

## SYNTHESIS

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# Prevalence and Predictors of Antibiotic Prescribing in Patients with COVID-19 – What We Know So Far

## Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). “What We Know So Far” documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., [ProMED](#), [CIDRAP](#), [Johns Hopkins Situation Reports](#)) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All “What We Know So Far” documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

## Key Findings

- A meta-analysis of 154 studies including 30,623 patients with COVID-19 estimated the prevalence of antibiotic prescribing to be 74.6% (95% confidence interval [CI]: 68.3-80.0). The estimated prevalence of bacterial co-infection was 8.6% (95% CI: 4.7-15.2) from 31 studies.
- Antibiotic prescribing prevalence was higher with increasing patient age (Odds Ratio [OR] 1.45 per 10 year increase, 95% CI: 1.18-1.77) and higher with an increasing proportion of patients requiring mechanical ventilation (OR 1.33 per 10% increase, 95% CI: 1.15-1.54). There was no clear difference with respect to geographic region.
- Antibiotic prescribing is substantially higher than the estimated prevalence of bacterial co-infection, suggesting unnecessary antibiotic use is common during the COVID-19 pandemic. Antibiotic overuse is associated with increased risk of adverse drug reactions, *Clostridioides difficile* (*C. difficile*) infections, and antimicrobial resistance, which could be a potential long-term consequence of the COVID-19 pandemic. Antibiotic stewardship interventions aimed at improving appropriateness of antibiotic use in this context are needed.

## Background

Antimicrobial overuse is associated with adverse drug events, *C. difficile* infections, and antimicrobial resistance. Concerns have been raised about the long-term impacts of the COVID-19 pandemic on

antimicrobial resistance due to potential antibiotic overuse in patients with COVID-19.<sup>1,2</sup> This is based on initial studies indicating that antibiotics are frequently prescribed to patients with COVID-19 despite a relatively low prevalence of bacterial co-infection (less than 10%).<sup>3-5</sup> To mitigate inappropriate antimicrobial use in patients with COVID-19, identifying opportunities for antibiotic stewardship interventions in this population will be crucial. A rapid systematic review was performed to determine the prevalence of antibiotic use and identify factors associated with antibiotic use in patients with COVID-19.

## Methods

A systematic search of MEDLINE, OVID Epub and EMBASE databases for English language literature published between January 1, 2019 to June 9, 2020 was performed. See Langford et al.<sup>6</sup> for a detailed description of methodology.

- Studies of individuals with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection across all healthcare settings and age groups were included. Randomized controlled trials (not evaluating antibiotic use as an intervention); cohort studies; case series with >10 patients; experimental or observational designs were included. Reviews, editorials, letters, case reports, and studies that did not report data on the number and percentage of patients receiving antibiotic use were excluded.
- The main outcome of interest was prevalence of antibiotic prescribing, defined as the number of patients prescribed at least one antibiotic during the course of their illness while under study observation, as a proportion of all patients with COVID-19. Prevalence was then stratified by geographical region, severity of illness (proportion of mechanically ventilated), study population (critically ill, hospitalized patients, mixed hospitalized/outpatient population), and age.
- Data were pooled using a random effects meta-analysis and univariable meta-regression was performed to predict the effect of specific patient characteristics on antibiotic prescribing.

## Results

Of 16,378 studies identified, after removal of duplicates, 7469 publications were screened. After screening, 154 studies (35,263 patients) were included in the final analysis.

- Most were retrospective cohort studies (n=135) and most took place in China (n=115). Studies were conducted between December 8, 2019 and May 21, 2020.
- The majority of studies included adults (n=132, 86%). The median proportion of females was 45% (interquartile range [IQR]: 39-51). Commonly reported comorbidities included diabetes (median 12%, IQR: 8-21), cardiovascular disease (median 12%, IQR: 6-18), chronic obstructive pulmonary disease (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). Some studies focused on specific patient subpopulations including obstetrical patients, healthcare workers, older adults and those with chronic conditions.
- Most studies included hospitalized patients (n=133, 30,212 patients). Fourteen studies evaluated a combined hospitalized and non-hospitalized outpatient population. While there were 9 studies focused on patients in the intensive care unit, there were no studies focusing on individuals residing in long-term care homes and no studies focusing exclusively on outpatients.

The median proportion of patients requiring mechanical ventilation support was 16% (IQR: 5-27, reported in 114 studies) and mortality was 5% (IQR: 0-18, reported in 133 studies).

## Prevalence of Antibiotic Prescribing in Patients with COVID-19

Of 35,263 patients, antibiotic data were available for 30,623 patients.

- The overall antibiotic prescribing prevalence was estimated to be 74.6% (95% CI: 68.3-80.0). Bacterial co-infection was estimated at 8.6% (95% CI: 4.7-15.2) from 31 studies.
- The prevalence of antibiotic prescribing was 63.1% (95% CI: 41.7-80.4) in Europe, 64.8% (95% CI: 54.0-74.2%) in North America (United States), 76.2% (95% CI: 66.8-82.3) in China, 86.0% (95% CI: 77.4-91.7) in the Middle East, and 87.5% (95% CI: 47.8-98.2) in East/Southeast Asia (excluding China).
- Twenty-eight studies (18.2%) provided data on antibiotic classes prescribed. The most common antibiotic classes prescribed were fluoroquinolones (20.0%), macrolides (18.9%), beta-lactam/beta-lactamase inhibitors (15.0%) and cephalosporins (15.0%).

## Predictors of Antibiotic Prescribing in Patients with COVID-19

The results of the meta-regression found the following predictors of antibiotic prescribing:

- Geographic region was not identified as a predictor of antibiotic prescribing prevalence differences; however, prescribing was lower in April 2020 compared to January 2020 (OR 0.28, 95% CI: 0.08-0.98).
- Patient sex (as measured by the proportion of female patients) and the proportion of patients with comorbidities (i.e., cardiovascular disease, diabetes, and COPD) were not associated with antibiotic prescribing.
- Antibiotic prescribing prevalence was lower in studies evaluating children (prescribing prevalence OR 0.10, 95% CI: 0.03-0.33), compared with studies examining only adults and higher with increasing median or average patient age (OR 1.45 per 10 year increase, 95% CI: 1.18-1.77).
- Compared to hospitalized patients, antibiotic prescribing was lower in mixed inpatient/outpatient populations (OR 0.51, 95% CI: 0.16-1.56).
- Antibiotic prescribing was higher with increasing proportion of patients requiring mechanical ventilation (OR 1.33 per 10% increase, 95% CI: 1.15-1.54), and with increasing proportion of patients that died (OR 1.45 per 10% increase, 95% CI: 1.21-1.74).

## Antimicrobial Stewardship Implications

This review found that antibiotics are prescribed in about three-quarters of patients with COVID-19 despite the low rate of co-infection, suggesting that there is a substantial amount of unnecessary antibiotic prescribing in this population. While most studies included in this review focussed on the hospital setting, in general, there is no proven benefit to using antibacterial agents in patients with COVID-19 in patients without bacterial co-infection.<sup>7</sup> Antimicrobial stewardship interventions can play a key role in helping to mitigate the potential impact on antimicrobial resistance in hospital and other healthcare settings including long-term care homes.

Antibiotic stewardship strategies were reported in only three studies in the review:<sup>8-10</sup>

- Two studies indicated that there were recommendations in place to avoid antibiotics in patients without suspected co-infection.
- One study reported reassessment and de-escalation of antibiotics when clinical additional data became available.

Additional strategies that have been highlighted in the literature to limit unnecessary use include:<sup>11</sup>

- Avoiding empiric antibiotic prescribing in confirmed COVID-19 patients with a low risk of bacterial co-infection.
- Obtaining microbiological tests before initiation of antibiotic therapy and selection of empiric therapy based on local epidemiology.
- Evaluating the appropriateness of therapy including route (i.e. intravenous to oral stepdown) and duration of therapy where continuation of antibiotic treatment is deemed necessary.

## Conclusion

Antibiotic prescribing occurs in three quarters of patients with COVID-19 despite the low rate of bacterial co-infection (<10%) in this population. Antimicrobial stewardship efforts in patients with COVID-19 in all healthcare settings are essential to help prevent the harms of antibiotic overuse during the pandemic.

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