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In 1918 Flu Pandemic, Timing Was a Killer

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American Red Cross workers collecting victims of the 1918 flu in St. Louis. A new study suggests why people in their late 20s were so vulnerable in that epidemic.

St. Louis Post-Dispatch



Carl Zimmer

Sometimes a virus can cause more devastation than all the world's armies. In 1918, at the end of World War I, influenza spread around the planet, reaching even Pacific islands and Arctic villages. The virus infected a third of all

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people on earth, and caused an estimated 50 million deaths — more than [three times the number of people killed in World War I](#).

Since 1918, four new global flu pandemics have struck. None have come anywhere close to 1918's toll, leaving scientists to puzzle about why 1918 was so deadly.

Adding to the mystery was that people in their late 20s were at greatest risk of dying in 1918. Typically, children and old people are more likely to die in flu outbreaks.

In a provocative new study [published](#) recently in The Proceedings of the National Academy of Sciences, a team of scientists argues that there wasn't anything particularly sinister about the 1918 virus. The pandemic was the result of some disastrously bad luck.

The mysteries that surround the 1918 flu inspired a hunt for the virus itself. In the mid-1990s, scientists [recovered its genes from tissue samples](#) still preserved in hospitals.

After comparing the genes of the 1918 flu virus to those of other flu viruses, some scientists argued that the pandemic started when a flu virus in birds jumped into humans.

Discovering the 1918 virus also led to some new ideas about why it killed so many young adults. When scientists infected mice and monkeys with that virus, the animals developed a dangerously strong immune response. That led some scientists to suggest that the 1918 flu



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virus set off a lethal overreaction. If that were true, then the people who had the strongest immune system would be at the greatest risk.

But [Michael Worobey](#), a biologist at the University of Arizona and an author of the new study, finds this explanation weak. “I just don’t buy it,” he said.

Teenagers and people in their early 20s also have strong immune systems. But they were at much less risk of dying in 1918 than people in their late 20s.

To get some new clues to the 1918 flu, Dr. Worobey recently launched an investigation with Guan-Zhu Han of the University of Arizona and [Andrew Rambaut](#) of the University of Edinburgh. The scientists conducted a detailed comparison of the 1918 virus to other flu viruses. Their evidence suggests that the 1918 virus did not, in fact, leap into humans right before the pandemic.

Instead, the virus became a human virus a decade earlier. This proto-1918 virus then inobtrusively circulated for years.

Influenza viruses sometimes produce hybrids. This occurs when two flu viruses infect the same cell. Their genes get mixed together as the cell makes new viruses.

The new study suggests that after a quiet decade, the proto-1918 virus mixed its genes with a bird flu virus. The result was the 1918 virus that caused the pandemic.

“That seems to tie a bunch of confusing observations together and makes sense of them,” said Dr. Worobey.

He argues that people under the age of 25 were protected from the new virus because they had already been exposed to its weaker version as their first experience with influenza.

When people have the flu, they make antibodies that can provide some protection to similar viruses years later. Some studies suggest that the first flu infection that children get has the biggest effect on their defenses later in life.

Children born after about 1900 would have been infected with that mild, proto-

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1918 virus. When the full-blown 1918 pandemic arrived, they had antibodies that protected them from a serious case of the stronger version of the virus.

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Older people were first exposed to influenza in the 19th century. To see how that first flu affected them, Dr. Worobey and his colleagues looked for clues to the nature of those earlier outbreaks.

The oldest people in 1918 would have been first infected with the flu in the early and mid-1800s. The research of Dr. Worobey and other researchers suggests that the flu viruses at that time were similar to the 1918 virus. In other words, old people in 1918 were protected from the new virus.

But in 1889, a new pandemic swept the planet. A few clues about its nature come from the antibodies that people made in response.

In the 1950s, scientists tested the antibodies of elderly people who had been alive during the 1889 pandemic, and found that their antibodies bound strongly to flu viruses that are only distantly related to the 1918 flu virus. That would suggest that people who were infected in the 1889 pandemic didn't get the protection to the 1918 virus that older and younger people did.

In other words, the people in their late 20s were the victims of timing. When they grew up, they didn't have strong defenses against the 1918 flu.

Other factors made the pandemic even worse for those young adults. Vulnerable soldiers were packed in battlefield trenches or aboard troop transport ships. The virus could spread easily from one host to another.

And in 1918, doctors could do little to treat the flu. They had no vaccines, no antiviral drugs and no antibiotics to stop the bacterial pneumonia that often came with bad cases of the flu.

Some flu experts hailed the new study by Dr. Worobey and his colleagues as a fascinating new way to think about the 1918 pandemic. But other scientists want more evidence.

"I'm not fully persuaded," said [Dr. David Morens](#), an expert on the 1918 flu at the National Institutes of Health. "It's fine to speculate over a beer, but when we do that, we should be very cautious and realize

that we're only speculating and brainstorming.”

The only way to gain a better understanding of what happened in 1918, Dr. Morens said, would be to track down the genes of flu viruses from the 19th century, not just the antibodies. “We have to have the viruses,” said Dr. Morens.

If Dr. Worobey is right, the story of the 1918 pandemic should actually be a cause for guarded optimism. The 1918 flu was not especially dangerous, but simply took advantage of some historical flukes.

Today, we are better prepared to battle a pandemic. Flu vaccines can protect people who did not get the right antibodies when they were young, for example.

The flu still remains a serious public health risk, killing [up to half a million people](#) worldwide every year. But Dr. Worobey suspects the ghost of 1918 pandemic can be put to rest.

“There are some hopeful signs here,” he said.

A version of this article appears in print on May 6, 2014, on page D3 of the New York edition with the headline: In 1918, Bad Timing Fed a Pandemic. Order Reprints | Today's Paper | Subscribe

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