SPECIAL REPORT

The 1918 flu virus is resurrected

The recreation of one of the deadliest diseases known could help us to prevent another pandemic. Or it might trigger one, say critics. Andreas von Bubnoff investigates whether the benefits outweigh the risks.

It is thought to have killed 50 million people, and yet scientists have brought it back to life. In this issue of *Nature*, scientists publish an analysis of the full genome sequence of the 1918 human influenza virus. And in this week's *Science*, researchers describe how they used that sequence to recreate the virus and study its effects in mice.

Some scientists have already hailed the work as giving unprecedented insight into the virus. Working out how it arose and why it was so deadly could help experts to spot the next pandemic strain and to design appropriate drugs and vaccines in time, they say.

But others have raised concerns that the dangers of resurrecting the virus are just too great. One biosecurity expert told *Nature* that the risk that the recreated strain might escape is so high, it is almost a certainty. And the publication of the full genome sequence gives any rogue nation or bioterrorist group all the information they need to make their own version of the virus.

Jeffery Taubenberger of the Armed Forces Institute of Pathology in Rockville, Maryland, is the lead author of the sequencing study. He says the work was necessary and the risks were low. The paper on page 889 gives details of the final three genes; the sequences of the rest have already been published.

The full sequence is strong evidence that the 1918 flu virus is derived wholly from an ancestor that originally infected birds. In contrast, the viruses that caused the flu pandemics of 1957 and 1968 arose when human and avian flu viruses infected the same person at the same time, allowing their genes to mix.

All eight of the genome segments from the 1918 virus differ in important ways from other human flu sequences, suggesting that none of the genome came from a strain that had previously infected people. "It is the most bird-like of all mammalian flu viruses," says Taubenberger.

Pinpointing exactly which genetic mutations allowed the virus to jump to humans will enable scientists to recognize other bird viruses that could trigger a pandemic. Taubenberger's team has already identified 25 changes in the protein sequences of the 1918 strain that have been present in subsequent human flu viruses. These mutations are likely to be particularly important, he says. One such change, in the polymerase gene *PB2*, was found in the virus isolated from the only human fatality in a 2003 outbreak of H7N7 bird flu in the Netherlands.

In the paper in *Science* (T. M. Tumpey *et al.* 310, 77–80; 2005), Terrence Tumpey at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and his co-workers have used Taubenberger's sequence to recreate the complete 1918 virus (see graphic).

When they used the strain to infect mice they found it was extremely virulent, and after 4 days had generated 39,000 times more virus particles in the animals' lungs than a modern flu strain (see 'How virulent is 1918 flu?'). "I didn't expect it to be as lethal as it was," says Tumpey.

The researchers compared the complete 1918 virus with strains in which some genes had been replaced by those of contemporary strains. They found that replacing the haemagglutinin gene, which helps the virus to enter cells, made it unable to kill mice. Replacing all three of the polymerase genes, which allow the virus to replicate, significantly reduced its virulence. The haemagglutinin gene is essential, says Tumpey. "But no single change or gene is the answer," adds Taubenberger. "It's a combination effect."

> "They have constructed a virus that is perhaps the most effective bioweapon known."

Future research will involve testing reconstructed viruses with and without certain mutations, to see which are the most important for virulence. Information from this type of study will hopefully be of use in vaccine and drug design, but so far the work is more about obtaining a basic understanding of the virus than any immediate health benefits.

The studies have been praised as groundbreaking. "It's a landmark," says Eddie Holmes, a virologist at Pennsylvania State University in University Park. "Not only is this the first time this has been done for any ancient pathogen, but it deals with the agent of the most important disease pandemic in human history."

The team got permission to do the work

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

'Fresh air' cures were used to fight flu in 1918, but reconstructing the virus may lead to more effective treatments.

BETTMANN/CORBIS

HOW VIRULENT IS 1918 FLU?

50 times as many virus particles are released from human lung cells a day after infection with the 1918 virus as are released after exposure to a contemporary strain called the Texas virus.

13% of body weight is lost by mice 2 days after infection with 1918 flu; weight loss is only transient in mice infected with the Texas strain.

39,000 times more virus particles are found in mouse lung tissue 4 days after infection with 1918 flu than are found with the Texas virus.

All mice died within 6 days of infection with 1918 flu; none died from the Texas strain.

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FISH PHEROMONES MADE IN THE LAB
Lampreys could be lured away from Great Lakes by artificial chemicals.
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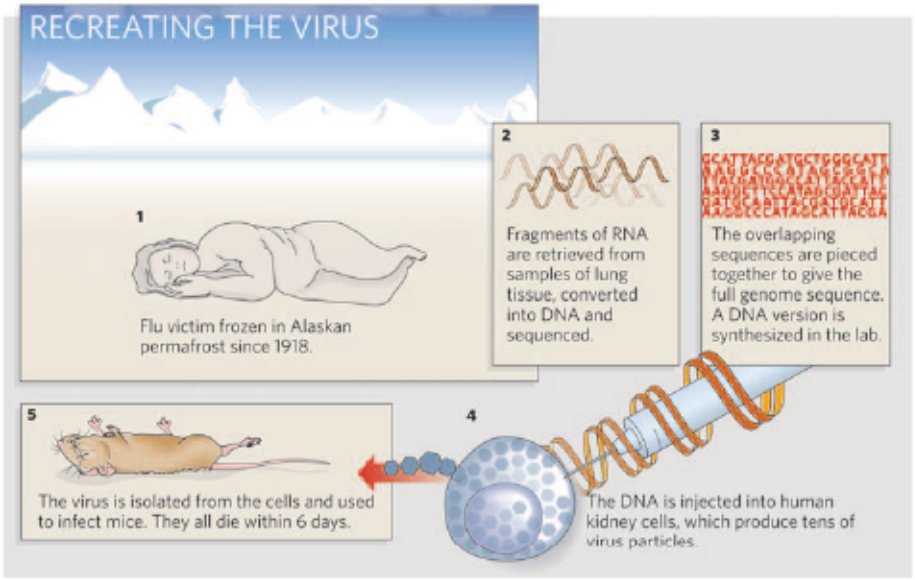

from CDC head Julie Gerberding and Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, based in Bethesda, Maryland.

But the studies have sparked fears among other researchers. "There most definitely is reason for concern," says Richard Ebright, a bacteriologist at Rutgers University in Piscataway, New Jersey, who serves on biosecurity panels. "Tumpey *et al.* have constructed, and provided procedures for others to construct, a virus that represents perhaps the most effective bioweapons agent now known."

"This would be extremely dangerous should it escape, and there is a long history of things escaping," says Barbara Hatch Rosenberg, a molecular biologist and member of the Federation of American Scientists' Working Group on Biological Weapons. "What advantage is so much greater than that risk?"

Ebright agrees that there is a significant risk, "verging on inevitability", of accidental release of the virus into the human population, or of theft by a "disgruntled, disturbed or extremist laboratory employee". And there is the danger that a hostile nation might reconstruct its own version of the virus, he says, pointing out that any of these scenarios could result in a large number of deaths.

Ebright also believes that using an enhanced biosafety level-3 lab for the work was inadequate. If the researchers were going to do the work at all, they should have used level 4, the strictest biosafety condition, he says. This requires experimenters to wear full body suits. In 2003, he points out, a SARS virus escaped accidentally from a level-3 lab in Singapore, and in 2004 two further escapes occurred from such labs in Beijing.

Tumpey counters that enhanced level 3, which requires upper body suits and respirators, is safe enough. Disgruntled employees aren't a concern either, he says, because he is the only one who works with the virus. The few researchers with access to the lab undergo extensive background checks, and retina and fingerprint scans are used to prevent any unauthorized entry to the lab.

He adds that even if the virus did escape, it wouldn't have the same consequences as the 1918 pandemic. Most people now have some immunity to the 1918 virus because subsequent human flu viruses are in part derived from it. And, in mice, regular flu vaccines and drugs are at least partly effective against an infection with reconstructed viruses that contain some of the genes from 1918 flu.

Publish and be damned?

The other potential threat comes from the availability of the full genome sequence, which has been put on the GenBank database — a condition of the paper's publication. Anyone can order DNA to be made to a certain sequence, points out Jonathan Tucker, a policy analyst at the Center for Nonproliferation Studies in Washington DC. There are currently no governmental controls on what sequences can be used, says Tucker, although some DNA synthesis companies now screen their orders for pathogenic sequences. If someone wants to reconstruct the virus, says Taubenberger, "the technology is available".

Philip Campbell, editor-in-chief of *Nature*, says that although he did not seek advice on whether to publish the work, he has done so for previous flu-virulence and pathogen genome papers. He says that the benefits clearly outweigh the risks. Donald Kennedy, editor-in-chief of *Science*, agrees about the merits of publication. "I think we are going to depend on this kind of knowledge," he says.

The US National Science Advisory Board for Biosecurity (NSABB) reached a similar conclusion about both studies, after calling an emergency meeting last week to consider the risks. But, concerned about public fears, it asked the authors of both papers to add a passage to the manuscripts stating that the work is important for public health and was conducted safely.

Campbell says he is worried that government agencies will start seeking to be involved in the publishing process. "We are happy to cooperate with the NSABB to consider the principles by which dual-use results can be published responsibly," he says. "But government bureaucracies and committees may push to avoid perceived risks, at the potential expense of benefits to public security."

Taubenberger admits that there can be no absolute guarantee of safety. "We are aware that all technological advances could be misused," he says. "But what we are trying to understand is what happened in nature and how to prevent another pandemic. In this case, nature is the bioterrorist." ■