9.3.0 Antimicrobial Resistance

Key Points

- There were 2,530 reports of invasive *E. coli* infection, an increase of 3% from 2,450 (2012):
 - The proportions of invasive *E. coli* resistant to 3rd generation cephalosporins (3GCs) (12.8%), ciprofloxacin (25.3%) and aminoglycosides (12.8%), those that were extended spectrum beta lactamase (ESBL) positive (10.5%) and those that exhibited multi-drug resistance (14.8%) were at their highest levels since surveillance began
- There were 1,094 reports of *S. aureus* bloodstream infection (BSI), an increase of 3% from 1,060 (2012). Of those, 222 (20.3%) were meticillin resistant *S. aureus* (MRSA):
 - For acute hospitals, the rate of MRSA BSI was 0.056 cases per 1,000 bed days used (BDU), a decrease from 0.060 (2012). Conversely, the rate of meticillin susceptible *S. aureus* (MSSA) BSI increased from 0.208 (2012) to 0.218 (2013)
 - Enhanced surveillance data revealed that 21% of *S. aureus* BSI were associated with infection related to central venous catheters (CVC) and 7% with peripheral venous catheter (PVC) infection
- There were 409 reports of *E. faecium* BSI, an increase of 4% from 392 (2012):
 - Vancomycin resistant *E. faecium* (VREfm) accounted for 43.1%, a decrease from 45.4% (2012)
- There were 326 reports of invasive *K. pneumoniae* infection, a decrease of 5.5% from 345 (2012):
 - The proportions of invasive *K. pneumoniae* resistant to 3GCs (21.2%) and those that were ESBL positive (18.4%) were at their highest levels since surveillance began
 - Two predominant clones have been identified among *K. pneumoniae* that are both ESBL positive and non-susceptible to ciprofloxacin and gentamicin. Some also produce

carbapenemases. Together, these are termed multi-drug resistant *K. pneumoniae* (MDRKP) and the proportion of invasive *K. pneumoniae* that were MDRKP further increased between 2012 and 2013: 5.3% (18 of 342 isolates) to 12.3% (40 of 325 isolates). An outbreak control team was established in October 2013 to investigate this emerging threat

- Two invasive *K. pneumoniae* isolates were carbapenemase producers, also known as carbapenem-resistant *Enterobacteriaceae* (CRE)
- There were 311 reports of invasive S. pneumoniae infection, a decrease of 3% from 321 (2012). Of those, 64 (20.7%) were penicillin-non-susceptible S. pneumoniae (PNSP), an increase from 19.6% (2012)
 - o The national rate of invasive infection was 6.8 per 100,000 population, compared to 7.0 (2012)
 - Serotype data were available for 271 of 311 invasive *S. pneumoniae* isolates (87%). Results indicate good coverage (71%) for the 23-valent pneumococcal polysaccharide vaccine (PPV-23) in its target population (adults ≥65 years)
- There were 207 reports of invasive *P. aeruginosa* infection, a decrease of 5.5% from 219 (2012) and resistance to all indicator antimicrobials decreased
- Enhanced surveillance data were provided on 1,908 cases from 11 laboratories, representing 36% of all reported cases in 2013
- See http://www.hpsc.ie for further details of EARS-Net, antimicrobial resistance and enhanced BSI surveillance in Ireland. European data are available at http://ecdc.europa.eu/en/activities/surveillance/ EARS-Net/Pages/Database.aspx

Introduction

The European Antimicrobial Resistance Surveillance Network (EARS-Net), previously the European Antimicrobial Resistance Surveillance System (EARSS), collects routinely-generated antimicrobial susceptibility testing data on seven important bacterial pathogens using the EARS-Net case definition. Participating laboratories in Ireland submit data on the "primary" or first isolate from blood or cerebrospinal fluid (CSF) per patient per quarter. EARS-Net does not distinguish clinically significant isolates from contaminants, nor does it distinguish between hospital-acquired, healthcare-associated and community-acquired infections. EARS-Net primarily serves as a surveillance system to measure national levels of antimicrobial resistance (AMR). In 2013, all 41 microbiology laboratories participated in EARS-Net resulting in complete coverage of the Irish population.

Escherichia coli

There were 2,530 reports of invasive *E. coli* infection (2,525 from blood and five from CSF) from 2,480 patients, an increase of 3.3% from 2,450 reports in 2012. **Table 1** displays the annual trends since 2004 in the proportion of *E. coli* isolates resistant to the four "indicator" antimicrobials/antimicrobial classes [ampicillin, third-generation cephalosporins (3GCs); cefotaxime, ceftriaxone, ceftazidime or cefpodoxime, fluoroquinolones (ciprofloxacin or ofloxacin) and aminoglycosides (gentamicin, amikacin or tobramycin)]:

- Of 2,528 isolates, 323 (12.8%) were resistant to 3GCs and of those, 256 were ESBL positive, with 65 ESBL negative
- Of 2,526 isolates, 640 (25.3%) were resistant to ciprofloxacin
- Of 2,525 isolates, 247 (9.8%) were resistant to gentamicin [325 (12.8%) of 2,530 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)]
- Two (0.2%) of 2,254 isolates were resistant to carbapenems, but both were confirmed not to be carbapenemase producers

In 2013, resistance to 3GCs, ciprofloxacin and aminoglycosides were at their highest levels since surveillance began (**Figure 1**). The trend in 3GC resistance has been upwards since 2004, which is highly significant (Chi² trend=187, P<0.0001).

In 2013, Ireland had moderately high levels (10 to <25%) of resistance to 3GCs (**Figure 2**), ciprofloxacin and aminoglycosides (ranking 13th, 13th and 11th, respectively, out of 30 countries reporting to EARS-Net). The median proportion for resistance among EARS-Net countries was 3GC (11.3%), ciprofloxacin (22.9%) and aminoglycosides (9.9%).

ESBLs are enzymes that confer resistance to most penicillins and cephalosporins (including 3GCs). ESBL positive bacteria (including *E. coli* and *K. pneumoniae*) are also often resistant to other classes of antimicrobials and have emerged as important causes of healthcare associated infection (HCAI). ESBLs were detected in 264 (10.5%) of 2,515 isolates tested. In 2013, ESBL production among *E. coli* isolates was at its highest level since surveillance began. The trend in ESBL production has been upwards since 2004, which was highly significant (Chi² trend=213, P<0.0001).

Of 2,524 isolates tested against all four "indicator" antimicrobials, 373 (14.8%) reported from 49 hospitals/ institutions were identified as multi-drug resistant (MDR); defined as resistance to three or more of indicator antimicrobials), an increase from 13.4% (2012):

- 151 resistant to ampicillin, 3GCs, ciprofloxacin and aminoglycosides. ESBL positive (138), ESBL negative (13)
- 105 resistant to ampicillin, 3GCs and ciprofloxacin. ESBL positive (87), ESBL negative (17)
- 110 resistant to ampicillin, ciprofloxacin and aminoglycosides. ESBL positive (1), ESBL negative (108)
- Seven resistant to ampicillin, 3GCs and aminoglycosides. ESBL positive (5), ESBL negative (2)

In 2013, MDR *E. coli* was at its highest level since surveillance began. Between 2009 and 2013, the trend in MDR was upwards, which was highly significant (Chi² trend=22.28, P<0.0001).

Females were slightly more likely (1.1-times) to have an invasive *E. coli* infection than males (z=2.63, P=0.01). The frequency of invasive *E. coli* infection increased with age, with the majority (n=1,884; 75%) occurring in adults aged over 60. The median age was 72 years (95%CI, 72-73).

Staphylococcus aureus

There were 1,094 reports of *S. aureus* BSI from 1,068 patients, an increase of 3.2% from 1,060 (2012). Of those, 222 (20.3%) were MRSA, which represents the lowest annual proportion since surveillance began in 1999. (**Table 1**). In 2010, the proportion was 24.4%, the first year that MRSA accounted for <25% of *S. aureus* BSI in Ireland, thus changing from red to orange on the EARS-Net map and 2013 was the seventh successive year in which a decrease was observed. The overall downward trend over this time period is highly significant (Chi² trend = 249, P<0.0001) (**Figure 3**). Overall, there was a 9.2% reduction in the number of reported MRSA BSI compared with 2012 (222 versus 242). In contrast, the total number of MSSA BSI increased by 6.6% compared with 2012 (872 versus 818).

Despite the decrease in numbers and proportion of MRSA BSI in 2013, Ireland still had one of the higher proportions of MRSA in Europe (see http://ecdc. europa.eu/en/activities/surveillance/EARS-Net/Pages/ Database.aspx for more detailed European data, including EARS-Net tables, charts and maps) (**Figure** 4). Ireland ranked 11th out of 30 countries reporting to EARS-Net, with the median proportion of MRSA BSI at 14.9%. All countries with MRSA proportions higher than

Pathogen	2004	2005	2006	2007	2008	Year 2009	2010	2011	2012	2013
Number laboratories by year-end	40	41	42	44	42	43	40†	41†	41	41
E. coli										
Number of isolates	1256	1445	1656	1785	1926	2064	2170	2210	2450	2530
%Ampicillin-R*	65.0	67.6	70.7	68.3	70.4	68.7	68.4	71.9	69.6	70.9
%3GC-R*	2.6	4.1	4.2	6.7	7.4	7.5	8.3	9.5	10.8	12.8
%ESBL-producers*	1.1 12.6	2.4 17.3	2.5 21.5	4.1 22.1	5.0 23.3	5.8 22.3	6.1 23.6	7.5 23.8	8.8 25.2	10.5 25.3
%Ciprofloxacin-R* %Gentamicin-R*	5.7	8.5	7.7	9.9	10.2	7.7	9.4	8.7	9.7	23.3 9.8
%Gentamicin/Amikacin/Tobramycin-R*	6.1	8.6	8.6	10.6	11.0	9.3	11.8	12.2	12.6	12.8
%Carbapenem ¹ -R*	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
%MDR*	5.6	7.7	9.0	11.3	12.1	10.4	11.7	13.0	13.4	14.8
Number laboratories by year-end S. aureus	41	42	42	44	43	43	40†	41†	41	41
Number of isolates	1323	1424	1412	1393	1303	1309	1251	1095	1060	1094
Number Meticillin-R (or MRSA)	553	592	592	536	439	355	305	263	242	222
%Meticillin-R (or MRSA)	41.8	41.6	41.9	38.5	33.7	27.1	24.4	24.0	22.8	20.3
Number laboratories by year-end E. faecium	40	41	42	44	42	43	40†	41†	41	41
Number of isolates	187	224	265	330	406	397	392	364	392	409
%Ampicillin-R*	95.7	92.3	93.9	93.1	95.1	92.9	95.6	95.9	92.9	93.2
%Vancomycin-R (VREfm)		31.7	37.1	33.4	35.7	38.3	39.3	37.4	45.4	43.1
%HLG-R*	58.0	51.4	44.3	35.2	28.1	39.1	39.6	36.8	39.3	41.4
%MDR*	18.5	25.6	25.6	22.7	16.2	26.7	24.9	21.1	20.3	19.6
Number laboratories by year-end E. faecalis	40	41	42	44	42	43	40†	41†	41	41
Number of isolates	242	290	294	280	301	289	298	265	298	336
%Ampicillin-R*	0.8	3.5	4.5	2.2	0.7	2.1	0.7	0.8	4.0	2.7
%Vancomycin-R (VREfa)	1.3	2.5	3.7	2.9	3.7	0.7	0.3	4.9	3.0	2.1
%HLG-R*	41.3	44.4	42.4	36.9	30.5	36.7	29.7	29.1	32.9	33.6
Number laboratories by year-end K. pneumoniae			36	39	41	42	40†	41†	41	41
Number of isolates			217	244	310	323	326	312	345	326
%Ampicillin-R*			97.7	99.2	99.7	99.7	99.1	100.0	98.5	99.1
%3GC-R*			10.2	9.9	11.4	11.2	10.5	8.0	11.9	21.2
%ESBL-producers*			8.6	3.7	7.7	8.2	5.0	5.6	8.8	18.4
%Ciprofloxacin-R*	No data	No data	15.3	18.1	12.8	13.0	10.5	13.2	11.9	20.9
%Gentamicin-R* %Gentamicin/Amikacin/Tobramycin-R*			7.8 9.2	9.9 11.1	10.7 10.7	11.1 11.1	6.8 7.1	7.4 8.3	9.9 9.6	16.9 17.5
%Carbapenem ¹ -R*			0.0	0.6	0.0	0.0	0.0	1.6	0.3	1.2
%MDRKP ^{2*}			1.7	2.9	3.9	4.3	2.2	4.6	5.3	12.3
%MDR*			11.2	11.9	10.6	11.9	8.0	8.4	9.9	19.4
Number laboratories by year-end	41	42	42	44	42	43	40†	41†	41	41
S. pneumoniae Number of isolates	400	401	407	438	447	356	314	327	321	311
%Penicillin-NS*	10.3	11.7	15.7	17.4	23.1	20.2	18.2	19.6	19.6	20.7
of which: %HLR		3.0	2.9	5.7	6.0	5.6	4.8	6.1	4.7	2.3
%Int	7.0	8.7	12.5	11.0	16.8	13.8	12.7	13.5	15.0	18.3
%Erythromycin-R*	14.4	12.1	16.1	16.4	16.7	17.3	15.7	18.9	16.9	17.9
%Penicillin-NS/Erythromycin-R	3.1	3.2	7.4	7.9	10.2	11.9	12.6	13.8	12.1	13.0
Number laboratories by year-end P. aeruginosa Number of isolates			36	39	41	42	40†	41†	41	41
Number of isolates %Piperacillin/tazobactam-R*			128 9.4	177 12.6	199 9.7	248 8.9	222 10.0	184 2.8	219 17.4	207 15
%Ceftazidime-R*			10.6	11.8	8.7	11.8	9.2	8.2	15.2	11
%Imipenem/meropenem-R*			11.8	12.2	9.3	10.2	8.3	12.0	19.6	12
%Ciprofloxacin-R*	No data	No data	18.0	22.9	21.8	12.1	13.2	12.6	20.6	15
% Gentamicin-R*			10.2	13.3	9.0	7.7	8.7	6.5	11.9	12
%Gentamicin/Amikacin/Tobramycin-R*			10.2	13.3	9.0	7.7	8.7	6.5	11.9	12
%MDR*			9.5	12.4	11.1	6.4	6.5	4.0	13.0	9
Number laboratories by year-end Acinetobacter spp.										41
Number of isolates										91
%Ciprofloxacin-R*										3
%Gentamicin-R*	No data	No data	No data	No data	Nodeta	No data	No data	No data	No data	0
%Gentamicin/Amikacin/Tobramycin-R*	No data	No data	No data	No data	No data	1				
%Carbapenem ¹ -R*										4
%MDR*										0

R, Resistant; NS, Non-Susceptible [includes isolates with intermediate (Int) and high-level resistance (HLR)] MRSA, Meticillin-Resistant S. aureus; VREfm, Vancomycin-Resistant E. faecium; VREfa, Vancomycin-Resistant E. faecalis HLG, High-Level Gentamicin; 3GC, 3rd-Generation Cephalosporin (includes cefotaxime, ceftriaxone, ceftazidime and cefpodoxime); ESBL, Extended-Spectrum Beta-Lactamase; MDR, Multi-Drug Resistant * Not all isolates tested † The number of laboratories processing blood cultures has changed on a number of occasions between 2006 and 2014; however, coverage of acute hospitals has remained at 100% ¹ Carbapenems include imigenem, meropenem and ertapenem

² MDRKP, MDR K. pneumoniae phenotype (ESBL-producer plus non-susceptibility to Ciprofloxacin and Gentamicin) OR carbapenemase-producer (e.g. KPC, OXA-48)

Ireland are located in Southern and Central/Eastern Europe.

No MRSA isolates with reduced susceptibility to vancomycin were detected at the National MRSA Reference Laboratory.

The MRSA rate for all acute hospitals in 2013 was 0.056 cases per 1,000 BDU, a decrease from 0.060 in 2012, while the MSSA rate increased from 0.208 to 0.218 [Rates are calculated from denominator data (bed days used) obtained from the HSE Business Intelligence Unit (BIU) for all acute public hospitals; and directly from private hospitals where available, where both numerator (*S. aureus* numbers) and denominator data have been provided].

Males were approximately 1.7-times more likely to have invasive *S. aureus* infection (2.3-times for MRSA, z=6.26, P<0.0001; 1.5-times for MSSA, z=6.38, P<0.0001) than females (z=8.43, P<0.0001). The frequency of invasive *S. aureus* infection increased with age, with the majority of infections (n=650; 60%) occurring in adults aged over 60. The median age for MRSA infection was 71 years (95%CI, 69-73) and for MSSA infection was 63 years (95%CI, 61-64). This was considered to be a significant difference, as the confidence intervals did not overlap.

Enterococcus faecium

There were 409 reports of *E. faecium* BSI from 399 patients, an increase of 4.3% from 392 (2012). **Table 1** displays the annual trends since 2004 in the proportion of *E. faecium* isolates resistant to the three "indicator" antimicrobials (ampicillin, vancomycin and high-level gentamicin).

- Of 399 isolates, 165 (41.4%) were resistant to high-level gentamicin (**Figure 5**)
- Of 408 isolates, 176 (43.1%) were resistant to vancomycin, with a decrease in the proportion of vancomycin resistant *E. faecium* (VREfm) from 45.4% (2012). Since 2008, Ireland has had the highest proportion of VREfm in Europe. In 2013, countries with the next highest proportions of



Figure 1. Trends for E. coli – total numbers of E. coli and percentage resistance to 3rd generation cephalosporins (3GCs), ciprofloxacin/ofloxacin (CIP/OFX), gentamicin (GEN) and gentamicin/amikacin/tobramycin (GEN/AMK/TOB) with 95% confidence intervals

. Table 2. Age and gender breakdown of patients by organism with major resistance profiles (data from laboratories participating in enhanced surveillance for 2013). Proportion of isolates detected <48 hours and >5 days post-admission is also shown.

		Total for 2013	Percent female	Mean age in years	Detected <48 hours after admission	Detected >5 days after admission
Staphylococcus aureus	Meticillin Resistant (MRSA)	97	25%	69.0	59%	34%
	Meticillin Susceptible	327	37%	57.7	66%	23%
Streptococcus pneumoniae	Penicillin non-Susceptible	21	29%	59.3	67%	19%
	Penicillin Susceptible	89	52%	61.5	90%	4%
Enterococci	Vancomycin Resistant	84	45%	66.2	18%	76%
	Vancomycin Sensitive	196	40%	65.3	41%	47%
Escherichia coli	Fluoroquinolone Resistant	234	46%	72.1	73%	22%
	Fluoroquinolone Susceptible	672	56%	67.7	77%	16%
Klebsiella pneumoniae		117	37%	65.7	49%	41%
Pseudomonas aeruginosa		71	44%	67.5	54%	34%

VREfm were; the United Kingdom (23%), Greece (23%) and Portugal (22%) (**Figure 6**), while the median proportion of VREfm in EARS-Net countries was just 5.6%.

• Of 398 isolates tested against the three "indicator" antimicrobials, 78 (19.6%) reported from 18 hospitals were resistant to all three and termed MDR, which represents a slight decrease from 20.3% (2012)

Males were approximately 1.4-times more likely to have invasive *E. faecium* infection than females (z=3.36, P<0.001). The frequency of invasive *E. faecium* infection increased with age, with the majority of infections (n=290; 71%) occurring in adults aged over 60. The median age was 68 years (95%CI, 65-70).

Klebsiella pneumoniae

There were 326 reports of invasive *K. pneumoniae* infection (323 from blood and three from CSF) from 317 patients, a decrease of 5.5% from 345 (2012). **Table 1** displays annual trends since 2004 in the proportion of *K. pneumoniae* isolates resistant to the four "indicator" antimicrobials (as for *E. coli* above) plus carbapenems (imipenem, meropenem or ertapenem).

- Of 326 isolates, 69 (21.2%) were resistant to 3GCs, 60 (18.4%) were ESBL positive and nine were ESBL negative. In 2013, the proportion of invasive ESBL positive *K. pneumoniae* infection was at its highest level since surveillance began, with an increase from 8.8% in 2012 (Figure 7)
- Of 325 isolates, 68 (20.9%) were resistant to ciprofloxacin
- Of 326 isolates, 55 (16.9%) were resistant

to gentamicin [57 (17.5%) of 326 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)]

 Of 326 isolates, four (1.2%) were resistant to carbapenems, with two confirmed to be carbapenemase producers, both reported from the same hospital (both OXA-48 type CRE) and two confirmed not to be carbapenemase producers. The two invasive OXA-48 *K. pneumoniae* isolates in 2013 followed the last reported invasive CRE isolates in 2011: OXA-48 (3) and KPC (1)

In 2013, resistance to 3GCs, ciprofloxacin and gentamicin/aminoglycosides were all at their highest levels since surveillance began.

Three invasive *K. pneumoniae* isolates were reported as susceptible to ampicillin, an unexpected finding as all *K. pneumoniae* is inherently resistant to ampicillin.

Of 326 isolates, 63 (19.4%) reported by 17 hospitals that were tested against all four "indicator" antimicrobials were identified as MDR, a large increase from 9.9% (2012):

- 42 resistant to ampicillin, 3GCs, ciprofloxacin and aminoglycosides. ESBL positive (38), ESBL negative (4). This represented a large increase from 16 isolates reported as resistant to all four antimicrobials in 2011
- Seven resistant to ampicillin, 3GCs and ciprofloxacin. All ESBL positive
- Six resistant to ampicillin, 3GCs and gentamicin. ESBL positive (5), ESBL negative (1)



Figure 2. Distribution of 3rd-generation cephalosporin resistant E. coli in EARS-Net countries in 2013

Map downloaded from ECDC's TESSy database on 28/07/2014: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx • Eight resistant to ampicillin, ciprofloxacin and aminoglycosides. All ESBL negative

In 2013, the Antimicrobial Resistance and Microbial Ecology (ARME) group at NUI Galway alerted HPSC to the presence of two predominant *K. pneumoniae* clones implicated in both patient infection and colonisation in a number of Irish hospitals. Both clones were simultaneously ESBL positive and non-susceptible to ciprofloxacin and gentamicin. Some were also found to produce carbapenemases. Together, these are termed multi-drug resistant *K. pneumoniae* (MDRKP) and the proportion of invasive *K. pneumoniae* that were MDRKP further increased between 2012 and 2013: 5.3% (18 of 342 isolates) to 12.3% (40 of 325 isolates), as displayed in **Figure 8**. An outbreak control team was established in October 2013 to evaluate this emerging threat.

Antimicrobial resistance in invasive *K. pneumoniae* isolates in Ireland were previously among the lowest in Europe, but this appears to be changing. In 2013, at 21.2% 3GC resistance, Ireland ranked 18th of 30 countries (up from a rank of 26th in 2012; 11.9%). At 21.2% fluoroquinolone resistance, Ireland ranked 21st (up from a rank of 25th in 2012; 11.9%). Aminoglycoside resistance in Ireland has also increased from 9.9% (ranking 19th of 29 countries) in 2012 to 17.5% (ranking 18th of 30 countries) in 2013. With only two reports of carbapenemase-producing *K. pneumoniae*, Ireland ranked 19th of 29 countries in 2013, with the median proportion among EARS-Net countries being 1.0% (**Figure 9**).

Males were approximately 1.5-times more likely to have an invasive *K. pneumoniae* infection than females (z=3.85, P=0.0001). The frequency of invasive *K. pneumoniae* infection increased with age with the majority of infections (n=220; 67%) occurring in adults aged over 60. The median age was 68 years (95%CI, 66-70).

Streptococcus pneumoniae

There were 311 reports of invasive *S. pneumoniae* infection (304 from blood and seven from CSF) from 310 patients, a decrease of 3.1% from 321 (2012). Table 1 displays annual trends since 2004 in the proportions of *S. pneumoniae* isolates non-susceptible/resistant to penicillin and erythromycin.

Penicillin-non-susceptible *S. pneumoniae* (PNSP) accounted for 20.7% (n=64) of all isolates tested against penicillin (n=309) in 2013. Of the PNSP isolates, 56 were intermediately-resistant (Int; MIC=0.1-1 mg/L for laboratories following the Clinical Laboratory Standards Institute (CLSI) old/oral guidelines and MIC=0.1-2mg/L for those following European Committee on Antimicrobial Susceptibility Testing (EUCAST) nonmeningitis guidelines) and eight were high-level resistant (HLR; MIC >1.0mg/L for CLSI and >2mg/L for EUCAST) to penicillin. Penicillin susceptibility was not determined for two isolates. Fifty-four (17.9%) of 302 isolates were resistant to erythromycin.

There was a slight increase in the proportion of PNSP isolates from 19.6% (2012) to 20.7% (2013) as displayed in **Figure 10**. However, the proportion that displayed penicillin HLR decreased from 4.7% (2012) to 2.6% (2013).

In 2013, Ireland remained among European countries with the highest proportions of PNSP (ranking 10th of 30 countries overall; and 6th of 22 countries reporting ≥50 isolates). In 2013, the median proportion among EARS-Net countries was 9.2%. However, it is important to consider that comparison with other EARS-Net countries is increasingly problematic due to the possibility of different interpretive criteria being applied to the data from different countries (and indeed from different laboratories within a country). Many Irish microbiology laboratories have recently switched or are currently in the process of switching from CLSI to EUCAST guidelines: 27 laboratories had switched by the



Figure 3. Trends for S. aureus – total numbers of S. aureus/MRSA and percentage MRSA with 95% confidence intervals

end of 2013, an increase from 15 by the end of 2012.

- CLSI provides three sets of breakpoints for interpreting penicillin susceptibility of *S. pneumoniae* isolates: meningitis, nonmeningitis and oral
- EUCAST provides two sets of breakpoints: meningitis and infections other than meningitis

In Ireland, EARS-Net data are reported using the "oral" CLSI breakpoints (which correspond to the original CLSI breakpoints) or the EUCAST breakpoints for infections other than meningitis, as these are broadly similar for epidemiological purposes and thus facilitate a more meaningful analysis of the data. This also permits a relatively consistent approach for comparing historical data.

Moderately high levels of erythromycin resistance were seen, with Ireland ranking 18th of 30 countries overall and 10th of 22 countries reporting 50 or more isolates. This is similar to the situation observed in much of Southern and Central/Eastern Europe. In 2013, the median proportion among EARS-Net countries was 18.0%.

Of 299 isolates tested against both penicillin and erythromycin, 39 (13.0%) were simultaneously PNSP (33



Figure 4. Distribution of MRSA in EARS-Net countries in 2013 Map obtained from ECDC on 28/07/2014: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx



Figure 5. Trends for E. faecium – total numbers of E. faecium and percentage resistance to vancomycin (VREfm) and high-level gentamicin (HLG) with 95% confidence intervals

Int, 6 HLR) and erythromycin-resistant in 2013, which is the highest proportion of penicillin/erythromycin coresistance since surveillance began.

In early 2007, a national pilot project was established as a collaborative initiative between RCSI/Beaumont Hospital, Children's University Hospital, Temple St and HPSC, with the aim of providing baseline serotyping data on invasive *S. pneumoniae* isolates. This project pre-dates the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) into the childhood immunisation schedule in September 2008 and PCV13 replaced PCV7 from September 2010.

In 2013, serotype data were available for 271 pneumococcal isolates reported by 31 of the 33 laboratories reporting pneumococcal isolates to EARS-Net, representing 87% of all pneumococcal isolates reported:

- Of 138 isolates from patients aged ≥65 years, 98 (71%) belonged to serotypes included in the PPV-23 vaccine
- Only 12 isolates were referred for typing from patients aged <2 years (the target population for the PCV13 vaccine) and eight of these were non-vaccine serotypes

The most common serotypes identified were; 7F (n=48), 19A (n=33), 3 and 22F (n=18 each), 8 (n=11), 14 and 23B (n=10 each) representing 55% of all isolates typed.

Of the 64 PNSP isolates, 55 were serotyped:

- Of 36 isolates from patients age ≥65 years, 24 (67%) belonged to serotypes included in the PPV-23 vaccine
- None of the serotyped PNSP isolates came from children <2 years (note: one PNSP isolate from a

child in this age group was not serotyped) Ongoing surveillance of the predominant serotypes is required, as strains with non-vaccine serotypes have been reported to increase in prevalence following the introduction of conjugate vaccines in other countries, hence the need for a fully-resourced Irish pneumococcal reference laboratory. The separate chapter on invasive pneumococcal disease (IPD) in Ireland in 2013 contains additional information on pneumococcal serotyping.

In 2013, the rate of IPD in Ireland was estimated at 6.8 cases per 100,000 population, compared with 7.0 in 2012 (Note that both rates were calculated using 2011 census data). The highest rates of IPD were observed at extremes of age; children aged <1 year (11.0 per 100,000) and 1 year (10.5 per 100,000) and adults aged 65-74 (20.3 per 100,000), 75-79 (39.2 per 100,000) and \geq 80 (40.5 per 100,000) as displayed in **Figure 11**. The IPD rates in all age groups were broadly similar to 2012, with the exception of ages 1 year (increase from 5.5 to 10.5) and \geq 80 years (decrease from 53.7 to 40.5).

Males were approximately 1.1-times more likely to have an invasive *S. pneumoniae* infection than females, but this was not statistically significant (z=0.97, P=0.33). The frequency of invasive *S. pneumoniae* infection increased with age, with the majority (n=182; 59%) occurring in adults aged over 60. The median age was 64 years (95%CI, 62-67).

Enterococcus faecalis

There were 336 reports of *E. faecalis* BSI from 327 patients, an increase of 12.8% from 298 (2012). **Table** 1 displays annual trends since 2004 in the proportions of *E. faecalis* isolates resistant to the three "indicator" antimicrobials (as for *E. faecium*):

 Of 334 isolates, seven (2.1%) were resistant to vancomycin (VREfa), with Ireland ranking 7th



Figure 6. Distribution of vancomycin-resistant E. faecium (VREfm) in EARS-Net countries in 2013 Map downloaded from ECDC's TESSy database on 28/07/2014: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx

among European countries for resistance. The median proportion in Europe was 0.4%, although the proportion of VREfa in Ireland has decreased from the highest reported proportion of 4.9% in 2011

• Of 318 isolates, 107 (33.6%) were resistant to high-level gentamicin

Nine isolates were reported resistant to ampicillin, which is suggestive of misidentification of species or misclassification, as resistance to ampicillin is rare in *E. faecalis*.

Males were approximately 2.1-times more likely to have invasive *E. faecalis* infection than females (z=6.74, P<0.0001). The frequency of invasive *E. faecalis* infection increased with age, with the majority of infections (n=236; 70%) occurring in adults aged over 60. The median age was 69 years (95%CI, 67-71).

Pseudomonas aeruginosa

There were 207 reports of invasive *P. aeruginosa* infection (206 from blood and one from CSF) from 205 patients, a decrease of 5.5% from 219 (2012). **Table 1** displays annual trends since 2006 in the proportion of *P. aeruginosa* isolates resistant to the five "indicator" antimicrobials/antimicrobial classes [piperacillin-tazobactam, ceftazidime, carbapenems (meropenem or imipenem), fluoroquinolones (ciprofloxacin or ofloxacin) and gentamicin]. In 2013, resistance to all five indicator antimicrobials decreased.

- Of 204 isolates, 31 (15.2%) were resistant to piperacillin-tazobactam
- Of 206 isolates, 22 (10.7%) were resistant to ceftazidime
- Of 206 isolates, 25 (12.1%) were resistant to imipenem or meropenem
- Of 207 isolates, 31 (15.0%) were resistant to ciprofloxacin

• Of 207 isolates, 24 (11.6%) were resistant to gentamicin [no additional isolates were resistant to the other aminoglycosides (amikacin or tobramycin)]

Nineteen (9.4%) of 203 isolates reported from 13 hospital and that were tested against all five "indicator" antimicrobials were identified as MDR, the highest since surveillance began:

- Three resistant to all five antimicrobial classes
- Ten resistant to four of five antimicrobial classes
- Six resistant to three of five antimicrobial classes

Antimicrobial resistance levels among *P. aeruginosa* isolates in Ireland are at moderately low levels in comparison with other European countries, with Ireland ranking 18th – 23rd of 30 countries for all five indicator antimicrobials.

Males were approximately 1.5-times more likely to have invasive *P. aeruginosa* infection than females (significant; z=2.91, P=0.004). The frequency of invasive *P. aeruginosa* infection increased with age, with the majority of infections (n=155; 75%) occurring in adults aged over 60. The median age was 71 years (95%CI, 69-73).

Acinetobacter spp.

In 2013, surveillance of invasive Acinetobacter spp. Infection began in Ireland, with 91 reports of invasive infection caused by Acinetobacter spp. (90 from blood and one from CSF) from 90 patients. **Table 1** displays the proportion of Acinetobacter spp. isolates resistant to the three "indicator" antimicrobials/antimicrobial classes [carbapenems (meropenem or imipenem), fluoroquinolones (ciprofloxacin or ofloxacin) and gentamicin]:



Figure 7. Trends for K. pneumoniae – total numbers of K. pneumoniae and percentage resistance to 3rd generation cephalosporins (3GCs) and ESBL-positivity with 95% confidence intervals

- Of 86 isolates, three were resistant to imipenem or meropenem
- Of 89 isolates, three were resistant to ciprofloxacin
- None of 89 isolates were resistant to gentamicin [no additional isolates were resistant to the other aminoglycosides (amikacin or tobramycin)]

Enhanced Surveillance

The voluntary EARS-Net enhanced surveillance programme was established in 2004. Laboratories that participate in EARS-Net are invited to provide additional demographic, risk factor and clinical data on invasive pathogens causing BSI.

In 2013, enhanced surveillance data on 1,908 individual records (cases or isolates under the EARS-Net definition) were submitted from 11 participating laboratories, representing 36% of all reports to EARS-Net. In late 2013, the layout of the enhanced surveillance data collection form was revised and piloted. The field structures were simplified to allow greater participation. **Table 2** displays demographic and other basic data for the major resistance profiles of pathogens reported to EARS-Net enhanced surveillance.

- 1. S. aureus BSI
- Healthcare associated infection was reported for the majority of MRSA (69%) and MSSA (63%) BSI
- From 2010 to 2012, a reduction in the proportion of *S. aureus* BSI due to CVC infection was observed (from 23% to 15%). However, the proportion increased to 21% in 2013. The proportion of *S. aureus* BSI due to PVC infection declined from 11% (2012) to 7% (2013)
 - MRSA BSI = 23% CVC & 3% PVC infection
 - o MSSA BSI = 20% CVC & 8% PVC infection
- The most common risk factors reported were recent

surgery, malignancy and stay in an intensive care unit

- 2. Enterococcal BSI
- Healthcare associated infection was reported for the vast majority of vancomycin resistant (92%) and vancomycin susceptible (74%) enterococcal BSI
- The most common primary sources of BSI were: CVC and intra-abdominal or gastrointestinal tract infection
- 3. S. pneumoniae BSI
- The proportion of PNSP detected within two days after admission decreased from 95% (2012) to 67% (2013), while the proportion of penicillin susceptible *S. pneumoniae* (PSSP) increased from 77% (2012) to 90% (2013). However, the number of PNSP BSI isolates for which enhanced information was reported was small, thus the results must be interpreted with caution
- Respiratory tract infection remained the most common source of pneumococcal BSI
- 4. E. coli BSI
- Healthcare associated infection was reported for the majority of fluoroquinolone resistant *E. coli* BSI, which contrasts with 44% for fluoroquinolone susceptible *E. coli*
- The most common source of *E. coli* bloodstream infection was urinary tract infection, with 5% reported in association with the presence of a urinary catheter



Figure 8. Trends for K. pneumoniae isolates with the MDRKP phenotype (simultaneously ESBL-producers and non-susceptible to both ciprofloxacin and gentamicin and/or a carbapenemase producer) — numbers and percentage with MDRKP phenotype with 95%CIs

Further information is available on the HPSC website: http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/EnhancedBacteraemiaSurveillance/

Conclusion

For the seventh consecutive year, the proportion of *S. aureus* BSI attributable to MRSA further declined to 20.3%, the lowest reported level since Ireland joined EARS-Net. Unfortunately, antimicrobial resistance in other important BSI causative pathogens increased further and remains a cause for concern.

For the sixth consecutive year, Ireland remained the European country with the highest proportion of VREfm BSI (43.1%), which was far in excess of the countries reporting the second highest proportion (UK and Greece, both at 23%).

Additionally, the proportions of ESBL positive and multi-drug resistant *Enterobacteriaceae* (*E. coli* and *K. pneumoniae*) reached the highest reported levels to date. In 2013, the ARME research group at NUI Galway alerted the HPSC to the detection of two *K. pneumoniae* clones causing both infection and colonisation in patients attending a number of Irish hospitals. These clones exhibited a multi-drug



Figure 9. Distribution of carbapenem-resistant K. pneumonie in EARS-Net countries in 2013 Map downloaded from ECDC's TESSy database on 28/07/2014: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx



Figure 10. Trends for S. pneumoniae – total numbers of S. pneumoniae/PNSP and percentage PNSP with 95% confidence intervals HLR, High-level resistant; I, Intermediately resistant

resistant phenotype, involving both ESBL production and non-susceptibility to both ciprofloxacin and gentamicin and have been termed MDRKP, with a smaller proportion also producing carbapenemases, hence the term CRE. Further analysis of EARS-Net data revealed a large increase in invasive K. pneumoniae that were MDRKP between 2012 and 2013 (from 5.3% to 12.3%), supporting the hypothesis of emergence and dissemination of MDRKP in Ireland. Given the extent of antimicrobial resistance exhibited by MDRKP, coupled with increasing concerns worldwide on both dissemination of multi-drug resistant organisms and paucity of effective antimicrobial treatments, in response to this data, a national outbreak control team was established by HPSC in October 2013 to evaluate this emerging threat.

In 2013, there were two reported cases of invasive carbapenemase-producing K. pneumoniae (CRE) infection in Ireland, with 24 of 29 EARS-Net participant countries reporting one or more cases and 15 countries reporting five or more cases. Greece (60%) and Italy (36%) remained the European countries with the largest proportion of invasive CRE infections (among K. pneumoniae). Additionally, significant increases were reported by Romania (22%) and Malta (15%). This clearly illustrates the successful dissemination of these highly resistant microorganisms in Europe, which may be contributed to by suboptimal infection prevention and control and antimicrobial stewardship practices in both acute and non-acute healthcare settings. To address the threat of MDR-Enterobacteriaceae, such as MDRKP, ESBLs and CRE to Ireland, it is vital that control measures are strengthened in both acute and non-acute healthcare settings, with implementation of the recommendations contained in the Guidelines for the prevention and control of multi-drug resistant organisms, other than MRSA, published in 2013 and the Guidelines for antimicrobial stewardship in hospitals, published in 2009.

The decline in the burden of MRSA BSI in recent years may be partly attributable to improvements in infection prevention and control interventions, such as increased emphasis on and improved healthcare worker awareness of the importance of compliance with standard and contact precautions, screening of patients for MRSA carriage and the availability of decolonisation regimens to eradicate MRSA carriage. The development of and strengthening of hospital antimicrobial stewardship programmes and restricted prescribing of certain broad spectrum antimicrobials, particularly in response to other healthcare associated infections, such as *Clostridium difficile* infection, may also have positively contributed to the decreasing proportion of MRSA BSI.

Since 2008, pneumococcal conjugate vaccines have been a component of the childhood immunisation programme, an intervention which has already resulted in a reduction in the burden of paediatric invasive pneumococcal disease (IPD) in Ireland. However, pneumococcal antimicrobial resistance remains a major problem in Ireland and the increasing number of reported invasive infections due to multi-drug resistant strains is of particular concern. Clearly, IPD manifesting as BSI or meningitis reflects the most severe form of pneumococcal infection and data on other more common manifestations of infection (e.g., pneumonia, sinusitis and otitis media) are not captured by EARS-Net. While data from invasive infections is extremely valuable in comparing national levels of AMR, the true burden of infection caused by antimicrobial resistant pneumococci may be underestimated.

The enhanced EARS-Net surveillance data are particularly useful in informing infection prevention and control programmes, both nationally and in those hospitals that participate in the surveillance scheme. Participation in enhanced surveillance can also help to identify risk factors and potentially preventable



Figure 11. Numbers and age-specific incidence rates of patients with invasive S. pneumoniae infection in 2013 compared with 2012

healthcare associated infections that can be targeted as part of preventative programmes (e.g., invasive medical device related infections).

Infections caused by antimicrobial resistant bacteria result in excess patient mortality, morbidity and costs to the healthcare system. Rising levels of AMR threaten many aspects of healthcare that we currently take for granted. It is critical that comprehensive infection prevention and control and antimicrobial stewardship programmes continue to be developed and maintained at all levels and settings within the Irish health service. To this end, it is vital that recommendations and guidelines produced by the HSE RCPI Clinical Advisory Group on HCAI and AMR are implemented.

HPSC thanks all the microbiology laboratories for their continued participation and enthusiasm for the EARS-Net project.

The data presented in this report were taken from the EARS-Net database on 1st September 2014.

9.3.0.1 Enhanced surveillance of Carbapenem Resistant *Enterobacteriaceae* (CRE) in Ireland – 2013

Summary:

- In 2013, enhanced surveillance data was received on 24 CRE cases. This represented a decrease compared with 2012, when enhanced surveillance data was received on 32 CRE cases. In contrast, the National Carbapenemase Producing Enterobacteriaceae (CPE) Reference Laboratory Service (CPEaRLS) at Galway University Hospital confirmed carbapenemase production in 48 Enterobacteriaceae isolates in 2013
- Just one patient (4%) had a history of hospitalisation in another jurisdiction (Northern Ireland: KPC-type CRE isolated)
- The clinical significance of the CRE isolate was reported for 20 patients (83%), representing colonisation in the majority (n=13). CRE infection was reported for the remaining seven patients

Carbapenem resistant *Enterobacteriaceae* (CRE) are multi-drug resistant Gram-negative bacteria that can be easily spread between patients in healthcare settings and have the ability to cause infections for which effective antimicrobial therapy may be lacking. Most CRE produce carbapenemase, an enzyme that breaks down the carbapenem class of antimicrobials (e.g. imipenem, meropenem). Carbapenemase production has spread worldwide in the past 15 years and is now a prominent resistance mechanism reported in many countries.

Detection of confirmed carbapenemase-producing CRE, hereafter known as CRE, became notifiable in Ireland in March 2011, under the category of 'unusual cluster or changing pattern of illness'. Upon amendment to the Infectious Diseases Regulations in September 2011, invasive CRE infection (blood, CSF or normally sterile site) became notifiable in its own category. The CRE enhanced surveillance scheme was established in June 2011 and reporting of CRE isolates from any site, whether colonisation or infection is encouraged.

In 2013, enhanced surveillance data was received from 11 laboratories on 24 confirmed cases of carbapenemase-producing CRE and one tertiary hospital reported a CRE outbreak. Figure 1 displays annual trends in CRE cases and types reported to enhanced surveillance since 2011. Of the 24 patients, 15 were male (63%). The average age was 67 years (range: 31 – 95). At the time of CRE detection, 21 patients (88%) were hospitalised, two were in the community (8%) and one was a nursing home resident (4%). Of the 21 hospitalised patients, 10 (48%) had been admitted from home, eight (38%) were transfers from another acute hospital, one had been admitted from long-term care (4%) and the source of admission was not provided for the remaining two patients (10%). Of the eight patients who had been transferred from

another acute hospital, one was repatriated from a hospital in another jurisdiction (Northern Ireland).

At the time of CRE detection, nine patients (38%) were already known to be colonised or infected with one or more other multi-drug resistant organisms (MDRO) and seven of those were inpatients.

Nine patients (38%) reported no foreign travel in the last 12 months and the travel history was unknown for the remaining 15 (62%).

Two patients had no identifiable risk factors for CRE colonisation or infection and risk factor data was not provided for two patients. Of the remaining 20 patients, 17 (85%) had more than one risk factor. Reported risk factors included; Hospitalisation in the past 12 months (15; 75%), history of surgery in the past six months (9; 45%), history of admission to intensive care in the last 12 months (3; 15%). Reported underlying co-morbidities included: immunocompromise (7 patients), renal disease (5 patients), diabetes mellitus (4 patients), liver disease (3 patients), chronic lung disease (1 patient) and urological abnormality (1 patient).

Antimicrobial exposure history prior to isolation of CRE was provided for 10 patients (42%), all of whom were hospitalised. Of those, nine had recent antimicrobials, with six having received more than one antimicrobial class:

- β lactam β lactamase inhibitor combination agents;
 9 (100%)
- •Carbapenems; 3 (33%)
- •Aminoglycosides; 3 (33%)
- •Cephalosporins; 2 (22%)
- •Fluoroquinolones; 2 (22%)

The clinical significance of the CRE isolate was reported for 20 patients (83%), representing colonisation in the majority (n=13). CRE infection was reported for the remaining seven patients, with three cases of urinary tract infection, two cases of surgical site infection and one case each of respiratory tract and intra-abdominal infection.

Half of CRE (n=12) were isolated from screening swabs (rectal or stoma). Five isolates were detected from urine (21%), two each from vascular catheter tips, respiratory specimens and tissue specimens and one from a superficial swab.

Outcome was reported for one of the three nonhospitalised patients (who survived) and for 17 of the 21 hospitalised patients (81%). Of those, nine (53%) were discharged home, two (12%) remained inpatients at the time the surveillance form was returned, one of whom had already had CRE infection and it is not known whether or not the second CRE colonised patient subsequently went on to develop CRE infection later in the hospital admission. Six patients died (35%). For two of the six deaths, the patient was reported to have had CRE infection. The potential contribution of CRE to patient death was not collected. Date of death was provided for four patients. Thus the interval between CRE positive specimen date and death could be calculated for four patients and was four, 17 and 19 days, respectively with CRE isolated from a post mortem specimen obtained from the final patient.

Length-of-stay could be calculated for all nine admitted patients. The median length-of-stay was 18 days (range: 3 - 77).

Klebsiella pneumoniae accounted for 20 CRE isolates. There were two cases each of *Escherichia coli* CRE and *Citrobacter freundii* CRE reported to enhanced surveillance.

The carbapenemase enzyme types reported to enhanced surveillance in 2013 were; OXA-48 (11), KPC (11) and NDM-1 (2). This contrasts with 48 CPE confirmed by the CPEaRLS in 2013, subdivided as follows: KPC (14), OXA-48 (29), NDM-1 (3), IMI (1) and IMP (1). Therefore, a significant proportion of confirmed CPE cases in 2013 were not reported to the enhanced surveillance scheme.

- •Carbapenems; Reported minimum inhibitory concentrations for meropenem and ertapenem ranged from 0.38 to >32 mg/L
- •Gentamicin; Reported on 23 isolates, with 9 resistant (39%)
- •Amikacin; Reported on 18 isolates, with 7 resistant (39%)
- •Fluoroquinolones; Reported on 21 isolates, with 15 resistant (71%) and one of intermediate susceptibility
- •**Tigecycline;** Reported on 16 isolates; with 5 resistant (31%) and 4 with intermediate susceptibility (25%)
- •Colistin; Reported on 15 isolates, with none resistant

In response to the emergence of CRE, Irish guidelines for the prevention and control of multi-drug resistant organisms, excluding MRSA, in the healthcare setting were developed under the auspices of the Royal College of Physicians of Ireland (RCPI) Clinical Advisory Group on Healthcare-Associated Infections and Antimicrobial Resistance and were first published in early 2013. In response to the changing epidemiology of CRE and other types of multi-drug resistance in Enterobacteriaceae in Ireland, the guidelines on screening for carriage of resistant Enterobacteriaceae were further updated in July 2014. The latest versions of the guidelines are available on the HPSC website at the following link: http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/StrategyforthecontrolofAntimicrobialResistanceinIrelandSARI/CarbapenemResistantEnterobacteriaceaeCRE/ScreeningforCREinIreland/

Please note that in the reduction in reported cases between 2012 and 2013 reflects under-reporting rather than a true decline in CRE. Twice as many isolates were confirmed by the CPEaRLS, Galway University Hospital (n=48) than were reported to the voluntary CRE enhanced surveillance scheme (n=24) in 2013.

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Sincere thanks to colleagues working in microbiology laboratories and infection prevention and control teams across Ireland for submitting enhanced surveillance data on patients with CRE.

Sincere thanks also to colleagues in the CPEaRLS, Galway University Hospital for data on confirmed carbapenemase producing *Enterobacteriaceae* in 2013 (Source: CPEaRLS annual report).



Figure 1. Annual trends in CRE cases and types reported to HPSC since enhanced surveillance of CRE commenced in 2011.