

Systematic Review

An umbrella systematic review of antibiotics therapy in COVID-19 patients: implications for antimicrobial resistance

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Received: 06 April 2025

Accepted: 02 May 2025

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ABSTRACT

Evidence from public health bodies describes extensive overuse of antibiotics during the COVID-19 pandemic worldwide, further worsening the spread of antimicrobial resistance (AMR). Umbrella review (CRD42024590181) of SRs that investigated the safety and efficacy of antibiotic drug therapies for treatment in COVID-19 patients irrespective of disease severity and age was conducted. Comprehensive searches were conducted between July 30, 2024, and October 26, 2024, covering PubMed and Cochrane databases, and other sources, such as, Coronavirus (COVID-19) Cochrane resources, and Google Scholar. The AMSTAR2 tool was used to assess the methodological quality of the included SRs. Review findings were synthesized narratively. The systematic search yielded a total of 3624 records from the electronic databases search. Ten original SRs, with 1-42 studies in each SR, were finally included. Sample size per SR ranged from 665-37,429 patients. Azithromycin was the most commonly administered antibiotic therapy. Overall, the studies included in this review reported no difference in all-cause mortality, time to clinical recovery, length of hospital stay, progression to severe disease, viral clearance, rate of co-infections or superinfections, and adverse events among patients treated with antibiotics compared to placebo/standard of care. Evidence suggests that use of antibiotics in COVID-19 patients is not associated with better outcomes. Further studies assessing prevalence of AMR and antibiotic usage during COVID-19 infection could aid in improving antimicrobial stewardship in clinical practice.

Keywords: Antimicrobial resistance, Antibiotics, COVID-19, SARS-COV-2, Infections, Global health

INTRODUCTION

Previously regarded as inconsequential, the human coronavirus became a defining health crisis of the 21st century when the severe acute respiratory syndrome Coronavirus (SARS-CoV) emerged from Wuhan, China in late December 2019 and transmitted globally, resulting

in alarming morbidity and mortality.¹ In 2020-2021 alone, deaths caused by Coronavirus disease 2019 (COVID-19) worldwide were estimated to be 14.8 million.² As of 2024, the COVID-19-induced death toll has reached a staggering 7 million.³ Throughout the pandemic, a multitude of therapeutic agents were employed against the RNA virus such as antivirals and immune therapies in

early stages of disease to corticosteroids and immune inhibitors in later stages of disease. However, current guidelines do not recommend the use of any of these treatments.⁴⁻⁷

During the first COVID-19 wave, uncertainty around the disease process, challenges in distinguishing between COVID-19 and bacterial pneumonia, a rapid increase in critically ill patients, and past experiences with bacterial coinfection in the setting of viral illness (such as the 1918 Spanish flu) led to a rise in empirical antibiotic use.⁸ While only 8% of COVID-19 patients actually developed secondary bacterial infections, the use of broad-spectrum antibiotics was very high as 72%.⁹ The most frequently used classes of antibiotics during the pandemic were macrolides, fluoroquinolones, and cephalosporins chosen for their efficacy against pneumococcal, atypical, and gram-negative respiratory infections.^{10,11} This injudicious use of antibiotics, fueled concerns about the rise of multidrug-resistant organisms. Prior to the pandemic, macrolides had already been a focus of antibiotic stewardship efforts due to their high potential for developing resistance.¹²

Antimicrobial resistance (AMR) is a major global health threat with severe human and economic consequences. According to the centres for disease control and prevention, AMR rates increased by 20% in 2021-2022, peaking in 2021.¹⁵ *Candida auris* cases, in particular, rose five times from 2019 to 2022.¹³ Recent meta-analyses report that during the pandemic, multidrug resistance (MDR) incidence rates increased from 24% to 37.5% between 2019 and 2021.

The highest resistance rates were observed in *Stenotrophomonas* spp., *Acinetobacter* spp., and *Klebsiella* spp.^{14,15} In the hierarchy of evidence, systematic reviews (SRs) are regarded as the highest level of evidence and are crucial for making well-informed decisions. With a growing number of SRs, especially for rapidly evolving diseases like COVID-19, having variable scopes and methodological quality, it is vital to have overviews that can further organize the literature, assess the quality of SRs and pinpoint key areas for decision-making.¹⁶

An umbrella review of SRs and meta-analyses was conducted to summarize and synthesize the existing evidence on antibiotics used for COVID-19 treatment. This review also aims to identify and present the types and trends of antibiotic classes evaluated in SRs over time for COVID-19 patients. The manuscript further weighs risks versus benefits of using antibiotic therapies in COVID-19 patients in the context of the evolving AMR dilemma.

METHODS

The protocol for this overview is registered with PROSPERO (CRD42024590181).

Inclusion exclusion criteria

We considered SRs that investigated safety and efficacy of antibiotic drug therapies for treatment in COVID-19 patients irrespective of disease severity and age.

Authors considered SRs on COVID-19 at any stage of disease severity, from asymptomatic to severe cases, and in any setting (outpatients and hospitalized patients). We considered for inclusion in this overview SRs irrespective of types of study designs included.

Targeted reviews with no clear methodological approach were excluded from this overview. SRs evaluating other drug therapies, vitamins or mineral interventions, Chinese medicine, herbal treatments and non-pharmacological therapies, including convalescent plasma therapies, were excluded. SRs evaluating post-exposure prophylaxis for COVID-19 were also excluded.

Information sources and search strategy

Keyword searches were conducted in PubMed and Cochrane databases. The search was supplemented with other sources like of Cochrane COVID-19 resource, Google Scholar, and cross-referencing of identified reviews. Comprehensive search strategies were developed using keywords for COVID-19, drug therapy, and SRs, as shown in the supplement.

Search terms were not restricted to antibiotic keywords to ensure that SRs reporting combined therapies, including antibiotics, are not missed during the search.

The electronic databases were searched for records published between January 1st, 2020, and July 30th, 2024, followed by an additional literature search on October 26th, 2024. The publications were restricted to English language publications only.

Screening and selection

The records retrieved by the searches were screened for relevance based on predefined eligibility criteria. The screening was conducted in duplicate by two reviewers at title/abstract stage and full text stage. Any disagreements or conflicts were resolved through discussion or by a third reviewer if needed.

Data items, collection, and quality assessment

A standardized data extraction form was used to extract data from included reviews.

The extraction form included general review characteristics, description of the target population, drug name and classification, comparators assessed, and data on outcomes and intervention effectiveness and safety. The overview aims to summarize the following outcomes.

Mortality rates

Overall survival or death rates in patients treated with antibiotics.

Time to clinical recovery

Duration taken for patients to recover from COVID-19 symptoms.

Hospitalization duration

Length of hospital stay.

Progression to severe disease

Whether patients progress from mild/moderate to severe COVID-19 symptoms.

Viral clearance

Time taken for SARS-CoV-2 to be undetectable in patients' samples (e.g., PCR tests).

Respiratory support requirements

Need for and duration of mechanical ventilation or oxygen therapy.

Incidence of secondary infections

Rate of co-infections or superinfections during antibiotic treatment.

Inflammatory markers

Changes in any inflammatory biomarkers.

Adverse events

Incidence and severity of any side effects associated with antibiotic use.

Quality of included SRs

The AMSTAR2 tool was used to assess the methodological quality of the included systematic reviews. Subsequently, the reviews were rated as high (No or one non-critical weakness), moderate (More than one non-critical weakness), low (One critical flaw with or without non-critical weaknesses), critically low (More than one critical flaw with or without non-critical weaknesses).

Full-text data extraction and quality assessment for all included reviews was conducted independently by 2 reviewers.

Data analyses

Review findings are synthesized narratively, and a quantitative analysis was not performed. The qualitative synthesis provides a breakdown of publication years of SRs, types of antibiotic drugs assessed in different severities of COVID-19, populations included, and countries of origin, the outcomes assessed and overall conclusion on effectiveness and safety of antibiotics for COVID-19 in literature.

RESULTS

SR study selection

The systematic search yielded a total of 3624 records from the electronic database search. After the removal of duplicates, 3591 records were assessed for eligibility based on title and abstract. After exclusion of 3582 records on title and abstract screening, a total of nine records were assessed for eligibility on full text. One study was excluded on full-text review due to not reporting outcomes of interest. Additionally, literature search from other sources was conducted on the 26th of October 2024, which identified two recent SRs. A total of 10 reviews that reported use of antibiotics in COVID-19 patients were finally included as part of the qualitative synthesis.¹⁷⁻²⁶ The PRISMA study selection process is summarized in Figure 1.

Characteristics of included SRs

All SRs were original reviews with no updates done by the authors. A summary of the included SR characteristics is presented in Table 1. The included studies in this review span a publication period from 2020-2024, with 1 study each published in 2023, 2022, and 2020, five studies were published in 2021 and two in 2024.

Six SRs further supplemented findings with meta-analysis with one of these reporting a network meta-analysis. The searches in the included SRs targeted a larger number of databases with the latest search date in one of the SR as of 31 March, 2024. The number of studies included in the SRs varied from one study in a SR from 2020 to 42 studies from a SR published in 2023. Majority of the SRs included both randomized and nonrandomized study designs. Only one SR included only hospitalized patients whereas all other SRs included patients from both, inpatient and outpatient settings.²⁰

The total sample size per SR ranged from 665 to 37,429. Six SRs also included patients under the age of 19 years. The included studies in the SRs reported a mix of patients with outpatient and inpatient settings. The included SRs considered articles without geographic restrictions. As per the World Bank Country classification, the included SRs were able to include studies from a high-income to low-middle-income countries with paucity of studies

conducted in low-income settings and studies from Africa.

Azithromycin was the most investigated antibiotic therapy in the included SRs. Other classes of antibiotics examined included penicillin, tetracyclines, cephalosporins and antimalarials. The outcomes reported included all-cause mortality, time to clinical recovery, length of hospital stay, progression to severe disease, viral clearance, respiratory support requirement, rate of co-infections or superinfections, inflammatory markers, and adverse events.

Summary of the effects and safety of interventions

Overall, the studies included in this review reported no clinical indication or superiority of using antibiotics over the standard of care/placebo as shown by comparable clinical efficacy outcomes and safety profiles. Azithromycin was the most commonly administered antibiotic therapy with mortality as the most commonly assessed clinical outcome.

Two SRs were published during 2024, which assessed efficacy of using antibiotics in COVID-19 patients.^{25,26} The SRs reported no significant improvement in clinical outcomes such as ICU admission rates, disease progression, length of stay, ventilator-associated pneumonia, in patients receiving Hydroxychloroquine plus Azithromycin, or Azithromycin alone when compared to standard of care.

In 2023, Debela et al published the only network meta-analysis and the largest of the included studies in this review.²² It comprised more than 37,000 patients from a total of 68 included studies. It reported Baricitinib plus Remdesivir to be more effective than other drugs in terms of clinical recovery at 14 days in COVID-19 patients. Analysis with regards to Azithromycin reported non-significant results for adverse events and mortality outcomes. In 2022, Granata et al published a systematic review with more than 26,000 patients which included the pediatric population as well.²³ It recommends that antibiotics should not be prescribed at home or for treating COVID-19 inpatients outside of RCTs.

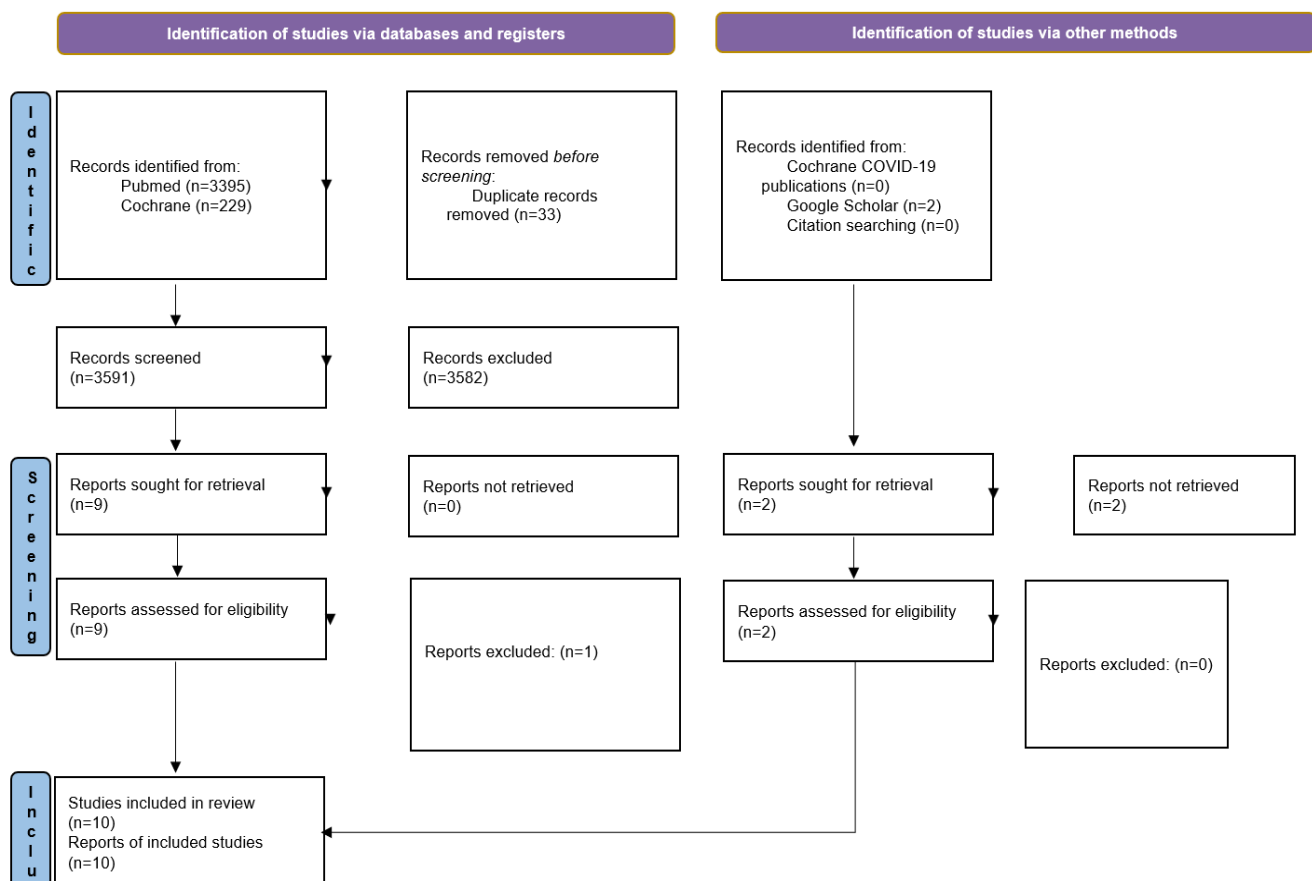


Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

Table 1: Characteristics of included systematic reviews (n=10).

Study (author, year)	Search date	No. Of databases searched	Total number of studies (n) and study designs included	Total number of patients included (n) and characteristics of study population.	Countries	Interventions assessed	Outcomes assessed	Conclusion	Amstar2 rating
Meta-analysis									
Ayerbe et al, 2021	July 5, 2021	6	16 (11 nrs and 5 RCTS)	22984 (most were inpatients)	USA, Spain, Turkey, Brazil, Uk, Iran, Spain, Italy, France.	Azithromycin vs standard of care	Mortality, length of hospital stay, care, hospital admission.	This study showed no difference in mortality and does not support the use of azithromycin in the management of COVID-19. They also show no evidence of any harm caused to patients who received it.	Low
Bhowmick et al, 2021	Feb 16, 2021	5	19 (12 NRS and 7 RCTS)	8754 (patients with multiple stages of covid-19)	Spain, Brazil, Usa, Peru, Iraq, Bangladesh, Italy, Egypt.	Ivermectin and doxycyclin as monotherapy and in combination vs standard care in seven and three studies respectively, two studies were placebo controlled; six studies did not have a comparator.	Duration of hospital stay, mortality, clinical progress or deterioration, requirement of oxygen or ventilator support, and days to clinical or symptomatic recovery, impact on viral load, safety.	Evidence is insufficient to either promote or refute the efficacy of IVM, doxy, or their combination in COVID-19 management.	Low
Kamel et al, 2021	Feb 12, 2021	7	7 RCTS	8822(four trials were conducted in hospital settings, and three trials were conducted in community settings. Only two studies included patients with severe COVID-19)	UK, Brazil, Qatar, Iran.	Azithromycin vs standard of care.	All-cause mortality up to 30 days, need for invasive mechanical ventilation, length of hospital stay, safety.	This study showed that the use of AZM was not associated with mortality, time to discharge, length of stay or the need for IMV in COVID-19 patient.	Critically low
Mangkul-iguna et al, 2021	March 2021	4	17 (12 NRS and 5 RCTS)	19189 (adults aged 45 to 83 years. Included patients had common	Italy, USA, Brazil, France, Qatar, Spain,	Azithromycin monotherapy or in combination vs the best available	Clinical improvement, hospitalization period, mortality,	Azithromycin did not result in a superior clinical improvement in COVID-19 patients, although it was well	Low

Continued.

Study (author, year)	Search date	No. Of databases searched	Total number of studies (n) and study designs included	Total number of patients included (n) and characteristics of study population.	Countries	Interventions assessed	Outcomes assessed	Conclusion	Amstar2 rating
				underlying conditions such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and cardiovascular disease. The severity of covid-19 ranged from mild to severe)	Uk, turkey.	therapy.	safety.	tolerated and safe to use.	
Popp et al, 2021	June 14, 2021	8	11 RCTS	11,281(mean age 54 years and 64% male, moderately ill patients according to who 4 to 5 and moderate to severe covid-19 according to who scale 4 to 7)	Brazil, usa, turkey, uk, qatar, egypt, iran.	Azithromycin, clarithromycin, lincomycin vs standard of care (only 2 studies used placebo)	All-cause mortality, serious adverse event, clinical status, and quality of life.	This study showed that the risk of death in covid-19 patients is not reduced by treatment with azithromycin. However, in the context of antimicrobial resistance, antibiotics should not be used for treatment of covid-19 outside well-designed rcts.	High
Network meta-analysis									
Debela et al, 2023	April 30, 2022	6	42 rcts	37429(mean age of 50.1years and 77% male)	China, Egypt, Nigeria, Brazil, UK, Hong Kong, Pakistan, Russia, Iran, India, Oman, US, France, Bangladesh, Guangzhou, Colombia.	Arbidol, azithromycin, baloxavir marboxil, baricitinib, chloroquine, daclatasvir, favipiravir, hydroxychloroquine, ivermectin, lopinavir–ritonavir, ribavirin, sofosbuvir, remdesivir, all as monotherapy and in combination vs	Time to clinical recovery, adverse events, all-cause mortality.	This study showed that ivermectin was the best top drug in terms of increasing clinical recovery rate at 14 days and azithromycin when used in combination had lower risks of ratio in terms of mortality than treating with standard of care.	Low

Continued.

Study (author, year)	Search date	No. Of databases searched	Total number of studies (n) and study designs included	Total number of patients included (n) and characteristics of study population.	Countries	Interventions assessed	Outcomes assessed	Conclusion	Amstar2 rating
						standard of care			
No meta-analysis									
Granata et al, 2024	1 January 2022 to 31 March 2024	2	4 (3 NRS and 1 RCT)	6570(both outpatients and inpatients with varying disease severity)	Italy, China, India	Doxycycline, azithromycin, suspension containing tobramycin sulfate, colistin sulfate, and amphotericin b vs standard of care (3 trials) and placebo (in 1)	Icu admission, disease progression, length of stay, ventilator associated pneumonia, safety.	Azithromycin does not improve disease progression and length of stay in covid-19 patients	Critically low
Sansone et al, 2024	December 2023	3	3 rcts	8877 hospitalized patients	Brazil, UK	Hydroxychloroquine plus azithromycin, and azithromycin alone versus standard of care	Clinical scores, clinical status and 28-day all-cause mortality.	Insignificant clinical improvement with hydroxychloroquine plus azithromycin, or azithromycin alone when compared to standard of care	Critically low
Granata et al, 2022	From January 2020 to October 30, 2022	2	36 (28 NRS and 8 RCTS)	26163 (mild moderate and severe, including outpatient and hospitalized.)	Brazil, UK, Egypt Denmark, US, Netherlands, Spain, Italy, Europe.	Azithromycin, clarithromycin, hydroxychloroquine , doxycycline vs standard of care	Clinical recovery, mortality, hospital admission rate, length of hospital stay, adverse events.	This study showed that antibiotics should not be prescribed during covid-19 unless there is a strong clinical suspicion of bacterial coinfection or superinfection as shown by no significant efficacy in inpatient and outpatient settings.	Critically low
Verdejo et al, 2020	August 6, 2020	39 (love platform)	1 RCT	432(hospitalized patients)	Brazil.	Azithromycin in combination with hydroxychloroquine compared to hydroxychloroquine alone vs placebo	All-cause mortality, need for ventilation or oxygenation, length of hospital stay, time to recovery, adverse events.	Macrolides in the management of patients with covid-19 showed no beneficial effects compared to the standard of care.	Low

Table 2: Summary of clinical guidelines' main recommendations on antibiotic treatment in COVID-19 patients.

Guideline	Last update	General recommendations on antibiotic treatment	COVID-19 Inpatients	COVID-19 Outpatients
World Health Organization (WHO)	November 2021	Antibiotic therapy not recommended in patients with mild COVID-19. In patients with moderate COVID-19 antibiotics should not be prescribed unless a bacterial infection is suspected	In patients with severe COVID-19, the guideline recommends empiric antibiotic treatment, based on clinical judgment, patient host factors and local epidemiology, as soon as possible	Guideline recommends considering empiric antibiotic treatment in the elderly, particularly in long-term care facility setting
National Institutes of Health (US)	May 2022	Empiric antibiotic treatment is not recommended	Guideline recommends following the guidelines established for non-COVID-19 patients	Antibiotic treatment is not recommended
The European Centre for Disease Prevention and Control (Europe)	February 2022	Consider antibiotic treatment only if bacterial coinfection is suspected/confirmed	Routine azithromycin administration is not recommended	Antibiotic treatment only if bacterial coinfection is suspected/confirmed
The National Institute for Health and Care Excellence (UK)	April 2022	Consider antibiotic administration only if bacterial coinfection is suspected or confirmed	Consider antibiotic administration only if bacterial coinfection is suspected or confirmed	Doxycycline is not recommended
Italian Society of Anti-infective Therapy and Italian Society of Pulmonology (Italy)	July 2021	Antibiotic administration is not recommended in the absence of a proven bacterial infection	Consider empirical antibiotic treatment if radiological signs of pulmonary consolidative lesions. Collection of samples for culture or molecular detection before antibiotic administration is recommended	Azithromycin is not recommended

In 2021, all five of the included studies had conducted meta-analyses. Ayerbe et al, published the largest study in this year's category with around 23,000 patients including the pediatric population.¹⁷ This study reported no difference in mortality in patients treated with or without azithromycin (OR: 0.95, 95% CI: 0.79-1.13). Bhowmick et al. publishing in the same year with a patient population of more than 8,000 patients reported no major safety concerns whilst concluding lack of strong evidence to report efficacy of ivermectin and doxycycline used alone or in combination.¹⁸ Kamel et al reported in their study of more than 8,000 patients that azithromycin compared to standard care was not associated with mortality (OR: 0.96, 95% CI: 0.88-1.05) in COVID-19 patients.¹⁹ This study aligns with the other included studies of our review that there is a lack of evidence on the efficacy of azithromycin hence is not recommended as a treatment. Mangkuliguna et al, report in their meta-analysis of more than 19,000 patients that mortality rate (OR: 0.95, 95% CI: 0.76-1.19), risk of secondary infection (OR: 1.23, 95% CI: 0.83-1.82), hypoglycemia (OR: 0.73, 95% CI: 0.38-1.40), and gastrointestinal problems (OR: 1.03, 95% CI: 0.73-1.45), did not significantly differ in Azithromycin group compared to control group hence the efficacy did not prove superior whilst the safety profile was favorable.²⁰

Popp et al, in their Cochrane systematic review of more than 11,000 patients reported that all-cause mortality (RR: 0.98, 95% CI: 0.90-1.06) and any adverse events (RR: 1.20, 95% CI: 0.92-1.57) during the study period, showed no difference in moderate to severe COVID-19 patients between azithromycin versus placebo/standard care.²¹ Further analysis of mild to asymptomatic COVID-19 patients yielded similar results. Lastly in 2020, Verdejo et al. published the only living and earliest SR reported in our study.²⁴ It comprised the lowest population size of 665 patients. It reported lower all-cause mortality in patients using azithromycin plus hydroxychloroquine versus hydroxychloroquine alone. Given this study included only 1 study, the results remain inconclusive.

Quality assessment of SRs (AMSTAR grading)

AMSTAR2 assessment was performed for the included SRs. Five SRs were assessed as of low quality, four SRs were of critically low quality while only one SR was assessed as of high quality. Most of the reviews were downgraded primarily for three weaknesses; no explanation of the study designs included, not providing a list of excluded studies and justifying their exclusions, and not reporting sources of funding for the studies included in the reviews. Additional details of assessments can be found in the supplement.

DISCUSSION

Main findings

This umbrella review includes 10 SRs published between the years 2020 and 2024, six of which were supplemented by meta-analyses. The sample sizes of these reviews ranged from 665 to over 37,000 patients. We found that azithromycin was the most commonly investigated antibiotic, with outcomes assessed including all-cause mortality, time to clinical recovery, length of hospital stay, progression to severe disease, viral clearance, respiratory support requirements, rates of co-infections or superinfections, inflammatory markers, and adverse events. Of all the included SRs, only one was deemed as of high quality.

The SRs conducted in 2024 found no significant improvement in progression of disease, ICU admissions, or ventilator-associated pneumonia among patients receiving azithromycin compared to those who did not receive azithromycin.^{25,26} Similarly, the 2023 network meta-analysis of over 37,000 patients reported no significant effect of azithromycin on mortality or adverse events.²² Earlier reviews also reported no improvements in clinical outcomes or safety profiles. Hence, the studies included in our umbrella review did not find any evidence supporting the use of azithromycin for improving clinical outcomes in patients with COVID-19.

Overuse of antibiotics during the COVID-19 pandemic and AMR

AMR is a growing global health threat by 2050, AMR is expected to result in 1.91 million deaths worldwide, with South Asia and Latin America projected to experience the highest mortality rates.²⁷ This was exacerbated during the pandemic, during which World Health Organization (WHO) reported widespread overuse of antibiotics in patients hospitalized with COVID-19 between 2020 to 2022, where only 8% of hospitalized patients with COVID-19 had bacterial co-infections requiring antibiotics, but 75% of patients were treated with antibiotics.²⁸

During the pandemic, antimicrobial resistance in the U.S. rose by 15%, with significant increases in carbapenem-resistant *Acinetobacter* (78%) and multidrug-resistant *Pseudomonas aeruginosa* (32%), as well as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).²⁹

Azithromycin was the most commonly administered antibiotic across the included systematic reviews. While large-scale randomized clinical trials, such as the RECOVERY and PRINCIPAL trials, have shown that azithromycin is ineffective in the treatment of COVID-19

both in the community and in hospitals-its empirical use persists widely.^{30,31}

This was demonstrated by the latest SRs by Granta et al, which discussed the widespread use of antibiotics during the pandemic, with usage rates ranging from 12% to 83%, despite the prevalence of coexisting bacterial infections being reported at only 3.6% to 17%.²⁵

Additionally, a retrospective cohort study in 2022 found that azithromycin use in patients with COVID-19 and pre-existing cardiovascular disease was significantly associated with an increased risk of acute heart failure and all-cause 30-day mortality, thus highlighting the importance for heightened vigilance when prescribing azithromycin.³²

This overuse of antibiotics seen during the pandemic can be attributed to several factors, such as the widespread panic worldwide owing to the unfamiliar nature of COVID-19, the overlap of symptoms with pneumonia and increased mortality rates.³³ Another study by Rawson et al also suggested that increased telehealth services contributed to excessive antibiotic use, as proper diagnostic criteria were unavailable due to the unknown nature of disease progression.³⁴ The widespread use of antibiotics during the COVID-19 pandemic accelerated the rise of AMR.

A SR by Yang et al that analyzed 173 studies involving 892,312 COVID-19 patients, found that 42.9% had multidrug-resistant organisms (MDROs), with the highest prevalence in the Middle East and North Africa (63.9%).³⁵ Antibiotics were used in 76.2% of patients, predominantly in South Asia (92.7%), with usage and MDRO prevalence higher in low- and middle-income countries. Therefore, it is important to highlight how these findings emphasize the need for improved antimicrobial stewardship to mitigate risks in future pandemics.

Comparison with existing guidelines

Table 2 provides a summary of recommendations on antibiotic use in COVID-19 from key organizations which was adapted from a SR by Granta et al (23). These guidelines on antibiotic use in COVID-19 emphasize the need for controlled administration to combat antimicrobial resistance.

The WHO advises against antibiotics for mild or moderate COVID-19 unless bacterial infection is suspected, with empiric treatment considered in severe cases or for elderly patients in long-term care facilities. On the other hand, the guidelines by NIH discourage empiric antibiotic use, recommending adherence to standard bacterial infection protocols for inpatients and no antibiotics for outpatients.

The European centre for disease prevention and control (ECDC), National institute for health and care excellence (NICE) and Italian guidelines recommend antibiotics only for suspected or confirmed bacterial coinfections, explicitly advising against routine use of azithromycin or doxycycline. Our studies findings are consistent with these guidelines which do not support the use of antibiotics especially Azithromycin because there is no improvement in clinical outcomes with a probability of treatment associated adverse effects.

Strengths and limitations

We conducted an extensive search for SRs across multiple sources, including studies having patients from both inpatient and outpatient settings, and also included adults and pediatric patients. Furthermore, we also used the AMSTAR-2 tool to ensure the quality of the included SRs. However, despite these efforts, there was a lack of studies from low-income countries, which limits the generalizability of the findings to these populations and interpretation of results.

Additionally, inconsistencies in defining bacterial coinfection and superinfection were evident, with some studies offering insufficient detail. Variability in the definitions of primary and secondary outcomes likely contributed to the substantial heterogeneity observed in certain results. Furthermore, some studies included meta-analyses while others did not, affecting the heterogeneity of the results.

Furthermore, only one of the 10 SRs was assessed as of high quality and there was an overlap in studies included across different systematic reviews. Lastly, the publications were restricted to English language publications only. Considering the global nature of the pandemic, there may be regional differences in epidemiology and high rates of AMR in parts of world that do not predominantly speak English.

Implications for future pandemic

To avoid unnecessary antibiotic use in COVID-19, several strategies can be employed at the individual, healthcare, and policy levels. Key strategies, such as accurate diagnosis through bacterial markers like procalcitonin (PCT) or C-reactive protein (CRP), can help determine a bacterial coinfection requiring antibiotics.³⁶ Another way could be to strengthen antibiotic stewardship through limiting the use of empiric or broad-spectrum antibiotics and having multidisciplinary teams to overlook the fair adherence to guidelines.³⁷

Developing these strategies should employ a mechanism to involve the healthcare workers and patients highlighting a need for educating them both regarding antibiotics abuse and the serious implications of growing AMR.³⁸

For healthcare workers, incorporation of decision support systems (DSS) with electronic medical systems (EMRs) could provide real-time data and evidence-based guidelines on antibiotics, which could aid them in their decision making.³⁹

Studies on DSS such as Schweitzer et al indicate that DSS incorporated into clinical workflows could decrease antibiotic misuse. There should also be proper surveillance of antibiotics prescribing behavior for example through regular audits and educational campaigns to raise more awareness regarding antibiotics exceeding use. These approaches would be vital in preventing the acceleration of AMR, which is a serious threat to global public health.³⁸⁻⁴¹

On the other hand, it is important to recognize that addressing the rising challenge of AMR requires international cooperation, as exemplified by the recent second high-level meeting held by the UN general assembly with various stakeholders.⁴²

This meeting highlighted the urgent need for global action to combat AMR, particularly in low- and middle-income countries, and aimed to lay the foundation for collaborative efforts to tackle the issue. More follow-up meetings involving different stakeholders and organizations from around the world to develop a more corroborative plan to fight the growing problem of AMR would be very beneficial in the long run.

CONCLUSION

This overview highlights that antibiotics use in COVID-19 patients is not associated with better outcomes such as mortality. This finding was also found to align with global guidelines discouraging their use, unless there is a strong clinical suspicion of bacterial co-infection or superinfection, since there is no significant improvement in patient outcomes.

However, the increased use of antibiotics during the pandemic has been associated with a surge in AMR and multidrug-resistant organisms, especially in low- and middle-income countries. This demands a seamless antimicrobial stewardship strategy, which includes accurate diagnostics using efficient markers, restricting empiric and broad-spectrum antibiotics, and having educational campaigns for healthcare providers and patients on antibiotic misuse and AMR, along with enhanced surveillance and steps to reduce infections.

However, the scarcity of data from low-income countries may affect the generalizability of these conclusions. There is research gaps related to prescribing trends, AMR patterns, and the effectiveness of antimicrobial stewardship programs, especially in resource-constrained environments that need to be addressed. Hence, there needs to be more high-quality SRs to address research gaps in low-income settings so the findings from these

could be used to help avoid this in case of a future pandemic/epidemic.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Irfan O, Amjad A, Qadir MA, Zakaria M, Rehman A, Rehman A, et al. An umbrella systematic review of antibiotics therapy in COVID-19 patients: implications for antimicrobial resistance. *Int J Community Med Public Health* 2025;12:2836-48.