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# Carbapenemase-producing *Enterobacteriaceae* in Europe: assessment by national experts from 38 countries, May 2015

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In 2012, the European Centre for Disease Prevention and Control (ECDC) launched the 'European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)' project to gain insights into the occurrence and epidemiology of carbapenemase-producing *Enterobacteriaceae* (CPE), to increase the awareness of the spread of CPE, and to build and enhance the laboratory capacity for diagnosis and surveillance of CPE in Europe. Data collected through a post-EuSCAPE feedback questionnaire in May 2015 documented improvement compared with 2013 in capacity and ability to detect CPE and identify the different carbapenemase genes in the 38 participating countries, thus contributing to their awareness of and knowledge about the spread of CPE. Over the last two years, the epidemiological situation of CPE worsened, in particular with the rapid spread of carbapenem-hydrolysing oxacillinase-48 (OXA-48)- and New Delhi metallo-beta-lactamase (NDM)-producing *Enterobacteriaceae*. In 2015, 13/38 countries reported inter-regional spread of or an endemic situation for CPE, compared with 6/38 in 2013. Only three countries replied that they had not identified one single case of CPE. The ongoing spread of CPE represents an increasing threat to patient safety in European hospitals, and a majority of countries reacted by establishing national CPE surveillance systems and issuing guidance on control measures for health professionals. However, 14 countries still lacked specific national guidelines for prevention and control of CPE in mid-2015.

## Introduction

The global rise of carbapenemase-producing *Enterobacteriaceae* (CPE) is alarming and represents

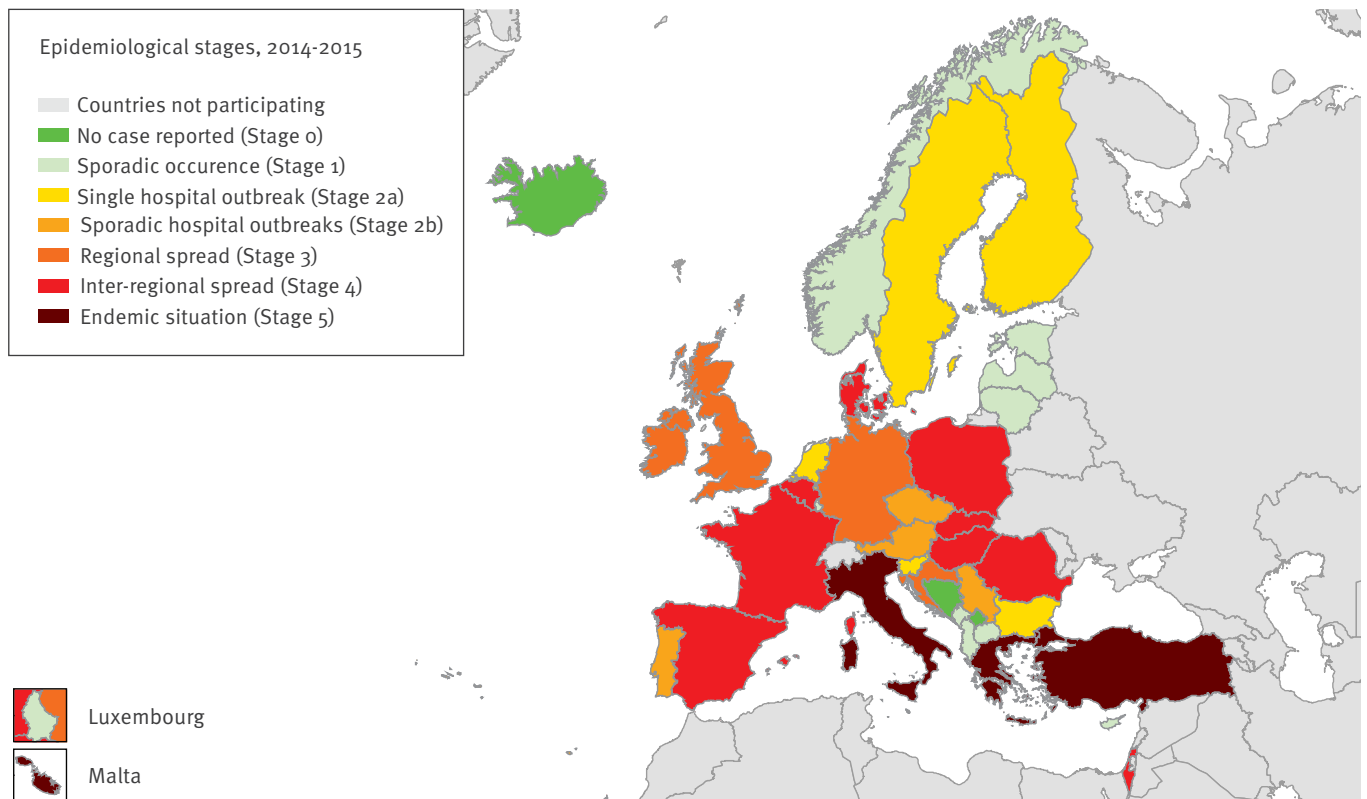
an increasing threat to healthcare delivery and patient safety in Europe and beyond.

In 2012, the European Centre for Disease Prevention and Control (ECDC) launched the 'European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)' project to improve the understanding of the occurrence and epidemiology of CPE, to increase awareness of the spread of CPE and to build laboratory capacity for diagnosis and surveillance in Europe.

In February 2013, a self-assessment questionnaire was sent to one national expert (NE) from each of the EuSCAPE participating countries (i.e. 28 European Union (EU) Member States, Iceland, Norway, the seven EU enlargement countries (Albania, Bosnia and Herzegovina, Kosovo\*, Montenegro, the former Yugoslav Republic of Macedonia, Serbia and Turkey) and Israel, to gather information on the current awareness of and knowledge about the spread of CPE, the public health responses and the available national guidelines on detection, surveillance, prevention and control, as well as on the capacity for laboratory diagnosis and surveillance. NEs were chosen based on their national and international laboratory and/or epidemiological experience in CPE among experts from national reference or expert laboratories, from the European Antimicrobial Resistance Surveillance Network (EARS-Net), and from the ECDC Coordinating Competent Bodies (National Focal Points for antimicrobial resistance and National Focal Points for microbiology) and ECDC National Correspondents for EU enlargement countries. The answers collected from the NEs showed that the epidemiological situation for CPE

**FIGURE 1**

Occurrence of carbapenemase-producing *Enterobacteriaceae* based on self-assessment by national experts, 38 European countries, May 2015



had worsened since 2010 and CPE continued to spread in European hospitals [1-3]. Answers also indicated that the knowledge and awareness of the spread of CPE and the laboratory capacity for diagnosis and surveillance were heterogeneous among countries [1,2]. These findings highlighted the urgent need for a coordinated European effort towards early diagnosis, active surveillance and guidance on infection control measures [1,2].

In September and October 2013, the EuSCAPE project supported laboratory capacity building for diagnosis and surveillance by hosting a ‘train-the-trainer’ workshop at the European level for national laboratory experts on the identification and confirmation of CPE, and by carrying out an external quality assessment (EQA) of national reference/expert laboratories. The workshop and the EQA aimed at ensuring performance quality, consistency and comparability of data between participating countries and laboratories. Between November 2013 and April 2014, 36 European countries participated in the first European-wide structured survey of CPE (data not shown). The participating reference/expert laboratories were asked to collect CPE isolates of *Klebsiella pneumoniae* and *Escherichia coli* together with clinical data on these CPE-related infections to gain an understanding on the prevalence and epidemiology of CPE, as well as the risk factors associated with CPE infections in Europe.

In March 2015, after the completion of the EuSCAPE project, a post-EuSCAPE feedback questionnaire was sent to the participating countries to document whether (i) knowledge and awareness regarding the occurrence and spread of CPE had increased, and (ii) national capacity for containment of CPE had changed in terms of surveillance, laboratory reference services, and availability of guidance on infection prevention and control measures for these bacteria, since February 2013.

In this report, we present the analysis of the NEs’ answers on behalf of their countries to the post-EuSCAPE feedback questionnaire and provide summaries of the current epidemiological situation of the spread of CPE in each country.

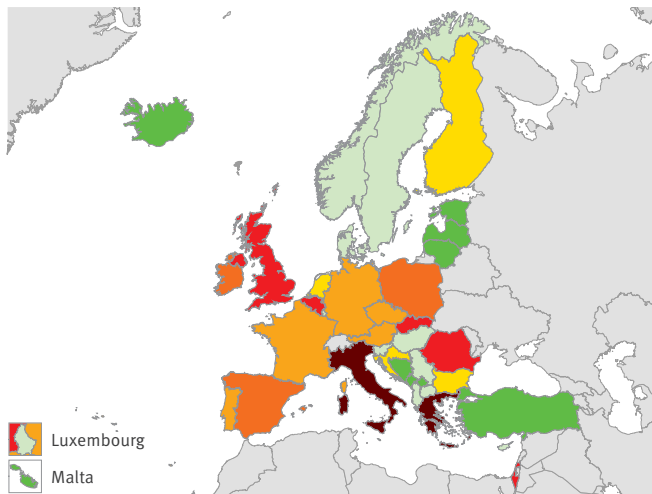
## Methods

The post-EuSCAPE feedback questionnaire was derived from the self-assessment questionnaire issued in February 2013 [1,2]. The questionnaire was divided in five sections. The first two sections explored awareness and knowledge about the occurrence of CPE in each country and collected information on the current national capacity for containment of CPE. The third and fourth sections collected the participants’ feedback on the EuSCAPE activities, e.g. laboratory capacity building workshop, EQA exercise and on the impact of the EuSCAPE project on collaborations and networking capacity, respectively. The fifth section investigated

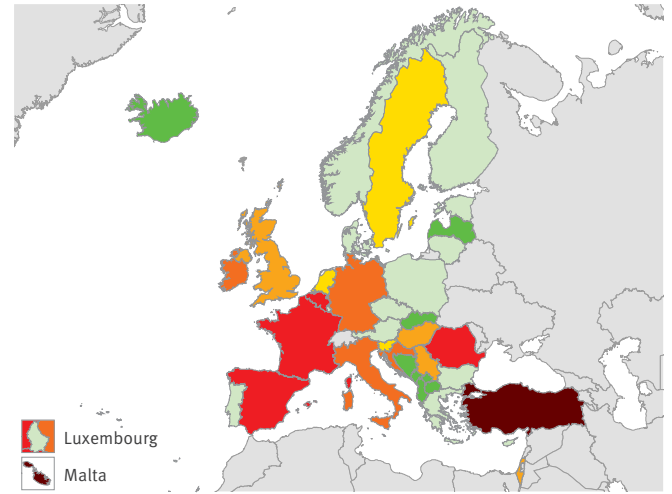
**FIGURE 2**

Geographic distribution of carbapenemase-producing *Enterobacteriaceae* by resistance mechanism, based on self-assessment by national experts, 38 European countries, May 201

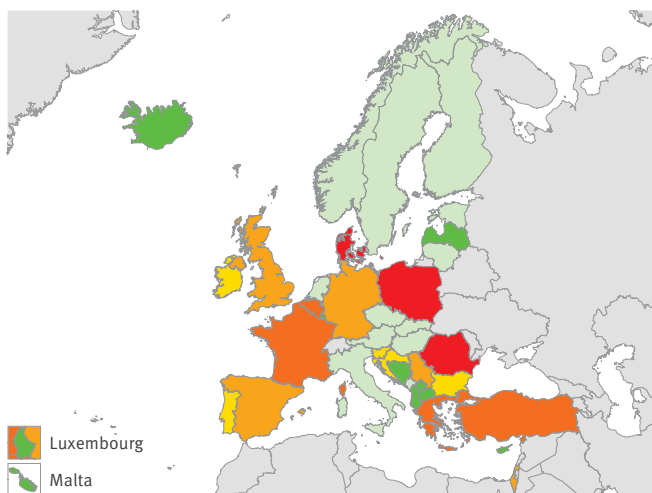
**A.** *Klebsiella pneumoniae* carbapenemase (KPC)



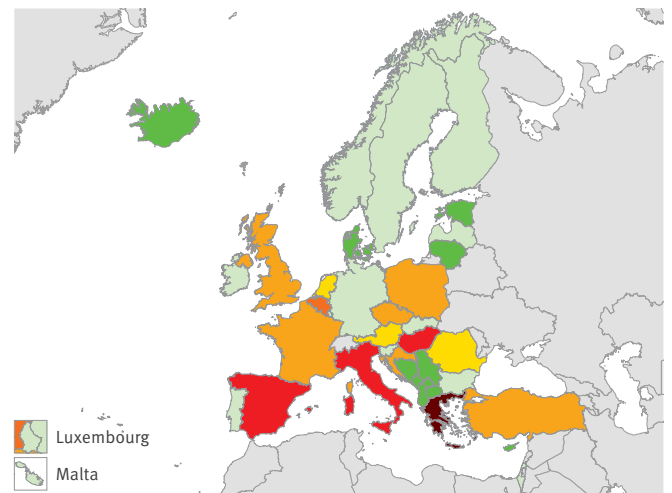
**B.** Oxacillinase-48 (OXA-48)



**C.** New Delhi metallo-beta-lactamase (NDM)



**D.** Verona integron-encoded metallo-beta-lactamase (VIM)



Epidemiological stages, 2014-2015

- Countries not participating
  - No case reported (Stage 0)
  - Sporadic occurrence (Stage 1)
  - Single hospital outbreak (Stage 2a)
- Sporadic hospital outbreaks (Stage 2b)
  - Regional spread (Stage 3)
  - Inter-regional spread (Stage 4)
  - Endemic situation (Stage 5)

desired areas for future ECDC activities on carbapenem-resistant Gram-negative bacteria. The questionnaire was sent to the same NEs who participated in a similar survey in February 2013, with the exception of France and the Netherlands. They were invited to coordinate their replies with colleagues in their countries i.e. the ECDC National Focal Points for antimicrobial resistance and the ECDC National Correspondents for EU enlargement countries) to reflect the national situation and to complete the questionnaire online between 3

March and 30 April 2015 (questionnaire available upon request from the corresponding author). They were also asked to provide a description of the emergence and spread of CPE in their country beyond *K. pneumoniae* and *E. coli* isolates collected during the EuSCAPE structured survey. The answers were based on their knowledge of national clinical and microbiological data and/or their personal judgement. When necessary, the respondents were contacted for clarification, and corrections were made accordingly. The latest data from

**TABLE 1***Epidemiological stages of carbapenemase-producing Enterobacteriaceae spread [1,3]*

Epidemiological scale	Description	Stage
No cases reported	No cases reported.	0
Sporadic occurrence	Single cases, epidemiological unrelated.	1
Single hospital outbreak	Outbreak defined as two or more epidemiologically-associated cases with indistinguishable geno- or phenotype in a single institution.	2a
Sporadic hospital outbreaks	Unrelated hospital outbreaks with independent, i.e. epidemiologically-unrelated introduction or different strains; no autochthonous inter-institutional transmission reported.	2b
Regional spread	More than one epidemiologically-related hospital outbreak confined to hospitals that are part of the same region or health district, suggestive of regional autochthonous inter-institutional transmission.	3
Inter-regional spread	Multiple epidemiologically-related outbreaks occurring in different health districts, suggesting inter-regional autochthonous inter-institutional transmission.	4
Endemic situation	Most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources.	5

EARS-Net provided an additional source of information on the percentage of carbapenem resistance in invasive isolates, in the EU/ European Economic Area (EEA) Member States.

For the presentation, countries were arbitrarily grouped in geographic entities independently of the epidemiological stages of CPE spread, geopolitical or economic considerations.

Using the same epidemiological staging system as in 2010 and 2013 (Table 1), all participating countries self-assessed their epidemiological situation of CPE, thereby documenting the progression of CPE within countries and dissemination in Europe between 2013 and 2015. All countries provided a self-assessment of the current national situation.

## Results

### Overall occurrence of carbapenemase-producing *Enterobacteriaceae*

Three countries reported not having identified one single case of CPE, whereas 13 reported regional and inter-regional spread, and four reported an endemic situation. Nine countries reported sporadic occurrence, five reported single hospital outbreak and four reported sporadic hospital outbreaks (Figure 1, Table 2).

Table 2 documents the epidemiological stages and dissemination for CPE within countries in the years 2010, 2013 and 2015 and indicates the changes in status between surveys in 2013 and 2015.

### Occurrence of carbapenemase-producing *Enterobacteriaceae* by type of carbapenemase

All countries were able to rate the occurrence and spread of CPE by type of carbapenemase. As of May 2015, *K. pneumoniae* carbapenemase (KPC)-producing

*Enterobacteriaceae* still had the widest dissemination in Europe, but carbapenem-hydrolysing oxacillinase-48 (OXA-48)-producing *Enterobacteriaceae* had almost reached the same spread, a change compared with February 2013, with eight countries reporting regional or inter-regional spread and another two countries reporting an endemic situation (Figure 2). The distribution of KPC- and OXA-48-producing *Enterobacteriaceae* varies and does not necessarily overlap, for example, Greece seeing predominantly KPC-producing *Enterobacteriaceae* and rarely OXA-48-producing *Enterobacteriaceae*, and Malta seeing almost exclusively OXA-48-producing *Enterobacteriaceae*.

The European epidemiology for CPE also changed between 2013 and 2015 for New Delhi metallo-beta-lactamase (NDM)-producing *Enterobacteriaceae*; five countries reported sporadic hospital outbreaks, and seven countries regional or inter-regional spread. No country reported an endemic situation. The epidemiological situation for Verona integron-encoded metallo-beta-lactamase (VIM)-producing *Enterobacteriaceae* remained stable with some minor country-specific changes. Imipenemase (IMP)-producing *Enterobacteriaceae* remained rare in Europe (Table 3).

### Description of the emergence and spread of carbapenemase-producing *Enterobacteriaceae*

The NEs participating in the EuSCAPE provided a description of the emergence and spread of CPE in their country beyond *K. pneumoniae* and *E. coli* isolates collected during the EuSCAPE structured survey.

#### Denmark, Iceland, Finland, Norway, Sweden and the Netherlands

In Denmark, only sporadic occurrence of CPE, mostly related to foreign travel, was observed until 2012 when the situation for CPE changed to sporadic hospital outbreaks with the spread of VIM-4 producing *E.*

**TABLE 2**

 Comparison of epidemiological stages of carbapenemase-producing *Enterobacteriaceae*, 38 European countries, 2010–2015

Country	Epidemiological stage for the spread of CPE			Change in epidemiological situation for CPE between 2013 and 2015
	2010 <sup>a</sup>	2013 <sup>b</sup>	2014–2015 <sup>c</sup>	
Albania	NA	2a	1	↓
Austria	0	2b	2b	→
Belgium	2b	3	4	↑
Bosnia and Herzegovina	1	1	0	↓
Bulgaria	0	2a	2a	→
Croatia	1	3	3	→
Cyprus	2a	2a	1	↓
Czech Republic	1	2b	2b	→
Denmark	1	2a <sup>d</sup>	4	↑
Estonia	0	2a	1	↓
Finland	1	2a	2a	→
France	3	3	4	↑
Germany	3	3	3	→
Greece	5	5	5	→
Hungary	3	4	4	→
Iceland	0	0	0	→
Ireland	1	4	3	↓
Israel	5	4	4	→
Italy	4	5	5	→
Kosovo*	NA	2b	0	↓
Latvia	1	1	1	→
Lithuania	1	1	1	→
Luxembourg	NA	1	1	→
Malta	1	5	5	→
Montenegro	NA	0	1	↑
The Netherlands	2a	2b	2a	↓
Norway	2a	2a	1	↓
Poland	4	3	4	↑
Portugal	1	1	2b	↑
Romania	1	1	4	↑
Serbia	1	1	2b	↑
Slovakia	NA	2a	4	↑
Slovenia	0	1	2a	↑
Spain	2b	3	4	↑
Sweden	2a	2b	2a	↓
The former Yugoslav Republic of Macedonia	NA	0	1	↑
Turkey	NA	2a	5	↑
United Kingdom	2b	3	3	→

 CPE: carbapenemase-producing *Enterobacteriaceae*; NA: not available.

↑: increase in the epidemiological stage between 2013 and 2015; ↓: decrease in the epidemiological stage between 2013 and 2015; →: unchanged epidemiological stage between 2013 and 2015.

Grey: countries with no data available.

Dark green: no case reported (Stage 0).

Light green: sporadic occurrence (Stage 1).

Light yellow: single hospital outbreak (Stage 2a).

Dark yellow: sporadic hospital outbreaks (Stage 2b).

Orange: regional spread (Stage 3).

Red: inter-regional spread (Stage 4).

Brown: endemic situation (Stage 5).

<sup>a</sup> The results were based on data obtained through a Europe-wide consultation during a workshop at the Dutch National Institute for Public Health and the Environment (RIVM) on 29–30 April 2010 [3].

<sup>b</sup> The results were based on data obtained through a self-assessment questionnaire (February 2013) to the national experts who participated in the 'European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)' project [1,2].

<sup>c</sup> This online survey (March–May 2015).

<sup>d</sup> Data provided in 2015.

\*This designation is without prejudice to positions on status, and is in line with United Nations Security Council resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.



*coli*, the identification of NDM-4 producing *E. coli* and an outbreak of NDM-1 producing *Citrobacter freundii* [4,5]. Since 2013, the number of CPE cases in Denmark has further increased with multiple epidemiologically-related hospital outbreaks of OXA-48- and NDM-producing *Enterobacteriaceae* in different regions of the country [6]. In 2014, most of the CPE cases had no history of recent travel abroad. Denmark is now facing an inter-regional spread of CPE.

The situation in **Iceland** has remained unchanged since 2010 despite active screening. Iceland is one of the few countries in Europe that has not reported any case of CPE.

In **Norway**, the occurrence of CPE, KPC-, OXA-48- and NDM-producing *Enterobacteriaceae*, has remained sporadic with still a small number of CPE cases (ca 10 cases per year, including colonisation) since 2013. The majority of the identified cases had a link with foreign travel.

In **Finland**, 74 CPE isolates from 66 patients have been obtained since 2009, with an increase from five cases in 2009 to 18 cases in 2014. About 70% of the patients with CPE had a history of foreign travel, mostly to Asia or southern Europe. Until 2013, the predominant CPE in Finland were OXA-48-producing *Enterobacteriaceae* [7]. In 2013, Finland experienced its largest and first outbreak of CPE, involving nine patients without direct link to travel abroad. This outbreak of colonisation was due to KPC-producing *K. pneumoniae* ST 512 making them the predominant CPE in Finland, although still at a very low prevalence [8]. In 2015, eight NDM-producing *Enterobacteriaceae*, six KPC-producing *Enterobacteriaceae* and four OXA-48-producing *Enterobacteriaceae* have been isolated so far (data not shown).

In **Sweden**, most identified cases had a history of foreign travel. In 2014, there was a slight increase in the number of CPE cases due to an outbreak that was only detected through identification of a secondary colonised case. Until 2013, the predominant CPE in Sweden were NDM-producing *Enterobacteriaceae* closely followed by OXA-48-producing *Enterobacteriaceae* [9]. Since 2014, OXA-48-producing *Enterobacteriaceae* became predominant over NDM-producing *Enterobacteriaceae*, however both are still at low level.

In **the Netherlands**, KPC-, OXA-48- and NDM-producing *Enterobacteriaceae* have so far only been responsible for single hospital outbreaks, although a recent inter-institutional outbreak of KPC-producing *K. pneumoniae* occurred following the transfer of a patient from a nursing home to a hospital [10,11].

#### **Estonia, Latvia and Lithuania**

The Baltic countries only recently started to report CPE cases [12,13].

In **Estonia**, the first case of CPE, i.e. German imipenemase (GIM)-producing *Enterobacter aerogenes*, was identified in 2015 (personal communication, Paul Naaber, 26 June 2015).

In **Latvia**, only three cases of CPE have been identified so far, of which the first two VIM-producing isolates were identified during the EuSCAPE structured survey (data not shown).

In **Lithuania**, surveillance of CPE became mandatory in 2014. Between 1 January and 31 December 2014, 13 CPE cases were reported, consisting of two cases of OXA-48-producing *K. pneumoniae*, nine cases of NDM-producing *Enterobacter cloacae*, one case of NDM-producing *E. aerogenes* and one case of VIM-producing *E. cloacae*.

#### **Ireland and United Kingdom**

In **Ireland**, sporadic occurrence of CPE, i.e. KPC-, VIM- and NDM-1-producing *Enterobacteriaceae*, had been reported until 2011, with the majority of cases being related to travel abroad [14-16]. In 2011, an outbreak of epidemiologically-related KPC-producing *K. pneumoniae* in two hospitals from two different regions resulted in epidemiological stage 4 of CPE spread in the country [17]. This was concomitant with the first hospital outbreak of OXA-48-producing *K. pneumoniae* [18]. Since 2013, although the spread of CPE was limited to regional spread in some regions, the overall national situation is considered to have worsened due to an increase in the overall number of reported CPE cases. Furthermore, increasing numbers of hospitals and regions where CPE had not been encountered before 2013, have since reported sporadic cases or outbreaks of CPE. Prior to 2013, KPC-producing *Enterobacteriaceae* were the main type of CPE responsible for hospital outbreaks, but from 2013 onwards, OXA-48- and NDM-producing *Enterobacteriaceae* were also responsible for outbreaks.

The **United Kingdom** (UK), reported the emergence and the spread of NDM-1-producing CPE soon after its first isolation in 2008 from a patient repatriated to Sweden from a hospital in India, and this led to a National Resistance Alert 3 notice by the Department of Health [19,20]. To date, the UK has reported the largest number of NDM-producing CPE cases among European countries and has seen multiple NDM variants. The number of CPE isolates received by the national reference laboratory has increased continuously since 2008. In 2014, an increasing number of NDM- or OXA-48-producing isolates was reported compared with previous years with a marked increase in carbapenemase-producing *E. coli*.

#### **Austria, Czech Republic, Germany, Luxembourg and Slovenia**

In **Austria**, the epidemiological situation worsened between 2010 and 2013, but has since remained unchanged with a low occurrence of CPE and sporadic hospital outbreaks [21-24]. Between 2010 and 2015, the most frequently confirmed carbapenemase genes by the reference laboratory were *bla*<sub>VIM</sub> and *bla*<sub>KPC</sub>, but also *bla*<sub>OXA-48</sub> and *bla*<sub>NDM</sub> were also found in low numbers. In April 2015, Austria initiated the Austrian surveillance project 'Carba-Net Austria' and organised four laboratory capacity building workshops on the identification of CPE and characterisation of carbapenemases based on the EuSCAPE protocols and training curriculum.

In the **Czech Republic**, the occurrence of CPE was rare until 2011 with only sporadic cases, and a total of three cases detected between 2009 and 2010. In 2011, however, the number of CPE increased due to the repatriation of patients from hospitals in Italy and Greece and an outbreak following the transfer of a patient from Italy [25]. To contain this increase, the national surveillance included CPE isolates from active screening samples as part of its surveillance scheme and the Ministry of Health issued, in 2012, official national guidelines for the control of CPE covering both infected and colonised cases. No further increase in the occurrence of CPE was observed in 2012 and 2013, and only one outbreak restricted to five patients and four sporadic cases was reported until mid-2013 [26]. During the EuSCAPE survey, the Czech Republic reported only two confirmed CPE cases, of which one involved NDM-1-producing *K. pneumoniae* from a patient transferred from Ukraine [27].

In **Germany**, there has been an increasing number of CPE referred to the German National Reference Laboratory for CPE and the German national antibiotic resistance surveillance has shown an increase of resistance to meropenem in *K. pneumoniae* from 0.1% in 2010 to 0.5% in 2014. Both observations possibly indicated an increase in the prevalence of CPE in Germany albeit on a low level. Several outbreaks with KPC-2-, KPC-3-, NDM-1- and OXA-48-producing *Enterobacteriaceae* have been documented; notably a protracted KPC-2 outbreak involving over 100 patients and a polyclonal KPC-2 outbreak involving other species besides *K. pneumoniae* [28]. The most prevalent CPE are in order of importance OXA-48-, KPC-2-, VIM-1-, NDM-1- and KPC-3-producing *Enterobacteriaceae*. Despite the dominance of OXA-48-producing *Enterobacteriaceae*, mostly KPC-producing *K. pneumoniae* outbreaks have been reported in Germany.

**Luxembourg** has only experienced sporadic cases of VIM-producing CPE [29].

In **Slovenia**, only sporadic cases of CPE were detected until 2013, with a large proportion of the cases being related to patient transfers from foreign hospitals [30]. The situation changed in October 2014 with the first outbreak of both OXA-48- and NDM-1-producing *E. coli* and *K. pneumoniae* affecting several wards in a single

hospital. While one of the first identified patients had been transferred from a foreign hospital, other patients had no history of travel abroad. Some CPE-positive patients belonging to this outbreak were transferred to other hospitals across the country, but no further spread occurred in these hospitals.

#### **Hungary, Poland, Romania and Slovakia**

In **Hungary**, ca 600 VIM-4-producing *Enterobacteriaceae* isolates – the predominant type of CPE in Hungary – have been collected since 2008. The first KPC-2-producing *K. pneumoniae* isolates were reported from 2008 to 2009 during a local outbreak in the north-eastern part of Hungary and the index case was a patient previously hospitalised in Greece [31]. About 20 KPC-producing isolates, from sporadic cases and mostly associated with medical treatment abroad, have since been collected, with an average of 1 to 2 isolates per year. These were KPC-producing *K. pneumoniae* until 2015 when the first KPC-producing *E. coli* was isolated. Only two small outbreaks caused by OXA-48-like-producing *K. pneumoniae* were reported, in 2012 and 2014, and both were linked to patient transfers from Romania and Ukraine, respectively [32]. In total, 20 OXA-48-producing *Enterobacteriaceae* have been identified so far in Hungary. Since 2013, only sporadic cases of NDM-producing CPE, primarily *E. cloacae*, have been identified, of which some but not all were linked to Romania.

In **Poland**, KPC-producing *K. pneumoniae* were predominant between 2008 and 2012 [33,34]. Since 2012, the epidemiology of CPE has changed with a decreasing number of KPC-producing *K. pneumoniae* and an increasing number of NDM-1-producing *K. pneumoniae*. The former primarily occurred in the regions that had experienced outbreaks of KPC-producing *K. pneumoniae* in 2008–2012. The latter was a consequence of a large inter-regional outbreak of NDM-producing *K. pneumoniae* that started at the end of 2012 [35], just a few months after the first case of NDM-1-producing *K. pneumoniae* was found in a patient with previous travel history to Africa [36].

In **Romania**, the first confirmed cases of OXA-48- and NDM-1-producing *Enterobacteriaceae*, mostly *K. pneumoniae*, were isolated in 2011 and both OXA-48- and NDM-1-producing *Enterobacteriaceae* were the predominant CPE in Romania until 2013. During the EuSCAPE structured survey, mostly OXA-48-producing *Enterobacteriaceae* were found (data not shown) [37-39].

Prior to 2013, **Slovakia** experienced only one small local epidemic in two hospitals, following an imported case of NDM-1-producing *K. pneumoniae* [40]. However, the situation changed in December 2013 after the identification of the first case of KPC-2-producing *K. pneumoniae* in a patient who had been hospitalised in Greece and the subsequent spread of CPE to more than



**TABLE 3**

 Comparison of epidemiological stages of carbapenemase-producing *Enterobacteriaceae* by type of carbapenemase, 38 European countries, 2010–2015

Country	Epidemiological stage for the spread of CPE by type of carbapenemase									
	KPC		OXA48		VIM		NDM		IMP	
	2013 <sup>a</sup>	2014–2015 <sup>b</sup>	2013 <sup>a</sup>	2014–2015 <sup>b</sup>	2013 <sup>a</sup>	2014–2015 <sup>b</sup>	2013 <sup>a</sup>	2014–2015 <sup>b</sup>	2013 <sup>a</sup>	2014–2015 <sup>b</sup>
Albania	1	1	2a	0	1	0	0	0	2a	0
Austria	1	2b	1	1	2b	2a	2a	1	0	0
Belgium	3	4	3	4	3	3	1	3	0	0
Bosnia and Herzegovina	0	0	0	0	0	0	0	0	0	0
Bulgaria	NA	2a	NA	1	2a	1	NA	2a	NA	0
Croatia	3	2a	1	3	1	2b	1	2a	1	1
Cyprus	NA	1	NA	1	NA	0	NA	0	1	0
Czech Republic	2b	2b	0	1	2a	2b	1	1	0	0
Denmark	1	1	1	1	2a <sup>c</sup>	0	1	4	0	0
Estonia	NA	0	NA	1	NA	0	NA	1	NA	0
Finland	2a	2a	1	1	1	1	1	1	0	1
France	2b	2b	3	4	2b	2b	2a	3	2a	1
Germany	3	2b	2b	3	2b	1	2a	2b	1	1
Greece	5	5	1	1	5	5	0	3	0	0
Hungary	3	1	1	2b	4	4	0	1	0	0
Iceland	0	0	0	0	0	0	0	0	0	0
Ireland	4	3	3	3	2a	1	1	2a	1	1
Israel	4	4	2b	2b	0	1	2a	2b	0	0
Italy	5	5	2b	3	4	4	2b	1	0	0
Kosovo*	2b	0	2b	0	0	0	1	0	0	0
Latvia	1	0	NA	0	NA	1	NA	0	NA	0
Lithuania	0	0	1	1	0	0	0	1	0	0
Luxembourg	1	1	0	1	1	1	0	0	NA	1
Malta	0 <sup>c</sup>	0	5	5	0 <sup>c</sup>	1	0 <sup>c</sup>	0	1	1
Montenegro	NA	0	NA	0	NA	0	NA	1	NA	0
The Netherlands	2a	2a	2b	2a	1	2a	1	1	1	1
Norway	2a	1	1	1	1	1	1	1	0	1
Poland	3	3	1	1	1	2b	1	4	0	DNK
Portugal	1	2b	0	1	1	1	0	2a	0	0
Romania	NA	4	1	4	NA	2a	1	4	NA	NA
Serbia	NA	1	NA	2b	NA	0	NA	2b	NA	0
Slovakia	NA	4	NA	0	NA	1	2a	1	NA	0
Slovenia	1	1	1	2a	1	1	1	2a	0	0
Spain	2b	3	3	4	3	4	1	2b	2b	1
Sweden	2a	1	1	2a	1	1	2a	1	0	1
The former Yugoslav Republic of Macedonia	NA	1	NA	0	NA	0	NA	0	NA	NA
Turkey	2b	0	1	5	1	2b	1	3	1	1
United Kingdom	3	4 <sup>d</sup>	3	2b	3	2b	2b	2b	1	0

CPE: carbapenemase-producing *Enterobacteriaceae*; DNK: do not know; IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; NA: not available; NDM: New Delhi metallo-beta-lactamase; OXA-48: carbapenem-hydrolysing oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Grey: countries with no data available.

Dark green: no case reported (Stage 0).

Light green: sporadic occurrence (Stage 1).

Light yellow: single hospital outbreak (Stage 2a).

Dark yellow: sporadic hospital outbreaks (Stage 2b).

Orange: regional spread (Stage 3).

Red: inter-regional spread (Stage 4).

Brown: endemic situation (Stage 5).

<sup>a</sup> The results were based on data obtained through a self-assessment questionnaire (February 2013) to the national experts that participated in the 'European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)' project [1,2].

<sup>b</sup> This online survey (March–May 2015).

<sup>c</sup> Data provided in 2015.

<sup>d</sup> For Scotland, it was not possible to determine the epidemiological stage for each enzyme at the time of the questionnaire however, KPC-producing *Enterobacteriaceae* are sporadic (Stage 1).

\*This designation is without prejudice to positions on status, and is in line with United Nations Security Council resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.

10 hospitals. The number of patients infected or colonised with KPC-2-producing *K. pneumoniae* has now reached 150. In addition, two small local outbreaks of VIM-producing *E. cloacae* and NDM-producing *K. pneumoniae* were reported up to 2015.

#### **Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Kosovo\*, Montenegro, Serbia and the former Yugoslav Republic of Macedonia**

**Albania** organised two laboratory capacity building workshops and urged hospitals not involved in the EuSCAPE project to initiate surveillance studies. This led to the identification of the first confirmed case of KPC-3-producing *K. pneumoniae* from a patient with no recent travel history, but with a previous admission in the intensive care unit at the University Hospital in Tirana in 2014 [41].

**Bosnia and Herzegovina** did not report any CPE, but NDM-1-producing *K. pneumoniae* had previously been reported in Croatia from a patient transferred from Bosnia and Herzegovina [42,43].

In **Bulgaria**, the occurrence of CPE has increased since 2012. KPC-2- and VIM-1-producing *K. pneumoniae* were isolated from a hospitalised patient in Varna and an outbreak caused by NDM-1-producing *E. coli* was reported from the Military Medical Academy Hospital of Sofia [44,45].

In **Croatia**, the first reported case of CPE was a NDM-1-producing *K. pneumoniae* isolated in 2009 in the University Hospital Centre of Zagreb from a patient repatriated from Bosnia and Herzegovina [42]. In February 2011, the first KPC-producing *K. pneumoniae* was isolated from a patient at the same hospital [46]. A multicentre study performed from 2011 to 2012 in four large hospital centres in Croatia identified a higher prevalence of VIM-1-producing *Enterobacteriaceae* than of NDM- and KPC-producing *Enterobacteriaceae* [47]. Since 2014, the epidemiology of CPE in Croatia has changed with the rapid spread of OXA-48-producing *Enterobacteriaceae* whereas incidence of KPC isolates declined.

**Kosovo\*** is one of the few countries that have not reported any cases of CPE isolated from normally sterile body fluids such as blood cultures and cerebrospinal fluid (CSF), although NDM-1-producing *K. pneumoniae* were previously reported in Austria, Belgium and in Germany from patients being transferred from hospitals in Kosovo\* [43,48,49].

In **Montenegro**, a laboratory capacity building workshop was organised and phenotypic methods of detection of CPE were implemented in the participating laboratories, leading to the identification of NDM-1-producing *K. pneumoniae* during the EuSCAPE structured survey (data not shown).

In **Serbia**, NDM- and OXA-48-producing *Enterobacteriaceae*, as well as NDM- and OXA-48- co-producing *Enterobacteriaceae* have been isolated during the EuSCAPE structured survey (data not shown). The latter type of CPE was also identified in a patient transferred from Serbia to Switzerland in December 2013 [50].

In the former Yugoslav Republic of Macedonia, only KPC-producing *K. pneumoniae* have been isolated so far through the EuSCAPE structured survey (data not shown).

#### **Belgium, France, Portugal and Spain**

In **Belgium**, the situation of CPE has seriously worsened with a rapid spread of CPE since 2012, i.e. a doubling in prevalence and incidence in acute care hospitals between 2012 and 2015 and more than 80% of the reported cases being confirmed as autochthonous acquisition, i.e. not travel-related. In addition, there has been an increase in the number of documented regional and inter-regional transmissions of epidemiologically related clusters and/or outbreaks, especially for OXA-48-producing *Enterobacteriaceae* and to a lesser extent for KPC-producing *Enterobacteriaceae*. There has also been an increase in the number of outbreaks with one third of the country's hospitals reporting outbreaks of CPE. Another major change in Belgium in 2015 was the marked increase, compared with 2013, in the number of non-travel-related NDM cases with inter-institution regional spread and multiple large difficult-to-control outbreaks occurring in several hospitals.

In **France**, the number of cases and outbreaks of CPE has steadily increased since 2009 with the sharpest increase during the last quarter of 2014. KPC-producing *Enterobacteriaceae* however, have been declining since 2012. Most cases were acquired abroad, i.e. through hospitalisation or travel. However, there has been an increase in the number of autochthonous cases, usually OXA-48-producing *Enterobacteriaceae*. In 2014, the most frequent CPE are OXA-48-producing *K. pneumoniae* and *E. coli*, followed by NDM-, VIM- and KPC-producing *Enterobacteriaceae*.

In **Spain**, the situation of CPE has worsened in the last few years with an increasing trend in the number of CPE cases and a wide geographic spread [51-54]. The spread of CPE has currently affected 34/50 Spanish provinces, resulting in a potential inter-regional spread of CPE [47,49, unpublished data]. The most predominant CPE are OXA-48- and VIM-producing *K. pneumoniae* [51-53]. In general, the prevalence of KPC- and NDM-producing *Enterobacteriaceae* in Spain is low but increasing [51,54]. Recently, an inter-hospital spread of NDM-7-producing *K. pneumoniae* that belonged to MLST type 437 was described in Madrid [51]. Although not frequent, detection of the polyclonal dissemination of OXA-48-producing *E. coli* is worrying.

In **Portugal**, only sporadic isolates or single hospital cases have been described. The most predominant CPE

**TABLE 4 A**

 National capacity for surveillance and containment of carbapenemase-producing *Enterobacteriaceae*, 38 European countries, May 2015

Country	National system for surveillance	Officially nominated national reference laboratory, or expert laboratory	National recommendation or obligation for reporting (notification) to health authorities	National plan for containment of (or preparedness to contain) CPE	National recommendation or guideline on infection control measures	Reference or URL for recommendation or guideline on infection control measures
Albania	.. <sup>a,b</sup>	.. <sup>a</sup>		.. <sup>a</sup>		
Austria	• <sup>c</sup>	•	• <sup>d</sup>		•	<a href="http://www.analyse.eu/content/inhalte/nationales_referenzzentrum/station%C3%A4re_patienten_mit_auslandsanamnese/index.html">http://www.analyse.eu/content/inhalte/nationales_referenzzentrum/station%C3%A4re_patienten_mit_auslandsanamnese/index.html</a>
Belgium	• <sup>e</sup>	•	• <sup>f</sup>	•	•	<a href="http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19074512.pdf">http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19074512.pdf</a> <a href="http://www.sante.belgique.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19074512_nl.pdf">http://www.sante.belgique.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19074512_nl.pdf</a>
Bosnia and Herzegovina	.. <sup>a,b</sup>		.. <sup>a</sup>	.. <sup>a</sup>		
Bulgaria	•	•	•	.. <sup>a</sup>	•	
Croatia	• <sup>e</sup>	•	• <sup>f</sup>	•	•	
Cyprus	.. <sup>e,g</sup>	• <sup>h</sup>				
Czech Republic	• <sup>e</sup>	•	• <sup>f</sup>	•	•	<a href="http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c8/2012_6865_2510_11.html">http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c8/2012_6865_2510_11.html</a> <a href="http://www.szu.cz/narodni-referencni-laborator-pro-antibiotika">http://www.szu.cz/narodni-referencni-laborator-pro-antibiotika</a>
Denmark	• <sup>c</sup>	•				
Estonia	.. <sup>g</sup>		• <sup>d</sup>			
Finland	• <sup>e</sup>	•	• <sup>f</sup>		•	<a href="http://urn.fi/URN:ISBN:978-952-302-260-7">http://urn.fi/URN:ISBN:978-952-302-260-7</a>
France	• <sup>e</sup>	•	• <sup>f</sup>	•	•	<a href="http://www.sante.gouv.fr/fichiers/bo/2014/14-02/ste_20140002_0000_0064.pdf">http://www.sante.gouv.fr/fichiers/bo/2014/14-02/ste_20140002_0000_0064.pdf</a>
Germany	• <sup>c</sup>	•	.. <sup>a</sup>		•	<a href="http://edoc.rki.de/documents/rki_ab/resuFmoGFF7o/PDF/210bND4dxM.pdf">http://edoc.rki.de/documents/rki_ab/resuFmoGFF7o/PDF/210bND4dxM.pdf</a>
Greece	• <sup>e</sup>	• <sup>h</sup>	• <sup>f</sup>	•	•	<a href="http://www.keelpno.gr/el-gr/vosimataθέματαυγείας/πολυανθεκτικαπαθογόναστονοσοκομεία.aspx">http://www.keelpno.gr/el-gr/vosimataθέματαυγείας/πολυανθεκτικαπαθογόναστονοσοκομεία.aspx</a>
Hungary	• <sup>e</sup>	• <sup>h</sup>	• <sup>f</sup>	.. <sup>a</sup>	•	<a href="http://www.oek.hu/oek.web?nid=1067&amp;pid=1&amp;to=&amp;lang=hun">http://www.oek.hu/oek.web?nid=1067&amp;pid=1&amp;to=&amp;lang=hun</a>
Iceland	• <sup>e</sup>	•	• <sup>f</sup>	•	•	
Ireland	• <sup>e</sup>	•	• <sup>d</sup>		•	<a href="http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,12922,en.pdf">http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,12922,en.pdf</a>
Israel	• <sup>e</sup>	•	• <sup>f</sup>	•	•	
Italy	• <sup>c</sup>	• <sup>h</sup>	• <sup>d</sup>	.. <sup>a</sup>	•	<a href="http://www.trovanorme.salute.gov.it/renderNormsanPdf?anno=0&amp;codLeg=45499&amp;parte=1%20&amp;serie=">http://www.trovanorme.salute.gov.it/renderNormsanPdf?anno=0&amp;codLeg=45499&amp;parte=1%20&amp;serie=</a>
Kosovo*	.. <sup>a,b</sup>	• <sup>h</sup>			.. <sup>a</sup>	
Latvia	• <sup>e</sup>	• <sup>h</sup>	• <sup>f</sup>	.. <sup>a</sup>		
Lithuania	• <sup>e</sup>	•				
Luxembourg	• <sup>c</sup>	• <sup>h</sup>	• <sup>d</sup>		•	
Malta	• <sup>e</sup>	• <sup>h</sup>		.. <sup>a</sup>	•	
Montenegro	.. <sup>a,b</sup>	.. <sup>a</sup>	• <sup>f</sup>			
The Netherlands	• <sup>c</sup>	• <sup>h</sup>		.. <sup>a</sup>	•	<a href="http://www.rivm.nl/dsresource?objectid=rivmp:46410&amp;type=org&amp;disposition=inline&amp;ns_nc=1">http://www.rivm.nl/dsresource?objectid=rivmp:46410&amp;type=org&amp;disposition=inline&amp;ns_nc=1</a>

 CPE: carbapenemase-resistant *Enterobacteriaceae*.

In the table cells, a dot signifies 'in place' and the absence of dot signifies 'absent'. Black colour indicates that the system or document was already in place in 2013. Blue colour indicates a change reported in 2015, as compared with 2013.

<sup>a</sup> In preparation.

<sup>b</sup> No national system for surveillance, but country reports carbapenem-resistant invasive isolates (*Klebsiella pneumoniae* and *Escherichia coli*) to the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR).

<sup>c</sup> Voluntary participation of the laboratories.

<sup>d</sup> Voluntary notification to health authorities.

<sup>e</sup> Mandatory participation of the laboratories (for the United Kingdom, only mandatory for Scotland).

<sup>f</sup> Mandatory notification to health authorities (for the United Kingdom, only mandatory for Scotland).

<sup>g</sup> No national system for surveillance, but country reports carbapenem-resistant invasive isolates (*K. pneumoniae* and *E. coli*) to the European Antimicrobial Resistance Surveillance Network (EARS-Net).

<sup>h</sup> An expert laboratory fulfils a similar role to that of a national reference laboratory.

<sup>\*</sup> This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the Internal Court of Justice Opinion on the Kosovo declaration of independence.

**TABLE 4 B**

 National capacity for surveillance and containment of carbapenemase-producing *Enterobacteriaceae*, 38 European countries, May 2015

Country	National system for surveillance	Officially nominated national reference laboratory, or expert laboratory	National recommendation or obligation for reporting (notification) to health authorities	National plan for containment of (or preparedness to contain) CPE	National recommendation or guideline on infection control measures	Reference or URL for recommendation or guideline on infection control measures
Norway	• <sup>e</sup>	•	• <sup>f</sup>	- <sup>a</sup>	•	<a href="http://www.fhi.no/dokumenter/9633178b9.pdf">http://www.fhi.no/dokumenter/9633178b9.pdf</a> <a href="http://www.fhi.no/eway/default.aspx?pid=239&amp;trg=List_6212&amp;Main_6157=6263:0:25,6493&amp;MainContent_6263=6464:0:25,6513&amp;List_6212=6453:0:25,6499:1:0:0:0:0">http://www.fhi.no/eway/default.aspx?pid=239&amp;trg=List_6212&amp;Main_6157=6263:0:25,6493&amp;MainContent_6263=6464:0:25,6513&amp;List_6212=6453:0:25,6499:1:0:0:0:0</a>
Poland	• <sup>e</sup>	•	• <sup>f</sup>		•	<a href="http://www.antybiotyki.edu.pl/pdf/kpc-20120713.pdf">http://www.antybiotyki.edu.pl/pdf/kpc-20120713.pdf</a>
Portugal	• <sup>e</sup>	•	• <sup>f</sup>	•	- <sup>a</sup>	
Romania	• <sup>c</sup>	• <sup>h</sup>			- <sup>a</sup>	<a href="http://www.srm.ro">http://www.srm.ro</a>
Serbia	• <sup>c</sup>	•				
Slovakia	• <sup>e</sup>	• <sup>h</sup>	• <sup>f</sup>	•	•	<a href="http://www.ruvztn.sk/OU%20MZ%20SR.pdf">http://www.ruvztn.sk/OU%20MZ%20SR.pdf</a>
Slovenia	- <sup>a, g</sup>	• <sup>h</sup>	- <sup>a</sup>		•	<a href="http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/mz_dokumenti/delovna_podrocja/zdravstveno_varstvo/zdravstveno_varstvo_v_posebnih/NAKOBO_oktober_2010/PRIPOROCILA_ESBL_26.10.10.pdf">http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/mz_dokumenti/delovna_podrocja/zdravstveno_varstvo/zdravstveno_varstvo_v_posebnih/NAKOBO_oktober_2010/PRIPOROCILA_ESBL_26.10.10.pdf</a>
Spain	• <sup>c</sup>	• <sup>h</sup>	• <sup>d</sup>	- <sup>a</sup>	•	<a href="http://www.aemps.gob.es/publicaciones/publica/docs/plan-estrategico-antibioticos.pdf">http://www.aemps.gob.es/publicaciones/publica/docs/plan-estrategico-antibioticos.pdf</a> <a href="http://www.madrid.org/cs/Satellite?blobcol=urldata&amp;blobheader=application%2Fpdf&amp;blobheadername1=Content-disposition&amp;blobheadername2=cadena&amp;blobheadervalue1=filename%3DPLAN+PREVENCION+C3%93N+Y+CONTROL+EPC+CM_v1_sept+2013.pdf&amp;blobheadervalue2=language%3Des%26site%3DPortalSalud&amp;blobkey=id&amp;blobtable=MungoBlobs&amp;blobwhere=1352838664739&amp;ssbinary=true">http://www.madrid.org/cs/Satellite?blobcol=urldata&amp;blobheader=application%2Fpdf&amp;blobheadername1=Content-disposition&amp;blobheadername2=cadena&amp;blobheadervalue1=filename%3DPLAN+PREVENCION+C3%93N+Y+CONTROL+EPC+CM_v1_sept+2013.pdf&amp;blobheadervalue2=language%3Des%26site%3DPortalSalud&amp;blobkey=id&amp;blobtable=MungoBlobs&amp;blobwhere=1352838664739&amp;ssbinary=true</a> <a href="http://safh.org/wp-content/uploads/2014/10/Programa-para-el-control-de-las-EPC_SSPA.pdf">http://safh.org/wp-content/uploads/2014/10/Programa-para-el-control-de-las-EPC_SSPA.pdf</a>
Sweden	• <sup>e</sup>	•	• <sup>f</sup>	•	•	<a href="http://www.folkhalsomyndigheten.se/page-files/17838/ESBL-producerande%20armbakterier.pdf">http://www.folkhalsomyndigheten.se/page-files/17838/ESBL-producerande%20armbakterier.pdf</a>
The former Yugoslav Republic of Macedonia	• <sup>e</sup>	• <sup>h</sup>	• <sup>f</sup>			
Turkey	•	• <sup>h</sup>	• <sup>d</sup>			
United Kingdom	• <sup>c, e</sup>	•	• <sup>d, f</sup>	•	•	<a href="https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-early-detection-management-and-control-toolkit-for-acute-trusts">https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-early-detection-management-and-control-toolkit-for-acute-trusts</a> <a href="http://www.documents.hps.scot.nhs.uk/hai/amr/cpe-guidance.pdf">http://www.documents.hps.scot.nhs.uk/hai/amr/cpe-guidance.pdf</a>

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In the table cells, a dot signifies 'in place' and the absence of dot signifies 'absent'. Black colour indicates that the system or document was already in place in 2013. Blue colour indicates a change reported in 2015, as compared with 2013.

<sup>a</sup> In preparation.

<sup>b</sup> No national system for surveillance, but country reports carbapenem-resistant invasive isolates (*Klebsiella pneumoniae* and *Escherichia coli*) to the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR).

<sup>c</sup> Voluntary participation of the laboratories.

<sup>d</sup> Voluntary notification to health authorities.

<sup>e</sup> Mandatory participation of the laboratories (for the United Kingdom, only mandatory for Scotland).

<sup>f</sup> Mandatory notification to health authorities (for the United Kingdom, only mandatory for Scotland).

<sup>g</sup> No national system for surveillance, but country reports carbapenem-resistant invasive isolates (*K. pneumoniae* and *E. coli*) to the European Antimicrobial Resistance Surveillance Network (EARS-Net).

<sup>h</sup> An expert laboratory fulfils a similar role to that of a national reference laboratory.

\* This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the Internal Court of Justice Opinion on the Kosovo declaration of independence.

were KPC-producing *Enterobacteriaceae*, but OXA-48-producing *Enterobacteriaceae* have also been recently reported [55,56].

#### Cyprus, Greece, Israel, Italy, Malta and Turkey

During the EuSCAPE structured survey, **Cyprus** collected only three CPE isolates (data not shown). In line with this, the latest data from the European

Antimicrobial Resistance Surveillance Network (EARS-Net) showed a decreasing trend in the percentage of carbapenem-resistant among invasive, i.e. blood and cerebrospinal fluid (CSF), *K. pneumoniae* isolates from 15.7% to 5% during 2011 to 2014 [12,57].

Since the early 2000s, **Greece** has been first facing a nationwide epidemic of polyclonal VIM-producing *K. pneumoniae* followed by a nation-wide occurrence of

mainly monoclonal KPC-2-producing *K. pneumoniae*. The first NDM-1-producing *K. pneumoniae* isolate was reported in 2012 in a patient repatriated from Albania [58,59]. Since 2012, NDM-producing *Enterobacteriaceae* have been isolated from patients in 15 Greek hospitals and several clonal outbreaks of NDM-1-producing *Enterobacteriaceae* have been reported with only a few cases in each outbreak, therefore of much smaller magnitude than earlier and concurrent outbreaks with KPC-producing *Enterobacteriaceae*. OXA-48-producing *Enterobacteriaceae* are still rarely isolated. According to EARS-Net data, Greece had the highest percentage of carbapenem-resistant isolates among invasive *K. pneumoniae* in Europe in 2014, with more than 62% of *K. pneumoniae* invasive isolates being carbapenem-resistant, but with a decreasing trend from 68.2% in 2011 to 62.3% in 2014.

In **Israel**, CPE were rarely detected until 2006 when the situation changed dramatically, with the nationwide spread of KPC-producing *K. pneumoniae*. This led the Ministry of Health to initiate a nationwide intervention plan aiming to contain the spread [60]. The situation of CPE is now stable and the spread of CPE has been contained for several years, but CPE are not eradicated. Recently, several reports have indicated that NDM- and OXA-48-producing *Enterobacteriaceae*, are now present in Israel [61-63].

In **Italy**, it was not until 2010 that CPE became a major issue when KPC-producing *K. pneumoniae* became endemic, due to a rapid countrywide diffusion mostly caused by strains of clonal complex 258 [64]. This increase in percentages of carbapenem resistance in invasive *K. pneumoniae* isolates has been documented by EARS-Net since 2010 and the latest data from EARS-Net reported that 32.9% of *K. pneumoniae* invasive isolates were carbapenem-resistant [12]. NDM-1- and OXA-48-producing *Enterobacteriaceae* have been reported but their dissemination was still limited and cases were mostly acquired abroad [65-67]. In an effort to control and prevent the further spread of CPE, the Ministry of Health issued a circular letter in 2013 asking the public health offices across the country to report all cases of bacteraemia caused by CPE to the regional and national authorities. Although there is still under-reporting of CPE, more than 2,000 CPE bacteraemia cases have been reported since publication of the circular letter. One worrisome recent development is the rapid and country-wide dissemination of resistance to colistin in KPC-producing *K. pneumoniae* [68] and the presence of pandrug-resistant (PDR) strains (data not shown).

In **Malta**, dissemination of OXA-48-producing *Enterobacteriaceae* had changed the country's epidemiological level from rare sporadic occurrence before 2010 to an endemic situation by 2013 [1,2]. It is thought that the influx of injured Libyan war victims to the intensive treatment unit of the country's only tertiary care hospital in 2011 contributed to the first outbreak and

spread of OXA-48-producing *Enterobacteriaceae* in the country [69]. Despite initial control of the outbreak, the situation rapidly became endemic in this hospital and OXA-48-producing *Enterobacteriaceae* spread to other health and residential care entities on the Maltese islands. Until 2014, no KPC- or NDM-producing *Enterobacteriaceae* were reported while during the same period more than 400 new cases of OXA-48-producing *Enterobacteriaceae* were identified. Since then, the number of new cases of OXA-48-producing *Enterobacteriaceae* has continued to increase. In addition, sporadic cases of VIM- and NDM- producing *Enterobacteriaceae* were recently identified, mainly acquired outside the country. EARS-Net data for Malta showed an increase in the percentage of invasive carbapenem-resistant *K. pneumoniae*, OXA-48 –producing *K. pneumoniae*, from 3.8% to 9.9% during the period 2011 to 2014 [12].

In **Turkey**, OXA-48-producing *Enterobacteriaceae* are endemic, and since 2013, an increasing number of reports have demonstrated the emergence of other types of CPE (e.g. NDM-1- and KPC-producing *Enterobacteriaceae*) [70]. This was confirmed by the results of the EuSCAPE structured survey (data not shown). Reports of NDM-1-producing *Enterobacteriaceae* cases have been increasing, especially in hospitals from cities close to the Syrian border. The latter development is in accordance with recent reports on both autochthonous and imported NDM-1-producing *Enterobacteriaceae* cases in Turkish hospitals [71,72]. In 2015, the first *K. pneumoniae* co-producing OXA-48 and NDM-1 was isolated from a patient treated in the hospital of Sanliurfa, a city close to the border with Syria [73].

#### **National capacity for surveillance and containment of carbapenamase-resistant *Enterobacteriaceae***

Table 4 summarises the existing surveillance and reference laboratory systems in place as well as the available national guidance documents for the containment of CPE in the participating countries at the time of the survey.

#### **Surveillance of carbapenamase-resistant *Enterobacteriaceae***

Twenty-five EU Member States, Norway and Iceland had a dedicated national system for surveillance of CPE. Three EU Member States did not have a dedicated national surveillance system but reported carbapenem-resistant *K. pneumoniae* and *E. coli* from blood and CSF to EARS-Net. Slovenia, one of these, reported that at the time it was developing a dedicated national system for surveillance of CPE for implementation by the end of 2015. The Netherlands, which has a system in place, reported that enhanced surveillance of CPE will take place from 2016 onwards. In order to increase laboratory participation and coverage as well as to improve data quality, the enhanced surveillance should further optimise diagnostic testing and integrate clinical, molecular and epidemiological data for all CPE cases to



determine relevant risk factors to target interventions and control potential spread.

All EU enlargement countries and Israel reported participating in the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR) network, a joint initiative of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Dutch National Institute for Public Health and the Environment (RIVM) and the World Health Organization Regional Office for Europe (WHO/Europe). However, only Serbia, the former Yugoslav Republic of Macedonia and Turkey have so far reported data to CAESAR using the EARS-Net methodology [74]. Israel, Serbia, the former Yugoslav Republic of Macedonia and Turkey had dedicated national systems for the surveillance of CPE, while Albania, Bosnia and Herzegovina, Kosovo\* and Montenegro were developing their surveillance system to be able to report data to CAESAR by 2015 or 2016.

Of 31 countries with a dedicated national surveillance system for CPE, 20 countries reported that surveillance of CPE was mandatory for all laboratories, nine countries reported that surveillance of CPE was voluntary and two countries did not specify. In Romania and Serbia, surveillance was voluntary and in form of a sentinel system of individual laboratories. In Ireland, laboratory participation was only mandatory for invasive disease caused by CPE, i.e. isolation from blood and CSF, but remained voluntary for CPE isolated from other body sites (Table 4).

#### **Laboratory capacity for carbapenamase-resistant *Enterobacteriaceae***

Thirty-four countries reported having an officially nominated national reference laboratory for CPE or a national expert laboratory that fulfilled a similar role. Both Albania and Montenegro reported that the national reference laboratory was in development for implementation by 2015–2016 (Table 4).

#### **Notification to health authorities for carbapenamase-resistant *Enterobacteriaceae***

Twenty-six countries reported having a national recommendation for reporting to health authorities CPE-positive patients identified by diagnostic laboratories. In most countries there is mandatory notification for all private and hospital laboratories and for all infections; only seven countries notified CPE cases on a voluntary basis. In two of the latter, notification of CPE cases was voluntary but notification of CPE outbreaks was mandatory. Slovenia and Germany reported that national recommendations or obligations for reporting were going to be implemented by the end of 2015, and for Bosnia and Herzegovina this is planned by 2016–2017 (Table 4).

#### **National plan for containment of and infection control measures for carbapenamase-resistant *Enterobacteriaceae***

Eleven countries had implemented a national plan for the containment or for preparedness to contain CPE, and another nine countries were developing national containment plans. Spain had no national but regional specific plans.

Twenty-four countries reported having national recommendations or guidelines for infection prevention and control measures to be applied for patients confirmed as being infected or colonised with CPE: for six countries this applied to single CPE cases, for 15 to single CPE cases and outbreaks, for Greece this only applied to outbreaks and two countries did not specify the scope of their recommendations. Twelve of the national recommendations or guidelines were specific guidance documents for prevention and control of CPE, while nine were included as part of a general guidance document for multidrug-resistant organisms (MDROs) that specifically referred to CPE and three included a general guidance document for MDROs not specifically referring to prevention and control of CPE. Kosovo\* and Portugal indicated that such recommendations or guidelines are in preparation for implementation by the end of 2015.

The most cited measures in such national recommendations or guidelines were isolation e.g. in single rooms, of suspected/colonised/infected patients and increased hand hygiene compliance (21 countries each), followed by active screening for early detection at admission of patients having been hospitalised abroad, implementation of contact precautions, for visitors and medical staff, and implementation of environmental hygiene procedures e.g. decontamination of equipment and disposal of waste (20 countries each), active screening for early detection of transferred patients from other wards/hospitals at admission (19 countries), cohorting of suspected/colonised/infected patients (18 countries), active screening for early detection of colonised patients at admission (16 countries), dedicated infection control teams (14 countries), separate cohort nursing care e.g. nurses, doctors (13 countries), specialised training for nursing staff in infection control (12 countries), implementation of an antibiotic stewardship programme (11 countries), and audit and feedback to local, regional or national health authorities (10 countries).

#### **Discussion**

In 2013, at the beginning of the EuSCAPE project, knowledge about the spread and occurrence of CPE was heterogeneous among European countries [1]. Moreover, some NEs expressed concerns that under-detection affected the epidemiological self-assessment of their country. Following EuSCAPE activities including a capacity building workshop and an EQA exercise to improve the detection of CPE and the identification of

the different carbapenemases circulating in Europe, the results of this follow-up survey provide evidence that the activities contributed to the desired improvement and increased awareness and knowledge of the epidemiology of CPE in many participating countries. After participation in the EuSCAPE project, all countries were able to self-assess their current situation, whereas only 26 countries could do so in 2013. In addition, all participating countries were able to rate the occurrence and spread of CPE according to the type of carbapenemase, while such data were only partially or not available in several European countries in 2013 [1,2].

In 2015, 13/38 countries reported inter-regional spread of or an endemic situation for CPE, compared with 6/38 countries in 2013. In addition, the survey documented the more frequent reporting of OXA-48- and NDM-producing *Enterobacteriaceae* compared with 2013. For OXA-48-producing *Enterobacteriaceae*, four countries had reported regional spread and only one country had reported an endemic situation in 2013, while in 2015, three countries reported regional spread, four reported inter-regional spread and two reported an endemic situation. Similarly for NDM-producing *Enterobacteriaceae*, only Italy and the UK had reported sporadic hospital outbreaks in 2013, while in 2015 six countries reported sporadic hospital outbreaks and seven countries reported regional and inter-regional spread. For the countries that were uncertain about their epidemiological stage in the 2013 survey, the results of this survey reflect an improved ability to detect CPE and identify the different carbapenemases. For the other countries, the changes in epidemiological stages observed between 2013 and 2015 likely reflect an increasing spread of CPE, as confirmed by the NEs. At the same time, increased awareness of CPE spread and surveillance might also contribute to increased detection and reporting of more advanced epidemiological stages. Indeed, countries with strict screening policies are more likely to report such advanced epidemiological stages.

The establishment of a surveillance system for CPE, based on the notification of CPE cases to health authorities, supported by reference laboratory confirmation and identification as well as, molecular typing services are the cornerstones of efficient monitoring and controlling of the spread of CPE. Many countries have developed dedicated surveillance systems and designated reference laboratories over the last two years, as well as implemented mandatory laboratory participation in CPE surveillance, or mandatory reporting of all cases of infections. However, despite the increased awareness and the worsening of the epidemiological situation in 2015, only 25 of the 38 countries that participated in the EuSCAPE project had enacted mandatory notification of CPE cases to health authorities. Active reporting of CPE cases should be encouraged by making all clinical cases notifiable to public health authorities.

Twenty countries had either implemented a national or regional plan for the containment of, or preparedness to contain, CPE or were developing national containment plans. However, national guidance documents on infection prevention and control of CPE were not available in 14 countries. In an effort to support health-care professionals, hospital administrators and public health professionals, ECDC published an online directory of guidance documents on prevention and control of carbapenem-resistant *Enterobacteriaceae* by EU/EEA Member States, ECDC, international and national agencies and professional societies [75,76].

A major impending threat to public health as a consequence of the expanding CPE epidemic in Europe is the emergence of PDR strains causing untreatable infections. Polymyxins, and particularly colistin, represent a last-line option for the treatment of patients infected with CPE. The latest data available from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) show that consumption of polymyxins, mainly colistin, in Europe, almost doubled between 2009 and 2013 [77]. In parallel to this increasing colistin consumption, colistin resistance is increasing in carbapenem-resistant *Enterobacteriaceae* [68,77,78]. In Italy, 43% of KPC-producing *K. pneumoniae* isolates collected during the EuSCAPE structured survey in 2013 to 2014 [68] and 13% of carbapenem-resistant *K. pneumoniae* isolates from blood cultures reported to EARS-Net in 2014 were resistant to colistin [12]. Approximately 20% of carbapenem-resistant *K. pneumoniae* isolates from blood cultures reported to EARS-Net in 2014 were resistant to colistin in Romania and Greece [12]. In February 2015, a Greek hospital reported an outbreak of PDR *Enterobacteriaceae*, via the acquisition of *bla*<sub>VIM</sub> by the naturally colistin-resistant *Providencia stuartii*, in an intensive care unit occurring in September to November 2011 [79].

The accumulation of other resistance markers in CPE strains in addition to colistin resistance makes it likely that Europe will soon witness an increasing number of outbreaks of extensively drug-resistant (XDR) or PDR *Enterobacteriaceae* [57], for which few or even no treatment options are available. The United States Food and Drug Administration (FDA) recently approved the use of a combination of a well-established  $\beta$ -lactam antibiotic, ceftazidime, with a novel  $\beta$ -lactamase inhibitor, avibactam, for treatment of serious infections caused by resistant Gram-negative pathogens. Ceftazidime-avibactam is active against OXA-48- and KPC-producing *Enterobacteriaceae* but not NDM- or VIM-producing *Enterobacteriaceae* and would offer a partial solution to treat infections due to XDR or PDR Gram-negative bacteria.

In conclusion, the EuSCAPE project and this follow-up survey confirm the urgent need for a coordinated European effort for surveillance, control and prevention of CPE in Europe. The project contributed to the improvement of the capacity and ability to detect CPE

in Europe by creating a European network of national reference/expert laboratories able to provide information for monitoring incidence and spread of carbapenemases in the 38 participating countries. Furthermore, results presented here show the need to develop an EU-wide system for public health surveillance of high-risk CPE clones and mobile genetic vectors of epidemic carbapenemases across the healthcare systems in Europe for informing risk assessment and control programmes.

*\*This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.*

#### **\*\*Authors' correction**

On 10 December 2015, upon request of the authors, the following text was added to the Acknowledgements section: 'The authors would like to thank Liselotte Diaz Högberg for providing data and the analysis of the data on the percentage of carbapenem resistance in invasive *Klebsiella pneumoniae* isolates in the European Union / European Economic Area Member States from the European Antimicrobial Resistance Surveillance Network (EARS-Net).'

[The European Survey of carbapenemase-producing Enterobacteriaceae \(EuSCAPE\) working group comprises the EuSCAPE national experts, ECDC National Focal Points for antimicrobial resistance, ECDC National Correspondents for EU enlargement countries, the EuSCAPE scientific advisory board and External consulted experts](#)

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#### **Conflict of interest**

None declared.

#### **Authors' contributions**

Barbara Albiger: modified, adapted and further developed the self-assessment questionnaire issued in February 2013 for the purpose of this study, supervised and coordinated the post-EuSCAPE survey collecting the data, performed the data analysis and wrote the manuscript.

Dominique L. Monnet: reviewed and provided feedback on the questionnaire and reviewed and approved the data, the analysis and the manuscript.

Marc J. Struelens: contributed to drafting and the review of the manuscript

Corinna Glasner and Hajo Grundmann: reviewed and provided feedback on the questionnaire and the manuscript.

The national experts, the ECDC National Focal Points for antimicrobial resistance and the ECDC National Correspondents for EU enlargement countries: answered the survey providing country specific data, provided country specific profile, approved the final data and the analysis, and reviewed and provided feedback the manuscript.

The EuSCAPE scientific advisory board and the external consulted experts: reviewed and provided feedback on the manuscript.



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