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Protective suits are required for work in the highest-rated biosafety-level-4 labs.

INFECTIOUS DISEASE

Japan imports deadly viruses

Ebola and other pathogens arrive ahead of the Olympics, but critics say the move is unnecessary.

BY MARK ZASTROW

Japan is preparing for tens of thousands of international tourists to descend on Tokyo for the Olympic Games next year — and that includes being ready for unwanted biological visitors.

Last month, Japan imported Ebola and four other dangerous viruses in preparation for a possible outbreak at the event. The Japanese health ministry says that researchers will use the samples, which include Marburg virus, Lassa virus and the viruses that cause South American haemorrhagic fever and Crimean–Congo haemorrhagic fever, to validate tests under development.

The viruses' arrival represents the first time that pathogens rated biosafety-level-4 (BSL-4) — the most dangerous rating — have been allowed to enter the Japanese National Institute of Infectious Diseases (NIID), the only facility in the country operating at that level.

Japan's medical-science community welcomes the move. Although infectious-disease scientists say that the risk of an outbreak during the Olympics isn't much higher than at any other time, access to the live viruses will boost the country's capacity to handle infectious diseases in general — and to prepare for a bioterror attack.

Although the NIID's laboratory in Musashimurayama, Tokyo, was built to BSL-4 specifications in 1981, it operated as a BSL-3 lab for decades because of opposition from residents. In 2015, the health ministry and Musashimurayama's mayor agreed that it could operate as a BSL-4 lab, but the decision to import the five viruses was finalized only in July.

> ***"An Ebola virus infection during the Olympics could have devastating consequences."***

Japan's ability to study the most dangerous pathogens has lagged behind that of other advanced nations — both the United States and Europe have more than a dozen BSL-4 labs in operation or under construction, and China is building a network of at least five BSL-4 labs, with one already operational in Wuhan.

"This is a landmark time, a landmark event" for NIID, says Masayuki Saijo, director of the NIID department that is responsible for haemorrhagic-fever viruses.

But not everyone is pleased about the imported viruses. Some local residents have told Japanese media that scientists and the government are using the Olympics as a pretext to import the pathogens. And Richard Ebright, a molecular biologist and biosecurity specialist at Rutgers University in Piscataway, New Jersey, says that BSL-4 labs can be prepared to handle outbreaks of hazardous agents without the need to bring them into the country ahead of time. Storing dangerous viruses, even in a highly secure lab, increases the risk of an accidental or deliberate release, he says.

WHAT'S THE RISK?

The NIID will use the live samples to validate tests it has developed to assess whether a person with one of the viruses is still infectious, says Saijo. The tests measure whether the person is generating antibodies that are capable of neutralizing the virus in question, which would suggest that they are recovering, and not infectious, he says. If there is a person with one of these viruses at the games, such a test could provide valuable information for assessing whether they can be discharged from hospital, he says.

The development of these tests will boost Japan's preparedness for such an event or a bioterror attack, says Saijo. Other Olympic host nations didn't have to specially import these viruses ahead of the games because they already had the pathogens in BSL-4 labs. The NIID will also continue developing more sensitive and accurate tests after the games. Saijo says that he understands opposition from local residents, but that the live viruses give Japanese researchers an important advantage in preparing against infectious diseases.

Elke Mühlberger, a microbiologist at Boston University in Massachusetts, thinks that a major outbreak of Ebola at the Olympics is unlikely because the infection is not transmitted through the air. But she says that Japan's plan to assess the NIID's tests with live viruses before the games makes sense, especially given the ongoing Ebola outbreak in the Democratic Republic of the Congo. "A report of an Ebola virus infection during the Olympics could have devastating consequences if the emergency responses were not professional," she says.

But Mühlberger is sceptical about the usefulness of neutralizing-antibody tests to evaluate whether a patient can be released. She says the easiest way to determine whether someone is virus-free is to look at the amount of viral RNA in their body fluids. "I don't believe anybody would release a patient just because they have developed neutralizing antibodies," she says.

ANIMAL RESEARCH

Now that the NIID is allowed to handle BSL-4 pathogens, researchers there will also be able to study other dangerous viruses that might emerge in the region, says Mühlberger. The latest genome-sequencing technologies are revealing that Ebola-like viruses are more

common than previously thought, she says. Three in the same family were discovered in animals in the past year: the Mengla virus in Chinese bats and two Ebola-like viruses found in fish in the East China Sea. "It is amazing how many animals are infected with viruses which are very closely related to very, very dangerous pathogens," she says.

It remains unknown whether these viruses can infect or harm humans, says Mühlberger. But their diversity is "pretty scary", she says. "These viruses are everywhere."

Virologist Ayato Takada at Hokkaido University in Sapporo, Japan, is also excited about being able to study BSL-4 pathogens in animals in Japan. Until now, researchers had to apply for access to BSL-4 labs overseas, which are in high demand. ■

GENOME EDITING

Errors in CRISPR-baby study

Geneticists retract paper that suggested first gene-edited babies might die early.

BY EWEN CALLAWAY

A study that raised questions over the future health of the world's first gene-edited babies has been retracted because of key errors that undermined its conclusion.

The research, published in June in *Nature Medicine*[1], had suggested that people with two copies of a natural genetic mutation that confers HIV resistance are at an increased risk of dying earlier than other people. It was conducted in the wake of controversial experiments by the Chinese scientist He Jiankui, who had attempted to recreate the effects of this mutation in the gene *CCR5* by using the CRISPR gene-editing technique in human embryos. The twin girls born last year as a result of the work did not end up carrying this exact mutation, but the research attracted attention because of its potential relevance to such experiments.

However, studies[2–4] that looked anew at the *Nature Medicine* research find no evidence that people with the mutation die early. The erroneous conclusion about *CCR5* was caused by errors in how the mutation was identified in a population-health database.

"I feel I have a responsibility to put the record straight," says Rasmus Nielsen, a population geneticist at the University of California, Berkeley, who led the study, which the authors retracted on 8 October. Nielsen also co-authored one of the papers rebutting its findings.

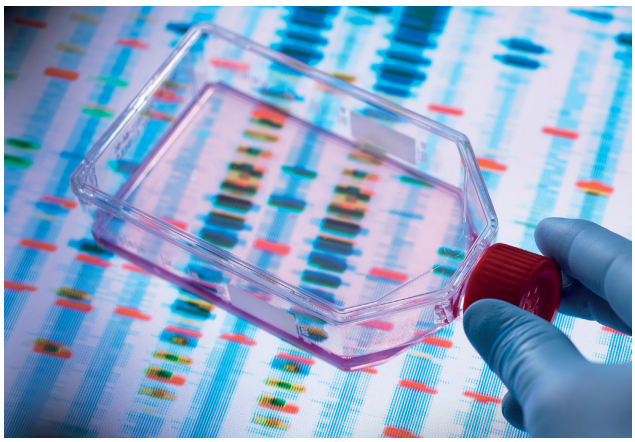
Some researchers stress that because the twins did not receive exactly the same mutation that occurs naturally, the original research and its retraction would not necessarily offer insights into their health anyway. But the episode raises questions about how best to assess the safety of future attempts to edit genes in human embryos.

He Jiankui shocked the scientific world when he announced, in November 2018, that his team had used CRISPR to disable the *CCR5* gene in two babies born that month. He, who was at the time a biophysicist at the Southern University of China in Shenzhen, said he targeted *CCR5* because people with a 32-DNA-letter deletion known as delta-32 in the gene are resistant to HIV but seem not to experience significant related health problems.

He has not published data supporting his work, but his announcement — presented at a scientific meeting — indicated that, for one twin, both copies of *CCR5* were altered, whereas the other twin carried edits in just one of her two copies. None of the changes exactly matched the delta-32 variation.

RESULTS NOT REPLICATED

Research has hinted that the delta-32 mutation, which is relatively common in people of European ancestry, might carry downsides — one small study[5] found that carriers were more likely than other people to die from influenza. To tackle the question in larger data sets, Nielsen and his Berkeley colleague Xinzhu Wei looked at the UK Biobank database, which contains genome and health data from 500,000 people.



GETTY

A 32-letter deletion in the gene *CCR5* confers resistance to HIV.

Their paper[1] reported that people with two copies of the delta-32 mutation were slightly more likely to die by the age of 76 than were those with one or no copies. They also found that the database harboured fewer people with two copies of the mutation than evolutionary theory predicted it should — a sign that individuals with two copies were dying earlier, on average, than the population at large, Wei and Nielsen argued. Questions over the conclusion emerged as soon as the paper was published. Sean Harrison, an epidemiologist at the University of Bristol, UK, attempted to replicate the findings that night. He did not have UK Biobank data on the gene variant that Wei and Nielsen used to identify carriers of delta-32, so he analysed genetic variants near it on the genome that should have given the same result (adjacent parts of the genome tend to be inherited together, allowing scientists to infer the presence or absence of a DNA sequence by analysing neighbouring variants). When they didn't, he described his findings in tweets and a blogpost.

The discrepancy piqued the interest of David Reich, a population geneticist at Harvard Medical School in Boston, Massachusetts, whose lab is studying *CCR5*. Working with Nielsen, his team discovered[2] that Nielsen and Wei's method had caused them to undercount the number of people in the UK Biobank with two copies of the delta-32 mutation, because the probe that measured the variant they were tracking did not always identify its target sequence. This — and not the supposed harmful effects of the mutation — explained the apparent absence of carriers from the UK Biobank database, says Nielsen.

Researchers emphasize that the unravelling of Wei and Nielsen's results does not mean it is a sound idea to target *CCR5* for gene editing. "It's very reasonable to expect that it might have a valuable function that we just don't know how to measure. It seems very unwise to edit it out," says Reich. ■

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