9.5 Antimicrobial Resistance

Key Points

- In 2015, there was a slight reduction in coverage of the Irish population by EARS-Net versus 2014, from 100% to 97%

- **There were 2,697 reports of invasive *Escherichia coli* infection:**
  - The proportion resistant to third-generation cephalosporins (3GC) at 12.5% and extended-spectrum beta lactamase (ESBL) producers at 10.6% reached the highest levels to date
  - There were two cases of carbapenemase-producing *E. coli* invasive infection, also known as carbapenem-resistant *Enterobacteriaceae* (CRE)

- **There were 401 reports of *Klebsiella pneumoniae* bloodstream infection (BSI)**, an increase from 358 in 2014:
  - The proportion resistant to 3GCs at 17.5% and ESBL producers at 13.3% increased from 2014 levels; 12.8% and 11.0%, respectively
  - In Ireland, *K. pneumoniae* that are both ESBL-producers and non-susceptible to ciprofloxacin and gentamicin are called multi-drug resistant *K. pneumoniae* (MDRKP). Some also produce carbapenemases. The proportion of invasive *K. pneumoniae* that were MDRKP increased from 8.2% in 2014 to 9.8% in 2015
  - There were seven cases of confirmed carbapenemase-producing *K. pneumoniae* invasive CRE infection

- **There were 201 reports of invasive *Pseudomonas aeruginosa* infection**, an increase from 2014. Resistance to most indicator antimicrobials, except carbapenems, decreased

- **There were 421 reports of *Enterococcus faecium* BSI**, an increase from 2014:
  - The proportion resistant to vancomycin (VREfm) at 45.6%, reflected one of the highest levels to date

- **There were 1,082 reports of *Staphylococcus aureus* BSI:**
  - The proportion that were meticillin-resistant *S. aureus* (MRSA) at 18.4% is the lowest annual proportion reported to date
  - The overall MRSA BSI rate for acute hospitals was 0.050 cases per 1,000 bed days used (BDU), a slight decrease from 0.055 in 2014. The meticillin-susceptible *S. aureus* (MSSA) BSI rate also decreased from 0.227 (2014) to 0.223 (2015)

- **There were 304 reports of invasive *Streptococcus pneumoniae* infection:**
  - The proportion deemed penicillin non-susceptible (PNSP) at 17.5% represented a slight increase from 17.1% in 2014
  - While the national rate of invasive pneumococcal infection at 6.8 per 100,000 population, represented a decrease compared to 7.2 in 2014
  - Serotype data was available for the majority of invasive *S. pneumoniae* isolates (n=276; 90.8%). Results indicate good coverage (67.1%) for the 23-valent pneumococcal polysaccharide vaccine (PPV23) in its target population (adults ≥65 years)

- Enhanced surveillance data were provided on 2,432 records (cases or isolates under the EARS-Net definition) from 22 laboratories, representing 45% of all reported cases in 2015

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/healthtopics/antimicrobial_resistance/database/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 2015, three of the 39 microbiology laboratories suspended their participation in EARS-Net for two quarters each, resulting in an estimated 97% coverage of the Irish population.

Escherichia coli

There were 2,697 reports of invasive *E. coli* infection (blood = 2,689 and CSF = 8) from 2,645 patients, compared with 2,771 reports in 2014. The observed decrease was due to lower population coverage in 2015 (see introduction). **Table 1** displays annual trends since 2008 in the proportion of *E. coli* isolates resistant to the five "indicator" antimicrobials/antimicrobial classes: ampicillin, third-generation cephalosporins (3GC; cefotaxime, ceftriaxone, ceftazidime or cefpodoxime), fluoroquinolones (ciprofloxacin or ofloxacin), aminoglycosides (gentamicin, amikacin or tobramycin) and carbapenems (meropenem or ertapenem):

- Of 2,686 isolates, 337 (12.5%) were 3GC resistant. Of those, 273 were ESBL producers and 64 were ESBL negative
- Of 2,688 isolates, 655 (24.4%) were resistant to ciprofloxacin
- Of 2,693 isolates, 295 (11%) were resistant to gentamicin [360 (13.4%) of 2,694 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)]
- Six (0.2%) of 2,678 isolates were resistant to carbapenems. Of those, two were confirmed carbapenemase-producers: NDM (1) and OXA-48 (1)

Resistance to 3GC has been increasing since 2004, reaching its highest level to date in 2015 (**Figure 1**). Resistance to ciprofloxacin and aminoglycosides decreased in 2015 compared with 2014. ESBLs were detected in 284 (10.6%) of 2,684 isolates tested. In 2015, ESBL production by invasive *E. coli* isolates was at its highest level since surveillance began. ESBL production has been increasing since 2004.

In 2015, Ireland had moderately high levels (10 to <25%) of resistance to 3GC (**Figure 2**), ciprofloxacin and aminoglycosides (ranking 16th, 17th and 13th, respectively, of 30 countries reporting to EARS-Net). The median proportions for resistance among EARS-Net countries were 12.5% for 3GC, 24.7% for ciprofloxacin and 12.5% for aminoglycosides.

Of 2,676 isolates tested against all five "indicator" antimicrobials, 389 (14.6%) reported from 46 hospitals/institutions were identified as multi-drug resistant (MDR) *E. coli*, defined as resistance to three or more of the indicator antimicrobials **OR** any isolate with resistance to carbapenems, a slight decrease from 15.0% in 2014. A significant increase in MDR-*E. coli* was observed from 2009 to 2014 (P<0.001). In 2015, MDR *E. coli* decreased slightly.

The frequency of invasive *E. coli* infection increased with female gender x 1.2 fold (P<0.001) and age, with the majority (n=2,040; 76%) occurring in those over 60 years (median = 72 years; 95%CI, 71-73).

Klebsiella pneumoniae

There were 401 reports of invasive *K. pneumoniae* BSI from 387 patients, an increase of 12% from 2013 (n=358). The observed decrease was due to lower population coverage in 2015 (see introduction). **Table 1** displays annual trends since 2008 in the proportion of *K. pneumoniae* isolates resistant to the five "indicator" antimicrobials (as described in section on *E. coli* above):

- Of 399 isolates, 70 (17.5%) were resistant to 3GC, of which 51 were ESBL producers and 19 were ESBL negative
- Of 399 isolates, 86 (21.6%) were resistant to ciprofloxacin
- Of 401 isolates, 68 (17.0%) were resistant to gentamicin [72 (18%) of 401 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)]
- Of 401 isolates, nine (2.2%) were carbapenem resistant. Of those, seven were carbapenemase-producers reported from four hospitals; OXA-48 (6) and KPC (1), an increase from two in 2014; OXA-48 (1) and KPC (1). The remaining two isolates were not carbapenemase-producers

Resistance to 3GC, ciprofloxacin and gentamicin/aminoglycosides all increased in 2015, compared with 2014. Resistance to ciprofloxacin and gentamicin/aminoglycosides reached the highest levels since surveillance began and 3GC-resistance the second highest level after 2013 (**Figure 3**).

Three invasive *K. pneumoniae* isolates were reported as susceptible to ampicillin, suggestive of misidentification of species or misclassification, as *K. pneumoniae* are inherently resistant to ampicillin.

ESBLs were detected in 53 (13.3%) of 398 isolates tested. In 2015, ESBL production by invasive *K. pneumoniae* isolates was at its second highest level (after 2013; 18.4%) since surveillance began.

Of 398 isolates, 79 (19.8%) reported by 24 hospitals that were tested against all five "indicator" antimicrobials were identified as MDRKP, an increase from 13.7% in 2014. In 2015, MDRKP reached its highest level since surveillance began.

In 2015, Ireland ranked 21st for both 3GC and fluoroquinolone resistance and 18th for aminoglycoside resistance among 30 countries reporting to EARS-Net. The median proportions among EARS-Net countries were 3GC (26.6%), fluoroquinolone (31.9%) and aminoglycosides (21.6%), respectively. With three cases of invasive carbapenem-resistant *K. pneumoniae* (0.8%) meeting the EARS-Net case

Pathogen	Year							
	2008	2009	2010	2011	2012	2013	2014	2015
Number laboratories by year-end	**42**	**43**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
E. coli								
Number of isolates	**1926**	**2064**	**2170**	**2210**	**2450**	**2530**	**2771**	***2697***
%Ampicillin-R*	70.4	68.7	68.4	71.9	69.6	70.9	69.9	***66.7***
%3GC-R*	6.7	7.1	8.0	9.1	10.3	12.3	12.0	***12.5***
%ESBL-producers*	5.0	5.8	6.1	7.5	8.8	10.5	10.2	***10.6***
%Ciprofloxacin-R*	23.3	22.3	23.6	23.8	25.2	25.3	26.2	***24.4***
%Gentamicin-R*	10.2	7.7	9.4	8.7	9.7	9.8	11.2	***11.0***
%Gentamicin/Amikacin/Tobramycin-R*	11.0	9.3	11.9	12.4	12.8	12.9	14.5	***13.4***
%Carbapenem[1]-R*	0.0	0.0	0.0	0.0	0.1	0.1	0.1	***0.2***
%MDR*	11.6	10.3	11.8	13.2	13.6	14.6	15.0	***14.5***
Number laboratories by year-end	**43**	**43**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
S. aureus								
Number of isolates	**1303**	**1309**	**1251**	**1095**	**1060**	**1094**	**1117**	***1082***
Number Meticillin-R (or MRSA)	**439**	**355**	**305**	**263**	**242**	**222**	**217**	***199***
%Meticillin-R (or MRSA)	33.7	27.1	24.4	24.0	22.8	20.3	19.4	***18.4***
Number laboratories by year-end	**42**	**43**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
E. faecium								
Number of isolates	**406**	**397**	**392**	**364**	**392**	**409**	**405**	***421***
%Ampicillin-R*	95.1	92.9	95.6	95.9	92.9	93.2	95.3	***94.3***
%Vancomycin-R (VREfm)	35.7	38.3	39.3	37.4	45.4	43.1	45.9	***45.6***
%HLG-R*	28.1	39.1	39.6	36.8	39.3	41.4	44.3	***49.5***
%Linezolid-R*	3.4	5.2	2.2	1.1	1.5	1.2	2.0	***0.7***
%MDR*	16.2	26.7	25.0	21.1	20.3	19.6	22.1	***21.3***
Number laboratories by year-end	**41**	**42**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
K. pneumoniae								
Number of isolates	**310**	**323**	**326**	**312**	**345**	**326**	**358**	***401***
%Ampicillin-R*	99.7	99.7	99.1	100.0	98.5	99.1	100.0	***99.3***
%3GC-R*	11.4	11.2	10.2	8.0	11.9	21.2	13.1	***17.5***
%ESBL-producers*	7.7	8.2	5.1	5.6	8.8	18.4	11.0	***13.3***
%Ciprofloxacin-R*	12.8	13.0	10.5	13.2	11.9	20.9	17.3	***21.6***
%Gentamicin-R*	10.7	11.1	6.8	7.4	9.6	16.9	12.6	***17.0***
%Gentamicin/Amikacin/Tobramycin-R*	10.7	11.1	7.1	8.3	9.9	17.8	13.2	***18.0***
%Carbapenem[1]-R*	0.0	0.0	0.0	1.9	0.3	1.2	1.1	***2.2***
%MDRKP[2]*	3.9	4.3	2.2	4.6	5.3	12.3	8.2	***9.8***
%MDR*	10.3	11.9	8.0	9.0	10.2	19.7	13.7	***19.8***
Number laboratories by year-end	**42**	**43**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
S. pneumoniae								
Number of isolates	**447**	**356**	**314**	**327**	**321**	**311**	**331**	***304***
%Penicillin-NS*	23.1	20.2	18.2	19.6	19.6	20.7	17.1	***17.5***
of which: %HLR	*6.0*	*5.6*	*4.8*	*6.1*	*4.7*	*2.6*	*2.4*	***0.3***
%Int	*16.8*	*13.8*	*12.7*	*13.5*	*15.0*	*18.0*	*14.5*	***17.2***
%Erythromycin-R*	16.7	17.3	15.7	18.9	16.9	17.9	13.8	***15.2***
%Penicillin-NS/Erythromycin-R	10.4	11.9	12.6	13.8	12.5	13.0	11.0	***10.8***
Number laboratories by year-end	**42**	**43**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
E. faecalis								
Number of isolates	**301**	**289**	**298**	**265**	**298**	**336**	**315**	***294***
%Ampicillin-R*	0.7	2.1	0.7	0.8	4.0	2.7	1.6	***0.7***
%Vancomycin-R (VREfa)	3.7	0.7	0.3	4.9	3.0	2.1	2.9	***1.4***
%HLG-R*	30.5	36.7	29.7	29.1	32.9	33.6	32.8	***28.0***
%Linezolid-R*	2.3	3.4	2.5	1.2	0.0	0.6	1.0	***0.4***
Number laboratories by year-end	**41**	**42**	**40†**	**41†**	**41**	**41**	**39†**	***38††***
P. aeruginosa								
Number of isolates	**199**	**248**	**222**	**184**	**219**	**207**	**182**	***201***
%Piperacillin/tazobactam-R*	9.7	8.9	10.0	2.8	17.4	15.7	16.5	***14.0***
%Imipenem/meropenem-R*	9.3	10.0	8.3	12.0	19.4	13.1	11.6	***16.4***
%Ciprofloxacin-R*	21.8	12.1	13.2	12.6	20.6	15.0	13.7	***13.5***
%Gentamicin-R*	9.0	7.7	8.7	6.5	11.9	11.6	4.9	***3.5***
%Gentamicin/Amikacin/Tobramycin-R*	9.0	8.1	8.6	6.5	11.9	11.6	5.5	***7.0***
%MDR*	11.1	6.4	6.5	4.0	13.0	9.4	6.7	***7.5***
Number laboratories by year-end						**41**	**39†**	***38††***
Acinetobacter spp.								
Number of isolates	*No data*	*No data*	*No data*	*No data*	*No data*	**91**	**93**	***87***
%Ciprofloxacin-R*						*3*	*8*	***7***
%Gentamicin-R*						*0*	*3*	***4***
%Gentamicin/Amikacin/Tobramycin-R*						*1*	*3*	***5***
%Imipenem/meropenem-R*						*4*	*4*	***6***
%MDR*						*0*	*2*	***3***

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)
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 up to 2014; however, coverage of acute hospitals has remained at 100%
†† Three laboratories each suspended their participation in EARS-Net for a period of two quarters; by the year-end two laboratories had re-commenced EARS-Net and coverage of acute hospitals in 2015 was estimated to be 97%
[1] Carbapenems include imipenem, 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)

definition for carbapenem resistance, which is less sensitive than that used in Ireland, Ireland ranked joint 16th of 30 countries in 2015, with the median proportion among EARS-Net countries being 0.9% (**Figure 5**).

The frequency of invasive *K. pneumoniae* infection increased with male gender x 1.7 fold (P=0.001) and age, with the majority of infections (n=293; 73%) occurring in those over 60 years (median = 69 years; 95%CI, 68-71).

Pseudomonas aeruginosa

There were 201 reports of invasive *P. aeruginosa* infection (blood = 200 and CSF = 1) from 195 patients, an increase of 10.4% from 2014 (n=182). The observed increase occurred despite lower population coverage in 2015 (see introduction). **Table 1** displays annual trends since 2008 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 aminoglycosides (gentamicin, amikacin or tobramycin)]:

- Of 200 isolates, 28 (14.0%) were resistant to piperacillin-tazobactam
- Of 201 isolates, 17 (8.5%) were resistant to ceftazidime
- Of 201 isolates, 33 (16.4%) were resistant to imipenem or meropenem
- Of 200 isolates, 27 (13.5%) were resistant to ciprofloxacin
- Of 201 isolates, seven (3.5%) were resistant to gentamicin [14 (7.0%) of 201 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)]

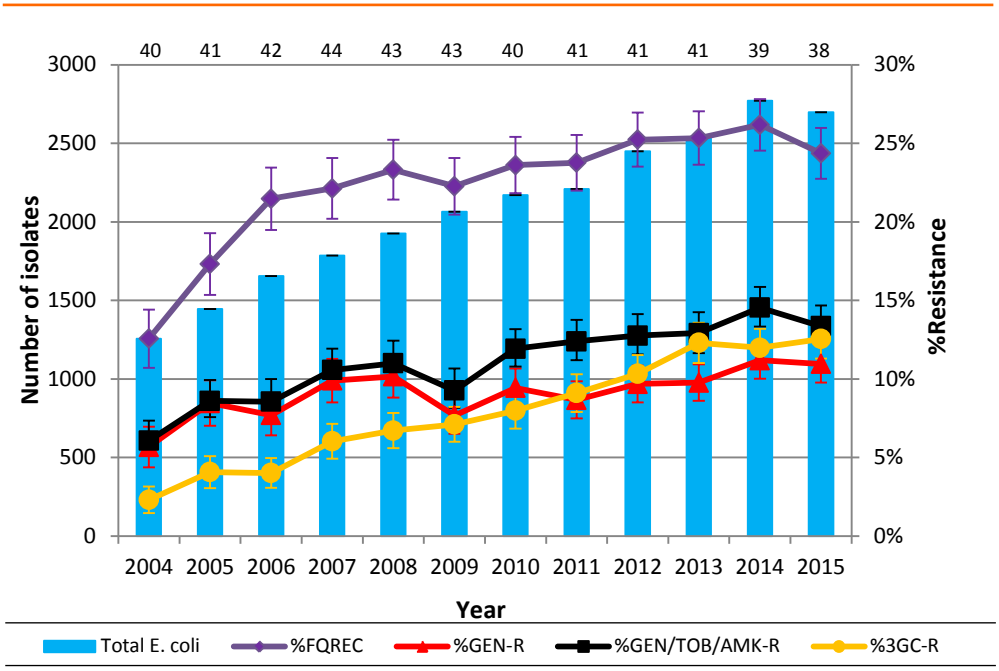


Figure 1. Trends for E. coli – total numbers of E. coli and percentage resistance to 3rd generation cephalosporins (3GCs), ciprofloxacin/ofloxacin (CIP/OFX), gentamicin (GEN) and gentamicin/amikacin/tobramycin (GEN/AMK/TOB) with 95% confidence intervals
Number of participating laboratories by year-end indicated above the bars

Table 2. Age and gender breakdown of patients by organism with major resistance profiles (data from laboratories participating in enhanced surveillance for 2015). The proportion of isolates detected <48 hours and >5 days post-admission is also shown

		Total for 2015	Percent female	Mean age in years	Detected <48 hours after admission	Detected >5 days after admission
Staphylococcus aureus	Meticillin Resistant (MRSA)	**97**	34%	69.5	47%	43%
	Meticillin Susceptible	**462**	40%	57.7	68%	22%
Streptococcus pneumoniae	Penicillin non-Susceptible	**25**	40%	61.3	96%	4%
	Penicillin Susceptible	**97**	51%	63.5	95%	5%
Enterococci	Vancomycin Resistant	**78**	35%	61.7	14%	77%
	Vancomycin Sensitive	**191**	41%	66.0	43%	48%
Escherichia coli	Fluoroquinolone Resistant	**285**	46%	73.5	74%	20%
	Fluoroquinolone Susceptible	**929**	59%	67.0	77%	17%
Klebsiella pneumoniae		**172**	39%	67.3	59%	32%
Pseudomonas aeruginosa		**96**	40%	69.5	59%	35%

In 2015, resistance to all but one of the indicator antimicrobials (imipemen/meropenem) decreased compared with 2014.

Fifteen (7.5%) of 200 isolates reported from 12 hospitals that were tested against all five "indicator" antimicrobials were identified as MDR *Pseudomonas aeruginosa*, defined as resistant to three or more of the indicator antimicrobials:

- Two resistant to all five antimicrobial classes
- Seven resistant to four of five antimicrobial classes
- Six resistant to three of five antimicrobial classes

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

The frequency of invasive *P. aeruginosa* infection increased with male gender x 1.5 fold (P=0.002) and age, with the majority of infections (n=144; 71.6%) occurring in those over 60 years (median = 68 years; 95%CI, 66-71).

Acinetobacter spp.
There were 87 reports of invasive infection caused by *Acinetobacter spp.* (blood = 85 and CSF = 2) from 86 patients, compared with 93 reports in 2014. The observed decrease was due to lower population coverage in 2015 (see introduction). **Table 1** displays annual trends since 2013 in the proportion of *Acinetobacter spp.* isolates resistant to the three "indicator" antimicrobials/antimicrobial classes [carbapenems (meropenem or imipenem), fluoroquinolones (ciprofloxacin or ofloxacin) and gentamicin]:

- Of 84 isolates, five were resistant to imipenem or meropenem
- Of 83 isolates, six were resistant to ciprofloxacin
- Of 81 isolates, three were resistant to gentamicin [four of 81 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)]

Two of 76 isolates reported from two hospitals were identified as MDR *Acinetobacter spp.*, i.e., resistant to all three "indicator" antimicrobials.

Enterococcus faecium
There were 421 reports of *E. faecium* BSI from 406 patients, an increase of 4% from 2014 (n=405). The observed increase occurred despite lower population coverage in 2015 (see introduction). **Table 1** displays the annual trends since 2008 in the proportion of *E. faecium* isolates resistant to the three "indicator" antimicrobials (ampicillin, vancomycin and high-level gentamicin):

- Of 419 isolates, 191 (45.6%) were resistant to vancomycin, which is similar to the proportion of vancomycin-resistant *E. faecium* (VREfm) in 2014 (45.9%) **(Figure 6)**
- Of 396 isolates, 196 (49.5%) were resistant to high-level gentamicin (**Figure 6**)
- Of 395 isolates tested against the three "indicator" antimicrobials, 84 (21.3%) were resistant to all three and termed MDR *E. faecium*. These were reported from 18 hospitals, with the majority from nine tertiary hospitals (n=67; 80%). This represents a slight decrease from the proportion of MDR *E. faecium* at 22.1% in 2014

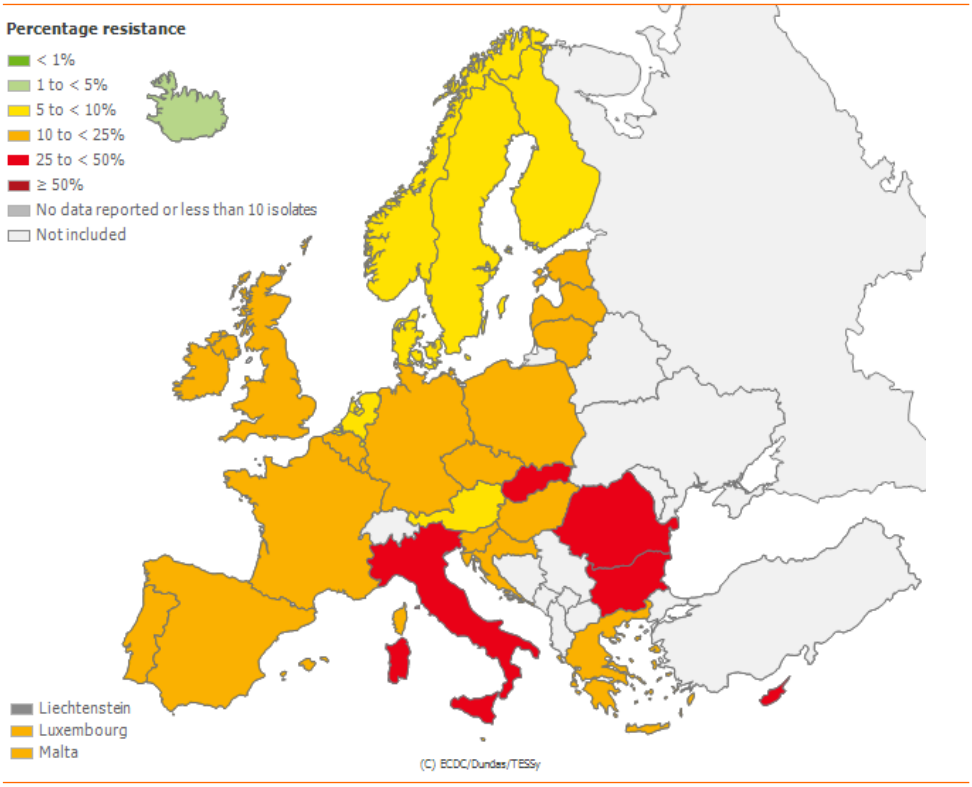


Figure 2. Distribution of 3rd-generation cephalosporin resistant E. coli in EARS-Net countries in 2015
Map downloaded from ECDC's TESSy database on 04/08/2016:
http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx

The proportion of VREfm first exceeded 40% in 2012 and has stayed between 43 and 45% since then. Since 2008, Ireland has had the highest proportion of VREfm in Europe. In 2015, countries with the next highest proportions of VREfm were: Cyprus (28.6%), Croatia (25.8%) and Romania (25.0%) (**Figure 7**). The median proportion of VREfm in EARS-Net countries was 9.9%, an increase from 4.5% in 2014.

The frequency of invasive *E. faecium* infection increased with male gender x 1.5 fold (P<0.001) and age, with the majority of infections (n=300; 71.3%) occurring in those over 60 years (median = 69 years; 95%CI, 67-72).

Enterococcus faecalis

There were 294 reports of *E. faecalis* BSI from 292 patients, a decrease from 315 reports in 2014. The observed decrease was due to lower population coverage in 2015 (see introduction). **Table 1** displays annual trends since 2008 in the proportions of *E. faecalis* isolates resistant to the three "indicator" antimicrobials (as described in section on *E. faecium*):

- Of 294 isolates, four (1.4%) were resistant to vancomycin (VREfa), with Ireland ranking 8th of European countries for resistance. The proportion of VREfa in Ireland has decreased from the highest reported proportion of 4.9% in 2011. In 2015, the median proportion in Europe was 0.3%
- Of 264 isolates, 74 (28.0%) were resistant to high-level gentamicin

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

The frequency of invasive *E. faecalis* infection increased with male gender x 1.4 fold (P=0.007) and age, with the majority of infections (n=198; 67.3%) occurring in those over 60 years (median = 70 years; 95%CI, 66-73).

Staphylococcus aureus

There were 1,082 reports of *S. aureus* BSI from 1,048 patients, compared with 1,117 reports in 2014. The observed decrease was due to lower population coverage in 2015 (see introduction). Of those, 199 (18.4%) were MRSA, which represents the lowest annual proportion since surveillance began in 1999 (**Table 1** shows data from 2008). 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 2014 was the eighth successive year in which a decrease was observed (significant downward trend, P<0.001) (**Figure 8**). Overall, there was an 8.3% reduction in MRSA BSI compared with 2014 (199 versus 217) and 1.9% reduction in MSSA BSI compared with 2014 (883 versus 900).

Despite the decrease in numbers and proportion of MRSA BSI in 2014, Ireland still had one of the higher proportions of MRSA in Europe (**Figure 9**). Ireland ranked 11th of 30 countries reporting to EARS-Net (compared to 12th of 30 countries in 2014), with the median proportion of MRSA BSI at 12.6%. All countries with MRSA proportions higher than Ireland are located in Southern and Central/Eastern Europe.

The overall rate of MRSA BSI in acute hospitals in 2015 was 0.050 cases per 1,000 BDU, a decrease from 0.055 in 2014, while the rate of MSSA BSI decreased from 0.227 to 0.223 [rates are calculated from denominator data (bed days used) obtained from the HSE's Business Information 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].

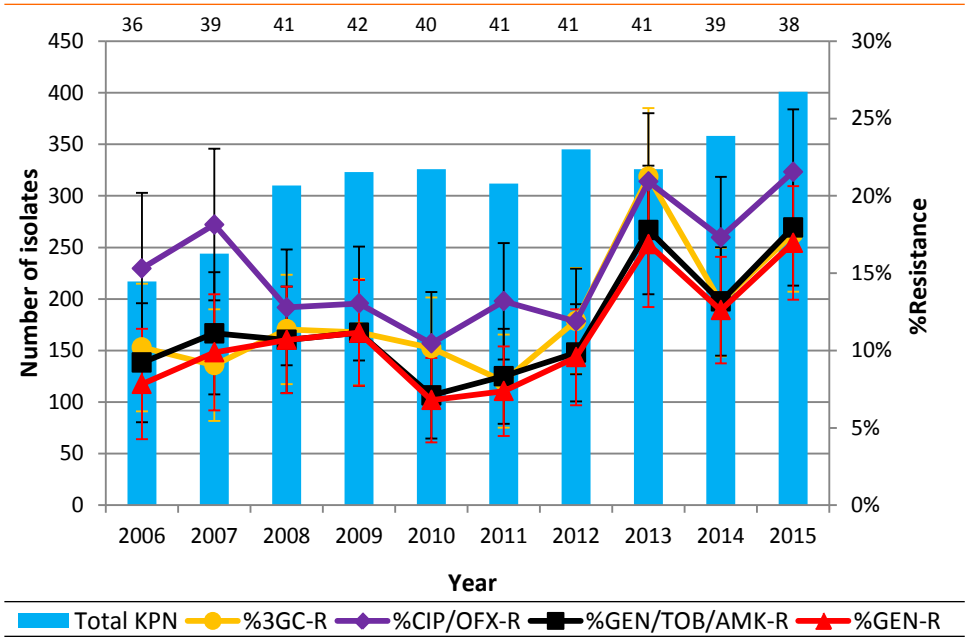


Figure 3. Trends for K. pneumoniae – total numbers of K. pneumoniae and percentage resistance to 3rd generation cephalosporins (3GCs), ciprofloxacin/ofloxacin (CIP/OFX), gentamicin (GEN) and gentamicin/amikacin/tobramycin (GEN/AMK/TOB) with 95% confidence intervals
Number of participating laboratories by year-end indicated above the bars

The frequency of invasive *S. aureus* infection increased with male gender x 1.7 fold (P<0.001) and age, with the majority of infections (n=657; 60.7%) occurring in those over 60 years. The median age for MRSA BSI = 73 years (95%CI, 70-76) was older than for MSSA BSI = 64 years (95%CI, 62-66). This was considered to be a significant difference, as the confidence intervals did not overlap.

Streptococcus pneumoniae

There were 304 reports of invasive *S. pneumoniae* infection (blood = 297 and CSF = 7) from 303 patients, compared with 331 reports in 2014. The lower population coverage attained in 2015 may have also contributed to this decrease (see introduction). **Table 1** displays annual trends since 2008 in the proportions of *S. pneumoniae* isolates non-susceptible/ resistant to penicillin and erythromycin.

Penicillin non-susceptible *S. pneumoniae* (PNSP) accounted for 17.5% (n=53) of all isolates tested against penicillin (n=302). Of the PNSP isolates, 52 were intermediately-resistant (Int; MIC=0.1-1 mg/L for laboratories following the Clinical Laboratory Standards Institute (CLSI) guidelines

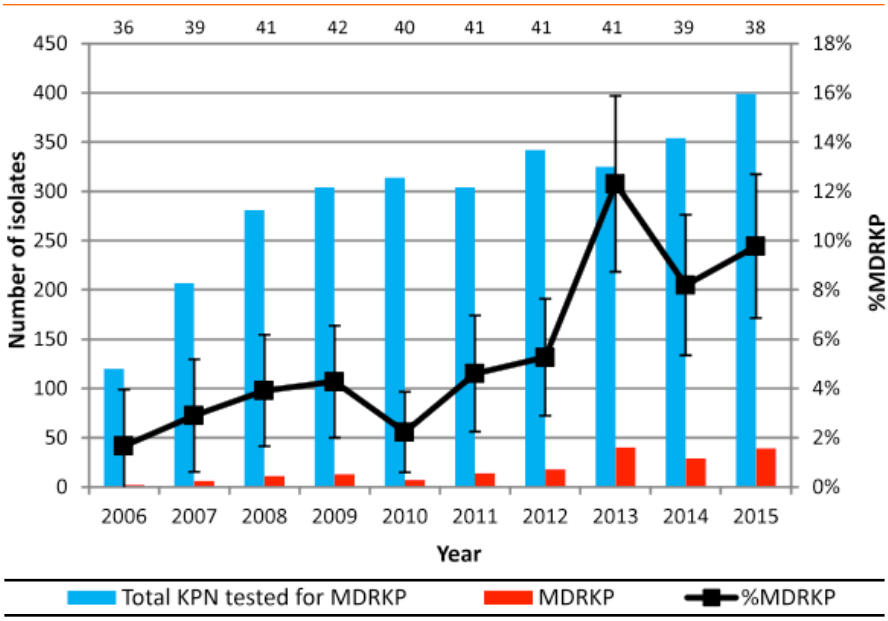


Figure 4. Trends for K. pneumoniae isolates with the MDRKP phenotype (simultaneously ESBL-producers and non-susceptible to both ciprofloxacin and gentamicin and/or a carbapenemase-producer) –– numbers and percentage with MDRKP phenotype with 95% confidence intervals
Number of participating laboratories by year-end indicated above the bars

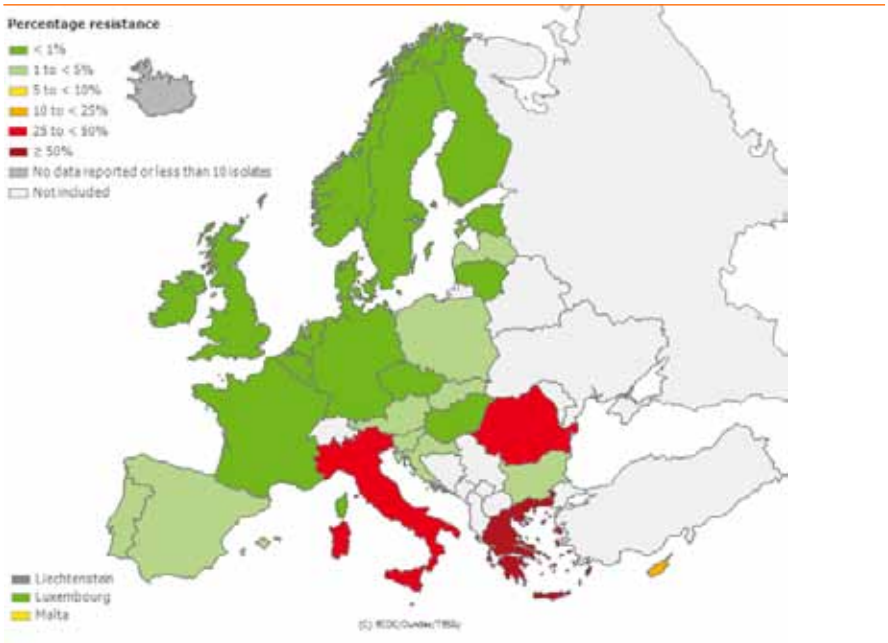


Figure 5. Distribution of carbapenem-resistant K. pneumoniae in EARS-Net countries in 2015
Map downloaded from ECDC's TESSy database on 04/08/2016:
http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx

(for non-meningitis syndrome via oral administration) and MIC=0.1-2mg/L for those following European Committee on Antimicrobial Susceptibility Testing (EUCAST) non-meningitis guidelines) and one was 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. Erythromycin resistance was seen in 45 of 297 isolates (15%).

There was a slight increase in the proportion of PNSP isolates from 17.1% in 2014 to 17.5% in 2015, as displayed in **Figure 10**. The proportion that displayed penicillin HLR decreased from 2.4% to 0.3%. In 2015, Ireland remained among European countries with higher proportions of PNSP, ranking 11th of 29 countries overall; and 5th of 22 countries reporting ≥50 isolates. In 2015, the median proportion of EARS-Net countries was 11.2%. However, it is important to consider that comparison with other EARS-Net countries can be 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):

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

Most Irish microbiology laboratories have already switched, or are currently in the process of switching, from CLSI to EUCAST guidelines: 33 laboratories had switched by the end of 2015 (unchanged from 2014). In Ireland, EARS-Net data are reported using the EUCAST breakpoints for infections other than meningitis or the CLSI breakpoints for "oral administration" (which correspond to the original CLSI breakpoints), 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 14th of 29 countries overall and 9th of 22 countries reporting 50 or more isolates. This is similar to the situation observed in much of Southern and Central/Eastern Europe. In 2015, the median proportion amongst EARS-Net countries was 14.4%.

Of 295 isolates tested against both penicillin and erythromycin in 2015, 32 (10.8%) were simultaneously PNSP (31 Int, one HLR) and erythromycin-resistant, which is a slight increase from 2014 (10.4%).

In 2007, a national pilot project was established as a collaborative initiative between RCSI, Beaumont Hospital, Children's University Hospital, Temple St and HPSC, to obtain 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. PCV13 replaced PCV7 from September 2010.

In 2015, serotype data were available for 276 pneumococcal isolates reported by 29 of the 30 laboratories reporting pneumococcal isolates to EARS-Net, representing 90.8% of all pneumococcal isolates reported:

- Of 158 isolates from patients aged ≥65 years, 106 (67.1%) belonged to serotypes included in the PPV23 vaccine
- Only 12 isolates were referred for typing from patients aged <2 years (the target population for the PCV13 vaccine) and three of these were serotypes included in the vaccine

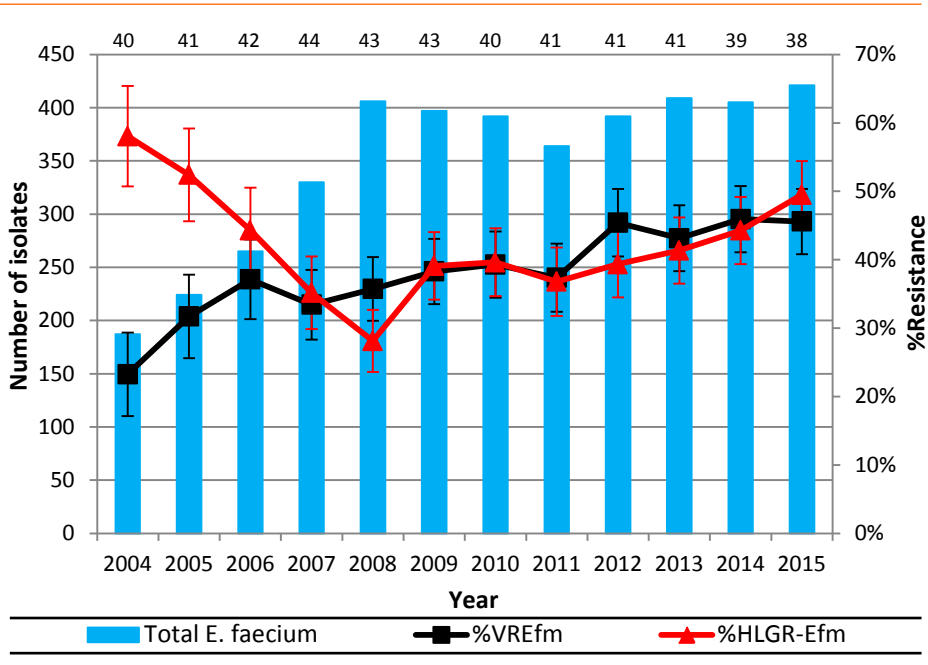


Figure 6. Trends for E. faecium – total numbers of E. faecium and percentage resistance to vancomycin (VREfm) and high-level gentamicin (HLG) with 95% confidence intervals
Number of participating laboratories by year-end indicated above the bars

- The most common serotypes identified were: 8 (n=28), 19A (n=27), 12F (n=24), 7F (n=22), 3 (n=21), 22F (n=18), 9N (n=13), 24F (n=12) and 35B (n=11) representing 68.8% of all isolates typed.

Of the 53 PNSP isolates, 47 (88.7%) were serotyped:

- Of 30 isolates from patients age ≥65 years, 13 (43.3%) belonged to serotypes included in the PPV23 vaccine
- Of three isolates from children <2 years, two belonged to serotypes included in the PCV13 vaccine
- The most common serotypes identified were: 19A (n=17), 35B (n=11) and 15B (n=6) representing 72.3% of all PNSP isolates typed.

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. Refer to the chapter on invasive pneumococcal disease (IPD) in Ireland in 2015 for additional information on pneumococcal serotyping.

In 2015, the rate of IPD in Ireland was estimated at 6.8 cases per 100,000 population, a decrease compared with 7.2 in 2014 [note that both rates were calculated using 2011 census data; the rate for 2015 is adjusted to account for the reduced population coverage (to 97%) by EARS-Net]. The highest rates of IPD were observed in the older age groups [adults aged 65-74 (22.0 per 100,000), 75-79 (33.3 per 100,000) and ≥80 (53.7 per 100,000)], with a smaller peak in young children [aged <1 year (6.9 per 100,000) and 1 year (9.6 per 100,000)] as displayed in **Figure 11**. The IPD rates in all age groups were broadly similar to 2014.

Males were approximately 1.2-times more likely to have an invasive *S. pneumoniae* infection than females, but this was not statistically significant (P=0.17). The frequency of invasive *S. pneumoniae* infection increased with age, the majority (n=196; 64%) occurring in those over 60 years (median = 68 years; 95%CI, 65-70).

EARS-Net Enhanced Surveillance

Since 2004, EARS-Net participants are invited to also provide enhanced demographic and clinical data on a voluntary basis regarding invasive pathogens causing BSI.

In 2015, enhanced surveillance data on 2,432 individual records (cases or isolates under the EARS-Net definition) were submitted from 22 participating laboratories, representing 45% of all reports to EARS-Net. **Table 2** displays demographic and other basic data for the major resistance profiles of pathogens reported to EARS-Net enhanced surveillance.

- ***S. aureus* BSI**
  - 71% of MRSA and 51% of MSSA BSI were reported as healthcare-associated
  - 25% of MRSA BSIs were reported as device-associated:
    - 11% CVC/PICC-associated and 4% PVC-associated
  - 16% of MSSA BSIs were reported as device-associated:
    - 6% CVC/PICC-associated and 5% PVC-associated
  - A recent antimicrobial exposure history was reported for 32% of patients with MRSA and 22% with MSSA BSI

- **Enterococcal BSI**
  - 95% of vancomycin-resistant enterococcal (VRE) and 66% of vancomycin-susceptible enterococcal (VSE) BSI were reported as healthcare-associated

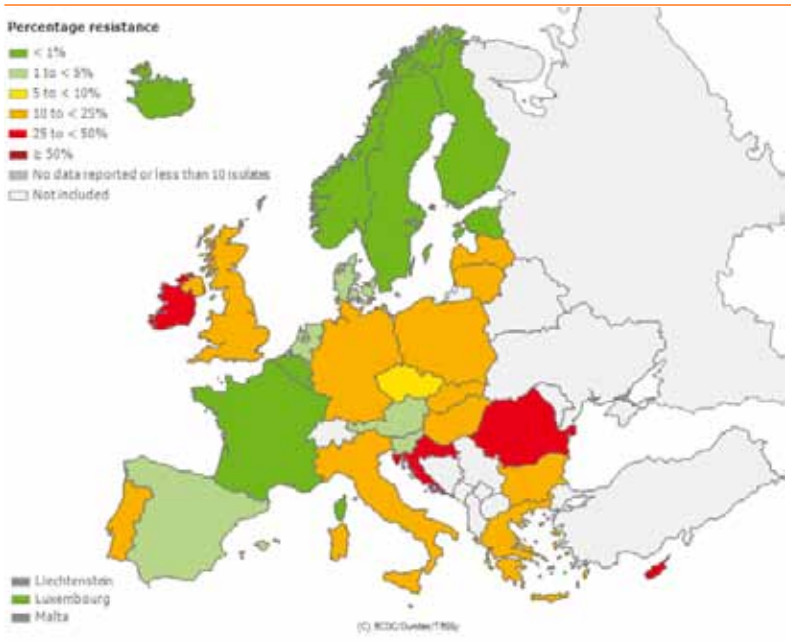


Figure 7. Distribution of vancomycin-resistant E. faecium (VREfm) in EARS-Net countries in 2015
Map downloaded from ECDC's TESSy database on 04/08/2016:
http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx

- 22% of VRE BSIs were reported as device-associated:
  - 15% CVC/PICC-associated
- 10% of VSE BSI were reported as device-associated:
  - 8% CVC/PICC-associated BSI
- A recent antimicrobial exposure history was reported for 21% of patients with VRE and 14% with VSE BSI

- ***S. pneumoniae* BSI**
  - The majority of both PNSP and PSSP BSIs were community-acquired
  - Respiratory tract infection remained the most common source of pneumococcal BSI

- ***E. coli* BSI**
  - 49% of fluoroquinolone-resistant *E. coli* (FQREC) BSI were reported as healthcare-associated versus 33% for fluoroquinolone-susceptible *E. coli (FQSEC)*
  - The most common source of *E. coli* BSI was urinary tract. Of FQREC and FQSEC BSI, 49% and 41% respectively occurred in setting of an indwelling urinary catheter
  - A recent antimicrobial exposure history was reported for 8% of patients with *E. coli* BSI

Conclusion

Antimicrobial resistance in key Gram-negative pathogens or *Enterobacteriaceae* causing invasive infection in Ireland, namely *E. coli* and *K. pneumoniae* increased further in 2015. As EARS-Net is limited to invasive isolates (blood and CSF), the true burden of infection caused by MDR-*Enterobacteriaceae* is likely to be far greater. These bacteria are among the most frequent causes of common infections, such as urinary tract infection and wound infection. They also form an important component of normal bowel flora (colonisation or carriage) in humans and animals. Therefore, carriers of MDR-*Enterobacteriaceae* tend to remain colonised indefinitely and may be an onward source of transmission to others. This poses a significant risk in healthcare settings, where infection caused by these pathogens is more difficult and more costly to treat and associated with increased patient morbidity and mortality.

Following the establishment of a national multi-drug resistant *K. pneumoniae* (MDRKP) outbreak control team (OCT) in 2013, reports were produced and correspondence issued to the acute hospitals between December 2013 and November 2014. Surveillance data indicated that MDRKP was now widely disseminated throughout acute and non-acute healthcare settings in Ireland, including primary and residential care. The OCT recommended that a national taskforce be set up, with recommended actions to be taken by the taskforce to address the threat of increasing antimicrobial resistance in Ireland. HSE established a national healthcare-associated infection (HCAI) & AMR taskforce, which convened in September 2015. The continued increase in antimicrobial resistance observed in *Enterobacteriaceae* requires close attention from both HSE and the Department of Health, given healthcare in Ireland is delivered by both the public and private sector. The increasing incidence of carbapenem resistant *Enterobacteriaceae* (CRE) in Ireland dates back to 2011 and a national strategy to curb dissemination of these highly antimicrobial resistant pathogens is urgently required. Data from other jurisdictions where invasive CRE infections have become commonplace report mortality rates in excess of 50%. It is vital that the recommendations contained in the "Guidelines for the prevention and control of multi-drug resistant organisms, other than MRSA", published in 2013 are adequately resourced and implemented and that infection prevention and control and antimicrobial stewardship

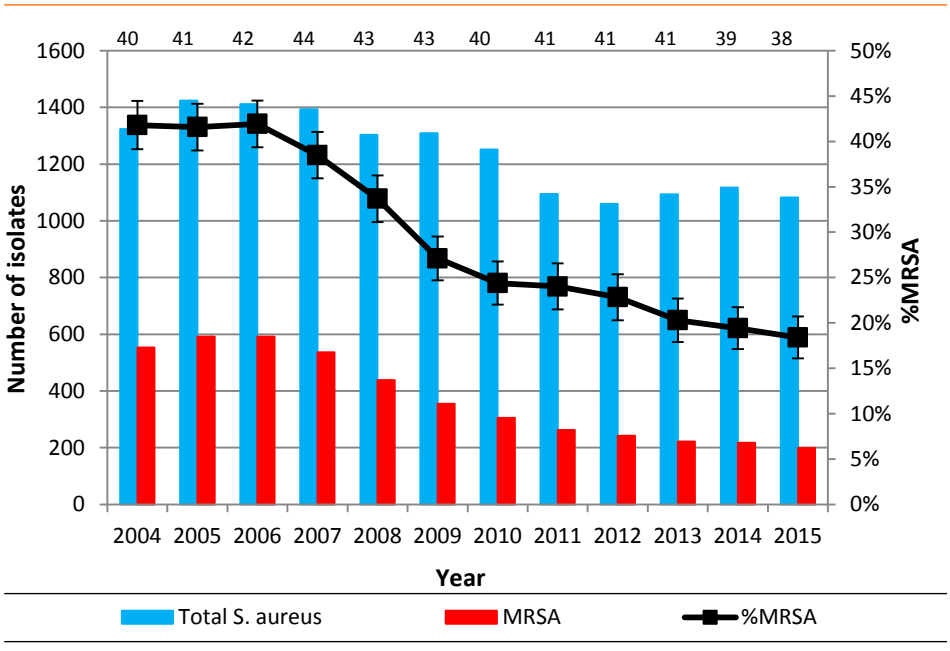


Figure 8. Trends for S. aureus – total numbers of S. aureus/MRSA and percentage MRSA with 95% confidence intervals

Number of participating laboratories by year-end indicated above the bars

resources are strengthened in acute hospitals and in the community, including primary and residential care (http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/).

For the ninth consecutive year, Ireland remained the European country with the highest proportion of VREfm BSI (45.6%), with Croatia, Cyprus and Romania also reporting proportions over 25% and therefore appearing red on the map.

For the ninth consecutive year, the proportion of *S. aureus* BSI attributable to MRSA further declined to 18.4%, the lowest reported level since Ireland joined EARS-Net in 1999.

EARS-Net enhanced surveillance data are particularly useful in informing infection prevention and control programmes, both nationally and in those hospitals that participate in the surveillance scheme.

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 2016**.

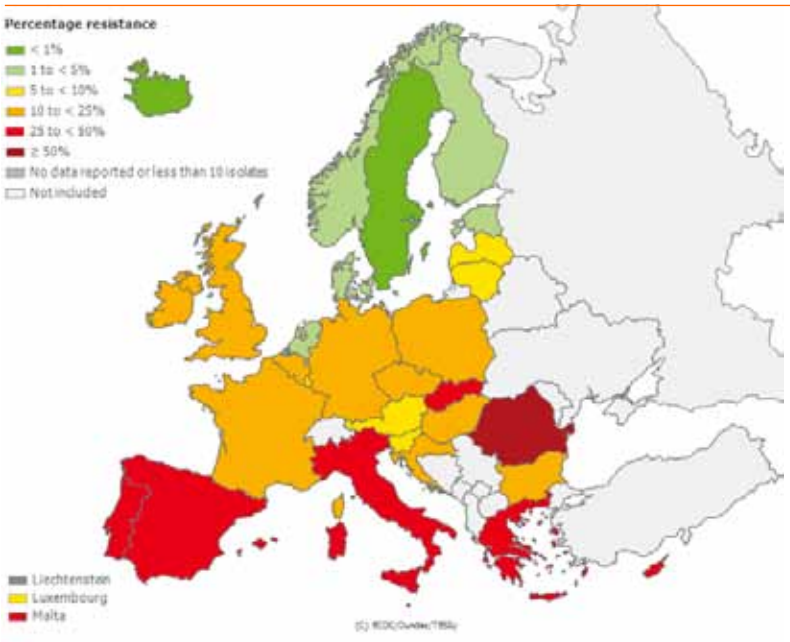


Figure 9. Distribution of MRSA in EARS-Net countries in 2015
Map obtained from ECDC on 04/08/2016:
http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx

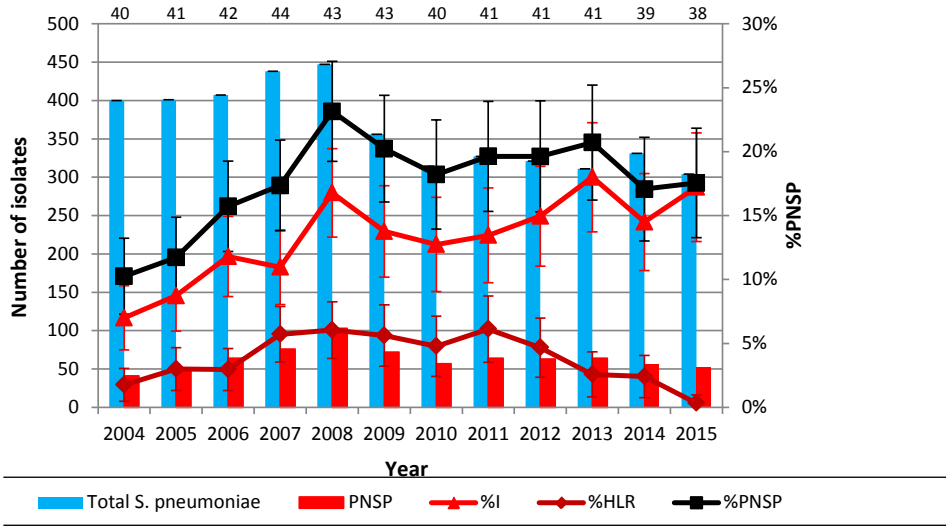


Figure 10. Trends for S. pneumoniae – total numbers of S. pneumoniae/PNSP and percentage PNSP with 95% confidence intervals
HLR, High-level resistant; I, Intermediately resistant
Number of participating laboratories by year-end indicated above the bars

Enhanced surveillance of Carbapenem Resistant *Enterobacteriaceae* (CRE)

Summary:

- In 2015, enhanced surveillance data was received on 98 cases of CRE, an increase from 2014 (n=61) and 2013 (n=26). In contrast, the national Carbapenemase Producing *Enterobacteriaceae* Reference Laboratory Service (CPEaRLS) at Galway University Hospital confirmed 140 CRE isolates as carbapenemase producers in 2015.
- Just four patients (4%) had a history of hospitalisation abroad: Bosnia and India: NDM; Romania: OXA-48 and Spain: KPC
- Clinical significance was reported for 91 patients, with the majority colonised with CRE at the time of reporting (n=66; 67%). However, CRE infection was reported for 25 patients

Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) are multi-drug resistant (MDR) Gram-negative bacteria. The term CRE includes *Enterobacteriaceae* that produce enzymes known as carbapenemases and *Enterobacteriaceae* resistant to carbapenems (e.g., meropenem) as a result of a combination of resistance mechanisms (e.g., ESBL or AmpC β-lactamase production with bacterial cell porin loss). Carbapenemases are encoded by genes transmitted between *Enterobacteriaceae* via mobile genetic elements, known as plasmids, resulting in colonisation or infection for which antimicrobial treatment options are very limited. 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.

Enhanced surveillance data

CRE cases reported to enhanced surveillance

In 2015, enhanced surveillance data was received from 13 microbiology laboratories on 98 patients with confirmed CRE. Of those, 59 were male (60%) with a median age of 71 years (range: 1 month – 93 years). No CRE outbreaks were reported in 2015. **Figure 1** displays annual trends in CRE cases and types reported to enhanced surveillance since 2011.

Patient location

At the time of CRE detection, 93 patients (95%) were hospitalised, four (3%) were in long-term care facilities and one was in the community. Of 93 inpatients, 47 (51%) had been admitted from home, 15 (16%) were transfers from another acute hospital, five had been admitted from long-term care/nursing homes (5%). Admission source was not provided for 26 patients (28%). Of 15 patients who had been transferred from another acute hospital, two were repatriated from hospitals abroad (in Bosnia and Spain). The median interval from hospitalisation to first positive CRE isolate for 86 of 93 inpatients was six days (range: 0 – 91).

Presence of other multi-drug resistant organisms (MDROs)

Known colonisation or infection with MDROs other than CRE was reported for 34 patients (35%), 33 of whom were inpatients: MRSA (n=19), VRE (n=17), ESBL-producing

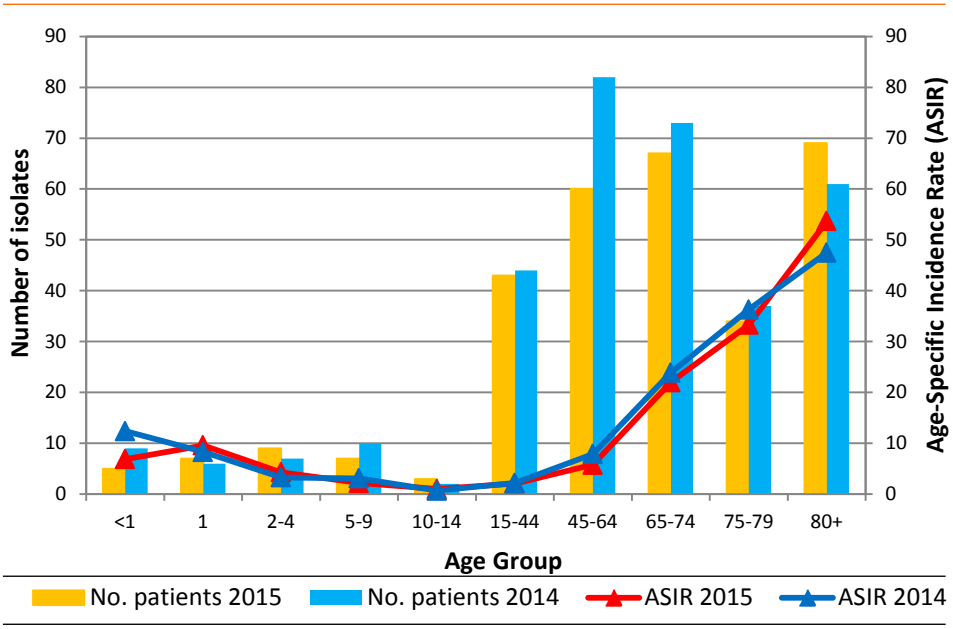


Figure 11. Numbers and age-specific incidence rates of patients with invasive S. pneumoniae infection in 2015 compared with 2014
ASIR, age-specific incidence rate

Enterobacteriaceae (n=12) and MDR *E. coli* (n=2). Twelve patients were colonised with ≥2 other MDROs.

Travel history
The travel history in the 12 months prior to CRE detection was unknown for the majority of patients (n=55; 56%). For 30 patients, there was no history of foreign travel (31%) and 13 (13%) reported foreign travel: Africa (country unspecified), Bosnia, Egypt, India, Lebanon, Pakistan, Romania, Spain and UK].

Risk factors
Risk factor data was provided on 86 patients, of whom 52 (60%) had more than one risk factor for CRE: hospitalisation in past 12 months (71; 83%); surgery in past six months (23; 27%); admission to intensive care in past 12 months (18; 21%). Reported co-morbidities included: immunocompromise (n=14); urological abnormality (n=14); diabetes mellitus (n=11); renal disease (n=11); chronic lung (n=7) and liver disease (n=1). Seven patients had no identifiable risk factors (8%) and risk factor data was unknown or not provided for the remaining 12 patients.

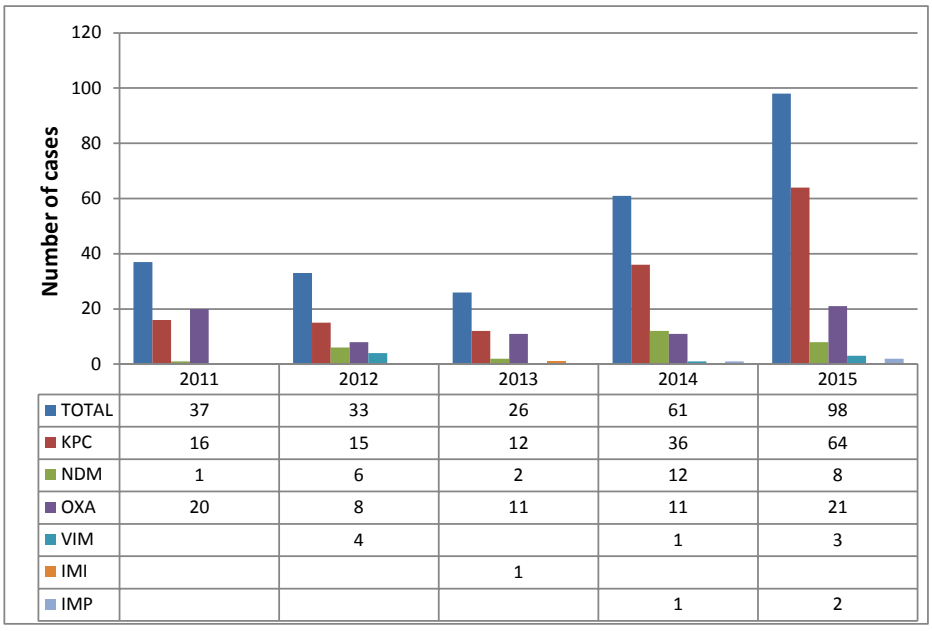
Prior antimicrobial exposure
Antimicrobial exposure history prior to isolation of CRE was provided for 59 patients (60%), 57 of whom were hospitalised and 13 of whom received more than one antimicrobial class:

- β-lactam/β-lactamase inhibitor combination agents - 46 (78%)
- Carbapenems - 10 (17%)
- Fluoroquinolones - 8 (14%)
- Aminoglycosides - 6 (10%)
- Cephalosporins - 6 (10%)
- Co-trimoxazole - 1 (2%)

Clinical significance and source of infection
The clinical significance of the CRE isolate was reported for 91 patients, representing colonisation in the majority (n=66; 73%). Infection was reported for 25 patients (27%), with urinary tract infection accounting for the majority (n=7), followed by respiratory tract (n=4) and intra-abdominal infection (n=4). It is important to note that patients who were colonised with CRE may have subsequently developed CRE infection after the case was reported to enhanced surveillance.

Specimen type
The majority of CRE isolates came from active surveillance or screening specimens; rectal or stoma swabs and faeces (n=76; 78%). Of CRE isolates from clinical specimens; eight came from blood (8%), eight from urine (8%), two from sputum and one each from a central vascular catheter tip, lung and wound swabs.

Outcome
Of 93 inpatients with CRE, outcome was reported for 68 (73%). Of those, 49 (59%) were discharged, 11 remained inpatients and eight subsequently died (12%). The contribution of CRE to patient death is not collected by enhanced surveillance. Five deaths occurred in patients with CRE infection. CRE was isolated in a post mortem microbiology specimen taken from one patient. Date of first CRE specimen and date of death was provided for five patients, with a median interval to death of 36 days (range = 6 - 68). Outcome was also reported for four of the five non-hospitalised patients, all of whom survived.



	2011	2012	2013	2014	2015
TOTAL	37	33	26	61	98
KPC	16	15	12	36	64
NDM	1	6	2	12	8
OXA	20	8	11	11	21
VIM		4		1	3
IMI			1		
IMP				1	2

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

Please note that the reduction in reported cases between 2012 and 2013 reflects under-reporting rather than a true decline in CRE. Almost twice as many isolates were confirmed by the CPEaRLS, Galway University Hospital in 2013 (n=48) and approximately one-third as many isolates in 2014 (n=82) and 2015 (n=139) than were reported to the voluntary CRE enhanced surveillance scheme

Carbapenemase types

The rank order of carbapenemase types reported to enhanced surveillance in 2015 correlates with CPE confirmed by the reference laboratory, although 30% of CPE confirmed by the reference laboratory did not have enhanced surveillance data submitted: KPC (n=64; 65%), OXA-48 (n=21; 21%), NDM (n=8; 8%), VIM (n=3) and IMP (n=2).

Antimicrobial susceptibility

Antimicrobial susceptibility data was provided on 94 of 98 isolates (96%):

- Carbapenems
  - Meropenem: reported on 94 isolates, with 72 resistant (77%); minimum inhibitory concentrations ranged from 0.25 to >32 mg/L
  - Ertapenem: reported on 91 isolates, with 89 resistant (98%); minimum inhibitory concentrations ranged from 0.25 to >32 mg/L
- Aminoglycosides: reported on 92 isolates, with 41 (45%) resistant to one or more of the aminoglycosides listed below
  - Gentamicin: reported on 91 isolates, with 33 resistant (36%)
  - Tobramycin: reported on 61 isolates, with 25 resistant (41%)
  - Amikacin: reported on 88 isolates, with 11 resistant (13%)
- Fluoroquinolones: reported on 88 isolates, with 35 resistant (40%)
- Tigecycline: reported on 82 isolates, with 15 resistant (18%)
- Colistin: reported on 83 isolates, with two resistant (2%)

Conclusion

In 2015, 98 cases of CRE colonisation/ infection were reported to the enhanced CRE surveillance system representing an increase of 61% from 61 cases in 2014. However, data from the CPEaRLS indicate that there were more confirmed CRE than were reported to enhanced surveillance.

Acknowledgements:

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 2015 (Source: CPEaRLS annual report 2015).