Published in "The Lancet Infectious Diseases 17(2): 153–163, 2017"
which should be cited to refer to this work.

Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study

Hajo Grundmann, Corinna Glasner*, Barbara Albiger, David M Aanensen, Chris T Tomlinson, Arjana Tambić Andrasević, Rafael Cantón, Yehuda Carmeli, Alexander W Friedrich, Christian G Giske, Youri Glupczynski, Marek Gniadkowski, David M Livermore, Patrice Nordmann, Laurent Poirel, Gian M Rossolini, Harald Seifert, Alkiviadis Vatopoulos, Timothy Walsh, Neil Woodford, Dominique L Monnet, and the European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group†*

Summary

Background **Gaps in the diagnostic capacity and heterogeneity of national surveillance and reporting standards in Europe make it difficult to contain carbapenemase-producing Enterobacteriaceae. We report the development of a consistent sampling framework and the results of the first structured survey on the occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in European hospitals.**

Methods **National expert laboratories recruited hospitals with diagnostic capacities, who collected the first ten carbapenem non-susceptible clinical isolates of *K pneumoniae* or *E coli* and ten susceptible same-species comparator isolates and pertinent patient and hospital information. Isolates and data were relayed back to national expert laboratories, which made laboratory-substantiated information available for central analysis.**

Findings **Between Nov 1, 2013, and April 30, 2014, 455 sentinel hospitals in 36 countries submitted 2703 clinical isolates (2301 [85%] *K pneumoniae* and 402 (15%) *E coli*). 850 (37%) of 2301 *K pneumoniae* samples and 77 (19%) of 402 *E coli* samples were carbapenemase (KPC, NDM, OXA-48-like, or VIM) producers. The ratio of *K pneumoniae* to *E coli* was 11:1. 1·3 patients per 10000 hospital admissions had positive clinical specimens. Prevalence differed greatly, with the highest rates in Mediterranean and Balkan countries. Carbapenemase-producing *K pneumoniae* isolates showed high resistance to last-line antibiotics.**

Interpretation **This initiative shows an encouraging commitment by all participants, and suggests that challenges in the establishment of a continent-wide enhanced sentinel surveillance for carbapenemase-producing Enterobacteriaceae can be overcome. Strengthening infection control efforts in hospitals is crucial for controlling spread through local and national health care networks.**

Funding **European Centre for Disease Prevention and Control.**

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Introduction

Carbapenemase-producing Enterobacteriaceae (CPE) are the most pervasive antibiotic resistance threat to health services worldwide. Because of the dearth of alternative drugs, patients are often left without effective treatment, revealing burgeoning resistance, long concealed by adaptive prescribing when doctors could still choose carbapenems as a last-line drug. Therefore, spread of CPE could be the tipping point when substantial morbidity and mortality from antibiotic resistance comes to the fore.[1]

Few alternative antibiotics (eg, colistin, fosfomycin, and tigecycline) remain,[2] and although resistance can extend even to agents still in development or recently approved,[3,4] public health efforts are beginning to emphasise containment of CPE in populations and health-care networks. This requires an understanding of the geographical distribution of CPE infections, their population reservoirs, and the risk factors for acquisition. However, there is little internationally comparable data.

The European Survey on CPE (EuSCAPE) was initiated with the aim of providing the first comparable and quality-controlled data on the occurrence of the most important CPE (*Klebsiella pneumoniae* and *Escherichia coli*) in Europe and neighbouring countries, and to establish a framework for future enhanced sentinel surveillance. It entailed the stepwise build-up of structures through identification of national expert laboratories (NELs),[5] a joint agreement on diagnostic standards, improvement of quality-assessed diagnostic capacity among NELs, and, as a proof of feasibility, a structured survey using a standard sampling protocol in all participating sites. We describe the execution and final results of the EuSCAPE structured survey.

Methods

Capacity building and proficiency testing

Technical staff from all NELs were trained to use a set of standard phenotypic and genotypic tests in accordance

*These authors contributed equally

†A list of the EuSCAPE Working Group can be found at the end of the manuscript and in the appendix

Department of Infection Prevention and Hospital Hygiene, Faculty of Medicine, University of Freiburg, Freiburg, Germany (Prof H Grundmann MD); **Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Netherlands** (Prof H Grundmann, C Glasner PhD, Prof A W Friedrich MD); **The Centre for Genomic Pathogen Surveillance, Wellcome Trust Genome Campus, Cambridgeshire, UK** (C Glasner, D M Aanensen PhD); **European Centre for Disease Prevention and Control, Stockholm, Sweden** (B Albiger PhD, D L Monnet PhD); **Department of Infectious Disease Epidemiology, School of Public Health,** (D M Aanensen), **and Department of Surgery and Cancer, South Kensington Campus** (C T Tomlinson PhD), **Imperial College London, London, UK; Department of Clinical Microbiology, University Hospital for Infectious Diseases, Zagreb, Croatia** (Prof A T Andrasević MD); **Servicio de Microbiología, Hospital Universitario**

Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain (Prof R Cantón MD); Unidad de Resistencia a Antibióticos y Virulencia Bacteriana asociada al Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain (Prof R Cantón); Division of Epidemiology, Tel-Aviv Sourasky Medical Centre, Tel-Aviv, Israel (Prof Y Carmeli MD); Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden (C G Giske MD); Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden (C G Giske); Department of Clinical Microbiology (Prof Y Glupczynski MD), and National Reference Laboratory for Antibiotic Resistance Monitoring in Gram-negative Bacteria (Prof Y Glupczynski), CHU Dinant-Godinne UCL, Namur, Université Catholique de Louvain, Yvoir, Belgium; Department of Molecular Microbiology, National Medicines Institute, Warsaw, Poland (Prof M Gniadkowski PhD); Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, Reference Microbiology Services, Public Health England, London, UK (Prof D M Livermore PhD, Prof N Woodford PhD); Norwich Medical School, University of East Anglia, Norwich, UK (Prof D M Livermore); INSERM U914 (Emerging Resistance to Antibiotics), Associated National Reference Center for Antibiotic Resistance, Faculté de Médecine et Université Paris-Sud, K Bicêtre, France (Prof P Nordmann PhD, L Poirel PhD); Medical and Molecular Microbiology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Switzerland (Prof P Nordmann, L Poirel); Dipartimento di Biotecnologie Mediche, Università di Siena, Siena, Italy (Prof G M Rossolini MD); SOD Microbiologia e Virologia, Azienda Ospedaliera-Universitaria Careggi, Fondazione Don Carlo Gnocchi, Firenze, Italy (Prof G M Rossolini);

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Research in context

Evidence before this study

On April 1, 2016, we search Pubmed with the terms "carbapenemase-producing Enterobacteriaceae" or "carbapenem-resistant Enterobacteriaceae", or "*Klebsiella pneumoniae*", "*Escherichia coli*", "Europe" and "surveillance" for reports published between Jan 1, 2000 and Jan 1, 2016, with no language restrictions. This search identified 72 publications. These consisted of larger national surveillance studies, reviews, or single case studies. None of the studies included comprehensive European coverage, standardisation of methods, or diagnostic quality assessment. Before this study, only anecdotal evidence existed for several countries with high endemicity. Since national reference laboratory structures were often absent and diagnostic standards differed between laboratories, cases remained unconfirmed leaving wide scope for ascertainment bias.

Added value of this study

We report data on the occurrence of carbapenemase-producing and last-line antibiotic resistant *K pneumoniae* and *E coli* using standardised procedures and provide the first comparable and laboratory-substantiated data on the incidence of these difficult-to-treat bacteria across Europe.

Implications of all the available evidence

K pneumoniae of nosocomial provenance is the main source of carbapenemase-producing Enterobacteriaceae (CPE) infection in Europe. The emergence and spread of antibiotic resistance against last-line antibiotics increasingly erodes the ability to successfully treat patients infected with CPE especially in countries where CPE prevalence in hospitals is high. At a time when novel and effective antibiotic compounds have not become available, containment of CPE is bound to rely on stricter infection control measures in hospitals.

with EUCAST guidelines.[6] Subsequently, all NELs were required to take part in an external quality assessment exercise, which was carried out and analysed by the UK National External Quality Assessment Service. Successful completion was a prerequisite for participation.

Structured survey

Each NEL recruited a defined number of hospitals with microbiologic diagnostic capacity, depending on the country's population; 20 sites were recruited in large countries (>15 million population), ten sites in medium-sized countries (2–15 million population), and one site in small countries (<2 million population). To prevent geographical bias, the NELs were asked to enrol hospitals in a geo-demographical representative manner (figure, appendix). NELs were asked to collect additional information about the participating hospitals for 2013, including number of beds, annual number of admissions, total number of patient-days, average bed occupancy, average length of stay, and estimated size of catchment population.

The sampling period was 6 months, starting on Nov 1, 2013, and ending on April 30, 2014. During this period, each sentinel site was required to collect the first ten consecutive primary isolates of *K pneumoniae* or *E coli* from clinical specimens from individual patients if local routine tests showed non-susceptibility to any carbapenem (imipenem, meropenem, or ertapenem). All clinical specimens were accepted, except for stool and surveillance screening samples. Each index isolate (ie, carbapenem-non-susceptible *K pneumoniae* or *E coli*) was matched to the first subsequent carbapenem-susceptible isolate of the same species irrespective of anatomical site, serving as a comparator isolate.

Isolates were dispatched to the NEL with additional information including sample date, anatomical origin of specimen, patient age and sex, clinical relevance of the isolate (colonisation or infection), patient location in the hospital (intensive care unit, ordinary ward, outpatient, or accident and emergency), and hospital admission and travel outside their country of residence in the past 6 months. Hospital acquisition was inferred when an isolate was sampled from patients after being admitted for more than 48 h, or community-associated otherwise. Instructions on the collection of isolates, and the ascertainment of clinical and epidemiological data were given by the structured survey protocol (appendix), which was translated by NELs into their respective language and distributed to the sentinel hospital laboratories if necessary.

The NELs confirmed species and phenotypic susceptibility and used PCR tests for four carbapenemase gene families (*Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], oxacillinase-48 [OXA-48-like], or Verona integron-encoded metallo-β-lactamase [VIM]). Antimicrobial susceptibility tests according to EUCAST guidelines variously included ampicillin, amoxicillin and clavulanic acid, piperacillin and tazobactam, cefotaxime, ceftazidime, cefepime, aztreonam, imipenem, meropenem, ertapenem, ciprofloxacin, trimethoprim and sulfamethoxazole (co-trimoxazole), gentamicin, amikacin, tobramycin, tigecycline, colistin, and fosfomycin. Phenotypic confirmation of carbapenemase production consisted of double disk synergy tests, combination disk tests, and Carba NP I or II test.[7] Methodological details for these tests are described in the appendix. Carbapenem non-susceptible isolates that were tested PCR-negative

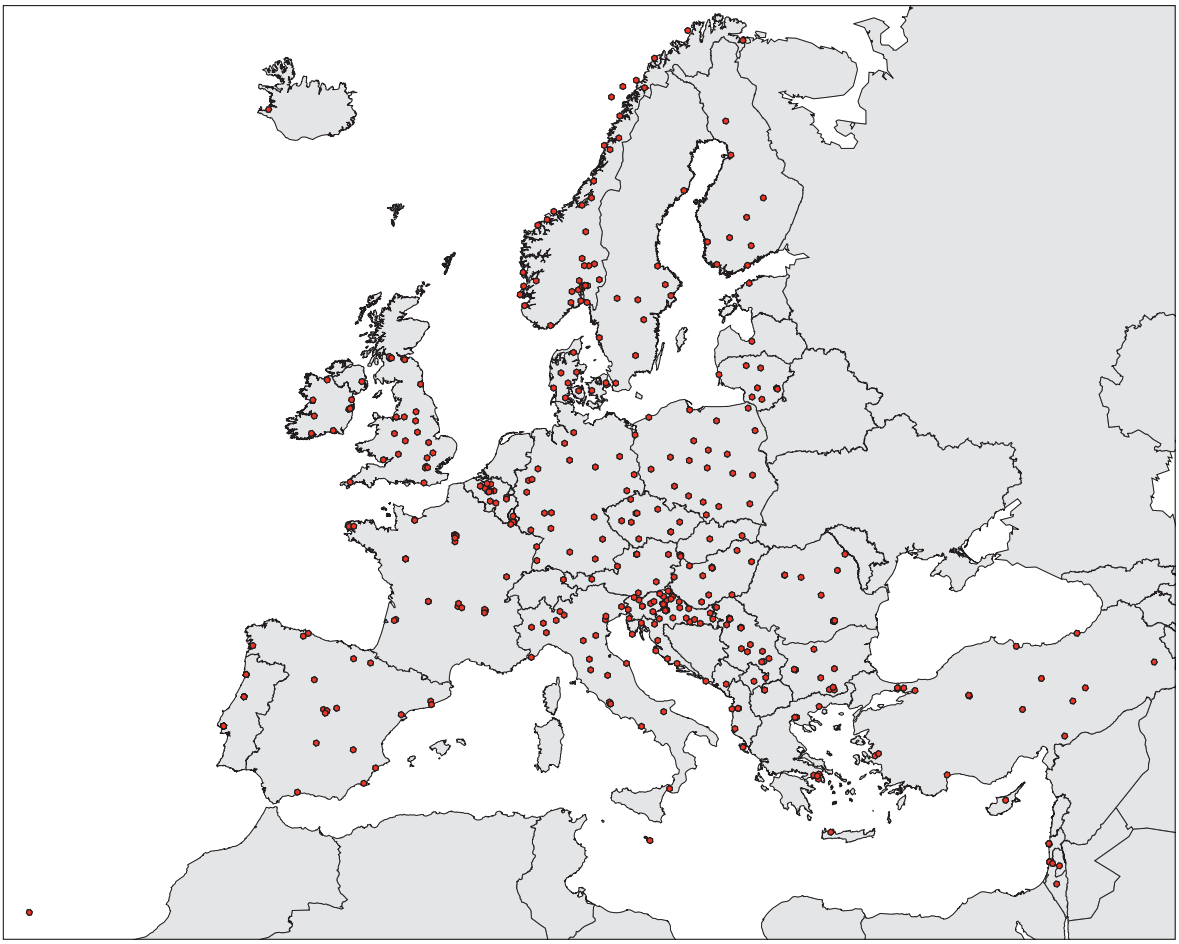

Figure: **Locations of participating sentinel hospitals**

were classified as "other". Results and epidemiological information were uploaded for central analysis using a password-protected web tool.

All data were anonymised and collected in accordance with the European Parliament and Council decisions on the epidemiological surveillance and control of communicable disease in the European Community.[8,9] Ethical approval and informed consent were thus not required.

Data analysis

Data were analysed with STATA version 13.1 (StataCorp, Texas, USA) using Mantel-Haenzel odds ratios and Pearson χ^2 test for univariate risk factor analysis and multiple logistic regression for multivariable analysis with log likelihood ratio tests after fitting interaction terms to identify effect modification. For hospitals that could not provide figures on the total number of patient days in 2013, we estimated this value as the product of the number of admissions and the average length of stay. Country-aggregated period prevalence estimates were reported as number of patients diagnosed with either carbapenemase-producing *K pneumoniae* or *E coli* per 10 000 hospital admissions. Country-aggregated incidence estimates were reported as number of patients diagnosed with either carbapenemase-producing *K pneumoniae* or *E coli* per 100 000 hospital patient-days. Confidence intervals for random errors are not provided because of heterogeneity of sampling density as a result of different diagnostic habits.

Role of the funding source

The study was funded by the European Centre for Disease Prevention and Control (ECDC) through a specific framework service contract (ECDC/2012/055) to the University Medical Center Groningen, Groningen, Netherlands. ECDC provided comments on the study design, suggested national coordinators, and provided comments on the analysis and the final report. The decision to submit for publication was jointly taken by all contributors.

Results

Between Nov 1, 2013, and April 30, 2014, 455 sentinel hospitals from 36 countries contributed to the

Institute for Medical Microbiology, Immunology and Hygiene, Cologne University, Cologne, Germany (Prof H Seifert MD); **German Center for Infection Research (DZIF), Braunschweig, Germany** (Prof H Seifert); **Department of Microbiology, National School of Public Health, Athens, Greece** (Prof A Vatopoulos MD); **and Section of Medical Microbiology IIB, School of Medical Sciences, Cardiff University, Heath Park Hospital, Cardiff, UK** (Prof T Walsh PhD)

Correspondence to:
Prof Hajo Grundmann, Department of Infection Prevention and Hospital Hygiene, Faculty of Medicine, University of Freiburg, 79106 Freiburg im Breisgau, Germany
hajo.grundmann@uniklinik-freiburg.de

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	Klebsiella pneumoniae			*Escherichia coli*			Sentinel hospitals (mean beds†)	Incidence per 10000 admissions‡		Incidence per 100000 patient-days§	
	Submitted non-susceptible isolates (n)	Confirmed carbapenemase-producing isolates* (n)	Comparator isolates (n)	Submitted non-susceptible isolates (n)	Confirmed carbapenemase producing isolates* (n)	Comparator isolates (n)		Rate (hospitals)	Rank	Rate (hospitals)	Rank
Albania	8	0	11	6	0	5	5 (586)	..	25	0 (5)	24
Austria	15	10	15	1	0	1	10 (968)	0 (1)	25	..	..
Belgium	48	33	49	13	5	13	15 (837)	1·2 (11)	8	1·74 (11)	8
Bulgaria	4	2	4	8	8	8	11 (538)	0·7 (11)	10	1·29 (11)	11
Croatia	48	7	52	2	1	2	32 (714)	0·29 (23)	16	0·44 (22)	18
Cyprus	1	1	1	2	2	2	1 (453)	2·45 (1)	6	4·09 (1)	6
Czech Republic	26	2	9	2	0	0	10 (1460)	0·09 (9)	21	0·14 (9)	21
Denmark	8	6	8	1	1	1	10 (..)	..	..	..	..
Estonia	9	0	8	3	0	3	1 (635)	0 (1)	25	0 (1)	24
Finland	1	0	1	6	0	10	9 (1126)	0 (8)	25	0 (7)	24
France	27	11	26	12	3	14	26 (763)	..	..	..	..
Germany	36	22	36	10	3	10	20 (1189)	0·56 (17)	13	0·6 (1)	16
Greece	86	79	79	1	1	1	10 (407)	5·78 (3)	2	17·3 (3)	1
Hungary	36	26	27	1	0	1	11 (1680)	0·68 (11)	11	1·04 (11)	12
Iceland	0	0	0	0	0	0	1 (612)	0 (1)	25	0 (1)	24
Ireland	12	6	10	10	0	9	10 (528)	0·44 (10)	15	0·67 (10)	15
Israel	39	34	36	6	6	4	8 (669)	..	..	..	..
Italy	195	192	198	5	5	5	22 (740)	5·96 (22)	1	7·8 (22)	3
Kosovo	0	0	0	0	0	0	2 (..)	..	..	..	..
Latvia	4	2	5	0	0	0	1 (826)	0·85 (1)	9	1·68 (1)	9
Lithuania	4	0	4	1	1	1	10 (780)	0·06 (9)	22	0·09¶ (9)	23
Luxembourg	10	8	10	0	0	0	5 (435)	1·45 (5)	7	2·25 (5)	7
Malta	9	9	9	1	1	1	1 (850)	..	..	..	..
Montenegro	10	10	10	0	0	0	1 (760)	5·65 (1)	3	9·27 (1)	2
Norway	5	1	5	5	1	5	45 (253)	0·02 (30)	24	..	..
Poland	34	4	28	0	0	0	21 (639)	0·15 (17)	19	0·25 (17)	19
Portugal	61	36	33	6	2	4	26 (721)	0·65 (26)	12	1·4¶ (24)	10
Romania	68	61	49	0	0	9	12 (891)	..	..	..	..
Serbia	67	43	46	5	5	5	18 (754)	3 (12)	5	4·35 (12)	5
Slovakia	22	1	22	2	0	2	6 (800)	0·1 (6)	20	0·15 (6)	20
Slovenia	12	3	10	2	0	2	12 (577)	0·25 (10)	17	0·54¶ (8)	17
Spain	116	102	122	14	4	24	20 (696)	4·01 (20)	4	5·88 (20)	4
Sweden	0	0	1	1	1	1	10 (978)	..	..	..	..
Macedonia	3	2	0	0	0	3	2 (1170)	0·51 (2)	14	0·85 (2)	13
Turkey	124	112	130	22	20	20	18 (980)	..	..	..	18
UK-England and Northern Ireland	47	25	36	29	6	25	18 (1176)	0·19 (18)	18	0·85¶ (18)	14
UK-Scotland	8	0	8	17	1	17	14 (428)	0·03 (13)	23	0·1 (13)	22
Total or average	1203	850	1098	194	77	208	455 (800)	1·3 (321)	..	2·51 (268)	..

*Confirmation included genes for the carbapenemase classes KPC, NDM, OXA-48-like, and VIM. †Mean number of beds per hospital for the financial year 2013. ‡Number of hospitals that provided the number of admissions per hospital for the financial year 2013. §Number of hospitals that provided the number of admissions and average length of stay for the financial year 2013. ¶For Lithuania, Portugal, Slovenia, and UK (England and Northern Ireland), the total number of patient days was calculated as average bed occupancy x number of beds x 365.

Table 1: **Clinical *Klebsiella pneumoniae* and *Escherichia coli* isolates submitted by country, and combined incidence estimates in European hospitals**

structured survey (figure). Participating countries included 27 European Union Member States, two European Economic Area countries, and six EU enlargement countries plus Israel. In the UK, Scotland participated on its own behalf. Albania, Finland, Israel, Latvia, Macedonia, Romania, Slovakia, Turkey, and the UK (England and Northern Ireland) did not reach their quota of participating sentinel hospitals, but Belgium, Bulgaria, Croatia, France, Hungary, Italy, Kosovo, Luxembourg, Norway, Poland, Portugal,

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Serbia, Slovenia, and UK (Scotland) recruited more hospitals.

During the 6-month period, 2301 *K pneumoniae* and 402 *E coli* isolates were collected (table 1). 1203 (86%) of 1397 index isolates submitted were *K pneumonia,* and 194 (14%) of 1397 isolates were *E coli*. Proportions of index and comparator isolates did not differ in terms of anatomical origin or specimen type except for bloodstream infections caused by *E coli,* for which carbapenem-susceptible isolates contributed substantially more infections (appendix). Therefore, the ability to cause infections seems not to be contingent on the resistance traits under study. Of all isolates submitted by the NELs as carbapenem non-susceptible, PCR

	Hospitals submitting carbapenem non-susceptible *K pneumoniae* isolates (n)	Number of submitted carbapenem non-susceptible *K pneumoniae* isolates	Confirmed carbapenemase-producing *K pneumoniae* isolates					Other (n, %)*
			KPC (n, %)	NDM (n,%)	OXA-48-like (n, %)	VIM (n, %)	Total (n, %)	
Albania	3	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Austria	6	15	6 (40·0)	2 (13·3)	2 (13·3)	0 (0)	10 (66·7)	5 (33·3)
Belgium	11	48	13 (27·1)	2 (4·2)	18 (37·5)	0 (0)	33 (68·8)	15 (31·3)
Bulgaria	3	4	0 (0)	2 (50·0)	0 (0)	0 (0)	2 (50·0)	2 (50·0)
Croatia	14	48	1 (2·1)	0 (0)	1 (2·1)	5 (10·4)	7 (14·6)	41 (85·4)
Cyprus	1	1	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Czech Republic	5	26	0 (0)	1 (3·8)	1 (3·8)	0 (0)	2 (7·7)	24 (92·3)
Denmark	3	8	1 (12·5)	3 (37·5)	2 (25·0)	0 (0)	6 (75·0)	2 (25·0)
Estonia	1	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (100)
Finland	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
France	11	27	1 (3·7)	0 (0)	10 (37·0)	0 (0)	11 (40·7)	16 (59·3)
Germany	13	36	8 (22·2)	2 (5·6)	12 (33·3)	0 (0)	22 (61·1)	14 (38·9)
Greece	10	86	56 (65·1)	12 (14·0)	2 (2·3)	9 (10·5)	79 (91·9)	7 (8·1)
Hungary	7	36	0 (0)	0 (0)	0 (0)	26 (72·2)	26 (72·2)	10 (27·8)
Ireland	7	12	2 (16·7)	2 (16·7)	2 (16·7)	0 (0)	6 (50·0)	6 (50·0)
Israel	7	39	31 (79·5)	2 (5·1)	1 (2·6)	0 (0)	34 (87·2)	5 (12·8)
Italy	22	195	187 (95·9)	1 (0·5)	1 (0·5)	3 (1·5)	192 (98·5)	3 (1·5)
Latvia	1	4	0 (0)	0 (0)	0 (0)	2 (50·0)	2 (50·0)	2 (50·0)
Lithuania	4	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)
Luxembourg	3	10	4 (40·0)	0 (0)	2 (20·0)	2 (20·0)	8 (80·0)	2 (20·0)
Malta	1	9	0 (0)	0 (0)	9 (100)	0 (0)	9 (100)	0 (0)
Montenegro	1	10	0 (0)	10 (100)	0 (0)	0 (0)	10 (100)	0 (0)
Norway	4	5	0 (0)	1 (20·0)	0 (0)	0 (0)	1 (20·0)	4 (80·0)
Poland	10	34	2 (5·9)	2 (5·9)	0 (0)	0 (0)	4 (11·8)	30 (88·2)
Portugal	17	61	36 (59·0)	0 (0)	0 (0)	0 (0)	36 (59·0)	25 (40·9)
Romania	8	68	4 (5·9)	5 (7·4)	50 (73·5)	2 (2·9)	61 (89·7)	7 (10·3)
Serbia	11	67	1 (·5)	33 (49·3)	9 (13·4)	0 (0)	43 (64·2)	24 (35·8)
Slovakia	5	22	1 (4·5)	0 (0)	0 (0)	0 (0)	1 (4·5)	21 (95·5)
Slovenia	4	12	0 (0)	1 (8·3)	1 (8·3)	1 (8·3)	3 (25·0)	9 (75·0)
Spain	20	116	9 (7·8)	0 (0)	81 (69·8)	12 (10·3)	102 (87·9)	14 (12·1)
Macedonia	1	3	2 (66·7)	0 (0)	0 (0)	0 (0)	2 (66·7)	1 (33·3)
Turkey	17	124	0 (0)	9 (7·3)	98 (79·0)	5 (4·0)	112 (90·3)	12 (9·7)
UK-England and Northern Ireland	15	47	14 (29·8)	3 (6·4)	7 (14·9)	1 (2·1)	25 (53·2)	22 (46·8)
UK-Scotland	4	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Total	251	1203	379 (31·5)	93 (7·7)	310 (25·8)	68 (5·7)	850 (70·7)	353 (29·3)

Iceland, Kosovo, and Sweden did not find any *K pneumonia* isolates that were suspected non-susceptible to carbapenems during the study period. *Other mechanism of carbapenem non-susceptibility, since none of the genes coding for the four major types of carbapenemases (KPC, NDM, OXA-48-like and VIM) were detected. All data are n, except where otherwise indicated.

***Table 2: Klebsiella pneumoniae* clinical isolates submitted as non-susceptible to carbapenems, confirmed as producing a carbapenemase and type of carbapenemase, by country**

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confirmed the presence of KPC, NDM, OXA-48-like, and VIM type genes for 850 (71%) of 1203 *K pneumoniae* isolates and 77 (40%) of 194 *E coli* samples. Among the 927 carbapenemase-producers, the ratio between *K pneumoniae* and *E coli* was 11:1.

Country-aggregated prevalence differed greatly between countries. Based on population-weighted averages, 1·3 patients per 10 000 hospital admissions and 2·5 patients per 100 000 hospital patient-days had a carbapenemase-producing *K pneumoniae* or *E coli*. High incidence countries included Greece, Italy, Montenegro, Spain, and Serbia.

KPC enzymes were detected in 393 (42%) of 927 CPE isolates, and were the most frequent carbapenemases. OXA-48-like enzymes were the second most frequent (353 [38%] of 927 isolates) and were the most prominent class of carbapenemases in eight countries. NDM genes were detected in 113 (12%) and VIM in 68 *K pneumoniae* isolates (7%).

In *K pneumoniae*, the most frequently detected carbapenemases were KPC enzymes (379 [45%] of 850 isolates), followed by OXA-48-like (310 isolates, 37%), NDM (93 isolates, 11%) and VIM (68 isolates, 8%). In *E coli*, the most frequently detected carbapenemases were

	Hospitals submitting carbapenem non-susceptible *E coli* isolates (n)	Number of submitted carbapenem non-susceptible *E coli* isolates (n)	Confirmed carbapenemase-producing *E coli* isolates					Other (n, %)*
			KPC (n, %)	NDM (n, %)	OXA-48-like (n, %)	VIM (n, %)	Total (n, %)	
Albania	2	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)
Austria	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Belgium	7	13	0 (0)	1 (7·7)	4 (30·8)	0 (0)	5 (38·5)	8 (61·5)
Bulgaria	1	8	0 (0)	8 (100)	0 (0)	0 (0)	8 (100)	0 (0)
Croatia	2	2	0 (0)	1 (50·0)	0 (0)	0 (0)	1 (50·0)	1 (50·0)
Cyprus	1	2	1 (50·0)	0 (0)	1 (50·0)	0 (0)	2 (100)	0 (0)
Czech Republic	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
Denmark	1	1	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Estonia	1	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)
Finland	1	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)
France	10	12	0 (0)	0 (0)	3 (25·0)	0 (0)	3 (25·0)	9 (75·0)
Germany	7	10	0 (0)	1 (10·0)	2 (20·0)	0 (0)	3 (30·0)	7 (70·0)
Greece	1	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Hungary	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Ireland	6	10	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (100)
Israel	3	6	6 (100)	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)
Italy	5	5	4 (80·0)	0 (0)	1 (20·0)	0 (0)	5 (100)	0 (0)
Lithuania	1	1	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Malta	1	1	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Norway	5	5	0 (0)	0 (0)	1 (20·0)	0 (0)	1 (20·0)	4 (80·0)
Portugal	4	6	2 (33·3)	0 (0)	0 (0)	0 (0)	2 (33·3)	4 (66·7)
Serbia	3	5	0 (0)	5 (100)	0 (0)	0 (0)	5 (100)	0 (0)
Slovakia	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
Slovenia	1	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
Spain	8	14	0 (0)	0 (0)	4 (28·6)	0 (0)	4 (28·6)	10 (71·4)
Sweden	1	1	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Turkey	11	22	0 (0)	1 (4·5)	19 (86·4)	0 (0)	20 (90·9)	2 (9·1)
UK-England and Northern Ireland	11	29	0 (0)	1 (3·4)	5 (17·2)	0 (0)	6 (20·7)	23 (79·3)
UK-Scotland	5	17	0 (0)	1 (5·9)	0 (0)	0 (0)	1 (5·9)	16 (94·1)
Total	105	194	14 (7·2)	20 (10·3)	43 (22·2)	0	77 (39·7)	117 (60·3)

Iceland, Kosovo, Latvia, Luxembourg, Montenegro, Poland Romania, and Macedonia did not find any *E coli* isolate that was suspected non-susceptible to carbapenems during the study period. *Other mechanism of carbapenem non-susceptibility since none of the genes coding for the four major types of carbapenemases (KPC, NDM, OXA-48-like and VIM) were detected. Data are n, unless specified otherwise.

***Table 3: Escherichia coli* clinical isolates submitted as non-susceptible to carbapenems, confirmed as producing a carbapenemase and type of carbapenemase, by country**

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OXA-48-like enzymes (43 [56%] of 77 isolates) followed by NDM (20 isolates, 26%) and KPC (14 isolates, 18%), albeit with substantial country-to-country variation in relative prevalence (table 2, table 3).

At country level, large proportions of KPC-positive *K pneumoniae* among carbapenem-non-susceptible isolates were found in Italy (187 [96%] of 195 isolates), Israel (31 [80%] of 39 isolates), Greece (56 [65%] of 86 isolates), and Portugal (36 [59%] of 61 isolates). These four countries, plus Cyprus, were the only countries where KPC genes were also detected in *E coli*, albeit very few. OXA-48-like enzymes were common in Turkey, where 98 (79%) of 124 carbapenem-non-susceptible *K pneumonia* and 19 (86%) of 22 *E coli* isolates had these enzymes, followed by Romania, where 50 (74%) of 68 carbapenem-non-susceptible *K pneumoniae* isolates had OXA-48-like enzymes. These enzymes were also frequent in Spain (81 [70%] of 116), Belgium (18 [38%] of 48), France (ten [37%] of 27), and Germany (12 [33%] of 36).

NDM was the most frequent carbapenemase in Serbia (33 [49%] of 67 isolates) and in Montenegro, where all ten submitted carbapenem non-susceptible *K pneumoniae* isolates were NDM-positive. In Greece, NDM was the second most frequent carbapenemase in

	Number of confirmed carbapenemase-producing *K pneumoniae* isolates	Colistin		Fosfomycin		Tigecycline		Total antibiotics tested*	Isolates resistant to all tested antibiotics (%)
		Tested	Resistant (%)	Tested	Resistant (%)	Tested	Resistant (%)		
Austria	10	10	3 (30·0)	10	2 (20·0)	0	..	17	1 (10·0)
Belgium	33	0	..	0	..	0	..	12	5 (15·2)
Bulgaria	2	2	0	2	0	2	0	18	0 (0)
Croatia	7	0	..	0	..	0	..	11	2 (28·6)
Cyprus	1	0	..	0	..	0	..	13	0 (0)
Czech Republic	2	2	1 (50·0)	2	0	2	0	18	0 (0)
Denmark	6	0	..	0	..	0	..	..	..
Estonia	0	0	..	0	..	0	..	18	..
Finland	0	0	..	0	..	0	..	18	..
France	11	11	2 (18·2)	11	2 (18·2)	11	1 (9·1)	18	0 (0)
Germany	22	22	8 (36·4)	16	7 (43·8)	22	2 (9·1)	17	0 (0)
Greece	79	21	4 (19·0)	0	..	21	4 (19·0)	13	15 (19·0)
Hungary	26	26	1 (3·8)	26	5 (19·2)	26	2 (7·7)	18	0 (0)
Ireland	6	6	1 (16·7)	6	1 (16·7)	6	1 (16·7)	18	0 (0)
Israel	34	34	4 (11·8)	34	3 (8·8)	0	..	17	0 (0)
Italy	192	192	77 (40·1)	149	99 (66·4)	192	2 (1·0)	16	11 (5·7)
Latvia	2	0	..	0	..	0	..	11	0 (0)
Lithuania	0	0	..	0	..	0	..	18	..
Luxembourg	8	4	1 (25·0)	1	1 (100)	1	0	15	0 (0)
Malta	9	9	0	9	2 (22·2)	9	1 (11·1)	18	0 (0)
Montenegro	10	0	..	9	5 (55·6)	1	0	12	1 (10·0)
Norway	1	1	0	1	0	1	0	16	0 (0)
Poland	4	3	1 (33·3)	0	..	4	0	16	0 (0)
Portugal	36	0	..	0	..	0	..	15	8 (22·2)
Romania	61	61	43 (70·5)	61	61 (100)	61	11 (18·0)	18	8 (13·1)
Serbia	43	43	6 (14·0)	41	5 (12·2)	38	11 (13·2)	17	2 (4·6)
Slovakia	1	1	0	0	..	1	0	15	0 (0)
Slovenia	3	3	0	3	3 (100)	3	0	18	0 (0)
Spain	102	102	10 (9·8)	102	70 (68·6)	102	19 (18·6)	18	1 (0·9)
Macedonia	2	2	0	0	..	0	..	12	1 (50·0)
Turkey	112	66	19 (28·8)	17	4 (23·5)	27	7 (25·9)	11	24 (21·4)
UK-England and Northern Ireland	25	25	2 (8·0)	0	..	25	3 (12·0)	16	0 (0)
UK-Scotland	0	0	..	0	..	0	..	14	..
Total	850	646	183 (28·3)	500	270 (54·0)	555	29 (5·2)	162	79 (9·3)

Albania, Iceland, Kosovo and Sweden did not find any K pneumoniae isolates that were suspected non-susceptible to carbapenems during the study period. *Mean number of antibiotics tested.

Table 4: **Resistance of confirmed carbapenemase-producing *Klebsiella pneumoniae* to last-line antibiotics and to all tested antibiotics**

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K pneumoniae (12 [14%] of 86). Other countries with notable proportions of NDM-producing *K pneumoniae* were Romania (five [7%] of 68) and Turkey (nine [7%] of 124). NDM-producing *K pneumoniae* were also isolated in another 12 European countries but in small numbers ranging between one and three isolates, though they were also the predominant carbapenemase-producing *K pneumoniae* isolates in Bulgaria and Denmark. In the case of *E coli*, small but noteworthy numbers of NDM-producing isolates were found in Bulgaria (eight [100%] of eight) and Serbia (five [100%] of five). Single isolates of NDM-producing *E coli* were identified in another seven countries.

VIM carbapenemases only found in *K pneumoniae* were the least frequent but represented most of the carbapenemase-producing isolates in Hungary (26 [72%] of 36) and Croatia (five [10%] of 48). Otherwise, only Greece (nine [11%] of 86) and Spain (12 [10%] of 116) had notable numbers of VIM-producing *K pneumoniae,* although these were also found in another seven countries, albeit in low numbers.

12 (33%) of the NELs tested the full panel of 18 recommended antibiotics. Some NELs found it difficult to obtain particular compounds, others used their routine reference service panel, and Denmark did not report any antibiotic susceptibility test results. Last-line antibiotics tested included colistin (tested in 22 NELs), tigecycline (tested in 20 NELs), and fosfomycin (tested in 18 NELs).

For *K pneumoniae,* the proportion of isolates that were reported resistant to all antibiotics varied between zero and 29% (mean 9%, table 4). Resistance to colistin was reported in 183 (28%) of 646 *K pneumoniae* isolates, fosfomycin resistance in 270 (54%) of 500 isolates, and tigecycline resistance (according to its EUCAST recommended breakpoint) in only 29 (5%) of 555. High proportions of *K pneumoniae* resistant to last-line antibiotics were found in Italy, Romania, Turkey, and Spain (table 4). Of the 77 *E coli* with carbapenemases, 57 were tested for susceptibility to colistin with three being resistant, 43 to fosfomycin (two isolates resistant), and 48 to tigecycline (one isolate resistant).

Carbapenem-susceptible comparator isolates of the same species were collected irrespective of anatomical site from clinical material submitted for diagnostic purposes from successive patients. These provided an important and unbiased sample, representative of the local susceptible population, and served as an appropriate control group. Univariate analysis identified six risk factors that were positively associated with carbapenemase-producing *K pneumoniae* or *E coli*, and two factors that were negatively associated (appendix). Four of these risk factors remained significantly and independently associated with carbapenemase-producing *K pneumoniae* or *E coli* in the multivariable model, which included intensive care therapy (OR=1·9, 95% CI 1·4–2·7), hospital admission in the preceding 6 months (OR=2·0, 1·5–2·7), hospital-acquisition (OR=2·6, 1·9–3·7), and travel outside the country of residence in the previous 6 months (OR=3·0, 1·6–5·7).

Discussion

Clinicians increasingly depend on carbapenem antibiotics for the treatment of infections due to otherwise multidrug-resistant bacteria. CPE have been implicated in hospital outbreaks and have the propensity to spread (or disseminate their plasmids) rapidly at local, regional, and international levels.[10–15]

We provide comprehensive survey results on the occurrence of carbapenemase-producing *K pneumoniae* and *E coli* between Nov, 2013, and April, 2014, from 455 hospitals in 34 European countries plus Turkey and Israel, together serving more than 270 million citizens out of a total population of 600 million. During the course of this investigation, NELs successfully expanded their capacity and adjusted workflows to accommodate new diagnostic tests.[16]

However, as with all sampling frameworks for bacteria and epidemiological data, important caveats remain. Despite decisions to minimise workload by concentrating on the two clinically most relevant species and reducing the amount of additional information, nine countries failed to recruit their quota of sentinel sites and an another eight countries did not provide crucial denominator data. In some cases this was because of financial constraints and because the workload could not be accommodated by some of the hospital laboratories that had initially agreed to participate. Some NELs with established routines could not manage to test additional antibiotics. As with other international surveillance systems (EARS-Net), this study relied on routinely available data. The precision of some of the estimates on the occurrence and risk factors of CPE in the European region could therefore still be improved. For example, some countries reported low numbers of index CPE isolates when, judging from previous publications and high endemicity in neighbouring countries, much higher rates would have been expected. In these countries, diagnostic habits might result in a lower sampling density or the recruited sentinel sites were less able to reliably identify carbapenem-non-susceptible isolates despite testing proficiency of the NELs, concealing the true incidence of CPE through these types of ascertainment bias. Moreover, 353 (29%) of 1203 *K pneumoniae* isolates and 117 (60%) of 194 *E coli* isolates that were submitted by the sentinel hospital laboratories as suspected carbapenem-non-susceptible had none of the four major carbapenemases (KPC, NDM, OXA-48-like, and VIM) and were reported as other. This lack of specificity could be the result of a carbapenemase not included in the test panel, or alternative mechanisms such as reduced permeability. At the same time, sentinel laboratories relied on their local routine antibiotic susceptibility tests that might also be the source of potential misclassification. Nevertheless, these first data

on CPE generated in a comprehensive manner will serve as a benchmark against which future initiatives and trends will be measured.

Prevalence of carbapenemase-producing *K pneumoniae* and *E coli* per 10 000 hospital admissions ranged from 6·0 in Italy, to 0·02 in Norway with an average of 1·3. The incidence per 100 000 hospital patient-days ranged from 17·3 in Greece to 0·09 in Lithuania, a mean of 2·5 across all countries. These values will underestimate total CPE incidence, because carbapenemases also occur in other Enterobacteriaceae, albeit less frequently than in *Klebsiella* spp.[17] Moreover, the absence of denominator data from eight countries cautions against our ranking of prevalence. Proportions of carbapenemase-positive bacteria considered in this study varied between countries and between the two species under investigation (table 2, table 3). This might be the result of the differential success of certain clonal lineages in different countries.[10,14] We found a clear association with health care since most isolates were either acquired in hospital, often associated with intensive care treatment, or isolated from patients with previous hospital admission. We also found an association with previous travel outside the country of residence (appendix). But when interpreting this finding, we must consider that many of the highly endemic countries could not provide information on previous travel, which might have led to an inflation of the risk estimate.

Incidence of carbapenemase-producing *K pneumoniae* and *E coli* was highest in southern and southeastern Europe. In Greece, VIM-positive *K pneumoniae* started to expand in the mid-2000s,[18] but that changed with the rapid spread of KPC-producing *K pneumoniae* from around 2007, which subsequently became the dominant CPE.[10] That NDM is now the second-ranking carbapenemase in Greece is striking and raises the concern that there could be a further replacement event by the more recently expanding carbapenemase.[19]

Carbapenemase-producing isolates were less common in *E coli* than in *K pneumoniae*. KPC enzymes were especially rare in *E coli* and were only identified in countries with high proportions of KPC-producing *K pneumoniae*, where they probably reflect a spill-over of resistance genes from the *K pneumoniae* reservoir. Large numbers of *E coli* with OXA-48-like enzymes were found in Belgium, France, Spain, Turkey, and the UK, and NDM carbapenemases in Bulgaria and Serbia. Penetration into *E coli* is of concern because *E coli* spreads in the community more readily than *K pneumoniae*, meaning that infection control interventions that mainly focus on hospitals are less likely to be effective. Moreover, *E coli* from the digestive tract are common vectors for promiscuous plasmids, which could also accelerate epidemic expansion.

In Romania, eight of 12 participating hospitals submitted *K pneumoniae* isolates with OXA-48-like enzymes and most were genetically indistinguishable by DNA fingerprinting, indicating countrywide spread of a single clone.[20] This finding might be analogous to the national expansion of *K pneumoniae* ST258-related clones with KPC-2 or KPC-3 enzymes in Greece, Italy, and Israel, for example, although with a different clonal lineage and carbapenemase type. OXA-48-like carbapenemases were frequent in Malta, Spain, France, and Belgium, where they appear to be repeatedly introduced from northern Africa. Genes coding for NDM seem also to be spreading in the Balkan region, with large numbers in Montenegro, Serbia, and Greece but also extending north into Slovenia and Austria. Surprisingly, no NDM-producing isolates were reported from Albania, Kosovo, or Macedonia, despite their occurrence in adjacent countries and reports from patients transferred from these countries to other European countries.[21]

Only 12 countries tested the complete panel of antibiotics recommended by the study protocol, which makes it difficult to establish the extent to which extensively drug-resistant or pan-drug-resistant Enterobacteriaceae phenotypes prevail in European hospitals.[22] Clinically more important than these epithets are the proportions of carbapenemase-producing isolates that are also resistant to last-line antibiotics such as colistin, fosfomycin, and tigecycline. We generally observed that high-CPE-incidence countries saw more resistance to these last-line antibiotics as well, perhaps reflecting greater use and selection pressure. However, there were exceptions. Germany, which has a moderate CPE incidence, reported much higher rates of colistin and fosfomycin resistance than other moderate incidence countries. More worrying is the fact that the overall proportions of fosfomycin resistance (54%) and colistin resistance (28%) have become so high among carbapenemase-producing *K pneumoniae* that even the so-called colistin-plus treatment regimens favoured for infections due to CPE are increasingly jeopardised, leaving little choice in many cases.[23,24]

As exemplified with this structured survey, the EuSCAPE project documented an encouraging degree of commitment from NELs, and shows that the political and logistical challenges of establishing a framework of enhanced sentinel surveillance for CPE can be overcome in Europe, Turkey, and Israel. There were large variations across Europe with respect to the distribution of the four major types of carbapenemases among clinical isolates of *K pneumoniae* and *E coli*. Clinicians should pay attention to antibiotic susceptibility testing results and be alerted when isolates show any degree of carbapenem non-susceptibility, which would require confirmation of carbapenemase production. For most isolates, there were still alternative options for patient treatment; however, resistance to all tested antibiotics was also reported, which is another reminder of the urgent need for prevention and control of CPE in Europe and emphasises the need for novel antibacterial agents that are active against carbapenem-resistant bacteria.

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Contributors

HG and DLM designed the study. HG, CG, BA, ATA, RC, YC, AWF, CGG, YG, MG, LP, GMR, HS, AV, TW, NW, DLM and the EuSCAPE Working Group modified the sampling frame and defined diagnostic procedures. HG and CG wrote the survey protocol. All members of the EuSCAPE Working Group recruited sentinel sites and collected isolates and epidemiological data and carried out diagnostic procedures. HG, CG, and all members of the EuSCAPE Working Group supervised and coordinated the survey. DMA, CTT, and CG developed tools for data collection. CG managed data and isolate collection. HG and CG analysed the data. HG and CG wrote the first draft manuscript. DML, DLM, NW, BA, AAT, RC, YC, AWF, CGG, YG, MG, PN, LP, GMR, HS, AV, TW, and the EuSCAPE Working Group provided feedback, contributed with comments, reviewed and edited the manuscript.

The members of the European Survey on Carbapenemase-Producing Enterobacteriaceae, (EuSCAPE) Working Group are:

EU Member States: *Austria*—Petra Apfalter and Rainer Hartl; *Belgium*—Youri Glupczynski and Te-Din Huang; *Bulgaria*—Tanya Strateva and Yuliya Marteva-Proevska; Croatia—Arjana Tambić Andrašević and Iva Butic; *Cyprus*—Despo Pieridou-Bagatzouni and Panagiota Maikanti-Charalampous; *Czech Republic*—Jaroslav Hrabak and Helena Zemlickova; *Denmark*—Anette Hammerum and Lotte Jakobsen; *Estonia*—Marina Ivanova and Anastasia Pavelkovich; *Finland*—Jari Jalava and Monica Österblad; *France*—Sophie Vaux and Laurent Dortet; *Germany*—Martin Kaase and Sören G Gatermann; *Greece*—Alkiviadis Vatopoulos and Kyriaki Tryfinopoulou; *Hungary*—Ákos Tóth and Laura Jánvári; *Ireland*—Teck Wee Boo and Elaine McGrath; *Italy*—Annalisa Pantosti and Monica Monaco; *Latvia*—Arta Balode and Mara Saule; *Lithuania*—Jolanta Miciuleviciene and Aiste Mierauskaite; *Luxembourg*—Monique Perrin-Weniger and Paul Reichert; *Malta*—Nina Nestorova and Sonia Debattista; *Poland*—Dorota Żabicka and Elżbieta Literacka; *Portugal*—Manuela Caniça and Vera Manageiro; *Romania*—Maria Damian and Brandusa Lixandru; *Slovakia*—Milan Nikš and Eva Schreterova; *Slovenia*—Mateja Pirš and Tjaša Cerar; *Spain*—Jesús Oteo and Belén Aracil; *Sweden*—Christian G Giske and Karin Sjöström; *England and Northern Ireland*—Neil Woodford and Katie Hopkins; *Scotland*—Camilla Wiuff and Derek J Brown.
EEA countries: *Iceland*—Hordur Hardarson; *Norway*—Ørjan Samuelsen and Bjørg Haldorsen.
EU enlargement countries: *Albania*—Andi Koraqi and Denada Lacej; *Kosovo**—Lul Raka and Arsim Kurti; *Montenegro*—Gordana Mijovic and Milena Lopicic; *Serbia*—Zora Jelesić and Anika Trudic; *Macedonia*—Ana Kraftandzieva and Elena Trajkovska-Dokic; *Turkey*—Deniz Gür and Aslı Cakar.
Other country: *Israel*—Yehuda Carmeli and Amos Adler.
*This designation is without prejudice to positions on status, and is in line with UNSCR 1244/1999 and the ICJ Opinion on the Kosovo declaration of independence.

Declaration of interests

BA and DLM are employed by the European Centre for Disease Prevention and Control (ECDC), the agency that provided funding for the survey, and manager of the corresponding specific framework service contract (ECDC/2012/055). YC or his institute received grants, honoraria, travel support, consulting fees, and other forms of financial support from MSD, AstraZeneca, DaVoltera, Intercell AG, Allecra Therapeutics, BioMerieux SA, Rempex Pharmaceuticals, Nariva, Proteologics; outside the submitted work. MG reports personal fees from Liofilchem, bioMérieux, groupH; outside the submitted work. DML reports grants, personal fees and other financial support from Merck, Meiji, AstraZeneca, Roche, Dechra, Allecra, Leo, Nordic, Pfizer, Curetis, Tetraphase, Achaogen, Shionogi, Auspherix, Discuva, VenatoRx Wockhardt, Accelerate, Centauri, AOP Orphan, Melinta; outside the submitted work. GMR reports grants, personal fees and non-financial support from Accelerate Achaogen, Alifax, Angelini ACRAF, AstraZeneca, Basilea, Becton Dickinson, bioMérieux, Biotest, Cepheid, Check-points, Curetis, Medivir, Menarini, Merck/Cubist Novartis, Pfizer, Rempex/TMCo, Venatorx, Zambon, Elitech, Nordic Pharma; outside the submitted work. HS reports personal fees for board memberships, consultancies, grants and lectures including service on speakers bureaus from Basilea Pharmaceutica International, FAB Pharma, Roche Pharma Switzerland, The Medicines Company, Astella Pharma, Cubist Pharmaceutical, Durata Therapeutics, Gilead Sciences Germany, Novartis Pharma, Novartis Pharma Germany, Pfizer Pharma Germany, Astellas Pharma Germany, AstraZeneca Germany, MSD Sharp and Dohme Germany; outside the submitted work. NW reports grants, personal fees and other support from the Department of Health (DH), Enigma, the European Centre for Disease Prevention and Control (ECDC), Birmingham University, Diagnostics Inc., AstraZeneca, Roche Ltd, Momentum Bioscience, Pharmaceuticals, USA, Bio-Rad, France, BioMerieux, Meiji Seika Pharma Co; outside the submitted work. All other authors declare no competing interests.

Acknowledgments

We thank the national expert/reference laboratories and all sentinel hospital laboratories for their voluntary participation in this study. We also acknowledge the support offered by Christine Walton and Vivienne Jones of UK-NEQAS and the execution of the external quality assessment exercise. We also thank Carola Schinkel from Tomorrow's Events for the organisation of the EuSCAPE project meetings and the capacity-building workshop. We thank Tjibbe Donker for technical support.

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