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Review

Impact of the COVID-19 pandemic on healthcare-associated infections and multidrug-resistant microorganisms in Italy: A systematic review

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ABSTRACT

Background: The diffused and prolonged SARS-CoV-2 transmission lead to high levels of hospitalization. During this period, the focus of sanitary structures was to contain COVID-19 mortality and this may have reduced the application of health associated infection (HAI) and multidrug resistant microorganism (MDRO) prevention programs.
Methods: A search was performed in PubMed, Science Direct, and Google Scholar databases to identify clinical observational studies that reported the impact of COVID-19 pandemic on the prevalence or incidence on HAIs and/or MDROs from December 2019 to August 2024 in Italy. Studies were included if they reported a comparison with pre-pandemic period and had a full-text available. Eligible studies were assessed for risk of bias and quality with NHI Quality Assessment Tool by two researchers independently. Data were represented in tables and a narrative synthesis was made in the text.
Results: Selected studies included 4 studies reporting data on HAI (1497 total patients) and 11 studies reporting data on MDRO (80388 total patients). The majority of the studies reported an increase in HAI prevalence (9–11.1 % range) and MDRO, in particular, gram negative MDRO had an increase range of 0.8 %-45.6 % and gram positive MDRO an increase range of 0.5 %-81.8 % from pre- to post-COVID-19 period in the different studies considered
Conclusion: These findings underscore the critical need for active surveillance in hospital wards, the implementation of antibiotic stewardship and prescribing programs to mitigate the impact of such crises on healthcare-associated infections and antimicrobial resistance. Furthermore, permanent training of healthcare personnel is necessary.

Contents

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Introduction

The diffused and prolonged SARS-CoV-2 transmission lead to high levels of hospitalization. During this period, the focus of sanitary structures was to contain COVID-19 related mortality and this may have reduced the application of health associated infection (HAI) and multidrug resistant microorganism (MDRO) prevention programs. The response to COVID-19 pandemic, moreover, may have caused a significant shortage of healthcare personnel and personal protective equipment that are very important for prevention measures.

Antimicrobial resistance (AMR) is the ability of microorganisms to survive and grow despite an antimicrobial agent that should inhibit or kill them. AMR is one of the most crucial public health threats and is associated with 4.95 million deaths with bacterial AMR and 1.27 million deaths attributable to bacterial AMR [1]. In Europe, 541 000 deaths (95 % UI 370 000–763 000) are associated with bacterial AMR and 133 000 deaths (90 100–188 000) are attributable to bacterial AMR in the whole WHO European region in 2019 [2]. The six leading pathogens for AMR associated-deaths are: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* and fungi, especially Candida, which are responsible for central line-associated bloodstream infections (CLABSIs), ventilator-associated pneumonia (VAP), urinary tract infections, peritonitis and meningitis [2–5].

AMR incidence and antibiotic consumption in Italy are among the highest in Europe. Antibiotics overuse and misuse play a major role in AMR, for this reason, implementing antimicrobial stewardship (AMS) programs may effectively reduce antimicrobial consumption and AMR risk [6].

The onset of coronavirus disease (COVID-19) pandemic has affected the health care department worldwide, in particular intensive care units (ICUs) suffered the most from the burden of the pandemic, due to the frequent requirement of ventilation support in COVID-19 patients. The considerable increase in ICU beds and supplies requirement, the shortage of healthcare personnel negatively affected some traditional activities. The organizational challenges due to COVID-19 pandemic, in particular, have limited the efficacy of traditional infection prevention and control protocols, in terms of lack of surveillance efforts, process measures and containment strategies and had an impact on healthcare-associated infection (HAIs) rates [7].

During COVID-19 pandemic, limited resources have been allocated also to the fight against antimicrobial resistant infections and antibiotic prescription raised considerably even if the rates of microbiologically confirmed bacterial co-infection were low and most patients received more than one type of antibiotics [8]. An increase in the rate of MultiDrug Resistant Organisms (MDROs) gram positive and gram negative bacteria during the COVID-19 pandemic was reported, whereas, there was a decrease of rate of extended-spectrum beta- lactamase inhibitor (ESBL)-producing Enterobacteriaceae and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) during the COVID-19 pandemic [9].

Nevertheless, evidence on the impact of COVID-19 on HAIs and *MDROs* is still limited and controversial. This review aims to examine the incidence of healthcare-associated infections (HAIs) and multidrug-resistant organisms (MDROs) in Italy, comparing data from before and during the COVID-19 pandemic.

Methods

Study design

This was a systematic review carried out according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement 2020 [10]. The systematic review was registered in Open Science Framework (OSF) Registries, registration DOI: https://doi.org/10.17605/OSF.IO/3VSNW.

Eligibility criteria

We considered for inclusion all clinical studies conducted in humans that reported the impact of COVID-19 pandemic on the prevalence or incidence of pandemic on HAIs and/or MDROs conducted from December 2019 to August 2024 in Italy. Studies that did not have a comparison with the pre-pandemic period were excluded. Pilot studies, preprint, correspondence, letters to editor, commentaries, unpublished studies, systematic reviews, meta-analyses and reviews were excluded from the study. Studies that presented comparisons with countries or cities outside Italy were also excluded

Search and selection process

This systematic review was conducted searching in PubMed, Medline, Science Direct and Google Scholar databases to select eligible studies, using the following keywords and terms used to identify eligible studies: (“Healthcare-Associated Infections” OR HAI OR “Multidrug resistant pathogens” OR “antibiotic resistance” OR “antimicrobial resistance” OR resistance OR “multidrug resistant organisms” OR “resistant organisms”) AND (“COVID-19 coronavirus pandemic” OR “COVID-19 pandemic” OR SARS-CoV-2 OR “Coronavirus infection” OR “Coronavirus disease 2019” OR “Severe acute respiratory syndrome coronavirus 2”) AND (Italy). The last search was performed on 2 Sep 2024.

The results from the different databases were combined, duplicates were removed, inclusion criteria were applied to title and abstract, and full text of relevant studies were included in the review.

Data extraction

The data were collected from the review of full text articles and inserted in a dedicated database that was used for table production. Literature search, screening of studies eligibility, data extraction and database completion was done by one reviewer and checked for accuracy by a second reviewer, disagreements were resolved by a third author.

Risk of Bias and quality assessment

Eligible studies were assessed for risk of bias and quality using the Quality Assessment Tool from the US National Health Institute (NHI), using those that were applicable to our study [11]. Two researchers independently checked the potential risk of bias associated with each study.

Data collected

The database contained the following items: reference (author name and publication year), setting (type of hospital or ward), type of study, localization (north, center or south of Italy), measure of frequency and/or association, specimen, number of patients involved in the study, period of the study, results of the comparison of HAIs or *MDROs* before and during or after the COVID-19 pandemic, type of microorganism detected. Data were represented in tables and a narrative synthesis was made in the text.

Results

Study selection

The search on Medline, Science Direct and Google Scholar databases allowed to retrieve a total of 1424 articles; 16 duplicates were removed after screening the title and abstracts. Non-duplicate articles (1408) articles were assessed for inclusion, 1388 of them studies were excluded because did not respect inclusion criteria, 20 full text were screened for eligibility and finally 14 eligible full-text articles were included in the review (Fig. 1).

Study characteristic

Selected studies included 4 reporting data on HAI (1497 total patients) and 11 reporting data on MDRO (80388 total patients). The selected studies rates as high or moderate/high quality. Most of the studies were conducted in South of Italy (n = 10); 2 were performed in center of Italy and 3 in the north. All the studies were observational and retrospective. Almost half of the studies (n = 6) included patients from intensive/acute care unit, 3 studies from hematology units, 4 studies from general hospital setting, 1 from geriatric unit and 1 from tertiary care setting. Blood samples (n = 10) was the most common specimen in the selected studies, followed by respiratory specimens (n = 7), including nasal, pharyngeal swab and sputum), rectal swab/stool (n = 8) and urine (n = 5).

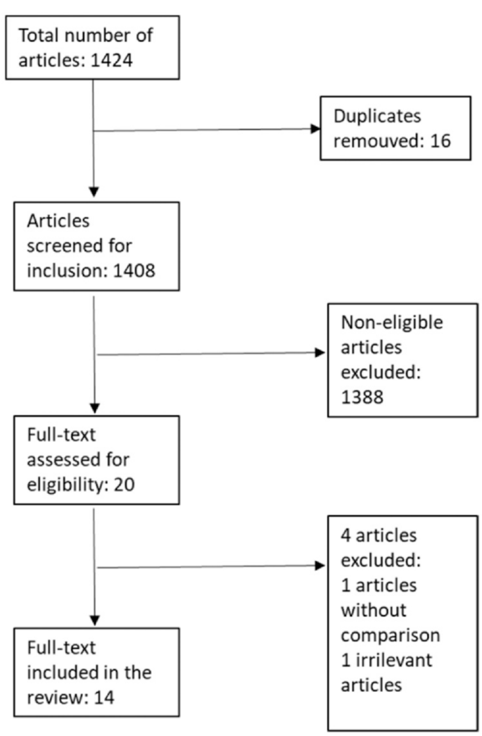

Fig. 1. Flow chart of articled screened and selected for inclusion in the review.

The majority of the studies reported an increase in HAI prevalence (9–11.1 % range) and MDRO, in particular, gram negative MDRO had an increase of 0.8 %-45.6 % and gram positive MDRO of 0.5 %-81.8 % from pre- to post-COVID-19 period.

Impact of COVID-19 pandemic on healthcare-associated infections

HAIs increase was reported in 3 out of 4 studies presented in this review [7,12,13] (Table 1). Only one study reported no significant variation in the prevalence of HAIs between 2019 and 2021 (38.5 % of HAIs in 2019 and 37.7 % in 2021, p = 0.910) [14].

As concerning the type of HAIs, one study reported that most infections were blood stream-related (85.8 %) and only 2 (14 %) device-related HAIs in the pre-pandemic period: one catheter-related bloodstream infections (CRBSI) and one catheter-associated urinary tract infections (CAUTI). In 2020, the HAIs registered were mainly ventilation-associated pneumonia (VAP, 37.8 %), followed by blood stream-related infections (31.1 %), CAUTI (22.2 %), *Clostridium difficile* infections (4.4 %), healthcare-associated pneumonia (2.2 %) and surgical site infections (2.2 %) [7].

Another study reported that pneumonia was the most common HAIs, followed by urinary tract infections and surgical site infections with a 47.5 % of infections that were device-related in COVID-19 pandemic period [12]. Ceparano and colleagues reported only device related HAIs: central/umbilical line associated bloodstream infections (CLABSI) and VAP both in pre- and pandemic period [13].

The most represented microorganism isolated were: *Acinetobacter baumannii, Enterococcus spp, Pseudomonas aeruginosa, Serratia marcescens, Klebsiella pneumoniae; Staphylococcus aureus* and *coagulase-negative Staphylococci* [7,12,13].

Impact of COVID-19 pandemic on multidrug resistant microorganism

MDROs increase was reported in all the 11 studies included in the review, including several types of microorganism (Table 2). Most frequently investigated MDRO*s* microorganism were: *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Enterococci.* In Table 3 were presented all the studies reporting an increase due to COVID-19 pandemic (Table 3).

Seven studies showed the increase of carbapenem-resistance of Gram negative bacteria as a consequence of COVID-19 pandemic. Three studies reported a significant increase in carbapenem-resistant *Acinetobacter baumannii* infection incidence from 0.3 % to 8 % pre pandemic to 1.7–11.8 in pandemic period ($P < 0.05$) [15–17]. Two studies described the increase of carbapenem-resistant *Pseudomonas aeruginosa* infections (1.5 % vs 5 %, $p < 0.05$) and one of carbapenem-resistant *Klebsiella pneumoniae* that increased (6.7 % vs 50 %, $p < 0.05$) from 2019 to 2020 [16,18]. The increase of carbapenem-resistance of Gram negative bacteria was observed also in a tertiary center and in an hospital setting [16,19].

In hematological department, there was a reduction of carbapenems-producing *Klebsiella pneumoniae* (15.5 % vs 52.56 % P,0.0001) and *Staphylococcus haemolyticus* vancomycin and teicoplanin resistant strains was observed (−49.3 % p = 0.016 and −51.3 % p = 0.015, respectively) during COCID-19 pandemic than in pre-pandemic period, whereas *Staphylococcus haemolyticus* had an increase in linezolid-resistant strains (+81.8 % $p < 0.001$) [14,20].

One study reported a significant reduction in the incidence of total MDROs bacterial infections during the pandemic compared to in pre-pandemic years ($p < 0.05$), however they also highlighted that there was a significantly higher incidence of *MDROs* bacterial infections in COVID-19 departments compared with other medical departments (29 % and 19 %, respectively) in the same period [21].

COVID-19 pandemic induced an increase also of carbapenem resistant *Klebsiella pneumoniae* (2 studies, 14 %-15.5 % vs 23 %-

Table 1
Characteristics and main results of Italian retrospective studies of COVID-19 impact on HAIs.

Reference	n. center /localization/ Frequency measure	Setting	Patients N.	Specimen	Period	Healthcare-Associated Infections	Type of microorganism identified in HAI
Baccolini et al., 2021 [7]	Single center, South Italy Incidence	Intensive care unit (ICU)	104	Blood, nasal swab, urine	Mar-Apr 2020 Vs 2019	The number of patients with at least one HAI was greater during the pandemic (27 patients, 43.6 %) than pre-pandemic (eleven patient, 26.2 %)	*Acinetobacter baumannii, Enterococci, Klebsiella pneumoniae, Enterobacteriaceae*
Deiana et al., 2022 [12]	Single center, South Italy Prevalence	Acute care wards	655	Blood, pharyngeal, nasal, rectal swab, urine, sputum	Nov-Dec 2021 Vs 2019	HAIs prevalence increased when compared to pre-pandemic values (9.0 %, vs 7.3 %)	*Pseudomonas aeruginosa, Klebsiella spp, Escherichia coli*
Ceparano et al., 2023 [13]	Single center, South Italy, Prevalence	Neonatal intensive care unit (NICU)	564	Blood, respiratory culture	Pre-pandemic Mar 2018-Feb 2019 and Mar 2019-Feb 2020 Vs Pandemic Mar 2020- Feb 2021 and Post pandemic Mar 2021- Feb 2022	HAI prevalence was greater during the pandemic (11 %) and post-pandemic (6.8 %) than pre-pandemic period (3 % in 2018–2019 and 3.4 % in 2019–2020).	*Serratia marcescens, Klebsiella pneumoniae, Staphylococcus aureus and coagulase-negative Staphylococci, Escherichia coli*
Petrone et al., 2024 [14]	Single center, South Ital Prevalence	Hematology	174	Blood, pharyngeal, nasal, rectal swab, urine, sputum	Jan-Dec 2019 Vs Ja-Dec 2021	No significant difference was found in HAI prevalence between the pre- (38.5 %) and post-pandemic period (37.7 %, p = 0.910).	*Enterococcus faecalis, Klebsiella pneumoniae, Escherichia coli, Candida albicans, Staphylococcus haemolyticus*

52.56 %, $p < 0.05$) and of Extended-spectrum β-lactamase *Klebsiella pneumoniae* (1 study, 4.8 % vs 10.6 %, $p < 0.05$) and *Escherichia coli* (1 study, 9 % vs 11.5 %) [16,20,21].

Four studies described an increase of *Staphylococcus aureus* because of COVID-19 pandemic, in particular, one resistant to oxacillin (22 % vs 41 %, $p < 0.05$) and 2 methicillin resistant (3.1 %-4.7 % vs 5 %-5.2 %) [16,17,19,22]. Increase of *Enterococci* vancomycin resistant (VRE) incidence was reporter in one study (4.3 % vs 7.1 %) after COVID-19 pandemic.

Discussion

This systematic review assessed the impact of the COVID-19 pandemic on healthcare-associated infections (HAIs) and multidrug-resistant organisms (MDROs) in Italy. Fourteen studies were included, with a limited number focusing on HAIs and more data available on MDROs. The selected studies rates as high or moderate/high quality. According to the most recent national prevalence study conducted before the pandemic, the HAIs prevalence in Italy was 8.0 %, whereas it increased during the pandemic, ranging from 9 % to 11.1 %, was reported in 3 out of 4 studies reviewed [7,12,13]. The most represented microorganism isolated were: *Acinetobacter baumannii* (31.6 % in 2019, 29.0 % in 2020), *Enterococcus spp* in 2019 (31.6 %), *Pseudomonas aeruginosa, Serratia marcescens* (5.0 % pre-pandemic), *Klebsiella pneumoniae* (5.0 % pre-pandemic); *Staphylococcus aureus* (22.5 % pandemic period) and coagulase-negative *Staphylococci* (12.5 % pandemic period) [7,12,13]. Petrone et al. reported no significant variation in HAIs prevalence between 2019 and 2021 [14]. This study was focused in hematology, whereas, the other studies that reported an increased HAI frequency were done in different hospital settings [7, 12, 1314].

Regarding MDROs, 11 studies reported a statistically significant increase in MDRO incidence during the pandemic, in particular, gram negative MDRO had an increase range of 0.8 %-45.6 % and gram positive MDRO increase range of 0.5 %-81.8 % from pre- to post-COVID-19 period [5,13–19,22,23]. One study noted a reduction in the overall incidence of MDRO bacterial infections during the pandemic compared to pre-pandemic years ($p < 0.05$), although it also highlighted a significantly higher incidence of MDRO infections in COVID-19 departments compared to other medical units (29 % vs. 19 %) [21].

Most frequently investigated *MDROs* microorganism were: *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, and Enterococci.* In particular, multivariable analyses showed a significantly increased risk of for *Acinetobacter baumannii* (adjusted odds ratio OR=1.37 in 2020 and 2.00 in 2021, $p < 0.001$), *Staphylococcus aureus* (OR = 1.43; $p = 0.02$ in 2020 and OR = 1.39; $p = 0.04$ in 2021) and *Klebsiella pneumoniae* isolation (OR = 1.43; P = 0.02 in 2020 and OR = 1.39; $p = 0.04$ in 2021), which were associated with factors such as age (> 46 years), Diagnosis-Related Group (DRG) weight, high-intensity care wards, and extended hospital stays [22].

Eight of the 11 studies reported an increase in carbapenem resistance among Gram-negative bacteria during the pandemic, particularly in *Acinetobacter baumannii* (0.3 %-8 % pre-pandemic vs. 1.7 %-11.8 % during the pandemic, $p < 0.05$), *Pseudomonas aeruginosa* (1.5 % vs. 5 %, $p < 0.05$), and *Klebsiella pneumoniae* (6.7 % vs. 50 %, $p < 0.05$) from 2019 to 2020 [14–19,22]. This increase was observed particularly in ICU settings. Two studies also reported a rise in carbapenem-resistant *Klebsiella pneumoniae* production (14 %-15.5 % pre-pandemic vs. 23 %-52.56 % during the pandemic, $p < 0.05$) [16,20]. These findings align with international data and are likely linked to COVID-19-related risk factors such as prolonged hospital stays, ICU admissions, invasive device use, and inappropriate antibiotic use, particularly cephalosporins and carbapenems [9,24].

Increase of methicillin resistant *Staphylococcus aureus* (MRSA) (3.1 %-4.7 % vs 5 %-5.2 %) was also observed because of COVID-19

Table 2
Characteristics and main results of Italian retrospective studies of COVID-19 influence on MDROs.

Reference	n. center /localization/ Frequency measure	Setting	Patients N.	Specimen	Period	Measure of frequency and/or association	Multidrug-Resistant Organisms
Amodio et al., 2024 [22]	Single center, South Italy, Incidence	Hospital	58427	Blood	Jan 2018-Dec 2019 Vs Jan 2020- Dec 2021	There was a statistically significant increase in the risk of MDR isolates (OR = 1.39; $P < 0.001$) during the COVID-19 pandemic period.	*Staphylococcus aureus, Acinetobacter baumannii* and *Klebsiella pneumoniae*
Micozzi et al., 2021 [20]	Single center, South Italy, Incidence	Hematology department	123	Blood	Nov 2019- Feb 2020 Vs Feb 2020- Aug 2020	During the pandemic the number of patients positive to carbapenems-producing *Klebsiella pneumoniae* was lower than that observed in pre-pandemic period (15.5 % vs 52.56 % $P < 0.0001$)	Carbapenems-producing *Klebsiella pneumoniae* (KPC-KP)
Gasperini et al., 2021 [5]	Single center, Center Italy, Incidence	Geriatric ward	73	Blood, urine	Dec 2019-Feb 2020 Vs May 2020-Jul 2020	MDRO was 50 % of the infections in pre-COVID-19 period (n = 18) and 59.6 % in the post-COVID-19 period (n = 28, p = 0.384). MDRO in bloodstream significantly increased in post-COVID-19 period (68.8 % vs. 40.0 % p = 0.038) and *Escherichia coli* was the main *MDROs* bacterium in both periods.	*Escherichia coli, Klebsiella spp. Enterococcus spp. Proteus spp. Pseudomonas spp. Enterobacter spp. Staphylococcus spp.* MRSA, ESBL, CPB
Pascale et al., 2021 [15]	Multi center, North Italy, Incidence	Intensive care units (ICUs)	2403	Sputum feces	Jan-Apr 2019 Vs Jan-Apr 2020	Incidences of infection with carbapenem resistant *Acinetobacter baumannii* were 5.1 per 10,000 patient days in pre-COVID-19 and 26.4 per 10,000 patient days post-COVID-19 period.	Carbapenems-producing *Enterobacteriaceae* (CPE) and carbapenem resistant *Acinetobacter baumannii* (CR-Ab)
Tiri et al., 2020 [18]	Single center, Center Italy, Incidence	Intensive care units (ICUs)	57	Feces	Jan 2019-Feb 2020 Vs Mar-Jun 2020	The incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) acquisition increased from 6.7 % in 2019–50 % in March–April 2020.	Carbapenem-Resistant *Klebsiella pneumoniae*
Shbaklo et al., 2022 [16]	Single center, North Italy, Incidence	Hospital		Sputum feces	Aug 2019-Jan 2020 Vs Mar 2020-Mar 2021	As significant increase was observed in all *MDROs* infections (p-value < 0.001) when comparing the COVID period to the previous period, particularly *Klebsiella pneumoniae* carbapenemase-producing isolates increased from (14 % vs 23 %), *Escherichia coli* isolates (9 % vs 11.5 %) and carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates (1.5 % vs 5 % and 3 % vs 4 % respectively).	*Klebsiella pneumoniae* carbapenemase-producing and extended-spectrum beta-lactamase *Escherichia coli* (ESBL-E. coli), methicillin resistant *Staphylococcus aureus* (MRSA), and carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (CR-PA; CR-AB).
Bentivegna et al., 2021 [21]	Single center, South Italy, Incidence	Hospital	1617	Stool	Pre pandemic Mar-Jun 2017–2018–2019 Vs Mar-Jun 2020 and 2021	There was a significantly higher incidence of *MDROs* bacterial infections in COVID-19 departments compared with other medical departments (19.2 % vs 29.2 % respectively $p < 0.05$), but they were lower than the pre-pandemic period (45.2 % in 2017, 44.2 % in 2018, and 41.4 % in 2019, $p < 0.05$)	Extended-spectrum β-lactamase *Klebsiella pneumoniae*, health care-associated *Clostridium difficile* (HA-CD), and *Acinetobacter baumannii*.
Fontana et al., 2022 [17]	Single center, South Italy, Incidence	Hospital	13125	Blood	Mar-May 2019 Oct-Dec 2019 vs Mar-May 2020 Oct-Dec 2020	Incidence rate of *MDROs* infection increased from 18.0 (pre-COVID-19) to 34.6 (COVID-19 period)	*Acinetobacter baumannii* and carbapenem-resistant enterobacteria (CRE), *staphylococci/ streptococci*-MLSB (MLSB), coagulase-negative *staphylococci* (CONS) resistant I/R to glycopeptides and *enterococci* vancomycin resistant (VRE)
Meschiari et al., 2022 [23]	Single center, North Italy, Incidence	Intensive care units (ICUs)	4164	Rectal swab	Jan 2015-Feb 2020 Vs Mar 2020-Nov 2021	Considering Gram-positive bacteria, an increase in the level of methicillin-resistant *Staphylococcus aureus* and was observed, though it did not reach statistical significance (0.72, 95 % CI 0.039–1.48, p = 0.062), this was also observed for *Clostridium difficile* (1.43, 95 %CI 0.002–2.863, p = 0.051). Among the Gram-negative isolates, there was a significant increase in carbapenem-susceptible *Pseudomonas aeruginosa* infections (1.477, 95 % CI 0.130–2.824, p = 0.032).	Carbapenem-resistant Gram negative bacteria (CR-GNB)

(*continued on next page*)

Table 2 (*continued*)

Reference	n. center /localization/ Frequency measure	Setting	Patients N.	Specimen	Period	Measure of frequency and/or association	Multidrug-Resistant Organisms
Petrone et al., 2024 [14]	Single center, South Italy, Prevalence	Hematology department	174	Blood, pharyngeal, nasal, swab, urine, sputum, feces	Jan-Dec 2019 VS Jan-Dec 2021	There was an increase in resistance to Carbapenems (Ertapenem: 48.8 % vs 94.4 %, p = 0.004; Imipenem: 19.5 % vs 44.4, p = 0.040; Meropenem: 41 % vs 50 %, p = 0.017). There was also a reduction in susceptibility of *Staphilococcus. haemolyticus* to glycopeptides (Vancomycin: 36.4 % vs 85.7 %, p = 0.016; Teicoplanin: 27.3 % vs 78.6 %, p = 0.015) and to linezolid (18.2 % vs 100 %, p < 0.001) and a reduction for vancomycin and teicoplanin resistace strains (63.6 % vs 14.3 %, p = 0.016 and 72.7 % vs 21.4 %, p = 0.015, respectively)	*Escherichia coli, Enterococcus faecalis and Staphylococcus haemolyticus.*
Caruso et al., 2021 [19]	Single center, South Italy, Prevalence	Tertiary care center, diabetic patients	225	Soft tissue	Jan-Dec 2019 Vs Jan-Dec 2020	2020 group had a significantly higher prevalence of antibiotic resistance than 2019 group (36 % vs 63 %, P < 0.001) in a population of patients with diabetic foot infection. In particular the prevalence of *Staphylococcus aureus* resistance to oxacillin (22 % vs 41 %, P = 0.022), *Corynebacterium striatum* resistance to vancomycin (70 % vs 95 %, P = 0.041) and linezolid (30 % vs 68 %, P = 0.031) were significantly higher in the 2020. Among Gram-negative pathogens, there was a significantly higher rate of resistance to carbapenems (15 % vs 41 %, P = 0.001), colistin (18 % vs 49 %, P = 0.010) and 3rd and 4th generation cephalosporins (25 % vs 45 %, P = 0.021) than in 2020.	*Staphylococcus aureus* resistance to oxacillin, *Corynebacterium striatum* resistance to vancomycin and linezolid, *Enterococcus faecalis* resistance to ampicillin and *Enterococcus faecium* resistance to vancomycin; Gram-negative, single or multiple resistance to carbapenems, colistin, 3rd and 4th generation cephalosporins, piperacillin/tazobactam and quinolones

MDRO: MultiDrug Resistant Organism. MRSA: Methicillin-resistant *Staphylococcus aureus*. ESBL: Extended Spectrum Beta-Lactamase Producing bacteria. CPB: Carbapenems-Producing Bacteria.

Table 3
The primary multidrug-resistant organisms (MDROs) increasing as a result of COVID-19 pandemic.

Reference	Microorganism MDROs	Pre-pandemic (%)	Pandemic (%)
	Klebsiella pneumoniae		
Tiri 2020	Carbapenem-Resistant *Klebsiella pneumoniae*	6.7	50
Micozzi 2021	Carbapenems-producing *Klebsiella pneumoniae*	15.5	52.56
Shbaklo 2022	Carbapenems-producing *Klebsiella pneumoniae*	14	23
Bentivegna 2021	Extended-spectrum β-lactamase *Klebsiella pneumoniae*	4.8	10.6
	Acinetobacter baumannii		
Pascale 2021	Carbapenem resistant *Acinetobacter baumannii* (CR-Ab)	0.3	1.7
Bentivegna 2021	*Acinetobacter baumannii*	3	5.3
Shbaklo 2022	Carbapenem-resistant *Acinetobacter baumannii*	3	4
Fontana 2022	Carbapenem-resistant enterobacteria *Acinetobacter baumannii*	8	11.8
	Pseudomonas aeruginosa		
Shbaklo 2022	Carbapenem-resistant *Pseudomonas aeruginosa*	2.9	3.7
	Escherichia coli		
Shbaklo 2022	Extended-spectrum beta-lactamase resistance	9	11.5
Petrone 2024	Resistance to Carbapenem	48.8	94.4
	Ertapenem	19.5	44.4
	Imipenem	41	50
	Meropenem		
	Staphylococcus aureus		
Caruso 2021	*Staphylococcus aureus* resistance to oxacillin	22	41
Shbaklo 2022	Methicillin resistant *Staphylococcus aureus* (MRSA)	3.1	5
Fontana 2022	Methicillin resistant *Staphylococcus aureus* (MRSA)	4.7	5.2
	Enterococci spp.		
Fontana 2022	*Enterococci* vancomycin resistant (VRE)	4.3	7.1
	Staphylococcus haemoliticus		
Petrone 2024	Resistance to Linozelide	18.2	100

pandemic [16,17]. MRSA incidence have sharply risen during COVID-19 pandemic, this could be due to the fact that *Staphylococcus aureus* is the most common pathogen causing co-infections and super-infections in patients affected by COVID-19 that resulted in a high rate of antibiotic use among patients with COVID-19 infection without a secondary confirmed bacterial infections [25,26].

There was also an increase in extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* (4.8 % pre-pandemic vs. 10.6 % during the pandemic, $p < 0.05$) and *Escherichia coli* (9 % vs. 11.5 %, $p < 0.05$) as well as vancomycin-resistant *Enterococci* (VRE) (4.3 % vs. 7.1 %) [16,21]. The rise in ESBL and VRE resistance is likely related to the increased use of empirical therapy against suspected secondary bacterial infections during the pandemic [25,26]. These findings highlight the critical need to strengthen infection control protocols and antimicrobial stewardship to reduce the transmission of ESBL and VRE infections.

In hematological departments with immunocompromised patients, stricter preventive measures were implemented, and these departments typically did not admit COVID-19 patients, which may explain the lack of significant differences in infection rates between the pre-pandemic and pandemic periods [21].

As concerning the geographical distribution of the selected studies, MDRO incidence increased in the north (n = 3), center (n = 2) and south (n = 4) of Italy, this increase involved in particular carbapenem resistance among Gram-negative bacteria during the pandemic, whereas, in two studies in the south of Italy a reduction was reported, this was referred in particular to *Sthaphylococcus aureus* and *Sthaphylococcus haemoliticus* [5,14–23]. HAI increase was reported in 3 out of the 4 studies selected that were made all in the south of Italy. These data may suggest the geographical localization was not pivotal in MRSA and HAI.

Several European countries reported the suspension of antimicrobial stewardship (AMS) programs during the pandemic. Despite low rates of confirmed bacterial co-infections during the pandemic, antibiotic prescription rates remained high, with many patients receiving multiple antibiotics [8]. Given the growing threat of antibiotic resistance, there is an urgent need to develop new antibiotic classes. However, the research and development process for new antibiotics is slow and complex, leaving a limited number of new antibiotic drugs available since 2017 [28] of maintaining AMS vigilance to curb antimicrobial resistance (AMR) [27].

Recent discoveries offer some hope. A German research group identified a new molecule, epifadin, produced by *Staphylococcus epidermidis*, which exhibits activity against competing bacteria, particularly Staphylococcus aureus [29]. Another promising discovery is zosurabalpin, a molecule that inhibits the LptB2FGC complex, which is crucial for the transmembrane transport of lipopolysaccharide and contributes to carbapenem resistance in *Acinetobacter baumannii* [30]. Xacduro, a combination of sulbactam and durlobactam, has also shown efficacy against carbapenem-resistant *Acinetobacter baumannii* (CRAB) strains [31].

Healthcare workers (HCWs) play a vital role in implementing infection prevention and control programs to combat HAIs and MDROs. Healthcare workers were under extreme pressure, which sometimes resulted in lapses in infection control protocols. The reallocation of healthcare staff to COVID-19 wards, many of whom were unfamiliar with ICU protocols, further weakened routine infection prevention strategies, exacerbating the risk of HAIs and the spread of MDROs. The surge in COVID-19 patients led to overcrowded hospitals, extended stays, and a higher demand for critical care, which increased the risk of HAIs. Intensive care units (ICUs) became overburdened, and infection prevention measures were often compromised due to limited space, personnel, and resources. This increased patient-to-patient transmission of pathogens.

Continuous, multidisciplinary, and targeted training of HCWs is essential for success [32]. The effectiveness of local and national AMR prevention protocols relies on HCWs' knowledge, attitudes, and practices. A study among Italian nurses found that AMR awareness varied by gender and region [33]. Multivariate analysis revealed that adequate knowledge of AMR prevention protocols was associated with participation in ward meetings to review active surveillance reports (OR=4.21, 95 % CI: 1.36–13.07). HCWs requested direct monitoring of compliance with hygiene protocols and the appointment of local HAIs managers to improve AMR prevention efforts. Enhanced training for HCWs is a key factor in preventing and containing HAIs spread [34].

Italian universities currently lack sufficient AMR management training, particularly for non-medical health workers. While several

European countries have implemented effective strategies against HAIs, Italy still lacks a national governance system for standardized HAIs surveillance and reporting. Although the COVID-19 pandemic likely influenced HAIs and MDRO rates, evidence on the long-term effects is limited, and further studies are needed to fully understand this issue.

The main limitations of this study were the inclusion only of full-text papers, they were all retrospective data collection in different period of time, where the COVID-19 variants may have different and the seriousness of the symptoms and of the hospital isolation may have been different. There was heterogeneity also of laboratory method of infection detection. Future studies are required to address these issues and to provide high quality and consistency or the impact of COVID-19 on HAI and MDRO.

Conclusion

The COVID-19 pandemic had a significant impact on healthcare-associated infections (HAIs) and multidrug-resistant organisms (MDROs) in healthcare settings globally. The pandemic's strain on healthcare systems, including increased patient volumes, resource limitations, and altered infection control practices, contributed to a rise in both HAIs and MDROs. These challenges highlight the need for reinforcing infection prevention and control strategies, strengthening surveillance, and maintaining robust antibiotic stewardship even during global health crises.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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