

Study identifies a key cellular mechanism that triggers pneumonia in humans

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Researchers have demonstrated that influenza virus impairs the immune response to pneumococcus, especially monocyte activity. A software tool developed with FAPESP's support was used to interpret the data. Credit: Liverpool School of Tropical Medicine

The relationship between influenza and pneumonia has long been observed by health workers. Its genetic and cellular mechanisms have now been investigated in depth by scientists in a study involving volunteers and conducted in the United Kingdom.

Published in the journal *Nature Immunology*, the paper describes for the first time a cellular mechanism that controls the proliferation of pneumococci—the *Streptococcus pneumoniae* bacteria that cause

pneumonia—and their movement from the nose to the lungs. It also reports that in humans, the inflammation caused by the influenza virus impairs the innate immune control of pneumococci.

The study was performed by scientists at the Center for Research on Inflammatory Diseases—CRID, a Research, Innovation and Dissemination Center—RIDC funded by São Paulo Research—FAPESP, and the Liverpool School of Tropical Medicine (LSTM) in the UK. It was supported by the Bill & Melinda Gates Foundation, the UK Medical Research Council (MRC), and the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES), as well as FAPESP.

"Based on our understanding and analysis of the cellular, genetic and immune response mechanisms, we were able to prove that most flu-related deaths are due to post-flu pneumonia rather than to influenza virus itself," said Helder Nakaya, a researcher affiliated with CRID and a coauthor of the paper.

The main reason, according to the results of the study, is that influenza virus silences the organism's innate immune response, in particular inhibiting the action of monocytes—the main type of leukocyte or white blood cell responsible for expelling foreign bodies such as viruses and bacteria. To conduct the study, the researchers recruited volunteers to be inoculated with attenuated influenza virus and pneumococcus. This procedure is permitted in the UK. No volunteers suffered from pneumonia during the study.

Researchers on the Brazilian side analyzed and interpreted genetic and cellular data using CEMiTool bioinformatics software developed at the University of São Paulo's Pharmaceutical Science School (FCF-USP) with [FAPESP's support](#) under the aegis of its Young Investigators grant program.

"The [software tool](#) enabled us to analyze the interaction among the various genes in a very large number of samples, given that 140 volunteers took part in the study," Nakaya said.

Journey of pneumococcus

Live attenuated influenza viruses were obtained from the flu vaccines (Fluenz/Flumist) administered every winter in the U.K. Three days after receiving the flu virus, the volunteers received pneumococcus via [nasal spray](#). Blood samples, nasal swabs and nasal cells from the volunteers were analyzed throughout the study, which lasted an entire winter.

"In order for pneumonia to develop, the bacterium must be in the lungs. This same bacterium can live in the nose for a long time without causing symptoms, especially in healthy adults. For some reason, however, especially in more vulnerable patients, the bacterium travels from the nose to the lungs. Our study focused precisely on the mechanisms that clear the bacteria from the nose and prevent it from traveling to the lungs, and on how influenza virus alters this process," said [Daniela Ferreira](#), a professor at LSTM and principal investigator for the study.

The findings showed that the number of bacteria in the nose increased significantly because of the influenza virus. "Another important point is that excessive multiplication of pneumococcus heightens the patient's predisposition to transmit it to other people," Ferreira said. "So there are two problems: an increase in individual susceptibility to pneumonia, and an increase in transmission of pneumococcus in the general population."

The bacteria multiply in the nose when the influenza virus impairs the immune response by inhibiting monocyte antibacterial activity.

"We analyzed the genes and mechanisms involved in the bacterium's journey to the lungs. We also identified biological markers that are more

expressed in an individual with the virus and uncontrolled bacterial infection. In future we'll be able to use all this information to develop better vaccines and therapies," Ferreira said.

Different in humans

The mechanisms of the immune response to colonization by pneumococcus have been thoroughly studied in mice but remain poorly understood in humans. Using for the first time a [human experimental challenge](#) model with the attenuated flu [virus](#) and pneumococcus, the researchers discovered that in humans, unlike mice, nasal bacterial infection leads quickly to the activation of neutrophils, another type of lymphocyte always present in the human nose, and to the recruitment of monocytes, which clear the nostrils of bacteria by rupturing their vesicles (lysis). Neutrophil recruitment results in control of the bacteria in mice, instead of monocyte recruitment.

This finding "underlin[es] the importance of confirming mouse findings with human data," the authors stress in the article.

Another finding was that the live attenuated [influenza](#) vaccine can be used to control pneumonia, which is a major global health problem and kills more children under five than any other disease. It is also particularly dangerous to the elderly and people with chronic lung disease, immunosuppression and viral coinfection.

"The most important point about this entire process is that people need to be immune to flu. The flu vaccine also proved beneficial to avoiding [pneumonia](#)," Ferreira said.

The researchers are now analyzing the converse situation when infection by the bacteria occurs first and is followed by [influenza virus](#) infection.

More information: Simon P. Jochems et al, Inflammation induced by influenza virus impairs human innate immune control of pneumococcus, *Nature Immunology* (2018). [DOI: 10.1038/s41590-018-0231-y](https://doi.org/10.1038/s41590-018-0231-y)

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