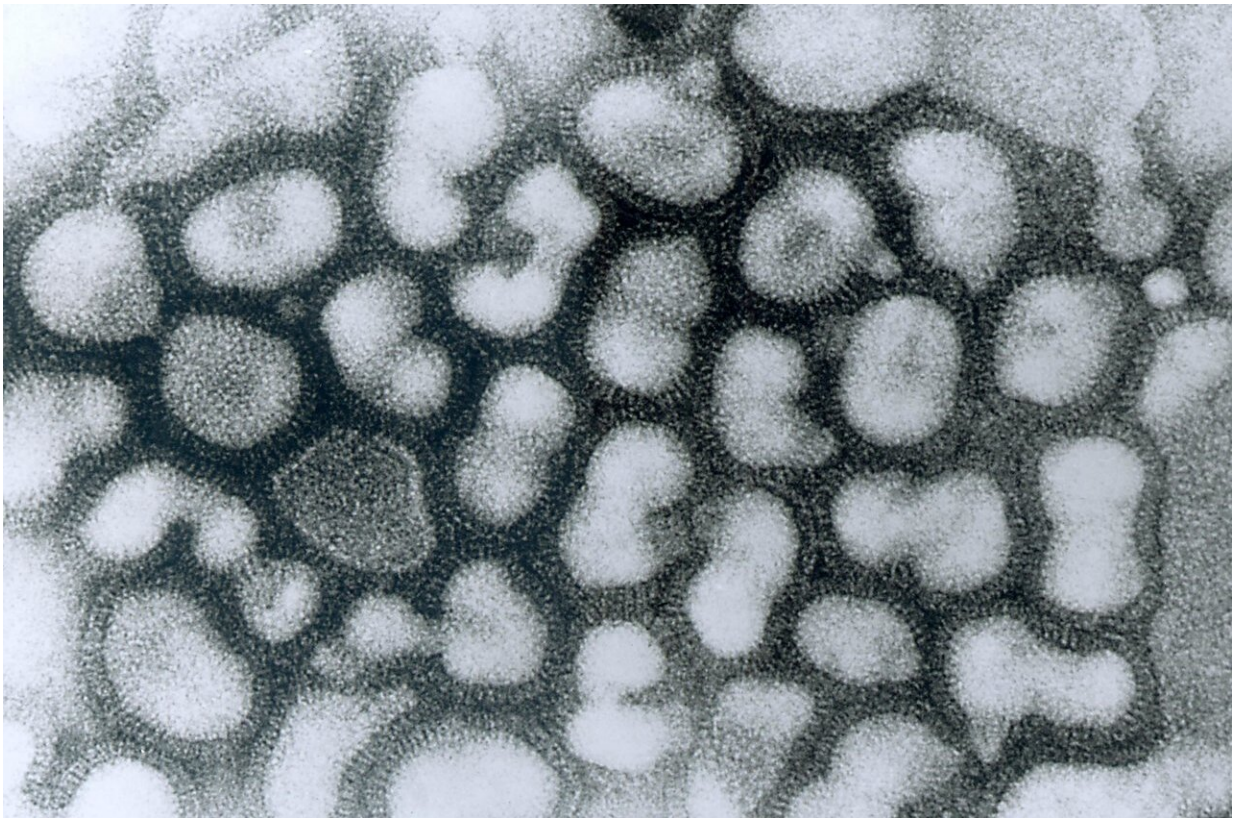


Spanish flu may have lingered two years before 1918 outbreak and vaccine could have treated it

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Transmission electron micrograph of influenza A virus, late passage. Credit: CDC

The most severe pandemic in recent history, killing some 50 million

people worldwide, the Spanish influenza, may have emerged up to two years earlier than previously believed. And, according to a new and influential study, its early manifestation was ignored at the time as a "minor infection".

It is believed that, if doctors had recognized that influenza was the cause of an illness which was killing soldiers in Etaples, France, and Aldershot, England, in 1916, scientists would then have had better grounds to embark on a two-year vaccination programme and some of the worst effects of the Spanish influenza could have been avoided. Such are the findings of a new paper, launched by Professor John S. Oxford, the UK's top expert on influenza, and Douglas Gill, a military historian.

Published in *Human Vaccines & Immunotherapeutics*, the study uses modern day scientific technology and delves through literature published in *The Lancet* from the time, to not only track the origins of the virus, but to seek how we can use this information to learn from the past to prevent the spread of an influenza pandemic.

In their quest, Oxford and Gill trace the origins of the Spanish influenza as it emerged in 1915 and 1916 in the Etaples Administrative District in northern France. At the time, up to 30,000 soldiers were admitted each year to British army hospitals in France and England, suffering from typical influenza symptoms. In early 1917, however, a medical group in Etaples treated hundreds of patients infected with what they described as an "unusually fatal disease" presenting "complex" respiratory symptoms.

In Aldershot, in the south of England, three senior physicians were also tackling a problem whose hallmarks looked very much the same. In both instances, the disease was characterized by a 'dusky' cyanosis, a rapid progression from quite minor symptoms to death—with death in any case usually resulting from a superinfection involving staphylococcus, streptococcus, etc.

Both medical groups were encountering a case fatality in the order of 50%, and they were learning from colleagues in England and France (who were publishing in *The Lancet* in 1917) that the malady was occurring elsewhere.

It is this information which has helped Oxford and Gill to track what was then believed to be a minor respiratory infection as the very origins of the biggest killing pandemic of the 20th century.

"We have identified long-neglected outbreaks of infection: outbreaks which, judged as minor at the time, can now be seen as increasingly important, and a portent of the disaster to come," explains Professor Oxford, of Queen Mary University, London.

"The research undertaken in the production of the Etaples paper was particularly exhaustive in its scope and depth. Not only were the usual examinations undertaken, of tissue and sputum, but a postmortem examination was conducted of every single soldier dying of disease, throughout a period of seven weeks in early 1917."

The findings of the literature as to the origins of the Spanish influenza are further supported in modern papers analysed by Oxford and Gill, wherein scientific methods, namely phylogenetic (the study of evolutionary relationships among biological entities—often species, individuals or genes) and molecular clock analysis, point to all eight genes of the H1N1 family of influenza A viruses as emerging in 1915-1916.

These modern studies have also shown that the 'emerging virus' began with aquatic geese, ducks, and swans as a reservoir. It is likely that this disease was then passed on to the soldiers through the faeces of migrating [water birds](#).

So what happened between 1915-1916 and 1918-1919 to make this pre-[pandemic virus](#) to become pandemic?

Professor Oxford explains.

"In essence, the virus must have mutated. It lost a great deal of its virulence, but gained a marked ability to spread. Recent experiments with a pre-pandemic 'bird flu' called H5N1, deliberately mutated in the laboratory, have shown that as few as five mutations could have permitted this change to take place."

"We appreciate today that a unique characteristic of a pre-pandemic virus lies in its inability to spread from person to person," Professor Oxford added. "The teams at Etaples and Aldershot, although strong in clinical diagnosis, were misled by the lack of spread of this infection. Accordingly, they failed to pinpoint influenza as the underlying cause."

There was, however, a silver lining to a very dark cloud.

"Pathologists in the United States and in France strove to construct the first universal vaccines against influenza. Their efforts were not misdirected, because the ultimate cause of death in nearly all cases flowed from superinfections with respiratory bacteria."

Oxford and Gill conclude: "We remain impressed by the care and initiative shown by our predecessors 100 years ago. Their efforts did have an impact on the level of fatalities, but—not unexpectedly—had no effect upon spread: the result, of course, of everyone's misunderstanding of the nature of the pathogen involved."

"Once the virus is able to spread from human to human, disaster strikes. With a generation time of two to three days, from just three patients who were infected originally, a million infections can be caused in around 40

days. And this is probably exactly what happened in 1918-1919."

Today, the World Health Organisation is on full alert; and every nation in the world has been asked to plan for a pandemic of bird influenza A (H5N1) or (H7N9).

By understanding the origins of the Spanish influenza via analyzing modern day research and papers written in 1917, it is hoped this study could help us prevent a new [influenza](#) pandemic.

Professor Oxford thinks that existing vaccines have a role to play.

"Something similar to what happened at the beginning of the twentieth century could easily be repeated. As a precaution, governments everywhere are stockpiling vaccines against the pneumococcus that usually develops as a secondary infection after the flu, and which causes fatalities on a very large scale."

More information: John S. Oxford et al, A possible European origin of the Spanish influenza and the first attempts to reduce mortality to combat superinfecting bacteria: an opinion from a virologist and a military historian, *Human Vaccines & Immunotherapeutics* (2019). [DOI: 10.1080/21645515.2019.1607711](#)

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