Enhanced Surveillance of Carbapenemase-Producing Enterobacterales (CPE), Q1-2 2019

Key points

- In December 2018, the Infectious Diseases Regulations were updated, with the addition of the first detection of CPE from a screening or diagnostic specimen, representing either colonisation or non-invasive infection to the long-standing requirement to notify every case of invasive CPE infection. At the time of finalising this report, work is ongoing to facilitate this expanded notification of CPE to Public Health Departments via Computerised Infectious Diseases Reporting (CIDR)
- The case definition for enhanced surveillance of CPE has been amended to avoid counting CPE cases more than once in a given year, to more accurately reflect the burden, particularly in hospitals
- In Q1-2 2019, 346 confirmed CPE isolates from 346 patients were reported by 31 (of 37) microbiology laboratories, with the majority detected from screening specimens (88%). Five laboratories reported zero CPE isolates and one laboratory did not provide data
- Hospital inpatients accounted for the vast majority of new CPE detections (n=310; 90%), followed by hospital outpatients (n=15), patients attending general practitioners (n=15) and long-term care facility (LTCF) residents (n=6)
- Information on patient placement within 24 hours of a suspected CPE laboratory result was not reported for 20% of inpatients. Where data was reported, most were isolated (n=221; 89%). Twenty-four patients (10%) were discharged before the laboratory result was available and four patients (2%) were not isolated within 24 hours

Introduction

Due to recent taxonomic changes, many of the species comprising the family *Enterobacteriaceae* have now been reclassified within the Order Enterobacterales. Carbapenemase-producing Enterobacterales (CPE), sometimes referred to as carbapenem-resistant Enterobacterales (CRE), are a growing threat to public health due to very limited options for treatment of infection. The European Antimicrobial Resistance Surveillance Network (EARS-Net), which is coordinated by the European Centre for Disease Prevention and Control (ECDC) monitors antimicrobial resistance trends in key pathogens causing bloodstream infections (BSI), which are a type of invasive infection. In addition to BSI, other more common infection types (e.g. urinary tract or wound infections), along with asymptomatic and often unrecognised colonisation contribute to the successful dissemination of CPE, particularly in healthcare settings. From EARS-Net data for European countries, the proportion of *K. pneumoniae* isolates causing BSI in 2015 that were CPE varied from 0% in some Nordic countries to 33% in Italy and 62% in Greece.

In 2011, invasive CRE infection was made notifiable in Ireland and a voluntary enhanced surveillance system for all CRE isolates was launched. In 2013, in response to an increasing trend in multi-drug resistant *K. pneumoniae* (MDRKP) invasive infections reported to EARS-Net, a proportion of which were also carbapenem resistant, a national MDRKP outbreak control team was established, along with an enhanced surveillance scheme for all MDRKP isolates (from screening and diagnostic specimens, including colonisation, non-invasive and invasive infections) from January 2014. To the end of 2016, MDRKP was reported by 88% of Irish hospitals, with cases also observed in primary and residential care.

The surveillance system indicated widespread dissemination of MDRKP in Ireland. Of particular concern was the rapid increase in the proportion of MDRKP that were also carbapenemase producers (a 195% increase in 2016 versus 2015). In response to this threat, the MDRKP and voluntary CRE surveillance schemes were replaced with a CPE enhanced surveillance scheme in January 2017. In December 2018, the Infectious Diseases Regulations were further updated, with the addition of newly-detected CPE from screening or

diagnostic specimens, representing colonisation or non-invasive infection to the requirement to notify every case of invasive CPE infection.

The National Carbapenemase Producing Enterobacterales Reference Laboratory Service (NCPERLS), based at Galway University Hospital has provided reference services since October 2012, with the annual total number of isolates from patients with newly-confirmed CPE submitted to the reference laboratory increasing from 50 in 2013 to 537 in 2018.

Revised case definition for enhanced surveillance of CPE

- The **first isolate per patient per year** of any Enterobacterales species that is a confirmed carbapenemase-producer from any specimen type, either infection or colonisation (e.g. if the first isolate is a screening specimen, a subsequent BSI due to the same isolate won't be counted in this surveillance system)
- If the same carbapenemase is found in isolates of two or more species from the same patient, then only the first species is included (e.g. OXA-48 *E. coli* followed by OXA-48 *Enterobacter cloacae*; only the OXA-48 *E. coli* will be counted in surveillance)
- If a different carbapenemase is found in an isolate of any species in a subsequent specimen from the same patient, then the first isolate with this other carbapenemase is included (e.g., OXA-48 *E. coli*, followed by NDM-1 *K. pneumoniae*; both will be counted in surveillance)
- If a carbapenemase gene is detected by direct PCR on the specimen, but an organism is not isolated or fails to grow, such cases should not be reported
- The case definition for enhanced surveillance does not distinguish between isolates from the same patient identified in different hospitals

Results

- As the case definition now only requires reporting of the first isolate of any Enterobacterales species with the same carbapenemase enzyme for the year, patients are counted once in the enhanced CPE surveillance programme, unless a subsequent isolate from the same patient is reported with a different carbapenemase
- At 346, the total patients reported to enhanced CPE surveillance in Q1-2 2019 was slightly higher than the NCPERLS total of 331 patients with newly-confirmed CPE:
    - The CPE enhanced surveillance reports on the first isolate of CPE per patient per year, based on the specimen collection date, while NCPERLS reports on newly-confirmed patients with CPE, based on the date the isolate was received by NCPERLS.
    - Of the 346 cases reported in Q1-2 2019, 328 were new cases with 18 cases having previously been first reported between 2017 and 2018
    - In CPE enhanced surveillance, it is not possible to definitively confirm when the same patient with CPE is identified across hospitals, due to the absence of a unique national patient identifier
    - CPE enhanced surveillance collects data on the patient's location at the time of CPE detection, which does not confirm that colonisation or infection was acquired at this location
    - Although CPE screening practice is now much more widespread and more uniform than formerly there is still variation in screening practice between hospitals and over time. This impacts on the number of CPE detections, as hospitals and hospital groups with higher rates of CPE screening may have higher rates of CPE detection and vice versa
- **Appendix 1** summarises the data reported by acute hospitals and hospital groups in Q1-2 2019. Thirty-one microbiology laboratories reported 346 CPE isolates from 346 patients, with five laboratories reporting zero isolates and one laboratory that did not submit data
- Nationally, the majority were OXA-48 (n=231, 67%), with KPC predominant in the University of Limerick (UL) hospital group (n=30; 71% of KPC isolates). In addition, the majority of OXA-181/232 and OXA-244 (both variants of OXA-48) and VIM cases were found in the Saolta hospital group (Figure 2). Three

species accounted for 76% of all CPE isolates: *E. coli* (31%), *Enterobacter cloacae* (23%) and *K. pneumoniae* (22%), as displayed in Table 1 and Figure 1

- Two patients had two different carbapenemases detected from the same screening specimen: one with OXA-48 and NDM and one with OXA-181 and NDM
- Males (59%) and patients aged ≥59 years (75%) accounted for the majority of cases
- The majority of isolates were detected from screening specimens (n=303; 88%), with the remainder from diagnostic specimens (n=43; 12%), of which six were from blood and two from other normally sterile sites (pleural fluid and bone)
- Inpatients in 36 acute hospitals accounted for the majority of CPE (n=310; 90%):
    - Admission and specimen collection dates were reported for 300 (97%), with a median interval between admission and detection of CPE of six days (range = 0-179)
    - CPE from diagnostic specimens were isolated from patients who had been inpatients (n=28), GP patients (n=12), outpatients (n=2) and LTCF residents (n=1). Of inpatients, information on antimicrobial therapy was provided for 20 cases (71%), with 13 patients (56%) prescribed antimicrobials with activity against CPE prior to case notification, suggesting CPE infection
    - For inpatients, information on patient placement within 24 hours of the laboratory reporting a suspected carbapenemase was provided for 249 isolates (80%), with the majority of patients isolated (n=221; 89%). Twenty-four patients were (10%) discharged by the time of the result. Four patients (2%) were not isolated within 24 hours. Isolation status was not reported for 61 (20%) of inpatient CPE isolates
- The remaining isolates were detected from outpatients (n=15), patients of general practitioners (GP) (n=15) and LTCF residents (n=6)
- Outcome data at the time of reporting the CPE to enhanced surveillance was sought for inpatients. Of 310 inpatients, 23 (7%) died. However, information on the contribution of CPE to the cause of death is not collected. Outcome data was not provided for 10% of inpatients
- A 26% increase in reported CPE cases was observed from 2017 to 2018 (from 449 to 565). While CPE detection from screening specimens increased by 39% (from 354 to 491), a 22% reduction in detection from diagnostic specimens (from 95 to 74) was observed. However, within that category, an increase in CPE detections from blood (from seven to ten) was noted

Table 1. Summary of Enterobacterales and carbapenemase type, Q1-2 2019

Enterobacterales species	Enzyme						Total
	OXA-48	KPC	NDM	OXA-48-Like*	VIM	Other**	
E. coli	76	2	19	10	0	1	**108**
Enterobacter cloacae	57	4	5	3	10	0	**79**
K. pneumoniae	44	15	12	3	1	1	**76**
Citrobacter spp.	20	16	0	1	1	0	**38**
K. oxytoca	26	1	0	2	1	0	**30**
Other Enterobacterales†	8	4	2	1	0	0	**15**
TOTAL	**231**	**42**	**38**	**20**	**13**	**2**	**346**

*includes 14 isolates with OXA-181/232 and six with OXA-244
** includes one isolate with both OXA-48 and NDM and one isolate with both OXA-181 and NDM
†includes five *Enterobacter* spp. three *K. variicola* isolates, two *Pantoea* spp. and one each of *other Escherchia* spp., *K. aerogenes*, *K. ascorbata*, *P. mirabilis* and *S. marcescens*

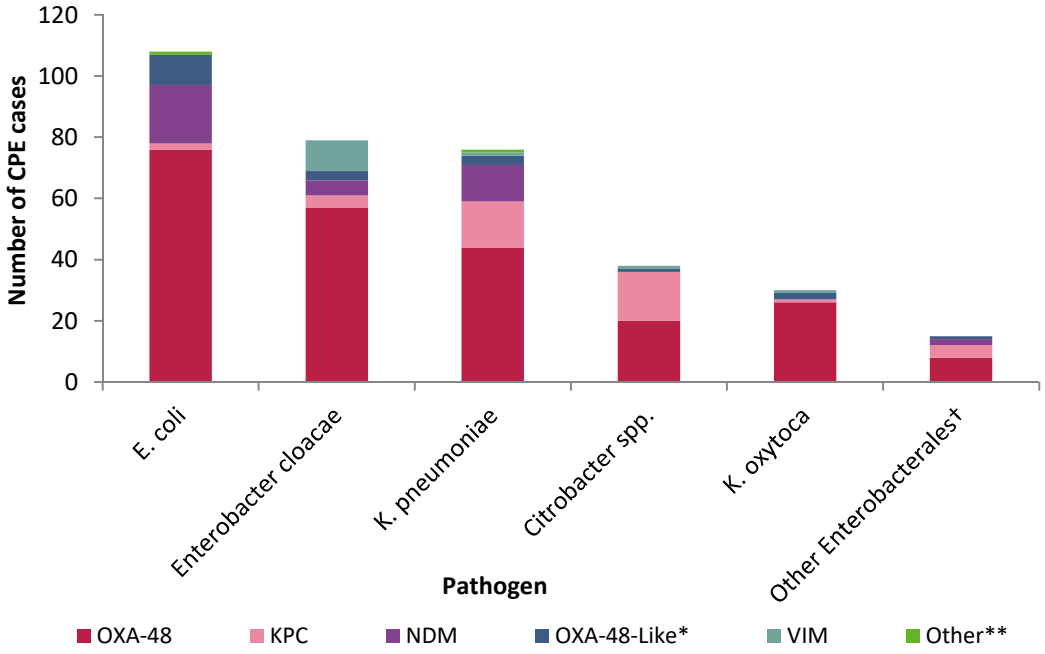

Figure 1. Enterobacterales and carbapenemase type, Q1-2 2019

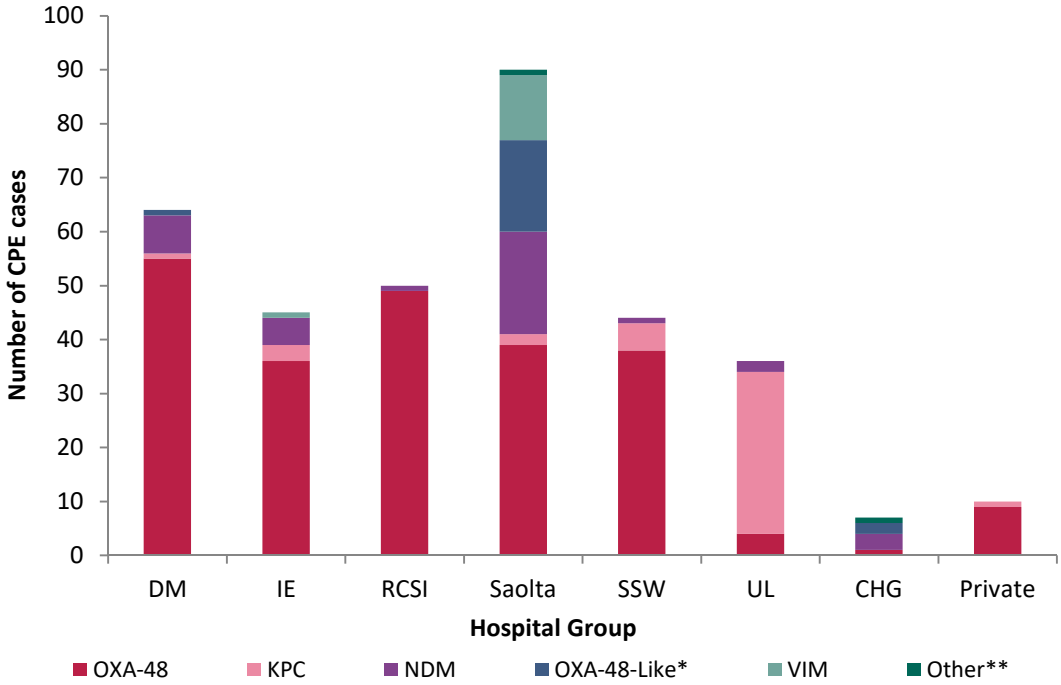

Figure 2. Distribution of carbapenemase type by Hospital Group, Q1-2 2019

DM, Dublin Midlands; IE, Ireland East; RCSI Hospitals; Saolta, West North-West; SSW, South South-West; UL, University of Limerick; CHG, Children's Hospitals

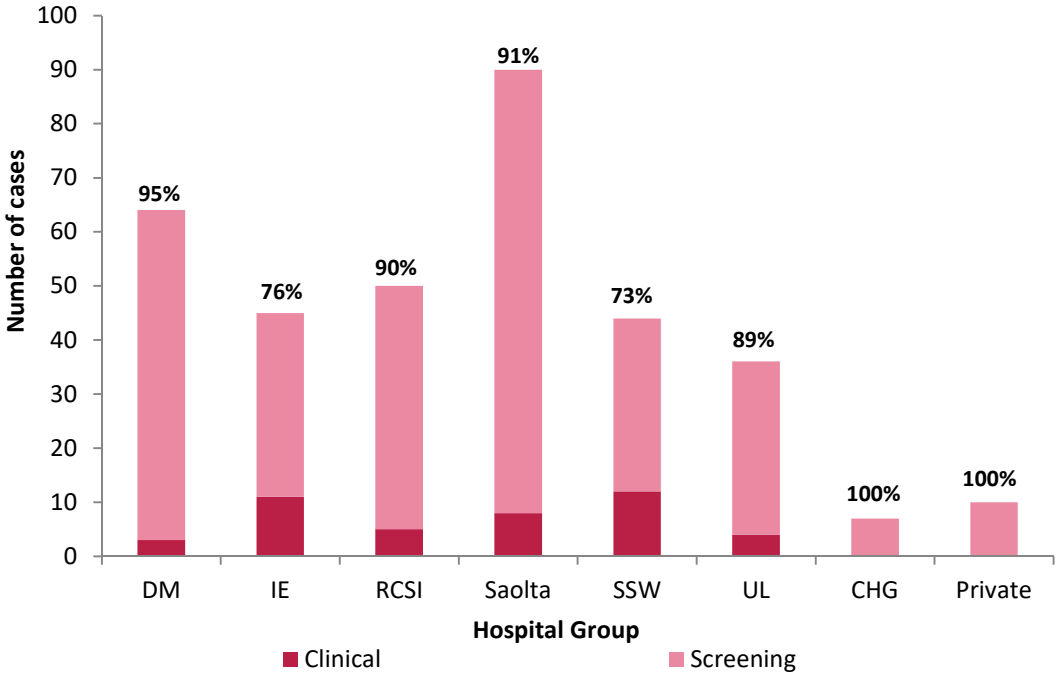

Figure 3. Distribution of CPE isolates from screening and diagnostic specimens (and proportion from screening) by Hospital Group, Q1-2 2019

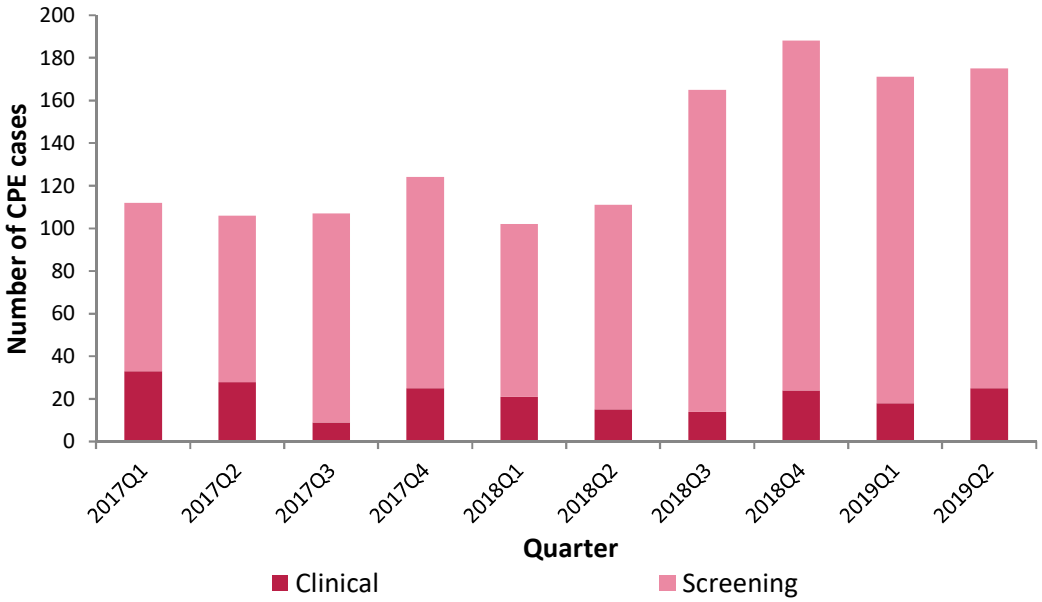

Figure 4. Quarterly distribution of CPE isolates from screening and diagnostic specimens (and proportion from screening), 2017-2019

Table 2. Summary of CPE (based on 1st isolate per patient **per year**, as per revised case definition), 2017, 2018 and 2019 (Q1-2 only)

	TIME PERIOD						
	2017		2018		2019Q1-2		COMMENT
	n	%	n	%	n	%	
CPE cases (based on case definition of 1st isolate per patient)	449		566		346		93% of all cases associated with 53 (of 60) acute hospitals, including outpatients (over all years)
Carbapenemase detected							
OXA-48	328	73%	393	69%	231	67%	
KPC	57	13%	91	16%	42	12%	
NDM	37	8%	27	5%	38	11%	
OXA-48-Like	3	1%	27	5%	20	6%	44 OXA-181/232 and 6 OXA-244
VIM	11	2%	20	4%	13	4%	
IMI	2	<1%	4	1%	0	0%	
IMP	9	2%	1	<1%	0	0%	
Combination of 2 enzymes	2	<1%	3	1%	2	1%	6 OXA-48/NDM and 1 OXA-181/NDM
First organism from each patient in which carbapenemase was detected							
E. coli	139	31%	155	27%	108	31%	
Enterobacter cloacae	94	21%	118	21%	79	23%	
K. pneumoniae	105	23%	133	23%	76	22%	
Citrobacter spp.	50	11%	67	12%	38	11%	
Klebsiellae oxytoca	43	10%	53	9%	30	9%	
Other *Enterobacter* species	5	1%	28	5%	5	1%	
Other *Enterobacterales* species	13	3%	12	2%	10	3%	
Diagnostic vs screening							
Diagnostic	95	21%	74	13%	43	12%	
Screening	354	79%	492	87%	303	88%	
Source (specimen type for Diagnostic isolates only)							
Blood/other normally sterile site	10	11%	11	15%	8	19%	
Urine	49	52%	44	59%	20	47%	
Sputum/respiratory	13	14%	8	11%	6	14%	
Swab/tissue/pus/other	23	24%	11	15%	9	21%	
Location							
Hospital*	408	91%	534	94%	325	94%	
Inpatient (non-ICU)	*325*	*72%*	*447*	*79%*	*282*	*82%*	
ICU	*26*	*6%*	*40*	*7%*	*8*	*2%*	
ED	*27*	*6%*	*28*	*5%*	*20*	*6%*	
Outpatient	*30*	*7%*	*19*	*3%*	*15*	*4%*	
Nursing home&LTCF/GP	41	9%	32	6%	21	6%	
Nursing home&LTCF	*29*	*6%*	*17*	*3%*	*6*	*2%*	
GP	*12*	*3%*	*15*	*3%*	*15*	*4%*	

Table 2 (continued). Summary of CPE (based on 1st isolate per patient **per year**, as per revised case definition), 2017, 2018 and 2019 (Q1-2 only)

	TIME PERIOD						COMMENT
	2017		2018		2019Q1-2		
Demographics							
Male	258	57%	326	58%	203	59%	
Age range	1-105		0-103		0-97		
Median age	69		71		71		
Inter-quartile range	57-80		61-80		59-80		75% of patients were aged 57 years or older in 2017 61 years or older in 2018 and 59 years or older in Q1-2 2019
Interventions (for in-patients only)							
*Total no. CPE cases from inpatients w/ diagnostic samples**	71		48		28		
Cases treated for CPE infection?							
Treated for infection	24	34%	22	46%	13	46%	
Not treated for infection	18	25%	14	29%	7	25%	
Not applicable (discharged before confirmed)			2	4%	2	7%	
Unknown/Not answered	29	41%	10	21%	6	21%	
Total no. CPE cases from inpatients †	378		515		310		
Isolation within 24 hours of CPE identified?							
Isolated within 24 hours	253	67%	383	74%	221	71%	
Not isolated within 24 hours	3	1%	7	1%	4	1%	
Not applicable (discharged before confirmed)	17	4%	29	6%	24	8%	
Unknown/Not answered	105	28%	96	19%	61	20%	
Potential association with hospital (for inpatients only)							
Proportion detected **>2 days** after admission, which may be indicative of potential acquisition in the facility		69%		68%		64%	Date of admission provided for 85%, 97% and 97% of inpatients in 2017, 2018 and Q1-2 2019, respectively
Outcome by time of reporting (for inpatients only)							
Died (but not known if cause of death)	28	7%	56	11%	23	7%	
Survived	248	66%	368	71%	255	82%	
Unknown/Not answered	102	27%	91	18%	32	10%	

* includes Inpatients (non-ICU), ICU, ED and Outpatients

† includes in-patient (non-ICU), ICU and ED

Appendix 1. Total CPE cases reported to enhanced CPE surveillance by acute hospitals, Q1-2 2019

Hospital Group	HOSPITAL	Category	Total CPE	GP or Long-term care	Outpatients	Hospitalised patients	% cases detected on screening	%Hospitalised diagnostic cases that were treated†	%Hospitalised cases that were isolated†
Dublin Midlands	Coombe Womens and Infants University Hospital	Specialist	1	0	1	0	100%	NA	NA
	Midland Regional Hospital, Portlaoise	General	2	0	0	2	100%	NA	50%
	Midland Regional Hospital, Tullamore	General	4	0	0	4	100%	NA	50%
	Naas General Hospital	General	4	0	0	4	100%	NA	75%
	St James's Hospital	Tertiary	27	4	2	21	89%	50%	100%
	St Luke's Hospital, Rathgar	Specialist	1	0	0	1	100%	NA	0%
	Tallaght University Hospital	Tertiary	25	0	0	25	100%	NA	*
Dublin North East (RCSI)	Beaumont Hospital	Tertiary	44	1	1	42	89%	100%	88%
	Cavan General Hospital	General	3	0	0	3	100%	NA	67%
	Connolly Hospital, Blanchardstown	General	2	0	0	2	100%	NA	100%
	Louth County Hospital, Dundalk	General	0	0	0	0	NA	NA	NA
	Our Lady of Lourdes Hospital, Drogheda	General	1	0	0	1	100%	NA	0
	Rotunda Hospital	Specialist	0	0	0	0	NA	NA	NA
Ireland East	Cappagh National Orthopaedic Hospital	Specialist	1	0	1	0	100%	NA	NA
	Mater Misericordiaie University Hospital	Tertiary	17	1	0	16	71%	0%	94%
	Midland Regional Hospital, Mullingar	General	1	0	0	1	100%	NA	100%
	National Maternity Hospital, Holles St.	Specialist	0	0	0	0	NA	NA	NA
	Our Lady's Hospital, Navan	General	1	0	0	1	100%	NA	*
	Royal Victoria Eye and Ear Hospital, Dublin	Specialist	1	0	1	0	100%	NA	NA
	St Columcille's Hospital, Loughlinstown	General	0	0	0	0	NA	NA	NA
	St Luke's Hospital, Kilkenny	General	5	0	0	5	80%	100%	100%
	St Michael's Hospital, Dun Laoghaire	General	3	0	0	3	67%	NA	*
	St Vincent's University Hospital, Elm Park	Tertiary	13	2	1	10	77%	100%	*
	Wexford General Hospital	General	3	0	0	3	67%	NA	67%
Midwest (UL)	Croom Hospital	Specialist	1	0	0	1	100%	NA	*
	Ennis Hospital	General	3	0	0	3	67%	NA	67%
	Nenagh Hospital	General	1	0	0	1	100%	NA	100%
	St John's Hospital, Limerick	General	1	0	1	0	0%	NA	*
	University Hospital Limerick	Tertiary	29	1	0	28	97%	*	*
	University Maternity Hospital Limerick	Specialist	1	0	1	0	0%	NA	NA

Appendix 1 (continued). Total CPE cases reported to enhanced CPE surveillance by acute hospitals, Q1-2 2019

Hospital Group	HOSPITAL	Category	Total CPE	GP or Long-term care	Outpatients	Hospitalised patients	% cases detected on screening	%Hospitalised diagnostic cases that were treated†	%Hospitalised cases that were isolated†
South/South West	Bantry General Hospital	General	0	0	0	0	NA	NA	NA
	Cork University Hospital	Tertiary	11	2	0	9	73%	100%	100%
	Kerry General Hospital, Tralee	General	0	0	0	0	NA	NA	*
	Kilkreene Orthopaedic Hospital, Co. Kilkenny	Specialist	0	0	0	0	NA	NA	NA
	Mallow General Hospital	General	0	0	0	0	NA	NA	NA
	Mercy University Hospital	General	4	0	1	3	75%	0%	100%
	South Infirmary/Victoria University Hospital, Cork	General	0	0	0	0	NA	NA	NA
	South Tipperary General Hospital, Clonmel	General	3	0	0	3	100%	NA	67%
	University Hospital Waterford	Tertiary	26	4	1	21	69%	100%	95%
Saolta (West/Northwest)	Galway University Hospitals	Tertiary	48	0	2	46	94%	67%	80%
	Letterkenny General Hospital	General	15	3	0	12	80%	NA	83%
	Mayo General Hospital, Castlebar	General	15	3	0	12	93%	NA	92%
	Portiuncula Hospital, Ballinasloe	General	1	0	0	1	100%	NA	100%
	Roscommon County Hospital	General	0	0	0	0	NA	NA	NA
	Sligo Hospital	General	11	0	1	10	91%	0%	50%
CHG	Children's University Hospital, Temple St.	Specialist	4	0	0	4	100%	NA	*
	Our Lady's Children's Hospital, Crumlin	Specialist	3	0	0	3	100%	NA	100%
	Tallaght Children's Hospital	Specialist	0	0	0	0	NA	NA	NA
Private	Aut Even Hospital, Kilkenny	Private	0	0	0	0	NA	NA	NA
	Beacon Hospital, Sandyford	Private	*	*	*	*	*	*	*
	Blackrock Clinic	Private	1	0	0	1	100%	NA	100%
	Bon Secours Hospital, Cork	Private	0	0	0	0	NA	NA	NA
	Bon Secours Hospital, Galway	Private	0	0	0	0	NA	NA	NA
	Bon Secours Hospital, Glasnevin	Private	2	0	0	2	100%	NA	*
	Bon Secours Hospital, Tralee	Private	0	0	0	0	NA	NA	NA
	Galway Clinic, Doughiska	Private	5	0	0	5	100%	NA	100%
	Hermitage Medical Clinic, Lucan	Private	0	0	0	0	NA	NA	NA
	Mater Private Hospital, Cork	Private	0	0	0	0	NA	NA	NA
	Mater Private Hospital, Dublin‡	Private	0	0	0	0	NA	NA	NA
	St Vincent's Private Hospital	Private	1	0	0	1	100%	NA	*
	Other acute (e.g. renal outpatient)/non-acute		1	0	1	0	100%	NA	NA
	Total		**346**	**21**	**15**	**310**	**88%**	**65%**	**71%**

CHG, Children's Hospital Group; † Data not necessarily complete for each hospital (% only calculated if response given to >50% of cases) and does not include cases where the patient was discharged before the result was known; ‡ No data provided for Q2 2019; * No data or insufficient data provided; NA, not applicable; It should not be assumed that the location of the patient at the time CPE is detected represents the location, including hospital or hospital group, in which colonisation or infection was acquired

Glossary of terms

Carbapenems	Broad spectrum beta lactam antibiotics often reserved for treatment of multi-drug resistant infections and infections in critically-ill patients. They bind to proteins in the bacterial cell wall, thereby stopping the cell wall from being synthesised. Examples include meropenem and ertapenem
Carbapenemases	Enyzmes produced by bacteria that hydrolyse or break down carbapenem antibiotics rendering them ineffective, thus enabling the bacteria to survive in their presence. Examples include KPC, OXA-48, NDM, VIM and IMP
CPE	**C**arbapenemase **p**roducing Enterobacterales (was ***E****nterobacteriaceae*)
CRE	**C**arbapenem **r**esistant Enterobacterales (was ***E****nterobacteriaceae*)
Enterobacteriaceae	Family of bacteria, often referred to as coliforms, which are found in the enteric tract/gut of humans and animals where they make up a large part of the normal flora and are usually harmless. They are important causes of infections such as; urinary tract and wound infections, BSI, meningitis and pneumonia. Examples include; *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter cloacae*
Enterobacterales	Recent taxonomic studies have narrowed the definition of the family *Enterobacteriaceae*. Some previous members of this family are now included in other families within the Order Enterobacterales*;* hence Enterobacterales is now more appropriate than *Enterobacteriaceae* for grouping the different species considered as coliforms
IMI	Less common type of carbapenemase
IMP	Less common type of carbapenemase
KPC	Common type of carbapenemase (***K****lebsiella* ***p****neumoniae*-**c**arbapenemase)
NDM	Common type of carbapenemase (**N**ew **D**elhi **m**etallo-beta-lactamase)
OXA-48	Common type of carbapenemase
OXA-181/232	Variant of OXA-48
OXA-244	Variant of OXA-48
VIM	Less common type of carbapenemase