Bacterial fingerprints across Europe

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CHAPTER 11

Carbapenemase-producing *Enterobacteriaceae* in Europe: a survey among national experts from 39 countries, February 2013

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Eurosurveillance. 2013 Jul 11;18(28). pii: 20525

ABSTRACT

The spread of carbapenemase-producing *Enterobacteriaceae* (CPE) is a threat to healthcare delivery, although its extent differs substantially from country to country. In February 2013, national experts from 39 European countries were invited to self-assess the current epidemiological situation of CPE in their country. Information about national management of CPE was also reported. The results highlight the urgent need for a co-ordinated European effort on early diagnosis, active surveillance, and guidance on infection control measures. The present report summarises the results from 39 European countries of a self-assessment of the epidemiological stage and the management of CPE at national level.

BACKGROUND

CPE are an emerging threat to healthcare and are frequently resistant to many other antibiotics besides carbapenems [1,2] leaving few treatment options. The extent, to which healthcare systems have already been affected, however, differs substantially from country to country. Following a previous initiative, a group of European experts is implementing the European Survey on CPE (EuSCAPE) in an effort to update assessments of the nature and scale of CPE spread in Europe [3]. The current programme receives financial support from the European Centre for Disease Prevention and Control (ECDC). The aim of this study is to obtain a more accurate and timely estimate of CPE prevalence in European countries and to support reference laboratory-capacity building to prevent and control the spread of CPE in Europe.

Development of a questionnaire and collection of information

A scientific advisory board of European experts in the field of carbapenemase-producing bacteria was invited to provide scientific advice in support of the EuSCAPE programme management team. A questionnaire was devised and modified from a 'field-tested' version used during previous similar surveys [3]. The questionnaire was divided into two sections. The first section (13 questions) explored the experts' knowledge and awareness of the current occurrence of CPE according to a previously-established epidemiological staging system [1,3]. In brief, the system captures seven consecutive stages in the national spread of these organisms. The seven stages are described in Table 1. The second section (22 questions) collected information about existing requirements, structures and guidance documents for reporting, surveillance, use of reference laboratory services and infection control for CPE. The questionnaire is available from the corresponding author.

In each of the 39 European countries (i.e. 27 European Union (EU) Member States, all European Economic Area (EEA)/ European Free Trade Association (ETFA) countries except Lichtenstein, and all EU enlargement countries, as well as Israel), a national expert (NE) with acknowledged laboratory and/or epidemiological experience was identified (for the United Kingdom two NEs participate in this questionnaire survey). The NEs were chosen among European Antimicrobial Resistance Surveillance Network (EARS-Net) contact points, experts from national reference diagnostic laboratories and ECDC-coordinating competent bodies. The list of NEs was validated by ECDC and represents the EuSCAPE Working Group. The NEs were invited to answer the questionnaire online (http://SurveyMonkey.net, SurveyMonkey Corporation, Portland, USA).

Answers from the NEs were compiled and analysed. When necessary, NEs were contacted by Email or telephone for clarification, and corrections were made accordingly. The epidemiological stage of some countries was considered as uncertain when (i) the NE reported a lack of awareness about the current epidemiology of CPE in their country, (ii) the answer of the NE indicated considerable underdetection and underreporting of CPE in their country, (iii) the comments made by the NE by E-mail or telephone indicated uncertainty and/or (iv) when frequent introductions into other countries have been described but the NE could not independently support this observation by own sources. In the maps (Figure), this uncertainty was indicated by displaying the respective country as hatched.

RESULTS

All NEs completed the online questionnaire. Thirty- seven NEs declared that they were aware of the current epidemiology of CPE in their country and all rated the occurrence and spread of CPE in their country using the previously established epidemiological staging system (Figure and Table 1). Nevertheless, only 26 NEs could self-assess their current situation with certainty. Three countries (Iceland, Montenegro and the Former Yugoslav Republic of Macedonia) reported no cases of CPE in their country. Sporadic cases, single or sporadic hospital outbreaks were reported by NEs from 22 countries. For 11 countries, regional or national spread was reported, whereas for three countries

(Greece, Italy and Malta) NEs reported that CPE are regularly isolated from patients in most hospitals, corresponding to the endemic stage (Table 2). Among the 31 countries that participated in both the 2010 and 2013 assessments, 17 reported a higher stage by 2013; likewise, by 2013, the number of countries with regional or inter-regional spread or an endemic situation increased from seven to 13 (Table 2). Some countries expressed concerns that underdetection or underreporting, or both, could affect the certainty of the stage of their countries (Figure).

Thirty-three of the NEs indicated that *Klebsiella pneumoniae* was the most frequent *Enterobacteriaceae* species to produce carbapenemases in their country. Overall, *K. pneumoniae* carbapenemase-producing *Enterobacteriaceae* (KPC) have attained the widest distribution, whereas strains with New Delhi metallo (NDM)-β-lactamase – although responsible for occasional hospital outbreaks in few countries – have not reached such a wide distribution in European countries (Figure). Table 3 displays the level of national management of CPE, based on existing surveillance, reference systems, and guidance in the 39 countries. Thirty and 28 of 39 countries reported having a dedicated surveillance system for CPE and a dedicated reference laboratory for CPE, respectively. Twenty-three reported having a system to notify CPE cases to health authorities, mostly on a mandatory basis. Only 21 countries reported having national recommendations or guidelines on infection control measures to prevent the spread of CPE; one country reported having such recommendation or guideline in preparation. Countries that were uncertain about their epidemiological stages had on average 1.9 national management documents regulating surveillance and response structures. In contrast, those who were more certain about their epidemiological stages had on average 4.7 (p-value < 0.001; Wilcoxon Rank Sum Test).

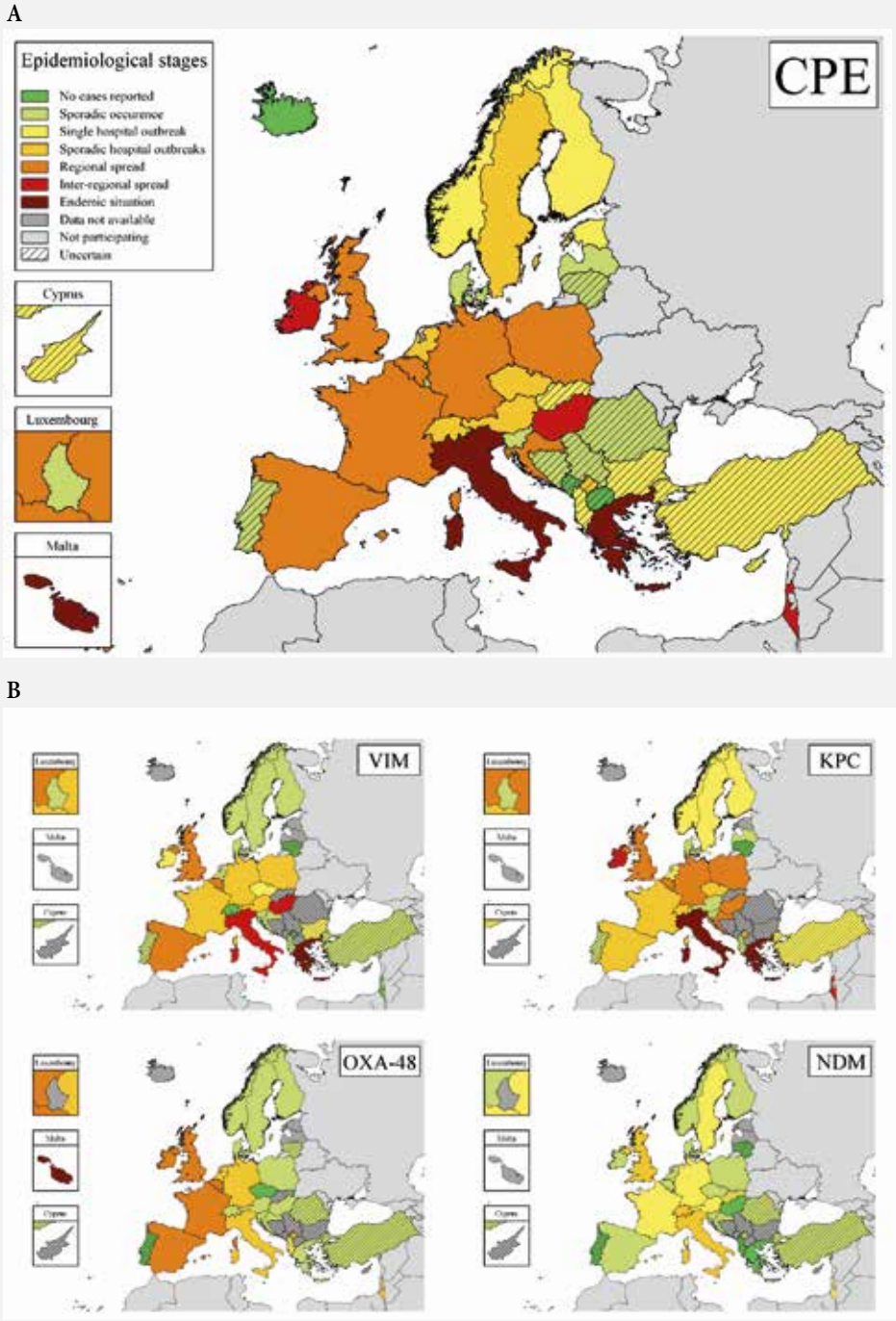

Figure. Occurrence of carbapenemase-producing *Enterobacteriaceae* (CPE) based on self-assessment by respective national experts, 2013. (A) Overall European situation regarding CPE using an epidemiological scale of nationwide expansion. **(B)** Geographic distribution of CPE by resistance mechanism using the same epidemiological scale.
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. More details on the epidemiological stages are given in the manuscript Table 1. In some countries, the epidemiological stage might not represent the true extent of the spread of CPE as it is a subjective judgment by national experts. Uncertainty about the epidemiological stage of a country is indicated by hatching. Results presented here reflect the uncertainty at the time of the survey. For Portugal, case notification and submission of isolates became mandatory on 21 February 2013.

Table 1. Description of the epidemiological stages of carbapenemase-producing *Enterobacteriaceae* (CPE)

Epidemiological scale	Description	Stage
No case reported	No case reported	0
Sporadic occurrence	Single cases, epidemiological unrelated	1
Single hospital outbreak	Outbreak defined as two or more epidemiological 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 a 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

The table was reproduced from reference [3].

The epidemiological staging system, developed in 2010, is based on seven levels [3]. Stage 0: no case reported; stage 1: sporadic occurrence whereby only single cases are reported; stage 2a: single hospital outbreak reported whereby an outbreak is defined as two or more epidemiologically-associated cases with indistinguishable geno- or phenotype; stage 2b: sporadic hospital outbreaks reported whereby more than one hospital outbreak is reported but all outbreaks are epidemiologically unrelated or caused by different clones (no autochthonous inter- institutional transmission); stage 3: regional spread whereby more than one epidemiologically-related hospital outbreak is reported, but confined to the same region or health district (regional autochthonous inter-institutional transmission); stage 4: inter-regional spread whereby multiple epidemiologically- related hospital outbreaks are reported from different regions or health districts (inter-regional autochthonous inter-institutional transmission); and stage 5: endemic situation whereby most hospitals in a country are constantly seeing cases admitted from autochthonous sources. The epidemiological stage of a country may not reflect the true extent of the spread of CPE, as it is based on the subjective judgment of the responding national expert in 2010 and 2013 and the opinion of the authors of a review in 2012. Some of the countries were not included in the 2010 survey and/or the 2012 review and their epidemiological stage is consequently indicated as 'not available' (NA).

NA: not available.

[a] The results were based on data obtained through a European- wide consultation during a workshop at the Netherlands's National Institute for Public Health and the Environment (RIVM) on 29 and 30 April 2010 [3].

[b] The results were based on the subjective analyses of the literature available at the time of the publication [1].

[c] This online survey (February 2013).

[d] ↑ = increase in the epidemiological stage, ↓ = decrease in the epidemiological stage and ➔ = unchanged epidemiological stage. A dash indicates that there are discrepancies between the results of the 2012 review and the 2013 survey, whereby no direction of change can be given.

[e] For France and Poland, discrepancies between results from the 2012 review and the 2013 survey are probably due to the subjective assessment by different experts.

[f] 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.

[g] For Montenegro and Turkey, discrepancies between results from the 2012 review and the 2013 survey underline the uncertainty of stage designation for these countries.

Table 2. Comparison of epidemiological stages of carbapenemase-producing *Enterobacteriaceae* (CPE) in 39 European countries, 2010, 2012 and 2013

Country	Epidemiological stage for spread of CPE			Direction of change (2010-2013)[d]
	Grundmann *et al.*, 2010[a]	Canton *et al.*, 2012[b]	2013[c]	
Albania	NA	NA	2a	NA
Austria	0	1	2b	↑
Belgium	2b	3	3	↑
Bosnia and Herzegovina	1	1	1	→
Bulgaria	0	NA	2a	↑
Croatia	1	1	3	↑
Cyprus	2a	NA	2a	→
Czech Republic	1	1	2b	↑
Denmark	1	1	1	→
Estonia	0	NA	2a	↑
Finland	1	1	2a	↑
France	3	4	3	–[e]
Germany	3	3	3	→
Greece	5	5	5	→
Hungary	3	2a	4	↑
Iceland	0	0	0	→
Ireland	1	1	4	↑
Israel	5	5	4	↓
Italy	4	5	5	↑
Kosovo[f]	NA	1	3	NA
Latvia	1	NA	1	→
Lithuania	1	NA	1	→
Luxembourg	NA	1	1	NA
Malta	1	NA	5	↑
Montenegro	NA	1	0	–[g]
Netherlands	2a	2b	2b	↑
Norway	2a	2a	2a	→
Poland	4	4	3	–[e]
Portugal	1	1	1	→
Romania	1	1	1	→
Serbia	NA	1	1	NA
Slovakia	NA	NA	2b	NA
Slovenia	0	1	1	↑
Spain	2b	2b	3	↑
Sweden	2a	2a	2b	↑
Switzerland	1	1	2b	↑
The Former Yugoslav Republic of Macedonia	NA	NA	0	NA
Turkey	NA	4	2a	–[g]
United Kingdom	2b	3	3	↑

Table 3. National management of carbapenemase-producing *Enterobacteriaceae* (CPE) in 39 European countries, 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
Albania						
Austria	•	•	•	•	•[b]	•
Belgium	•	•	•	•	•[b]	•
Bosnia and Herzegovina						
Bulgaria	•				•[c]	
Croatia	•	•	•	•	•[c]	•
Cyprus	•					
Czech Republic	•	•	•	•	•[c]	•
Denmark	•	•	•	•		
Estonia	-[d]					
Finland	•	•	•	•	•[c]	
France	•	•	•	•	•[c]	•
Germany	•	•		•		•
Greece	•	•	•	•	•[c]	•[e]
Hungary	•	•	•	•	•[c]	•
Iceland	•	•	•	•	•[c]	•
Ireland	•	•	•	•	•[c]	•[e]
Israel	•	•			•[c]	•
Italy	•				•[c, f]	•
Kosovo[g]		•	•			•[e]
Latvia	-[d]	•			•[c]	
Lithuania	•	•		•		
Luxembourg	•	•		•	•[c]	
Malta	•	•	•	•		•[e]
Montenegro						
Norway	•	•	•	•	•[c]	•
Poland	•	•	•	•	•[c]	•
Portugal	•	•	•	•	•[c]	•
Romania	-[d]	•				
Serbia	•	•				
Slovakia	•	•			•[b]	
Slovenia			•	•		•
Spain	•	•	•	•	•[b]	
Sweden	•	•	•	•	•[c]	•
Switzerland	•			•		
The Former Yugoslav Republic of Macedonia	•	•			•[c]	
The Netherlands	•		•	•	•[b]	•
Turkey						
United Kingdom	•	•	•	•		•

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

[a] Agreed criteria or policy (including minimum inhibitory concentration (MIC) cut-off, species and resistance confirmation, epidemiological typing) to submit CPE isolates to a national reference laboratory.

[b] Voluntary notification to health authorities.

[c] Mandatory notification to health authorities.

[d] Country reporting carbapenem-resistant invasive isolates (*Klebsiella pneumoniae* and *Escherichia coli* to the European Antimicrobial Resistance Surveillance Network (EARS-Net)).

[e] Only in case of outbreaks.

[f] Only for bacteraemia cases.

[g] 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.

DISCUSSION

The results of this online survey, performed in February 2013, show that, based on the knowledge and judgment of NEs, CPE are continuing to spread in Europe. Although most countries reported only single hospital outbreaks, the epidemiological situation has deteriorated over the past three years. Among the 31 countries that participated in both 2010 and 2013 assessments, 17 countries were upgraded to a higher epidemiological stage (Table 2). Three countries that reported sporadic occurrence or single hospital outbreaks 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 by nature 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 carbapenem-hydrolysing oxacillinase (OXA)-48-positive *Enterobacteriaceae* (M. Borg, personal communication, April 2013). In Italy, a sporadic occurrence of Verona integron-encoded metallo-beta-lactamase (VIM)- producing *Enterobacteriaceae* from 2008, accentuated by a single hospital outbreak, has been overtaken by the wide dissemination of KPC-positive *K. pneumoniae* strains to many healthcare institutions [4-9]. The situation in Hungary has evolved in the opposite direction: in 2010, concern centred upon a single clone of KPC-2-positive *K. pneumoniae* that had attained regional distribution, whereas VIM-4-positive strains were only reported sporadically, but have now spread nation- wide [3,10]. Overall, KPC-positive *Enterobacteriaceae* still have the widest distribution among CPE in Europe, but rising numbers of OXA-48-positive isolates are reported, making OXA-48 the most frequently detected carbapenemase in Belgium, France and Malta. Despite the attention that NDM has received when associated with introductions from the Indian subcontinent, the current numbers of reports by European countries are still relatively modest compared to the other carbapenemases [11]. The United Kingdom, however, continues to report more NDM-positive isolates than most other European countries [3,12].

The NEs completed the questionnaire to the best of their knowledge, but these were subjective assessments that may have underestimated the true extent of the spread of CPE. Underdetection and underreporting were pointed out by respondents in several countries, leading to uncertainty about the true epidemiological stage (Figure). In particular, this applied to countries from which introductions into other countries have been described but where NEs could not independently assess the extent of CPE spread. Underdetection and underreporting of CPE also coincided with weaker reference laboratory infrastructures and the absence of national recommendations for submission to national reference laboratories and for reporting to health authorities, thus suggesting that the true extent of CPE occurrence 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 the comparability of the assessment.

The keys to success in preventing the establishment of CPE are, firstly, early detection through good diagnostic practices, secondly, containment of spread through patient and contact screening as well as infection control measures. An increasing number of countries have reacted and implemented measures as indicated by the increasing availability of a recommendation or guideline on infection control measures to prevent the spread of CPE [12]. Still 18 countries surveyed lacked such guidance and the same number of countries lacked relevant guidance for submission of isolates to national reference laboratories [12]. The results of the present report underscore the urgent need for an upgrading of laboratory standards to enable active surveillance and preventive action. To this purpose, the EuSCAPE programme aims to build a laboratory-based network for CPE detection in Europe.

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PART 4

‘So eine Arbeit wird eigentlich nie fertig, man muß sie für fertig erklären,
wenn man nach Zeit und Umständen das Mögliche getan hat.’
Goethe (1749-1832)