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." ■

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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.

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

Moderna, both have a reported efficacy of about 95% after two doses. But data Pfizer provided last month showed an efficacy of just 52.4% between the first and second dose of its vaccine, below FDA's threshold for emergency use given the result's statistical uncertainty.

Slaoui floated a different change to expand supply of the Moderna vaccine: cutting both doses in half. Moderna has data showing its vaccine stimulated a strong immune response in people between ages 18 and 55 at half the usual dose, he notes. But FDA doesn't like that idea, either. "There are some possible challenges with reliability and interpretation of the data that Slaoui based this on," says Peter Marks, who heads FDA's Center for Biologics Evaluation and Research. And in much of the United States, logistical problems, rather than supply shortages, are currently the main limiting factor in the vaccination campaign.

Doses of the AstraZeneca-Oxford COVID-19 vaccine, made at the Serum Institute of India, are stored in a cold room.

In India, meanwhile, the Central Drugs Standard Control Organisation (CDSCO) created a furor on 3 January by granting "restricted emergency approval" for a vaccine containing killed, or "inactivated," SARS-CoV-2, based on early trials showing immune responses but not efficacy, as well as animal data. A phase III trial of the vaccine, produced by Bharat Biotech, hasn't even completed recruiting. Vineeta Bal of India's National Institute of Immunology calls the decision "unconscionable."

But CDSCO's director, V. G. Somani, said the approval was out of "abundant precaution," in case it was needed to protect the country against B.1.1.7. CDSCO also approved a local version of the AstraZeneca-Oxford vaccine, even though it hasn't fully analyzed data from a "bridging study" designed to show that the vaccine triggers an immune response in Indians comparable to that seen in trials elsewhere.

China's Sinovac and Sinopharm added to the confusion with their COVID-19 vaccines, which are based on whole, killed copies of SARS-CoV-2. A press release early last month from the United Arab Emirates said that a candidate from Sinopharm's China National Biotec Group was safe and had "86% efficacy against COVID-19 infection" in a UAE trial that involved 31,000 participants. But on 30 December, the state-owned company reported that the vaccine had 79.34% efficacy "against the disease."

Its statement contained no other important scientific information. Nevertheless, China gave the vaccine "conditional approval," instructing Sinopharm to complete the efficacy studies it has underway in UAE and several other countries. (The company did not reply to queries from *Science*.)

A similar muddle surrounds Sinovac's vaccine. On 23 December, investigators in Brazil announced that a trial with 13,000 participants had shown greater than 50% efficacy. But they said a contractual agreement with Sinovac prohibited them from revealing more information and the company wanted to compare results from other countries. One day later, researchers in Turkey revealed interim data, which were far more preliminary, from a Sinovac vaccine trial that suggested an efficacy of 91.25%.

Mauro Schechter, an infectious disease researcher at the Federal University of Rio de Janeiro, College City, says "the perception that Turkish investigators are at liberty to divulge their data but Brazilians are not" contributes to what he calls "an atmosphere of distrust" for Sinovac's vaccine, one of Brazil's only options now. And that's the last thing needed as the pandemic takes its deadly toll. ■

With reporting by Priyanka Pulla in India.

EUROPE

Brexit deal secures U.K. access to research funds

Horizon Europe program will be open to U.K. researchers

By **Nicholas Wallace**

The Brexit cliffhanger has ended with a favorable outcome for U.K. researchers. Just 1 week before a 1 January deadline, negotiators struck a long-term agreement on trade and cooperation that will ease the United Kingdom's exit from the European Union. The deal also includes a hoped-for provision for science. In exchange for a contribution to the EU budget, the United Kingdom will join the forthcoming Horizon Europe research program, which will spend €85 billion over the next 7 years.

"I am unbelievably relieved," says Vivienne Stern, director of advocacy group Universities UK International (UUKI). She says failure to reach agreement on Horizon Europe "would've been a tragedy" for U.K. researchers, and that the outcome is "a relief to the European and international research community."

Mike Galsworthy, co-founder of anti-Brexit campaign group Scientists for EU and a visiting researcher at the London School of Hygiene & Tropical Medicine, is also pleased about access to Horizon Europe. But he laments the loss of U.K. influence over the program and how the money is spent, because those decisions will only be made by EU countries.

U.K.-based researchers were among the largest beneficiaries of Horizon 2020, Horizon Europe's predecessor. They hoped that after Brexit, the country would pay for "associate" status, which allows researchers in non-EU countries such as Switzerland and Israel to apply for and receive EU funding. But there were fears that associate membership might be too costly.

Association fees are calculated on the basis of gross domestic product, but after Swiss and Israeli researchers won more from Horizon 2020 than their govern-

PHOTO: FRANCIS MASCARENHAS/REUTERS

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