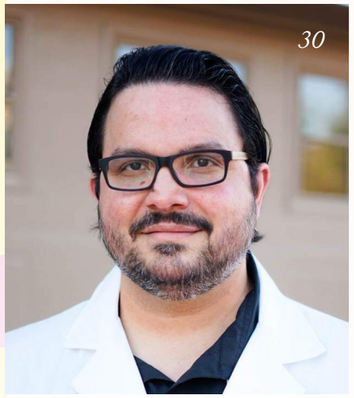
APRIL 2023 # 01

ID Transmission

In association with the Pathologist

We've Got ID Covered

ID Transmission – our new microbe-obsessed media hub – and The Pathologist join forces for a whistle-stop tour of the infectious disease landscape



We've Got ID Covered

Casting a wider net over infectious diseases – and creating a hub for everyone working across this diverse field

Follow us on social media (@IDTransmission or @pathologistmag) and head to www.idtransmission.com or www.thepathologist.com for even more content, or get in touch at olivia.gaskill@texerepublishing.com.

Although Disease X – an unknown pathogen with future pandemic potential – was coined by the World Health Organization back in 2018, it was COVID-19 that threw a spotlight on infectious diseases that's unlikely to dim anytime soon.

Since its official launch earlier this year (though its history dates back to 2020 in the form of The COVID-19 Curator newsletter), ID Transmission has been committed to delivering the latest hot topics and news from across the vast infectious disease landscape – without shying away from the hard-hitting and thorny subjects via plenty of interviews with the great and the good of the ID community. Our ambitious goal? To become a hub for everyone involved in tackling infectious diseases – no matter where or how you work with (or against!) them.

The Pathologist, on the other hand, has spent the past nine years amplifying the voices of laboratory medicine professionals who often go largely overlooked – by both patients and their peers – in the patient care pathway.

"We've Got ID Covered" – a special issue brought to you by ID Transmission and The Pathologist – explores the intersection of two areas of expertise. In this issue, we highlight the critical role that laboratory medicine plays in the detection, diagnosis, and treatment of infectious diseases. At the same time, we dig into the emerging science behind infectious diseases – exploring the potential threats posed by new pathogens, how they spread, and the measures we can take to mitigate them.

A few of my particular highlights of this issue include Stuart M. Levitz's take on the lack of antifungal vaccines (page 12), Emma Hannay and Karishma Saran's deep dive into pandemic preparedness (page 14), and my interview with mpox expert Dimie Ogoina (page 36) – and there's so much more to get stuck into. Sharing their first-hand insights and experiences, the experts featured in this issue offer valuable perspectives on the challenges and opportunities facing the field and the people who work in it.

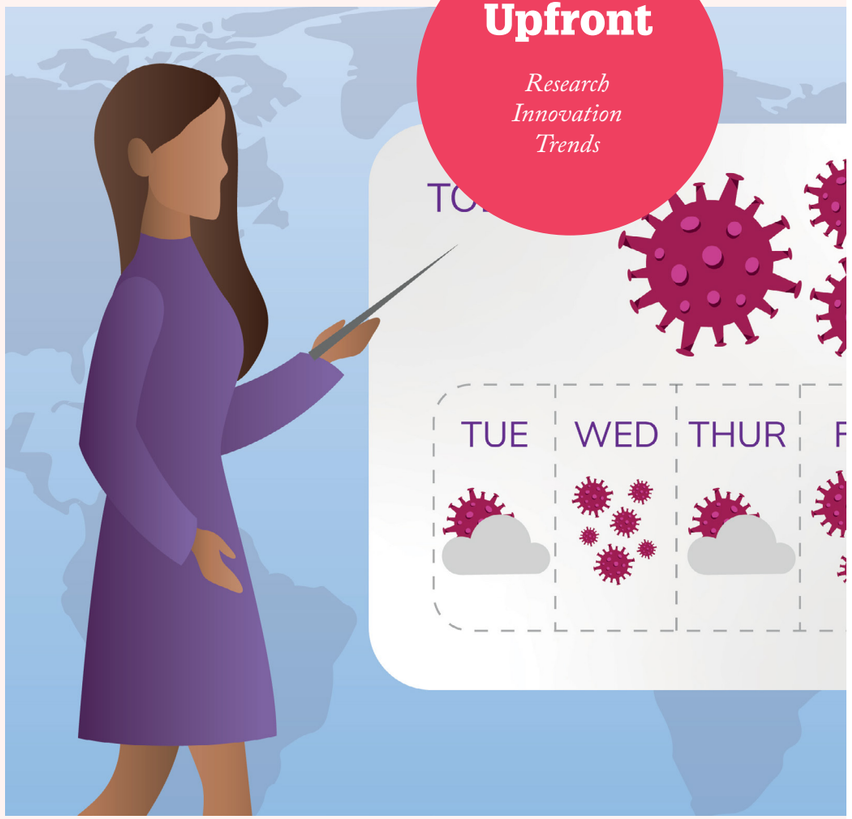
"We've Got ID Covered" is being released at an opportune moment as we descend on Copenhagen, Denmark, for the 33rd European Congress of Clinical Microbiology & Infectious Diseases. As the world's leading ID and clinical microbiology conference, the event will provide an ideal platform for scientists, researchers, and healthcare professionals to share their latest findings and discuss trends that have emerged since the last time we gathered.

As such, ID Transmission and The Pathologist are excited to share our joint collaboration with the masses and hope that it will serve as a valuable resource for those of you with a vested interest in infectious disease. We welcome you to our community of readers!

Liv Gaskill
Editor, ID Transmission

A Weather Forecast for Disease

With recent advances in tracking, data, and surveillance technology, is an infectious disease forecast system possible?



In a world where pandemics and lockdowns are still fresh in people's minds, there has never been more of an appetite for real-time tracking of infectious disease. With new advances in genomics, as well as epidemiological and clinical data, modern surveillance techniques allow for unprecedented insight into the current status of disease. But although the technology may exist, the infrastructure for disease forecasting is a still fledgling science. One group of researchers, in a bid to support the creation of such a system, has outlined their perspective on the steps needed to design a successful disease forecast in the future.

First, it's vital to address the looming threat of antimicrobial resistance. To date, disease forecasts have been unable to incorporate predictions on pathogen diversity – but, to ensure that the models are useful to practitioners and policymakers, they must be able to describe current infectious agents and their risk of resistance diversification. Pathogens evolve fast – and we need to keep up if we want to effectively monitor our antimicrobials' ability to keep us safe.

So what can we do? The authors propose a marriage between disease forecasting and genomic data. Sequencing technology is faster and cheaper than ever, and our ability to handle large volumes of data is only increasing. We're also expanding our understanding of resistance mechanisms, causative mutations, and predictive parameters. As turnaround times decrease and access to sequencing technology increases, we can track the evolution of the most pressing pathogens and the effectiveness of our antibiotic treatments against them. Embedding this data into prediction models and refining them over time in light of real-time pathogen evolution could significantly improve the accuracy and utility of infectious disease forecasting.

Despite the availability of extensive public pathogen sequence databases and the range of projects underway to compare sequences and combat resistance, the authors highlight that differences in sampling strategies and lack of context can impact the data's forecasting utility. To remedy this, they recommend continual sampling in the context of long-term surveillance – but standardized approaches to sampling, sequencing, and reporting (including metadata) could also help. Although mathematical modeling for epidemiology has grown significantly more accurate in recent years, there are still improvements to be made – and real-world observations, particularly in genomics, don't always match up with the math. In light of the expanding opportunities, the authors call for the incorporation of molecular data – genetics, genomics, and ultimately phylodynamics – into disease forecasting to ensure that our predictions, and the actions we take as a result, are as accurate and well-considered as possible.

Fishing for Viruses with DNA Nanobait

A new test detects multiple respiratory viruses at once, including SARS-CoV-2 variants

Respiratory tract infections are one of the leading causes of deaths from infectious diseases worldwide – but many viruses have similar symptoms, making it more challenging to choose the appropriate treatment. Using self-assembled DNA "nanobait" that can simultaneously detect multiple short RNA targets, a new test can identify different common respiratory viruses using a single sample (1).

For those of us who are unfamiliar with the concept of DNA nanobait, we asked senior author Ulrich F. Keyser from the University of Cambridge to give us the lowdown: "We can use DNA to build small structures – like molecular Lego," he says. "Viruses use RNA to store their genetic code – and RNA is chemically compatible with DNA, so we can use DNA to build a nanobait that only binds to RNA originating from one virus, such as SARS-CoV-2."

When asked what inspired his team to develop a test able to simultaneously identify multiple viruses and variants, Keyser says, "During the COVID-19 lockdown, we started to work on a viral RNA test and our co-author Stephen Baker, Principal Research Associate at the University of Cambridge, pointed out that one main issue was to be able to distinguish different viruses as quickly as possible."

In terms of SARS-CoV-2, the nanobait was able to accurately determine whether the virus was present or absent in samples taken from patient oropharyngeal swabs. But as well as concurrently identifying different viruses, the nanobait can be easily reprogrammed to distinguish between SARS-CoV-2 variants, for example, with single-nucleotide resolution.

Importantly, the technology is able to detect viral RNA without the time-consuming or convoluted steps that gold-standard tests, such as PCR, require. Moreover, although highly accurate, PCR tests can only test for one virus at a time and can take hours to deliver results. In contrast, the nanobait test returns highly accurate results in under an hour. The test also offers high specificity and sensitivity because it can detect multiple targets from the same viral RNA, as demonstrated when detecting SARS-CoV-2 in clinical samples.

Rapidly testing for viral RNA could also play a role in treatment selection – particularly when infections could be caused by two different types of pathogens. Keyser and his team are currently working on this endeavor; "A test that can tell if a patient has a bacterial or viral infection in a couple of hours could help streamline and improve patient care," says Keyser. "Furthermore, if one can tell which virus it is, the appropriate medication can be easily chosen – and, in terms of antimicrobial resistance, if the infection is not viral and one can tell what bacterial infection it is, healthcare workers can choose the correct antibiotic, potentially reducing the prescription of antimicrobial drugs."

Next on the agenda for Keyser is to develop a similar test that can be used in low- and middle-income countries, which he plans to collaborate on with Baker. It's this collaborative and curious nature that led him here in the first place. "This work was enabled by fundamental, curiosity-driven research over the past 15 years in my Cambridge lab," Keyser highlights. "Combining our knowledge with the expertise of people in different fields allowed us to move fast and go far beyond the original goal of a test for COVID-19."

Reference

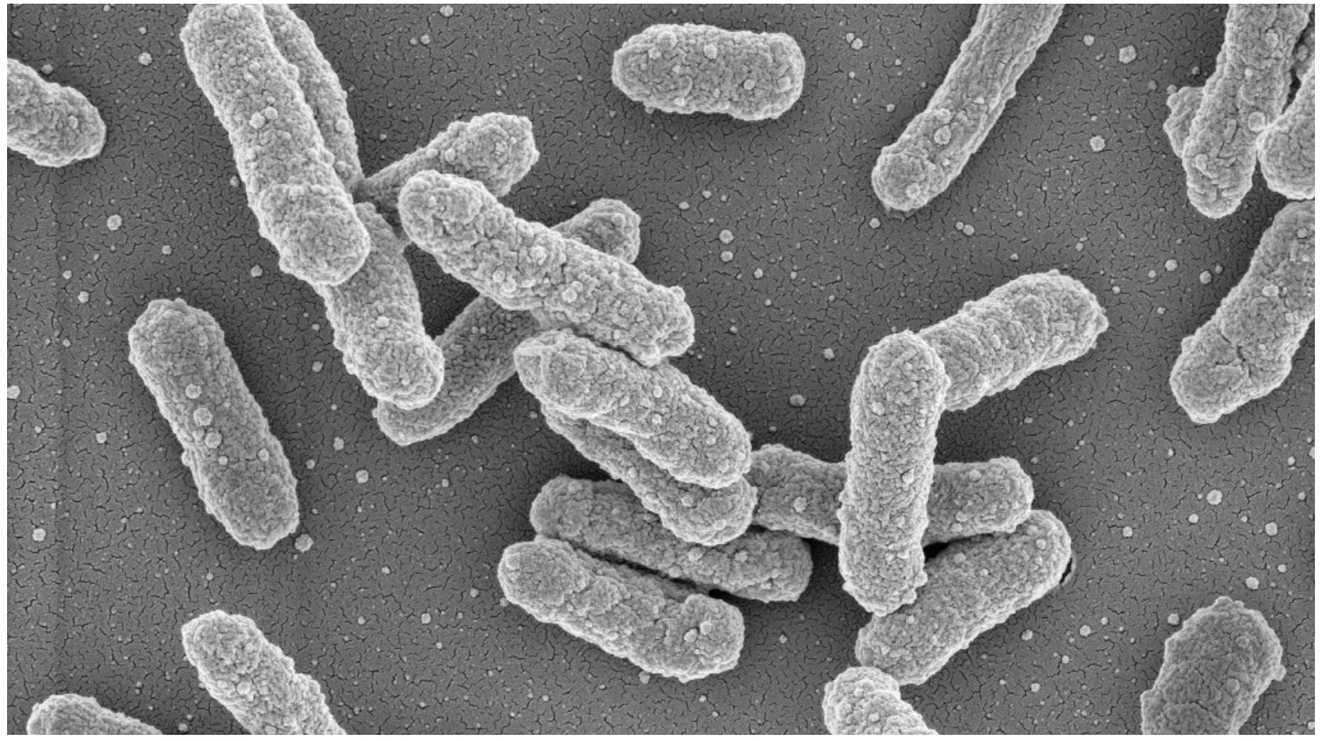
1. *F Bošković et al., "Simultaneous identification of viruses and viral variants with programmable DNA nanobait," Nat Nanotechnol, [Online ahead of print] (2023). PMID: 36646828.*

mRNA Vaccines: Beyond Viruses

Researchers have developed a highly effective mRNA vaccine against *Yersinia pestis*, demonstrating mRNA's potential against bacterial pathogens

Although plenty of research focused on mRNA technology before 2020, it wasn't until SARS-CoV-2 spread through the population that mRNA-based vaccines took center stage, with an unsurprising focus on viral pathogens. But with antimicrobial resistance plaguing already strained health systems, could mRNA vaccines offer new routes for treating – and preventing – bacterial infections?

For the first time, researchers have successfully developed an mRNA lipid nanoparticle (LNP) vaccine that is highly effective against a bacterial pathogen – namely, *Yersinia pestis* (1). To find out more, we spoke with one of the researchers, Dan Peer, Professor and Director of the Laboratory of Precision NanoMedicine at Tel Aviv University.



Credit: Muhsin Özel, Gudrun Holland, Rolf Reissbrodt/RKI.

What inspired you to develop a mRNA-LNP vaccine against a bacterial pathogen?

Bacterial pathogens pose a great threat to human health and, though many bacterial infections can be resolved with antibiotics, the global emergence of antibiotic-resistant bacterial strains necessitates the development of alternative countermeasures. The recently approved mRNA-LNP vaccine platform has been evaluated extensively against viral pathogens, but few reports demonstrate the effectiveness of this platform against bacterial agents. Given the ability of the mRNA-LNP platform to elicit robust humoral and cellular immune responses, we hypothesized that it could be harnessed for bacterial infections.

Why did you choose *Yersinia pestis* for your proof of concept?

Our study was performed in close collaboration with the Israel Institute for Biological Research, which has gained tremendous knowledge and experience with various bacterial pathogens, including *Y. pestis*. Our motivation was that, if we successfully demonstrated the efficacy of the mRNA-LNP platform against a highly lethal bacterium such as *Y. pestis*, it could open new avenues toward the development of novel prophylactic approaches against other bacterial pathogens.

What are the challenges associated with developing mRNA vaccines against bacterial pathogens?

As evidenced by the limited reports regarding the efficacy of mRNA vaccines against bacterial pathogens, designing a bacterial antigen to be encoded by the mRNA vaccine is more complex than a viral antigen. Though viruses exploit the host's translation machinery to produce their own proteins and subsequent production of virus particles, bacteria rely on their endogenous replication system, which does not involve eukaryotic pathways. Therefore, expression of a bacterial protein in mammalian cells could result in a protein which, although encoded by the same identical mRNA sequence, carries different modifications, which may alter its immunogenicity. Designing bacterial mRNA vaccines therefore requires deep understanding and molecular optimization of the relevant antigen.

Can you please summarize the main findings and lessons of your research?

In our study, we demonstrate the design of an effective mRNA vaccine against *Y. pestis* – the causative agent of plague. The vaccine is based on a major protective antigen, the F1 capsular protein, which was optimized to elicit robust immune responses. Through codon optimization, increased G/C content, human Fc conjugation, and removal of signal peptide, we were able to obtain very high anti-F1 IgG titers which, in the well-established plague mouse model, conferred full protection against a lethal challenge with *Y. pestis*. Importantly, the elicited immune responses were so robust that a single vaccination was sufficient to confer 100 percent protection.

As for lessons, I'd emphasize that the design and construction of mRNA vaccines against bacterial pathogens requires extensive adaptation and modification of the relevant antigen.

How might the target bacterium affect mRNA vaccine efficacy?

The life cycle of the bacterium is important. Intracellular bacteria are more similar to viruses in that they are capable of hiding from circulating antibodies (at least during the primary adaptive response). A cellular immune response – for example, CD8+ – is therefore crucial for successful elimination of intracellular bacteria (and viruses). Neutralizing antibodies will assist in controlling later phases of infection by blocking further spread of progeny viruses or bacteria – or during subsequent infection.

In contrast, extracellular bacteria generally do not "hide" inside host cells and are prone to binding by neutralizing antibodies. Therefore, humoral responses are generally highly effective against extracellular bacteria. One major advantage of the mRNA vaccine platform is its ability to elicit both humoral and cellular immune responses.

What are the strengths of mRNA vaccines for bacteria over traditional recombinant protein vaccines?

Compared with recombinant protein vaccines, mRNA vaccine production is relatively rapid, simple, inexpensive, and does not require cell culture and tedious purification stages. The mRNA vaccine platform also enables quick adaptation to emerging strains of the pathogen. We believe that our proof-of-concept study will pave the way for the development of additional mRNA vaccines against bacterial pathogens, especially in light of the global health threat of antibiotic resistance.

When might we see approved mRNA vaccines against bacteria, such as *Y. Pestis*?

In our study, we tested the ability of the mRNA vaccine to protect animals against bubonic plague; next, we aim to evaluate the vaccine's ability to confer protection against pneumonic plague, which is the most serious form of the disease. Unlike SARS-CoV-2, approval of an mRNA vaccine against *Y. pestis* may take a long time because plague disease is mostly sporadic and does not resemble the recent global pandemic affecting millions of people.

What are your predictions for mRNA-based vaccines for other bacteria given the success of your research so far?

We believe that the data collected in our study will facilitate the development of mRNA-based prophylaxis against additional bacterial pathogens. Although the modifications we applied to the *Y. pestis* antigen greatly increased its ability to induce robust immune responses, it is possible that other bacterial pathogens will require additional or different antigen alterations or sequence optimization. Therefore, the successful development of mRNA vaccines for other bacteria will require deep understanding of the pathogen's biology and its potential antigens.

Reference

1. *E Kon et al., "A single-dose F1-based mRNA-LNP vaccine provides protection against the lethal plague bacterium," Sci Adv, 9, eadg1036 (2023). PMID: 36888708.*

Prenatal Insights of SARS-CoV-2

Using MRI as an in vivo tool to explore the effects of SARS-CoV-2 infection on both fetus and placenta

It is already known that SARS-CoV-2 infection during pregnancy is associated with fetus complications (1) – but most research has been limited to histopathological investigation of the placenta. Furthermore, pathological study only allows placental development to be measured ex vivo toward the end of development. Delivering high tissue contrast, magnetic resonance imaging (MRI) represents an excellent non-invasive tool for identifying placental abnormalities in vivo before birth, so researchers applied it to the challenge of understanding the impact of SARS-CoV-2 infection during pregnancy. Specifically, they wanted to understand if it was capable of visualizing the effect of infection on the fetus and placenta (2).

Between July 2020 and July 2022, MRI examinations were performed on pregnant women an average of 83 days after a positive SARS-CoV-2 PCR result. Twenty infections were classified as pre-Omicron variants (Wildtype, Alpha, Delta, unknown but pre-Omicron); 18 infections were Omicron.

Placentas in the pre-Omicron infection group demonstrated more frequent lesions (lobulation and hemorrhages). However, compared with noninfected controls, globular shape changes of the placenta were evident in both the pre-Omicron and Omicron groups. As well as higher frequency of lobulation and hemorrhages in the pre-Omicron group, a significant increase in placental thickening was also found. Two fetuses in the pre-Omicron group (wildtype) showed perinatal cerebrovascular fetal lesions. Furthermore, fetal growth restriction (FGR) was found in 5.6 percent of Omicron fetuses and 25 percent of pre-Omicron fetuses. The pre-Omicron FGR cases were found to correlate with globular placental expressions.

In the paper, the researchers suggest that thickening of the placenta with globular shape changes could be "a compensatory mechanism in placental insufficiency" – which has been linked with vascular causes. From this, the researchers deduced that the effects on the fetus are caused by malperfusion of placental vessels.

Two potential explanations offered for the differing rates of placental lesions across variants are Omicron's lower pathogenicity and higher vaccination coverage at later stages of the pandemic, though both of these variables were not measured. Furthermore, pre-existing maternal risk factors and diseases were not available for all cases.

Overall, the study demonstrates the potential of MRI as a reliable in vivo diagnostic tool for examining the effects of SARS-CoV-2 on the placenta and fetus. Specifically, there is evidence of placental lesions based on vascular malperfusion following SARS-CoV-2 infection during pregnancy, which is more prominent in pre-Omicron variants, and could explain associated fetal morbidities, such as FGR.

References

1. *E MyClymont et al., "Association of SARS-CoV-2 Infection During Pregnancy With Maternal and Perinatal Outcomes," 327, 1983 (2022). PMID: 35499852.*
2. *P Kienast et al., "SARS-CoV-2 variant-related abnormalities detected by prenatal MRI: a prospective case–control study," Lancet Reg Health Eur, [Online ahead of print] (2023). PMID: 36713638.*

RSV Racing

FDA advisors recommended both Pfizer and GSK's RSV vaccines within days of each other – but who will cross the finish line first?

Amid rising cases of respiratory syncytial virus (RSV) over the winter months, the lack of an approved vaccine was all the more apparent. But within a few days of each other, FDA advisors recommended both Pfizer and GSK's RSV vaccines for adults aged 60 years and over (1,2).

"In older adults, RSV can result in serious illness, hospitalization, or even death, so there is a significant need to protect this at-risk population," said Pfizer's Senior Vice President and Chief Scientific Officer of Vaccine Research and Development, Annaliesa Anderson (1). "We are encouraged by the outcome of today's [Vaccines and Related Biological Products Advisory Committee] meeting as it is a testament to the strength of our science and dedication to bringing this important vaccine candidate to the market. We look forward to working with the FDA as it completes the review of our application."

The advisory committee voted 7-4 in favor of the safety and effectiveness of Pfizer's vaccine, with one member abstaining from the vote (1). For GSK's vaccine, the committee voted unanimously in favor of the vaccine's effectiveness and 10-2 in favor of its safety data (2).

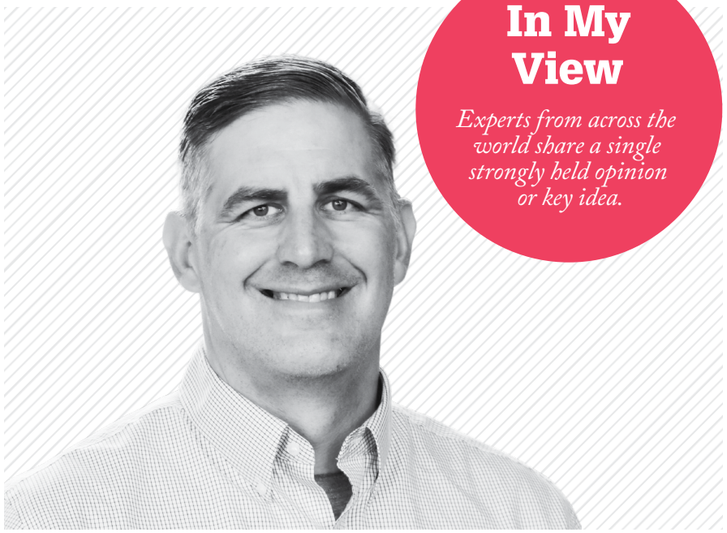
"Today's vote brings us an important step closer to delivering one of the world's first vaccines for RSV – a respiratory virus that causes potentially debilitating disease and imposes a major burden on healthcare systems," said Phil Dormitzer, Global Head of Vaccines R&D at GSK (2). "Thousands of older adults in the US are impacted by RSV and those with underlying health conditions, like respiratory and heart diseases and diabetes, are at increased risk of severe complications. We're delighted that the Advisory Committee recognized the strength of our vaccine's data and its potential to make a positive public health impact with a unanimous vote on the effectiveness of the vaccine."

Two's company, three's a crowd – nevertheless, Moderna has also entered the race (albeit a little late), announcing at the start of 2023 that its investigational RSV vaccine MRNA-1345 met primacy endpoints in its ConquerRSV Phase III trial (3).

Who will cross the finish line first? Will we need a photo finish? We'll be watching from the stands.

References

1. *Pfizer, "Pfizer Receives Positive FDA Advisory Committee Votes Supporting Potential Approval for Vaccine Candidate to Help Combat RSV in Older Adults" (2023). Available at: bit.ly/3yQ8Ozd.*
2. *GSK, "US FDA Advisory Committee votes to support effectiveness and safety of GSK's respiratory syncytial virus older adult vaccine candidate" (2023). Available at: bit.ly/3lvBw5x.*
3. *Moderna, "Moderna Announces Mrna-1345, An Investigational Respiratory Syncytial Virus (Rsv) Vaccine, Has Met Primary Efficacy Endpoints In Phase 3 Trial In Older Adults" (2023). Available at: bit.ly/40hZQGO.*



In My View

Experts from across the world share a single strongly held opinion or key idea.

What's in a Name?

Infectious disease naming conventions should aim to prevent stigma and discrimination – and improve public health responses

By Brad Hutton, Public Health Consultant at Hutton Health Consulting, New York, and Former New York State Deputy Commissioner of Public Health, New York, USA.

Given my career as an infectious disease epidemiologist, and my avid interest in history, I am particularly intrigued about the origin of pathogen names, the impact they have on society, and how history continues to repeat itself.

In the 14th century, before syphilis was named after a literary character with the disease, countries at war named the disease after their enemies; Russians referred to the disease as the "Polish Disease," the Polish called it the "German Disease," and Italians called it the "French Disease." This practice of naming a disease after a country and blaming its residents for its spread had the intended effect of promoting hostility and divisiveness. Unfortunately, the previous US President evoked the same hostile reaction when he referred to the SARS-CoV-2 virus as the "China Virus" and "Wuhan Virus," which has resulted in significant anti-Asian discrimination, harassment, and violence.

In the 20th century, newly discovered pathogens were often named based on the population impacted by the initial outbreak; for example, *Legionella pneumophil*a, which was discovered to be the bacteria behind an outbreak among attendees at an American Legion convention in 1976. Diseases were also named based upon the small geographic area where cases were first reported, including Lyme disease in Lyme, Connecticut; Norovirus in Norwalk, Ohio; and Pontiac fever in Pontiac, Michigan. Similarly, the Ebola virus was named after an outbreak in 1976 near the Ebola River in the Democratic Republic of Congo.

Although residents of these towns, cities, and countries are likely not pleased to have diseases named in such a way, other infectious disease names have been much more stigmatizing and discriminatory because they focused on who was primarily contracting the pathogen. For example, in 1982, what we now refer to as the human immunodeficiency virus (HIV) was often referred to as GRID, for "gay-related immunodeficiency." Recognizing the harm that could come from poorly named pathogens, the World Health Organization (WHO) established best practices for naming infectious diseases in 2015, stating that names should not negatively impact "trade, travel, tourism, or animal welfare" and should "avoid causing offense to any cultural, social, national, regional, professional, or ethnic groups" (1). The WHO acknowledged that the discovering scientists traditionally name new pathogens and encouraged them to use the new nomenclature standards.

Although the WHO's effort was a step in the right direction, there are still numerous infectious diseases that were named prior to 2015, including monkeypox, now "mpox." Mpox was initially discovered and reported in the 1950s as the virus responsible for an outbreak in a colony of monkeys being used for laboratory studies in Denmark. The scientists who named it "monkeypox" should not be faulted for failing to foresee the stigma the name could have when used in future decades; however, that does not mean we can allow it to happen today. Because of "racist and stigmatizing language online, in other settings and in some communities," the WHO recommended this pathogen be renamed "mpox" in November 2022.

"We need to proactively take action to reduce the potential for stigma by reviewing legacy infectious pathogen names."

Moving forward, it is critical that we be cognizant of how naming an infectious pathogen can lead to stigmatization, discrimination, and violence against those infected or from a certain region, and to populations disregarding the necessary protocols to contain a disease outbreak. Historically, stigma affected efforts to quarantine individuals exposed to SARS in 2003, the public health response to the 2014 Ebola outbreak in West Africa, and the approach to treating tuberculosis for centuries.

We need to proactively take action to reduce the potential for stigma by reviewing legacy infectious pathogen names and renaming those that are either inflammatory or have the potential to cause harm before an outbreak or pandemic occurs. The WHO uses the term "Pathogen X" to refer to yet-to-be-discovered pathogens that could cause future pandemics. They have convened scientists and thought leaders to discuss "Pathogen X;" explore research gaps that must be addressed to enable rapid development of testing, vaccines, and therapeutics; and glean lessons from the COVID-19 pandemic and other recent outbreaks to improve public health responses to new or re-emerging pathogens in the future.

However, our greatest threat may not be one that can be addressed in laboratories or through clinical trials; it is the ongoing effort to discredit public health and spread misinformation. The US Surgeon General Vivek Murthy issued an advisory on confronting health misinformation in July 2021, stating that, "Health misinformation is a serious threat to public health. It can cause confusion, sow mistrust, harm people's health, and undermine public health efforts. Limiting the spread of health misinformation is a moral and civic imperative" (2).

Working in public health for nearly 30 years, I couldn't agree more. It is imperative that "Pathogen X" discussions include the identification of pathogens and diseases most likely to result in stigma and misinformation. In particular, I think Middle East Respiratory Syndrome – or MERS – should be at the top of our renaming priorities due to the potential stigmatization of people from that region of the world.

Dedicated efforts to change pathogen names and launch health information campaigns to address and prevent stigma are needed just as urgently as efforts to develop diagnostics, vaccines, and therapeutics.

References

1. *World Health Organization, "World Health Organization Best Practices for the Naming of New Human Infectious Diseases" (2015). Available at: https://bit.ly/3uQfOtS.*
2. *VH Murthy, "Confronting Health Misinformation" (2021). Available at: https://bit.ly/3YbULy4.*

Adventure Science

Searching for the next zoonotic viruses

By Brittany Niccum, Senior Commercial Product Manager at Integrated DNA Technologies, Indianapolis, USA, and Han Wei, Market Development Scientist at Beckman Coulter Life Sciences, Indianapolis, USA.

Scientists know a great deal about zoonotic diseases – sicknesses that move between animals and humans, such as rabies, West Nile virus, and Lyme disease. But the human race is still vulnerable to the next virus – and the next pandemic – because we don't know enough. Six out of 10 infectious diseases, and three out of four emerging diseases, are zoonotic (1). We can avoid being caught unprepared by actively looking for them.

Due to population growth, the ease of global travel, and the human thirst for unique experiences, humans are invading areas previously inhabited exclusively by animals. The two groups are interacting in unprecedented ways – and exploring these interactions can help us understand the conditions that cause the sharing and spread of disease.

To gain information about new viruses and how to deal with them, we need a holistic approach that takes into account the fact that human health is connected to the health of animals, plants, and the environment. This kind of transdisciplinary approach isn't new; it's called One Health and it allows scientists, governments, and health agencies around the world to collaborate for the benefit of human health.

For example, if a lot of birds are dying of West Nile virus in Africa, local scientists who know the ecosystem should lead the research to understand the cause of the

outbreak. The national government could provide funding and disseminate public health information while avian experts provide research support. Maybe a US lab with specialized equipment can cost-effectively process samples and share findings. All of this serves a common goal – to learn how to prevent the birds from getting West Nile virus so they don't pass it onto other animals and then to us. By empowering scientists in local communities to research and ultimately contain a virus before it gets on a plane and travels to the other side of the world, everyone – human or animal – is safer.

Achieving optimal health outcomes requires us to move away from a reactive approach. For zoonotic diseases we've already studied, such as Lyme disease or West Nile virus, we have learned to identify symptoms in the infected animals, warning signs that indicate a person has been infected, and treatments. Both humans and animals are protected because we have done that work ahead of time – and we can make use of it rapidly when an outbreak hits.

The spread of COVID-19 taught us that we can rapidly develop vaccines, get them to the right places, and contain the spread of disease. But it also revealed a fundamental lack of information about the source of the disease and how it spread. We knew that coronaviruses could be a problem because of the SARS outbreak in 2003 and the rise of MERS some years later, and viral trials completed at the time might have allowed us to be more prepared for the arrival of SARS-CoV-2.

"The spread of COVID-19 taught us that we can rapidly develop vaccines, get them to the right places, and contain the spread of disease. But it also revealed a fundamental lack of information about the source of the disease and how it spread."

Lessons learned from a small outbreak of mpox in the United States in 2003 – the first report of the disease outside Africa – illustrate the need for a One Health approach in our interconnected world. Prairie dogs, purchased from a sketchy exotic animal dealer, passed the disease on to their new owners in six states. Scientists knew that the virus was similar enough to smallpox that using the same vaccines and treatments contained the spread. That same information is now preventing the spread of the virus in the US and elsewhere. But we still don't know the source of the misnamed mpox virus – its reservoir. We know that monkeys can be infected and pass it on to other animals, including humans, but what animal is infecting monkeys? We won't know until we go looking.

Research gives us the information we need to prepare for a public health crisis. It also helps us prevent crises by caring for the animals and environment and maybe even eliminate the threats they can pose. To stay ahead of the next outbreak, we need a One Health approach supported by worldwide scientific and medical collaboration – working together for the global good.

References

1. *Centers for Disease Control and Prevention, "Zoonotic Diseases" (2021). Available at: bit.ly/3g0roz6.*

Where Are the Antifungal Vaccines?

Developing vaccines for fungal diseases is a multifaceted challenge that demands a multifaceted solution

By Stuart M. Levitz ,Professor of Medicine, Microbiology, and Physiological Systems at the UMass Chan Medical School, and an attending physician at UMass Memorial Medical Center, Worcester, Massachusetts, USA.

It's true that fungi don't seem to get as much attention as viruses, bacteria, and other infectious pathogens – why? Serious fungal infections (mycoses) occur mostly in persons who are immunocompromised; in contrast, many viruses, bacteria, and parasites are primary pathogens that can infect and kill people with intact immune systems.

If you think back 100 years ago, lethal fungal infections were rare because there weren't many immunocompromised patients – but that's no longer our reality. Tens of millions of people worldwide live with HIV/AIDS. People with solid organ transplants need immunosuppressive medications to prevent rejection. Cancer chemotherapy can lead to profound immunosuppression. Corticosteroids and other biologics are commonly used to treat diseases characterized by excessive inflammation, such as autoimmune diseases. As a result, the at-risk population has skyrocketed – worldwide, an estimated 1.5 million people a year die from fungal infections. Recognition from medical professionals and the public of the importance of tackling fungal infections is slowly increasing, but challenges still remain.

One of the problems encountered with fungal diseases is that there are currently no clinically approved antifungal vaccines. But there are dozens of fungal vaccines in development. We can categorize fungal vaccines by the pathogen(s) they are directed against. Some vaccines in development aim to protect against multiple pathogens by targeting components shared by most medically important fungi; one such component is β-D-glucan, which is found on fungal cell walls. Others seek to protect against a single fungal disease, such as coccidioidomycosis.

We can also categorize fungal vaccines by their general composition. For example, some vaccines are composed of whole organisms that are attenuated or killed, while others are made from crude extracts or defined antigens. Some subunit vaccines take advantage of RNA technology akin to what is used in COVID-19 vaccines.

Multifaceted challenges

The lack of fungal vaccines can be broken down into two distinct challenges: scientific and logistical. On the scientific side, fungi are complex pathogens with a large genome; identification of immunoprotective antigens in an organism that expresses over 5,000 proteins is not trivial. Whole-organism vaccines run the risk of triggering autoimmunity because fungi and humans are eukaryotic and, as such, share many cellular features. Host defenses against many medically important fungi rely primarily on T cell immunity, but T cell vaccines are challenging to develop, partly because approved vaccine adjuvants mostly stimulate antibody responses. In addition, responses to T cell vaccines can be heterogeneous because of the many HLA alleles in the human population. But perhaps the biggest scientific challenge is developing vaccines that are potent enough to stimulate robust responses in immunocompromised individuals.

Perhaps the least challenging fungus targeted in vaccine development is Coccidioides species. This fungus causes coccidioidomycosis – an endemic mycosis that often afflicts those with apparently intact immune systems. The incidence is high enough that efficacy trials are feasible and immunocompetent subjects could be enrolled – but unfortunately that's not the case with most other fungi. Each fungus presents unique challenges with vaccine development. Fungi that rarely cause infection are challenging because clinical vaccine trials need to enroll large numbers of subjects to evaluate efficacy. Fungi that predominantly infect severely immunocompromised persons are challenging because of the uncertainty surrounding whether one can elicit an adequate immune response.

When it comes to logistics, vaccine trials are very expensive. Pharmaceutical companies have not shown strong interest in supporting fungal vaccines. In addition to the scientific hurdles, for many vaccines they do not see a pathway to profits because most people who would benefit reside in resource-poor countries.

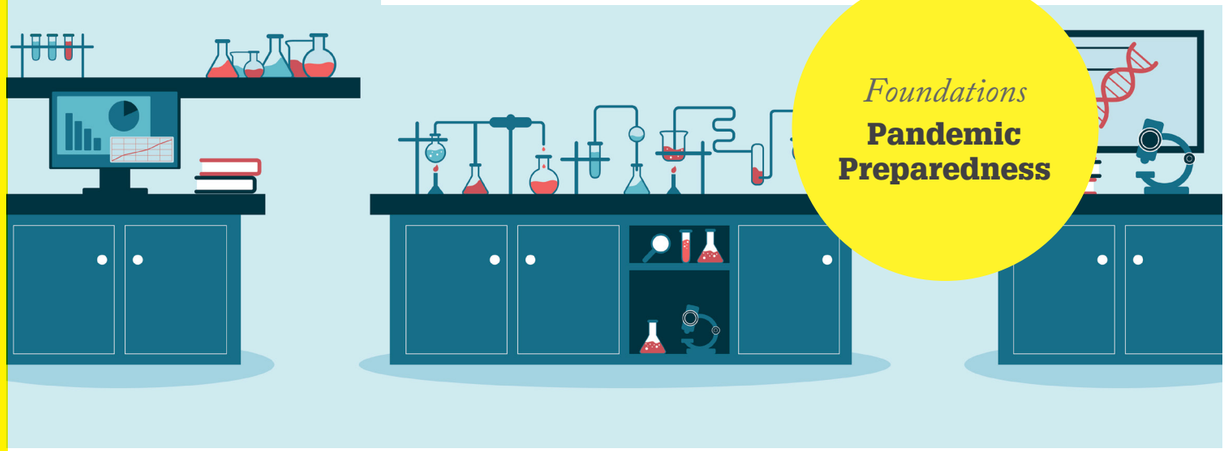
Overcoming hurdles

To overcome the challenges presented by antifungal vaccine development, strategies must be developed and individualized according to: i) the vaccine and ii) the target population. A vaccine designed for an immunosuppressed population could be administered prior to anticipated immunosuppression; for example, before an anticipated organ transplantation. Using newer adjuvants that elicit strong T cell responses to vaccine antigens should be considered for vaccines against fungi. Autoimmunity risk can be minimized by targeting molecules with no homologies to human cells. And finally, scientists must form partnerships with pharmaceutical companies, governmental agencies, and non-government organizations to bring promising vaccines to clinical trials.

Recent significant breakthroughs make me hopeful of a future filled with antifungal vaccines. For example, new adjuvants that promote strong antibody and T cell responses to fungal proteins have had very promising results in rodent studies, and dogs were protected in a trial of a live-attenuated Coccidioides vaccine. Also, a vaccine to prevent recurrences of vulvovaginal candidiasis was successfully tested in women – demonstrating the feasibility of human fungal vaccine trials.

The World Health Organization has significant influence worldwide, so when it published its fungal priority pathogens list in 2022, it brought much-needed attention to the importance of fungal diseases. This need extends beyond vaccines; there is also an urgent need for better diagnostics, therapeutics, and prevention measures – and we need to make the already existing measures available to all who need it. Many countries cannot afford first-line antifungal drugs and simple diagnostic tests, such as fungal cultures, are not readily available.

I'm optimistic that the increased awareness of the need for fungal vaccines will direct more resources towards development. But – reflecting on my point above – when vaccines do find their way through approvals, they need to be made available to the whole globe and especially the populations most in need.



Foundations
Pandemic Preparedness

Fail to Prepare, Prepare to Fail

Are global health systems ready for another pandemic?

By Emma Hannay, Chief Access Officer at FIND, Geneva, Switzerland, and Karishma Saran, Senior Manager of Advocacy and Communications at FIND, Geneva, Switzerland.

Healthcare workers were among the first respondents to the COVID-19 pandemic. Because their occupations required them to be on the frontlines, many lost their lives during the early days and others still suffer from post-viral symptoms or from the psychological aftereffects of the pandemic. The situation highlighted just how unprepared the world was to provide equitable access to medical countermeasures such as tests, vaccines, personal protective equipment, and therapeutics. However, we saw a triumph of science in the diagnostic landscape – accurate PCR tests for confirming SARS-CoV-2 infection were available in laboratories within eight days of the World Health Organization (WHO) declaring COVID-19 a Public Health Emergency of International Concern. But when it came to making these tests available to all of the healthcare centers and hospitals that urgently needed them, especially during the early phases of the pandemic, this victory was over as quickly as it came.

A changing world

Test manufacturing and supply has traditionally been very centralized; before COVID-19, research, development, and demand for diagnostic tests left the world with limited manufacturing capacity, unstable supply chains, and poor distribution and use of tests globally. Now, key industry players are coming forward to develop and grow local manufacturing capacities coupled with enhanced technology transfer. However, the same cannot be said for many other disease diagnostics. COVID-19 demonstrated what can be achieved when public and private partners work together; now, we need to develop these partnerships further so that new testing technologies can be rapidly introduced in most, if not all, countries.

The pandemic triggered the largest-ever global expansion of genomic surveillance capacity and demonstrated the powerful potential of next-generation sequencing technologies to transform disease surveillance and public health readiness for epidemics and pandemics. However, this expansion exposed existing inequities in disease surveillance systems, marked by uneven distribution and gaps in diagnostic testing and genome sequencing capacities in low- and middle-income countries (LMICS).

After almost three years of battling COVID-19, governments must see the value in systematically building diagnostic capacity, prioritizing testing in national health strategies, investing in local manufacturing, and ensuring that effective mechanisms for real-time disease surveillance are in place. Although this need is clear, a survey by the World Innovation Summit for Health (WISH) revealed that lack of access to equipment is a key threat facing national health systems (1). We feel strongly about improving access to accurate and affordable diagnostics simply because no tests exist for 60 percent of the "Blueprint" pathogens identified by the WHO as having the greatest outbreak potential (2). This lack of availability and access to reliable, high-quality tests threatens our ability to respond to health emergencies and jeopardizes the achievement of universal health coverage.

Lessons learned

The next pandemic is always just around the corner, but countries have learned some tough lessons from COVID-19 that will help them going forward. Speaking at WISH 2022, Commonwealth Secretary-General Patricia Scotland said, "We were all in the same storm, but we were definitely not in the same boat" (3). The virus doesn't respect borders and we must work hand-in-hand to ensure that nobody – no matter where they are in the world – is left behind. To combat this, one of the early partnerships formed was the ACT-Accelerator, a global collaboration to accelerate the development, production, and equitable access to COVID-19 tests, treatments, and vaccines. From research to rollout, the ACT-Accelerator remains the world's only end-to-end solution aimed at ending the COVID-19 pandemic.

With inequitable access to vaccines, therapeutics, and tests, many LMICs in the global south were largely left out in the cold during the pandemic. Groups such as the United Nations, European Commission, and WHO need to invest in data-enabled health systems for all on an ongoing basis, not only in the time of a crisis or pandemic. These institutions came together to form the ACT-Accelerator, the learnings from which continue to inform our thinking about new pandemic instruments, financing, and core capacities needed for future countermeasures. However, although mpox has been prevalent in certain regions for decades now, it only became an issue of global concern once its effects reached high-income nations. Clearly, existing health inequities are not only a matter of preparedness, but also one of prioritization.

COVID-19 taught us that nothing is impossible when there's a combination of funding and political will. We have seen research and development occur on extremely accelerated timelines because it affected everyone, everywhere. Investing in laboratories and strengthening national surveillance systems has better prepared countries for new waves of COVID-19 and served as a strong foundation for resilient pandemic preparedness.

From a supply chain perspective, we learned that centralized manufacturing does not lead to resilience – revealing how convoluted and fragile our supply chains are. The first few rapid COVID-19 tests were produced from one country, which proved extremely stressful because the whole world depended on a single supply source. All COVID-19 tests require a swab for sampling but, at the start of the pandemic, most swabs were produced in just two factories – one in Lombardi, Italy, and one in the US. The US put export restrictions on those swabs and, when it came down to country equity issues, high-income countries were able to move quickly, not only on the procurement and supply of diagnostic tests, but also on understanding how to use those tests in different circumstances. This meant that LMICs were already falling behind in their testing rates due to a lack of steady supply. Overwhelmed health systems also caused competition for funding and a grave neglect of diseases such as tuberculosis, HIV, and malaria, which then suffered significant setbacks as health systems shifted testing priorities.

Now, many countries around the world rapidly manufacture tests themselves, but this must continue to be an integral part of future pandemic preparedness to ensure supply chain resiliency. Manufacturing hubs and their partners must have a strong access plan to make sure people can get their hands on the necessary tools to keep themselves safe.

Barriers to success

Despite many diagnostic successes during the pandemic, the global testing effort still had many shortcomings. Significant challenges remain to be understood and addressed, particularly the global inequity of accessing tests, treatments, and vaccines – especially in remote areas and LMICs.

Testing is the essential first step in any pandemic preparedness plan – identifying the enemy and directing the development of vaccines and treatments. Like many others involved in diagnostic preparedness, we are now working closely with the Coalition for Epidemic Preparedness Innovations (CEPI) on the 100 Days Mission in five key areas (4):

1. Developing diagnostic test kits for high-priority pathogens that can be quickly adapted to any emerging pathogen.
2. Normalizing regular diagnostic testing.
3. Ensuring global access to diagnostic testing through reliable local manufacturing capacity and investments in LMIC testing networks.
4. Global surveillance systems to detect and monitor emerging and re-emerging pandemic threats.
5. Global cooperation and coordination in areas such as testing policy, emergency regulatory authorization, and global data sharing.

Most importantly, pathologists and lab medicine professionals are our gatekeepers; we rely on their warning signals and identification of future threats that may have pandemic potential. Looking ahead, we are interested in exploring the potential of multiplex testing rather than binary testing – a world in which patients and healthcare providers find a quick answer to the question, "What disease does the patient have?" rather than, "Does the patient have X disease?" It sounds futuristic, but we believe it's an achievable vision within the next few years – as long as diagnostics remain high on our collective agenda.

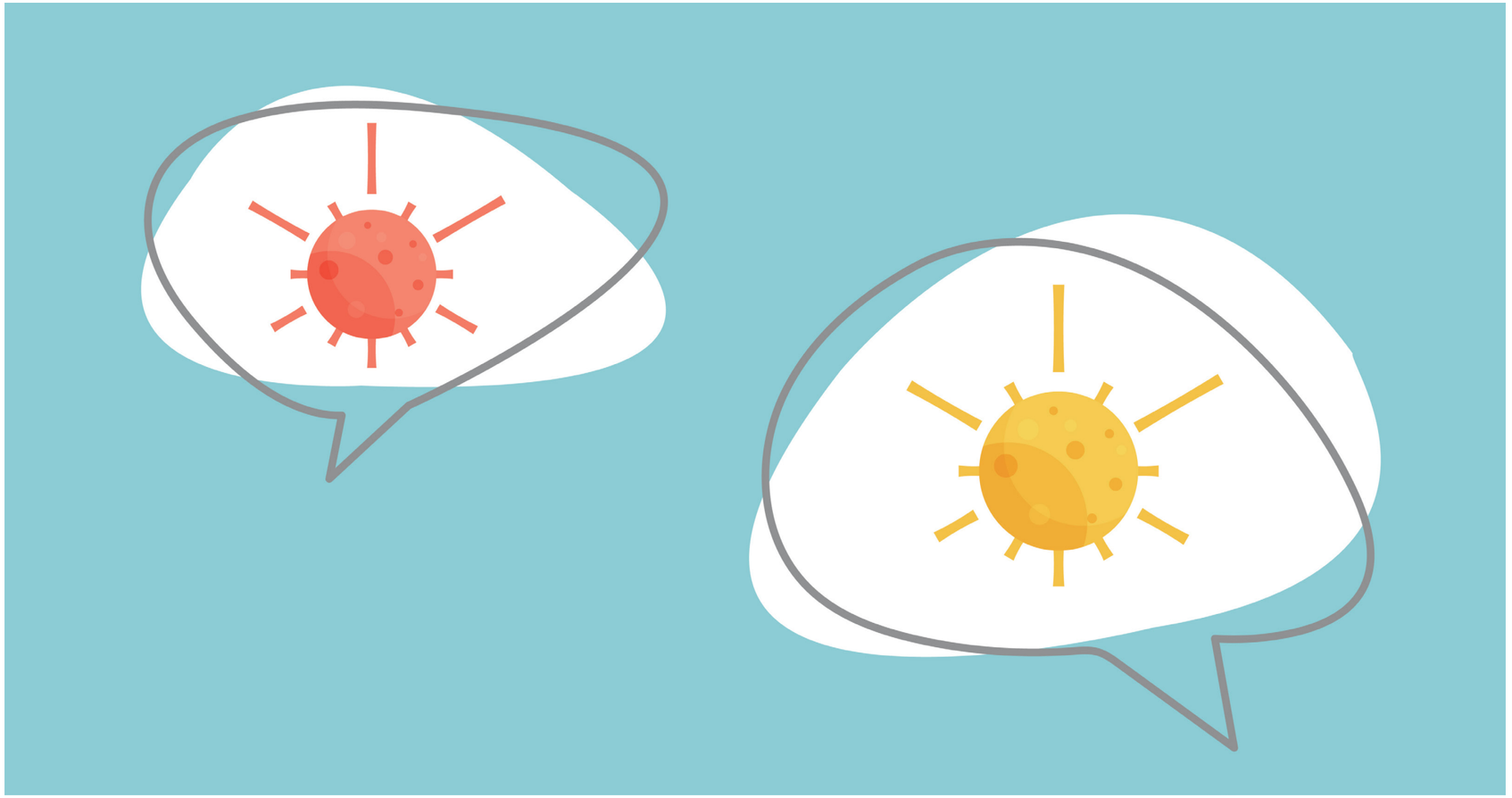
References

1. *WISH, YouGov, "WISH-commissioned study on pandemic preparedness, health system resilience, and healthcare practitioners' experiences from working through COVID 19" (2022). Available at: https://bit.ly/3UICoAg.*
2. *World Health Organization, "Prioritizing diseases for research and development in emergency contexts" (2022). Available at: https://bit.ly/3DlrKI9.*
3. *The Commonwealth, "At H20 Summit, Commonwealth Secretary-General calls for solidarity and collaboration to tackle global health challenges" (2022). Available at: https://bit.ly/3DoK1Ep.*
4. *B Rodriquez, "Accelerating diagnostic test development and deployment to prevent a future pandemic" (2022). Available at: http://bit.ly/3tmurVf.*

The Virus Hunters

Practicing viral vigilance will help scientists detect and contain future outbreaks

By Marwan Alsarraj, Biopharma Segment Manager, Digital Biology Group, Bio-Rad Laboratories, Hercules, California, USA.



Imagine how different the COVID-19 pandemic might have been if scientists had been armed with more information about the virus before the first major human outbreaks occurred…

Although humankind has faced many viruses and other pathogens for millennia, modern outbreaks have increasing potential to spread internationally and wreak havoc on every aspect of society – the stark reality presented by COVID-19. In early 2022, the IMF estimated that the cost of the pandemic will exceed US$12.5 trillion by 2024 (1) – and that's not to mention the unquantifiable cost of lives lost, long-lasting health effects, and disruption in education, socialization, technological advancement, and more.

The acceptance of mRNA technology has opened the door to other rapid-fire vaccine development platforms, which enables preemptive vaccine design and rapid deployment for future epidemics. One modeling study estimated that almost 600,000 COVID-19 deaths could have been prevented if vaccination efforts had reached the World Health Organization's 40 percent coverage target by the end of 2021 (2) – a feat made easier if more vaccines had been available sooner.

Looking ahead, a key component of pandemic preparedness will involve proactive monitoring of viruses as they evolve and circulate between different populations and species. "Virus hunting" will require significant funding and effort from a broad coalition, but it is a worthwhile cost to prevent or mitigate the next pandemic.

How do outbreaks occur?

Viruses that originated in animals and jumped the species barrier – aka "zoonotic spillover" – accounts for 60–75 percent of infectious diseases that plague humans (3), including HIV, Dengue fever, and SARS. Any interaction between humans and wild animals can increase the risk for zoonotic spillover, including hunting, exotic pet trades, and habitat encroachment that results from deforestation and urban expansion. And it's not just new viruses we have to worry about – outbreaks can also come from familiar pathogens already circulating in human populations; for example, polio, ebola, Zika virus, and mpox.

The risk of new outbreaks is also high in areas of inequitable vaccination access or low uptake, which creates higher concentrations of unvaccinated individuals who can rapidly spread the disease to those around them.

Tracking down viruses

Virus hunting requires strategic, multi-pronged approaches. It is unrealistic to sample every animal and human population; however, the risk of new outbreaks isn't evenly distributed. Some virus hotspots are far more likely to produce new, mutated viruses and create opportunities for spillover – making them targets for closer monitoring. Generally, these hotspots include areas where a large number of species co-habitat, such as jungles and rainforests.

Virology expert Ed Rybicki from the University of Cape Town (located at the heart of the South African viral hotspot) says an ideal testing plan for novel viruses would include scans of wildlife and domestic animals within a given area, using samples collected from feces, forest and farm runoff, and sewage. This type of environmental surveillance is much more efficient and comprehensive than testing individual animal specimens or humans. Once scientists have a virus' genetic sequence from agnostic environmental sampling and laboratory testing of known diseases, they can use simpler, cheaper tools for ongoing monitoring. Rybicki points out that hotspots are often widely distributed in remote locations, so monitoring cities is a good "tripwire" to detect viruses that begin spreading from rural points of origin. He suggests that small devices could be installed on public transport and in community settings such as hospitals and schools to monitor the viral "airome" via miniaturized sensors or chips with genetic sequences that are shared between known viruses.

However, although airome sampling presents an intriguing concept for respiratory pathogens, wastewater surveillance is the most robust and established epidemiological tool for broad community monitoring. Scientists have been using the technique for decades to track diseases, such as polio, but the method has advanced in recent years with extra-sensitive technologies, such as Droplet Digital PCR, which not only detects specific viruses but accurately quantifies how prevalent they are at a given time point. This has proved its utility and gained recognition throughout the COVID-19 pandemic, allowing scientists to track new variants as they emerged and providing early warning of surges to enable proactive public health measures and hospital preparation.

Worth the up-front investment?

The next pandemic is a matter of when, not if. Therefore, pandemic preparedness is a sure investment rather than unnecessary caution. With strategic resource allocation and surveillance integration into existing research programs, it doesn't have to be costly relative to overall expenditures on other research and healthcare – or compared with the costs of unmanaged outbreaks.

"We could put a sequencing laboratory in each hotspot worldwide to sequence thousands of viruses per day. We could probably automate subunit vaccine development for each of those viruses – whether we needed them or not," says Barry Holtz, Chief Scientific Officer at Phylloceuticals and a leading expert in the development of fast-track vaccines using plants. "The budget would be mere pixie dust compared with the trillions of dollars the COVID-19 pandemic has already cost the world."

References

1. *A Shalal, "IMF sees cost of COVID pandemic rising beyond $12.5 trillion estimate" (2022). Available at: reut.rs/3YZK2sd.*
2. *OJ Watson et al., "Global impact of the first year of COVID-19 vaccination: a mathematical modelling study," Lancet Infect Dis, 22, 1293 (2022). PMID: 35753318.*
3. *JH Ellwanger, JAB Chies, "Zoonotic spillover: Understanding basic aspects for better prevention," Genet Mol Biol, 44, e20200355 (2021). PMID: 34096963.*

Why Is It Always Bats?

Researchers may have just uncovered why bats can tolerate and co-exist with viruses that are harmful to humans

By Liv Gaskill

Bats have been in the spotlight since the start of the COVID-19 pandemic, given that scientists think SARS-CoV-2 may have made the cross-species jump into humans via bats. These small creatures host an array of viruses that can be harmful to humans, yet they manage to evade risk themselves.

In a new study, researchers have created induced pluripotent stem cells from bats to uncover insights into the entanglement between bats and viruses – and they found some pretty neat results (1). I spoke with Thomas P. Zwaka, senior author on the study and Professor at Icahn School of Medicine at Mount Sinai, New York, USA, to find out more…

What inspired you to investigate the relationship between bats and viruses?

Our inspiration began during the early days of the COVID-19 pandemic when we were involved in SARS-CoV-2 infection studies using human pluripotent stem cell-derived lung cells. At the time, I realized it would be fascinating to explore similar studies using bat pluripotent stem cells as a starting point. This approach would enable us to compare the mechanisms by which bats are resistant to these viruses and don't become sick, despite being natural reservoirs for many viruses.

Why is it so important that we study this relationship?

Studying the relationship between bats and viruses is crucial; bats are known to carry and transmit many deadly viruses, including Ebola, Hendra, Nipah, and coronaviruses like SARS-CoV and SARS-CoV-2. Understanding the molecular and cellular mechanisms underlying their virus resistance could provide us with valuable insights for developing effective therapies and preventive measures against these viruses.

Furthermore, bats possess many unique features, such as longevity, extreme metabolism, and cancer resistance, which make them an ideal model for studying aging and disease resistance. Thus, studying bat pluripotent stem cells could lead to a deeper understanding of the mechanisms behind these traits, which could then have significant implications for human health.

Talk me through the research process…

Once we had bat fibroblasts (connective tissue cells), we applied the stem cell reprogramming process developed by Nobel prize laureate Shinya Yamanaka, which involves introducing specific genes into the cells to "reset" them to a pluripotent stem cell state. Once we obtained stable stem cell lines, we began characterizing them to understand their properties and functions.

What issues did you encounter along the way – and how did you overcome them?

Some issues were related to the pandemic; when COVID-19 hit, we were all under lockdown, which made it challenging to carry out our research. We needed special permits to come to work in Manhattan, New York, and the researcher in Spain who caught the bats for us also needed a number of permits to do the work because Spain was hit particularly hard during those early months.

In addition to pandemic-related challenges, we also faced technical challenges in finding the right tissue culture conditions. Despite following Shinya Yamanaka's established reprogramming process, we had to make several modifications to optimize the process for bat cells, which took longer than expected. We had to troubleshoot and try various techniques until we found the right combination of factors to successfully reprogram the cells.

Could you please summarize the main findings?

One of the main findings was that bats have evolved a unique set of adaptations that allow them to live with viruses and tolerate them without getting sick. Specifically, we found that bats have a genetic adaptation that appears to weaken their immune response to viruses, which may explain why they do not experience the severe symptoms that humans and other animals do when infected with certain viruses.

Our research also revealed that bat pluripotent stem cells have an unusual feature that may be related to their virus resistance: the cells look like they are under viral attack, even when they have not been exposed to any viruses.

We also found that many ancient viral sequences embedded in the bat genome were reawakened when we turned the bat fibroblasts into stem cells, suggesting that there is a long-term co-evolutionary relationship between bats and viruses.

Were you surprised by these findings?

Yes! There were actually many surprising findings about our bat pluripotent stem cells. First, we were surprised by the unusual stem cell state that the bat cells were in. We did not know beforehand how similar or different bat cells would be from human or mouse cells. We had to optimize the reprogramming process to work for bat cells, and the stem cells that we obtained were in a unique state that had not been observed before.

Additionally, we were surprised by the reactivation of endogenous viruses in the bat cells. This was unexpected because it suggested that there is a co-evolutionary relationship between bats and viruses that goes back millions of years.

We were also surprised by the unusual tissue culture protocol we had to develop to maintain the stem cells. This protocol was different from what we had used previously for human or mouse cells and required a lot of experimentation and optimization to get right.

And the question on everyone's mind: why is it always bats?

One theory is that bats' ability to fly may have played a role in their ability to carry and spread viruses. Bat habitats often involve large numbers of individuals living in close proximity, which can facilitate the transmission of viruses between individuals. Perhaps bats have evolved unique immune systems that allow them to coexist with viruses without getting sick. As mentioned, bats have a lower immune response to viruses compared with other animals, which may be an adaptation to prevent excessive inflammation and tissue damage that can occur during a robust immune response.

It's possible that bats have co-evolved with viruses over millions of years, and that viruses have played a role in shaping the bats' immune systems and other biological adaptations. This could explain why bats seem to carry so many viruses without getting sick.

What implications will your findings have on our understanding of zoonotic diseases and spillover events?

One of the main implications is that bats are genetically hardwired to tolerate and co-exist with viruses. Furthermore, our research suggests there is a co-evolutionary relationship between bats and viruses, and that understanding this relationship is important for predicting and preventing future spillover events. By studying the molecular and cellular mechanisms that underlie bat virus resistance, we can identify potential targets for developing therapeutics and vaccines to prevent and treat zoonotic diseases.

Our research also highlights the importance of studying zoonotic diseases in their natural hosts to understand how they coexist with viruses and to identify potential transmission pathways. This can help us develop effective strategies for preventing spillover events and reducing the risk of outbreaks.

What are the next steps for your research?

We are now exposing our bat cells to different viruses to investigate how their response differs from humans. By doing so, we hope to gain a deeper understanding of the mechanisms that underlie bat virus resistance and identify potential targets for developing therapeutics and vaccines. We also plan to continue investigating the unusual features of bat pluripotent stem cells, such as the reactivation of endogenous viruses.

Reference

1. *M Déjosez et al., "Bat pluripotent stem cells reveal unusual entanglement between host and viruses," Cell, [Online ahead of print] (2023). PMID: 36812912.*

Foundations

Diagnostics and Surveillance

The Wind of Change Is Blowing

Could blowing into a tissue be a viable replacement for a nasal swab?

By George Francis Lee

Mucus, saliva, blood – we've all spent the last few years offering our bodily fluids into tubes, cartridges, and swabs to monitor for potential SARS-CoV-2 infection. With the need for millions to self-administer tests during the pandemic, most people are now intimately aware of how our bodies' output can be used to track disease.

Some might assume that scientists have exhausted the human body's available options for disease detection. But there's a new contender – tissues. Not the kind you find in a lab, but the ones you use to wipe away tears, clean up spills, and – most importantly for our story – blow your nose.

Could a used tissue offer information on the state of someone's infection? It's not the first time nose tissues have been considered as a viable testing tool. A 2012 study using a variety of alternative sampling methods found that tissues could detect upper respiratory tract infections at a similar rate to nasopharyngeal and nasal swabs (1). Four years earlier, researchers found that *Streptococcus pneumoniae* sampling through nose-blowing had a sensitivity of up to 94 percent for children with visible secretions (2).

It's this promising beginning that inspired Vincent Thibault, Professor of Virology at the University Hospital of Rennes in Brittany, France, to address the question. After he presented his work at last year's European Society of Clinical Virology (ESCV) conference, we caught up with him to find out whether this line of research was blown out of proportion, or whether it is truly nothing to sniff at.

Could you please introduce your work?

Basically, we are in charge of all viral analyses for inpatients and outpatients at our hospital. Our expertise includes serological testing, but nowadays, we cover many molecular biology diagnostic approaches, from simple PCR detection up to full viral genome analysis by next-generation sequencing.

What prompted your study into nose tissue diagnostics?

I was always impressed by forensic scientists and their ability to detect minute amounts of human DNA on a piece of tissue paper. Using this idea, I started to test for viral infections on family members' disposable tissues when they felt sick. I was surprised to notice that I was able to easily detect viral genomes on any analyzed tissue using PCR techniques available in our laboratory. As I accumulated compelling data on this approach, I decided to file a patent for the technology, encompassing the entire process from nose-blowing to tissue collection and processing. I then applied this strategy to detecting viruses on tissues collected from young infant communities and was able to identify many circulating viruses throughout the year.

For those who weren't at ESCV, can you summarize your study and its findings?

We demonstrated that it was possible to detect viral genomes and obtain reliable diagnoses from used tissues. We began by collecting used tissues from a daycare center and then from a kindergarten on a weekly basis and analyzing them with our in-house method. In both communities, we were able to document viral circulation and demonstrate that the circulating viruses were different in the different age classes. Moreover, in the first year (2018, well before the COVID-19 pandemic), tissue analysis in the daycare center detected the flu five weeks before it was picked up in the general population.

We believe our approach could be an interesting tool to document the emergence of any epidemic, particularly in infant communities where seasonal viruses mostly propagate. Informing parents about the circulation of one specific seasonal virus may have many benefits. It explains their children's symptoms, may limit the need for visits to the doctor, and can even reduce the use of unnecessary antibiotics. At the individual level, tissue testing is cheap, easy to perform, does not require a medical professional for sample collection, and is as sensitive as a standard nasal swabbing. Moreover, used tissues can be shipped anywhere through regular mail for remote diagnosis (using appropriate infection control precautions, of course).

What challenges did you face during your study?

Curiously, the most difficult thing was collecting used tissues! I think used tissues have a bad reputation to most people. Consequently, most patients were reluctant to send me their tissues after being diagnosed with a respiratory viral infection. When it comes to the laboratory, we had to invent all of the devices needed to process the collected tissues. We got to use all kinds of unexpected tools!

One unexpected problem was the challenge of communicating our results to non-specialists. It might be frightening to hear that your child is infected with a parainfluenza 3 virus! That's why deploying such a strategy also requires an understanding of how to tailor scientific communications to the public.

"One unexpected problem was the challenge of communicating our results to non-specialists."

Your findings seem like a solid proof of concept. What's the next step?

As mentioned earlier, this approach is almost too simple! It seems that patients expect some kind of medical intervention for diagnosis and, on the face of it, blowing into a tissue seems much less professional than getting a nasal swab. Our data indicate that nasal swabbing may not always be performed perfectly and nose-blowing suffers no more shortcomings than standard methods. Moreover, unlike nasal swabbing, nose-blowing has no side effects. The main difficulty I perceive is in encouraging patients (and doctors) to accept that this approach is as "real" as the current standard of care. One way to convince them is to demonstrate noninferiority via a large-scale study. Performing such an investigation is a big challenge and requires a lot of time and money. To demonstrate the potency of our approach, we must take into account the rate of positivity for a viral infection; it is usually around 20 percent. In other words, to collect 20 positive tissues, we need to test at least 100 patients. That offers an idea of the study size required! A relevant study would be to test 1,000 patients (i.e., approximately 200 positive) who both undergo nasal swabbing and blow into a tissue – not a simple task given all the hurdles of a clinical trial.

Do you see this kind of nose tissue diagnostic being used at scale?

Obviously, I will give you a biased answer! Just ask anyone who has undergone nasal swabbing; the vast majority would likely have preferred to blow into a tissue. Think about athletes during multi-day competitions who are tested on a daily basis; wouldn't blowing into a tissue be simpler and less invasive? Pediatricians, too, are keen to evolve toward this kind of testing.

What problems might prevent this kind of process from taking off?

I have not mentioned the extra work needed in the lab. Obviously, nose tissue testing requires some additional work and is not yet automated. I am confident that we could optimize the process to limit the burden for technicians, but it does have to be taken into consideration. However, tissues are much less expensive than nasal swabs and do not require any medical input.

Our data indicate that viral genomes are very stable when dried on a tissue, giving this approach another advantage – albeit one that we will need to formally demonstrate via another large-scale study. I have spread the word about our approach because I firmly believe that it is a robust alternative to swab testing. I hope other scientists will test our strategy and confirm our findings. I also hope that this approach will ease the diagnostic process for patients and professionals. I am convinced that the ability to diagnose more viral infections with greater ease will benefit us all. Staying informed about viral circulation is reassuring for the public, but this noninvasive approach to detection could also help promote preventative measures, limit unnecessary medical attention, and curtail the overuse of antibiotics.

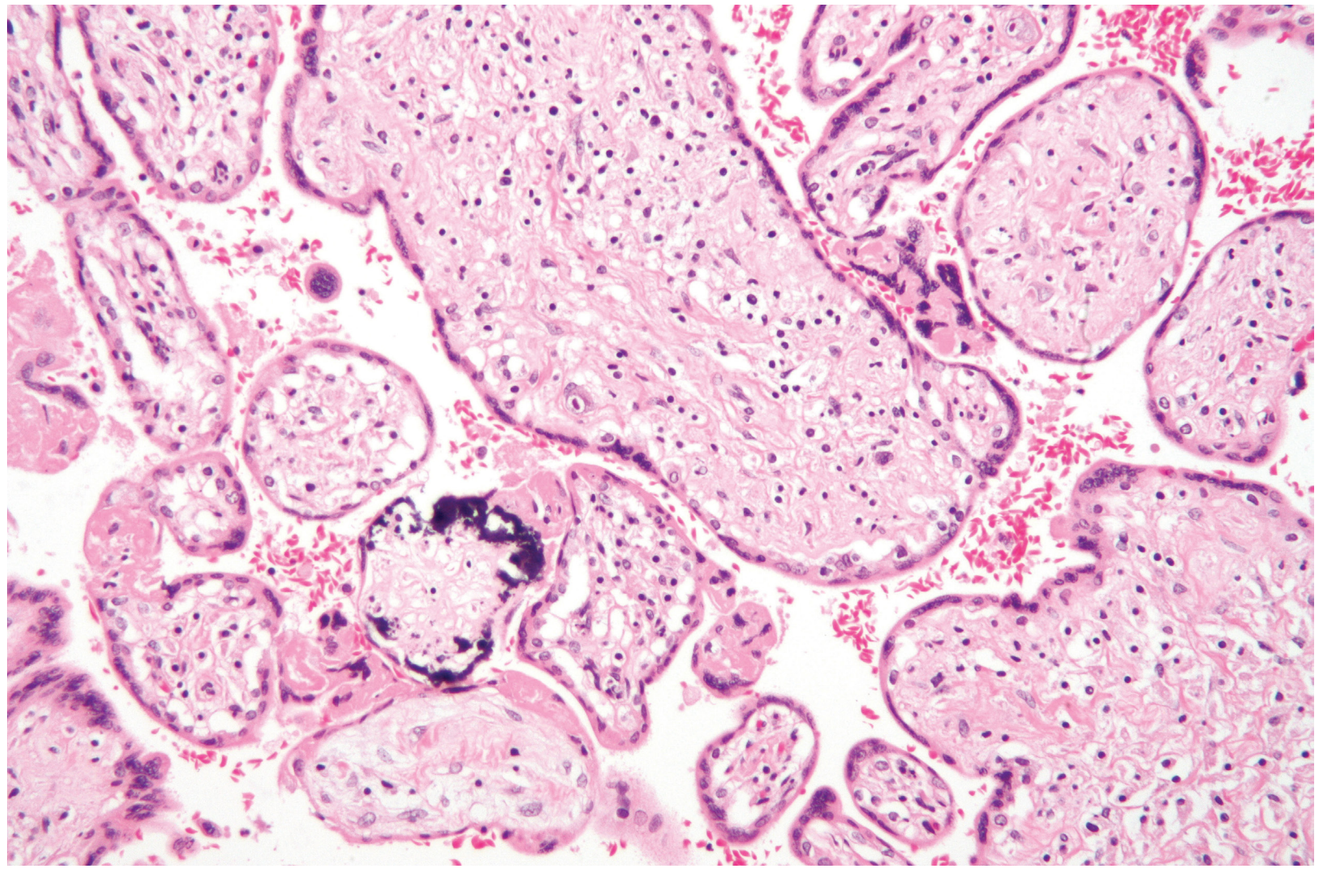
References

1. *MR van den Bergh et al., "Alternative Sampling Methods for Detecting Bacterial Pathogens in Children with Upper Respiratory Tract Infections," J Clin Microbiol, 50, 4134 (2012). PMID: 23052306.*
2. *AJ Leach et al., "Comparison of Nasal Swabs with Nose Blowing for Community-Based Pneumococcal Surveillance of Healthy Children," J Clin Microbiol, 46, Issue 6, 2081 (2008). PMID: 18385438.*

Coming Out Screening

Overcoming testing challenges for congenital cytomegalovirus

By Michelle Tabb, Chief Scientific Officer at DiaSorin Molecular LLC, Cypress, California, USA.



Credit: ©2009 Michael Bonert. You are free to share and adapt this image as per CC BY-SA 3.0.

Cytomegalovirus (CMV) is a common cause of infection in humans, but it's not typically a cause for concern. In fact, experts estimate that half of US adults become infected with CMV by the time they reach 40 years old (1), but adult infections tend to be mild – often unnoticeable – and the virus then usually becomes dormant. However, CMV infection in a newborn is far more serious.

CMV is the most common infectious cause of congenital defects in the United States. About one in every 200 babies is born with congenital CMV (2). CMV can be transmitted from mother to baby during pregnancy or postnatally. Although cases of congenital CMV can be deadly or have lifelong neurodevelopmental impacts, infections acquired after birth have less severe outcomes. Unfortunately, early detection for congenital infection is challenging; almost all babies born with CMV appear healthy, but one in five are at risk of dying from infection-related complications. Those who survive are more likely than their healthy counterparts to suffer from hearing loss or developmental delays later in life.

Universal newborn screening for CMV infection would help identify patients in need of antiviral treatment, but CMV is not currently included in US federal screening guidelines. Universal newborn hearing screening is in place (as recommended by the American Academy of Pediatrics), but many infected newborns pass the initial hearing test only to later exhibit hearing loss due to undetected CMV infection. Some states do offer CMV screening for newborns that fail the hearing test, but the recommendations and approaches vary significantly by geography. So far, Minnesota is the only state to pass legislation requiring CMV screening for all newborns. The Vivian Act was passed by the Minnesota state legislature in July 2021 – adding congenital CMV to the Minnesota newborn screening panel.

Clearly, there is a pressing need to improve newborn CMV testing to detect cases as early as possible. Identifying that CMV infection was acquired before birth must be done before the baby is approximately one month old. After that time, newborns can be infected via other exposures after birth where the consequences of infection are much less severe. Treatment in the first month of life with medications such as valganciclovir or ganciclovir can improve a baby's health outcome, mitigating future hearing loss or developmental delays (3, 4).

What type of testing is best? Molecular testing could offer notable improvement over less sensitive test methods (such as viral culture) that can take weeks to complete, giving healthcare professionals a better chance at detecting congenital CMV early enough to make a significant difference. PCR tests – the most robust molecular diagnostic technology – can be deployed with either saliva swabs or urine samples, which are currently recommended by the CDC for diagnosing and confirming congenital CMV in newborns (5). Developers of rapid, easy-to-use molecular diagnostics are also making strides toward commercially available CMV assays that would generate highly accurate results with both sample types.

The sample-to-answer approach

Though there are many types of molecular diagnostic tests, one approach may hold great potential for moving toward universal CMV screening in newborns using saliva swab specimens. Sample-to-answer systems are molecular test platforms in which all steps, including most sample preparation and processing, are performed automatically. Users simply load the sample and ready-to-use reagents into a consumable or cartridge, insert it into the testing instrument, and press start.

These systems offer a number of benefits – their automated approach typically leads to rapid results (sometimes in as little as one hour) and, because they require minimal training, they are easier for clinical lab teams to install, validate, and run. For clinical labs with limited bench space, these flexible systems can be a good way to maintain a broad test menu without adding lots of new equipment.

Adopting a sample-to-answer approach would enable labs to expand their CMV testing capabilities rather than being limited to relying on those facilities with sufficient resources to develop and validate a PCR-based laboratory-developed test. Because these platforms are offered by commercial diagnostic developers, the assays are typically cleared by the FDA as in vitro diagnostic assays, minimizing the validation required for clinical laboratory use.

As recognition of the challenges associated with congenital CMV detection increases, more diagnostic manufacturers are developing molecular tests for newborns. As the utility and accuracy of these assays are confirmed in clinical studies, commercial test availability may finally bring CMV screening to more babies – perhaps even to all newborns if CMV can be incorporated into universal screening recommendations. This would represent a huge step forward in providing early interventions for better outcomes in one of our most vulnerable populations.

> *"There is a pressing need to improve newborn CMV testing to detect cases as early as possible."*

References

1. *MJ Cannon et al., "Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection," Rev Med Virol, 20, 202 (2010). PMID: 20564615.*
2. *US Akpan, LS Pillarisetty, Congenital Cytomegalovirus Infection. StatPearls Publishing: 2022.*
3. *Centers for Disease Control and Prevention, "Babies Born with Congenital Cytomegalovirus (CMV)" (2022). Available at: https://bit.ly/3zLuKgb.*
4. *SA Ross, D Kimberlin, "Clinical outcome and the role of antivirals in congenital cytomegalovirus infection," Antiviral Res, 191, 105083 (2021). PMID: 33964331.*
5. *Centers for Disease Control and Prevention, "About Cytomegalovirus (CMV)" (2022). Available at: https://bit.ly/3dZXUjb.*

NGS: Hot on the Trail

How is next-generation sequencing supporting outbreak surveillance efforts?

By Nick Downey, NGS Collaborations Lead at Integrated DNA Technologies, Coralville, Iowa, USA.

COVID-19 brought infectious disease management and research into the public eye, illustrating how crucial these tools are for combating current and future pandemics. The implementation of next-generation sequencing (NGS) has been key to these efforts, allowing scientists to detect and track the spread of new variants. Indeed, with its breadth of information and ability to show genomic structural changes, NGS has become crucial for tracking the evolution of SARS-CoV-2 and other viruses. The smaller size of viral genomes makes them easier to sequence than other pathogens, but NGS can also be more precisely targeted to biologically important regions – such as antibiotic resistance genes – when it comes to larger pathogen genomes.

By revealing insight into the genetic structure of a pathogen, NGS allows mutations to be tracked and for the development of new strains to be monitored. Right now, NGS serves two main applications within the infectious disease community: individual patients and wastewater surveillance. At the patient-level, sequencing reveals not only what pathogen the patient has, but also the strain – allowing us to track a disease through the population, while observing how its structure and clinical presentation evolves. This has been particularly useful during the COVID-19 pandemic; NGS has been used to track the evolution of the SARS-CoV-2 spike protein and detect new variants able to evade vaccine immunity. Tracking spike protein mutations using NGS also allowed new vaccines to be developed to address these changes.

A new frontier for public health

By sampling from a pool of DNA from a particular population, NGS-based wastewater surveillance – a relative newcomer to the field – can reveal which pathogens are present in that population and serve as a warning signal for emerging outbreaks. It is particularly useful when regional testing efforts are low and an outbreak could be spreading undetected; by identifying a pathogen using wastewater surveillance, health officials can make informed decisions and mobilize a response more quickly.

Using NGS for assessing individual patients goes hand-in-hand with population sequencing. Both inform public health officials on the pathogen behind current outbreaks and alert them about emerging waves and, together, they provide the information needed to quickly launch an effective response.

Despite its importance in public health, broad adoption of wastewater surveillance presents significant challenges. The first challenge is economic – unsurprisingly, sequencing efforts require a source of funding. Fortunately, some government bodies have stepped up to the plate, but there is still a way to go.

The second challenge is technical. Determining the optimal sequencing method – direct, amplification, or hybrid capture – for each situation can be difficult. The third challenge is procedural – we need to address how we handle potentially infectious samples at scale. The safety of those working with these samples is of utmost importance when developing a sensitive assay. Some labs have faced issues when trying to sequence mpox or polio samples because they don't have the biosafety certifications required to handle those types of samples.

The future utility of NGS

It's not hard to see why surveillance activities will increase significantly in the coming years – boosted by their effectiveness during the COVID-19 pandemic. Notably, there will be more pathogens and antibiotic resistance markers being screened as we try to understand the probability of a potential outbreak. There has been a surge of interest in global research networks that enable sharing of data across a range of viruses to extract insights that could be applied to future epidemics.

Additionally, patient sequencing could find new uses in future – for example, sequencing the pathogens from those who are not responding well to treatment. Testing could reveal that they have a different strain that evades the drug's potency, while genomic information might provide clues about the mechanism of resistance and support the development of new therapies for patients with drug-resistant infections.

Over the years, NGS has developed into an important tool for the infectious disease community – from detecting and sequencing pathogens to tracking them through the population and identifying outbreaks early. The information generated from NGS gives health officials time to educate the public and spring into action with interventions to curb disease spread. Going forward, the ID community is pushing for a more collaborative approach to establish networks that will advance the field even further – working with researchers, policymakers, and industry leaders to improve NGS research assays, form cross-discipline collaborations, and promote continuous conversation on improving infectious disease research and management.

Foundations

Antimicrobial Stewardship

Credit: Image sourced from Unsplash.com.

Resisting the Resistance

The drug-resistance crisis is becoming an increasing burden to healthcare systems – could rapid phenotypic testing help?

By Nick Arab, CEO and co-founder of Pattern Bioscience, Austin, Texas, USA.

When COVID-19 turned the world upside down, we were already on a troubling trajectory with drug-resistant superbugs – but the pandemic spurred doctors around the world to prescribe more broad-spectrum antibiotics to prevent and treat secondary bacterial infections, accelerating the potential for resistance. The long-term solution to this growing problem goes well beyond developing new antibiotics; what the global healthcare community desperately needs is access to rapid, reliable data about each patient's infection to guide antibiotic treatment and other clinical care decisions. Ultimately, this approach could allow healthcare teams to rein in the unnecessary use of broad-spectrum antibiotics and help reverse the drug-resistance trajectory.

This concept would require profiling each pathogen's antibiotic susceptibility to rule out treatments – or, more importantly, rule in targeted options. However, current tests cannot provide comprehensive antibiotic susceptibility profiles rapidly enough to guide initial antibiotic selection. Culture-based tests provide the necessary data, but can take days to return results; genotypic tests are much faster, but do not provide definitive guidance about which antibiotics will work.

The need is clear – a test that offers phenotypic results at the speed of a rapid genotypic test. Ideally, a rapid phenotypic test would, like culture-based methods, expose the collected pathogen(s) to a variety of antibiotics and measure response to guide patient-specific treatment selection.

The crisis at hand

The rise of drug-resistant superbugs is no secret in healthcare – but just how bad is it? According to a recent analysis, in 2019 alone, 1.27 million deaths were attributable to drug-resistant bacteria (1). And even before COVID-19, experts believed this would rise significantly in the coming years (2). The crisis is largely fueled by standard treatment protocols in hospitals; because there is no commercially available test that can identify the bacterial strain and profile its antibiotic susceptibility within a few hours, physicians often prescribe a cocktail of broad-spectrum antibiotics to patients with a presumed bacterial infection.

Resistance to key drugs used for empiric treatment in hospitalized patients has also been creeping up, and recent studies indicate that a large proportion of all antibiotic treatment decisions in the hospital are either incorrect or inappropriate (3). It's also becoming more common to find superbugs that are resistant to all available classes of antibiotics. Scientists are well aware of the need to develop new antibiotics as a solution but, though new options would be helpful for a time, they would not address the root cause of the issue. We must curb unnecessary antibiotics use to conserve the effectiveness of the treatments we have today and give future treatments a better chance of remaining effective.

The testing gap

Many physicians would use narrow-spectrum antibiotics if they were confident of their efficacy – but that requires rapid, reliable diagnostics to demonstrate which treatments would be effective for each patient. Today's tests cannot meet this need. With turnaround times of days or more, culture-based testing is often only useful for auditing treatments patients are already taking. Meanwhile, studies have shown that critically ill patients with drug-resistant infections are significantly more likely to die with even a 24-hour delay in receiving effective antibiotics (4).

Rapid genotypic tests – typically based on polymerase chain reaction (PCR) – are marketed as a solution to the slow culture process. However, though they do produce faster results, they are limited by their reliance on genetic resistance markers. I think of this as the "MRSA illusion." For methicillin-resistant *Staphylococcus aureus* (MRSA), there is one prevailing resistance mechanism — the *mecA* gene. Because there is only one thing to test for (and PCR does it well), genotypic testing for MRSA has become commonplace. Along the way, it has contributed to the misconception that resistance testing for all pathogens is equally straightforward, which is not the case – there are thousands of resistance genes across bacterial pathogens with complex interactions that can confer resistance. Making things more complicated is the constant evolution and gene-sharing that give even well-characterized bacterial strains new modes of resistance. Genotypic testing cannot keep up with the speed at which bacteria evolve new capacities for drug resistance.

"Making things more complicated is the constant evolution and gene-sharing that give even well-characterized bacterial strains new modes of resistance."

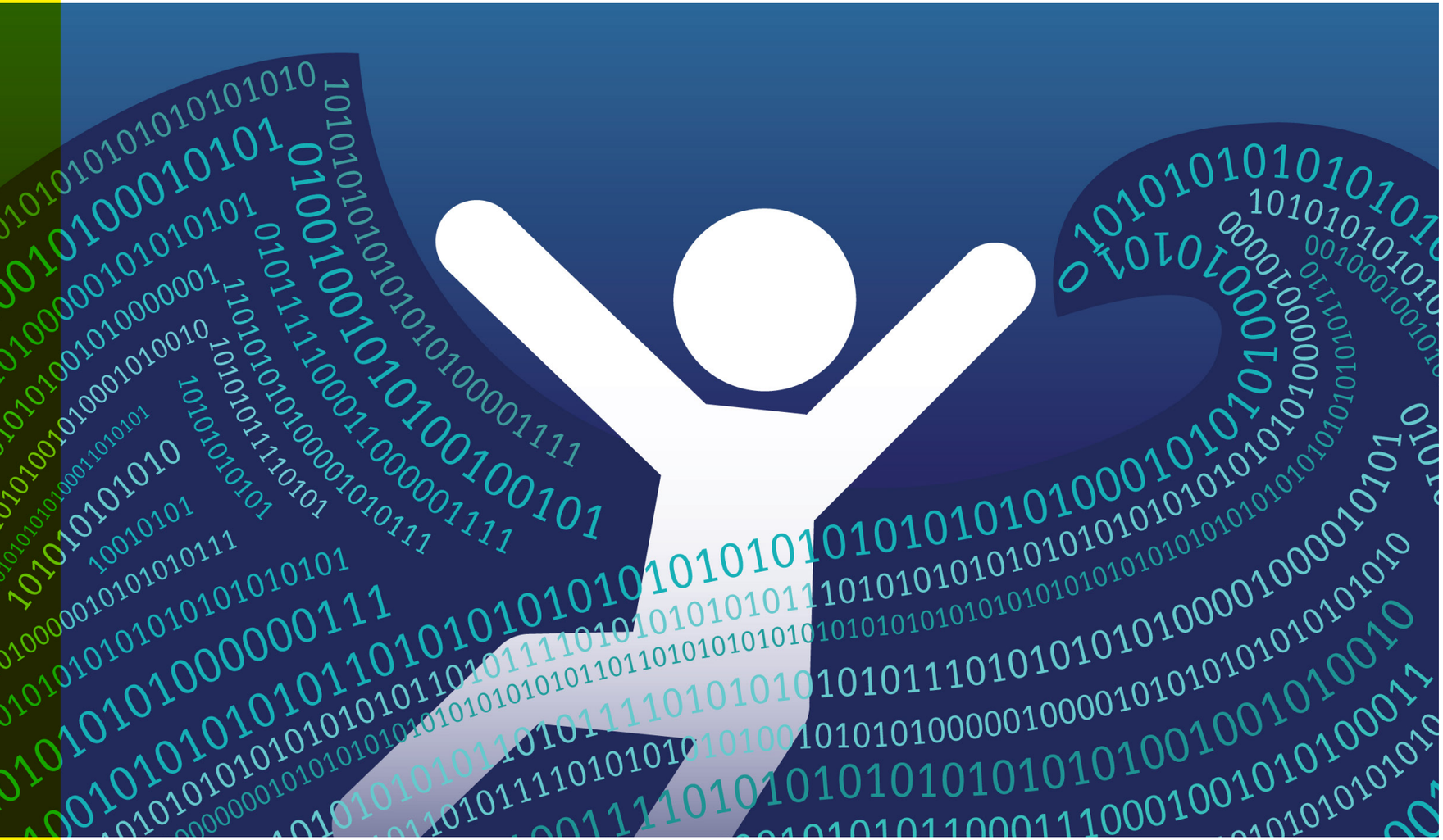
A phenotypic approach

The ideal test would provide complete information about a pathogen's species and its antibiotic susceptibility in just a few hours, meaning that results could guide treatment selection as early as possible in the patient care journey. For optimal results, these tests would expose the patient's pathogen to an array of antibiotics so physicians could clearly see which treatments wouldn't work – and which would. Each patient's treatment plan could then be custom-tailored to their specific infection, allowing physicians to prescribe the most narrow-spectrum antibiotics possible for each case.

This kind of approach has not been possible before but, thanks to recent advances in cell partitioning, single-cell analysis, and artificial intelligence, we have finally reached a point where rapid phenotypic testing should soon be feasible. With exciting innovation happening in diagnostics development, rapid phenotypic testing for infectious diseases could be a realistic alternative in the coming years.

References

1. *AMR Review (2016). Available at: bit.ly/3MuqYg9.*
2. *Antimicrobial Resistance Collaborators, "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis," Lancet, 399, 629 (2022). PMID: 35065702.*
3. *SS Magill et al., "Assessment of the appropriateness of antimicrobial use in US hospitals," JAMA Netw Open, 4, e212007 (2021). PMID: 33734417.*
4. *M Iregui et al., "Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia," Chest, 122, 262 (2002). PMID: 12114368.*



Dealing with a Data Deadlock

Research into WHO's priority pathogens is booming, but it's futile without actionable insights

By Liv Gaskill

Drug resistance is on the rise, and a somewhat dry pipeline of new antibiotics doesn't paint a much rosier picture. In fact, the most recently discovered class of antibiotics was in 1987, and the FDA hasn't approved a new antibiotic since 2019. Back in 2017, the World Health Organization (WHO) published the first ever list of antibiotic-resistant "priority pathogens," which highlighted the 12 families of bacteria that represent the greatest threat to human health and placed them into three groups: critical, high, and medium. The list aimed to address urgent public health needs by guiding and promoting research and development of novel antibiotics. But what triggered the pipeline drought in the first place? It seems a number of issues are to blame.

"In the 1950s and 1960s, there was a huge boom in antimicrobial drug discovery, during which the 'easy wins' were identified," says Thibault Géoui, Senior Director of Discovery Biology and Predictive Risk Management at Elsevier. "The challenge of finding new antibacterial compounds in the decades since has been twofold. First, investment in innovation declined due to a perceived saturation of the market in the 1990s – a time when a wide range of effective antimicrobials were available. Second, rising resistance has rendered many of the recently discovered compounds useless."

In an effort to understand the impact of WHO's priority pathogens list, Géoui and his team at Elsevier conducted an internal project on research activity surrounding the listed bacteria (1). Using data from Scopus, Elsevier's abstract and citation database, they revealed that 227,808 research papers have been published on the priority pathogens since 2017, with *Acinetobacter baumannii* (public enemy number one) benefiting from the biggest boost in published papers between 2017 and 2021. Although *Staphylococcus aureus* (methicillin-resistant, vancomycin-intermediate and -resistant) rose at a slower rate over the years, the bacteria still came out on top in terms of numbers of published papers, with a whopping total of 83,165.

Certainly, research into priority pathogens is not lacking, but with such high research activity comes an even higher volume of data. Although data availability isn't the issue, Géoui highlights a particular barrier to putting it into action. "The recent analysis shows that data on antimicrobials and the WHO's 12 priority pathogens is increasing year-on-year and flooding the scientific domain. It is impossible for researchers in the field to read the quarter of a million articles published in the past ten years, which risks valuable insights being missed."

Results hidden within could inform future research, help accelerate drug discovery, or simply prevent duplication of efforts – all possibly helping humanity unlock a new antibiotic. But how can we find the most informative and valuable papers – the needles in many haystacks? In an increasingly digital world, Géoui believes that artificial intelligence (AI) and related technologies could help researchers extract valuable insights from what has become big data. "Cutting-edge AI and natural language processing technologies help make sense of the information available by incorporating the data generated in experiments and published in scientific papers, along with data being held in and added to high-quality databases daily," he says. "These technologies will accelerate drug discovery by helping to identify targets, forecast clinical side effects, and prioritize compounds of interest. During the COVID-19 pandemic, we realized the capabilities of AI in analyzing disease networks and helping to identify existing drugs which could be repurposed (2) – there is no reason a similar approach could not be employed for antimicrobial resistance."

First, however, scientists and researchers working with priority pathogens need to be supported from the top. "The WHO has done an excellent job of raising awareness of the threat of antimicrobial resistance, but the onus is really on governments and policymakers to incentivize innovation in the field," Géoui says. "We saw during the COVID-19 pandemic what can be achieved when public and private institutions band together to develop new therapies and know that it can be achieved. There is no arguing that drug development is expensive and, although using modern technologies to make workflows more efficient will be a part of the next phase of antimicrobial drug discovery, proper funding and incentives will be the key drivers."

References

1. *PharmiWeb, "Antimicrobial Awareness Week 2022: Research into Priority Pathogens Explodes, But Now Scientists Face the Challenge of Using It," (2022). Available at: bit.ly/3w3XXk3.*
2. *S Richman et al., "Old drugs, new tricks: leveraging known compounds to disrupt coronavirus-induced cytokine storm," NPJ Syst Bio Appl, 8, 38 (2022). PMID: 36216820.*

Profession

Your career
Your business
Your life

Putting the Mic in Microbiology

Luis Plaza takes us behind the scenes of his microbiology podcast, Let's Talk Micro

Liv Gaskill interviews Luis Plaza

Tell us about Let's Talk Micro…

Let's Talk Micro is a podcast that's heavily focused on clinical microbiology – from organisms and biochemicals to media and processes – and anything else I have learned throughout my laboratory career. My aim is to provide listeners with new knowledge they can incorporate into their own work. There are many subspecialties within microbiology outside of the clinical setting, such as environmental microbiology and marine microbiology, among others, but there's not much awareness around them – people either find out by accident or after they have already graduated. This is problematic because, although we do great work, microbiology is very understaffed and few people know what we do. I want to bring attention to these areas – all while raising awareness of the medical laboratory sciences profession as a whole.

The target audience spans all career levels – from students to clinical directors and everyone in between. I like to explain concepts in an easy-to-understand manner without getting too technical so that both early-career and experienced professionals can both understand.

What inspired you to start a podcast?

I have always wanted to go beyond the scope of my job and understand the processes behind why we do things, why we use specific media, or why organisms get worked up in certain ways. Working in microbiology is all about practice and repetition, and you start to see and learn more over the years in the lab. It was this need for information that inspired me to start Let's Talk Micro – and I wanted to share this knowledge with the world.

Years ago, there was a big divide in microbiology between the senior clinical lab scientists who had been in the field for 20–30 years and the recent graduates. At the time, I thought about making a club or some space where those of us who were just starting out could meet and share what we had recently learned, but that never came to fruition and I progressed in my career. Eventually, I decided that this field moves too fast sometimes and you don't always get answers to your questions, so why not collate all the information and put it out there in one resource that everyone can easily access? From that, Let's Talk Micro was born.

How do you promote the podcast without the help of sponsors?

I have just passed 22,000 downloads which is an impressive feat because Let's Talk Micro is an independent podcast – I don't have any sponsors, so it's all self-promotion and word of mouth. I'm happy that so many people have listened to us and I hope they continue to do so. I have mostly used social media for marketing and promotion; Twitter has worked particularly well because there's a high concentration of academics and microbiologists across all levels. Once you have guest episodes that also helps because if they have a good experience on the podcast they retweet and promote the podcast to their followers.

I have previously been invited by schools and institutions to talk to university students about microbiology and clinical lab sciences, which also gave me the opportunity to promote the podcast. More proactively, I also reach out to specific schools and departments and invite them to check out the podcast – sometimes they respond, but I've found I have gotten a better response rate as the podcast continues to grow and I release more episodes. When I sent invitations at the beginning, I only had six or seven episodes for them to listen to, but now that we're almost 80-episodes in they have a whole backlog of episodes to choose from.

There is always so much going on in microbiology and laboratory sciences. How do you choose which topics to cover?

My current goal is to cover the basic understanding of organisms and biochemicals, the media in clinical microbiology, antimicrobials, and more. This will provide the audience with a basic understanding of microbiology and how elements work together, which could help them in their own work or learning journey. Further to that, if I come across any publications that I think will be beneficial to clinical microbiologists, students, or other professionals, I reach out to the authors and invite them to interview. No one has declined so far, which I'm hugely grateful for!

The podcast caters to a wide target audience in microbiology and anyone can be a guest as long as they have a topic that is useful for our listeners. I have guests from all around the world and I'm considering the possibility of recording a few in Spanish. Until now, our episodes have been mainly in English, but there are so many incredible microbiologists in Latin America who might not feel comfortable having to speak English as a guest – I speak Spanish, so why not use this skill to expand the podcast? That way, we can bring on more microbiologists from Latin America and other Spanish-speaking countries and make them feel included in the podcast.

How important are science-focused podcasts, particularly in this modern age of information and social media?

Years ago, before podcasts started to take off, I never thought about the importance of audio media. Everyone is so attached to their phones and on social media all the time and, although it's a great way to convey information, there is so much out there when you Google a topic that it can be hard to know where to go, what to read first, or what is accurate.

Everyone is busy with their daily lives – it's hard to sit and dedicate time to reading journals, news articles, or books, but podcasts avoid this problem entirely. If you put the content into a 20–30 minute audio format, people can listen on their commute, in the shower, cleaning the house – any task! If they hear something that piques their interest they can search for more information after; I usually signpost listeners to further resources at the end of each episode so they don't get lost in the pages of a search engine.

What is your favorite part of running Let's Talk Micro?

I enjoy learning more about the mechanisms behind organisms or diving deep into topics I might not usually encounter at work, so one of my favorite parts of the podcasting process is the research. I don't like editing episodes (I find it difficult to listen to myself for 30 minutes, I start to pick apart my voice!) but I love recording them, especially when I'm talking with other guests. It's a great feeling because, without the podcast, I might not have had the chance to connect with so many interesting people; now I find myself talking to microbiologists from all around the world!

What advice can you offer to someone who wants to start their own podcast?

If you want to start a podcast, I say go for it! Just make sure the information you put out there is accurate. Set a goal for each episode of what you want to talk about and, before you hit record, make sure you know the topic you'll be discussing and have gathered as much information about it as possible – even if you're already a subject matter expert or interviewing an expert.

It's hard work but it's very rewarding; you need to have discipline because it can be challenging and time-consuming, especially editing episodes. You must also be consistent because if you want to reach as many people as possible you have to put in the promotional work and talk about it on social media – otherwise no one will know about it. It took me a while to finally get Let's Talk Micro out there but it has been a great experience. I'm the type of person who can be closed off in my own world – I'm a good listener but I probably won't be the one to start the conversation. The podcast has been a great challenge for me to get out there and force myself to talk with fellow microbiologists and come out of my shell.

And what would you like to say to potential listeners?

First, thank you in advance! Second, if you do listen to the podcast or subscribe, please leave a comment or get in touch and let me know what you think. Likewise, if you have any topic or guest suggestions let me know – and if you think you've done something in your work that could benefit others and you want to share it, I want to hear from you! Let's Talk Micro is all about sharing knowledge and breaking down barriers to accessing information!

You can listen to Let's Talk Micro on Apple Podcasts, Spotify, or wherever you get your podcasts – and you can find Luis on Twitter at @Letstalkmicro1.

Pathologists at the Table: Keeping Our Place After COVID-19

The work of pathologists has been vital in the response to COVID-19 – but are we soon to be forgotten?

By Gary Procop, CEO of the American Board of Pathology and a Consulting Pathologist and Professor of Pathology at Cleveland Clinic, Cleveland, Ohio, USA.

The COVID-19 pandemic put pathologists, laboratory professionals, and testing front and center. It reminds me of a favorite, albeit paraphrased, quote by William Osler: "There are three phases of treatment – diagnosis, diagnosis, diagnosis." We must not allow health system leadership to forget that it was through engaged laboratory leadership that frontline providers had the best testing available – not to mention that this was achieved in an evidence-based manner and under extreme, unprecedented conditions.

If the importance of the laboratory in the era of high-quality care fades into the background, we will have only ourselves to blame. Now is the time to push our way to "the table" if necessary and remind hospital leadership about what we bring, what we can bring, and what we have already delivered. We cannot, however, rest on the laurels of our performance during COVID-19. Instead, we must turn our attention to improving the healthcare delivery issue du jour at our institutions. I know these words may not be for every pathologist, but they are a battle cry for health system leaders to arise from within our ranks.

Regarding the "winding down" of COVID-19, the relaxation – and reimposition – of precautionary measures now and in the future must be evidence-based. They must consider viral transmissibility, disease prevalence, population density, and more. There have been many appropriately critical after-action reports regarding the national response to this pandemic. It is a hope – one unfortunately not likely based in reality – that the US could review these findings and use that learning to devise an evidence-based response strategy, separate from politics, that has a chance of working. I have faith in the expertise and professionalism of our community and believe that, at some point in the future, we will find our standing in the house of medicine better than ever.

That said, the uncertainties that lie ahead concern how we secure our place in that house of medicine. Are we viewed as important colleagues and key contributors to healthcare delivery (as became evident during the COVID-19 pandemic) or are our services viewed as commodities that can be outsourced and performed remotely? I am convinced that healthcare delivery is improved when pathologists and laboratory professionals are at the table and engaged in systems-level issues – and I'm sure my colleagues in the field are, too.

But, for that to happen, we have to be at the table in the first place. We must obtain positions on our health systems' decision-making committees and maintain them by being more than just great pathologists. The surgeons, internists, and pediatricians who are currently CEOs and CMOs of health systems began by excelling in their craft while learning new skills in management, leadership, and large-scale healthcare delivery. Pathologists need to do the same, and we are fortunate to have some great pioneers in this regard whose example we can follow. Consider, by way of example, Jeffrey Myers from the University of Michigan; he is not only a world-renowned pulmonary pathologist, but also Vice Chair of Clinical Affairs and Quality at that institution and the Chair of the Patient Champions Steering Committee for ASCP. Leaders such as these, as well as pathologists in mid-level leadership positions, have opportunities to underscore the value of high-quality, on-site pathology and laboratory medicine services that benefit both the individual patient and the healthcare system in its entirety.

In Practice

Technology
Quality
Workflow

How to Name Your Bacterium

The process of naming bacteria follows specific rules – but do you know what they are?

By Aharon Oren, Professor of Microbial Ecology at the Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Israel. Aharon is also list editor, nomenclature reviewer, and past editor-in-chief of the International Journal of Systematic and Evolutionary Microbiology and past chair of the International Committee on Systematics of Prokaryotes.

Many of you will have diagnosed infectious diseases before – perhaps caused by well-known pathogens like *Staphylococcus aureus* or less common ones like *Gemella morbillorum*. But have you ever wondered how these bacteria obtain their names? The process is more organized than you may think…

Naming and classifying

Bacteria have no "official" classification scheme – but they do have formal nomenclature, which is regulated by internationally accepted rules. These rules are fixed in the International Code of Nomenclature of Prokaryotes (1). The International Committee on Systematics of Prokaryotes (ICSP) is responsible for updating and implementing the rules of the Code. Principle 1(4) of the Code states, "Nothing in this Code may be construed to restrict the freedom of taxonomic thought or action." What does that mean? Essentially, that anyone is free to design their own system of classifying bacteria; the Code only deals with the way species, genera, and higher taxa of prokaryotes are named. In recent years, extensive comparative studies of prokaryotic genomes have led to the establishment of the Genome Taxonomy Database (2). The impressive classification system proposed there is widely accepted today; many bacteriologists even consider it "official," even though such a thing does not exist.

To obtain standing in the nomenclature, names of new taxa of prokaryotes must be published in the International Journal of Systematic and Evolutionary Microbiology (IJSEM), an official publication of the ICSP. There are two ways of doing this. The first is to publish an original paper describing the new taxon in the IJSEM. In addition to the usual scientific peer review, the proposed names are checked by the journal's nomenclature reviewers to ensure that they are formed in accordance with the rules of the Code. However, not everyone may wish to publish in that journal – and, of course, authors are free to publish wherever they wish.

The newly proposed names are then considered "effectively published." To obtain the status of "validly published," the authors must then take the second route: a copy of the publication must be sent to the IJSEM editorial office with the request to include the names in the journal's bimonthly Validation List. Such requests must be accompanied by further documentation – in particular, proof that the type strain of the new species and any subspecies are available from at least two culture collections in different countries. The list editors of the journal will check the documents and, if all conditions for valid publication are met, the names will be listed in the next Validation List.

The knowledge of ancient Greek and Latin can play an important role in the process of naming a new prokaryote – but many scientists have only a rudimentary knowledge of classical languages. In fact, the number of microbiologists who have i) the necessary command of Latin and Greek, ii) an interest in nomenclature issues, and iii) most importantly, sufficient time to assist colleagues worldwide in proposing correctly formed names is very small. Most papers describing new bacterial taxa come from Asian countries in which microbiologists are rarely, if ever, exposed to the classical languages. Often, prospective authors consult me or one of my colleagues in our "nomenclature quality control team" (3). The editors of some microbiological journals also routinely consult us before they accept taxonomic papers for publication. The final stage is valid publication of the names in the IJSEM following quality control by the nomenclature reviewers and list editors of the journal.

Molecular biology in the lead

Molecular biology is the gold standard of current classification. Since Carl Woese pioneered the use of molecular sequences (notably those of ribosomal RNA molecules) in the late 1970s, molecular data have been used for the classification of bacteria and archaea. The Genome Taxonomy Database is entirely based on sequence data – and, as much as possible, on complete genomes. The results of molecular sequence comparisons do not always agree with the older classification schemes. As a result, many species have been reclassified in new genera as "comb. nov." (*combinatio nova*, new combination) taxa. In some cases, this has led to considerable confusion. We must remember that the older validly published names retain their standing in the nomenclature. An example of importance in medicine is the reclassification of *Clostridium difficile* as *Clostridioides difficile*. This reclassification was necessary when it became apparent that *Clostridium difficile* is only distantly related to *Clostridium butyricum*, the type species of the genus *Clostridium*.

Renaming medically important bacteria by reassigning them to new genera based on molecular sequence data may cause problems for the medical profession – especially for those involved in diagnosis, classification, and treatment selection. In addition to the case of *Clostridium* versus *Clostridioides*, the genus *Mycobacterium* was recently split into five genera, including the newly proposed *Mycolicibacterium*, *Mycolicibacter*, *Mycolicibacillus*, and *Mycobacteroides*. Some members of the genus *Mycoplasma* were reclassified into the new genera *Malacoplasma*, *Mesomycoplasma*, and *Metamycoplasma*. These names and the new combinations were validly published, but that does not prevent anyone from continuing to use the old names.

Rule 56a of the International Code of Nomenclature of Prokaryotes allows experts to propose the rejection of names "whose application is likely to lead to accidents endangering health or life or both or of serious economic consequences." Only the Judicial Commission of the ICSP can place names on the list of rejected names.

As a service to the medical community, Diagnostic Microbiology & Infectious Diseases periodically publishes a paper entitled, "Proposed Nomenclature or Classification Changes for Bacteria of Medical Importance – Taxonomic Update." The fifth such update, which is now in press, covers the period from 2018 to 2020 and lists 32 names. That may not seem like a lot – but novel pathogens are even rarer. The number of validly published names of newly described human pathogens annually in recent years is in the single digits. Unfortunately, many more names of new pathogenic bacteria are effectively published in the literature, but never submitted to the IJSEM for validation.

References

1. *"International Code of Nomenclature of Prokaryotes", Int J Syst Evol Microbiol, 69, S1 (2019). PMID: 26596770.*
2. *"Genome Taxonomy Database" (2019). Available at: bit.ly/2VHV72J.*
3. *Microbiology Society, "International Journal of Systematic and Evolutionary Microbiology – Editorial Board" (2020). Available at: bit.ly/2W7Ghlg.*

The Torchbearer for Nigeria's Healthcare

Sitting Down With… Dimie Ogoina, Infectious Disease Physician at the Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State, Nigeria

What inspired you to become an infectious disease physician?

I developed an interest in microbiology during my fourth year of medical school, following the inspiring lectures given by the late Laszlo Egler, Professor of Medical Microbiology and Medicine at Ahmadu Bello University, Zaria, Kaduna State, Nigeria. Meanwhile, during my first posting in clinical medicine, I became interested in bedside medical practice and enthralled with internal medicine because it offered me the opportunity to hone my analytical skills. It was a no-brainer then that being an infectious disease physician was my calling – providing an opportunity to learn about microbiology while practicing bedside medicine.

You were featured in Nature's 10 in 2022. How did you feel when you found out – and how has it been for you since it was announced?

I felt very honored and privileged; it was a pleasant surprise and very unexpected. My listing in Nature's 10 was a new height in both my professional career and personal life; however, the recognition was not just for me, but also for my institution, state, and country. The successful response to the 2017 mpox outbreak in Nigeria was a collective effort of many individuals and institutions, including the Federal and State governments and their various ministries of health. I was happy that our observations and sacrifices during the outbreak were recognized – and although I may have been the torchbearer, there were many behind me who equally deserved praise and commendation.

Since the announcement, my professional visibility has grown significantly. I suspect some of the scientific collaborations, interviews, and guest speaker invitations are partly due to my being featured in Nature's 10. However, I take the recognition as a challenge to stay focused and excellent. I always tell myself: "Dimie, you are listed in Nature's 10 – you must break new ground and avoid mediocrity!"

For me, Nature's 10 has opened a door in my journey to make a real difference in science and medicine.

We hear a great deal about health inequities in low- and middle-income countries. How do you think that affects infectious disease care in Nigeria?

There are health inequalities throughout the whole chain of healthcare in Africa, including Nigeria, especially in response to infectious diseases of public health concern. The COVID-19 pandemic and 2022 mpox outbreak illustrated various aspects of this inequity; for example, there are stark inequities in i) vaccine and therapeutic manufacturing capacity, ii) decision-making regarding which diseases and population(s) will be treated, iii) access to medical countermeasures, iv) funding for procuring treatments and vaccines, v) distribution of available countermeasures, and vi) which populations are selected to receive and use these resources.

It has been almost a year since the 2022 mpox outbreak first began, yet Nigeria and many other countries in Africa known to be endemic for mpox have still not received access to mpox therapeutics and vaccines. However, it is important to emphasize that African countries should not always wait for handouts from the developed world. We must invest in our health systems, show commitment, and take ownership of the response to public health threats in our continent. Nobody cares about us more than us.

What lessons do you think other countries could learn from health professionals in Nigeria?

Our capacity to work successfully in difficult situations and environments, our creativity, and our relentless pursuit for knowledge. Nigeria health professionals are among the best-trained in the world; they can work in any environment – and do so excellently.

What has been the biggest challenge you've faced in your career?

I take the challenges I have faced as opportunities to learn, develop resilience, and become well equipped for what life offers me. In particular, there are two major challenging situations in my career of note.

The first challenge was when I received a provisional pass in an exam – part two of a dissertation for an immunology and infectious disease fellowship at the West African College of Physicians. The examiners raised concerns about my approach to the statistical analysis of my data and requested that I reanalyzed my results before I could be given a clear pass. This singular event was instrumental to what I have learnt today about medical statistics and has helped me in analyzing research data for publishing – without the need to consult a statistician.

The delay in my appointment as a consultant and medical lecturer after qualifying as an infectious disease physician was also challenging. I was discouraged that I completed my training but had no employment for close to six months. Thankfully, I was able to secure an appointment thereafter, but the waiting period taught me some lessons about life and how opportunities are not always related to skill or knowledge, but rather dependent on grace.

Read the first part of this interview at: tp.txp.to/dimie-ogoina