Carbapenemase Producing *Enterobacterales* (CPE) in Ireland: 2017

Key points

- The case definition has been amended to avoid counting CPE cases in the same hospital more than once and thus more accurately reflect the burden on CPE in Ireland, particularly in Irish hospitals
- In 2017, 449 confirmed CPE isolates were reported by 32 microbiology laboratories, with the majority detected from screening specimens (79%). Seven laboratories reported zero isolates
- The distribution by patient location at specimen collection was: hospital inpatient (n=378; 84%), hospital outpatient (n=30), long-term care facility resident (n=29) and patients attending general practitioners (n=12)
- Data on patient isolation status within 24 hours of a suspected CPE laboratory result was not reported for 28% of inpatient cases. Where data was reported, the majority of inpatients were isolated (n=254; 92%), with 20 (7%) who were discharged prior to the laboratory result being available. Three patients were not isolated

Introduction

Due to recent taxonomic changes, many of the species comprising the family *Enterobacteriaceae* have now been re-classified within the Order *Enterobacterales*). Carbapenemase producing *Enterobacterales* (CPE), often interchangeably known as carbapenem resistant *Enterobacterales* (CRE) are a growing threat to public health due to very limited options for treatment of infection.

In 2015, the proportion of invasive carbapenem resistant *K. pneumoniae* isolates causing bloodstream infection (BSI) reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net) varied from 0% in some Nordic countries to 33% in Italy and 62% in Greece. However, BSI represent the tip of the iceberg, as other more common infection types (e.g., urinary tract or wound infections) and asymptomatic and often unrecognised enteric/gut colonisation also contribute to the successful dissemination of CPE, particularly in healthcare settings.

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 invasive multi-drug resistant *K. pneumoniae* (MDRKP) infections, a proportion of which were also carbapenem resistant, a national MDRKP outbreak control team was established, along with a mandatory enhanced surveillance scheme for all MDRKP isolates (from invasive and non-invasive infections, colonisation and active screening) 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 observed increase in the proportion of MDRKP that were also carbapenemase producers (195% increase in 2016 versus 2015). In response to this threat, the mandatory MDRKP and voluntary CRE surveillance schemes were replaced with the mandatory CPE enhanced surveillance scheme in January 2017. 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 patients with newly-confirmed CPE increasing from 50 in 2013 to 433 in 2017.

Revised case definition

- The **first isolate per patient** of any *Enterobacterales* species that is a confirmed carbapenemase-producer from any specimen type, either infection or carriage: (e.g., if first isolate is a screening specimen, a subsequent BSI due to the same isolate won't be counted in surveillance)
- 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 an organism is not isolated or fails to grow, but a carbapenemase is detected by direct PCR on the specimen, such CPEs should not be reported
- The case definition for enhanced surveillance does not distinguish between isolates from the same patient identified in different hospitals.

Results

Appendix 1 summarises the data reported by acute hospitals and Hospital Groups in 2017.

Thirty-two microbiology laboratories reported 449 isolates from 447 patients, with seven laboratories reporting zero isolates. In 2017, one laboratory did not submit data for quarters 3 and 4 due to on-going resource issues and another laboratory did not submit data for quarter 4.

- If probable duplicate patients between hospitals are excluded (based on date-of-birth, gender or specific information supplied), the total number of patients reported to enhanced CPE surveillance in 2017 was 427, which is similar to the NCPERLS total of 433 patients with newly-confirmed CPE. It is noteworthy that there are differences in what is counted: NCPERLS reports based on the date an isolate is received, while CPE enhanced surveillance is based on the specimen collection date and reports on the first isolate per patient per year, which may include more than newly-confirmed patients (i.e., when a patient was previously known with CPE in the preceding year)
- As the case definition now only requires reporting of the first isolate of any *Enterobacterales* species with the same enzyme for the year, patients are only counted once in this surveillance programme, unless a subsequent isolate from the same patient is reported with a different enzyme:
    - Two patients had two different carbapenemases reported: both with OXA-48 and NDM isolated from the same screening specimens
    - Two patients had two different carbapenemases reported from two separate specimens:
        - OXA-48 *Enterobacter cloacae* from a clinical specimen and VIM *E. cloacae* from a screening specimen where both specimens taken on the same date
        - OXA-48 *E. coli* from a screening specimen and OXA-181/232 *E. coli* from a subsequent clinical specimen
- Nationally, the majority were OXA-48 (73%), with KPC predominant in the mid-west (n=45; 79% of KPC isolates). Three species accounted for 75% of all CPE isolates: *K. pneumoniae* (31%), *E. coli* (23%) and *Enterobacter cloacae* (21%), as displayed in Table 1 and Figure 1
- Males (57%) and patients aged ≥57 years (75%) accounted for the majority of cases
- The majority of isolates were detected from screening specimens (n=353; 79%), with the remainder from clinical specimens (n=96; 21%), of which seven were from BSI
- Inpatients in 33 hospitals accounted for the majority of carbapenemases (n=378; 78%):
    - Admission and specimen dates were reported for 321 (85%), with a median interval between admission and first positive result of eight days (range = 0 – 458)

- Of clinical specimens, the majority were detected from inpatients (n=72; 75%). Of those, information on antimicrobial therapy was provided for 45 (63%), with 25 of those (60%) having required antimicrobial therapy active against a carbapenemase for suspected infection prior to case notification. However, for over one-third of clinical isolates from inpatients (37%), information on antimicrobial therapy by the time of case notification was not reported
- Information on inpatient isolation status within 24 hours of the laboratory reporting a suspected carbapenemase was provided for 277 isolates (73%), with the majority of patients isolated (n=254; 92%) and 16 who were (8%) discharged prior to the result. In three cases, the patient was not isolated within 24 hours. However, for 28% of inpatient isolates (n=105), isolation status was not reported
- In 2017, the majority of inpatient CPEs were reported from screening specimens (rectal swab or faeces). The following hospitals accounted for the majority of reported CPE and all also reported and managed CPE outbreaks in 2017:
  - Tallaght Hospital (n=76; 97% on screening)
  - Galway University Hospital (n=45; 88% on screening)
  - University Hospital Limerick (n=39; 87% on screening)
  - Beaumont Hospital (n=33; 74% on screening)
  - St James's Hospital (n=33; 76% on screening)
  - University Hospital Waterford (n=26; 69% on screening)
  - St Luke's Hospital, Kilkenny (n=17; 76% on screening)
  - Naas General Hospital (n=16; 100% on screening)
  - St Vincent's University Hospital (n=15; 78% on screening)
  - In 2017, additional CPE outbreaks were notified to Departments of Public Health by the Mater Misericordiae University Hospital, Our Lady's Hospital, Navan, Sligo University Hospital and the Beacon Hospital, as well as by two long-term care facilities (LTCF) in different regions

- The remaining isolates were detected from outpatients attending 12 hospitals (n=30), LTCF residents (n=29) and patients attending general practitioners (GP) (n=12)
- Outcome data at the time of reporting was not provided for 27% of inpatient isolates. Of 276 inpatients, 28 (10%) were reported to have died at the time of reporting. However, cause of death was not ascertained

Table 1. Summary of *Enterobacterales* and carbapenemase type in 2017

Enterobacterales species	Enzyme						
	OXA-48	KPC	NDM	VIM	IMP	Other*	Total
E. coli	118	4	16			1	**139**
K. pneumoniae	68	20	15			2	**105**
Enterobacter spp.	72	9	2	9	4	3	**99**
Citrobacter spp.	29	18	1		1	1	**50**
K. oxytoca	33	3	1	2	4		**43**
*Other Enterobacterales***	8	3	2				**13**
TOTAL	**328**	**57**	**37**	**11**	**9**	**7**	**449**

*includes two isolates with both OXA-48 and NDM, two isolates with IMI, two isolates with OXA-181/232 and one with OXA-181

**includes six isolates *of K. variicola*, three isolates of *Serratia* spp., two isolates of *P. stuartii* and one each of *P. mirabilis* and *Leclercia adecarboxylata*

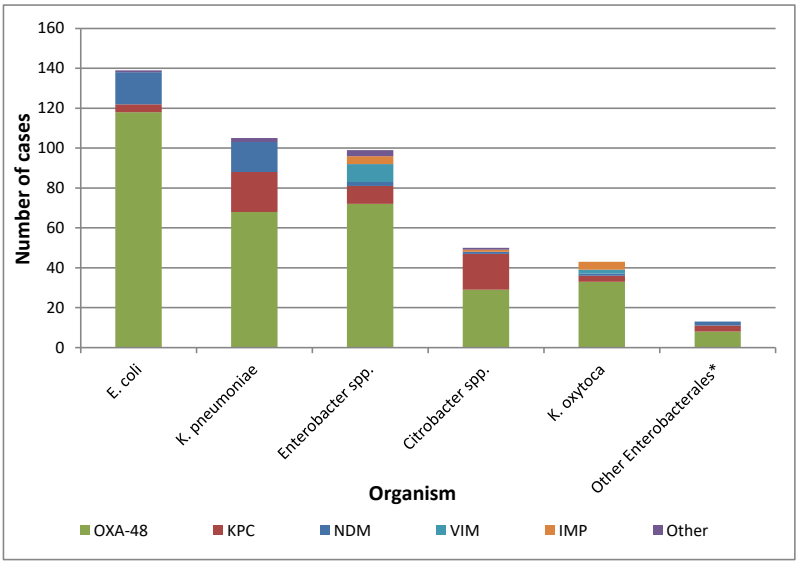

Figure 1. *Enterobacterales* and carbapenemase type in 2017

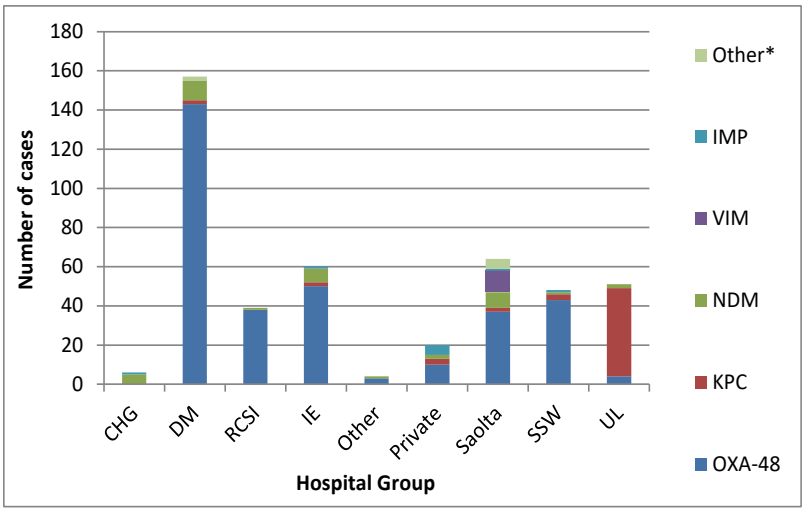

Figure 2. Distribution of carbapenemase type by Hospital Group in 2017

CHG, Children's Hospital Group; DM, Dublin Midlands Group; DNE, RCSI, RCSI Group; IE, Ireland East Group; Other, Other non-acute; Saolta Group, West North-West Group; SSW, South South-West Group; UL, University of Limerick Group

*Other=IMI, OXA-181/232, OXA-48/NDM

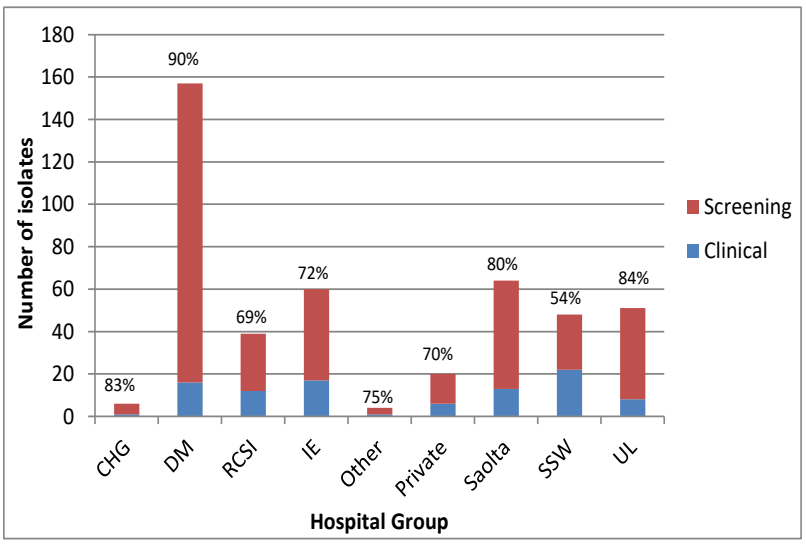

Figure 3. Distribution of isolates from screening and clinical specimens (and proportion from screening) by Hospital Group in 2017

Table 2. Summary of CPE (based on 1st isolate per patient, as per revised case definition) in 2017

	TIME PERIOD 2017 n	%	COMMENT
CPE cases (based on case definition of 1st isolate per patient)	449		of which 418 cases (91%) associated with 40 (of 60) acute hospitals (including outpatients)
Carbapenemase detected			
OXA-48	328	73%	
KPC	57	13%	
NDM	37	8%	
VIM	11	2%	
IMP	9	2%	
Other	7	2%	3 OXA-181/232, 2 IMI, 2 OXA-48/NDM
First organism from each patient in which carbapenemase was detected			
E. coli	139	31%	
K. pneumoniae	105	23%	
Enterobacter spp.	99	22%	
Citrobacter spp.	50	11%	
Klebsiellae oxytoca	43	10%	
Other Enterobacterales species	13	3%	
Clinical vs screening			
Clinical	96	21%	
Screening	353	79%	
Source (specimen type for clinical isolates only)			
Blood/other normally sterile site	10	10%	
Urine	50	52%	
Sputum/respiratory	13	14%	
Swab/tissue/pus/other	23	24%	
Location			
Hospital*	408	91%	
Inpatient (non-ICU)	*325*	*72%*	
ICU	*26*	*6%*	
ED	*27*	*6%*	
Outpatient	*30*	*7%*	
Nursing home&LTCF/GP	41	9%	
Nursing home&LTCF	*29*	*6%*	
GP	*12*	*3%*	
DEMOGRAPHICS			**COMMENT**
Male	258	57%	
Age range	1-105		
Median age	69		
Inter-quartile range	57-80		75% of patients are aged 57 years or older
Interventions (for in-patients only)			
*Total no. CPE cases from inpatients w/ clinical samples***	*72*		
Cases treated for CRE infection?			
Treated for infection	25	35%	
Not treated for infection	18	25%	
Unknown/Not answered	29	40%	
*Total no. CPE cases from inpatients***	*378*		
Isolation within 24 hours of CRE identified?			
Isolated within 24 hours	254	67%	
Not isolated within 24 hours	3	1%	
Not applicable (discharged before confirmed)	16	4%	
Unknown/Not answered	105	28%	
Potential association with hospital (for inpatients only)			
Proportion detected >3 days after admission, which may be indicative of potential acquisition in the facility		63%	Date of admission provided for 321 of 378 inpatients
Outcome by time of reporting (for inpatients only)			
Died (but not known if cause of death)	29	8%	
Survived	247	65%	
Unknown/Not answered	102	27%	

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

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

Appendix 1. Total CPE cases reported by acute hospitals in 2017

Hospital Group	HOSPITAL	Category	Total CPE	GP or Long-term care	Outpatients	Hospitalised patients only	% of cases detected on screening	%Hospitalised, clinical cases that were treated†	%Hospitalised cases that were isolated†
Dublin Midlands	Coombe Womens and Infants University Hospital	Specialist	1	0	1	0	0%	NA	NA
	Midland Regional Hospital, Portlaoise	General	0	0	0	0	NA	NA	NA
	Midland Regional Hospital, Tullamore	General	1	1	0	0	0%	NA	NA
	Naas General Hospital	General	16	0	0	16	100%	NA	100%
	St James's Hospital	Tertiary	35	1	1	33	74%	71%	100%
	St Luke's Hospital, Rathgar	Specialist	3	0	0	3	100%	NA	100%
	Tallaght Hospital	Tertiary	101	12	13	76	95%	NA	NA
Dublin North East (RCSI)	Beaumont Hospital	Tertiary	35	1	1	33	74%	50%	97%
	Cavan General Hospital	General	0	0	0	0	NA	NA	NA
	Connolly Hospital, Blanchardstown	General	2	0	0	2	50%	NA	100%
	Louth County Hospital, Dundalk	General	0	0	0	0	NA	NA	NA
	Our Lady of Lourdes Hospital, Drogheda	General	2	1	0	1	0%	NA	NA
	Rotunda Hospital	Specialist	0	0	0	0	NA	NA	NA
Ireland East	Cappagh National Orthopaedic Hospital	Specialist	0	0	0	0	NA	NA	NA
	Mater Misericordiaie University Hospital	Tertiary	12	0	1	11	67%	75%	91%
	Midland Regional Hospital, Mullingar	General	1	0	0	1	100%	NA	100%
	National Maternity Hospital, Holles St.	Specialist	1	0	1	0	0%	NA	NA
	Our Lady's Hospital, Navan	General	3	0	0	3	33%	100%	NA
	Royal Victoria Eye and Ear Hospital, Dublin	Specialist	0	0	0	0	NA	NA	NA
	St Columcille's Hospital, Loughlinstown	General	0	0	0	0	NA	NA	NA
	St Luke's Hospital, Kilkenny	General	17	0	0	17	76%	100%	100%
	St Michael's Hospital, Dun Laoghaire	General	1	0	0	1	100%	NA	NA
	St Vincent's University Hospital, Elm Park	Tertiary	18	0	3	15	78%	0%	83%
	Wexford General Hospital	General	7	0	1	6	71%	NA	100%
Midwest (UL)	Croom Hospital	Specialist	0	0	0	0	NA	NA	NA
	Ennis Hospital	General	1	0	0	1	100%	NA	100%
	Nenagh Hospital	General	0	0	0	0	NA	NA	NA
	St John's Hospital, Limerick	General	2	0	0	2	100%	NA	100%
	University Hospital Limerick	Tertiary	48	9	0	39	83%	0%	100%
	University Maternity Hospital Limerick	Specialist	0	0	0	0	NA	NA	NA
South/South West	Bantry General Hospital	General	0	0	0	0	NA	NA	NA
	Cork University Hospital	Tertiary	4	2	0	2	0%	100%	100%
	Kerry General Hospital, Tralee[1]	General	0	0	0	0	NA	NA	NA
	Kilkreene Orthopaedic Hospital, Co. Kilkenny	Specialist	0	0	0	0	NA	NA	NA
	Mallow General Hospital	General	1	0	0	1	0%	100%	100%
	Mercy University Hospital	General	5	0	0	5	20%	25%	100%
	South Infirmary/Victoria University Hospital, Cork	General	0	0	0	0	NA	NA	NA
	South Tipperary General Hospital, Clonmel	General	8	0	0	8	88%	NA	100%
	University Hospital Waterford	Tertiary	30	4	0	26	60%	100%	100%
Saolta (West/Northwest)	Galway University Hospitals	Tertiary	48	0	3	45	88%	60%	100%
	Letterkenny General Hospital	General	5	4	0	1	80%	100%	NA
	Mayo General Hospital, Castlebar	General	4	1	0	3	25%	50%	100%
	Portiuncula Hospital, Ballinasloe	General	0	0	0	0	NA	NA	NA
	Roscommon County Hospital	General	2	0	0	2	100%	NA	100%
	Sligo Hospital	General	5	1	1	3	40%	0%	100%
CHG[2]	Children's University Hospital, Temple St.	Specialist	1	0	0	1	100%	NA	100%
	Our Lady's Children's Hospital, Crumlin	Specialist	5	0	3	2	80%	NA	100%
	Tallaght Hospital (National Children's Hospital)	Specialist	0	0	0	0	NA	NA	NA
Private	Aut Even Hospital, Kilkenny	Private	1	0	0	1	100%	NA	NA
	Beacon Hospital, Sandyford[3]	Private	8	0	0	8	75%	50%	100%
	Blackrock Clinic	Private	0	0	0	0	NA	NA	NA
	Bon Secours Hospital, Cork	Private	2	0	0	2	100%	NA	100%
	Bon Secours Hospital, Galway	Private	0	0	0	0	NA	NA	NA
	Bon Secours Hospital, Glasnevin	Private	1	0	0	1	100%	NA	100%
	Bon Secours Hospital, Tralee	Private	1	0	0	1	0%	NA	NA
	Galway Clinic, Doughiska	Private	5	0	0	5	60%	0%	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	2	0	1	1	50%	NA	NA
	St Vincent's Private Hospital	Private	0	0	0	0	NA	NA	NA
	Other non-acute		4	4	0	0	75%	NA	NA
	Total		**449**	**41**	**30**	**378**	**79%**	**58%**	**99%**

† Data not necessarily complete for each hospital (% only calculated if response given to >50% of cases); * No data or insufficient data provided; N/A, not applicable

[1] No data for Q3-4 2017 due to resource issues; [2] CHG, Children's Hospital Group; [3] No data submitted for Q4 2017

Glossary of terms

Carbapenems	Broad spectrum beta lactam antibiotics often reserved for treatment 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 beta lactam 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
VIM	Less common type of carbapenemase