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REVIEW

Antibacterial agents used in COVID-19: A systematic review and meta-analysis

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Abstract
There have been speculations regarding rise in antimicrobial resistance (AMR) globally owing to indiscriminate antibiotic usage during the COVID-19 pandemic. To curb the menace through decisive policies, it is essential to assess the antibiotics, particularly the antibacterial agents. This systematic review and meta-analysis were performed to assess antibiotic use in COVID-19 patients. A thorough systematic search was undertaken in databases like PubMed, Cochrane library, Google Scholar, World Health Organization (WHO) database and clinicaltrials.gov by two independent reviewers for articles in English published from January 1, 2019 to October 31, 2020. Studies were included if they assessed confirmed COVID-19 cases and mentioned the use of antibiotics. The primary outcome was the proportion of COVID-19 patients subjected to specific antibacterial agents. An attempt to stratify the data based on study settings and disease severity was also performed. Of the total 6012 studies screened, 40 were eligible for qualitative review and 19 for meta-analysis. Specific antibacterial agents were mentioned in 23 studies (57.5%). In the random effect meta-analysis, pooled prevalence of azithromycin use was 24.5% (95% CI 22.9–26.2%) followed by cephalosporins as 26.6% (95% CI 24.9–28.4). None of the studies clearly specified indications for antibiotic use. Ten studies (25%) mentioned empirical use of antibiotics. Bacterial co-infections/secondary infections were documented in four studies with mean prevalence of infection of 1.9% (95% CI 1.2–2.8%). There is lack of data on use of specific antibacterial agents, indications for their use based on severity of infections and microbiological evidence of bacterial co-infections.

Keywords Antibiotics · Empirical · Bacterial co-infections · Azithromycin · Cephalosporins · COVID-19 · Antimicrobial resistance

Introduction

The global unpreparedness for tackling a pandemic of such magnitude like the coronavirus disease 2019 (COVID-19) has led to several direct and indirect challenges. Many of these challenges might not seem impending at the current stage of the pandemic but could have grave consequences even after the pandemic is contained. In this regard, there have been speculations that indiscriminate use of antibacterial agents or antibiotics during the pandemic without proper indications will impact antimicrobial resistance (AMR) particularly in bacteria (Getahun et al. 2020; Rossato et al. 2020). There are multiple threats of this pandemic towards a probable rise in AMR. On one side, increased hospital admissions due to the pandemic might lead to increase in healthcare associated infections and antibiotic use as a pre-emptive measure both in the community and hospitals. On the other side, widespread use of biocides against the virus in the community might result in an upsurge of drug resistant organisms, thus forming a vicious cycle (Caselli 2020). Evidence have suggested that the pandemic is 'exacerbating' the existing burden of AMR and antibiotics have been used beyond their indications (Strathdee et al. 2020). While appropriate management protocols for severe infections in COVID-19 and for bacterial coinfections remained largely unknown, there were sufficient gaps in expertise for differentiating COVID pneumonia and bacterial pneumonia,

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which in turn initiated unnecessary use of antibiotics (Nature Microbiology 2020). In order to tackle these problems, it is very essential to formulate effective and appropriate policies for judicious use of antibiotics. To decide on the policies, preliminary data on the trends in use of antibiotics in COVID-19 after almost 10–11 months of the ongoing pandemic is essential. To meet this end, we planned a systematic review to assess the proportions of various antibiotics, specifically the antibacterial agents used in COVID-19 patients.

Methods

Search strategy

Electronic databases particularly PubMed, Cochrane library, Google Scholar, World Health Organization (WHO) database and clinicaltrials.gov. were searched for articles that have been published between January 1, 2019 to October 31, 2020. The search terms and keywords used included "COVID-19", "Covid-19", "covid-19", "SARS-CoV-2", "antibiotics", "antimicrobials" as per the search criteria of the individual databases.

Inclusion and exclusion criteria

All articles on COVID-19 patients across hospitals, in community or any long-term care facilities mentioning antibiotics were included. Studies only in English language within the said time period were considered. Studies with unreliable or overlapping data were excluded. Abstract only papers were also excluded. Besides, case reports, systematic or narrative reviews, opinions, editorials were not considered.

Study selection

All published studies in English comprising of randomised and non-randomised controlled trials, case control studies, cohort studies, cross-sectional studies with sufficient data on antibiotic use in COVID-19 patients were included. Letter to Editor with results of original observational studies or randomised control trials (RCT) were also included. Preprints and 'not yet peer-reviewed' articles on MedRix-V were included if they contained relevant data. All duplicate studies were removed. The literature search as well as the screening of all the titles and abstracts of the included articles was independently done by two reviewers (SS and AS). All the full text articles were then reviewed by 2 independent reviewers (TB and SS/AS) for final inclusion. Disagreements were resolved by consensus, failing which the decision of the third reviewer was accepted. The reference section as well as the articles citing the selected articles were manually searched and checked for eligibility by the two independent reviewers. Authors were contacted by mail for any missing data in the selected articles. Reporting was done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic review (Moher et al. 2009).

The study protocol was registered in PROSPERO register (CRD42020220042).

Data extraction

From the included studies, data was extracted by two independent reviewers (TB and AS) using a Microsoft Xcel spreadsheet and doubly cross checked for accuracy. Data was extracted under the following heads: first author, year of study, article type, study design, study setting, country of study, sample size, gender distribution, age of the study population, severity of COVID-19 in affected patients, number of patients on antibacterial therapy, antibacterial agents used, and indications of antibacterial therapy, presence of bacterial coinfections.

Data synthesis and statistical analysis

The primary outcome that was assessed was the overall proportions of antibacterial agents used in COVID-19 patients. We also tried to stratify the data based on the study settings and severity of COVID-19 in terms of mild, moderate or severe disease. Proportion data across all studies were pooled using a random effects meta-analysis with DerSimonian-Laird method. Results were displayed using forest plots for demonstration of the study effects along with the confidence intervals (CI). Heterogeneity was determined by I^2 statistic. Heterogeneity was graded as considerably high at 75–100%, substantial at 50–90%, moderate at 30–60% and low at below 40% (Higgins et al. 2019). Publication bias was evaluated using the funnel plots. All categorical variables were expressed as relative frequencies and proportions. Continuous variables were expressed as mean or median with dispersion. All statistical analyses were performed using software STATA version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) and R package version 4.0 [R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria].

Results

Screening of studies

A total of 6012 search articles were screened of which 40 articles finally qualified for the systematic review (Table 1). Studies that were included consisted of confirmed

Table 1 Summary of the studies included in systematic review

S. no.	First author	Article type	Study setting	Country	Type of study	Sample size	Female (N, %)	Age of patients	Whether specific antibacterial agent mentioned	Whether severity of COVID-19 mentioned
1.	Williams et al	Pre-print	Hospital	UK	Retrospective observational	368	147, 39.95%	75 (median)	Y	N
2.	An et al	Pre-print	Hospital	South Korea	Retrospective cohort	226	143, 63.27%	43.48 ± 15.5 (mean)	Y	Y
3.	Mason et al	Pre-print	Hospital	UK	Retrospective cohort	800	304, 38.00%	68 (median)	N	N
4.	Mancilla-Galindo et al	Pre-print	Hospital	Mexico	Retrospective cohort	136,855	70,172, 51.27%	44.2 ± 16.8 (mean)	N	N
5.	Buetti et al	Published	ICU	Switzerland	Retrospective observational	48	11, 22.92%	66.6 (median)	Y	Y
6.	Yin et al	Pre-print	Hospital	China	Retrospective cohort	1613	887, 54.99%	57,54 (median)	N	Y
7.	Hung et al	Published	Hospital	Hong Kong	RCT	127	59, 46.46%	52 (median)	Y	N
8.	Wei et al	Pre-print	Hospital	US	Observational	147	60, 40.82%	52 (mean)	Y	Y
9.	Borba et al	Published	Hospital	Brazil	RCT	62	2, 3.23%	51.1 (mean)	Y	Y
10.	Tang et al	Published	Hospital	China	RCT	150	68, 45.33%	46 (mean)	N	Y
11.	Spinner et al	Published	Hospital	Multiple Countries	RCT	584	227, 38.87%	56,58,57 (median)	Y	N
12.	Gautret et al	Published	Hospital	France	RCT	36	21, 58.33%	45.1 (mean)	Y	Y
13.	Davoudi-Mon Farad et al	Published	Hospital	Iran	RCT	81	24, 29.63%	56.5, 61 (median)	Y	Y
14.	Mato et al	Published	Hospital	Multi-center	Cohort	198	73, 36.87%	70.5 (median)	Y	Y
15.	Sekhavati et al	Published	Hospital	Iran	RCT	111	51, 45.95%	54.3 ± 15.92, 59.89 ± 15.55 (mean)	Y	N
16.	Sadeghi et al	Published	Hospital	Iran	RCT	66	34, 51.52%	58 (median)	N	Y
17.	Abd-Elsalam et al	Published	Hospital	Egypt	RCT	194	104, 53.61%	40.72 ± 19.32 (mean)	Y	Y
18.	Calderon et al	Published	Hospital	Mexico	Observational	20	0, 0.00%	25.5 ± 4.6 (mean)	Y	Y
19.	Furtado et al	Published	Hospital	Brazil	RCT	397	262, 65.99%	59.4, 60.2 (median)	Y	Y
20.	Seaton et al	Published	Hospital	UK	Point prevalence	531	257, 48.40%	72 (median)	Y	Y
21.	Khamis et al	Published	Hospital	Oman	Case series	63	1, 1.59%	48 ± 16 (mean)	Y	Y
22.	Staub et al	Published	Hospital	US	Retrospective observational	131	52, 39.69%	56 ± 17.4 (mean)	N	N
23.	Huang et al	Published	Hospital	China	Retro case series	40	2, 5.00%	41 (median)	Y	Y
24.	Yu et al	Published	Hospital	China	Retrospective observational	550	262, 47.64%	68 (median)	N	Y

Table 1 (continued)

S. no.	First author	Article type	Study setting	Country	Type of study	Sample size	Female (N, %)	Age of patients	Whether specific antibacterial agent mentioned	Whether severity of COVID-19 mentioned
25.	Hu et al	Published	Hospital	China	Retrospective observational	1254	613, 48.88%	56 (median)	N	N
26.	Lehmann et al	Published	Hospital	US	Retrospective	321	177, 55.14%	60 (median)	N	N
27.	Chen et al	Published	Hospital	China	Observational	3309	1667, 50.38%	62 (median)	N	Y
28.	Santoro et al	Published	Hospital	Italy	Prospective	110	37, 33.64%	58 ± 14 (mean)	Y	N
29.	Karami et al	Published	Hospital	Netherland	Retrospective cohort	925	333, 36.00%	70 (median)	Y	N
30.	Jin et al	Published	Hospital	China	Retrospective observational	651	320, 49.16%	46.14 ± 14.19, 45.09 ± 14.45 (mean)	N	Y
31.	Lian et al	Published	Hospital	China	Retrospective observational	465	222, 47.74%	45 (median)	Y	Y
32.	Yang et al	Published	Hospital	China	Retrospective case series	136	70, 51.47%	56 (median)	Y	Y
33.	Sun et al	Published	Hospital	China	Retrospective observational	55	24, 43.64%	44 (median)	N	Y
34.	de Melo et al	Published	Hospital	Brazil	Retrospective cohort	181	110, 60.77%	55.3 ± 2.1 (mean)	N	N
35.	Piva et al	Published	Hospital	Italy	Observational cohort	33	3, 9.09%	64 (median)	Y	Y
36.	Prata-Barbosa et al	Published	Hospital	Brazil	Observational prospective	79	36, 45.57%	4 (median)	N	N
37.	Feng et al	Published	Hospital	China	Retrospective observational	476	205, 43.07%	53 (median)	N	Y
38.	Tian et al	Published	Hospital	China	Retrospective case control	90	42, 46.67%	64 (median)	N	Y
39.	Stevens et al	Published	Hospital	US	Retrospective cohort	346	297, 85.84%	45 ± 18 (mean)	Y	Y
40.	Ji et al	Published	Hospital	China	Retrospective observational	101	53, 52.48%	51 (median)	N	N

Where Y = yes and N = no

COVID-19 cases by reverse transcriptase polymerase chain reaction (RT-PCR) and excluded suspected cases based on clinical presentations. Of these, 19 articles were considered for the meta-analysis. The study flow diagram has been shown in Fig. 1. The 40 articles for review comprised of 16 observational studies, 10 RCTs, 9 cohorts, 3 case series, 1 case control and 1 point-prevalence study. In this 1 article in 'Letter to Editor' and 1 in 'Review" article format was also included due to relevance. This collection of 40 articles comprised of 35 published and 5 preprints 'yet to be peer reviewed' articles. The geographical distribution of the study locations has been shown in Fig. 2. Majority of the studies were from China, the epicentre of the pandemic. The summary of the articles has been shown in Table 1. All the

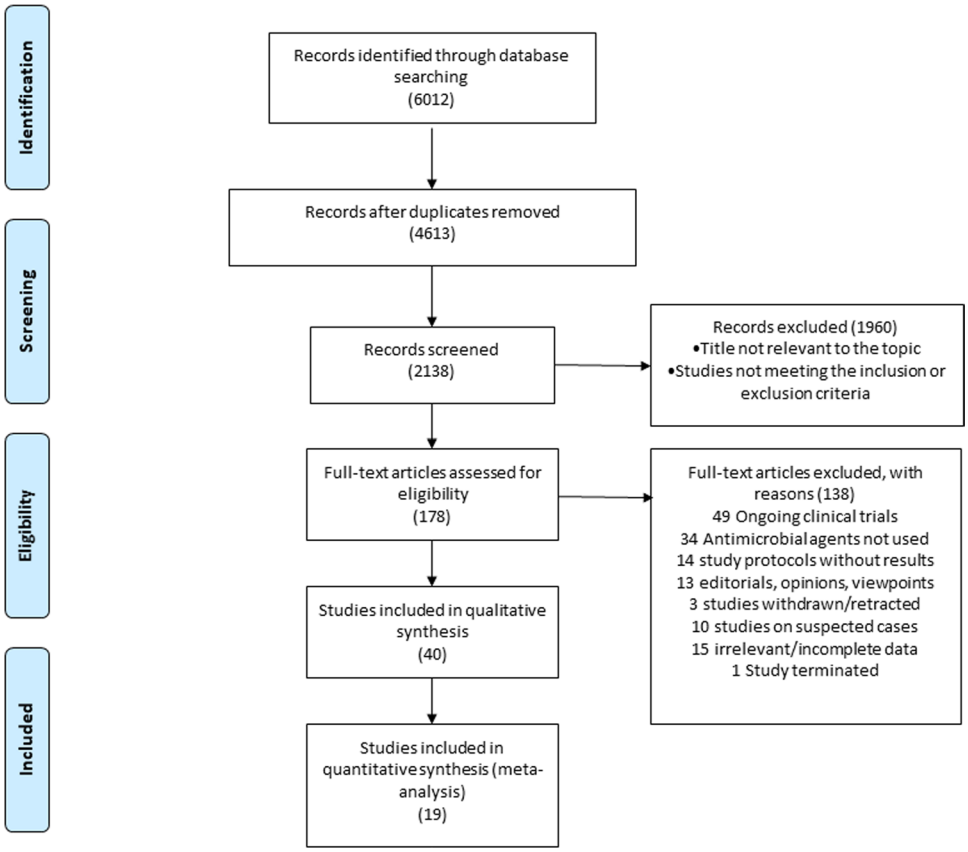

Fig. 1 Study flow diagram based on PRISMA guidelines

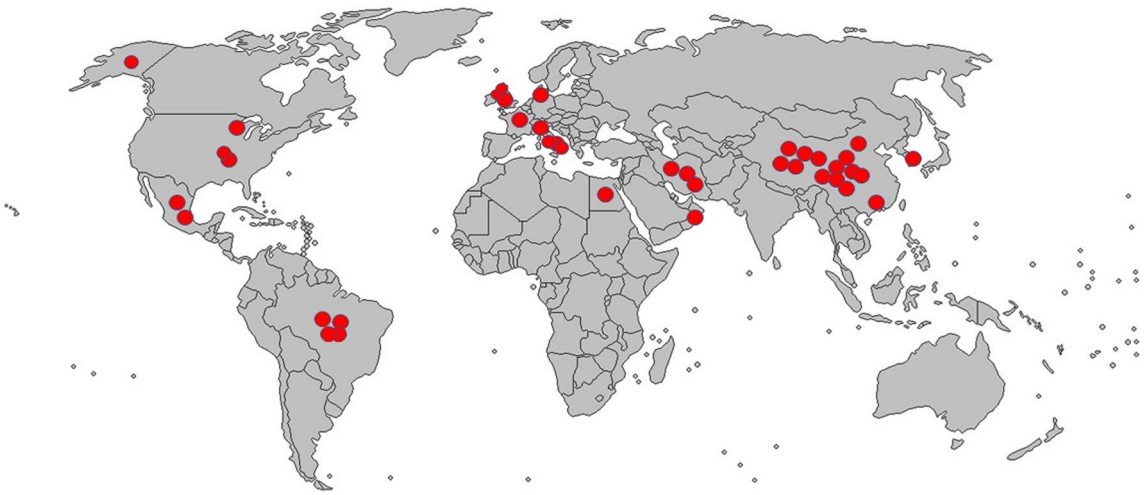

Fig. 2 Distribution of selected articles across the globe

studies were hospital based with only 1 specifically being an intensive care unit (ICU) based study. Sample size of the studied population varied from 20 to 136,855.

Meta-analysis of antibacterial agents used The names of specific antibacterial agents were mentioned in 23 of the 40 studies (57.5%) while the remaining studies mentioned only the use of 'antibiotics' without specifying the category of the antibacterial agents. In the random effect meta-analysis, pooled prevalence of azithromycin use was 24.5% (95% CI 22.9–26.2%), cephalosporins was 26.6% (95% CI 24.9–28.4) as shown in Table 2. There was considerable heterogeneity across all studies for all the antibacterial agents (I^2 = 96–99%) with moderate heterogeneity in proportions of carbapenems use. The summary estimate of pooled prevalence of individual antibacterial agents has been shown in Fig. 3. Only two of the studies quantified antibiotic usage in terms of daily defined doses (DDD).

Indications for use of antibacterial agents None of the studies clearly specified indications for antibiotic use. While 10 studies (25%) mentioned empirical use of antibiotics, remaining studies did not specify the reason for use. Bacterial co-infections/secondary infections were documented in four studies only comprising of a sample size of 1323 cases where co-infections were seen in 26 (1.9%, 95% CI

Table 2 Prevalence of antibacterial agents used in COVID-19 as per systematic assessment

Antibacterial agent	Studies (N)	Sample size (N)	No. of patients who received the antibiotic (n)	Prevalence (95% CI)
Macrolides	14	2699	750	27.7% (26.1–29.5)
Cephalosporins	8	2432	649	26.6% (24.9–28.4)
Azithromycin	12	2646	694	24.5% (22.9–26.2)
Fluoroquinolones	6	1200	122	10% (8.5–12)
Ceftriaxone	5	1992	181	9% (7.8–10.4)
Doxycycline	3	1004	82	8.1% (6.5–10)
Piperacillin/tazobactam	4	1067	86	8% (6.5–9.8)
Amoxycillin/clavulanate	4	1631	118	7.2% (6–8.6)
Carbapenem	4	763	33	4.3% (3–6)

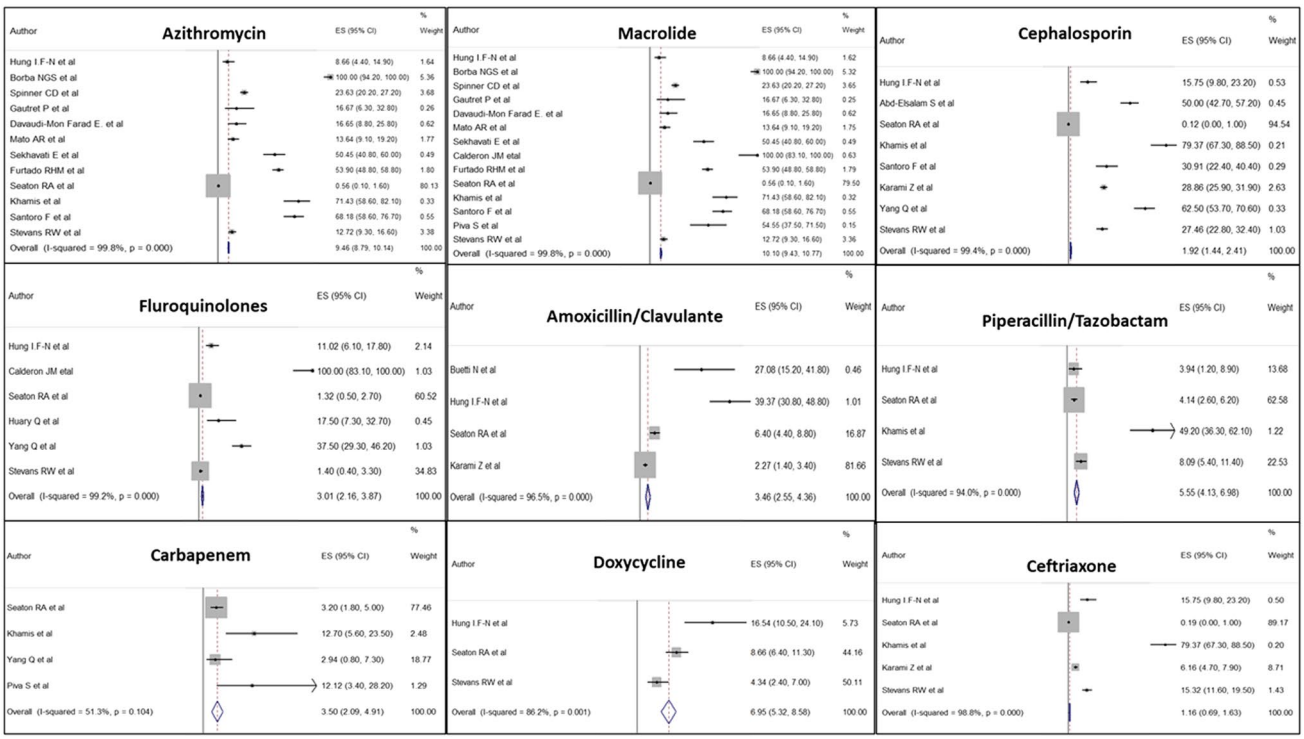

Fig. 3 Forest plots showing pooled prevalence of individual antibacterial agents

1.2–2.8%, $I^2 = 44.2$, moderate heterogeneity) of the cases (Fig. 4).

Severity of COVID-19 infections in the studies In 14 of the 40 studies, severity of COVID-19 infections as mild, moderate and severe was not mentioned. In the remaining studies, use of antibiotics based on severity of infections was mentioned only in two studies. However, in both the studies specific antibacterial agents for each category were not mentioned.

Assessment of bias

As detected by the funnel plots in Fig. 5, there was no bias in selection of studies on cephalosporin, carbapenem, amoxycillin-clavulanate and doxycycline while asymmetrical funnel plots were seen for azithromycin and macrolides, fluoroquinolones, piperacillin-tazobactam. There was no bias in article selection for antibacterial agents used in bacterial coinfections vis-a-vis empirical therapy.

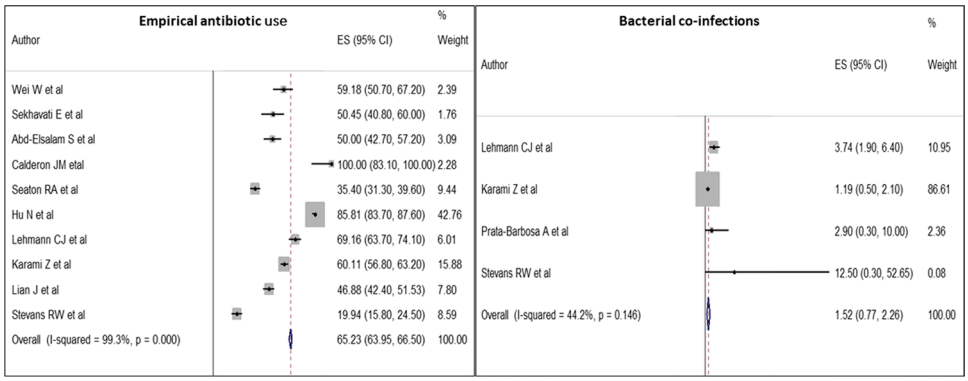

Fig. 4 Forest plots showing empirical antibiotic use and documented bacterial co-infections in COVID-19 patients

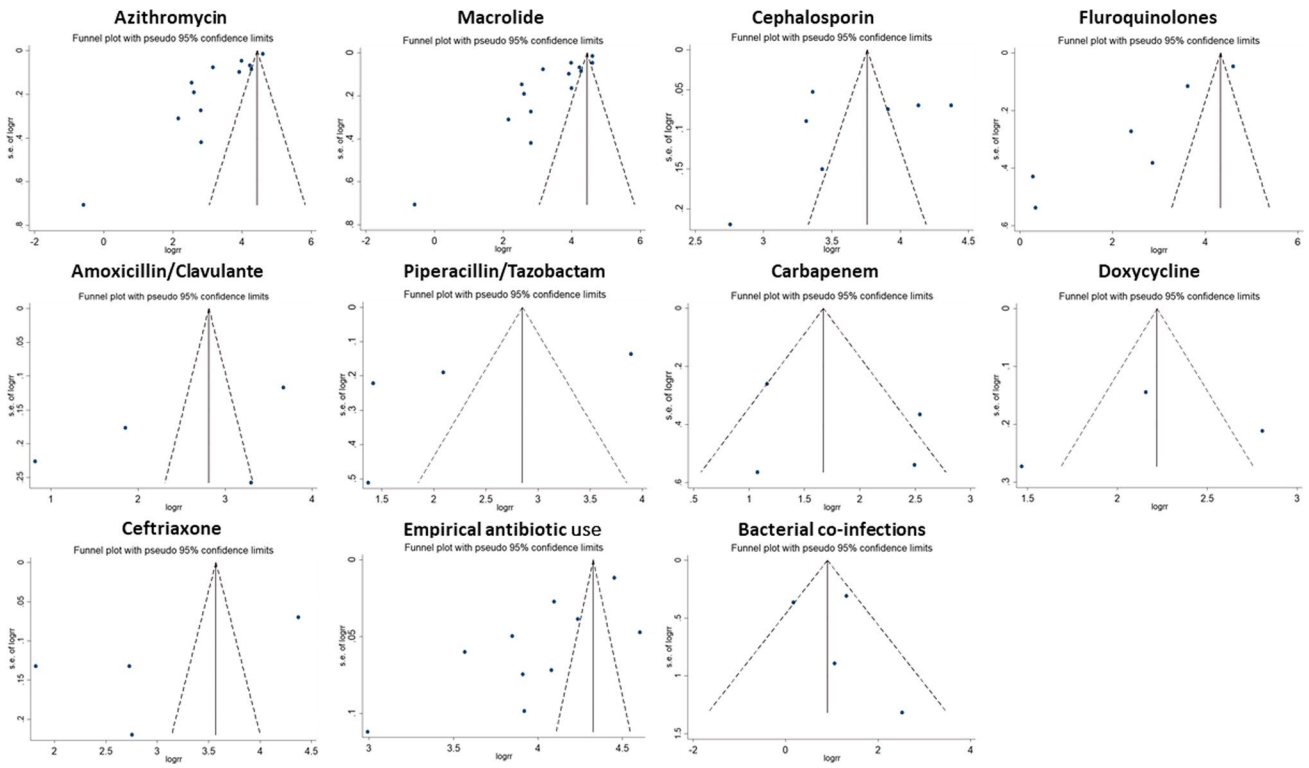

Fig. 5 Funnel plots showing assessment of publication bias for individual antibacterial agents

Discussion

This systematic review on the antibacterial agents used in COVID-19 patients tried to identify the specific agents that have been used and their indications to generate a baseline data on antibiotic use in COVID-19. As speculations on inappropriate and excessive usage of antibiotics is remarkably high, this review paves the way for early recognition of several problems related to antibiotic consumption, research studies documenting them and prevailing antibiotic policies and stewardship programmes during the pandemic. Systematic reviews on antibacterial agents used in the pandemic are not previously available in literature.

The review clearly showed that azithromycin was the most frequently used antibacterial agent during the pandemic. While the role of azithromycin in treatment of COVID-19 has been debatable throughout, there has been evidence of increase in its consumption in the community against a background of decrease in consumption of other antibiotics (Gagliotti et al. 2020). Efficacy of azithromycin is well established in cases of community acquired pneumonia (CAP), but it is effects on viruses lacks evidence (Sultana et al. 2020). Besides azithromycin, clarithromycin has also been used in COVID-19 patients (Calderón et al. 2020). WHO has also reported the widespread use of azithromycin especially with hydroxychloroquine even beyond recommendations (WHO 2020, NICE 2020).

Empirical use of cephalosporins, especially third generation cephalosporins, in ICUs has been common entity even before the pandemic (Hariri et al. 2017; Banerjee et al. 2013, 2018). While the pandemic has mostly concentrated on repurposing and repositioning of the drugs, consumption of antibiotics for presumptive co-infections might have already changed the existing AMR scenario. In this regard, among the cephalosporins, cefuroxime has also been proposed for repurposing (Durojaiye et al. 2020). This drug has also been used in 220 patients out of the 556 cases of empirical therapy in one of the studies (Karami et al. 2020). Another repurposed drug in this aspect is doxycycline which has been used with the reason that tetracyclines possess both antiviral and anti-inflammatory properties that might help to fight COVID-19 (Yates et al. 2020). Broad spectrum antibiotics in form of cephalosporins and fluoroquinolones have been used empirically in nearly 74% of the patients as suggested by another meta-analysis on bacterial coinfection in COVID-19 (Langford et al. 2020). The same analysis has shown that against this high antibiotic prescribing attitude, co-infections and secondary bacterial infections were demonstrated only in 3.5% and 14.3% of the COVID-19 cases respectively, despite recommendations for antibiotic use specifically in cases of documented infections (WHO 2020). In this systematic review too, of the included studies only four studies discussed the prevalence of lower rate of documented bacterial infections against high empirical antibiotic use.

The major strength of this study is that it is the first documentation of the specific antibacterial agents used in COVID-19, a preliminary step for necessary actions to curb the menace of AMR. However, the study was not without limitations. Though 19 studies were identified for meta-analysis, use of antibiotics might have been underrepresented as majority of the studies focussed on other aspects of treatment of COVID-19, not specifying antibiotic therapy. Besides, antibacterial agents have also been used in clinically suspected patients of COVID-19 which were not included in this review. The classes of antibiotics used had not been mentioned in most of the studies and data on use of antibacterial agents based on disease severity was lacking. Unequal distribution of the studies throughout the globe might have affected the results owing to variations in local policies prevailing in the regions, besides differences in patient population (Huttner et al. 2020). The considerable heterogeneity in the study effects could have resulted from the wide differences in the study designs of the selected articles among other factors affecting heterogeneity (Glasziou and Sanders 2002).

Nevertheless, the study clearly reveals that azithromycin and cephalosporins have been the most frequently used antibiotics in the pandemic despite evidence of low bacterial co-infection rates. To meet this increase in antibiotic consumption in healthcare set ups, initiation of 'One Health' approach is very essential along with a concomitant curb on antibiotic use in agribusiness (Strathdee et al. 2020). Speculating a rise in AMR based on these preliminary findings, we need to prioritize antimicrobial stewardship at double the existing pace to combat the impending crisis in the post-COVID era. Surge in AMR is likely to affect low- and middle-income countries (LMIC) drastically as some of them are also the major producers of antibiotics (Nature Microbiology 2020). Epidemiological studies with more and more evidence of actual quantity and indication of antibiotic use should be encouraged along with justifications for use based on severity of COVID-19.

It should be mentioned that AMR is a worldwide threat that incurs huge expenditures on the world economy and global health. The major concern is the fact that LMIC which are the major facilitators for easy dissemination of AMR are also the ones most affected by the burden of infections. Therefore, we suggest that utmost importance should be given to the implementation of antimicrobial stewardship in hospitals even in low resource countries based on our understanding of pathogenesis of the SARS-CoV-2 virus. Prudent and judicious use of antibacterial agents are necessary to curb the already existing menace of AMR. Lastly,

it is always advisable to follow policies based on evidence and therefore, documentation of the real need for antibacterial therapy in cases of bacterial co-infections should be prioritized.

Conclusion

This study showed that among the COVID-19 patients, azithromycin and cephalosporins have been used mostly on empirical basis in hospitals. There is lack of data on the use of specific antibacterial agents as most of the studies have not mentioned the name of the antimicrobial agents administered. Though presumptive antibacterial therapy for suspected bacterial co-infections was the commonest indication for their use, documented microbiological evidence of bacterial co-infections was not mentioned in majority of the studies. The data from the available studies had also not specified the administration or indication of antibacterial therapy based on the severity of the COVID-19. Though it was evident that azithromycin and cephalosporins were the commonest antibacterial agents used during the pandemic, dearth of details on several aspects could not predict their exact role in AMR. Therefore, future studies should consider these lacking details for better analysis of the situation.

Author contributions SS and AS have performed literature search. SS, AS and TB have done final selection for articles. AS and TB have extracted data. SS and TB have synthesized data and performed statistical analysis. SS, AS and TB have finally drafted the manuscript.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

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