



Systematic review

Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis

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ABSTRACT

Background: The proportion of patients infected with SARS-CoV-2 that are prescribed antibiotics is uncertain, and may contribute to patient harm and global antibiotic resistance.

Objective: The aim was to estimate the prevalence and associated factors of antibiotic prescribing in patients with COVID-19.

Data Sources: We searched MEDLINE, OVID Epub and EMBASE for published literature on human subjects in English up to June 9 2020.

Study Eligibility Criteria: We included randomized controlled trials; cohort studies; case series with ≥ 10 patients; and experimental or observational design that evaluated antibiotic prescribing.

Participants: The study participants were patients with laboratory-confirmed SARS-CoV-2 infection, across all healthcare settings (hospital and community) and age groups (paediatric and adult).

Methods: The main outcome of interest was proportion of COVID-19 patients prescribed an antibiotic, stratified by geographical region, severity of illness and age. We pooled proportion data using random effects meta-analysis.

Results: We screened 7469 studies, from which 154 were included in the final analysis. Antibiotic data were available from 30 623 patients. The prevalence of antibiotic prescribing was 74.6% (95% CI 68.3–80.0%). On univariable meta-regression, antibiotic prescribing was lower in children (prescribing prevalence odds ratio (OR) 0.10, 95% CI 0.03–0.33) compared with adults. Antibiotic prescribing was higher with increasing patient age (OR 1.45 per 10 year increase, 95% CI 1.18–1.77) and higher with increasing proportion of patients requiring mechanical ventilation (OR 1.33 per 10% increase, 95% CI 1.15–1.54). Estimated bacterial co-infection was 8.6% (95% CI 4.7–15.2%) from 31 studies.

Conclusions: Three-quarters of patients with COVID-19 receive antibiotics, prescribing is significantly higher than the estimated prevalence of bacterial co-infection. Unnecessary antibiotic use is likely to be high in patients with COVID-19. **Bradley J. Langford, Clin Microbiol Infect 2021;27:520**

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Introduction

With millions of cases globally, the COVID-19 pandemic has had an immediate and devastating impact on the healthcare system and society as a whole. The long-term repercussions of COVID-19 on antimicrobial resistance have been raised as a grave concern due to elevated antibiotic use in patients infected with SARS-CoV-2 [1,2]. Despite the viral nature of this syndrome, initial studies indicate that antibiotics are prescribed frequently to patients with COVID-19, largely due to suspected bacterial co-infections [3–5].

Despite frequent antibiotic prescribing to patients with COVID-19, the prevalence of bacterial co-infection and secondary infection in patients hospitalized with COVID-19 is relatively low at 3.5% and 14.3%, respectively [5]. The gap between the prevalence of bacterial infection and frequency of antibiotic prescribing highlights the potential for significant antibiotic overuse in these patients. Over-prescribing of antibiotics in patients infected with SARS-CoV-2 can result in increased selective pressure for antimicrobial resistance. Antibiotic misuse coupled with a strained healthcare workforce and a reduced surveillance capacity for antibiotic-resistant organisms may lead to antimicrobial resistance as a lasting consequence of the COVID-19 pandemic [6,7].

Antibiotic stewardship interventions aimed at improving the appropriateness of antibiotic use are associated with reduced antibiotic utilization, and decreased incidence of drug-resistant infections [8]. Understanding patterns and predictors of antibiotic prescribing in COVID-19 can help to identify opportunities for interventions, and target antibiotic stewardship strategies to improve the quality and safety of antibiotic use. Our objective was to determine the prevalence of antibiotic use and identify the predictors of antibiotic use in patients with COVID-19.

Materials and methods

We conducted a rapid review based on modified Cochrane Rapid Reviews Methods Group guidance [9] to determine the proportion of patients with COVID-19 that were prescribed an antibiotic during the course of their illness, herein referred to as *prevalence* of antibiotic use in patients with confirmed COVID-19 infection. We selected rapid review as the optimal methodology to synthesize knowledge in a timely fashion for this emergent issue because we aimed to help clinicians apply the learnings to COVID-19 management strategies efficiently during the pandemic.

We included studies of humans with laboratory-confirmed SARS-CoV-2 infection, across all healthcare settings (i.e. hospital, community, long-term care) and age groups (paediatric and adult patients) as defined by study authors.

We included cohort studies, case series with ten or more patients and randomized controlled trials (not evaluating antibiotic use as an intervention), but excluded reviews, editorials, letters and case studies. We considered studies to be eligible regardless of experimental or observational design, and irrespective of their primary objective. However, we excluded studies that did not report data on the number and percentage of patients receiving antibiotics. This protocol was registered under PROSPERO, the international registry of systematic reviews (ID CRD42020192286).

Data Sources

We performed systematic searches of MEDLINE, OVID Epub, and EMBASE databases for published literature in the English language from 1 January 2019 to 9 June 2020 with assistance from a medical library information specialist. The limitation to English language articles was based on Cochrane Rapid Review Methods Group guidance [9] aimed at improving the timeliness while maintaining

broad representation of the review. The search was structured to include COVID-19 terms and antibiotic, co-infection, bacterial infection, respiratory infection, epidemiology, or descriptive cohort study terms. The complete search strategy is described in the supplementary material. 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. For quality assurance, three other authors (M.S., S.R. or N.D.) then randomly selected 25% of the identified studies for duplicate screening. Disagreements that could not be resolved via consensus were reviewed independently by another author who had not participated in the screening. All full text studies meeting initial criteria were then reviewed by one of the authors (B.L., M.S., S.R. or N.D.) for final inclusion in the rapid review. Studies potentially describing overlapping data were noted (e.g., same hospital and population during an overlapping time period).

Data extraction

One of five authors (B.L., M.S., S.R., V.L. or D.M.) independently extracted data from included studies using a standardized data collection form. For quality assurance, two authors (V.L. or D.W.) then randomly sampled 25% of data extraction forms to confirm accuracy and completeness. We collected data on the following variables for demographics and setting: author; country of study; start and end dates; name(s) of healthcare facility; study design (retrospective vs. prospective); healthcare setting (inpatient ICU vs. non ICU, outpatient); sample size; age group; patient population; mean or median age; and proportion of female patients. Regarding clinical characteristics, we collected information on COVID-19 severity; proportion of patients requiring mechanical ventilation; proportion of patients that were smokers; number of patients with comorbidities (chronic obstructive pulmonary disease, cardiovascular disease or malignancy); and number of patients who were prescribed an antibiotic. We also collected information on the following parameters if reported: antibiotic classes prescribed; duration of therapy; timing of antibiotic initiation (on admission or empiric vs. after admission); antibiotic stewardship interventions; and prevalence of respiratory or bloodstream bacterial co-infections.

Data synthesis

The main outcome of interest was the overall prevalence of antibiotic prescribing among patients with COVID-19. We evaluated the number of patients prescribed an antibiotic at any point during the course of their illness while under study observation as a proportion of all patients with laboratory-proven COVID-19. First, we stratified by region to identify differences in prescribing practices based on geography. Second, we stratified prescribing by severity of COVID-19 illness based on the study's quartile of the proportion of mechanically ventilated patients and by study population: (a) critically ill patients (admitted to intensive care unit); (b) all hospitalized patients; and (c) mixed hospitalized/outpatient population. Third, we stratified by the month in which the study completed follow-up to determine if antibiotic prescribing decreased as the pandemic progressed, as more information became available regarding the low rates of co-infection in patients

with COVID-19. Fourth, we stratified by study age group to evaluate differences in antibiotic prescribing between paediatric and adult patients. We pooled proportion data across studies via a random-effects meta-analysis using a generalized linear mixed model (GLMM) with logit link approach [10,11]. Results were illustrated using forest plots. Heterogeneity was assessed by I^2 statistic, with <40% considered low heterogeneity, 30–60% considered moderate heterogeneity, 50–90% considered substantial heterogeneity and 75–100% considered considerable heterogeneity [12]. All analyses were carried out using R version 3.6.0 with the packages *metafor* and *meta*. The statistical code for this analysis is made available online [13].

Meta-regression

To predict the effect of specific patient characteristics on antibiotic prescribing, we performed univariable meta-regression evaluating patient demographic characteristics (age, sex, comorbidities), markers of severity (mechanical ventilation, healthcare setting), geography (grouped by China, Middle East, East/Southeast Asia, Europe, North America, multiple countries), Healthcare Access and Quality Index (a novel measure of health system quality for 195 countries based on age-standardized mortality for 32 conditions with largely avoidable cause of death [14]), and end month of study. Prevalence differences in antibiotic prescribing for each variable were described in terms of the prevalence odds ratio (OR).

Assessment of bias

We considered a formal assessment for risk of bias to be of limited utility, given the lack of appropriate assessment tool (e.g. most appraisal questions are not applicable). Although a risk of bias tool has been developed for meta-analyses of disease prevalence [15], there are no tools that are directly relevant to our research question addressing the prevalence of antibiotic prescribing. Therefore, our modified rapid review approach incorporated study quality into our sensitivity analysis by estimating the quality of antibiotic prescribing data based on whether the study reported detail on antibiotic classes. In additional sensitivity analyses, we removed studies focusing exclusively on populations where antibiotic prescribing may differ from the general population (i.e. transplant, malignancy, obstetrics, older age (i.e. 60 years or older), chronic obstructive pulmonary disease (COPD), diabetes, fatal COVID infection, HIV, surgery, dialysis and acute kidney injury), and we removed studies with potentially overlapping patient cohorts (studies occurring in the same patient population in the same hospital during the same time frame).

Role of the funding source

University of Toronto, Department of Medicine, Network Seed Funding Grant supported the role of a research coordinator (D.W.) to provide research project management. The University was not involved in study concept, analysis or synthesis of evidence, nor the decision to publish.

Results

Of 16 378 studies identified, after duplicate removal, we reviewed a total of 7469 studies via title and abstract screening, 523 of which were assessed via full-text screening. We included 154 studies in the final analysis [16–40, 41–80, 81–100, 101–135, 136–169] (Fig. 1). Study design was primarily retrospective in nature ($n = 135$), followed by prospective cohort ($n = 11$), randomized controlled ($n = 6$) and mixed prospective and retrospective design

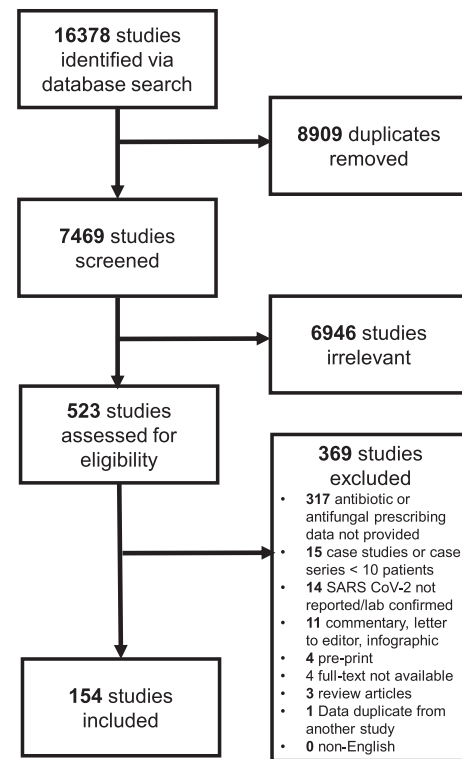


Fig. 1. Study flow diagram.

($n = 1$). Studies were conducted between 8 December 2019 and 21 May 2020.

Study geography

Most studies took place in China ($n = 115$ studies; 21 852 patients), followed by the United States ($n = 12$ studies, 2302 patients), Italy ($n = 11$ studies, 3785 patients) and South Korea ($n = 4$ studies, 5321 patients). A complete list of all study details and locations is available in Table 1.

Patient characteristics

A total of 35 263 patients with laboratory-confirmed COVID-19 were included across the 154 studies. The median patient age was 53 years (IQR 44–61, range 3–72). The majority of studies evaluated exclusively adults ($n = 91$) whereas a smaller number of studies ($n = 10$) included only children. Females comprised a median 45% of patients (IQR 39–51%) (Table 1). Commonly reported comorbidities included diabetes (median 12%, IQR 8–21%), cardiovascular disease (median 12%, IQR 6–18%), COPD (median 4%, IQR 2–7%) and malignancy (median 3%, IQR 1–6%). A history of smoking was reported in a median of 10% of patients (IQR 6–19%).

Although most studies evaluated a range of patients with varying demographics and comorbidities, some studies focused on COVID-19 in specific patient subpopulations. They included organ transplant ($n = 6$ studies, 96 patients); obstetrics ($n = 6$ studies, 547 patients); healthcare workers ($n = 3$ studies, 107 patients); older adults ($n = 2$ studies, 309 patients); malignancies ($n = 2$ studies, 156 patients); HIV ($n = 2$ studies, 74 patients); COPD ($n = 1$ study, 1048 patients); diabetes ($n = 1$ study, 258 patients); cystic fibrosis ($n = 1$ study, 40 patients); surgery ($n = 1$ study, 34 patients); and acute kidney injury ($n = 1$ study, 30 patients).

Table 1
Predictors of antibiotic prescribing in patients with COVID-19

Characteristic	Prevalence odds ratio	95% confidence interval	Studies included
Region			154
China	reference		115
Middle East	6.05	0.29–126.87	2
East/Southeast Asia	1.94	0.38–9.88	6
Europe	0.54	0.21–1.40	18
North America	0.60	0.19–1.85	12
Multiple	0.54	0.01–21.63	1
Healthcare access/quality score (10-point increase) change)	0.77	0.46–1.28	152
End month			154
January	reference		14
February	0.61	0.29–1.88	72
March	0.37	0.11–1.24	33
April	0.28	0.08–0.98	29
May	0.45	0.05–3.71	4
Not specified	0.18	0.01–2.90	2
Setting			154
Hospital	reference		133
Hospital ICU	2.55	0.68–9.49	9
Hospital/outpatient	0.51	0.16–1.56	12
Age group			154
Adults	reference		91
Children	0.10	0.03–0.33	10
Adults and Children	0.33	0.17–0.65	41
Not specified	0.48	0.16–1.39	12
Age (10-year change)	1.45	1.18–1.77	153
Female (10% change)	0.97	0.78–1.20	154
Mechanical Ventilation (10% change)	1.33	1.15–1.54	115
Smoker (10% change)	1.08	0.68–1.72	51
COPD (10% change)	1.04	0.52–2.05	81
CVD (10% change)	1.01	0.83–1.22	115
Diabetes (10% change)	1.15	0.90–1.49	120
Deaths (10% change)	1.45	1.21–1.74	133

Severity of COVID-19 illness

Most studies evaluated hospitalized patients ($n = 133$ studies, 30 212 patients) including a mix of both general ward and critically ill patients. A smaller group of studies evaluated a mixed inpatient/outpatient population ($n = 12$ studies, 4084 patients) or patients exclusively in the intensive care unit ($n = 9$ studies, 967 patients). The median proportion of patients requiring mechanical ventilation support was 16% (IQR 5–27%), based on 114 studies that reported this variable. Among studies that reported mortality ($n = 133$), 5% (IQR 0–18%) of patients died during follow up.

Antibiotic prescribing in patients with COVID-19

Out of total of 35 263 patients, 30 623 were assessed for antibiotic prescribing, of whom 19 102 (62.4%) received at least one antibiotic agent. The random effects meta-analysis of all combined studies estimated the antibiotic prescribing prevalence 74.6% (95% CI 68.3–80.0%), with considerable heterogeneity ($I^2 = 99%$) (Fig. S1).

Of all included studies 28 (18.2%) provided data on antibiotic classes prescribed. In these studies, 4721 patients were evaluated and 2482 patients received 3058 antibiotic agents. Of ten classes of antibiotics studied, the most common antibiotic classes prescribed were fluoroquinolones ($n = 612$, 20.0%), macrolides ($n = 579$, 18.9%), β -lactam/ β -lactamase inhibitors ($n = 459$, 15.0%) and cephalosporins ($n = 459$, 15.0%) (Fig. 2). All studies provided data on the number of patients receiving antibiotics ($n = 154$); however, only five studies (3.2%) [29,33,47,51,142] provided additional metrics including duration ($n = 5$), single vs. combination therapy ($n = 1$), time to empiric antibiotic therapy ($n = 1$) and antibiotics started within 48 hr vs. antibiotics continued beyond 48 hr ($n = 1$). Antibiotic use was classified by authors as empiric or started on

admission in 49 studies (31.8%), post-admission in 13 studies (8.4%) and not specified in 92 studies (59.7%). Antibiotic stewardship strategies were reported in three studies (1.9%) [23,24,40], indicating that there were recommendations to avoid antibiotics in patients without suspected co-infection ($n = 2$) or to de-escalate antibiotics when additional data became available ($n = 1$).

Antibiotic prescribing by region

The prevalence of antibiotic use across regions had considerable heterogeneity with $I^2 = 99%$. In order of increasing prevalence of use, antibiotic prescribing in Europe was 63.1% (95% CI 41.7–80.4%), in North America (USA) 64.8% (95% CI 54.0–74.2%), in China 76.2% (66.8–82.3%), Middle East 86.0% (95% CI 77.4–91.7%) and in East/Southeast Asia (excluding China) 87.5% (47.8–98.2%) (Fig. 3).

Antibiotic prescribing by age

Antibiotic prescribing prevalence increased along with increasing age. The prevalence of antibiotic prescribing was lowest in children (38.5%, 95% CI 26.3–52.3%), moderate in all age groups combined (61.5%, 95% CI 48.3–73.3%) and highest in adults (83.4%, 95% CI 76.6–88.5%). (Fig. 4).

Antibiotic prescribing by setting/severity

Antibiotic prescribing was lowest in the mixed inpatient/outpatient setting at 59.3% (95% CI 38.7% to 77.1%), followed by the inpatient hospital setting at 74.8% (95% CI 67.8–80.7%) and highest in the ICU setting at 86.4% (95% CI 73.7–93.6%) (Fig. 5). The prevalence of antibiotic prescribing varied based on the proportion of patients requiring mechanical ventilation. Prescribing was lowest in studies not reporting ventilation status at 56.7% (95% CI

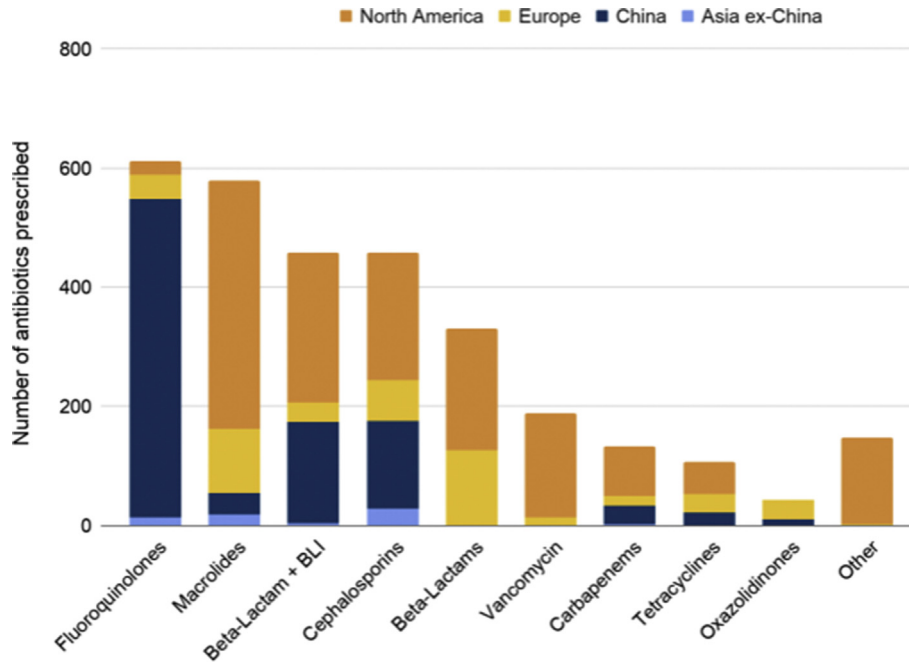


Fig. 2. Classes of antibiotic prescribing in patients with COVID-19 by region. BLI, β-lactamase inhibitor. One course of polymyxins was prescribed in China.

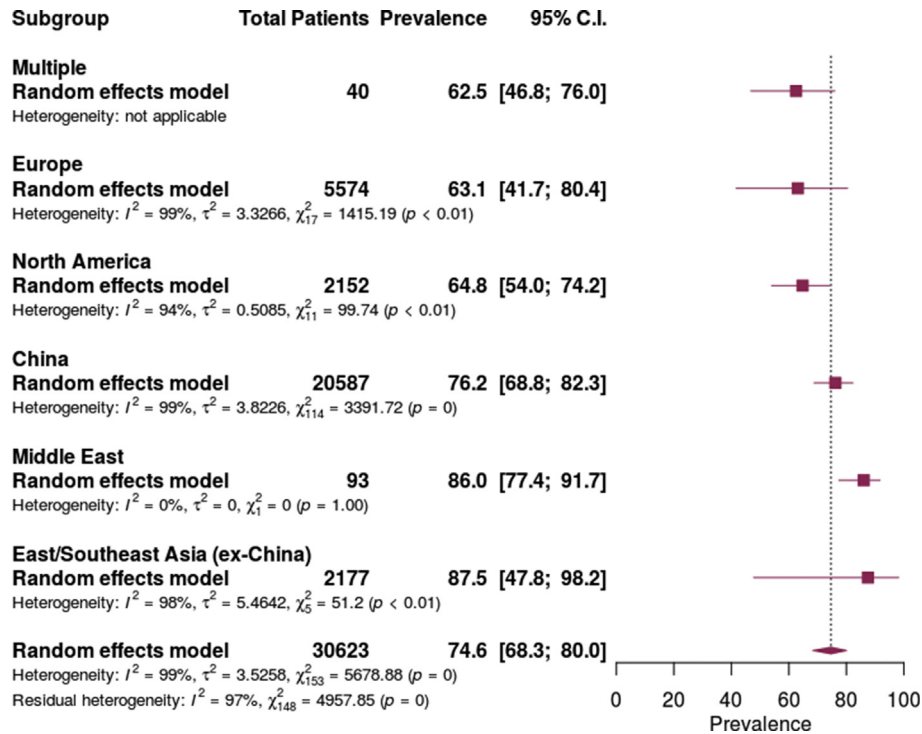


Fig. 3. Antibiotic prescribing in patients with COVID-19 by region.

41.2–70.9) and the lowest quartile of patients requiring mechanical ventilation at 64.4 (95% CI 49.8–76.8) but higher in patients in the highest three quartiles of patients requiring mechanical ventilation. (Fig. 6).

Antibiotic prescribing by date

There was a trend towards reduced antibiotic prescribing as the pandemic progressed. Studies ending enrolment and/or follow-up

in January showed the highest prescribing prevalence (85.8%, 95% CI 67.9–94.6%) and studies ending in April showed the lowest (62.6%, 95% CI 50.7–73.1%) (Fig. 7).

Sensitivity analyses

As an estimate of antibiotic prescribing data quality, studies reporting information on antibiotic classes prescribed showed numerically higher prevalence of prescribing (82.1%, 95% CI

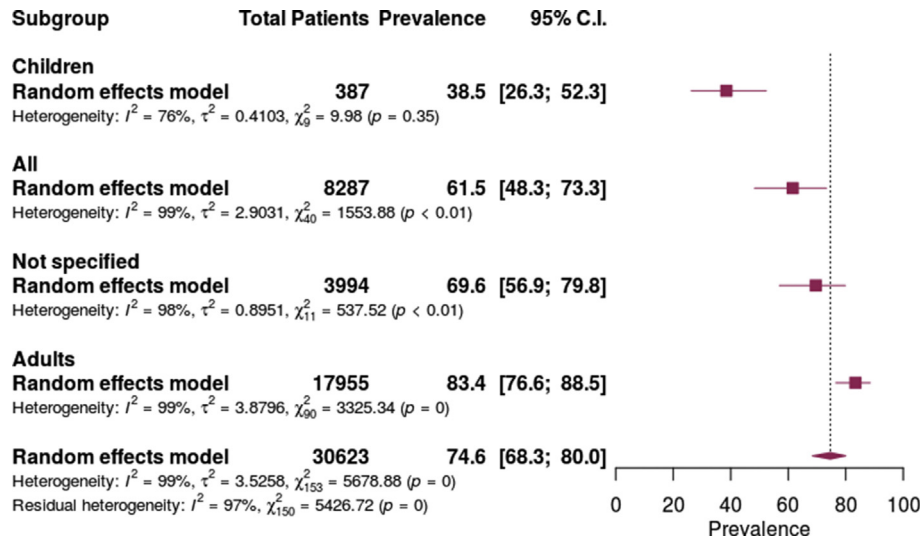


Fig. 4. Antibiotic prescribing in patients with COVID-19 by age group.

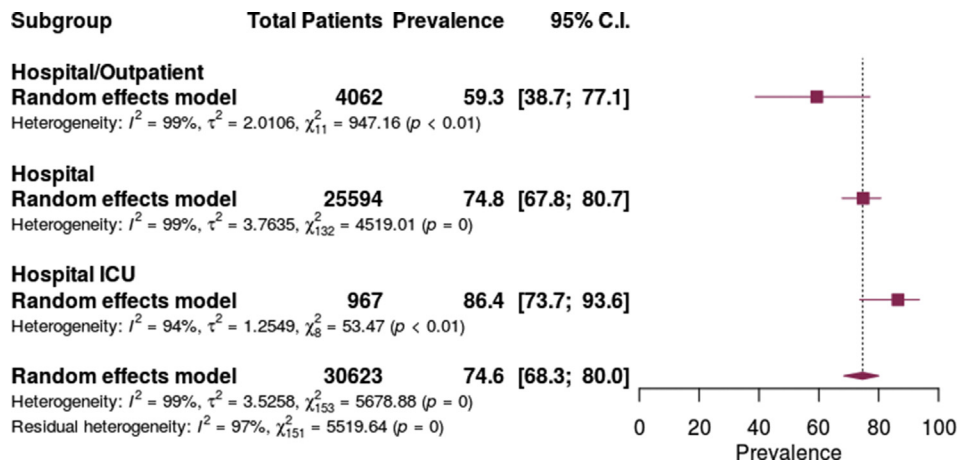


Fig. 5. Antibiotic prescribing in patients with COVID-19 by healthcare setting.

67.3–91.1%) compared with the studies that did not report this additional data (72.8%, 95% CI 65.8–78.9%). When removing studies focusing exclusively on patient populations at higher risk of antibiotic use (i.e. transplant, malignancy, obstetrics, older age, COPD, diabetes, fatal infection, HIV, acute kidney injury, surgery, dialysis and acute kidney injury, $n = 29$ studies) overall antibiotic prescribing did not differ significantly (71.8%, 95% CI 64.4–78.2%) from the overall estimate. Similarly, when removing studies with potentially overlapping patient populations ($n = 16$ studies) the estimate of antibiotic prescribing (72.5%, 95% CI 65.6–78.5%) was similar to the overall estimate (Figs S2–4).

Meta-regression antibiotic prescribing prevalence in COVID-19

In the meta-regression, geographic region was not identified as a predictor of antibiotic prescribing prevalence differences. In terms of study date, prescribing was noted to be lower in April 2020 (OR 0.28, 95% CI 0.08–0.98) than in January 2020. Antibiotic prescribing was also lower in studies evaluating children (prescribing prevalence OR 0.10, 95% CI 0.03–0.33) and combined children and adults (OR 0.33, 95% CI 0.17–0.65) compared to studies examining only adults. Antibiotic prescribing was higher with increasing

median or mean patient age (OR 1.45 per 10 year increase, 95% CI 1.18–1.77), higher with increasing proportion of patients requiring mechanical ventilation (OR 1.33 per 10% increase, 95% CI 1.15–1.54) and higher with increasing proportion of patients that died (OR 1.45 per 10% increase, 95% CI 1.21–1.74) (Table 1). Quantile–quantile plots of univariable model residuals are available in Fig. S5.

Bacterial Co-Infection or secondary infection

The number of patients with COVID-19 and concomitant bacterial infection was reported in 31 studies. Pooled data from all studies reporting bacterial infection indicated that the prevalence was 8.6% (95% CI 4.7–15.2%). There was a considerable degree of heterogeneity between studies $I^2 = 96\%$.

Discussion

In this large rapid review and meta-analysis evaluating patients with COVID-19 in the first 6 months of the global pandemic, we found that nearly three-quarters of patients received antibiotic therapy. Prescribing was very heterogeneous but overall

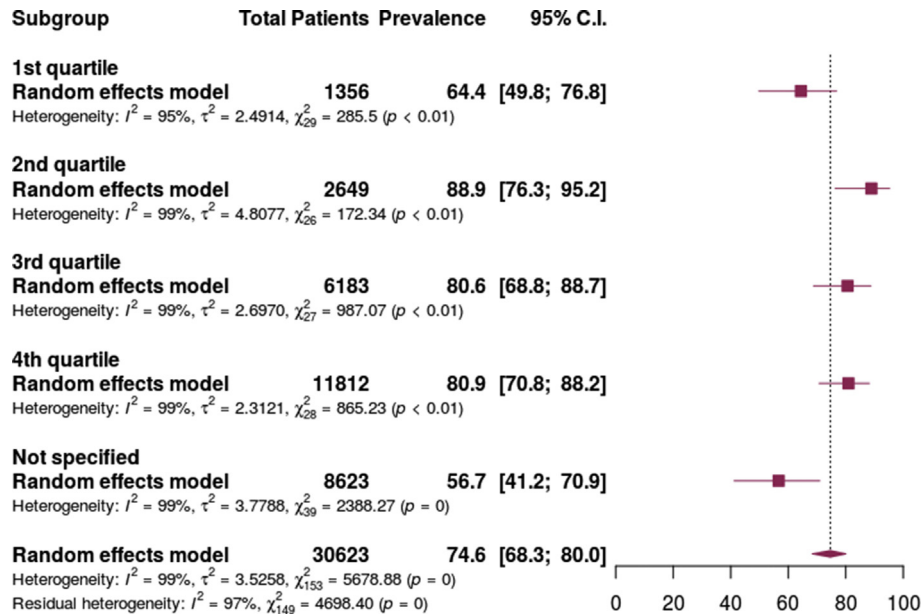


Fig. 6. Antibiotic prescribing in patients with COVID-19 by study quartile of proportion of patients requiring mechanical ventilation.

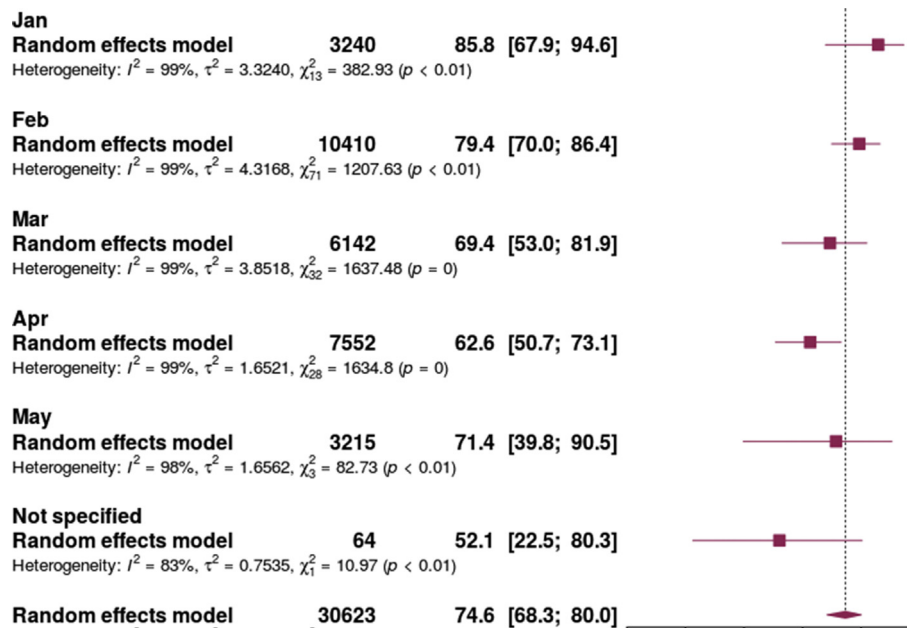


Fig. 7. Antibiotic prescribing in patients with COVID-19 by study end date.

consistently high across healthcare setting and geography. Prescribing was elevated in older age groups and those with higher severity of illness, as marked by proportion of patients requiring mechanical ventilation and fatal infections. Consistent with our data, bacterial co-infection rates for SARS-CoV-2 have been estimated between 6.1% and 8.0% [4,5,170,171]. As such, antibiotic prescribing is significantly higher than the prevalence of bacterial co-infection suggesting a large number of antibiotic prescriptions are unnecessary, increasing the risk of preventable harm including adverse events, *Clostridium difficile* infection, and antimicrobial resistance.

Although the risk of co-infection appears to be lower in patients with SARS-CoV-2 than in those with influenza, our findings raise

similar, if not greater, concerns for antibiotic overuse than in patients with influenza. On average, an estimated 23% of hospitalized patients with influenza experience bacterial co-infection [172], while antibiotic use far exceeds this estimate. In a cohort study of 322 hospitalized patients with influenza, 65.5% of patients received antibiotics on admission and 34.5% of those were continued without evidence of bacterial infection [173].

The impact of COVID-19 on global antimicrobial resistance (AMR) is uncertain, and likely to be unevenly distributed across disease epicentres and populations. Pandemic-associated changes in human behaviour and healthcare practices, including decreased travel, physical distancing, hospital and clinic avoidance, improved infection prevention and control, hand hygiene and environmental

cleaning may alleviate some of the impact of COVID-19-mediated antibiotic use on AMR [174]. However, disproportionately high use of antibiotics in patients with COVID-19 has the potential to exacerbate this public health threat [175], particularly in areas where AMR is already a significant problem, such as China [176], Italy [177] and the United States [178].

Regardless of the net impact of COVID-19 on AMR, antimicrobial stewardship principles should guide the antibiotic management of patients with COVID-19 [7]. As there is significant diagnostic uncertainty in identifying bacterial infection in patients with COVID-19, guidelines can support appropriate empiric prescribing decisions. Several guidelines advocate for the use of empiric antibiotics for patients with severe COVID-19 [179,180], whereas others have more tailored approach to antibiotic use based on patient presentation [181]. Our findings support the need for clear and consistent guidance on which patients with COVID-19 would derive greatest benefit from empiric antibiotics, and in which patients the risks of antibacterial therapy exceed the benefits. Prospective studies evaluating the role of initiating antibiotics in patients with severe COVID-19, and to identify appropriate parameters for safe antibiotic discontinuation (e.g. based on imaging, clinical criteria and/or biomarkers) are needed.

Key strengths of our review include the large number of studies spanning several months of the COVID-19 pandemic. The meta-regression identifies key factors associated with antibiotic use and highlights opportunities for improvement. Limitations include the disproportionate representation from Asia, potentially limiting the generalizability of the results to other countries affected by COVID-19. However, representation of over ten studies each from Europe and North America (USA) provides adequate data and it appears antibiotic use is consistently high across regions. Additionally, the antibiotic prescribing data are of uncertain quality and we found limited data on antibiotic prescribing details other than number of patients receiving antibiotics (e.g. antibiotic classes, duration). Further information on indication, selection, timing and duration could be helpful to better estimate the appropriateness of antibiotic therapy and the quality of the data. For example, empiric antibiotic therapy may be appropriate in severely ill patients with COVID-19 but upon follow-up with laboratory, imaging and microbiological data, antibiotic therapy can be re-assessed and discontinued promptly to prevent unnecessary exposure. Finally, we were unable to identify an appropriate risk of bias tool for this research question; however, our sensitivity analyses evaluating the quality and quantity of antibiotic data, different patient populations, and potential for study overlap were robust to our initial estimates.

Opportunities for future work include improved co-infection diagnostics, evaluation of bacterial co-infection, providing additional detail on antibiotic prescribing including timing, duration and indication, estimating antibiotic appropriateness, and identifying successful antimicrobial stewardship initiatives in patients with COVID-19.

Conclusion

Antibiotics are prescribed in three-quarters of patients with COVID-19. Given the low rate of co-infection in these patients, there is a high risk for unnecessary antibiotics. Predictors of increased antibiotic use in COVID-19 include advanced age, use of mechanical ventilation and fatal COVID-19 infections. Antimicrobial stewardship

efforts are urgently needed to help mitigate the impact of COVID-19 on antimicrobial resistance.

Transparency declaration

The authors have no conflicts of interest to declare. Funding: University of Toronto, Department of Medicine, Network Seed Funding Grant. Registration: PROSPERO (ID CRD42020192286).

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.2020.12.018>.

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