

News in focus

Evanston, Illinois. “This is an important paper for the field,” she adds.

But some researchers argue that smaller BWAS studies still have value. Peter Bandettini, a neuroscientist at the National Institute of Mental Health in Bethesda, Maryland, says that studies such as the ones Marek’s team simulated looked for correlations between crude measurements of behaviour or mental health (self-reported surveys, for example) and brain scans whose conditions might vary

from participant to participant, diluting bona fide associations.

By selecting participants carefully and analysing brain-imaging data using sophisticated approaches, it might be possible to find associations between brain scans and behaviour that are stronger than those identified in the study, says Stephen Smith, a neuroscientist at the University of Oxford, UK, who leads the UK Biobank’s brain-imaging efforts. “I fear this paper may be overestimating unreliability.”

MORGUE DATA HINT AT COVID’S TRUE TOLL IN AFRICA

About 90% of bodies tested at a Lusaka facility during coronavirus surges were positive for SARS-CoV-2.

By Freda Kreier

Almost one-third of more than 1,000 bodies taken to a morgue in Lusaka in 2020 and 2021 tested positive for SARS-CoV-2, with much higher numbers during viral surges, implying that many more people died of COVID-19 in Zambia’s capital than official figures suggest¹. Some scientists say that the findings further undermine the ‘African paradox’, a narrative that the pandemic was less severe in Africa than in other parts of the world.

This idea arose after health experts noticed that sub-Saharan nations were reporting lower case numbers and fewer COVID-19 deaths than might be expected. But researchers say that the findings from Zambia could reflect a broader truth – that a deficit of testing and strained medical infrastructure have masked COVID-19’s true toll on the continent. The findings have not yet been peer reviewed.

Ignoring the true extent of COVID-19 in Lusaka and beyond “is so wrong. People were ill. They’ve had their families destroyed,” says



A health-care worker in Lusaka is vaccinated against COVID-19.

co-author Christopher Gill, a global-health specialist at Boston University in Massachusetts. One of his colleagues in Zambia died from COVID-19 while working on the project.

“It’s not hypothetical to me,” says Gill.

The relatively low numbers of reported COVID-19 cases in sub-Saharan Africa led to the perception “that severe debilitation and deaths caused by COVID-19 were somehow less in Africa compared to other continents”, says Yakubu Lawal, an endocrinologist at the Federal Medical Centre Azare in Nigeria.

Lawal and other scientists speculated² that the relative youth of Africa’s population might have helped to spare the continent, but also suspected that official numbers were under-reported. The question was by how much.

Missing COVID cases

Gill and his colleagues in Zambia tested bodies in one of Lusaka’s largest morgues for SARS-CoV-2 in 2020 and 2021. Test positivity was 32% overall – and reached around 90% during the peak of the waves caused by the Beta and Delta variants. Only 10% of the people whose bodies were found to contain the virus after death had tested positive while still alive.

Gill and his colleagues can’t confirm that all of these people died of COVID-19, but the results still contrast sharply with official numbers. So far, there have been fewer than 4,000 confirmed COVID-19 deaths in Zambia, home to around 19 million people. Separate findings published³ on 10 March suggest that Zambia’s ‘excess’ deaths – those above what would usually be expected – in 2020 and 2021 exceeded 80,000.

The Lusaka numbers mesh with statistics from South Africa, where a 2021 study found that only 4–6% of SARS-CoV-2 infections in two communities were officially documented⁴. Further study⁵ of the same communities showed that 62% of participants had been infected at least once from July 2020 to August 2021. Co-author Cheryl Cohen, an epidemiologist at the University of the Witwatersrand in Johannesburg, South Africa, says that many of these infections were asymptomatic, but that people with symptoms might have gone undetected as well.

Gill suspects that a major reason for the gap between his results and official counts is that most people in Zambia who die of COVID-19 do so outside medical care. Four out of five people tested in the study were never admitted to a hospital.

But not everyone is convinced that the Lusaka findings invalidate the idea of the African paradox. In Ethiopia, for instance, “our experience is people get infected with the virus, are asymptomatic or have mild symptoms, and recover”, says Amare Abera Tareke, a physiologist at Wollo University in Dessie. “While it is difficult to ignore the

current finding, we have to take it cautiously.”

Gill worries that the idea that Africa was spared the worst of the pandemic might have led people to take unnecessary risks or contributed to “the lack of urgency” in supplying African nations with vaccines.

“I suppose this could be unique to Lusaka,” he says, “But boy, you’d really have to try

hard to explain why.”

1. Gill, C. J. et al. Preprint at medRxiv <https://doi.org/10.1101/2022.03.08.22272087> (2022).
2. Lawal, Y. *Int. J. Infect. Dis.* **102**, 118–122 (2021).
3. COVID-19 Excess Mortality Collaborators. *Lancet* [https://doi.org/10.1016/S0140-6736\(21\)02796-3](https://doi.org/10.1016/S0140-6736(21)02796-3) (2022).
4. Kleyhans, J. et al. *Emerg. Infect. Dis.* **27**, 3020–3029 (2021).
5. Cohen, C. et al. *Lancet Infect. Dis.* [https://doi.org/10.1016/S1473-3099\(22\)00069-X](https://doi.org/10.1016/S1473-3099(22)00069-X) (2022).

ARE ‘COVID TOES’ ACTUALLY CAUSED BY THE CORONAVIRUS?

Study adds to evidence suggesting that SARS-CoV-2 doesn’t trigger chilblains in toes.

By Cassandra Willyard

In March 2020, just as COVID-19 cases began to surge in Boston, Massachusetts, Esther Freeman noticed something peculiar – a deluge of people with discoloured toes requesting appointments. Freeman, director of global health dermatology at Massachusetts General Hospital, had seen these kinds of toes before. The itchy red and purple patches are a classic sign of chilblains, a skin condition that typically appears in cold weather. But usually, she would see one or two cases each winter. “Suddenly, I was seeing 15, 20 patients a day,” she says. Intriguingly, the surge – seen by physicians around the globe – seemed to coincide with the rise of the COVID-19 pandemic.

Yet, when physicians examined people with what the media began calling ‘COVID toes’, most didn’t test positive for a coronavirus SARS-CoV-2 infection. Scientists were stumped, and have been looking for answers ever since.

The latest study, published on 25 February¹, is an immunological deep dive, examining 21 people who developed chilblains during the early months of the pandemic in Connecticut. Although the results don’t rule out a direct connection between COVID-19 and chilblains, the authors couldn’t find any immunological evidence of a past SARS-CoV-2 infection in 19 of those people. The report adds to the argument by some researchers that ‘COVID toe’ could have been caused by something unrelated to the virus. For instance, it might have arisen from people in lockdown “being at home, not wearing shoes and socks”, says Jeff Gehlhausen, a dermatologist and immunologist at Yale School of Medicine in New Haven, Connecticut, and first author of the study.

Still, the results raise “some very interesting questions that deserve further study”,



Researchers are debating whether ‘COVID toes’ are triggered by an infection with the coronavirus SARS-CoV-2.

says Freeman, who was not involved in the research. For instance, the study doesn’t exclude the possibility that people exposed to the virus could have fought it off using an innate immune response – a first-line defence that would not prompt the body to produce detectable antibodies and T cells against SARS-CoV-2.

How chilblains arise isn’t entirely clear. “We think of it as a cold-weather-related injury,” says Patrick McCleskey, a dermatologist and researcher at Kaiser Permanente in Oakland, California. Researchers think that the cold probably leads to a restriction in blood flow, causing some cells to die and kicking off an

inflammatory process.

Most of the people in the latest study developed ‘COVID toes’ between April and May 2020, when COVID-19 cases surged in Connecticut. About one-third reported having some symptoms of COVID-19 before developing the condition, and one-third reported that they had been in contact with a person confirmed or suspected to have been infected with SARS-CoV-2.

The researchers used a variety of methods to look for antibodies and T cells specific for the coronavirus – signs of the body having what’s called an adaptive immune response to a pathogen. These people were months past the onset of their chilblains, so their immune systems would have had plenty of time to respond to SARS-CoV-2 if they had been infected. But the team picked up signs of a past infection only in two people, one of whom had initially tested positive.

Unsolved mystery

“The team did a fantastic, really extraordinary job,” Freeman says. But she emphasizes that the study is small – and therefore not necessarily generalizable – and that much larger epidemiological studies^{2,3} have shown a connection between chilblains and SARS-CoV-2.

Dermatologist Thierry Passeron, at Côte d’Azur University in Nice, France, still thinks COVID toes are triggered by the virus. His team found⁴ that people who developed chilblains during the pandemic showed evidence of a strong innate immune response.

With the link between COVID-19 and chilblains still in question, some researchers point to the theory that people spent more time at home barefoot early in the pandemic and got cold feet, literally. Or perhaps all the media coverage of COVID toes led to more people than usual seeking medical attention.

The debate has become strangely polarizing, Gehlhausen says. But the hypotheses are not mutually exclusive. “It’s possible that all these things are true,” he says.

It’s also possible the problem might be fading. “We’re still seeing patients with new chilblains, but it seems to be kind of back to the old background rate,” says Yale dermatologist William Damsky, an author on the paper.

In the end, the issue makes for an intriguing scientific debate, McCleskey says, but irrespective of whether a person had COVID-19, chilblains generally go away on their own in two or three weeks.

“Honestly, I think maybe we can chill out about chilblains,” he says.

1. Gehlhausen, J. R. et al. *Proc. Natl. Acad. Sci. USA* **119**, e2122090119 (2022).
2. Mascitti, H. et al. *Eur. J. Clin. Microbiol. Infect. Dis.* **40**, 2243–2248 (2021).
3. Visconti, A. et al. *Br. J. Dermatol.* **184**, 880–887 (2021).
4. Hubiche, T. et al. *JAMA Dermatol.* **157**, 202–206 (2021).