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Global antimicrobial resistance and antibiotic use in COVID-19 patients within health facilities: a systematic review and meta-analysis of aggregated participant data

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Abstract

Objectives: The COVID-19 pandemic has posed a significant threat to the global healthcare system, presenting a major challenge to antimicrobial stewardship worldwide.

Methods: We conducted a systematic review to determine the prevalence of antimicrobial resistance (AMR) and antibiotic usage among COVID-19 patients receiving treatment in healthcare facilities. Our search encompassed the PubMed, Web of Science, Embase, and Scopus databases, spanning studies published from December 2019 to May 2023. We utilized random-effects meta-analysis to assess the prevalence of multidrug-resistant organisms (MDROs) and antibiotic use in COVID-19 patients, aligning with both the WHO's priority list of MDROs and the AWaRe list of antibiotic products. Estimates were stratified by region, country, and country income. Meta-regression models were established to identify predictors of MDRO prevalence and antibiotic use in COVID-19 patients. The study protocol was registered with PROSPERO (CRD 42023449396).

Results: Among the 11,050 studies screened, 173 were included in the review, encompassing a total of 892,312 COVID-19 patients. MDROs were observed in 42.9% (95% CI 31.1%-54.5%, I^2=99.90%) of COVID-19 patients: 41.0% (95% CI 35.5%-46.6%) for carbapenem-resistant organisms (CRO), 19.9% (95% CI 13.4%-27.2%) for methicillin-resistant Staphylococcus aureus (MRSA), 24.9% (95% CI 16.7%-34.1%) for extended-spectrum beta-lactamase-producing organisms (ESBL), and 22.9% (95% CI 13.0%-34.5%) for vancomycin-resistant Enterococcus species (VRE), respectively. Overall, 76.2% (95% CI 69.5%-82.9%, I^2=99.99%) of COVID-19 patients were treated with antibiotics: 29.6% (95% CI 26.0%-33.4%) with "Watch" antibiotics, 22.4% (95% CI 18.0%-26.7%) with "Reserve" antibiotics, and 16.5% (95% CI 13.3%-19.7%) with "Access" antibiotics. The MDRO prevalence and antibiotic use were significantly higher in low- and middle-income countries than in high-income countries, with the lowest proportion of antibiotic use (60.1% (95% CI 52.1%-68.0%)) and MDRO prevalence (29.1% (95% CI 21.8%-36.4%)) in North America, the highest MDRO prevalence in the Middle East and Africa (63.9% (95% CI 46.6%-81.2%)), and the highest proportion of antibiotic use in South Asia (92.7% (95% CI 90.4%-95.0%)). The meta-regression identified antibiotic use and ICU admission as a significant predictor of higher prevalence of MDROs in COVID-19 patients.

Conclusions: This systematic review offers a comprehensive and current assessment of MDRO prevalence and antibiotic use among COVID-19 patients in healthcare facilities. It underscores the formidable challenge facing global efforts to prevent and control AMR amidst the backdrop of the COVID-19 pandemic. These findings serve as a crucial warning to policymakers, highlighting the urgent need to enhance antimicrobial stewardship strategies to mitigate the risks associated with future pandemics.

Keywords: antimicrobial resistance; antibiotic; COVID-19; multidrug-resistant organisms; global health

Introduction

The high disease burden and economic losses resulting from antimicrobial resistance (AMR) represent a serious threat to global health, necessitating international cooperation. The COVID-19 pandemic, as a major public health emergency, has garnered widespread global attention and significantly impacted the management of antibiotics and the surveillance of AMR.[1,2] Due to the similarities between the symptoms of COVID-19 and bacterial pneumonia, along with the occurrence of secondary bacterial infections, clinicians may encounter challenges in adhering to antibiotic prescription guidelines. These difficulties could potentially lead to irrational or increased antibiotic use in hospitalized patients, further exacerbating AMR.[3-5]

The inappropriate use of antibiotics in patients with COVID-19 is a significant concern.[6,7] Previous studies have estimated the proportion of bacterial infections and antibiotic use in COVID-19 patients since the pandemic began.[7-12] Despite a low overall prevalence of bacterial co-infection (3–8%), antibiotic use was found to be high (50–75%) in COVID-19 patients.[7] However, there is considerable heterogeneity in the results of previous studies, stemming from regional representation and differing publication times of literature. Moreover, the trends in AMR among COVID-19 patients have varied during the pandemic, and no studies have comprehensively covered the entire COVID-19 pandemic period to provide a holistic picture of overall antibiotic resistance and use. Therefore, additional evidence is required to investigate potential global disparities in AMR prevalence and antibiotic use among COVID-19 patients, with adequate coverage of data throughout the entire pandemic.

As we transition to the long-term management of the COVID-19 pandemic, it is crucial to remain vigilant and establish evidence-informed measures to prevent and control emerging infectious diseases, including COVID-19.[13,14] A better understanding of AMR prevalence and antibiotic usage among COVID-19

patients could aid in improving antimicrobial stewardship in clinical practice. Therefore, our aim is to provide a comprehensive and up-to-date picture of AMR and antibiotic use in COVID-19 patients, supporting policymakers and clinical practitioners in developing and enhancing appropriate antimicrobial stewardship.

Methods

Search Strategy

We conducted this study to evaluate the prevalence of multidrug-resistant organisms (MDROs) and antibiotic use in COVID-19 patients using existing literature. A comprehensive search was performed in the PubMed, Web of Science, Embase, and Scopus databases for English-language publications on human subjects, spanning from December 2019 to May 2023. The search involved three key themes: COVID-19, antibiotics, and antibiotic resistance, utilizing a combination of Medical Subject Headings (MeSH) and text words. Appendix One provides a complete list of the search strategies employed.

Selection Criteria

The inclusion criteria encompassed observational studies (retrospective, prospective, and cross-sectional studies) with more than 10 patients. Excluded were reviews, editorials, letters, randomized controlled trials, case studies, preprints, dissertations, and poster presentations. Studies lacking clinical details were also excluded.

Eligible studies needed to meet the following conditions:

1. Patients confirmed positive for SARS-CoV-2 with active infection across all age groups and healthcare settings;
2. For COVID-19 patients with resistant bacterial infection, AMR was confirmed through susceptibility tests;
3. For COVID-19 patients receiving antibiotics, comprehensive antibiotic prescribing information was available.

If condition 1) was met, studies meeting either condition 2) or 3) were included. Studies failing the following criteria were excluded:

1. COVID-19 identified solely by serological or antigen tests;
2. Chronic bacterial infections (e.g., tuberculosis) or suspected resistant bacterial infection without performed susceptibility tests, or colonization of drug-resistant bacteria;

3. Uncertain or unavailable antibiotic prescribing information for COVID-19 patients receiving antibiotics.

The acquired studies were imported into a literature management website (https://www.rayyan.ai/), where three authors (XY Yang, XY Li, and SY Qiu) independently screened titles and abstracts, and conducted a comprehensive examination of full texts based on predetermined eligibility criteria. In cases of conflicting judgments, a third party (LP Yang) was involved to make the final decision. The study protocol was registered with PROSPERO, the International Registry of Systematic Reviews (CRD 42023449396).

Data extraction

We extracted essential information from studies, including author, year, country, region, country income, dates of study, study design, sample size, and healthcare settings. Demographic characteristics encompassed age, sex, severity of COVID-19, comorbidities and complications, and bacterial infection (site of infection, species, and antibiotic resistance).

Antibiotic Information: Details on antibiotics included categories of antibiotics, reasons for antibiotic use, duration of antibiotics prescribed, individual vs. multiple antibiotics, antibiotic prescribing indicators and calculations, and the presence or absence of antibiotic stewardship measures.

Antimicrobial Resistance Information: For resistance information, we included AMR indicators and calculations, and infection risk factors (e.g., ventilation and catheter) and their effect sizes on AMR. Bacteria were classified as multidrug-resistant if they were not susceptible to at least one drug across three or more antibiotic classes. The presence of specific bacterial infections such as carbapenem-resistant organisms (CRO), vancomycin-resistant Enterococcus species (VRE), extended-spectrum beta-lactamase-producing organisms (ESBL), and methicillin-resistant Staphylococcus aureus (MRSA) also led to classification as multidrug-resistant bacterial infections.

Data Extraction Process: For studies meeting the inclusion criteria, three authors (XY Yang, XY Li, and SY Qiu) independently extracted basic information and research content using a data extraction table. Any disagreements were resolved through discussion. If further questions arose regarding one or more included articles, a third party (LP Yang) reviewed and made the final decision.

Bias risk assessment

The risk of bias assessment was independently conducted by SY Qiu and XY Li at the data point or outcome level. They utilized a validated 11-item AHRQ Bias risk assessment tool to evaluate the quality

of included studies, focusing on selection bias, performance bias, detection bias, attrition bias, and reporting bias. Study quality was categorized by two authors as high (score ≥8), moderate (5–7), or low (0–4) based on assessment criteria specific to each study's research design.[15] Conflicts were resolved through consensus or discussion with a third reviewer (XY Yang).

Data Analysis

Two outcome indicators were assessed in this study: the proportion of antibiotic use in COVID-19 patients and the prevalence of MDROs in COVID-19 patients. The proportion of COVID-19 patients receiving antibiotic prescriptions was calculated by dividing the number of patients receiving antibiotics by the total number of COVID-19 patients in each study. The prevalence of antibiotic resistance was presented using: 1) the proportion of COVID-19 patients with MDRO infections calculated by dividing the number of patients with MDRO infection by the total number of COVID-19 patients with bacterial infection; 2) the proportion of drug-resistant strains calculated by dividing the number of resistant strains by the total number of isolated strains. Antibiotic resistance was further categorized according to the WHO priority list, and antibiotics were classified into three groups ("Access", "Watch", "Reserve") based on the WHO AWaRe classification (2021).[16] The "Access" group includes antibiotics that are effective against common pathogens and have low resistance potential, while the "Watch" group includes antibiotics with high resistance potential and/or high risk of selective resistance and the "Reserve" group is dedicated to treating confirmed or suspected infections caused by multidrug-resistant bacteria as a treatment option of last resort.

A random-effects meta-analysis was performed to estimate the proportion of COVID-19 patients receiving antibiotic treatment and the prevalence of antibiotic-resistant infections. Subgroup analyses were conducted based on national income level, region, publication date, ICU admission, and severity of COVID-19.

Meta-regression analysis was conducted to identify predictors of antibiotic resistance and antibiotic use at both the study and patient levels. For study-level variables, a generalized linear model with a log link was fitted, incorporating an offset term to account for differing sample sizes. Patient characteristic variables were transformed into proportions as continuous variables in the regression model, with odds ratios (OR) obtained by exponentiating the regression coefficient.

To explore the potential impacts of study quality on estimated outcomes, sensitivity testing of the findings was conducted using a sample that excluded studies deemed 'low quality'.

The meta-analysis utilized StataSE (version 12). Visualization was conducted using the ggplot2 package in R (version 4.2.2), while regression analysis was performed using the stats package in R (version 4.2.2). Heterogeneity was deemed significant if $I^2 > 50\%$, prompting the adoption of a random-effects model; otherwise, a fixed-effect model was employed. Statistical significance was defined as a p-value of < 0.05 (two-tailed).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Out of the 11,050 studies identified, 782 underwent full-text screening, of which 173 ultimately met the inclusion criteria (Figure 1). The years of publication for the included studies were distributed as follows: 2020 (n = 9, 5.2%), 2021 (n = 48, 27.7%), 2022 (n = 86, 49.7%), and 2023 (n = 30, 17.3%). All included studies were observational, with the majority (n = 133, 76.9%) being retrospective.

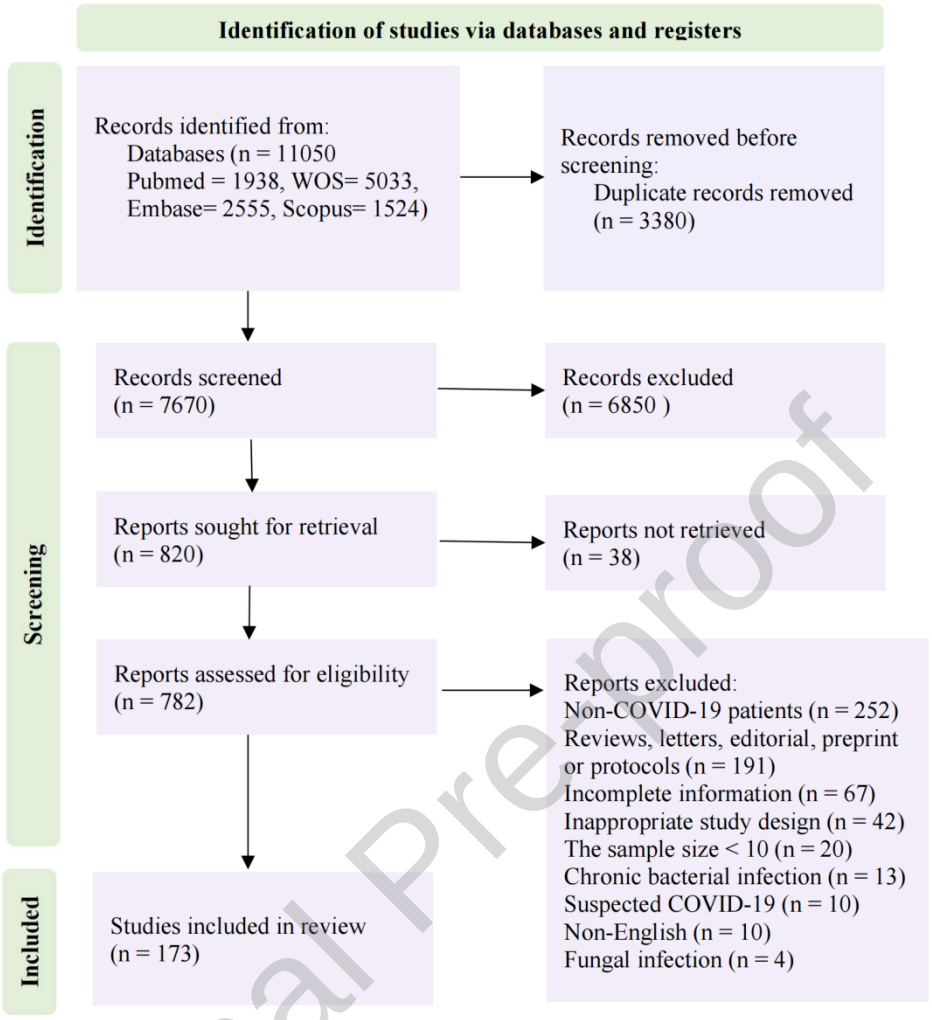

Figure 1: PRISMA flow diagram

The included studies were conducted in 52 countries. Most studies were conducted in Europe and Central Asia (n = 81, 46.8%), followed by the Middle East & North Africa (n = 26, 15.0%) and South Asia (n = 25, 14.5%). Based on the World Bank classification, 85 studies (49.1%) were conducted in high-income countries, 57 (32.9%) in lower-middle-income countries, 28 (16.2%) in upper-middle-income countries, and 3 (1.7%) in low-income countries.

The majority of studies (137, 79.2%) were conducted in tertiary hospitals. Among these, 86 (49.7%) focused exclusively on patients in ICUs, while 29 (16.8%) encompassed both ICU departments and general wards. Additionally, more than half of the studies (n = 89, 51.4%) specifically targeted patients with severe COVID-19.

The bias assessments revealed that 34.7% (60/173) of the studies were classified as high quality, 64.2% (111/173) as medium quality, and 1.2% (2/173) as low quality. Further details are provided in Appendices (2), (3), and (4).

The 173 included studies comprised a total of 892,312 patients with COVID-19. Patient age was reported in 118 (67.8%) studies, with an average age of 63 years (IQR: 18.6–37.7). Gender ratio was reported in 139 (80.3%) studies, indicating a median proportion of male participants at 64.4% (IQR: 56–72). Several comorbidities were reported across the studies: Diabetes was reported in 83 studies, with a prevalence of 27% (IQR: 18.6–37.7); Hypertension was reported in 71 studies, with a prevalence of 45.9% (IQR: 36.7–56.7); Chronic kidney disease was reported in 55 studies, with a prevalence of 8.5% (IQR: 5.5–13.5) and Obesity (BMI > 30) was reported in 21 studies, with a prevalence of 40% (IQR: 22.7–48.8).

Table 1: Characteristics of included studies

	Studies (n=173)	
Study design, n (%)	n	Proportion (%)
Retrospective study	138	79.80%
Cross-sectional study	24	13.90%
Prospective study	11	6.40%
Year of publication, n (%)		
2020	9	5.20%
2021	48	27.70%
2022	86	49.70%
2023	30	17.30%
Country income, n (%)		
High income	85	49.10%
Lower middle income	57	32.90%
Upper middle income	28	16.20%
Low income	3	1.70%
Region, n (%)		
Europe & Central Asia	81	46.80%
Middle East & North Africa	26	15.00%
South Asia	25	14.50%
East Asia & Pacific	14	8.10%
North America	12	6.90%
Latin America & Caribbean	10	5.80%
Sub-Saharan Africa	5	2.90%
Healthcare settings, n (%)		
Tertiary care hospitals	137	79.20%
Primary care institutions	3	1.70%

Secondary care hospitals	3	1.70%
Quaternary medical centers	2	1.20%
Not specified	28	16.20%
ICU admission, n (%)		
Yes	86	49.70%
No	58	33.50%
Mix	29	16.80%
Severity of COVID-19, n (%)		
Severe	89	51.40%
Critical	3	1.70%
Mix	48	27.70%
Not specified	33	19.10%

Drug-resistant bacterial infections in COVID-19 patients were reported in 76.30% (132/173) of the included studies, with 48.4% (64/132) involving MDROs. The types of infections primarily included bloodstream infections, upper respiratory tract infections, lower respiratory tract infections, urinary tract infections, and others. Notably, literature on bloodstream infections constituted 9.24% (16/173) of the total publications analyzed, while studies on respiratory tract infections accounted for 6.94% (12/173). The remaining studies investigated various mixed types of infections. Antibiotic use was studied in 64.16% (111/173) of the articles, revealing antibiotic usage in 71.17% (79/111) COVID-19 patients.

Table 2: Subgroup meta-analysis of MDRO infection prevalence

	Studies (n)	Prevalence* (%)	95% CI	I^2	*p*-value for heterogeneity	*p*-value between groups
Total	64	42.9	(31.1, 54.5)	99.90%	<0.0001	..
Country income level						<0.0001
Low and middle income	32	48.8	(29.3, 68.4)	99.95%	<0.0001	..
High income	32	36.2	(30.3, 42.1)	98.15%	<0.0001	..
Region of study*						0.013
East Asia & Pacific	5	38.6	(-11.4, 88.6)	99.89%	0.13	..
Europe & Central Asia	26	39.8	(31.2, 48.5)	98.65%	<0.0001	..
Latin America & Caribbean	9	35.5	(15.7, 55.4)	99.25%	<0.0001	..
Middle East & North Africa	11	63.9	(46.6, 81.2)	99.01%	<0.0001	..
North America	6	29.1	(21.8, 36.4)	88.53%	<0.0001	..
South Asia	7	42.8	(18.5, 67.1)	99.37%	0.001	..
Year of publication						<0.0001
2020	2	66.5	(59.1, 73.9)	..	..	..
2021	16	45.5	(22.7, 68.3)	99.79%	<0.0001	..

2022	30	31.7	(25.4, 38.0)	99.20%	<0.0001	..
2023	16	57.0	(38.5, 75.4)	99.54%	<0.0001	..
ICU admission						0.036
Yes	35	33.8	(22.4, 45.1)	99.59%	<0.0001	..
No	23	52.3	(27.0, 77.6)	99.96%	<0.0001	..
Mix	6	59.5	(42.4, 76.5)	98.81%	<0.0001	..
Severity of COVID-19						0.063
Severe / Critical	43	36.2	(31.0, 41.5)	98.60%	<0.0001	..
Mix	13	47.8	(28.6, 67.0)	99.76%	<0.0001	..
Not specified	8	65.1	(38.8, 91.3)	99.73%	<0.0001	..

Notes: * refers to the prevalence of MDROs, which is the number of MDROs detected divided by the total number of strains. Bacteria were classed as multidrug-resistant if they were not susceptible to at least one drug across three or more antibiotic classes (or as defined by study authors). Due to the small number of studies, Sub-Saharan Africa studies were combined with Middle East & North Africa studies.

Table 3: Subgroup meta-analysis on the proportion of antibiotic use in COVID-19 patients

	Studies (n)	Proportion* (%)	95% CI	I^2	*p-value* for heterogeneity	*p-value* between groups
Total	79	76.2	(69.5, 82.9)	99.99%	<0.0001	…
Country income level*						<0.0001
Lower-middle income	21	87.9	(86.5, 89.2)	99.24%	<0.0001	…
Upper-middle income	14	84.1	(58.6, 109.6)	99.96%	<0.0001	…
High income	44	70.0	(62.0, 78.1)	99.94%	<0.0001	…
Region of study*						<0.0001
East Asia & Pacific	9	68.6	(42.4, 94.9)	99.94%	<0.0001	…
Europe & Central Asia	39	75.2	(67.2, 83.2)	99.81%	<0.0001	…
Latin America & Caribbean	6	84.5	(44.5, 124.6)	99.97%	<0.0001	…
Middle East & North Africa	10	81.4	(73.7, 89.1)	99.16%	<0.0001	…
North America	7	60.1	(52.1, 68.0)	99.47%	<0.0001	…
South Asia	8	92.7	(90.4, 95.0)	99.00%	<0.0001	…
Year of publication						<0.0001
2020	5	78.7	(65.5, 92.0)	98.28%	<0.0001	…
2021	29	76.3	(70.3, 82.2)	99.92%	<0.0001	…
2022	34	74.0	(60.6, 87.3)	99.99%	<0.0001	…
2023	11	82.6	(76.0, 89.2)	98.67%	<0.0001	…
ICU admission						<0.0001
Yes	39	84.8	(82.8, 86.9)	99.21%	<0.0001	…
No	31	71.4	(55.7, 87.0)	99.99%	<0.0001	…
Mix	9	70.7	(53.1, 88.2)	99.90%	<0.0001	…
the severity of COVID-19						<0.0001
Severe / Critical	38	81.9	(77.9, 85.8)	99.31%	<0.0001	..

Mix	24	75.2	(68.1, 82.2)	99.98%	<0.0001	..
Not specified	17	67.7	(52.6, 82.9)	99.94%	<0.0001	..
Healthcare settings						<0.0001
Secondary/Tertiary hospitals	74	77.0	(70.1, 83.9)	99.99%	<0.0001	..
Quaternary medical centers	2	91.3	(90.5, 92.2)	..	..	..
Primary Health Cares	3	52.1	(25.5, 78.7)	..	..	..

Notes: * refers to the total proportion of antibiotic use in COVID-19 patients which is the number of COVID-19 patients receiving antibiotic divided by the total number of patients. Due to the small number of studies, low-income studies were combined with lower-middle income studies, and Sub-Saharan Africa studies were combined with Middle East & North Africa studies.

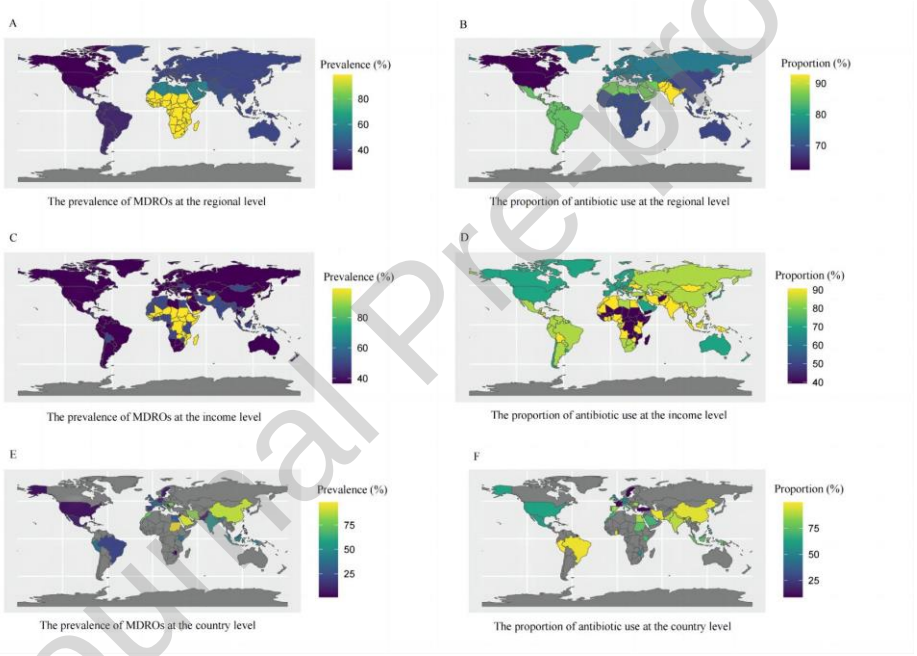

Figure 2: Estimates of MDRO prevalence and antibiotic use at country, regional, and income levels

Notes: A: The prevalence of MDROs at the regional level; B: The proportion of antibiotic use at the regional level; C: The prevalence of MDROs at the income level; D: The proportion of antibiotic use at the income level; E: The prevalence of MDROs at country level; F: The proportion of antibiotic use at country level. Grey indicates the countries/regions without relevant data.

The meta-analysis of 64 articles revealed that the prevalence of MDROs in COVID-19 patients was 42.9% (31.1%, 54.5%) (Table 2). When considering national income levels, the prevalence of MDROs in COVID-19 patients from low- and middle-income countries (48.8% (29.3%, 68.4%)) significantly

surpassed that from high-income countries (36.2% (30.3%, 42.1%)). In terms of regions, North America demonstrated the lowest MDRO prevalence at 29.1% (21.8%, 36.4%), while the Middle East & North Africa exhibited the highest MDRO prevalence at an alarming level of 63.9% (46.6%, 81.2%). According to the publication time, the highest prevalence of MDROs was found in 2020 at 66.5% (59.1%, 73.9%), while the lowest was found in 2022 at 31.7% (25.4%, 38.0%). The estimated highest prevalence of MDROs occurred when the studies mixed ICU departments and general hospital wards, reaching up to 59.5% (42.4%, 76.5%).

The meta-analysis of the 79 studies reporting overall antibiotic use showed that the overall proportion of antibiotic use in COVID-19 patients was 76.2% (69.5%, 82.9%), ranging from 74.0% (60.6%, 87.3%) in 2022 to 82.6% (76.0%, 89.2%) in 2023 (Table 3). Regarding income levels, lower-middle income, upper-middle income, and high-income countries had overall antibiotic usage of 87.9% (86.5%, 89.2%), 84.1% (58.4%, 109.6%), and 70.0% (62.0%, 78.1%), respectively. Among different regions, North America had the lowest overall proportion of antibiotic use at 60.1% (52.1%, 68.0%), and South Asia had the highest at 92.7% (90.4%, 95.0%). The highest proportion of antibiotic use was 84.8% (82.8%, 86.9%) in ICUs. The proportion of antibiotic use was higher in severe/critical COVID-19 patients at 81.8% (77.9%, 85.8%).

Figure 2 shows significant differences in both the overall proportion of antibiotic usage and MDRO prevalence across countries, regions, and country income. Heterogeneity of the included studies was high (I^2 > 95%) for both MDRO prevalence and antibiotic usage.

Table 4: Prevalence of antimicrobial resistance of various strains in COVID-19 patients: results of meta-analysis of random effects

Drug-resistant strains	Studies (n)	Strains (n/N) [a]	Prevalence (95% CI)	Heterogeneity (I^2)
CRO	57	4731/17606	41.0% (35.5-46.6)	99.59%
MRSA	35	3835/32165	19.9% (13.4-27.2)	99.19%
ESBL	29	2902/31939	24.9% (16.7-34.1)	99.46%
VRE	21	1241/24381	22.9% (13.0-34.5)	99.32%
Acinetobacter baumannii (aba)				
Any resistance	46	2186/6547	59.9% (44.9-74.0)	99.21%
CR-aba	30	1558/4909	63.7% (44.9-80.7)	99.28%
GCR-aba	4	108/138	78.8% (19.9-100.0)	97.45%
MDR-aba	9	496/1125	54.1% (21.4-85.0)	99.21%
Colistin-aba	3	24/375	6.8% (0.1-13.5)	79.88%
Klebsiella pneumoniae (kpn)				
Any resistance	55	1624/6035	42.5% (31.6-53.9)	98.58%

CR-kpn	24	878/3997	37.2% (28.4-46.0)	99.59%
GCR-kpn	12	242/335	78.9% (61.5-92.5)	90.93%
ESBL-kpn	10	246/1087	29.8% (14.8-44.8)	98.55%
MDR-kpn	6	174/384	41.1% (6.7-75.4)	99.20%
Colistin-kpn	3	84/232	30.4% (3.9-56.9)	93.49%
Escherichia coli (eco)				
Any resistance	30	742/4228	23.7% (13.5-35.5)	98.26%
CR-eco	10	255/1110	22.6% (5.9-45.0)	97.92%
ESBL-eco	10	147/2229	12.8% (8.0-17.7)	96.66%
GCR-eco	6	270/496	49.6% (32.9-66.3)	84.61%
MDR-eco	4	70/393	30.2% (11.0-49.4)	97.79%
Pseudomonas aeruginosa (pae)				
Any resistance	49	1465/11214	26.0% (18.4-34.3)	98.49%
CR-pae	26	773/8689	27.9% (18.3-38.6)	98.52%
MDR-pae	12	192/1121	23.7% (12.8-34.6)	98.44%
GCR-pae	7	453/1057	36.1% (13.2-59.0)	98.56%
colistin-pae	2	3/135	1.6% (-0.5-3.8)	-
ESBL-pae	2	44/212	20.8% (15.3-26.2)	-
Enterobacterales				
Any resistance	36	899/9652	29.4% (25.0-33.8)	99.41%
CRE	18	417/8300	22.0% (17.2-26.8)	99.47%
GCR-Enterobacterales	8	390/646	62.3% (42.6-82.0)	97.38%
ESBL-Enterobacterales	4	21/352	8.1% (0.6-15.6)	80.30%
MDR-Enterobacterales	4	47/264	17.8% (1.5-34.1)	91.58%
Colistin-Enterobacterales	2	24/90	26.6% (17.5-35.7)	-
Staphylococcus aureus (sau)				
Any resistance	40	3966/32631	20.2% (14.0-27.1)	99.10%
MRSA	35	3835/32165	19.9% (13.4-27.2)	99.19%
MDR-Staphylococcus aureus	4	94/362	20.4% (4.7-36.2)	90.14%
Amoxicillin-Staphylococcus aureus	1	37/104	35.6% (26.4-45.6)	-

Abbreviation: CRO: carbapenem-resistant organisms; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum beta-lactamase-producing organisms; VRE: vancomycin-resistant Enterococcus species; GCR: Cephalosporin resistance; MDR: multi-drug resistance.

Notes: [a] n refers to the number of drug-resistant strains, while N represents the total cases with bacterial infection.

Table 5: Proportion of antibiotic usage in COVID-19 patients: Results of meta-analysis of random effects

WHO AWaRe Category	Times (n) [a]	Patients (n/N) [b]	Proportion of usage (95% CI)	Heterogeneity (I^2)
Access	43	8663/48792	16.5% (13.3, 19.7)	99.53%

Watch	136	27915/85475	29.6% (26.0, 33.4)	99.52%
Reserve	29	5265/34910	22.4% (18.0, 26.7)	99.65%
Antibiotic class				
Third-generation-cephalosporins	43	7357/34895	31.5% (26.0-37.0)	99.64%
Carbapenems	41	10665/30205	29.7% (22.8-37.1)	99.15%
Macrolides	38	14388/76079	34.7% (20.5, 48.9)	99.96%
Fluoroquinolones	28	3485/27624	15.5% (12.5-18.5)	98.75%
Beta-lactam/beta-lactamase-inhibitor	23	22763/47355	24.2% (12.3-36.2)	99.96%
Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	23	2501/10029	30.8% (24.5-37.1)	97.81%
Glycopeptides	21	6358/41615	33.1% (28.4-37.8)	99.82%
Penicillins	13	3752/66420	17.9% (15.2-20.6)	99.47%
Tetracyclines	10	2965/22876	27.9% (14.0-41.9)	99.80%
Aminoglycosides	9	72/935	9.0% (4.2-13.9)	94.64%
Polymyxins	9	755/1785	30.4% (12.1-48.6)	99.55%
Oxazolidinones	8	552/14813	24.2% (12.4-36.0)	99.05%
Fourth-generation-cephalosporins	4	146/6061	9.6% (3.5-15.7)	94.33%
Imidazoles	4	133/827	22.4% (-3.1-47.9)	99.05%
Sulfonamide-trimethoprim-combinations	3	25/477	7.0% (1.0-13.0）	58.86%
Antibiotic				
Ceftriaxone	26	2758/8269	38.3% (24.0-52.7)	99.74%
Azithromycin	22	4981/8626	46.2% (26.0-58.5)	99.83%
Piperacillin/tazobactam	22	2309/9776	28.4% (23.2-33.5)	96.51%
Meropenem	19	1232/3780	29.5% (15.9, 45.3)	98.98%
Vancomycin	13	5774/21444	34.7% (22.1-47.3)	99.75%
Amoxicillin/clavulanic-acid	12	2335/13730	14.6% (6.3-22.9)	99.61%
Levofloxacin	10	346/3461	18.1% (11.0-25.2)	98.11%
Doxycycline	9	2881/8944	31.0% (22.8-39.2)	98.51%
Colistin_IV	7	233/721	28.5% (10.1-46.9)	98.55%
Linezolid	6	522/14549	28.4% (13.4-43.4)	99.30%
Amikacin	5	26/690	3.1% (1.0-5.1)	63.81%
Ceftazidime/avibactam	5	32/280	9.1% (3.4-14.7)	75.75%

Notes: [a] refers to the number of times the antibiotic appeared in the included study. [b] n refers to the number of patients who received antibiotic treatments, while N refers to the total number of patients.

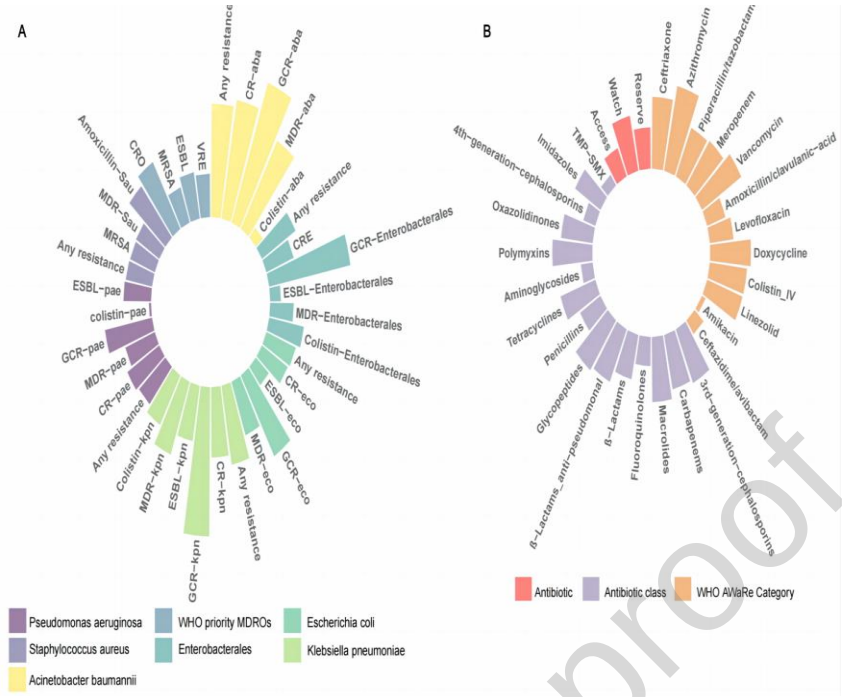

Figure 3: Subgroup analysis of prevalence of antibiotic resistance and proportion of antibiotic use in patients with COVID-19

Notes: Different colors represent the strains of resistant bacteria and the types of antibiotic, and each column represents the magnitude of the prevalence of resistant bacteria and the proportion of antibiotics use in COVID-19 patients. A: Subgroup analysis on the prevalence of antibiotic resistance in COVID-19 patients. B: Subgroup analysis on the proportion of antibiotic usage in COVID-19 patients.

Table 4 and Figure 3A presents the prevalence of various drug-resistant bacteria in COVID-19 patients, including four multidrug-resistant bacteria identified by the WHO priority list: carbapenem-resistant organisms (CRO: 41.0% (35.5%, 46.6%)), methicillin-resistant Staphylococcus aureus (MRSA: 19.9% (13.4%, 27.2%)), extended-spectrum beta-lactamase-producing organisms (ESBL: 24.9% (16.7%, 34.1%)), and vancomycin-resistant Enterococcus species (VRE: 22.9% (13.0%, 34.5%)).

To be specific, the resistance of gram-negative bacteria to cephalosporins was particularly notable: Acinetobacter baumannii - 78.8% (19.9%, 100.0%), Klebsiella pneumoniae - 78.9% (61.5%, 92.5%), Escherichia coli - 49.6% (32.9%, 66.3%), Pseudomonas aeruginosa - 36.1% (13.2%, 59.0%), and Enterobacterales - 62.3% (42.6%, 82.0%). Regarding high-grade antibiotics, carbapenem resistance was more prevalent in Acinetobacter baumannii and Klebsiella pneumoniae: 63.7% (44.9%, 80.7%) and 37.2%

(28.4%, 46.0%), respectively. Additionally, Klebsiella pneumoniae and Enterobacterales exhibited high resistance to colistin, with a prevalence of 30.4% (3.9%, 56.9%) and 26.6% (17.5%, 35.7%), respectively. Table 5 and Figure 3B presents the proportion of three types of antibiotics used in COVID-19 patients categorized by the WHO AWaRe classification. The Access category accounted for 16.5% (13.3%, 19.7%) of antibiotic usage, while the Watch category had the highest proportion at 29.6% (26.0%, 33.4%). The Reserve level constituted 22.4% (18.0%, 26.7%) of antibiotic use. Macrolides had the highest proportion of usage at 34.7% (20.5%, 48.9%), followed by Glycopeptides at 33.1% (28.4%, 37.8%) and third-generation cephalosporins at 31.5% (26.0%, 37.0%). The top three antibiotics utilized were azithromycin 46.2% (26.0%, 58.5%), ceftriaxone 38.3% (24.0%, 52.7%) and vancomycin 34.7% (22.1%, 47.3%). There existed moderate or high heterogeneity (I^2 ranging from 63.81%% to 99.96%%) in the studies of antibiotic usage in COVID-19 patients.

Table 6: Predictors of MDRO prevalence in patients with COVID-19: Results of meta regression

	Studies (n)	Odds ratio	95% CI	*p* value
Country income				
High income	32	Ref.[a]	Ref.	..
Low and middle income	32	0.869	(0.752, 1.007)	0.060
Region of study				
East Asia & Pacific	5	Ref.	Ref.	..
Europe & Central Asia	26	0.825	(0.698, 0.978)	0.026
Latin America & Caribbean	9	0.858	(0.720, 1.021)	0.085
Middle East & North Africa	11	1.676	(1.415, 1.989)	< 0.001
North America	6	0.678	(0.552, 0.834)	< 0.001
South Asia	7	0.553	(0.463, 0.660)	< 0.001
Year of publication				
2020	2	Ref.	Ref.	..
2021	16	0.925	(0.687, 1.282)	0.623
2022	30	0.48	(0.358, 0.664)	< 0.001
2023	16	0.971	(0.719, 1.350)	0.856
ICU admission				
Mix	6	Ref.	Ref.	..
Yes	35	0.728	(0.636, 0.835)	< 0.001
No	23	0.635	(0.561, 0.718)	< 0.001
the severity of COVID-19				
mix	13	Ref.	Ref.	..
critical / severe	43	0.685	(0.611, 0.769)	< 0.001
not specified	8	1.072	(0.962, 1.195)	0.208

Patient or treatment characteristics [b]				
Age (average)	47	0.987	(0.984, 0.991)	< 0.001
Diabetes (%)	33	1.011	(1.008, 1.014)	< 0.001
Hypertension (%)	31	1.011	(1.007, 1.015)	< 0.001
COPD (%)	19	0.957	(0.948, 0.965)	< 0.001
Chronic kidney disease (%)	17	1.002	(0.995, 1.008)	0.591
Obesity (BMI > 30) (%)	12	1.003	(0.996, 1.010)	0.478
Charlson Comorbidity Index	5	1.646	(1.319,2.046)	< 0.001
Antibiotic treatment [b]				
Antibiotics (%)	30	1.004	(1.002, 1.006)	< 0.001
Duration of antibiotics (d)	6	1	(0.982, 1.016)	0.983
Multiple antibiotics (%)	4	1.029	(1.022, 1.037)	< 0.001

Notes: [a] Ref= Reference. [b] Odds ratios in these groups are for every 1% increase in the proportion of patients with specific characteristics. (Where the unit of the variable "Charles Index" is the median, and the unit of the variable "antibiotic duration" is "day".) The variables of Country income, Region of study, Year of publication, ICU admission and the severity of COVID-19 are included in one equation to fit the multivariable meta-regression, and the variables in part of “patient or treatment characteristics” are fitted to the univariable meta-regression respectively.

Table 7: Predictors of antibiotic use in patients with COVID-19: Results of meta regression

	Studies (n)	Odds ratio	95% CI	*p* value
Country income				
High income	44	Ref.[a]	Ref.	..
Upper middle income	14	1.458	(1.376, 1.544)	< 0.001
Lower middle income	21	2.047	(1.925, 2.176)	< 0.001
Region of study				
East Asia & Pacific	7	Ref.	Ref.	..
Europe & Central Asia	39	2.005	(1.926, 2.089)	0.002
Latin America & Caribbean	6	0.581	(0.543,0.622)	< 0.001
Middle East & North Africa	7	1.113	(1.036, 1.196)	0.003
North America	9	1.880	(1.778, 1.988)	< 0.001
South Asia	8	1.306	(1.238, 1.379)	< 0.001
Year of publication				
2020	5	Ref.	Ref.	..
2021	29	1.220	(1.162, 1.282)	< 0.001
2022	34	1.008	(0.962, 1.056)	0.741
2023	11	1.116	(1.035, 1.202)	0.004
ICU admission				
Mix	31	Ref.	Ref.	..
Yes	39	1.299	(1.243, 1.356)	< 0.001

No	9	1.142	(1.087, 1.200)	< 0.001
the severity of COVID-19				
Mix	24	Ref.	Ref.	..
Critical / severe	38	0.958	(0.919, 0.998)	0.039
Not specified	17	0.864	(0.829, 0.901)	< 0.001
Healthcare settings				
Primary Health Cares	3	Ref.	Ref.	..
Quaternary medical centers	2	2.153	(1.995, 2.324)	0.003
Secondary / Tertiary hospitals	74	2.383	(2.255, 2.519)	< 0.001
Patient characteristics [b]				
Age (average)	58	1.100	(1.098, 1.103)	< 0.001
Gender (male %)	69	0.967	(0.966, 0.968)	< 0.001
Diabetes (%)	42	1.005	(1.004, 1.006)	< 0.001
Hypertension (%)	36	0.995	(0.994, 0.996)	< 0.001
COPD (%)	23	1.004	(1.001, 1.007)	0.013
Chronic kidney disease (%)	30	1.086	(1.081, 1.091)	< 0.001
Obesity (BMI > 30) (%)	14	1.040	(1.038, 1.041)	< 0.001
Charlson Comorbidity Index	8	1.161	(1.138, 1.184)	< 0.001

Notes: [a] Ref= Reference. [b] Odds ratios in these groups are for every 1% increase in the proportion of patients with specific characteristics. (Where the unit of the variable "Charlson Comorbidity Index" is the median.) The variables of Country income, Region of study, Year of publication, ICU admission and the severity of COVID-19 are included in one equation to fit the multivariable meta-regression, and the variables in part of "patient characteristics" are fitted to the univariable meta-regression respectively.

Table 6 presents predictors at both population and patient characteristic levels for MDRO infection. In comparison to East Asia & Pacific, studies conducted in the Middle East & North Africa (1.676 [95% CI 1.415-1.989]) showed higher odds of MDRO infection, while North America (0.678 [95% CI 0.552-0.834]), South Asia (0.553 [95% CI 0.463-0.660]), and Latin America & Caribbean (0.858 [95% CI 0.720-1.021]) had lower odds. Additionally, MDRO infections were more likely to be detected in the ICU department (0.728 [95% CI 0.636-0.835]) compared to non-ICU.

At the patient characteristic level, factors such as age, diabetes, hypertension, COPD, and Charlson Comorbidity Index were significantly associated with MDRO infection in COVID-19 patients. The use of antibiotics (1.004 [95% CI 1.002-1.006]) and multiple antibiotics (1.029 [95% CI 1.022-1.037]) were also associated with a higher risk of MDRO infection.

Table 7 shows predictors at population and patient characteristic levels for total antibiotic use in COVID-19 patients. Compared with high-income countries, lower middle-income countries (2.047 [95% CI 1.925-2.176]) and upper middle-income countries (1.458 [95% CI 1.376-1.544]) had a higher risk of antibiotic use. The proportion of antibiotic use was higher secondary and tertiary hospitals (2.383 [95% CI 2.255-2.519]), in particular in the ICU (1.299 [95% CI 1.243-1.356]). Age, diabetes, COPD, chronic kidney disease, obesity and the Charlson Index were all predictors of antibiotic use in COVID-19 patients. The sensitivity testing using a sample that removed studies of low quality showed no significant changes in the estimation of the proportion of antibiotic use (76.2% VS 75.7%) and the prevalence of MDROs (42.9% VS 42.8%) in COVID-19 patients (Appendix 5-6). The meta regression also generated similar results.

Discussion

Our meta-analysis, comprising 173 studies and encompassing information from 892,312 patients across 52 countries, provides a comprehensive systematic review offering a thorough and up-to-date assessment of AMR and antibiotic use among COVID-19 patients globally. The study spans the entire duration of the COVID-19 pandemic, concluding with the WHO's declaration of the end of the global health emergency for COVID-19. The review sheds light on the substantial impact of the COVID-19 pandemic on global efforts in preventing and controlling AMR and antibiotic stewardship.

The estimated prevalence of MDROs among COVID-19 patients was found to be 42.9%, underscoring the significant challenge posed by multidrug-resistant bacterial infections during the pandemic. Furthermore, the total proportion of antibiotic use among COVID-19 patients was estimated at 76.2%. Noteworthy disparities in the prevalence of AMR and antibiotic usage were identified across countries, regions, and income levels. Low- and middle-income countries, particularly in Africa and South Asia, confronted heightened challenges in their healthcare systems due to a higher proportion of antibiotic use and AMR prevalence, compounded by limited clinical microbiology laboratory capacity and insufficient infection prevention and control measures throughout the COVID-19 pandemic.[17-20]

Multidrug-resistant bacterial infections have emerged as a primary concern for the WHO due to their heightened mortality rate and disease burden.[21,22] This study aimed to estimate the prevalence of priority MDROs, including CRO, ESBL, MRSA, and VRE, in COVID-19 patients. The estimated prevalence of CRO was found to be 41.0%, the highest among those tested. This underscores the need for specific

attention to carbapenem resistance, particularly observed in Acinetobacter baumannii and Klebsiella pneumoniae, emphasizing their resistance to carbapenems.

Among COVID-19 patients, the prevalence of ESBL-producing bacteria was determined to be 24.9%, with a notable proportion infected with Klebsiella pneumoniae. These findings are consistent with previous research results,[23-25] reinforcing the significance of monitoring and addressing specific multidrug-resistant organisms to guide targeted interventions and mitigate the impact on patient outcomes.

Optimizing the use of antimicrobials stands as a key priority in the global strategy to combat AMR. To enhance the development of tools for antibiotic stewardship at local, national, and global levels, and to address AMR effectively, the WHO introduced the Access, Watch, Reserve (AWaRe) classification of antibiotics.[26] A review study argued that the seven most frequently prescribed antibiotics in COVID-19 patients were all on the "Watch" list of the WHO AWaRe classification. [27] Consistent with this finding, our study revealed that the prevalence of antibiotics categorized under the "Watch" level was the highest among COVID-19 patients, followed by the "Reserve" level. These underscores notable usage of higher-level antibiotics among COVID-19 patients, highlighting the necessity for further evaluation of antibiotic use rationality.

Although the effectiveness of hydroxychloroquine, alone or with azithromycin for treating COVID-19 is in doubt,[28-30] azithromycin use has been commonly reported in our included studies, highlighting potential overuse of antibiotics. The proportion of azithromycin use in COVID-19 patients reached 46.2% according to the findings of our study, which is comparable to the data extracted from the Premier Bank database in the United States (46.6%), lower than the Spanish estimate (57.9%), but much higher than the Chinese estimate (4.9%).[31,32] Some regional treatment protocols for COVID-19 did include empirical antimicrobials such as ceftriaxone and azithromycin.[33] A series of studies showed that the overall antibiotic use in COVID-19 patients had declined as the pandemic evolved,[27,34] consistent with our findings.

Notably, we observed that a high proportion of antibiotic use was accompanied by a high prevalence of infection caused by bacteria resistant to these antibiotics. For instance, cephalosporins, commonly prescribed for COVID-19 patients, presents a significant challenge of resistance, with the highest resistance rates noted across various types of bacteria studied. Approximately 28.5% of COVID-19 patients received treatment with polymyxin, and correspondingly, the prevalence of polymyxin-resistant

bacteria was higher than in other groups. The irrational use of antibiotics is considered a crucial factor contributing to bacterial resistance, compounded by other factors that collectively have complex effects on AMR development.[35,36] This study identified increased antibiotic usage, longer durations of antibiotic treatment, and a higher proportion of combined antibiotic treatment as predictors for MDRO prevalence. This adds global evidence to the association between antibiotic resistance and antibiotic use among COVID-19 patients, emphasizing the need for further verification with additional primary evidence in the future.

Low- and middle-income countries are more susceptible to pandemics due to healthcare resource shortages, leading to increased complexity in managing AMR in these regions. However, due to the limited number of relevant studies and the lack of surveillance information, this issue has not been extensively discussed. A meta-analysis of antibiotic use among COVID-19 patients in low- and middle-income countries indicated that the proportion of COVID-19 patients prescribed antibiotics was 80% (95% CI: 72%-88%), highlighting widespread inappropriate antibiotic use.[37] The ratio of sources included in this current study is approximately 1:1 between high-income countries and lower-middle-income countries, improving geographical representation. Building on this, we observed that the proportion of COVID-19 patients using antibiotics in middle-income countries is significantly higher than that in high-income countries. Additionally, the prevalence of MDROs in middle- and low-income countries is also significantly higher than that in high-income countries. This emphasizes the urgent need to strengthen AMR monitoring and antibiotic stewardship in underdeveloped regions.

Patients in intensive care units (ICUs) face an elevated risk of MDRO infections due to their complex health conditions, impaired organ function, and compromised immune systems.[22] Consistent with previous studies,[38-40] our research identified a higher prevalence of antibiotic-resistant infections among COVID-19 patients in ICUs compared to those in general wards. Comorbidities such as diabetes, hypertension, and obesity further amplify the risk of drug resistance in these individuals, aligning with previous research findings.[7,41-44] We observed the highest proportion of antibiotic use at 84.8% (82.8%, 86.9%) in ICU patients, with critical COVID-19 patients at 81.8% (77.9%, 85.8%). While the rationale for antibiotic use in the ICU is sometimes uncertain and may not always indicate a bacterial infection, these findings underscore the importance of exercising caution and ensuring appropriate antibiotic use for severe and critical COVID-19 patients or those with multiple comorbidities. Additionally, they emphasize the imperative for enhanced monitoring and diagnosis of antibiotic resistance in these settings.

To the best of our knowledge, this systematic review and meta-analysis currently stands as the largest in terms of sample size, encompassing the highest number of countries and incorporating the highest number of studies on AMR in COVID-19 patients. This global perspective study covers the entire pandemic period, from January 2020 to May 2023, filling evidence gaps in the later stages of the pandemic. The study adopts a balanced inclusion of regions, maintaining nearly equal proportions between low-middle-income countries and high-income countries. This approach facilitates a more systematic and accurate assessment of AMR among COVID-19 patients and the status of antibiotic usage, allowing for further exploration of differences across various countries, regions, and income levels.

However, the study has some limitations. Firstly, the complexity of outcome measures provided by included studies poses a challenge to estimation and synthesis. To address this issue, we propose employing comprehensive indicators such as the prevalence of MDROs and the overall proportion of antibiotic use, encompassing a wide range of information from included studies. Additionally, we categorized and used international standards to enrich results; for example, we employed the WHO AWaRe Category and priority lists for further subgroup analysis. Secondly, despite maintaining a similar proportion of studies in low- and middle-income countries compared to high-income countries from a global perspective, there is limited literature available for low-income countries, affecting our estimates of antibiotic resistance in COVID-19 patients in these regions. Thirdly, there existed high heterogeneity in the included studies due to variations in study settings and study design. We have tried to address the challenge through subgroup analyses, meta-regression, and sensitivity testing. Fourthly, the quality of included studies varies, and there may be selection bias due to the attention on bacteria with serious resistance issues. There may be many potential antibiotics uses in COVID-19 patients that have not been estimated. We cannot exclude the possibility of publication bias either, because we did not search for unpublished data. We excluded low-quality studies to re-estimate the prevalence of MDROs infection and antibiotic use in patients with COVID-19 and found no significant changes in the estimates. Lastly the study participants of the included studies were biased toward hospitalized patients. This approach lacks attention to primary healthcare institutions or retail pharmacies.

Despite these limitations, the comprehensive and systematic assessment of AMR and antibiotic use during the COVID-19 pandemic provides helpful evidence to highlight the global issue of serious AMR. It underscores the need for close monitoring of changes in AMR, especially in the context of public health emergencies that challenge healthcare systems.

Contributors

XYY, XYL, SYQ and LPY conceived the study and take responsibility for all its aspects. LPY and XYY initially designed the study, with support from CJL, GBT, GL, JC, SQC, SFY and JKZ. XYY, XYL and SYQ led the data collection. XYY, SL, YCZ and LPY provided data management, statistical analysis and methodology support. LPY, XYY and CJL conceived this article. XYY, XYL and SYQ wrote the manuscript, with further contributions from CJL, GBT, GL, JC, SFY, SQC, SL, YCZ, HHX and JKZ. All authors interpreted results, contributed to critical revisions, and approved the final version of the Article.

Conflict of Interests

All authors declared no competing interests.

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Data sharing statement

The materials and datasets analysed during the current study are available from the corresponding author on reasonable request.

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Highlights

- Our study included 892,312 patients with COVID-19 across 173 studies spanning over 50 countries.
- It revealed a substantial prevalence of MDRO infection (42.1%) in COVID-19 patients, and a notable overall proportion of antibiotic use (76.2%).

- Low- and middle-income countries have higher prevalence of MDRO and higher proportion of antibiotic use, especially in the Middle East, Africa and South Asia.
- Antibiotic resistance was further categorized according to the WHO priority list, and antibiotics were classified based on the WHO AWaRe (2021).
- The findings serve as a crucial warning to policymakers, highlighting the urgent need to enhance antimicrobial stewardship to mitigate the risks associated with future pandemics.