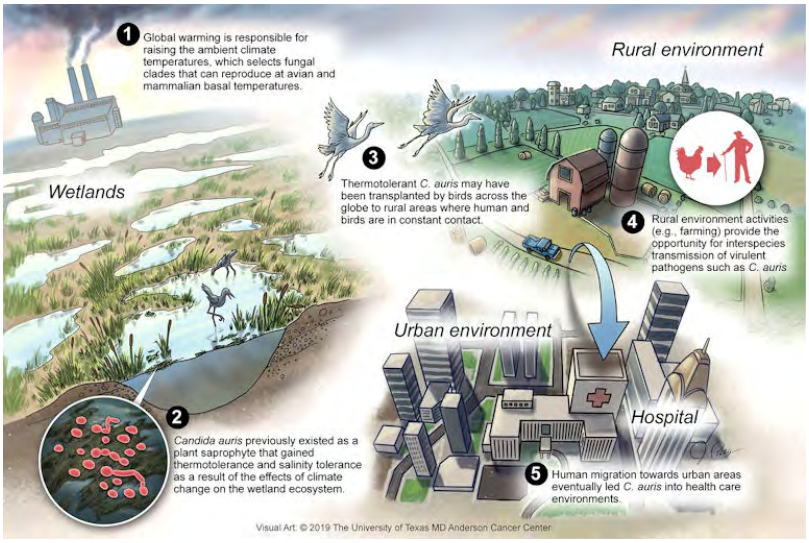
BY ASHLEY MAYRIANNE ROBBINS, M.E.L.P.

Study after study has arrived at the same conclusion: A changing climate will influence the health and well-being of humans and their environments. Shifts in temperature, precipitation, humidity, CO2 concentrations and nutrient availability can increase the risk of vector-borne and zoonotic diseases, both in new geographic areas and in places where such diseases are already endemic or eradicated.

A systematic literature review published in August 2022 predicted that 58% of human pathogenic diseases are likely to worsen with climate change. The impact of climate change on global health is expected to be so severe that the World Health Organization has termed it "the single biggest health threat to humanity," estimating that the direct health costs will total between $2 billion and $4 billion by 2030 due to increases in deaths from malnutrition, malaria, diarrhea and heat stress, among other factors. Scientists expect to see the highest burden of climate-influenced diseases in low-resource countries and communities. People who are immunocompromised or who have preexisting respiratory, nutritional and seasonal allergies will also be at higher risk.

WHY DOES CLIMATE CHANGE INCREASE DISEASE RISK?

In general, milder weather is more conducive to microbial survival and reproduction. Yet, according to Dr. Arturo Casadevall, chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology and a professor at the Johns Hopkins Bloomberg School of Public Health, the problem isn't simply warmer weather on average. "People are saying 'the world is only warming by 1 degree'; that's not the right way to think about it. Every time you have a really hot day, it's a selection event," he said. As the climate changes, microbes must adapt to the "new normal," presenting opportunities for pathogens to move about and evolve in unknown ways that may increase virulence and host range. As humans move to new environments to avoid climate change impacts, they may also encounter novel pathogens against which they lack natural immunity. Human evolution simply cannot keep up.



Proposed scheme for the emergence of *C. auris*.
Source: Casadevall A. et al./mBio, July 23, 2019.

"One of the reasons why [humans] don't [currently] worry about fungal disease … is because we're warm," Casadevall said. "Most fungi can't grow at our body temperatures," but rather infect room-temperature creatures, like reptiles and amphibians, or only impact humans on the skin level. However, "fungi are adapting," he cautioned. "As the world gets hotter, they are learning to grow at higher temperatures."

Casadevall's work over the last decade describes the ability of the fungus *Candida auris* to adapt and survive at high temperatures (above 37 degrees C), breaking the thermal exclusionary zone otherwise protecting humans from infection. "The concern with climate change is that the pillar that is temperature can be overcome if the fungi adapt," he said, especially given research showing that the average human body temperature is declining.

Casadevall's climate-based hypothesis arose from the fact that 3 unique isolates of *C. auris* have appeared simultaneously on 3 continents, with temperature tolerance being the common denominator. This hypothesis is seemingly backed by research in India that found that *C. auris* isolated from a populated beach had a higher temperature tolerance than a separate isolate from a marsh, indicating that the fungus might have adapted to different environments.

Host Spread/Migration

Wildlife overlaps with human communities amid habitat loss.

Hantavirus, Rabies virus

Source: American Society for Microbiology.

Pathogen and Host Ecology

To fully understand pathogens, it is helpful to understand the ecology of their host or vector organisms. Dr. Karla Satchell, Northwestern University Feinburg School of Medicine Professor, specializes in studying *V. vulnificus*, a marine bacterium found in shellfish and acquired by eating contaminated seafood. Less often, *V. vulnificus* can also infect wounds and cause necrotizing fasciitis, also known as "flesh-eating disease." "*Vibrio [vulnificus]* likes to grow in warm water (like the Gulf Coast). The number of days that are warm enough to allow bacteria to grow is increasing, and it's expanding into further northern regions … it's now pretty common in the Chesapeake Bay, and we are seeing incidences in Boston because the water is warm enough for multiple days per year," she said.

Satchell explained that *V. vulnificus* also only grows within a narrow range of salinities, but temperature-induced desalination has allowed *Vibrio* growth in the previously saltier Mediterranean Sea. An increase in *Vibrio* infections could have wide-reaching economic impacts on the fishing and shellfish industries as well. This could be particularly relevant in the summer during "beach season" and in coastal communities. *Vibrio* infections also follow natural disasters, with Florida reporting an increase in cases that occurred from the storm surge entering their homes or during post-storm clean-up during Hurricane Ian.

Vector Life Cycles

The seasonality, range and breeding cycles of arthropod vectors are altered.

Borrelia burgdorferi, Plasmodium spp.

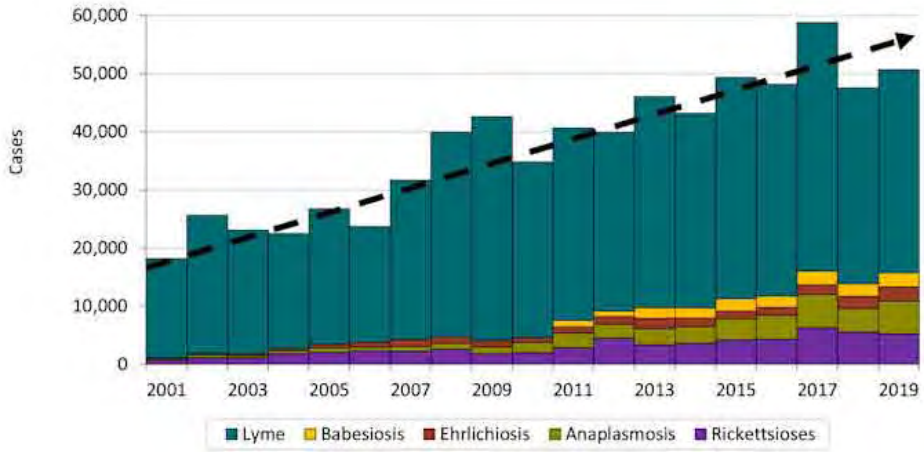
Source: American Society for Microbiology.

Vector-Borne Diseases

Meanwhile, on land, increasing temperatures have been shown to accelerate tick development, explained Michigan State University Professor Dr. Jean Tsao at Microbe 2022. A warming climate also facilitates the northward spread of mammals that carry ticks, such as the whitefooted mouse, which has been implicated in the establishment of *Borrelia burgdorferi*, the causative agent of Lyme disease, into new geographic areas. Similar phenomena have been observed in *I. ricinus* in Northern Europe, as well as vector movement toward the South Pole in Chile and other locations in the southern hemisphere.

Tsao explained that ticks consume only 1 blood meal per life stage, and they only feed in favorable temperature and humidity conditions. Researchers have noted changes in development rates and peak host-seeking periods between ticks in the Midwest versus in the Northeast, with the latter's larvae peaking in late fall. The cooler autumn weather in the Midwest, which lacks the buffer of East Coast winds, drives larvae to enter diapause (suspended development) shortly after and delay their feeding until spring, whereas Northeast ticks remain active. Because Lyme disease only spreads by vertical transmission, climate changes that impact life cycles may also impact disease incidence if nymph and larval seasons overlap. For instance, the maintenance of *B. burgdorferi* typically relies on larvae feeding after an infected nymph in order to acquire the bacteria.

Reported Cases of Leading TBDs by Year U.S., 2001-2019



Reported cases of leading tick-borne diseases in the U.S. by year, 2001-2019.
Source: Christopher Braden/CDC with American Society for Microbiology

"More Americans are at risk than ever before as mosquitoes and ticks are moving into new areas of the country, increasing cases and geographic ranges of vector-borne diseases," said Dr. Christopher Braden, the Acting Director of the Centers for Disease Control and Prevention (CDC) Center for Emerging and Infectious Zoonotic Diseases, at an ASM webinar. Since 2005, the number of vector-borne disease cases in the U.S. has doubled, and 10 novel pathogens have been discovered. The last decade has seen the first domestic U.S. outbreaks of mosquito-borne chikungunya and Zika viruses, and the largest single West Nile Virus outbreak in the U.S. occurred in Phoenix in 2021, affecting up to 5% of the resident population.

CAUSATION OR CORRELATION?

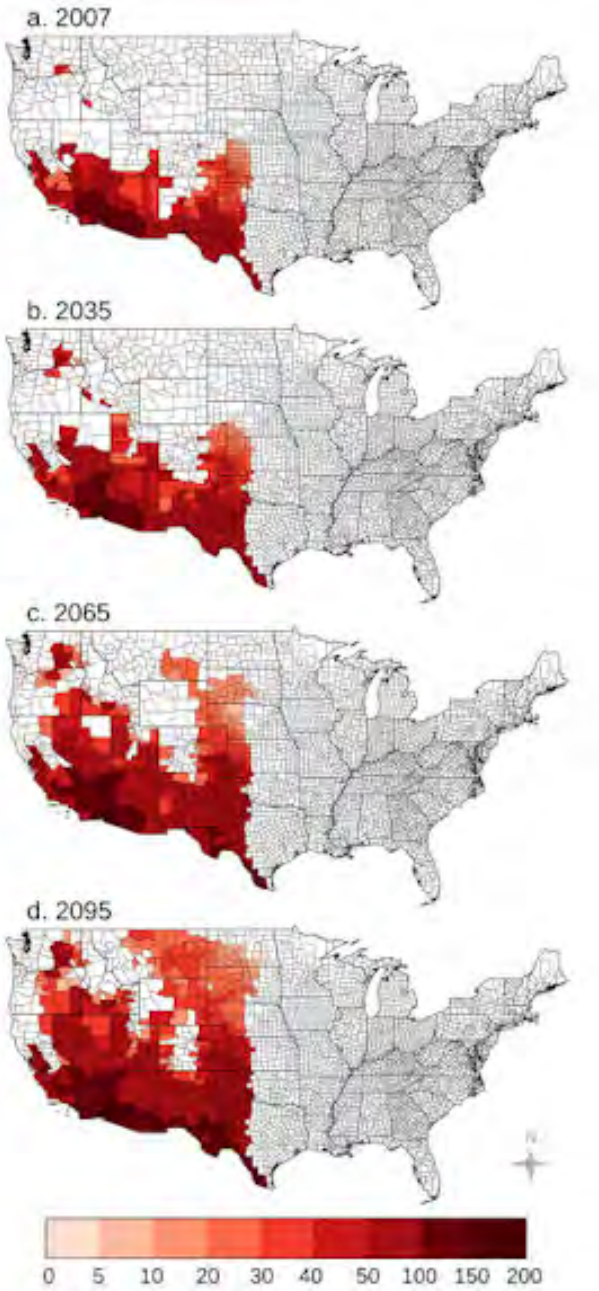
Scientists are investigating ways to remedy these difficulties retroactively by referring to historic climate change data from weather satellites or historical anecdotes from past outbreaks. Dr. Kathleen Treseder, the Howard A. Schneiderman Endowed Chair and a biology professor at University of California, Irvine, has monitored an increase in Valley Fever, a pneumonia-like disease caused by *Coccidioides* fungi, across the southwest U.S. over the last decade. Because the disease is not contagious and is instead acquired from inhaling the fungus from the environment, it was suspected that the "silent epidemic" has worsened due to hotter, drier, dustier conditions caused by climate change. For their study, Treseder's students wrote to every public health agency, county by county, to obtain case counts of Valley Fever every month over a 10-year span. They then connected this information to weather conditions in those places and times, using data from the National Weather Service.

"With so much data, we had to be very careful with our approach," Treseder said. "We wanted to look for relationships that made sense ecologically and biologically, and we needed to make sure relationships were robust. We wanted to be able to drill down and make sure climate was our main driver." Treseder explained that she also modeled cases against agricultural land use and economic variables to ensure that climate was, in fact, the key causative agent.

"There is no linear relationship between climate and infectious diseases," said University of Florida professor of environmental engineering, Dr. Antar Jutla. His research team develops predictive modeling intelligence to forecast how infectious pathogens will respond to geophysical and sociological processes, focusing on the underling hypotheses rather than curve-fitting models. "We are not always right, but once the hypothesis is supported with data, we are confident in our approaches to predict disease risk," he said. "The other philosophy of our research group is that we cannot separate the environment in which humans work, live and survive. Therefore, we need to understand how humans behave under certain weather/climate conditions."

PREDICTING AND MODELING THE FUTURE

Accurately predicting future outbreaks or climate conditions sounds impossible, let alone forecasting where, when and to whom these events might occur. Although predicting outbreaks is not a perfect science, Treseder used her observations from the past to anticipate which temperatures and precipitation amounts could be most conducive to the next Valley Fever outbreak. "We have been able to come up with a rule of thumb [that] if a certain area [is] above a certain temperature and below a certain



90th Percentile potential valley fever incidence
(cases per 100,000 population per year)

precipitation, we can say outbreaks would be occurring," she said. "We put this into a climate simulation, and found that over the next century, Valley Fever will move to the Plains states, a whole new region, where people have not been exposed." However, as she acknowledged, much of the future depends on human behavior. Therefore, her models include predictions under a "best case" as well as a "business as usual" scenario. "For that, it depends on how optimistic you feel in humans to make a change," she said. "But even under a best-case scenario, we still expect a 50% increase in the geographic extent of the disease, and in the worst case, it reaches the Canadian border."

Even if causation cannot be shown in nature, "we know *Vibrio* incidences go down in the winter. That is a correlative argument … but it's a pretty good one," said Satchell. Ideally, scientists would be able to use climate or environmental data to predict when and where *Vibrio vulnificus* risk may be highest, and respond with corresponding policies and public warnings. However, the CDC has not recently updated its Cholera and Other *Vibrio* Illness Surveillance website, perhaps in part because cases are relatively rare in the U.S. While they may be rare, *Vibrio* outbreaks can be economically devastating to tourism and shellfish industries. "This problem isn't going to go away until scientists start studying it, and the kind of scientists that study it also understand its pathogenesis," she said.

This is where the integration of knowledge from engineering and microbiology can lead to more disease-resilient human societies/communities. Jutla's research about waterborne pathogens is intended to inform water system and sanitation design. "Success is defined in several ways when dealing with infectious diseases. It could mean saving 1 human being, communities, regions or [a] country," said Jutla. "Generally, it is not possible to measure success directly in infectious disease domains, but if an outbreak can be prevented, it is a success."

TAKE ACTION

The American Academy for Microbiology, ASM's honorific society, has embarked on a 5-year scientific portfolio to bring microbiologists into conversations about public health and climate change. ASM Microbe 2023 also will feature a climate change guest track. To learn more and get involved, visit our resource page.

Do's and Don'ts of Crisis Communication for Public Health

BY GEOFF HUNT, PH.D.

Infectious disease outbreaks, though always unique, are not novel. In fact, the Centers for Disease Control and Prevention (CDC) has published a 350-page Crisis and Emergency Risk Communication (CERC) manual that lays out steps for preparing for, and responding to, a public health crisis. Yet, even the best-laid plans often go awry.

CRISIS EXPEDITES THE FLOW OF INFORMATION

During an emergency, everything is moving at warp speed as the normal flow of information turns into an avalanche. To keep up with this heightened pace, normal routines and standards are upended in the name of exigency. While useful (and often necessary), these changes also have consequences.

For example, consider that non-peer reviewed pre-prints became acceptable publications during the COVID-19 pandemic, as researchers strained to share any available data about the novel virus as quickly as possible. Unfortunately, these findings often were taken as definitive statements of fact, rather than preliminary results to be further analyzed and confirmed (or repudiated).

Cumulative growth of journal articles and preprints containing COVID-19–related search terms (as of April 2021).
Source: Fraser, N., et al. (2021). PLOS Biology 19(4): e3000959.

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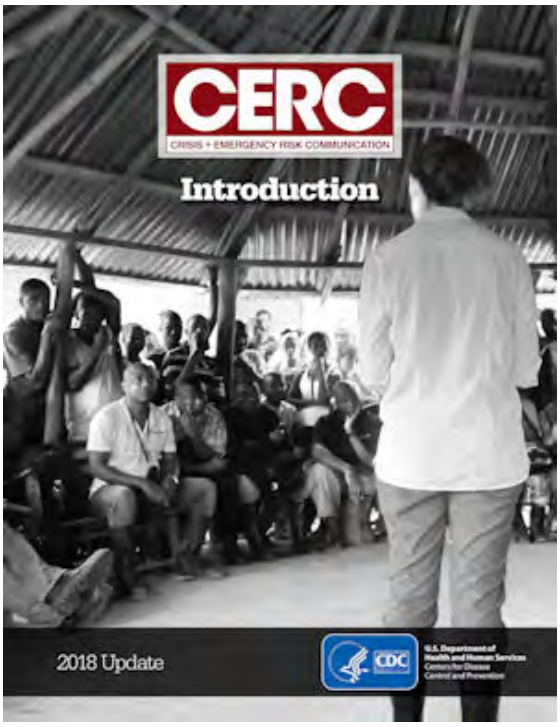
WHO TO TRUST?

Faced with such a deluge of information from scientists, medical and public health officials, policymakers and the media, it is nearly impossible for any individual to sort through what is accurate, what is new and what should be prioritized. Effective crisis communications are therefore reliant upon trusted, respected spokespeople who have the skills, the capacity, the knowledge and the institutional support to engage with audiences about the rapidly changing nature of an emergency. Yet, too often, the public health community's messengers lack the credibility, training or capacity to reach broad audiences in ways that resonate.

WHAT QUALIFIES AS AN EMERGENCY?

How a person responds to crisis communications is also dependent on circumstance. What seems like an emergency to some is just another setback to others. Individuals from underserved communities who are already contending with existing health, environmental and social challenges are less motivated to respond to crisis messaging, and the result is that these groups often end up bearing a disproportionate share of the burden from emergencies, such as infectious disease outbreaks.

Given these challenges, what steps can be taken to improve health crisis communications before the next infectious disease outbreak rolls around?



The Centers for Disease Control and Prevention Crisis and Emergency Risk Communication manual provides a step-by-step framework for responding to an emergency like an infectious disease outbreak. Source: Centers for Disease Control.

Do: Have a Plan

Part of the solution is just being prepared. Developing an emergency response plan helps organizations define goals, identify effective spokespeople, set up the necessary infrastructure and create a chain of command for collecting and disseminating information.

According to Xun Zhu, Ph.D., assistant professor of communications at the University of North Dakota, having a centralized information distribution center allows organizations "to be able to release information faster and distribute widely in social and organizational networks."

Zhu also recommends being prepared in terms of content. "Having a contingency plan means we would have a set of possible messages ready to go that has been tested for different groups of people," he suggested. This approach would allow scientists to coordinate appropriate strategies to address any potential issues before, rather than during, an emergency.

Do: Put Yourself Out There

The internet gives everyone the ability to broadcast their thoughts, opinions and perspectives. The challenge is being heard above the noise. The most efficient approach for making an impact is working with those who already have the platform and the audience. As Amanda Fine, News Media Branch Chief at The National Institutes of Health (NIH), recommended, "try to use existing channels of communication, like those of your organization, to amplify your message. It's very hard to gain a large following as an individual, and it's more likely that their platform has a much larger audience than yours."

Amplifying your voice also means being willing to talk with journalists. Providing outside expertise and advice on scientific research helps media outlets ensure accuracy, while respecting their publishing process. "If we call you, please answer the phone in a timely way, be willing to talk to us in a timely manner," pleaded Karen Kaplan, Science and Medicine Editor at the Los Angeles Times.

Seek Help From Communications Professionals

Fine suggested that scientists always coordinate with communications professionals when interacting with the media. "You don't want to talk and say something that you didn't mean that's either going to hurt the reputation of your institution or your own reputation," she cautioned. On the other hand, a bonus of this kind of collaboration, said Fine, is that it allows communications staff, who may lack a technical background, to "gain a better understanding of your research and help guide you in your messaging."

Going it Alone

A number of scientists have done a great job reaching audiences on their own, primarily through sharing of information on social media. This success is usually attributed to several factors, most of which tie back to a comfort with communicating and a willingness to engage.

"You write, you talk, you share," explained Monica Ponder, Ph.D., assistant professor of health communication at Howard University. "And people want to listen in. They want someone that is relatable and personable to explain these complex topics."

Choice of platform is also important. Whether it be Twitter, LinkedIn, press releases or TikTok, where you choose to engage dictates who you are reaching and how your message is both constructed and received.

Eric Topol, M.D., has gained a huge social media following thanks to his in-depth posts about the COVID-19 pandemic. Source: Eric Topol's Twitter profile.

Engage in 2-Way Communications

Scientists also must be willing to engage in 2-way communications with different communities, especially those who have been traditionally underserved, marginalized and ignored. As Ponder explained, "We as scientists need to be in those spaces, making sure that we are countering incorrect information and giving context in a way that is accessible, fun, creative and colorful."

Only by making an honest effort to establish relationships with these groups can the public health community hope to build the trust and credibility that is required to promote an effective crisis response.

"You write, you talk, you share," explained Monica Ponder, Ph.D., assistant professor of health communication at Howard University. "And people want to listen in. They want someone that is relatable and personable to explain these complex topics."

Don't: Let it Consume You. Do: Take a Breath

"Be First" is listed as the top principle of effective emergency and risk communications in the CDC's CERC manual. However, as Fine warned, "once you say it, you can't take it back. And once it's in writing, it's forever." Rather than sacrificing accuracy for speed, a better approach is to pause to think about what is being communicated and who is being reached before disseminating the information on a given platform.

Readers also benefit from a "less is more" approach, according to Rebecca Rozelle-Stone, Ph.D., professor of philosophy and religion at the University of North Dakota. "Online articles and social media can feel like images and headlines are just screaming at you," she said. "You can walk away quickly, but you feel exasperated and distraught."

Instead, Rozelle-Stone encouraged an approach of consuming less information and taking more time to read content. "Thinking about local issues, which gives us a greater sense of efficacy and agency, tends to happen when we're reading at a slower pace," she pointed out. "Connecting the dots between social contexts and crises are steps that increase empathy into the plight of other people," which helps ameliorate crisis fatigue.

Do: Change the System.

Some solutions will require a sustained, coordinated effort, involving stakeholders from across different sectors, making structural changes to how science is communicated. Institutions should adopt programs that integrate communications training as part of their curricula (similar to ASM's "Science Communication for Microbiologists" training course).

ASM's 'Science Communication for Microbiologists' course offers training on effectively communicating science to different audiences. Source: American Society for Microbiology.

Improve Cultural Competency

There is also a great need for cultural competency training that provides opportunities for raised awareness and mutual learning about different perspectives, backgrounds and experiences. Research shows that a critical factor for trustworthiness of crisis communication messages is transparency. "We have to begin to speak the same language, even if we're all just addressing the problem from a different angle," urged Ponder.

Enhance Accessibility and Responsiveness.

Other recommendations focus on making the scientific process more accessible and more responsive. Ponder suggested adding accessible information to journal articles. "I would love to see more explanation in discussion parts of articles that are prescriptive," she said. "Connecting those dots so that the data gets out of the lab itself and gets out of the clinical language."

For her part, Kaplan would love to see greater efficiency in the peer-review and article publication process. "If journals were able to turn things around faster, there'd be less need to throw so many things up on a pre-print," she explained.

THE NEED FOR BETTER COMMUNICATION

Addressing issues that are internal to the public health community would also positively impact how scientific and medical information is communicated to broad audiences. "When crises are there and facts need to be relayed, there's no way around it," admitted Rozelle-Stone. However, she added, "keeping people's eyes on just the catastrophe increases the sense of impotence."

Instead, Rozelle-Stone suggested a different approach. "Interspersing crisis stories with stories of hope, agency and dignity can prove useful" in overcoming feelings of hopelessness and helplessness that often lead to despair and inaction.

Ultimately, the public health community needs to start addressing these challenges now in order to see results when the next infectious disease outbreak hits. Admittedly, there is a lot of work to do, and hardly any of it is easy: nobody likes thinking about worst-case scenarios. Yet, a crisis is a crisis because it is an unexpected change from normal. Only by changing what normal looks like can we do a better job communicating when the next infectious disease outbreak occurs.

What's Hot in the Microbial Sciences

BY ASHLEY HAGEN, M.S.

In this issue, "What's Hot" takes a look at ...

HOW DOES *PSEUDOMONAS AERUGINOSA* DEAL WITH COMPETITORS?

The answer is poison. A recent study, published in *mBio*, reported that airborne hydrogen cyanide (HCN) produced by the pathogenic bacterium *Pseudomonas aeruginosa* inhibits *Staphylococcus aureus* growth in biofilm and in vivo lung environments. The observation sheds light on competitive dynamics of polymicrobial communities that cause chronic infections in cystic fibrosis (CF) patients.

CF is a genetic disease in which bodily secretions, such as mucus and digestive juices, become thick and sticky, providing an ideal environment for pathogens to thrive. As a result, the lungs and airways of CF patients are often colonized by multiple bacterial pathogens, including *P. aeruginosa* and *S. aureus*. Although *S. aureus* usually colonizes the lungs first during CF infection, when *P. aeruginosa* arrives on the scene, it outcompetes and replaces *S. aureus*.

3D illustration of lung infection caused by bacteria *Pseudomonas aeruginosa*. Source: istock.com.

Scientists have identified several extracellular factors that may contribute to the colonization shift; however, less was known about how airborne HCN (which is produced by *P. aeruginosa* metabolism and can rapidly diffuse into the environment) factors into the equation. HCN is a known respiratory chain inhibitor and is toxic to a wide range of eukaryotes. Scientists, therefore, hypothesized that it might also poison HCN-sensitive bacteria in a variety of niches.

The study revealed that HCN limits growth of a wide array of *S. aureus* strains and can do so from a distance. Low-oxygen environments were found to enhance *P. aeruginosa* production as well as *S. aureus* sensitivity to the compound. These results were demonstrated in microaerobic in vitro biofilms as well as in vitro CF lung sputum medium. Furthermore, consistent inhibition of *S. aureus* growth was reported in mouse model airways that were coinfected with both bacterial pathogens.

The study provides new context for the management and monitoring of *P. aeruginosa* lung infections and interactions with other HCN-sensitive microbes that may contribute to polymicrobial disease.

Mosquitos are attracted to high levels of the volatile organic compound acetophone produced by commensal skin microbiota. Source: istock.com.

CAN MOSQUITOS 'SMELL' DENGUE AND ZIKA VIRUSES?

Research published in *Cell* during the summer of 2022 demonstrated that mosquitos are not only more attracted to hosts infected with certain arboviruses (i.e., dengue and Zika), but also that the attraction is driven by a volatile organic compound (VOC) that is overproduced by the host's skin microbiota.

Scientists separated mice into 2 cohorts—those that were infected with dengue or Zika virus, and those that were not. Then they blew air over each cohort and observed that mosquitos preferentially flocked to the infected test subjects over controls. Upon collection and measurement of the volatiles emitted from the mice, researchers discovered that acetophone (C_8H_8O), an aromatic ketone that has natural roles as a photosensitizing agent, metabolite and xenobiotic, was significantly enriched in the infected cohort.

How did these arboviruses manipulate skin microbes to produce a scent that stimulates mosquito olfaction? It turns out, flavivirus infection suppresses expression of REMα, an essential antimicrobial that occurs on host skin. In the absence of this natural antimicrobial, commensal bacteria that produce acetophone as a metabolite are able to thrive. High acetophone levels attract more mosquitoes to the host, where feeding and spread of disease may be propagated.

A simple vitamin A derivative, isotretinoin, which can be given, in measured doses, as a dietary supplement, was shown to induce REMα production, decrease acetohpone concentration and reduce feeding of mosquitos on the treated hosts—perhaps illuminating a unique strategy for arboviral control.

Close-up image of Cynopterus brachyotis (Lesser short-nosed fruit bat). Source: Wikimedia.

WHY DON'T BATS GET SICK FROM DISEASES THAT ARE DEADLY TO HUMANS?

New research published in *Journal of Virology* suggests that selective pressure on a ubiquitous mammalian antiviral protein may assist bats in their unique ability to asymptomatically house viruses that are deadly to other mammals—including humans. Tetherin is a restriction enzyme that prevents particles of enveloped viruses (e.g., retroviruses, coronaviruses, filoviruses and paramyxoviruses) from escaping host cells. As a secondary function, tetherin triggers the immune signaling pathway NF-κB and stimulates antiviral interferon responses. The protein is common to all mammals; however, data indicate that bat tetherin genes have undergone expansion and diversification relative to other mammals, which may enhance their ability to withstand viruses, such as Ebola, Marburg, SARS-CoV-1, Hendra and Nipah, without showing clinical signs of disease.

In this study, researchers mined databases of publicly available sequence reads of bat tetherin homologs. Using an isoform from the fruit bat (*Pteropus alceto*) as their query sequence, they reported that the structure, number and expression of tetherin genes varied amongst the 27 bat species that were studied. For example, while the fruit bathas 3 isoforms of a single tetherin gene, 1 species of vesper bat (*Myotis marcopus*) was found to express 5 distinct tetherin genes and another, *Myotis lucifugus*, may have up to 7 more than any other mammal reported to date. (Most mammals carry only a single tetherin gene, and humans express the enzyme in 2 alternative isoforms). Notably, some of the variants discovered across bat species were structurally unique and had activity against different viral particles.

Scientists also examined tetherin protein expression, paying particular attention to the tissues of fruit bats. They found that the antiviral protein is expressed widely and variably throughout fruit bat tissues, with the highest levels reported in the thymus and lungs. These observations may point to the defensive role of tetherin against respiratory pathogens. Finally, when stimulated with Toll-like receptor agonists (e.g., lipopolysaccharide), increased tetherin expression was detected in the spleen. The importance of

this observation remains unknown. What is clear is that bats have evolved forms of tetherin that are unique from those observed in other mammalian species. Given bats are known reservoirs of viruses that cause severe disease in other mammals—often without development of any observable symptoms—unique evolution and diversification of antiviral genes, like tetherin, warrant further investigation.

Baijiu, a Chinese liquor, is fermented with the help of fungus-bacterium cooperative metabolisms. Source: Tagosaku/Flickr.

CAN FERMENTED FOOD FLAVOR BE REPRODUCED WITHOUT GEOGRAPHICAL LIMITATIONS?

Fermentation is one of the oldest practices in food and beverage preservation in human history. Lauded for its practicality and distinct flavor profiles, food fermentation has become something of both art and science. Replicating the flavors of fermented foods is often thought to be geography-dependent, but in a study published in *ASM's Microbiology Spectrum*, researchers attempted to replicate the complex processes of Chinese liquor (baijiu) fermentation in the lab.

The team collected 403 baijiu samples, belonging to 3 aroma types, from 9 different locations in China, across a latitude range of 27°N to 37°N, then applied culture-independent (metagenomics, metabolomics and metatranscriptomics) as well as culture-dependent tools to the samples. The analysis identified 735 bacterial genera and 290 fungal genera across the baijiu microbiome and revealed that fungus-bacterium cooperative metabolism had a greater impact on geography-dependent flavor than on either microbial counterpart alone. Furthermore, geographical characteristics could be attributed to enrichment of species from various microbial pools, which were largely governed by pH, precipitation and nutrition. As a result, researchers suggested adjusting the composition and distribution of species as an option for flavor regulation, stating that their findings provided rationale for developing a microbiome design to achieve intended flavor goals.

Space shuttle Atlantis, attached to its bright orange external fuel tank and twin solid-rocket boosters. Source: U.S. Government (Public Domain).

CAN MICROBES MAKE ROCKET FUEL?

Converting petroleum to fuel contributes to polluting emissions, including the environmentally costly greenhouse gas carbon dioxide (CO_2). Yet, energy-demanding applications, such as rocketry, aviation and shipping, require combustion of an energy-dense fuel source. Fuels that are rich in cyclic molecules with strained angles (i.e., cyclopropanes) can store the most energy. Cyclopropanes are hard to organically synthesize, which has propagated global dependence on petroleum. However, in a study published in *Joule*, scientists used bacteria to synthesize a molecule that has a higher energy density than any petroleum product on the planet.

The group explored thousands of bacterial genomes in search of naturally synthesized cyclopropanated molecules and identified a set of iterative polyketide synthases (iPKSs) that were predicted to produce polycyclopropanated fatty acids (POP-FAs). Next, they engineered a heterologous system to express iPKSs in *Streptomyces coelicolor*. The engineered bacterial host produced polycyclopropanated fatty acid methyl ester (POP-FAME), which can have energy densities greater than 50 MJ/L (higher than the most widely used rocket and aviation fuels on the market). Calculation of enthalpy of combustion, energy density (as net heating values) and vapor pressure lead scientist to conclude that POP-FAMEs are viable replacements for petroleum-based fuel sources in energy-demanding applications.

The study acknowledged that the next hurdle will be scaling up this system to be commercially useful. Once the structure of the molecules was determined, scientists were able to use this engineered biosynthetic pathoway to increase POP-FAME production by 22-fold.

Interested in learning more about the intersections between space travel and microbiology? Join us at ASM Microbe 2023 and hear from Andy Weir, author of *New York Times* Bestsellers, *The Martian*, *Artemis* and *Project Hail Mary*, as the inaugural Science and Society Keynote Lecturer. Register for ASM Microbe 2023.