

Study uncovers a lethal secret of 1918 influenza virus

In a study of non-human primates infected with the influenza virus that killed 50 million people in 1918, an international team of scientists has found a critical clue to how the virus killed so quickly and efficiently.

Writing this week in the journal *Nature*, a team led by University of Wisconsin-Madison virologist Yoshihiro Kawaoka reveals how the 1918 virus - modern history's most savage influenza strain - unleashes an immune response that destroys the lungs in a matter of days, leading to death.

The finding is important because it provides insight into how the virus that swept the world in the closing days of World War I was so efficiently deadly, claiming many of its victims people in the prime of life. The work suggests that it may be possible in future outbreaks of highly pathogenic flu to stem the tide of death through early intervention.

The study "proves the 1918 virus was indeed different from all of the other flu viruses we know of," says Kawaoka, a professor in the UW-Madison School of Veterinary Medicine and at the University of Tokyo.

The new study, conducted at the Public Health Agency of Canada's National Microbiology Laboratory in Winnipeg, Manitoba, utilized the 1918 flu virus, which has been reconstructed by researchers using genes obtained from the tissues of victims of the great pandemic in a reverse genetics process that enables scientists to make fully functioning viruses.

"In 1918, the existence of viruses had barely been recognized. In fact, the influenza virus wasn't identified until 1933. Thanks to recent technological advancements, we are now able to study this virus and how it wreaked havoc around the globe," explains Darwyn Kobasa, research scientist with the Public Health Agency of Canada and lead author of the new study. "This research provides an important piece in the puzzle of the 1918 virus, helping us to better understand influenza viruses and their potential to cause pandemics."

By infecting monkeys with the virus, the team was able to show that the 1918 virus prompted a deadly respiratory infection that echoed historical accounts of how the disease claimed its victims.

Importantly, the new work shows that infection with the virus prompted an immune response that seems to derail the body's typical reaction to viral infection and instead unleashes an attack by the immune system on the lungs. As immune cells attack the respiratory system, the lungs fill with fluid and victims, in essence, drown. The mechanisms that contribute to the lethality of the virus were uncovered by University of Washington researchers using functional genomics, a technique in which researchers analyze the gene functions and interactions. Learning more about the virulence mechanisms of the 1918 flu virus may help researchers understand how to keep the virus from causing such a severe immune response.

"This study in macaques, combined with our earlier research showing the host response in mice infected with the 1918 flu, suggests that the host immune response is out of control in animals infected with the virus," said Michael G. Katze, professor of microbiology at the University of Washington in Seattle, who led the functional genomics portion of the new study and led the previous mouse-based study. "Our analysis revealed potential mechanisms of virulence, which we hope will help us develop novel antiviral strategies to both outwit the virus and moderate the host immune response."

The same excessive immune reaction is characteristic of the deadly complications of H5N1 avian influenza,

the strain of bird flu present in Asia and which has claimed nearly 150 human lives but has not yet shown a capacity to spread easily among people.

"What we see with the 1918 virus in infected monkeys is also what we see with H5N1 viruses," Kawaoka says, suggesting that the ability to modulate immune response may be a shared feature of the most virulent influenza viruses.

In the new study, conducted in a high-level biosafety laboratory (BSL 4) at the Public Health Agency of Canada's National Microbiology Laboratory, seven primates were infected with the reconstructed 1918 virus. Clinical signs of disease were apparent within 24 hours of infection and within eight days euthanization was necessary. The rapid course of the disease mirrors how quickly the disease ran its course in its human victims in 1918.

Upon infection, the virus grew rapidly in the infected animals, suggesting the agent somehow sets the stage for virulent infection: "Somehow, early in infection, this virus does something to the host that allows it to grow really well," says Kawaoka. "But we don't know what that is."

Knowing that the virus does something early in infection to trigger such a devastating immune response may provide biomedical researchers with clues about how to intervene and stop or mitigate the virus' potentially lethal effects, Kawaoka says.

"Things may be happening at an early time point (in infection), but we may be able to step in and stop that reaction."

Source: University of Wisconsin-Madison

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