



Commentary

Influenza and Community-acquired Pneumonia Interactions: The Impact of Order and Time of Infection on Population Patterns

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Discoveries made during the 1918 influenza A pandemic and reports of severe disease associated with coinfection during the 2009 hemagglutinin type 1 and neuraminidase type 1 (commonly known as H1N1 or swine flu) pandemic have renewed interest in the role of coinfection in disease pathogenesis. The authors assessed how various timings of coinfection with influenza virus and pneumonia-causing bacteria could affect the severity of illness at multiple levels of interaction, including the biologic and population levels. Animal studies most strongly support a single pathway of coinfection with influenza inoculation occurring approximately 7 days before inoculation with *Streptococcus pneumoniae*, but less-examined pathways of infection also may be important for human disease. The authors discussed the implications of each pathway for disease prevention and what they would expect to see at the population level if there were sufficient data available. Lastly, the authors identified crucial gaps in the study of timing of coinfection and proposed related research questions.

community-acquired infections; influenza, human; pneumococcal infections; pneumonia

Abbreviation: CAP, community-acquired pneumonia.

Community-acquired pneumonia (CAP) often follows influenza infection. The hypothesized synergistic interaction resulting from coinfection with influenza and agents of CAP is thought to be a major factor in the severity of the 1918 influenza A pandemic (1, 2). Today, up to 20% of persons who have CAP show evidence of recent exposure to the influenza virus (3), and pneumonia is a leading indicator of influenza severity (4). Although *Staphylococcus aureus* is a relatively uncommon cause of CAP after influenza infection, methicillin-resistant *S. aureus* has been considered an important pathogen in deaths of coinfecting pediatric patients. Data from the Centers for Disease Control and Prevention on the 2004–2007 influenza seasons showed that methicillin-resistant *S. aureus* was present in 60% of the 20 pediatric patients who died from *S. aureus* coinfection, with the highest rate during the 2006–2007 season (5), which suggests that the problem of antibiotic resistance among children with CAP in this age group is growing.

Influenza is transmitted via respiratory droplets, through either direct or indirect contact, and is highly infectious. Each year, seasonal influenza infects hundreds of thousands of people worldwide and accounts for an estimated 36,000 deaths in the United States (6), with pandemic strains often resulting in higher mortality rates (7, 8). Complications from influenza are most severe in the young, the elderly, and persons with compromised immune systems (9). Bacteria that cause CAP are transmitted through person-to-person direct contact; however, the rates of infectivity and progression to pneumonia are thought to be lower than those of influenza, and many of the CAP-causing bacteria are found in healthy individuals. The most common causes of CAP are *Staphylococcus pneumoniae*, *S. aureus*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, although there are regional variations (10). Although investigators performing studies in which they used animals and experimental systems have begun to address

how coinfection may enhance pathogenesis, there is little in the literature on the impact of coinfection on transmission of or susceptibility to bacteria. Perhaps most importantly, although population-level synergy has been observed, the timing of transmission related to the order of infection from each agent has not been definitively established (11, 12). Understanding the order and timing of this synergistic relation and the resulting population-level effects is especially relevant to epidemiologists who are engaged in planning for pandemics.

In the present commentary, we use *S. pneumoniae*, the most common cause of CAP, as a model organism to explore the relation between influenza A and CAP. With over 90 identified serotypes and multiple licensed vaccines, *S. pneumoniae* remains one of the best researched of the pneumonia-causing bacteria (13). We present 3 pathways to coinfection and discuss the impact of order and timing of coinfection on what epidemiologic patterns might be observed. We close with a discussion of outstanding research questions and their implications for CAP prevention.

PATHWAYS TO COINFECTION

There are 3 possible pathways to coinfection: 1) infections with both etiologic agents occur essentially simultaneously; 2) *S. pneumoniae* colonization precedes influenza infection; and 3) influenza infection precedes *S. pneumoniae* colonization (Figure 1). Each of these pathways is possible (although they likely occur at different frequencies); however, we expect the resulting population patterns to differ depending on the relative frequency of each pathway, as will the implications for control measures (discussed below).

Simultaneous acquisition of influenza and *S. pneumoniae*

Viruses and bacteria can be transmitted together through coughing or sneezing (11, 14–16). However, the extent to which simultaneous infections with influenza and *S. pneumoniae* lead to CAP is uncertain. In one of the few animal studies in which simultaneous infections were studied, investigators found no evidence of lethal synergy in mice infected with sublethal titers of both influenza and *S. pneumoniae* (17). In humans, influenza infection alone increases cough, potentially facilitating transmission of both viruses and bacteria (4). Additionally, influenza replicates more rapidly than does bacteria, so even if the infections are acquired simultaneously, the clinical manifestations in an individual would appear sequentially. At the population level, we might expect little or no lag between peaks in influenza and pneumonia occurrence after simultaneous infection. Potential course-of-infection and research questions related to concurrent infection are presented in Table 1.

S. pneumoniae colonization preceding influenza

If *S. pneumoniae* colonization precedes influenza infection, changes in the upper and lower respiratory tracts resulting from the influenza infection would enable the colonizing strain of *S. pneumoniae* to successfully avoid a host immune

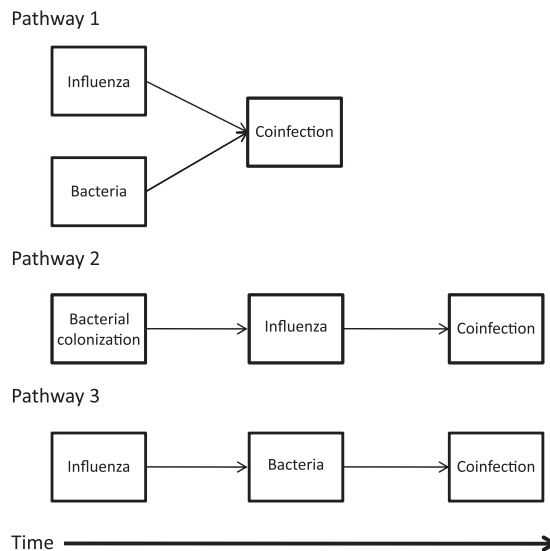


Figure 1. Schematic of 3 pathways of influenza and bacterial pneumonia exposure that lead to coinfection.

response, invade the lung, and cause pneumonia. Although it is assumed that bacteria that colonize the nasopharynx frequently enter the lungs, the host immune response is usually sufficient to prevent infection. The introduction of influenza primes the lungs for bacterial colonization and adversely affects the host response, leading to secondary pneumonia (4, 11, 18). In this case, the endogenous bacteria exploit an opportunity that may not have presented itself in the absence of an influenza infection. The prevalence of *S. pneumoniae* colonization ranges from 19% in children (19) to approximately 11% in adults in the United States (10). Thus, for pneumonia caused by *S. pneumoniae*, the relative contribution of coinfection would be age-dependent and rely upon rates of colonization among the elderly or adult interaction with children who had an *S. pneumoniae* infection.

There have been few animal models in which this pathway was studied directly. In one mouse model, the introduction of influenza A 3 days after inoculation with *S. pneumoniae* led to an increase in the presence of pneumonia and facilitated influenza transmission to littermates (12). However, in a second mouse model, investigators found that *S. pneumoniae* colonization before influenza infection was protective compared with influenza infection before *S. pneumoniae* colonization (17). These studies seem to suggest that *S. pneumoniae* can facilitate transmission of influenza, but they provide insufficient evidence for any synergy in terms of coinfection.

At the population level, we would expect a limited time lag before the onset of bacterial pneumonia (Table 1). Because the bacterial agent has had a chance to proliferate in the host, we would expect more rapid proliferation once the lungs were no longer able to clear the bacteria. However, because acquisition of a new bacterial isolate is required, we could anticipate that the onset of coinfection would be much more variable and would be associated with individuals with high risk of exposure, such as those who had contact with young children.

Table 1. Examples of Relevant Research Questions for Each Pathway of Influenza and Bacterial Pneumonia Coinfection

Pathway	Relevant Research Questions	Population Implications
Cotransmission	Is a cough or sneeze sufficient for simultaneous infection, or must fomites play a role? Does bacterial survival depend upon droplet size?	Short or no lag observed between peak of influenza infection and peak of bacterial pneumonia infection
Bacterial colonization followed by influenza infection	Does the body exert more effort to keep certain bacteria in check? If so, is an individual with those bacteria more likely to become infected after influenza infection? Can probiotics or prebiotics be used to prevent colonization with pneumonia-causing bacteria?	Short lag between peak of influenza infection and peak of bacterial pneumonia infection
Influenza infection followed by bacterial colonization	What role do children play in transmitting bacteria to influenza-infected adults? How can we prime the immune system to prevent secondary infection from bacterial pathogens?	Long lag between peak of influenza infection and peak of bacterial pneumonia infection

Influenza infection preceding *S. pneumoniae* colonization

Clinically, it is assumed that bacterial pneumonia associated with influenza results from a bacterial infection that follows the influenza infection. Within an individual, the typical course of secondary bacterial pneumonia involves initial recovery from influenza followed by secondary symptoms, such as cough or fever, 4–14 days later (20). Results from animal models support this clinical observation. When mice are exposed to both wild-type and laboratory influenza strains and various strains of *S. pneumoniae* and *S. aureus*, there is an increased number of pneumonia infections, as well as an increased likelihood of death, compared with when any agent is given alone (11, 17, 21–23). In the aggregate, these experiments strongly support the idea of a synergistic interaction between influenza and *S. pneumoniae* (and *S. aureus*) when infection occurs sequentially.

At the population level, we would expect to see a relatively long lag time between influenza infection and the presence of CAP because of the time needed for the influenza to reduce the ability of the lungs to clear a bacterial infection. This lag time would enable partial recovery before the bacteria could infect the individual. The bacterial agent would then have to proliferate within the host before the host began to show symptoms of CAP. This lag was observed when data from the 1918 pandemic were reanalyzed. A graph of the timing from influenza infection to death found a lag period of 7–21 days (24), which suggests that affected individuals recovered before developing a more severe bacterial infection. Other research on data from the 1918 influenza A pandemic that suggests the role that secondary bacteria may have played has been supported by similar death curves created from data from infection with bacterial pneumonia alone through the 1920s and 1930s (25).

RESEARCH QUESTIONS AND IMPLICATIONS

Specifying the pathways to coinfection may help to identify new research questions about the interaction between influenza and CAP (Table 1) that can only be answered through basic science, clinical, and population studies. Basic laboratory

science studies of the interactions within animal models have provided the most information to date for understanding the interactions between influenza and *S. pneumoniae* because unlike in human populations, experiments in laboratories can control the timing of exposure to influenza and secondary bacterial infection. Animal research has also shed light on specific cytokine pathways, such as mediation of infection with influenza by interleukin-10 (26) and inhibition of the pulmonary system's ability to fight infection by interferon-gamma (27, 28), that provide testable hypotheses for an inflammatory response that might occur in humans. Further, in animal studies, investigators can explore what combinations of influenza strains and *S. pneumoniae* serotypes may result in greater risks to human populations (11, 13, 29, 30).

Seasonal influenza and pneumococcal vaccinations can protect elderly populations against hospitalization for either influenza or pneumonia, and the effects are additive. We see the fewest hospitalizations among individuals who have had both vaccinations, but persons with either the influenza vaccine or the *Streptococcus* vaccine have lower rates of hospitalization than do unvaccinated individuals (31). The novel 2009 hemagglutinin type 1 and neuraminidase type 1 influenza (commonly known as H1N1 or swine flu) pandemic provided a natural experiment in a naive population not previously exposed to the influenza strain. Specifically, the lethality of the strain in an unexposed population and potential immunity among the elderly who had been previously exposed to an H1N1 strain provided information about risk of coinfection (8, 32, 33). The pandemic also started a robust debate about when it is appropriate to provide antibiotics to prevent secondary infection and how to ration them (34–36). Because etiology is determined in only 30%–50% of patients with CAP who are tested (16) and antibiotics are often given without identifying the bacterial agent, clinical research studies will need to include bacterial surveillance. Additionally, determining the effectiveness of neuraminidase inhibitors and specific age groups to target to prevent a secondary pneumonia infection is needed to provide evidence of which populations will benefit the most from limited resources.

Historical research into the role that bacterial infections played in the deaths from the 1918 influenza A pandemic

provides a baseline for our understanding of coinfection at the population level (24, 25, 37) but little insight into the role of order and timing of the infections. Although current recommendations to stay home after influenza infection have been suggested to prevent secondary influenza infections, following the same advice may also prevent subsequent exposure to novel bacteria (pathway 3 in Figure 1) that can cause secondary pneumonia—a major cause of death in 1918. More recent data on the timing between influenza infection and bacterial pneumonia are needed to determine whether antibiotic and antiviral treatments have changed the basic timing and relation at the population level.

We described 3 pathways to CAP associated with influenza and the biologic evidence that supports the potential for each of these pathways to lead to coinfection. By exploring the implications of each pathway and examining coinfection at the biologic, clinical, and population levels, we should be able to identify key signals for predicting and preventing CAP. Although most animal models are currently used to test and support a sequential infection with influenza followed by exposure to bacteria, translating that research to a human model is not straightforward. The interaction between colonization with bacteria and infection, as well as real-life variability in the timing to transmission, means that much further research needs to be conducted for a true understanding of how this coinfection occurs in humans. However, by thinking about the interaction between influenza and pneumonia-causing bacteria in terms of timing of transmission, we are able to raise questions about where to target future human research. Creation of public health recommendations to reduce transmission among at-risk populations and determination of the effectiveness of vaccinations and treatments can be guided by using results from current animal models with a goal of shaping population-level studies. With the majority of historical deaths from influenza pandemics attributable to bacterial infection (2), sorting out the relative contribution of each pathway to disease is a project too important to ignore.

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