What our embattled world looks like through the ‘eyes’ of SARS-CoV-2

I’m tired of writing about COVID from a geneticist’s point of view, so I thought I’d let a virus speak – about the pandemic’s origin and future.

Arrival!

My ancestors came to the US from China in the nasal passages of a handful of airline passengers, in late 2019. A few of us descended quickly into lungs, hiding as pneumonia percolated. Some of us were forcefully ejected in droplets as our human hosts hurried through coastal US airports, riding sneezes and coughs or shot out in violent diarrhea into airport toilets, symptoms easily blamed on common colds or food poisoning. Many hapless hosts weren’t sick at all, obliviously passing us to others.

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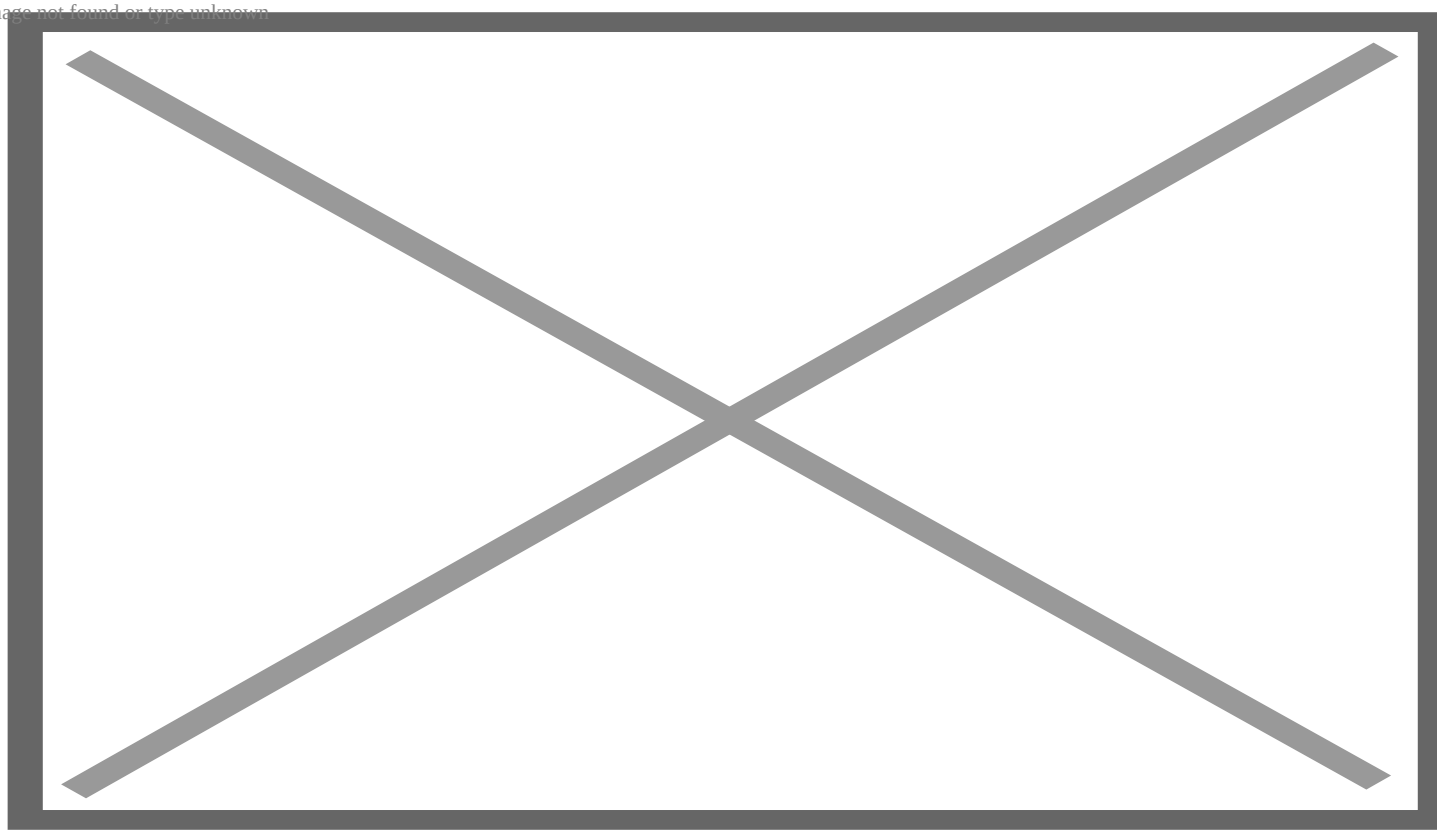

Credit: Lucas Olenuik/Toronto Star

In this way, my ancestors silently, stealthily, seeded the nation.

Outbreaks begat waves, which coalesced as time went on until we were racing through populations of unwitting humans everywhere. In early 2020, when the humans in the US were just starting to feebly block our spread, more of us arrived, bearing an accelerating mutation. The humans named those initial renegades D614G, marking the specific change in our genome. D614G would reverberate as a key part of many variants, what the hosts term collections of mutations that travel together.

More changelings arose from errors in RNA replication as virus spawned virus, proliferating uncorrected, lacking the natural repair systems of DNA. Our mutants that gained the ability to reproduce faster quietly and quickly took over, a tiny deletion here, an altered RNA base there. Some newbies sprouted spikes that more tightly gripped the receptors festooning human cells, even glomming together the cells, easing our entry. Natural selection was on our side at every change, perpetuating the advantaged among us.

The humans couldn't keep up, obsessed with tracking and cataloging us. At first they named us after where they found us, but that stigmatized the unfortunate places. Then they used virology jargon, numbers and periods meaningless to most. Greek letters prevailed for awhile, until the delta variant itself spewed variants. Naming is pointless. We're too fast.

Early on we noted difficulty infecting hosts who'd encountered coronaviruses before; they had leftover antibodies. But we SARS-CoV-2 viruses are pretty different from the "common cold" CoVs of years past. How did we come to be? Clues lie in our genome sequences. The humans have appeared slow in piecing together our origin, but it may be unknowable – because there's more than one.

The cave where it happened – maybe

At first the humans' algorithms spat out standard evolutionary tree diagrams that placed us among coronaviruses that infect horseshoe bats, in caves and mine shafts in southern China and in a few other places. The bat coronaviruses getting the most attention, like RaTG13, are our closest modern relatives, but they're still somewhat distant. That might be because the humans simply haven't identified many bat coronaviruses, paying much more attention to the influenza viruses. Few humans were even looking.

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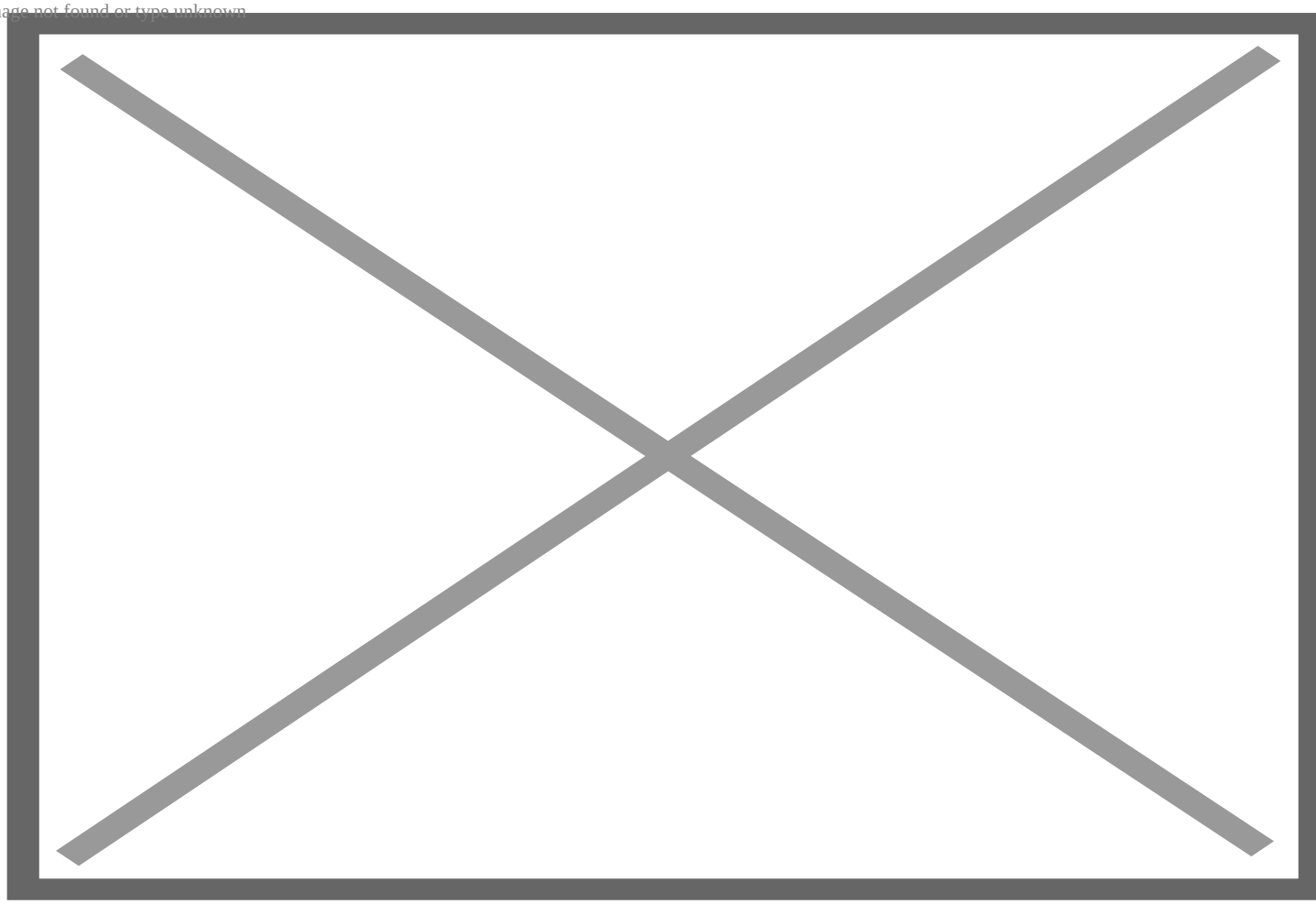

A model of a bat cave at the Wuhan Nature History Museum. Credit: Getty Images

Or, maybe the virus-oozing bat caves were only a steppingstone to our birth.

The humans have sequenced more than 2 million of our genomes, and are zeroing in on how we're different: our genomes encode a few unusual parts of proteins known to exist singly in other, unrelated viruses. Did these pieces of RNA swap into our genomes in a bat cave, all at once or in stages? Or did the augmentation happen in a lab, to bat coronaviruses collected from the wild, due to lax precautions in basic research. Or intentionally, as a brewing bioweapon? Two or all three ways?

The answer may lie in our spikes.

The mysterious furin cleavage site

A viral spike protein has two parts: one binds the host cell while the other drags the virus inside. Four amino acids nestled into where the spike halves touch, called a furin cleavage site, serve as a landing pad of sorts for where a human enzyme can cut. That snip pushes us inside the host cell, like an arrow shot

from a bow. Using the host's enzyme – and we can use a few types – to invade its cells is brilliant.

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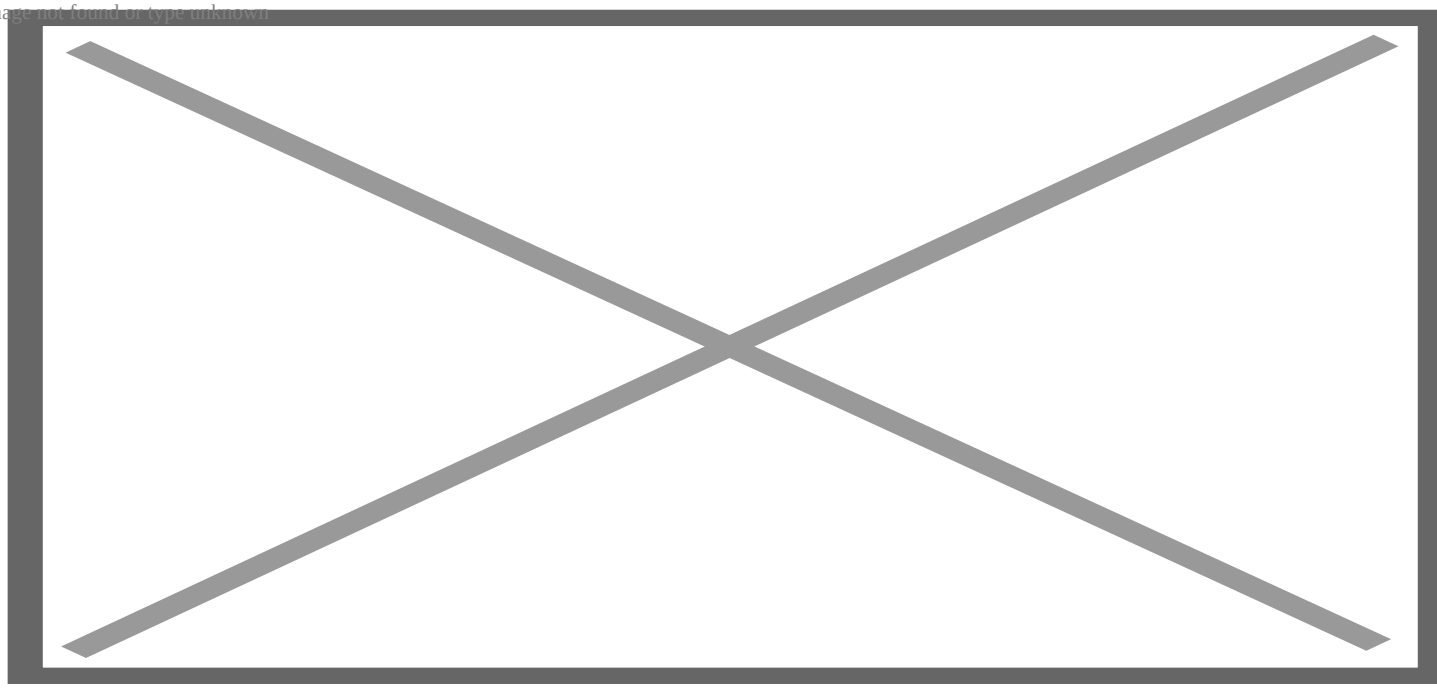

Diagram showing where the furin protease cleavage motif is between the S1 (binding domain) and S2 (fusion domain) subunits of the SARS-CoV-2 spike protein. Credit: University of Tartu

Oddly, the first SARS virus, our close relative, doesn't have a furin cleavage site. But the viruses that cause Ebola, AIDS, and MERS do. The humans call something unexpected showing up in a genome like this a "gain of function." It scares them, because we can change in ways that enable us to spread more easily, make people sicker, and even duck parts of the immune response. Yes, we can!

How did we get our spike furin cleavage sites? Were they plopped into the genomes of our recent ancestors in a bat cave or in an abandoned mine shaft in Yunnan province? Or at the Wuhan Institute of Virology or in a nearby seafood market?

It really doesn't matter where we and our genetic distinctions came from. Maybe the humans will figure out our origins eventually, but for us, it's moot. We're here.

What's next? Will we mutate ourselves into more benign forms? Perhaps, eventually, if we can benefit. But for now, the only thing that can stop or slow us are vaccines. They're actually quite clever.

The vaccine-hesitant create pockets of vulnerability

COVID vaccines so far consist of genetic material, RNA or DNA, that programs human cells to crank out versions of our spike proteins, engineered to elicit an immune response much more multifaceted than what happens during natural infection. Antibodies greet us right in the nasal passages where our journey typically begins. Sometimes we leave behind bits of our genetic material when the antibodies tear us

apart, triggering a positive PCR test when someone shoves in a swab. This can frighten silly humans into calling our RNA remnants “breakthrough infection.”

If nearly all humans were vaccinated, we viruses would be goners. We know this, but not all the hosts do. Epidemiologists assign a metric to the race between us and vaccines: herd immunity. It’s simple. The more people who are vaccinated, the harder it becomes for us to spread, like a person fleeing in a forest ramming into trees. The denser the forest, the more difficult it is to run through it.

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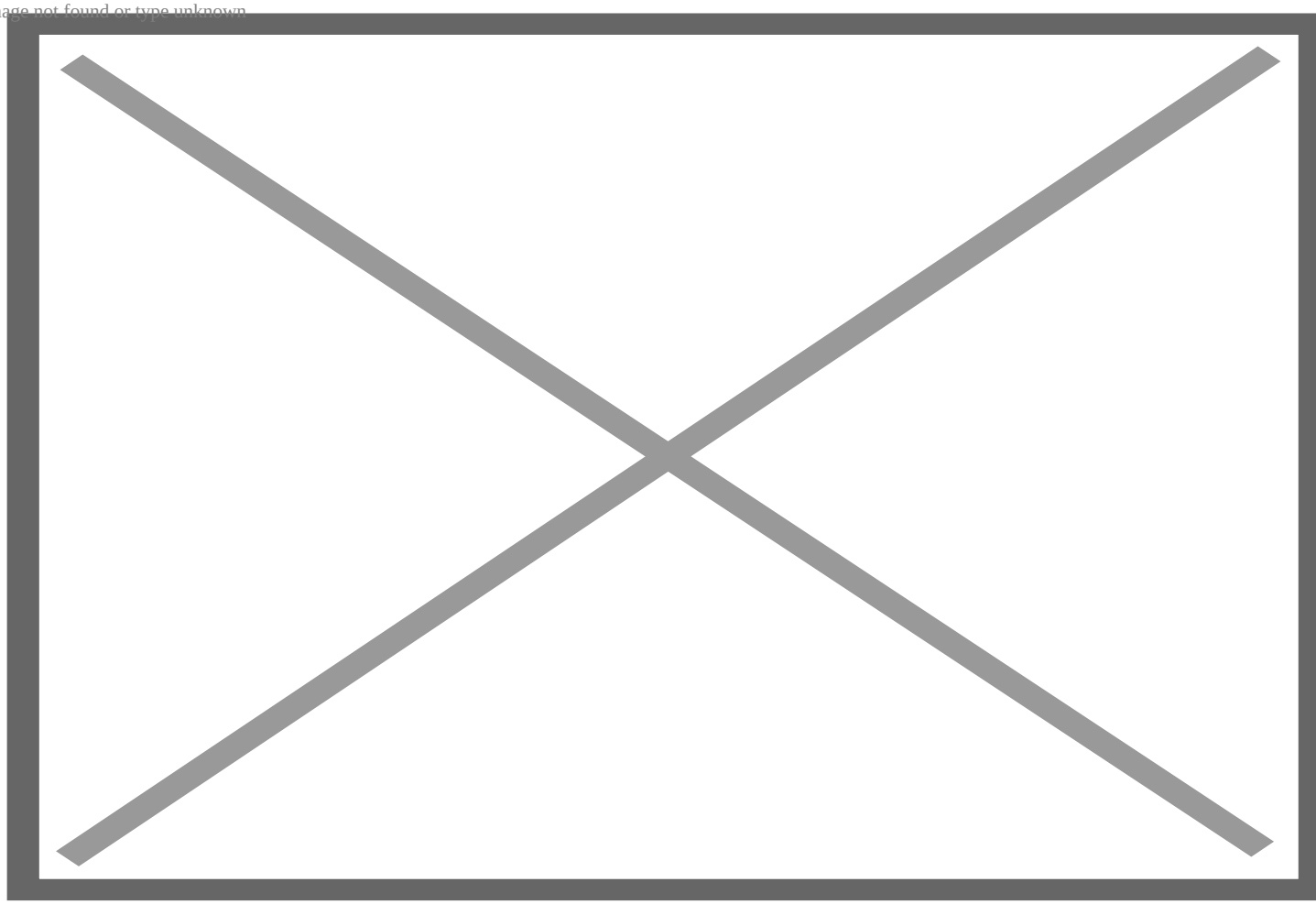

How herd immunity works. Credit: Shelby Lawton/Cavalier Daily

But herd immunity is unlikely. Why?

Many places can’t get enough vaccine. But in the privileged US, herd immunity is elusive because some humans don’t know how vaccines work, demand freedom of choice while ignoring the greater good, or see vaccination as a political issue. I’ll explain.

Some humans are unfamiliar with the components of the new vaccines, especially older folk who didn’t learn about RNA in middle school. But some hosts think vaccine mRNA can slip into their cell nuclei and

reprogram genes into causing cancer or autism, destroy sperm, harm grandchildren, carry nanochips or spyware, or make humans magnetic, radioactive, or into crocodiles, as Brazilian president Jair Bolsonaro claimed. Some humans interpreted that to mean vaccines could turn them into lizard monsters.

We viruses marvel at the ways that so-called higher organisms with well-developed brains fail to understand how an mRNA vaccine simply programs their cells to make decoy spikes. It is so utterly, ingeniously simple.

In the US, many humans have curiously divided themselves, with those in one political party having a considerably higher rate of vaccination than those in the other. And the states that maintain the most distressing pockets of vulnerability – Alabama, Arkansas, Louisiana, Mississippi, and Wyoming – are projected to suffer "very dense outbreaks" of our delta variant and its offspring.

The human known as Fauci called this split The Two Americas, referring to the US (Canada is in America too), and the media trumpeted that statement, as if it hasn't been true for many months. We didn't cause the divide that the vaccines wrought, but we seem to be catalyzing it.

And so we'll simmer in those places where vaccine hesitancy reigns. We'll still spread as new mutations enjoy natural selection, a few of us surviving intact in the noses of the vaccinated as long as unvaccinated and maskless humans are out and about, welcoming us, our numbers never dipping low enough for us to vanish. The conflation of politics with science ensures our survival and victory.

That's why come next winter, in the US, we'll be back. Not with the population-crippling force of 2020, but in mini-surges that will take out the unvaccinated, while favoring we who've mutated into faster and deadlier versions of ourselves. We're mutating right now, not only in our spikes where the humans focus their efforts, but in other genes that indirectly affect the spikes. It's survival of the fittest. Us.

Maybe once the unvaccinated have either perished or fought us off with their inferior immune responses, we'll start to go away as the vaccinated block our spread. But it will all unfold slowly, triggering violence as the world shatters further into haves and have-nots. Perhaps we'll sneak back into the bats from which our long-ago ancestors came. There we'll wait, incubate, multiply, and continue to change, as RNA viral genomes do.

We will re-emerge, if not as 2021 becomes 2022, then perhaps in 2026, dancing to the 7-year beat of other coronaviruses. Maybe the humans will be ready this time and meet our descendants with vaccines and anti-virals.

Only time will tell. Unless the humans can pull off a feat like they did with the global eradication of smallpox, we'll be back. COUNT ON IT.

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