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# Bacterial and viral co-infections complicating severe influenza: Incidence and impact among 507 U.S. patients, 2013–14

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ABSTRACT

*Background:* Influenza acts synergistically with bacterial co-pathogens. Few studies have described co-infection in a large cohort with severe influenza infection.
*Objectives:* To describe the spectrum and clinical impact of co-infections.
*Study design:* Retrospective cohort study of patients with severe influenza infection from September 2013 through April 2014 in intensive care units at 33 U.S. hospitals comparing characteristics of cases with and without co-infection in bivariable and multivariable analysis.

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*Results:* Of 507 adult and pediatric patients, 114 (22.5%) developed bacterial co-infection and 23 (4.5%) developed viral co-infection. *Staphylococcus aureus* was the most common cause of co-infection, isolated in 47 (9.3%) patients. Characteristics independently associated with the development of bacterial co-infection of adult patients in a logistic regression model included the absence of cardiovascular disease (OR 0.41 [0.23–0.73], p = 0.003), leukocytosis (>11 K/μl, OR 3.7 [2.2–6.2], p < 0.001; reference: normal WBC 3.5–11 K/μl) at ICU admission and a higher ICU admission SOFA score (for each increase by 1 in SOFA score, OR 1.1 [1.0–1.2], p = 0.001). Bacterial co-infections (OR 2.2 [1.4–3.6], p = 0.001) and viral co-infections (OR 3.1 [1.3–7.4], p = 0.010) were both associated with death in bivariable analysis. Patients with a bacterial co-infection had a longer hospital stay, a longer ICU stay and were likely to have had a greater delay in the initiation of antiviral administration than patients without co-infection (p < 0.05) in bivariable analysis.
*Conclusions:* Bacterial co-infections were common, resulted in delay of antiviral therapy and were associated with increased resource allocation and higher mortality.



## 1. Background

Influenza results in significant morbidity and mortality in the U.S and worldwide [1], and this is exacerbated by bacterial co-infections during both seasonal and pandemic influenza years [2–4]. During the most severe influenza pandemic recorded, in 1918–1919, when an estimated 675,000 people died in the United States [5,6], epidemiologic, clinical and pathologic data indicate that the majority of influenza patients died from bacterial pneumonia rather than from the influenza virus itself. Bacterial co-infections should thus be studied in order to devise effective preventative and therapeutic strategies [2,3,7].

Influenza virus has been shown to have complex effects on the human lung, priming the respiratory tract for synergistic pathogenesis with a bacterial co-infection [8]. Morbidity and mortality are increased when bacterial pneumonia complicates influenza infection as compared with bacterial pneumonia in the absence of influenza infection [9,10].

During the 1918 and 1968–1969 pandemics, *Streptococcus pneumoniae* was likely the most common co-pathogen [3,11]. In the 1957–1958 pandemic, many reports identified *Staphylococcus aureus* as the most frequently cultured co-pathogen [3,12,13]. More recently *S. aureus* has been increasingly found in cases of fulminant pneumonia complicating influenza infection [14,15]. *Haemophilus influenzae*, with the introduction of the *H. influenzae* type B conjugate vaccine in 1985 [16], and *Streptococcus pyogenes* have decreased in prevalence over time [17]. Vaccination, novel antibiotics, and probably more importantly, viral or bacterial strain-related differences account for shifts in etiology of the most common bacterial co-infections [8].

A novel pandemic influenza A strain, influenza A (H1N1) pdm09, emerged in 2009. Reported rates of bacterial co-infection among severely ill patients varied between 17.5% and 25% for community-acquired influenza patients in the 2009–2010 season [18,19] and 33% in a study of combined community-acquired and hospital-acquired influenza patients [20]. In these and other studies the most common community-acquired pathogens included *S. pneumoniae* and then *S. aureus* [10]. The risk of co-infection and spectrum of bacterial species has not been studied during the 2013–2014 season, the first postpandemic year in which influenza A (H1N1) pdm was the predominant circulating influenza strain.

## 2. Objectives

We recently completed a retrospective study of 507 patients with severe influenza treated in intensive care units (ICUs) of 33 U.S. hospitals during the 2013–2014 influenza season [21]. The objectives of the present study were to evaluate bacterial and viral co-infection in this cohort, to describe the spectrum of co-infections and to determine their clinical impact.

## 3. Study design

We performed a retrospective cohort study of all patients with laboratory confirmed influenza A and/or influenza B infection who were diagnosed with influenza during an ICU stay or within 30 days prior to an ICU admission between September 1, 2013 and April 1, 2014 at 33 U.S. study sites that made up the Severe H1N1 Influenza Consortium (SHIC) [21]. Laboratory testing may have been with a PCR-based test, a rapid test or viral culture. Complete laboratory data were accessed from infection control records, an enterprise data warehouse or directly from the clinical microbiology laboratory. Institutional review boards approved the study at each of the participating sites.

### 3.1. Data collected

Data for this study were abstracted by a physician from each center's electronic health record (EHR) and entered into a REDCap database [22]. Data abstracted and study site information were previously described [21].

Bacterial co-infection was defined in patients having one or more isolates obtained from a blood culture and/or a pleural fluid, sputum, tracheal or bronchoscopic sample if the isolate was a pathogen thought to be causing a true infection in the opinion of the treating physician and if the isolate was collected within 30 days of ICU admission or present on arrival to the ICU. Viral co-infection was defined in patients having a positive PCR or appropriate antibody test for a viral pathogen other than influenza. Bacterial co-infections cultured within 48 h of hospital admission were defined as community-acquired; those cultured after 48 h were considered to be hospital-acquired. Bacterial identification and susceptibility testing were performed by methods determined by institutional guidelines. For all patients, management was according to institutional practices.

### 3.2. Statistical analysis

STATA v12 (College Station, TX: StataCorp LP) was used for all analyses. Outliers were reexamined in the EHR to ensure data accuracy. No subject with outlying values was excluded from any analysis. Descriptive statistics were tabulated. Bivariable analyses were used to compare potential risk factors for bacterial co-infection diagnosed during the 30 days after ICU admission or present on admission. A multivariable logistic regression model was developed to determine which of the variables significantly associated in bivariable analyses (p < 0.05) were independently