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REVIEW ARTICLE

Carbapenem-resistant *Klebsiella pneumoniae* in the Balkans: Clonal distribution and associated resistance determinants

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ABSTRACT

Carbapenems are considered to be among the last line antibiotics against extended-spectrum β-lactamase producing *Enterobacterales*. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has been frequently reported and its spread in Europe is indisputable and poses an enormous threat to hospitalized patients which is of growing concern. This review aims to record prevalence of CRKP in the Balkan region and to review the current knowledge about this life-threatening pathogen. In this review, we summarize data about clinical isolates of carbapenem-resistant *K. pneumoniae* from Greece, Croatia, Romania, Bulgaria, Serbia, Slovenia, Montenegro, Bosnia-Herzegovina and Albania from published reports between 2000 and 2023. Among Balkan countries, Greece and Romania are the ones with the most reports about CRKP. Since 2007, KPCs are the dominant carbapenemases in both countries. KPC-2 and NDM-1-producing *K. pneumoniae* strains have been identified as the most frequent CRKP in Croatia, Bulgaria, Serbia, and Slovenia. OXA-48 enzyme has been identified in most Balkan countries. In addition, since 2018, CRKP sequence type 11 (ST11) seems to have replaced ST258 in Balkan Peninsula, while ST15 continues to thrive throughout the years. Not only efficacy of colistin against CRKP has decreased dramatically during the last ten years but colistin resistance mechanism is based on alterations of chromosomal *mgrB* gene, rather than the already known *mcr* genes.

Moreover, ceftazidime-avibactam-resistant CRKP were detected mostly in Greece. Emergence of CRKP poses a severe threat to the Balkan countries. Due to the narrow therapeutic window, it is essential to prevent the spread of multiresistant *K. pneumoniae* strains.

KEYWORDS

carbapenem-resistant *Klebsiella pneumoniae*, Balkans

INTRODUCTION

Klebsiella pneumoniae is a member of Enterobacterales and it usually colonizes the gastrointestinal tract, and rarely the nasopharynx. *K. pneumoniae* is a major pathogen both in community-acquired and in nosocomial infections [1]. *K. pneumoniae* is also included in the group of ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species*), which are considered responsible for the rise of antimicrobial drug resistance in hospitals and healthcare facilities [2, 3].

The wide expansion of extended-spectrum β-lactamase (ESBL)-producing Enterobacterales over the past decades, dramatically limited the therapeutic options leading to the

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increased use of carbapenems. Hence, the emergence of carbapenemase-producing *Enterobacterales* (CPE) is a worldwide threat for both hospitalized and community patients [4]. It is therefore critical to deeply understand population and diversity of *K. pneumoniae,* so as to interprete clinical and public health surveillance data and intensify intervention strategies against this life-threatening pathogen.

Among the 4 classes of β-lactamases defined by the Ambler classification system, the carbapenemases that confer carbapenem resistance in *Enterobacterales* belong to 3 of them: Class A (*K. pneumoniae* carbapenemase, KPC), Class B (metallo-β-lactamase, MBL including New Delhi metallo-β-lactamase, NDM and the Verona integron–encoded metallo-β-lactamase, VIM) and Class D (oxacillinase β-lactamase-48, OXA-48-like carbapenemase) [5].

It is important to assess the dissemination of antibiotic resistant *K. pneumoniae*. In this study, the aim is to evaluate the prevalence of carbapenem-resistant *K. pneumoniae* (CRKP) in the Balkans. More specifically, data relevant to the carbapenemase-producing *K. pneumoniae* pathogens and their resistant genes have been collected and categorized for every Balkan country in chronological order. The Balkans, also known as the Balkan Peninsula, is the geographical area that encompasses Greece, Albania, Bulgaria, Serbia, Bosnia and Herzegovina, North Macedonia, Kosovo, Montenegro, Croatia, Slovenia and Romania.

MATERIAL AND METHODS

Study design

The study design was based on the PRISMA 2020 statement [6] and reviewed reports from Greece, Romania, Albania, Croatia, Bulgaria, Serbia, Slovenia, Montenegro, Bosnia-Herzegovina, Kosovo and North Macedonia over the last 23 years (from 2000 to 2023). A preliminary search was conducted using the search tools of selected databases. Reports which did not include human samples in the study population, nor were related to carbapenemase-producing *K. pneumoniae* resistance or prevalence and were not related to any of the aforementioned Balkan countries, were excluded. Subsequently, a significant number of reports were excluded by the authors, according to the exclusion criteria that was mentioned above. The results were distributed chronically for each country.

Methods

The reports have been selected from two major databases: “PubMed” and “Scopus”. The initial search query for both of databases included the keywords: «carbapenem», «resistant», «klebsiella pneumoniae», “Greece”, “Croatia”, “Romania”, “Albania”, “Bulgaria”, “Serbia”, “Slovenia”, “Montenegro”, “Bosnia-Herzegovina”, “Kosovo” and “North Macedonia” and the time limitation: “from 2000 until today”. Before authors proceeded to screening of the results, they removed manually duplicate reports that appeared in both databases.

The automatic screening followed, using additional filters separately for “PubMed” and “Scopus”. These filters included: samples “only humans”; language: “English” and “Greek”; types: “Articles”, “Reviews” and Meta–Analyses”.

The following step included manual evaluation. Authors categorized each report by country and by chronological order. Reports that could not be retrieved were dismissed. Finally, the excluded criteria comprised the following: no human sample in the study population; no relation to carbapenemase-producing *K. pneumoniae* resistance or/and prevalence; no reference to any of the aforementioned Balkan countries. The flow diagram (Fig. 1. Workflow) reveals step by step the screening procedure of studies.

RESULTS

The total number of reports identified was 386. Two hundred and seventeen publications out of 386 in total were retrieved from the PubMed database, while the rest 169 from the Scopus database. After the essential screening and the adjustments based on the limitations and exclusion criteria, the final number of the included records came to 134. The number of reports that were obtained from each country were distributed as follows: 76 reports were referred to Greece, 19 to Romania, 17 to Croatia, 10 to Serbia, 6 to Bulgaria, 3 to Bosnia - Herzegovina, 2 to Slovenia and finally 1 to Albania. The analytical distribution of CRKP for each country follows. Table 1 records the chronological order of the emergence CRKP genes. Table 2 summarizes the distribution of CRKP sequence types (STs) in the Balkans.

Greece

In their review, Vatopoulos et al. [7] claimed that there had been a major increase in imipenem resistant *K. pneumoniae* from 2000 to 2006. According to their data regarding Intensive Care Units (ICUs) in Greek hospitals, the spread of imipenem-resistant *K. pneumoniae* rose to 50%, and the VIM-producing *K. pneumoniae* were the predominant strains. During the same period (2000 – 2006), Falagas et al. [8] conducted a matched case–control study of 106 patients in two Greek hospitals. Based on their results, the use of fluoroquinolones and antipseudomonal penicillins was an independent risk factor for infections caused by CRKP.

From 2007 to 2008 Mouloudi et al. [9] carried out case-control studies in patients hospitalized in ICU with Bloodstream infection (BSI) caused by carbapenemase-producing *K. pneumoniae*. The researchers concluded that BSI due to CRKP led to increased mortality in the ICU. During the same time frame: Poulou et al. [10] recorded for the first time the spread of a VIM-1-producing *K. pneumoniae* strain in the community; Tsakris et al. and Cuzon et al. [11, 12] reported the first incidences of KPC-2-possessing *K. pneumoniae* in Greece; Pournaras et al. [13] reported for the first time in Europe the emergence and spead of strains of KPC-2-producing *K. pneumoniae* in a Greek hospital. From 2005 to 2009, six studies were published regarding the spread of

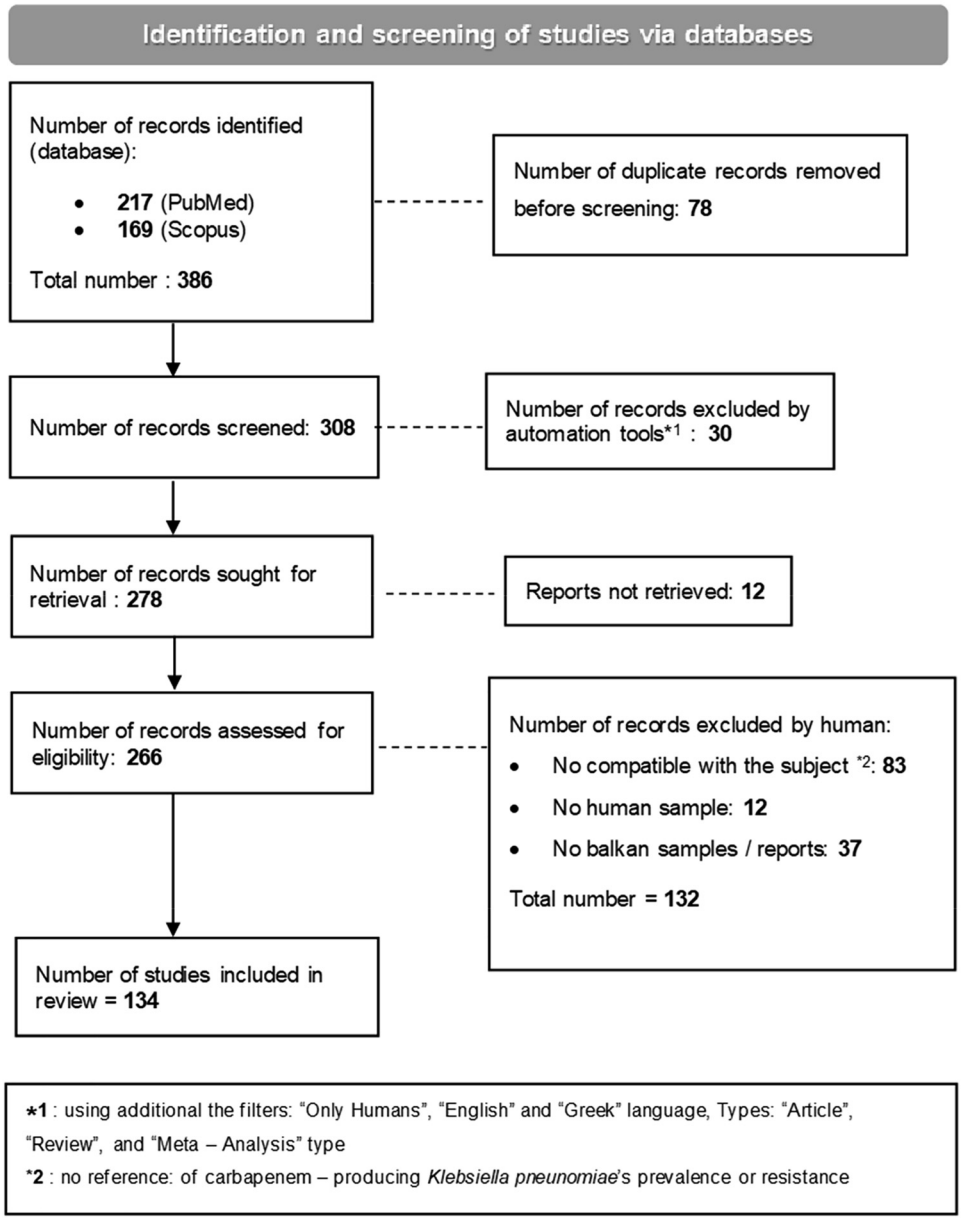

Fig. 1. Workflow. The steps of identification and screening of studies that were included in this review

VIM-producing *K. pneumoniae* and one clinical study regarding the spread of KPC-2-producing *K. pneumoniae* in several Greek hospitals [14–19].

Moreover, 2 clinical studies recorded a remarkable reduction of the efficacy of fosfomycin, aminoglycosides, fluoroquinolones and colistin against carbapenemase-producing *K. pneumoniae* isolates in Greek University Hospitals [20, 21]. From 2001 to 2009 Grundmann et al. [22] reported a polyclonal epidemic of multidrug- resistant or even pan-drug resistant strains of carbapenemase-producing *K. pneumoniae*. Souli et al. and the European Antimicrobial Resistance Surveillance System (EARSS) [23] agreed with the above data. Specifically, in 2007, the rates of resistance to carbapenems among *K. pneumoniae* isolates amounted to 46%. Also, during the first months of 2010, the emergence of VIM and KPC – producing *K. pneumoniae* isolates were reported [23]. Similar results were reported by several researchers, while studies also focused on community-onset urinary tract infections caused by CRKP in pediatric patients and infants following Neonatal Intensive Care Unit [NICU] hospitalisation [24, 25].

In 2010 the "Prokroustes" nationwide action plan was established by the Hellenic Center for Disease Control and Prevention [HCDCP] to surveille and restrain the increasing *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* antibiotic resistance proportions in greek hospitals. Three years after the onset of the action plan, *K. pneumoniae's* carbapenem resistance rates had been increased [26]. In 2011, Greece held the first place in Europe having the highest number of carbapenemase producing *Enterobacterales* (CPE) isolates, with *K. pneumoniae* being dominant [27, 28]. Voulgari et al. (2011–2012) [29] studied for the first time the outbreak of

Table 1. Chronological distribution of CRKP genes in the Balkans

Country	CRKP resistant genes through the years					
	2000–2007	Ref.	2007–2014	Ref.	2014–2023	Ref.
Greece	$bla_{VIM,}$ $bla_{KPC-1,-2}$	[7, 11–13, 19]	$bla_{VIM,}$ bla_{KPC} bla_{OXA-48}	[14–19, 23, 29–33]	$bla_{VIM,}$ bla_{KPC} bla_{OXA-48} bla_{NDM-1}	[32, 41, 44–48, 50–53, 56, 58, 60–64, 66]
Croatia	*NR	NR	bla_{VIM} bla_{KPC} bla_{NDM} bla_{OXA-48}	[81, 82, 86]	bla_{KPC} bla_{OXA-48}	[89, 90, 92, 93]
Romania	$bla_{VIM,}$ $bla_{KPC-1,-2}$	[94–97]	bla_{VIM} bla_{KPC} bla_{NDM-1} bla_{OXA-48}	[98, 99]	bla_{NDM-1} bla_{OXA-48}	[106–108, 110]
Bulgaria	*NR	NR	bla_{KPC} bla_{NDM-1} bla_{OXA-48}	[115–117]	bla_{KPC-2} bla_{NDM-1}	[117, 118, 120]
Serbia	NR	NR	bla_{KPC} bla_{NDM-1} bla_{OXA-48}	[123, 124]	bla_{NDM-1} bla_{OXA-48}	[125, 126]
Slovenia	NR	NR	NR	NR	bla_{NDM-1} bla_{OXA-48}	[133, 134]
Bosnia - Herzegovina	NR	NR	NR	NR	bla_{OXA-48}	[136]
Albania	NR	NR	NR	NR	NR	NR
Montenegro	NR	NR	NR	NR	NR	NR
North Macedonia	NR	NR	NR	NR	NR	NR
Kosovo	NR	NR	NR	NR	NR	NR

*__NR: No Records__ found according to the inclusion criteria of this review.

OXA-48-producing *K. pneumoniae* in Greece. However, many other studies conducted during that period stressed the predominance of KPC-producing *K. pneumoniae* [30, 31]. Kolonitsiou et al. [32] isolated 207 CRKP from 1732 patients with bloodstream infection, whereas most of the pathogens were harbouring the bla_{KPC} gene. According to a multi-center clinical study conducted from 2009 to 2013, there was an emergence of NDM-1-producing *K. pneumoniae* whereas the production of KPC carbapenemases was estimated to be 60.9% [33].

Within the same period, another 6 studies were conducted in hospitalized patients, which pointed out an outbreak of the CRKP isolates and correlated the infections from CRKP pathogens with limited treatment options and high mortality during hospitalization. Also, these studies revealed a gradual increase in colistin-resistant bacteria, which undermines its efficacy. On the contrary ceftazidime-avibactam was an efficient agent against *K. pneumoniae* isolates [34–39]. In 2013 Rolain et al. [40] declared that the percentage of CRKP isolates aroused at an endemic rate for Romania, Italy, and Greece, with Greece once again coming first.

Between November 2014 and April 2016, Galani et al. [41] studied 300 carbapenem-resistant *K. pneumoniae* isolates from 300 patients in 14 Greek hospitals. The predominant strain remained the KPC-producing *K. pneumoniae*, followed by NDM-producing *K. pneumoniae*. The writers, also, pointed out that plazomicin, an aminoglycoside antibiotic, was an effective agent against CRKP. In the meantime, Galani et al. [42] evaluated the resistance of non-MBL-producing *K. pneumoniae* to relebactam and other antibiotics in 314 isolates selected from 18 Greek hospitals. Almost all isolates were found to be resistant to imipenem, doripenem and meropenem. On the other hand, the combinations imipenem/sulbactam and ceftazidime/avibactam seemed to be effective against most of the bla$_{KPC}$-harboring *K. pneumoniae* isolates. During the course of 8 years (2010–2017), the European Antimicrobial Resistance Surveillance Network (EARS-Net), the Greek Electronic System for the Surveillance of Antimicrobial Resistance - WHONET-Greece and 4 more clinical studies reported a severe decrease in susceptibility of CRKP strains and other gram-negative pathogens to carbapenems and other antibiotics such as ampicillin/sulbactam, colistin, fosfomycin, etc. [44–49].

Papadimitriou-Olivgeris et al. [43], from 2015 to 2018, studied Greek patients with bloodstream infections (BSIs) caused by CRKP who were treated with ceftazidime/avibactam and observed changes in the genetic pattern of carbapenemase-producing *K. pneumoniae* leading to a change in the palette of carbapenemases by replacing KPC with MBL-producing isolates. Specifically, MBL-producing *K. pneumoniae* isolates were more frequent in 2018 compared to 2015–17. Between 2016 and 2018,

Table 2. Chronological distribution of CRKP sequence types (STs) in the Balkans

Country	CRKP sequence types (ST)s through the years					
	2009–2012	Ref.	2013–2018	Ref.	2019–2023	Ref.
Greece	ST258/512 ***(D)***	[76]	ST258/512 ST39 ST15 ST11	[74–76]	ST258 ST147 ST39 ST15 ST323 ST11***(D)***	[66, 67, 69, 73, 76]
Croatia	ST37, ST258	[81, 82, 84]	*NR	NR	ST101	[94]
Romania	ST525, ST101	[98]	NR	NR	NR	NR
Bulgaria	ST15 ***(D)*** ST76 ST1350 ST101 ST258 ST151	[117]	ST15 ST76 ST1350 ST101 ST258 ST151 ST16 ST391 ST11***(D)***	[117–119]	NR	NR
Serbia	NR	NR	ST101 ST888 ST437 ST336 ST307 ST340 ST258	[123, 125, 126]	NR	NR
Slovenia	NR	NR	ST437 ***(D)*** ST147 ST15 ST3390	[133, 134]	NR	NR
Bosnia - Herzegovina	NR	NR	NR	NR	NR	NR
Albania	NR	NR	NR	NR	NR	NR
Montenegro	NR	NR	NR	NR	NR	NR
North Macedonia	NR	NR	NR	NR	NR	NR
Kosovo	NR	NR	NR	NR	NR	NR

* **NR: No Records** found according to the inclusion criteria of this review.
* ***(D)*:** The **Dominant** ST during this period.

Chatzidimitriou et al. [44] selected 47 CRKP strains from two tertiary teaching hospitals in Greece in order to study the susceptibility to the novel ceftazidime/avibactam and eravacycline. The bla_{KPC} gene was found in more than half the strains, followed by the bla_{NDM} and the bla_{VIM} genes. These antimicrobial agents were found to be reliable for treatment, due to most of the strains being susceptible to these antibiotics. During a six-month study [from October 2017 to March 2018], Sakkas et al. [45] investigated the ratio and the antibiotic resistance of pathogens isolated in sewage samples in Northwestern Greece's hospitals. Among the 70 resistant isolates identified, 19 were found to be carbapenemase-producing *K. pneumoniae*. One out of the total isolates was found to be resistant to tigecycline, 79.2% of them encoded class A (KPC) carbapenemase and class B (NDM and VIM) enzymes, and 42.1% co-produced both KPC and MBL genes. In 10 clinical studies carried out from 2003 to 2018 in hospitalized patients in Greece, a plethora of carbapenemase-producing *K. pneumoniae* subtypes, such as VIM, NDM-1, KPC and OXA-48-producing *K. pneumoniae*, were isolated for the first time. The most prevalent carbapenemase continued to be KPC. CRKP rates again fluctuated at endemic levels, while the Balkans were considered to be the reservoir of resistant strains [32, 46–54]. Kachalov et al. [55] conducted a major survey about the spread of ESBL and CRKP in the hospital and the community of 30 countries in the European region, based on ECDC data. Greece and Italy seemed to be on the top, with the prevalence of carbapenem resistance soaring higher than 30%. Until 2020, the predominance of bla_{KPC} genes and the co-production of more than one carbapenemases resulting in multi-resistant strains from hospitalized patients were once again reported in 6 studies [56–61]. In addition, there had been reports of NDM-producing *K. pneumoniae* emergence among adult patients in Greek hospitals [62, 63].

In a ten-year (2010–2019) retrospective study based in the intensive care unit (ICU) of a Greek hospital, Olivgeris et al. [64] indicated tigecycline as an efficient monotherapy for bloodstream infections caused by carbapenemase-producing *K. pneumoniae*. Once again, the majority of

carbapenemase-producing *K. pneumoniae* isolates produced KPC carbapenemase, followed by VIM – producing *K. pneumoniae* isolates, co-producing KPC and VIM *K. pneumoniae* isolates and last NDM – producing *K. pneumoniae* isolates. At the same time, Kofteridis et al. [65] conducted a retrospective single-center cohort study from 2010 to 2018 and supported the efficiency of tigecycline combined with carbapenemases against *K. pneumoniae, A. baumannii*, and *P. aeruginosa*. From 2018 to 2020, several studies isolated and perfomed molecular characterization of ceftazidime/avibactam - resistant carbapenemase - producing *K. pneumoniae* strains [66–69], while many researchers aimed to test the efficacy of the synergetic activity of old and new antimicrobial agents [70–73]. More specifically, during 2020 ceftazidime-avibactam-resistant *K. pneumoniae* strains harbouring bla_{KPC} gene were isolated belonging to ST39, ST258 and ST147 [66, 67, 69, 73]. Furthermore, Maraki et al. reported decreased efficacy of aztreonam in combination with ceftazidime/avibactam against 40 MDR, MBL-producing, and serine-β-lactamases co-producing *K. pneumoniae* [69]. During 2018–2022 numerous studies conducted in Greek hospitals indicated that ST15, ST323, ST39 and ST11 *K. pneumoniae* isolates were widely expanded. The isolates included a variety of KPC, VIM, NDM and OXA-48 producing *K. pneumoniae* strains [74, 75].

Finally, Tryfinopoulou et al. [76] combined data from three surveys in Greek hospitals and showed a shift in clonal distribution of CRKP throughout the years. Over the last 10 years, ST11 and ST258/512 CRKP clones were widely spread among Greece. In 2009 and 2010, ST258/512 was the most frequent ST among CPKP while in 2022 CPKP ST11 dominated. Moreover, from 2018 to 2019 *K. pneumoniae* ST39 isolates harbouring bla_{KPC-2} and bla_{VIM-1} were detected. Finally, in 2022, *K. pneumoniae* ST323 harbouring bla_{KPC-2} emergence was identified.

Croatia

In a yearlong survey (2001–2002) that took place in a university hospital of Croatia, Tonkic et al. [77] noticed an emergence of *Escherichia coli* and *K. pneumoniae* resistant strains to a variety of antibiotics, except to carbapenems. Similarly, from 2002–2007, the data that was extracted from several croatian hospitals, involving both adults and paediatric patients, did not reveal any resistance to meropenem or imipenem for *K. pneumoniae*. On the other hand, high resistance levels of *K. pneumoniae* were reported to ceftazidime, cefepime and gentamicin [78–80].

This changed in 2009 and 2011, when the two first reports of carbapenemase-producing *K. pneumoniae* in Croatia were made. The genomic analysis reported that *K. pneumoniae* isolates carried bla_{KPC}, bla_{TEM}, and bla_{SHV} and bla_{NDM} resistance genes. The KPC-producing strains belonged to ST37 clone [81, 82].

From 2011 to 2012, according to Zujić Atalić et al. [83], there had been a sporadic rise of carbapenemase-producing *K. pneumoniae* and other *Enterobacterales* with reduced susceptibility to carbapenems in several regions of Croatia. In 2012, Brkic et al. [84] recorded the first carbapenemase-producing *K. pneumoniae* ST 258 clone outbreak in Croatia. During 2011 to 2013, Jelic et al. [85] supported that the outbreak of CRKP in Croatia was just beginning. The researchers reported a multidrug - resistant phenotype from all their carbapenemase-producing *K. pneumoniae* isolates. However, the proportion between susceptibility and resistance to carbapenems varied. In a retrospective study during the same period, there had been speculation of an undergoing outbreak of CRKP carrying the bla_{OXA-48} resistance gene [86].

Matovina et al. [87] conducted a three-year retrospective study from 2012–2014 and noted the reduction of susceptibility to ertapenem and the presence of multidrug resistance in all *K. pneumoniae* isolates. An emergence of tigecycline resistance in many of their isolates was also reported, whereas the most effective antibiotic appeared to be colistin.

Bedenic et al. [88], with their molecular analysis in 2016, supported that the rise of the resistant *Enterobacterales* (*K. pneumoniae* included) to carbapenems had escalated. Moreover, from 2016 to 2018, *K. pneumoniae* isolates of several Croatian hospitals were analyzed. Most of them were found to be OXA-48 positive, instead of VIM-1 strains that had been dominating in the past years [89, 90].

During the period of 2014–2022, records of KPC-producing and OXA-producing *K. pneumoniae* isolates emerged from different regions of Croatia. All the isolates exhibited resistance to meropenem and ertapenem, while their susceptibility to gentamicin, sulfamethoxazole/trimethoprim, colistin and ceftazidime/avibactam varied [91, 92].

Nowadays, the proliferation of OXA-48 producing *K. pneumoniae* seems to have an impact on non-hospitalized patients as well. Suto et al. [93] conducted a study in 2022 in which they underlined the spread of OXA-48 producing *K. pneumoniae* to long-term care facilities and communities in Croatia. Finally, in 2023 Rubik et al. [94] indicated that KPC-producing *K. pneumoniae* ST101 clone was the predominant clone in southern Croatia. According to their results, all isolates exhibited a multidrug-resistant phenotype. Moreover, many of them appeared to be resistant to colistin due to alterations in the chromosomal *mgrB* gene.

Romania

In the early 2000s, there were only a few clinical records regarding the dissemination of CRKP in Romania. According to European surveillance programs of CRE in Europe, from 2004 to 2013 Romania was included in the top six countries with high transmission rates of *K. pneumoniae* resistant to tigecycline and carbapenems. In the same period, the most dominant carbapenemases in Romania and many other European countries, were KPC-2/3 and VIM-type [95–97].

Between 2010 and 2012, Szekely et al. [98] made the first report of bla_{NDM-1}, bla_{OXA-48} and $bla_{OXA-181}$ producing *K. pneumoniae* strains in Romania. The sequence type of

these isolates corresponded to ST525 and ST101 clones. During the same years, Gheorghe et al. [99] recorded the geographical distribution of OXA-48 and NDM-1 - producing *K. pneumoniae* isolates. From November 2013 to April 2014, Lixandru et al. [100] isolated 65 carbapenemase-producing *K. pneumoniae* strains from eight Romanian hospitals. Most of the isolates carried the $bla_{\text{OXA-48}}$ resistance gene, followed by the $bla_{\text{NDM-1}}$, $bla_{\text{KPC-2}}$ and finally $bla_{\text{VIM-1}}$ genes. Gavriliou et al. [101] conducted a retrospective study in order to record the resistance and susceptibility rates of *K. pneumoniae* over a five-year time period (from 2010 to 2015). Regarding carbapenems, in 2010 there were no records of resistance, whereas in 2015, researchers isolated one resistant strain.

According to studies, a remarkable reduction in *K. pneumoniae's* suscebtibility to carbapenems was recorded in Romanian hospitals over the next years [102–105]. The resistant genes $bla_{\text{OXA-48}}$ and $bla_{\text{NDM-1}}$ were identified in carbapenemase-producing *K. pneumoniae* strains by many researchers until 2019 [106–109]. From 2021 until 2022, many investigators recorded the spread of carbapenemase-producing *K. pneumoniae* strains to patients who were hospitalized in the ICU. The majority of carbapenemase-producing *K. pneumoniae* was characterized as OXA-48 producers. Moreover, increased resistance rates were observerd in a variety of antibiotics (fluoroquinolones, carbapenemes, aminoglycosides). Most of the isolates were susceptible to colistin [110–114].

Bulgaria

Prior to 2011, little is known about the prevalence of CRKP in Bulgaria. In 2014, Sabtcheva et al. [115] recorded for the very first time an OXA-48-producing *K. pneumoniae* isolate in Bulgaria. The same year, Todorova et al. [116] were the first researchers that confirmed the emergence of NDM-1-producing *K. pneumoniae* strains in two different bulgarian hospitals. In a three-year survey that was conducted, involving hospitalized patients (2012–2015), Markovska et al. [117] isolated CRKP with multidrug-resistant phenotypes in most of their samples. The researchers recorded a variety of clonal types. The dominant type was ST15, followed by ST76 and ST1350. ST101, ST258, and ST151 carbapenemase-producing *K. pneumoniae* isolates were also detected. Most of the isolates were multridrug resistant and harbored bla_{TEM}, bla_{KPC}, $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-9}}$ genes. The majority of *K. pneumoniae* ST15 clone produced both KPC-2 and CTX-M-15 enzymes, while the researchers reported the first occurrence of OXA-48 producing ST101 *K. pneumoniae* in Bulgaria.

From 2015 to 2016, Savov et al. [118] conducted a survey in a large medical center in Sofia, providing evidence of the first polyclonal outbreak of NDM-1-producing *K. pneumoniae* in the country. The dominant clonal type was ST11, while ST16, ST15 and ST391 were also detected. In their wide-scale study, including eight medical centers in five bulgarian cities from 2014 to 2018, Markovska et al. [119] identified KPC-2, NDM-1 and multiclonal OXA-48 – producing *K. pneumoniae* strains as the most dominant. Half of KPC-2-producing *K. pneumoniae* isolates belonged to ST258 and all of the NDM-1 producing strains to ST11.

From 2017 until 2021, two more studies reported CRKP strains bearing bla_{KPC}, bla_{NDM} and bla_{VIM} resistance genes [120, 121].

Serbia

Data about CRKP were first recorded in Serbia in 2013, when Djuric et al. [122] reported the distribution of many multidrug resistant pathogens in Belgrade. During the same year, Seiffert et al. [123] were the first to identify the co-producing NDM-1 and OXA-48 *K. pneumoniae* ST101 from a Serbian hospital.

Moreover, Trudic et al. [124] isolated 121 *K. pneumoniae* strains in 14 hospitals in Serbia from November 2013 to May 2014. Out of these 121 isolates, 58 produced carbapenemases. Specifically, 33 carbapenemase-producing *K. pneumoniae* were identified harbouting bla_{NDM}, 10 were harbouring $bla_{\text{OXA-48}}$, 1 was harbouring bla_{KPC} and 7 carbapenemase-producing *K. pneumoniae* carried both $bla_{\text{OXA-48}}$ and bla_{NDM}.

Novonic et al. [125] conducted a three-year survey (2013–2016) and isolated 27 colistin- and carbapenem-resistant *K. pneumoniae* strains in three Serbian tertiary care hospitals and in one private laboratory. The resistant gene $bla_{\text{CTX-M-15}}$ was found in all isolates, while many ST101, ST888, ST437, ST336, and ST307 strains harboured $bla_{\text{OXA-48}}$ and only ST340 was $bla_{\text{NDM-1}}$ positive. Moreover, ST336 clone was detected with a premature stop codon in the *mgrB* gene, while none of *mcr* genes were identified. In the same period (2013–2017), Palmiery et al. [126] obtained 2,298 clinical *K. pneumoniae* isolates from five serbian cities. Four hundred and twenty-six of them were resistant to at least one carbapenem. ST437, ST336, ST340, ST258 and the newly emerging ST101 *K. pneumoniae* sequence types were isolated. The only carbapenemase that was produced from *K. pneumoniae* ST101 was OXA-48, while KPC-2 was associated with ST258. Regarding colistin resistance, all isolates except ST101 showed numerous *mgrB* mutations but did not harbor any *mcr* gene.

On a case-control study from 2007 to 2019 in abdominal surgical patients with hospital-acquired pneumonia, there was no detection of any resistant *K. pneumoniae* strain to carbapenems. On the contrary, all tested strains were highly resistant to fluoroquinolones, penicillins and cephalosporins [127].

On the other hand, since 2019, five more studies presented the expansion of carbapenems resistant *K. pneumoniae* strains and the emergence of CRKP carrying $bla_{\text{OXA-48-like}}$, bla_{KPC} and bla_{NDM} genes, Some of these studies detected an increase in resistance of CRKP strains to ceftazidime/avibactam and colistin [128–132].

Other Balkan countries

In Slovenia, the available resources referred to CRKP dissemination are limited. Between 2010 and 2014 there

have been only few reports of carbapenem-resistant *Enterobacterales* [133]. The first outbreak of CRKP in Slovenia was recorded by Pirs et al. [134] from October 2014 to April 2015. The investigators isolated OXA-48 and/or NDM-producing *K. pneumoniae* strains (ST437 and ST147 types) from 38 patients of the tertiary teaching hospital University Medical Centre Ljubljana. Between 2014 and 2017, Benulic et al. [133] studied the resistance and the production of carbapenemases of 32 *K. pneumoniae* isolates from the Slovenian national expert laboratory. The researchers detected 10 different sequence types. The first and most frequently identified type was ST437, followed by ST147, ST15 and eventually ST3390. Moreover, they confirmed the existence of $bla_{\text{OXA-48}}$ resistance gene in 53.1% of the isolates, bla_{NDM-1} in 15.6%, and a combination of $bla_{\text{OXA-48}}$ and $bla_{\text{NDM-1}}$ in 21.9% of the isolates.

In 2006, Custovic et al. [135] conducted a study at a University Clinical Center in Bosnia - Herzegovina, in order to report the resistance levels of gram-positive and gram-negative pathogens in a variety of antibiotics. The authors observed a low rate of resistance of *K. pneumoniae* to imipenem. Ten years later, Granov et al. [136] reported the outbreak of OXA-48 producing *K. pneumoniae* in 2017 and 2018 in the Clinical Center University of Sarajevo. Finally, a retrospective study (2020–2021) pointed out a severe increase in the prevalence of CRKP strains in bosnian hospital settings [137].

In Albania, only one study refering to carbapenems resistance in *Enterobacterales* was reported in 2015, at a tertiary care hospital of Tirana. However, the authors found all *K. pneumoniae* strains susceptible to carbapenems [138].

In Montenegro, Kosovo and North Macedonia no reports on prevalence of carbapenemase-producing *K. pneumoniae* clinical isolates were recorded, neither in PubMed nor in Scopus databases.

DISCUSSION

Greece has the highest rates of carbapenem-resistant *K. pneumoniae* in the Balkans. Since 2000, an escalation of CRKP has been reported. VIM-1 was the first carbapenemase to be identified produced by *K. pneumoniae* [7, 10]. The first occurrence of KPC-producing-*K. pneumoniae* was reported in 2007 [11, 12]. Ever since, KPCs seemed to be the enzymes mainly produced by CRKP and ST258/512 CRKP were the dominant clones [11, 12, 47–53]. In 2011, OXA-48-producing *K. pneumoniae* was detected for the first time [29]. In the last five years, several reports revealed the emergence of bla_{NDM} resistance gene [44]. Moreover, since 2022, CRKP ST11 was identified as the most frequent type, while since 2018, *K. pneumoniae* ST39 isolates harbouring $bla_{\text{KPC-2}}$ and $bla_{\text{VIM-1}}$ and *K. pneumoniae* ST323 harbouring $bla_{\text{KPC-2}}$ were detected [76]. Since 2009, many studies mentioned a decrease of colistin's efficacy against CRKP [34–39]. In addition, there has been a rapid spread of multidrug-resistant *K. pneumoniae* isolates in Greek hospitals [44]. During the last three years, ceftazidime-avibactam-resistant CRKP were detected [66, 67, 69, 73].

Similar to Greece, the CRKP outbreak in Romania began in the early 2000's, with the most dominant carbapenemases recorded to be KPC-2/3 and VIM-type [93–95]. From 2010 to 2019, OXA-48 and NDM-1-producing *K. pneumoniae* isolates replaced the aforementioned. The sequence types of the isolates detected were ST525 and ST101 [98–100, 106–108] whereas colistin resistance has not been reported at all [110–114].

In Croatia, the first two studies on carbapenemase-producing *K. pneumoniae* were published in 2009 and 2011 respectively, almost ten years after Greece. These studies revealed that ST37 *K. pneumoniae* isolates carried the bla_{KPC} and bla_{NDM} resistance genes [88, 89] whereas until 2013, such cases were only sporadically mentioned. After 2013, an undergoing expansion of carbapenemase-producing *K. pneumoniae* harbouring $bla_{\text{OXA-48}}$ gene was speculated [92, 93]. The escalation and the final outbreak of carbapenemase-producing *K. pneumoniae* was reported after 2016. Nowdays in Croatia, OXA-48 producing *K. pneumoniae* strains seem to be widely spread, while KPC-producing *K. pneumoniae* ST101 clone dominates in southern Croatia. In addition, mutations in the *mgrB* gene seem to be responsible for the increase of CRKP resistance to colistin [94, 97, 98, 101, 110].

Although the first data of Bulgaria was recorded after 2011, the distribution of resistant genes of CRKP seems to follow the trend of Greece and Romania. The first OXA-48-producing and NDM-1-producing *K. pneumoniae* strains were isolated in 2014 [122, 124]. Before that, the dominant carbapenemase was the KPC-2 type [124]. The dominant clonal types were ST15, followed by ST76 and ST1350, ST101, ST258, and ST151. The first outbreak of NDM-1-producing *K. pneumoniae* was reported between 2015 and 2016 [125]. Moreover, ST11 was the most frequent clonal type, while ST16, ST15 and ST391 were also detected. Since 2014 and until now, KPC-2 and NDM-1-producing *K. pneumoniae* strains were dominant in Bulgaria [124, 127]. In Serbia and Slovenia, until 2014, newly emerging CRKP harbouring $bla_{\text{NDM-1}}$ and/or bla_{oxa-48} isolates gradually replaced the older $bla_{\text{KPC.}}$ [129, 131, 133, 140, 141]. In Slovenia, the emergence of ST101 *K. pneumoniae* was correlated to the dominance of OXA-48 carbapenemase. The same clone showed resistance to colistin due to alterations in *mgrB* gene [126]. An outbreak of OXA-48 producing *K. pneumoniae* was also recorded in Bosnia - Herzegovina in 2017 and 2018 [143].

Meletis et al. were the first to urge caution on the emergence of carbapenemases in Balkans. According to their review, until 2013 NDM-1-producing *Enterobacterales* dominated the Balkan countries. However, publications on carbapenemases from Serbia, Bosnia and Herzegovina, Kosovo, Montenegro, Albania and FYROM (North Macedonia) were scarce [139]. The reported conclusions of our study referring to Greece and Romania seem to come in agreement with the aforementioned study and similar data in the rest of Europe. In 2013, CRKP proportions reached

endemic rates in only three countries out of 27: Romania was the third, Italy was second and Greece ranking first in Europe [40]. In the last 10 years, Romania, Poland, and Denmark are the countries with the highest rates of NDM-producing *K. pneumoniae* and *E. coli* in Europe. Spain, Italy, and Hungary report that the expansion of the VIM type carbapenemase has reached endemic levels [4].

In the United States, Latin America, Canada, and India, NDM-1-producing *K. pneumoniae* is the most common strain [4, 140]. On the other hand, KPC-producing *Enterobacterales* thrive in Mediterranean countries, especially in Italy and Greece, while also in Asia, especially in China, South and Central America. Moreover, almost every state in the United States has reported the emergence of KPC-producing *Enterobacterales*, including KPC-producing-*K. pneumoniae* [141–143]. Until now, evidence suggests that the prevalence of OXA-48 producing-*K. pneumoniae* remains in low levels in the United States whereas they are widely spread in the Mediterranean region and in several countries of Europe [5, 144, 145]. The authors of this review spotted a severe emergence of OXA-48 carbapenemase in the Balkans, initiated in 2011 [29, 85, 99, 115, 124, 136]. In addition, a clear shift is observed in the epidemiology of CRKP strains regarding the production of KPC and MBLs. While during the years 2018–2019, the dominant resistance mechanism was the production of carbapenemase KPC, either alone or in combination with VIM, during the years 2020–2021, there were more strains producing carbapenemase NDM.

Regarding the distribution of CRKP sequence types, ST258 was the dominant type in United States and worldwide until 2014 [146]. During the same period in Europe, ST11, ST15, ST101, and especially, ST258/512 were considered to be the high-risk CRKP clones [147]. According to our study, the same pattern was observed in most Balkan countries since 2014. ST258 was the most common type of CRKP in Greece [76] and was recorded by many researhers in Croatia, Bulgaria and Serbia [18, 81, 82, 84, 118, 119, 123, 125]. During the following years, new sequence types and some of the already known emerged in Balkans. Since 2018, ST11 became the most frequent in Greece and Bulgaria [66, 67, 69, 73, 76, 119]. On the other hand, ST437 dominated in Slovenia [134]. Moreover, the expansion of ST15 was observed in the aforementioned three Balkan countries [73, 76, 119, 134]. Nowadays, many countries all over the world recorded the severe emergence of ST11, ST15 and ST14 [148].

To conclude, carbapenem resistant *K. pneumoniae* emergence poses a severe threat not only to the Balkans but also to all countries in Europe. Greece and Romania have been at an endemic level for the last 20 years. CRKP harbouring bla_{KPC}, are the most common in these two countries. Regarding the rest of the region, the spread of CRKP initiated approximately 10 years later, with metallo-β-lactamases (MBL) being the protagonists. OXA-48 producing *K. pneumoniae* has been spotted in most of the countries. In addition, since 2018, ST11 seems to have replaced the ST258 of CRKP in Balkan peninsula, while ST15 continues to thrive throughout the years. Concerning CRKP susceptibility to other drugs, colistin's efficacy has decreased dramatically during the last ten years. Further investigation is strongly recommended, as the resistance mechanisms to colistin seem to be based on alterations in *mgrB* gene, rather than the already known *mcr* genes. Moreover ceftazidime-avibactam-resistant CRKP were detected mostly in Greece. Given our therapeutic options are significantly restricted, it is essential to design measures in order to monitor and control infections caused by superbugs. Future studies should focus in development of strategies that would be able to restrict and hopefully prevent the outbreak of CRKP in Europe and further expansion to Balkan countries.

Reviewing current knowledge upon life-threatening CRKP is the most important finding of this study pointing out that this problem needs to be urgently addressed as it constitutes a serious issue of patient safety in Balkan hospitals. Tracking emerging antimicrobial resistance threats, as well as assessing the effectiveness of the control efforts in use are issues extremely essential.

LIMITATIONS

This study includes reports from only two databases, "PubMed" and "Scopus", and therefore bias due to no-reporting data should be considered. The authors recorded data strictly from the Balkan region over the last 23 years. The reports were retrieved, categorized and screened separately for each Balkan country in order to minimize any bias in the selection of the data. In addition, the excluded criteria were checked twice. A preliminary query was conducted using the search tools and the proper limitations of the databases, while the second assessment was conducted manually, according to the exact same criteria. Publications written in the native languages of each country have been dismissed, since the authors were able to study only English and Greek. All the above contributed in the effort to eliminate any risk of bias due to confounding and to improve the quality of the reported results.

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