Enhanced Surveillance of Carbapenemase-Producing *Enterobacterales* (CPE), 2018

Key points

- The case definition was amended to avoid counting CPE cases more than once in a given year and thus to more accurately reflect the burden, particularly in hospitals
- In 2018, 565 confirmed CPE isolates from 564 patients were reported by 30 (of 39) microbiology laboratories, with the majority detected from screening specimens (87%). Eight laboratories reported zero CPE isolates and one laboratory did not provide data
- Hospital inpatients accounted for the vast majority of new CPE detections (n=514; 91%), followed by hospital outpatients (n=19), long-term care facility (LTCF) residents (n=17) and patients attending general practitioners (n=15)
- Data on patient isolation status within 24 hours of a suspected CPE laboratory result was not reported for 19% of inpatients. Where data was reported, the majority were isolated (n=382; 91%), with 29 patients (7%) who were discharged before the laboratory result was available. Seven patients (2%) were reported as not isolated within 24 hours
- The overall numbers of CPE increased in 2018 due to a 35% increase in cases from screening. This was mirrored by a 27% decrease in clinical cases, which may signal that screening and control measures are starting to make an impact. Despite this, the number of cases from bloodstream infections increased from 7 in 2017 to 10 in 2018

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 *K. pneumoniae* isolates causing bloodstream infection (BSI) that were CPE, as 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 represents 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 an 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 MDRKP and CRE surveillance schemes were replaced with the 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 isolates from patients with newly-confirmed CPE submitted to the reference laboratory increasing from 50 in 2013 to 433 in 2017 and 537 in 2018.

Revised case definition

- 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 first the 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

Appendix 1 summarises the data reported by acute hospitals and Hospital Groups in Q1-4 2018.

Twenty-nine microbiology laboratories reported 565 isolates from 564 patients, with eight laboratories reporting zero isolates. In 2018, one laboratory did not submit data.

- 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:
    - One patient had two different carbapenemases (OXA-48 and NDM) reported from two different screening specimens
- The total number of patients reported to enhanced CPE surveillance in 2018 was 564, which is higher than the NCPERLS total of 537 patients with newly-confirmed CPE. The CPE enhanced surveillance reports on the first isolate per patient per year, while NCPERLS reports on newly-confirmed patients. In CPE enhanced surveillance, it is also not possible to definitively identify where the same patient with CPE is identified across hospitals due to the absence of a unique national patient identifier
- This surveillance system collects data on the patient's location when CPE is detected, which is not an indicator that colonisation or infection was acquired at this location. The origin of colonisation or infection may be in another hospital or hospital group
- Screening practices are known to differ between hospitals and hospital groups and this can have an impact on the overall numbers of CPE detected: hospitals and hospital groups with higher screening rates may have higher CPE numbers as a consequence of better screening; while those with lower screening rates may have lower CPE numbers
- Nationally, the majority were OXA-48 (n=393, 70%), with KPC predominant in the University of Limerick (UL) hospital group (n=60; 66% of KPC isolates). In addition, the majority of VIM and OXA-181/232 (a variant of OXA-48) cases were found in the Saolta hospital group (Figure 2). Three species accounted for approx. 72% of all CPE isolates: *E. coli* (27%), *Enterobacter cloacae* (24%) and *K. pneumoniae* (21%), as displayed in Table 1 and Figure 1
- Four patients had two different CPEs (OXA-48 and NDM) reported from the same screening specimen
- Males (58%) and patients aged ≥61 years (75%) accounted for the majority of cases
- The majority of isolates were detected from screening specimens (n=491; 87%), with the remainder from clinical specimens (n=73; 13%), of which 10 were from BSI and one from another normally sterile site (bile)
- Inpatients in 40 hospitals accounted for the majority of CPE (n=513; 91%):

- Admission and specimen dates were reported for 495 (96%), with a median interval between admission and first positive result of eight days (range = 0-389)
- Of clinical specimens, the majority were detected from inpatients (n=48; 65%). Of those, information on antimicrobial therapy was provided for 38 (79%), with 22 of those (58%) having required antimicrobial therapy active against a CPE for suspected infection prior to case notification. However, for one-quarter of clinical isolates from inpatients (26%), 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 418 isolates (81%), with the majority of patients isolated (n=382; 91%) and 29 who were (7%) discharged prior to the result. In seven cases (2%), the patient was not isolated within 24 hours. However, for 17% of inpatient isolates (n=96), isolation status was not reported
- In 2018, most inpatient CPE was detected in screening specimens (rectal swab or faeces). The following hospitals accounted for the majority (76%) of reported CPE and all also reported or managed ongoing CPE outbreaks in 2018:
  - Tallaght Hospital (n=78; 99% on screening)
  - Galway University Hospital (n=61; 95% on screening)
  - University Hospital Limerick (n=54; 91% on screening)
  - Beaumont Hospital (n=49; 86% on screening)
  - St James's Hospital (n=45; 73% on screening)
  - Mater Misericordiae University Hospital (n=33; 82% on screening)
  - Sligo University Hospital (n=33; 94% on screening)
  - University Hospital Waterford (n=32; 75% on screening)
  - Cork University Hospital (n=21; 86% on screening)
  - St Vincent's University Hospital (n=21; 67% on screening)
  - In 2018, additional CPE outbreaks were notified to Departments of Public Health by the Beacon Hospital, Cavan General Hospital; Mallow General Hospital, St Luke's Hospital, Kilkenny; South Tipperary General Hospital; and Mercy University Hospital

- The remaining isolates were detected from outpatients attending nine hospitals (n=19), LTCF residents (n=17) and patients attending general practitioners (GP) (n=15)
- Outcome data at the time of reporting or discharge was not provided for 18% of inpatients. Of 423 inpatients, 56 (13%) were reported to have died at the time of reporting. However, information on the contribution of CPE to the cause of death is not collected
- Between 2017 and 2018, the overall number of CPE reported increased by 26% from 449 to 565. This is predominantly due to an increase in the number from screening samples (354 vs 491, an increase of 39%), while the number from clinical samples decreased (95 vs 74; a decrease of 22%). This could be an indication that increased screening and measures to control CPE are starting to make an impact. However, there was an increase in the number of CPE cases from blood (10 in 2018 vs seven in 2017), which are indicative of the most serious types of infections

Table 1. Summary of *Enterobacterales* and carbapenemase type in Ireland, 2018

Enterobacterales species	Enzyme						Total
	OXA-48	KPC	NDM	OXA-181/232	VIM	Other*	
E. coli	126	10	11	4	1	3	**155**
Enterobacter cloacae	93	16	5	2	13	3	**132**
K. pneumoniae	75	31	8	2	2		**118**
K. oxytoca	49	3		12	2	1	**67**
Citrobacter spp.	20	26	2	3	2		**53**
Other *Enterobacter* spp.	23	2		2		1	**28**
Other Enterobacterales**	7	3		1		1	**12**
TOTAL	**393**	**91**	**26**	**26**	**20**	**9**	**565**

*includes four isolates with IMI, one with IMP and four with both OXA-48 and NDM

**includes four *K. variicola* isolates, three *S. marcescens;* two *Raoultella ornithinolytica* and one each of *Hafnia alvei*, other *Klebsiella spp.* and *M. morganii*

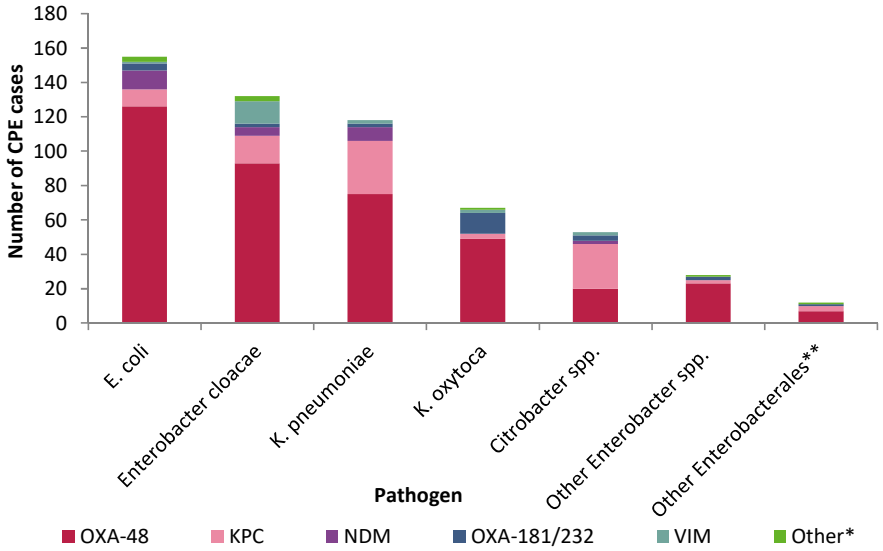

Figure 1. *Enterobacterales* and carbapenemase type in Ireland, 2018

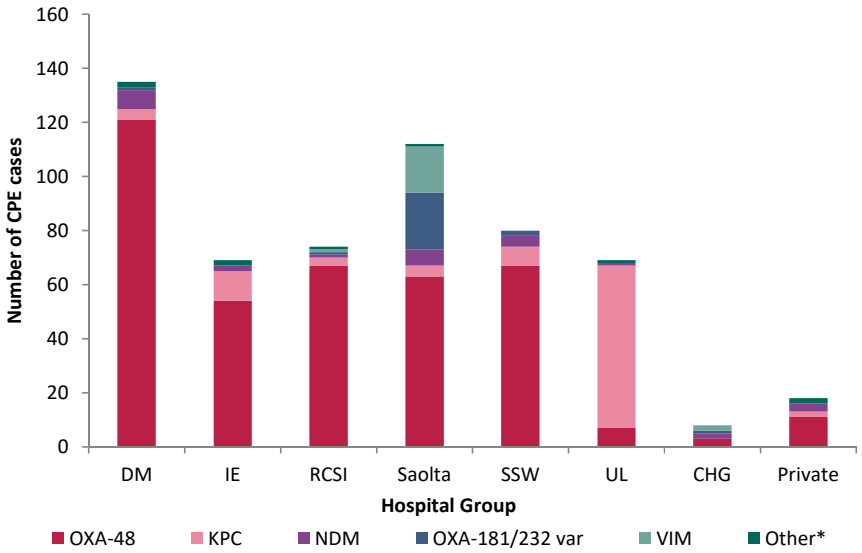

Figure 2. Distribution of CPE type by Hospital Group in Ireland, 2018
DM, Dublin Midlands Group; IE, Ireland East Group; RCSI, RCSI Group; Saolta Group, West North-West Group; SSW, South South-West Group; UL, University of Limerick Group; CHG, Children's Hospital Group

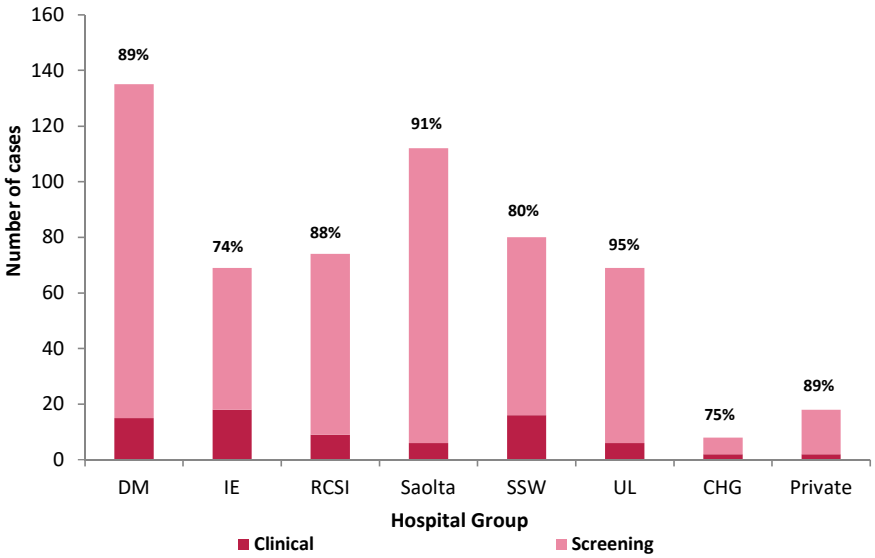

Figure 3. Distribution of CPE isolates from screening and clinical specimens (and proportion from screening) by Hospital Group in Ireland, 2018

Table 2. Summary of CPE (based on 1st isolate per patient **per year**, as per revised case definition) in Ireland, 2017 & 2018

	TIME PERIOD				
	2017		2018		COMMENT
	n	%	n	%	
CPE cases (based on case definition of 1st isolate per patient)	449		565		93% of all cases associated with 49 (of 60) acute hospitals, including outpatients (over both years)
Carbapenemase detected					
OXA-48	328	73%	393	70%	
KPC	57	13%	91	16%	
NDM	37	8%	26	5%	
OXA-181/232	3	1%	26	5%	
VIM	11	2%	20	4%	
IMI	2	<1%	4	1%	
IMP	9	2%	1	<1%	
OXA-48/NDM together	2	<1%	4	1%	
First organism from each patient in which carbapenemase was detected					
E. coli	139	31%	155	27%	
K. pneumoniae	105	23%	132	23%	
Enterobacter cloacae	94	21%	118	21%	
Citrobacter spp.	50	11%	67	12%	
Klebsiellae oxytoca	43	10%	53	9%	
Other *Enterobacter* species	5	1%	28	5%	
Other *Enterobacterales* species	13	3%	12	2%	
Clinical vs screening					
Clinical	95	21%	74	13%	
Screening	354	79%	491	87%	
Source (specimen type for clinical isolates only)					
Blood/other normally sterile site	10	11%	11	15%	
Urine	49	52%	44	59%	
Sputum/respiratory	13	14%	8	11%	
Swab/tissue/pus/other	23	24%	11	15%	
Location					
Hospital*	408	91%	533	94%	
Inpatient (non-ICU)	*325*	*72%*	*446*	*79%*	
ICU	*26*	*6%*	*40*	*7%*	
ED	*27*	*6%*	*28*	*5%*	
Outpatient	*30*	*7%*	*19*	*3%*	
Nursing home&LTCF/GP	41	9%	32	6%	
Nursing home&LTCF	*29*	*6%*	*17*	*3%*	
GP	*12*	*3%*	*15*	*3%*	
DEMOGRAPHICS					**COMMENT**
Male	258	57%	325	58%	
Age range	1-105		0-103		
Median age	69		71		
Inter-quartile range	57-80		61-80		75% of patients were aged 57 years or older in 2017 and aged 61 years or older in 2018
Interventions (for in-patients only)					
*Total no. CPE cases from inpatients w/ clinical samples***	71		48		
Cases treated for CPE infection?					
Treated for infection	24	34%	22	46%	
Not treated for infection	18	25%	14	29%	
Not applicable (discharged before confirmed)			2	4%	
Unknown/Not answered	29	41%	10	21%	
*Total no. CPE cases from inpatients***	378		514	91%	
Isolation within 24 hours of CPE identified?					
Isolated within 24 hours	253	67%	382	74%	
Not isolated within 24 hours	3	1%	7	1%	
Not applicable (discharged before confirmed)	17	4%	29	6%	
Unknown/Not answered	105	28%	96	19%	
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%	Date of admission provided for 85% and 97% of inpatients in 2017 and 2018, respectively
Outcome by time of reporting (for inpatients only)					
Died (but not known if cause of death)	28	7%	56	11%	
Survived	248	66%	367	71%	
Unknown/Not answered	102	27%	91	18%	

* 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 Ireland, 2018

HOSPITAL	Category	Total CPE	GP or Long-term care	Outpatients	Hospitalised patients	% cases detected on screening	%Hospitalised clinical cases that were treated†	%Hospitalised cases that were isolated†
Coombe Womens and Infants University Hospital	Specialist	0	0	0	0	NA	NA	NA
Midland Regional Hospital, Portlaoise	General	0	0	0	0	NA	NA	NA
Midland Regional Hospital, Tullamore	General	5	2	0	3	60%	NA	100%
Naas General Hospital	General	4	0	0	4	100%	NA	100%
St James's Hospital	Tertiary	45	4	0	41	73%	88%	88%
St Luke's Hospital, Rathgar	Specialist	3	0	0	3	100%	NA	100%
Tallaght University Hospital	Tertiary	78	1	2	75	99%	*	*
Beaumont Hospital	Tertiary	49	2	0	47	86%	25%	81%
Cavan General Hospital	General	18	1	0	17	100%	NA	100%
Connolly Hospital, Blanchardstown	General	5	0	0	5	100%	NA	80%
Louth County Hospital, Dundalk	General	0	0	0	0	NA	NA	NA
Our Lady of Lourdes Hospital, Drogheda	General	1	1	0	0	0%	NA	NA
Rotunda Hospital	Specialist	1	0	1	0	0%	NA	NA
Cappagh National Orthopaedic Hospital	Specialist	0	0	0	0	NA	NA	NA
Mater Misericordiaie University Hospital	Tertiary	33	2	1	30	82%	0%	100%
Midland Regional Hospital, Mullingar	General	2	1	0	1	100%	NA	100%
National Maternity Hospital, Holles St.	Specialist	0	0	0	0	NA	NA	NA
Our Lady's Hospital, Navan	General	3	1	0	2	67%	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	10	0	0	10	60%	*	80%
St Michael's Hospital, Dun Laoghaire	General	0	0	0	0	NA	NA	NA
St Vincent's University Hospital, Elm Park	Tertiary	21	9	0	12	67%	0%	*
Wexford General Hospital	General	1	0	0	1	100%	NA	100%
Croom Hospital	Specialist	1	0	1	0	100%	NA	NA
Ennis Hospital	General	3	0	0	3	67%	*	100%
Nenagh Hospital	General	5	0	0	5	100%	NA	100%
St John's Hospital, Limerick	General	6	0	0	6	100%	NA	100%
University Hospital Limerick	Tertiary	54	2	3	49	91%	67%	100%
University Maternity Hospital Limerick	Specialist	0	0	0	0	NA	NA	NA
Bantry General Hospital	General	1	0	0	1	100%	NA	0%
Cork University Hospital	Tertiary	21	1	1	19	86%	100%	95%
Kerry General Hospital, Tralee	General	1	0	0	1	100%	NA	*
Kilkreene Orthopaedic Hospital, Co. Kilkenny	Specialist	0	0	0	0	NA	NA	NA
Mallow General Hospital	General	2	0	0	2	100%	NA	100%
Mercy University Hospital	General	14	0	2	12	79%	100%	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	75%	*	63%
University Hospital Waterford	Tertiary	32	2	1	29	75%	100%	97%
Galway University Hospitals	Tertiary	61	0	2	59	95%	100%	80%
Letterkenny General Hospital	General	8	0	0	8	100%	NA	88%
Mayo General Hospital, Castlebar	General	8	0	1	7	88%	0%	86%
Portiuncula Hospital, Ballinasloe	General	2	0	0	2	100%	NA	50%
Roscommon County Hospital	General	0	0	0	0	NA	NA	NA
Sligo Hospital	General	33	3	0	30	94%	100%	100%
Children's University Hospital, Temple St.	Specialist	0	0	0	0	NA	NA	NA
Our Lady's Children's Hospital, Crumlin	Specialist	6	0	2	4	83%	100%	100%
Tallaght Children's Hospital	Specialist	2	0	0	2	50%	*	*
Aut Even Hospital, Kilkenny	Private	0	0	0	0	NA	NA	NA
Beacon Hospital, Sandyford	Private	*	*	*	*	*	*	*
Blackrock Clinic	Private	2	0	0	2	100%	NA	50%
Bon Secours Hospital, Cork	Private	3	0	0	3	100%	NA	100%
Bon Secours Hospital, Galway	Private	0	0	0	0	NA	NA	NA
Bon Secours Hospital, Glasnevin	Private	2	0	0	2	100%	NA	50%
Bon Secours Hospital, Tralee	Private	0	0	0	0	NA	NA	NA
Galway Clinic, Doughiska	Private	6	0	1	5	100%	NA	80%
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	1	0	0	1	100%	NA	NA
St Vincent's Private Hospital	Private	3	0	0	3	67%	0%	33%
Other non-acute		1	0	1	0	0%	NA	NA
Total		**565**	**32**	**19**	**514**	**87%**	**61%**	**74%**

CHG, Children's Hospital Group; † Data not necessarily complete for each hospital (% only calculated if response given to >50% of cases)
* 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 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
VIM	Less common type of carbapenemase