Influenza Circulation in United States Army Training Camps Before and During the 1918 Influenza Pandemic: Clues to Early Detection of Pandemic Viral Emergence

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Background. Surveillance for respiratory diseases in domestic National Army and National Guard training camps began after the United States' entry into World War I, 17 months before the "Spanish influenza" pandemic appeared.

Methods. Morbidity, mortality, and case-fatality data from 605 625 admissions and 18 258 deaths recorded for 7 diagnostic categories of respiratory diseases, including influenza and pneumonia, were examined over prepandemic and pandemic periods.

Results. High pandemic influenza mortality was primarily due to increased incidence of, but not increased severity of, secondary bacterial pneumonias.

Conclusions. Two prepandemic incidence peaks of probable influenza, in December 1917–January 1918 and in March–April 1918, differed markedly from the September–October 1918 pandemic onset peak in their clinical-epidemiologic features, and they may have been caused by seasonal or endemic viruses. Nevertheless, rising proportions of very low incidence postinfluenza bronchopneumonia (diagnosed at the time as influenza and bronchopneumonia) in early 1918 could have reflected circulation of the pandemic virus 5 months before it emerged in pandemic form. In this study, we discuss the possibility of detecting pandemic viruses before they emerge, by surveillance of special populations.

Keywords. 1918 influenza; epidemiology; military; pandemic influenza; pneumonia.

United States Army statistics on influenza and pneumonia have been recorded since the middle 1800s [1]. Surveillance for influenza and pneumonia in domestic National Army and National Guard training camps began after the United States' entry into World War I, in April 1917. Seventeen months later, the "Spanish influenza" pandemic appeared [2]. Although the vast majority of pandemic influenza cases in the general population were of a self-limited nature, similar to cases seen in influenza epidemics before and since, a small percentage (in the range of 1 percent) were fatal, and nearly all of these were complicated by severe secondary bacterial pneumonias [3].

Human influenza A viruses were first identified in 1933 [4], and the virus responsible for the 1918 pandemic was first identified in 1997 [5], when its RNA genome was sequenced from preserved and frozen human tissues [6]. By studying the reconstructed 1918 influenza virus, important insights into its origin and pathogenesis were found [7]. Understanding the 1918 pandemic also requires understanding the epidemiology of its occurrence, complications, and mortality. It is of particular value to examine, using standardized approaches, clinical and epidemiologic aspects of influenza-like illnesses and complications in large, healthy, homogeneous populations under continuous and intense surveillance before and during the pandemic. In this study, we examine data on

respiratory illnesses and deaths in US military training camps during World War I.

METHODS

Data were abstracted from a 1925 report of the US Army Surgeon General's Office summarizing admissions and deaths attributable to influenza, pneumonia, and other respiratory diseases, in 39 US military training camps from April 1917 to December 1919 [8]. Data were tabulated by month for each individual camp. Troop strengths by month and by camp were also recorded. Because most camps were not yet fully operational between April and September 1917, and because camps were largely demobilized between April and December 1919, data from these periods, although available in the Surgeon General's report [8], are not considered here.

Original 1917–1919 diagnostic categorization of soldiers' illnesses reflected military providers' clinical diagnoses and military epidemiologists' judgments about diagnostic categorization. There appear to have been no standardized criteria for diagnosis or diagnostic categorization, but because of rapid and broad Army-wide dissemination of medical information, including exchange of information between Army camps, diagnostic criteria may be reasonably inferred from clinical descriptions and Army reports of the time [9]. Because the cause of influenza was unknown in this era, diagnoses could not be confirmed by viral culture, serology, or molecular-based diagnostic tests, although complications of pneumonia were readily diagnosed by radiography and by bacterial culture of pleural fluid, blood, or tissue at autopsy. Disease misclassifications seem to have been uncommon with the possible exceptions, discussed below, of lobar versus bronchopneumonia in the prepandemic months, and of some of the specific diseases subsumed within the Common respiratory diseases category. Data abstracted from original diagnoses of respiratory tract diseases were placed by military epidemiologists in the 1917–1919 era into the following 7 diagnostic categories: (1) Influenza, uncomplicated, (2) Influenza and lobar pneumonia, (3) Influenza and bronchopneumonia, (4) Influenza and other complications, (5) Bronchopneumonia, (6) Lobar pneumonia, and (7) Common respiratory diseases.

"Influenza, uncomplicated" referred to fever and malaise with or without upper respiratory symptoms. Soldiers admitted with Influenza, uncomplicated who subsequently developed complications were to be recategorized according to the complication, but such recategorizations were apparently not always made [1]. "Bronchopneumonia" was distinguished from "Lobar pneumonia" by clinical signs of diffuse lower respiratory tract involvement without evidence of early lung consolidation [9]. "Influenza and other complications" referred to involvement of organs outside the respiratory tract including heart, brain, gastrointestinal tract, and kidneys, eg, complications resulting from secondary bacteremia. "Common respiratory diseases"

were included in some of the analyses because of the possibility that, if not correctly diagnosed, sporadic cases of mild influenza, or cases seen in small influenza outbreaks, might be categorized under this rubric, which also included noninfluenza diagnoses of pharyngitis, tonsillitis, bronchitis, and presumed viral "colds" [1]. Postmeasles lobar pneumonia and bronchopneumonia, including those cases diagnosed during Army-wide measles epidemics in late 1917 and early 1918 [10], were recorded in separate diagnostic categories and were not considered here. Of the 605 651 admissions and 18 354 deaths recorded in the 7 categories noted above, made between October 1917 and March 1919, 122 diagnoses (26 admissions and 96 deaths) appeared to be inaccurate and were omitted from analyses. In these instances, the number of monthly deaths in a category were greater than admissions in that category for the concurrent and preceding months.

Statistical Analysis

Diagnostic category-specific attack rates (number of admissions per 1000 troops), mortality rates (number of deaths per 100 troops), and case-fatality rates (number of deaths per 100 admissions), with 95% confidence intervals (CIs), were calculated in each month for all camps combined. Confidence intervals were calculated using the binomial distribution [11].

In some analyses, certain of the original diagnostic categories were combined in order to consider effects of their specificity or sensitivity. The original 7 respiratory diagnostic categories were combined as 1 diagnostic category referred to below and in the Figures and Tables as "All influenza illnesses", meaning all 7 of the diagnostic categories combined, all of which were believed to contain at least some influenza cases. The 4 original diagnostic categories thought to contain cases of influenza complicated by pneumonia (Influenza and bronchopneumonia, Influenza and lobar pneumonia, Bronchopneumonia, and Lobar pneumonia) were combined in some analyses and termed "Influenza complicated by pneumonia." The latter 2 of these categories (Bronchopneumonia, and Lobar pneumonia), in which a diagnosis of influenza had not been made, were included in such analyses because presenting postinfluenza bacterial pneumonias might not have been correctly associated with antecedent influenza illnesses. Diagnostic categories believed to contain cases of influenza that were not complicated by pneumonia or other complications (Influenza, uncomplicated, and Common respiratory diseases) were combined in some analyses and termed "Influenza not complicated by pneumonia."

The 4 original diagnostic categories believed to be most specific for influenza infection (Influenza, uncomplicated; Influenza and lobar pneumonia; Influenza and bronchopneumonia; and Influenza and other complications) were combined and termed "Specified influenza infection." The 2 original diagnostic categories thought to be most specific for postinfluenza pneumonia (Influenza and lobar pneumonia and Influenza
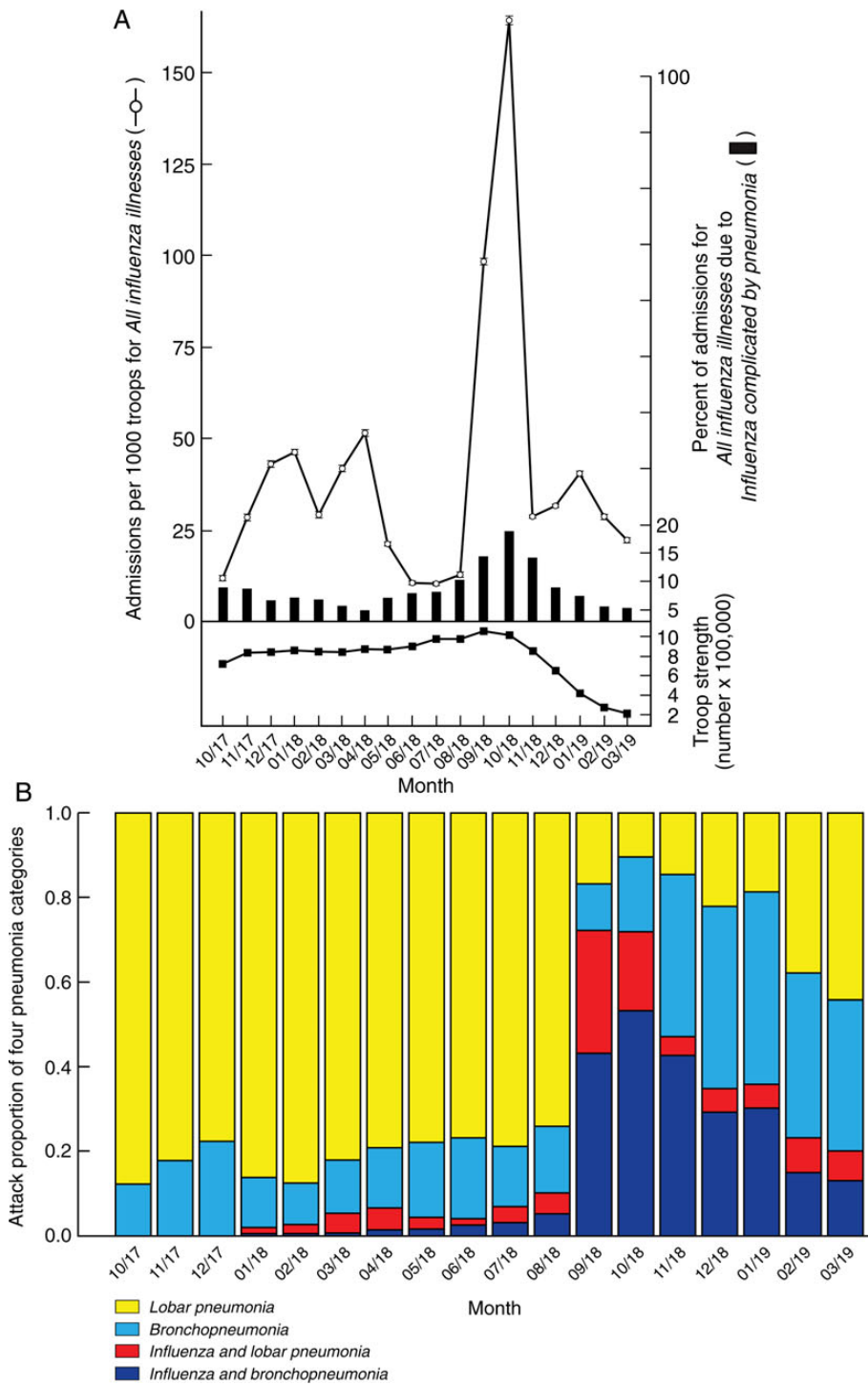
Figure 1. A, Incidence rates of admissions for All influenza illnesses; percentages of admissions for All influenza illnesses due to Influenza complicated by pneumonia; troop strength, in all US Army training camps combined, October 1917–March 1919. The line-graph on the upper section of the figure (left y-axis) represents the number of admissions per 1000 troops for All Influenza Illnesses (7 diagnostic categories combined including Influenza, uncomplicated; Influenza and lobar pneumonia; Influenza and bronchopneumonia; Influenza and other complications; Bronchopneumonia; Lobar pneumonia; and Common respiratory diseases). Error bars (barely visible) represent the 95% confidence interval. The bar graph (upper part of right y-axis) represents the percentage of admissions for All influenza illnesses due to Influenza complicated by pneumonia (4 pneumonia categories combined including Influenza and bronchopneu-monia, Influenza and lobar pneumonia, Bronchopneumonia, and Lobar pneumonia). The line-graph on the lower section of the figure (lower part of right y-axis) represents troop strength. B, Proportion of pneumonia admissions by original 4 pneumonia diagnostic categories, all Army training camps combined, October 1917–March 1919. Dark blue bars represent the proportion of pneumonia admissions for Influenza and bronchopneumonia. Red bars represent the proportion of pneumonia admissions for Influenza and lobar pneumonia. Light blue bars represent the proportion of pneumonia admissions for Bronchopneumonia. Yellow bars represent the proportion of pneumonia admissions for Lobar pneumonia.

Table 1. Odds of Disease Admission, Mortality, and Case Fatality for Original and Combined Respiratory Diagnostic Categories, in all US Army Training Camps Combined, During September–October 1918, Relative to December 1917–April 1918

Original Diagnostic Categories	Admission OR (95% CI)	Mortality OR (95% CI)	Case-Fatality OR (95% CI)
1. Influenza, uncomplicated	7.26 (7.19–7.33)	44.27 (20.40–96.07)	6.54 (2.99–14.31)
2. Common respiratory diseases	0.62 (0.61–0.62)	18.9 (11.26–29.37)	18.41 (11.25–30.13)
3. Influenza and bronchopneumonia	784.98 (620.64–992.84)	862.83 (527.97–1410.07)	1.15 (0.65–2.04)
4. Influenza and lobar pneumonia	78.33 (69.36–88.46)	146.22 (108.10–197.78)	2.78 (1.96–3.94)
5. Bronchopneumonia	10.68 (10.09–11.29)	15.05 (13.39–16.92)	1.55 (1.34–1.80)
6. Lobar pneumonia	1.38 (1.33–1.43)	2.50 (2.32–2.68)	2.03 (1.86–2.22)
7. Influenza and other complications	6.81 (6.47–7.18)	31.42 (15.23–64.80)	5.34 (2.57–11.11)
Combined Diagnostic Categories			
1 and 2. Influenza not complicated by pneumonia	2.88 (2.86–2.90)	25.00 (16.69–37.44)	8.44 (5.63–12.66)
3 through 6. Influenza complicated by pneumonia	9.45 (9.25–9.66)	15.32 (14.57–16.10)	1.77 (1.68–1.88)
1 through 7. All influenza illnesses	3.25 (3.23–3.27)	15.50 (14.76–16.29)	4.90 (4.66–5.15)

Abbreviations: CI, confidence interval; OR, odds ratio.

and bronchopneumonia) were combined and termed "Specified influenza and pneumonia." Rates of death from Influenza and bronchopneumonia alone among individuals with Specified influenza infection (deaths from Influenza and bronchopneumonia per 100 admissions for Specified influenza infection) were compared with rates of death from Specified influenza and pneumonia (deaths from Specified influenza and pneumonia per 100 admissions for Specified influenza infection).

Logistic regression analyses compared odds of admission, mortality, and case fatality among 4 different periods of respiratory disease activity that had been selected by us beforehand based on (1) the known period of annual winter activity and (2) on published Army data indicating 3 separate peaks of influenza-like activity in the winter-spring preceding and during the 1918 pandemic onset: the prepandemic 1917–1918 "influenza season" (December 1917–April 1918), the prepandemic winter of 1917–1918 (December 1917–February 1918), the prepandemic spring of 1918 (March–April 1918), and the peak of the 1918–1919 influenza pandemic (September–October 1918). Given possible differences between camps due to geographical or other factors, a random effects model accounting for potential differences between camps was used. Log odds ratios (ORs) were converted to ORs with associated 95% CI.

RESULTS

Admission Rates

Admission rates of All influenza illnesses during the 1917–1918 influenza season (December 1917–April 1918) peaked in January 1918 at 46 cases per 1000 troops and peaked again in April 1918 at 51 cases per 1000 troops (Figure 1A). In both the January 1918 peak and the April 1918 peak, Influenza complicated by pneumonia made up a relatively small proportion of All

influenza illnesses (7% and 5.5%, respectively; Figure 1A). Admission rates of All influenza illnesses peaked again during the pandemic in October 1918 at 164 cases per 1000 troops (Figure 1A). At this time, Influenza complicated by pneumonia accounted for a significantly larger proportion of All influenza illnesses (19%; Figure 1A), primarily due to Influenza and bronchopneumonia (53%; Figure 1B).

Odds of admission to camp hospitals in September–October 1918 relative to December 1917–April 1918 were increased in 6 of the 7 original diagnostic categories, the exception being Common respiratory diseases (Table 1). Odds of admission for Influenza complicated by pneumonia were elevated approximately 10-fold in September–October 1918 relative to December 1917–April 1918 (OR, 9.45; 95% CI, 9.25–9.66) (Table 1), and relative to the March–April 1918 period (OR, 10.04; 95% CI, 9.72–10.37), with odds of admission for Influenza and bronchopneumonia being exceptionally high (OR, 784.98; 95% CI, 620.64–992.84).
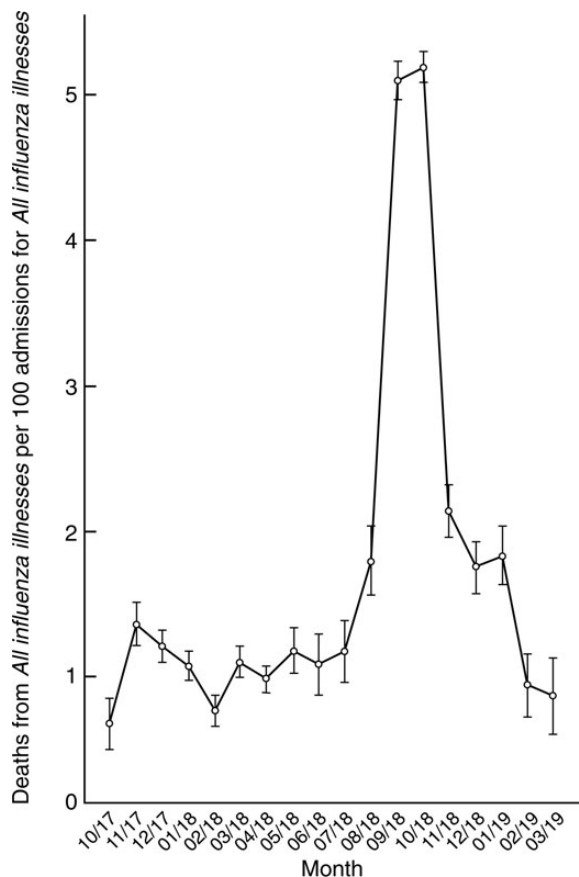
Mortality Rates

Mortality rates of All influenza illnesses were 0.05% during the December 1917 and April 1918 mortality peaks (Figure 2A). Most deaths during these times (98% in December 1917 and 99% in April 1918) were due to Influenza complicated by pneumonia (Figure 2A). Mortality rates of All influenza illnesses peaked again during the October 1918 pandemic at 0.85%, with nearly all deaths (98%) attributable to Influenza complicated by pneumonia (Figure 2A). Significantly, unlike the earlier periods, the largest proportion of these deaths (48%) was due to Influenza and bronchopneumonia (Figure 2B).

Odds of mortality in September–October 1918 relative to December 1917–April 1918 were increased in each of the 7 original diagnostic categories (Table 1). Mortality odds for Influenza complicated by pneumonia in September–October 1918 relative
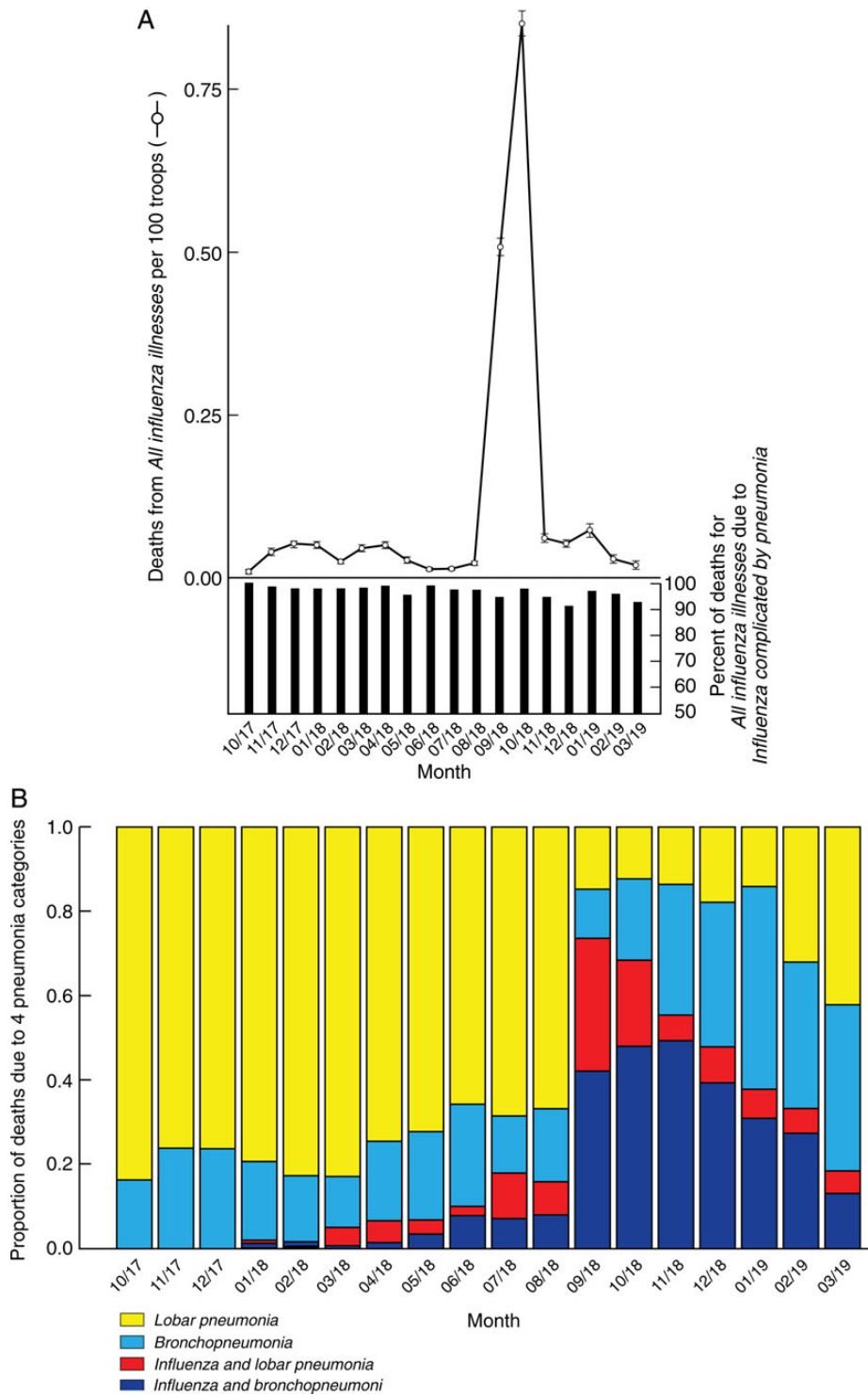
Figure 2. A, Mortality rates of All influenza illnesses, and percentage of deaths due to Influenza complicated by pneumonia, in all US Army training camps combined, October 1917–March 1919. The line-graph (left y-axis) represents number of deaths from All influenza illnesses (7 diagnostic categories combined including influenza, uncomplicated; influenza and lobar pneumonia; influenza and bronchopneumonia; influenza and other complications; bronchopneumonia; lobar pneumonia; and common respiratory diseases) per 100 troops. Error bars (barely visible) represent the 95% confidence interval. The bar graph (lower right y-axis) represents the percent of deaths from All influenza illnesses due to Influenza complicated by pneumonia (4 pneumonia categories combined including Influenza and bronchopneumonia, Influenza and lobar pneumonia, Bronchopneumonia, and Lobar pneumonia). B, Proportion of pneumonia deaths by original 4 pneumonia diagnostic categories, all Army training camps combined, October 1917–March 1919. Dark blue bars represent the proportion of pneumonia deaths due to Influenza and bronchopneumonia. Red bars represent the proportion of pneumonia deaths due to Influenza and lobar pneumonia. Light blue bars represent the proportion of pneumonia deaths due to Bronchopneumonia. Yellow bars represent the proportion of pneumonia deaths due to Lobar pneumonia.

Figure 3. Case-fatality rates of All influenza illnesses in all US Army training camps combined, October 1917–March 1919. The graph represents number of deaths from All influenza illnesses (7 diagnostic categories combined including Influenza, uncomplicated; Influenza and lobar pneumonia; Influenza and bronchopneumonia; Influenza and other complications; Bronchopneumonia; Lobar pneumonia; and Common respiratory diseases) per 100 admissions for All influenza illnesses. Error bars represent 95% confidence intervals.

to December 1917–April 1918 were significantly increased (OR, 15.32; 95% CI, 14.57–16.10) (Table 1), as they were when comparing the March–April 1918 period (OR, 14.00; 95% CI, 13.03–15.04), largely because of deaths from Influenza and bronchopneumonia (OR, 862.83; 95%, CI 527.97–1410.07). It was not possible to comprehensively examine the "W-shaped" mortality curve [2] in this population because most of the soldiers were young adult men.

Case-Fatality Rates

Case-fatality rates of All influenza illnesses remained approximately 1 percent throughout winter–spring 1917–1918, peaking in November 1917 at 1.4% and then again in the September–October 1918 pandemic onset at 5.2% (Figure 3).

Increased case-fatality odds were observed in 6 of the 7 original diagnostic categories, the exception being *Influenza and*

bronchopneumonia (Table 1). Case-fatality odds were most elevated for the individual categories Common respiratory diseases (OR, 18.41; 95% CI, 11.25–30.13) and Influenza, uncomplicated (OR, 6.54; 95% CI, 2.99–14.31). Misclassification of 1918 pandemic influenza cases into the Common respiratory diseases category during September–October 1918 likely accounted for the observed increase in case-fatality odds in this category. Although mild cases of illness in the Common respiratory diseases category and in the Influenza, uncomplicated category were supposed to be reclassified according to subsequent complications per US Army guidelines [1], this clearly this was not always accomplished. Increased case-fatality odds were most prominently observed in the combined category of Influenza not complicated by pneumonia (Table 1) given that this category is a combination of Common respiratory diseases and Influenza, uncomplicated, and All influenza illnesses for which the majority of cases derive from the Common respiratory diseases and Influenza, uncomplicated categories.

Relative to the prepandemic December 1917–April 1918 influenza season, the odds of death among soldiers admitted for All influenza illnesses during September–October 1918 were approximately 5-fold higher (OR, 4.90; 95% CI, 4.66–5.15) (Table 1), as were the odds of dying when comparing the March–April 1918 period alone (OR, 4.92; 95% CI, 4.58–5.28). However, it is noteworthy that soldiers admitted with Influenza and bronchopneumonia in September–October 1918 were no more likely to die than those admitted with the same diagnosis in December 1917–April 1918 (OR, 1.15; 95% CI, 0.65–2.04) (Table 1).

Fatal Complication Rates

The fatal complication rate from Influenza and bronchopneumonia among individuals with Specified influenza infection (Influenza, uncomplicated; Influenza and lobar pneumonia; Influenza and bronchopneumonia; and Influenza and other complications, combined) peaked at 0.06% in January 1918 and dropped to 0.02% in March 1918 (Figure 4). However, during the 5 months preceding the pandemic peak (April–August 1918), the fatal complication rate from Influenza and bronchopneumonia rose steadily despite low incidence of Specified influenza infection among the general troop population during late spring and summer (May–August 1918) (Figure 4). The fatal complication rate from Influenza and bronchopneumonia peaked in October 1918 at 2.8% and remained elevated through February 1919 in the 2%–3% range, even as influenza admissions returned to very low levels. Among individuals with Specified influenza infection, the fatal complication rate from Specified influenza and pneumonia (Influenza and bronchopneumonia and Influenza and lobar pneumonia combined) followed a pattern similar to that of Influenza and bronchopneumonia alone, except during February–April 1918. During February–April 1918, elevated
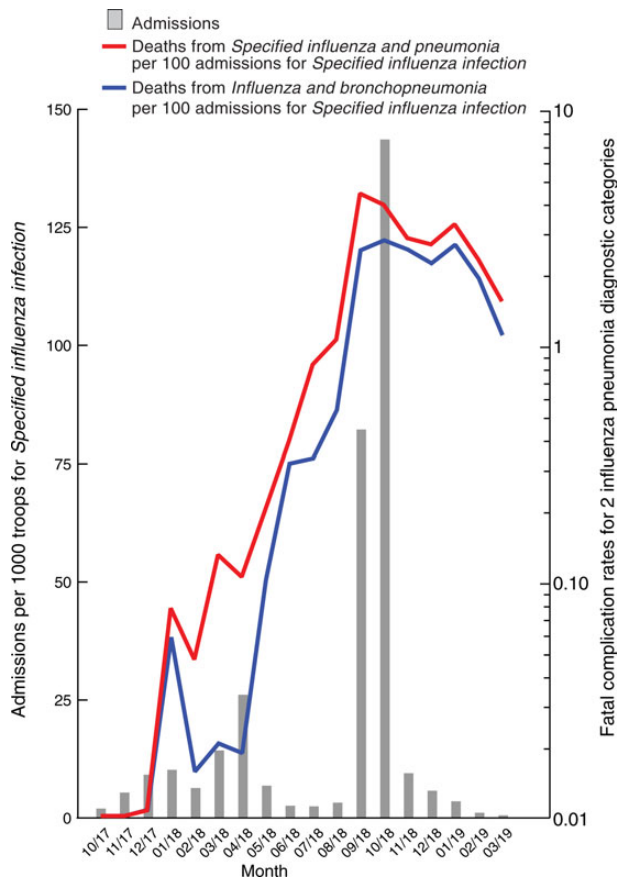
Figure 4. Incidence rates of Specified influenza infection and fatal complication rates of Influenza and bronchopneumonia and of Specified influenza and pneumonia, in all US Army training camps combined, October 1917–March 1919. The bar graph (left y-axis) represents the number of admissions per 1000 troops for Specified influenza infection. The red line represents the number of deaths from Specified influenza and pneumonia (Influenza and bronchopneumonia and Influenza and lobar pneumonia combined) per 100 admissions for Specified influenza infection (4 influenza-specific diagnostic categories combined including Influenza, uncomplicated; Influenza and lobar pneumonia; Influenza and bronchopneumonia; and Influenza and other complications) (right y-axis, log scale). The blue line represents the number of deaths from Influenza and bronchopneumonia per 100 admissions for Specified influenza infection (right y-axis, log scale).

fatal complication rates from Influenza and lobar pneumonia contributed to high fatal complication rates from Specified influenza and pneumonia (Figure 4).

DISCUSSION

Analyses of respiratory disease admission incidence, mortality, case fatality, and complications in 39 domestic US Army training camps were performed to characterize patterns of respiratory illnesses and deaths among US soldiers during World War I. We examined 7 original respiratory diagnostic categories including 4 pneumonia subcategories, the latter singly and combined.

Separating and combining the 4 pneumonia categories in some analyses was considered necessary because of the possibility that physicians could have missed diagnosing antecedent influenza in soldiers presenting with Lobar pneumonia or with Bronchopneumonia, and because of potential misclassifications between Lobar pneumonia and Bronchopneumonia. The data showed 3 distinct peaks of respiratory disease admission incidence preceding and during the pandemic onset. Mortality rates from All influenza illnesses in December 1917 and in April 1918 were both 0.05%. By comparison, mortality rates from All influenza illnesses in September–October 1918 were significantly higher (0.85%), and they were consistent with age-specific pandemic mortality rates in 1918 US civilian populations [2].

Excess mortality in September–October 1918 resulted from a combination of high influenza admission rates, more frequent case progression to secondary bacterial pneumonia, especially bronchopneumonia, and high but typical pneumonia case-fatality rates. During the 1918 pandemic, many military and civilian observations made it clear that severe and fatal postinfluenza pneumonia was linked with high frequency to bronchopneumonia specifically [12]. During September–October 1918, the odds of being admitted with Influenza complicated by pneumonia were approximately 10-fold higher than in December 1917–April 1918 (OR, 9.45; 95% CI, 9.25–9.66), even though the odds of dying from Influenza complicated by pneumonia, once it occurred, were only modestly elevated (OR, 1.77; 95% CI, 1.68–1.88). These data support the notion, widely cited in the medical literature of the 1918 era [13], that high pandemic influenza mortality rates during fall 1918 resulted primarily from increased frequency of postinfluenza bacterial pneumonia rather than increased lethality of such pneumonias, and further that the case fatality of postinfluenza pneumonia in 1918–1919 was not remarkably different from general pneumonia case-fatality rates observed in the years before and after the pandemic [13, 14].

Of the 4 pneumonia categories, the role of Influenza and bronchopneumonia in excess influenza mortality in September–October 1918 stands out. Soldiers were approximately 785 times more likely to develop Influenza and bronchopneumonia during September–October 1918 relative to December 1917–April 1918 (OR, 784.98; 95% CI, 620.64–992.84), even though they were no more likely to die from it (OR, 1.15; 95% CI, 0.65–2.04). Experience with highly fatal measles epidemics in the same US Army training camps in the months immediately preceding the 1918 influenza pandemic had shown that postviral bronchopneumonia was a fundamentally different disease than lobar pneumonia. The 1917–1918 Army measles and the 1918 influenza epidemics advanced understanding of the natural history and pathogenesis of postviral bronchopneumonia as a virally induced cytolytic process that begins in the upper airway, extends to the lower airway, becomes complicated

by invasive bacterial infection, and in some cases manifests as a confluent infectious process resembling lobar pneumonia clinically or radiographically [15].

The slow spring–summer 1918 increase in the percent of All influenza illnesses attributable to Influenza complicated by pneumonia (Figure 1A), and the concomitant rise in the proportion of cases and deaths of Influenza complicated by pneumonia attributable to Influenza and bronchopneumonia (Figures 1B and 2B), could indicate early emergence of the pandemic virus, which was later shown, during the fall 1918 pandemic peak, to be associated with a high rate of severe and fatal postinfluenza bronchopneumonia. During the spring months of 1918, military providers recognized and evaluated rare cases of severe pneumonia that retrospectively fit the clinical and epidemiologic pattern of early pandemic viral emergence on the background of outbreaks of mild influenza-like illnesses. These data seem consistent with the presence of at least 2 epidemiologically and clinically distinct respiratory diseases occurring between October 1917 and March 1919: (1) low- to intermediate-incidence influenza-like illnesses with few pneumonia complications and low mortality, peaking in January and April 1918, and (2) high-incidence pandemic influenza associated with a high rate of pneumonia complications, but with typical postinfluenza pneumonia case-fatality rates, peaking in September–October 1918. The low rates of postinfluenza complications and deaths during December 1917–April 1918 suggest that the predominant virus circulating in the prepandemic months was distinct from the September–October 1918 pandemic virus.

The initial recognized appearance of the Spanish influenza pandemic in Northern Europe in summer 1918 [16] suggests that the pandemic virus must have been circulating below the level of detection well before emergence. However, the data examined here do not strongly support the possibility that the pandemic virus was the cause of most influenza-like illnesses in US Army camps in spring 1918, which some have called "a" or "the" "spring wave" [17, 18]. Unlike the pandemic that emerged in summer–fall 1918, spring influenza cases tended to be mild, not complicated by pneumonia, and rarely fatal; the spring outbreaks were limited in progression, even in intensely crowded military camps during a season (winter–spring) historically favorable to influenza spread [19].

Alternative explanations for the limited spring outbreaks of mild influenza-like illnesses that occurred sporadically and disappeared quickly on the US East Coast, in parts of Europe, and in US Army camps include the possibility that the responsible viruses were noninfluenza respiratory viruses [9]; that they were seasonal or endemic influenza viruses; that the responsible virus was the 1918 pandemic virus of stable virulence at the time, whose later high pathogenicity, in the 1918–1921 period, reflected unknown and transient nonviral cofactors; or that early in its emergence, at some time after spring 1918, the

pandemic virus mutated to enhanced virulence. This latter possibility appears problematic in several respects, including early (May 1918) influenza viral hemagglutinin gene sequences that are little-changed from the sequences of viruses studied at the pandemic peak, and which were derived from cases with clinical courses and histopathologic characteristics indistinguishable from later pandemic cases; [20] and the seemingly spontaneous pandemic emergence within a narrow window of time in summer–fall 1918, in a pathogenic form widely dispersed geographically, consistent with global pre-seeding of the virus [21].

Although none of the 4 emergence scenarios mentioned above can be conclusively ruled out, the data presented here appear most consistent with the possibility that the December 1917–February 1918 and the March–April 1918 influenza-like illness activities were both largely due to 1 or more unrelated influenza viruses, exhibiting properties of typical seasonal influenza viruses, their lowly pathogenic outbreak properties masking the very slow, simultaneous, emergence of a pathogenic but low-incidence pandemic virus (Figure 4). The data also appear consistent with the notion that this latter virus remained almost undetectable in its mortality impact (Figure 2A) while nevertheless causing rare, but increasingly more frequent, cases of severe and fatal bronchopneumonia in the epidemiologic background, consistent with an emerging pandemic virus (Figure 4).

Others have observed an association between presumed respiratory viral exposure in spring 1918 and reduced rates of infection and death in fall but not winter 1918 [22]. This apparent protection might be attributable to inter- or intra-subtypic influenza humoral immunity, T-cell immunity, or short-term innate antiviral responses. Viral genetic and immunologic data derived from the 1918 era would be required to reliably address this issue as ecological studies, where inferences about the nature of individuals are deduced from inference for the group are subject to significant bias.

Attempts to understand these decades-old pandemic phenomena are of importance in our efforts to understand pandemic emergence today. Simple mathematics indicates that pandemic viruses must circulate in 1 or more human populations for months before emergence, allowing an opportunity for early detection. This finding is consistent with observations made since the 1957 pandemic. Detecting such pandemic viruses when they are still circulating at a low prepandemic level is a critical public health goal because it would potentially provide significantly more time to develop vaccines and formulate prevention and mitigation strategies.

Our interpretation of the 1917–1919 US Army data suggests the theoretical feasibility of detecting a modern pathogenic prepandemic virus by aggressive surveillance in selected human populations during nonpandemic periods. Viewed in retrospect, the 1917–1919 Army data seem to be consistent with a "signal" of an approaching pandemic 5 months before it appeared when, in spring 1918, rare cases of severe and fatal

Influenza and bronchopneumonia began to be detected in the midst of outbreaks of mild influenza-like illnesses. Had this happened in the modern era, severe cases of respiratory viral illness detected in emergency rooms, inpatient hospital wards, or intensive-care units could be confirmed by viral culture or molecular diagnostic assay. Influenza A virus subtypes, other than those predominantly circulating, could be rapidly genetically sequenced, allowing detection of a novel influenza virus. Early detection would lead to enhanced virus-specific surveillance and to public health strategies to prevent and control pandemic emergence (ie, vaccine development and distribution).

CONCLUSIONS

The importance of detecting pandemic viruses as early as possible in the course of their months-long emergence cannot be overstated. Early detection shortens the lag time in vaccine development, policy and strategy development, and education of providers, the public, and other key groups. Understanding how pandemic viruses emerge and development of early detection strategies are key elements of effective prevention and control. The 1917–1919 data presented here should stimulate additional discussions aimed at optimizing pandemic detection and response.

Acknowledgments

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