What Really Happened during the 1918 Influenza Pandemic? The Importance of Bacterial Secondary Infections

To the Editor—Plans for responding to an influenza pandemic are based on estimates of the effects that a 1918-like pandemic would have in modern populations and settings [1–4]. Most recent descriptions of the 1918 pandemic emphasize the unique clinical expressions of the H1N1 pandemic strain—particularly the rapid progression to respiratory failure and death—and suggest that such cases were the predominant causes of death [1–4]. Recent reviews have stated that most of the fatalities during the pandemic were due to respiratory failure with a characteristic hemorrhagic alveolitis [1], that the majority of these deaths were caused by a virus-induced cytokine storm that led to acute respiratory distress syndrome (ARDS),[2] that bacterial superinfections caused perhaps one-third of all deaths [1–4], and that currently available antibiotics and bacterial vaccines would not be particularly useful should a 1918-like pandemic recur [1–3]. Given these views, it is not surprising that most plans for responding to an influenza pandemic minimize or disregard the importance of preventing and treating secondary bacterial infections.

However, in their recent review, Morens and Fauci noted that the causes of death during the 1918 pandemic were “similar to those during other pandemics” and that “most fatalities had secondary pneumonias caused by common bacteria or, in a minority of cases, ARDS-like syndromes” [5, table 1 on p. 1019]. Indeed, until recently, most descriptions of the 1918 pandemic (including nearly all contemporaneous reports) emphasized that fatal cases had variable and often prolonged clinical courses, that fulminant cases with rapid progression were relatively uncommon, and that secondary bacterial infections were the likely causes of most deaths. The following descriptions from Great Britain, the United States, and New Zealand are illustrative.

**Great Britain.** In their review of the 1918 pandemic, medical leaders in Great Britain at the time concluded that the clinical courses of fatal cases were highly variable and that bacterial infections were the predominant causes of death. A report from 1920 noted that “pneumonic complications ... would develop at any period of the influenza attack; there was no rule” [6, p. 71]. Regarding bacterial infections, the report stated that “the organisms responsible for the infections of the respiratory tract, to which its chief terrors are due, are well known. They are Pfeiffer’s bacillus [now known as *Haemophilus influenzae*], the pneumococcus, streptococci, and especially streptococci of hemolytic type, and more occasionally staphylococci, and other organisms to be mentioned in due course.... The uncomplicated disease ... is rarely of itself fatal. ... The complications to which the epidemic has owed its abnormal fatality have been due to secondary infections” [7, pp. 122, 123, 125].

**United States.** Numerous accounts of local outbreaks and systematic reviews of experiences across US Army installations during 1918 revealed that cases of hemorrhagic pneumonitis that rapidly progressed to death were relatively uncommon, that most deaths occurred after relatively long clinical courses, and that the most fatal cases were thought to be due to secondary bacterial infections [8–10]. After the pandemic, a detailed review by the US Army medical department concluded that nearly all deaths were due to “secondary pneumonias” and that “very few” died as a result of primary infections [10, p. 68]. The report cautioned that assessments of relationships between the influenza virus and “secondary invaders” required consideration of “the duration of the disease before the fatal ending and the stage of the epidemic wave at which the onset of the disease occurred” [10, p. 148]. At the peaks of outbreaks, most of the cases had average durations that were decidedly longer than those of the purely hemorrhagic type, and these cases “comprise[d] a majority of deaths” [10, p. 148]. A recent estimate of the distribution of times from infection to death during the 1918 pandemic—based on the reports of 94 autopsies of US soldiers—suggests that fewer than 4% of deaths occurred within 3 days, and nearly half of the deaths occurred more than 10 days, after estimated times of infection [11].

**New Zealand.** In November 1918, an influenza epidemic at a military camp in New Zealand resulted in 3220 hospitalizations and 163 deaths (case fatality, 5.1%) among ~8000 soldiers. A recent analysis revealed that the average time from onset of illness to death was 6–7 days (few cases died within 3 days) [12]. The authors suggested that “an important cause of death was likely to have been from secondary bacterial pneumonia—as opposed to the primary influenza viral pneumonia or acute respiratory distress syndrome (for which death may have tended to occur more promptly)” [12, p. 6]. By many mechanisms, influenza increases the risk and severity of bacterial respiratory infections [8, 13, 14]. Yet preparations for responding to the next influenza pandemic pay little attention to the prevention and treatment of bacterial infections. This may be due to widespread misperceptions regarding the importance...
of bacterial infections during the 1918 pandemic.

In many places, modern antivirals and strain-specific vaccines may be inaccessible and/or too costly—and other preventive methods (e.g., social distancing) may be ineffective—in response to an influenza pandemic. In such settings, currently available and relatively inexpensive bacterial vaccines and antibiotics may be accessible, affordable, and lifesaving—before, during, and after future influenza pandemics [15–17].

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References


Potential conflicts of interest: none reported.
The opinions or assertions herein are the private views of the authors and should not be construed as official or as reflecting the views of the US Department of Defense, the Department of the Army, or the Australian Defence Force.

Reply to Brundage and Shanks

To the Editor—We thank Drs. Brundage and Shanks for their comments, which agree with our view that most deaths from influenza during the 1918–1919 pandemic were associated with severe secondary bacterial pneumonia [1]. Building on data from the 1917–1918 US epidemics of measles/bacterial pneumonia, scientists studying influenza a year later generated voluminous data supporting the notion that bacterial pneumonia epidemics were precipitated by prevalent respiratory agents. Referring to the fatal outbreaks of bacterial pneumonia in US Army camps, the American pathologist W. G. MacCallum called influenza the “pre-disposing disease,” concluding that influenza infection somehow gave nasopharyngeal bacteria access to the lungs, where they multiplied to a degree unprecedented in noninfluenza pneumonias. MacCallum regarded these as secondary infections [2] and added that combinations of influenza and particular bacteria determined the anatomic type of pneumonia (lobar, lobular, or bronchopneumonia). In one of the best controlled autopsy studies producing results consistent with MacCallum’s views, Hirsch and McKinney not only provided data on the antemortem nasopharyngeal carriage of bacteria but also documented its importance in fatal influenza pneumonias, by obtaining, often in pure culture, postmortem lung isolates of either Streptococcus pneumoniae or S. pyogenes from 164 of 167 subjects who died during the 1918 pandemic [3].

Despite their rigor, however, pathologic and bacteriologic studies of military populations produce data that are probably not representative of what would be found in civilian populations. The constant influx of young military recruits regularly led to widespread nasopharyngeal carriage of bacterial pathogens in the camps. These “carriage epidemics” probably played a key role in the unusually high mortality rate due to influenza in military populations. Neither the incidence of bacterial carriage in civilian populations nor the bacteriology of fatal pneumonias was examined as rigorously, although the results of published studies appear to be in accord with those of MacCallum [2, 4].

Two additional problems bear directly on the points made by us and by Brundage and Shanks. If, as we have suggested [4], severe primary viral pneumonia during 1918–1919 was a risk factor for severe secondary bacterial pneumonia, then, to design optimal treatments, we need a better understanding of the pathogenesis and natural history of influenza viral pneumonia itself. Without fully understanding the pathogenesis of influenza-related