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Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness

John F Brundage

It is commonly believed that the clinical and epidemiological characteristics of the next influenza pandemic will mimic those of the 1918 pandemic. Determinative beliefs regarding the 1918 pandemic include that infections were expressed as primary viral pneumonias and/or acute respiratory distress syndrome, that pandemic-related deaths were the end states of the natural progression of disease caused by the pandemic strain, and that bacterial superinfections caused relatively fewer deaths in 1918 than in subsequent pandemics. In turn, response plans are focused on developing and/or increasing inventories of a strain-specific vaccine, antivirals, intensive care beds, mechanical ventilators, and so on. Yet, there is strong and consistent evidence of epidemiologically and clinically important interactions between influenza and secondary bacterial respiratory pathogens, including during the 1918 pandemic. Countermeasures (eg, vaccination against pneumococcal and meningococcal disease before a pandemic; mass uses of antibiotic(s) with broad spectrums of activity against common bacterial respiratory pathogens during local epidemics) designed to prevent or mitigate the effects of influenza-bacterial interactions should be major focuses of pandemic-related research, prevention, and response planning.

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Introduction

The influenza pandemic of 1918 accounted for an estimated 40–100 million deaths worldwide.[1,2] The emergence and international spread of coronavirus-associated severe acute respiratory syndrome (SARS),[3] of H5N1 influenza among domestic and wild avian species,[4–8] and of avian influenza among human beings have alarmed public health and clinical professionals.[4–8]

Plans for responding to the next influenza pandemic are guided by beliefs regarding the 1918 pandemic including that the pandemic was caused by a highly virulent, efficiently transmitted influenza virus that evolved from an avian strain;[2,6–10] that infections with the pandemic strain were expressed as primary viral pneumonias and/or acute respiratory distress syndrome (ARDS);[6–8,11] that pandemic-related deaths were the end states of the natural progression of disease caused by the pandemic strain;[6–8,11,12] that bacterial superinfections caused relatively fewer deaths in 1918 than in subsequent influenza epidemics;[6–8,13] and that the clinical and epidemiological characteristics of the next pandemic will closely mimic those of the 1918 pandemic.[6,7] In turn, vaccines and antivirals (which are in short supply and/or may not be effective) are the mainstays of prevention planning, and the availability of intensive care beds and mechanical ventilators to treat rapidly progressing viral pneumonias and ARDS are central to clinical preparations.[6–8,14]

However, outside of highly controlled laboratory settings, the clinical and pathophysiological characteristics of most infectious diseases are much more complex than implied by a simple "one germ, one disease" model because the pathophysiological effects of many infectious agents—and particularly influenza viruses—modify the effects of coinfecting agents.[15–29] The mechanisms involved in such interactions include breakdowns of physical barriers to tissue invasion; decreased mucociliary clearance activity; destruction, depression, and/or dysregulation of immune system components; enhanced expressions of receptors by, and/or increased adherence to, epithelial cells; increased aerosolisation and dispersion of coinfecting agents; production of antibodies that block immune responses to other agents; up-regulation of expressions of genes that code for toxins; and so on[15–29] (figure 1). In turn, interactions among influenza and coinfecting bacterial respiratory pathogens, for example, often determine clinical attack rates, the nature and severity of clinical expressions, and the mode, direction, and velocity of spread of coinfecting agents in various populations, locations, and settings.

I review some of the clinically and epidemiologically significant interactions between influenza and common respiratory bacterial pathogens, particularly in relation to the 1918 pandemic. Contemporaneous reports regarding the 1918 pandemic bacteriological findings, and interpretations of their clinical and epidemiological relevance, must be interpreted cautiously because, for

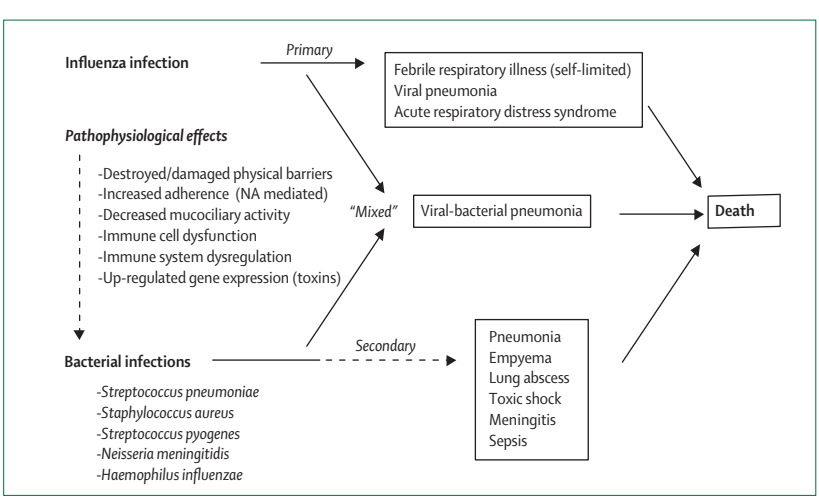

Figure 1: **Examples of pathophysiological interactions between influenza and bacterial respiratory pathogens and various clinical expressions**

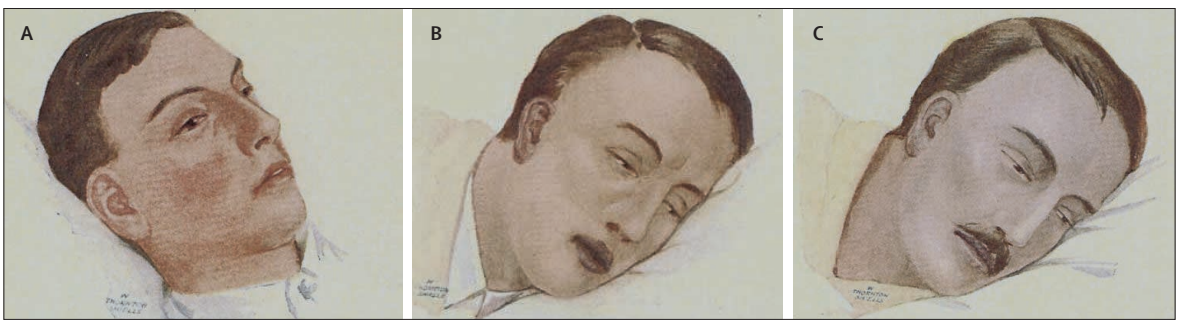

Figure 2: **Faces of "influenzo-pneumonic septicaemia"**
(A) "An early case in which the facial colour is frankly red, and the patient might not appear ill were it not for the drooping of the upper eye-lids and a half-closed appearance to the eyes." (B) "Cyanosis in which the colour of the lips and ears arrests attention in contrast to the relative pallor of the face. The patient may yet live for twelve hours or more." (C) "The heliotrope cyanosis. The patient is not in physical distress, but the prognosis is almost hopeless." Reproduced from reference 32.

example, bacteria were thought to cause most influenza and pneumonia cases, influenza viruses had not yet been discovered, and in general only severe and/or fatal hospitalised cases were included in summary reports, thus limiting the generalisability of findings. Still, the bacteriological findings and clinical impressions of medical officers—eg, regarding the timing and severity of the clinical courses of many cases—from widely dispersed outbreaks during the 1918 pandemic period are relevant, informative, and potentially useful.

"Purulent bronchitis" in British army camps, 1916–17

In the winter of 1916–17, a highly virulent respiratory illness ("purulent bronchitis") attacked a large British army camp at Etaples in northern France. The clinical presentation was "so distinctive as to constitute a definite clinical entity".[30] At the height of the epidemic, purulent bronchitis accounted for nearly half of all necropsies that were done in the affected area. Cultures of 20 sputum specimens from purulent bronchitis cases revealed *Bacterium influenzae* (now *Haemophilus influenzae*; 90%), pneumococcus (65%), streptococcus (25%), and staphylococcus (15%). Of note, specimens that yielded high numbers of *B influenzae* were nearly always coinfected with pneumococci.[30]

About the same time, a similar illness was affecting soldiers in large numbers at the British army camp in Aldershot, England. The clinical course was characterised by profound respiratory distress, "a peculiar dusky heliotrope type of cyanosis"[31] (figure 2) and high case fatality (approximately 50%). In eight consecutive cases, seven had "copious growths of *B influenzae*" associated with pneumococci.[31] Medical officers at the camp concluded that "these patients suffer from a primary invasion of their lung tissues by the *B influenzae*, and that pneumococci, present at the same time, are at first of low virulence … Exaltation of the virulence of the pneumococci by symbiotic growth with *B influenzae* would appear to follow."[31] The emergence of a distinctive, highly virulent disease in military camps in France and England suggested to Abrahams and colleagues[31] that purulent bronchitis "is more widespread than has hitherto been recognized".

Beginning in October 1917, there was a substantial rise in influenza-related morbidity among American troops in France. After his review of clinical and necropsy findings from US Army hospitals in France, MacNeal[33] had "little, if any, doubt" that the disease that attacked American soldiers late in 1917 was essentially the same as the purulent bronchitis that attacked British camps in France and England earlier that year.

In 1919, Abrahams and colleagues[32] reviewed their extensive experience during the 1918–19 influenza pandemic. They reported that *Streptococcus pyogenes longus* (36%), pneumococcus (29%), and *B influenzae* (25%) were recovered relatively frequently from cultures (n=28) of lung tissue of fatal "influenzal pneumonia" cases. They noted that "in essentials the influenza-pneumococcal 'purulent bronchitis' that we and others described in 1916 and 1917 is fundamentally the same condition as the 'influenzal pneumonia' of this present pandemic." In both conditions, the virulence of the secondary organisms appears "to be exalted by the initial influenzal infection".

Recently, Oxford and colleagues[34] postulated that the outbreaks of purulent bronchitis in military camps in France and England in 1916–17 were progenitors of the nearly simultaneous outbreaks of influenza that affected countries throughout the world in 1918–19.

Influenza and bacterial pneumonias in the US military, 1918

In the USA, the influenza pandemic was first manifested on a large scale in late winter of 1918 at Camp Funston, KS. In March, approximately 1100 soldiers assigned to the camp were hospitalised for influenza—approximately 22% developed pneumonias (>90% lobar), of which approximately 20% were fatal. Opie and colleagues[35] reported that "the greatest incidence of pneumonia affecting troops in this camp occurred … coincident and immediately following the outburst of influenza, the maximum of pneumonia being five days after the maximum for influenza".

In the autumn of 1918, "an epidemic of epidemics" attacked military camps in general.[36] Within 8 days of the start of the index epidemic at Camp Devens, MA, 11 other camps had been affected; by the end of September, 31 camps had been attacked; and by the end of October, all large camps in the continental USA had been affected (figure 3).[36]

The natures, dynamics, and effects of the epidemics that affected the widely separated camps were remarkably similar. In general, they had explosive onsets, nearly as rapid declines, and durations of 3–4 weeks (figure 4). Within approximately 1 week after the start of each epidemic, there was an "ominous prevalence of pneumonia. The pneumonia [did] not exist as a separate epidemic, but it [was] always a follower of influenza".[36] At the various camps, the epidemic curves of pneumonias and deaths lagged by approximately 7–10 days behind those of influenza (figure 4). Overall, there was a remarkably strong relation between cases of influenza each week and pneumonia-related deaths the following week (pneumonia-related deaths each week=0·0635 × influenza cases the previous week; R^2=0·98).[36] Soper[36] concluded that "the influenza paves the way for the pneumonia, if it does not actually produce it".

Descriptions of epidemics at various camps—and impressions of medical officers who responded to them—were also remarkably similar. For example, at Camp Devens, in 1 month beginning September 12, approximately one-quarter of all troops were diagnosed with influenza; of them, approximately 17% developed pneumonias, of which approximately 35% were fatal.[36,40] *B influenzae* were found in pure culture in at least one lobe in 43% of 37 necropsies; and pneumococci (65%), *Streptococcus haemolyticus* (7·5%), *H influenzae* (2·5%), and *Staphylococcus aureus* (1·3%) were recovered from 80 post-mortem cultures of heart blood. Medical officers felt that "considerable importance must be placed on the secondary invaders, the pneumococcus and in this hospital rarely the *S hemolyticus,* which are found in such a large percentage of cases examined, both during life and post mortem".[40]

At Camp Logan, TX, from September 13 to October 8, there were 2487 hospitalisations for influenza; of them, approximately 17% developed pneumonias, of which approximately 4% were fatal.[36,41] Of 302 sputum cultures of influenza and pneumonia patients, the predominant organism by far was pneumococcus. In nine post-mortem examinations, pneumococci were the most frequently recovered organisms from lungs (44%), pleural cavities (67%), and heart blood (33%).[41]

At Fort Riley, KS, between September 15 and the end of October, approximately one-quarter of the camp's population were affected by influenza; of them, approximately 17% developed pneumonias, of which approximately 36% were fatal.[36,42] Medical officers reported that there were "no deaths during the epidemic except from pneumonia or its complications".[42] They concluded that "influenza bacillus or some unknown

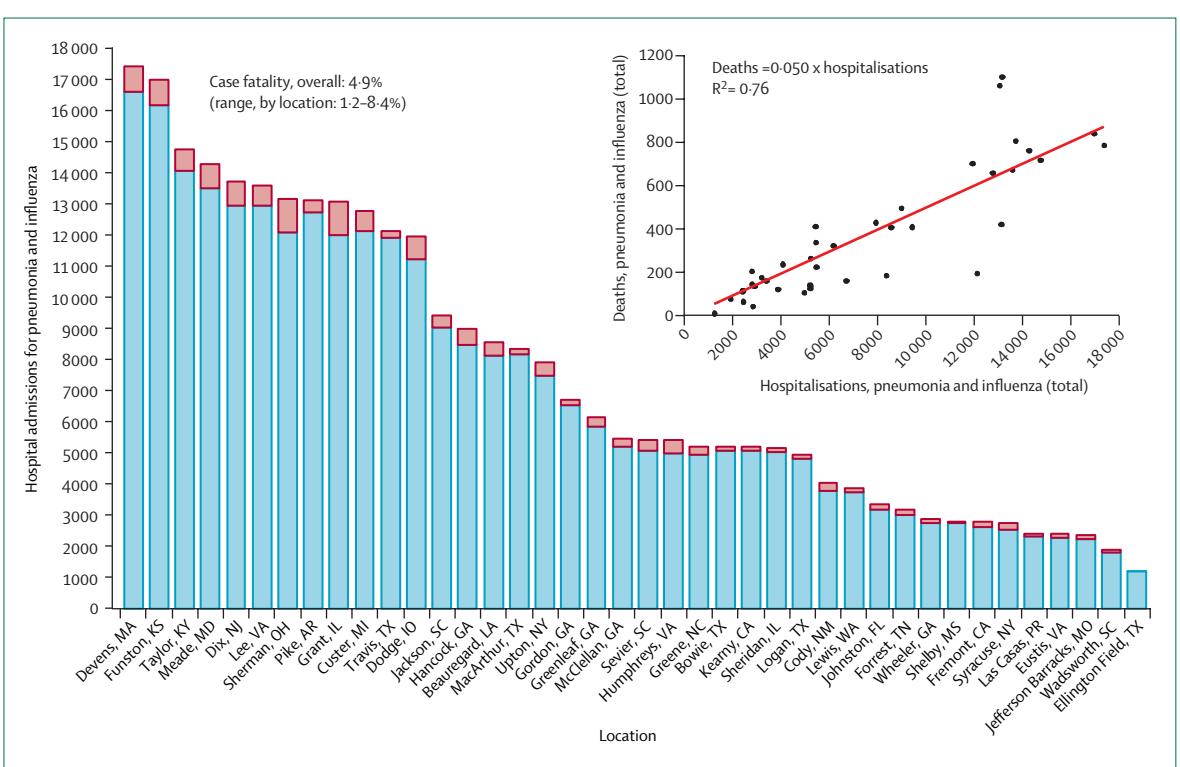

Figure 3: Hospitalisations for, deaths due to, and variability of case fatality of pneumonia and influenza at 40 large US army camps during the autumn of 1918[37]

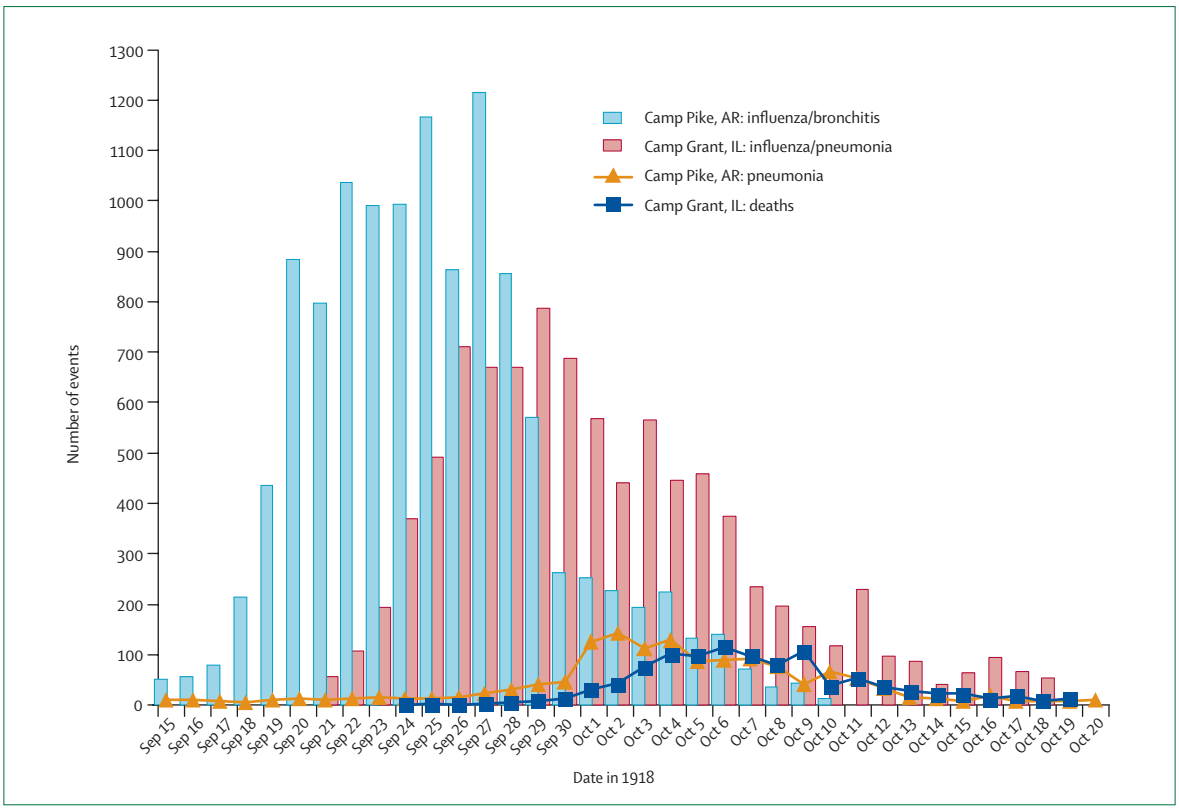

Figure 4: **Between Sept 15 and Oct 20, 1918, there were approximately 7–10 day lags between the epidemic curves of "influenza/bronchitis" and "pneumonias" at Camp Pike, AR,[38] and "influenza/pneumonia" and associated "fatalities" at Camp Grant, IL[39]**

virus merely served to predispose to pulmonary infection with organisms commonly known to produce pneumonia such as the pneumococcus and *Streptococcus hemolyticus*".[42]

At Camp Jackson, SC, from approximately September 15 through mid-October, about one-fifth of the camp's population were hospitalised with influenza; of them, about 17% developed pneumonias, of which approximately 31% were fatal.[36,43] The most frequent isolate from sputum of pneumonia cases was *Streptococcus pneumoniae*; remarkably, nearly half of 312 post-mortem lung cultures revealed *S aureus*. Medical officers postulated that "the primary epidemic infection depresses the hematopoietic system to such a degree that it is unable to react normally to infection by bacteria".[43]

At Camp Pike, AR, between September 20 and October 19, nearly one-quarter of the camp's population were treated for influenza; of them, approximately 12% developed pneumonias of which approximately 31% were fatal (figure 4).[36,38] From clinical and autopsy findings, Opie and colleagues[38] concluded that "pneumonia follows influenza because the disease renders the air passages susceptible to the invasion of a variety of micro-organisms, among which those commonly found are pneumococci, hemolytic streptococci, and staphylococci".

At Camp Dix, NJ, from mid-September through October, approximately one-fifth of the troops were hospitalised for influenza; of them, approximately 18% developed pneumonias, of which approximately 50% were fatal.[36,39] There were 20 cases of frank empyema and several lesions of pleura that would have resulted in empyema had the patients lived longer. Medical officers noted that "a large variety of organisms has been encountered in cultures and smears from the lung substance, from the bronchial mucous membrane, and from the sputum. Streptococci and pneumococci have been most frequently found".[39]

At Camp Custer, MI, from late September through October, more than one-quarter of all troops were diagnosed with influenza; of them, approximately 21% developed pneumonias, of which approximately 28% were fatal.[36,44] Of 740 cultures of sputum of pneumonia patients, 26% and 17% were positive for pneumococcus and haemolytic streptococcus, respectively. Post-mortem cultures of lung and heart blood specimens from 280 fatal pneumonia cases revealed that 28% of each were positive for pneumococcus, and 27% and 22%, respectively, were positive for haemolytic streptococcus. The authors noted that "without exception the deaths from this respiratory epidemic have been due to secondary pneumonia. In no instance has a case come to necropsy in which death occurred from influenza infection alone".[44] They concluded that bacteria recovered from pneumonic lungs were "secondary invaders, the field being prepared by the

lowering of resistance incident to a preceding disease, which in this epidemic was in most instances influenza".[44]

At Camp Grant, IL, in approximately 1 month following September 21, about one-quarter of all troops were hospitalised for influenza; of them, approximately 22% developed pneumonias, of which approximately 46% were fatal (figure 4).[36,45] Post-mortem cultures of exudates of consolidated lungs and heart's blood often revealed "purely fine green colonies containing gram positive, lancet shaped diplococci".[45] 45 of 90 blood cultures of living patients revealed "a gram-positive diplococcus in pure strain without exception ... all the morphologic and cultural characteristics of a pneumococcus".[45] The authors concluded that "the epidemic of bronchopneumonia at Camp Grant is due to infection by a virulent strain of pneumococcus. The virulence of this organism exceeds greatly that of strains usually identified in pneumonia".[45]

At Camp Fremont, CA, in 6 weeks beginning October 8, there were 2418 hospitalisations for respiratory diseases; of them, approximately 17% developed pneumonias, of which approximately 36% were fatal.[36,46] Cultures of nasopharynges or sputum of 158 pneumonia cases revealed *B influenzae* (38%), pneumococci (41%), and streptococci (29%). Post-mortem cultures of lungs in 20 lobar pneumonia cases revealed pneumococci (45%) and staphylococci (10%). Post-mortem examinations of bronchopneumonia cases revealed that "pus streamed from their tracheas when the lungs were removed. Small areas ... of consolidated tissue were scattered uniformly throughout the lungs ... a drop of pus could be expressed from the center of each."[46] The authors concluded that the primary infection caused lower resistance to certain secondary organisms; secondary lobar pneumonias were due to pneumococci and streptococci—pneumococci predominating; and bronchopneumonias were due to *B influenzae*.[46]

In his review of clinical reports from 72 US Army hospitals throughout the USA, Conner[47] noted "the multiplicity of types of the infecting micro-organisms" and emphasised the "close relation which exists between the purely clinical aspects of the disease and the nature of the dominating organism in the lung. This relation seems to be especially important in the case of *Streptococcus hemolyticus* and of *Staphylococcus aureus*."

In his review of the effects of the pandemic at 37 large army camps between September 12 and October 31, Soper[36] estimated that 22% of all soldiers were diagnosed with influenza; of them, approximately 17% developed pneumonias, of which approximately 34% were fatal. Across all camps, the mean influenza attack rate was 23% (median 22%; quartiles 15–28%), the mean percentage of influenza cases that developed pneumonias was 16% (median 17%; quartiles 10–20%), and the mean percent of pneumonia cases that were fatal was 34% (median 33%; quartiles 22–41%).[36]

Finally, in his review of the pandemic's effects on the American Expeditionary Forces in Europe, MacNeal[32] reported that "influenza bacilli, pneumococci of various types, hemolytic and non-hemolytic streptococci have occurred most frequently in the infiltrated lungs ... In many cases, two or more of these organisms were isolated from the same tissue." He concluded that "the disease has been essentially due to an invasion of the respiratory tract by influenza bacilli, followed by and associated with other pharyngeal organisms, and the fatal outcome, in most instances, has been brought about particularly by these secondary invaders, in some instances streptococci, in others pneumococci".

Descriptions of the pandemic's effects at US Navy installations were similar. For example, in the annual report of the Surgeon General of the US Navy for 1918,[48] the epidemic that affected the submarine base in San Pedro, CA, was described as "influenza complicated by streptococcus infection". In the same report, Borden and Leopold noted that "no case of pandemic pneumonia ... failed to present the clinical signs of influenza well before any pneumonic symptoms were recognized, thus demonstrating a distinct relationship between the causative factor in the uncomplicated influenza and the post influenzal pneumonia".

During the epidemic at the Puget Sound Navy Yard, WA, in the fall of 1918, streptococci were recovered from 44% of 52 blood cultures of living cases. During 20 post-mortem examinations, haemolytic streptococci were recovered from heart blood (85%), the lungs (70%), and the pericardium (60%). The authors concluded that at the Puget Sound Navy Yard, the disease called influenza was due to an organism that "should be classed as a hemolytic streptococcus".[49]

At the US Naval Hospital at League Island, PA, during 1 week in mid-September, 600 patients were hospitalised with influenza; of them, approximately 28% developed pneumonias, of which 29% were fatal. Pneumococci were recovered from "the majority of cultures" of sputum, whereas *B influenzae*, streptococci, and staphylococci were recovered less often. Devers and colleagues[50] noted that "the presence of these organisms, especially the pneumococcus and streptococcus ... is interesting in view of the very common complication of pneumonia".

At the First Naval District in Massachusetts, Rapaport[51] found that 54·5% of 295 convalescent influenzal pneumonia patients (versus 9·6% of 300 controls) had antibodies to *B influenzae*.

In the *US Naval Medical Bulletin*, Hare[52] reported that "in the vast majority of cases, the illness was not the result of infection by one pathogenic organism, but was a multiple infection in which one of several organisms was the chief agent or in which all were approximately equally responsible ... the physical signs of disease, the symptoms, and the lesions recognized at autopsy were much more those of the *Streptococcus hemolyticus* than of any of the other associated organisms".

In summary, medical officers at military installations throughout the USA and Europe were consistent in their

impressions that primary infections with influenza increased susceptibility to bacterial respiratory pathogens, that secondary bacterial infections were common and were clinically expressed with unusual virulence, and that bacteria accounted for many, if not most, of the pneumonias and deaths. By contrast with many recent reports,[6,7,13] there were few, if any, contemporaneous descriptions of epidemics at military camps in 1918 that did not emphasise the importance of secondary bacterial infections.

In this regard, it is worth noting Conner's mention[47] of a "clinical type which, in a few camps, notably at Camp Sherman, was sufficiently common to form an outstanding feature of the epidemic. The patients ... showed extreme cyanosis, high fever, and intense air hunger, and died in from 24 to 48 hours. The chest was filled with coarse, bubbling rales, and pinkish, frothy serous fluid often poured from the mouth and nostrils. The postmortem findings in the lungs were those of intense congestion and edema, without actual pneumonia. Friedlander compares the clinical picture to that seen after severe exposure to chlorin gas." Such cases have become the focus of most current pandemic preparedness planning.

The pandemic's effects in civilian populations were generally similar to those in the military. For example, in December 1918, a house-to-house survey of 112 958 people in eight locations throughout the USA found that approximately 28% were affected by influenza and approximately 30% of associated pneumonias were fatal.[53]

Between September 23 and October 29, in Chicago, more than 2000 patients were hospitalised for influenza at Cook County hospital—nearly one-third of them died. Most fatalities were among young adults between 25 and 35 years old. Pneumococci were isolated from 70% of sputum, 74% of throat, and 73% of 15 lung puncture specimens of living patients. Pneumococci were also isolated from 75% of lung cultures post-mortem. Nuzum and colleagues[54] concluded that "the high percentage of pneumococci obtained during life and at necropsy and predominating in the sputum, tracheal mucosa, and lung tissue both early and late in the course of the disease suggest that this organism is at least the most important secondary invader and is responsible for many of the rapidly fatal pneumonias".

Influenza and bacterial pneumonias post-1918

Reports of associations between influenza and bacterial pneumonias of unusual virulence are not limited to the 1918 pandemic. For example, Burgess and Gormley[55] reported three cases of staphylococcal pneumonia that rapidly progressed to death during an influenza epidemic in January 1929. *S aureus* was recovered from the sputum of all three patients (and from the lungs of the only case examined post-mortem).[55]

In December through January 1941, during an epidemic of influenza A in Boston, Finland and colleagues[56] reported 66 cases (32% fatal) of *S aureus* pneumonia. During the same period, 22 patients were admitted to the same hospital with pneumococcal lobar pneumonias—all had onsets of pneumonia 1–10 days after symptoms of influenza.[56] During the same epidemic, Pearson and colleagues[57] found high titres of antibodies against influenza A virus (suggestive of recent infection) in 34 of 82 (41%) patients hospitalised with pneumococcal pneumonia and seven of nine (78%) patients hospitalised with staphylococcal pneumonia. Of patients who had paired serum samples, five of 21 (24%) patients with pneumococcal pneumonia and all six with staphylococcal pneumonia had changes in titres indicative of recent influenza A infection. The authors noted the possibility that "in certain of these patients, at least, influenza represented a factor predisposing to the pneumonia".[57] During the same period, Michael[58] described five staphylococcal pneumonia cases with fulminating clinical courses. In three of the cases, serological tests confirmed that influenza A infection immediately preceded the pneumonia. Michael concluded that "*S aureus* pneumonia often occurs as a complication of influenza" and suggested that "chemotherapy might have little effect unless given prophylactically during influenzal epidemics".

In 1944, Dingle and colleagues[59] observed that "outbreaks of pneumonia in camps and institutions were usually preceded by waves of influenza-like infection". They postulated that influenza infections increased susceptibility to pneumococcal infections and/or enhanced the transmission of pneumococci in affected populations. To clarify the relation, they studied acute and convalescent sera of patients involved in a pneumonia outbreak in a small town in New York and found that influenza B pre-existed in the community. They concluded that some localised outbreaks of acute bacterial pneumonia were secondary manifestations of influenza epidemics and that an increased prevalence of pneumonia may be a useful clue to identifying and studying outbreaks of influenza.

During the 1957 Asian influenza pandemic in the USA, there were substantial increases in hospitalisations and deaths from respiratory illnesses in general and pneumonias in particular. A case series analysis revealed that the most frequently isolated bacteria from patients with post-influenzal pneumonias were *S pneumoniae*, *H influenzae*, and *S aureus*.[60] During the same period in the Netherlands, Hers and colleagues[61] studied 158 fatal cases of Asian influenza. *S aureus* and pneumococci were recovered from 59% and 15% of lung cultures, respectively. Approximately two-thirds (n=56) of the pneumonia-related deaths attributable to *S aureus* were in individuals between 6 and 40 years old. "Pure" influenza pneumonia was considered the cause of death in 20% of the fatal cases.[61]

During the 1968 Hong Kong influenza pandemic in the USA, there was an estimated threefold increase in the incidence of staphylococcal pneumonias and a strong

correlation between staphylococcal pneumonia risk and prior influenza infection. Much of the excess mortality during the pandemic was attributed to the increased incidence of bacterial pneumonias.[62] In Rochester, MN, influenza A Hong Kong/68 virus was isolated from 127 patients; of these, 16% developed pneumonias, of which 40% were fatal. *S aureus* or *Pseudomonas aeruginosa* was recovered from six of eight fatal cases.[63]

In 1996, Kim and colleagues[64] reported results of a community-wide surveillance of respiratory diseases in Houston. Among adults, they found significant correlations between the occurrence of pneumococcal disease and the isolation of influenza, respiratory syncytial virus, and other viruses ($p<0·001$). Recently, in a controlled trial among South African children, Madhi and colleagues[65] found that pneumococcal vaccine prevented 31% of all pneumonias associated with a variety of respiratory viruses. They concluded that pneumococci were important in the pathogenesis of viral pneumonias, and that viruses were important in the pathogenesis of bacterial pneumonias.

In summary, over decades in various populations and settings worldwide, there have been strong and consistent relations between influenza and secondary pneumonias, particularly due to pneumococcus, *S aureus, S pyogenes,* and *H influenzae*.

Influenza and meningococcal disease

Interactions between influenza and *Neisseria meningitidis* have also been well documented. For example, during mobilisation for World War 1 (which included the influenza pandemic period), there were historically high numbers and rates of meningococcal disease in US civilian and military populations. In the US Army, recruits in initial training camps and soldiers who had recently disembarked from troop ships were at highest risk.[66]

In October 1918, the weekly bulletin of the American Expeditionary Forces in Europe documented a sharp rise in reports of cerebrospinal meningitis approximately 1 week after sharp increases in reports of influenza and pneumonia. The bulletin noted that "it has been a usual observation that when infections of the upper respiratory tract prevail, the incidence of meningitis in the community increases soon after and this rule prevails at present".[67]

Since 1918, there have been numerous reports of clusters of meningococcal disease that occurred during or shortly after outbreaks of influenza or influenza-like illnesses. For example, in 1972, Young and colleagues[68] described 11 cases (three fatal) of serogroup B meningococcal meningitis among 55 residents of a mental institution during a community outbreak of influenza A. Both nasopharyngeal carriage and systemic infections with *N meningitidis* were significantly associated with serological evidence of recent influenza infections ($p=0·054$ and $p=0·029$, respectively). In 1976, Mackowiak and colleagues[69] reported four cases of meningococcaemia that occurred simultaneously in a family of six. The family members were affected by influenza-like illnesses before the outbreak of meningococcemia.[69] In 1986, Schubiger and colleagues[70] reported an outbreak of group B meningococcal disease among boarding school students. Each affected student had serological evidence of concomitant influenza infection. The authors concluded that "the viral infection made way for the outbreak of the meningococcal disease and for the high rate of secondary meningococcal infection". In February 1986, within 2 days, five children who rode the same school bus developed group C meningococcal disease. All of the affected children had recent influenza-like illnesses, and cases had higher titres of antibodies to influenza B than non-affected students on the same bus.[71] In January 1996, ten cases of group C meningococcal disease occurred within 6 days among 1034 air force recruits in Greece. The peak of the outbreak was approximately 3 days after the peak of a large outbreak of influenza B among the recruits.[72]

Relations between influenza and meningococcal disease incidence have also been documented at population levels. For example, in November–December 1989, during an influenza outbreak in the UK, Cartwright and colleagues[73] noted a striking increase in the number of meningococcal strains submitted to the national reference laboratory. Sera from 28% of 43 meningococcal disease cases (compared with 9% of 67 other cases) had antibodies to the epidemic strain of influenza A. During the same period, rates of meningococcal disease were increased and case fatality rates were exceptionally high throughout southwest England.[73] In 1957 and 1976, in England and Wales, approximately 2 weeks separated large outbreaks of influenza A from increases in reports of meningococcal meningitis.[74] From 1985 through 1990 in France, the incidence of meningococcal disease during a given week correlated with rates of influenza-like syndrome during the preceding (but not the following) 5 weeks. Also, there were significant spatiotemporal associations between the spread of influenza-like syndrome throughout the country and subsequent increases in meningococcal disease rates ($p<0·05$). Finally, meningococcal cases had more severe clinical outcomes during and up to 2 months following outbreaks of influenza-like syndrome compared with other times.[75]

In summary, in many locations, populations, and settings over many decades, important relations have been documented between influenza incidence and subsequent rates and severities of meningococcal disease.

Influenza and staphylococcal toxic shock syndrome

Influenza has been associated with increased risk of staphylococcal toxic shock syndrome. In 1987, Sperber and Francis[76] reported a fatal case of staphylococcal toxic shock syndrome in an 18-year-old boy with bilateral

S aureus pneumonitis and ulcerative tracheobronchitis following a 3-day history of influenza-like illness. The fatal illness occurred during an outbreak of influenza B in the boy's community. In the same year, Macdonald and colleagues[77] reported nine cases of staphylococcal toxic shock syndrome during influenza outbreaks (primarily type B) in Minnesota during one winter season. Eight of the cases occurred within 1–4 weeks of peaks of influenza activity in the same communities; and seven of the cases had *S aureus* isolates that produced toxic shock syndrome toxin 1 or enterotoxin B. The authors surmised that toxic shock syndrome can occur in patients "who have a toxigenic strain of *S. aureus* in their respiratory tracts during influenza-like illness".

"Cloud adults" and "superspreaders"

In 1960, Eichenwald and colleagues[78] reported that newborns whose noses were colonised with *S aureus* dispersed large numbers of bacteria ("cloud baby") and were highly contagious ("superspreaders") when coinfected with common respiratory viruses. In 1972, Gwaltney and colleagues[79] documented 25 transmissions of *S pneumoniae* between family members. 14 (56%) of these donors had symptomatic upper respiratory infections around times of transmission. In 1996, Sherertz and colleagues[80] documented the "cloud" phenomenon in adults. Investigation of an outbreak of MRSA in a surgical intensive care unit revealed that one of 64 workers in the unit was a nasal carrier of the outbreak strain. The carrier had a minor upper respiratory illness during the outbreak; and after experimental inoculation with a rhinovirus, he had a 40-fold increase in dispersion of the carriage strain of *S aureus*. In 2004, Bassetti and colleagues[81] reported that university students with persistent nasal carriage of *S aureus* increased dispersal by twofold (with peak increases up to 34-fold) after experimental infection with a rhinovirus.

During outbreaks of SARS coronavirus in 2003, some infected individuals transmitted the virus much more efficiently than others. The few superspreaders were epidemiologically important.[82] For example, during the outbreak in Hong Kong, the index case—a super-spreader—presented with a runny nose, a relatively uncommon clinical manifestation of SARS coronavirus. Bassetti and colleagues[83] postulated that the trans-missibility of SARS coronavirus may be substantially enhanced by coinfections with other respiratory viruses.

Studies in animals and natural experiments in human beings suggest that influenza spreads from person-to-person through aerosols of droplet nuclei ("virus clouds").[84] It is likely (but not documented) that influenza increases the transmissibility of bacteria and/or viruses that colonise or coinfect the respiratory tracts of coinfected hosts; and that infections with other viruses and/or bacteria (eg, pertussis) may increase the aerosolisation—and hence the transmissibility—of coinfecting influenza.

Interactions model: public health and clinical implications

The epidemiology and clinical expressions of respiratory infectious diseases depend on characteristics of and interactions among co-circulating infectious agents, infected and at-risk human hosts, and the environments in which they interact. Narrow epidemiological models that do not account for agent, host, and environmental interactions unnecessarily restrict opportunities for prevention, treatment, and control.

During the 1918 pandemic (and subsequent pandemics and epidemics) of influenza, a large proportion of deaths were likely attributable to bacterial respiratory infections. Unlike 1918, however, we now have safe and effective vaccines against the most prevalent strains of *S pneumoniae* and *N meningitidis*. In addition, we now have antibiotics that have been used safely and effectively to prevent severe bacterial respiratory illnesses (eg, invasive group A streptococcal disease, acute rheumatic fever, pneumonia, empyema, cerebrospinal meningitis) in individuals, groups, and settings considered to be at high risk.[85–93] During future pandemics, virtually all members of general populations will be at high risk of influenza infection, and all those infected (regardless of age or prior health) will be at exceptionally high risk of fulminant clinical expressions of secondary bacterial respiratory infections.

The prevention of secondary bacterial infections with currently available vaccines and antibiotics would seem to be "low hanging fruit" for pandemic preparedness. Fock and colleagues[94] have noted that "even if suitable influenza vaccines and virostatic agents are not sufficiently available at the start of a pandemic, it is still possible to at least prevent an outbreak of two of the most feared secondary infections that accompany influenza: pneumococcal pneumonia or meningitis and illnesses resulting from *Haemophilus influenzae*".

Yet, there is relatively little knowledge regarding—and little research specifically focused on defining—the public health and clinical implications of interactions between influenza viruses in general (or H5N1 specifically) and bacterial respiratory pathogens. Vaccines and antibiotics may be useful adjuncts to current influenza epidemic countermeasures. Research on prevention and treatment measures specifically related to bacterial infections that occur secondary to influenza should be a high priority.

Conflicts of interest

I declare that I have no conflicts of interest.

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