

A hypothesis: the conjunction of soldiers, gas, pigs, ducks, geese and horses in Northern France during the Great War provided the conditions for the emergence of the “Spanish” influenza pandemic of 1918–1919

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Abstract

The Great Influenza Pandemic of 1918–1919 was a cataclysmic outbreak of infection wherein over 50 million people died worldwide within 18 months. The question of the origin is important because most influenza surveillance at present is focussed on S.E. Asia. Two later pandemic viruses in 1957 and 1968 arose in this region. However we present evidence that early outbreaks of a new disease with rapid onset and spreadability, high mortality in young soldiers in the British base camp at Etaples in Northern France in the winter of 1917 is, at least to date, the most likely focus of origin of the pandemic. Pathologists working at Etaples and Aldershot barracks later agreed that these early outbreaks in army camps were the same disease as the infection wave of influenza in 1918.

The Etaples camp had the necessary mixture of factors for emergence of pandemic influenza including overcrowding (with 100,000 soldiers daily changing), live pigs, and nearby live geese, duck and chicken markets, horses and an additional factor 24 gases (some of them mutagenic) used in large 100 ton quantities to contaminate soldiers and the landscape. The final trigger for the ensuing pandemic was the return of millions of soldiers to their homelands around the entire world in the autumn of 1918.

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The automobile manufacturer, Henry Ford, expostulated that ‘History is bunk’. A more accurate and certainly more useful attitude is to re-visit the past, not to dwell but to learn from it for the future. It is with this in mind that we and others have researched the Edwardian and following era of 1901–1919 to focus on the origin, evolution, and spread of the so-called forgotten influenza pandemic of 1918 [1–4].

It is also clear that societies can forget the huge problems of the past. How else can we explain the forgotten pandemic of 1918–1919 which killed 4 times more humans than the Great

War itself [5,6]? Yet the 1914–1918 war is remembered yearly at the armistice ceremony on 11th November throughout Europe, the USA, Canada, Australia and New Zealand. Huge museums and libraries, photo, movie and sound archives are devoted to the subject. Probably tens of thousands of books have been written, and still are being written, about the Great War. In contrast, only a handful of books have analysed the effects of the Spanish influenza pandemic. We are appreciating, perhaps for the first time, the cataclysmic effects the outbreak had in virtually every community of the world with the possible exception of Western Samoa where an extensive quarantine excluded the virus [7,8].

The object of this brief review is to examine what can be learnt about the origin and subsequent spread of this virus and

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to deduce whether this information is of use to us today for pandemic planning. In scientific terms can a particular virulence gene of influenza be identified which could help early identification of new pandemic influenza A viruses arising anywhere in the world and with capacity to spread? In retrospect the H5 viruses, which caused six deaths in Hong Kong in 1997 and the recent outbreaks (March 2003 and 2004) lacked a crucial ability to spread from person to person [9]. The two most recent pandemics, 1957 and 1968 appeared to have started in Asia. But the origin of the greatest outbreak of all, the so-called Spanish Influenza of 1918, has been rather obscure. The resolution of the geographical epicentre could be most important for pandemic planning because most scientific attention is directed towards Hong Kong and China as a breeding focus for a new pandemic influenza A virus. But should we also be increasing surveillance in other countries that may have the requisite group of biological and geographic factors? Finally, we ask the question as to what these factors are.

Genetic analysis of influenza viral RNA from autopsy lung material of victims of the 1918–1919 outbreak

The advent of reverse transcription and the polymerase chain reaction (PCR) has allowed amplification of the minute quantities of RNA and DNA present in formalin preserved tissues thereby opening up new opportunities in the search for the origins of infectious disease agents and the range of illnesses they cause. Most medical schools have large collections of human tissue retained after post mortem examinations. Certainly, until the 1940s post mortems were carried out on most patients dying from any cause in British and other hospitals. Most often the lung, spleen, brain and kidney are preserved as small formalin-fixed paraffin-embedded tissue blocks, with stained sections or microscope slides stored separately. The records of the morbid anatomist and pathologist are often detailed and highly instructive. In this manner, lung samples from victims of the 1918–1919 influenza pandemic have been located at the Armed Forces Institute in Washington and The Royal London Hospital, London [1–4]. To date two research teams have exploited these archives to obtain nucleotide sequence analysis of four genes of influenza A virus recovered from victims who died early in 1918, October–November 1918 and early 1919 [2,4].

Four of the eight genes of influenza have now been sequenced and there is no clear genetic indication of why this virus was so virulent, though the NS1 gene-product may have played a role [10]. Therefore, we need to examine the particular circumstances of 1918, such as population movements and major events of the time. Obviously, the unique circumstance of that period was the Great War. Could the special circumstances engendered in the war itself have allowed or caused the emergence, evolution and spread of a pandemic virus?

The geographical origin of the “Spanish” influenza pandemic of 1918–1919

At present, most attention is directed towards China and Hong Kong as a potential source of a new pandemic influenza A virus. There are several reasons why virologists surmise that Hong Kong is an important epicentre for the emergence of pandemic influenza.

1. A large and young human population living in crowded conditions with ideal opportunities for viral spread by the respiratory route.
2. Outbreaks of avian influenza H5N1 have been documented in the live chicken, geese, and duck markets and on several occasions influenza A viruses have spread directly to humans [9]. The virus appears to be endemic in avians in S.E. Asia.
3. At least one pandemic virus namely A/Hong Kong/1/68 (H3N2) either originated in Hong Kong or alternatively used the city as a gateway to the rest of the world [6].

The preceding pandemic virus, the so-called ‘Asian’ influenza of 1957 originated not in Hong Kong but Japan. For the 1889 pandemic, there are a number of definitive descriptions of the virus first appearing in Russia and spreading westwards. There has been no dispute in the literature to date about the place of origin of the latter pandemic-causing virus. However, the origin of the 1918–1919 virus, that caused by far the greatest outbreak of all to date, is the centre of vigorous debate and some disagreement. At the time, there was undoubted agreement of a Spanish origin whereas, most recently, army camps in the USA have been blamed [5]. Whatever the precise “Western” source of the virus, most recent authorities agree that the 1918–1919 virus infection did not begin in China or the Far East but indeed spread eastwards towards China (reviewed in [7]).

Our analysis of the simultaneous outbreaks of influenza in the autumn of 1918 in so many countries around the world suggested to us that the virus could have seeded itself earlier. Furthermore, analysis of the rates of evolution of the neuraminidase (NA) and haemagglutinin (HA) genes suggested a possible emergence in 1915–1916 [2]. We searched the scientific literature for early outbreaks of influenza but we did not restrict our attention to the descriptive noun ‘influenza’. In earlier times, this acute infection was more often called epidemic bronchitis, epidemic catarrh or 3-day fever, or simply pyrexia of unknown origin (PUO).

We, therefore, investigated explosive outbreaks of respiratory disease that affected young people in the winter periods of 1916–1918, and focussed on those with descriptions of clinical heliotrope cyanosis and with high mortality. All these features were characteristic of the 1918–1919 influenza pandemic.

Hammond et al. [11] described an outbreak of respiratory infection, termed at the time ‘purulent bronchitis’, in a British army base at Etaples, near the coast south of Boulogne in



Fig. 1. The huge military camp and hospital base at Etaples.

Northern France (Fig. 1), during the winter of 1916. The base consisted, principally, of a huge reinforcement camp, through which British and other infantry passed to and from the front; plus a dozen or so base hospitals, placed close together along the Northern fringes of the camp. The copious records kept by the Etaples medical and administrative staff permit an hour-by-hour examination of events throughout the war. Those records depict an immense traffic of young soldiers (more than one million of them by September 1917) moving up towards the front; in the hospitals, sick and wounded men and women undergoing treatment up to 23,000 of them at any given time. They depict, in addition, a degree of dangerous overcrowding. A score or so of fit young men in each and every tent, plus the sick and wounded tightly packed together, not only in the tented wards, but laid out in palliasses in the corridors, mess and recreation rooms. They depict, not least, pathologists and physicians, including Captain Rolland, and Lieutenants Hammond and Shore, conducting a scientific study of disease, debating findings, and writing up their work [12].

In the outbreak from December 1916 to March 1917, soldiers were admitted to the base hospitals, suffering from an acute respiratory infection, high temperature, and cough at a time when recognised influenza was present. Clinical examination showed, in most cases, signs of bronchopneumonia, and pathology history showed an acute purulent bronchitis. This outbreak was further characterised clinically by heliotrope cyanosis described extensively in the ensuing 1918 outbreak, and very high mortality. Undoubtedly, overcrowded conditions on the western front and in the camp, with most of the 100,000 soldiers being housed in tents or temporary wooden barracks, were ideal for spread of a respiratory virus. At this time, ambulance trains were arriving day and night from the Somme battlefield (Fig. 2). The camp also had an extensive piggery whilst in nearby villages soldiers could purchase live geese, chickens and ducks (Fig. 3). Therefore, the requisite conditions for cross species transfer of avian influenza A virus existed at the camp alongside large numbers of young soldiers in



Fig. 2. Overcrowded conditions on the Western Front 1914–1918. (A) A typical base camp hut used for convalescence. (B) Ambulance trains ferried thousands of sick and wounded men into the Etaples base camp each day during the Battle of the Somme, 1916. There were up to 10 trains each night.

overcrowded conditions and many with a compromised respiratory system after gas attacks. In total, two million soldiers camped in this small region of Northern France, and six million soldiers occupied stretches of the 10 mile wide trench system from the English Channel to Switzerland.

An almost identical epidemic of purulent bronchitis with bronchopneumonia, with cases showing the peculiar dusky heliotrope cyanosis and mortality rates of 25–50%, was also documented for Aldershot barracks in March 1917 [14]. The pathologist at Etaples and the nearby pathology laboratory carried out transmission experiments in 1918 on monkeys and this scientific group was perhaps the first to identify the causative agent of the pandemic as a filter-passing virus [15]. Abrahams, one of the co-authors of the 1917 purulent bronchitis paper, having experienced the large 1918–1919 outbreak concluded that both outbreaks had the same causation. “We emphasise our view 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 1918 pandemic” [16]. Therefore, not only are we considering a forgotten pandemic but a forgotten and overlooked origin. The circumstances of 1916–1918, particularly the war on the Western Front, were

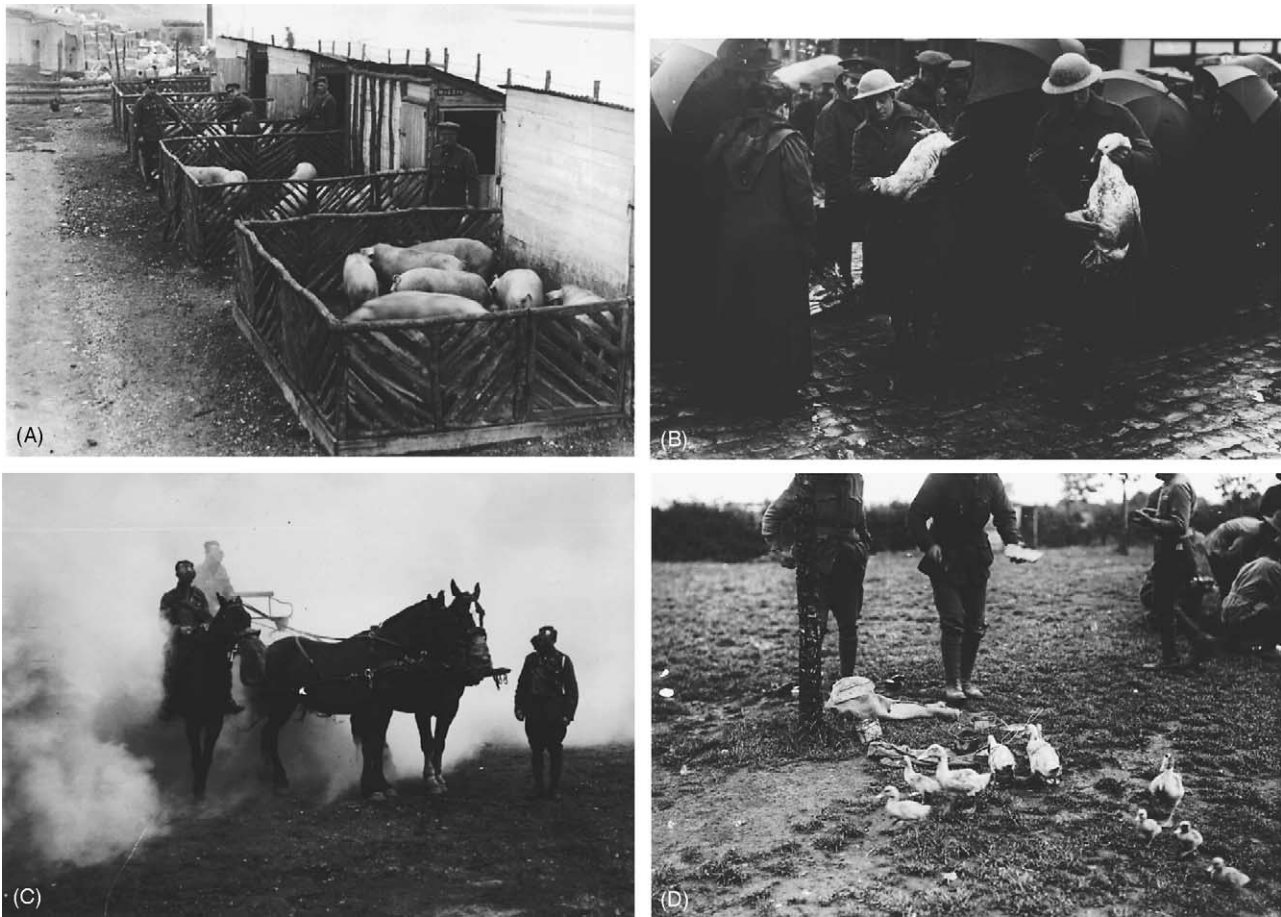


Fig. 3. Illustrations of the range of horses, pigs and live birds in the British Army 1914–1918 and contact with soldiers. (A) Pig farm in the base camp at Etaples. (B) Soldiers purchasing live geese and ducks. (C) Horse with gas mask. (D) Soldiers feeding ducks.

unprecedented [17,18]. A population of physically and mentally stressed soldiers existed due to overcrowding and the unsanitary and inhospitable landscape (contaminated with thousands of tons of respiratory irritants such as chlorine and phosgene and 23 other gases, some of them mutagenic) created by the fighting (Tables 1 and 2: 18). About 12,000 tons of the most mutagenic mustard gas (dichlorethyl sulphide) was used following its introduction in 1917 and caused 400,000 casualties. Overcrowding would have allowed rapid “passage” of influenza in literally millions of young soldiers and

provided the opportunity for an avian influenza virus zoonosis and adaptation to humans. Stepwise mutational changes would have been important factors in the evolution of the virus into a particularly infectious/virulent form resulting, at the time of the armistice, in the worldwide pandemic. Mustard gas is mutagenic [20] but whether it could accelerate mutations in viruses such as influenza has not been investigated.

The protracted period, almost 2 years, we postulate for the emergence of the “Spanish” influenza pandemic of 1918 may have been due to the absence of air travel and the effects of travel restrictions during the Great War. The new virus could have maintained itself in small civilian and military outbreaks while increasing virulence in a stepwise manner, similar to virus adaptation in animal models where hundreds of passages can be required to increase virulence of a pneumotropic strain. Several authors refer to “multiple outbreaks” in army camps at this time and we have preliminary evidence of early 1917 outbreaks in the German army in Eastern Europe (D. Gill, unpublished data). Demobilisation in the autumn of 1918 would have provided ideal opportunities for further intimate person-to-person spread and wide dispersion as soldiers returned home by sea and rail to countries around the globe (Fig. 4). Family parties organised to celebrate a

Table 1
Demographics of the Great War 1914–1918 relevant to influenza infection

Total number of soldiers	65×10^6
Total number of soldiers who died	8×10^6
Total number of soldiers who died of disease	2×10^6
Total number of civilian deaths who died of starvation and disease	6.6×10^6
Quantity of asphyxiating gases used by both sides (tons)	119×10^3
Number of soldiers who were gassed	1.2×10^6
Number of soldiers who died from gas asphyxiation	91×10^3

From [18–20].

Table 2
Factors in the military camp at Etaples which would have contributed to the emergence of the pandemic influenza A virus

Factor	Comment
Respiratory distress	Up to 1500 tons of gas were used in the months immediately prior to the winter of 1916/1917 including phosgene, diphosgene, chlorpicrin, xylyl bromide, trichlormethylchloroformate, brom methyl ethyl ketones, ethyl iodo acetate, acrolein, stannic chloride, benzyl bromide, bromacetone, hydrogen sulphide, hydrocyanic acid, phenyldichlorarsine, phenylcarbylamine chloride, dichlordemethyl ether, methylsulphuryl chloride, dimethyl sulphate, dichlorethyl sulphide (mustard)
Overcrowding	At least 100,000 soldiers per day at the Etaples camp. Continual movement of troops. Twenty thousand wounded soldiers of all nations in hospitals at the 12 sq km site
Pigs as a mixing vessel for reassortant viruses	A new experiment of the British army to move pig farms into the camp
Ducks, geese and chicken as the origin of avian pandemic influenza A viruses	Photographic evidence of soldiers of all nationalities buying fowl, plucking them, etc.
Horses	A vital component of all the fighting and transportation

From [19].

soldier's homecoming would have further exacerbated the situation.

At present, most surveillance for influenza pandemics is focused on China and Hong Kong. Chinese labourers were present in the Etaples camp in 1918, and their animal husbandry practices could have increased animal-human contact. However, Vera Brittain's classic description of the overcrowded and fraught conditions at Etaples, where she worked, identifies soldiers, administrative, and medical staff of European and Indian origin only, thereby limiting Chinese/non-Chinese contact during the time the first outbreaks were described in 1916–1917 [13]. Further, Chinese data of the period indicates that the 1918 influenza virus did not originate in China. On the contrary, most reports track movement of the virus from the Western world to China [7]. This has led us, and others [7], to exclude the possibility of a Chinese origin of the "Spanish" influenza pandemic. Most recently, Barry [21] has postulated that the virus arose in March 1918 in USA army camps but there is no published pathology evidence to support this. To the contrary, there was military traffic from Europe to the USA during 1917 as the USA prepared to enter the war. We acknowledge that definitive proof of any origin (Etaples included) would require a pathology block lung sample and identification of H1N1 RNA. Many pathology samples were exemplified at Etaples but to date we have not located a clinical sample from this 1917 period.

Therefore, we conclude that the previous four influenza pandemics (1889, 1918, 1957, 1968) have originated in Rus-



Fig. 4. Unprecedented number of young soldiers returning home in 1918.

sia, France, Japan and China, respectively. Common factors linking these four sites would be relatively large young human populations, living in crowded accommodation and in close contact with domesticated animals, notably chickens, geese, ducks and pigs. Additionally, in Russia in 1889 and France in 1916–1918 there would have been large numbers of horses (Fig. 3) perhaps reaching equivalence in some regions to the human population and even exceeding it although the significance of equine influenza viruses in pandemic emergence is unknown and deserves immediate attention.

Conclusions

To return to Henry Ford, we can assert that in the context of the great pandemic his comment was a serious misjudgement. Our search of the relevant literature from the early 20th century shows that some major discoveries were made at British army bases in 1916–1918, relating to the "Spanish" influenza pandemic of 1918–1919. A research programme was initiated to identify the new respiratory microbe of 'epidemic bronchitis' and the pathologists involved became some of the most experienced in the world. They identified Etaples as the focus of the pandemic and at the nearby laboratories in Abbeville

showed the agent of influenza to be a filter passing virus, not a bacillus. In fact, the author of the latter study had his life taken by the disease he studied [15].

The evidence presented for ‘seeding’ of the 1918–1919 influenza pandemic up to 2 years earlier and the lack of a Chinese/Far East origin contains lessons for the future. In terms of advance planning for the next influenza pandemic, it should be recognised that it could emerge anywhere in the world when particular combinations of factors arise. The epicentre could be Hong Kong but it could equally be Saudi Arabia, Pakistan, Uruguay and other South American countries, Africa, Thailand and even some regions of modern day Europe. Influenza pandemic surveillance could be increased in all these regions.

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