MONKEYPOX CASES RISING IN AFRICA

Decade	Confirmed cases caused by the viral strain that emerged in Central Africa	Confirmed cases caused by the viral strain that emerged in West Africa
1970–79	38	9
1980–89	355	1
1990–99	520	0
2000–09	92 10,027 suspected*	47
2009–19	85 18,788 suspected*	195

* The Democratic Republic of the Congo primarily reported suspected monkeypox cases, rather than confirmed cases, during these periods.

SOURCE: BUNGE, E. M. *ET AL. PLOS NEG. TROP. DIS.* **16**, E0010141 (2022)

and laboratory technicians. Other researchers *Nature* spoke to also said the shots could help to curb monkeypox in Africa if they were given to people with compromised immune systems and those who frequently encounter wildlife.

A lack of investment

Some health officials in sub-Saharan Africa worry that they will continue to be left behind, judging by their experience of vaccine inequity during the COVID-19 pandemic. Although case numbers are going up, only 18.5% of people in Africa have been vaccinated against the coronavirus SARS-CoV-2, compared with 75.7% in high-income countries elsewhere.

Member nations of the World Health Organization (WHO) have pledged more than 31 million smallpox-vaccine doses to the agency for smallpox emergencies — but these have never been distributed to Africa for use against monkeypox. Part of the reason, says Rosamund Lewis, the technical lead for monkeypox at the WHO, is that some of the agency's pledged stockpile is made up of 'first generation' vaccines; these can have severe side effects and are not recommended for monkeypox, which is less deadly than smallpox.

She also cites "regulatory issues", because some member nations have licensed the vaccines only for use against smallpox, not monkeypox. (Although the vaccines are considered safe and effective for use in people with smallpox infection, they have had limited testing against monkeypox.)

"The investment has perhaps not been what we would want it to be, but it's not been nothing," Lewis says of efforts to address monkeypox in Africa. She adds that the WHO has been coordinating with African countries that have monkeypox outbreaks to improve surveillance and diagnostics.

Last month, the WHO recognized the inequity in the global attention that monkeypox is receiving. On 17 June, the agency announced it would no longer report monkeypox cases and deaths for sub-Saharan Africa and the rest of the world separately, reflecting the "unified response that is needed". And after researchers published a proposal to change the name of monkeypox viral strains — currently called the West African clade and the Congo Basin clade — WHO director-general Tedros Adhanom Ghebreyesus came out in support of the changes, to reduce stigma. He promised to "make announcements about the new names as soon as possible".

Yet even if sub-Saharan African nations procure vaccines, inoculation alone will not eradicate monkeypox, says Oyewale Tomori, an independent virologist in Ibadan, Nigeria. He cautions that vaccination is only effective if health officials understand the local epidemiology of the pathogen — and there are still many questions about how isolated cases of the disease have continued to pop up all over the affected countries in sub-Saharan Africa. He recommends supporting research to investigate the animal reservoir of monkeypox so that health officials can devise more precise measures to curb the spread of the virus. "Without addressing the fundamental issues, you'll end up using all your vaccines toward monkeypox," he says, instead of dealing with the source of the problem — contact between wildlife and humans.

Equally important are strategies to speed up testing for monkeypox, because the faster that a case can be confirmed, the sooner that public-health officials can begin containment countermeasures, Ogoina says. These advances can't come soon enough for sub-Saharan Africa, he adds. "Isolated solutions that fix the problem for developed countries alone and leave out developing countries will lead us through the same cycle again," he warns, pointing to past outbreaks where a pathogen continues to re-emerge. "It's just a matter of time."

FAST-EVOLVING COVID VARIANTS COMPLICATE VACCINE UPDATES

Emerging viral lineages and fickle immune reactions mean it's not clear what new jabs should look like.

By Ewen Callaway

As countries brace for another Omicron wave driven by the variants BA.4 and BA.5, calls to update COVID-19 vaccines are growing louder.

Existing vaccines based on the version of the virus SARS-CoV-2 that emerged in Wuhan, China, in late 2019 are a poor match to current Omicron strains. As a result, the vaccines now offer only short-lived protection from infection — although they seem to be holding up against severe disease.

This week, an advisory panel to the US Food and Drug Administration (FDA) will meet to discuss whether COVID-19 vaccines should be updated — and what the upgraded vaccines should look like.

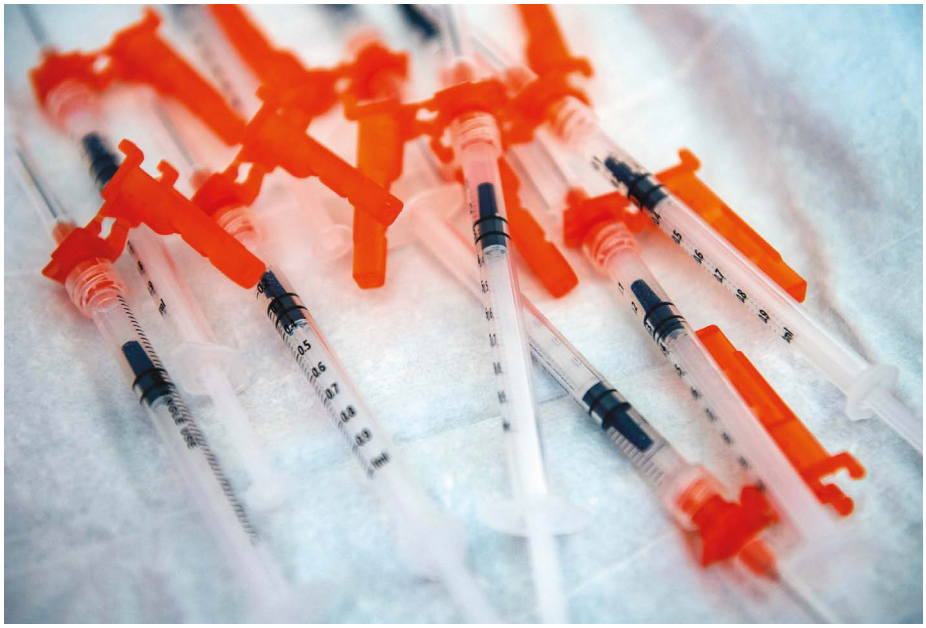
Many — although by no means all — scientists agree that COVID-19 vaccines are overdue for change. But constantly emerging variants and hard-to-predict immune responses mean that it's far from clear what the new jabs ought to look like.

"I think it's time," says Meagan Deming, a virologist and vaccine scientist at the University of Maryland School of Medicine in Baltimore. "The virus is changing, and what worked two years ago may not work for future variants." But she and other scientists caution that updating COVID-19 vaccines won't be as simple as swapping genetic material based on the Wuhan strain for that matching Omicron.

Shifting sands

Omicron has altered the course of the pandemic and spawned a series of offshoots, with BA.4 and BA.5 the latest. Each has eroded the immunity earnt from vaccination and infection with previous strains, including earlier versions of Omicron.

So if upcoming vaccines are based on the original Omicron, called BA.1, there is a real possibility that by the time they are rolled out later this year, circulating Omicron strains will be different. "BA.1 is yesterday's news," says John Beigel, a physician-scientist at the US National Institute of Allergy and Infectious



JOSEPH PREZIOSO/AFP/GETTY

Vaccines might become more effective if they target newer variants of the SARS-CoV-2 virus.

Diseases (NIAID) in Bethesda, Maryland, who is leading a trial of potential vaccine updates.

It is also possible — and some scientists say likely — that an entirely new variant will pop up from a distant part of the SARS-CoV-2 family tree. "My concern is that there's this huge focus on Omicron, and the assumption that Omicron is what we will be dealing with in the future," says Penny Moore, a virologist at the University of the Witwatersrand in Johannesburg, South Africa. "We have a strong track record of getting that wrong."

As a result of such uncertainty, scientists say the next COVID-19 vaccines need to cast a wide net, ideally eliciting an immune response that can recognize variants past, present and future. "The broadest response is definitely what I want," says Deming.

Mix and match

How to achieve such breadth is the million-dollar question. Moderna, the biotechnology company in Cambridge, Massachusetts, that co-developed a successful mRNA-based vaccine with NIAID, is trialling an updated jab that encodes two versions of the SARS-CoV-2 spike protein: the original formulation and a version based on BA.1.

On 25 June, the company posted results from the trial[1], which gives a booster of this 'bivalent' vaccine to people who have had three doses of the original Moderna vaccine, and compares their immune responses with those seen in people who receive a fourth dose of the original vaccine. But other data announced last month suggest that the updated vaccine triggered antibody responses that were 75% more potent against BA.1 and 24% stronger against a version of SARS-CoV-2 from the early months of the pandemic, compared with an extra dose of the original vaccine. "This is a clearly superior booster," the company's president, Stephen Hoge, told investors on 8 June.

And late last month, Moderna added that the bivalent vaccine generates antibodies that still block BA.4 and BA.5, although their levels were about three times lower than those against BA.1. However, the company did not provide a comparison with responses triggered by an extra dose of the original vaccine.

Other vaccine manufacturers, including Pfizer in New York City and its collaborator BioNTech in Mainz, Germany, as well as Novavax in Gaithersburg, Maryland, are testing their own Omicron-based vaccines. In a 25 June press release, Pfizer–BioNTech reported that an Omicron BA.1-only vaccine generated neutralizing antibody responses against BA.1 that were around 2–3 times more potent than an extra dose of the original vaccine; their bivalent vaccine, similar to Moderna's, generated BA.1 responses that were about 1.5 to 2-fold stronger. BA.4 and BA.5 sapped these responses similarly to the Moderna vaccine.

> **"Having the vaccine as close as possible to the circulating virus will generally be better."**

Beigel says that the Moderna trial shows why now is the time to update COVID-19 vaccines.

But John Moore, a vaccine scientist at Weill Cornell Medicine in New York City, wonders whether the improvements the updated vaccines offer are worth it. "The question the FDA advisers have to decide on is whether this modest increase is enough to justify the expense and complexity of a composition switch," Moore says. "I've seen nothing in the Pfizer and Moderna data to obviously justify a composition switch to Omicron."

Beigel and his colleagues will soon report the first results from a NIAID-funded trial that is testing combinations of vaccines based on a range of variants, including Omicron, Beta, Delta and the original strain. This trial, called COVAIL, includes mRNA vaccines manufactured by Moderna and Pfizer–BioNTech, as well as an experimental protein-based booster developed by Sanofi in Paris and GSK in London.

Surprise entrant

Beigel says that we shouldn't presume that the original vaccine is the best way to trigger a response against earlier non-Omicron strains. He hopes his study will shine a light on the ideal combinations. Another trial found that Sanofi–GSK's booster, which is based on the Beta variant, triggered strong neutralizing-antibody responses against all variants, including BA.1 and Delta[2]. This hints that Beta shouldn't be ruled out as a component of future updates, scientists say.

The quest for an updated formulation is also complicated by the possibility that vaccines based on a particular strain, such as Omicron, might not always trigger a potent immune response against that strain. Some recent studies[3] have found that Omicron infections after vaccination recall the same antibodies that vaccines triggered against earlier strains, instead of eliciting all-new responses to Omicron. But it's not yet clear whether updated vaccines will behave in the same way. Preclinical studies of Omicron-based vaccines in animals showing little difference between Omicron and original-strain boosters suggest that they might, says Moore.

A similar phenomenon, known as imprinting, affects how people respond to influenza vaccination and infection, causing levels of protection to vary between people and from year to year. Nonetheless, health officials attempt to match the make-up of seasonal vaccines to the strains most likely to be in circulation.

This strategy makes sense with SARS-CoV-2, says Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Center in Seattle, Washington. "We can safely assume that having the vaccine as close as possible to the circulating virus will generally be better."

But decisions about the composition of flu vaccines are based on a solid understanding of how those viruses evolve, says Beigel. "We know the rules of flu and we can predict that very well. For COVID, we don't."

1. Chalkia, S. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.06.24.22276703 (2022).
2. Launay, O. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.05.25.22274904 (2022).
3. Reynolds, C. J. *et al*. *Science* https://doi.org/10.1126/science.abq1841 (2022).