

UCLA

UCLA Previously Published Works

Title

Development of secondary bacterial pneumonia in adults presenting with influenza versus noninfluenza viral respiratory infection.

Permalink

<https://escholarship.org/uc/item/9gc1q4n2>

Authors

Melamed, Kathryn

Williams, Justin

Wang, Xiaoyan

et al.

Publication Date

2020

DOI

10.1177/1753466620963026

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial License, available at <https://creativecommons.org/licenses/by-nc/4.0/>

Peer reviewed

Development of secondary bacterial pneumonia in adults presenting with influenza *versus* noninfluenza viral respiratory infection

Kathryn H. Melamed, Justin Williams, Xiaoyan Wang, Scott Hu, Christopher Nguyen, Jing Cui and Jane C. Deng 

Ther Adv Respir Dis

2020, Vol. 14: 1–10

DOI: 10.1177/
1753466620963026

© The Author(s), 2020.

Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract

Background: Respiratory viral infections, particularly influenza, are known to cause significant morbidity and mortality, often due to secondary infections. Our aim was to comparatively analyze the incidence, epidemiology, and outcomes of secondary pneumonia in adult patients hospitalized with influenza *versus* noninfluenza viral infections and determine whether influenza particularly predisposes to secondary infections.

Methods: This was a retrospective analysis from a single tertiary medical center of adult patients admitted to the hospital between 2008 and 2010 with respiratory viral infections. Microbiological patterns and clinical outcomes were compared between those with influenza (VI, $n=57$) and those with noninfluenza (NI, $n=77$) respiratory viral infections.

Results: The NI group was older (60.6 ± 14.0 *versus* 53.3 ± 19.7 years, $p=0.019$) with higher rates of lung transplantation (29% *versus* 9%, $p=0.009$) than VI. Overall, 35% developed secondary pneumonia, higher among NI (44%) than VI (23%, $p=0.017$). *Staphylococcus aureus* was the most common cause of pneumonia in VI, whereas Gram-negative rods were most frequently identified in NI. The NI group had longer hospital [median 10 (interquartile range (IQR) 6–19) *versus* 6 (IQR 4–15) days, $p=0.019$] and intensive care unit [median 4 (IQR 0–12) *versus* 0 (IQR 0–8) days, $p=0.029$] stays compared with VI. Further, the NI group was more likely to be admitted to the intensive care unit compared with VI (62% *versus* 39%, $p=0.011$). A trend towards increased mortality was observed in viral infections complicated by secondary pneumonia than primary viral infections (28% *versus* 15%, $p=0.122$).

Conclusion: Secondary pneumonia is common among adults hospitalized with viral respiratory infections. Within our population, NI results in more frequent secondary pneumonia and longer hospital stays than those with VI. Given the high number of infections caused by Gram-negative rods, monitoring local epidemiology is critical for guiding initial antibiotic selection in empirical treatment of secondary infections.

The reviews of this paper are available via the supplemental material section.

Keywords: bacterial pneumonia, influenza, polymicrobial infections, secondary infections, viral pneumonia

Received: 18 February 2020; revised manuscript accepted: 7 September 2020.

Introduction

Respiratory viral infections contribute to significant morbidity and mortality annually.^{1,2} Causes of death include lung injury, exacerbation of chronic conditions, and bacterial superinfections.^{1,3,4} With

influenza, data from seasonal epidemics and pandemics reflect that secondary bacterial pneumonia is responsible for the majority of deaths during pandemic influenza, whereas respiratory and circulatory comorbidities in the elderly account for the

Correspondence to:

Jane C. Deng
Pulmonary and Critical
Care Medicine, Veterans
Affairs Ann Arbor
Healthcare System,
2215 Fuller Road, 111G
(Pulmonary), Ann Arbor,
MI 48105, USA

Division of Pulmonary and
Critical Care Medicine,
University of Michigan, Ann
Arbor, MI, USA
jcdeng@med.umich.edu

Kathryn H. Melamed
Scott Hu
Division of Pulmonary and
Critical Care Medicine,
University of California at
Los Angeles, Los Angeles,
CA, USA

Justin Williams
Department of
Biostatistics, University of
California at Los Angeles,
Los Angeles, CA, USA

Xiaoyan Wang
Department of General
Internal Medicine and
Health Services Research,
David Geffen School
of Medicine at UCLA,
University of California,
Los Angeles, CA, USA

Christopher Nguyen
Department of Pulmonary
Medicine, Kaiser Oakland
Medical Center, Oakland,
CA, USA

Jing Cui
Department of
Cardiothoracic
Anesthesiology,
Morristown Medical
Center, Morristown,
NJ, USA

majority of deaths from seasonal flu.^{1,3,5,6} In addition, seasons with higher prevalence of H3N2 strains have increased rates of invasive pneumococcal disease, perhaps resulting from higher viral neuraminidase activity.⁷⁻⁹ Nevertheless, given that secondary pneumonia is a potentially preventable complication, an improved understanding of the incidence and epidemiology of secondary infections following viral infections would have significant management implications.

Even in the modern era, secondary infections remain a significant problem, with surveys from the 2009 H1N1 influenza pandemic [caused by the influenza A(H1N1)pdm09 virus], revealing incidence of bacterial coinfections ranging from 26% to 43%.¹⁰⁻¹⁶ In addition to *Streptococcus pneumoniae* and *Staphylococcus aureus* as the main bacterial pathogens, *Aspergillus* species are emerging as a cause of secondary pneumonia after influenza.¹⁷ While the incidence and causative agents of secondary pneumonias following influenza have been well characterized,^{6,18-20} the epidemiology and prevalence of secondary infections complicating other viral infections are less well established. With noninfluenza respiratory viral infections, although secondary infections or coinfections with bacteria have been reported, most studies have examined pediatric populations.²¹⁻²³ Similar to what has been observed in animal studies of influenza, murine studies have demonstrated that respiratory viruses such as respiratory syncytial virus (RSV) impair bacterial clearance, thereby predisposing mice to secondary infections.²⁴ Our group has also reported that simply activating an antiviral immune response increases susceptibility to bacterial pneumonia,²⁵ and thus, it perhaps is somewhat surprising that secondary infections after noninfluenza viral infections are not better recognized. Multiple studies have demonstrated that coinfections significantly increase mortality rates compared with single viral or bacterial infection,^{22,26} but whether secondary bacterial pneumonia occurs more frequently after influenza as compared with other respiratory viral infections remains unclear. Moreover, how the microbiology and outcomes of secondary pneumonias following noninfluenza viral infections compare with influenza are incompletely understood.

Therefore, we performed a retrospective analysis of a 3-year period at our institution to examine microbiological patterns and outcomes of secondary infections, and to test the hypothesis that

influenza infections do not uniquely predispose to secondary bacterial infections. We included a period overlapping with the 2009 influenza pandemic, given the increased risk of secondary pneumonias during pandemic flu.^{1,3,6} We also analyzed clinical outcomes among hospitalized patients with respiratory viral infections. We specifically focused on studying patients with severe presentations that required hospitalization, reasoning that this cohort is at highest risk for poor outcomes and hence the population of greatest interest to study.

Methods

Study patients

Data from hospital admissions to Ronald Reagan UCLA Medical Center between 1 January 2008 and 31 December 2010, were reviewed. This included two influenza seasons and part of the 2009 influenza pandemic. Initial screening was by ICD-9 codes (480-488.1, except 481-482), which included respiratory viral infections or pneumonia organisms not otherwise specified. Patients under 18 years of age or whose hospital stay extended beyond the designated period were excluded.

A total of 3316 patients' medical records, which were selected by the ICD-9 codes listed above, were reviewed. From this group, patients were ultimately included for study if upon manual chart review they were found to have respiratory symptoms upon admission and positive results from viral studies within the first 10 days of admission. Respiratory symptoms included cough, rhinorrhea, shortness of breath, or hypoxia. As this was a retrospective review, exact criteria for admission to a hospital ward or the intensive care unit (ICU) was left to the clinical judgment of the provider, and pneumonia risk scores were not systemically used to justify patient disposition. Positive viral testing included Focus Diagnostics Influenza polymerase chain reaction (PCR) swab [influenza A, influenza B, and influenza A(H1N1)pdm09]; QIAGEN ResPlex II Panel v2.0 respiratory viral panel PCR [RSV A and B, parainfluenza virus types 1-4, human metapneumoviruses A and B, rhinovirus, adenovirus serogroups B and E, rhinovirus, coronavirus (serogroups NL63, HKU1, 229E, and OC43), coxsackie and echoviruses, and bocavirus]; and respiratory cytomegalovirus and herpes simplex virus PCR swabs. Patients without respiratory symptoms at admission or viral testing, or with negative respiratory viral PCR results were

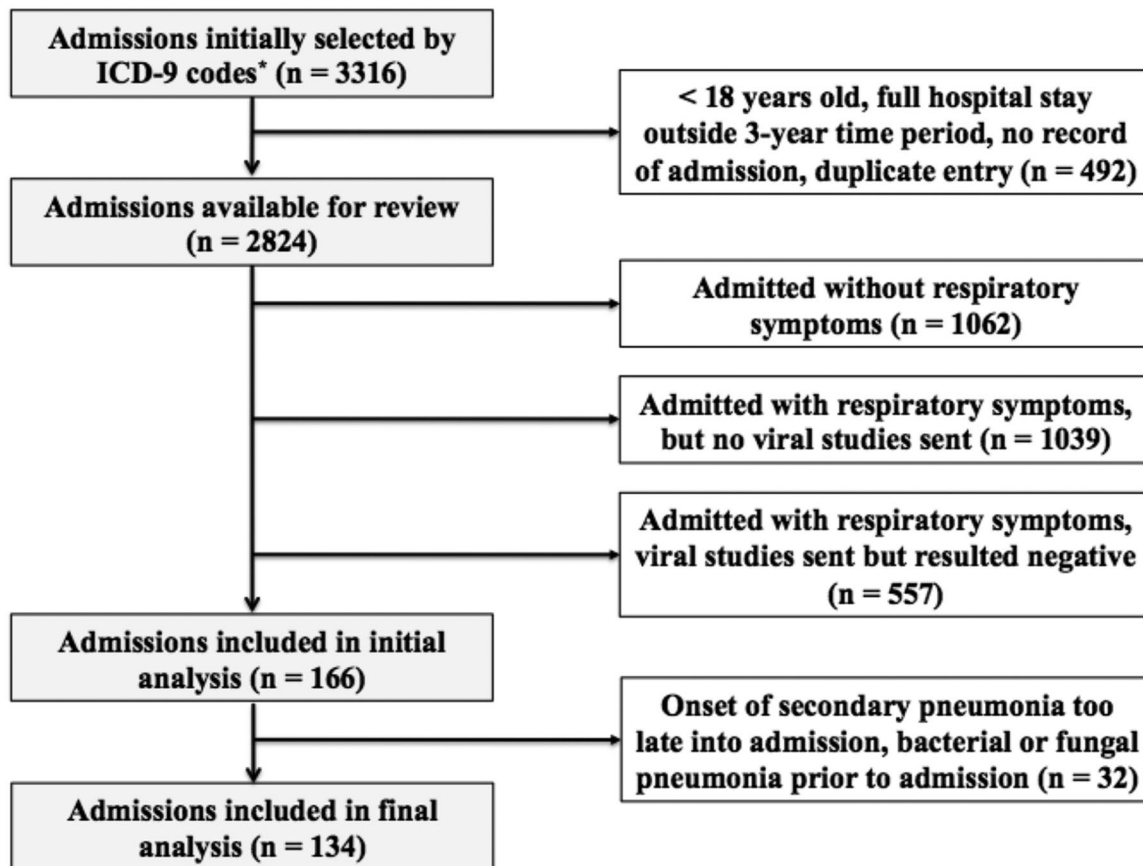


Figure 1. Study population. Subjects with acute respiratory viral infection were identified on the basis of having both acute respiratory symptoms and positive microbiologic testing, as described in the Methods section.

*International Classification of Diseases 9 codes used were all 480–488.1 codes, except 481 and 482.

excluded. Patients with onset of secondary pneumonia late into the admission (defined as more than 2 weeks) or who had documented bacterial or fungal pneumonia or colonization prior to the admission were also excluded (Figure 1). Respiratory infections occurring outside of this time window were excluded to avoid capturing hospital-acquired infections unrelated to the primary viral respiratory infection, which is consistent with other reports of secondary pneumonia after viral respiratory infection.^{13–19} A waiver of consent was obtained because this was a retrospective chart review. The study was approved by UCLA Institutional Review Board (#11-003110).

Data collection

The following data were collected: age, sex, comorbid medical conditions, type of respiratory viral infection, presence and type of secondary

bacterial or fungal pneumonia, immune status (immunosuppressed or normal immune function), total hospital and ICU days, and survival at discharge. Immunosuppression was defined as those with an immunosuppressive condition (e.g. HIV) or taking immunosuppressive medications (e.g. equivalent of prednisone 20 mg or more per day, chemotherapeutic agents). Secondary pneumonia was diagnosed by positive bacterial or fungal respiratory (e.g. sputum, bronchoscopy) cultures (excluding *Candida* species) and clinical diagnosis of pneumonia by the treating physician (e.g. antibiotics and positive radiological studies). Follow up was until death or time of discharge from the hospital, whichever occurred first.

Data analysis

The patients were divided into two groups, viral influenza (VI) and noninfluenza (NI) viral

Table 1. Distribution of viral infections among the VI and NI groups.

Group	Virus type	n (%)
VI		57 (100%)
	Influenza A(H1N1)pdm09	30 (52.6%)
	Influenza A – non-A(H1N1)pdm09	21 (36.9%)
	Influenza B	6 (10.5%)
NI		77 (100%)
	Respiratory syncytial virus	16 (20.7%)
	Rhinovirus	13 (16.9%)
	Cytomegalovirus	11 (14.3%)
	Herpes simplex virus	10 (13.0%)
	Parainfluenza virus	10 (13.0%)
	Coxsackie/echovirus	7 (9.1%)
	Adenovirus	4 (5.2%)
	Coronavirus	3 (3.9%)
	Human metapneumovirus	2 (2.6%)
	Bocavirus	1 (1.3%)

NI, noninfluenza; VI, viral influenza.

respiratory infections based upon viral testing. Patients coinfecting with VI and NI were assigned to the VI group, as the premise we were testing was whether influenza infections increased risk of secondary bacterial pneumonia compared to NI infections.

The VI and NI groups were compared across age, sex, obesity (defined as body mass index $>30\text{ kg/m}^2$), presence of pulmonary disease, history of lung transplant, immune status, and Charlson comorbidity index.²⁷ Rates and microbial etiology of secondary pneumonia were collected for each group. Finally, clinical outcomes (total hospital days, total ICU days, and mortality rate) were compared between VI and NI subgroups (i.e. with and without pneumonia).

Statistical analysis

T-tests, Chi-squared tests, and Fisher exact tests were used to compare baseline characteristics by viral infection (VI *versus* NI). Univariate analysis included logistic regression models that iteratively

analyzed each variable of interest with the respective outcome. Variables included in a final multivariate logistic regression model were chosen using univariate results and clinician expertise.

A Chi-squared test was used to test whether NI was associated with higher rates of secondary pneumonia. To control for possible confounders, multivariate logistic regression was used to account for age, sex, and Charlson index. Variance inflation factors testing showed no evidence of multicollinearity among the variables in our model.

Finally, binary clinical outcomes (e.g. mortality) were tested using Chi-squared tests, while continuous clinical outcomes (e.g. hospital and ICU days), were tested using Wilcoxon rank-sum test or Kruskal–Wallis test by ranks as length of stay (LOS) was substantially right-skewed.²⁸ For all analyses, tests for significance were two-tailed with significance set at p -value <0.05 . All analyses were conducted using R software version 3.4.2²⁹ or GraphPad Prism 7.0 (San Diego, CA, USA).

Results

From 1 January 2008 to 31 December 2010, 2824 adult patients were hospitalized with a diagnosis of respiratory viral infection based on ICD-9 code. On further chart review, 1062 of these patients did not have respiratory symptoms on admission. Of the remaining 1762 patients, 723 patients had viral studies sent, of whom 557 had negative results. After excluding 32 patients who had late onset of pneumonia or pneumonia preceding hospitalization, a total of 134 cases were included in the study (Figure 1).

Among subjects with confirmed viral infections, 57 had influenza (VI) and 77 had NI viral infection. Among those with VI, 30 cases were influenza A(H1N1)pdm09, 21 cases were influenza A (non-A(H1N1)pdm09), and 6 cases were influenza B. The NI group included several viruses (Table 1), with RSV being the most common, followed by rhinovirus.

Clinical characteristics

Patient demographic data are presented in Table 2. The NI group was older (60.6 ± 14.0 *versus* 53.3 ± 19.7 years, $p=0.019$), more often had undergone lung transplantation (29% *versus* 9%, $p=0.009$), and had a higher

prevalence of immunosuppression (81% *versus* 63%, $p=0.041$). Multivariate logistic regression confirmed that a 10-year increase in age was associated with developing NI [odds ratio (OR) 1.339, 95% confidence interval (CI) 1.058–1.695, $p=0.015$], and patients with lung transplants were more likely to have NI compared with those without lung transplants (OR 7.690, 95% CI 2.321–29.781, $p=0.002$). However, patients who were immunosuppressed but did not have a lung transplant were not at increased risk of developing NI (OR 1.95, 95% CI 0.788–5.010, $p=0.153$).

The groups had equal proportion of women, similar rates of underlying lung disease, and similar measures of comorbid illness as indicated by Charlson score. Of note, the majority of patients were immunosuppressed (73% overall).

Secondary pneumonia

We next examined whether influenza resulted in higher rates of secondary bacterial pneumonia compared with NI respiratory viral infections. The overall incidence of secondary pneumonia (including fungal infections) was 35% (47 of 134), with a 30% (40 of 134) incidence of secondary bacterial pneumonia. Patients with NI had increased incidence of secondary pneumonia (44% *versus* 23%, $p=0.017$) and secondary bacterial pneumonia (38% *versus* 19%, $p=0.035$) as compared with VI. This difference remained significant after multivariate logistic regression to control for age, sex, and Charlson score (OR 2.59, 95% CI 1.191–5.867, $p=0.019$). Risk factors for development of secondary bacterial pneumonia were lung transplantation (34% *versus* 13%, $p=0.007$) and NI (72% *versus* 49%, $p=0.017$), as shown in Table 3.

Specific microbiologic patterns of pneumonia also differed depending on the initial viral infection. *S. aureus* infections were the most common secondary infection in those with influenza (implicated in 46% of secondary infections, and solely responsible for 23% of secondary infections), whereas the NI group had increased pneumonia caused by Gram-negative rods, including *Pseudomonas* sp. (29% of secondary infections, Figure 2). From the VI group, 10% (3 of 30) of the influenza A patients and 14% (3 of 21) of the influenza A(H1N1)pdm09 were infected with were infected with *S. aureus* (3 of 6 were

Table 2. Demographic and baseline characteristics.

Characteristic	Total (n = 134)	VI (n = 57)	NI (n = 77)	p-value
Age (years)	57.5 ± 17.0	53.3 ± 19.7	60.6 ± 14.0	0.019
Female sex, n (%)	55 (41)	27 (47)	28 (36)	0.270
Obesity, n (%)	6 (4)	2 (3)	4 (5)	0.999
Charlson index ^a	2.26 ± 1.8	1.95 ± 2.1	2.49 ± 1.6	0.099
Underlying lung disease, n (%)	61 (45)	27 (47)	34 (44)	0.846
Lung transplantation, n (%)	27 (20)	5 (9)	22 (29)	0.009
Immunosuppressed, n (%)	98 (73)	36 (63)	62 (81)	0.041

^aThe Charlson comorbidity index is a composite of several factors including age and medical comorbid disease that predict a patient's 1-year mortality, and it has been validated elsewhere.²⁷

NI, noninfluenza respiratory viral infection; VI, viral influenza respiratory infection.

methicillin-resistant *S. aureus*). The remainder of the infections for the VI group were as follows: the influenza A group had three fungal infections, one enterococcal infection, one mycobacterial infection, and one other Gram-negative infection; the influenza A(H1N1)pdm09 had three pseudomonal infections, two fungal infections, and one other Gram-negative infection; and the influenza B group had one pseudomonal and fungal coinfection. Notably, the diversity of organisms isolated from NI viral-infected patients with secondary infections was higher. Overall, five (9%) patients in the VI group and 13 (17%) patients in the NI group had evidence of polymicrobial infections.

Clinical outcomes

Clinical outcomes were analyzed by VI and NI groups, and further divided into subgroups by those with (VIp, NIp) and without (VIo, NIo) secondary pneumonia (Table 4). The patient with NI were more likely to be admitted to the ICU (62% *versus* 39%, $p=0.011$). Patients with NI had longer hospital [median LOS 10 (IQR 6–19) *versus* 6 (IQR 4–15) days, Wilcoxon rank-sum = 2715.5, $p=0.019$] and ICU [median LOS 4 (IQR 0–12) *versus* 0 (IQR 0–8) days, Wilcoxon rank-sum = 2653.5, $p=0.029$] stays compared with those with VI (Figure 3). When divided into subgroups by those with and without secondary pneumonia, there was a trend towards longer hospital

Table 3. Risk factors associated with development of secondary bacterial pneumonia.

Characteristic	All patients (n = 134)	Pneumonia (n = 47)	No pneumonia (n = 87)	p-value
Age (years)	57.52	58.57	56.95	0.568
Charlson score ^a	2.26	2.62	2.07	0.126
Female, n (%)	55 (41%)	19 (40%)	36 (41%)	1.000
Obesity, n (%)	6 (4%)	4 (9%)	2 (2%)	0.222
Lung disease, n (%)	61 (45%)	22 (47%)	39 (45%)	0.970
Lung transplant, n (%)	27 (20%)	16 (34%)	11 (13%)	0.007
Other solid organ transplant, n (%)	30 (22%)	7 (15%)	23 (26%)	0.189
Bone marrow transplant, n (%)	18 (13%)	8 (17%)	10 (11%)	0.529
All immunosuppressed, n (%)	98 (73%)	38 (81%)	60 (69%)	0.202
Immunosuppressed non-lung transplant, n (%)	71 (53%)	22 (47%)	49 (56%)	0.383
Hematologic malignancy, n (%)	29 (22%)	9 (19%)	20 (23%)	0.768
Solid malignancy, n (%)	13 (10%)	8 (17%)	5 (6%)	0.072
Noninfluenza, n (%)	77 (57%)	34 (72%)	43 (49%)	0.017

^aThe Charlson comorbidity index is a composite of several factors including age and medical comorbid disease that predict a patient's 1-year mortality, and it has been validated elsewhere.²⁷

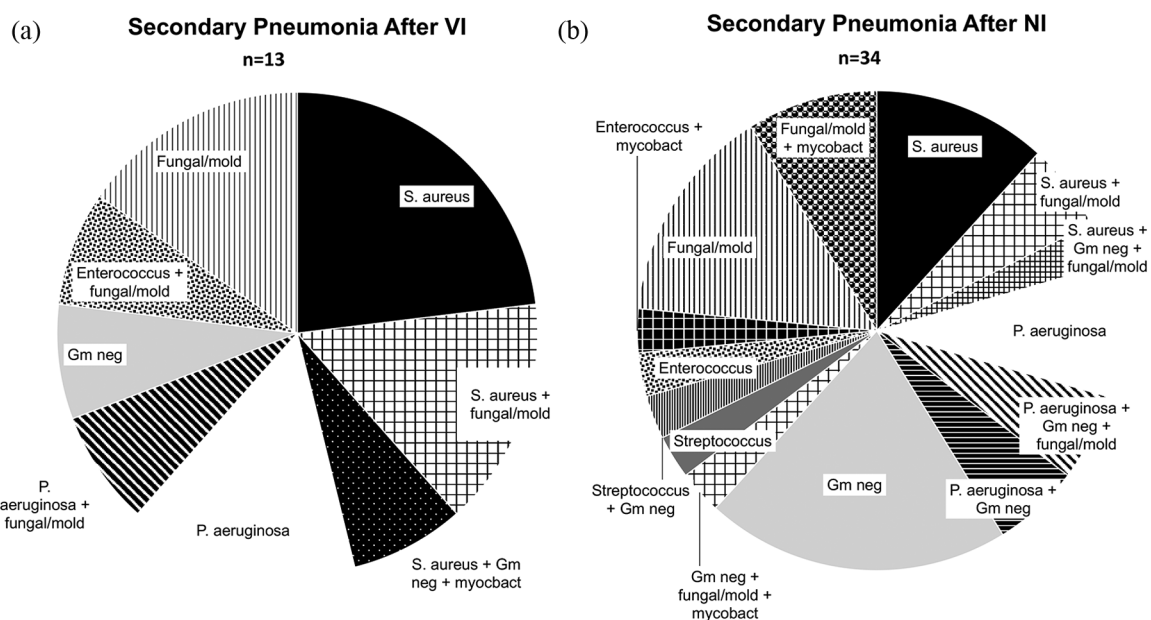


Figure 2. Distribution of microbiological isolates from respiratory cultures following VI (a) versus NI (b) viral infections. The VI group most often was coinfecting with *Staphylococcus aureus*, whereas those with NI viral infections developed secondary Gram-negative rod infections, particularly *Pseudomonas* species. There were 5 (9%) patients in the VI group and 13 (17%) patients in the NI group infected with more than one pathogen. Gm neg, Gram-negative rods; mycobact, *Mycobacterium*; NI, noninfluenza; VI, viral influenza.

Table 4. Clinical outcomes of those with viral respiratory infections and secondary pneumonia.

	VI (n=57)	NI (n=77)		p-value	
Mortality, n (%)	9 (15.8)	17 (22.1)		0.491	
Hospital days, med (IQR)	6 (4, 15)	10 (6, 19)		0.019	
ICU days, med (IQR)	0 (0, 8)	4 (0, 12)		0.029	
ICU admission, n (%)	22 (39)	48 (62)		0.011	
	VIp (n=13)	VIo (n=44)	NIp (n=34)	NIo (n=43)	p-value
Mortality, n (%)	3 (23.1)	6 (13.6)	10 (29.4)	7 (16.3)	0.322
Hospital days, med (IQR)	6 (5, 21)	5.5 (4, 13.5)	10.5 (6, 20.8)	10 (6, 15.5)	0.086
ICU days, med (IQR)	0 (0, 8)	0 (0, 6.75)	3 (0, 14.2)	6 (0, 11.5)	0.181
	Pneumonia (n=47)		No pneumonia (n=87)		p-value
Mortality, n (%)	13 (28)		13 (15)		0.122
Hospital days, med (IQR)	10 (5, 21)		7 (4, 15)		0.162
ICU days, med (IQR)	3 (0, 13.5)		0 (0, 11)		0.442

ICU, intensive care unit; IQR, interquartile range; med, median; NI, noninfluenza respiratory viral infection; NIo, NI without secondary pneumonia; NIp, NI with secondary pneumonia; VI, viral influenza respiratory infection; VIo, VI without secondary pneumonia; VIp, VI with secondary pneumonia.

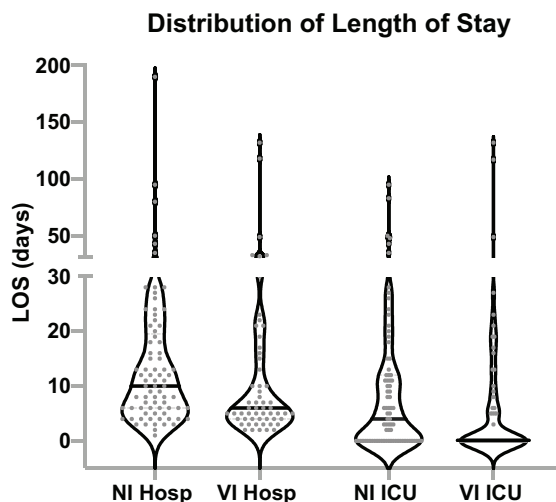


Figure 3. Hospital days and ICU days for patients admitted to the hospital with VI versus NI viral infections. The distributions of hospital stay and ICU stay for those with influenza and NI respiratory viral infections are depicted in violin plots. Those with NI viral respiratory infections had longer length of hospital stay (median LOS 10 days *versus* 6 days, $p=0.019$) and ICU stay (median LOS 4 days *versus* 0 days, $p=0.029$) compared with those with influenza. Median LOS values are indicated by black bars. ICU, intensive care unit; LOS, length of stay; NI, noninfluenza; VI, viral influenza.

stay among those who developed pneumonia [median LOS VIp: 6 (IQR 5–21) days, VIo: 5.5 (IQR 4–13.5) days, NIp: 10.5 (IQR 6–20.8) days, and NIo: 10 (IQR 6–15.5) days, $p=0.086$]. The overall mortality rate was 19% (26 of 134). There was a trend towards increased mortality in the group with secondary pneumonia *versus* no secondary pneumonia (28% *versus* 15%, $p=0.122$). There was no difference in mortality between the NI and VI groups (22.1% *versus* 15.8%, $p=0.491$).

Discussion

Among adult patients with acute respiratory viral infections admitted to a tertiary medical center over a 3-year period, we observed a 35% overall incidence of secondary pneumonia, of which 85% were bacterial. Rates of secondary pneumonia following influenza were 23%. These rates of secondary infection are consistent with those previously reported.^{10–16} However, the subgroup infected with NI respiratory viruses had a higher incidence of secondary pneumonia than previously reported, 44% compared to the published 11–33%.^{4,22,30–32} Research in adult and pediatric populations suggests that differences in rates of secondary pneumonia depend upon the initial

respiratory viral infection.^{21,30,33,34} In addition, more patients in the NI group were immunosuppressed, with a higher percentage of lung transplant recipients compared with the VI group. The immune status of this cohort is notable, as the mechanisms underlying the development of secondary infections following NI viral infections may differ from those underlying influenza-mediated susceptibility to secondary pneumonia.

While these findings may not be generalizable to the all patients, understanding patterns of secondary infections that affect this immunosuppressed population is increasingly important as the number of organ transplants per year and total population of living organ transplant recipients grows each year. It is reasonable to posit that hosts who develop severe NI respiratory viral infections have weakened immune responses, and thus are prone to opportunistic infections, including Gram-negative rods, fungi, and mycobacteria. Alternatively, baseline microbial colonization patterns of the upper respiratory tract are also likely to differ among patients with different immune states, which may be reflected in the epidemiology of secondary pneumonias observed in our cohort. Given that this is the population that is most at risk for complicated respiratory viral infections, longitudinal studies examining the changes in the upper respiratory microbiome will be of clinical significance, in order to understand how the dynamics of host immune responses and new viral infections interact to result in secondary pneumonias.

Although recent studies report *S. pneumoniae* to be the most common pathogen in cases of secondary pneumonia,^{11–14,16} our influenza-infected patients were most commonly infected with *S. aureus*. Interestingly, we reported no cases of pneumococcal pneumonia in the influenza group. There is not a clear explanation for our findings, but our results may reflect bacterial colonization patterns in our cohort. Additionally, a smaller study of critically ill patients with influenza A(H1N1)pdm09 similarly found that *S. aureus* was the most common cause of secondary pneumonia.⁵ We also had a substantive number of fungal/mold infections and *Pseudomonas aeruginosa* and other Gram-negative infections following viral infections. It is possible that our immunosuppressed population was more susceptible to hospital-acquired and opportunistic pathogens than the general population. Other small cohort studies have similarly demonstrated a variety of secondary bacterial

infections and a notable proportion of Gram-negative bacterial infections.^{4,22,30} Whether the development of Gram-negative pneumonia is due to acquisition of Gram-negative bacteria after admission or baseline colonization as a result of immunosuppressed state is unknown. Taken together, our data confirm the importance of *S. aureus* as a causative pathogen in secondary bacterial pneumonia after influenza infection. In addition, in immunocompromised patients, consideration should be given to empiric coverage for Gram-negative pathogens, including *P. aeruginosa*, and underscore the importance of individual centers evaluating local epidemiological patterns to tailor empirical antibiotic therapy for secondary pneumonias appropriately.

Outcomes among the NI population are worse than VI, marked by longer hospital stays and increased ICU days. These differences seem to be driven by patients who develop secondary pneumonia, putting a premium on early identification and appropriate antimicrobial treatment. Our data also demonstrated a trend towards increased in-hospital mortality rates among patients with secondary infections compared with primary viral infections, consistent with previous studies.^{22,26}

Our study is limited by its retrospective nature and moderate sample size. For example, exact criteria necessitating admission to the hospital ward or ICU were not standardized and left to the discretion of the treating clinician. Further work should examine additional risk factors for secondary pneumonia after viral infection, with a focus on host immune status and longitudinal changes in bacterial colonization patterns. This is particularly important as such a large proportion of our cohort was immunosuppressed or were organ transplant recipients. Additionally, given the atypical microbial profile of secondary infection after NI viral infection, the relationship between empirical antibiotic choice and clinical outcomes in this group lends itself to future study. Earlier and broader empiric antimicrobial coverage in high-risk patients with viral respiratory infections may shorten hospital stay and improve clinical outcomes. Lastly, given that we do not have histological evidence of respiratory infection, it is possible that the positive respiratory viral, bacterial, and fungal studies could represent viral shedding or microbial colonization rather than true infection. However, we took care to ensure that

all patients did have symptoms consistent with a respiratory infection on time of presentation, so we presume that these microbial isolates are pathogenic. Future confirmatory studies with lung biopsy or autopsy could help distinguish viral shedding or bacterial colonization from true invasive infection.

In summary, early identification of respiratory viral infection and secondary pneumonia remains important, since at least one in three patients presenting to the hospital with any respiratory viral infection will develop bacterial or fungal pneumonia. Our work demonstrates an even higher rate of secondary pneumonia among NI respiratory viruses, illustrating the clinical significance of these viral infections, particularly among the immunosuppressed. Further study of this group is warranted to better illuminate risk factors for development of secondary infections, which portends a poor prognosis.

Author contribution(s)

Kathryn H. Melamed: Conceptualization; Data curation; Investigation; Methodology; Writing-original draft; Writing-review & editing.

Justin Williams: Data curation; Formal analysis; Methodology; Writing-review & editing.

Xiaoyan Wang: Data curation; Formal analysis; Methodology; Writing-review & editing.

Scott Hu: Data curation; Formal analysis; Investigation; Methodology; Writing-review & editing.

Christopher Nguyen: Data curation; Investigation; Methodology; Writing-review & editing.

Jing Cui: Conceptualization; Data curation; Investigation; Writing-review & editing.

Jane C. Deng: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing-original draft; Writing-review & editing.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Jane C. Deng  <https://orcid.org/0000-0002-0476-1283>

Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. van der Sluijs KF, van der Poll T, Lutter R, *et al.* Bench-to-bedside review: bacterial pneumonia with influenza - pathogenesis and clinical implications. *Crit Care* 2010; 14: 219.
2. Thompson WW, Moore MR, Weintraub E, *et al.* Estimating influenza-associated deaths in the United States. *Am J Public Health* 2009; 99 Suppl 2: S225-S230.
3. Thompson WW, Shay DK, Weintraub E, *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003; 289: 179-186.
4. Choi SH, Hong SB, Ko GB, *et al.* Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med* 2012; 186: 325-332.
5. Dominguez-Cherit G, Lapinsky SE, Macias AE, *et al.* Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009; 302: 1880-1887.
6. Morens DM, Taubenberger JK and Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis* 2008; 198: 962-970.
7. Zhou H, Haber M, Ray S, *et al.* Invasive pneumococcal pneumonia and respiratory virus co-infections. *Emerg Infect Dis* 2012; 18: 294-297.
8. Peltola VT, Murti KG and McCullers JA. Influenza virus neuraminidase contributes to secondary bacterial pneumonia. *J Infect Dis* 2005; 192: 249-257.
9. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev* 2006; 19: 571-582.
10. Song JY, Cheong HJ, Heo JY, *et al.* Clinical, laboratory and radiologic characteristics of 2009 pandemic influenza A/H1N1 pneumonia: primary influenza pneumonia versus concomitant/secondary bacterial pneumonia. *Influenza Other Respir Viruses* 2011; 5: e535-e543.

11. Shieh WJ, Blau DM, Denison AM, *et al.* 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. *Am J Pathol* 2010; 177: 166–175.
12. Mauad T, Hajjar LA, Callegari GD, *et al.* Lung pathology in fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med* 2010; 181: 72–79.
13. Echenique IA, Chan PA, Chapin KC, *et al.* Clinical characteristics and outcomes in hospitalized patients with respiratory viral co-infection during the 2009 H1N1 influenza pandemic. *PLoS One* 2013; 8: e60845.
14. Cilloniz C, Ewig S, Menendez R, *et al.* Bacterial co-infection with H1N1 infection in patients admitted with community acquired pneumonia. *J Infect* 2012; 65: 223–230.
15. Centers for Disease C and Prevention. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May–August 2009. *MMWR Morb Mortal Wkly Rep* 2009; 58: 1071–1074.
16. Alsadat R, Dakak A, Mazlooms M, *et al.* Characteristics and outcome of critically ill patients with 2009 H1N1 influenza infection in Syria. *Avicenna J Med* 2012; 2: 34–37.
17. Wauters J, Baar I, Meersseman P, *et al.* Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. *Intensive Care Med* 2012; 38: 1761–1768.
18. Bisno AL, Griffin JP, Van Epps KA, *et al.* Pneumonia and Hong Kong influenza: a prospective study of the 1968-1969 epidemic. *Am J Med Sci* 1971; 261: 251–263.
19. Oswald NC, Shooter RA and Curwen MP. Pneumonia complicating Asian influenza. *Br Med J* 1958; 2: 1305–1311.
20. Luria DB, Blumenfeld HL, Ellis JT, *et al.* Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza. *J Clin Invest* 1959; 38: 213–265.
21. Hall CB, Powell KR, Schnabel KC, *et al.* Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. *J Pediatr* 1988; 113: 266–271.
22. Crotty MP, Meyers S, Hampton N, *et al.* Epidemiology, co-infections, and outcomes of viral pneumonia in adults: an observational cohort study. *Medicine (Baltimore)* 2015; 94: e2332.
23. Tristram DA, Miller RW, McMillan JA, *et al.* Simultaneous infection with respiratory syncytial virus and other respiratory pathogens. *Am J Dis Child* 1988; 142: 834–836.
24. Stark JM, Stark MA, Colasurdo GN, *et al.* Decreased bacterial clearance from the lungs of mice following primary respiratory syncytial virus infection. *J Med Virol* 2006; 78: 829–838.
25. Tian X, Xu F, Lung WY, *et al.* Poly I:C enhances susceptibility to secondary pulmonary infections by gram-positive bacteria. *PLoS One* 2012; 7: e41879.
26. Burk M, El-Kersh K, Saad M, *et al.* Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. *Eur Respir Rev* 2016; 25: 178–188.
27. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
28. Chazard E, Ficheur G, Beuscart JB, *et al.* How to compare the length of stay of two samples of inpatients? A simulation study to compare type I and type II errors of 12 statistical tests. *Value Health* 2017; 20: 992–998.
29. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2017.
30. Jung HS, Kang BJ, Ra SW, *et al.* Elucidation of bacterial pneumonia-causing pathogens in patients with respiratory viral infection. *Tuberc Respir Dis (Seoul)* 2017; 80: 358–367.
31. Coisel Y, Bousbia S, Forel JM, *et al.* Cytomegalovirus and herpes simplex virus effect on the prognosis of mechanically ventilated patients suspected to have ventilator-associated pneumonia. *PLoS One* 2012; 7: e51340.
32. Jain S, Self WH, Wunderink RG, *et al.* Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015; 373: 415–427.
33. Wolf DG, Greenberg D, Shemer-Avni Y, *et al.* Association of human metapneumovirus with radiologically diagnosed community-acquired alveolar pneumonia in young children. *J Pediatr* 2010; 156: 115–120.
34. Wolf DG, Greenberg D, Kalkstein D, *et al.* Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. *Pediatr Infect Dis J* 2006; 25: 320–324.