

Cross-Protection between Successive Waves of the 1918–1919 Influenza Pandemic: Epidemiological Evidence from US Army Camps and from Britain

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Background. The current worst-case scenario for pandemic influenza planning is based on the catastrophic 1918–1919 pandemic. In this article, we examine the strength of cross-protection between successive waves of the 1918–1919 pandemic, which has remained a long-standing issue of debate.

Method. We studied monthly hospitalization and mortality rates for respiratory illness in 37 army camps, as well as the rates of repeated episodes of influenza infection during January–December 1918 in 8 military and civilian settings in the United States and Britain.

Results. A first wave of respiratory illness occurred in US Army camps during March–May 1918 and in Britain during May–June, followed by a lethal second wave in the fall. The first wave was characterized by high morbidity but had a lower fatality rate than the second wave (1.1% vs. 4.7% among hospitalized soldiers; $P < .001$). Based on repeated illness data, the first wave provided 35%–94% protection against clinical illness during the second wave and 56%–89% protection against death ($P < .001$).

Conclusion. Exposure to influenza in the spring and summer of 1918 provided mortality and morbidity protection during the fall pandemic wave. The intensity of the first wave may have differed across US cities and countries and may partly explain geographical variation in pandemic mortality rates in the fall. Pandemic preparedness plans should consider that immune protection could be naturally acquired during a first wave of mild influenza illnesses.

Most readers know George Santayana's admonition "Those who cannot remember the past are condemned to repeat it" [1]. Fewer are likely to know George Bernard Shaw's observation that "We learn from history that men never learn anything from history" [2].

Whether the policy makers, public health experts, and scientists who are now planning for a possible future influenza pandemic end up heeding Santayana's warning or proving Shaw correct depends on just how wisely they interpret the experience of the 1918–1919 pandemic. Yet, some important data that affect our understanding of this pandemic have never been reviewed in

the modern scientific literature, whereas other studies published in the 1920s and 1930s seem to have been forgotten or, in some cases, misinterpreted.

A key question involves the temporal pattern in which the pandemic influenza A/H1N1 virus moved through the human population and the implications for pandemic planning. Traditionally, the 1918–1919 pandemic has been described as coming in 3 waves in the United States and Europe: a mild first wave in spring or summer 1918, an extremely lethal second wave in fall 1918, followed by a less severe third wave in winter and spring 1919 [3]. Speculation has attributed these closely spaced waves to either entirely different viruses or sequential variants of the A/H1N1 pandemic virus [4].

Epidemiological and medical reports suggest that a widespread outbreak of influenza-like illness began in March 1918 in the US military and spread rapidly through Army training camps. The outbreak disseminated to civilian communities, mostly in the eastern United States, but was associated with far less mortality than were later outbreaks in the fall [5–7]. By June, outbreaks of respiratory illness had seemingly disappeared

Received 14 February 2008; accepted 30 May 2008; electronically published 12 September 2008.

Potential conflicts of interest: none reported.

Financial support: National Institutes of Health, intramural program (to C.V.); George Washington University (to L.S.); Sloan Foundation (to J.M.B.).

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The Journal of Infectious Diseases 2008;198:1427–34

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0022-1899/2008/19810-0003\$15.00

DOI: 10.1086/592454

from civilian communities in the continental United States, but explosive outbreaks of mild influenza-like illnesses were described during the summer in Europe, peaking in June and July in England, Switzerland, Scandinavia, and parts of the Pacific rim [8–11]. In addition to these reports of outbreaks of influenza-like illness in early 1918, quantitative studies involving civilian populations in New York, New York [12]; Louisville, Kentucky [13]; and Copenhagen, Denmark [8], have provided epidemiological evidence that these early waves had the classical signature of the A/H1N1 pandemic virus, with the highest mortality rate occurring in young adults.

Historical evidence from the virus specimens involved in the successive waves is not available for comparison that might shed light on the patterns of spread and their implications. However, if it can be demonstrated that illness during the spring and summer 1918 pandemic waves conferred protection against illness during the fall 1918 wave, this would provide epidemiological evidence of cross-immunity between viruses circulating during these waves. This in turn would suggest that these viruses were genetically related—probably sequential variants of the emerging A/H1N1 pandemic virus. Unfortunately, there has been no quantitative review of the relevant epidemiological evidence so far, and thus little is understood about the different viruses involved and the acquisition of immunity in populations facing successive attacks of pandemic influenza.

In this article, we attempt to fill this void by conducting a quantitative review of cross-protection in successive outbreaks of respiratory illness during 1918, using detailed morbidity and mortality data from US Army camps, British military data, and data from British civilian communities. We discuss the implications of our findings in the context of pandemic planning.

METHODS

General Approach

Monthly hospitalization and mortality data for respiratory illness were used to study the spatiotemporal patterns and impact of the successive pandemic waves in US Army training camps during 1918 [14, 15]. Army documents listed hospitalizations and deaths specifically attributed to “influenza,” but we refrained from analyzing those data after noticing that the criteria used to diagnose influenza differed between camps. Approximately 1.3 million enlisted men passed through these camps during 1918, of whom ~475,000 (36.1%) fell ill with respiratory illness and ~24,000 (1.9%) died of such illness.

We also used more detailed reports that described the disease status of each individual during successive pandemic waves in the US Army camps [15, 16], the British Grand Fleet [10], and British civilian communities [11] to quantify cross-protection between successive waves. For the sake of simplicity, the outbreaks of influenza-like illness during March–August 1918 in the United States and Britain are referred to as the first pandemic

wave. Later outbreaks in September–November 1918 are referred to as the second pandemic wave.

Overall Epidemic Patterns of the 1918 Pandemic in US Army Training Camps

Monthly statistics from US Army training camps. Disease surveillance was in place in 37 of the 39 largest US Army camps for all months during January–December 1918. These camps ranged in size from roughly 20,000 to 60,000 troops; most camps held 25,000–40,000 troops. We studied monthly rates of hospitalization and death for respiratory illness in these 37 training camps, as reported by medical authorities [17]. Because recruits entered these camps for training and then went to France, the camp populations fluctuated widely over the study period (for example, the Camp Cody population ranged from 3,000 to 25,000 troops); because of these fluctuations, we used monthly population estimates [17].

Magnitude of pandemic waves. For each of the 37 US Army training camps studied, we estimated the hospitalization rate for respiratory illness during the first wave in the spring, defined as March–May 1918. We then computed the corresponding rate for the second wave in the fall, September–November 1918. Because of substantial variability in baseline hospitalization rates between camps, even in the absence of outbreaks of respiratory illness, we could not directly compare rates. Instead, we compared the relative incidence of respiratory disease during the first and second waves. Accordingly, we identified the camps with the greatest amount of illness during the first wave, i.e., those camps where hospitalization rates during the first wave were $\geq 50\%$ as high as the rates during the second wave.

Cross-Protection between Successive Pandemic Waves, 1918–1919

Attack rates in US Army personnel, according to time enlisted. In the fall of 1918, US Army clinicians and epidemiologists immediately recognized differences between new recruits (defined by Army epidemiologists as individuals with < 1 month of service) and seasoned troops (defined as individuals with > 1 month of service) with respect to influenza-related morbidity and mortality rates [5, 6, 14]. These observations suggested a protective effect at work in seasoned personnel, who had presumably been naturally immunized by prior influenza exposure during the first wave, while in the Army.

Five US Army camps provided detailed data for influenza illnesses and deaths during the second wave, as a function of length of tenure in the Army, which allowed comparison between new recruits and seasoned troops (Camp Grant, Illinois; Columbus Barracks, Ohio; Fort McDowell, California; Camp Pike, Arkansas; and Camp Lee, Virginia) [7, 14, 16]. In addition, 2 regiments of seasoned troops that were trained at Camp Dodge in the fall were compared: one regiment had been exposed to the first wave

while stationed in Hawaii during the spring, whereas the other had escaped it because it was stationed in Alaska [16].

Repeated episodes of illness in the British Grand Fleet. One publication provided the numbers of sailors in the British Grand Fleet who were sick with influenza during each of the 2 waves (in May and September 1918) and during both waves. Unlike the US Army training camp populations, this population remained constant at 90,000 individuals. [10]

Repeated episodes of illness in British civilian communities. For 25,000 individuals in 12 British civilian communities, we compiled the rates of successive influenza illnesses for the first wave in June 1918, the second wave in September–October 1918, and the third wave in winter 1918–1919. [11]

Estimates of cross-protection. To quantify cross-protection, we relied on methods used for estimating the protective effect of vaccination in cohort studies, comparing the relative risk (RR) of disease in vaccinated and unvaccinated cohorts. We compared the risk of developing influenza during the second wave among individuals who had been sick with influenza in the first wave (i.e., the “naturally immunized” cohort), relative to individuals who remained influenza-free during the first wave (i.e., the cohort not naturally immunized). We used a similar approach for Army camp data, comparing the risk of influenza illness or death among seasoned personnel who had presumably been exposed to influenza during the first wave versus new recruits who had not. Point estimates and 95% confidence intervals (CIs) for the effectiveness of cross-protection were estimated as $1 - RR$.

RESULTS

Overall Epidemic Patterns of the 1918 Pandemic in US Army Training Camps

Hospitalization rates. A peak in hospitalization for respiratory illness occurred in March–April 1918 and subsided in May 1918, followed by a second peak in September–November (figure 1A). Across all camps, 11.8% (143,986/1,219,359) of the personnel were hospitalized for respiratory illness during the first wave in March–May, whereas 27.5% (437,224/1,591,835) were hospitalized during the second wave in September–November (figure 1A). The mean hospitalization rate was ~3.4-fold lower during the first wave than it was during the second wave (range, 1.1–9.4 hospitalizations per 100 individuals). However, in 10 (27%) of the 37 camps, hospitalization rates during the first wave exceeded 50% of the rates observed during the second wave. During the peak of the first wave, hospitalization rates had more than doubled in comparison with the February 1918 hospitalization rates in 16 camps. The monthly data for the 3 camps that experienced the most pronounced first waves of illness are presented in figure 1B. In one of these camps (Camp Wheeler), the

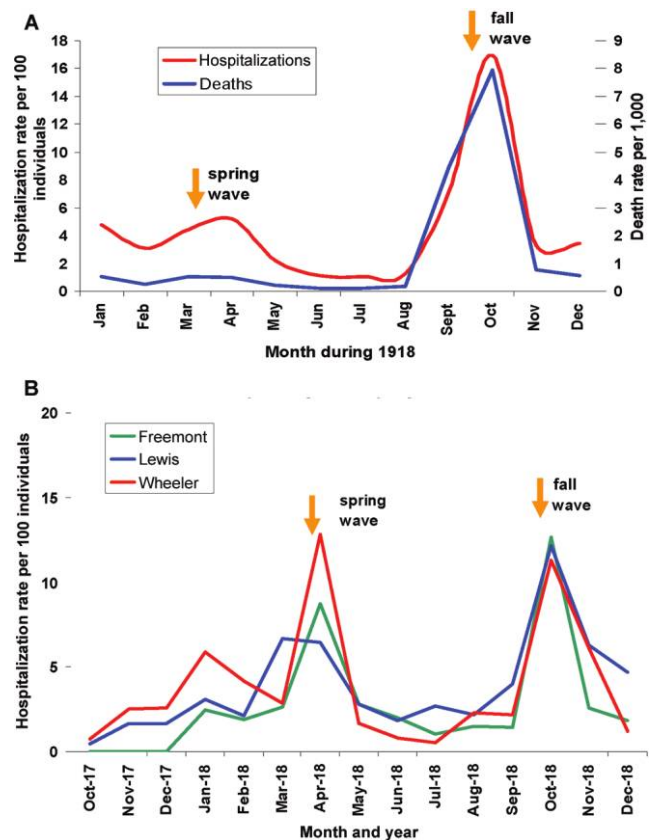


Figure 1. Morbidity and mortality from respiratory illness in US Army training camps. *A*, Monthly rates of hospitalizations and deaths among enlisted men in US Army training camps, January–December 1918 (total for all 37 camps). *B*, Monthly rates of hospitalization for October 1917–December 1918 for the 3 US Army training camps that experienced the most pronounced spring wave of illness, relative to the amount of illness in the fall.

monthly peak hospitalization rate was even higher during the first wave than during the second wave.

We note that in 6 camps, the hospitalization rate in January 1918 was more than double the February 1918 rate. On the basis of the coding for the hospitalizations in January, we could rule out a measles epidemic (a widespread measles epidemic had spread through many camps in the preceding months), but we could not distinguish between the increased activity of a seasonal influenza virus, a pandemic influenza virus, or the activity of another respiratory pathogen. Although contemporary investigators noted this January peak, none associated it with pandemic influenza. This is consistent with reports of a typical seasonal influenza outbreak in January 1918 in New York City, with the highest excess mortality occurring among individuals >65 years of age [12].

Mortality rates. In all of the US camps studied, there was a small increase in death rates from respiratory illness that peaked in March–April 1918, and a large peak in the fall that coincided with the second pandemic wave (figure 1A). Combining the morbidity and mortality data, we estimated that the case-fatality

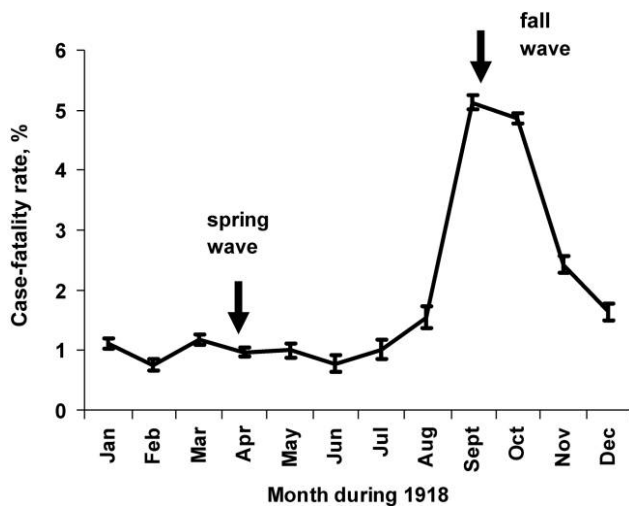


Figure 2. Monthly case-fatality rate among individuals hospitalized for respiratory illness, for all enlisted men in US Army camps, 1918. *Black bars*, 95% confidence intervals. Arrows point to the time of the spring and fall pandemic waves; note the lack of elevation above the background case-fatality rate in the spring and the large elevation above the background rate in the fall.

rate among US Army soldiers hospitalized for respiratory illness peaked at 5.1% in September 1918, up from baseline levels of 0.8%–1.5% earlier that year (figure 2). Overall, the first wave was rather mild, with a ~5-fold lower case-fatality rate, compared with the second wave (1.1% during March–May vs. 4.7% during September–November; $P < .001$).

Cross-protection between successive pandemic waves, 1918–1919

Attack rates in US Army personnel based on time enlisted.

Five US army camps gave detailed data on influenza-related morbidity and mortality during the second pandemic wave, as a function of length of tenure in the Army (table 1). Protection

against death during the second wave was estimated at 56% (95% CI, 51%–61%) and 89% (95% CI, 66%–97%) in seasoned personnel from Camp Grant and Columbus Barracks, respectively. Protection against clinical illness during the second wave was estimated to range between 49% and 94% (95% CI, 48%–97%) in seasoned personnel from 3 camps: Camp Pike, Camp Lee, and Fort McDowell.

In addition, we could estimate protection in a sixth camp, Camp Dodge, where one regiment of seasoned troops had experienced the first wave, while another seasoned regiment had escaped it. Among troops exposed in the spring, 6.6% (198 of an estimated 3000 troops) became sick with influenza in the fall. In contrast, among the troops not exposed in the spring, 48.5% (1455 of an estimated 3000 troops) became sick with influenza in the fall at Camp Dodge ($P < .001$). In this comparison, which adjusts for length of tenure in the army, age, and housing conditions, we estimated that prior exposure afforded 86% protection (95% CI, 84%–88%) against influenza illness in the fall.

Repeated episodes of illness in the British Grand Fleet. In the British Grand Fleet population comprising 90,000 sailors, approximately 10,313 (11.5%) came down with clinical influenza during the first wave in May–June of 1918. We estimated that influenza illness in the spring provided 72% protection (95% CI, 68%–76%) for these sailors against illness in the fall, relative to sailors who had not been ill during the first wave (table 2).

Repeated episodes of illness in British civilian communities. In 12 British communities (population 24,706) where repeated episodes of clinical influenza illness were monitored during 1918, there were 2863 individuals (11.6%) with influenza during the first wave in summer 1918 (table 2). We estimated that summer illnesses were associated with 35% protection against illness during the second wave in the fall (95% CI, 27%–43%), relative to those who had escaped illness in summer.

Table 1. Influenza-related morbidity and mortality among US Army personnel during the second 1918 pandemic wave, according to length of tenure in the Army.

US Army training camp	Outcome measured during fall wave	Troops affected, proportion (%)		Protective effect ^a (95% CI)
		>1 month, seasoned troops	<1 month, new recruits	
Camp Grant	Death	510/30,000 (1.7)	780/20,000 (3.9)	56%(51%–61%)
Columbus Barracks	Death	3/929 (0.3)	55/1814 (3.0)	89%(66%–97%)
Fort McDowell ^b	Influenza illness	14/684 (2.0)	339/969 (35)	94%(90%–97%)
Camp Pike	Influenza illness	4461/28,782 (15.5)	7267/23,749 (30.6)	49%(48%–51%)
Camp Lee ^c	Influenza illness	711/16,100 (4.4)	1000/3220 (31.1)	86%(84%–87%)

NOTE. Data from Vaughan [7, 14], and the Office of Medical History, Office of the Surgeon General [16]. All $P < .001$. CI, confidence interval.

^a The protective effect was calculated as $1 - \text{relative risk (RR)}$, where RR equals the percentage of seasoned troops affected/percentage of new recruits affected.

^b Seasoned troops at this camp are the permanent staff.

^c Percentage data information from Hall [16] combined with data from a British pandemic report [11].

Table 2. Clinical illness during the first wave of the 1918 pandemic in the spring and summer and protective effect against illness during the second wave in fall 1918, British military and civilian communities.

Population, illness status	Illness in fall	No illness in fall	RR (95% CI)	Protective effect (95% CI)	<i>P</i>
British Grand Fleet^a (N = 90,000)					
Illness in spring	186	10,127	0.28 (0.24–0.32)	72% (68%–76%)	<.001
No illness in spring	5195	74,492			
Twelve civilian British communities^b (N = 24,706)					
Illness in summer	240	2623	0.65 (0.57–0.73)	35% (27%–43%)	<.001
No illness in summer	2831	19,012			

^a Data on influenza illness in May and September 1918 [10].

^b Data from a British pandemic report [11].

In these communities, influenza illnesses were also monitored during the third pandemic wave in winter 1918–1919. We noted that illness during the first wave did not protect against illness during the third wave (estimated protective effect, –9% [95% CI, –23% to 3%]), nor did illness during the second wave protect against illness during the third wave (estimated protective effect, 3% [95% CI, –10% to 14%]) (table 3).

DISCUSSION

Our quantitative review of epidemiological data from military and civilian communities in the United States and Britain strongly points to cross-protection between outbreaks of respiratory illness during spring and early summer of 1918 and the influenza pandemic wave in the fall of 1918. The cross-protection effect was estimated to range from 35% to 94% for clinical illness and from 56% to 89% for mortality. Cross-protection was observed for both mortality and mild morbidity outcomes, suggesting that factors beyond viral virulence were at play. Of note, the estimated level of protection is comparable to that conferred by modern influenza vaccines, which are ~70%–90% effective against laboratory-confirmed influenza in healthy adults [18].

There are several limitations to our study. We stratified influenza outcomes during the pandemic wave in fall 1918 by length of tenure in the Army, assuming that seasoned troops were exposed to the first wave in spring while in Army training camps, whereas new recruits were not. We think it likely that most new recruits were not exposed to the spring wave as civilians. In only a few places in the United States did the spring wave cause enough illnesses to be recognized contemporaneously, and investigators looking retrospectively for early signs of the pandemic did not find widespread disease among US civilians [12, 13, 16]. In a comprehensive survey of the literature, Edwin Jordan observed that in civilian communities “a striking feature of the first wave was that. . . it lacked the extreme diffusive vigor of the pandemic. . . showing a tendency to die out.” [19, p. 96]. In contrast, we have shown that a widespread spring wave of influenza-like infections sickened ~12% of the military personnel in large US Army camps. The reason why spring outbreaks did not die out in Army camps remains unclear but may be related to high population mixing or a continuous influx of influenza-naive recruits. In Camp Funston, in Kansas, 5 consecutive outbreaks of influenza-like illness occurred between early March and summer 1918, coinciding with the arrival of large numbers of

Table 3. Protective effect of illness during the first and second pandemic waves against illness during the third wave (winter 1918–1919), based on data from 12 civilian British communities (population 24,706).

Seasonal wave, illness status	Illness in winter	No illness in winter	RR (95% CI)	Protective effect (95% CI)	<i>P</i>
Summer wave					
Illness	270	2579	1.09 (0.97–1.23)	–9% (–22% to 3%)	.15
No illness	1895	19,962			
Fall wave					
Illness	262	2813	0.97 (0.86–1.10)	3% (–10% to 14%)	.68
No illness	1895	19,736			

NOTE. Data from a British pandemic report [11]. CI, confidence interval; RR, relative risk. Slight differences between data for British civilians in tables 2 and 3 are the result of rounding errors in converting the percentages in the report [11] into numbers.

Table 4. Population structure in US Army camps in fall 1918, stratified by pandemic mortality during the fall wave.

Mortality index	Camp population by length of tenure in the Army, %	
	>1 month, seasoned troops	<1 month, new recruits
Severe	59	41
Moderately severe	69	31
Moderately mild	78	22
Mild	84	16

NOTE. Data are as reported in Hall [16]. If camp populations were divided into groups according to mortality in the fall, mortality was found to correlate with the proportion of new recruits. For instance, in camps with mildest mortality impact, a disproportionate 84% of the camp population was seasoned troops, whereas 16% was new recruits. This may be explained by seasoned troops having acquired protective immunity during exposure to influenza in spring and summer of 1918. Only percentages were available from Hall [16].

new recruits; a similar pattern was observed elsewhere [14; 16, p. 135]. These arguments support the comparison of seasoned troops and new recruits as proxies for differential exposure to influenza in the spring of 1918.

Our analysis may involve some misclassification of spring exposure to influenza because some recruits could have been exposed as civilians, whereas some seasoned troops could have escaped the spring wave. However, any misclassification bias would go *against* showing protection and our estimates of protective effect may somewhat underestimate the true benefits.

Unfortunately, in most US Army camps analyses we could not adjust for differences in living conditions and age between and within regiments, which may have affected the risk of contracting influenza in the fall. However, a comparison of 2 groups of seasoned troops who lived side by side in the same conditions at Camp Dodge and differed only in their exposure to influenza in the spring also yielded a high estimate of cross-protection (84% [95% CI, 82%–86%]). In addition, to increase manpower availability, the US Army raised the maximum age of eligible draftees from 30 years to 45 years in September 1918, so that troops newly drafted in the fall were likely to be older than seasoned troops. Because older adults fared better in the pandemic, this potential age difference would also underestimate the true level of cross-protection.

Despite these caveats, and in line with the intuition of contemporary Army epidemiologists, we found protection against influenza-related morbidity and mortality in seasoned troops during the second pandemic wave in fall 1918, compared with new recruits. It is interesting to note that camps with the highest proportion of new recruits had the highest fall mortality rates (table 4), an observation that agrees with our findings,

Analyses based on data from the British Grand Fleet and British civilian communities are also likely to underestimate the true

protective effect of the first pandemic wave. We relied on non-specific reports of clinical influenza illness without laboratory confirmation, and the contribution of other respiratory pathogens or asymptomatic infections would attenuate the estimated protective effect.

Taken together, this set of quantitative analyses based on data from civilian and military settings in 2 countries, performed using a robust and conservative statistical approach [11, 20], suggests that influenza illness during the first pandemic wave provided protection against illness during the second wave. Interestingly, in the course of our analysis, we revisited epidemiological evidence from 12 British civilian communities and obtained an estimated 35% protection (95% CI, 27%–43%), which is somewhat lower than the estimate of 54% published in the original study [11]. Analysis of a subset of these same data was later cited as evidence against protection [21], but this subanalysis does not corroborate the conclusions of the larger study [11].

We think the most parsimonious explanation for the observed cross-protection is that both pandemic waves—the first in spring-summer 1918 and the second in fall 1918—were caused by sequential variants of A/H1N1 viruses. Given the high level of clinical protection evidenced in our study, it is unlikely that non-specific or heterosubtypic immunity played a role (e.g., by means of a related neuraminidase antigen or internal proteins [22, 23]). The influenza virus circulating during the first wave in March-April 1918 in the United States was perhaps not fully adapted to the human host, because it apparently did not spread effectively in civilian populations. In parallel, the case-fatality rate for respiratory disease in US Army camps increased from ~1% during the first wave to ~5% during the fall wave, suggesting an increase in virus virulence over time. This pattern corroborates similar findings from Copenhagen, where the case-fatality rate of pandemic influenza was lower in summer than fall (~0.35% vs. ~2.3%) [8]. Alternatively, it is possible that cocirculating respiratory bacterial pathogens increased disease severity in the fall, while nearly identical influenza viruses circulated during both waves. For instance, mouse models have demonstrated lethal synergy between influenza A virus and *S. pneumoniae* [24].

A key area for future research is to investigate how widespread the outbreaks of pandemic influenza were in US cities during the first wave during March-April 1918 and whether virulence patterns mirrored those observed in US Army camps. A telltale signature of the 1918 pandemic virus was increased mortality in young adults [8, 12]; only 2 studies of civilian populations documented unusually high mortality risk in young adults as early as March 1918 in New York City and Louisville [12, 13]. Such studies require morbidity and mortality data with fine age and time resolution, which are, unfortunately, not available for most US cities. In the military, because virtually all troops were young adults, the age signature of the respiratory pathogens circulating during 1918 could not be investigated.

For reasons not fully understood, pandemic mortality rates during the fall 1918 wave varied almost 4-fold among US cities [25]. Recent studies have suggested that most of this variation could be explained by differences in the intensity and timing of nonpharmaceutical public health interventions [26–28]. However, this interpretation has recently been debated [28–30]. In this study, we propose that geographical differences in population immunity acquired during the first wave could have contributed to the observed variation during the second wave. For example, New York City and Louisville experienced a first wave during March–April 1918 [12, 13] and a relatively low mortality or morbidity impact during the second wave [28, 31].

Another possible explanation of pandemic variation across the United States is the timing of the fall wave. Later peaks were associated with a lower mortality burden [26], which may indicate declining virulence of A/H1N1 viruses during the fall–winter of 1918–1919. Furthermore, the risk of severe influenza outcome could also be affected by general health status, nutrition, comorbidities, and health care [32]. More quantitative studies are needed to elucidate the relative contribution of the following factors: (1) nonpharmaceutical interventions, (2) the timing of the fall pandemic wave and how it relates to virus evolution, (3) baseline health and socioeconomic conditions, and (4) “natural immunization” resulting from prior exposure to a pandemic influenza variant in the spring–summer.

Evidence is accumulating that several countries experienced mild pandemic waves in spring and summer 1918, which partially immunized the population. The pattern of successive pandemic waves also occurred in the 1889, 1957, and 1968 pandemics [33]; thus, the possibility of multiple waves of varying severity should be considered in pandemic planning efforts. The policy implications are complex. First, these findings highlight that timely virological and epidemiological surveillance are key to characterizing influenza in the early phase of a pandemic with respect to transmissibility, virulence, and the specific age groups affected. Second, if indeed a mild first wave is documented, the benefits of cross-protection during future waves should be considered before implementing public health interventions designed to limit exposure. In the meantime, we should continue to explore the vast amount of epidemiological information hidden in historic archives around the world.

Acknowledgments

We thank our colleagues John Greenwood, US Army historian; Don Olson; and Viggo Andreasen for stimulating discussions.

References

1. Santayana G. *The life of reason; or, the phases of human progress*. New York, New York: Scribner's, 1905:284.
2. Shaw GB. *Selected plays*. Vol I. New York, New York: Dodd Mead, 1948: 485.

3. Barry JM. *The great influenza: the epic story of the deadliest plague in history*. New York, New York: Viking Penguin, 2004.
4. Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. *Emerg Infect Dis* 2006; 12:15–22.
5. US Navy Bureau of Medicine and Surgery. Record group 52, entry 12, index card 126811. US National Archives; College Park, Maryland.
6. US Navy Bureau of Medicine and Surgery. Analysis of the course and intensity of the epidemic in Army camps. Record group 112, entry 29, box 394. US National Archives; College Park, Maryland.
7. Vaughan VC. *Epidemiology and public health*. St. Louis, MO: C. V. Mosby Company, 1922:358–9.
8. Andreasen V, Viboud C, Simonsen L. Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. *J Infect Dis* 2008; 197: 270–8.
9. Chowell G, Ammon CE, Hengartner NW, Hyman JM. Estimation of the reproductive number of the Spanish flu epidemic in Geneva, Switzerland. *Vaccine* 2006; 24:6747–50.
10. Hill R. Influenza in the Grand Fleet. *J Royal Navy Med Serv* 1919; 142–149:1060.
11. Report on the mortality from influenza in England and Wales during the epidemic of 1918–1919: supplement to the eighty-first annual report of the Registrar General of Births, Deaths and Marriages. London, UK: H. M. Stationary Office, 1920: 48–80.
12. Olson DR, Simonsen L, Edelson PJ, Morse SS. Epidemiological evidence of an early wave of the 1918 influenza pandemic in New York City. *Proc Natl Acad Sci U S A* 2005; 102:11059–63.
13. Crosby AW. *America's forgotten pandemic: the influenza of 1918*. Cambridge: Cambridge University Press, 2003.
14. Vaughan W. Influenza: an epidemiologic study. *Am J Hygiene, Monograph Series*. 1921:173.
15. Secretary of War. Annual Report of the Surgeon General, US Army. Excerpts on the influenza and pneumonia pandemic of 1918 from war department. Washington, DC: US Army, 1919.
16. Hall MM. Chapter II: inflammatory diseases of the respiratory tract (bronchitis, influenza, bronchopneumonia, lobar pneumonia). In: Siler JF, Ireland M, eds. *The Medical Department of the United States Army in the World War*. Vol IX. Communicable diseases. Washington, DC: US Government Printing Office, 1928:61–169.
17. Office of Medical History, Office of the Surgeon General. The US Army Medical Department and the influenza pandemic of 1918. Available at: http://history.amedd.army.mil/default_index2.html. Accessed 27 May 2008.
18. Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2008; CD006297.
19. Jordan EO. *Epidemic influenza*. Chicago, IL: American Medical Association, 1927.
20. Sonoguchi T, Naito H, Hara M, Takeuchi Y, Fukumi H. Cross-subtype protection in humans during sequential, overlapping, and/or concurrent epidemics caused by H3N2 and H1N1 influenza viruses. *J Infect Dis* 1985; 151:81–8.
21. Morens DM, Fauci AS. The 1918 influenza pandemic: insights for the 21st century. *J Infect Dis* 2007; 195:1018–28.
22. Roti M, Yang J, Berger D, Huston L, James EA, Kwok WW. Healthy human subjects have CD4+ T cells directed against H5N1 influenza virus. *J Immunol* 2008; 180:1758–68.
23. Sandbulte MR, Jimenez GS, Boon AC, Smith LR, Treanor JJ, Webby RJ. Cross-reactive neuraminidase antibodies afford partial protection against H5N1 in mice and are present in unexposed humans. *PLoS Med* 2007; 4:e59.
24. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon- γ during recovery from influenza infection. *Nat Med* 2008; 14:558–64.

25. Pearl R. Influenza studies: further data on the correlation of explosiveness of outbreak of the 1918 epidemic. *Public Health Rep* **1921**; 36:273–98.
26. Bootsma MC, Ferguson NM. The effect of public health measures on the 1918 influenza pandemic in U.S. cities. *Proc Natl Acad Sci U S A* **2007**; 104:7588–93.
27. Hatchett RJ, Mecher CE, Lipsitch M. Public health interventions and epidemic intensity during the 1918 influenza pandemic. *Proc Natl Acad Sci U S A* **2007**; 104:7582–7.
28. Markel H, Lipman HB, Navarro JA, et al. Nonpharmaceutical interventions implemented by US cities during the 1918–1919 influenza pandemic. *JAMA* **2007**; 298:644–54.
29. Barry JM. Nonpharmaceutical interventions implemented during the 1918–1919 influenza pandemic. *JAMA* **2007**; 298:2260–1.
30. Barry JM. Comments on the nonpharmaceutical interventions in New York City and Chicago during the 1918 flu pandemic. *J Transl Med* **2007**; 5:65.
31. Frost WH. Statistics of influenza morbidity. *Public Health Rep* **1920**; 7: 584–97.
32. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. *Lancet* **2006**; 368: 2211–8.
33. Simonsen L, Olson DR, Viboud C, et al. Pandemic Influenza and mortality: past evidence and projections for the future. In: Knobler S, Mack A, Mahmoud A, Lemon SM, eds. *The threat of pandemic influenza: are we ready?* Washington, DC: The National Academies Press, **2005**: 89–114.