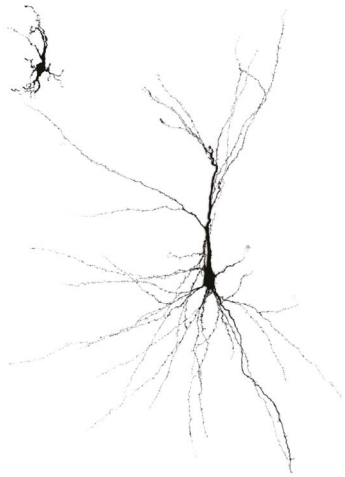

Human neurons created from stem cells and transplanted into a rat brain (right) grow more fully than those cultivated in a dish (left).

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become fully integrated into the rats' brains. But when they examined the animals' brains at the end of that time, they saw that the integration had been so successful that it was almost like adding "another transistor to a circuit", Pasca said at a 10 October press conference.

Paola Arlotta, a molecular biologist at Harvard University in Cambridge, Massachusetts, is excited about the results. "It's an important step in allowing organoids to tell us more complex properties of the brain," she says, although she thinks that the transplantation procedure is probably still too expensive and complex to become a standard research tool. The next step, Arlotta adds, will be to work out how individual human neurons — not just fully developed organoids — are integrated into the rat brain.

Behavioural trigger

In their report, published in *Nature*, the researchers describe how they genetically engineered the neurons in the organoids to fire when stimulated with light from a fibre-optic cable embedded in the rats' brains (O. Revah *et al. Nature* **610**, 319–326; 2022). The team trained the rats to lick a spout to receive water while the light was switched on. Afterwards, when the researchers shone the light on the hybrid brains, the rats were prompted to lick the spout, meaning that the human cells had become integrated well enough to help drive the animals' behaviour. Furthermore, when the researchers prodded the rats' whiskers, the human cells in the sensory cortex fired in response, meaning the cells could pick up sensory information.

To demonstrate the promise of their work for studying brain disorders, Pasca and his colleagues also created brain organoids from the stem cells of three people with a genetic condition called Timothy syndrome, which can cause symptoms similar to some seen in autism. The tiny structures looked the same as any other brain organoids grown in a dish, but when the researchers transplanted them into rats, they did not grow as large as others and their neurons didn't fire in the same way.

Rusty Gage, a neuroscientist at the Salk Institute for Biological Studies in La Jolla, California, is glad to see these results. In 2018, he and a team of researchers reported that transplanted human brain organoids could be integrated into the brains of adult mice (A. A. Mansour *et al. Nature Biotechnol.* **36**, 432–441; 2018). Mice don't live as long as rats, and Pasca and his colleagues hoped that because newborn rat pups' brains are more plastic than those of adult animals, they would be better able to receive the new cells.

"We've got challenges out there for us," Gage says. "But I do believe the transplantation procedure will be a valuable tool."

Some of the challenges are ethical. People are concerned that creating rodent–human hybrids could harm the animals, or create animals with human-like brains. Last year, a panel organized by the US National Academies of Sciences, Engineering, and Medicine released a report concluding that human brain organoids are still too primitive to become conscious, attain human-like intelligence or acquire other abilities that might require legal regulation. Pasca says that his team's organoid transplants didn't cause problems such as seizures or memory deficits in the rats, and didn't seem to change the animals' behaviour significantly.

But Arlotta, a member of the National Academies panel, says that problems could arise as science advances. "We can't just discuss it once and let it be," she says. She adds that concerns about human organoids need to be weighed against the needs of people with neurological and psychiatric disorders. Brain organoids and human–animal hybrid brains could reveal the mechanisms underlying these illnesses, and allow researchers to test therapies. "I think we have a responsibility as a society to do everything we can," Arlotta says.

LABS THAT HANDLE DANGEROUS PATHOGENS SURGE IN WAKE OF COVID

India, Singapore and the Philippines are among those building new laboratories at biosafety level 3 or above.

By Smriti Mallapaty

In the wake of the COVID-19 pandemic, plans are afoot to build more than 40 high-level biosafety laboratories around the world, in places including India, the Philippines and Singapore. Investments in biosafety labs often follow epidemics, but many researchers are concerned about the growing number of facilities that will handle some of the world's most dangerous pathogens.

Some scientists worry about the huge cost of maintaining biosafety-level-3 (BSL-3) and BSL-4 facilities, whereas others fear the risks posed by these labs, such as the possibility of making pathogens more dangerous or of microorganisms escaping.

But researchers in the countries that plan to build these laboratories say the facilities are needed. The lack of high-security labs in some regions became particularly apparent during the pandemic, because work on the live virus that causes COVID-19, SARS-CoV-2, must be done at a BSL-3 or BSL-4 facility.

"The pandemic exposed the weakness of health systems worldwide in recognizing and responding to emerging threats in public health," said Bharati Pawar, India's minister for health and family welfare, at a ceremony to mark the start of construction for one of the nation's new BSL-3 labs in Bengaluru last month. "In this light, the critical element of any preparedness programme is lab preparedness," she said.

Around the world

India's plans are among the most ambitious. The country is in the process of building five BSL-3 facilities and is planning at least another nine. Four institutions have also said they will construct BSL-4 labs with the highest level of containment. India currently has only one such facility that is operational. And the government has committed to building four new national institutes of virology, two of which will eventually handle BSL-4 pathogens.

BSL-3 laboratories are designed so that scientists can safely work with potentially lethal and inhalable pathogens in a contained environment. Experiments are done in sealed workspaces in which the air is filtered and not recirculated, and the entrance to the facility is typically secured by self-closing doors. BSL-4 facilities, in which researchers work with fatal

AKOS STILLER/BLOOMBERG VIA GETTY

The lack of high-security labs in some regions became apparent during the pandemic.

pathogens that can spread through aerosols, and for which vaccines or treatments are lacking or limited, require extra security measures. These labs are isolated from other sections of a building and have a dedicated air supply, and researchers change their clothes and shower before entering and leaving the premises.

The pandemic has raised public awareness of emerging diseases and the need for labs, creating a favourable environment for these investments, says Pragya Yadav, a virologist who heads the BSL-4 facility at the Indian National Institute of Virology in Pune. A country of India's size needs more high-containment facilities, she says.

Elsewhere in Asia, Kazakhstan, Singapore and the Philippines have announced plans to build their first BSL-4 facilities. Beyond the region, the United States has committed to adding another BSL-4 lab to its existing group of about a dozen maximum-containment facilities. And Russia announced last year that it will build 15 BSL-4 labs, although details are scant.

Since the COVID-19 pandemic began, plans to build 27 BSL-4 labs have been announced worldwide, say two researchers who have tracked the number and distribution of BSL-4 facilities globally, Gregory Koblenz, a biodefence researcher at George Mason University in Arlington, Virginia, and Filippa Lentzos, a biosecurity researcher at King's College London. "These will likely take several years to design, build and commission," says Lentzos.

Endemic diseases

Researchers hope that the new biosafety labs will support more research into drugs and vaccines, particularly for infectious diseases that affect these countries, including tuberculosis, dengue virus and Kyasanur forest disease, a viral haemorrhagic fever spread by ticks. "It is important to have the lab capacity to study endemic diseases," says Kathrin Summermatter, who operates a BSL-3 lab at the University of Bern.

The new labs will improve working conditions for researchers, too. Before the pandemic, Raju Mukherjee, a biochemist at the Indian Institute of Science Education and Research in Tirupati, and his students used to travel for five hours by bus to the nearest BSL-3 lab, in Bengaluru, several times a year. He would spend about a month there at a time — adding up to four months a year away from his family — to study drug resistance in *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis, and develop treatments. Mukherjee is one of five researchers in India to receive government funding to build a new BSL-3 facility, and construction in Tirupati should start by March 2023.

> **"The pandemic exposed the weakness of health systems worldwide."**

Super expensive

But some researchers question the need for so many extra BSL-3 and BSL-4 labs and note the hefty cost of maintaining them.

Illich Mombo, a virologist at the International Centre for Medical Research of Franceville in Gabon, says that roughly 10% of his lab's budget goes on experiments, whereas around 90% is spent on checking, maintaining and repairing the facility. When instruments break, they cost a lot to fix, and there are no trained technicians in the region. Researchers are sometimes sent to work elsewhere, says Mombo.

Thomas Ksiazek, a virologist who heads the high-containment operations at Galveston National Laboratory in Texas, a BSL-4 facility, says that his team's lab receives close to US$12 million a year from the National Institute of Allergy and Infectious Diseases just for maintenance and operations, some $2 million of which is spent on 24-hour security. And about $2 million is required to power the ventilation, heating and air conditioning, as well as to operate the BSL-3 portion of the lab.

Rohani Navarro, a veterinarian at the Philippines National Institute of Molecular Biology and Biotechnology in Manila, says that she and her colleagues are constantly writing grant applications just to maintain their BSL-3 operations. Annual certification, which involves a thorough safety review, costs some $40,000, she says. "High-containment facilities can become like a white elephant that isn't used."

Some researchers also worry that having more of these labs will increase the risks associated with them, including the chances of workers being infected. Scientists say labs often struggle to find well-trained staff to run high-containment facilities. Kim Sales, who researches health policy and health systems at the non-profit organization Alliance for Improving Health Outcomes in Manila, says a survey of lab practices in the Philippines found that biosafety officers had only a weak understanding of biosafety. The country plans to build a BSL-4 lab.

High-risk experiments

More labs could also lead to more high-risk research such as gain-of-function studies, in which pathogens are sometimes modified, potentially making them more dangerous to people, says Lentzos.

A large body of evidence suggests that SARS-CoV-2 jumped to humans from wild animals, probably at a live-animal market in Wuhan, China, but some scientists say they cannot exclude the possibility that the pandemic started with an enhanced virus that escaped from a lab, raising broader concerns about the risks of gain-of-function research. Wuhan is also home to the Wuhan Institute of Virology, a BSL-4 lab.

However, some researchers say that the development of new biosafety labs could lead to better safety practices. "These laboratories help researchers work more safely than they could without them," says Gigi Gronvall, a biosecurity scientist at Johns Hopkins University in Baltimore, Maryland. "Assuming that people are trained well and equipment is updated, I am not concerned by the array of BSL-3 laboratories."