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Antimicrobial Resistance in the UK

Neil Woodford

Antimicrobial Resistance & Healthcare Associated Infections (AMRHAI) Reference Unit

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UK 5-year AMR Strategy 2013-18: Seven key areas for action

DH – High Level Steering Group

PHE
Human health

Defra
Animal health

DH

1. **Optimising prescribing practice**
2. **Improving infection prevention and control**
3. **Improving professional education, training and public engagement**
4. **Better access to and use of surveillance data**

- **Improving the evidence base through research**
- **Developing new drugs, vaccines and other diagnostics and treatments**
- **Strengthening UK and international collaboration**

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Mechanisms of antibiotic resistance

- Intrinsic or acquired
- Drug inactivation
- Drug modification
- Drug *target* modification
- Reduced accumulation of drug
  - reduced cell permeability (less in)
  - efflux (more pumped out)
- Alternative metabolic pathways (by-pass)

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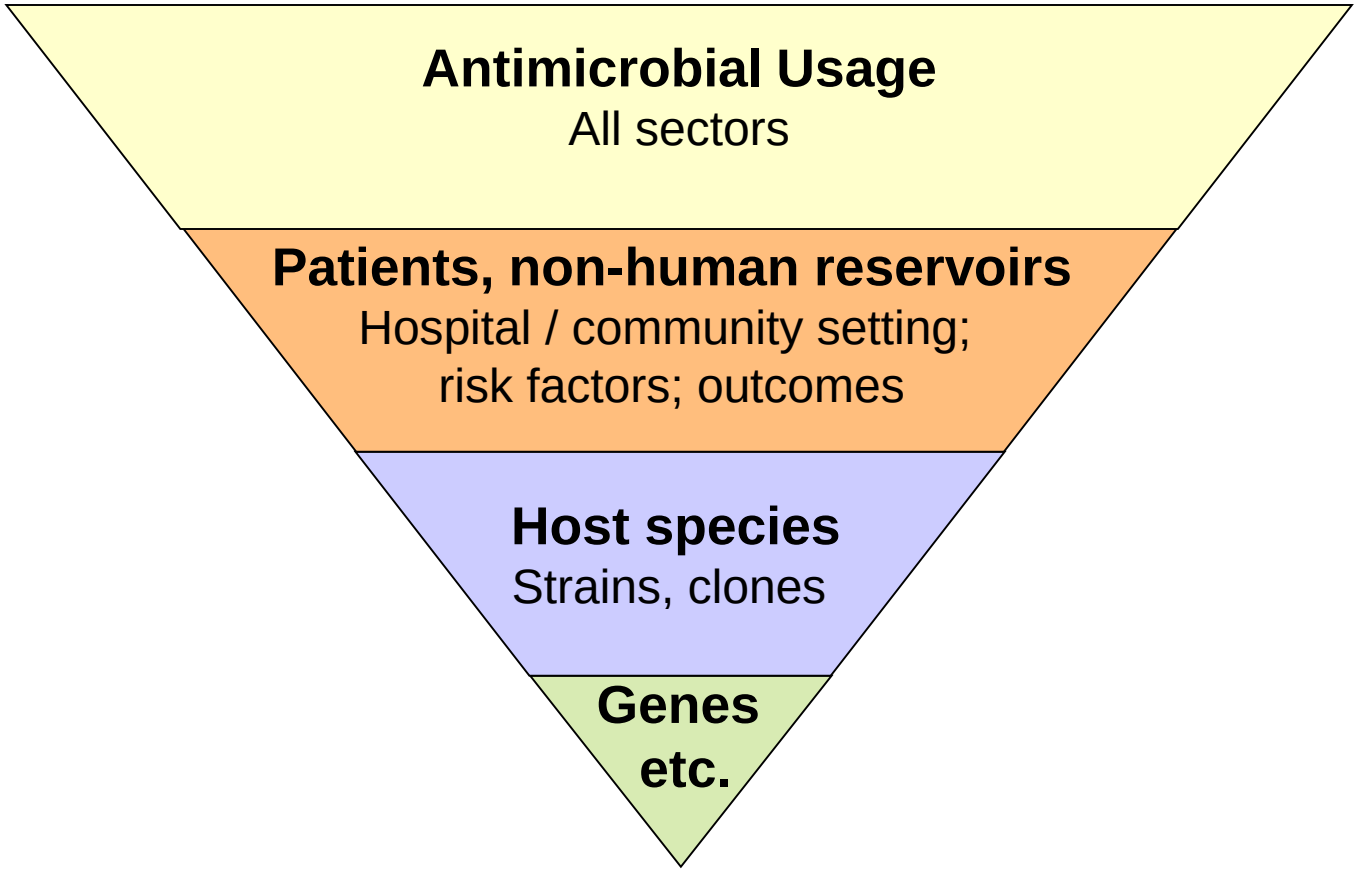
The complexities of AMR epidemiology



Three strands for surveillance of AMR

1. data on **consumption of antibiotics** in both humans and animals, […] which would help understand the link between antimicrobial use and the development of resistance.
2. data on **resistance rates** for various drug–bug combinations and their impact on patients' health.
3. **molecular biological data** to explain the biological basis of resistance, through characterisation of the types of resistant bacteria and the genetic reasons for their resistance.

- This information should be **gathered within a 'one health' perspective**, covering animals and humans and the environment to provide a complete picture

Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

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The resistance ratchet keeps turning

Pathogen	Established problems	Emerging threats
E. faecium	VRE, HLGR, Amp-R	Lin-R, Dap-R, Tig-R
S. aureus	MRSA (ha/ca)	Van-R, Lin-R, Dap-R
Klebsiella	ESBLs	Carbapenemases, Col-R
Acinetobacter	MDR, Carbapenemases	Tig-R, Col-R
Pseudomonas	MDR, except Col	Carbapenemases, Col-R
Enterobacter	AmpC, ESBLs	Carba-R, Carbapenemases
E. coli	Cip-R, ESBLs	Carbapenemases

- Historic focus on Gram-positives

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AMR mechanisms in Gram-positives (examples)

Antibiotic class	Staphylococci	Enterococci	Pneumococci (and viridans)	Beta-haem streps (A,C,G)
Penicillins	Penicillinase (common)	PBP-mediated (E. faecium); Penicillinase (very rare)	PBP-mediated (common)	*No reports of resistance*
Pen'ase- stable penicillins	PBP-mediated (*mecA/mecC*)	-	-	-
3rd-generation cephalosporins	PBP-mediated (*mecA/mecC*)	Intrinsic	PBP-mediated (rarer than Pen-R)	*No reports of resistance*
Vancomycin	Mutations (rare); VanA (very rare)	VanA; VanB; VanC (intrinsic); other rarer *van* types	*No reports of resistance*	*No reports of resistance*
Teicoplanin	Intrinsic (some CoNS); mutations (rare); VanA (very rare)	VanA; VanB; VanC (intrinsic); other rarer *van* types	*No reports of resistance*	*No reports of resistance*

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AMR mechanisms in Gram-positives (examples)

Antibiotic class	Staphylococci	Enterococci	Pneumococci (and viridans)	Beta-haem streps (A,C,G)
Aminoglycosides	AMEs	Intrinsic; AMEs (high level)	Intrinsic	Intrinsic
Macrolides	Erm(A,C); Msr	Erm(B)	Erm(B); Mef	Erm(B)
Lincosamides	Erm(A,C); Lnu	Intrinsic; Erm(B); Lnu	Erm(B); Lnu	Erm(B); Lnu
Tetracyclines	Tet(K,L,M)	Tet(M)	Tet(M)	Tet(M)
Mupirocin	Mutations; Mup(A,B)	-	-	-
Rifampicin	Mutations	Mutations	Mutations	-
Daptomycin	Rare (mutations)	Rare (mutations)	-	-
Linezolid	Rare: mutations; *cfr; optrA*	Rare: mutations; *cfr; optrA*	-	-
Synercid	Vat(A,B,C); efflux	Intrinsic (*E. faecalis*); Vat(D,E)	-	-

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E. coli	**Cip-R, ESBLs**	**Carbapenemases**

- 5 of 7 ESKAPEEs are Gram-negative
- Increasing reliance on carbapenems
- *The* resistance issue for the next 5-10 years

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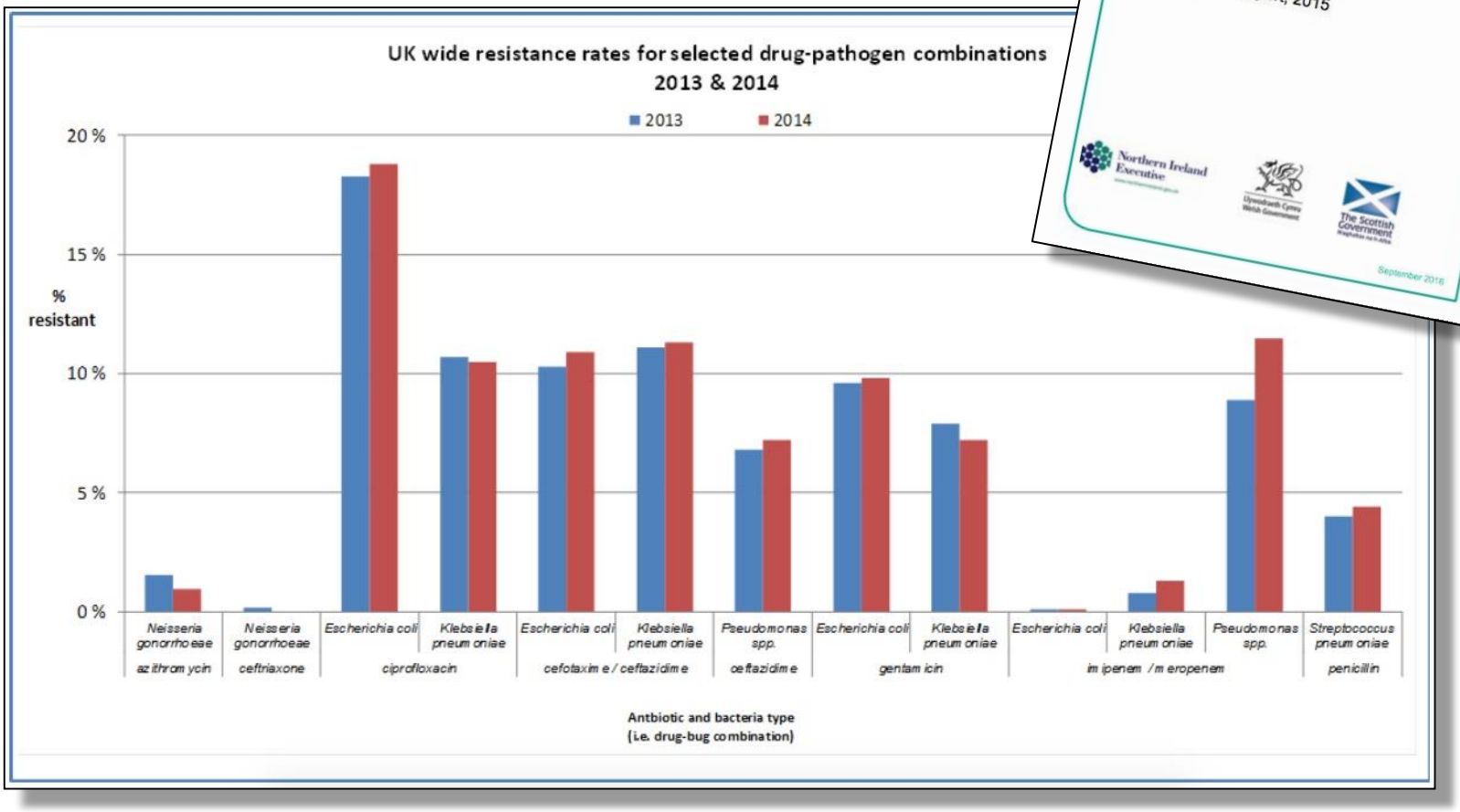
UK resistance rates



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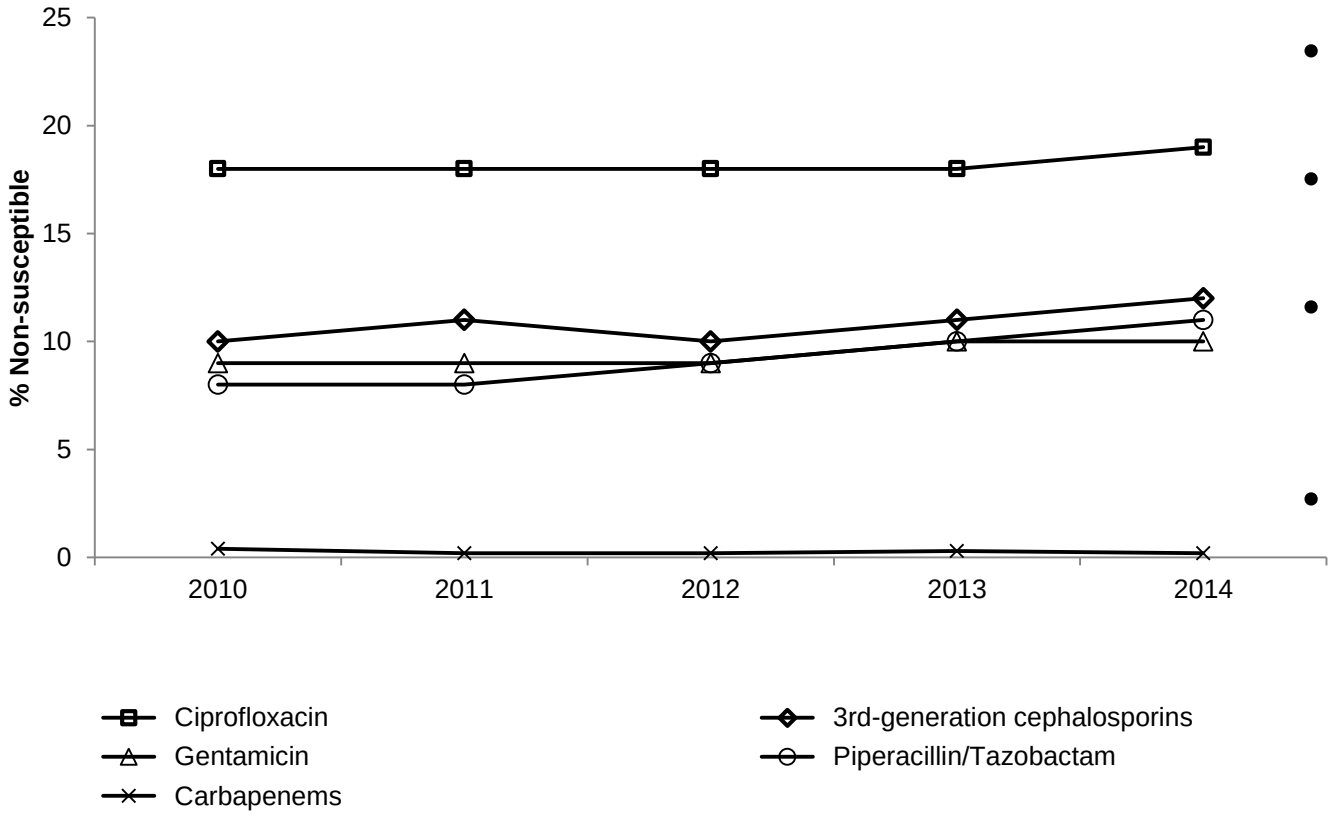
E. coli BSI resistance, 2010-14



- 'Little change'
- 'Largely stable'
- 'Slight upwards trend'
- PTZ – difficult to interpret

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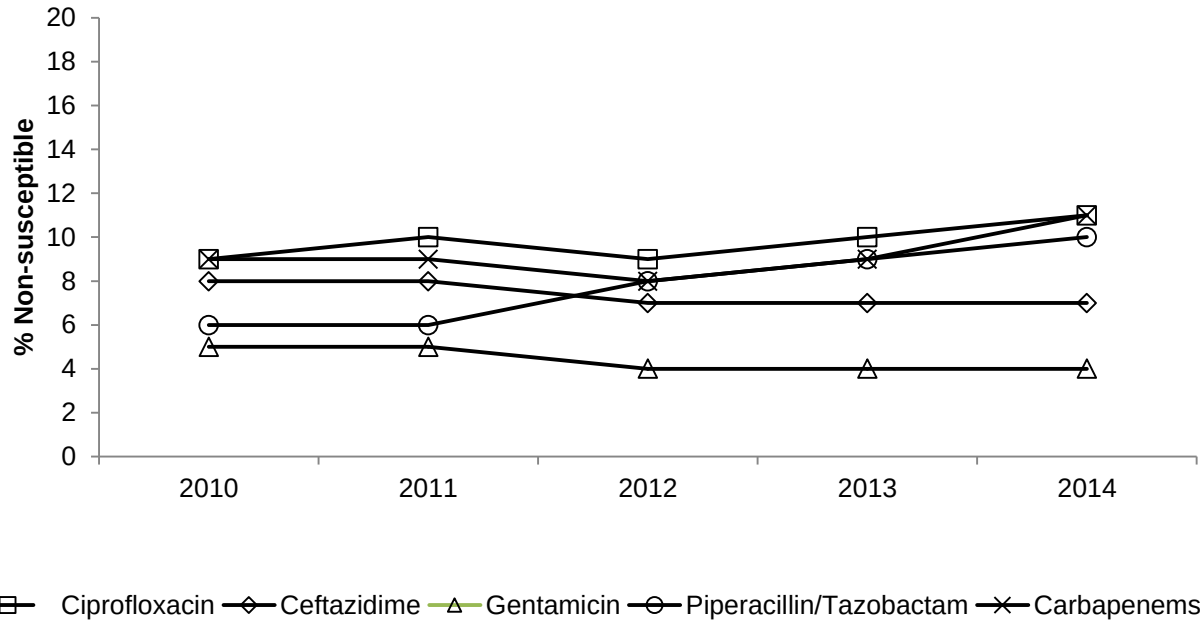
Pseudomonas BSI resistance, 2010-14



- ‘Little change’
- ‘Largely stable’
- ‘Slight upwards trend’
- PTZ – difficult to interpret

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Resistance to beta-lactams

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Can you distinguish TEM-1 from CTX-M-15 ?

Enzyme	Examples	Confer resiatance to
Penicilllinases	**TEM-1**/-2, SHV-1, OXA-1/-30	Penicillins; early cephalosporins; overexpression affects penicillin-inhibitor combinations
ESBLs	TEM-, SHV-, OXA-, **CTX-M**, VEB, PER	All generation cephalosporins (not cephamycins)
pAmpC	CMY, ACC, DHA, FOX, MOX, ENT / EBC	3rd gen cephs (not 4th); cephamycins

- Carbapenems remain active against producers of these enzymes and are increasingly used for treatment

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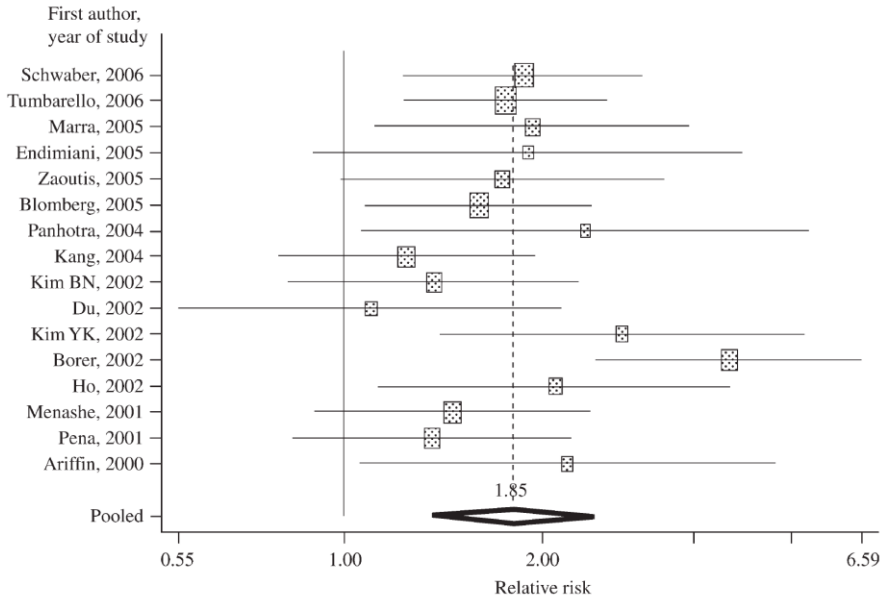
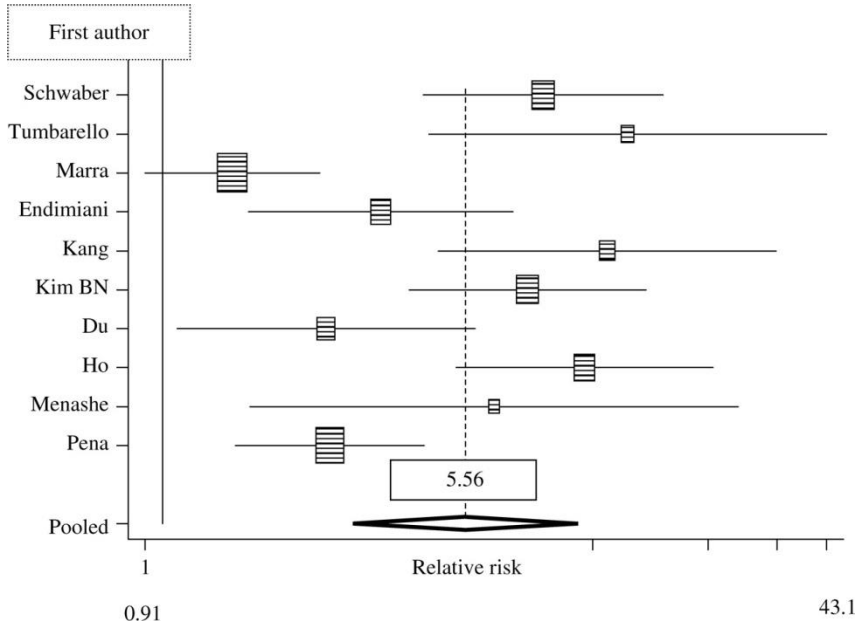
ESBL *vs.* non-ESBL bacteraemia



Mortality



Delayed appropriate Rx

Schwaber & Carmeli, *JAC* 2007; **60:** 913

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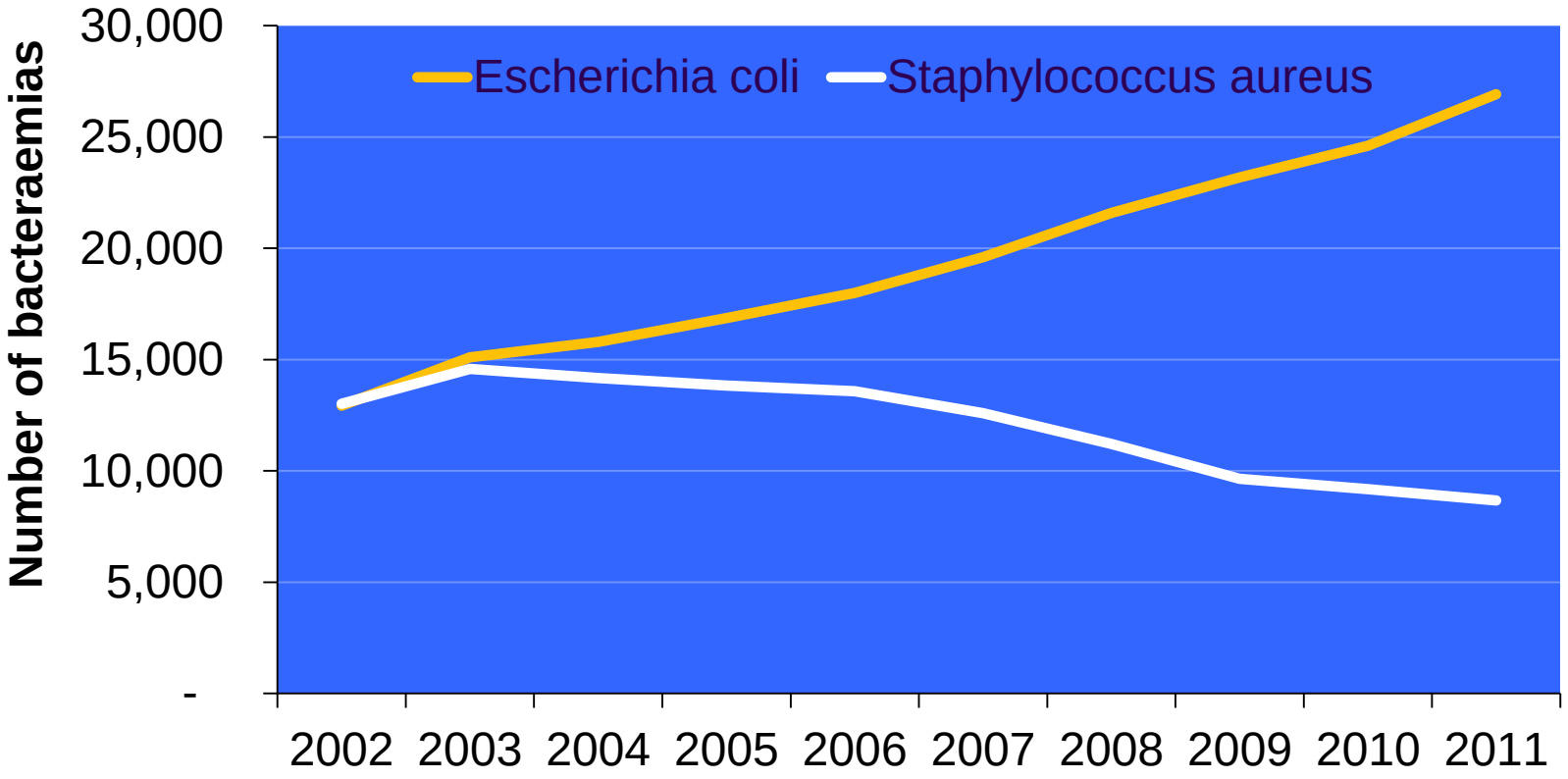
Rising numbers of *E. coli* bacteraemias



- *E. coli* bacteraemia continues to rise: >35000 cases in 2015
  - c. 3500 'cephalosporin-resistant infections' p.a.; most ESBLs

LabBase2 data, England only

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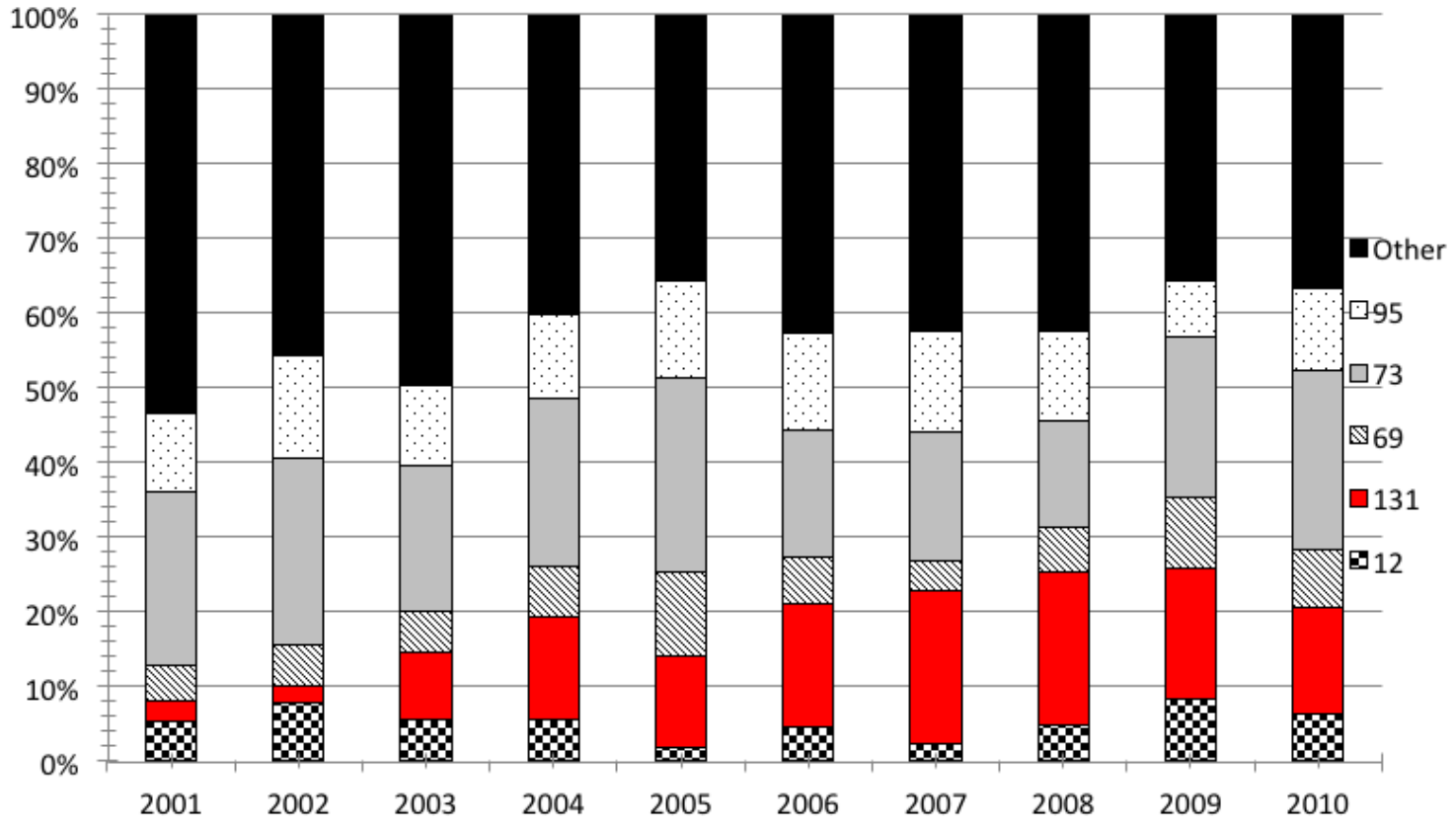
A few *E. coli* STs predominate among BSIs



Day et al. 2016 JAC

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AMR is not equally distributed among *E. coli* STs

		Non-susceptibility (%)									β-lactamase (%)				
CC	Total no.	AMX	AMC	PTZ	CTX[c]	CAZ	CIP	GEN	TIG[c]	IMI	CTX-M other[d]	CTX-M gp 1	CTX-M gp 9	Other	Non-ESBL
73	449	55.9	27.8	9.1	1.5	1.8	1.3	1.6	0.2	0.0	0.0	0.0	0.0	1.1	98.9
131	302	83.4	59.3	22.2	35.0	29.5	64.2	20.2	0.0	0.0	0.3	32.5	0.3	1.0	65.9
95	245	45.3	13.9	2.9	0.0	0.0	0.4	2.4	0.0	0.0	0.0	0.0	0.0	0.0	100
69	149	81.9	32.2	10.1	1.4	2.0	6.7	4.0	0.7	0.0	0.0	0.7	0.0	0.0	99.3
12	119	71.4	28.6	7.6	1.8	5.0	0.8	3.4	0.0	0.0	0.0	0.8	0.0	0.0	97.5
other[a]	902	60.9	27.7	9.3	5.3	5.3	15.2	6.4	0.1	0.2	0.2	2.2	0.1	0.1	96.5
TOTAL	**2166**	**63.3**	**30.9**	**10.3**	**7.2**	**7.1**	**16.1**	**6.6**	**0.1**	**0.1**	**0.1**	**5.5**	**0.1**	**0.1**	**93.4**

Day et al. 2016 JAC

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High-Risk Clones (HiRiCs)

- The risk of development of resistance during therapy (mutation-selection) is small in most cases
- Most problems of antibiotic resistance derived from the spread and further acquisition of particular clones, HiRiCs, able to efficiently colonize the host or be transmitted between hosts
- World-wide clonal epidemics
- HiRiCs might persist and acquired resistance genes as well disseminate among local clones its antibiotic resistance genes (horizontal gene transfer), favoring endemicity

Baquero & Coque. FEMS Rev 2011 35:705

Courtesy, Jordi Vila

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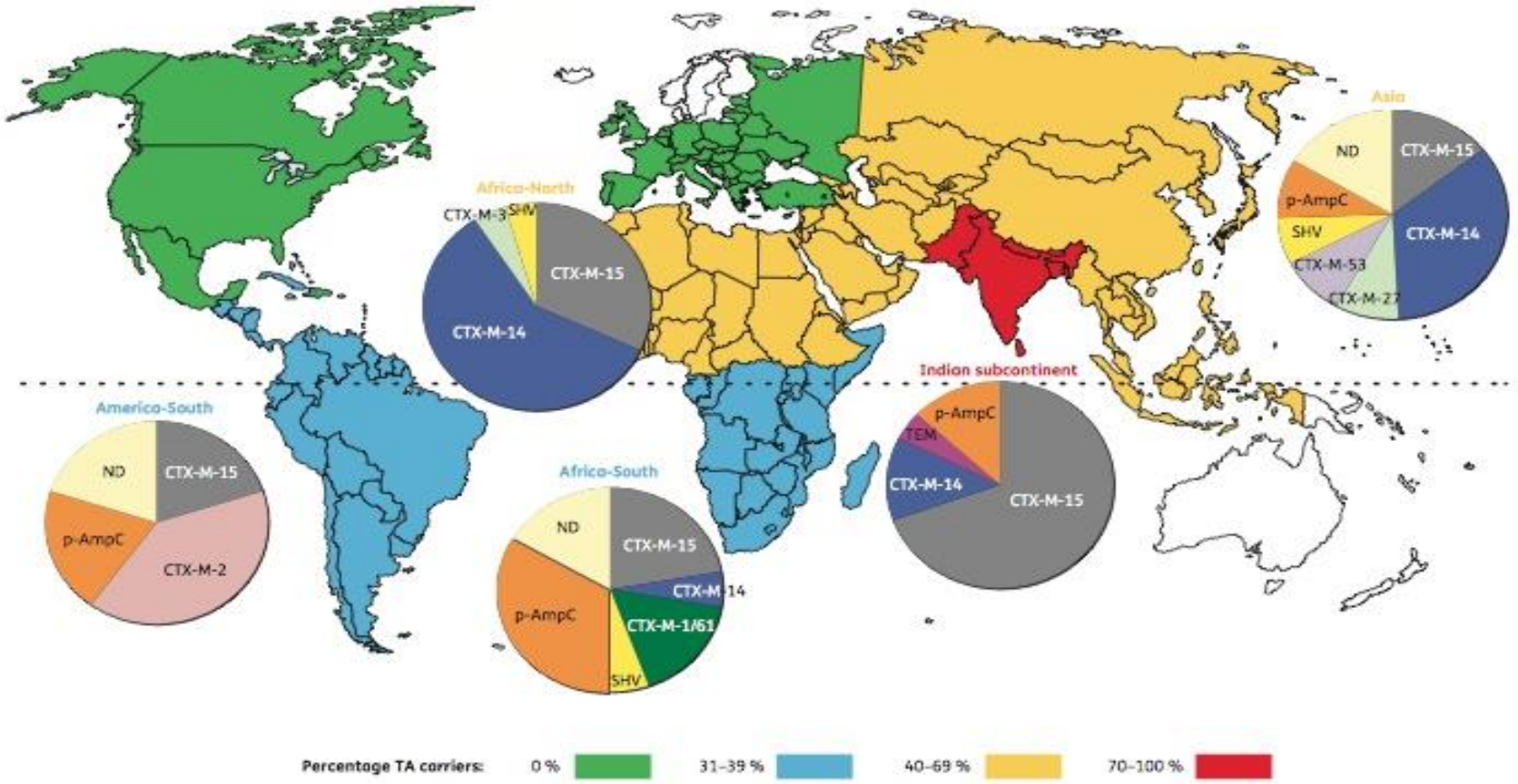
Destination influences risk and type of resistance



Ostholm-Balkhed et al. JAC 2013; 68: 2144-53

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Carbapenemases

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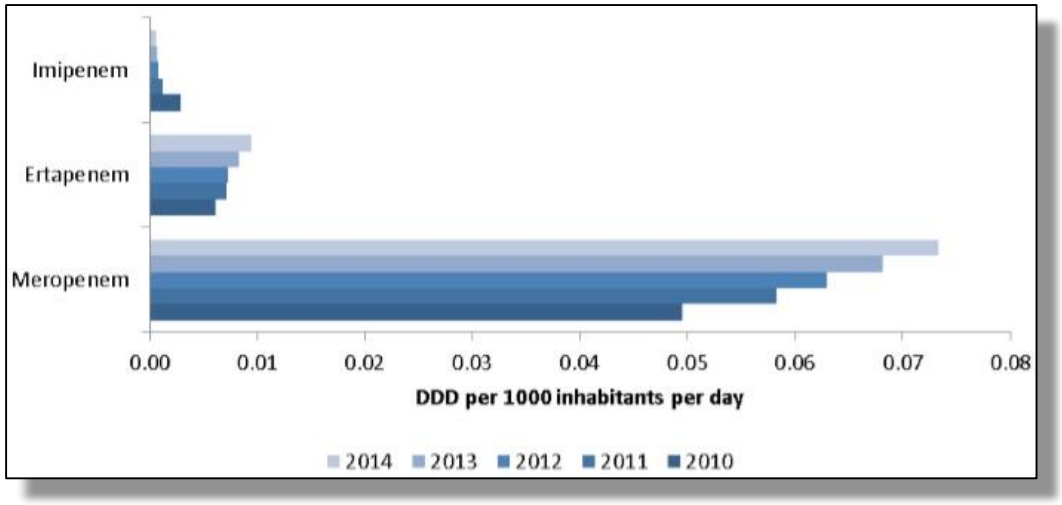
Carbapenem usage is increasing



- Carbapenems = 0.3% of total antibiotic consumption in 2013
- BUT use increased by 31.3% in England between 2010 and 2013
- Mostly in the hospital sector, <1% in primary care.
- MEM = c. 90% of carbapenem use

- ↑ use of carbapenems
- new selective pressures, …with consequences

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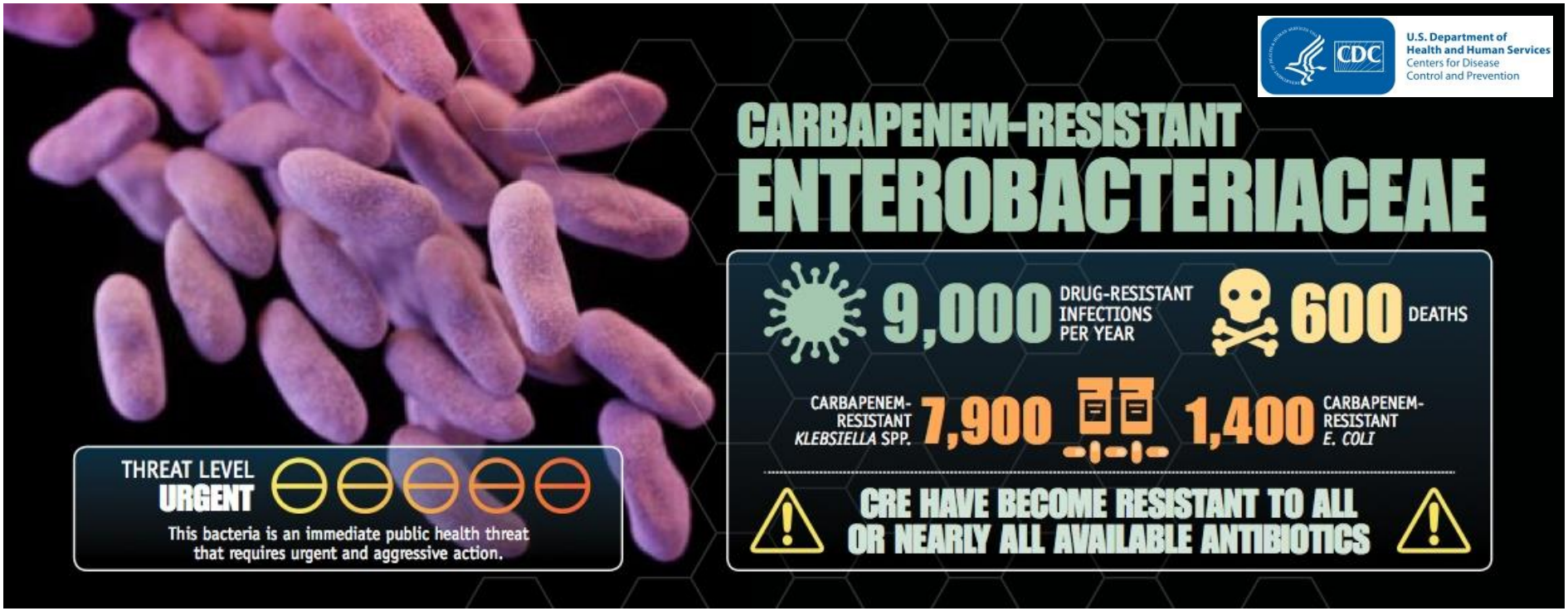
The apex of *current* resistance problems ?



- only colistin is currently active against 90% of CRE (UK data)
- colistin resistance is a growing threat

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Acquired carbapenemases

Class	Carbapenemase	Enterobacteriaceae	Non-fermenters
A (non-metallo)	**KPC**	**+++**	+
	BIC, GES, IMI, NMC, SME	+	+/-
B (metallo)	**IMP*, VIM***	**+++**	**+++**
	NDM	**+++**	++
	AIM, DIM, GIM, SIM, SPM, TMB	-	++
D (non-metallo)	**OXA-48-like**	**+++**	+/-
	OXA-23, -40, -58, -143, -235	+/-	**+++**

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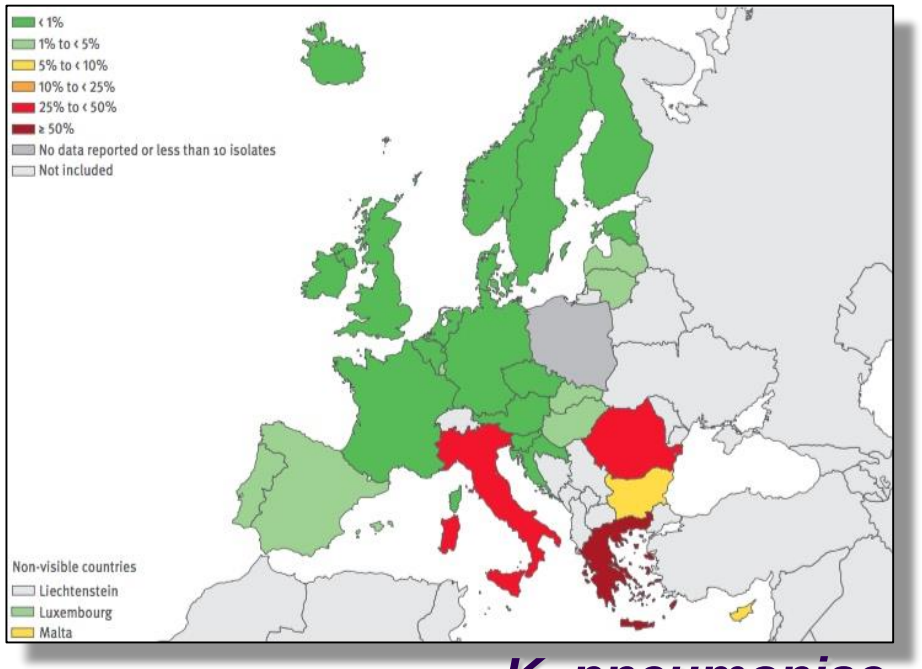
Carbapenem non-susceptibility, EARS-Net 2014

E. coli



K. pneumoniae

- 'green' data risk giving a false sense of security to non-experts
- only 9% of UK carbapenemase producers are from blood cultures

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Enhancing surveillance with reference microbiology

- Reference laboratory provides specialist microbiology that seeks to explain trends
  - Is at the centre of a national / regional laboratory network
  - Benefits from a ‘spider’s web effect’
  - Monitors new and emerging AMR issues, long before they register in surveillance programmes

Data, courtesy Prof Alan Johnson

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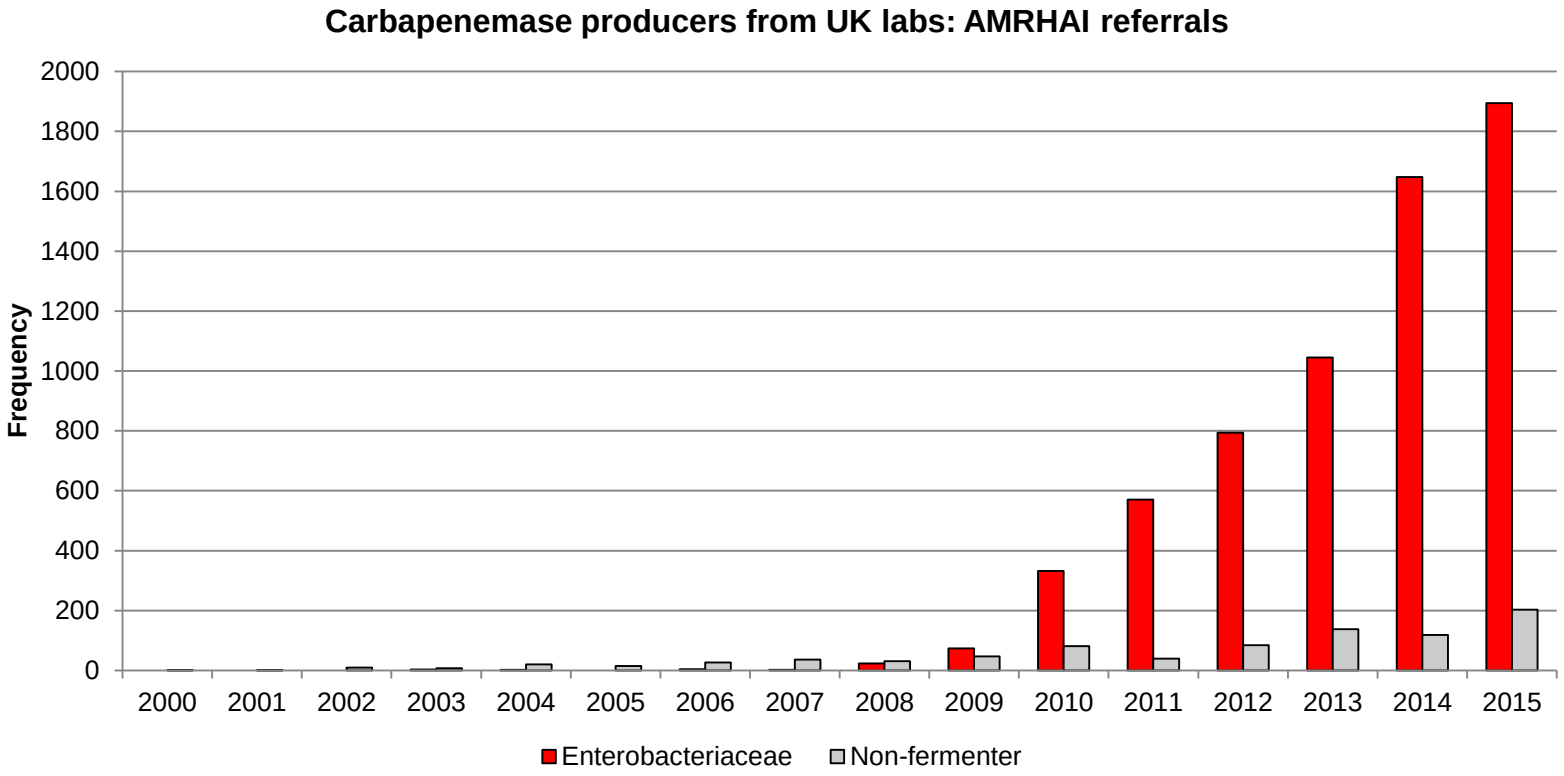
Most ‘CPOs’ in the UK are Enterobacteriaceae



AMRHAI, Unpublished data

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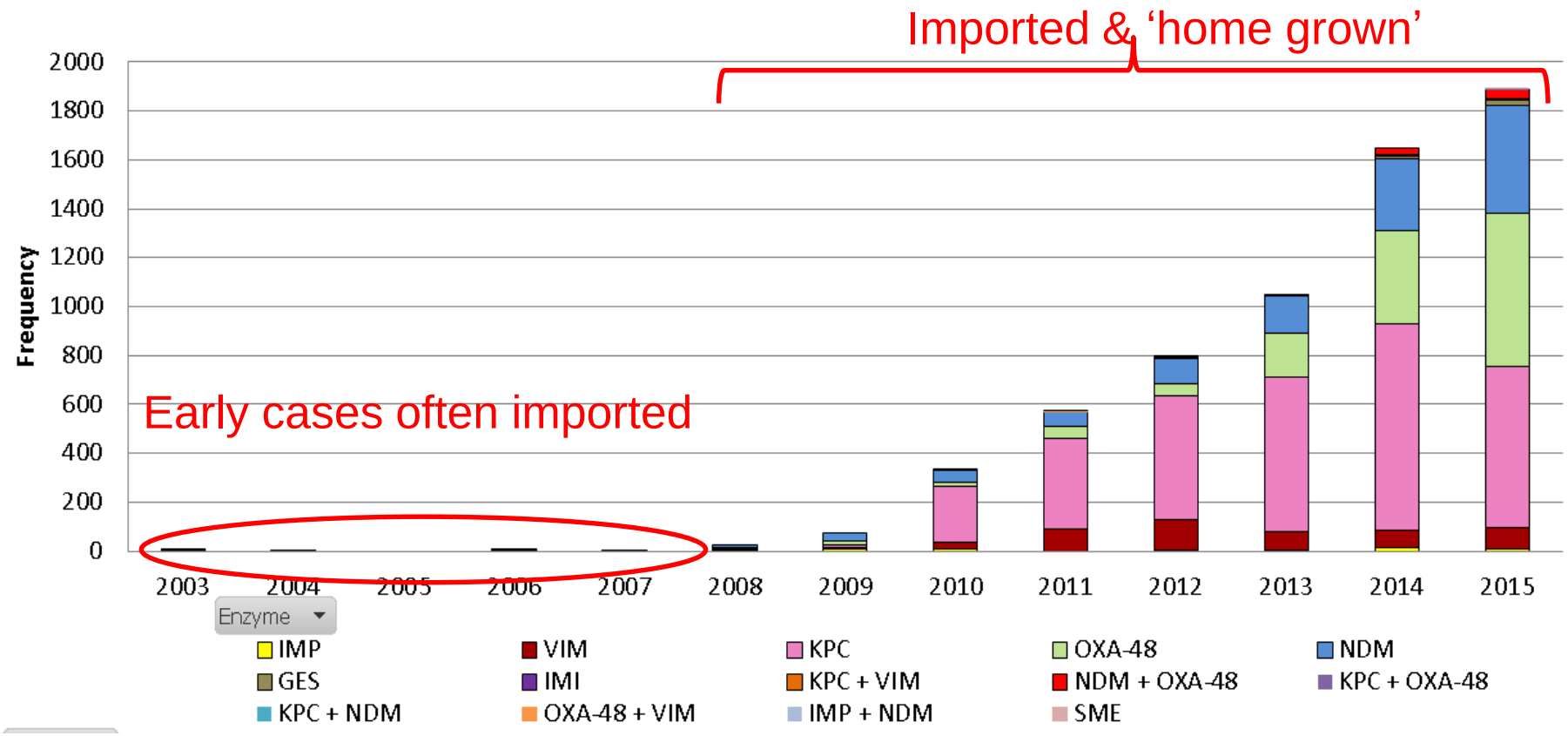
CPE in the UK, 2000-2015



Klebsiella spp. 69%; *E. coli* 18%, *Enterobacter* spp., 9%; others 4%

AMRHAI, Unpublished data

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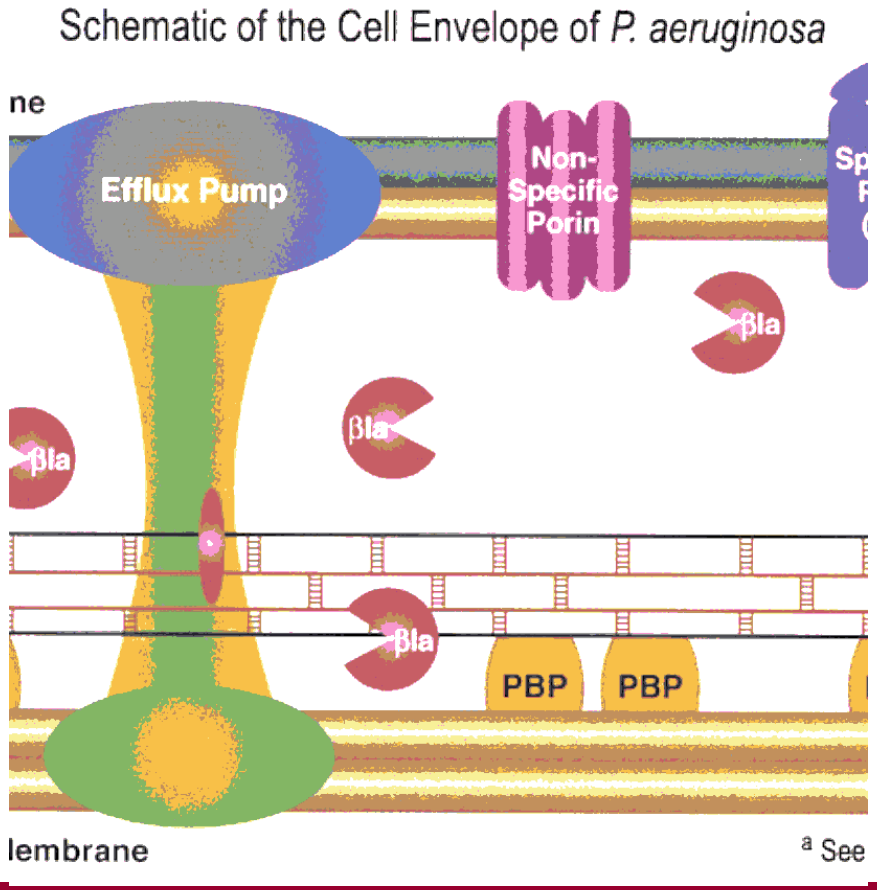
Impermeability, efflux & carbapenem^{R}



- Only *P. aeruginosa* readily develops carbapenem resistance
  - imipenem: loss of D2 porin expression
  - meropenem: up-regulated efflux (MexAB-OprM) and D2 loss

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MBL +ve *P. aeruginosa* lineages are widespread

Table 1. Typing data for the six main VNTR complexes identified ($n=251$)

VNTR complex	VNTR type[a]	No. of different VNTR profiles	MLST type(s) (no. of isolates tested)	No. of isolates[b]	No. of submitting laboratories	MBLs detected (no. of isolates)
A	11,3,4,3,2,2,x,4,x	6	ST111 (11)	75	25	VIM (70) IMP (5)
B	13,3,6,4,5,1,x,2,x	16	ST235 (18)	52	25	VIM (46) IMP (6)
C	12,3,4,5,3,1,x,2,x	11	ST233 (10)	26	16	VIM (26)
D	11,3,2,15,3,1,x,3,x	6	ST654 (10), ST964 (1)	19	11	VIM (17) IMP (1) NDM (1)
E	13,2,1,5,2,3,6,x,x	7	ST357 (9)	30	9	VIM (30)
F	12,4,6,5,3,1,10,x,x	3	ST773 (5)	13	11	VIM (13)
Others	diverse	26	not done	36	25	VIM (25) IMP (10) VIM and NDM (1)

[a]x represents loci where the repeat number varies between isolates within a complex.
[b]One isolate per patient was included; these numbers include 4 isolates (complex B), 14 isolates (complex E) and 1 isolate (complex F) where the MBL-positive organisms were no longer available in the archive for VNTR analysis, but which were previously found to share a PFGE profile, and are from the same hospital outbreak as other isolates in the respective complex. Isolates were also received from an additional 39 patients at London_17 with a PFGE profile corresponding to complex A. These are not included here as they had not been screened for MBL genes and were no longer available in our archives.

Wright et al. JAC 2014: Epub ahead of print

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Polymyxin resistance

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Most CPE are multi-resistant, 2014

Antibiotic	Proportion of susceptibility, % [a]					
	Metallo-enzyme producers (NDM, VIM, IMP) (n=c. 400)			Non-metallo-enzyme producers (KPC, OXA-48, GES, IMI) (n=c. 1250)		
	E. coli	*Klebsiella*	*Enterobacter / Citrobacter*	*E. coli*	*Klebsiella*	*Enterobacter / Citrobacter*
Imipenem (IPM)	3	2	3	48	7	40
IPM-EDTA [b]	100	88	94	69	17	42
Meropenem	6	5	8	73	12	51
Ertapenem	3	0	3	4	0	1
Ampicillin	0	0	0	0	0	0
Co-amoxiclav	1	0	0	1	0	0
Piperacillin (PIP)	0	0	1	0	0	1
PIP-tazobactam	2	0	1	1	0	1
Cefotaxime	1	0	0	10	3	13
Ceftazidime	1	0	0	25	7	34
Aztreonam	13	13	23	15	7	34
Ciprofloxacin	17	6	20	61	30	68
Gentamicin	31	24	24	51	56	66
Tobramycin	22	7	8	51	47	59
Amikacin	49	33	62	92	82	96
Colistin	100	93	93	100	94	100
Tigecycline	99	52	73	98	59	80

a. Susceptibility defined using BSAC v. 13 (June 2014) breakpoints
b. Diagnostic test to distinguish metallo- from non-metallo- enzymes; not for therapeutic use

Active in vitro against <50% isolates
Active in vitro against 50-90% isolates
Active in vitro against >90% isolates

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The Italian experience …one we'd sooner not share

- 178 KPC-KP isolates
- **76 (43%) were resistant to colistin**
- (increased from 22% in 2010)
- **Col-R KPC-KP detected in all 21 participating laboratories**
- nationwide dissemination of Col-R KPC-KP not yet reported in most other settings of high KPC-KP endemicity

Monaco et al. Euro Surveill. 2014;19(42):pii=20939.

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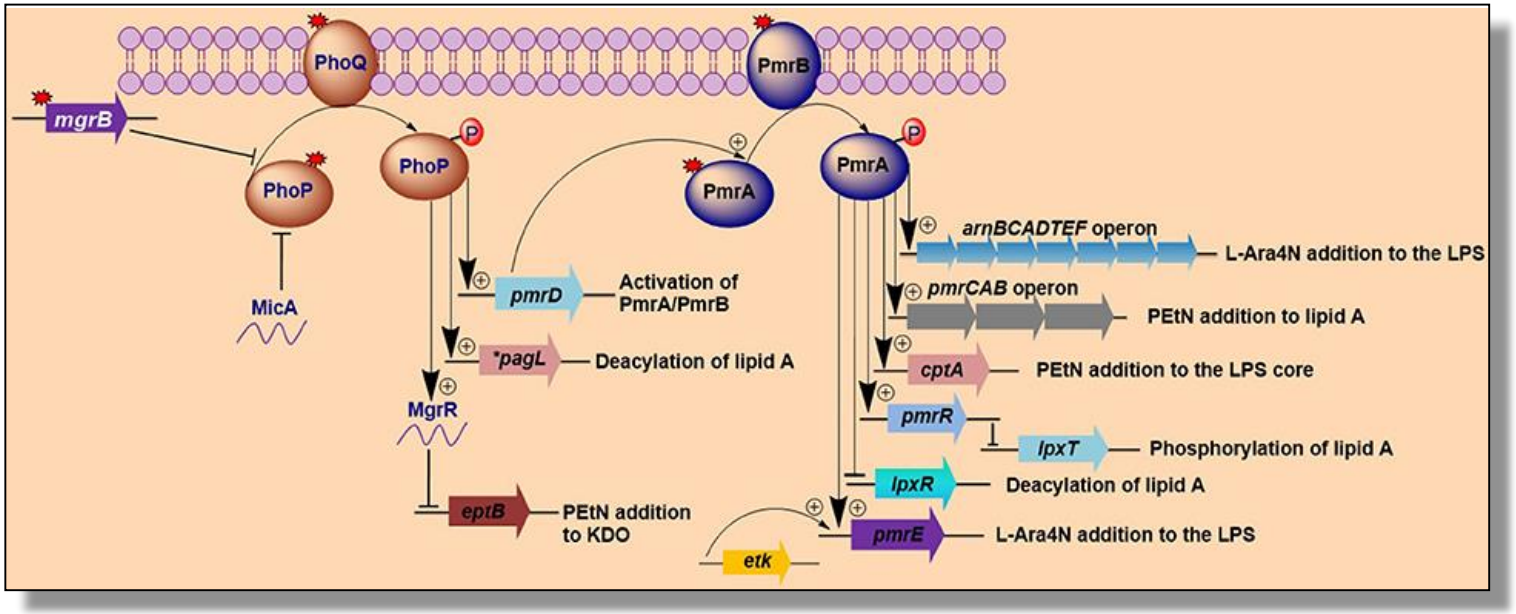
Chromosomal colistin resistance



- Diverse mutations affecting LPS structure
- Enterobacteriaceae and other non-fermenters
- Also underlies much intrinsic COL-R (*Serratia*, *Proteus*, *Morganella* etc.)

Olaitan *et al. Front. Microbiol.*, 26 November 2014

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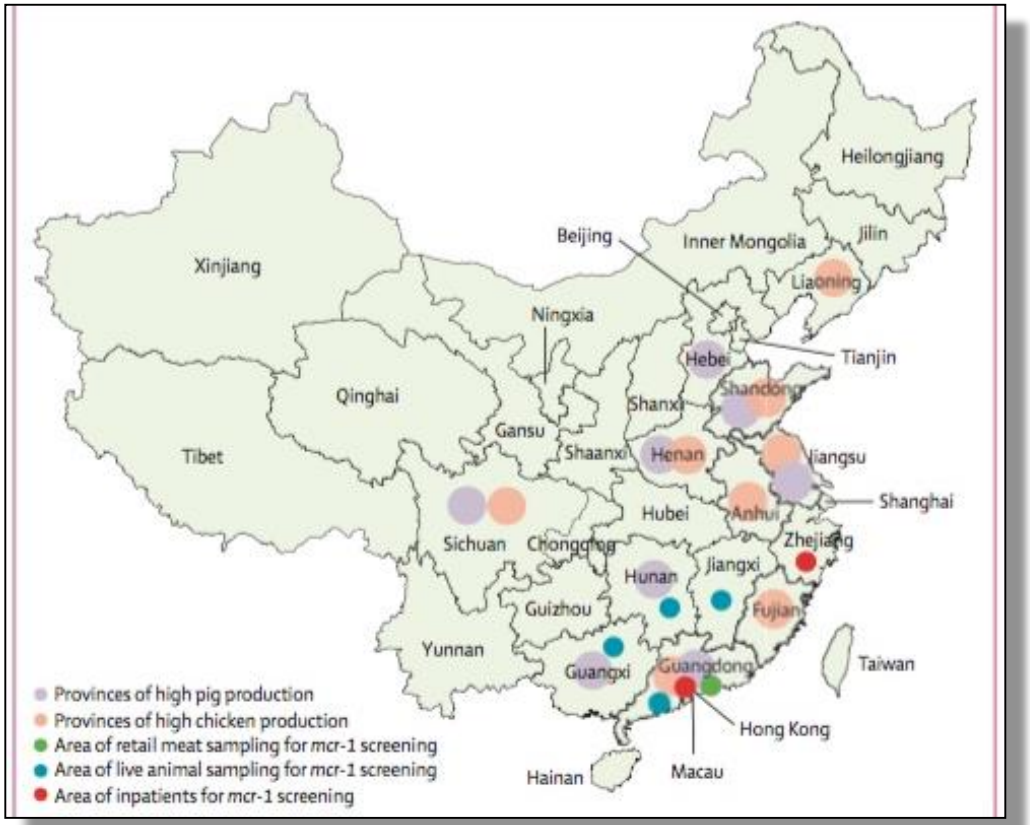
…and now plasmidic colistin resistance; *mcr-1*



	Year	Positive isolates (%)/number of isolates
Escherichia coli		
Pigs at slaughter	All	166 (20·6%)/804
Pigs at slaughter	2012	31 (14·4%)/216
Pigs at slaughter	2013	68 (25·4%)/268
Pigs at slaughter	2014	67 (20·9%)/320
Retail meat	All	78 (14·9%)/523
Chicken	2011	10 (4·9%)/206
Pork	2011	3 (6·3%)/48
Chicken	2013	4 (25·0%)/16
Pork	2013	11 (22·9%)/48
Chicken	2014	21 (28·0%)/75
Pork	2014	29 (22·3%)/130
Inpatient	2014	13 (1·4%)/902
Klebsiella pneumoniae		
Inpatient	2014	3 (0·7%)/420

Table 2: Prevalence of colistin resistance gene *mcr-1* by origin

Liu et al. *Lancet Infect Dis*. 2015 Nov 18. pii: S1473-3099(15)00424-7

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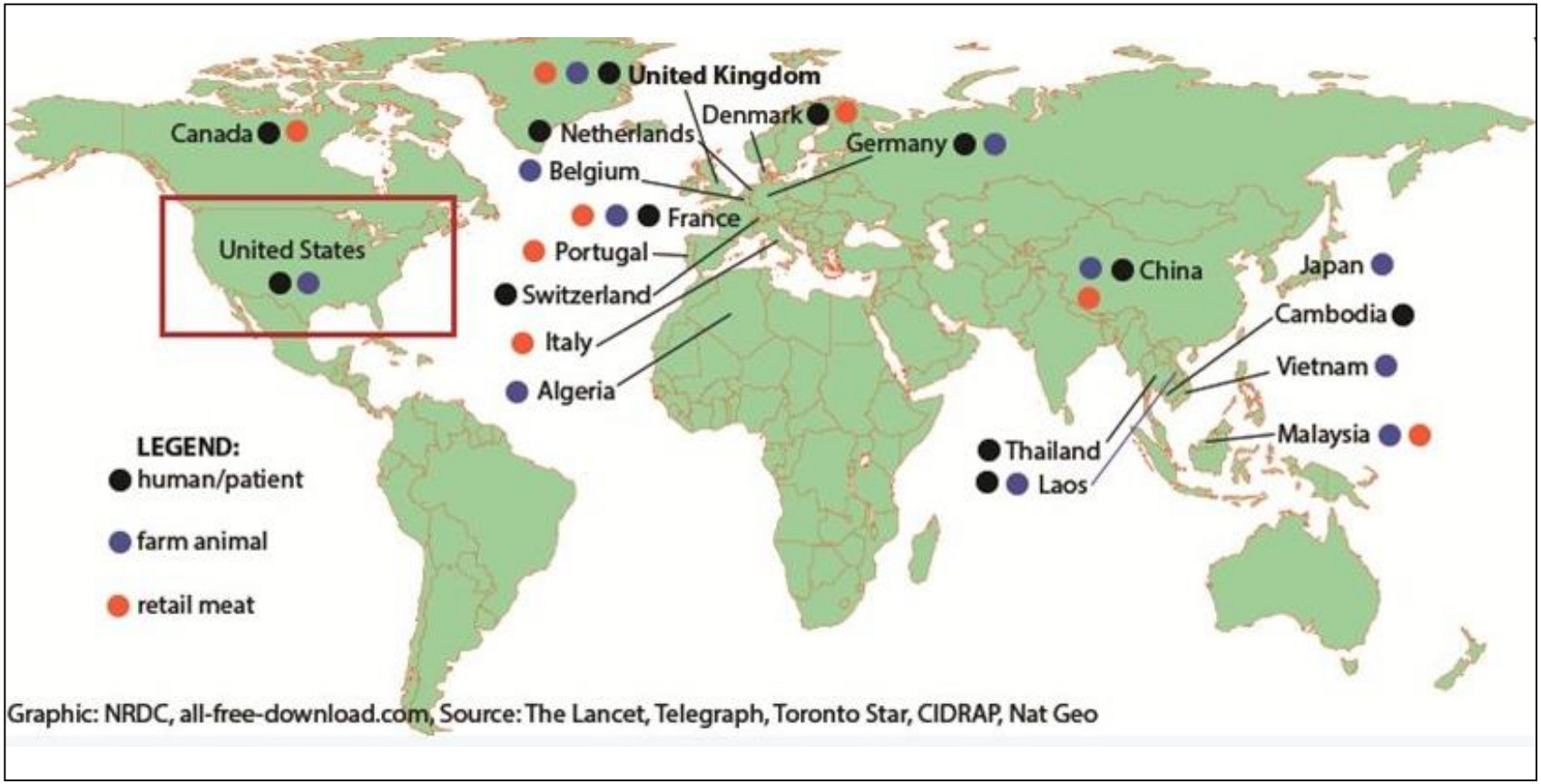
Global reports of *mcr-1*



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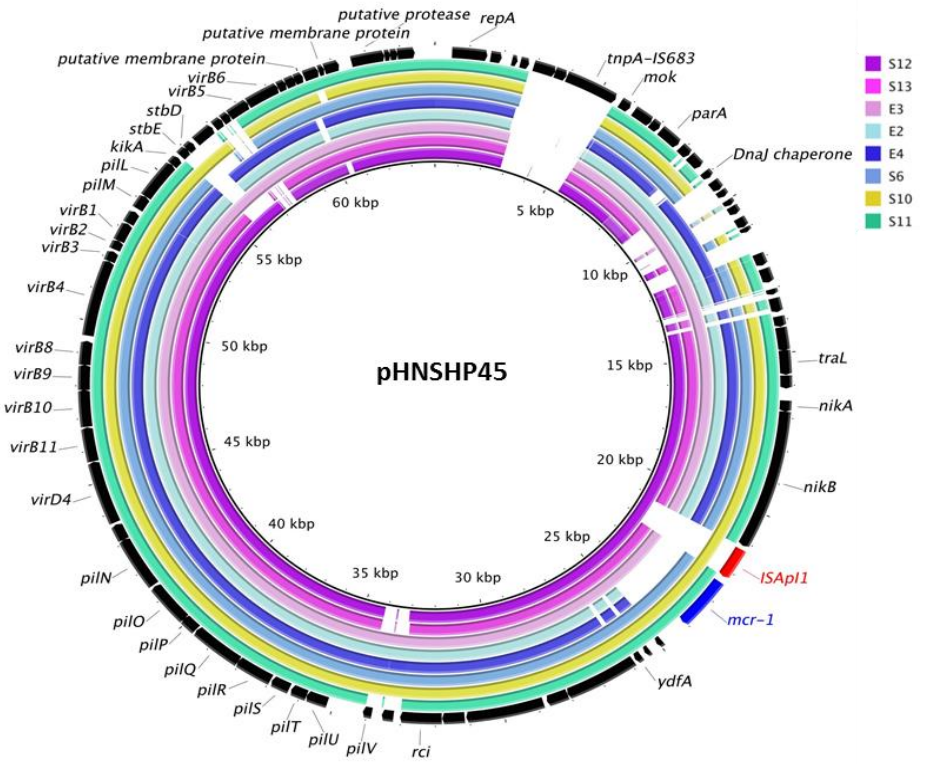
mcr-1-positive bacteria from humans in the UK

- 1st phase: 24K genomes mined
  - 3 +ve *E. coli*
  - 12 +ve diverse *Salmonella*
- 2nd phase: c. 450 COL^R isolates screened (2014-2015)
  - Enterobacteriaceae + non-fermenters with acquired COL^R
  - 0 positives !!
- **At present *mcr-1* is rare in the UK, even among COL-R isolates sent to the national reference laboratory.**



Doumith et al. *JAC* 2016

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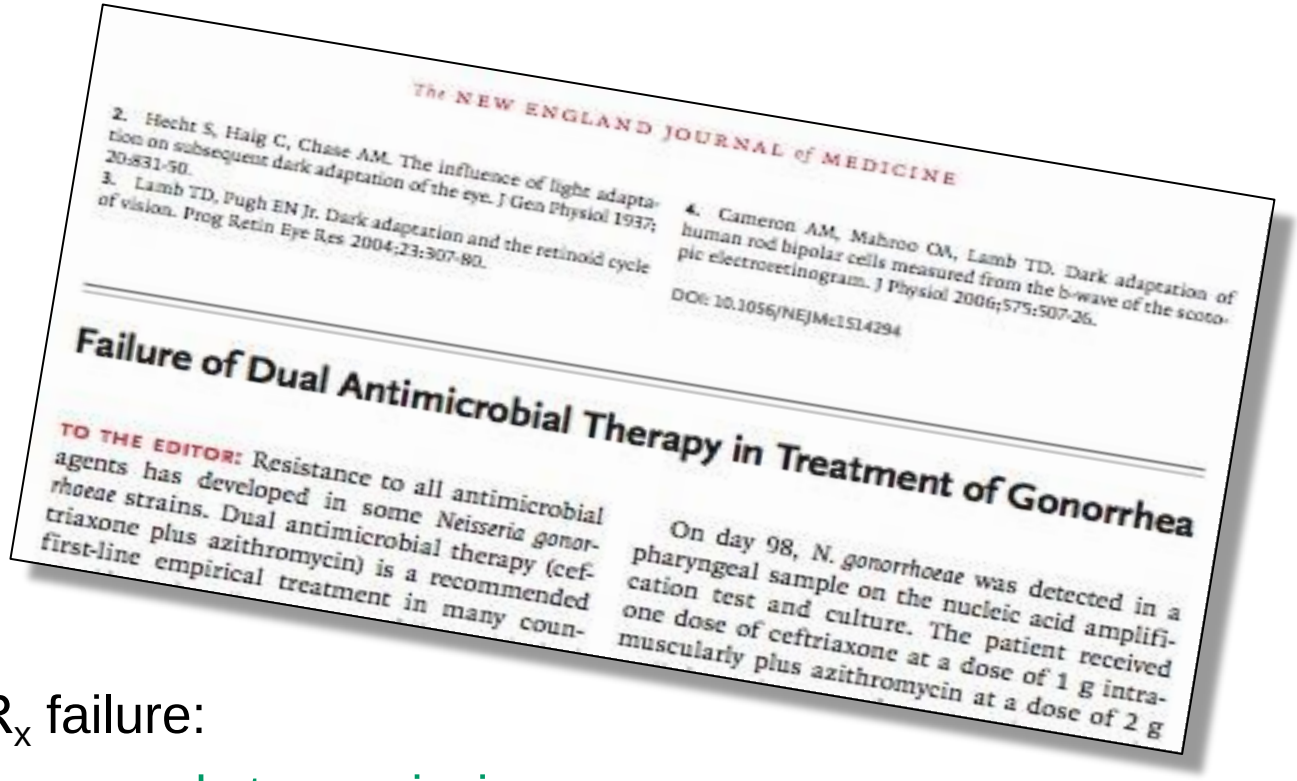
N. gonorrhoeae



The NEW ENGLAND JOURNAL of MEDICINE

2. Hecht S, Haig C, Chase AM. The influence of light adaptation on subsequent dark adaptation of the eye. J Gen Physiol 1937; 20:831-50.
3. Lamb TD, Pugh EN Jr. Dark adaptation and the retinoid cycle of vision. Prog Retin Eye Res 2004;23:307-80.
4. Cameron AM, Mahroo OA, Lamb TD. Dark adaptation of human rod bipolar cells measured from the b-wave of the scotopic electroretinogram. J Physiol 2006;575:507-26.

DOI: 10.1056/NEJMc1514294

Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea

TO THE EDITOR: Resistance to all antimicrobial agents has developed in some *Neisseria gonorrhoeae* strains. Dual antimicrobial therapy (ceftriaxone plus azithromycin) is a recommended first-line empirical treatment in many coun-

On day 98, *N. gonorrhoeae* was detected in a pharyngeal sample on the nucleic acid amplification test and culture. The patient received one dose of ceftriaxone at a dose of 1 g intramuscularly plus azithromycin at a dose of 2 g

- World's first dual R_x failure:
  - Single case, no onwards transmission
  - MICs, CTR 0.25 mg/L; AZI 1 mg/L (both R by EUCAST)

- Outbreak of HL-AZI-R gonorrhoea
  - MICs, >256 mg/L (not a formal criterion)

Fifer et al. NEJM 2016; 374: 2504-6

Public Health England

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

WGS-based genotypic antibiograms

- EUCAST Subcommittee on the role of whole genome sequencing (WGS) in antimicrobial susceptibility testing of bacteria
  - Chair: Neil Woodford, London UK; report to be published in early 2017

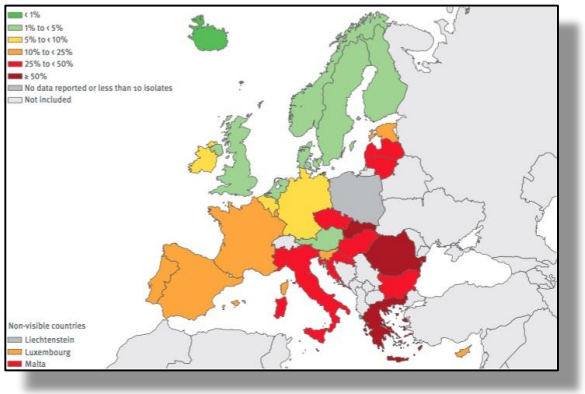
- could ‘soon’ replace much AST for surveillance purposes
  - low impact of the low error rate
- could ‘soon’ reduce need for AST in *reference* laboratories unless
  - to guide treatment
  - for agents with poorest genotypic/phenotypic concordance
  - comparative in-vitro activity of new agents

Public Health England

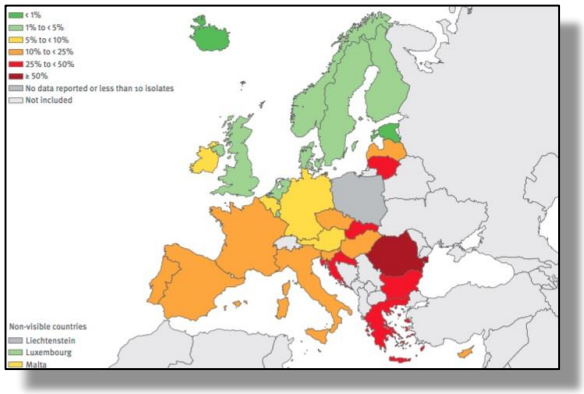
A future of pan-drug-resistant (PDR) Gram-negatives ?

E. coli

K. pneumoniae



P. aeruginosa



- MDR increasingly seen in BSI across Europe
- PDR also a reality, but low numbers in most countries
- MBL + ESBL (all beta-lactams) + 16S RMTase (aminoglycosides)
- + resistance to colistin + upregulated efflux

  EARS-Net, 2014