IN DEPTH

A family of cynomolgus macaques in the wild in Cambodia.

PHOTO: GERMAN VOGEL/ALAMY

ANIMAL RESEARCH

Indictment of monkey importers could disrupt U.S. research

Alleged Cambodian smuggling ring poses dangers to wild macaques and the drug studies they're used in

By **David Grimm**

The indictment of several members of an alleged international monkey smuggling ring is sending ripples through the U.S. biomedical community. The U.S. Department of Justice (DOJ) has charged two Cambodian wildlife officials and several members of a Hong Kong–based primate supply company with illegally exporting hundreds—and potentially more than 2000—cynomolgus macaques, an endangered species, to the United States for research. The animals were reportedly captured from the wild in Cambodia and falsely labeled as captive-bred.

The indictment, which carries multiple felony charges, will likely exacerbate the shortage of these monkeys, used in everything from drug safety testing to vaccine research, says Dave O'Connor, a virologist at the University of Wisconsin, Madison, who uses cynomolgus macaques to study infectious disease. Still, he says, the main priority should be stopping this illegal trade, for the sake of research and the animals themselves. "These sorts of unscrupulous actors give a black eye to an already heavily scrutinized industry."

Animal advocacy groups are pushing to ban further monkey imports until more is known about their provenance. And some experts in the biomedical community are suggesting moving the breeding of this species of macaque to the United States and collecting more genetic and pedigree information on the monkeys that come from overseas. They also say labs should find ways to use fewer of these animals.

It's unclear how many of the animals in question have been used in research, but one of two companies that received them is the largest private supplier of monkeys to U.S. research labs, *Science* has learned. The company, Inotiv, tells *Science* that "while we do not yet know if these allegations will be proven true, Inotiv strongly condemns any and all unauthorized trading/importation of endangered species. … To confirm our screening processes are (and were) solid, we have plans in place to conduct the necessary audits to ensure excellence and provide transparency."

Cynomolgus macaques, also known as long-tailed macaques or cynos, are—by far—the monkey species most imported to the United States. Nearly 30,000 entered the country last year, according to data from the U.S. Centers for Disease Control and Prevention (CDC), which regulates the import of nonhuman primates. Most cynos are used by pharmaceutical and biotechnology companies. (Rhesus macaques, another species common in U.S. biomedical research, are mostly used by the academic community, which largely obtains them from national primate research centers.) Cynos are also the main monkey species imported to Europe for research. They are typically bred in large facilities in Asia.

China used to be the main supplier of cynos—exporting approximately 30,000 in 2018—but the country has shut off its supply, which experts have attributed to the trade war with the United States and China's desire to beef up its own biomedical industry. Several countries, mostly in Southeast Asia, stepped in to fill the gap. Cambodia now exports the largest share of cynos—more than 29,000 in 2020, the vast majority of which were shipped to the United States.

Though the actual number of cynos in the wild is unclear, the International Union for Conservation of Nature downgraded the status of the monkeys from vulnerable to endangered this year, citing growing demand from the research industry as a factor that could incentivize illegal trade.

The need for cynos has indeed grown, especially during the pandemic. The species was

one of the main animal models employed to test COVID-19 vaccines, and researchers are increasingly using the monkeys to study Alzheimer's, Parkinson's, and other diseases. "There is a sky-high demand for these animals," O'Connor says.

That may be what's fueling the alleged illegal trade in Cambodia. According to the DOJ indictment, two high-ranking employees of Vanny Resources Holdings, a Hong Kong–based company that breeds monkeys for research, paid millions to black market suppliers and Cambodian wildlife officials to capture thousands of cynos from national parks and other protected areas of Cambodia, and to fake their paperwork to indicate the animals had been bred in captivity.

Nearly 1500 of these "laundered" cynos arrived in the United States from 2018 to 2020, according to the indictment, with potentially hundreds more in 2021. They appear to have ended up at facilities in Florida and Texas. The companies running the facilities are not named in the indictment, but in a filing with the U.S. Securities and Exchange Commission, Inotiv disclosed that its principal supplier of nonhuman primates was the target of the DOJ probe, indicating that the company gets most of its monkeys from Vanny.

Last year, Inotiv purchased the major research animal supplier Envigo (under fire recently for a series of animal welfare violations at one of its beagle breeding facilities), making it the world's largest supplier of nonhuman primates for research. The company currently houses more than 9000 monkeys—the vast majority cynos—which it sells to private and academic labs.

Cindy Buckmaster, spokesperson for Americans for Medical Progress, which advocates for the use of animals in scientific studies, says there's not much that companies like Inotiv—or the labs they sell to—can do to check the provenance of the animals they receive. "We have to take the documentation at face value," she says.

Still, she calls the alleged illegal import of cynos "horrible" for the animals, and a violation of the trust both the scientific community and the public put in animal research. She says wild-caught monkeys carry viruses that could infect other animals they're housed with, or humans. And they're prone to stress just from being around people for the first time, which could result in "very different data."

The animal rights group People for the Ethical Treatment of Animals has asked CDC to suspend all nonhuman primate exports from Cambodia. It also asked the U.S. National Institutes of Health "to determine the precise origin of every [cyno] imported from Cambodia since 2017 and currently in publicly funded laboratories."

In a statement, Cambodia's ministry of agriculture said it was "surprised and saddened" by the indictment, and is committed to upholding all laws governing the international trade of animals. It also denied that any of its exported monkeys had been captured from the wild.

"If this is the reaction from the supply side, then we think there needs to be much stricter controls on the demand side," says Eric Kleiman, a researcher at the Animal Welfare Institute, an animal advocacy group that has closely followed the issue. "If monkeys are to be used in research in the U.S., there is a responsibility to ensure they are well cared-for … and sourced responsibly."

> **"There is a sky-high demand for these animals."**
> **Dave O'Connor**, University of Wisconsin, Madison

Sarah Kite, co-founder of Action for Primates, a U.K.-based advocacy organization, agrees. She notes the European Union is poised to pass a law that will ban the import of all wild-caught animals and their offspring. "That's the only way to ensure they're not getting wild-caught animals," she says. "The research community needs to be held accountable for what's happening to this species."

O'Connor suggests one solution: ensuring that all captive-bred animals have extensive pedigree records, which could be kept in a global registry. He also suggests genotyping every monkey used in research studies to better trace their origins.

Major pharmaceutical and biotech companies contacted by *Science* either declined to comment on the issue or did not respond.

"I think [the indictment] is going to constrict the pipeline even more," says a U.S. consultant on industry and academic monkey research who has worked in the field for decades but asked not to be named because of concerns of damaging relationships with his clients. The U.S. biomedical community should invest in breeding these animals domestically, he says. "We need to migrate away from shipping an animal from halfway around the world, where we can't control where it came from."

But the community also needs to work to reduce the number of monkeys it uses, he says. That could be accomplished by designing studies to require fewer animals, and working with regulators to require fewer animals for research such as drug safety studies. "That's easier, faster, and less expensive than building up a bigger pipeline." ■

BIOLOGY

CRISPR is so popular even viruses may use it

Thousands of phages appear to have stolen the gene-cutting mechanism

By **Mitch Leslie**

The gene-editing tool CRISPR started out as a bacterial defense against invading viruses. But it turns out the intended targets have stolen CRISPR for their own arsenals. A new study reveals that thousands of the bacteria-attacking viruses known as bacteriophages (phages, for short) contain the CRISPR system's genetic sequences, suggesting they may use them against rival phages. The finding could boost CRISPR's laboratory usefulness.

The discovery "opens doors for possible new applications of CRISPR systems," says genomicist Mazhar Adli of Northwestern University's Feinberg School of Medicine, who wasn't connected to the research.

Like other viruses, phages cannot reproduce on their own. Instead, they hijack bacteria's molecular machinery, often killing their hosts in the process. The CRISPR system enables bacteria to fight back. It includes repetitive stretches of DNA that match sequences of previously encountered phages. If these same phages attack a bacterium again, it uses this repetitive DNA to encode strands of RNA that can steer a partner enzyme, which acts like a pair of genetic scissors, to cut the phage's genome at specific places.

For about the past decade, scientists have been working to turn this microbial immune defense into a gene-editing technique for myriad uses, including improving crop defenses, detecting pathogens, and fighting diseases such as cancer.

Characteristic DNA that encodes components of the CRISPR system had previously turned up in a handful of phages. At first, scientists regarded these finds as mere "curiosities," says structural biologist Jennifer Doudna of the University of California (UC), Berkeley, who shared the 2020 Nobel Prize in Chemistry for showing how to tailor the CRISPR system to target particular se-