

Researchers find long-lived immunity to 1918 pandemic virus

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Aug 19, 2008 (CIDRAP News) – A study of the blood of older people who survived the 1918 influenza pandemic reveals that antibodies to the strain have lasted a lifetime and can perhaps be engineered to protect future generations against similar strains.

The findings appeared online Aug 17 in *Nature*. Study collaborators hail from several institutions: Vanderbilt University, Mount Sinai School of Medicine, University of Medicine and Dentistry of New Jersey (UMDNJ), the Centers for Disease Control and Prevention (CDC), and Scripps Research Institute.

Inspiration for the study came from an unlikely source, an episode of an old medical television show that portrayed a town protecting itself from the 1918 virus outbreak by using blood from an elderly survivor, the Associated Press (AP) reported yesterday. The storyline prompted Eric Altschuler, MD, a professor of physical medicine and rehabilitation at UMDND to ask the National Institutes of Health (NIH) for a grant to test people over age 90 for the 1918 flu antibodies, according to the AP report. The NIH funded much of the study and enlisted the expertise of other experts.

The group collected blood samples from 32 pandemic survivors aged 91 to 101. The multipronged study had four components, to:

- Determine if the survivors still had antibodies to the virus
- See if the B cells—the ones that produce the antibodies—could be cultured and produce antibodies to a 1918 virus protein
- Attempt fusing cells having the highest levels of activity with myeloma cells to create a hybrid cell line that secretes monoclonal antibodies
- Evaluate if the antibodies could protect mice infected with the 1918 influenza virus

The people recruited for the study were 2 to 12 years old in 1918 and many recalled sick family members in their households, which suggests they were directly exposed to the virus, the authors report. The group found that 100% of the subjects had serum-neutralizing activity against the 1918 virus and 94% showed serologic reactivity to the 1918 hemagglutinin.

The investigators generated B lymphoblastic cell lines from the peripheral blood mononuclear cells of eight subjects. Transformed cells from the blood of 7 of the 8 donors yielded secreting antibodies that bound the 1918 hemagglutinin.

Author James E. Crowe, Jr, MD, professor of pediatrics and director of the Vanderbilt Program in Vaccine Sciences, said in a press release from Vanderbilt that the researchers were surprised by the findings.

"The B cells have been waiting for at least 60 years—if not 90 years—for that flu to come around again," he said. "That's amazing, because it's the longest memory anyone's ever demonstrated."

From the B cells of three donors, the research group generated five monoclonal antibodies that not only strongly neutralized the 1918 virus, but also cross-reacted with proteins related to the 1930 swine flu virus. However, the antibodies did not react against more contemporary influenza strains.

In the final arm of the study, the researchers infected mice with the reconstructed 1918 virus and the next day tested the five monoclonal antibodies at various doses to see if the therapy protected the animals. The mice receiving the lowest dose of the 1918 monoclonal antibody died, as did the ones receiving the control antibody. All given the highest antibody doses survived.

Dr Tshidi Tsibane, a study author and postdoctoral fellow in Mount Sinai School of Medicine's microbiology department, said in a press release from Mount Sinai that though there is no need for a new treatment for 1918 influenza virus infections, the results are still useful.

"These findings could serve as potential therapy for another 1918-like virus," said Dr Tsibane in the statement.

The authors point out that it is difficult to be certain that the monoclonal antibodies they isolated were first stimulated during the 1918 influenza pandemic. However, they write that the subjects' clinical histories and the high affinity of the monoclonal antibodies for the 1918 strain "strongly suggest that recent exposures do not account for this immunity." They add that exposure to similar viruses circulating during first part of the 20th century probably bolstered the subjects' B cell function.

Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, said recent studies have projected that immunity lasts several decades; the current study provides proof, the AP reported. "This is the mother of all immunological memory here," he told the AP.

Xiaocong Y, Tsibane T, McGraw P, et al. Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. *Nature* 2008 (published online Aug 17) [[Abstract \(http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature07231.html\)](http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature07231.html)]

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