Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Impact of COVID-19 pandemic on multidrug resistant gram positive and gram negative pathogens: A systematic review

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ABSTRACT

Background: There is paucity of data describing the impact of COVID-19 pandemic on antimicrobial resistance. This review evaluated the changes in the rate of multidrug resistant gram negative and gram positive bacteria during the COVID-19 pandemic.

Methods: A search was conducted in PubMed, Science Direct, and Google Scholar databases to identify eligible studies. Studies that reported the impact of COVID-19 pandemic on carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum beta-lactamase inhibitor (ESBL)-producing *Enterobacteriaceae*, vancomycin-resistant *enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Pseudomonas aeruginosa* (CPE) were selected. Studies published in English language from the start of COVID-19 pandemic to July 2022 were considered for inclusion.

Results: Thirty eligible studies were selected and most of them were from Italy (n = 8), Turkey (n = 3) and Brazil (n = 3). The results indicated changes in the rate of multidrug resistant bacteria, and the changes varied between the studies. Most studies (54.5%) reported increase in MRSA infection/colonization during the pandemic, and the increase ranged from 4.6 to 170.6%. Five studies (55.6%) reported a 6.8–65.1% increase in VRE infection/colonization during the pandemic. A 2.4–58.2% decrease in ESBL *E. coli* and a 1.8–13.3% reduction in ESBL *Klebsiella pneumoniae* was observed during the pandemic. For CRAB, most studies (58.3%) reported 1.5–621.6% increase in infection/colonization during the pandemic. Overall, studies showed increase in the rate of CRE infection/colonization during the pandemic. There was a reduction in carbapenem-resistant *E. coli* during COVID-19 pandemic, and an increase in carbapenem-resistant *K. pneumoniae*. Most studies (55.6%) showed 10.4 – 40.9% reduction in the rate of CRPA infection during the pandemic.

Conclusion: There is an increase in the rate of multidrug resistant gram positive and gram negative bacteria during the COVID-19 pandemic. However, the rate of ESBL-producing Enterobacteriaceae and CRPA has decrease during the pandemic. Both infection prevention and control strategies and antimicrobial stewardship should be strengthen to address the increasing rate of multidrug resistant gram positive and gram negative bacteria.

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Introduction

Antimicrobial resistance was one of the major public health challenges in the twenty first century prior to the COVID-19 pandemic [1,2]. Antimicrobial resistance is a global public health crisis that threatens several advancement in medical sciences inluding surgery, dialysis and chemotherapy that rely on the availability of effective antimicrobial agents [3]. Infections caused by antimicrobial resistant pathogens are associated with morbidity and mortality [4]. In the United States (US), three million multidrug resistant infections with 35,000 deaths are reported each year [3]. Globally, antimicrobial resistant pathogens cause an estimated 700,000 deaths every year and the mortality is projected to increase to 10 million deaths a year by 2050 in the absence of interventions to mitigate the rising trend of antimicrobial resistance [5]. Prior to the COVID-19 pandemic, the rate of healthcare-associated infections, especially in developing countries was high [6,7], and some of these infections were caused by multidrug resistant pathogens [7]. Prior to the COVID-19 pandemic, antimicrobial stewardship and infection control and prevention strategies were used as mitigation strategies against antimicrobial resistance [3,5]. However, the emergence of COVID-19 pandemic has caused major disruptions in healthcare systems that threaten the effectiveness these mitigation strategies [2,8–10]. The diversion of traditional infection control resources and measures such as, active surveillance; screening programme to detect colonization, and isolation of patients with multidrug resistant infections, to the management of the pandemic coupled with the high rate of antibiotic use among COVID-19 patients are precursors for the emergence and transmission of resistant pathogens [1,2,9,10]. In contrast, improvement in hand and environmental hygiene, decrease in local and international travels due to lockdowns and decrease in elective invasive procedures may reduce antimicrobial resistance [1,9]. In addition to the disruption of infection prevention and control measures, inappropriate use of antimicrobial agents prior to the pandemic [11,12] and during the pandemic [13] may contribute to the emergence and spread of antimicrobial resistance.

Currently, the impact of disruptions in healthcare systems during the COVID-19 pandemic on antimicrobial resistance is still unclear [14,15]. Limited resources have been allocated to the fight against antimicrobial resistant infections during the COVID-19 pandemic [1,16]. This has raised some concerns due to the obvious burden and threat posed by multidrug-resistant infections before the pandemic. The burden of antimicrobial resistance varies from one microorganism to the other. However, multidrug resistant gram positive and gram negative pathogens are recognised at the top of the global priority pathogens list for research and development. Gram negative pathogens including carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and third-generation cephalosporin-resistant and carbapenem-resistant *Enterobacteriaceae* (CRE) are listed as critical priority pathogens [17]. High priority pathogens include gram positive bacteria such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* [17]. Similarly, the Centers for Disease Control and Prevention (CDC) also categorised these pathogens as “urgent” and “serious” public health threats in the US [3]. These pathogens are difficult to treat due to limited choices of antibiotics and are associated with high morbidity and mortality rates. Therefore, the impact of COVID-19 on these multidrug resistant gram positive and gram negative pathogens remains an important issue during the pandemic. Data describing the changing in the trends of multidrug resistant pathogens during the COVID-19 pandemic are scarce [18]. The objective of this systematic review was to describe the impact of COVID-19 pandemic on multidrug resistant gram positive and gram negative pathogens including MRSA, vancomycin-resistant *Enterococci* (VRE), CRAB, CRPA, CRE, and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

Methods

Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement 2020 [19].

Eligibility criteria

All studies conducted in humans reporting the impact of COVID-19 pandemic on the prevalence of multidrug resistant pathogens using a quasi-experimental or interrupted time series analysis were considered for inclusion. Studies published from the start of the COVID-19 pandemic in December 2019 to July 2022 were eligible for inclusion. Studies that reported the prevalence of multidrug resistant pathogens during the COVID-19 pandemic without a pre-COVID-19 pandemic data and vice versa were excluded. Only studies

published in English language and available as free full-text were selected. Previous systematic reviews and meta-analyses, unpublished studies including preprints, correspondence and letter to editor were excluded. Only studies that compared the prevalence/incidence of multidrug-resistant pathogens such as CRAB, CRE, CRPA, ESBL-producing *Enterobacteriaceae*, MRSA and VRE between pre-pandemic and during the pandemic periods were selected.

Information sources

PubMed and Scopus databases were searched using the keywords and terms described below to identify eligible studies. Google scholar was also searched to find additional studies. The reference list of the selected studies was also examined for potentially eligible studies.

Search strategy

The relevant keywords for antimicrobial resistance and COVID-19 pandemic were combined using Boolean indicators (AND/OR). The following keywords were used in both PubMed and Scopus databases: Antimicrobial resistance OR resistance OR antibiotic resistance OR Multidrug resistant pathogens OR multidrug resistant organisms OR resistant organisms AND SARS-CoV-2 OR COVID-19 OR Coronavirus disease 2019 OR Severe acute respiratory syndrome coronavirus 2 OR Coronavirus infection OR coronavirus pandemic OR COVID-19 pandemic. The last search date was 27th July 2022.

Selection process

The results from PubMed, Scopus and Google Scholar searches were combined and screened for duplicates. The title and abstract of the non-duplicate studies was assessed based on the inclusion and exclusion criteria and irrelevant studies were removed. Full-text studies that fulfilled the eligibility criteria were selected and reviewed for data collection.

Data collection process

The data was collected using a predesigned data collection form. Data collection was conducted through review of the full-text article. The data was collected by one reviewer and a second reviewer verified the collected data for accuracy. Disagreement between the reviewers were resolved either by consensus or by inviting a third reviewer.

Data items

The following data items were extracted from the selected articles: author name and year of publication, country involved, study setting/number of centre, study design, period of the study, number of participants, characteristics of the patients, specific hospital units involved, prevalence of antimicrobial resistance before COVID-19 pandemic and during COVID-19 pandemic, type of microorganisms involved.

Results

Study selection

PubMed and Science Direct databases search yielded 4441 and 13,618 articles, respectively. However, only the first 1000 articles from Science Direct were assessed for inclusion. Therefore, only 5441 articles were retrieved from the two databases. Seventy eight additional articles were identified after screening the results from Google Scholar searches. A total of 5519 articles were retrieved from all the databases and 64 duplicates were removed. After screening the title and abstracts of the non-duplicate articles, 78 articles were assessed for inclusion in the review. Finally, 30 eligible full-text articles were selected and included in the review. Fig. 1 shows the article screening and selection process flowchart.

Study characteristics

Most of the studies were conducted in Italy (n = 8), Turkey (n = 3), Brazil (n = 3), China (n = 2) and Indonesia (n = 2). Europe accounted for 46.7% of the studies (n = 14). Most of the studies were conducted in a single centre (n = 18). The study setting included ICU (n = 7), geriatric ward (n = 1), psychiatric ward (n = 1) and haematology ward (n = 1). Twelve studies reported the inclusion of non-duplicate specimens. The guidelines used in the selected studies include the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (n = 9) and the Clinical and Laboratory Standard Institute (CLSI) (n = 8). The data source included surveillance data (n = 8) and hospital electronic or microbiology records (n = 10). Respiratory specimen including sputum, tracheal aspirate, endotracheal aspirate, and bronchoalveolar lavage (BAL) were the most common specimens included in the selected studies (n = 17). This was followed by blood (n = 16), urine (n = 11) and rectal swab (n = 5). Table 1 summarises the characteristics of the selected studies.

Changes in the rate of multidrug resistant bacterial pathogens during the COVID-19 Pandemic

Carbapenem-resistant Acinetobacter baumannii (CRAB)

Twelve studies reported the impact of COVID-19 pandemic on CRAB, with six of them indicating changes in the prevalence of CRAB infections [20–31]. Four studies described the impact of COVID-19 pandemic on CRAB using incidence density per patient-days [21–23,29]. Most of the studies (n = 7) reported an increase in the rate of CRAB infection/colonization during the pandemic [21–27] while two studies reported no changes in the rate of CRAB infection/colonization [20,28]. A 6.33% - 42.7% decrease in the rate of CRAB infection/colonization was reported in two studies[29,30]. Three studies reported a 107–621.6% increase in the incidence density of CRAB infection/colonization per 1000/100,000 patient-days during the pandemic [21–23]. Similarly, three studies reported a 5.87–56.9% increase in the prevalence of CRAB [24–27]. Table 2 shows the changes in CRAB infection/colonization during the COVID-19 pandemic.

Carbapenem-resistant Pseudomonas aeruginosa (CRPA)

A total of nine studies described the impact of COVID-19 disruption in healthcare systems on the rate of CRPA. Seven studies reported changes in the prevalence of CRPA infections during the pandemic, and four of them demonstrated a 10.4 – 40.9% reduction in the prevalence [20,24–26]. Overall, five studies (55.6%) showed 10.4 – 40.9% reduction in the prevalence/incidence of CRPA infections during the pandemic [20,21,24–26]. In one study, the incidence of CRPA infections in the wards increased from 0.41 per 1000 patient-days before the pandemic to 0.49 per 1000 patient-days during the pandemic [29]. However, the incidence of CRPA infections in the ICU declined by 25.4% during the pandemic [29]. Three studies demonstrated 2.9 – 22.2% rise in the prevalence of CRPA infections during the COVID-19 pandemic. Table 3 illustrates the impact of COVID-19 pandemic on CRPA infections.

Carbapenem-resistant Enterobacteriaceae (CRE)

Nineteen studies reported the impact of COVID-19 pandemic on CRE . Ten studies described the changes in CRE infections during the pandemic while the remaining seven demonstrated the changes in either carbapenem-resistant *K. pneumoniae* or carbapenem-resistant

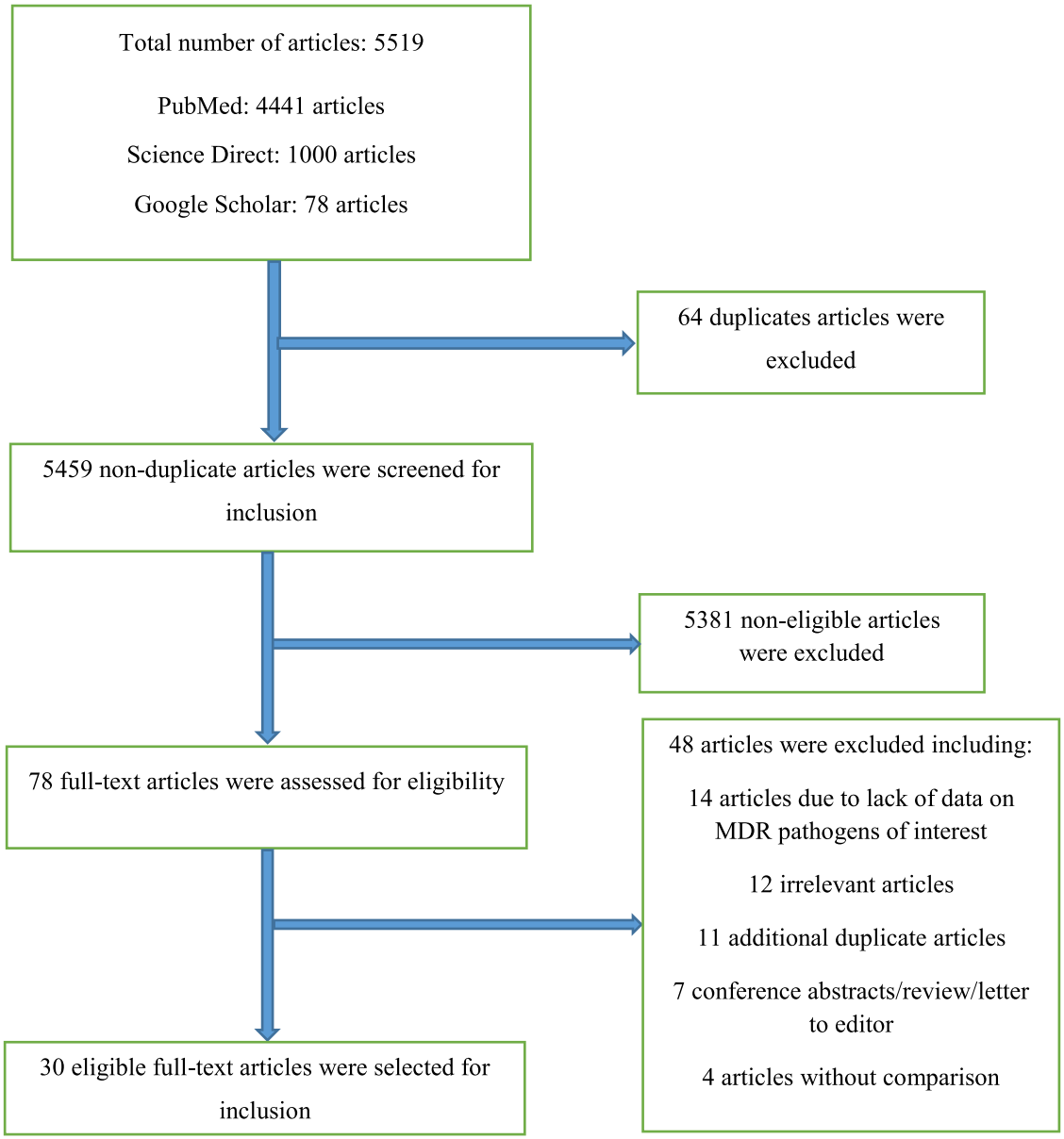

Fig. 1. Flow chart for the screening and selection processes.

E. coli or both. Five studies showed that CRE infections/colonization increased during the pandemic [21,23,29,37,44] and the increase ranged from 6.9% to 314.8% [21,29,37,44]. Two studies demonstrated decrease in carbapenem-resistant *E. coli* infection during the COVID-19 pandemic [20,25]. For carbapenem-resistant *K. pneumoniae*, most of the studies (n = 5) reported increase in the rate of infections [23,25,26,42,45] while two studies showed decrease in the rate of CR-KP infections during the COVID-19 pandemic [20,39]. Table 4 demonstrates the changes in CRE infection/colonization during the pandemic. [20,39].

Extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae

Twelve studies described the changes in ESBL-producing-*Enterobacteriaceae* infection/colonization during COVID-19 pandemic. Of this, eight studies reported the changes in *ESBL-producing-E. coli* [20,23,25,27,33,35,43] while seven studies showed the changes in ESBL-producing-*K. pneumoniae* [20,25,27,28,31]. A retrospective single centre study revealed that the rate of ESBL-producing *Enterobacteriaceae infection* decreased from 20.76% before the pandemic to 20.74% during the pandemic [37]. Five studies reported a 2.4–58.2% decrease in the prevalence of ESBL-*producing E. coli* infections during the pandemic [20,33,35,43] while one study demonstrated an increase in the prevalence of ESBL-producing-*E. coli* [23]. Three studies reported a 1.8–13.3% reduction in the prevalence of ESBL-producing-*K. pneumoniae* infections during the COVID-19 pandemic [20,27,28]. Table 5 shows the changes in the prevalence or incidence of ESBL-producing-*Enterobacteriaceae* infections during the COVID-19 pandemic.

Vancomycin resistant enterococci (VRE)

Nine studies reported the impact of COVID-19 pandemic on VRE infections. Six studies demonstrated changes in the rate of VRE infections [25–27,32,36,37]. Three studies indicated an increase in the rate of VRE infections during the pandemic [25–27,36] while one study showed no changes in the rate of VRE infections [32]. In one study, the rate of VRE infection decreased by 4.1% during the first quarter of the pandemic compared to the first quarter of the previous year (2019) [36]. However, an increase was found when the rate of VRE infections during the second quarter of 2020 was compared with the second quarter of the previous year [36]. In three

Table 1
Characteristics of the studies included in the review.

S/No.	Author and year	Country and continent	Study setting/No of centres	Study design	Period of the study	Number of participants	Characteristics of participants	Type of specimen	Guideline used	Source of data	Non-duplicate specimen
1	Caruso et al., 2021[32]	Italy, Europe	Single centre	Retrospective study	1st January 2019–31 st December 2020.	105 in the pre-pandemic period and 120 patients during the pandemic period	Hospitalized diabetic patients with diabetic foot infections	Soft tissue or bone biopsy	NA	Clinical isolates	NA
2	Lemenand et al., 2021[33]	France, Europe	Multicentre (1022 clinical laboratories)	Retrospective study	1st Jan 2019–17 th March 2020 (pre-pandemic period) to 11th May to 31st Dec 2020 (pandemic period)	505, 945 isolates in the pre-pandemic period and 259, 388 isolates during the pandemic period	Nationwide clinical microbiology surveillance system for primary care and nursing home residents.	Urine and others	EUCAST	Surveillance database	Yes
3	Hirabayashi et al., 2021[34]	Japan Asia	Multicentre / all units	Retrospective study	2018 – 2019 (pre-pandemic period) and 2020 (pandemic period)	16.7 million samples from 5.9 million hospitalized patients	NA	Blood, urine, stool and respiratory specimen	CLSI	Surveillance data	NA
4	Hessel Dias et al., 2022[24]	Brasil South America	Multicentre (99 adult ICUs)	Retrospective study	1st January 2019–31 st December 2020.	11,248 device associated infections	Hospitalized adult patients in the ICU diagnosed with DAIs	Blood, urine respiratory specimen	CLSI or EUCAST	Surveillance data	Yes
5	Polly et al. 2022[21]	Brasil South America	Acute care hospital (single centre)	Retrospective study	2017–2019 (pre-pandemic period) to 2020 (pandemic period)	2641 HCAIs caused by MDR organisms	Hospital HCAI surveillance data for both ICU and non-ICU wards	NA	CLSI	Hospital surveillance database	NA
6	Cole et al., 2021[35]	USA North America	Single centre	Retrospective study	January to June 2020	NA	Hospitalized patients with hospital acquired infections caused by MDRO	Urine, wound, blood and sputum	NA	Clinical isolates	NA
7	Hamidi et al., 2021[20]	Turkey Europe	Single centre	Retrospective study	1st January 2020–30 th April 2020	3384 specimens in the pre-pandemic period and 2170 specimen in the pandemic period	NA	Blood, urine, BAL, sputum, ETA	EUCAST	Clinical isolates	Yes
8	Pascale et al., 2021[22]	Italy Europe	Multicentre / ICU	Retrospective study	Jan – Apr 2019 (pre-pandemic period) Jan – Apr 2020 (pandemic period)	1252 patients (pre-pandemic) and 1151 patients (pandemic)	Adult patients admitted to the ICU	Tracheal aspirate and BAL, rectal swab, blood	EUCAST	Hospital administrative records and the databases of the microbiology laboratories.	Yes
9	Shbaklo et al., 2022[23]	Italy Europe	Single centre / Medical, surgical, and ICU wards	Retrospective and prospective study	1st Aug 2019 – 30th January 2020 (pre-pandemic period) To 1st February 2020 – 30th March 2021 (pandemic period)	NA	Patients with HAIs admitted to surgical, medical, and intensive careunits, from August	Blood, rectal swab and respiratory specimen	EUCAST	Hospital record	NA
10	Jeon et al., 2022[29]	Korea Asia	Multicentre / medical ward and ICU	Retrospective study	March 2018 to September 2019 (pre-pandemic period) March 2020 to September 2021 (pandemic period)	209,107 hospitalized patients	Hospitalized patients	NA	CLSI	Clinical data warehouse	Yes
11	Fontana et al., 2022[36]	Italy Europe	Single centre / inpatient and outpatient unit	Retrospective study	NA	Specimen from inpatient and outpatient	NA	Blood and others	NA	Epidemiological information system	NA

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Table 1 (*continued*)

S/No.	Author and year	Country and continent	Study setting/No of centres	Study design	Period of the study	Number of participants	Characteristics of participants	Type of specimen	Guideline used	Source of data	Non-duplicate specimen
12	Sinto et al., 2022[25]	Indonesia Asia	Single centre / hospital wide	Retrospective study	Jan – Dec 2019 (pre-pandemic) to Jan – Dec 2020 (pandemic period)	1895 hospitalized patients with bloodstream infections	Hospitalized patients	Blood	CLSI	Hospital information system	Yes
13	Karatas et al., 2021[37]	Turkey Europe	Single centre	Retrospective study	15th December 2019–15 th March 2020 (pre pandemic) And 15th March 2020 to June 2020 (pandemic)	3532 hospitalized patients and 4859 culture positive isolates. 3034 and 1702 samples	Hospitalized patients	Blood, respiratory tract, urinary tract, and other samples such as gastrointestinal tract, tissue, normally sterile fluids cultures	EUCAST	Microbiological database record	NA
14	Wee et al., 2021[38]	Singapore Asia	Multicentre / all units	Retrospective study	Jan 2018 – Jan 2020 (pre-pandemic) 01st February 2020 – 31st August 2020 (pandemic)	NA	Hospitalized patients	NA	NA	Surveillance data	NA
15	Micozzi et al., 2021[39]	Italy Europe	Single centre / haematology unit	Retrospective study	Nov 2019 – Feb 2020 (pre-pandemic) And Mar 2020 to Aug 2020 (pandemic)	203 patients with haematological malignancies	Hospitalized patients with haematological malignancies	Rectal swab, blood	NA	Surveillance data	NA
16	Gaspar et al., 2021[40]	Brazil South America	Single centre / Adult ICU	Retrospective study	Jan 2018 – Jan 2020 (pre-pandemic) and Feb – July 2020 (pandemic)	466 clinically positive samples	Adults admitted into ICU	Blood, surgical wound, urine, catheter tip, rectal swab and tracheal secretion	BrCAST	Electronic data record and from microbiology lab record	NA
17	Yang et al., 2021[41]	China Asia	Single centre /psychiatric unit	Retrospective study	2016 – 2020	NA	Respiratory specimen	Respiratory specimen (sputum and throat swab)	CLSI	NA	Yes
18	Tiri et al., 2020[42]	Italy Europe	Single centre / ICU	Retrospective study	1st January 2019 to June 2020	NA	All patients admitted into ICU	Rectal swab, urine and BAL	NA	Surveillance data	NA
19	Wardoyo et al., 2021[43]	Indonesia Asia	Single centre / private microbiology lab	Retrospective study	Sept 2019 – 1th March 2020 (pre-pandemic) and March 2020 to Sept 2020 (pandemic period)	308 Gram negative isolates in group Aand 243 Gram negative isolates in group B.	All clinical specimen	Blood, sputum, pus and urine	CLSI	NA	NA
20	AlDiba et al., 2021[44]	Saudi Arabia Asia	Single centre / hospital wide	Retrospective study	1st Jan 2019–31 st December 2020	249 patients (2019) and 264 patients (2020)	Inpatients and outpatients with positive culture	Urine, blood, swab, respiratory specimen, and wound	CLSI	Record from microbiology department	NA
21	Ullrich et al., 2021[30]	Germany Europe	National surveillance data	Retrospective study	2016–2020	NA	NA	NA	NA	Surveillance database	NA
22	Polemis et al. 2021[26]	Greece Europe	Multicentre /	Interrupted time series study	January 2018 to March 2021 January 2018 to March 2020 (pre-pandemic) and April 2020 to March 2021 (pandemic period)	17,837 g positive and negative bacterial isolated from blood and respiratory specimen among hospitalized patients	Hospitalized patients with Gram positive and negative bacterial isolates in 9 tertiary hospitals	Blood and respiratory specimen	CLSI or EUCAST	Surveillance data	Yes

(*continued on next page*)

Table 1 (*continued*)

S/No.	Author and year	Country and continent	Study setting/No of centres	Study design	Period of the study	Number of participants	Characteristics of participants	Type of specimen	Guideline used	Source of data	Non-duplicate specimen
23	Bentivegna et al., 2021[31]	Italy Europe	Single centre / hospital wide	Case control study	2017 to June 2020	1617 hospital discharges	NA	NA	NA	NA	NA
24	Lo´pez-Ja´come et al., 2022[45]	Mexico South America	Multicentre	NA	1st January 2019–31 st December 2019 (pre-pandemic) and 1st January 2020–31 st December 2020	NA	NA	blood, urine, respiratory samples, and from all specimens	CLSI	Hospital laboratory records	Yes
25	Cheng et al., 2022[46]	China Asia	Multicentre / hospital wide	Retrospective study	2012 – 2019 (pre-pandemic) and 2020 – 2021 (pandemic)	NA	Hospitalized patients with positive blood culture	Blood	NA	Hospital electronic database	Yes
26	Gasperini et al., 2021[47]	Italy Europe	Multicentre / Geriatric wards	Retrospective study	Dec 2019 – Feb 2020 (pre-pandemic) and May 2020 – July 2020 (pandemic)	73 geriatric patients	Hospitalized geriatric patients with at least a positive blood or urine culture	Blood and urine	EUCAST	Electronic and laboratory database	Yes
27	Bahçe et al., 2022[28]	Turkey Europe	Single centre / ICU	Retrospective study	1st April 2019–31 st March 2020 (pre-pandemic) and 1st April 2020–31 st March 2021 (pandemic period)	971 and 602 hospitalized patients in the pre- and during pandemic period, respectively	Hospitalised ICU patients with positive endotracheal aspirate	Endotracheal aspirate	EUCAST	NA	Yes
28	Lai et al., 2021[27]	Taiwan Asia	Single centre / hospital wide	Retrospective study	Jan – Jun 2019 (pre-pandemic) and Jan – Jun 2020 (pandemic)	NA	Both inpatient and outpatients were included	Various clinical sources	NA	NA	NA
29	Amarsy et al., 2022[48]	France Europe	Multicentre /	NA	Jan – April 2019 (pre-pandemic) and Jan – April 2020 (pandemic period)	NA	Hospitalized patients with blood culture sample	Blood	EUCAST	Laboratory information system	NA
30	Meschiari et al., 2022[49]	Italy Europe	Single centre	Interrupted time series study	Jan 2015 – Feb 2020 (pre-pandemic period) and March 2020 – November 2021 (pandemic period)	NA	Hospitalized patients with bloodstream infection	Blood	NA	Surveillance data	Yes

Table 2
Impact of COVID-19 pandemic on carbapenem-resistant *Acinetobacter baumannii* (CRAB).

Author	Pre-pandemic period (%)	Pandemic period (%)	Difference (%)
Studies that reported changes in the prevalence of CRAB during COVID-19 pandemic			
Hessel Dias et al., 2022[24]	7.9	12.4	+ 56.9
Hamidi et al., 2021[20]	100	100	0
Sinto et al., 2022[25]	46	48.7	+ 5.87
Ullrich et al., 2021[30]	-	-	-42.7
Polemis et al. 2021[26]	96.6[a] 97.7[b]	100[a] 99.2[b]	+ 3.52 + 1.54
Bahçe et al., 2022[28]	100	100	0
Lai et al., 2021[27]	3.35	4.24	+ 26.6
Studies that reported changes in incidence density of CRAB			
Polly et al. 2022[21]	0.53 *	1.10	+ 107
Pascale et al., 2021[22]	5.1[#; α] 5.1[#; β]	36.8[#; α] 26.4[#; β]	+ 621.6 + 417.6
Shbaklo et al., 2022[23]	0.32 *	2.0 *	+ 525.0
Jeon et al., 2022[29]	0.79 *; c 8.94 *; d	0.74 *; c 7.28 *; d	-6.33 -18.6

* = cases per 1000 patient days; # = cases per 10,000 patient days; α = colonization only; β = infection only; [a] = blood specimen; [b] = respiratory specimen; [c] = ward data; [d] = ICU data

studies, changes in VRE infections was described using incidence density per 1000 patient-days [21,29,35]. A 10–80% decrease in the incident-density of VRE infections was reported in two studies [21,35] while one study showed a 50% increase in the incident density per 1000 patient-days. Overall, five studies reported increase in VRE infections during the pandemic compared to the pre-pandemic period [25–27,29,36] while three studies demonstrated reduction in VRE infections during the pandemic [21,35,37]. Table 6 summarizes the impact of COVID-19 pandemic on VRE infection/colonization.

Methicillin resistant Staphylococcus aureus (MRSA)

Twenty two studies described the changes in the prevalence/incidence of MRSA infections/colonization during the COVID-19 pandemic. Of the 22 studies, 11 studies described the changes in the prevalence of MRSA infections [20,25–27,32,36,37,41,44,45,47] with eight of them reporting increase in the prevalence of MRSA infections [25–27,37,41,44,45,47]. Eight studies showed the changes in MRSA infections during COVID-19 pandemic using incidence density per 1000 or 10,000 patient-days [21,23,29,31,35,38,46,48], and four of them demonstrated increase in the incidence density of MRSA infections during the pandemic [21,23,46,48]. Overall, most of the studies (54.5%) reported increase in the prevalence/incidence of MRSA infections/colonization during the COVID-19 pandemic and the increase ranged from 4.6% to 200.0%. Table 7 reveals the impact of COVID-19 pandemic on MRSA infections/colonization.

Discussion

This systematic review evaluated the impact of COVID-19 pandemic on multidrug resistant gram positive and gram negative pathogens. Thirty studies were included in the review. There was limited number of studies that evaluated the impact of COVID-19 pandemic on multidrug resistant pathogens. Most of the studies were conducted in Europe and Asia. There was paucity of data from Africa, North America and South America. This highlights the need for more studies, especially from Africa to provide an insight into the trend of multidrug resistant infections during the COVID-19 pandemic. In the current study, the impact of COVID-19 pandemic on CRAB infections varied between the studies. The variations could be due to differences in the prevalence and the trend of CRAB infections before the COVID-19 pandemic and the differences in the effectiveness of the infection prevention and control measures implemented during the pandemic. Most of the studies demonstrated that there was an increase in the rate of CRAB infections during the COVID-19 pandemic. This could be attributed to an increase in the risk factors for CRAB infections during the COVID-19 pandemic including the use of immunosuppressive therapy, use of invasive devices such as ventilation, and central and peripheral catheters, and increase in ICU admissions [50–55]. In addition, the shortage of protective personal equipment during the COVID-19 pandemic compromised infection control practices in hospitals, thereby increasing the risk of CRAB transmission [56,57]. Furthermore, the inappropriate use of carbapenems among COVID-19 patients may be another reason for increase in CRAB infections and colonization during the pandemic [13]. Studies have shown that A. *baumannii* is a common pathogens isolated among COVID-19 patients with co-infections and those with secondary infections [58,59]. Therefore, infection control and prevention strategies such as flagging of patients at high risk of CRAB infections or colonization for early contact precaution, hygiene and isolation to prevent cross-transmission is recommended.

Available evidence showed increasing rate of VRE infections prior to the COVID-19 pandemic [60,61]. The current review revealed that most studies demonstrated an increase in VRE infections and colonization during the COVID-19 pandemic. The increase may be a continuation of the rising trend of VRE infections before the pandemic, and may not be linked to the failure of the infection

Table 3
Impact of COVID-19 pandemic on carbapenem-resistant *Pseudomonas aeruginosa* infections.

Author	Pre-pandemic period (%)	Pandemic period (%)	Difference (%)
Studies that reported changes in the prevalence of CRPA			
Sinto et al., 2022[25]	27	24.2	-10.4
Hessel Dias et al., 2022[24]	3.3	2.6	-21.2
Hamidi et al., 2021[20]	47.1	34.6	-26.5
Polemis et al. 2021[26]	62.9	37.2	-40.9
Lai et al., 2021[27]	0.9	1.1	+ 22.2
Bahçe et al., 2022[28]	47.4	50.0	+ 5.5
Studies that reported changes in incidence density of CRPA			
Polly et al. 2022[21]	0.42 *	0.36 *	-14.3
Shbaklo et al., 2022[23]	0.69 *	0.71 *	+ 2.9
Jeon et al., 2022[29]	0.41 *; a 2.95 *; b	0.49 *; a 2.20 *; b	+ 19.5 -25.4

* = cases 1000 patient days;
[a] = ward data;
[b] = ICU data

Table 4
Impact of COVID-19 pandemic on the prevalence of carbapenem-resistant *Enterobacteriaceae* infections/colonization.

Author	Pre-pandemic period (%)	Pandemic period (%)	Difference (%)
Studies that reported changes in the prevalence of carbapenem-resistant *Enterobacteriaceae*			
Fontana et al., 2022[36]	8.7[a]	10.6[a]	+ 21.8
	17.1[b]	13.2[b]	-22.8
Karatas et al., 2021[37]	2.97	3.64	+ 22.6
AlDiba et al., 2021[44]	5.4	22.4	+ 314.8
Ullrich et al., 2021[30]	NA	NA	-34.6
Studies that reported changes in prevalence of carbapenem-resistant *E. coli*			
Hamidi et al., 2021[20]	7.2	6.2	-13.9
Sinto et al., 2022[25]	16.3	10.8	-33.7
Studies that reported changes in prevalence of carbapenem-resistant *K. pneumoniae*			
Hessel Dias et al., 2022[24]	6.4	6.4	± 0.0
Hamidi et al., 2021[20]	23.9	18.1	-24.3
Sinto et al., 2022[25]	34.0	38.0	+ 11.8
Micozzi et al., 2021[39]	52.5	15.5	-70.5
Polemis et al. 2021[26]	87.8	88.6	+ 0.9
Lo´pez-Ja´come et al., 2022[45]	13.0	23.4	+ 80.0
Tiri et al., 2020[42]	4.0[α]	53.0[α]	+ 1225
Shbaklo et al., 2022[23]	3.41 *[c]	4.46 *[c]	+ 30.8
Studies that reported changes in incidence density of carbapenem-resistant *Enterobacteriaceae*			
Polly et al. 2022[21]	1.29 *	1.38 *	+ 6.9
Pascale et al., 2021[22]	47.3[#; α]	40.2[#;α]	-15.0
	3.83[#β]	2.29[#β]	- 40.2
Jeon et al., 2022[29]	0.23 *	0.28 *	+ 21.7
Wee et al., 2021[38]	11.2 *	10.2 *	-8.9
Gaspar et al., 2021[40]	22 *	15.1 *	-31.4

[a] indicates first quarter pre-COVID-19 versus first quarter of COVID-19 pandemic; [b] = second quarter pre-COVID-19 versus second quarter of COVID-19 pandemic; [α] = colonization only; [β] = infections only; * = cases per 1000 patient days; [#] = cases per 10,000 patient days; [c] refers to *K. pneumoniae*

Table 5
Impact of COVID-19 pandemic on the prevalence of ESBL-producing-*Enterobacteriaceae*.

Author	Pre-pandemic period (%)	Pandemic period (%)	Difference (%)
Studies that reported changes in incidence density of ESBL *enterobacteriaceae*			
Karatas et al., 2021[37]	20.76	20.74	-0.09
Studies that reported changes in prevalence of ESBL producing *E. coli*			
Lai et al., 2021[27]	0.90	0.90	0.0
Hamidi et al., 2021[20]	40.5	35.2	-13.1
Sinto et al., 2022[25]	76	74.2	-2.4
Lemenand et al., 2021[33]	3.1	2.9	-6.5
Wardoyo et al., 2021[43]	50	20.9	-58.2
Cole et al., 2021[35]	1.4 *	1.1 *	-21.4
Shbaklo et al., 2022[23]	2.12 *	2.26 *	+ 6.6
Hirabayashi et al., 2021[34]	20,506[a]	19,892[a]	-2.99
	20,630[b]	20,748[b]	+ 0.6
Studies that reported changes in rate of ESBL *enterobacteriaceae*			
Bentivegna et al., 2021[31]	9.4[#; α]	4.8[#; α]	-48.9
	9.4[#; β]	10.6[#; β]	+ 12.8
Sinto et al., 2022[25]	85.3	82.5	-3.3
Hamidi et al., 2021[20]	68.2	64.9	-4.8
Bahçe et al., 2022[28]	90.5	88.9	-1.8
Lai et al., 2021[27]	1.3	1.50	-13.3
Hirabayashi et al., 2021[34]	3142[a]	3595[a]	-14.4
	4357[b]	4357[b]	+
Amarsy et al., 2022[48]	0.02[#; c]	0.04[#; c]	+ 100
	0.03[#; d]	0.09[#; d]	+ 200

* = cases per 1000 patient-days; [#] = cases per 100 patient-days/discharges; [α] = pre-pandemic versus non-COVID-19 wards; [β] = pre-pandemic versus COVID-19 wards; [a] = second quarter pre-COVID-19 versus second quarter of COVID-19 pandemic; [b] = third quarter pre-COVID-19 versus third quarter of COVID-19 pandemic; [c] = March 2019 versus March 2020; [d] = April 2019 versus April 2020.

prevention and control measures during the pandemic. Increase in VRE infections despite improved hand and environmental hygiene, and the use of face masks by patients and healthcare workers may be explained by the inappropriate use of vancomycin among COVID-19 patients for empirical therapy against secondary bacterial infections [13]. Therefore, infection control and prevention measures must be strengthened coupled with antimicrobial stewardship to mitigate the emergence and transmission of VRE infections during the pandemic. This review also demonstrated that most of the studies reported a decline in the prevalence of ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae* during COVID-19 pandemic. This was in contrast to the rising trend of ESBL-producing *Enterobacteriaceae* infections prior to the COVID-19 pandemic [62,63]. This implies that there was a reduction in the prevalence of ESBL-producing *Enterobacteriaceae* during the COVID-19 pandemic. The reduction in ESBL-producing *Enterobacteriaceae* could be explained by multiple factors with infection prevention and control strategies, and antimicrobial stewardship contributing to this trend. In addition, national lock downs implemented by governments across the world to control the transmission of COVID-19 caused reduction in international and local travels which is a major risk factor for the transmission of ESBL-producing *Enterobacteriaceae* infections [64,65]. With the easing of the COVID-19 restrictions such as the resumption of international travels, additional studies are required to evaluate the trend of ESBL-producing *Enterobacteriaceae* infection during the pandemic.

The prevalence of MRSA infections was declining before the COVID-19 pandemic began [66,67]. However, this trend was not universal because an increasing trend was observed in some countries [68,69]. In the current review, more than 50% of the studies revealed increase in the prevalence of MRSA during the COVID-19 pandemic and this increase ranged from 4.6% to 200%. The change in the trend of MRSA during the pandemic suggests that the COVID-19 pandemic has caused an increase in the prevalence of MRSA. Increase in the prevalence of MRSA during the pandemic can be

Table 6
Impact of COVID-19 pandemic on the prevalence of vancomycin-resistant *Enterococci*.

Author	Pre-pandemic period (%)	Pandemic period (%)	Difference (%)
Studies that reported changes in the prevalence of VRE			
Sinto et al., 2022[25]	0	20	+
Fontana et al., 2022[36]	7.4[a] 4.3[b]	7.1[a] 6.0[b]	-4.1 + 39.5
Caruso et al., 2021[32]	0	0	± 0
Karatas et al., 2021[37]	2.11	1.29	-38.9
Polemis et al. 2021[26]	35.4	47.2	+ 33.3
Lai et al., 2021[27]	0.74	0.79	+ 6.8
Studies that reported changes in incidence density of VRE			
Polly et al. 2022[21]	0.65 *	0.59 *	-10.2
Cole et al., 2021[35]	0.5 *	0.1 *	-80
Jeon et al., 2022[29]	0.46 *	0.69 *	+50

* = per 1000 patient days; [a] = first quarter pre-COVID-19 versus first quarter of COVID-19 pandemic; b = second quarter pre-COVID-19 versus second quarter of COVID-19 pandemic

explained by the high rate of empirical antibiotic use among patients with COVID-19 infection without a commensurate high risk of secondary bacterial infections [13]. Evidence from a previous meta-analysis demonstrated that there is an association between antibiotic exposure and MRSA infections [70]. Therefore, strategies to promote appropriate use of antibiotics among COVID-19 and non-COVID-19 patients is recommended to prevent the emergence of MRSA strains in healthcare facilities. The finding of this review implies that compliance with hand and environmental hygiene, and the use of facemask during the pandemic did not reduce the prevalence of MRSA infections. The disruption of certain infection control measures including active surveillance, isolation of MRSA carriers, and contact precautions by healthcare providers could explain the rising prevalence of MRSA during the COVID-19 pandemic.

There was an increase in the prevalence of carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant K. *pneumoniae* during the COVID-19 pandemic and this has multifactorial explanations. First, available evidence demonstrate a rising rate of CRE infections before the COVID-19 pandemic [3,71], and this suggests that the increase in CRE during the pandemic may be a continuation of the rising trend before the pandemic. Secondly, the risk factors for CRE infections including prolonged hospital admission, use of invasive devices, exposure to cephalosporins and carbapenems, and intensive care unit admission [71] are common among hospitalized COVID-19 patients. This could also explain the increase in the prevalence of CRE infections during the pandemic. Inappropriate use of empirical antibiotics among COVID-19 patients is a precursor for the emergence and transmission of CRE infections [13]. There was a reduction in the prevalence of carbapenem-resistant *E. coli* during the COVID-19 pandemic and the reasons for this is not clear. However, the decrease could be attributed to improvements in hand and environment hygiene, use of facemasks and decrease in hospital admissions for non-COVID-19 diseases during the pandemic. Additional studies are required to unravel the factors that contributed to the decline in the rate of carbapenem-resistant *E. coli* infections during the COVID-19 pandemic.

Most of the studies reported a reduction in the prevalence of CRPA during the pandemic. Evidence has shown that previous use of carbapenem, use of medical devices and ICU admission are major risk factors for CRPA infection [54]. The reduction could be attributed to improved hand and environmental hygiene in the ICU during the COVID-19 pandemic which may limit the transmission of CRPA within and outside the ICU. However, the reduction in the prevalence of CRPA despite an increase in the use of carbapenems

Table 7
Impact of COVID-19 pandemic on the prevalence/incidence of MRSA.

Author	Pre-pandemic period (%)	Pandemic period (%)	Difference (%)
Studies that reported changes in the prevalence of MRSA			
Caruso et al., 2021[32]	41.0	22	-86.3
Hamidi et al., 2021[20]	17.6	14.3	-18.8
Sinto et al., 2022[25]	3.4	9.2	+ 170.6
Karatas et al., 2021[37]	1.75	2.35	+ 34.3
Yang et al., 2021[41]	2.3	20.6	+ 795.6
AlDiba et al., 2021[44]	16.1	17.2	+ 6.8
Lopez-Ja´come et al., 2022[45]	15.2	36.9	+ 142.8
Gasperini et al., 2021[47]	0.0	2.1	+
Lai et al., 2021[27]	2.41	2.69	+ 11.6
Polemis et al. 2021[26]	34.3%	44.8%	+ 30.6
Fontana et al., 2022[36]	9.1[a] 4.7[b]	6.0[a] 5.2[b]	-34.1 + 10.6
Studies that reported changes in incidence density of MRSA			
Polly et al. 2022[21]	0.24 *	0.46 *	+ 91.7
Cole et al., 2021[35]	1.2 *	0.7 *	-41.7
Shbaklo et al., 2022[23]	0.75 *	0.97 *	+ 29.3
Jeon et al., 2022[29]	0.86 *; [c] 6.27 *; [d]	0.9 *; [c] 4.30 *; [d]	+ 4.6 -31.4
Wee et al., 2021[38]	11.7[#]	6.4[#]	-45.3
Ullrich et al., 2021[30]			-28
Bentivegna et al., 2021[31]	14[α]	4.2[α]	-70
Cheng et al., 2022[46]	27.76[β; e] 25.66[β; f]	31.34[β; e] 29.72[β; f]	+ 12.9 + 15.8
Hirabayashi et al., 2021[34]	40,758 [g] 40,158 [h]	35264 [g] 35,111 [h]	-13.5 -12.6
Amarsy et al., 2022[48]	0.01[α; l] 0.01[α; j]	0.02[i] 0.03[j]	+ 100 + 200
Meschiari et al., 2022[49]	-	-	NA

* = cases per 1000 patient days; [#] = cases per 10,000 patient days; [a] = first quarter pre-COVID-19 versus first quarter of COVID-19 pandemic; [b] = second quarter pre-COVID-19 versus second quarter of COVID-19 pandemic; [c] = ward data; [d] = ICU data; [α] = cases per 100 patient-days/discharge; [β] = cases per 100,000 admissions; [e] = community-acquired bacteremia; [f] = hospital-acquired bacteremia; [g] = second quarter pre-COVID-19 versus second quarter of COVID-19 pandemic; [h] = third quarter pre-COVID-19 versus third quarter of COVID-19 pandemic; [i] = March 2019 versus March 2020; [j] = April 2019 versus April 2020.

among COVID-19 patients highlights the need for additional studies to explore the factors responsible for this reduction [13]. The current review has a number of limitations which should be considered when interpreting the results. First, only open access articles were selected for inclusion and more than 90% of articles from science direct were not assessed for inclusion. These factors led to the limited number of studies from Africa, and North and South America, which may limits the generalizability of the study. Second, there was heterogeneity in the study design, duration of study, method of detection and the laboratory guidelines used in the selected study and this increase the risk of assessment bias. Third, there was also lack of consistency in the measurement used in the studies; some studies reported the changes in the rate of multidrug resistant pathogens using prevalence while some used incidence per 1000 or 10,000 patient days. These differences make it difficult to conduct a quantitative summary of the impact of COVID-19 pandemic on antimicrobial resistance. Fourth, most of the selected studies described the impact of COVID-19 pandemic on multidrug resistant pathogens in hospital setting. There is limited data to describe the trend of the organisms in the community. Fifth, few studies reported the differences between the impact of COVID—9 pandemic on multidrug resistant pathogens in the ICU and non-ICU settings. Future studies should address these limitations to provide quality and consistent data to summarize the impact of COVID-19 pandemic on antimicrobial resistance.

Conclusion

COVID-19 pandemic has caused disruption in infection control and prevention measures and this had an impact on the rate of multidrug resistant pathogens. There is limited studies that evaluated the impact of COVID-19 pandemic on antimicrobial resistance from Africa, North America, South America and Asia. There is an increase in the rate of CRAB, CRE, VRE, and MRSA infection/colonization during the COVID-19 pandemic. However, the rate of ESBL-producing *Enterobacteriaceae* and CRPA has decreased during the pandemic. Disruptions of contact precaution, active surveillance, isolation of infected or colonized patients coupled with the high rate of antibiotic use among COVID-19 patients are the possible reasons for the increase in multidrug resistant pathogens during the COVID-19 pandemic compared to the period before the pandemic. Infection prevention and control measures and antimicrobial stewardship interventions are recommended to mitigate against the rising rate of multidrug resistant pathogens.

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