



Prevalence and Clinical Disease Severity of Respiratory Coinfections During the Coronavirus Disease 2019 Pandemic

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KEYWORDS

• Coinfection • Superinfection • COVID-19 • Respiratory virus • SARS-CoV-2 • Influenza

KEY POINTS

- An increased use of multiplex polymerase chain reaction–based assays has challenged the notion of a single respiratory pathogen always being responsible for a given disease.
- Rates of coinfection between severe acute respiratory syndrome coronavirus 2 and other respiratory viruses is highly variable based on etiology and patient population.
- Rates of coinfection or superinfection with bacteria are generally lower in patients with coronavirus disease 2019 than for those with influenza or respiratory syncytial virus.
- Higher rates of bacterial and fungal pneumonia in ventilated patients with coronavirus disease 2019 in the intensive care unit warrants increased diagnostic testing and empirical antibiotic therapy.
- Low rates of community-acquired respiratory coinfections, and higher rates of antimicrobial resistance, warrant greater antibiotic stewardship for patients with nonsevere coronavirus disease 2019.

INTRODUCTION

Respiratory tract infections represent a major global health concern. Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 470 million confirmed cases and approximately 6 million deaths worldwide [1]. Since the beginning of COVID-19 pandemic, the presence of more than 1 pathogenic organism in the respiratory tract of patients with COVID-19 has been widely recognized owing to the availability of advanced molecular detection technologies, such as multiplex polymerase chain reaction (PCR) and next-generation sequencing.

However, the association between the occurrence of multiple pathogen infections and clinical disease severity remains unclear. In the study of disease evolution, multiple infections fall into 2 broad categories: coinfection and superinfection. Coinfection occurs when a person is found to be infected by two or more micro-organisms, but which infection was established first cannot be clearly determined, while superinfection is an infection arising when one or more infections is already present. A substantial number of patients with COVID-19 were also coinfecting with various pathogens, including other respiratory viruses, bacteria, and fungi, which can influence infectious disease dynamics. This

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review presents an overview of the prevalence and clinical disease severity of respiratory coinfections and superinfections (Table 1) and discusses possible mechanisms of the interactions between viral infections, including SARS-CoV-2, and bacterial infections during the COVID-19 pandemic.

RESPIRATORY VIRAL COINFECTIONS

In late 2019, an acute respiratory disease, COVID-19, emerged in humans caused by a novel coronavirus, SARS-CoV-2. Unlike previously known coronaviruses, SARS-CoV-2 combines greater pathogenicity with high transmissibility during the presymptomatic or asymptomatic period [2]. COVID-19 has spread rapidly across the globe and has become a major pandemic disease. The increasing number of infections prompt the need to use rapid antigen-based assays and real-time reverse transcription PCR technology to rapidly detect SARS-CoV-2 RNA and confirm the clinical diagnosis of COVID-19 [3].

Respiratory virus infections are associated with a wide spectrum of clinical symptoms. This classical thinking that a single virus is associated with clinical symptoms has been challenged by the more advanced multiplexed PCR-based assays, which may simultaneously identify multiple pathogens associated with one clinical syndrome [4]. Broad respiratory syndromic testing is widely used to identify viral pathogens that cocirculate with SARS-CoV-2. Coinfections involving viruses are recognized to influence the disease dynamics that occur relative to a single infection [5].

Prevalence of respiratory viral coinfections

Respiratory viral coinfection with SARS-CoV-2 refers to the simultaneous infection of other respiratory viruses at the time of COVID-19 diagnosis. Previous reports have shown viral coinfection and superinfection are rare [6]. This article focuses on the prevalence and outcome of viral coinfection.

Viral coinfection in adults

The overall rate of coinfection of SARS-CoV-2 and other respiratory viruses in adults is considerably variable as reported. The rate of viral coinfection depends on the cocirculation of respiratory viruses in the specific time of the year and the geographic region where the study was conducted. In the beginning of COVID-19 pandemic, Yue and colleagues [7] carried out an epidemiologic study in Wuhan, China, between January 12 and February 21, 2020, and reported that the prevalence of SARS-CoV-2 and influenza coinfections was as high

as 57.3% (176/307 cases), although the diagnosis of influenza was based on IgM serologic testing alone. From March 3 through 25, 2020, Kim and colleagues [8] conducted a study to assess the prevalence of coinfections in Northern California. A total of 1217 nasopharyngeal swabs of symptomatic adult patients were tested by multiplex real-time reverse transcription PCR assays for SARS-CoV-2 and other respiratory pathogens. Of the 116 specimens positive for SARS-CoV-2, 24 were positive for 1 or more additional pathogens including influenza, rhinovirus, enterovirus, respiratory syncytial virus (RSV), and non-SARS-CoV-2 coronaviridae. The rates of coinfection between SARS-CoV-2 and other respiratory pathogens were 20.7%.

When the California Department of Public Health assessed influenza activity in California during the 2020 to 2021 influenza season, their analyses revealed that, among the 255 positive influenza cases, 58 persons were coinfecting with SARS-CoV-2. The occurrence of influenza and SARS-CoV-2 coinfections was 23%, with influenza B being the predominant type (39/58 [67%]) [9]. The report indicated that SARS-CoV-2 testing was prioritized over influenza virus testing and infrequent influenza testing might have contributed to underestimates of influenza transmission [9]. Since the highly transmissible SARS-CoV-2 virus became the predominant circulating respiratory virus in humans, its impact on the circulation of other respiratory viruses has been evaluated [10]. The majority of cocirculating respiratory viruses seem to be less prevalent since the onset of the COVID-19 pandemic. This finding might be attributable to both intrinsic viral characteristics and viral interference [10].

Viral coinfection in children

The prevalence of viral coinfections is significantly higher in children than adults. A study from 6 US children's hospitals located in areas with high COVID-19 incidence during July and August 2021 found viral coinfections with SARS-CoV-2 was common (113/713 [16%]) in pediatric patients aged less than 18 years. The coinfection rate was even higher among infants (32.4%) and young children aged 1 to 4 years (36.1%). The predominant (>65%) viral coinfections were caused by RSV [11].

Children with COVID-19 present with distinct epidemiologic and clinical characteristics that differ from adults. They may be asymptomatic or symptomatic with generalized clinical manifestations, like fever, cough, and nasal congestion. This pattern of symptoms makes it difficult to distinguish children with COVID-19 from those with infection of other common

TABLE 1
Prevalence of common coinfections in patients with COVID-19

Coinfections	Geography	Patient Population	Diagnostic Method for Coinfected Agents	No. of Patients	No. of Coinfected Case	Coinfection Rate	Reference ^a
Viral coinfection							
SARS-CoV-2 coinfecting with influenza A/B	China	Aged ≥ 50 y	IgM serology	213	97	45.5%	Cheng et al, ²⁵ 2021
	Spain	Adults	NAAT	255	7	2%–8%	Garcia-Vidal et al, ¹³ 2021
	Japan	Adults	NAAT	298	28	9.4%	Ishiguro et al, ¹⁴ 2021
	USA	Adults	NAAT	116	1	0.9%	Kim et al, ⁸ 2020
	Turkey	Adults	Direct fluorescent antibody	1103	6	0.5%	Ozaras et al, ¹⁷ 2020
	USA	Adults	NAAT	255	58	22.8%	Rizzo et al, ⁹ 2021
	China	Children	NAAT	34	1	2.9%	Wu et al, ¹² 2020
	China	Adults	NAAT	145	2	1.4%	Xiang et al, ²⁶ 2021
SARS-CoV-2 coinfecting with RSV	China	Adults	IgM serology	307	176	57.3%	Yue et al, ⁷ 2020
	Spain	Adults	NAAT	256	1	0.4%	Garcia-Vidal et al, ¹³ 2021
	USA	Adults	NAAT	116	6	5.2%	Kim et al, ⁸ 2020
	USA	Children	NAAT	713	75	10.5%	Wanga et al, ¹¹ 2021
	China	Children	NAAT	34	3	8.8%	Wu et al, ¹² 2020
	Bacterial coinfection						
Community-acquired coinfections	Spain	Adults	Culture	989	25	2.5%	Garcia-Vidal et al, ¹³ 2021
	Sweden	Adults	Culture, NAAT antigen	1243	46	4.0%	Hedberg et al, ⁵⁸ 2022
	USA	Adults	Culture, NAAT antigen	1705	59	3.5%	Vaughn et al, ⁶³ 2021
Community-acquired coinfections (72 h)	USA	Adults	Culture	3028	183	6.0%	Kubin et al, ⁶⁴ 2021

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TABLE 1
(continued)

Coinfections	Geography	Patient Population	Diagnostic Method for Coinfected Agents	No. of Patients	No. of Coinfected Case	Coinfection Rate	Reference ^a
Community-acquired pneumonia	USA	Adults	Culture, NAAT antigen	1705	26	1.7%	Vaughn et al, ⁶³ 2021
	USA	Adults	Culture	3796	35	0.9%	Weidmann et al, ⁶⁰ 2022
Health care-associated superinfections (>72 h)	USA	Adults	Culture	3028	350	11.6%	Kubin et al, ⁶⁴ 2021
Hospital-acquired superinfections	Spain	Adults	Culture	989	38	3.8%	Garcia-Vidal et al, ¹³ 2021
Ventilator-associated lower respiratory tract superinfections	Sweden	Intubated Adults	Culture	426	129	29.4%	Hedberg et al, ⁶¹ 2022
Ventilator-associated pneumonia	USA	Intubated Adults	Culture	631	246	39.0%	Weidmann et al, ⁶⁰ 2022

Abbreviation: NAAT, nucleic acid amplification test.

^a References included in the review are arranged alphabetically within each type of coinfection.

respiratory viruses. A retrospective study of previous healthy children exposed to SARS-CoV-2 in their household, who subsequently tested positive for SARS-CoV-2, reported 19 of 34 children (51%) coinfecting with other respiratory pathogens [12].

Clinical outcomes of respiratory viral coinfections

The COVID-19 pandemic has caused great challenges for health care systems globally. Viral coinfections are commonly seen in hospitalized patients [13]. A retrospective study found that, even though viral coinfection was common at 30.5% in patients hospitalized with COVID, coinfection was not an independent risk factor for the severity of hospital admission, need for high-flow oxygen therapy or mechanical ventilation, or mortality [14]. Another study analyzed inpatient data and revealed that patients positive for SARS-CoV-2 had a lower rate of coinfection with other respiratory viruses compared with those positive for other respiratory viruses (1.4% vs 4.8%). Patients with COVID-19 testing positive for other viruses including rhinovirus, parainfluenza, and seasonal coronavirus presented with mild disease and did not progress to pneumonia [15]. The proportion of SARS-CoV-2 coinfecting patients requiring care in the intensive care unit (ICU) (4/21 [19%]) was significantly lower than the proportion of those infected with SARS-CoV-2 alone (113/280 [47%]), indicating that coinfection with other respiratory viruses might not worsen the outcome of SARS-CoV-2-associated respiratory disease [16].

The clinical disease severity of respiratory viral coinfections in patients with COVID-19 could be impacted by the specific organism(s) causing of coinfection.

Coinfection with influenza

Influenza virus is a frequent cause of community-acquired pneumonia (CAP). Coinfection with SARS-CoV-2 may worsen COVID-19 symptoms and increase mortality, especially for the elderly [9]. Patients coinfecting with SARS-CoV-2 and influenza B virus have presented with symptoms of fatigue (13%), abnormalities on a computed tomography scan of the chest (100%) or decreased lymphocytes and poor prognosis compared with SARS-CoV-2 single positive patients [7]. Ozaras and colleagues [17] reported 6 patients with COVID-19 who were coinfecting with influenza and suffered from pneumonia. A thoracic computed tomography scan showed multiple lesions in the lung in 2 cases, bilateral lung lesions in 3 cases, and a single central lesion in 1 case [17]. A recent research study using an animal model for SARS-CoV-2 infection demonstrated

that coinfection with influenza A virus causes more severe and prolonged pneumonia in SARS-CoV-2-infected hamsters [18]. The research team examined the respiratory organs of coinfecting hamsters using immunohistochemical stain and found the infected regions were clearly divided into SARS-CoV-2-patterned and influenza-patterned areas and both viruses never coexisted at the same site in these organs, indicating that each virus may have distinct cell tropism and can efficiently spread in the respiratory organ without interference with the other [18].

Coinfection with Respiratory Syncytial Virus

RSV is the most common cause of bronchiolitis and pneumonia in children younger than 1 year of age. Patients coinfecting with SARS-CoV-2 have been reported and hospitalized [11]. A retrospectively study found that 6 of 32 hospitalized children (18.7%) less than 24 months of age coinfecting with SARS-CoV-2 and RSV, and had a significantly longer length of stay (7 days vs 3 days) than those without [19]. However, there was no difference in the need for intensive care or mechanical ventilation or mortality [19]. Similar findings were presented by Giannattasio and colleagues [20] among 6 infants aged 18 days to 9 months coinfecting with both SARS-CoV-2 and RSV. The infants experienced mild fever and respiratory symptoms with an uncomplicated resolution [20]. RSV, which can cause more severe disease in infants, caused relatively mild disease in coinfecting infants in this study of limited size. The authors speculate that this finding could be due to increased infectivity and replication of SARS-CoV-2, which may suppress RSV replication and clinical expression [20].

Virological mechanisms that determine viral persistence or exclusion during coinfections

Viral competition for resources in the respiratory tract

Molecular methods of viral detection and their increased sensitivity over culture have led to increased diagnoses of viral respiratory infections. This increase has also led to a greater frequency of viral coinfections being detected. When looking at the interactions between individual viruses during viral-viral respiratory coinfections, there seem to be both cases of inhibition and enhancement of one virus over another.

In the case of inhibition, it has been demonstrated through mathematical modeling that one virus can block infection with another virus by being the first to infect a cell [21]. In addition, the replication speed of the virus played a role with a rapidly replicating virus,

such as rhinovirus, decreasing the replication of other viruses and a slow-growing virus, such as parainfluenza virus, being out-competed and subsequently suppressed in a viral–viral coinfection model [21]. This pattern is consistent with reports of viral coinfections seen during the pandemic, with 1 study reporting 8% of cases as coinfecting, with rhinovirus comprising 6% and influenza virus comprising 2% of SARS-CoV-2 coinfections [22].

Ferret models of SARS-CoV-2 and influenza A virus coinfection showed that influenza A outcompeted SARS-CoV-2 in both viral titers and infectivity when coinfecting ferrets were cohoused with uninfected ferrets [23]. Additional animal studies in murine models also showed increased influenza viral loads in coinfections and increased mortality, which could be ameliorated by prior immunity to influenza [24].

Studies in humans have been more ambiguous, with some studies showing similar clinical outcomes in patients infected with SARS-CoV-2 alone versus with a viral coinfection [25] and others showing higher rates of viral–viral coinfections in patients with severe cases of COVID-19 [7,26,27] or who had died [28]. Data published before the pandemic looking at influenza viral coinfections suggested that detection of more than 1 virus correlated with less severe disease [29] or had no difference in clinical disease severity [30]. This finding will need to be investigated in the context of SARS-CoV-2 coinfections. One large observational study in more than 21,000 positive specimens found that, although viral coinfection was not associated with an increase in viral load when compared with single-virus infections, there was evidence of viral competition that decreased the viral load [31].

Epithelial and organ damage

Although the significance of viral coinfection is unknown, the mechanisms of coinfection include virus-induced airway damage, decreased mucociliary clearance, and damage to the immune system [32].

Animal models of SARS-CoV-2 and influenza A virus coinfection led to significantly more weight loss and more severe inflammation in both the nose and lungs when compared with animals singly infected with each virus [23,33]. In addition, influenza A virus preinfection led to an increase in SARS-CoV-2 infectivity in cell-based models and also led to more lung damage and higher viral loads in mouse models [34]. Other models of epithelial, endothelial, and mononuclear cells have also shown infectivity with high viral loads, leading to cell damage and deterioration of barrier function [35].

Impact on the pattern of immune responsiveness

Because of the damage to the immune system caused by the coinfection, the presentation of patients who are positive for both SARS-CoV-2 and other viruses may be more severe [36]. It has been shown that SARS-CoV-2 infection leads to epithelial cell damage and the release of interferon [35]. Increases in proinflammatory cytokine levels early in infections have been linked to worse outcomes, with severe COVID-19 being linked with an increased cytokine response throughout disease progression [37].

When looking at influenza A and SARS-CoV-2 coinfection, one study showed an increase in serum cytokines (interleukin-2R [IL-2R], IL-6, IL-8, and tumor necrosis factor- α), cardiac troponin I, and a higher incidence of lymphadenopathy in patients solely infected with SARS-CoV-2 [25]. A hamster model of SARS-CoV-2 and influenza coinfection also showed a higher histology score for pulmonary edema, vasculitis, and inflammatory cell infiltration than single-virus infected animals [33]. Additionally, looking at the impact of influenza A and SARS-CoV-2 coinfections in adult inpatients showed that coinfection led to an increased odds of acute heart failure, multilobar infiltrates, acute kidney injury, secondary bacterial infection, and ICU admission. Coinfecting patients also had a relatively higher SARS-CoV-2 viral load based on relative cycle threshold values than patients singly infected with SARS-CoV-2, which significantly correlated with acute kidney injury and acute respiratory distress syndrome [38].

BACTERIAL COINFECTION IN THE SETTING OF RESPIRATORY VIRAL ILLNESS

Respiratory viral infection may predispose hosts to bacterial pneumonia, but the degree to which this occurs varies widely based on the viral pathogen. We will examine 3 commonly occurring respiratory viral pathogens—influenza virus, RSV, and SARS-CoV-2—to understand how each affects risk for bacterial coinfection, outcomes associated with coinfection, and the mechanisms underlying these associations.

Influenza-associated bacterial coinfection

As a long-known cause of seasonal epidemics and occasional pandemics, the association of influenza with bacterial superinfection has long been established, with review of autopsy findings from the 1918 Spanish Flu pandemic displaying that bacterial superinfection was

likely a central risk factor for mortality [39]. A variety of studies have attempted to characterize the rates of bacterial coinfection or superinfection in the setting of influenza, yet many of these have been limited to a single influenza season [40,41]. A metaanalysis found rates varying from 2% to 65%; however, when the studies contributing the majority of heterogeneity were removed the range was 11% to 35% [42]. More recently, a prospective multicenter study from Spain has assessed rates of bacterial pneumonia from 2009 to 2015, including years of both pandemic and seasonal epidemic influenza [43]. These authors found lower rates of bacterial coinfection during 2009 (11.4%), associated with the H1N1 pandemic during that year, relative to increased rates in subsequent years (17.3%–23.4%) [43]. A metaanalysis focusing on pandemic H1N1 influenza during 2009 found that 19% of hospitalized patients were found to have secondary bacterial pneumonia and that this rate increased to 23% when looking at autopsy specimens from fatal influenza cases [41].

Outcomes in patients with influenza have been found to be consistently worse in the setting of bacterial coinfection. Authors of the 2009 to 2015 Spanish study finding an adjusted odds ratio (OR) of 1.9 (95% CI, 1.5–2.5) for hospital mortality, whereas another retrospective study of 209 patients hospitalized with influenza from the Netherlands, 41 of whom had community-acquired bacterial coinfection (19.6%), found an adjusted hazard ratio of 2.6 (95% confidence interval [CI], 1.252–5.480) for mortality associated with bacterial coinfection [44]. Of note, this latter study found a large difference in mortality by bacterial species responsible for coinfection, with *Staphylococcus aureus* producing a mortality (adjusted hazard ratio) of 6.267 (95% CI, 2.679–14.662). A smaller study comparing mortality rates in patients with bacterial pneumonia in the setting of influenza (VI; n = 57) or other types of respiratory viral illness (NI; n = 77), they found that VI patients had lower rates of bacterial pneumonia than NI patients (23% vs 44%), as well as overall lower length of hospital and ICU stay, but no significant trends associated with bacterial pneumonia status [45].

A large portion of bacterial pneumonia in the setting of influenza has been found to be community acquired. One study involving 4313 patients with influenza hospitalized between 2010 and 2015 at 179 US hospitals found a CAP rate of 10.6%, with *S aureus* presenting as the most common etiology, and a mortality adjusted OR of 3.00 (95% CI, 2.17–4.16) [46]. Bacterial isolates identified were also more consistent with CAP, with the largest study of all types of bacterial pneumonia in

patients with influenza identifying *Streptococcus pneumoniae* as the most common etiology (51.0%) by a large margin [43], and the most comprehensive meta-analysis of this subject has also found *S pneumoniae* as the most common etiology (35%), although *S aureus* made a more significant contribution (28%) [42].

There are a number of pathways by which influenza has been identified in both animal and human studies to increase susceptibility to bacterial pneumonia, including (1) depletion of alveolar macrophages by 90% during the first week of influenza infection in mice [47], (2) inhibition of the phagocytic activity of macrophages and neutrophils through induction of type 1 IFN responses [48,49], (3) inhibition of Th17 T cells that modulate the immune surveillance of pathogenic bacteria via type 1 IFN signaling, as well as (4) an increase in bacterial binding sites in the upper and lower respiratory tract produced by neuraminidase cleavage of sialic acid [50], and upregulation of surface receptors recognized by bacteria from the host inflammatory response and wound healing [51,52]. Interestingly, the mortality rates for influenza with bacterial pneumonia have been found to be highest in animal studies when bacterial infection occurs during the first week of viral infection [53], which in conjunction with high rates of CAP and the mechanisms listed elsewhere in this article, suggest that viral and bacterial infection act synergistically to decrease pulmonary function and inhibit host responses.

RSV-associated bacterial coinfection

Before the COVID-19 pandemic, RSV represented the leading cause of lower respiratory tract infection in children, with an estimated 2.7 to 3.8 million cases in 2015, causing higher rates of hospitalization and mortality relative to influenza in children under 5 years [54]. A wide range of bacterial coinfection rates is associated with RSV. One study of children with bronchopulmonary RSV found that 43.6% had a concurrent respiratory culture positive for pathogenic bacteria [55], with the most common pathogens being *Haemophilus influenzae* (43.9%), *S pneumoniae* (36.6%), and *Moraxella catarrhalis* (29.3%). A larger study of children with RSV pneumonia between 2010 and 2019 found that 32.4% had a concurrent respiratory bacterial infection, the most common etiologies of which were *S pneumoniae* (40.8%), *S aureus* (40.8%), and *H influenzae* (25.4%) [56]. This study also assessed the effect of bacterial coinfection on clinical outcomes in children with bacterial coinfection compared with RSV alone, finding significantly higher rates of invasive ventilation (3.0% vs 0.0%) and ICU care (11.9% vs 6.4%), although

mortality was not reported. One study focusing on 165 patients with RSV who were intubated and treated in the ICU found similarly high rates of respiratory culture positivity (42.6%); however, they used quantitative culture to separate bacterial coinfection (21.8%) and low bacterial growth or possible coinfection (20.8%) based on whether their cultures grew greater or less than 10^5 CFU/mL, respectively [57]. Although there was no significant difference in mortality rates, this study found a small but significant increase in length of mechanical ventilation in the bacterial coinfection group (6 days vs 4 days).

Interestingly, a retrospective cohort study concluding within the past year has directly compared rates of CAP in admitted adult patients testing positive for Influenza, RSV, or SARS-CoV-2 [58]. Hedberg and colleagues (2022) [58] found that roughly similar proportions of adults with influenza or RSV had concurrent CAP, 27% and 29% respectively, whereas only 4% of patients with SARS-CoV-2 had CAP. For all 3 viral infections, no significant differences in length of stay, ICU admission, or 30-day mortality between patients with or without CAP were seen, except a lower adjusted hazard ratio of being discharged alive for patients with influenza and CAP relative to those without CAP (0.76; 95% CI, 0.64–0.90). Of note, this study assessed only adult patients, whereas most studies of coinfection in the setting of RSV have focused on pediatric patients. Therefore, in adults, RSV infection involves high rates of bacterial pneumonia, similar to or increased in prevalence compared with influenza coinfection; however, exacerbation of outcomes by coinfection in pediatric populations is modest in comparison with that of influenza.

SARS-CoV-2–associated bacterial coinfection

The literature to date on bacterial coinfection in the setting of SARS-CoV-2 has shown significant differences from influenza or RSV coinfection. One study of 4267 patients hospitalized with COVID-19 in New York City found that only 2.1% had positive respiratory cultures and 1.9% had positive blood cultures, although 71% received at least 1 dose of an antibiotic [59]. Whereas Hedberg, Johansson, and colleagues [58] reported a CAP coinfection rate of 4% with SARS-CoV-2, other studies assessing CAP have found significantly lower rates. A multicenter study of 1705 patients hospitalized with COVID-19 in Michigan found that only 1.5% qualified as having CAP (defined as positive culture <3 days from admission). Another study of 3796 hospitalized patients with COVID-19 in New York

City found that only 0.9% of patients with COVID-19 had CAP (defined as positive culture <2 days from admission), which only represented 12.2% of bacterial pneumonia cases in patients with COVID-19, whereas the large majority of cases were due to ventilator-associated pneumonia (VAP, 85.7%) [60]. This study also found that a significantly higher proportion of bacterial pneumonia in patients with COVID-19 was ventilator-associated relative to patients who did not have COVID. Rates of bacterial pneumonia among ventilated patients were also found to be significantly higher for those testing positive for SARS-CoV-2, was also seen in an independent study of a large cohort in Sweden [61]. Although meta-analyses have only looked at overall rates of bacterial coinfection in the setting of SARS-CoV-2, the largest of these found considerable heterogeneity between studies, with subgroup analyses showing rates of 4% in all hospitalized patients and 14% for ICU patients alone, consistent with the largest individual studies described elsewhere in this article [59,62,63].

Although Hedberg and colleagues did not report significant differences in the risk of ICU admission or 30-day mortality for patients with COVID-19 with CAP relative to those without, another large observational study looking specifically at clinically confirmed CAP found significantly increased rates of ICU admission (rate ratio = 4.45), mechanical ventilation (rate ratio = 6.74), higher rates of septic shock (rate ratio = 4.60), longer length of stay (mean 7 vs 5 days) and greater mortality (47.5% vs 18.0%) for patients with CAP [63]. A study specifically assessing hospital-acquired respiratory coinfections with bacterial or fungal pathogens found that that they occurred in 6.8% of patients with COVID-19, and more than 10-fold as many positive respiratory cultures relative to community-acquired infections [64]. For both hospital- and community-acquired infections, the vast majority were associated with bacterial etiologies, with only 4% of community-acquired and 2% of health care-associated pathogens involving fungal isolates (*Aspergillus*). Few other studies have directly assessed the rate of fungal respiratory infection in the setting of hospitalized patients with COVID-19. Of these, Nori and colleagues [59] represents the largest and also found low rates of coinfection with fungal pathogens, with 3 of 112 (2.7%) positive respiratory isolates of fungal etiology (*Candida* and *Aspergillus* spp). However, high rates of pulmonary aspergillosis have been demonstrated among patients with COVID-19 admitted to an ICU, with 1 meta-analysis of 30 studies covering 3441 patients demonstrating a pooled incidence rate of 14%

(95% CI, 11%–17%) with a case fatality rate of 52% (95% CI, 47%–56%) [65].

The etiologies of bacterial respiratory infections also reflect a relatively high proportion of health care-associated and/or ventilator-associated pathogens in patients with COVID-19, relative to pathogens found in patients with influenza. Although *S pneumoniae* represented the most common bacterial pneumonia pathogen for patients with influenza, *Staphylococcus*, *Pseudomonas*, and Enterobacterales spp (such as *Klebsiella*) represented the most common etiologies in patients with COVID-19 found by studies looking at both community-acquired and health care-associated pneumonia [59,60,64]. In a large observational study looking specifically at CAP in patients with COVID-19, bacterial pathogen profiles were more similar to that of patients with influenza, with the most common pathogen being *S pneumoniae* (28%), albeit far lower than coinfection in patients with influenza (56%), and with patients with COVID-19 with CAP having a higher proportion of *S aureus* as the second-most common pathogen (26% vs 19%) [58].

Despite the lower rates of bacterial respiratory coinfection in patients with COVID-19 relative to patients with influenza and RSV, high rates of early antibiotic therapy have been observed in these patient populations. The 3 largest such studies, including 4267, 3028, and 1705 patients with COVID-19 from Spring 2020, respectively, found that 71%, 67%, and 57% of patients received some form of antibiotic therapy during their treatment [59,63,64]. Interestingly, the smallest of these studies found that 54% of those patients with COVID-19 started on early antimicrobial therapy had it discontinued within 1 day after SARS-CoV-2 tests returned positive, but of those remaining on antimicrobial therapy, only 7.4% had a community-onset bacterial infection confirmed [63]. Another meta-analysis of 24 studies including 3338 patients also found that 72% of patients received antibiotics (95% CI, 56%–88%). However, most of the studies have looked at cases dating from the first or second wave of the COVID-19 pandemic in 2020, when effective antivirals were not available, and it remains to be seen whether such high rates of antibiotic therapy have continued into 2021 to 2022.

Nori and colleagues (2021) [59] also assessed antibiotic use in health care-associated infections, finding that 79% of patients who had a positive bacterial culture (blood or respiratory) had received antibiotics in the 30 days before positive culture, and all 21 patients with multi-drug resistant pathogens were in this group. Kubin and colleagues (2021) [64] found increasing

rates of antimicrobial resistance in isolates recovered later in patients' hospital stay, 33% of *S aureus* isolates were methicillin resistant, 76% of which were respiratory isolates, 42% of Enterobacterales were cephalosporin resistant and 7% were carbapenem resistant (the majority of which were respiratory isolates). However, a study from the same institution comparing rates of antimicrobial resistance for bacterial respiratory isolates in patients with and without COVID-19 found no significant increase in any of these categories except for patients with COVID-19 with methicillin-resistant *S aureus* and overall resistance to penicillin class antibiotics [60]. Thus, antimicrobial resistance rates seemed comparable for COVID-19 and patient populations without COVID-19, with the exception of methicillin-resistant *S aureus*, but increasing risk of resistance with hospital stay further highlights the need for stewardship in early antibiotic treatment, particularly for nonintubated patients. This finding is corroborated by health care-associated infection risk factors assessed in Kubin and colleagues (2021), the leading of which were invasive mechanical ventilation (OR, 6.0; 95% CI, 3.7–10.0), ICU care (OR, 4.1; 95% CI, 2.5–6.8), and steroid treatment (OR, 1.9; 95% CI, 1.4–2.6).

Although there are a host of mechanisms by which influenza has been found to predispose human epithelia to bacterial coinfection, with high rates of CAP to support the manifestation of these mechanisms in real-world settings, there is a paucity of research into which of these mechanisms may also operate in the setting of SARS-CoV-2 infection. However, observational studies have found far lower rates of CAP in SARS-CoV-2 relative to patients with influenza, and instead prolonged exposure to health care settings and particularly mechanical ventilation seem to be driving the majority of bacterial and fungal pneumonia cases seen in patients with COVID-19. Respiratory culture ordering and antibiotic use should, therefore, be primarily considered in severe COVID-19 disease requiring ICU-level care and invasive mechanical ventilation.

DISCLOSURE

The authors have nothing to disclose.

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