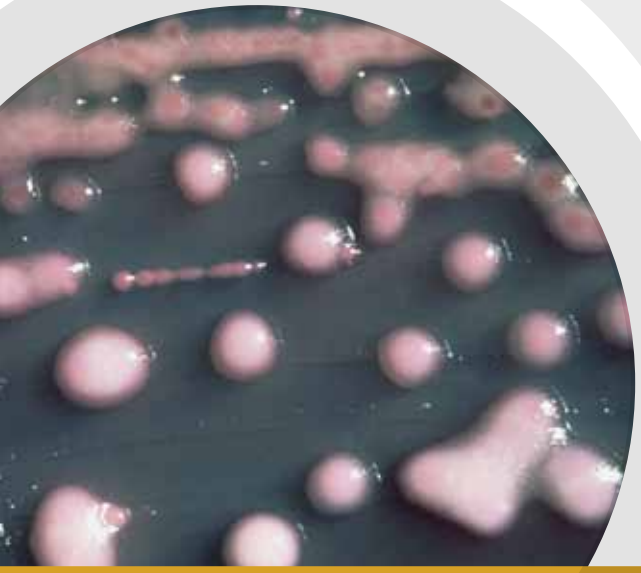

TECHNICAL REPORT

Carbapenemase-producing bacteria in Europe

Interim results from the European survey on carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) project 2013

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ECDC TECHNICAL REPORT

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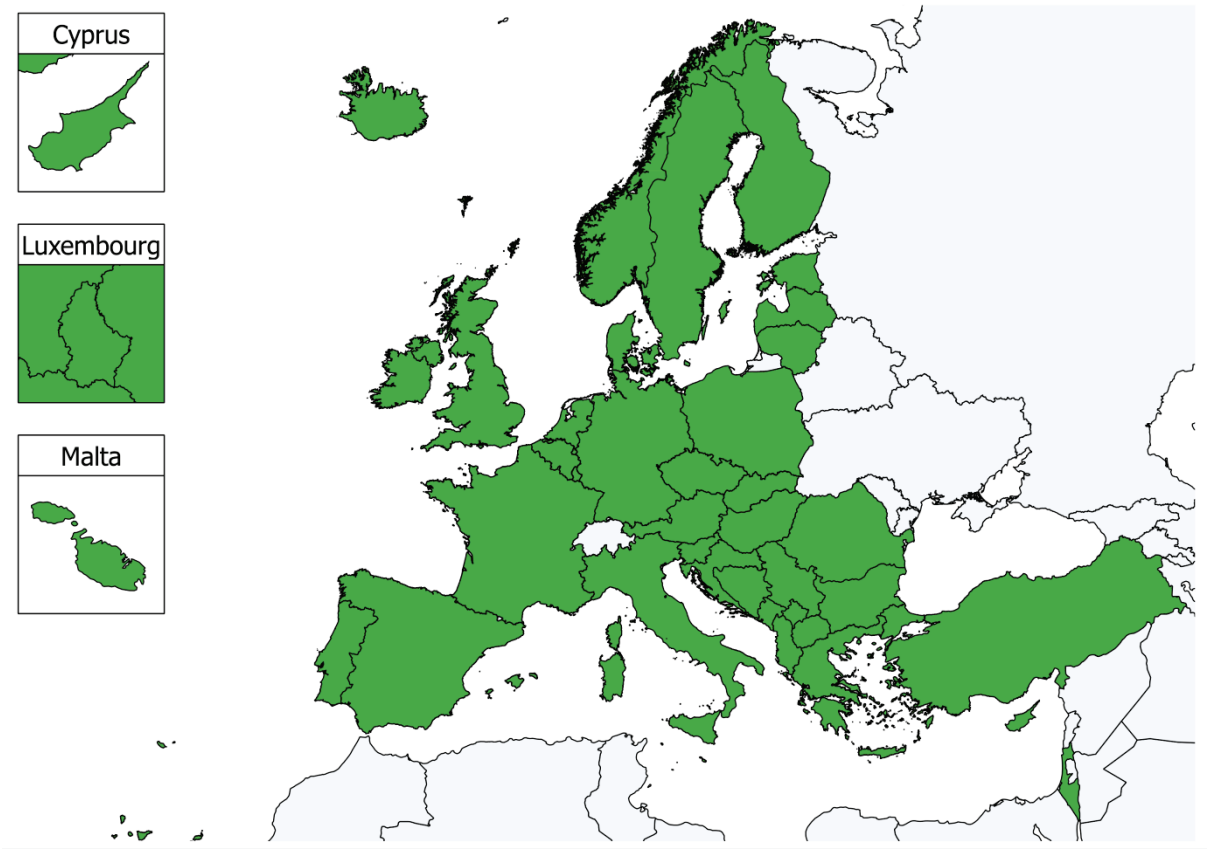
Abbreviations

AST	Antimicrobial susceptibility testing
CSF	Cerebrospinal fluid
CPE	Carbapenemase-producing *Enterobacteriaceae*
CRA	Carbapenem-resistant *Acinetobacter* spp.
CRAb	Carbapenem-resistant *Acinetobacter baumannii*
EEA/ETFA	European Economic Area/European Free Trade Association
ECDC	European Centre for Disease Prevention and Control
EARS-Net	The European Antimicrobial Resistance Surveillance Network
ESBL	Extended spectrum beta-lactamase
EU	European Union
EuSCAPE	European Survey on Carbapenemase-Producing *Enterobacteriaceae*
HAI	Healthcare-associated infections
IMP	IMP-type metallo-beta-lactamase
KPC	*Klebsiella pneumoniae* carbapenemase
NDM	New Delhi metallo-beta-lactamase
NE	National Expert
NEL	National Expert Laboratory
NRL	National Reference Laboratory
OXA-48	Carbapenem-hydrolysing oxacillinase-48
RIVM	Dutch National Institute for Public Health and the Environment
VIM	Verona integron-encoded metallo-beta-lactamase
UK	United Kingdom

Participating countries

Figure 1. Countries participating in the survey, March 2013



Participating countries are represented in green.

Executive summary

The spread of carbapenem-non-susceptible bacteria, more specifically of carbapenemase-producing *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii*, is a threat to healthcare and patient safety in Europe, although its exact prevalence in healthcare facilities and within the community in Europe is unknown.

The European Centre for Disease Prevention and Control (ECDC) is currently funding a project on carbapenemase-producing bacteria in Europe. The first part of the project was a survey to gather information about the spread of carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *A. baumannii* (CRAb) in Europe, on public health responses and on available national guidance on detection, surveillance, prevention and control. The survey also investigated the laboratory capacity for diagnosis and surveillance at the national level.

Between 8 February and 14 March 2013, 39 national experts from the 28 European Union (EU) Member States, Iceland, Norway, the seven EU enlargement countries and Israel were invited to complete the survey. The present report summarises the results of this survey and demonstrates that CPE and CRAb are increasingly spreading in Europe, highlighting the urgent need for a coordinated European effort on early diagnosis, active surveillance, and guidance on infection prevention and control measures.

Introduction

The *Enterobacteriaceae* form part of the commensal human gut flora and are frequently the cause of community- and healthcare-associated infections (HAI). *Acinetobacter* species are opportunistic pathogens that are being increasingly isolated from healthcare settings, mostly from intensive care units and from immunocompromised patients. Treatment of infections due to *Acinetobacter* spp. has become more challenging, since a large percentage of these bacteria have become resistant to many and sometimes all antibiotics to which they were once susceptible.

Over the last decade, Gram-negative bacteria in Europe and worldwide (i.e. *Enterobacteriaceae* and *Acinetobacter* spp.) have become increasingly resistant to first- and second-line antibiotics (e.g. beta-lactam antibiotics, fluoroquinolones and aminoglycosides) [1]. Resistance to extended-spectrum beta-lactam antibiotics (e.g. third-generation cephalosporins) due to the production of extended-spectrum beta-lactamases (ESBLs) continues to increase in *Enterobacteriaceae* [1]. Carbapenems are a class of beta-lactam antibiotics with very broad activity and have therefore become the empirical treatment option in countries where infections due to ESBL-producing bacteria are common, as well as an important treatment option for multidrug-resistant *Acinetobacter* spp.. Resistance to carbapenems in *Enterobacteriaceae* and in *Acinetobacter* spp. is linked to either decreased permeability or to the enzymatic breakdown of the antibiotic by carbapenemases. The most frequent carbapenemases in *Enterobacteriaceae* reported in Europe are: the *Klebsiella pneumoniae* carbapenemase (KPC), the Verona integron-encoded metallo-beta-lactamase (VIM), the IMP-type metallo-beta-lactamase (IMP), the New Delhi metallo-beta-lactamases (e.g. NDM-1) and the OXA-48-like carbapenem-hydrolysing oxacillinases [2,3]. The following *Acinetobacter* species, *A. baumannii*, *A. nosocomialis* and *A. pittii*. belong to the *Acinetobacter baumannii* group. For the remainder of this report, these three species will be collectively designated as *A. baumannii sensu lato*. *A.baumannii* possesses the intrinsic oxacillinase OXA-51 that confers resistance to carbapenems only when over-expressed. The most frequent mechanism leading to carbapenem resistance in *A. baumannii* is mediated by the acquired oxacillinases OXA-23-like, OXA-24-like, OXA-58-like, OXA-143-like and OXA-235. Metallo-β-lactamases, such as IMP, VIM and others have only rarely been encountered in *A. baumannii*, although NDM-producing *A. baumannii* isolates have increasingly been reported in Europe [4-6].

The rapid and global expansion of CPE and CRAb is a threat to healthcare and patient safety worldwide, as it seriously curtails the ability to cure infections. Infections due to CPE are associated with higher in-hospital mortality [7-9].

During the annual meeting of the European Antimicrobial Resistance Surveillance System in Athens in 2009, the need for a European-wide consultation about the increasing occurrence of CPE was recognised among European experts. At a follow-up workshop at the Dutch National Institute for Public Health and the Environment (RIVM) in April 2010, experts in the surveillance of antimicrobial resistance in *Enterobacteriaceae* from 31 European countries established a novel epidemiological staging system to describe the magnitude of CPE and provided recommendations to address this public health issue in a concerted manner [10]. Following the meeting, a survey was carried out, providing valuable insights into the prevalence of different carbapenemases and the degree of spread of CPE in the EU Member States and three European Economic Area (EEA)/European Free Trade Association (EFTA) countries [10].

In November 2010, ECDC published a risk assessment on the spread of NDM-1-producing *Enterobacteriaceae* in the EU Member States, which also reported on the availability of national guidance on detection, surveillance, notification and control of NDM-1 and other carbapenemase-producing *Enterobacteriaceae* in these countries [11]. In 2011, ECDC issued an update of this risk assessment and published a broader risk assessment on the spread of carbapenemase-producing *Enterobacteriaceae* (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer [12,13]. In 2012, Canton et al. estimated the extent and spread of CPE in Europe based on available published data [14]. Most recently, Levy Hara et al. published recommendations from an international working group for the detection, treatment and prevention of CPE [15]. The increasing number of reports on CRAb outbreaks and the emergence of new CRAb clones in European hospitals suggest that CRAb has become another menace in European hospitals [4,6,16-27]. There is consensus among experts that surveillance of CPE and CRAb is crucial for the implementation of effective infection prevention and control.

In April 2012, ECDC published an open call for tender for a European project on carbapenemase-producing bacteria with the following aim: to improve the understanding of the epidemiology and occurrence of carbapenemase-producing bacteria in Europe; to build laboratory capacity for diagnosis and surveillance at the national and European level; and to develop a laboratory-based network in the EU Member States and EEA and the EU enlargement countries that is capable of providing information on the prevalence of carbapenemase-producing bacteria in Europe.

The European Survey on carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) project is implementing some of the recommendations published in 2010, such as assessing the existing laboratory capacity, building the capacity of reference diagnostics, standardising the detection of carbapenemase-producing bacteria, and developing a structured survey to obtain a more accurate estimate of carbapenemase-producing bacteria in Europe [10,28].

The EuSCAPE project is divided into three parts, whose goals are:

- To gather information about the spread of CPE and CRAb in Europe on; public health responses; on available national guidance on detection, surveillance, prevention and control; and about the laboratory capacity for diagnosis and surveillance using a survey sent to 39 national experts in 38 European countries, (8 February 2013–14 March 2013)
- To host a capacity building workshop for national laboratory experts to be further informed about the identification and confirmation of CPE (5–6 September 2013, Vari, Greece)
- To carry out an external quality assessment followed by a structured survey collecting European isolates of CPE together with data on CPE-related infections in 38 European countries (November 2013–May 2014).

This interim report summarises the results of the survey amongst the national experts from the 28 Member States, Iceland, Norway, the seven EU enlargement countries and Israel.

Methodology

The purpose of the survey was to gather information about the spread of CPE and CRAb in Europe, on public health responses and on available national guidance on detection, surveillance, prevention and control. The survey also assessed the laboratory capacity for diagnosis and surveillance at the national and European level.

Description of the survey

The survey was derived from a field-tested version used during previous similar surveys [10,11]. It was based on a questionnaire and divided into three sections:

- **Section 1:** 13 questions exploring the experts' knowledge and awareness of the current occurrence of CPE and CRAb and supporting a self-assessment of the spread of CPE and CRAb according to a previously established epidemiological staging system (Table 1);
- **Section 2:** 22 questions gathering information about existing national guidance documents for reporting, surveillance, use of reference laboratory services and infection control for CPE and CRAb;
- **Section 3:** 26 questions gathering information about the existing laboratory capacity at the national level in each country in preparation of the second and third phase of the EuSCAPE project, i.e. the capacity building workshop (5-6 September 2013) and the structured survey (November 2013 – May 2014).

The survey questions were discussed and validated by an expert panel, composed of the EuSCAPE Management Team, the EuSCAPE Scientific Advisory Board and ECDC (Annex 1). Three types of questions were included: yes/no, multiple choice and open questions with possibility of free text answers (for details about the questionnaire, please see Annex 2).

Table 1 The epidemiological stages of nationwide expansion of carbapenemase-producing *Enterobacteriaceae* (CPE)

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 related cases 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 outbreak confined to hospitals that are part of regional referral network, 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

Composition of the Scientific Advisory Board

A panel of scientific experts (Scientific Advisory Board) was invited to provide expert support to the EuSCAPE project (Annex 1). The members of the EuSCAPE Scientific Advisory Board were selected for their broad expertise in the field of CPE and CRAb.

Some members of the Scientific Advisory Board also represented relevant scientific and professional organisations in the field of antimicrobial resistance, i.e. the European Committee on Antibiotic Susceptibility Testing (EUCAST), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European Network On Carbapenemase-producing bacteria, the European Surveillance for Antimicrobial Resistance (EARS-Net), and the European Study Group for Antimicrobial Resistance Surveillance (ESGARS). Care was taken to choose experts from different geographical regions for an adequate European perspective (Annex 1). Additional expert support to the EuSCAPE project was provided by two independent external experts (Annex 1).

Selection of the national experts

In each of the 38 European countries, a national expert (NE) with acknowledged laboratory and/or epidemiological experience was identified. Twenty-three of these NEs are employed at reference laboratories. The NEs were chosen among EARS-Net contact points, experts from national reference laboratories and ECDC Coordinating Competent Bodies (National Focal Point for antimicrobial resistance and National Focal Points for microbiology). The United Kingdom was represented by two NEs. The list of NEs was validated by ECDC and represents the EuSCAPE Working Group (Annex 1).

Description of the survey tool

The NEs were invited to answer the questionnaire online between 8 February and 14 March 2013 using the Survey Monkey software and questionnaire tool

Analysis, evaluation and representation of the answers to the survey

Answers from the NEs were compiled in a database. When necessary, NEs were contacted by e-mail or telephone for clarification, and corrections were made accordingly. The NEs answered the questionnaire based on their knowledge of the national clinical and microbiological data or on their personal judgement.

Since there were concerns from some of the NEs that under-detection and/or under-reporting most likely affected the certainty of the staging of their country, stage designations for CPE were considered uncertain if two or more of the following criteria were met:

- the NE reported a lack of awareness about the current epidemiology of CPE in the country;
- the NE reported potential under-detection and under-reporting of CPE in the country;
- the NE expressed uncertainty during the clarifications sought by e-mail or telephone;
- when CPE had been reported to or from other countries but NEs could not independently verify existing sources in their own country.

Uncertainty for the epidemiological stage of CPE is represented on the maps presented in this report (Figure 3 and Figure 5).

As surveillance and reporting of CRAb are not performed routinely at this time, and because fewer national reference laboratory structures for CRAb are in place in European countries, most NEs highlighted that the exact epidemiology of CRAb remains uncertain in their country. There is a clear need for data on CRAb for all participating countries and therefore, the stage designations for CRA might be taken with caution for all participating countries. Hence, it was chosen not to highlight uncertainty in the corresponding map (Figure 7).

The answers of the NEs are presented individually for each country in all tables and figures, except for Figures 2, 4 6, 8 and 9, where the answers were aggregated. The answers of the NEs were based on their knowledge of the epidemiological situation of CPE and CRAb at the time of the survey (8 February–14 March 2013). This situation might have evolved and be different at the time of the publication of this report. If so, and if informed by the NEs, the changes are presented in the discussion.

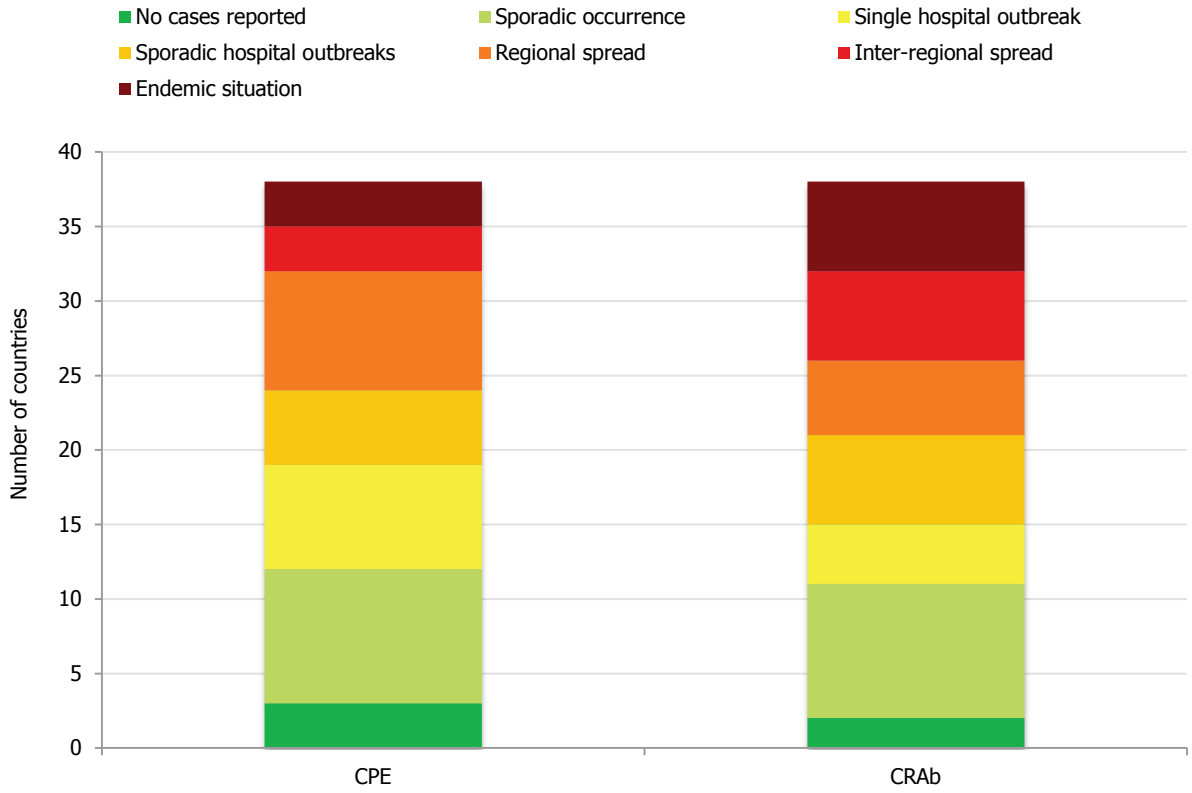
Results

Epidemiology of carbapenemase-producing bacteria in Europe

All NEs completed the online questionnaire and applied the epidemiological staging system (Table 1) to describe the magnitude of the spread of CPE and CRAb in their respective countries (Figure 2).

Comparison of the epidemiological stages of CPE and CRAb suggests that CRAb have a broader dissemination than CPE in Europe. For CRAb, 12 countries reported stage 4 or 5 (inter-regional spread or an endemic situation), whereas only six countries reported the same extent for CPE (Figure 2).

Figure 2. Comparison of the epidemiological stages of carbapenemase-producing *Enterobacteriaceae* and carbapenem-resistant *A. baumannii* based on self-assessment of the national experts in the participating countries, March 2013

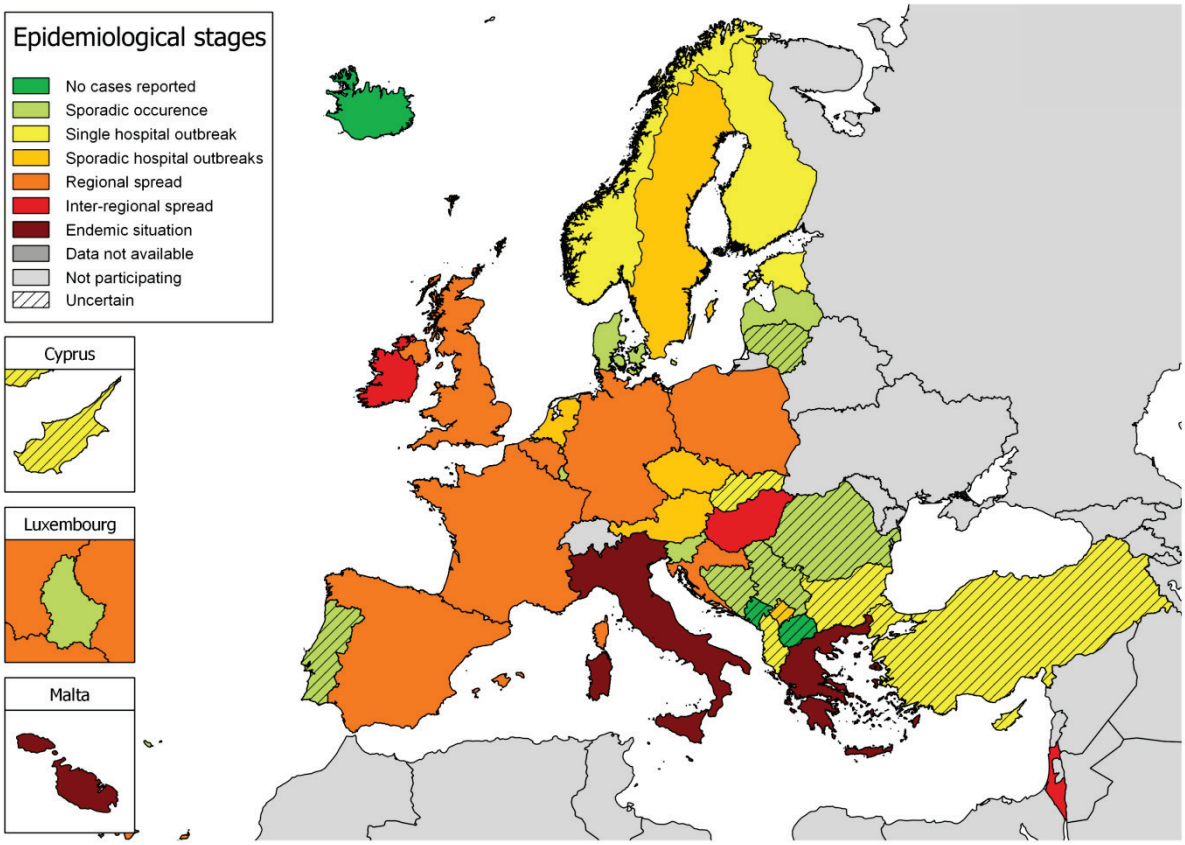


Occurrence of carbapenemase-producing *Enterobacteriaceae*, March 2013

All 39 NEs rated the occurrence and spread of CPE for their respective country and 37 of the NEs declared that they were fully aware of the current epidemiology of CPE in their country (Table 2 and Figure 3). Twenty-six of the 38 countries could self-assess their current situation with certainty (Figure 3).

Three NEs (representing Iceland, Montenegro and the former Yugoslav Republic of Macedonia) reported no case of CPE in their country. Sporadic cases, single or sporadic hospital outbreaks were reported by NEs from 21 countries. For 11 countries, regional or national spread was reported, whereas NEs of three countries (Greece, Italy and Malta) reported that CPE are regularly isolated from patients in most hospitals, corresponding to an endemic situation (Table 2).

Figure 3 Occurrence of carbapenemase-producing *Enterobacteriaceae* in 38 European countries based on self-assessment by the national experts, March 2013



In some countries, the epidemiological stage might not represent the exact extent of the spread of CPE as it is a subjective judgment by national experts. Results presented here reflect the uncertainty at the time of the survey.

Table 2. Comparison of the epidemiological stages of carbapenemase-producing *Enterobacteriaceae* in European countries, 2010 and 2013

Country	Epidemiological stage for spread of CPE		Direction of change (2010 compared to 2013)[c]
	2010 [10][a]	2013[b]	
Albania	NA	2a	NA
Austria	0	2b	↑
Belgium	2b	3	↑
Bosnia and Herzegovina	1	1	→
Bulgaria	0	2a	↑
Croatia	1	3	↑
Cyprus	2a	2a	→
Czech Republic	1	2b	↑
Denmark	1	1	→
Estonia	0	2a	↑
Finland	1	2a	↑
France	3	3	→
Germany	3	3	→
Greece	5	5	→
Hungary	3	4	↑
Iceland	0	0	→
Ireland	1	4	↑
Israel	5	4	↓
Italy	4	5	↑
Kosovo[d]	NA	2b	NA
Latvia	1	1	→
Lithuania	1	1	→
Luxembourg	NA	1	NA
Malta	1	5	↑
Montenegro	NA	0	NA
Netherlands	2a	2b	↑
Norway	2a	2a	→
Poland	4	3	↓
Portugal	1	1	→
Romania	1	1	→
Serbia	NA	1	NA
Slovakia	NA	2a	NA
Slovenia	0	1	↑
Spain	2b	3	↑
Sweden	2a	2b	↑
the former Yugoslav Republic of Macedonia	NA	0	NA
Turkey	NA	2a	NA
United Kingdom	2b	3	↑

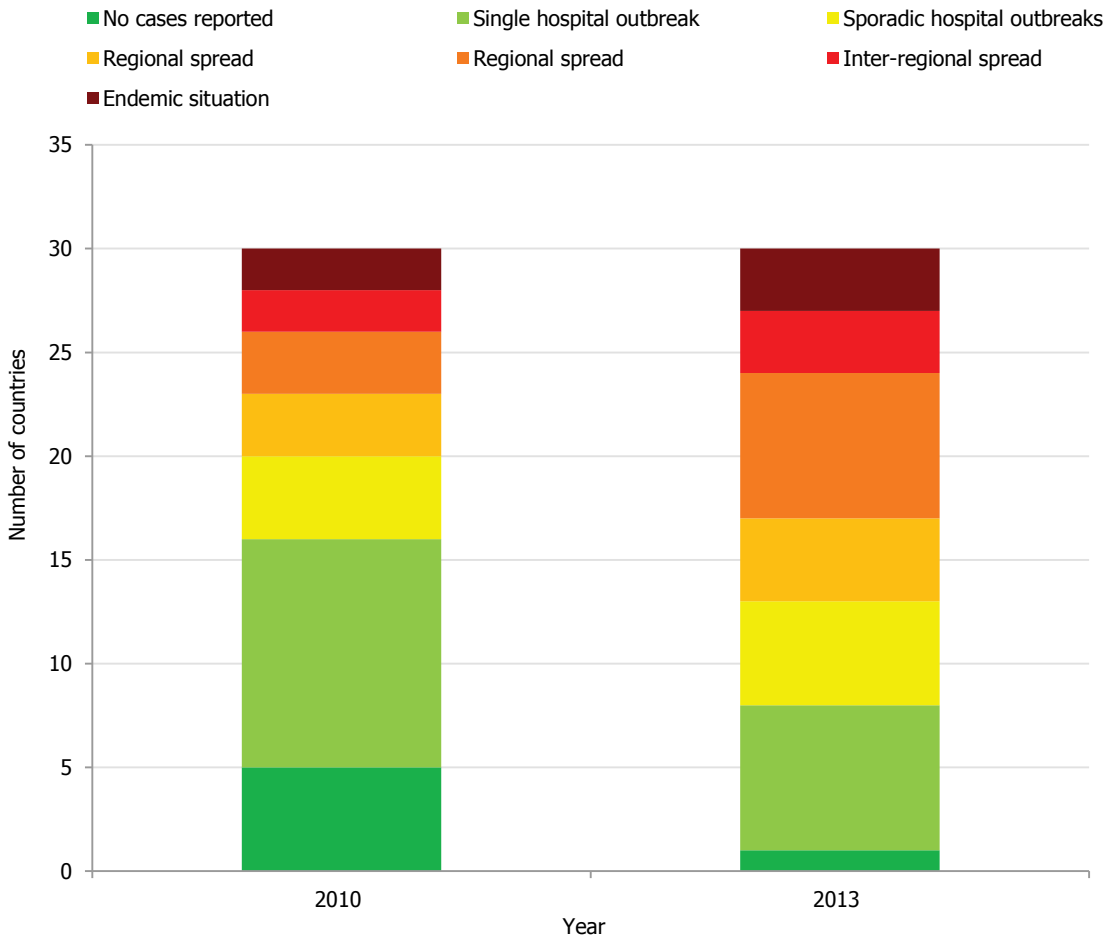
The epidemiological stage of a country may not reflect the exact extent of the spread of CPE. Some of the countries were not included in the 2010 survey and their epidemiological stage and the direction of change between 2010 and 2013 are consequently indicated as 'not available' (NA).

[a] *The results were based on data obtained through a European-wide consultation during a workshop at the RIVM on 29 and 30 April 2010 [10].*
[b] *This online survey (February – March 2013) [28].*
[c] ↑ *increase in the epidemiological stage,* ↓ *decrease in the epidemiological stage and* → *unchanged epidemiological stage.*
[d] *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.*

The self-assessment was based on an epidemiological staging system, previously established, during a workshop at the RIVM in 2010, for a similar exercise involving experts from European countries [10]. It allows possible comparison of results of these two self-assessments (Table 2).

Caution must be taken as some, but not all, experts participated in both self-assessments and therefore staging might reflect subjective variation. When comparing the epidemiological stages of the 30 countries that participated in both self-assessments (2010 and 2013), 16 reported a higher stage in 2013 compared to 2010. Likewise, by 2013, there was an increased number of countries – from seven countries in 2010 to 14 countries in 2013 – reporting regional or inter-regional spread, or even an endemic situation (Table 2 and Figure 4). These results suggest that CPE are increasingly spreading in Europe.

Figure 4. Comparison of the epidemiological stages of carbapenemase-producing *Enterobacteriaceae* between 2010 and 2013.

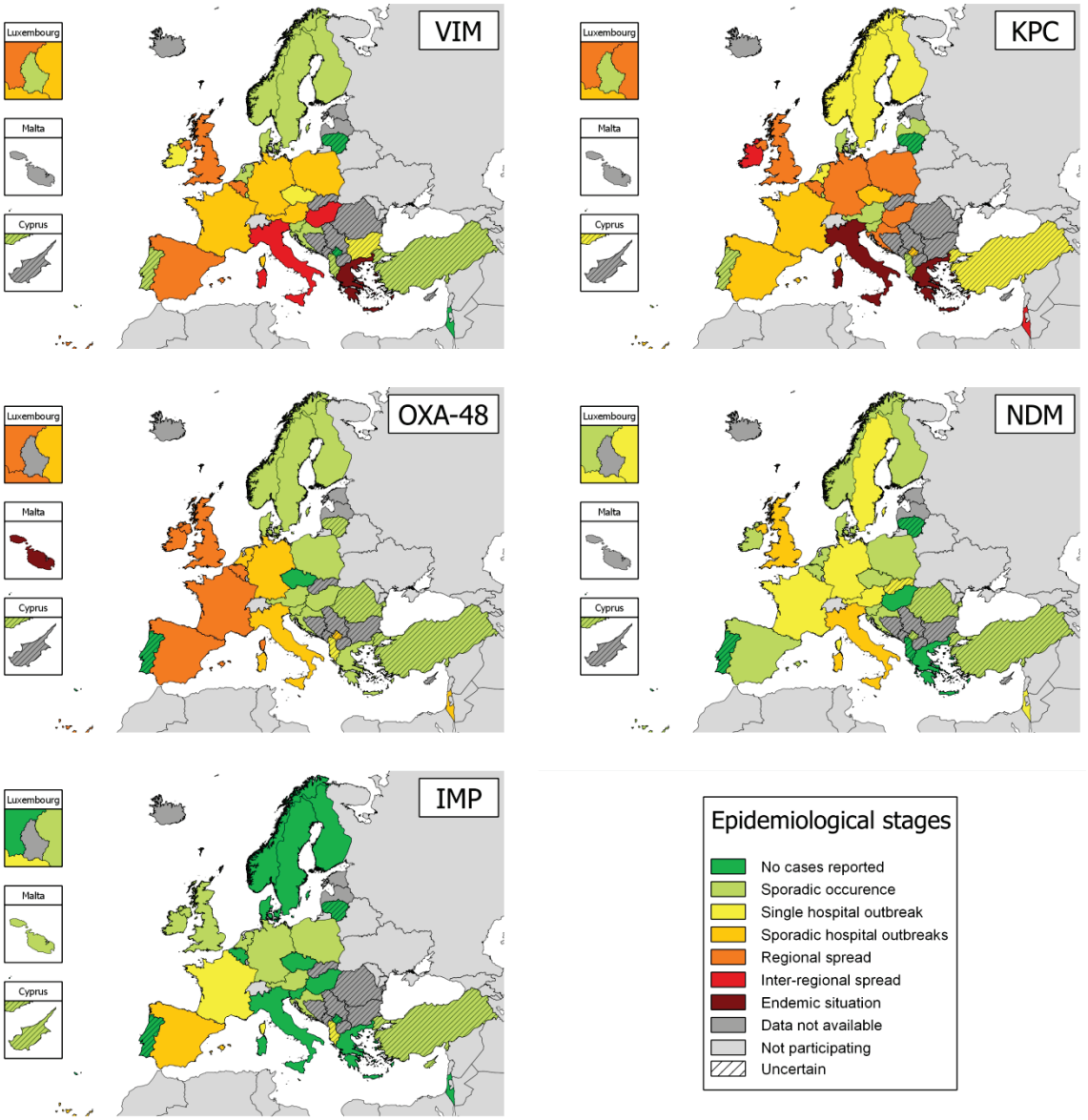


Thirty-three of the NEs indicated that *Klebsiella pneumoniae* was the most frequent *Enterobacteriaceae* species harbouring carbapenemases in their country. Estonia and Lithuania reported that the predominant species among CPE was *Enterobacter* spp., whereas Albania reported that it was *E. coli*. Iceland reported not having identified any CPE yet.

IMP, KPC, NDM, OXA-48 and VIM are the five most common carbapenemases in *Enterobacteriaceae* and thirty-three of the NEs reported that one or more of these most common carbapenemases could be isolated in their country. They rated the occurrence and spread of CPE in their country according to each of these carbapenemases (Figure 5 and Figure 6). In five countries (Bosnia and Herzegovina, Estonia, Montenegro, Serbia and the former Yugoslav Republic of Macedonia), these data were not available.

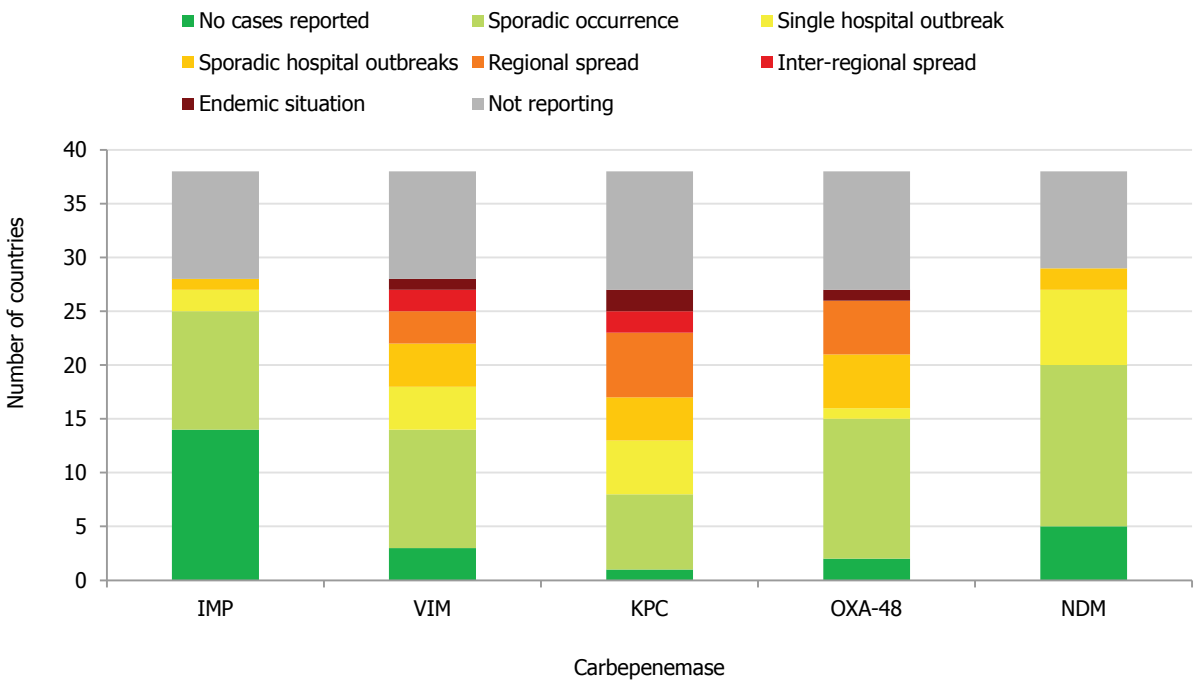
As of March 2013, KPC-producing *Enterobacteriaceae* had attained the widest dissemination, whereas NDM-producing strains, although responsible for occasional hospital outbreaks in few countries, had not reached such a wide dissemination in European countries. OXA-48 was the most frequently detected carbapenemase in Belgium, France and Malta, and increasing numbers of OXA-48 positive isolates were also reported in Ireland, Spain and the UK (Figure 5 and Figure 6).

Figure 5. Occurrence of carbapenemase-producing *Enterobacteriaceae* by type of carbapenemases in 38 European countries based on self-assessment by the national experts, March 2013



KPC: Klebsiella pneumoniae *carbapenemase-producing* Enterobacteriaceae*; NDM: New Delhi metallo-beta-lactamase; OXA-48: carbapenem-hydrolysing oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase. In some countries, the epidemiological stage might not represent the exact extent of the spread of CPE as it is a subjective judgment by national experts.. Results presented here reflect the uncertainty at the time of the survey.*

Figure 6. Rating of the spread of carbapenemase-producing *Enterobacteriaceae* by type of carbapenemases in 38 European countries based on self-assessment by the national experts, March 2013

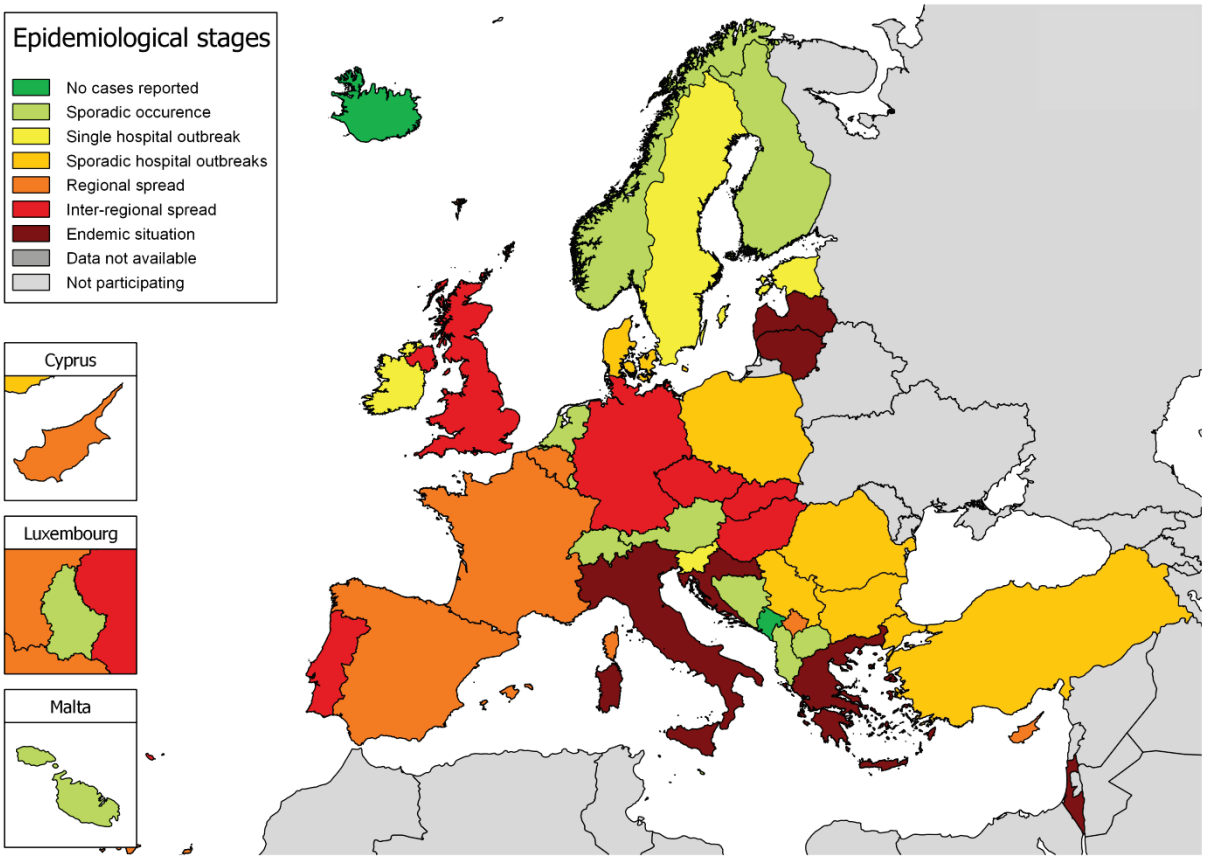


Occurrence of carbapenem-resistant *A. baumannii*, March 2013

All 39 NEs rated the occurrence and spread of CRAb for their respective country using the same epidemiological staging system as for CPE (Figure 7). Most NEs highlighted that the exact epidemiology of CRAb remains uncertain in their country, because surveillance and reporting of CRAb are not performed routinely in their country, and because fewer national reference laboratory structures for CRAb exist in European countries. Sixteen and 28 countries reported that neither surveillance nor reporting of CRAb is performed routinely in their country, respectively (Table 6).

Two NEs (representing Iceland and Montenegro) reported no case of CRAb in their country. Sporadic cases, single or sporadic hospital outbreaks were reported by NEs from 19 countries. For 11 countries, regional or national spread was reported, whereas NEs of six countries (Croatia, Greece, Israel, Italy, Latvia, and Lithuania) reported that CRAb are regularly isolated from patients in most hospitals, corresponding to an endemic situation (stage 5) (Figure 7 and Table 3).

Figure 7. Occurrence of carbapenem-resistant *A. baumannii* in European countries based on self-assessment by the national experts, March 2013



The stage designations for CRAb should be taken with caution for all 38 participating countries. Most NEs highlighted that the exact epidemiology of CRAb remains uncertain in their country, because at the time of the survey, surveillance and reporting of CRAb are not performed routinely in their country, and because fewer national reference laboratory structures for CRAb exist in European countries.

Table 3. Epidemiological stages of carbapenem-resistant *A. baumannii* in 38 European countries based on self-assessment by the national experts, March 2013

Country	Epidemiological stage for spread of CRA
Albania	1
Austria	1
Belgium	3
Bosnia and Herzegovina	1
Bulgaria	2b
Croatia	5
Cyprus	3
Czech Republic	4
Denmark	2b
Estonia	2a
Finland	1
France	3
Germany	4
Greece	5
Hungary	4
Iceland	0
Ireland	2a
Israel	5
Italy	5
Kosovo	3
Latvia	5
Lithuania	5
Luxembourg	1
Malta	1
Montenegro	0
Netherlands	1
Norway	1
Poland	2b
Portugal	4
Romania	2b
Serbia	2b
Slovakia	4
Slovenia	2a
Spain	3
Sweden	2a
the former Yugoslav Republic of Macedonia	1
Turkey	2b
United Kingdom	4

National management of carbapenemase-producing bacteria in Europe

The second section of the questionnaire collected information regarding notification to health authorities, existing national surveillance and reference laboratories and services, as well as guidance documents for reporting, surveillance, reference services and infection control measures at the national level.

National management of carbapenemase-producing *Enterobacteriaceae*

Table 4 summarises the available national guidance documents for the management of CPE, and existing surveillance and reference systems in the 38 participating countries.

Table 4. Available national documents on the management of carbapenemase-producing *Enterobacteriaceae* in 38 European countries, March 2013

Country	National system for surveillance	Officially nominated national reference laboratory	National recommendation or guideline for submitting isolates to national expert or reference laboratories	Agreed criteria or a policy for submitting isolates to national expert or reference laboratories[a]	National recommendation or obligation for reporting (notification) to health authorities	National recommendation or guideline on infection control measures	Comments	Reference or URL for recommendation or guideline on infection control measures
Albania		[d]						
Austria	•[b]	•	•	•	•[e]	•		http://www.analyse.eu/nationales-referenzzentrum/carbapenemasen.html
Belgium	•[b]	•	•	•	•[e]	•	Guidelines for infection control, prevention of cross-transmission and outbreak management under revision (Extension of guidelines for chronic sector and community)	http://www.nsih.be/surv_carba/carbapenemase_fr.asp
Bosnia and Herzegovina								
Bulgaria	•[c]	[d]	•		•[f]			
Croatia	•[b]	•	•	•	•[f]	•	Guideline for infection control available only for KPC positive patients. Guideline for all multidrug resistant bacteria in preparation.	
Cyprus	•[c]							
Czech Republic	•[c]	•	•	•	•[f]	•		http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c8/2012_6865_251011.html
Denmark	•[b]	•						

Country	National system for surveillance	Officially nominated national reference laboratory	National recommendation or guideline for submitting isolates to national expert or reference laboratories	Agreed criteria or a policy for submitting isolates to national expert or reference laboratories[a]	National recommendation or obligation for reporting (notification) to health authorities	National recommendation or guideline on infection control measures	Comments	Reference or URL for recommendation or guideline on infection control measures
Estonia	[g]						Guideline for infection control for multidrug resistant bacteria available only at hospital levels.	
Finland	● [c]	●	●	●	● [f]		Guideline for infection control in preparation.	
France	● [b]	●	●		● [f]	●	Results and guidelines for surveillance, early warning, infection control and outbreak management are regularly updated.	http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=372
Germany	● [b]	●		●		●		http://www.rki.de/DE/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Gramneg_Erreger.pdf
Greece	● [b]	●	●	●	● [f]	● [h]		http://www.keelpno.gr/el-gr/νοσήματαθέματαυγείας/πολυανθεκτικάπαθογόναστανοσοκομεία.aspx
Hungary	● [b]	●	●	●	● [f]	●		
Iceland	● [b]	●	●	●	● [f]	●		
Ireland	● [c]	●	●	●	● [f]	● [h]		http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,12922,en.pdf
Israel	● [c]	●			● [f]	●		http://www.old.health.gov.il/Download/pages/postacotic.pdf
Italy	● [b]	[d]			● [f, i]	●		http://www.trovanorme.salute.gov.it/renderNormsanPdf?anno=0&codLeg=45499&parte=1%20&serie=
Kosovo		●				● [h]		
Latvia	[g]	●			● [f]			
Lithuania	● [b]	●		●				
Luxembourg	● [c]	●	●	●	● [f]			
Malta	● [b]	●	●	●		● [h]		
Montenegro							A national reference laboratory is under development	

Country	National system for surveillance	Officially nominated national reference laboratory	National recommendation or guideline for submitting isolates to national expert or reference laboratories	Agreed criteria or a policy for submitting isolates to national expert or reference laboratories[a]	National recommendation or obligation for reporting (notification) to health authorities	National recommendation or guideline on infection control measures	Comments	Reference or URL for recommendation or guideline on infection control measures
Netherlands	●[b]	[d]	●	●	●[e]	●		www.wip.nl
Norway	●[c]	●	●	●	●[f]	●		http://www.fhi.no/dokumenter/96331178b9.pdf
Poland	●[c]	●	●	●	●[f]	●		http://www.antybiotyki.edu.pl/pdf/kpc-20120713.pdf
Portugal	●[c]	●	●	●	●[f]	●		http://www.dgs.pt/
Romania	[g]	●						
Serbia	●[b]	●						
Slovakia	●[b]	●			●[e]			
Slovenia	[g]	[d]	●	●		●		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
Spain	●[b]	●	●	●	●[e]			
Sweden	●[c]	●	●	●	●[f]	●		http://www.socialstyrelsen.se/smittskydd/sjukdomar/lagstiftningensfyrakategorier/smittsparningsplikt iga
the former Yugoslav Republic of Macedonia	●[c]	●			●[f]			
Turkey								
United Kingdom	●[b, c]	●	●	●		●	Guideline for infection control under revision.	http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/CarbapenemResistance/GuidanceOnCarbapenamProducers/

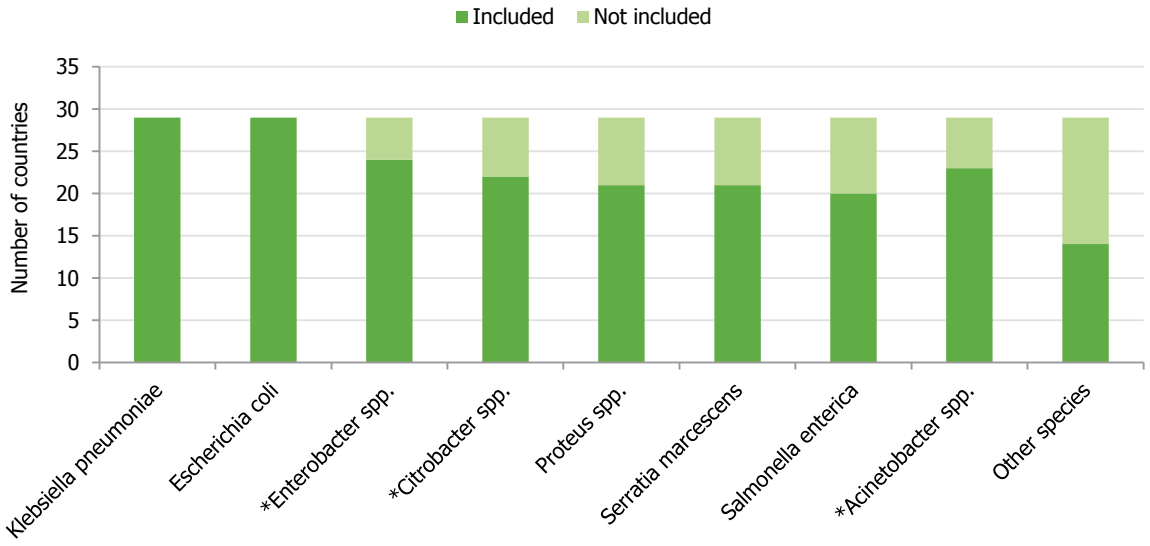
In the table cells, a dot signifies 'in place' and the absence of dot signifies 'absent'

[a] *Agreed criteria or policy (including MIC cut-off, species and resistance confirmation, epidemiological typing) to submit CPE isolates to a national reference laboratory (for the UK, only for Scotland);*
[b] *Voluntary participation of laboratories;*
[c] *Mandatory for all laboratories (for the UK, only mandatory in Scotland);*
[d] *Presence of a national expert laboratory that fulfils a similar role than the national reference laboratory;*
[e] *Voluntary notification to health authorities;*
[f] *Mandatory notification to health authorities;*
[g] *Country reporting carbapenem-resistant invasive isolates (*K. pneumoniae *and* E. coli*) to the European Antimicrobial Resistance Surveillance Network (EARS-Net);*
[h] *Only in case of outbreaks;*
[i] *Only for bacteremia cases;*

Surveillance

Twenty-nine of the 38 countries reported having a national surveillance system for CPE (Table 4). Nine countries (Albania, Bosnia and Herzegovina, Estonia, Kosovo, Latvia, Montenegro, Romania, Slovenia and Turkey) do not have a dedicated national surveillance system for CPE, of which four countries (Estonia, Latvia, Slovenia and Romania) report carbapenems-resistant invasive *K. pneumoniae* and *E. coli* from blood and cerebrospinal fluid (CSF) to EARS-Net. All Member States, Norway and Iceland participate and report to EARS-Net (Note: Croatia participated for the first time in the EARS-Net data collection in 2013 with current and retrospective data [38]). Thirteen countries with a national surveillance system for CPE reported that surveillance of CPE is mandatory for all laboratories and for an additional 16 countries, it is voluntary or best described as a sentinel system of individual laboratories. In the UK, surveillance of CPE is only mandatory in Scotland. All 29 existing national surveillance systems include *K. pneumoniae* and *E. coli* (Figure 8 and Table 5). Some national surveillance systems collect data on others species, i.e. *Enterobacter* spp., *Citrobacter* spp., *Proteus* spp., *Serratia marcescens*, *Salmonella enterica, Acinetobacter* spp. and *Pseudomonas aeruginosa* in their surveillance schemes (Figure 8 and Table 5). In general, national surveillance systems collect data about CPE from all clinical specimens (16 countries), from bloodstream isolates (33 countries), and from respiratory specimens (16 countries) and urine (16 countries). Other data (i.e. baseline demographic data, epidemiological data, incidence or incidence-density, type of resistance mechanism) are less frequently collected.

Figure 8. Bacterial species in the surveillance scheme of 29 European countries, March 2013



**In the UK, only the surveillance scheme of Scotland includes* Enterobacter *spp.,* Citrobacter *spp. and* Acinetobacter *spp. The surveillance schemes of England, Northern Ireland and Wales only include* Klebsiella *spp. and* E. coli*.*

Table 5. Bacterial species in the surveillance scheme by countries, March 2013

Country	*E. coli*	*K. pneumoniae*	*Enterobacter* spp.	*Citrobacter* spp.	*Proteus* spp.	*Serratia marcescens*	*Salmonella enterica*	*Acinetobacter* spp.	Others (e.g., *Pseudomonas aeruginosa*)
Albania									
Austria	•	•	•	•	•	•	•	•	•
Belgium	•	•	•	•		•		•	•
Bosnia and Herzegovina									
Bulgaria	•	•			•			•	•
Croatia	•	•	•	•	•	•	•	•	•
Cyprus	•	•	•	•	•	•	•	•	
Czech Republic	•	•	•	•	•	•	•		
Denmark	•	•	•	•	•	•	•	•	•
Estonia									
Finland	•	•	•	•	•	•	•	•	•
France	•	•						•	
Germany	•	•	•	•	•	•	•	•	•
Greece	•	•	•	•	•	•	•	•	
Hungary	•	•	•	•	•	•	•	•	•
Iceland	•	•	•					•	
Ireland	•	•	•	•	•	•	•		•
Israel	•	•	•	•	•	•	•		
Italy	•	•						•	
Kosovo	•	•	•	•	•	•	•	•	
Latvia									
Lithuania	•	•					•		
Luxembourg	•	•	•	•	•	•	•	•	•
Malta	•	•	•	•	•	•		•	•
Montenegro									
Netherlands	•	•	•	•	•	•	•		
Norway	•	•	•	•	•	•	•	•	•
Poland	•	•	•	•	•	•	•	•	
Portugal	•	•	•	•	•	•	•	•	•
Romania									
Serbia	•	•						•	
Slovakia	•	•	•	•	•	•	•	•	
Slovenia									
Spain	•	•	•					•	
Sweden	•	•	•	•	•	•	•		•
the former Yugoslav Republic of Macedonia									
Turkey									
United Kingdom	•	•	•	•				•	

In the table cells, a dot signifies 'included' and the absence of dot signifies 'not included' in the national surveillance scheme

National reference laboratories

Twenty-eight of the 38 countries reported having an officially nominated national reference laboratory (NRL) for CPE (Table 4). Five countries (i.e. Albania, Bulgaria, Italy, Slovenia and the Netherlands) did not have an officially nominated NRL for CPE, but had a national expert laboratory (NEL) that fulfilled a similar role. A NRL for CPE was under development in Montenegro. Only 21 countries with NRL or NEL also had national recommendations or guidelines for submitting isolates to the NEL or NRL, and had agreed criteria (including minimum inhibitory concentration cut-off, species, resistance confirmation and epidemiological typing) to submit isolates to the NEL or NRL. Ten countries with NRLs (Belgium, Bulgaria, Finland, Greece, Hungary, Ireland, Poland, Spain, Sweden and UK) reported that epidemiological typing is a routine requirement in outbreak situations. The 28 NRLs and five NELs reported collecting additional information when receiving CPE isolates from peripheral laboratories for reference analysis, such as date of specimen collection (100% of the cases), reason for submission (94%), type of specimen (94%), species identification (94%), antimicrobial susceptibility testing (AST) results (91%), basic demographic data (age and sex, 94%), site of infection (62%), etiological significance (i.e. colonisation versus infection, 56%), community versus healthcare-associated (53%), and in case of healthcare- associated, association with an outbreak (35%), but also travel history (47%), patient location within the hospital (56%), patient referral history (previous hospital admissions, 18%), mortality at 14 or 30 days after isolation of the incriminated pathogen (9%), severity of current disease (e.g., APACHE II or nurse dependency scores, 3%), underlying disease (e.g., Charlson comorbidity index, 3%).

Notification to health authorities

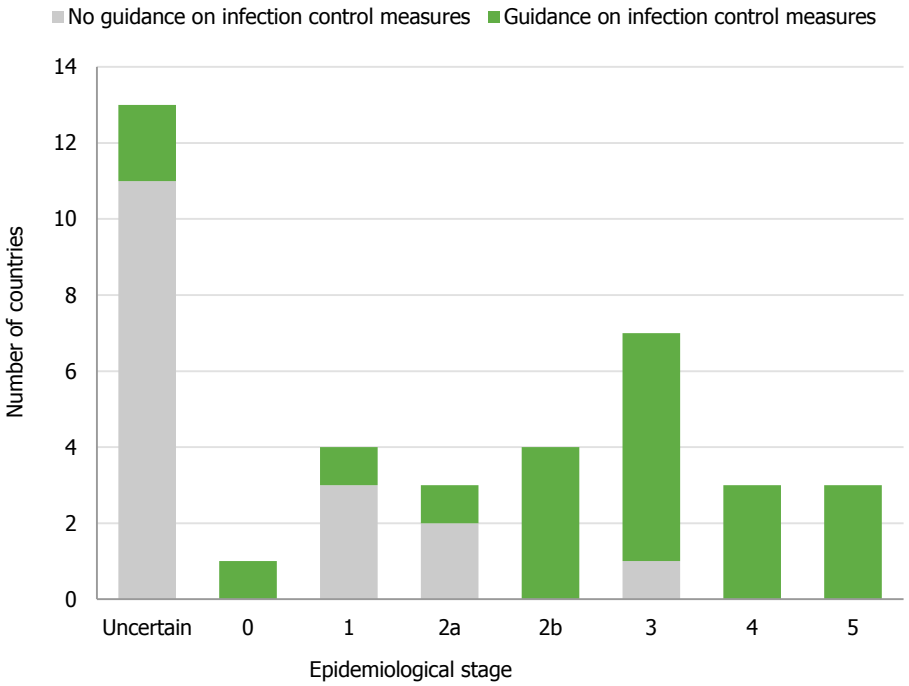
Twenty-three countries reported having a system to notify CPE cases to health authorities, mostly on a mandatory basis. Only five countries notified CPE cases on a voluntary basis (Table 4). A majority of countries declared reporting to national health authorities, whereas a minority of countries reported to regional, municipal health authorities or other bodies (i.e. tertiary hospital units). Both under-detection and under-reporting were highlighted by many NEs.

Infection prevention and control measures

Only 21 countries reported having national recommendations or guidelines on infection prevention and control measures to prevent the spread of CPE; Finland informed having such recommendations or guidelines in preparation (Table 4).

The epidemiological stage of 13 countries was considered to be uncertain. These countries had an average of 1.9 national management documents regulating surveillance and response structures in place and 11 of them still lacked national recommendations or guidelines on infection control measures to prevent the spread of CPE. The countries that were more certain about their epidemiological stages had on average 4.7 national management documents (p-value < 0.001; Wilcoxon Rank Sum Test) (Figure 2, Figure 9 and Table 4).

Figure 9. Presence or absence of national recommendations or guidelines on infection control measures to prevent the spread of carbapenemase-producing *Enterobacteriaceae* by epidemiological stage, 2013



National management of carbapenem-resistant *Acinetobacter* spp. (CRA)

Less information is available on the level of management of CRA compared to CPE (Table 6) and surveillance and reporting of CRA are not performed routinely in the participating countries. Twenty-two of 38 countries reported performing some type of surveillance for CRA (Table 5 and 6 and Figure 8). In the UK, surveillance of CRA is only performed in Scotland.

Only 21 countries reported having an officially nominated NRL for CRA (Table 6). Austria, Bulgaria, Finland, Ireland, Italy, the former Yugoslav Republic of Macedonia, the Netherlands and Slovenia did not have an officially nominated NRL for CRA, but reported that a NEL fulfilled a similar role. A NRL for CRA is under development in Montenegro. Six countries with NRLs (Belgium, Bulgaria, Greece, Hungary, Norway and UK) reported that epidemiological typing is a requirement in outbreak situations.

Ten countries reported having a system to notify CRA cases to health authorities (Table 6). Both under-detection and under-reporting were reported by many NEs.

Only two countries (Germany and Iceland) reported having national recommendations or guidelines on infection prevention and control measures to control and prevent the spread of CRA. Three countries (France, Slovenia and Sweden) specifically reported that there are no such recommendations or guidelines in their country and three countries (Croatia, Finland and Poland) reported having such recommendations or guidelines in preparation (Table 6).

Table 6. National management of carbapenems-resistant *Acinetobacter* spp. in 38 European countries, March 2013

Country	National system for surveillance	Officially nominated national reference laboratory	Epidemiological typing in outbreak situation[a]	National recommendation or obligation for reporting (notification) to health authorities	National recommendation or guideline on infection control measures	Comments
Albania						
Austria	●	[b]				
Belgium	●	●	●			
Bosnia and Herzegovina						
Bulgaria	●	[b]	●	●		
Croatia	●					Guidelines for all MDR in preparation.
Cyprus	●					
Czech Republic		●				
Denmark	●	●				
Estonia						
Finland	●	[b]				Guidelines for infection control in preparation.
France	●	●		●		No guidelines for CRA
Germany	●	●			●	
Greece	●	●	●	●		
Hungary	●	●	●	●		
Iceland	●	●		●	●	
Ireland		[b]				
Israel		●				
Italy	●	[b]				
Kosovo	●	●				
Latvia						
Lithuania		●				
Luxembourg	●	●				
Malta	●	●				
Montenegro						
Netherlands		[b]		●		
Norway	●	●		●		
Poland	●	●	●	●		Guidelines for infection control in preparation.
Portugal	●	●		●		
Romania		●				
Serbia	●	●				
Slovakia	●	●				
Slovenia		[b]				No guidelines for CRA
Spain	●					
Sweden		●				No guidelines for CRA

Country	National system for surveillance	Officially nominated national reference laboratory	Epidemiological typing in outbreak situation[a]	National recommendation or obligation for reporting (notification) to health authorities	National recommendation or guideline on infection control measures	Comments
the former Yugoslav Republic of Macedonia		[b]		•		
Turkey						
United Kingdom	•[c]	•	•			

In the table cells, a dot signifies 'in place' and the absence of dot signifies 'absent'

a national recommendation or national guideline prescribing a clear demand for epidemiological typing for CRA in outbreak situations
b Presence of a national expert laboratory that fulfils a similar role than the national reference laboratory.
c for Scotland only

Laboratory capacity for reference investigation of carbapenemase-producing *Enterobacteriaceae* in Europe

In preparation of the capacity building workshop on the identification and confirmation of CPE, the third section of the questionnaire investigated the capacity for reference services and for expert advice, as well as for the identification and confirmation methods used in the participating laboratories. The results are summarised in Tables 7 and 8.

In brief, most participating laboratories reported providing reference services that are additional investigations not normally carried out at local diagnostic laboratories. They also reported providing recommendations towards containment and control of transmission of CPE as well as for treatment of patients infected with CPE (Table 7).

All of the NELs, with the exception of Bosnia and Herzegovina, reported using standardised common phenotypic methods for antimicrobial susceptibility testing such as the Etest or other gradient strips, and regular disk diffusion testing. Other methods including automated test systems, microdilutions, the Hodge test, combo disk and double-disk diffusion were also used by approximately 50% of the NELs. The most recently developed test, the Carba NP test was currently only used by seven NELs [29,30]. Single and multiplex PCR were the most common molecular techniques used for identification and confirmation of carbapenemase production. Real-time PCR, product sequencing or newly developed ligation amplification techniques were seldom used by NELs (Table 8).

The laboratory capacity assessment highlighted that the NRLs and NELs are under pressure with regards to their budget and personnel.

Table 7. Reference services provided by the participating laboratories

Country	Reference services[a]				Expert advice[b]	
	Species identification	Antimicrobial susceptibility testing (AST)	Genetic resistance determinant	Molecular typing	Public health advice on infection control	Clinical advice for treatment
Albania						
Austria	●	●	●	[c]	●	●
Belgium	●	●	●	[c]	●	●
Bosnia and Herzegovina						
Bulgaria	●	●	●	[c]		●
Croatia	●	●	●	[c]	●	●
Cyprus					●	●
Czech Republic	●	●	●	●	●	●
Denmark	●	●	●	[c]	●	●
Estonia					●	
Finland	●	●	●	●		
France	●		●	[c]	●	●
Germany	●	●	●	[c]	●	●
Greece	●	●	●	[c]	●	
Hungary	●	●	●	●	●	●
Iceland	●	●				●
Ireland	●	●	●	[c]	●	●
Israel	●	●	●	[c]	●	
Italy	●	●	●	●	●	●
Kosovo	●	●	●		●	●
Latvia	●	●				
Lithuania	●	●	●			●
Luxembourg	●	●	●			
Malta	●	●	●		●	●
Montenegro					●	●
Netherlands			●			
Norway	●	●	●	[c]	●	●
Poland	●	●	●	[c]	●	●
Portugal	●	●	●	[c]		
Romania	●	●	●			
Serbia	●	●			●	●
Slovakia	●	●	●			●
Slovenia	●	●	●	●	●	●
Spain	●	●	●	●	●	●
Sweden	●	●	●	●	●	●
the former Yugoslav Republic of Macedonia	●	●	●			
Turkey						
United Kingdom	●	●	●	●	●	●

a Reference services are additional investigations not normally carried out at local diagnostic laboratories
b Provision of recommendations towards containment and control of transmission of CPE and for treatment of patients infected with CPE
c Only for outbreaks

Table 8. Methods used by the participating laboratories for identification and confirmation of carbapenem-resistance of the submitted carbapenemase-producing *Enterobacteriaceae* isolates

	Phenotypic identification									Genotypic identification and/or confirmation					Chromatographic or spectrometric identification and/or confirmation	
Country	Gradient strips (e.g., E-test)	Disk diffusion	Double-disk diffusion	Hodge test	Combo disk	Microdilution	Agar dilution	Carba NP test	Automated test systems	Single PCR	Multiplex PCR	Real-time PCR	Product sequencing	Ligation techniques (e.g. Check-Points)	MALDI-TOF	Others or none
Albania		●				●			●							●
Austria	●	●	●	●	●					●	●		●	●	●	
Belgium	●	●			●	●		●	●	●	●	●	●	●	●	
Bosnia and Herzegovina									●							●
Bulgaria	●	●	●	●			●		●	●	●	●				●
Croatia	●	●	●	●		●			●	●			●			●
Cyprus	●								●							●
Czech Republic	●	●	●			●				●	●	●	●		●	
Denmark	●	●		●	●	●		●			●		●			●
Estonia	●	●	●							●	●	●			●	
Finland	●	●	●		●					●	●		●			●
France	●						●	●			●		●			●
Germany	●	●	●	●	●	●				●	●		●	●		●
Greece	●	●	●	●						●			●			●
Hungary	●	●	●	●	●	●	●	●		●	●		●			●
Iceland	●	●	●	●	●											●
Ireland	●	●			●					●	●	●				●
Israel	●	●		●		●	●	●	●	●	●	●	●			
Italy	●	●	●		●	●			●	●	●	●	●		●	
Kosovo		●							●					●		●
Latvia	●	●		●						●						●
Lithuania	●	●		●	●	●			●	●	●					●
Luxembourg	●	●									●	●			●	
Malta	●			●	●				●							●
Montenegro		●							●	●		●				●
Netherlands	●			●	●						●					●
Norway	●	●		●	●				●	●	●	●	●	●		●[a]
Poland	●	●	●		●	●	●		●	●	●		●		●	
Portugal		●	●			●				●			●			●
Romania	●	●	●	●		●			●	●	●	●	●			●
Serbia	●	●		●		●	●		●							●
Slovakia				●		●				●		●	●		●	
Slovenia	●	●		●	●			●	●	●	●		●		●	
Spain	●	●	●	●	●	●	●	●	●	●	●		●			●
Sweden	●	●			●					●		●		●	●	
the former Yugoslav Republic of Macedonia	●	●	●	●					●	●	●	●				●
Turkey	●	●							●	●	●					●
United Kingdom	●			●			●			●	●			●	●	

[a] *For Norway, spectrophotometric analysis for carbapenem hydrolysis are performed*

Limitation of the survey

The NEs completed the questionnaire to the best of their knowledge and, in some cases, based on their knowledge of the national clinical or microbiological data. As only one NE was chosen per country, the answers of the NEs could represent subjective assessments that may have underestimated the exact extent of the spread of CPE and CRAb.

Under-detection and under-reporting pointed out by respondents in several countries, lead to uncertainty about the exact epidemiological stage of CPE and CRAb. In particular, this applied when CPE had been reported to or from other countries but NEs could not independently verify existing sources in their own country. Under-detection and under-reporting of CPE and CRAb coincided with weaker reference laboratory infrastructures and the absence of national recommendations for submission to NRLs and for reporting to health authorities, thus confirming that the exact extent of the occurrence of CPE and CRAb in Europe is still underestimated. At the same time, countries with strict screening policies and good surveillance are more likely to report advanced epidemiological stages also affecting comparability of countries in this assessment.

The answers of the NEs are based on their knowledge of the epidemiological situation of CPE and CRA at the time of the survey (8 February–14 March 2013). This situation might have evolved and be different at the time of the publication of this report. If so, and if informed by the NEs, the changes are presented in the discussion.

Discussion

The rapid and global expansion of carbapenem-resistant Gram-negative bacteria (i.e. carbapenemase-producing *Enterobacteriaceae* and carbapenems-resistant *A. baumannii*) during the past decade is a worrisome trend and a threat to healthcare and patient safety in Europe and globally. The consequences for patients infected with these bacteria are fewer options for treatment, and increased morbidity and mortality [7-9]. Given that there are few novel antimicrobial agents that are likely to become available for clinical use in the short to medium term, the risks to public health are not difficult to fathom [31].

The overarching goal of the EuSCAPE project is to generate comprehensive data about carbapenemase-producing bacteria, to improve the understanding of their epidemiology and occurrence in Europe, to stimulate laboratory capacity for diagnosis and surveillance at the national and European level, and to develop a laboratory-based network in EU Member States, EEA countries and EU enlargement countries, that will be capable of providing information on the prevalence of carbapenemase-producing bacteria in Europe.

The results of the present survey, carried out in February-March 2013, show that CPE are continuously spreading in European hospitals and that the epidemiological situation for CPE has deteriorated over the past three years. Among the 30 countries that participated in both assessments (2010 and 2013 assessments), 16 countries reported a higher epidemiological stage (Table 2). Croatia, Ireland and Malta who had only reported sporadic occurrence of CPE in 2010 are now witnessing regional or inter-regional spread, or even an endemic situation.

Malta moved from having sporadic cases to an endemic situation, although because of its small size, the intermediate epidemiological stages have little relevance. The influx of injured refugees from Libya in 2011 is believed to have contributed to an increase in OXA-48-producing *Enterobacteriaceae* (M. Borg, personal communication, April 2013).

In Italy, a sporadic occurrence of VIM-producing *Enterobacteriaceae* from 2008, accentuated by a single hospital outbreak, has been overtaken by the wide dissemination of KPC-producing *K. pneumoniae* strains to many healthcare institutions [32-34]. Italy is now witnessing an endemic situation of CPE.

In 2010, Hungary was only concerned by a single clone of KPC-2-producing *K. pneumoniae* that had attained regional distribution, whereas at the same time, VIM-4-producing strains were only reported sporadically. In 2013, VIM-4-producing strains have spread nationwide [35-37].

In Poland, retrospective laboratory studies demonstrated that the wide spread of VIM-producing strains occurring at the time of the survey had not been taken into account when rating the occurrence and spread of CPE in the country. While Poland only reported regional spread of CPE in March 2013, the epidemiological stage of Poland was corrected to being inter-regional spread of CPE based on these retrospective laboratory studies.

Although data collected by EARS-Net are limited to invasive (i.e. blood and CSF) isolates and EARS-Net does not collect data on carbapenemase production in carbapenem-resistant isolates, the latest EARS-Net data on carbapenem susceptibility of invasive *E. coli* and *K. pneumoniae* isolates support the results of the EuSCAPE survey. The population-adjusted EU/EEA mean percentage of carbapenem resistance in invasive *K. pneumoniae* isolates increased significantly over the past four years from 3.2% in 2009 to 6.2% in 2012. In comparison, the population-adjusted EAU/EEA mean percentage of carbapenem resistance in invasive *E. coli* isolates remained very low (0.1%) in 2012 [38]. During the past four years, Cyprus, Greece, Hungary, Italy, Malta and Romania reported the highest percentages of carbapenem resistance in invasive *K. pneumoniae* isolates to EARS-Net. With the exception of Romania, this is in accordance with the results of the EuSCAPE self-assessments of inter-regional spread (Hungary) or the endemic situation (Greece, Italy and Malta) in these countries [38]. Romania reported only sporadic occurrence of CPE in the EuSCAPE survey.

Overall, KPC-producing *Enterobacteriaceae* still have the widest distribution among CPE in Europe, but rising numbers of OXA-48-producing isolates are reported, making OXA-48 the most frequently detected carbapenemase in Belgium, France, Malta and Spain (Figures 4 and 5) [39-41]. Most of the OXA-48-producing isolates observed in France are associated with travel and/or hospitalisation in North African countries; these countries are facing endemic situations of OXA-48-producing strains [42-45]. Despite the media attention that NDM has received when associated with introductions from the Indian subcontinent, the current numbers of reports by most European countries are still relatively modest compared to the other carbapenemases [46]. The United Kingdom, however, continues to report more NDM-producing isolates than other European countries [12,13,28].

Results from this survey also indicate that CRAb are more widely disseminated in Europe than CPE (Figures 2, 3 and 7). Because surveillance and reporting of CRAb are not performed routinely, and because fewer national reference laboratory structures for CRA exist in European countries, the exact epidemiology of CRA in Europe remains uncertain. A large Europe-wide initiative - the ECDC Point Prevalence Survey (PPS) on healthcare-associated infections (HAI) and antimicrobial use in acute care hospitals conducted in 2011–2012 in more than 1 000 hospitals in 30 European countries showed that, while *Acinetobacter* spp. only accounted for

3.6% of all microorganisms isolated in HAI, 81.2% of all *Acinetobacter* spp. isolates reported in were non-susceptible to carbapenems [47]. In comparison, whereas *E. coli* and *Klebsiella* spp. together accounted for 24.6% of all microorganisms isolated in HAI, only 9.3% of these isolates were non-susceptible to carbapenems.

Another line of concern is the increasing number of reports of CRAb outbreaks and the emergence of new CRAb clones in European hospitals [4,6,16-27]. When asked which bacterial species the NEs would consider as a priority in an active surveillance of antimicrobial susceptibility in their respective country, *Acinetobacter* spp. scored third as most important after *E. coli* and *K. pneumoniae*. Due to the obvious need to assess the level of resistance in *Acinetobacter* spp. in Europe, EARS-Net is currently exploring the feasibility of including this bacterium in its surveillance panel. EARS-Net has been piloting the collection of susceptibility data for all *Acinetobacter* spp. isolates from bloodstream infections since January 2013 (2012 data), regardless of the sub-species identification as *A. baumannii*, *A. nosocomialis* and *A. pittii*. This pilot project will end on 31 December, 2014. As of September 2013, eighteen of the 30 EARS-Net participating countries were able to report susceptibility data for *Acinetobacter* spp. in 2012. Large inter-country variations in the percentage of carbapenem-resistant *Acinetobacter* spp. isolates were noted. Generally, high resistance percentages were reported from south-eastern and southern Europe compared to northern and western Europe, where low percentages or no isolate with carbapenem resistance were reported [38]. With a few exceptions, the percentages of carbapenem-resistant *Acinetobacter* spp. reported to EARS-Net for 2012 was coherent with the self-assessment of CRAb by the NEs in the EuSCAPE project. However, the inter-regional spread reported to EuSCAPE by the UK and Germany was not reflected in the *Acinetobacter* spp. data reported to EARS-Net, and the high percentages of carbapenem resistance reported to EARS-Net by Bulgaria and Romania were not reflected in the EuSCAPE self-assessment. As resistance data in *Acinetobacter* spp. have only been collected by EARS-Net for less than one year, and because only a small number of isolates were reported from most countries, data interpretation and comparison with the EuSCAPE self-assessment should be made with caution.

The increasing availability of recommendations or guidelines on infection control measures to prevent the spread of CPE (Table 4) is an indication that public health authorities are gradually understanding the need for prevention and control of CPE. Still, 17 of the surveyed countries lacked such guidance in 2013 and the same number of countries lacked relevant guidance for submission of isolates to national reference or expert laboratories [28].

Only 22 of the 38 countries reported performing some type of surveillance for CRA, with the consequence that the exact epidemiology of CRAb in Europe still remains uncertain. Although there is a consensus among European experts that CRAb is increasingly spreading in Europe, only two countries reported having specific national recommendations or guidelines on infection prevention and control measures to prevent the spread of CRAb. This highlights the need to fully assess the level of resistance in *Acinetobacter* spp. in Europe, and countries that participated to the ECDC PPS and the EARS-pilot gained an insight of the situation of CRA in their country, e.g. Poland is upgrading its staging of CRAb from sporadic hospital outbreaks to inter-regional spread.

Conclusions and perspectives

The key to success in preventing the establishment of CPE and CRAb is early detection through good diagnostic practices, and containment of spread through patient and contact screening as well as infection prevention and control measures [5,13]. Antibiotic stewardship might be considered as a preventive measure but its role in the development of carbapenem resistance and in the management of outbreaks of CPE in hospitals is still not fully understood [5].

The assessment of the existing laboratory capacity and the answers from the NEs about the workload and constraints encountered at the national level demonstrated that there are gaps in the European laboratory capacity and an urgent need for an upgrading of laboratory standards to enable active surveillance. The assessment also provided important information for the preparation of a curriculum for a capacity building workshop on the identification and confirmation of CPE that took place on 5-6 September 2013 in Vari, Greece. The capacity building workshop for one national laboratory expert from each participating country sought to provide training in various diagnostic techniques, as well as to promote a unified approach for the identification and confirmation of CPE in Europe. This shall enhance existing capacities in participating NRLs and NELs and pave the way for a comprehensive European-wide enhanced surveillance system.

Although, there is an urgent need for a coordinated European effort on early diagnosis, active surveillance, and guidance on infection prevention and control measures, the EU is facing serious economic challenges due to the financial crisis that affects some Member States. These challenges were highlighted by most NEs, as they expressed their concerns that the ability to carry out necessary reference services and/or the ability to build the capacity for reference services in their country were hindered by budget limitations for staff, consumables, and necessary investments. To the question 'did your budget suffer from austerity measures imposed on your laboratory during the last years', the NEs answered that indeed their budget suffered and that these cost savings threatened the ability to control the spread of carbapenemase-producing bacteria in their country.

The capacity building workshop therefore promoted easy-to-use and cost-effective methods and techniques for the identification and confirmation of CPE and carpanemase production such as commercially available and in-house disk diffusion, double-disk diffusion and combination disk testing, as well as the Carba NP I & II tests for phenotypic identification. For the molecular identification, a set of in-house primers for single PCR for the four major carbapenemase was designed and suggested to all NELs.

The first step towards a laboratory-based network for CPE detection in Europe is to conduct a structured survey (including an external quality assessment) by collecting isolates of CPE and data on CPE-related infections in 38 European countries, which is scheduled for November 2013–April 2014. Because public health budgets continue to be under pressure across Europe, this structured survey will promote easy to use and cost-effective methods and techniques for the identification and confirmation of CPE and carpanemase production.

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Annex 2: Questionnaire

PART I (13 questions): Knowledge and awareness about the current epidemiology of carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *Acinetobacter* spp. (CRA) in your country

1. You have been identified as the National Expert, please choose for which country *(pull-down list with countries)*
2. Please also state your e-mail address
3. Would you be aware of the current epidemiological situations of carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *Acinetobacter* spp. (CRA) in your country?
   For CPE
   - ❑ Yes
   - ❑ No

   For CRA
   - ❑ Yes
   - ❑ No

   Free Text
4. In your country and based on your knowledge, how would you describe the situation with regards to the epidemiology of carbapenemase-producing *Enterobacteriaceae* (CPE)*?*
   Please choose the current level of occurrence in your country based on the staging system below. *(*outbreak defined as two or more epidemiologically associated cases with indistinguishable geno- or phenotype)*

Stage	Definition of stage
Stage 0	no cases reported
Stage 1	only single cases reported (sporadic occurrence)
Stage 2a	a single hospital outbreak reported*
Stage 2b	more than one hospital outbreak reported but outbreaks are/were epidemiologically unrelated or caused by different clones (no autochthonous inter-institutional transmission)
Stage 3	more than one epidemiologically-related hospital outbreak reported but confined to the same region or health district, (regional autochthonous inter-institutional transmission)
Stage 4	multiple epidemiologically-related hospital outbreaks reported from different regions or health districts (inter-regional autochthonous inter-institutional transmission)
Stage 5	most hospitals in a country are constantly seeing cases admitted from autochthonous sources

5. If you can discriminate between the most important resistance determinants among carbapenemase-producing *Enterobacteriaceae* (CPE), i.e. KPC, NDM, VIM, OXA-48 and IMP), please also indicate their level of occurrences in *Enterobacteriaceae*. See question 4 for the description of the various stages.

Stage	KPC	NDM	VIM	OXA-48	IMP
Stage 0					
Stage 1					
Stage 2a					
Stage 2b					
Stage 3					
Stage 4					
Stage 5					

6. Do you have knowledge about the introduction of patients with CPE from another country to hospitals in your country?
   - ❑ Yes
   - ❑ No
7. If yes, what was (were) the year(s), the resistance types(s) and the countries of origin (provide reference if published)?
   - ❑ Year
   - ❑ Resistance type (e.g. KPC, NDM, etc.)
   - ❑ Country of origin
   - ❑ Reference (if published)

   - ❑ Year
   - ❑ Resistance type (e.g. KPC, NDM, etc.)
   - ❑ Country of origin
   - ❑ Reference (if published)

   - ❑ Year
   - ❑ Resistance type (e.g. KPC, NDM, etc.)
   - ❑ Country of origin
   - ❑ Reference (if published)

8. If there were more than 3 events, please list the year, resistance type and country of origin (e.g. 2009, NDM, India, etc.)

   Free Text

9. Do you have knowledge about patients with CPE who have been referred from your own country to hospitals outside your country?
   - ❑ Yes
   - ❑ No

10. If yes, what was (were) the year(s), the resistance types(s) and the countries of origin (provide reference if published)?
    - ❑ Year
    - ❑ Resistance type (e.g. KPC, NDM, etc.)
    - ❑ Country of origin
    - ❑ Reference (if published)

    - ❑ Year
    - ❑ Resistance type (e.g. KPC, NDM, etc.)
    - ❑ Country of origin
    - ❑ Reference (if published)

    - ❑ Year
    - ❑ Resistance type (e.g. KPC, NDM, etc.)
    - ❑ Country of origin
    - ❑ Reference (if published)

11. If there were more than 3 events, please list the year, resistance type and destination country (e.g. 2008, NDM, India, etc.)

    Free Text

12. In your country, which species do you believe is the most predominant (most frequent) among the CPE:
    - ❑ *Escherichia coli*
    - ❑ *Klebsiella* spp.
    - ❑ *Enterobacter* spp.
    - ❑ *Citrobacter* spp.
    - ❑ *Proteus* spp.
    - ❑ *Serratia marcescens*
    - ❑ *Salmonella enterica*
    - ❑ All of the above
    - ❑ Other, please specify

    Free text

13. In your country and based on your knowledge, how would you describe the situation with to the epidemiology of carbapenem-resistant *Acinetobacter* spp. (CRA)? Please choose for CRA the current level of occurrence in your country based on the staging system below. *(*outbreak defined as two or more epidemiologically associated cases with indistinguishable geno- or phenotype)*

Stage	Definition of stage
Stage 0	no cases reported
Stage 1	only single cases reported (sporadic occurrence)
Stage 2a	a single hospital outbreak reported*
Stage 2b	more than one hospital outbreak reported but outbreaks are/were epidemiologically unrelated or caused by different clones (no autochthonous inter-institutional transmission)
Stage 3	more than one epidemiologically-related hospital outbreak reported but confined to the same region or health district, (regional autochthonous inter-institutional transmission)
Stage 4	multiple epidemiologically-related hospital outbreaks reported from different regions or health districts (inter-regional autochthonous inter-institutional transmission)
Stage 5	most hospitals in a country are constantly seeing cases admitted from autochthonous sources

PART II (22 questions): Information on reporting to health authorities, surveillance scheme and reference laboratory services in your country

A. Reporting

1. In your country, is there a national recommendation or obligation for reporting (**notification of health authorities**) if patients with CPE and CRA have been identified by diagnostic laboratories? Note: a national recommendation, guideline or obligation is issued or supported by a national body (ministry, national institute of health or reference centre) or professional organisation (society of microbiology etc.)

   For CPE
   - ❑ Yes
   - ❑ No

   For CRA
   - ❑ Yes
   - ❑ No

2. If yes, is the reporting. (tick more than one, if applicable)
   - ❑ voluntary for all laboratories (private and hospital laboratories)?
   - ❑ mandatory for all laboratories (private and hospital laboratories)??
   - ❑ mandatory for outbreaks only ?

3. Who receives these reports?
   - ❑ regional or municipal health authority
   - ❑ national health authority
   - ❑ other

   Free Text

4. Please provide URL/web address of guideline or document about the recommendation/obligation to report
5. Are you convinced that there is substantial under-detection in diagnostic laboratories?

   For CPE:
   - ❑ Yes
   - ❑ No

   For CRA:
   - ❑ Yes
   - ❑ No

6. Are you convinced that there is substantial under-reporting at the national level

   For CPE:
   - ❑ Yes
   - ❑ No

   For CRA:
   - ❑ Yes
   - ❑ No

7. In your country, is there a national recommendation or guideline specifying measures **for infection control** in case a patient or patients with CPE or CRA are reported?
   - ❑ Yes, for single cases
   - ❑ Yes, in case of outbreaks
   - ❑ No

   Free Text

8. Please provide URL/web address of guideline or document about the advice to recommended infection control procedures (if applicable).

B. Surveillance

9. n your country, do you have a national system **for surveillance** of CPE or CRA?
   - ❑ Yes
   - ❑ No

10. If yes, what are the incentives for participation?
    - ❑ participation is voluntary and is best described a sentinel system of individual laboratories
    - ❑ participation is mandatory for all laboratories

11. For what species do you do surveillance? (please tick more than one box, if applicable)
    - ❑ *Escherichia coli*
    - ❑ *Klebsiella* spp.
    - ❑ *Enterobacter* spp.
    - ❑ *Citrobacter* spp.
    - ❑ *Proteus* spp.
    - ❑ *Serratia marcescens*
    - ❑ *Salmonella enterica*
    - ❑ *Acinetobacter* spp.
    - ❑ Other, please specify

    Free Text

12. What information is collected through this surveillance system? (please tick more than one, if applicable)
    - ❑ proportion of carbapenemase-producing or carbapenem-resistant isolates among defined species isolated of **all clinical specimens** received by the laboratories
    - ❑ proportion of carbapenemase-producing or carbapenem-resistant isolates among defined species isolated from **bloodstream infections**
    - ❑ proportion of carbapenemase-producing or carbapenem-resistant isolates among defined species isolated from **respiratory specimens**
    - ❑ proportion of carbapenemase-producing or carbapenem-resistant isolates among defined species isolated from **urine**
    - ❑ **baseline demographic data** of patients from which carbapenemase-producing and carbapenem-resistant isolates were isolated
    - ❑ **epidemiological details** (i.e., hospital or community onset, previous hospital stay, previous travel outside the country, exposure to animal or food products, nursing home care, etc.)
    - ❑ **incidence or incidence-density** of carbapenemase-producing and carbapenemase-resistant isolates per admission to hospitals or per number of inpatient-days
    - ❑ **type of resistance mechanism** for all reported cases

13. If you handle different sampling frames depending on species (e.g. different sources or collect different information), please explain shortly in the text box

14. Please provide URL/web address of guideline or document (URL/website) about the recommendation to perform surveillance.

C. Reference services

15. In your country, do you have a national recommendation or guideline on submitting isolates of CPE or CRA to **national expert/reference laboratories**?

    - ❑ Yes
    - ❑ No

    Free Text

16. Please provide URL/web address of guideline or document about the recommendation to submit isolates of CPE and/or CRA to national expert/reference laboratories.

17. If yes, to which species does this policy apply?
    - ❑ *Escherichia coli*
    - ❑ *Klebsiella* spp.
    - ❑ *Enterobacter* spp.
    - ❑ *Citrobacter* spp.
    - ❑ *Proteus* spp.
    - ❑ *Serratia marcescens*
    - ❑ *Salmonella enterica*
    - ❑ *Acinetobacter* spp.
    - ❑ All of the above
    - ❑ Other,

    Please specify **Free Text**

18. In your country, do you have an officially nominated **national reference laboratory** for CPE and/or CRA

    For CPE:

    - ❑ Yes
    - ❑ No

    For CRA:

    - ❑ Yes
    - ❑ No

19. In your country, do you have agreed criteria or a policy (such as minimum inhibitory concentration cut-off) **for submitting isolates of CPE or CRA** to national experts or reference laboratories for reference services (species confirmation, resistances confirmation, epidemiological typing)?
    - ❑ Yes
    - ❑ No

20. Please provide URL/web address of guideline or document (URL/website) about the agreed criteria to submit isolates of CPE and CRA to national expert or reference laboratories.

21. Does your national recommendation or guideline prescribe a clear demand for epidemiological typing for CPE and CRA in outbreak situations?

    For CPE:

    - ❑ Yes
    - ❑ No

    For CRA:

    - ❑ Yes
    - ❑ No

22. In your country, what information is provided by the submitting laboratory when an isolate is sent for reference services in terms of epidemiological, clinical and microbiological detail? (please tick more than one box if applicable)
    - ❑ reason for isolate submission
    - ❑ date of specimen collection
    - ❑ type of specimen incl. screening sample
    - ❑ site of infection
    - ❑ species identification
    - ❑ antimicrobial susceptibility test (AST) results
    - ❑ basic demography (age, sex) of patients
    - ❑ epidemiological context (community onset or hospital acquisition)
    - ❑ and if hospital acquisition, size of the transmission chain (outbreak)
    - ❑ travel history
    - ❑ patient location within hospital
    - ❑ Patient transfer history (through different wards)
    - ❑ mortality at 14 or 30 days after isolation of the incriminated pathogen
    - ❑ severity of disease
    - ❑ underlying diseases
    - ❑ Other, please specify

    Free text

PART III (26 questions): Laboratory capacity assessment

A. Participation in a European laboratory-based study on the occurrence of CPE and CRA

1. Which bacterial species would you give priority to be included in a more active surveillance in your country? Please rank the following species from 1 to 8, where 1 is the least important and 8 the most important.
    - ❑ *Escherichia coli*
    - ❑ *Klebsiella* spp.
    - ❑ *Enterobacter* spp.
    - ❑ *Citrobacter* spp.
    - ❑ *Proteus* spp.
    - ❑ *Serratia marcescens*
    - ❑ *Salmonella enterica*
    - ❑ *Acinetobacter* spp.

2. Would you find it desirable if you could directly upload your results and information and receive immediate feedback in the future?
    - ❑ Yes
    - ❑ No

3. In case of your participation in a European network, would you deem it important to be included into an external quality assurance exercise (EQA) and regularly receive a panel of well-characterised strains of particular public health importance?
    - ❑ Yes
    - ❑ No

4. Do you think that you can identify an appropriate number of laboratories in your country (depending on the size of your country, whereas the appropriate number of participating laboratories would be a minimum of 1 for small countries (<2 million inhabitants), a minimum of 10 for medium countries (2-15 million inhabitants) and a minimum of 20 for large countries (>15 million inhabitants)) that could collect a finite number of clinical isolates of CPE and CRA and epidemiological data from source patient during the structured survey from October 2013 until March 2014?
    - ❑ Yes
    - ❑ No

    Free text

B. Preparation for laboratory capacity building: details about your own laboratory

5. Does your laboratory provide "reference services" for CPE and/or CRA to other laboratories in your country? *Note: Reference services are additional investigations not normally carried out at local diagnostic laboratories.*

   For CPE

   - ❑ Yes
   - ❑ No

   For CRA

   - ❑ Yes
   - ❑ No

6. If yes, what are the reasons that your laboratory provides reference services for CPE and CRA? (please tick more than one box if applicable)
   - ❑ You have acknowledged expertise and competence in the field
   - ❑ You have been nominated by governmental bodies to function as a reference centre
   - ❑ You have been nominated by governmental bodies to function in the role the expert for epidemiology and surveillance for CPE and/or CRA
   - ❑ Your laboratory is part of a governmental institution that includes the National Institute for Public Health

   Free text

7. How are your references services for CPE and/or CRA reimbursed? (please tick more than one box if applicable)
   - ❑ by the government
   - ❑ by the client (sending laboratory or hospital)
   - ❑ not reimbursed
   - ❑ others, please specify

   Free text

8. What do these reference services include? (please tick more than one box if applicable)
   - ❑ Species identification and confirmation
   - ❑ repeat antimicrobial susceptibility testing and confirmation
   - ❑ Molecular typing routinely
   - ❑ Molecular typing in cases of outbreak
   - ❑ Others, please specify)

   Please specify **free text**

9. In terms of public health advice, do you or someone else in your reference laboratory provide clients with recommendations towards containment and control of transmission of CPE and/or CRA?
   - ❑ Yes
   - ❑ No

10. In terms of clinical advice, do you or someone else in your reference laboratory provide clinicians with treatment recommendations?
    - ❑ Yes
    - ❑ No

C. Inventory of reference services provided by your own laboratory (for preparation of laboratory capacity building workshop)

11. How many laboratories request reference services for isolates of CPE and CRA from your laboratory per year (2012)? (please provide accurate number or your best estimate)

    Free text

12. This number is:
    - ❑ accurate
    - ❑ the best estimate

13. How many isolates, suggestive of CPE and/or CRA, were submitted to your reference laboratory in 2012?

	<10	<100	>100
E. coli			
Klebsiella spp			
Enterobacter spp.			
Other *Enterobacteriacaea*			
Acinetobacter spp.			

Free text

14. What proportion of these isolates were confirmed CPE and/or CRA by your laboratory in 2012? (best estimate in %)

15. How many outbreak investigations did you support in 2012?
    - ❑ In hospitals ……
    - ❑ In nursing homes ……

16. For CPE, what phenotypic techniques do you currently use in your laboratory? (please tick more than one box if applicable)
    - ❑ Disk diffusion
    - ❑ Automated test systems (Vitek, Phoenix, etc.)
    - ❑ Microdilution (MIC determination)
    - ❑ Agar dilution (MIC determination)
    - ❑ Etest or other gradient strip (MIC determination)
    - ❑ Hodge Test
    - ❑ Combo Disk
    - ❑ Double Disk Diffusion
    - ❑ Carba NP test
    - ❑ Others, please specify

    Free text

17. For CPE, what chromatographic or mass spectrometry identification techniques do you use in your laboratory? (please tick more than one box if applicable)
    - ❑ MALDI-TOF (for resistance determination and/or species identification)
    - ❑ None
    - ❑ Other, please specify

    Free text

18. For CPE, what genotypic techniques do you use in your laboratory? (please tick more than one box if applicable)
    - ❑ PCR
    - ❑ Multiplex-PCR
    - ❑ Real-time PCR
    - ❑ Product sequencing
    - ❑ Ligation amplification techniques (Checkpoints)
    - ❑ Others, please specify

    Free text

19. For CRA, how do you identify *Acinetobacter* spp. at species level and how do you determine susceptibility?
    Free text

20. Does your laboratory have access to the following equipment? (please tick more than one box if applicable)
    - ❑ MALDI-TOF (Please name manufacturer)
    - ❑ Real-time PCR machine (Please name manufacturer)
    - ❑ Sequencer (Please name manufacturer)

21. Do you maintain strain collections for future investigation?
    - ❑ Yes, in -80ºC freezers
    - ❑ Yes, in -20ºC freezers
    - ❑ Yes, on slant agar or in form of agar stab cultures (room temperature)
    - ❑ No

D. Preparation for laboratory capacity building: constraints, wishes and aspirations

22. Please rate the following constraints that inhibit your ability to carry out your desired reference services, whereby 1 is the least important and 5 is the most important constraints:

Constraints	1	2	3	4	5
too many isolate submissions and service requests					
financial constraints to cover for necessary consumables					
financial constraints to make necessary investments (equipment, laboratory structure)					
too few personnel because of inability to attract adequate candidates					
too few personnel because of budget limitations					

23. **Free Text to comment**

24. Did your budget suffer from austerity measures imposed on your laboratory during the last three years?
    - ❑ Yes
    - ❑ No

25. Do you believe that these cost savings jeopardize the ability to control the spread of CPE and/or CRA in your country?
    - ❑ Yes
    - ❑ No

26. Knowing the currently available techniques, which could you envisage adding to your repertoire and want the capacity (know-how) built up in your laboratory?
    Free text