Le Infezioni in Medicina, n. 2, 85-106, 2014

Rassegna

Review

Carbapenemase reports from the Balkans: a systematic review

Microrganismi produttori di carbapenemasi nei Balcani: una rassegna sistematica

Georgios Meletis[1], Efstathios Oustas[1], Maria Bagkeri[2]

[1]Department of Clinical Microbiology, St. Paul General Hospital of Thessaloniki, Thessaloniki, Greece;
[2]Department of Internal Medicine, St. Demetrios General Hospital of Thessaloniki, Thessaloniki, Greece

BACKGROUND

Transferable carbapenemases (enzymes which inactivate carbapenems together with other beta-lactams and can be disseminated via horizontal gene transfer) are a major public health threat causing worldwide concern. Since their first detection in the early 1990s they have spread through all continents and Southern Europe is one of the areas in which their presence is well documented [1, 2]. In 2010, a consultation of European experts highlighted the need, amongst others, for proper data collection on the dissemination and introduction of strains with particular health importance and indicated the likelihood of several European and especially Balkan countries underreporting carbapenemase-producing isolates [3]. Two years later, the European Network on Carbapenemases commented on the fact that some European countries publish frequent reports on carbapenemases whereas data and epidemiological information from others are not available [4]. Consequently, the presence of carbapenemases in these cases is usually revealed after patient transfer abroad. Moreover, in the same paper, Canton et al. noticed that countries with very active investigators tend to have a larger number of reports compared to others.

Corresponding author
Meletis Georgios
E-mail: meletisg@hotmail.com

The Balkan Peninsula, popularly referred to as the Balkans, is the geographical region that comprises Greece, the Turkish region of Eastern Thrace, Albania, Bulgaria, Serbia, Bosnia and Herzegovina, the Former Yougoslav Republic of Macedonia (FYROM), Kosovo, Montenegro, Croatia, Slovenia and Romania. As Greece, of these countries, is considered endemic for KPC and VIM carbapenemases, the "Prokroustes" Nationwide Action Plan has been in place since 2010. However, data from other Balkan countries related to this significant health problem seem to be scarce in the international literature. Livermore et al. presented evidence that the Balkans may be a second important reservoir for the NDM-1 carbapenemase following that of the Indian subcontinent despite the lack of internationally available epidemiological data [5]. The present systematic review aims to evaluate the literature data accessible on PubMed regarding the report of carbapenemases from each of the Balkan countries and the occurrence of carbapenemase-producing bacteria dissemination to other parts of Europe via patient transfer from the Balkan Peninsula.

Literature search

We searched for relevant studies indexed in the PubMed database reporting at least one of the most frequently encountered carbapenemases in the Balkan region and published since the year in which the first carbapenemase reports in Europe were issued until May 2013 (01/01/1999-05/31/2013) [6, 7].

Our search terms included the words ([All Fields]) 'carbapenemase*', 'KPC', 'IBC', 'GES', 'VIM', 'IMP', 'NDM-1', 'OXA-23', 'OXA-48', 'OXA-58', 'OXA-72' and 'Greece', 'Bulgaria', 'Romania', 'Albania', 'Croatia', 'Serbia', 'Slovenia', 'Bosnia', 'Montenegro', 'Kosovo', 'FYROM', 'Macedonia' and 'Balkan*'. Even though Eastern Thrace is part of the Balkan Peninsula and belongs to Turkey, it was not included in the research criteria because the region itself is small in respect to the whole Turkish territory and its inclusion could lead to bias in assessing the report of carbapenemases from the Balkans. No limits were applied for language. The PRISMA guidelines were followed for search, selection and inclusion/exclusion criteria of the related publications [8]. In the present review, studies are referred with the first author's name and year of publication. The name of the second and third authors are mentioned where appropriate to distinguish studies with the same first author and year of publication and studies with the same first and second author and year of publication, respectively. Our search retrieved 204 publications for Greece, 0 for Albania, 17 for Croatia, 1 for Bosnia, 12 for Bulgaria, 9 for Slovenia, 14 for Romania, 0 for Macedonia or FYROM, 22 for Serbia, 2 for Montenegro and 9 for Balkan* (Figure 1).

Reviewed publications by country

Greece

After the first screening, 25 publications were excluded as being completely unrelated to carbapenemases. These publications showed up in our search results mainly because the abbreviated names of some carbapenemases are identical to other abbreviations used in different medical specialties such as oncology and immunology (for example VIM for vimentin; IBC for inflammatory breast cancer, ipsilateral breast cancer, intrahepatic biliary cystadenoma, invasive breast carcinoma; IMP for imidazolyl phenol, carvedilol impurities; GES for glucuronyl esterases). The same strategy was applied for the early exclusion of studies from the other countries' datasets.

Twenty publications were excluded as reviews and 33 as articles presenting methodological approaches to the study of carbapenemases rather than reporting the isolation of carbapenemase-producing bacteria. In this category we included articles on infection control strategies, detection methods, gene or plasmid characterization and molecular typing of carbapenemase-producing isolates. Eighteen more articles were excluded as they represented drug and treatment research or studied the patient outcomes of infections caused by carbapenemase-producing pathogens. Six articles were rejected because they simply mentioned Greece in their background or discussion section whereas three showed up in our search results due to the participation of Greek affiliated authors in foreign studies. Finally, 99 publications were included, 20 of which were reports from other countries due to patient transfer from Greek hospitals [9-28]. The other 79 were divided into two categories:

1) large studies (prospective and retrospective, case-control studies and outbreaks, reporting or studying generally >3 isolates);
2) case reports or case series (presenting ≤3 isolates). Forty-nine publications met the criteria of the first category [29-77]. Thirty publications were considered as case reports or case series [78-107].

Croatia

Five out of 17 results for Croatia were excluded as unrelated to carbapenemases. Two papers were classified as reviews, one as a methodological article and another was excluded because Croatia was simply mentioned in its main text. Therefore, eight publications were included for final evaluation. Seven of them were from Croatian studies: five large studies [108-112] and two case reports [113, 114]. The remaining publication was a report of patient introduction from Bosnia and Herzegovina to Croatia [115].

Bosnia and Herzegovina

Only one publication showed up in our search for Bosnia and proved to be unrelated to our study. However, the above patient transfer to Croatia was considered as a case report to be attributed to Bosnia and Herzegovina [115].

Bulgaria

Six out of 12 papers from our search for Bulgaria were not related to carbapenemases. Interestingly, in two studies investigating carbapenem resistance, the authors did not detect the presence of carbapenemases [116, 117]. Three large studies and one case report were finally included [118-121].

Slovenia

Nine papers were screened for Slovenia and

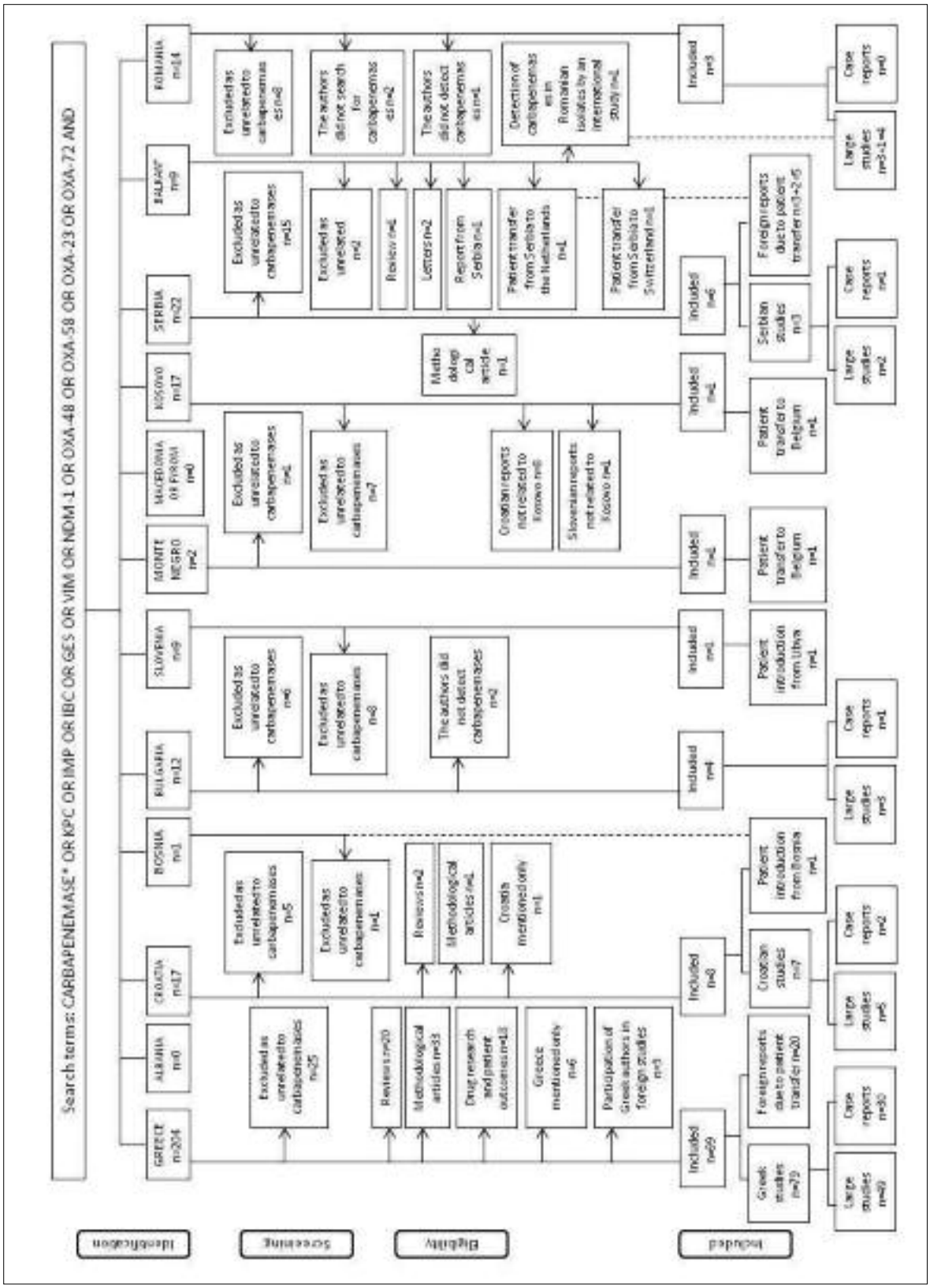

Figure 1 - Flow diagram of retrieved publication.

eight of them were excluded as not related to our study. The remaining publication was a report of a carbapenemase-producing *Klebsiella pneumoniae* introduction from Libya [122].

Romania
Eight out of 14 publications were unrelated to carbapenemases. In three studies on antibiotic resistance, the authors either did not search for carbapenemases or they did not detect any [123]. Finally, three large-scale studies were included for evaluation [124-126].

Kosovo
The search for Kosovo revealed seven unrelated publications and nine double results not related to patients or hospitals in Kosovo. Eight of them were from Croatia and one from Slovenia [108-115, 122]. These publications were excluded in this step because they had been previously evaluated. The remaining paper was a report of patient transfer from Kosovo to Belgium [127].

Serbia
Fifteen out of 22 search results were excluded because they represented fields of medical research other than antibiotic resistance; one was excluded as it was an article on methodology. Three foreign reports were included due to patient transfer from Serbia together with two large studies and one case report from Serbian investigators [127-132].

Montenegro
One out of two search results was unrelated to carbapenem resistance and the other was a report of patient transfer to Belgium [127].

*Balkan**
Two publications were excluded as unrelated and one as review. One previously evaluated double result from Serbia was found and excluded along with the letter of Livermore et al. and its commentary by Gecaj-Gashi et al. [5, 131, 133]. In the study of Marqué et al., OXA carbapenemases were reported in Romanian Acinetobacter isolates. Thus these findings were added to Romania [134]. The remaining two publications reported patient transfers from Serbia to the Netherlands and to Switzerland [135, 136]. These two publications were added to the total sum of foreign reports due to patient transfers from Serbia raising the final number from four to six.

Evaluation of the reviewed data
A brief description of the study type and results of the evaluated publications is presented in Table 1. Greece presents the highest number of reports due to patient transfers abroad, more frequently associated with KPC- or VIM-producing *K. pneumoniae.* The large number of domestic studies reflects the endemic status of the country regarding the presence of carbapenemase-producing gram negatives and the interest of several Greek scientific groups in this regard. Indeed, carbapenemases of all molecular classes have been found in Greece mainly among *K. pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. This is in accordance with the data of the European Antimicrobial Resistance Surveillance Network (EARS-Net) on carbapenem resistance in Greece (rates of carbapenem resistance increased from 27.8% in 2005 to 68.2% in 2011 for *K. pneumoniae* and from 38.7% in 2005 to 54.0% in 2011 for *P. aeruginosa* whereas these remained relatively stable 1.1-0.1% for *E. coli* between 2000 and 2011). Studies from Croatia indicate that despite the sporadic isolation of VIM-2-producing *P. aeruginosa* and KPC-2-producing *K. pneumoniae*, these enzymes are not disseminated as in the case of Greece (EARS-Net data of carbapenem resistance: 0-22% for *K. pneumoniae* and 21.9-28.6% for *P. aeruginosa* between 2009 and 2011). On the contrary, serious outbreaks have been reported in Zagreb and Split due to *A. baumannii* bearing OXA-type carbapenemases. Carbapenem-resistant *A. baumannii* producing OXA carbapenemases represents the main finding in Bulgarian studies as well. It is of interest that negative results concerning carbapenemase detection in *P. aeruginosa* were reported in two distinct studies: Vatcheva-Dobrevska et al., and Strateva et al. found no transferable carbapenemases among 29 multi-drug-resistant (MDR) isolates from seven hospitals and 203 clinical isolates from five hospitals, respectively (EARS-Net rates of carbapenem resistance: 0% for *K. pneumoniae* and from 37.5% in 2005 to 29.2% in 2011 for *P. aeruginosa*) [116, 117].
The only case report of carbapenemase-producing *K. pneumoniae* found for Slovenia was due to patient introduction from Libya [122]. The country's EARS-Net rates of carbapenem resistance for *K. pneumoniae* were stable (0-0.5% between 2005 and 2011). Carbapenem resistance rates for *P. aeruginosa*, however, rose from 13.2% in 2005 to 23.7% in 2011.
Four large studies were evaluated for Romania

Table 1 - Study type and results of the evaluated publications per country.

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
	Mougkou et al., 2013 [29]	Gr	FT	214 high-risk children from 8 neonate ICUs, 2 pediatric ICUs, 3 oncology units and 1 transplant unit in Athens screened for rectal colonization by carbapenemase-producing bacteria	(1) VIM-producing *K. pneumoniae*
	Alexopoulou et al., 2013 [30]	Gr	FT	47 cases of spontaneous bacterial peritonitis studied retrospectively in Athens	(4) KPC-producing *K. pneumoniae*
	Koutsogiannou et al., 2013 [31]	Gr	FT	Study of 240 MDR *P. aeruginosa* isolates from an outbreak in Patras	(46) VIM-2 and (3) VIM-1 *P. aeruginosa*
	Voulgari, Zarkotou et al., 2013 [32]	Gr	FT	Study of 13 ertapenem resistant *K. pneumoniae* that were negative for KPC and MBL production in Athens	(13) OXA-48+OXA-1+CTXM-15 *K. pneumoniae*
	Mavroidi, Miriagou et al., 2012 [33]	Gr	FT	Study of 106 ciprofloxacin-resistant *E. coli* in Larissa	(4) KPC-2 *E. coli*
Large Studies	Papadimitriou, Olivgeris et al., 2012 [34]	Gr	FT	Prospective observational study of 405 patients admitted to an ICU in Patras regarding the enteric colonization with KPC-*K. pneumoniae*	(52) patients colonized with KPC-*K. pneumoniae* upon ICU admission
	Poulou et al., 2012 [35]	Gr	FT	Report of the dissemination and control of carbapenemase-producing *K. pneumoniae* between 2009-2011 in Serres	(52) KPC-2, (12) VIM-1 and (9) KPC-2+VIM-1 *K. pneumoniae*
	Liakopoulos et al., 2012 [36]	Gr	FT	174 carbapenem-resistant *A. baumannii* isolated between 2010-2011 in Larissa	(125) OXA-23, (48) OXA-58 and (1) OXA-23+OXA-58 *A. baumannii*
	Zagorianou et al., 2012 [37]	Gr	FT	570 carbapenemase-producing *K. pneumoniae* reported between 2004-2010 in a hospital of Thessaloniki	(267) VIM-producing, (301) KPC-producing and (2) VIM+KPC-producing *K. pneumoniae*
	Galani, Souli, Panagea et al., 2012 [38]	Gr	FT	3/1534 *K. pneumoniae* and 3/734 *P. mirabilis* from a university hospital in Athens found to bear the rmt-B gene	(2/3) *K. pneumoniae* co-harbored KPC-2 and OXA-10 and (1/3) *P. mirabilis* co-harbored VIM-1 and OXA-10 →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
	Mavroidi, Miriagou, Malli et al., 2012 [39]	Gr	FT	15 carbapenem-non susceptible *E. coli* studied from a hospital and a long term care facility in Larissa	(10) KPC-producing *E. coli* plus 5/20 fecal carriers from the long term care facility were found
	Papagiannitsis et al., 2012 [40]	Gr	FT	256 *K. pneumoniae* from 8 hospitals in 2010 studied for β-lactamase production	(90) KPC-2, (15) VIM-1, (5) VIM-19, (2) VIM-27, (6) KPC-2+VIM-1 and (1) KPC-2+VIM-19 *K. pneumoniae*
	Gogou et al., 2011 [41]	Gr	FT	Study of the evolutionary and genetic relatedness of *A. baumannii* clonal lineages from 8 hospitals during a 10 year period	(67/94) OXA-58 *A. baumannii*
	Koratzanis et al., 2011 [42]	Gr	FT	Study of VIM-producing bacteria isolated in an ICU in Athens during 1.5 years	(77) VIM-1 *K. pneumoniae* (2) VIM-1 *E. cloacae* (1) VIM-1 *C. freundii* (2) VIM-2 *P. aeruginosa*
	Tsakris, Poulou et al., 2011 [43]	Gr	FT	Study of 9 MDR K. oxytoca isolated between 2005-2007 in Serres	(3) VIM-1 *K. oxytoca*
Large Studies	Giakkoupi et al., 2011 [44]	Gr	FT	Study of 378 KPC-2 *K. pneumoniae* from 40 hospitals isolated between 2009-2010	(18) KPC-2+VIM-1 or VIM-4 *K. pneumoniae*
	Poulou et al., 2010 [45]	Gr	FT	157 *K. pneumoniae* isolated from outpatients in Serres studied for carbapenemase production	(24) *K. pneumoniae* isolates from 12 patients were found to be VIM-1 positive
	Kontopoulou et al., 2010 [46]	Gr	FT	Description of an outbreak in Thessaloniki	(7) KPC-2 *K. pneumoniae* resistant to colistin
	Zioga et al., 2010 [47]	Gr	FT	Study of 42 carbapenem resistant *K. pneumoniae* isolated in 2009 in Athens	(16) KPC-2 and (12) VIM-1 and (14) KPC-2+VIM-1 *K. pneumoniae*
	Souli et al., 2010 [48]	Gr	FT	Description of a 2007-2008 outbreak in Athens	(50) KPC-2 *K. pneumoniae* cases
	Papa et al., 2009 [49]	Gr	FT	Study of 164 carbapenem resistant *A. baumannii* isolated between 2001-2008 in Thessaloniki	(159) OXA-58 *A. baumannii*
	Tsakris, Poulou, Kristo et al., 2009 [50]	Gr	FT	Study of 45 carbapenem resistant *P. aeruginosa* outpatient urinary tract infections between 2005-2008 in Serres	(45) VIM-2 *P. aeruginosa* →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
	Pournaras, Protonotariou et al., 2009 [51]	Gr	FT	Description of an outbreak during 2007-2008 in Thessaloniki	(47) KPC-2 *K. pneumoniae*
	Giakoupi et al., 2009 [52]	Gr	FT	2008 survey in 40 hospitals for KPC-producing *K. pneumoniae*	KPC-2 found in isolates from 173 patients in 18 hospitals
	Maltezou et al., 2009 [53]	Gr	FT	Description of an outbreak in 2007 in Heraklion	(22) KPC-2 *K. pneumoniae*
	Siarkou et al., 2009 [54]	Gr	FT	Study of 29 MDR *P. aeruginosa* isolated between 2004-2005 in Thessaloniki	(13) VIM-17 and (1) VIM-2 *P. aeruginosa*
	Zappas et al., 2008 [55]	Gr	Ab	Study of 112 imipenem resistant *P. aeruginosa* isolated between 2002-2003 in Athens	(32) VIM-2 *P. aeruginosa*
	Tsakris, Ikonomidis et al., 2008 [56]	Gr	FT	Study of 31 imipenem resistant *A. baumannii* isolated between 2005-2007 in Serres	(19) VIM-1+OXA-58+OXA-66 and (5) VIM-4+OXA-58+OXA-69 and (2) OXA-58+OXA-69 and (5) OXA-66 *A. baumannii*
	Loli et al., 2008 [57]	Gr	FT	Description of an outbreak in 2005-2006 in Piraeus	(6) VIM-1+OXA-58+OXA-51 *A. baumannii*
Large Studies	Tokatlidou et al., 2008 [58]	Gr	FT	Description of an outbreak in 2006-2007 in Thessaloniki	(9) VIM-12+CMY *K. pneumoniae*
	Ikonomidis et al., 2008 [59]	Gr	FT	87 *A. baumannii* isolates tested for phenotypically hidden MBL gene presence in Larissa	(2) VIM-1 *A. baumannii*
	Psichogiou et al., 2008 [60]	Gr	FT	178 *K. pneumoniae* blood isolates from 3 teaching hospitals of Athens tested for MBL production	(45) VIM-1+SHV-5 and (22) VIM-1 *K. pneumoniae*
	Tsakris, Ikonomidis, Poulou et al., 2007 [61]	Gr	FT	Study of 155 carbapenem resistant *P. mirabilis* community-onset clinical infections during 2005-2006 in Serres	(12) VIM-1 *P. mirabilis*
	Ikonomidis, Pournaras et al., 2007 [62]	Gr	FT	Study of 150 *A. baumannii* from 5 Greek hospitals	(130) OXA-66 and (18) OXA-69 and (2) OXA-65 *A. baumannii*
	Horianopoulou et al., 2006 [63]	Gr	FT	35 ICU patients in Athens studied for respiratory tract colonization by MBL-producing bacteria	(6) VIM-2 *P. aeruginosa*
	Poirel et al., 2006 [64]	Gr	FT	Study of 12 carbapenem resistant *A. baumannii* isolated between 2003-2005 in a pediatric hospital in Athens	(12) OXA-58 *A. baumannii* →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
Large Studies	Vourli et al., 2006 [65]	Gr	FT	Study of 7 imipenem resistant *P. mirabilis* isolated between 2004-2005 in Thessaloniki	(7) VIM-1 *P. mirabilis*
	Tsakris et al., 2006 [66]	Gr	FT	Study of 5 positive IMP-EDTA test *A. baumannii* isolated between 2004-2005 from 2 Greek hospitals in Thessaloniki and Larissa	(2) VIM-1+OXA-66+OXA -58 and (2) VIM-1+OXA-66 and (1) VIM-1 *A. baumannii*
	Pournaras et al., 2006 [67]	Gr	FT	Study of 17 imipenem resistant *A. baumannii* isolated in 2002 in Athens	(12) OXA-51+OXA-58 and (3) OXA-51 and (2) OXA-58 *A. baumannii*
	Ikonomidis et al., 2005 [68]	Gr	FT	Study of 27 positive IMP-EDTA test *K. pneumoniae* isolated in Larissa and Thessaloniki between 2004-2005	(27) VIM-1 *K. pneumoniae*
	Pournaras, Maniati et al., 2005 [69]	Gr	FT	Study of 13 meropenem resistant and ceftazidime susceptible *P. aeruginosa* isolated in 2003 in Larissa	(1) VIM-2 *P. aeruginosa*
	Scoulica et al., 2004 [70]	Gr	FT	Study of 4 MBL producing *E. coli* isolated in Heraklion	(4) VIM-1 *E. coli*
	Tsakris et al., 2003 [71]	Gr	FT	Study of 24 carbapenem resistant *Pseudomonas spp* isolated between 1998-2000 in Thessaloniki	(1) VIM-2 *P. aeruginosa* and (1) VIM-2 *P. putida*
	Giakkoupi, Xanthaki et al., 2003 [72]	Gr	FT	Study of 17 MBL producing *K. pneumoniae* isolated in 2002 from 3 hospitals in Athens	(17) VIM-1 *K. pneumoniae*
	Pournaras et al., 2003 [73]	Gr	FT	Study of 53 carbapenem resistant *P. aeruginosa* isolated between 2001-2002 in Larissa	(47) VIM-producing *P. aeruginosa*
	Tzelepi et al., 2003 [74]	Gr	FT	79 *K. pneumoniae* and 124 *E. coli* isolated in 2001 in Athens and Thessaloniki examined for ESBL production	(1) IBC-1+SHV-5 and (2) IBC-1 *K. pneumoniae*
	Giakkoupi, Petrikos et al., 2003 [75]	Gr	FT	Study of 58 imipenem non-susceptible *P. aeruginosa* isolated in 2001 from 15 hospitals	(36) VIM-producing *P. aeruginosa*
	Kartali et al., 2002 [76]	Gr	FT	Study of 27 ceftazidime resistant *E. cloacae* isolated in a neonatal ICU in Thessaloniki between 1998-2000	(19) IBC-1 *E. cloacae*
	Tsakris et al., 2000 [77]	Gr	FT	Study of 6 high-level carbapenem resistant *P. aeruginosa* isolated between 1996-1998 in Thessaloniki	(6) VIM-1 *P. aeruginosa*

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	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
Case Reports	Sianou et al., 2012 [78]	Gr	FT	Co-infection case by *K. pneumoniae*, *E. coli* and *E. cloacae* in Thessaloniki	(1) VIM-1 *K. pneumoniae* and (1) VIM-1 *E. coli* and (1) VIM-1 *E. cloacae*
	Mavroidi et al., 2011 [79]	Gr	FT	Isolation of *C. koseri* and *K. pneumoniae* by the same patient in Larissa	(1) KPC-2 *C. koseri* and (1) KPC-2+VIM-1 *K. pneumoniae*
	Papagiannitsis, Kotsakis et al., 2011 [80]	Gr	FT	Report of a VIM-1 variant in Larissa	(3) VIM-27 *K. pneumoniae*
	Papadimitriou et al., 2011 [81]	Gr	Ab	Isolation of a carbapenem-resistant *E. coli* from rectal swab of a neonate in a neonate ICU in Athens	(1) VIM-1 *E. coli*
	Papagiannitsis et al., 2010 [82]	Gr	FT	Report of a *K. pneumoniae* co-producing more than one carbapenemases in Athens	(1) VIM-4+KPC-2+CMY-4 *K. pneumoniae*
	Panopoulou et al., 2010 [83]	Gr	FT	Study of 3 MBL-producing *E. cloacae* from Alexandroupolis	(1) VIM-12 and (2) VIM-1 *E. cloacae*
	Galani et al., 2010 [84]	Gr	FT	Report of qnrA1-positive *K. pneumoniae* and qnrB2-positive *E. coli* harboring MBLs isolated in Athens	(1) VIM-1 *K. pneumoniae* and (1) VIM-1 *E. coli*
	Pournaras, Poulou et al., 2010 [85]	Gr	FT	Report of a *K. pneumoniae* co-producing more than one carbapenemases in Serres	(1) VIM-19+KPC-2+ CMY-2+CTXM-15 *K. pneumoniae*
	Tsakris, Voulgari et al., 2010 [86]	Gr	FT	Report of in vivo acquisition of KPC-2 in *S. marcescens*	(3) KPC-2+TEM-1 *S. marcescens* and (1) KPC-2+TEM-1 *K. pneumoniae*
	Meletis et al., 2010 [87]	Gr	FT	Report of a *K. pneumoniae* co-producing more than one carbapenemases in Thessaloniki	(1) VIM-1+KPC-2+TEM+SHV *K. pneumoniae*
	Miriagou et al., 2008 [88]			Study of MBL-producing *S. liquefaciens* and *K. oxytoca* isolated in Athens	(1) VIM-1+SHV-5 *S. liquefaciens* and (1) VIM-1 *K. oxytoca*
	Tsakris, Kristo et al., 2008 [89]	Gr	FT	Report of a KPC-producing *K. pneumoniae* isolated in Serres	(1) KPC-2+SHV-12 *K. pneumoniae*
	Protonotariou et al., 2008 [90]	Gr	FT	Study of an MBL-producing *C. freundii* isolated in Thessaloniki	(1) VIM-1 *C. freundii*
	Kontou et al., 2007 [91]	Gr	FT	Report and characterization of a new VIM variant in Thessaloniki	(1) VIM-12 *K. pneumoniae* →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
	Ikonomidis, Spanaki et al., 2007 [92]	Gr	Ab	Study of an MBL-producing *E. cloacae*	(1) VIM-4+SHV-2a *E. cloacae*
	Maniati et al., 2007 [93]	Gr	FT	Study of an MBL-producing *P. aeruginosa* isolated in Larissa	(1) VIM-4 *P. aeruginosa*
	Tsakris, Ikonomidis, Spanakis et al., 2007 [94]	Gr	FT	Study of an MBL-producing *M. morganii*	(1) VIM-1 *M. morganii*
	Galani et al., 2007 [95]	Gr	FT	Study of MBL-producing *E. coli*, *E. aerogenes* and *P. mirabilis* isolated from different patients in the same hospital in Athens	(1) VIM-1+TEM *E. coli* and (1) VIM-1+SHV *E. aerogenes* and (1) VIM-1+TEM *P. mirabilis*
	Sofianou et al., 2005 [96]	Gr	FT	Study of an MBL producing *A. xylosoxidans*	(1) VIM-2 *A. xylosoxidans*
	Pournaras, Ikonomidis et al., 2005 [97]	Gr	FT	Report of a novel VIM variant in Thessaloniki	(1) VIM-12+CMY +TEM-1+SHV-1 *K. pneumoniae*
	Miriagou et al., 2005 [98]	Gr	FT	Study of 4 colistin-only susceptible *K. pneumoniae* isolated in Athens	(4) VIM-1+SHV-5 *K. pneumoniae*
Case Reports	Galani et al., 2005 [99]	Gr	FT	Study of an MBL-producing *E. cloacae* isolated in Athens	(1) VIM-1 *E. cloacae*
	Galani et al., 2004 [100]	Gr	FT	Study of an MBL-producing *E. coli* isolated in Athens	(1) VIM-2+IBC-1 *E. coli*
	Vourli et al., 2004 [101]	Gr	FT	Study of an *E. coli* and a *K. pneumoniae* with decreased susceptibility to carbapenems isolated in Athens	(1) GES-3 E. coli and (1) GES-4 *K. pneumoniae*
	Vourli et al., 2003 [102]	Gr	FT	Study of a class 1 integron in an *E. coli* stool isolate in Athens	(1) IBC-1 *E. coli*
	Miriagou, Tzelepi et al., 2003 [103]	Gr	FT	Study of an *E. coli* with decreased susceptibility to carbapenems isolated in Piraeus	(1) VIM-1 *E. coli*
	Pournaras et al., 2002 [104]	Gr	FT	Report of a novel VIM variant in Larissa	(1) VIM-4 *P. aeruginosa*
	Mavroidi et al., 2001 [105]	Gr	FT	Report of a novel IBC variant in Thessaloniki	(1) IBC-2 *P. aeruginosa*
	Mavroidi et al., 2000 [106]	Gr	FT	Study of a carbapenem resistant *P. aeruginosa*	(1) VIM-2 *P. aeruginosa*
	Giakkoupi et al., 2000 [107]	Gr	FT	Study of a MDR E. cloacae isolated in Thessaloniki	(1) IBC-1 *E. cloacae* →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
	Chan et al., 2013 [9]	Gr	FT	Patient transfer to Canada	(1) KPC-2 *K. pneumoniae*
	Karah et al., 2011 [10]	Gr	FT	Study of 13 carbapenem resistant *A. baumannii* isolated between 2004-2007 in Sweden	(3) OXA-58like *A. baumannii* imported from Greece
	Hrabák et al., 2011 [11]	Gr	FT	Patient transfer to Czech Republic	(1) KPC-2 *K. pneumoniae*
	Bogaerts et al., 2011 [12]	Gr	FT	Patient transfer to Luxemburg	(1) VIM-27 *K. pneumoniae*
	Vaux et al., 2011 [13]	Gr	FT	Study of carbapenemase-producing Enterobacteriaceae between 2004-2011 in France	(3) VIM- and (7) KPC-producers transferred from Greece
	Samuelsen et al., 2011 [14]	Gr	FT	Characterization of eight VIM-producing *K. pneumoniae* identified in Scandinavia during 2005-2008	6 imported from Greece: (1) VIM-1+CTXM-3+ SHV-11+TEM-1, (1) VIM-1+SHV-11+ TEM-1, (1) VIM-1+SHV-5, (1) VIM-26+ SHV-5, (1) VIM-1+ SHV-11, (1) VIM-19, CTXM-gr.1+SHV-1
Patient Transfer	Babouee et al., 2011 [15]	Gr	FT	Report of 4 KPC-producing *K. pneumoniae* in Switzerland	(1) KPC-2 *K. pneumoniae* imported from Greece
	Bogaerts et al., 2010 [16]	Gr	FT	Report of the first 3 KPC-2-producing K. pneumoniae in Belgium	(3) KPC-2 *K. pneumoniae* imported from Greece
	Kassis-Chikhani et al., 2010 [17]	Gr	FT	Report of an outbreak in France after patient transfer from Greece	(1) VIM-1 *K. pneumoniae* imported from Greece
	CDC, 2010 [18]	Gr	FT	Patient transfer in the USA	(1) VIM-producing *K. pneumoniae*
	Wendt et al., 2010 [19]	Gr	FT	Report of the first KPC-2-producing *K. pneumoniae* outbreak in Germany	(1) KPC-2 *K. pneumoniae* imported from Greece
	Barbier et al., 2010 [20]	Gr	FT	Report of the in vivo transfer of blaKPC-2 between intensive care unit-acquired and a commensal strain of *K. pneumoniae* in a French patient after repatriation from Greece	(1) KPC-2 *K. pneumoniae* imported from Greece
	Carbonne et al., 2010 [21]	Gr	FT	Report of a KPC-2-producing *K. pneumoniae* outbreak in France	(1) KPC-2+SHV-12 *K. pneumoniae* imported from Greece →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
Patient Transfer	Samuelsen, Toleman et al., 2010 [22]	Gr	FT	Molecular epidemiology of MBL-producing *P. aeruginosa* isolates from Norway and Sweden	(1) VIM-2 and (1) VIM-4 *P. aeruginosa* imported from Greece
	Samuelsen, Naseer et al., 2009 [23]	Gr	FT	Report of KPC-producing *K. pneumoniae* isolates in Norway and Sweden	(4) KPC-2+SHV-11+SHV-12+TEM-1 *K. pneumoniae* transferred from Greece to Norway
	Osterblad et al., 2009 [24]	Gr	FT	Report of the first 2 KPC-producing *K. pneumoniae* isolates in Finland	(1) KPC-2+SHV+TEM-1 *K. pneumoniae* imported from Greece
	Cuzon et al., 2008 [25]	Gr	FT	Report of a KPC-producing *K. pneumoniae* isolate in France	(1) KPC-2+TEM-1 *K. pneumoniae* imported from Greece
	Wybo et al., 2007 [26]	Gr	FT	Report of an MDR *A. baumannii* outbreak in Belgium	(2) OXA-58 *A. baumannii* imported from Greece
	Kassis-Chikhani et al., 2006 [27]	Gr	FT	Report of an MDR *K. pneumoniae* outbreak in France	(1) VIM-1+SHV-5 *K. pneumoniae* imported from Greece
	Libisch et al., 2004 [28]	Gr	FT	Report of the first MBL producing *P. aeruginosa* in Hungary	(1) VIM-4 *P. aeruginosa* imported from Greece
Large Studies	Sardelic et al., 2012 [108]	Cr	FT	Study of 169 imipenem resistant *P. aeruginosa* in Split	(6) VIM-2 *P. aeruginosa*
	Goic-Barisic et al., 2011 [109]	Cr	FT	Description of a carbapenem resistant *A. baumannii* outbreak in 2009 in Split	(32) OXA-72+OXA-90 *A. baumannii* after introduction of an OXA-51type producing isolate from Bosnia and Herzegovina
	Franolić-Kukina et al., 2011 [110]	Cr	FT	Outbreak of 34 carbapenem resistant *A. baumannii* in 2008 in Zagreb	(33) OXA-72 and (1) OXA-58 *A. baumannii*
	Bedenic et al., 2010 [111]	Cr	Ab	1510 Gram-negative pathogens screened for meropenem resistance between 2002-2007 in Zagreb and Split	(3) OXA-58like *A. baumannii* from Zagreb and (6) OXA-51 *A. baumannii* from Split
	Bosnjak et al., 2010 [112]	Cr	Ab	100 *P. aeruginosa* with reduced susceptibility to carbapenems isolated in Zagreb were tested for MBL production	(6) VIM-2 *P. aeruginosa*
CR	Bedenić et al., 2012 [113]	Cr	Ab	Report of a KPC-producing *K. pneumoniae* in Zagreb	(1) KPC-2+SHV+TEM *K. pneumoniae*
	Sardelic et al., 2003 [114]	Cr	FT	Report of 2 MBL-producing *P. aeruginosa* in 2000 in Split	(2) VIM-2 *P. aeruginosa* →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
Large Studies	Strateva et al., 2012 [118]	Bu	FT	Study of 70 MDR *A. baumannii* isolated between 2005-2011 in Sofia	(49) OXA-23 *A. baumannii*
	Stoeva et al., 2009 [119]	Bu	FT	Study of 11 carbapenem resistant and 2 carbapenem susceptible *A. baumannii* isolated in 2006 in Sofia	(8) OXA-23 and (3) OXA-58 *A. baumannii*
	Stoeva et al., 2008 [120]	Bu	FT	Study of 29 carbapenem resistant *A. baumannii* isolated between 1999-2006 in Pleven	(29) OXA-23 *A. baumannii*
CR	Schneider et al., 2008 [121]	Bu	FT	Report of novel VIM variants in *P. aeruginosa* from Germany and Bulgaria	(1) VIM-15 *P. aeruginosa* isolated in Sofia
PT	Pirš et al., 2011 [122]	Sl	FT	Case report of an OXA-48 producing *K. pneumoniae* imported from Libya	(1) OXA-48 *K. pneumoniae*
	Bonnin et al., 2011 [124]	Ro	FT	Study of 13 carbapenem resistant *A. baumannii* isolated between 2009-2010 in Arad, Resita and Timisoara	(3) OXA-23+OXA-69 and (3) OXA-23+TEM-1+OXA-66 and (2) OXA-23+OXA-66 and (2) OXA-23+PER-1+TEM-1+OXA-66 and (1) OXA-23+TEM-1+OXA-69 and (1) OXA-58+OXA-64 and (1) OXA-58+OXA-69
	Mereuţă, Tuchiluş et al., 2011 [125]	Ro	Ab	84 *P. aeruginosa* isolated in Iasi between 2007-2011 tested for MBL production	(24) VIM-producing *P. aeruginosa*
	Mereuţă et al., 2007 [126]	Ro	Ab	28 *P. aeruginosa* and *A. baumannii* collected between 2003-2007 from 5 hospitals in Iasi, Bacau and Galati tested for MBL production	(1) VIM-2 and (1) IMP-13 *P. aeruginosa*
	Marqué et al., 2005 [134]	Ro	FT	Study of 48 carbapenem non susceptible *Acinetobacter* spp collected from 6 European countries between 1997-2004	(10) OXA-58 and (2) OXA-23 and (1) OXA-40 *A. baumannii* and (1) OXA-23+OXA-58 *A. junii* isolated in Iasi, Romania
LS	Jovcic, Vasiljevic et al., 2011 [130]	Se	FT	526 *P. aeruginosa* isolates from a pediatric hospital in Belgrade tested for MBL production	(58) VIM-2 *P. aeruginosa*
	Jovcic, Lepsanovic et al., 2011 [131]	Se	FT	Report of NDM-1-producing *P. aeruginosa* isolated in Belgrade	(7) NDM-1 *P. aeruginosa*
CR	Lepsanovic et al., 2008 [132]	Se	Ab	Report of VIM-producing *P. aeruginosa* isolated in Belgrade	(1) VIM-2 *P. aeruginosa* →

	Reference	*Country*	*Evaluation of*	*Brief study description*	*(No.) of isolates and carbapenemases + other β-lactamases found in the study*
	Flateau et al., 2012 [128]	Se	FT	Patient transfer to France	(1) NDM-1 *P. aeruginosa* imported from Serbia
	Poirel et al., 2012 [129]	Se	FT	Study of an NDM-1-producing *A. baumannii* isolated in Switzerland	(1) NDM-1 *A. baumannii* imported from Serbia
PT	Bogaerts et al., 2011 [127]	Se	FT	Report of 5 NDM-1-producing Enterobacteriaceae in Belgium	(1) NDM-1+CTXM-15+ TEM-1+OXA-1 *M. morganii* and (1) NDM-1+CTXM-15+TEM-1+SHV-12 *E. cloacae* isolated from a patient consecutively hospitalized in Serbia and in Kosovo
	Halaby et al., 2012 [135]	Se	FT	2 cases of NDM-1-producing *K. pneumoniae* in the Netherlands	(1) NDM-1 *K. pneumoniae* imported from Serbia
	Poirel et al., 2011 [136]	Se	FT	4 NDM-1-producing Enterobacteriaceae found among 20 isolates with decreased susceptibility to ertapenem in Geneva, Switzerland	(1) NDM-1+TEM-1+OXA -1+CMY-30 *E. coli* and (1) NDM-1+CTXM-15+ TEM-1+SHV- 28+OXA-1 *K. pneumoniae* isolated from a Serbian patient
	Bogaerts et al., 2011 [127]	Mo	FT	Report of 5 NDM-1-producing Enterobacteriaceae in Belgium	(1) NDM-1+CTXM-15+ TEM-1+OXA-1+OXA-9+SHV-12 *K. pneumoniae* and (1) NDM-1+CMY-16+TEM-1+OXA-10 *E. coli* isolated from a patient previously hospitalized in Montenegro
PT	Mazzariol et al., 2012 [115]	Bo	FT	Report of an NDM-1–producing *K. pneumoniae* in Croatia	(1) NDM-1+CTXM-15+CMY-16 *K. pneumoniae* imported from Bosnia and Herzegovina
PT	Bogaerts et al., 2011 [127]	Ko	FT	Report of 5 NDM-1-producing Enterobacteriaceae in Belgium	(1) NDM-1+CTXM-15+TEM-1+OXA-1 *M. morganii* and (1) NDM-1+CTXM-15+TEM-1+SHV-12 *E. cloacae* isolated from a patient consecutively hospitalized in Serbia and in Kosovo

Legenda: Gr: Greece, Cr: Croatia, Bu: Bulgaria, Sl: Slovenia, Ro: Romania, Ko: Kosovo, Se: Serbia, Mo: Montenegro, Bo: Bosnia and Herzegovina, FT: Full Text, A: Abstract, LS: Large Studies, CR: Case Reports, PT: Patient Transfer, ICU: Intensive Care Unit, MDR: Multi-Drug-Resistant, MBL: Metallo-beta-lactamase

Figure 2 - Number of studies per country and carbapenemase types detected in or from the Balkan Peninsula.

Table 2 - Number of evaluated studies per country and foreign reports due to patient transfers abroad

	Total domestic studies	*Large studies*	*Case reports*	*Foreign reports of patient transfer*
Greece	78	48	30	20
Croatia	7	5	2	0
Bulgaria	4	3	1	0
Slovenia	0	0	0	0
Romania	4	4	0	0
Serbia	3	1	2	5
Bosnia & Herzegovina	0	0	0	1
Kosovo	0	0	0	1
Montenegro	0	0	0	1
Albania	0	0	0	0
FYROM	0	0	0	0

reporting OXA type carbapenemase-producing *A. baumannii* [124, 134] and VIM-producing *P. aeruginosa* [125, 126]. In another study, the authors searched for KPC-producing *K. pneumoniae* and *Escherichia coli* among 498 urinary tract infection isolates and reported negative results [123]. Indeed, Romanian data from EARS-Net present 0-0.5% carbapenem resistance for *K. pneumoniae* between 2005 and 2011; 0-3.0% carbapenem resistance for *E. coli* between 2002 and 2011 and a worrying 70% for *P. aeruginosa* in 2010 followed by a decrease to 60% in 2011.

Publications from Serbia report MBL-producing *P. aeruginosa* and include the first identification of NDM-1 in this pathogen [131]. Interestingly, five foreign papers report the identification of NDM-1 (in *P. aeruginosa, A. baumannii, Morganella morganii, Enterobacter cloacae, E. coli* and *K. pneumoniae*), providing strong evidence for the presence of an important NDM reservoir in this area [127-129, 135, 136]. Unfortunately, Serbia, like the rest of the remaining Balkan countries, is not a member of the EARS-Net and additional data are not available on an international level.

Research papers on carbapenemases from Bosnia and Herzegovina, Kosovo, Montenegro, Albania and FYROM were not found using our search terms on PubMed. However, there are valuable reports of NDM-1-producing *K. pneumoniae* imported from Bosnia and Herzegovina, Kosovo and Montenegro (Figure 2) [115, 127]. The number and study types for each of the Balkan countries are presented in Table 2.

Concluding remarks

Our review of the literature showed that even though carbapenemase-producing bacteria are present in the Balkans, the actual situation in some countries is not well, or in some cases, not at all documented, leaving unanswered questions about this considerable public health threat. More research is required in order to assess the prevalence of carbapenemases and especially that of NDM enzymes among gram negative pathogens in this area, and in the absence of political will and adequate funding, the contribution of active investigators is of utmost importance in this regard.

Conflict of interest

None to declare

Keywords: carbapenemases, Balkans, systematic review.

SUMMARY

The spread of carbapenemase-producing bacteria constitutes a worldwide problem of major importance to public health. The detection of these enzymes is often reported by most European countries and infection control measures are implemented in order to limit their dissemination. Despite the strong evidence indicating the Balkans as a reservoir for carbapenemase-encoding genes, especially for NDM-1, data published in the English literature seem to be scarce for many of the Balkan countries. We systematically reviewed studies on carbapenemase-producing bacteria from each country of the Balkan Peninsula and correlated them with foreign reports on carbapenemase detection due to patient transfer from the Balkans to the rest of Europe.

RIASSUNTO

La diffusione di microrganismi produttori di carbapenemasi rappresenta un problema di grande portata per la salute publica a livello mondiale. L'osservazione di questi enzimi è spesso riportata dalla maggior parte dei paesi europei e, nel tentativo di limitarne la diffusione, sono applicate delle misure di controllo. Nonostante le forti evidenze che indicano nei Balcani un reservoir *di geni codificanti le carbapenemasi, NDM-1 in particolare, per molti dei paesi balcanici i dati pubblicati nella letteratura anglofona sono scarsi. In questa rassegna abbiamo esaminato gli studi inerenti ai batteri produttori di carbapenemasi di tutti i paesi della penisola balcanica, correlandoli alle segnalazioni straniere sulla rilevazione di carbapenemasi avvenuta a seguito di pazienti trasferitisi dai Balcani al resto dell'Europa.*

I nostri risultati hanno evidenizato la necessità impellente di compiere maggiori ricerche nei paesi balcanici al fine di determinare la reale prevalenza delle carbapenemasi nell'ambito dei patogeni gram negativi in quest'area del continente europeo.

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