

SHORT REPORT

Enhanced risk of illness during the 1918 influenza pandemic after previous influenza-like illnesses in three military populations

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SUMMARY

The reasons for the unprecedented mortality during the 1918 influenza pandemic remain poorly understood. We examined morbidity records from three military cohorts from years prior to and during the 1918 pandemic period to assess the effects of previous respiratory illnesses on experiences during the pandemic. Clinical registers and morbidity lists were examined to identify all medical encounters for acute respiratory illnesses in students at two U.S. military officer training academies and Australian soldiers deployed in Europe. Influenza-like illness prior to the major pandemic wave of 1918 predisposed Australian soldiers [relative risk (RR) 1·37, 95% confidence interval (CI) 1·18–1·60, $P < 0\cdot0001$] and US officer trainees at West Point (RR 3·10, 95% CI 2·13–4·52, $P < 0\cdot0001$) and Annapolis (RR 2·03, 95% CI 1·65–2·50, $P < 0\cdot0001$) to increased risks of medically treated illnesses in late 1918. The findings suggest that susceptibility to and/or clinical expressions of the 1918 pandemic influenza virus depended on previous experiences with respiratory infectious agents. The findings are consistent with observations during the 2009 pandemic in Canada and may reflect antibody-dependent enhancement of influenza infection.

Key words: influenza, military, mortality, 1918 pandemic.

The reasons for the unprecedented mortality during the 1918–1919 influenza pandemic remain poorly understood. Of note in this regard, the 1918 pandemic preferentially killed young adults; moreover, the natures and effects of interactions in the different waves of the 1918–1919 pandemic are unclear [1]. Several Canadian studies have reported that immunization with a mismatched seasonal influenza vaccine

increased illness during the subsequent 2009 H1N1 pandemic [2, 3]. In a related study in swine, influenza immunization was associated with severe illness during subsequent infection with a different influenza strain. The study's authors hypothesized that non-neutralizing antibodies to haemagglutinin increased viral fusion through an antibody-dependent enhancement mechanism [4]. To gain insight into the interrelationships of events during 1916–1919, military health records of individuals in the Australian Imperial Force (AIF) in Europe, U.S. Military Academy, West Point, New York (USMA) and U.S. Naval Academy, Annapolis, Maryland (USNA)

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were reviewed to document all acute respiratory illnesses (ARIs) in cohort members. In all three cohorts, medically treated influenza-like illnesses (ILIs) during 1916–1918 increased the risk of clinically significant respiratory illness during the late 1918 pandemic period.

A previous report has summarized the ARI experiences of a subset of soldiers of the AIF during the First World War. For the report, ILIs were identified from the digitalized medical records of members of two infantry battalions ($n = 2063$), the medical and nursing corps ($n = 1360$), engineers ($n = 1334$) and the flying corps ($n = 1437$) who were in Europe continuously from late 1916 until the end of the war in 1918 [5]. For this report, the same records from the same subset of AIF soldiers were used to compare their respiratory illness experiences during a pre-pandemic (November 1916–April 1917) and the pandemic (September 1918–June 1919) periods.

For each individual enrolled at the USMA or USNA in late 1918, records in the historical archives of the respective academies were reviewed to ascertain dates of and reasons for all of their medical encounters prior to and during late 1918 [6, 7]. Specifically, for USMA cadets, respiratory illnesses consistent with influenza were ascertained from records of sick call visits documented in medical clinic logbooks during calendar years 1916–1920. For USNA midshipmen, respiratory illnesses consistent with influenza were ascertained from records of sick call visits documented in the personnel records of members of the graduating classes of 1919, 1920 and 1921 who were present during late 1918.

For purposes of this study, cases were defined as medical encounters of members of the study cohorts for ARIs that were possibly due to influenza (e.g. grippe, flu, influenza, pneumonia). Judgements as to whether medical encounters were case-defining were based solely on diagnoses recorded in the relevant records since no signs, symptoms, or illness histories were available. ARIs that were not likely influenza or influenza-related (e.g. mumps, measles) were not considered cases for this analysis. For consistency, a single physician made final case determinations when diagnostic labels were uncertain. Because all records were identified by the dates of case-defining illness episodes and the affected individuals, relationships between case illness experiences prior to and during late 1918 could be assessed.

Australian Imperial Force. Of the cohort of AIF members considered here ($n = 6193$), those affected by ILI

during November 1916–April 1917 were nearly 40% more likely to be affected during September 1918–June 1919 [relative risk (RR) 1.37, 95% confidence interval (CI) 1.18–1.60, $P < 0.0001$]. The magnitude of the increased risk in the AIF cohort overall was generally consistent across all military occupation-defined subgroups (occupation-specific subgroups, range of RRs: 1.42–1.91); of note, the RR estimates in nurses and in one infantry battalion did not statistically significantly exceed 1.0. Interestingly, the infantry battalion in which illness during the pre-pandemic period did not statistically significantly increase risk during the pandemic period had markedly low mortality during the pandemic period. In contrast, in the other infantry battalion included in the AIF cohort overall, ILI during the pre-pandemic period was associated not only with increased illness risk (RR 1.43, 95% CI 1.06–1.92, $P < 0.01$) but also with high influenza-related mortality during the pandemic period. [5]

U.S. Military Academy. At the USMA, West Point, New York, there were sharp peaks of ARI during 1916, 1917, early 1918, and late 1918–1919 (Fig. 1). Because many USMA cadets were sent to the war in Europe prior to their scheduled graduation dates, only 511 cadets were present at West Point both in early 1918 (first pandemic wave period) and late 1918 (second pandemic wave period). Of those who were present throughout 1918, 154 were affected by influenza during late 1918 (illness attack rate 30.1%). No cadet present at the beginning of 1918 died during the influenza pandemic.

There was no association between influenza-like respiratory disease during the first wave period (February–April 1918) (illness attack rate 24.1%) and ILI during the second wave period (September–October 1918) [illness attack rate during autumn 1918: 30% in previously ill vs. 32% in not previously ill (RR 0.95, 95% CI 0.70–1.29, $P = 0.72$)]. However, of the 227 cadets who had been at the academy throughout both 1917 and 1918, those who were treated for influenza-like respiratory disease during early 1917 were three times more likely than their counterparts to be treated for ILIs during late 1918 (ILI attack rate in late 1918 in relation to experience in 1917: 67% in those affected in 1917 vs. 22% in those not affected in 1917 (RR 3.10, 95% CI 2.13–4.52, $P < 0.0001$). Three cadets died during the 1918–1919 influenza pandemic period: one in November 1918 and two during January–February 1919. All three cadets who died had entered the academy in

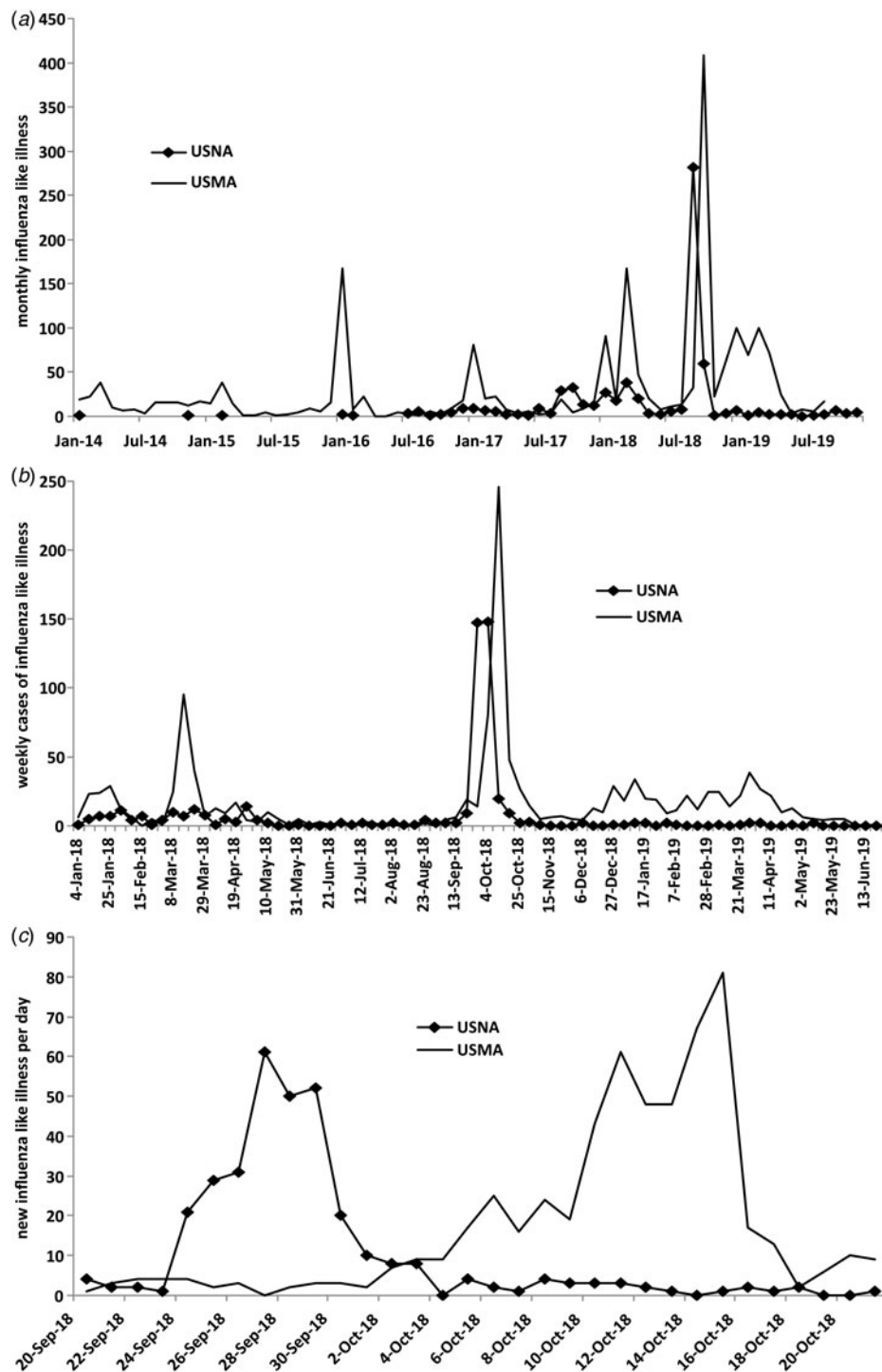


Fig. 1. (a) Monthly (1914–1919), (b) weekly (1918–1919) and (c) daily (September–October 1918) influenza-like illnesses at U.S. Military Academy, West Point, New York (USMA) and U.S. Naval Academy, Annapolis, Maryland (USNA).

November 1918; as such, none were at the academy during previous respiratory disease epidemics.

U.S. Naval Academy. At the USNA, there were only small increases of ILI during autumn 1917 and early 1918. In late 1918, influenza-like respiratory disease

cases suddenly increased on 24 September (one day after the start of the academic year), peaked on 27 September, and returned to baseline on 4 October. During the late 1918 epidemic, 313 midshipmen were treated for ILIs; the overall illness attack rate during the epidemic was 26% (Fig. 1).

At the time of the late 1918 outbreak, there were three graduation year-defined classes at the USNA: 1920, 1921, and 1922. Because members of the class of 1922 entered the academy in mid-1918, only members of the classes of 1920 and 1921 ($n = 1190$) were present during all of 1918. Unlike cadets at USMA, midshipmen at USNA did not experience a distinct influenza-like respiratory disease wave in early 1918 (Fig. 1). However, midshipmen who had been medically treated for ILI anytime between October 1917 and April 1918 (13.5% illness attack rate) were twice as likely as their counterparts to be affected by ILI during autumn 1918 [illness attack rate in autumn 1918: 48% in those affected in October 1917–April 1918 vs. 24% in those not affected in October 1917–April 1918 (RR 2.03, 95% CI 1.65–2.50, $P < 0.0001$)].

Members of the classes of 1920 and 1921 participated in training cruises during the summer of 1918. Six midshipmen who had been on training cruises died during the epidemic; two of these had been on the same ship. The training cruises embarked 7 June and returned 30 August. The academic year at the academy began 23 September, the index case of the epidemic was hospitalized on 24 September, the academy was quarantined on 26 September, and the first death was on 3 October. From 3 to 21 October 1918, ten midshipmen died of influenza-related illnesses. Eight of the ten deaths occurred within 7 days (3–10 October), and the first three deaths occurred on 3 consecutive days and affected one member of each class. During the epidemic, there were four deaths in the most senior class (class of 1920, cumulative mortality: 0.82%), two deaths in the class of 1921 (cumulative mortality 0.30%), and four deaths in the most recently enrolled class (class of 1922, cumulative mortality 0.42%). The cumulative mortality percent in midshipmen overall was 0.47%. Only one midshipman who died had a previously recorded influenza-like respiratory disease episode (in March 1917) while at the USNA.

In this review of all medical encounters of three geographically separate cohorts of young adult men during and prior to 1918, previous ILIs consistently increased risk of medically treated ARIs during the 1918 pandemic period. The underlying causes of this unexpected finding are unclear. In other settings, antibodies produced after exposures to certain infectious agents alter the clinical expressions of infections with antigenically different strains of the same agents ('antibody-dependent enhancement'). Unfortunately, no archived clinical specimens are available for

investigation of such a hypothesis in regard to the experiences documented here. Fortunately, complete records of the natures and dates of all medical encounters of three epidemiologically closed cohorts have survived. Such records allow determinations of the ARI experiences of all cohort members during the 2 years preceding the lethal wave of the 1918 influenza pandemic. In each of the cohorts, medically treated episodes of ARI in 1916 to mid-1918 markedly increased clinically significant ILIs during late 1918.

The findings are counterintuitive and unexpected. For example, several authors have suggested that episodes of ILI during spring–early summer 1918 ('first wave') provided immunological protection from infection with the highly lethal pandemic strain during the 1918–1919 autumn–winter seasons ('second and third waves'). However, both the AIF and USMA were affected by outbreaks of ARI in early 1918; and in both cohorts, influenza-like respiratory illnesses during spring–summer 1918 did not change illness attack rates during autumn–winter 1918–1919 [5].

At USNA, there were no distinct outbreaks of ARI during the first wave period (spring–summer) of 1918. In USNA midshipmen, the 'previous illnesses' assessed as possible risk factors for ILIs in autumn–winter 1918–1919 were ascertained during a broad interval (October 1917–April 1918). Illnesses that affected midshipmen during this interval markedly increased risk of ILI in late 1918; the effects resembled those observed in AIF and USMA members who had medically treated ILIs in late 1916–1917 (Fig. 1).

These findings of this report are consistent with those of studies of pandemic-related mortality as opposed to morbidity in U.S. Army soldiers. Illness in early 1918 could protect against mortality in late 1918 as observed in Australian soldiers in France as well as in U.S. Army soldiers recruited from the states of Indiana and Kansas. For example, compared to their urban counterparts, US soldiers who resided in rural areas of Indiana and Kansas prior to the pandemic had much higher influenza/pneumonia-related death rates in late 1918–1919. It is likely that residents of urban areas were exposed to greater numbers and more antigenically diverse respiratory infectious agents prior to entering military service in mid-1918 [8, 9].

Of note in this regard, AIF soldiers who were medically treated for ARIs during April–July 1918 ('pandemic first wave') had similar illness rates, but were much less likely to die than their counterparts (OR 0.37, 95% CI 0.25–0.53, $P < 0.001$) during late

1918–1919 [5]. The simplest explanation of the findings is that at least two influenza virus strains circulated during 1916–19; this conjecture is consistent with recently reported genomic data showing multiple lines of influenza were present in 1918 [10] as well as a spatio-temporal study of both pandemic waves in the British Armies in France in 1918 [9]. These data coupled with the lack of protection from illness in late 1918 by ILI in early 1918 in both the AIF and USMA suggest that at least two immunologically distinct influenza viruses were circulating in 1918.

There are limitations to this study that should be considered when interpreting the findings. For example, the data analysed for the report were related to three different military groups whose clinically attended illnesses were documented in different manners in records that were archived and retrievable. Because comparable records of the experiences of other groups are very rare, it is difficult to assess the generalizability of the findings here to other populations and settings.

Moreover, the observation times of the cohorts of interest for this report varied. For each cohort, the illness experiences that were documented in detail prior to the 1918 pandemic period focused on times when high rates of ARI affected the group. It is plausible that influenza viruses caused many or most of the epidemics of ILIs in the pre-1918 pandemic period. However, the assertion cannot be validated because the pre-1918 period preceded the discovery of influenza viruses, and relevant clinical materials from the period are not available for modern analyses. Undoubtedly, some ILIs that were considered cases for this report were due to non-influenza respiratory pathogens.

In most cases since the 1918–1919 pandemic, serial influenza infections have not resulted in enhanced subsequent illness. The contrasting findings of this report document a unique characteristic of the 1918–1919 pandemic that is poorly understood but potentially relevant for preventing or responding to future pandemics.

In the three closely followed military cohorts described herein, some but not all ILIs during the previous 2 years increased risk of medically treated illness during autumn–winter 1918–1919. We hypothesize that the observed effects were related, at least in part, to antibody-dependent enhancement. This could have resulted when cross-reactive antibody binding to a new influenza virus created an immune complex which was then better able to infect

additional cells through increased viral membrane fusion activity. In a swine influenza model, severe clinical outcomes after immunization were caused by antibody-dependent enhancement [4]. Such experiences in swine support the potential of antibody-dependent enhancement after sequential influenza infections in humans. Other mechanistic possibilities such as T-cell mediated hypersensitivity exist, but we think that given the time-course of the events described that the observations are more likely to be explained by antibodies. Further studies to assess the potential for and determinants of antibody-dependent enhancement of the clinical expressions of influenza infections after immunizations of humans are indicated.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Morens DM, Fauci AS.** The 1918 influenza pandemic: insights for the 21st century. *Journal of Infectious Diseases* 2007; **195**: 1018–1028.
2. **Janjua NZ, et al.** Seasonal influenza vaccine and increased risk of pandemic A/H1N1-related illness: first detection of the association in British Columbia, Canada. *Clinical Infectious Diseases* 2010; **51**: 1017–1027.
3. **Skowronski DM, et al.** Association between the 2008–09 seasonal influenza vaccine and pandemic H1N1 illness during spring–summer 2009: four observational studies from Canada. *PLoS Medicine* 2010; **7**: e1000258.

4. **Khurana S, et al.** Vaccine-induced anti-HA2 antibodies promote virus fusion and enhance influenza virus respiratory disease. *Science Translational Medicine* 2013; **5**: 200ra114–200ra114.
5. **Shanks GD, et al.** Mortality risk factors during the 1918–19 influenza pandemic in the Australian army. *Journal of Infectious Diseases* 2010; **201**: 1880–1889.
6. **US Army.** Annual report of the Superintendent United States Military Academy, 1919. West Point, NY: USAMA.
7. **US Navy.** Report of the commandant of the US Naval Academy, 1919. Annapolis: USNA.
8. **Paynter S, Ware RS, Shanks GD.** Host and environmental factors reducing mortality during the 1918–1919 influenza pandemic. *Epidemiology and Infection* 2011; **139**: 1425–1430.
9. **Shanks GD, et al.** Opinion: spatiotemporal investigation of the 1918 influenza pandemic in military populations indicates two different viruses *Epidemiology and Infection* 2015; **143**: 1816–1825.
10. **Worobey M, Han G, Rambaut A.** Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus. *Proceedings of the National Academy of Science USA* 2014; **111**: 8107–8112.