Lessons from the Global South's fight against COVID-19

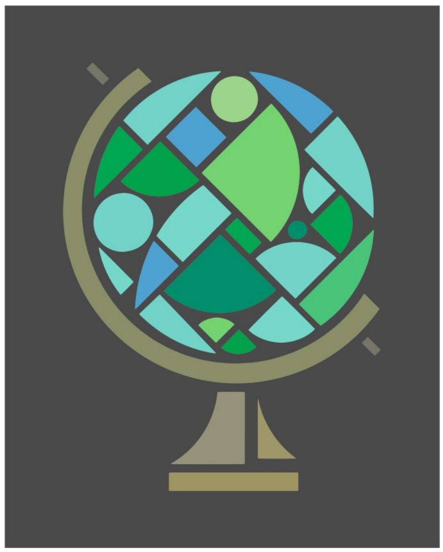
Against the backdrop of its many battles with infectious disease, the Global South applies networking and creative grit to face COVID-19.

Vivien Marx

As tragedies go, COVID-19 has been a dark one, especially in the under-resourced, under-vaccinated Global South, where some authorities are weighing the use of a 'dose-sparing' COVID-19 vaccine regimen. It's unclear whether stretching supplies with a lower than recommended dose can ward off severe disease and mortality. With all its death and harm, the pandemic has no bona fide silver lining, but it does have silver-shimmery speckles, especially related to the Global South. In the way they tap into the power of networking and embed their deep experience with infectious disease into their emergency responses, researchers' dogged determination in the Global South sends positive messages. It's setting the stage for longer-term fixes.

In March 2020, as COVID-19 spread, "Europe was terrified," says Koussay Dellagi, scientific advisor to the Pasteur Network, which connects Institut Pasteur in Paris and partners around the world devoted to infectious disease. European healthcare systems became overwhelmed and catastrophe loomed for Africa's much more fragile healthcare system. "It was not the case, thanks to God," he says. Perhaps the continent's younger demographic — only 3% of the African population is over 65 — helped avoid catastrophe, he says. Perhaps African descent means having a genome with variations that lower susceptibility to this virus. Now, the role of genetic diversity "is recognized," he says. COVID-19 is also a reminder that our planet's range of humid, cold and arid ecosystems has exposed us to dissimilar ecosystems of bacteria, viruses and parasites. "They leave behind an immune system that has been educated," he says, which can help explain variable responses to pathogens.

COVID-19 links the Global South and North in new ways. In regional epidemics, unaffected neighbors can lend helping hands, but COVID-19 is a global matter. "Things will be solved in the whole world or things will not be solved," says Dellagi. This global awareness facilitates new types of collaboration that won't end when



Setting the stage for longer-term fixes, researchers in the Global South tap into their deep experience with infectious disease and the power of networking. Credit: CSA-Printstock / Getty Images

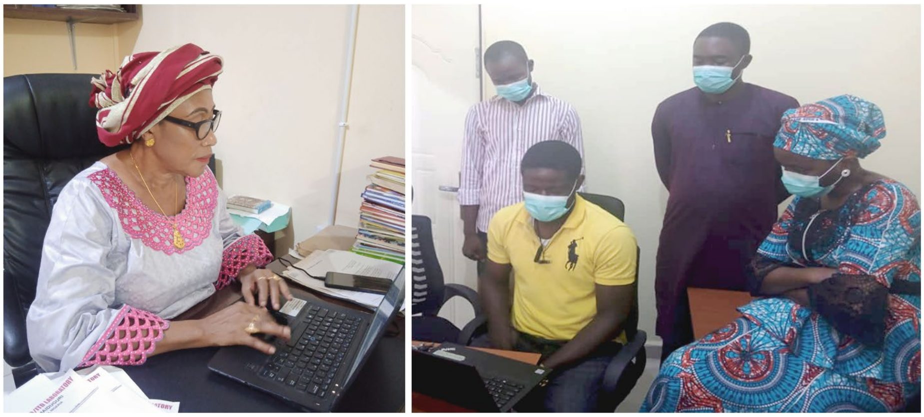
pandemic flames burn lower. "We are aware as never of the effect of emerging infectious disease," he says. "I'm very optimistic," says Rana Dajani, a molecular cell biologist at Hashemite University in Zarqa, Jordan. "COVID has shown us a lot of things we thought are impossible, or 'no we can't do this,'" she says, "we can, if we really want to." As scientists across the Global South raced to the public health frontlines of COVID-19, they developed protocols, scaled up infrastructure, trained personnel, kept their governments and populations apprised and maintained their research programs, too.

Collaborative supply chain

"Supply chain has been a major problem for most countries," says virologist Erik Karlsson from the Institut Pasteur du Cambodge in Phnom Penh, Cambodia, who works on respiratory viruses such as avian flu and SARS-CoV-2. Others in Cambodia turned to them for expertise and help to set up COVID-19 testing centers and surveillance systems and to act as a referral lab for developing and validating new assays. The country's heat and humidity meant that stockpiled personal protective equipment was sometimes too brittle to use safely for scaled-up work with SARS-CoV-2. When flights and shipping were scaled back, transportation costs soared and options grew slim. Ethanol was needed for RNA extraction, but as a 'dangerous good' — it's flammable — it must be packaged and transported in certain ways. The scientists searched unsuccessfully for options, says Karlsson, then chartered a plane to move supplies from Singapore to Cambodia. Supply chain issues have gotten better, says Veasna Duong, who heads the virology unit at the institute, where they use BSL-2 and 3 facilities for avian flu, tuberculosis and zoonotic disease research. Duong has spent two decades studying bat coronaviruses and mosquito-borne arboviruses. When the government asked for advice and support, he says, they had "family-level" coronavirus PCR assays ready. In January 2020, with the SARS-CoV-2 genome sequence in hand, they could quickly begin testing and surveillance.

In Kampala, Uganda, Thomas Egwang, director general of Med Biotech Laboratories, has tried to source diagnostic kits, but contacting companies led to runarounds. "It's been impossible," he says. To get kits, reagents and consumables for RT-PCR and sequencing, he and his colleagues tapped into their collaborative networks, he says.

In Nigeria, across research facilities and hospital labs, equipment and know-how to test COVID-19 samples was lacking, says virologist Marycelin Baba, from the University of Maiduguri in Maiduguri, northeastern Nigeria. Even at her university's teaching hospital, "those things were not there." When COVID-19 struck Nigeria, the government asked her to optimize labs for testing, and some were opened that were not up to the task. She was asked certify one where even the most basic biosafety was lacking. "I said 'never'; I refused," says Baba. "Even if I was to be



When COVID-19 emerged, virologist Marycelin Baba (left) helped build labs and train people across Nigeria. She studies many virus types, especially arboviruses. Right, a training session to optimize a lab for COVID-19 testing at University of Maiduguri Teaching Hospital (UMTH). Credit: University of Maiduguri

killed, I don't mind." The issues she flagged were corrected and she eventually certified the lab.

In 2020, many labs in Nigeria were unfit, but, she says, now more than 50 labs across the country are well equipped to handle COVID-19 and other infectious diseases. In her World Health Organization (WHO)-accredited and WHO-sponsored lab, she had supplies, equipment and personnel, know-how for viral RNA extraction, and ability to perform quantitative RT-PCR. Using BSL-2 facilities, she and her team work on infectious diseases such as yellow fever, West Nile, dengue, chikungunya and Zika viruses. In separate labs at University of Maiduguri Teaching Hospital, work is done on HIV and polio. Although Nigeria is polio-free, now and then variants rear their ugly heads. When COVID-19 emerged, "we swung into action," she says. Her lab could not do large-scale genomic analysis, so the researchers sent SARS-CoV-2 isolates to a sequencing center in western Nigeria. She began collaborating with Christian Happi at Redeemer's University in Ede, Nigeria, who also directs the African Centre of Excellence for Genomics of Infectious Diseases. His lab sequenced the first SARS-CoV-2 genome from Africa in 2020 and shared the data via GISAID, a global virus-tracking resource.

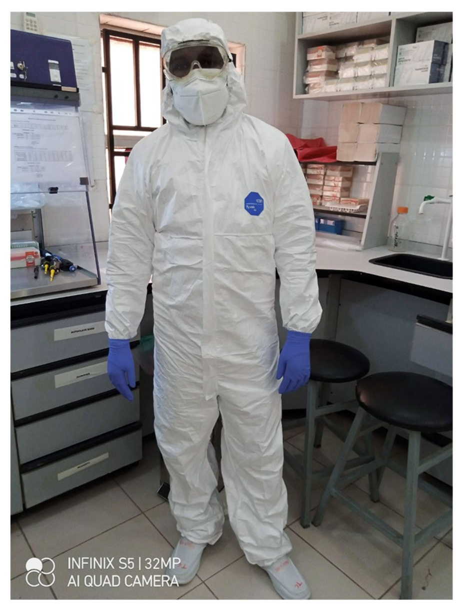
Sequence to win

"I'm only as good as I have the reagents in place, as good as I get the sequencers serviced, as good as I can get things in a timely fashion," says George Githinji, a bioinformatician at Kenya Medical Research Institute (KEMRI), a governmental organization with centers across the country. He is in the KEMRI–Wellcome Trust Research Programme (KWTRP) in KEMRI's Centre for Geographic Medicine Research in Kilifi, Kenya. KWTRP is one of the regional sequencing hubs for the Africa Centres for Disease Control and Prevention (Africa CDC). It builds capacity with PhD-level training in East Africa in sequencing, bioinformatics, modeling and public engagement in infectious disease. Supply chain issues have been a nightmare. "In the Global South, you're kind of getting the short end of the stick," says Githinji. Large sequencing companies do not maintain a physical presence in Africa; they sell through resellers. For instrument maintenance, technicians fly to Nairobi from the Middle East or Europe. Even in ordinary times, that means delays; COVID-19 made things worse. "We'd love to see that change," he says. He hopes companies will set up physical presences in Africa.

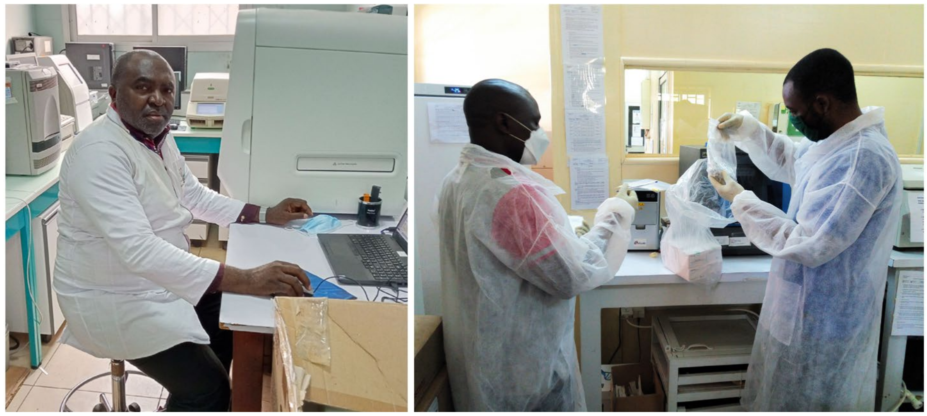
Before COVID-19, Githinji and other KEMRI colleagues had been building and expanding sequencing and bioinformatics infrastructure. In 2015, they installed an Illumina MiSeq sequencer; a year later, they added Oxford Nanopore instruments. When COVID-19 struck in China, the scientists knew it might reach Kenya in a few months. But first came the massive outbreak in Italy and France. Before Kenya's first case, collaborators in France sent Githinji and colleagues an inactivated SARS-CoV-2 isolate, which they used to set up the detection and sequencing assays.

For reagents, kits and other supplies, Githinji plugged into existing partnerships with the Kenyan government, Africa CDC, companies, the Wellcome Trust and labs in the North. Both Illumina and Oxford Nanopore donated supplies. Githinji also leveraged contacts in the Advancing Real-Time Infection Control (ARTIC) network, an international collaboration devoted to molecular epidemiology and outbreak response. They develop and share wet-lab and software protocols for characterizing SARS-CoV-2 on nanopore sequencers. When the first Kenyan COVID-19 case was detected in March 2020, "we were prepared," says Githinji. Since then they have been tracking variants circulating in Kenya. Working with others, they tracked the spread of SARS-CoV-2 and distribution of viral lineages on the Kenyan coast and shared the analysis pipeline[1]. The Kenyan Ministry of Health asked KEMRI for weekly briefs to inform policy. "That has been really good, I think, for our genomics surveillance work," he says.

At the beginning of the pandemic, Cameroon's research labs and hospitals generally lacked capability to run RT-PCR tests, says Mirdad Kazanji, who directs the Centre Pasteur in Yaoundé, Cameroon. With French government support, the scientists helped to set up labs, recruit people and train them at 17 sites around the country, and build a software pipeline for real-time virus analysis and surveillance. "We were already ready because we have the equipment, we have the techniques, we have know-how," says Richard Njouom, who directs virology at the institute, which is the regional reference lab for polio and yellow fever, a national reference lab for flu, and a WHO reference center for polio. The scientists are regularly tasked with surveillance of infectious diseases, mainly through serological analysis. A grant from US Health and Human Services during



Ayodele Israel is dressed to test samples for SARS-CoV-2 at UMTH's lab, which also studies polio. Credit: University of Maiduguri the Obama administration had helped them set up 'sentinel sites' for infectious disease surveillance across Central Africa to follow flu, including avian flu. The Trump administration cancelled the funding. When COVID-19 arrived in Cameroon, these facilities were re-activated. The team continues to build capacity in Cameroon to follow SARS-CoV-2 and to run sample analyses in the lab. They are setting up sequencing capability with Illumina and Oxford Nanopore platforms. "This new program is to follow, in real time, the evolution of different variants of COVID across the country," says Kazanji. Capacity building for COVID-19 has led to facilities, testing and training programs. They have built on existing expertise in many infectious diseases that can now be brought to bear on research into other infectious diseases. "I think this is the positive point of COVID," he says.



Virologist Richard Njouom (left) at the Centre Pasteur in Cameroon and team helped colleagues (right) at Bamenda Regional Hospital, 300 kilometers away, build capacity for RT-PCR-based detection of SARS-CoV-2. Credit: Centre Pasteur du Cameroun.

Networked network

To track SARS-Cov-2 takes reagents, such as RT-PCR primers. Delivery came to the scientists in Cameroon from colleagues at the HKU-Pasteur Research Pole, which is the Pasteur Network's unit at Hong Kong University and part of university's School of Public Health. The Pasteur Network set up the REPAIR project, devoted to sero-epidemiology, molecular epidemiology and outbreak modeling. Njouom heads projects to assess the dynamic of circulating virus and detects variants. Other efforts focus on serological assays. The team developed a loop-mediated isothermal amplification (LAMP) test that is now undergoing evaluation. LAMP involves no thermocycling. Instead a looped DNA structure develops and 'self-primes' as it advances. The Pasteur Network connections between institutes and people have been very helpful, says Njouom.

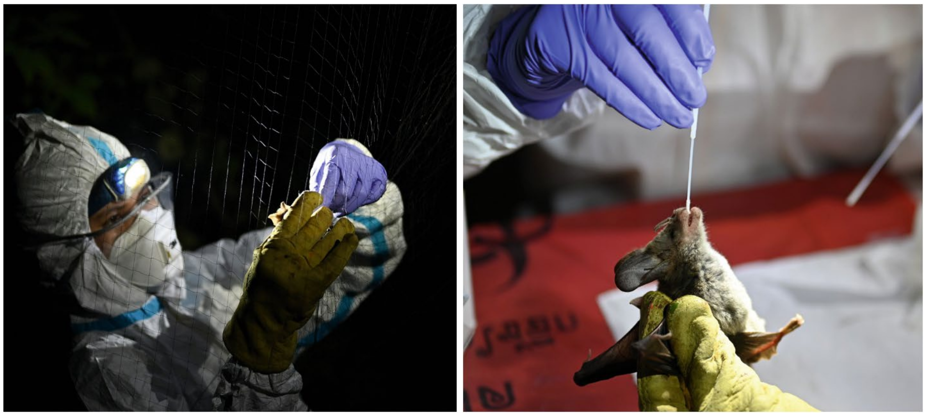
The Pasteur Network connects 33 institutions. "It was actually a creation of the French empire," says Dellagi. When it was set up in the late nineteenth century, research institutes were modeled after the Institut Pasteur in Paris. Many, such as those in sub-Saharan Africa and Southeast Asia, addressed needs in the French colonies. As countries achieved independence from France, the institutes kept "Pasteur" somewhere in their name, but they are not branches of the institute in Paris. Each is independent. What stayed is a sharing culture between network members, which has been particularly powerful in the COVID-19 pandemic. For instance, says Dellagi, the Pasteur Network's team in Hong Kong and Institut Pasteur scientists provided a team in Tunis with the cloned gene for producing the virus's spike and nucleocapsid proteins for enzyme-linked immunosorbent assay (ELISA) tests.

"This network did not develop in one day," says Leo Poon, who co-directs the Hong Kong University Pasteur Research Pole. The network has grown over years, and "we know each other quite well." Poon's lab identified SARS-CoV in 2003, and it also detected MERS-CoV, H5N1 avian influenza and the causes of other zoonotic diseases in the lab's sequencing center. Given this history, when the news from Wuhan emerged about a cluster of pneumonia-like illness, "we started to worry," says Poon. The 2003 experience with SARS made everyone in Hong Kong especially alert. The scientists quickly began sharing pipette tips, supplies needed for sequencing, and kits of various types with other labs. When the SARS-CoV-2 genome sequence was made public, the researchers developed an RT-PCR diagnostic protocol. "We also made a big batch of reagents," he says. They shared them across the Pasteur Network and elsewhere. By May 2020, he says, they had been sent to 170 labs in 77 countries. Some assays are faster than RT-PCR and cheaper but can be less sensitive or specific. For pandemics and epidemics, it takes all assay classes, he says. For surveillance of infectious diseases, "we need to do this in parallel; I think we need all of them."

Poon is happy with the sharing that took place across the Pasteur Network and beyond. Within a sharing network, one node can pick up when others run into issues. For his research, he is keen on developing new types of diagnostic assays for infectious diseases, as well for studying their basic biology. Among the around 30 faculty at HKU's School of Public Health, 20 work in infectious disease. "I look forward to attract more people to join the force to combat emerging infectious disease," he says. Science must learn from COVID-19. "I hope COVID can give us a good lesson and then also to policymakers," says Poon. After SARS, many sought continued surveillance of zoonotic diseases, he says, but most of the funding collapsed. People have "short-term memory" on infectious disease, especially when a pathogen may seem to disappear. But with Ebola, dengue, Zika or COVID-19, it's best to not talk about infectious disease in the past tense, says Poon. "We should try to allocate resources better," he says, including having countries spend more of their gross national product on health-related research to prevent infectious disease such as the kind that stems from animal-to-human transmission. With faster platforms for vaccine development, diagnostics and medication, "we can try to find a better way to control it or reduce the risk," he says. COVID-19 has shown that preventive measures are superior to a scramble to address an emergency. "We learned something now," says Poon, also about the need for health infrastructure.

"Viruses are clever cell biologists, and they exploit multiple pathways to replicate and infect other cells," says Roberto Bruzzone, who co-directs the HKU-Pasteur Research Pole with Poon. Before COVID-19, the group ran a training course on the global health risks coronaviruses pose. Bruzzone is a cell biologist who studies host–virus interactions and the mechanisms that underpin viral pathogenicity. The research community should think beyond COVID-19 and SARS-CoV-2, he says. If the research scope had been narrow, there might be no RNA vaccine. Plenty of resources have been reallocated to COVID.

From the first year of the pandemic alone, the database PubMed shows over 100,000 COVID-oriented papers, "as many as for HIV/AIDS after 20 years since the clinical description," he says. To avoid overlapping research efforts, he hopes for more coordination between research groups. With predictions, he says, there is a tendency to look at things through the magnifying lens of the latest episode. COVID-19 shows healthcare needs a re-think. Most people did not need hospitalization, but hospitals were overwhelmed because alternatives were lacking. "We also need to consider mechanisms to scale up resources," he says. "This is the real preparedness."



Virologist Veasna Duong (left) at the Institut Pasteur du Cambodge in Cambodia has long studied bat coronaviruses. When the government turned to him and his colleagues for advice about COVID-19, they had family-level coronavirus PCR assays ready. Credit: Institut Pasteur du Cambodge

Building capacity

"Building capacity on biological techniques is like my food," says Baba, who has been advising other labs and was tasked with building capacity and training in Nigeria. Skills for working with pathogens are transferable. Once you know virology, she says, it takes only "a small boost" to apply RT-PCR and other techniques to yellow fever, dengue, HIV or Ebola. Her fascination rests with viruses, especially arboviruses. With one mosquito bite, *Aedes aegyptii* can transmit arboviruses including Zika, chikungunya, yellow fever and dengue. "Nigeria is mosquito island," says Baba. Fevers in Nigeria are often assumed to be malaria, and people self-medicate with openly available anti-malaria drugs. But fever can also indicate yellow fever or dengue, which need different and urgent treatment. Now that COVID-19 testing is routine in Nigeria, she hopes other tests can follow for viral infections. ELISAs can cost $1,000 per test, which is why better and cheaper ways are needed to detect and track these diseases. She was glad to evaluate a LAMP test developed by New England Biolabs (NEB) and optimized for COVID-19 in a consortium. "It is very good," says Baba. She likes that the assay requires no instruments or highly skilled personnel.

Many quick turnaround assays have been developed to address the need for rapid and widespread COVID-19 testing and are especially important in resource-constrained regions. COVID is not a positive, says Tom Evans, who directs research at New England Biolabs, but what is a positive is that "labs have the attention of their governments." NEB donated LAMP reagents to the International Centre for Genetic Engineering and Biotechnology (ICGEB), an organization established by United National Industrial Development Organization that runs labs in South Africa, India and Italy and has members across the Global South.

The company had previously developed a LAMP kit to target and amplify regions on DNA or RNA. When COVID-19 emerged, together with ICGEB and financed by the Bill and Melinda Gates Foundation, they sent a LAMP assay to researchers in Cameroon, Ethiopia, Kenya and Nigeria for comparison to the 'gold standard,' which is quantitative RT-PCR. KEMRI's Eric Lelo has pointed out the LAMP assay reduces turnaround time for diagnosis, treatment and contact tracing, thus enabling better disease containment. The colorimetric assay was developed in NEB's parasitology division, which company founder Don Comb initiated to study diseases in low- and middle-income countries such as elephantiasis, river blindness and diseases caused by parasitic nematodes. Nathan Tanner and Tilde Carlow have developed colorimetric LAMP diagnostics to help track infection prevalence. The tests are for research use only but can hint at which tests one might choose next.

Along with the Wuhan Institute of Virology, NEB published a preprint in February 2020. "We started getting a ton of inquiries," says Tanner, such as how to use the LAMP assay and whether it worked with saliva. The demand led to gLAMP, a global consortium led by Cornell University researcher Christopher Mason, who pivoted his lab work to explore LAMP-based COVID-19 testing. gLAMP now involves 100 investigators who share their findings[2]. A lab at Massachusetts General Hospital developed a simplified extraction buffer. Eventually the researchers found a way to avoid expensive and time-consuming extraction and apply the test directly to saliva or blood spots dabbed on paper. As assay tweaking and evaluation continued, "it led to learning a lot really quickly," says Tanner. As part of a CLIA certification process, to date, around 700 individuals have tested it 30,000 times. When compared to RT-PCR, "it compared extremely favorably," says Evans. NEB is not a diagnostics company nor does it plan to become one, he says; the team just hopes this work can help establish rapid tests for many types of infectious diseases.

Africa has an urgent need for better, cheaper tests, and COVID-19 has provided "activation energy" to make this happen, says Evans. The technology is flexible. With different primers and validation studies, it could be used for insect vectors, for example. There is much to figure out, including transport in humid conditions, issues at customs, and distribution. Assays can't just be shipped to a big warehouse in Cape Town, says Tanner. "That's not getting things to Tanzania where they're needed." Says Evans, "right now we've just been giving away the kits for free." COVID could, he hopes, lead to a sustainable ecosystem for such tests so those who need them can get them. "They can't be expensive." Beyond the practicalities of assays, there are some science fundamentals that researchers in the Global South would like to see addressed.

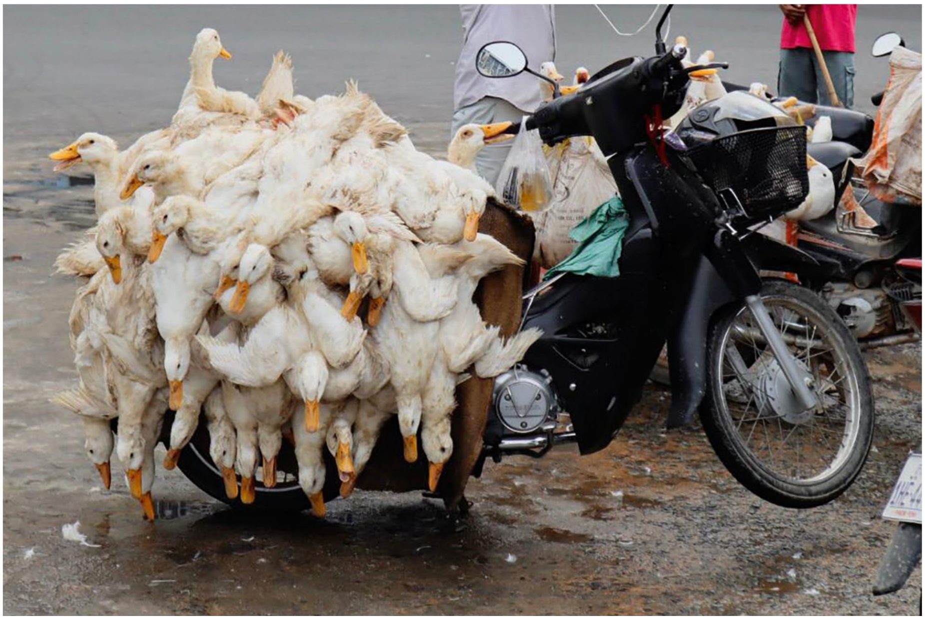
Diversity spotlight

The human reference genome "is actually a Caucasian genome," says KIMRI's Githinji. It's not representative of human genome diversity, particularly in terms of African genetic diversity and other under-represented groups. He's hopeful about pan-genome-oriented research and tool development underway. A more diverse human genome reference and perhaps pan-genomes of microbes and viruses too will enable stronger research on infectious disease. The pan-genome data structure lets scientists capture and query data such as relevant mutations that may have accumulated in certain populations.

In Jordan, Dajani studies ethnic minorities — Circassians and Chechens who fled persecution elsewhere over a century ago. Before COVID-19, she assessed differences between metabolic disease in these populations and in Jordan's Arab inhabitants. She is now returning to these data and will check in with the participants. She wants to explore genetic indicators of disease severity in COVID-19. "We have data that we can go back to, and look for example at the ACE receptor: is there a difference between severity and ACE?" she says about the cellular receptor the virus uses to enter cells. "This is something we are working on right now."

Some studies indicate that having had malaria may protect against severe COVID-19, an aspect that calls for more research, says Egwang. He and his colleagues have been helping to build Uganda's infectious disease research infrastructure and are involved in training people at the graduate and PhD level. "We live in an environment where we have many parasitic diseases," says Egwang. Especially in low- and middle-income countries, people can harbor parasitic helminths, which include round- and flatworms. Together with Tonny Jimmy Owalla, a research associate in his lab, and Margaret Kemigisha from nearby Kiruddu Referral Hospital in Kampala, Egwang has pointed out that helminth infections polarize the immune response[3]. They polarize the immune response toward T_H2 immunity, he says. That increases IgE antibodies, eosinophils, mast cells and basophils. And specific cytokines are activated, such as interleukins 4, 5 and 13. People whose immune system is biased in this way may not be able to mount a potent and robust immune response to pathogens. "SARS-CoV-2: it's quite established that you need a T_H1 kind of response," says Egwang. He and his team are looking into links between helminths and COVID-19 severity.

Cleared helminth infections likely leave a partial T_H2 bias in a person's immune response. "We don't know," he says. "That's something that we would need to find out." In the rush of vaccine development, to his knowledge, COVID-19 vaccine trials didn't assess the influence of helminth infection on vaccine response. But it's known that helminth infections impair the response to cholera and hepatitis vaccines. This impression has also arisen with experimental malaria vaccines. This all matters for discussions about dose-sparing vaccines and for assessing vaccine



In Cambodia, scientists run virus surveillance systems at 'wet markets' where pathogenic viruses may jump from animals to humans. Credit: Institut Pasteur du Cambodge

response, including booster scheduling in immunocompromised people such as those with HIV. "Do they get impaired responses; are antibodies short lived?" he asks. The same could apply to those who have or have had helminth infections.

"I agree absolutely with him," says Dellagi about Egwang's points on helminth infections. Dellagi hopes such aspects can now receive greater attention. Helminth infections, leishmaniasis, schistosomiasis and other neglected tropical diseases are the "endemic diseases of poverty," he says. These diseases might not kill, but they disable all too many people. Work on such diseases has taken a back seat to COVID-19, which is understandable. But he hopes that gains made with these diseases and progress on others including polio, rubella and measles will not see a COVID-related setback. COVID-19 has, he says, made clear how important it is to study diversity. The story on the dangers that pathogenic viruses pose hasn't ended with COVID-19. Now, the world has to understand what happened in different regions of the globe as well. "The story is just starting, I think."

The Global South and North have taken away many hard lessons from this pandemic, but perhaps a few positives, or at least shimmery bits, include the power of networking in infectious disease. Predictions are tough to get right, particularly ones on outbreaks and pandemics. It's impossible to accurately predict the next outbreak or to be optimally prepared, says Kazanji. COVID-19 has taught everyone how important it is to be careful and to focus on "the real information on the pathogens and the science." Reacting quickly is always complicated, but COVID-19 might have made it easier to see how important quick reactions are for public health measures and accelerated vaccine and drug development.

Right now is likely an "inter-pandemic period," says Njouom. The WHO and government authorities have put in place 'One Health' preparedness plans in Cameroon and elsewhere. This bundles modeling and surveillance of infectious disease, high awareness of animal reservoirs of potential human pathogens, and environmental factors that can accelerate pathogen spread. Work on infectious diseases means constant preparedness to enable fast ramp-up of measures such as the ones put in place at COVID-19's peak. Next time, they must be faster and more efficient. When the current pandemic quiets down, he says, "we'll not sleep." ❐

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