Streets in downtown Glasgow were deserted on 5 January after the United Kingdom imposed a strict lockdown to curtail the spread of a new SARS-CoV-2 variant.

PHOTO: ANDY BUCHANAN/AFP/GETTY IMAGES

COVID-19

Viral evolution may herald new pandemic phase

Scientists worry about another 'very, very bad' wave, argue for stricter control measures

By **Kai Kupferschmidt**

For COVID-19 researchers, the new year brings a strong sense of déjà vu. As in early 2020, the world is anxiously watching a virus spread in one country and trying to parse the risk for everyone else. This time it is not a completely new threat, but a rapidly spreading variant of SARS-CoV-2. In southeastern England, where the B.1.1.7 variant first caught scientists' attention last month, it has quickly replaced other variants, and it may be the harbinger of a new, particularly perilous phase of the pandemic.

"One concern is that B.1.1.7 will now become the dominant global variant with its higher transmission and it will drive another very, very bad wave," says Jeremy Farrar, an infectious disease expert who heads the Wellcome Trust. Whereas the pandemic's trajectory in 2020 was fairly predictable, "I think we're going into an unpredictable phase now," as a result the virus' evolution, Farrar says.

The concern has led some countries to speed up vaccine authorizations or discuss dosing regimens that may protect more people rapidly (see p. 109). But as the new variant surfaces in multiple countries, many scientists are calling for governments to strengthen existing control measures as well. U.K. Prime Minister Boris Johnson announced tough new restrictions on 4 January, including closing schools and asking people not to leave their homes unless strictly necessary. But other countries have hesitated. "I do feel like we are in another situation right now where a lot of Europe is kind of sitting and looking," says virologist Emma Hodcroft of the University of Basel. "I really hope that this time we can recognize that this is our early alarm bell, and this is our chance to get ahead of this variant."

In announcing the U.K. restrictions, Johnson said the new variant is between 50% and 70% more transmissible. But researchers have been careful to point out uncertainties. Cases have soared in the United Kingdom over the past month, but the rise occurred while different parts of the country had different levels of restrictions and amid changes in people's behavior and regional infection rates in the run-up to Christmas—"a complex scenario" that makes it hard to pinpoint the effect of the new variant, says evolutionary biologist Oliver Pybus of the University of Oxford.

Yet evidence has rapidly increased that B.1.1.7's many mutations, including eight in the crucial spike protein, do enhance spread. "We're relying on multiple streams of imperfect evidence, but pretty much all that evidence is pointing in the same direction now," says Adam Kucharski, a modeler at the London School of Hygiene & Tropical Medicine. For instance, an analysis by Public Health England showed about 15% of the contacts of people infected with B.1.1.7 in England went on to test positive themselves, compared with 10% of contacts of those infected with other variants.

If other countries that have detected B.1.1.7 also see it surge, it will be "the strongest evidence we will have," Pybus says. Data from Denmark, which leads the European Union in the sequencing of SARS-CoV-2, are not reassuring. Routine surveillance there has picked up the variant dozens of times; its frequency went from 0.2% of sequenced genomes in early December to 2.3% 3 weeks later. "We have had what looks like a poster child example

of exponential growth these last 4 weeks in Denmark," says genomicist Mads Albertsen of Aalborg University.

The lack of evidence—so far—that the new variant makes people sicker is little consolation. Increased transmissibility of a virus is much more treacherous than increased pathogenicity because its effects grow exponentially, Kucharski says. "If you have something that kills 1% of people but a huge number of people get it, that's going to result in more deaths than something that a small number of people get but it kills 2% of them."

If the U.K. estimates of a 50% to 70% increase in the virus' reproduction number, or R, hold true, "keeping the virus from spreading has become a lot harder," says Viola Priesemann, a physicist at the Max Planck Institute for Dynamics and Self-Organization who has been modeling the pandemic and the effects of nonpharmaceutical interventions, such as physical distancing and school closures. "In Germany you would need two big additional measures to keep the reproduction number below 1," Priesemann says.

Isolating patients and tracing, quarantining, and testing their contacts is one part of any attempt at doing so; those measures alone can reduce R from about 2 to about 1, Priesemann has shown for Germany. But that effect breaks down when case numbers reach a critical threshold and public health authorities are overwhelmed, which means tougher measures now can help contain spread of the new variant later. "It's yet another reason to go for very low numbers," says Priesemann, who co-authored a December 2020 letter to in *The Lancet* calling for Europe to adopt a joint strategy to bring down infections fast. Hodcroft agrees. "The case has never been stronger," she says. "What's the worst-case scenario here? We overshoot and we get cases so low that we can get rid of a lot of restrictions."

Curtailing infections sharply has the added benefit of reducing the chances for the virus to evolve even further. Already other variants have emerged, notably one called 501Y.V2 in South Africa, that are just as worrying as B.1.1.7, Farrar adds. "It is essentially a numbers game: The more virus is circulating, the more chance mutants have to appear," he says. In the long term, mutations could arise that threaten the efficacy of vaccines.

It's dispiriting to feel like the world is back where it was in early 2020, says epidemiologist William Hanage of the Harvard T.H. Chan School of Public Health. "But we have to stop this virus. … Fatalism is not a nonpharmaceutical intervention." ■

COVID-19

Dosing debates, transparency issues roil vaccine rollouts

U.K. decision to delay booster shots sparks concerns

By **Jon Cohen**

Last-minute vaccine dosing changes that could gamble away proven COVID-19 protection and undermine public trust. Controversial approvals without any efficacy data. Vaccinemakers at odds with countries hosting their clinical trials. The COVID-19 vaccine landscape keeps changing almost daily, simultaneously raising hopes and triggering confusion and scientific debates. "It's crazy," says vaccine researcher John Moore of Weill Cornell Medicine. "Every morning, it's just, 'What's going on?'"

Over the past few weeks, COVID-19 vaccines developed in the United Kingdom, China, and India moved toward widespread rollout, offering new weapons in the face of fast-spreading viral variants that threaten to deepen the crisis (see p. 108). But many came with controversies, and U.K. regulators sparked a debate when they endorsed a sharp departure from the expected dosing schedule for a newly authorized vaccine from AstraZeneca and the University of Oxford and one from Pfizer and BioNTech. The pandemic has driven most COVID-19 vaccinemakers to aim for a short 3 or 4 weeks between prime and booster shots, but the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) said second shots can be given up to 12 weeks later.

Science's COVID-19 reporting is supported by the Pulitzer Center and the Heising-Simons Foundation.

Biostatistician Natalie Dean of the University of Florida thinks MHRA moved too quickly and without enough explanation of its dosing decision. "Clearly there were deliberations that the U.K. had about this, but we don't have access to those discussions."

MHRA didn't cite the fast-spreading B.1.1.7 variant of SARS-CoV-2 in its dosing decision, announced last week when the agency authorized the AstraZeneca-Oxford vaccine. But some scientists say the strain's threat, which led this week to a U.K.-wide lockdown, justifies delaying the booster to expand the population that can receive at least one dose of vaccine.

MHRA said an "exploratory analysis" of some participants in AstraZeneca-Oxford phase III trials in Brazil and the United Kingdom found an efficacy of 73% after a single dose of the vaccine, which uses an adenovirus to deliver a gene that codes for the surface protein, spike, of SARS-CoV-2. This, oddly, was higher than the 62% efficacy after two full doses reported in *The Lancet*. Oxford's Adrian Hill, who co-led the vaccine's development, notes its efficacy trials started earlier than other groups, which may explain the discrepancy. "I'm afraid it's possible that what's happening is efficacy is declining over time," Hill says. (The 62% figure has itself brought confusion, as the vaccine had a reported 90% efficacy when the first dose was halved.)

For all two-dose vaccines, intervals between a prime and booster are somewhat arbitrary, says pediatrician Paul Offit of the Children's Hospital of Philadelphia, a member of an independent U.S. vaccine advisory committee. But some physicians and scientists worry that last-minute debates on dosing strategies will increase vaccine hesitancy. "Mixed messages and lack of evidence will inevitably lead to undermining the public trust in the vaccine and could negatively impact on uptake," the Doctors' Association UK wrote in a letter of concern to the U.K. health minister.

The British Society for Immunology issued a statement supporting MHRA's "pragmatic" dosing schedule, but urged the government to launch a "robust" monitoring program to determine how the different intervals affect efficacy. Several scientists also called for more direct clinical trial comparisons of dosing intervals.

The United States seems unlikely to follow the U.K. example. "The MHRA has taken quite a significant risk," says Moncef Slaoui, chief scientist for the U.S. government's Operation Warp Speed program, which is now staging its own 30,000-person trial of the AstraZeneca-Oxford vaccine. "After the first dose, quite a lot of people actually are not primed," he adds. The U.S. Food and Drug Administration (FDA) issued a statement that made similar scientific arguments, adding that the move could backfire if people who are not fully protected begin to increase their risk of exposure.

Nor do data on the two U.S. authorized vaccines, which both use messenger RNA encoding spike, clearly support a delayed booster. Made by Pfizer and BioNTech and

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Science **371** (6525), 108-109.
DOI: 10.1126/science.371.6525.108