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Systematic review

Predictors and microbiology of respiratory and bloodstream bacterial infection in patients with COVID-19: living rapid review update and meta-regression

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ABSTRACT

Background: The prevalence of bacterial infection in patients with COVID-19 is low, however, empiric antibiotic use is high. Risk stratification may be needed to minimize unnecessary empiric antibiotic use. **Objective:** To identify risk factors and microbiology associated with respiratory and bloodstream bacterial infection in patients with COVID-19.

Data sources: We searched MEDLINE, OVID Epub and EMBASE for published literature up to 5 February 2021.

Study eligibility criteria: Studies including at least 50 patients with COVID-19 in any healthcare setting.

Methods: We used a validated ten-item risk of bias tool for disease prevalence. The main outcome of interest was the proportion of COVID-19 patients with bloodstream and/or respiratory bacterial co-infection and secondary infection. We performed meta-regression to identify study population factors associated with bacterial infection including healthcare setting, age, comorbidities and COVID-19 medication.

Results: Out of 33 345 studies screened, 171 were included in the final analysis. Bacterial infection data were available from 171 262 patients. The prevalence of co-infection was 5.1% (95% CI 3.6–7.1%) and secondary infection was 13.1% (95% CI 9.8–17.2%). There was a higher odds of bacterial infection in studies with a higher proportion of patients in the intensive care unit (ICU) (adjusted OR 18.8, 95% CI 6.5–54.8). Female sex was associated with a lower odds of secondary infection (adjusted OR 0.73, 95% CI 0.55–0.97) but not co-infection (adjusted OR 1.05, 95% CI 0.80–1.37). The most common organisms isolated included *Staphylococcus aureus*, coagulase-negative staphylococci and *Klebsiella* species.

Conclusions: While the odds of respiratory and bloodstream bacterial infection are low in patients with COVID-19, meta-regression revealed potential risk factors for infection, including ICU setting and mechanical ventilation. The risk for secondary infection is substantially greater than the risk for co-infection in patients with COVID-19. Understanding predictors of co-infection and secondary infection may help to support improved antibiotic stewardship in patients with COVID-19. **Bradley J. Langford, Clin Microbiol Infect 2022;28:491**

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Introduction

There is rising concern about the long-term impact of COVID-19 on antimicrobial resistance. While bacterial co-infection rates in patients presenting with COVID-19 have been found to be low (<5%) [1,2], the majority (50–75%) of hospitalized patients with COVID-19 receive antibiotics [3,4]. The rates of secondary bacterial infection, those that occur later on in illness, tend to be higher (10–20%), but are typically related to healthcare-associated infections involving invasive devices, such as ventilators and central venous access [1,5,6]. There are limited data describing the causative pathogens and their susceptibility patterns among COVID-19 patients with bacterial co-infections.

Despite the low rate of infection early in illness, a large observational study found that 57% of patients with COVID-19 received early empiric antibiotics and 46% of these patients had their antibiotics continued after a positive COVID-19 PCR test. Of those who had antibiotics continued despite no confirmed bacterial infection, 64% had antibiotics continued for 5 or more days [3].

The vast discrepancy between the rate of proven bacterial infection and antibiotic use suggests an urgent need for antimicrobial stewardship. However, there are several diagnostic challenges that drive antibiotic overuse in COVID-19, most notably the difficulties in (a) differentiating viral from bacterial infection prior to the COVID-19 test result, and (b) definitively ruling out bacterial co-infection in those after a positive COVID-19 test.

A better understanding of the population-level predictors of bacterial co-infection and secondary infection can help identify situations where antibiotics are more likely to provide benefit, and uncover opportunities for antimicrobial stewardship. Additionally, a characterization of the common organisms identified in early versus late bacterial infection in a COVID-19 patient may help clinicians optimize prescribing, particularly regarding when and which empiric treatment may be beneficial. As the standard of care for COVID-19 infection evolved rapidly over the course of the pandemic, including the life-saving measures of respiratory support and use of immunotherapy based on emerging evidence, it was deemed important to update our analysis reflecting this change in practice. Our objective was to build upon our previously published rapid review to describe the prevalence and microbiological characteristics of respiratory and bloodstream co-infection and secondary infection and to use meta-regression to identify study-level predictors of bacterial infections in patients with COVID-19.

Materials and methods

We conducted a rapid systematic review guided by the Cochrane Rapid Reviews Methods Group [7] to evaluate concomitant bacterial infection in patients with COVID-19. We included studies of humans with COVID-19, across all healthcare settings (i.e., hospital, community, long-term care) and age groups (paediatric and adult patients).

We included cohort studies, case series with 50 or more patients and randomized controlled trials that did not evaluate antibiotic use as an intervention, but excluded reviews, editorials, letters and case studies. We excluded studies that (a) included patients with non-laboratory-proven COVID-19, (b) tested for co-infection using only nasopharyngeal swabs, (c) did not differentiate between bacterial infection and other co-infections or secondary infections (e.g., fungal), (d) indicated bacterial infection was presumed or suspected (e.g., use of white blood cell count, biomarkers) and (e) used serology as a bacterial infection diagnostic approach. This protocol was registered under PROSPERO, the international registry of systematic reviews (ID CRD42021241098).

Data sources

We performed systematic searches of MEDLINE, OVID Epub and EMBASE databases for published literature in any language from 1 January 2019–5 February 2021 with assistance from a medical library information specialist. The expanded timeline aimed to capture new publications since the systematic search we performed for our earlier review (1 January 2019–16 April 2020) [1]. The current search was structured to include COVID-19 terms co-infection, bacterial infection, respiratory infection, epidemiology or descriptive cohort study terms. The complete search strategy is described in the Online Supplement. The results of the search were imported into Covidence (Covidence, Melbourne, Australia), an online software tool for systematic reviews. Duplicate records were removed using Covidence.

Study selection

Initial screening of titles and abstracts from the search were shared by two authors (B.L. or V.L.) who independently identified studies that met all inclusion criteria and none of the exclusion criteria. All full text studies meeting initial criteria were then reviewed by one of the authors (B.L., M.S., V.L., S.R., T.K., J.L. or D.M.) for final inclusion in the rapid review. Single screening was utilized given the high volume of citations and the substantial kappa agreement (0.62–0.68) from our team for previous rapid reviews in which duplicate screening was performed [9].

Data extraction

One of seven authors (B.L., M.S., V.L., S.R., T.K., J.L. or D.M.) independently extracted data from included studies using a standardized data collection form. For quality assurance, one of three authors (E.L., V.L. or B.L.) then verified all extracted data to confirm accuracy and completeness. We collected data on the following variables for demographics and setting: author; country of study; start and end dates; study design; healthcare setting (inpatient intensive care unit (ICU) vs. non-ICU outpatient); sample size; age group; patient population; mean or median age; and number of female patients. Regarding clinical characteristics, we collected information on COVID-19 severity; number of patients requiring mechanical ventilation; number of patients that were smokers; number of patients with comorbidities (chronic obstructive pulmonary disease, cardiovascular disease or diabetes); and number of patients who were prescribed corticosteroids, interleukin-6 (IL-6) inhibitors (i.e., tocilizumab or sarilumab) and antibacterial agents. We extracted respiratory and bloodstream microbiology data, including specimen source and identification, if the information was available.

Assessment of bias

We used a validated ten-item risk of bias tool for disease prevalence [10]. Risk of bias was categorized as low (score ≥ 8), moderate (score 5–7) or high (score 0–4). A sensitivity analysis was performed stratifying proportion of bacterial infection by study risk of bias. Additional sensitivity analyses were performed to (a) remove studies where bacteriological testing method and bacterial infection source were not specified and (b) to stratify studies based on whether they used a clinical definition for bacterial infection (e.g., differentiated infection from colonization or contamination using clinical criteria).

Data synthesis

The main outcome of interest was the overall prevalence of respiratory and bloodstream bacterial co-infection or secondary

infection among patients with COVID-19. We evaluated the number of patients developing a bacterial infection at any point during the course of their illness while under study observation as a proportion of all patients with COVID-19.

First, studies were categorized based on whether they evaluated co-infection (authors used the term co-infection and/or specified that infection was assessed on admission or at the time of health care visit), secondary infection (authors used the term secondary infection, super-infection, healthcare-associated infection and/or indicated that infection was identified >48 hr after initial assessment). Studies that did not specify co-infection or secondary infection were grouped with co-infection. To estimate overall bacterial infection, for studies reporting both co-infection and secondary infection, we selected the higher proportion of the two. Second, the source of infection was categorized as respiratory, bloodstream, both respiratory and bloodstream or not specified. Infections specified from other sources (e.g., urine, skin) were not included. For the purposes of this study, both co-infection and secondary infection were limited to respiratory and/or bloodstream specimens to estimate the prevalence of infections closely linked to COVID-19 while limiting bias due to variability in diagnosis of other less relevant conditions (e.g., skin and soft tissue infections and urinary tract infections). Third, studies were categorized based on the bacteriological testing method (culture, nucleic acid amplification, a combination of approaches, or not specified).

We pooled proportion data across studies via a random-effects meta-analysis using a generalized linear mixed model (GLMM) with logit link approach [11,12]. Results were illustrated using forest plots stratified by healthcare setting and infection type. Heterogeneity was assessed by the I^2 statistic [13]. All analyses were carried out using R version 4.1.1 with the packages *metafor* and *meta*. The statistical code for this analysis is made available online [14].

Meta-regression

To predict the effect of specific population-level variables on bacterial infection, we performed univariable meta-regression evaluating patient characteristics (age, sex, comorbidities, use of medication for treatment of COVID-19), markers of severity (e.g., mechanical ventilation), healthcare setting, geographic region (Asia, Middle East, Europe, North America, South America) and end-month of study. Differences in prevalence of antibiotic prescribing for each variable were described in terms of the prevalence odds ratio (OR) compared with reference, per 10% increase for continuous variables and per 10-year increase for age. Multi-variable meta-regression was then performed to account for key factors mediating the risk of infection including mean/median patient age [15] and severity of COVID-19 (an index including the highest value of % of patients with ARDS; % of ICU patients; % of mechanical ventilation patients) [16]. One model per variable was constructed, and only studies where both the variable of interest and the adjustment variables were reported were included. We used the same subset of studies with available data for both the unadjusted and adjusted analyses. Given studies that did not report whether they evaluated co-infection versus secondary infection were grouped with co-infection, a sensitivity analysis was performed to remove these studies with unspecified outcome to determine the robustness of our findings.

Results

Of 56 767 studies identified via searching, after duplicate removal, we reviewed a total of 33 345 studies via title and abstract screening, 1798 of which were assessed via full-text screening. We included 171 studies in the final analysis [1,3–7,9–16], [17–45], [46–77], [78–108], [109–130], [131–156], [157–185] (Fig. 1). Study design was primarily

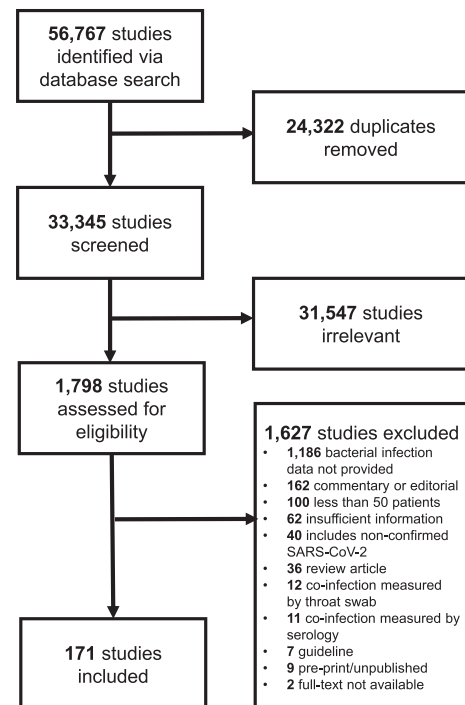


Fig. 1. PRISMA study flow diagram.

retrospective in nature ($n = 149$), with fewer prospective cohorts ($n = 19$), or randomized controlled trials ($n = 3$). COVID-19 study data was collected from December 2019 to October 2020.

Study geography

The majority of studies took place in Europe (67, 39%), followed by Asia (55, 32%), North America (34, 20%), Middle East (10, 6%), South and Central America (3, 2%) and multiple regions (2, 1%).

Healthcare setting

Most studies took place in a general hospital setting (129, 75%), followed by only ICU patients (33, 19%), mixed hospitalized patients and outpatients (9, 5%) and a single study limited to outpatients (1, 1%).

Patient characteristics

A total of 171 262 patients were evaluated for bacterial infection across the 171 studies. A median 41% of participants were female (interquartile range (IQR) 33–48%). The median age was 61 years (IQR 53–64, range 5–85). Only four studies included a population with a median age less than 18 years. Studies included a median of 25% ICU patients (IQR 13–100%) and a median of 21% (IQR 10–52%) patients receiving mechanical ventilation. Smokers comprised a median of 9% (IQR 5–22%) of the study populations. Common comorbidities included chronic respiratory disease (median 6%, IQR 4–12%), cardiovascular disease (median 14%, IQR 6–20%) and diabetes (median 21%, IQR 12–32%).

Bacterial infection assessment in COVID-19

Most studies did not specify how bacterial infection was detected (82, 48%), followed by studies using culture methods (72, 42%), combined approach using culture with nucleic acid

amplification and/or urinary antigen testing (16, 9%) and nucleic acid amplification alone (1, 1%). Sources assessed for infection included a combination of respiratory and bloodstream isolates (75, 44%), respiratory only (38, 22%), blood only (22, 13%) and unclear site of infection (35, 20%). The minority of studies (66, 39%) employed a clinical definition for diagnosis of bacterial infection. A total of 86 studies (59 explicitly used co-infection terminology, and 27 not specified) including 137 325 patients evaluated for co-infection, and 95 studies including 40 843 patients evaluated for secondary infection. This includes ten studies that assessed patients for both co-infection and secondary infection.

Microbiological characteristics of bacterial infections in COVID-19

A total of 76 studies specified organism identification for bacterial infections (co-infections $n = 1319$ and secondary infections $n = 2016$). For co-infections, the most common bacterial organisms identified included *Staphylococcus aureus* (332, 25%), coagulase-negative *Staphylococcus* (CNST) (217, 16%) and *Klebsiella* species (113, 9%). For secondary infections, identified organisms were more diverse but the most common organisms were similar including *S. aureus* (315, 16%) and *Klebsiella* species (233, 11%). Fig. 2 contains complete details for all organisms identified.

Prevalence of bacterial infection in patients with COVID-19

When pooling bacterial infection across all 171 262 patients with COVID-19, the prevalence of overall respiratory and/or bloodstream bacterial infection was 8.8% (95% CI 6.9–11.1%). Bacterial co-infection occurred in 5.1% (95% CI 3.6–7.1%) of patients and increased with the level or intensity of care, from mixed hospital/outpatient populations (1.9%, 95% CI 0.5–7.1%), to hospitalized patients (4.4%, 95% CI 3.0–6.4%), to intensive care only (15.4%, 95% CI 10.5–22.0%). Secondary bacterial infection was more common at 13.1% (95% CI 9.8–17.2%). While mixed hospital/outpatient populations (11.1%, 95% CI 1.4–52.3%) and hospitalized populations (8.2%, 95% CI 6.3–10.7%) experienced a lower risk of secondary infection, secondary bacterial infection was more common in ICU populations (41.9%, 95% CI 29.5–55.4). The degree of heterogeneity in the prevalence of bacterial co-infection and secondary infection was substantial ($I^2 = 98%$) (Fig. 3).

The prevalence of bacterial infection differed depending on the site of infection reported: respiratory and blood isolates (co-infection 6.2%, 95% CI 3.6–10.5%; secondary infection 16.3%, 11.9–22.0%), blood alone (co-infection 6.0%, 95% CI 3.4–10.3%; secondary infection 10.7%, 95% CI 3.4–28.8%) and respiratory isolates alone (co-infection 2.9%, 95% CI 1.6–4.9%; secondary infection 12.2%, 95% CI 4.9–27.1%) (Fig. 4).

Meta-regression: predictors of co-infection and secondary infection in COVID-19

COVID-19 co-infection rates were higher in studies with a higher proportion of ICU patients (adjusted OR 6.96, 95% CI 2.14–22.65) and secondary infection (adjusted OR 32.10, 95% CI 2.66–387.30) than those not admitted to an ICU. Studies with a higher proportion of mechanically ventilated patients were associated with a greater odds of both co-infection (adjusted OR 1.24, 95% CI 1.11–1.40) and secondary infection (adjusted OR 1.44, 95% CI 1.32–1.57). Advanced study population age did not appear to be associated with a greater odds of co-infection (adjusted OR 1.06, 95% CI 0.87–1.28 per 10-year increase) or secondary infection (adjusted OR 1.24, 95% CI 0.93–1.66 per 10-year increase). A higher proportion of female patients appeared to be protective for secondary infection (adjusted OR 0.73, 95% CI 0.55–0.97) but not co-infection (adjusted OR 1.05, 95% CI 0.80–1.37). There was no association between the proportion of study corticosteroid use and bacterial infections (co-infection adjusted OR 1.07, 95% CI 0.88–1.29, secondary infection adjusted OR 0.99, 95% CI 0.87–1.12) or IL-6 inhibitor use (co-infection adjusted OR 1.06, 95% CI 0.85–1.31, secondary infection adjusted OR 0.98, 95% CI 0.87–1.10) and bacterial infection in patients with COVID-19 (Table 1).

Sensitivity analyses

Although the overall estimate of bacterial infection was similar when stratified by study risk of bias, studies with a moderate risk of bias reported numerically higher rates of bacterial infections in ICU patients (44.2%, 95% CI 28.8–60.8) than the same population in studies with high (18.8%, 95% CI 13.9–25.0%) and low risk of bias (24.5%, 95% CI 15.2–36.9%) (Fig. S1). However, this difference was not statistically significant upon meta-regression in either unadjusted or adjusted analyses. Studies with a high risk of bias had a greater odds of co-infection (adjusted OR 2.45, 95% CI 1.05–5.72) but not secondary infection (adjusted OR 0.67, 95% CI 0.26–1.71) (Table 1).

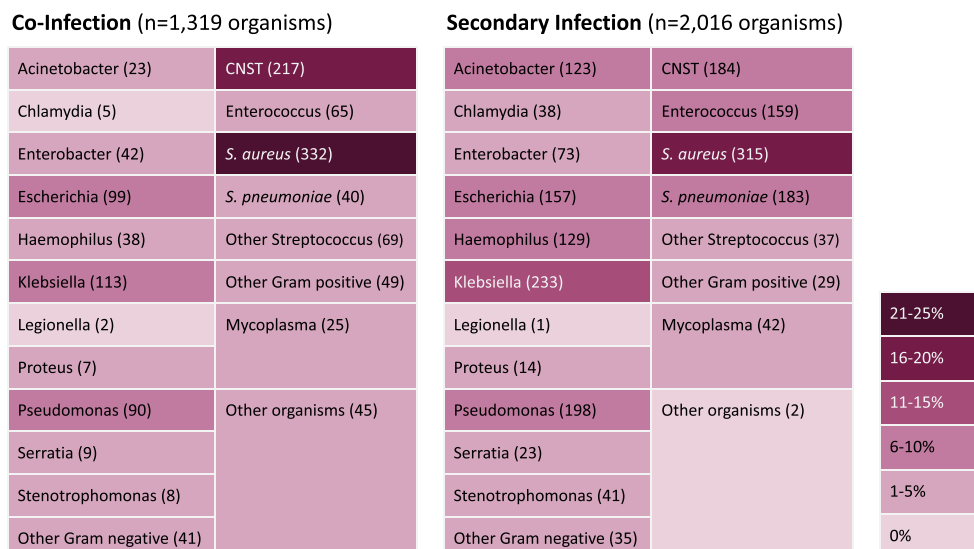
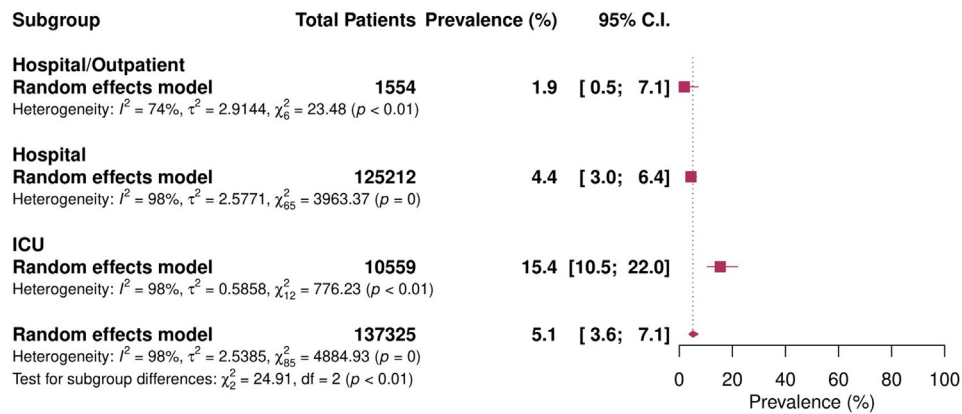


Fig. 2. Microbiological characteristics of bacterial infection in patients with COVID-19. CNST, coagulase negative *Staphylococcus* spp.

Co-Infection



Secondary Infection

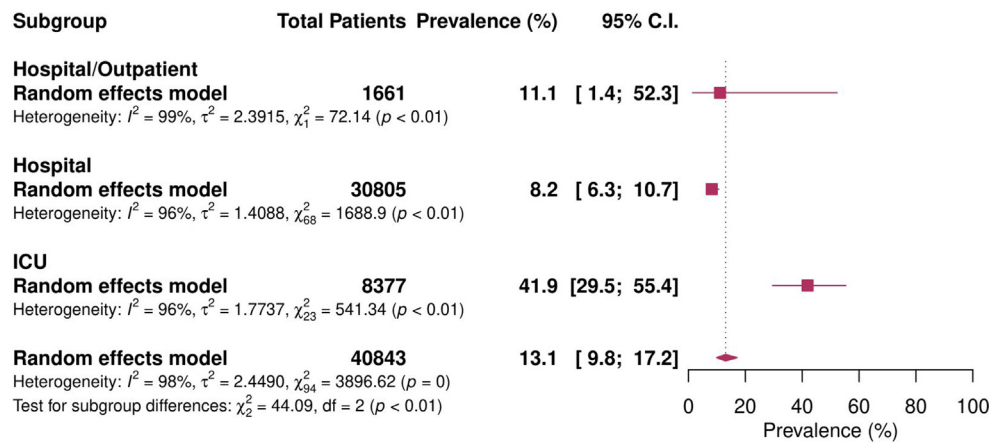


Fig. 3. Forest plot of co-infection and secondary infection prevalence based on healthcare setting co-infection.

Estimates of proportion of bacterial infection were similar when removing studies where bacteriological testing method and bacterial infection source were not specified (Fig. S2). Studies that employed a clinical definition for bacterial infection appeared to report prevalence of infection similar to those without this definition (Fig. S3).

When removing studies that did not explicitly state whether they evaluated co-infection versus secondary infection, the findings were similar, with one key exception. ICU setting did not appear to be associated with co-infection risk after removing these studies (adjusted OR 3.61; 95% CI 0.46–28.36); however, the association between ICU setting and secondary infection risk persisted, (adjusted OR 32.10; 95% CI 2.66–387.30) (see Supplementary Table 2).

Antibiotic prescribing in patients with COVID-19

Out of 31 802 patients evaluated for antibiotic prescribing, the prevalence of antibiotic use in patients with COVID-19 was 76.2% (95% CI 67.3–83.2%). There did not appear to be an appreciable change in prescribing over time during the period January to September 2020. There was substantial heterogeneity between studies in the prevalence of antibiotic prescribing ($I^2 = 99\%$) (Fig. S4).

Discussion

We previously conducted a rapid review/meta-analysis on the prevalence of bacterial co-infection and another on the antibiotic prescribing based on literature published in the first few months of the pandemic [1,4]. The current update included literature published up to the beginning of February 2021—over a year since SARS-CoV-2 was first identified. In this analysis, the pooled estimated prevalence of bacterial co-infection in 5.1%, and increased with the severity of COVID-19 infection. The prevalence of secondary infections was estimated to be 13%, more than double that of co-infection. With meta-regression, this updated analysis provides a more comprehensive and granular picture on the predictors of bacterial infections in COVID-19 while confirming our earlier findings. Furthermore, compared with pandemic influenza which has been associated with a risk of bacterial co-infection of at least 19% [186,187] the risks of bacterial co-infection and secondary infections from SARS-CoV-2 appear to be lower.

A series of pivotal studies established two classes of immunotherapy, systemic corticosteroids and IL-6 inhibitors, as standards of care for patients with moderate to severe acute respiratory distress syndrome requiring hospitalization requiring respiratory support [188–191]. Given their immunomodulatory effects,

Table 1
Study-level predictors of bacterial co-infection, secondary infection and overall bacterial infection in patients with Covid-19 (prevalence OR, 95% CI)

Characteristic	Co-infection (n = 86)		Secondary infection (n = 95)		Bacterial infection (n = 171)		No. of studies
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Overall
Setting (reference = Hospital/ Outpatient)	Reference	Reference	Reference	Reference	Reference	Reference	8
Hospital	1.74 (0.64–4.71)	1.49 (0.54–4.12)	3.53 (0.28–44.19)	4.16 (0.36–48.82)	2.89 (1.07–7.78)	2.31 (0.86–6.24)	120
ICU	8.40 (2.65–26.65)	6.96 (2.14–22.65)	28.63 (2.22–369.50)	32.10 (2.66–387.30)	24.79 (8.57–71.74)	18.83 (6.48–54.77)	32
Study end month (reference = Jan to May 2020)	Reference	Reference	Reference	Reference	Reference	Reference	134
Jun to Oct 2020	1.66 (0.53–5.15)	1.28 (0.48–3.44)	1.14 (0.43–2.98)	1.14 (0.54–2.41)	1.48 (0.67–3.25)	1.18 (0.63–2.20)	19
Region (reference = North America)	Reference	Reference	Reference	Reference	Reference	Reference	29
Europe	1.35 (0.57–3.20)	1.03 (0.48–2.18)	1.81 (0.76–4.34)	1.46 (0.72–2.96)	1.68 (0.82–3.41)	1.28 (0.72–2.27)	62
Asia	0.96 (0.39–2.36)	1.51 (0.67–3.41)	0.69 (0.27–1.76)	0.99 (0.46–2.12)	0.80 (0.38–1.69)	1.18 (0.64–2.18)	49
Middle East	0.98 (0.14–7.05)	2.39 (0.37–15.39)	0.70 (0.17–2.90)	0.66 (0.21–2.08)	0.96 (0.27–3.39)	1.01 (0.36–2.85)	8
South and Central America	1.52 (0.20–11.45)	2.04 (0.35–11.82)	2.37 (0.11–49.18)	0.71 (0.06–8.03)	1.31 (0.19–9.07)	1.07 (0.22–5.13)	3
Multiple	11.08 (0.84–145.78)	3.81 (0.39–37.42)	0.03 (0.00–0.92)	0.08 (0.00–1.30)	0.67 (0.07–6.94)	0.47 (0.07–3.13)	2
Risk of bias (reference = Low)	Reference	Reference	Reference	Reference	Reference	Reference	52
Moderate	1.17 (0.59–2.33)	1.57 (0.87–2.86)	1.20 (0.58–2.49)	1.02 (0.58–1.79)	1.22 (0.69–2.15)	1.20 (0.76–1.89)	82
High	1.72 (0.64–4.61)	2.45 (1.05–5.72)	0.60 (0.18–2.00)	0.67 (0.26–1.71)	0.91 (0.38–2.15)	1.13 (0.57–2.26)	19
Age (10-year increase)	1.20 (0.97–1.48)	1.06 (0.87–1.28)	1.53 (1.07–2.18)	1.24 (0.93–1.66)	1.37 (1.12–1.69)	1.12 (0.94–1.34)	153
% Female (10% increase)	0.74 (0.58–0.93)	1.05 (0.80–1.37)	0.50 (0.37–0.67)	0.73 (0.55–0.97)	0.58 (0.47–0.71)	0.87 (0.71–1.07)	152
% Mech. ventilation (10% increase)	1.26 (1.13–1.41)	1.24 (1.11–1.40)	1.45 (1.33–1.58)	1.44 (1.32–1.57)	1.42 (1.32–1.53)	1.41 (1.30–1.52)	124
% Smoker (10% increase)	0.89 (0.58–1.37)	0.72 (0.46–1.14)	0.85 (0.52–1.37)	0.79 (0.55–1.12)	0.89 (0.63–1.27)	0.73 (0.54–0.98)	58
% COPD (10% increase)	1.02 (0.55–1.90)	0.86 (0.49–1.51)	1.27 (0.71–2.29)	1.02 (0.64–1.64)	1.39 (0.89–2.16)	1.08 (0.74–1.57)	106
% CVD (10% increase)	0.98 (0.67–1.45)	0.86 (0.57–1.31)	1.27 (0.90–1.77)	1.11 (0.80–1.52)	1.18 (0.90–1.54)	1.00 (0.77–1.30)	100
% Diabetes (10% increase)	1.18 (0.97–1.45)	1.10 (0.88–1.37)	1.33 (1.00–1.76)	1.00 (0.77–1.28)	1.24 (1.03–1.50)	1.03 (0.86–1.23)	126
% Corticosteroid (10% increase)	1.12 (0.91–1.39)	1.07 (0.88–1.29)	1.11 (0.95–1.30)	0.99 (0.87–1.12)	1.14 (0.99–1.30)	1.01 (0.91–1.14)	103
% IL-6 inhibitor (10% increase)	1.27 (1.00–1.61)	1.06 (0.85–1.31)	1.05 (0.89–1.23)	0.98 (0.87–1.10)	1.12 (0.97–1.28)	0.99 (0.89–1.10)	65

Adjusted analysis accounts for median/mean study age, and severity index (% of patients with severe COVID-19).
Setting and mechanical ventilation are only adjusted for age.

concern has been raised regarding their role in secondary infections in COVID-19. Our analyses did not identify a significantly higher odds of secondary bacterial infections among patients exposed to corticosteroids or IL-6 inhibitors. These findings may reflect the fact that other drivers, such as the inflammatory response to SARS-CoV-2 and invasive devices, are more significant contributing factors of bacterial infections in patients with COVID-19 [192] and as such there may be limited benefit of empiric antibiotics in the absence of proven infection for patients receiving these agents. Alternatively, our study may not be adequately powered to detect the impact of these immunomodulatory agents on secondary infections, given the relatively low rate of bacterial infection events.

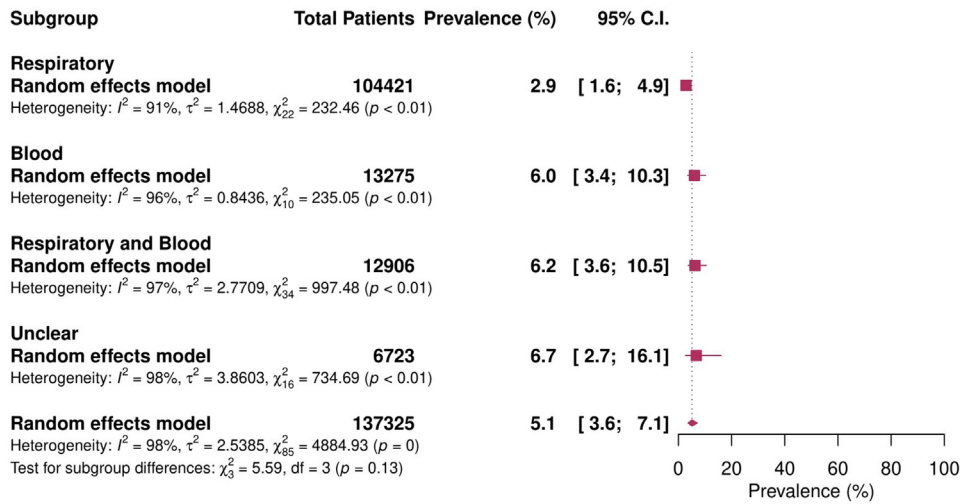
The most common organisms identified in patients with both co-infection and secondary infection are *S. aureus*, CNST and *Klebsiella* species. These pathogens reflect those seen in hospital-acquired pneumonia and bloodstream infections also seen outside of the context of COVID-19 [193,194]. However, given most studies did not attempt to differentiate infection from contamination, CNST may represent contamination in many cases [174].

At 77%, the prevalence of antibiotic prescribing was high and incongruent with the relatively low prevalence of bacterial infections. This outcome remained consistent with our previous publication [4]. Of note, clinical guidelines for COVID-19 recommendations varied with respect to the use of empiric antibiotics, particularly in critically ill patients [195–198]. Differences in the recommended approach to antibiotic prescribing may explain why the use of antibiotics remained higher than prevalence of bacterial infections. Our findings support a more judicious approach, particularly in patients outside of the ICU.

A limitation of this review is that these findings are constrained by the quality of the underlying primary literature, as less than one third of included studies were considered to be at low risk of bias. We also noted a high degree of heterogeneity across studies, of which it is not clear whether this reflects a difference in clinical characteristics, diagnostic approaches and/or clinical practice across settings. However, our findings are relatively consistent across study risk of bias rating and align with those in recent large high-quality observational cohort studies [83,161]. A second limitation is our focus on microbiological identification of bacterial infection. There may be a risk of under-estimating the true prevalence of co-infection and secondary infection given that only a proportion of patients receive microbiological testing to confirm the presence of bacterial infection. On the other hand, a microbiological definition alone may overestimate infection in the setting of colonization without evidence of a true respiratory infection. Finally, the distinction between bacterial co-infection and secondary infection is not always consistent across the literature [199]. Terms may be used interchangeably or not at all, leading to a risk of misclassification bias. To address this risk, we reported both an estimate of co-infection and secondary infection, as well as overall bacterial infection, the latter of which reduces the impact of imprecision associated with terminology chosen by study authors.

Over a year into the pandemic, these findings provide further supporting evidence for the relatively low rate of bacterial infection in COVID-19 and may serve an impetus for antimicrobial stewardship initiatives, such as risk stratification for early empiric antibiotics, and early discontinuation in patients with COVID-19 and lack of confirmed concomitant bacterial infection.

Co-Infection



Secondary Infection

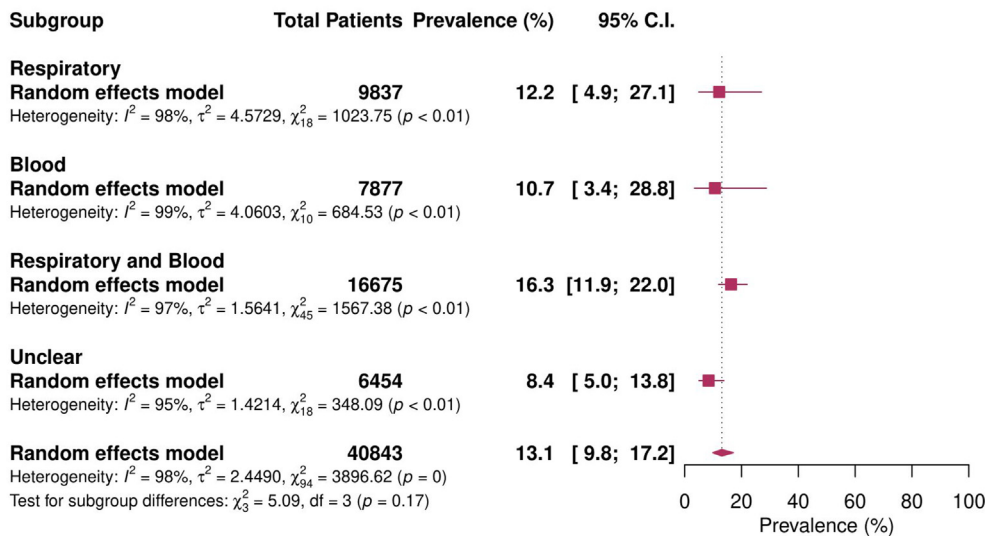


Fig. 4. Forest plot of co-infection and secondary infection prevalence based on specimen source.

Conclusion

While the odds of respiratory and bloodstream bacterial infection are low in patients with COVID-19, potential risk factors for infection include ICU setting and mechanical ventilation. The risk for secondary infection is substantially greater than the risk for co-infection in patients with COVID-19. Antibiotics appear to continue to be overprescribed in COVID-19. Understanding predictors of co-infection and secondary infection may help to support improved antibiotic stewardship in patients with COVID-19.

Transparency declaration

The authors have no conflicts of interest to declare. Funding: This project was carried out as part of routine work.

Author contributions

Concept and design: All authors. Acquisition, analysis or interpretation of data: All authors. Drafting of the manuscript: Langford, So. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Soucy, Langford. Administrative, technical or material support: All authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.11.008>.

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