9.3.0 Antimicrobial Resistance

Key Points

- In 2012, 2,450 reports of invasive *E. coli* infection were submitted from Ireland to the European Antimicrobial Resistance Surveillance Network (EARS-Net), an increase of 11% from 2,210 reports in 2011. The proportion of *E. coli* isolates displaying resistance to third-generation cephalosporins (10.8%), to ciprofloxacin (25.2%), to aminoglycosides (12.6%) along with those reported to produce extended-spectrum beta-lactamases (8.8%) and to exhibit multi-drug resistance (13.4%) were at their highest levels since surveillance began

- In 2012, there were 1,060 reports of *Staphylococcus aureus* bloodstream infection (BSI), a decrease of 3% from 1,095 reports in 2011. Of these, 242 (22.8%) were meticillin-resistant *S. aureus* (MRSA), a decrease of 8% from 263 reports in 2011. For acute hospitals, the rate of MRSA BSI was 0.060 cases per 1,000 bed days used, a decrease from 0.066 in 2011. Over the same period, the rate of meticillin-susceptible *S. aureus* (MSSA) BSI remained stable at 0.208.

- Enhanced surveillance data revealed that 15% of *S. aureus* BSI were associated with central vascular catheters (CVCs) and 11% with peripheral vascular catheters

- In 2012, there were 392 reports of *Enterococcus faecium* BSI, compared with 364 in 2011. This represents an increase of 8%. Vancomycin-resistant *E. faecium* (VREfm) accounted for 45.4% of reports, which was at its highest level since surveillance began and was the highest proportion among countries reporting to EARS-Net in 2012

- In 2012, there were 345 reports of invasive *Klebsiella pneumoniae* infection compared to 312 in 2011, an increase of 11%. The proportions of *K. pneumoniae* isolates displaying resistance to third-generation cephalosporins (11.9%) and those reported to produce extended-spectrum beta-lactamases (8.8%) were at their highest levels since surveillance began. There were no reports of carbapenem resistant invasive *K. pneumoniae* isolates in 2012

- In 2012, there were 321 reports of invasive *S. pneumoniae* infection compared to 327 in 2011, a decrease of 2%. Of these, 63 (19.6%) were penicillin-non-susceptible *S. pneumoniae* (PNSP), which is similar to the situation in 2011 (n=64; 19.6%). The national rate of invasive pneumococcal infection was 7.0 per 100,000 population, which is comparable to 7.1 in 2011. The numbers of reports and rates of infection in children aged under two years, the target group for the 13-valent pneumococcal conjugate vaccine (PCV13), were broadly similar to those seen in 2011

- Serotype data were available on 306 of 321 invasive pneumococcal isolates (95%) and results indicate good coverage (80%) for the 23-valent polysaccharide (PPV23) vaccines in its target population (adults ≥65 years). Coverage for PCV13 in its target population was broadly similar to 2011

- In 2012, there were 219 reports of invasive *Pseudomonas aeruginosa* infection, compared to 184 in 2011, an increase of 19%. Resistance to piperacillin-tazobactam (17.4%), ceftazidime (15.2%) and meropenem (19.6%) all reached their highest levels since surveillance began

- Enhanced surveillance data were provided on 1,765 cases from nine laboratories, representing 35% of all cases submitted to EARS-Net in 2012

9.3.0.1 European Antimicrobial Resistance Surveillance Network (EARS-Net)

Introduction

In Ireland, 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 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 healthcare-associated infections from those associated with the community. EARS-Net primarily serves as a surveillance system to measure national levels of antimicrobial resistance (AMR). In 2012, all 41 microbiology laboratories participated in EARS-Net, resulting in complete coverage of the Irish population.

Escherichia coli

In 2012, there were 2,450 reports of invasive *E. coli* infection (2,447 from blood and three from CSF) from 2,388 patients, an increase of 10.9% from 2,210 reports in 2011. **Table 1** displays 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)] by year since 2004.

Of the 2,441 isolates for which 3GC susceptibility testing data was reported, 264 (10.8%) were resistant to 3GCs, of which 195 were reported as extended spectrum beta lactamase (ESBL)-positive and 64 as ESBL-negative. Just over one quarter (25.2%); 616 of 2,441 were ciprofloxacin resistant; and 236 (9.7%) of 2,437 were gentamicin-resistant [307 (12.6%) of 2,437 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)].

In 2012, 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 (Chi^2 trend=143, P<0.0001).

The proportion of invasive *E. coli* isolates with 3GC resistance in Ireland is moderately-high levels (10 to <25%) on the EARS-Net European map (**Figure 2**). Also, 2012 data resulted in a colour change for Ireland on the EARS-Net European map from yellow in 2011 (5 to <10% 3GC resistance) to orange (10 to <25% 3GC resistance). With regard to 3GC, ciprofloxacin and aminoglycoside resistance Ireland ranks 18th, 12th and 13th, respectively, out of 30 countries reporting to EARS-Net in 2012.

ESBLs are enzymes that confer resistance to most penicillins and cephalosporins (including 3GCs). ESBL-producing bacteria (including *E. coli* and *K. pneumoniae*) are often resistant to other classes of antimicrobials and have emerged as important causes of infections both in hospitals and the community. ESBLs were detected in 215 (8.8%) of 2,444 isolates tested. In 2012, 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 (Chi^2 trend=161, P<0.0001).

Of 2,428 isolates tested against all four "indicator" antimicrobials, 326 (13.4%), from 46 hospitals/ institutions, were identified as multi-drug resistant (MDR), which is defined as resistance to three or more of these indicator antimicrobials, a slight increase from 13.0% in 2011. In 2012, MDR *E. coli* was at its highest level since surveillance began. Between 2009 and 2012, the trend in MDR was upwards, which was highly significant (Chi^2 trend=10.97, P=0.0009).

- 114 with resistance to ampicillin, 3GCs, ciprofloxacin and aminoglycosides (105 ESBL-positive, 9-negative)
- 85 with resistance to ampicillin, 3GCs and ciprofloxacin (70 ESBL-positive, 14 -negative)
- 124 with resistance to ampicillin, ciprofloxacin and aminoglycosides (7 ESBL-positive, 117 -negative)
- Three with resistance to ampicillin, 3GCs and aminoglycosides (two ESBL-positive, one -negative)

Females were slightly more likely (1.05-times) to have an invasive *E. coli* infection than males (z=1.31, P=0.19). The frequency of invasive *E. coli* infection increased with age, with the majority of infections (n=1,840; 75%) occurring in adults over 60 years. The median age was 72 years (95%CI, 71-73).

Staphylococcus aureus

In 2012, there were 1,060 reports of *S. aureus* bloodstream infection (BSI) from 1,038 patients, a decrease of 3.2% from 1,095 reports in 2011. Of these, 242 (22.8%) were meticillin resistant *S. aureus* (MRSA) (**Table 1**). This represents the lowest annual proportion since surveillance began in 1999. In 2010, the proportion was 24.4%, which was the first time MRSA accounted for <25% of *S. aureus* BSI in Ireland, and thus marked a change from red to orange on the EARS-Net European map. This is the sixth successive year in which a decrease has been observed and the overall downward trend over this time period is highly significant (Chi^2_{trend}=196.6, P<0.0001) (**Figure 3**). Overall, there was an 8% reduction in the number of MRSA BSI reports compared with 2011 (242 vs. 263). The total number of meticillin-susceptible *S. aureus*

Table 1. Summary of EARS-Net data by pathogen and year, 2004-2012

Pathogen	2004	2005	2006	2007	2008	2009	2010	2011	2012
Number laboratories by year-end	40	41	42	44	42	43	40†	41††	41
E. coli									
Number of isolates	1256	1445	1656	1785	1926	2064	2170	2210	2450
Ampicillin-R*	65.0%	67.6%	70.7%	68.3%	70.4%	68.7%	68.4%	71.9%	69.6%
3GC-R*	2.6%	4.1%	4.2%	6.7%	7.4%	7.5%	8.3%	9.3%	10.8%
ESBL-producers*	1.1%	2.4%	2.5%	4.1%	5.0%	5.8%	6.1%	7.5%	8.8%
Ciprofloxacin-R*	12.6%	17.3%	21.5%	22.1%	23.3%	22.3%	23.6%	23.8%	25.2%
Gentamicin-R*	5.7%	8.5%	7.7%	9.9%	10.2%	7.7%	9.4%	8.7%	9.7%
Gentamicin/Amikacin/Tobramycin-R*	6.1%	8.6%	8.6%	10.6%	11.0%	9.3%	11.8%	12.2%	12.6%
Carbapenem‡-R*	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
MDR*	5.6%	7.7%	9.0%	11.4%	12.1%	10.4%	11.7%	13.0%	13.4%
Number laboratories by year-end	41	42	42	44	43	43	40†	41††	41
S. aureus									
Number of isolates	1323	1424	1412	1393	1303	1309	1251	1095	1060
Number Meticillin-R (or MRSA)	553	592	592	536	439	355	305	263	242
Meticillin-R (or MRSA)	41.8%	41.6%	41.9%	38.5%	33.7%	27.1%	24.4%	24.0%	22.8%
Number VISA	0	0	2	1	0	0	0	0	0
VISA*	0.0%	0.0%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
Number laboratories by year-end	40	41	42	44	42	43	40†	41††	41
E. faecium									
Number of isolates	187	224	265	330	406	397	392	364	392
Ampicillin-R*	95.7%	92.3%	93.9%	93.1%	95.1%	92.9%	95.6%	95.9%	92.9%
Vancomycin-R	23.2%	31.7%	37.1%	33.4%	35.7%	38.3%	39.3%	37.4%	45.4%
HLG-R*	58.0%	51.4%	44.3%	35.2%	28.1%	39.1%	39.6%	36.8%	39.3%
MDR*	18.5%	25.6%	25.6%	22.7%	16.2%	26.7%	24.9%	21.1%	20.3%
Number laboratories by year-end			36	39	41	42	40†	41††	41
K. pneumoniae									
Number of isolates			217	244	310	323	326	312	345
Ampicillin-R*			97.7%	99.2%	99.7%	99.7%	99.1%	100.0%	98.5%
3GC-R*			10.2%	9.9%	11.4%	11.2%	10.5%	8.0%	11.9%
ESBL-producers*			8.6%	3.7%	7.7%	8.2%	5.0%	5.6%	8.8%
Ciprofloxacin-R*	No data	No data	15.3%	18.1%	12.8%	13.0%	10.5%	13.2%	11.9%
Gentamicin-R*			7.8%	9.9%	10.7%	11.1%	6.8%	7.4%	9.9%
Gentamicin/Amikacin/Tobramycin-R*			9.2%	11.1%	10.7%	11.1%	7.1%	8.3%	9.6%
Carbapenem‡-R*			0.0%	0.6%	0.0%	0.0%	0.0%	1.6%	0.3%
MDR*			11.2%	11.9%	10.6%	11.9%	8.0%	8.4%	9.9%
Number laboratories by year-end	41	42	42	44	42	43	40†	41††	41
S. pneumoniae									
Number of isolates	400	401	407	438	447	356	314	327	321
Penicillin-NS*	10.3%	11.7%	15.7%	17.4%	23.1%	20.2%	18.2%	19.6%	19.6%
of which: HLR	1.8%	3.0%	2.9%	5.7%	6.0%	5.6%	4.8%	6.1%	4.0%
Int	7.0%	8.7%	12.5%	11.0%	16.8%	13.8%	12.7%	13.5%	15.6%
Erythromycin-R*	14.4%	12.1%	16.1%	16.4%	16.7%	17.3%	15.7%	18.9%	16.9%
%Penicillin-NS/Erythromycin-R	3.1%	3.2%	7.4%	7.9%	10.2%	11.9%	12.6%	13.8%	12.2%
Number laboratories by year-end	40	41	42	44	42	43	40†	41††	41
E. faecalis									
Number of isolates	242	290	294	280	301	289	298	265	298
Ampicillin-R*	0.8%	3.5%	4.5%	2.2%	0.7%	2.1%	2.0%	0.8%	4.0%
Vancomycin-R	1.3%	2.5%	3.7%	2.9%	3.7%	0.7%	0.3%	4.9%	3.0%
HLG-R*	41.3%	44.4%	42.4%	36.9%	30.5%	36.7%	29.7%	29.1%	32.9%
Number laboratories by year-end			36	39	41	42	40†	41††	41
P. aeruginosa									
Number of isolates			128	177	199	248	222	184	219
Piperacillin/tazobactam-R*			9.4%	12.6%	9.7%	8.9%	10.0%	2.8%	17.4%
Ceftazidime-R*			10.6%	11.8%	8.7%	11.8%	9.2%	8.2%	15.2%
Imipenem/meropenem-R*	No data	No data	11.8%	12.2%	9.3%	10.2%	8.3%	12.0%	19.6%
Ciprofloxacin-R*			18.0%	22.9%	21.8%	12.1%	13.2%	12.6%	20.6%
Gentamicin-R*			10.2%	13.3%	9.0%	7.7%	8.7%	6.5%	11.9%
MDR*			9.5%	12.4%	11.1%	6.4%	6.5%	4.0%	13.0%

MRSA, Meticillin-Resistant S. aureus; VISA, Vancomycin-Intermediate S. aureus
R, Resistant; NS, Non-Susceptible [includes isolates with intermediate (Int) and high-level resistance (HLR)]
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
† In 2010, 3 laboratories stopped processing blood cultures, however coverage of acute hospitals remained at 100%
†† In Q3 2011, one additional laboratory started reporting data
‡ Carbapenems include imipenem, meropenem and ertapenem

(MSSA) BSI reports decreased by 1.7% in 2012 compared to 2011 (818 vs. 832).

Despite the decrease in numbers and proportion of MRSA, Ireland still had one of the higher proportions of MRSA in Europe in 2012 (see http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx for European data, including EARS-Net tables, charts and maps) (**Figure 4**). Ireland ranked 12th out of 30 countries reporting to EARS-Net. All of the countries with higher MRSA proportions than Ireland are in Southern and Central/Eastern Europe.

No MRSA isolates with reduced susceptibility to vancomycin were detected by the National MRSA Reference Laboratory in 2012.

The rate of MRSA BSI for all acute hospitals in 2012 was 0.060 cases per 1,000 bed days used, representing a decrease from 0.066 in 2011, whilst the rate of MSSA BSI remained stable at 0.208 [Rates are calculated taking into account denominator data (bed days used) obtained from the Business Intelligence Unit at the Health Services Executive for all acute public hospitals and directly from the private hospitals where available, where both numerator (*S. aureus* BSI numbers) and denominator data have been provided].

Males were approximately 2.1-times more likely to get an invasive *S. aureus* infection (2.3-times for MRSA, z=6.72, P=0.0001; 2.1-times for MSSA, z=10.84, P<0.0001) than females (z=12.73, P<0.0001). The frequency of invasive *S. aureus* infection increased with age, with the majority of infections (n=623; 59%) occurring in adults over 60 years. The median age for patients with an MRSA infection was 73 years (95%CI, 69-76) while the median age for patients with MSSA was 61 years (95%CI, 59-63). This was considered to be a significant difference as the confidence intervals did not overlap.

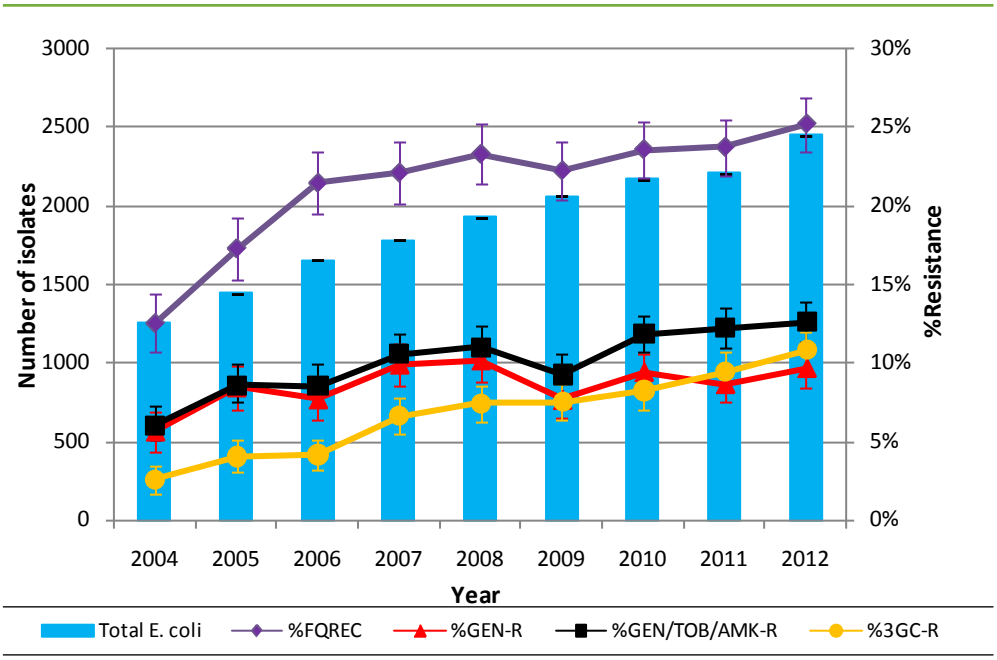

Figure 1. Trends for E. coli. Total numbers & percentage resistance to 3GCs, ciprofloxacin/ofloxacin (CIP/OFX), gentamicin (GEN), any aminoglycoside: gentamicin/amikacin/tobramycin (GEN/AMK/TOB), and percentage ESBL-positive with 95% confidence intervals.

Table 2. Age and gender breakdown of patients by organism with major resistance profiles (data from laboratories participating in enhanced surveillance for 2012). Proportion of isolates detected <48 hours and >5 days post-admission is also shown.

		Total for 2012	Percent female	Mean age in years	Detected <48 hours after admission	Detected >5 days after admission
Staphylococcus aureus	*Meticillin Resistant (MRSA)*	**75**	**32%**	**68.3**	**56%**	**36%**
	Meticillin Susceptible	*250*	*34%*	*58.7*	*66%*	*20%*
Streptococcus pneumoniae	*Penicillin non-Susceptible*	*31*	*35%*	*57.6*	*65%*	*26%*
	Penicillin Susceptible	*108*	*40%*	*63.2*	*79%*	*8%*
Enterococci	*Vancomycin Resistant*	*67*	*40%*	*67.4*	*19%*	*70%*
	Vancomycin Sensitive	*179*	*40%*	*66.1*	*34%*	*50%*
Escherichia coli	*Fluoroquinolone Resistant*	*225*	*43%*	*72*	*60%*	*28%*
	Fluoroquinolone Susceptible	*637*	*58%*	*68.3*	*68%*	*16%*
Klebsiella pneumoniae		*122*	*47%*	*63.9*	*45%*	*41%*
Pseudomonas aeruginosa		*71*	*45%*	*67.9*	*55%*	*32%*

Enterococcus faecium

In 2012, there were 392 reports of *E. faecium* BSI from 386 patients, an increase of 8% from 364 reports in 2011. **Table 1** displays the annual proportions of *E. faecium* isolates resistant to the three "indicator" antimicrobials (ampicillin, vancomycin and high-level gentamicin) by year since 2004.

Of the 392 invasive *E. faecium* isolates, 178 (45.4%) were resistant to vancomycin. The proportion of isolates that were vancomycin-resistant *E. faecium* (VREfm) increased from 37.4% in 2011, which was a significant finding (Chi^2=5.03; P=0.025). Of 389 isolates with reported susceptibility test results for high-level gentamicin, 153 (39.3%) were resistant (**Figure 5**).

Since 2008, Ireland has had by far the highest proportion of VREfm in Europe. This remained the case in 2012, with the next highest proportions reported by Portugal (23%), Greece (18%) and Germany (16%) (**Figure 6**).

Of 389 isolates tested against the three "indicator" antimicrobials, 79 (20.3%) isolates from 20 hospitals were resistant to all three and therefore classed as MDR. This represents a slight decrease from 21.1% in 2011.

Males were approximately 1.6-times more likely to have an invasive *E. faecium* infection than females (z=4.67, P=<0.0001). The frequency of invasive *E. faecium* infection increased with age with the majority of infections (n=277; 71%) occurring in adults over 60 years. The median age was 69 years (95%CI, 67-71).

Klebsiella pneumoniae

In 2012, there were 345 reports of invasive *K. pneumoniae* infection (343 from blood and two from CSF) from 338 patients, an increase of 11% from 312 reports in 2011). **Table 1** displays the proportion of *K. pneumoniae* isolates resistant to the four "indicator" antimicrobials (as for *E. coli* above) plus carbapenems (imipenem, meropenem or ertapenem) since 2004. Forty-one (11.9%) of 344 isolates were resistant to 3GCs, 30 of which were ESBL-positive and 10 were ESBL-negative; 41 (11.9%) of 345 were ciprofloxacin-resistant; and 33 (9.6%) of 345 were gentamicin-resistant [34 (9.9%) of 345 were aminoglycoside-resistant (i.e. resistant to gentamicin, tobramycin or amikacin)].

Between 2011 and 2012, resistance to 3GCs and gentamicin/aminoglycosides increased. In 2012, resistance to 3GCs was at its highest level since surveillance began.

Five isolates were reported as ampicillin-susceptible, an unusual finding, as *K. pneumoniae* are regarded as inherently resistant to this antimicrobial.

ESBLs were detected in 30 (8.8%) of 342 isolates tested, representing an increase from 5.6% in 2011.

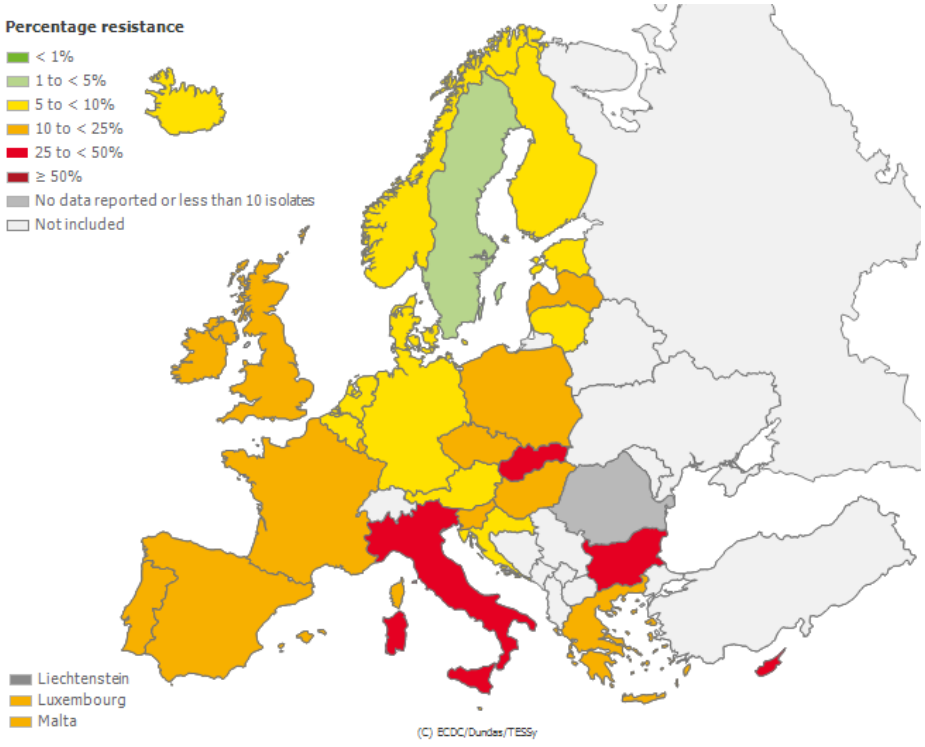

Figure 2. Distribution of third generation cephalosporin (3GC) resistant E. coli in EARS-Net countries in 2012. Map downloaded from ECDC's TESSy database on 16/10/2013: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.as

In 2012, ESBL-production was at its highest level since surveillance began.

No carbapenem-resistant invasive *K. pneumoniae* isolates (termed carbapenem-resistant *Enterobacteriaceae*, or CRE) were reported in 2012. In 2011, four invasive *K. pneumoniae* CRE isolates were reported due to carbapenemase production: three OXA-48 from one hospital and one KPC from another hospital. These carbapenemase-producing CRE isolates were the first reports of invasive infection due to these organisms in Ireland.

Thirty-four, or 9.9%, of 343 isolates tested against all four "indicator" antimicrobials from 21 hospitals were identified as MDR, an increase from 8.4% in 2011:

- 19 with resistance to ampicillin, 3GCs, ciprofloxacin and aminoglycosides (18 ESBL-positive, one -negative)
- Five with resistance to ampicillin, 3GCs and ciprofloxacin (3 ESBL-positive, one -negative)
- Five with resistance to ampicillin, 3GCs and gentamicin (all ESBL-positive)
- Five with resistance to ampicillin, ciprofloxacin and aminoglycosides (all ESBL-negative)

The number with resistance to all four "indicator" antimicrobials increased from 16 in 2011 to 19 in 2012. Antimicrobial resistance levels among *K. pneumoniae* isolates in Ireland have been among the lowest in Europe, with Ireland ranking 26th and 25th out of 30 countries in 2012 for 3GC and fluoroquinolone resistance, respectively. However, between 2011 and 2012, aminoglycoside resistance in Ireland has increased from 7.6% (ranking 24th highest of 29 countries) to 12.6% (ranking 13th of 30 countries).

Males were approximately 1.4-times more likely to have an invasive *K. pneumoniae* infection than females (z=3.00, P=0.003). The frequency of invasive *K. pneumoniae* infection increased with age with the majority of infections (n=216; 63%) occurring in adults over 60 years. The median age was 65 years (95%CI, 63-67).

Streptococcus pneumoniae

In 2012, there were 321 reports of invasive *S. pneumoniae* infection (315 from blood and six from CSF) from 319 patients, a decrease of 1.8% from 327 reports in 2011. **Table 1** displays the annual proportions of *S. pneumoniae* isolates non-susceptible/resistant to penicillin and erythromycin by year since 2004.

Penicillin-non-susceptible *S. pneumoniae* (PNSP) accounted for 19.6% (n=63) of all isolates tested against penicillin (n=321) in 2012 (**Table 1**). Of the 63 PNSP isolates, 48 were intermediately-resistant (Int) with a minimum inhibitory concentration (MIC) to penicillin between 0.1-1.0mg/L and 15 were high-level resistant (HLR) with a MIC >1.0mg/L to penicillin. Fifty-three (16.9%) of 313 isolates were resistant to erythromycin. Between 2011 and 2012, the proportion of PNSP in Ireland remained stable at 19.6% (**Figure 7**). The proportion of isolates that displayed HLR to penicillin decreased from 6.1% in 2011 to 4.7% in 2012. In 2012, Ireland had one of the highest proportions of PNSP (ranking 9th out of 30 countries, and 5th out of 21 countries reporting 50 isolates or more).

Comparison of *S. pneumoniae* susceptibility data between Ireland and other countries reporting to EARS-Net is increasingly problematic due to the possibility of different interpretive criteria being applied to the susceptibility testing data in different countries (and indeed by different laboratories within

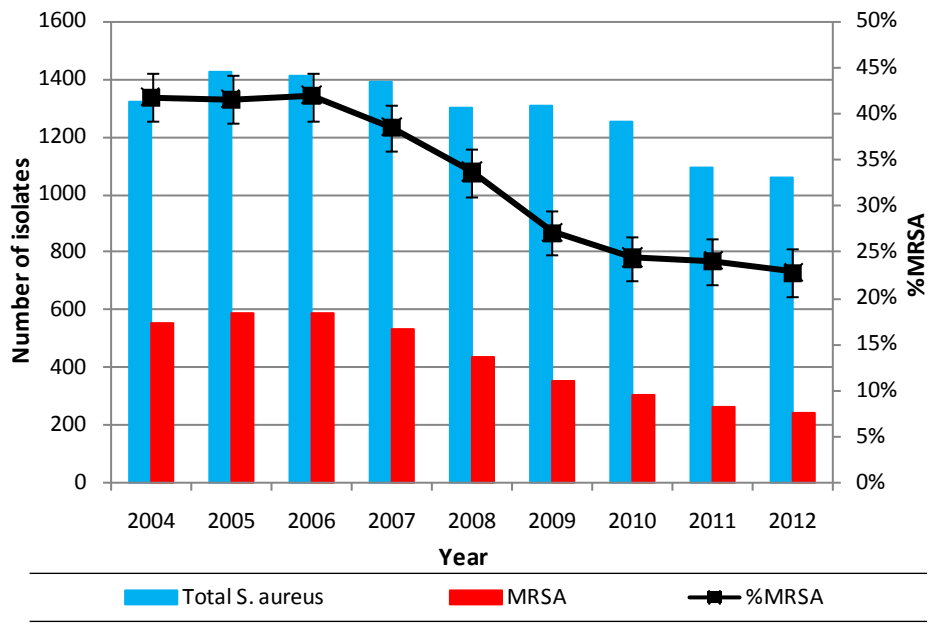

Figure 3. Trends for S. aureus. Total numbers of S. aureus/MRSA and percentage MRSA with 95% confidence intervals

the same country). Irish microbiology laboratories are currently in the process of changing over to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. By the end of 2012, 15 laboratories had completed the switch over from the American Clinical Laboratory Standards Institute (CLSI) guidelines. CLSI provides three sets of breakpoints for interpreting penicillin susceptibility of *S. pneumoniae* isolates: meningitis, non-meningitis and oral; while 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 to facilitate a more meaningful analysis of the data. This approach also permits a relatively consistent approach for comparing historical data.

Moderately-high levels of erythromycin resistance were seen in *S. pneumoniae* in 2012 (with Ireland ranking 16th out of 30 countries, and 11th out of 20 countries reporting 50 isolates or more), similar to the situation observed in much of Southern and Central/Eastern Europe.

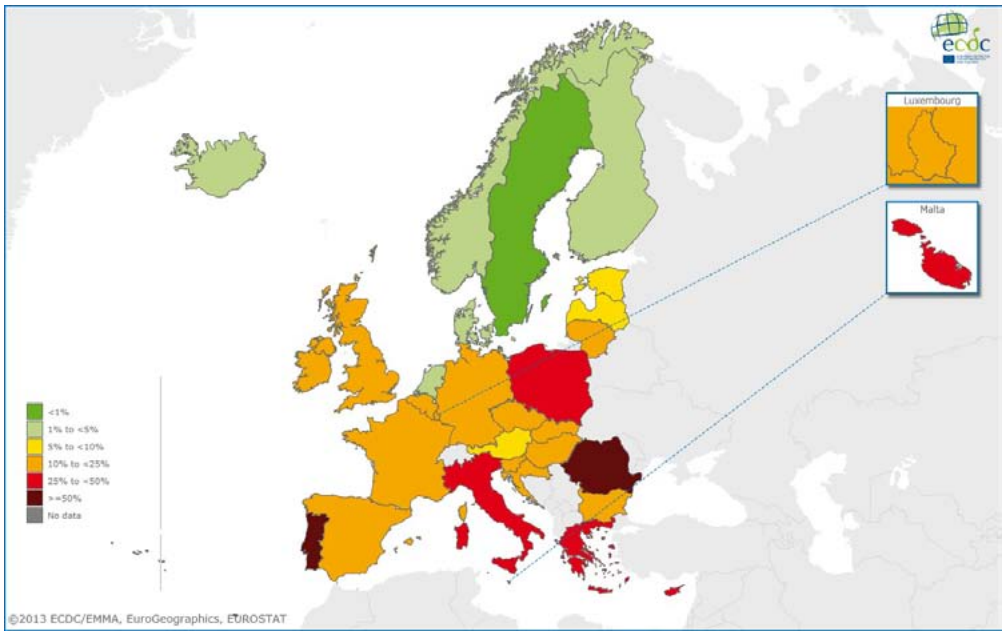

Figure 4. Distribution of MRSA in EARS-Net countries in 2012. Map obtained from ECDC on 16/10/2013: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx

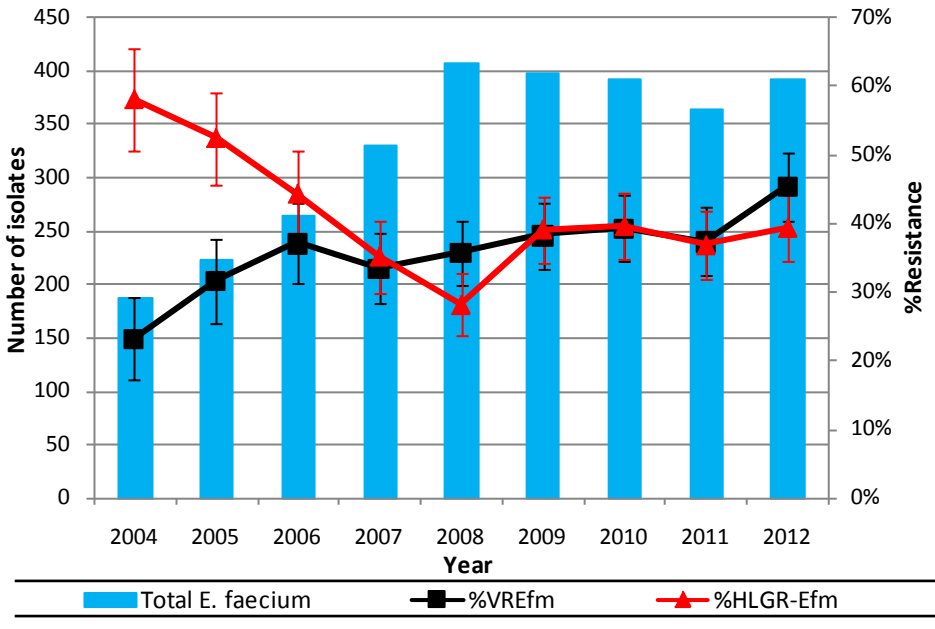

Figure 5. Trends for E. faecium. Total numbers of E. faecium and percentage resistance to high-level gentamicin (HLG) and vancomycin (VAN) with 95% confidence intervals

Of isolates tested against both penicillin and erythromycin (n=312), 38 (12.2%) were simultaneously PNSP (29 Int, 9 HLR) and erythromycin-resistant in 2012. Prior to the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) into the childhood immunisation schedule in September 2008, a national pilot project was established early in 2007 as a result of 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. From September 2010, PCV7 was replaced with PCV13. For 2012, serotype data were available on 306 pneumococcal isolates from all 30 laboratories that reported pneumococcal isolates to EARS-Net in 2012, representing 95% of all pneumococcal isolates reported. Overall, 243 (79%) isolates belonged to serotypes covered by the pneumococcal polysaccharide vaccine (PPV23; target population: adults ≥65 years and at risk groups), while 158 (52%) were covered by the conjugate vaccine (PCV13; target population: children <2 years). From adults aged ≥65 years, 138 of 172 (80%) isolates were covered by PPV23, while from children <2 years, 6 of 13 (46%) isolates were covered by PCV13 (compared with 7 of 13 isolates, or 56%, in 2011). Of the 63 PNSP isolates for which serotyping data were available, 18 of 28 (64%) from adults ≥65 years were covered by PPV23 while three of the four isolates from children <2 years were covered by PCV13. On-going surveillance of the predominant serotypes is required as strains with serotypes other than those in the vaccine have been reported to increase in prevalence following the introduction of conjugate vaccines in other countries. Hence the need for a fully resourced national pneumococcal reference facility.

The rate of invasive pneumococcal disease (IPD) in Ireland in 2012 was estimated to be 7.0 cases per 100,000 population, comparable to 7.1 in 2011 (note: both rates calculated using the 2011 census data). The highest rates of IPD were observed in children <1 year (12.4 cases per 100,000) and adults aged 65-74 years (21.7 cases per 100,000), 75-79 years (44.1 cases per 100,000) and ≥80 years (53.7 cases per 100,000) (**Figure 8**). The rates in all age groups were broadly similar to the data for 2011 with the exception of the 75-79 year age group, which increased from 31.4 cases per 100,000.

Males were approximately 1.1-times more likely to have an invasive *S. pneumoniae* infection than females, but this was not significant (z=0.84, P=0.4). The frequency of invasive *S. pneumoniae* infection increased with age with the majority of infections (n=210; 65%) occurring in adults over 60 years. The median age was 68 years (95%CI, 65-71).

Enterococcus faecalis

In 2012, there were 298 reports of *E. faecalis* BSI from 298 patients, an increase of 12% from 265 reports in 2011. **Table 1** displays the annual proportions of *E. faecalis* isolates resistant to the three "indicator" antimicrobials (as for *E. faecium* above) by year since 2004.

Nine (3.0%) of 298 isolates were resistant to vancomycin (vancomycin resistant *E. faecalis* – VREfa) and 95 (32.9%) of 289 isolates were resistant to high-level gentamicin.

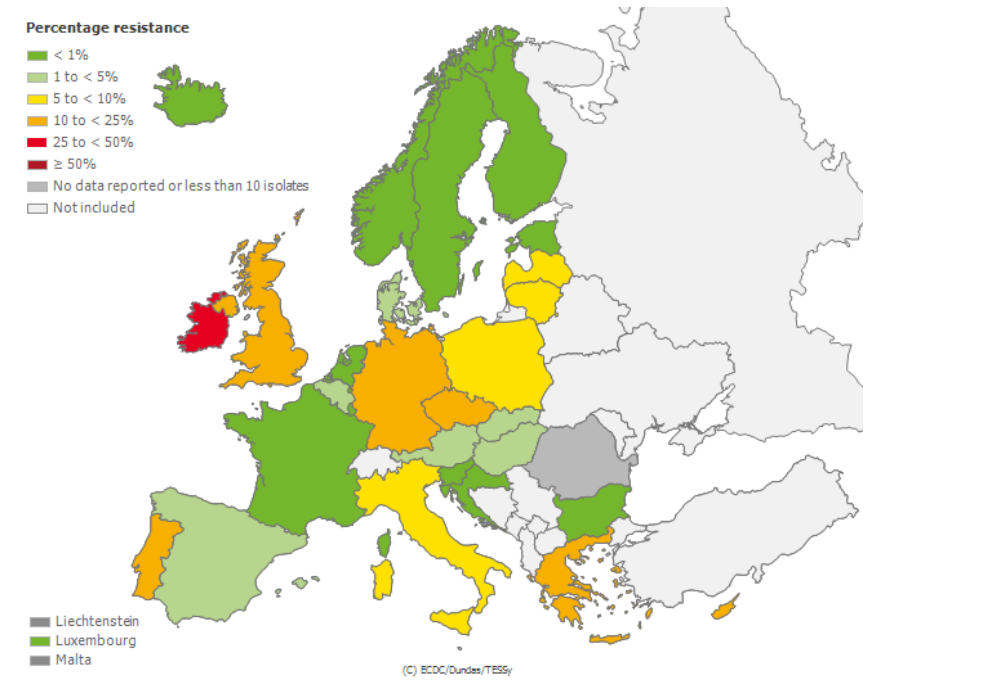

Figure 6. Distribution of vancomycin-resistant E. faecium in EARS-Net countries in 2012. Map downloaded from ECDC's TESSy database on 16/10/2013: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx

The highest proportion of VREfa in Ireland (4.9%) was reported in 2011. In 2012, Ireland had the second highest proportion of VREfa in Europe after Greece (7.9%).

Twelve isolates were reported as ampicillin-resistant, which suggests that these isolates were either misidentified as *E. faecalis* or misclassified as ampicillin-resistant, as resistance to ampicillin is rare in *E. faecalis*. Males were approximately two times more likely to have an invasive *E. faecalis* infection than females (z=6.15, P<0.0001). The frequency of invasive *E. faecalis* infection increased with age with the majority of infections (n=197; 66%) occurring in adults over 60 years. The median age was 68 years (95%CI, 66-72).

Pseudomonas aeruginosa

In 2012, there were 219 reports of invasive *P. aeruginosa* infection (217 from blood and two from CSF) from 219 patients, an increase of 19% from 184 reports in 2011. **Table 1** displays 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] since 2006.

Thirty-eight (17.4%) of 219 isolates were resistant to piperacillin-tazobactam; 33 (15.2%) of 217 were resistant to ceftazidime; 42 (19.4%) of 216 were resistant to imipenem or meropenem; 45 (20.6%) of 218 were resistant to ciprofloxacin; and 26 (11.9%) of 218 were resistant to gentamicin [no additional isolates were resistant to the other aminoglycosides (amikacin or tobramycin)].

In 2012, resistance to all five indicator antimicrobials increased, with resistance to piperacillin-tazobactam, ceftazidime and meropenem reaching their highest levels since surveillance began.

Twenty-eight (13.0%) of 215 isolates tested against all five "indicator" antimicrobials, from 14 hospitals, which was the highest since surveillance began:

- Four with resistance to all five required antimicrobials
- 11 with resistance to four of the five required antimicrobials
- 13 with resistance to three of the five required antimicrobials

Antimicrobial resistance levels among *P. aeruginosa* isolates in Ireland have been increasing in comparison with other European countries, with Ireland ranking between 16th and 20th out of 30 countries for all five indicator antimicrobials.
Males were approximately 1.6-times more likely to have an invasive *P. aeruginosa* infection than females (significant; z=3.63, P<0.001). The frequency of invasive *P. aeruginosa* infection increased with age with the majority of infections (n=155; 71%) occurring in adults over 60 years. The median age was 71 years (95%CI, 68-73).

Enhanced EARS-Net Surveillance

The enhanced EARS-Net surveillance programme was established in 2004 and involves voluntary participation by hospitals that provide additional demographic, risk factor and clinical data on invasive pathogens causing BSI. In 2012, there were 1,765 individual records (cases or isolates under the EARS-Net definition) submitted

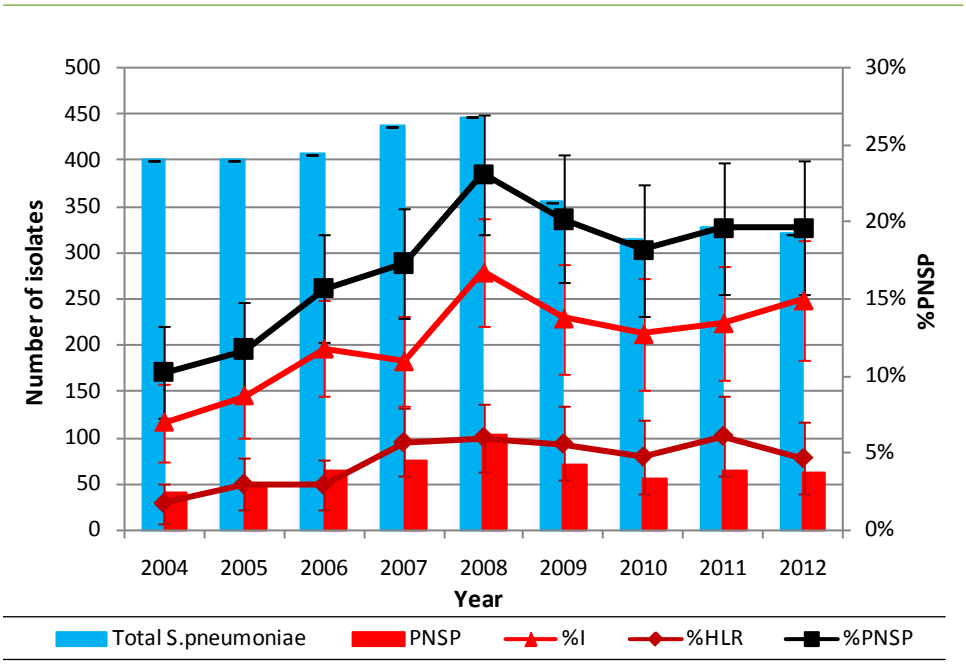

Figure 7. Trends for S. pneumoniae. Total numbers of S. pneumoniae/PNSP and percentage PNSP with 95% confidence intervals. HLR = High-level resistant; I = Intermediate resistance

from nine participating laboratories. The total number of records thus far for 2012 represents 35% of the total core EARS-Net dataset. Demographic and other basic data for the major resistance profiles of EARS-Net pathogens are shown in **Table 2**.

1. ***S. aureus* BSI**
   - Of the *S. aureus* BSI, 69% of MRSA and 61% of MSSA were classified as healthcare-associated in 2012
   - Between 2010 and 2012, there was an annual reduction in the proportion of *S. aureus* BSI due to central vascular catheter (CVC) infection (23% to 15%). However, there was an increase in the proportion of *S. aureus* BSI due to peripheral vascular catheter infection (6% to 11%)
   - The most common reported risk factors for *S. aureus* BSI were; recent surgery, malignancy and stay in an intensive care unit
   - Endocarditis, abscess & septic arthritis were the most commonly recorded clinical features

2. **Enterococcal BSI**
   - Of the enterococcal BSI, the majority of vancomycin resistant (83%) and vancomycin sensitive (73%) were healthcare-associated
   - The commonest primary sources of enterococcal BSI were CVCs and intra-abdominal/ gastrointestinal tract infections
   - Between 2010 and 2012, there was an increase in VRE bloodstream infection due to a CVC infection

3. **Pneumococcal BSI**
   - For penicillin non-susceptible *S. pneumoniae* (PNSP), the proportion of isolates that were detected within two days after admission decreased from 95% in 2011 to 65% in 2012. For penicillin susceptible *S. pneumoniae* (PSSP) this also decreased from 93% in 2011 to 79% in 2012. Between 2011 and 2012, the proportion of isolates that were detected after five days post-admission increased from 0% to 26% for PNSP and from 5% to 8% for PSSP. These changes have resulted in an increasing proportion of PNSP BSI in particular, being classed as "acquired in the reporting hospital" (5% in 2011 to 32% in 2012). However, the overall number of PNSP BSI isolates for which there is enhanced information is small and these results must be interpreted with caution
   - Respiratory tract infection remains the most common source of pneumococcal BSI
   - Of pneumococcal BSI, 5% were associated with meningitis

4. ***E. coli*, *K. pneumoniae* and *P. aeruginosa* BSI**
   - The majority of fluoroquinolone resistant *E. coli*, *K. pneumoniae* and *P. aeruginosa* BSI were healthcare-associated, in contrast to 43% of fluoroquinolone susceptible *E. coli* BSI
   - The most common source of *E. coli* BSI was urinary tract infection, with 5% associated with the presence of a urinary catheter
   - The most common source of *K. pneumoniae* BSI was intra-abdominal/gastro intestinal tract, followed by urinary tract infection
   - The most common source of *P. aeruginosa* BSI was respiratory tract infection

For further details, go to the HPSC website: www.hpsc.ie and click on "Topics A-Z", then "Enhanced Bacteraemia Surveillance

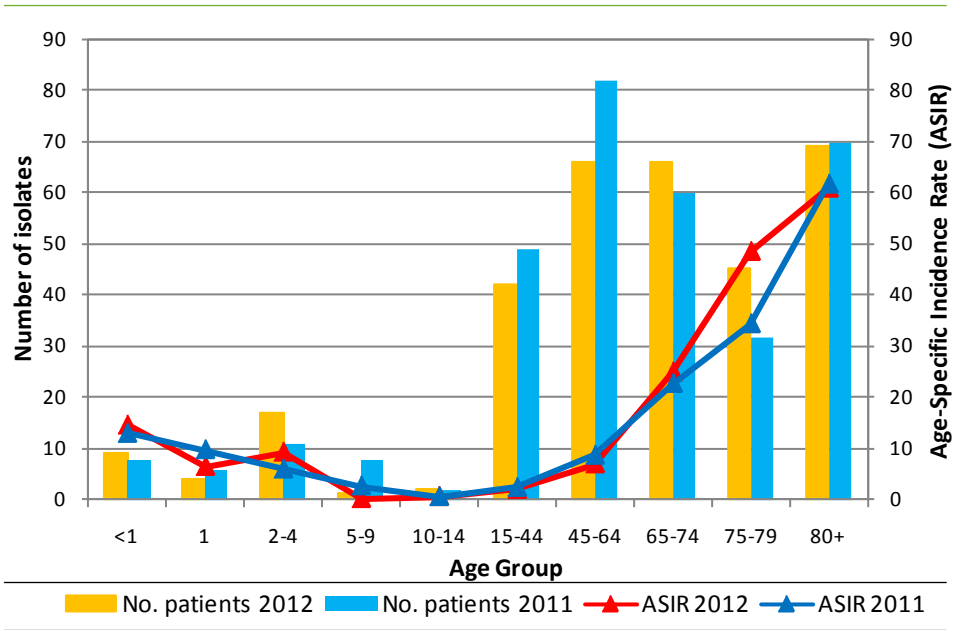

Figure 8. Numbers and age-specific incidence rates of patients with invasive S. pneumoniae infection in 2012 compared with 2011

Conclusion
Ongoing monitoring of trends in Ireland's EARS-Net surveillance data provides important information.
A welcome trend is the continued decrease in the proportion of *S. aureus* BSI due to MRSA for the sixth consecutive year to the lowest level yet (22.8%) in 2012. However, antimicrobial resistance to key antimicrobials in invasive infections caused by the *Enterobacteriaceae* (*E. coli, K. pneumoniae*), *P. aeruginosa* and *Enterococcus faecium* continues to increase, reaching the highest levels yet in 2012. Indeed, for 2012, Ireland had the highest proportion of VREfm (45.4%) of any EARS-Net country.

Improvements in infection prevention and control resources and interventions, along with hospital antimicrobial stewardship programmes, have probably contributed to reducing the burden of MRSA BSI in Ireland since 2006. The introduction of pneumococcal conjugate vaccines into the childhood immunisation programme since September 2008 has already resulted in a reduction in the burden of invasive pneumococcal disease in children. Despite these successes, the issue of antimicrobial resistance remains a major problem in Ireland. In addition, the increasing number of reported invasive infections due to multi-drug resistant bacteria is of particular concern. It should also be noted that antimicrobial resistance is an issue for other bacterial species (not captured within the EARS-Net surveillance) as well as for infections occurring at sites other than blood and/or CSF (not captured within the EARS-Net surveillance). Whilst EARS-Net surveillance data on key pathogens from invasive infections is extremely valuable in comparing antimicrobial resistance at a national level, it is likely to underestimate the true burden of infections caused by drug-resistant pathogens.

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

Infections caused by antimicrobial resistant bacteria result in excess patient mortality, morbidity and costs to the healthcare system. Rising levels of resistance 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 health service. To this end, it is vital that recommendations and guidelines produced by the HSE/RCPI AMR and HCAI Clinical Advisory Group 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 October 2013**.
For further details of EARS-Net and antimicrobial resistance in Ireland see www.hpsc.ie
European data are available at http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx

9.3.0.2 Enhanced Surveillance of Carbapenem resistant *Enterobacteriaceae* (CRE) in Ireland

Key points:

- In 2012, enhanced surveillance data was received on 32 CRE cases. This represented a small decrease compared with 2011, when enhanced surveillance data was received on 37 CRE cases (out of a total of 39 cases reported that year)
- Six patients (19%) had a history of hospitalisation abroad – UK (4 VIM-type CRE, all of whom were cared for in the same UK hospital) and India (2 NDM-type CRE with no epidemiological links)
- The clinical significance of the CRE isolate was reported for 30 patients (94%), representing colonisation in the majority (n=27) and CRE infection was reported for three patients

Carbapenem resistant *Enterobacteriaceae* (CRE) are multiple-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 antibiotic therapy may be lacking. Most CRE produce carbapenemase, an enzyme that breaks down the carbapenem class of antibiotics (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 2012, 32 confirmed cases of carbapenemase-producing CRE and three CRE outbreaks were reported;

1. Two KPC outbreaks, both reported from acute hospitals, affecting seven and three patients, respectively
2. One OXA-48 outbreak, which occurred in a long-term care facility affecting two residents

Completed enhanced surveillance forms were received from eight laboratories on 32 patients, 18 of whom were male (56%). The average age was 50 years (range: 1 to 95 years). At the time of CRE detection, 22 patients

(68%) were hospitalised, eight were in the community (25%) and two were nursing home residents. Of the 22 hospitalised patients, nine (41%) had been admitted from home, five (23%) were transfers from another acute hospital and the source of admission was not provided for the remaining eight patients. Of the five patients who had been transferred from another acute hospital, three were repatriated from hospitals abroad; UK (2) and India (1).

At the time of CRE detection, 10 patients (31%) were already known to be colonised or infected with one or more other multi-drug resistant organisms (MDRO). Six patients (19%) had a history of recent hospitalisation abroad; UK (4) and India (2).

Fifteen patients (47%) reported no foreign travel in the last 12 months and the travel history was unknown for nine patients (28%). Eight patients reported a history of foreign travel within the past 12 months:

- UK – Five patients; VIM (4) and KPC (1). Four of those had been hospitalised in UK
- India; Two patients with NDM-1. Both had been hospitalised in India
- Philippines; One patient with KPC who had not been hospitalised whilst abroad

Two patients had no identifiable risk factors for CRE colonisation or infection and risk factor data was not provided for six patients. Of the remaining 24 patients, 14 (58%) had more than one risk factor. Reported risk factors included; Hospitalisation in the past 12 months (21; 88%), history of surgery in the past six months (6; 25%), history of admission to intensive care in the last 12 months (4; 17%). Eleven patients (46%) had underlying co-morbidities [chronic lung disease, diabetes mellitus, urological abnormality or immunocompromise].

Of the 32 patients, antimicrobial exposure history prior to isolation of CRE was provided for 23 (72%), which included the majority of the 22 hospitalised patients (n=19; 86%). Fourteen patients had received more than one antimicrobial class.

- β lactam - β lactamase inhibitor combination agents; 19 (83%)
- Cephalosporins; 8 (35%)
- Fluoroquinolones; 6 (26%)
- Carbapenems; 4 (17%)
- Aminoglycosides; 3 (13%)

The clinical significance of the CRE isolate was reported for 30 patients (94%), representing colonisation in the majority (n=27). CRE infection was reported for three patients, with two cases of urinary tract infection and one case of respiratory tract infection.

The majority of CRE (21; 66%) were detected from screening rectal swabs or faeces. Eight isolates were detected from urine (25%), two from superficial swabs and one from intra-abdominal pus.
Outcome was reported for only one of the eight non-hospitalised patients (survived) and for 16 of the 24 hospitalised patients (66%). Of those, eleven (68%) were discharged home, two (13%) remained inpatients at the time the surveillance form was returned and it is not known whether or not those CRE colonised patients subsequently went on to develop CRE infection later in the hospital admission. Three patients died (19%). For one of the three deaths, the patient was reported to have had CRE infection. The potential contribution of CRE to patient death was not collected.

Of the eleven patients who were discharged home, length-of-stay could be calculated for nine. The median length-of-stay was 26 days (range: 12 to 120 days). *Klebsiella pneumoniae* accounted for 23 and *K. oxytoca* for one CRE isolate. There were six cases of *E. coli* CRE and one case each of *E. cloacae* and *C. freundii* CRE reported.

The reported carbapenemase enzyme types reported in 2012 were; KPC (14 cases), OXA-48 (8 cases), NDM-1 (6 cases) and VIM (4 cases).

- Carbapenems; Reported minimum inhibitory concentrations for meropenem and ertapenem ranged from 1.5 to >32 mg/L
- Gentamicin; Reported on all 32 isolates, with 13 resistant (40%)
- Amikacin; Reported on 26 isolates, with 16 resistant (62%) and four with intermediate susceptibility
- Fluoroquinolones; Reported on 28 isolates, with 23 resistant (82%)
- Tigecycline; Reported on 25 isolates; with 10 resistant (40%) and five with intermediate susceptibility
- Colistin; Reported on 20 isolates, with one resistant (5%)

No case of carbapenemase-producing infection of blood or CSF was reported in Ireland in 2012. In 2012, 25 of 29 EARS-Net countries reported one or more case of invasive carbapenem resistant *K. pneumoniae* infection, with 13 countries reporting five or more cases. In 2012, the proportions of invasive *K. pneumoniae* isolates with carbapenem resistance were highest in Greece (62%) and Italy (31%). This clearly illustrates that this is an evolving problem throughout Europe. Increases in the prevalence of CRE are largely related to overuse of broad spectrum antimicrobials and suboptimal infection prevention and control practices, particularly in hospital and long-term care settings. Prudent antimicrobial stewardship and aggressive infection prevention and control interventions are required to prevent transmission of carbapenemase-producing *Enterobacteriaceae*.
In response to the emergence of CRE, screening

guidelines were issued in 2011. Subsequently, Irish guidelines for the prevention and control of multi-drug resistant organisms, excluding MRSA, in the healthcare setting have been developed under the auspices of the Royal College of Physicians of Ireland (RCPI) Clinical Advisory Group on Healthcare-Associated Infections and Antimicrobial Resistance. Latest available information on CRE in Ireland and the guidelines are available on the HPSC website at the following link:
http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/StrategyforthecontrolofAntimicrobialResistanceinIrelandSARI/CarbapenemResistantEnterobacteriaceaeCRE/