Select-agent status could slow development of anti-SARS therapies

Saudi Arabian doctors scrambled last month to treat a third person who had fallen ill from a new strain of coronavirus that emerged earlier this year in the Middle East. The man survived with the help of supportive care from his physicians, but one of the other two patients who fell victim to the mysterious virus—a pathogen that resembles the coronavirus responsible for severe acute respiratory syndrome (SARS)—was not so fortunate.

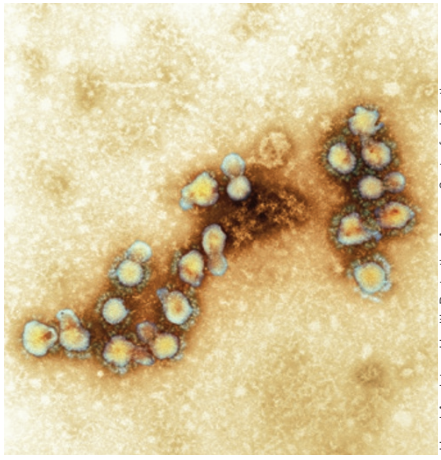
These recent cases drive home an all too stark reality: a decade on from the SARS outbreak that killed close to 800 people worldwide, scientists still have no proven effective vaccines or drugs that can stop the spread of SARS or SARS-like viruses, let alone mitigate their symptoms. Now, to make matters worse in the face of an emerging threat, a new reclassification of the bioterrorism risk posed by SARS may hamper efforts at novel medical strategies.

"Many labs are going to destroy their [SARS] virus instead of continue to work on it because the burden of regulation is quite high," says Rachel Roper, a microbiologist at East Carolina University Brody School of Medicine in Greenville, North Carolina.

Roper has worked with SARS since the global pandemic ten years ago. She led the team that sequenced the virus's genome (*Science* **300**, 1399–1404, 2003), and, more recently, she and her colleagues created two experimental vaccines: a whole, killed SARS virus shot and an adenovirus-based vector carrying key SARS structural proteins. Both products elicited some degree of immune response and partially prevented viral replication in mice (*J. Gen. Virol.* **87**, 641–650, 2006) and ferrets (*J. Gen. Virol.* **89**, 2136–2146, 2008). However, the protection was incomplete.

She had been working to improve both strategies and was already struggling with how she would advance a lead candidate into the clinic in the absence of any natural human SARS challenge against which to test it. Then, on 5 October, the US government announced plans to add SARS to its list of select agents. This reclassification, which went into effect on 4 December, requires labs to now obtain additional licenses and adhere to stricter levels of biosafety and biosecurity to conduct any experiments with the virus. Although Roper recognizes that the move was made in the interest of protecting public health, for her this was the last straw. She says she no longer plans to work on SARS, opting to destroy her live virus instead of seeking certification for her lab.

"The reason we know so much about SARS now is because so many labs could start working on it" after the 2002–2003 outbreak, says Matthew Frieman, a microbiologist at the University of Maryland School of Medicine in Baltimore who is seeking select-agent certification to advance two compounds he discovered last year that inhibit SARS replication (*PLoS One* **6**, e28479, 2011). Following the government's reclassification, however, "the next time something like this happens, even fewer people will be ready to jump to start working on it."



Hazel Appleton, Health Protection Agency Centre for Infections

Status update: SARS becomes a select agent.

To work on a select agent in the US, a lab must submit safety and security response plans for approval to the US Centers for Disease Control and Prevention (CDC). The country's Federal Bureau of Investigation must also conduct a background check on anyone who has access to the virus.

According to Rob Weyant, director of the CDC's Division of Select Agents and Toxins in Atlanta, the agency has been in touch with 36 labs that work with SARS in the US, and all but four are registered to work with select agents. Fourteen more labs still need to be contacted, and the CDC has pledged to help any researchers that need assistance fulfilling the new requirements. "We will assign one of our inspectors to each of these entities to provide hand-holding and individual attention," Weyant says.

A shot of reality

Microbiologist Ralph Baric leads one such lab at the University of North Carolina–Chapel Hill School of Medicine that the CDC has already visited to start the recertification process. He is currently revamping his infrastructure for the tighter security controls, during which time much of his microarray and proteomics work has been halted. He expects the renovations to cost in excess of $400,000, and, even after his lab is up to code, there could still be problems ahead for his research program.

On page 1815 of this issue of *Nature Medicine*, Baric and his colleagues describe their latest vaccine strategy, in which they knocked out a key proofreading enzyme in the SARS genome to create a crippled virus capable of triggering an immune response in mice but one that does not cause disease itself. To advance the product further, Baric had hoped to test the experimental vaccine on larger animals, such as hamsters, ferrets or primates. Yet, the development of the vaccine requires collaboration with other labs, including the one at Vanderbilt University in Nashville, Tennessee, that analyzed SARS RNA for the latest paper. For that collaboration to continue, these labs will also have to upgrade their facilities to achieve biosafety level 3 (BSL3) status.

Not all SARS research will be necessarily affected by the government's reclassification, though. At Novavax, for example, researchers are forging ahead with an experimental vaccine that combines two structural proteins—one from SARS, the other from the influenza virus—but does not involve a live virus. The Maryland-based company does not have a BSL3 lab, nor do they need one. Last year, for the mouse experiments demonstrating that the vaccine offers protection from an otherwise lethal challenge of SARS (*Vaccine* **29,** 6606–6613, 2011), the Novavax scientists simply teamed up with virologist Dale Barnard at Utah State University in Logan, which has BSL3 facilities.

Wayne Marasco, an immunochemist at the Dana-Farber Cancer Institute in Boston, has similarly gotten along just fine studying SARS from the comfort of his low-security office. He's been working on developing neutralizing antibodies that can fight SARS infections, but his work to date has mostly involved computer modeling to find the best designs.

Even so, Marasco is wary of what the new regulations will do for SARS research given the nature of the virus. "Very basic research needs to continue to work on human coronaviruses, because they may continue to evolve," he says. The recent cases out of the Middle East certainly prove this point.

Susan Matthews