

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

John S. Oxford and Douglas Gill

Blizard Institute, Queen Mary University London, Whitechapel, London

ABSTRACT

When we reconsider the virology and history of the Spanish Influenza Pandemic, the science of 2018 provides us with tools which did not exist at the time. Two such tools come to mind. The first lies in the field of ‘gain of function’ experiments. A potential pandemic virus, such as influenza A (H5N1), can be deliberately mutated in the laboratory in order to change its virulence and spreadability. Key mutations can then be identified. A second tool lies in phylogenetics, combined with molecular clock analysis. It shows that the 1918 pandemic virus first emerged in the years 1915–1916.

We have revisited the literature published in Europe and the United States, and the notes left by physicians who lived at the time. In this, we have followed the words of the late Alfred Crosby: who wrote that “contemporary documentary evidence from qualified physicians” is the key to understanding where and how the first outbreaks occurred. In our view, the scientists working in Europe fulfill Crosby’s requirement for contemporary evidence of origin.

Elsewhere, Crosby also suggested that “the physicians of 1918 were participants in the greatest failure of medical science in the twentieth century”. Ours is a different approach. We point to individual pathologists in the United States and in France, who 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.

ARTICLE HISTORY

Received 21 January 2019

Revised 22 March 2019

Accepted 9 April 2019

KEYWORDS

Spanish Influenza Origin; Influenza Epidemics in 1917; New Vaccines; Etaples Administrative District; Hospital Beds in the Great War; Hygiene in the Great War

Introduction

In January 1917, the main force of the British army was deployed in France, along the Western Front. In a line of trenches stretching from Dunkirk, on the North Sea, to the headwaters of the Somme, two million officers and men were gathered in cramped, cold, and insanitary conditions. The risks to health were clear. Typhoid, dysentery, and pneumonia had long been the real enemies of soldiers. Accordingly, the medical resources of the British Isles had been gravely depleted, and the finest minds sent to France. Bacteriologists and sanitary officers – respected scientists and administrators – undertook day to day inspections of billets, encampments, hospital wards, trenches, indeed every location where soldiers were found. Their work was preventative. The army had 150,000 beds in which to care for the wounded and sick.¹ And, during the opening weeks of 1917, it seems that, in many hospital centers, the sick were present in preponderant numbers, and respiratory problems had very much come to the fore.

Until 1917, the new science of pathology had identified the bacteria causing disease, and had rapidly formulated vaccines. Most soldiers were inoculated against cholera, typhoid, and smallpox before they crossed over to France, and chemicals based on chlorine were applied in large quantities to surfaces, food, and drinking water.²

One important infection, however, had been tackled neither by disinfectants nor vaccines. That disease was influenza. During each

of the years 1915 and 1916, some thirty odd thousand soldiers were admitted to army hospitals, suffering from influenza. Not a large total, perhaps, given that the figure of two million soldiers, as set out above, was simply the total at any given time, and concealed an ever-shifting flow of young men. In early 1917, however, the situation suddenly and unexpectedly changed. In the course of our researches, 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. After all, within 18 months, the most serious influenza pandemic in history had killed some fifty million people.

Early outbreaks in 1917

Two papers were published in *The Lancet* in 1917 describing an outbreak of disease constituting “almost a small epidemic”. The first paper was written by physicians at a hospital center in northern France,³ and the second by a team at an army hospital in Aldershot,⁴ in southern England. In both instances, the disease was characterized by a ‘dusky’ cyanosis, a rapid progression from quite minor symptoms to death – which death in any case usually resulting from a superinfection involving staphylococcus, streptococcus, etc.

The first outbreak to be recorded and published took place in the so-called ‘Etaples Administrative District’, an area extending across some eighty square miles along a forgotten area of the

French coast. In the complex of hospitals there – the largest in the British army at the time⁵ – comprising more than twenty thousand beds, physicians encountered an “unusually fatal disease” accompanied by “a symptom complex so distinctive as to constitute a definite clinical entity”. The research undertaken in the production of this 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. Clinically, it seemed, an ordinary case of minor respiratory infection moved on to bronchitis, pneumonia, and thence rapidly to death – a death ushered in by dyspnea and cyanosis. The problem may have been even more widespread. At that same time, from a viewpoint closer to the trenches, a senior consultant had written to Sir William Leishman, the British Army’s chief pathologist. He had seen, he said, “some very severe and rapidly fatal cases of Bronchitis”, which he thought were “Influenza in type”.

From Aldershot, in the south of England, three yet more senior physicians were also tackling a problem whose hallmarks looked very much the same. Throughout the winter of 1916–1917, they wrote, they were encountering deaths through respiratory disease which seemed in every way to reflect the symptoms of those dying at Etaples: a form of bronchitis in which cyanosis and lung block so often supervened. They were encountering a case fatality in the order of 50%, and they were learning from colleagues in England and France that the malady was occurring elsewhere. Throughout their paper, they pointed to one clinical symptom above all which typified the faces of those who were destined to die: “a peculiar dusky heliotrope type of cyanosis of the face, lips, and ears, so characteristic as to hall-mark the nature of the patient’s malady”.

These physicians remained puzzled by the epidemiology of the outbreaks which they faced. All showed high mortality – in excess of 40%, it was reported from Etaples – but with little or no spread from person to person. No doctor or nurse, for instance, died, and there were no reports of an outbreak in the civil population. So what diagnosis did these physicians make? In truth, they lacked the science to understand the underlying cause. We believe that they could have suspected influenza, but that the lack of spread confused them. The bacteriologists of that era had accepted Pfeiffer’s proposition that the Russian influenza pandemic of 1889 had been caused by a Gram-negative bacillus – a bacillus which came to bear his name. The authors of 1917 hesitated, therefore, to call the outbreak ‘influenza’; and, in any case, the word was not in common useage in scientific circles at the time. In the years since the outbreak of 1830, physicians preferred to use terms such as ‘epidemic catarrh’ or ‘epidemic bronchitis’.

When they looked back, in 1919, after clinically examining tens of thousands of cases, the Aldershot team emphasizes that “in essentials the influenza pneumococcal purulent bronchitis that we and others described in 1916 and 1917 is fundamentally the same condition as the influenza pneumonia of this present pandemic”.⁶

A modern-day scientific interpretation of the epidemics in 1916 and 1917

How differently would the world react today, were it to be armed with reports of outbreaks such as these! A present-day virologist or

pathologist would fit together the scenario of an emerging influenza pandemic, using China and the two bird influenza viruses, H5N1 and H7N9, as a current model. Today, the World Health Organisation (WHO) 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). And this despite the fact that, in China, fewer than a thousand deaths have been detected in a population of two billion; and that neither H5N1 nor H7N9 is spreading in the community. In other words, we appreciate today that a unique characteristic of a pre-pandemic virus lies in its inability to spread from person to person. We also know that pandemic influenza A virus is an ‘emerging virus’, with aquatic geese, ducks, and swans as a reservoir. The outbreak in 1997 in Hong Kong showed us that such viruses can cross the species barrier directly, from birds to humans, but cannot easily take the next step, and move from human to human. We deduce that these first ‘in man’ influenza viruses can replicate deep down in the lung, rather than in the upper airways, where coughing enables the virus to spread from person to person. Once the virus has mutated and can move from the base of the lung to the upper airways, then, necessarily, a pandemic can break out. And we know, from ‘gain of function’ experiments^{7,8} (whereby the virus H5N1 is deliberately mutated in a laboratory) that the virus would only need four to five mutations in the HA gene to enable it to trigger person-to-person spread. With an R0 of 3, and a Generation Time of two to three days, a million infections can be caused in 40 days and nights, in an immune-naive population.

The third piece of evidence supports our hypothesis about the timing of the emergence of the Spanish flu virus in 1916. Michael Worobey et al. have applied phylogenetic and molecular clock analysis to all eight genes of the H1N1 family of influenza viruses,⁹ which we know now caused the pandemic because genes of this subtype have been detected in clinical lung samples from 1918 victims in the United States, and London. Worobey hypothesized that seven genes of a bird virus emerged directly in 1916 from a migrating waterbird and reassorted with an already established epidemic influenza A H1 gene, itself having emerged and reassorted around 1907. Thus, a brand-new potentially pandemic virus entered the human population. Still, as we noted above, it is likely that further mutations allowed wider dissemination of the virus. We consider that the 1916 virus would have exchanged high lethality for a higher level of infectiousness as it moved in a grand circle from Etaples to the United States and back, in the bodies of the men of General Pershing’s Expeditionary Force. We also deduce that the emerged 1907 H1 virus could not itself have spread widely. In the same way, today, the bird influenza H5N1 which emerged in 1997 has not left south-east Asia and become widespread. Had this not been the case, and the 1907 H1 had indeed spread, the wider population would have developed a real measure of protection by the year 1918.

Could the Spanish influenza have arisen in China or the United States?

Two alternative geographical hypotheses have been widely aired in North America.¹⁰ These propose either the State of Kansas, or an area in northern China, as the places where the virus first emerged. Suffice it to say that we anticipate that, in any such focal area, there would be a large population of

youngsters, perhaps crowded and stressed, and in contact with geese and ducks, most likely because of a nearby migratory flight path. It should be recalled that new influenza viruses are carried as enteric infections in migrating water birds, and move to domesticated birds, and thence to humans. Alfred Crosby demanded a scientific publication to back up any claim of Spanish influenza emerging anywhere in the world. However, there are no scientific publications backing up either the Chinese or Kansas hypotheses – merely a brief observation in Kansas by a general practitioner of a local winter respiratory outbreak, and, in China, reports filed by a doctor for routine administrative purposes rather than for a scientific or medical journal. Olson and colleagues¹¹ have presented epidemiological evidence of a herald, or warning, wave of influenza in New York in the winter of 1917–18. In clinical terms, their description fits the signature of the 1918 influenza pandemic – namely, high numbers of deaths in young people. However, Olson and colleagues do not propose that city as the source of the pandemic. Nor do they endorse the view that the pandemic emerged in the State of Kansas in the USA. That view, they write, “has become widely accepted without vigorous re-evaluation of the original evidence”.

A question is whether the precise origin of these earlier pandemics merits scientific attention. In our opinion, clarification of the factors of geography, demographic mix, migration, farmers, and markets is crucial; and this knowledge would allow us to identify a new virus in likely hotspots before it becomes widespread.

Forgotten development of influenza vaccines in 1917

The pathologists at Etaples, in describing their treatment of ‘purulent bronchitis’, mentioned their need for a vaccine, as a prophylactic. They reported on the progress they had made to identify the pathogens causing mortality in the camp, and pointed specifically to streptococcus, pneumococcus, staphylococcus, and Pfeiffer’s bacillus. They then undertook small-scale cultivation of these bacteria, and subsequently heat-treated them to prepare a safe vaccine. By the time the vaccine was ready, however, the “small epidemic” was nearing its end, having caused a mere one hundred deaths between ten and twenty thousand hospital patients.

Fifteen months later, military pathologists were to be found investigating the efficacy of similar ‘mixed’ catarrhal vaccines (MCV). A relatively large-scale investigation was carried out in this field. The vaccine contained seven different heat-treated organisms: *pneumococcus*, *streptococcus*, *B. influenzae*, *staphylococcus aureus*, *M. catarrhalis*, *B. pneumoniae*, and *B. septus*. It was prepared in two dosage strengths, delivered ten days apart. In September 1918, John Eyre, a co-author of the Aldershot purulent bronchitis paper, together with a colleague, immunized 16,000 New Zealand recruits and used another 5000 as unimmunized controls. By this procedure, the risk of death in severe and complicated cases was reduced from 23% to 8%.¹²

By late 1918, Sir William Leishman had become Director of Pathology at the War Office in London. He now recommended that bacterial vaccines be used on a wider scale. One such vaccine contained three types of bacterium: *B. influenzae*, 400 million per millilitre; streptococci 80 million; and pneumococci

200 million. 15,624 men were vaccinated, whereas 43,520 were not. Deaths were reduced from 2.25 per thousand, in the control group, to 0.12 per thousand in the vaccinated group. Lung complications were reduced on a similar scale. As Leishman put it, the results “had best be left to speak for themselves”.¹³ In modern terms, the trial can be criticized as poorly controlled, in that the two vaccine groups were not matched, and soldiers were immunized on an ‘every other one’ basis. Even so, as recent recruits, they were similar in age and health.

In New York, the bacteriologist William Park was carrying out work of an entirely similar kind.¹⁴ His experimental vaccine contained *B. influenzae*, pneumococcus types 1 and 2, and hemolytic streptococcus. He prepared small batches of vaccine and immunized 60 people. In the control, non-immunized group, ten developed pneumonia, three of whom died. In contrast, only three of the vaccinated group developed pneumonia, none of whom died. In a quite separate North American project, at Camp Upton, in 1919, Synnott and Clark produced a vaccine containing types 1, 2, and 3 pneumococci.¹⁵ They noted “not only a successful immunization against pneumococci of the three types mentioned, but also distinct protection against streptococcal pneumonia, the incidence of which among the vaccinated cases was very low.”¹⁵

At the Royal Army Medical Corps scientific center in London, a large-scale vaccine project was underway; but the dislocation arising at the end of the war – the demobilization of medical personnel, for example – led to the project folding. The virus, however, had not stopped evolving, and caused a further large outbreak during February 1919, and thereafter outbreaks at yearly intervals right through until the year 1933. In that year, a group of scientists at Saint Bartholomew’s hospital isolated a filter-passing virus as the true cause of influenza, and thus allowed the first virus-containing vaccines to be developed.¹⁶

Contemporary influenza vaccines

By 1946, the first killed whole virus and live-attenuated influenza vaccines had been tested in both the United States and the Soviet Union. By 1960, the HA and NA proteins of the influenza virus had been separated by ultracentrifugation, to make sub-unit vaccines. Such vaccines require formulation yearly and are not wholly effective.

We can note that, rather unexpectedly, the vaccination of soldiers in 1918 with a mixed bacterial vaccine reduced pneumonia and deaths in those infected with the influenza virus. This can be explained by the observation that then, and now, over half of the victims of pandemic influenza virus die because of deep-seated superinfection with respiratory bacteria.¹⁷ Today, pneumococcus vaccines are stockpiled for use in influenza pandemics, as well as for yearly outbreaks among children and the elderly. But more research is needed with streptococcal and pneumococcal vaccines.

In modern times, the ingenuity of immunologists and molecular biologists has been applied to the design of so-called ‘universal influenza vaccines’. There is the hope of a broader-based immune response, even covering new pandemic viruses. Many of these new vaccines are composed of peptides of the influenza hemagglutinin, particularly from the stalk region, which is antigenically related between the HA subtypes.¹⁸ Other researchers have made experimental vaccines, using the internal influenza

virus proteins M, NP, and polymerase PA, PB1, PB2, and also M2e.^{19–23} An underlying research strategy is to formulate novel vaccines to increase the magnitude of CD8 and CD4 T-cell memory to influenza proteins. Two such vaccines have reached clinical testing in the community in the European Union.²²

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. Even so, we can speculate that, had the two RAMC groups concluded that influenza was the underlying problem, in Etaples and Aldershot in 1916, they would have had better scientific grounds to embark on a two-year vaccination programme.²³

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

- Macpherson WG. History of the great war, medical services, general history. London, England: His Majesty's Stationery Office; 1923.
- Macpherson WG, Leishman WB, Cummins CB. History of the great war, medical services, pathology. London, England: His Majesty's Stationery Office; 1923.
- Hammond JAR, Rolland W, Shore THG. Purulent bronchitis a study of cases occurring amongst the British troops at a base in France. *Lancet*. 1917;2:41–45. doi:10.1016/S0140-6736(01)56229-7.
- Abrahams A, Hallow NF, Eyre JWH, French H. Purulent bronchitis, its influenza and pneumococcal bacteriology. *Lancet*. 1917;2:377–80. doi:10.1016/S0140-6736(01)52169-8.
- Gill D, Putkowski J. The British base camp at Etaples 1914–1918. Etaples (France): Musée Quentovic; 1997.
- Abrahams A, Hallows N, French H. A further investigation into influenza-pneumococcal and influenza-streptococcal septicaemia: epidemic influenza 'pneumonia' of highly fatal type and its relation to 'purulent bronchitis'. *Lancet*. 1919;193:1–11. doi:10.1016/S0140-6736(01)22115-1.
- Herfst S, Schrauwen EJ, Linster M, Chutinimitkul S, de Wit E, Munster VJ, Sorrell EM, Bestebroer TM, Burke DF, Smith DJ, et al. Airborne transmission of influenza A/H5N1 virus between ferrets. *Science*. 2012;336:1534–41. doi:10.1126/science.1213362.
- Imai M, Watanabe T, Hatta M, Das SC, Ozawa M, Shinya K, Zhong G, Hanson A, Katsura H, Watanabe S, et al. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5HA/H1N1 virus in ferrets. *Nature*. 2012;486:420–28. doi:10.1038/nature10831.
- Worobey M, Han GZ, Rambaut A. Genesis and pathogenesis of the 1918 pandemic (H1N1) influenza A virus. *Proceedings of the National Academy of Science*; 2014; 111: 8107–12.
- Crosby AW. America's forgotten pandemic: the influenza of 1918. Cambridge, England: Cambridge University Press; 1989.
- Olson DR, Simonsen L, Edelson PJ, Morse SS. Epidemiological evidence of an early wave of the 1918 influenza pandemic in New York City. *Proceedings of the National Academy of Science*. 2005;102:11059–63. doi:10.1073/pnas.0408290102.
- Eyre JWH, Cronin E, Lower E. Report upon the autumn influenza pandemic (1918) as it affected the NZEF in the UK. *Lancet*. 1920; i:366–68.
- Leishman WB. The results of protective vaccinations against influenza: the army at home. *Lancet*. 1920;i:380–90.
- Park WH. Bacteriology of recent pandemic of influenza and other complicating infections. *J Am Med Assoc*. 1919;73:318–20. doi:10.1001/jama.1919.02610310012004.
- Sajous L. Recent gleanings relative to the prophylaxis and treatment of influenza. *N Y Medl J*. 1919 July 26;163–66.
- Stuart-Harris H, Schild GC, Oxford JS. Influenza, the viruses and the disease. London, England: Edward Arnold; 1985.
- Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza. *J Infect Dis*. 2008;198:962–70. doi:10.1086/593027.
- Impagliazzo A, Milder F, Kuipers H, Wagner MV, Zhu X, Hoffman RM, van Meersbergen R, Huizingh J, Wanningen P, Verspuij J, et al. A stable trimeric influenza hemagglutinin stem as a broadly protective immunogen. *ScienceExpress*. 2015; 349: 1301–06.
- Fiers W, De Filette M, Birkett A, Neiryck S, Min Jou W. A 'universal' human influenza A vaccine. *Virus Res*. 2004;103:173–76. doi:10.1016/j.virusres.2004.02.030.
- Yassine HM, Boyington JC, McTamney PM, Wei CJ, Kanekiyo M, Kong WP, Gallagher JR, Wang L, Zhang Y, Joyce MG, et al. Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection. *Nat Med*. 2015 August;1–6.
- Krammer F, Palese P, Steel J. Advances in universal virus vaccine design and antibody mediated therapies based on conserved regions of the hemagglutinin. *Curr Top Microbiol Immunol*. 2015;386:301–21. doi:10.1007/82_2014_408.
- Ortiz JR, Hickling J, Jones R, Donabedian A, Engelhardt OG, Katz JM, Madhi SA, Neuzil KM, Rimmelzwaan GF, Southern J, et al. Report on eighth WHO meeting on developments of influenza vaccines that induce broadly protective and long-lasting immune responses: Chicago, 23–24 August 2016. *Vaccine*. 2018;36:932–38. doi:10.1016/j.vaccine.2017.11.061.
- Oxford J, Gill D. Unanswered questions about the 1918 influenza pandemic: origin, pathology, and the virus itself. *Lancet Infect Dis*. 2018 June 20;18:e348–e354. doi:10.1016/S1473-3099(18)30359-1.