Clinical Bacteriology Update

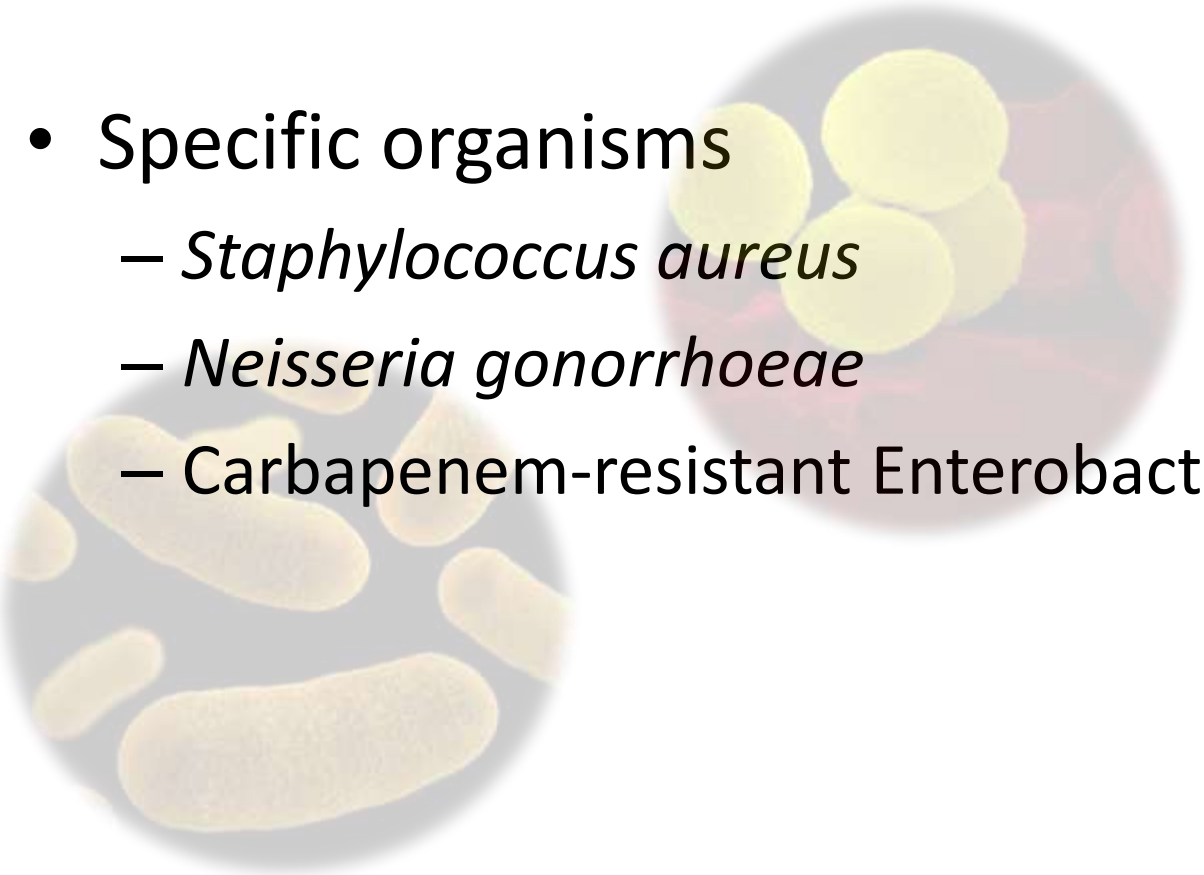
James Hatcher

Imperial College Healthcare NHS
NHS Trust

OUTLINE

- Antibiotic resistance and case

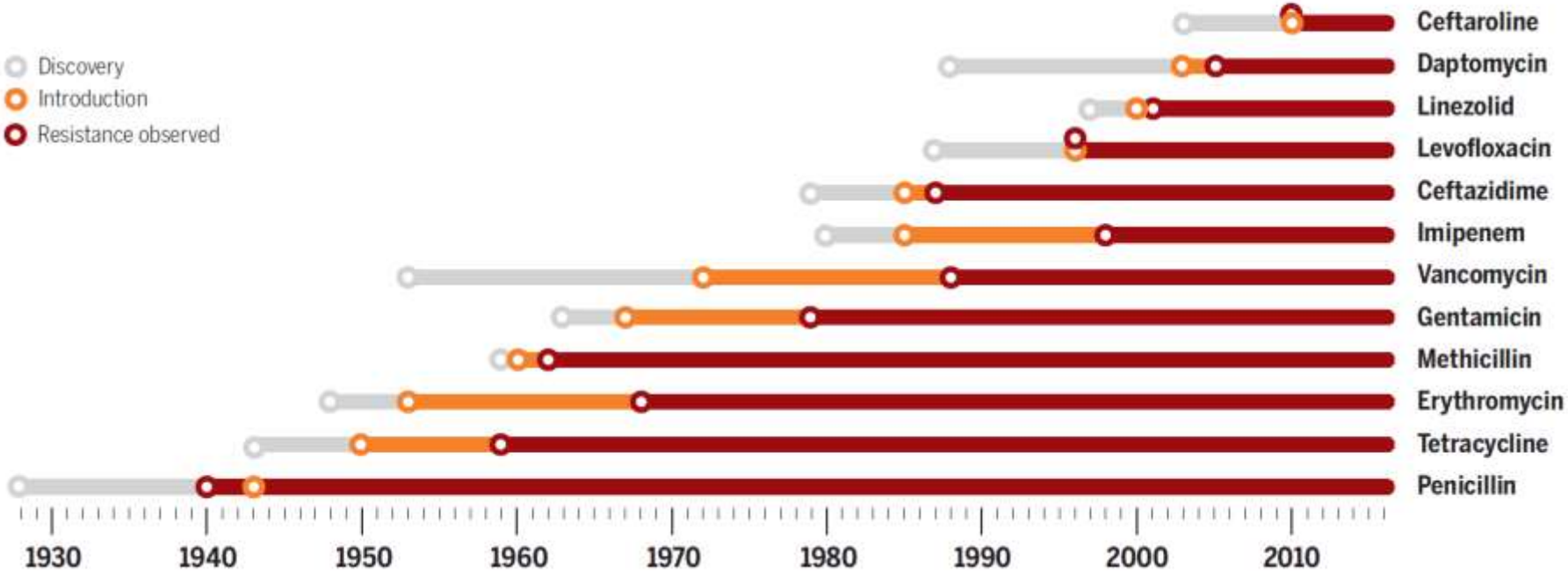
- Specific organisms
  - *Staphylococcus aureus*
  - *Neisseria gonorrhoeae*
  - Carbapenem-resistant Enterobacteriaceae



Images from CDC Public Health Image Library

The rise of resistance

Bacteria have developed resistance to every antibiotic discovered so far, sometimes even before the drug reached the market. The appearance of resistance does not mean that a drug has become completely useless.

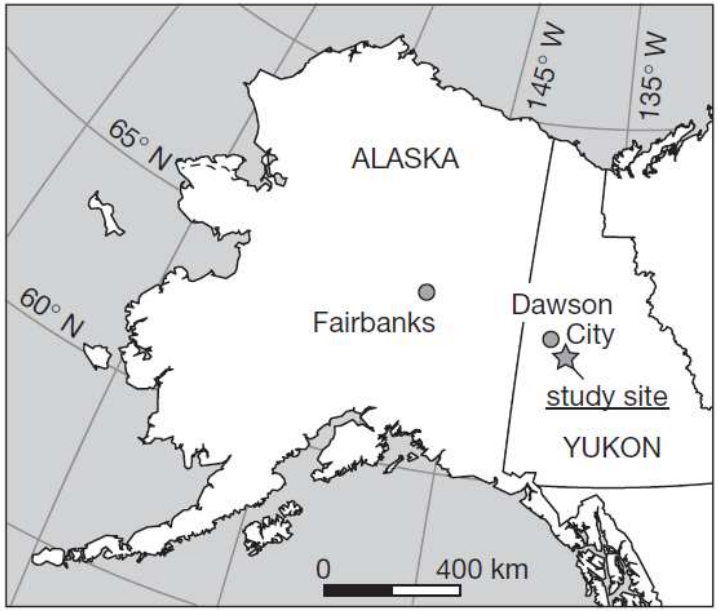


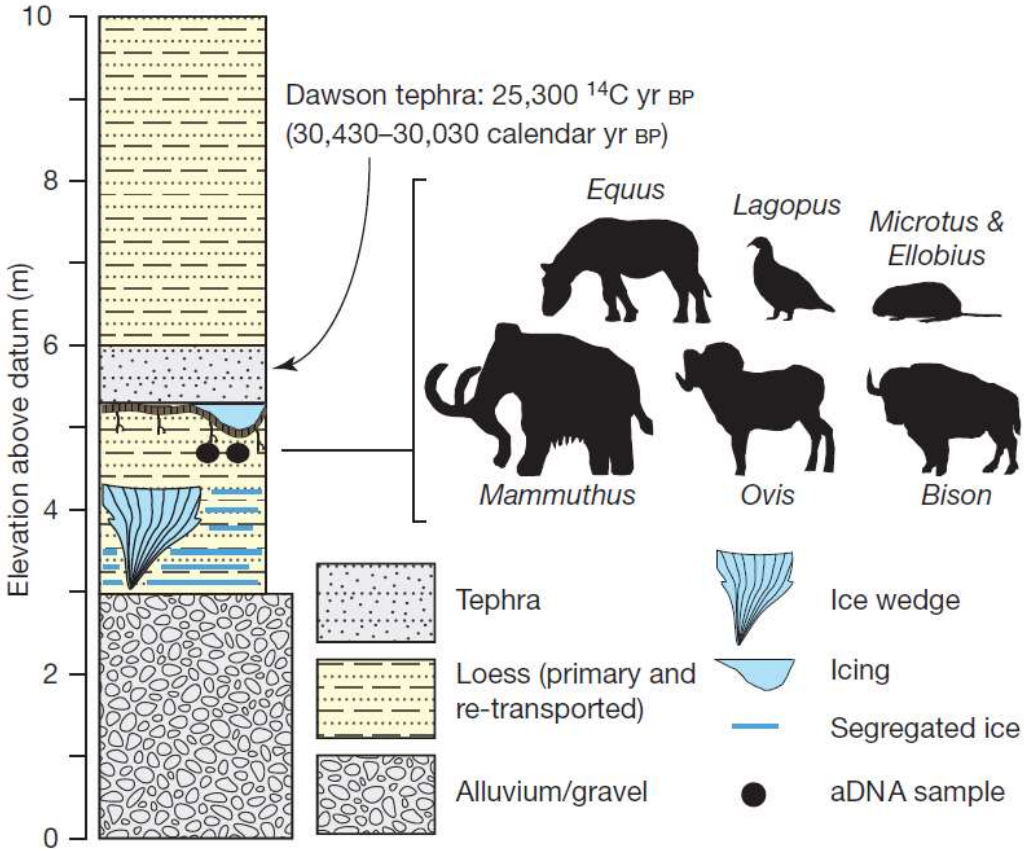
SCIENCE
13 MAY 2016 • VOL 352 ISSUE 6287

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

22 SEPTEMBER 2011 | VOL 477 | NATURE | 457





PCR amplification:

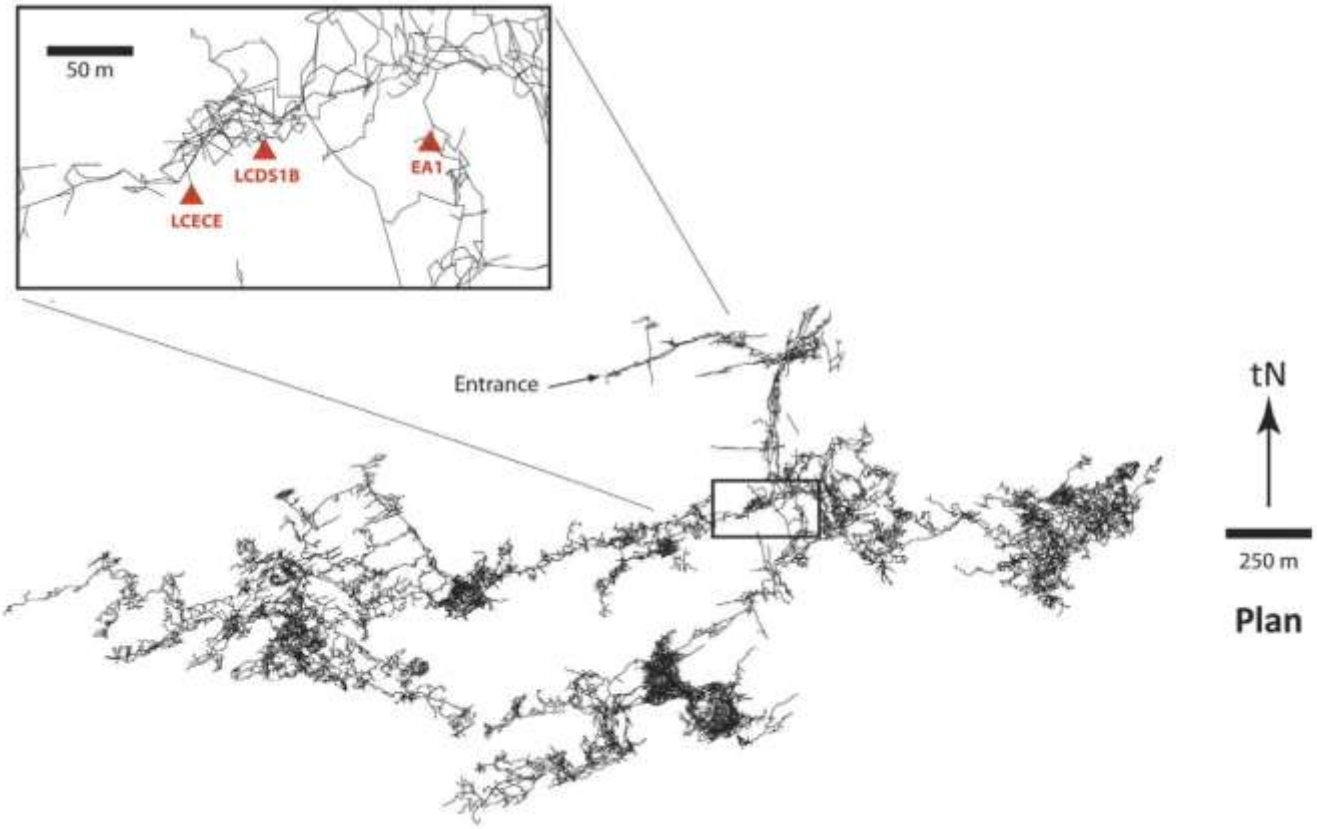
*van*X = glycopeptide resistance

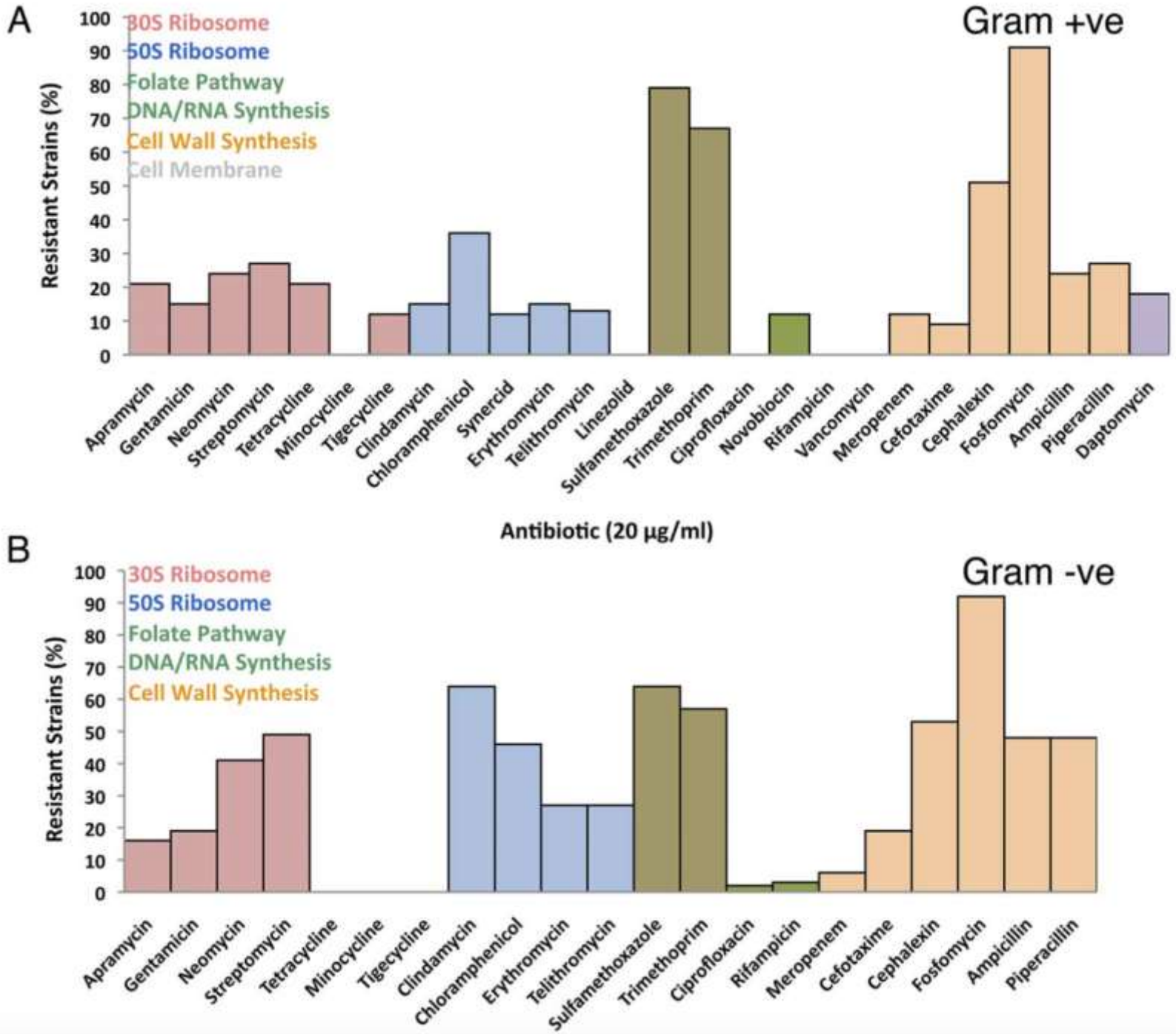
*tet*M = tetracycline resistance

bla = beta-lactam resistance

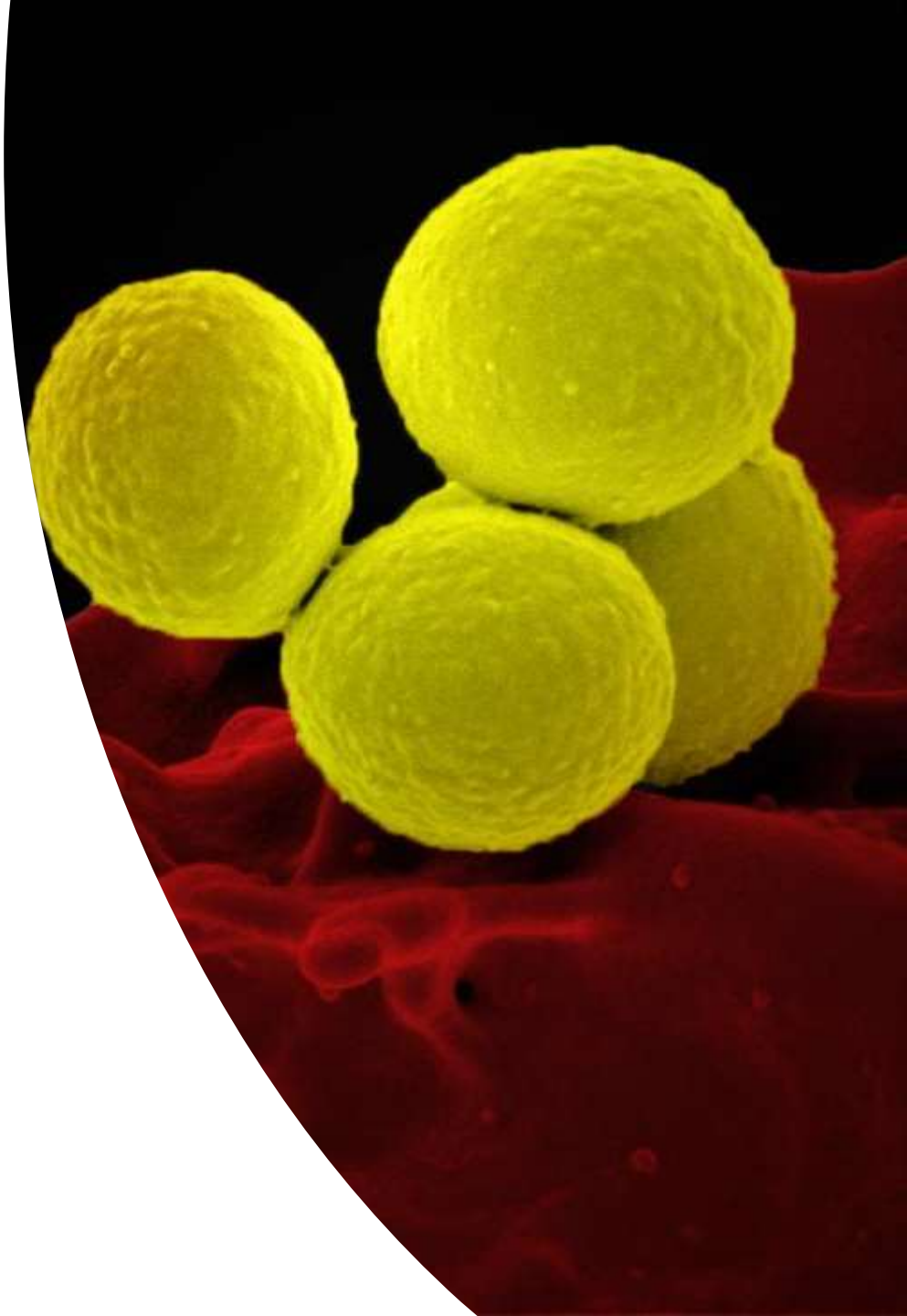
Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

Kirandeep Bhullar[1], Nicholas Waglechner[1], Andrew Pawlowski[1], Kalinka Koteva[1], Eric D. Banks[2], Michael D. Johnston[2], Hazel A. Barton[2], Gerard D. Wright[1]*




A
Gram +ve
30S Ribosome
50S Ribosome
Folate Pathway
DNA/RNA Synthesis
Cell Wall Synthesis
Cell Membrane
Resistant Strains (%)
100
90
80
70
60
50
40
30
20
10
0
Apramycin
Gentamicin
Neomycin
Streptomycin
Tetracycline
Minocycline
Tigecycline
Clindamycin
Chloramphenicol
Synercid
Erythromycin
Telithromycin
Linezolid
Sulfamethoxazole
Trimethoprim
Ciprofloxacin
Novobiocin
Rifampicin
Vancomycin
Meropenem
Cefotaxime
Cephalexin
Fosfomycin
Ampicillin
Piperacillin
Daptomycin
Antibiotic (20 µg/ml)
B
Gram -ve
30S Ribosome
50S Ribosome
Folate Pathway
DNA/RNA Synthesis
Cell Wall Synthesis
Resistant Strains (%)
100
90
80
70
60
50
40
30
20
10
0
Apramycin
Gentamicin
Neomycin
Streptomycin
Tetracycline
Minocycline
Tigecycline
Clindamycin
Chloramphenicol
Erythromycin
Telithromycin
Sulfamethoxazole
Trimethoprim
Ciprofloxacin
Rifampicin
Meropenem
Cefotaxime
Cephalexin
Fosfomycin
Ampicillin
Piperacillin

Staphylococcus aureus



69 year old male

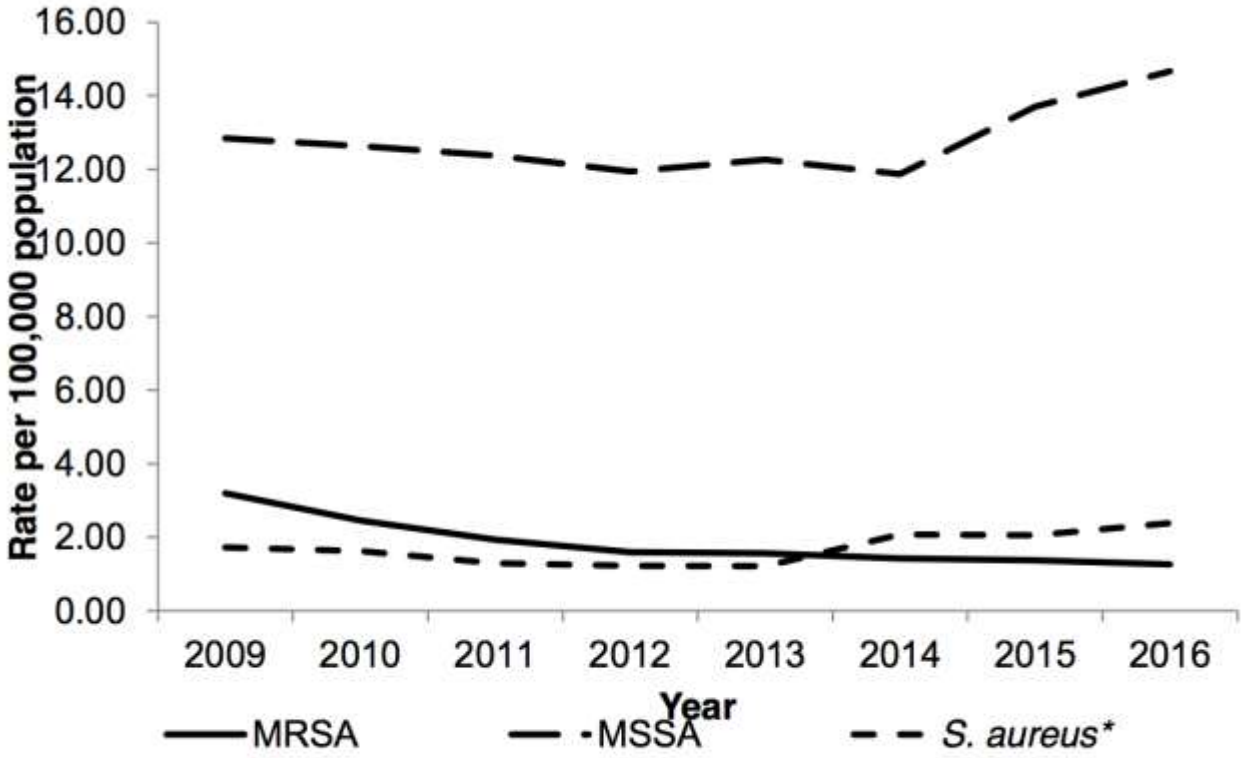
- Admitted with fever and hypotension
- Recent minor abrasion
- No PMhx
- Penicillin allergic – unknown reaction
- ECHO – aortic valve vegetation

- Blood culture – meticillin-sensitive *Staphylococcus aureus*
- What Abx treatment would you recommend?

Public Health England

Laboratory surveillance of *Staphylococcus aureus* bacteraemia in England, Wales and Northern Ireland: 2016

Health Protection Report
Volume 11 Number 29
18 August 2017



S. aureus where susceptibility to methicillin was not reported

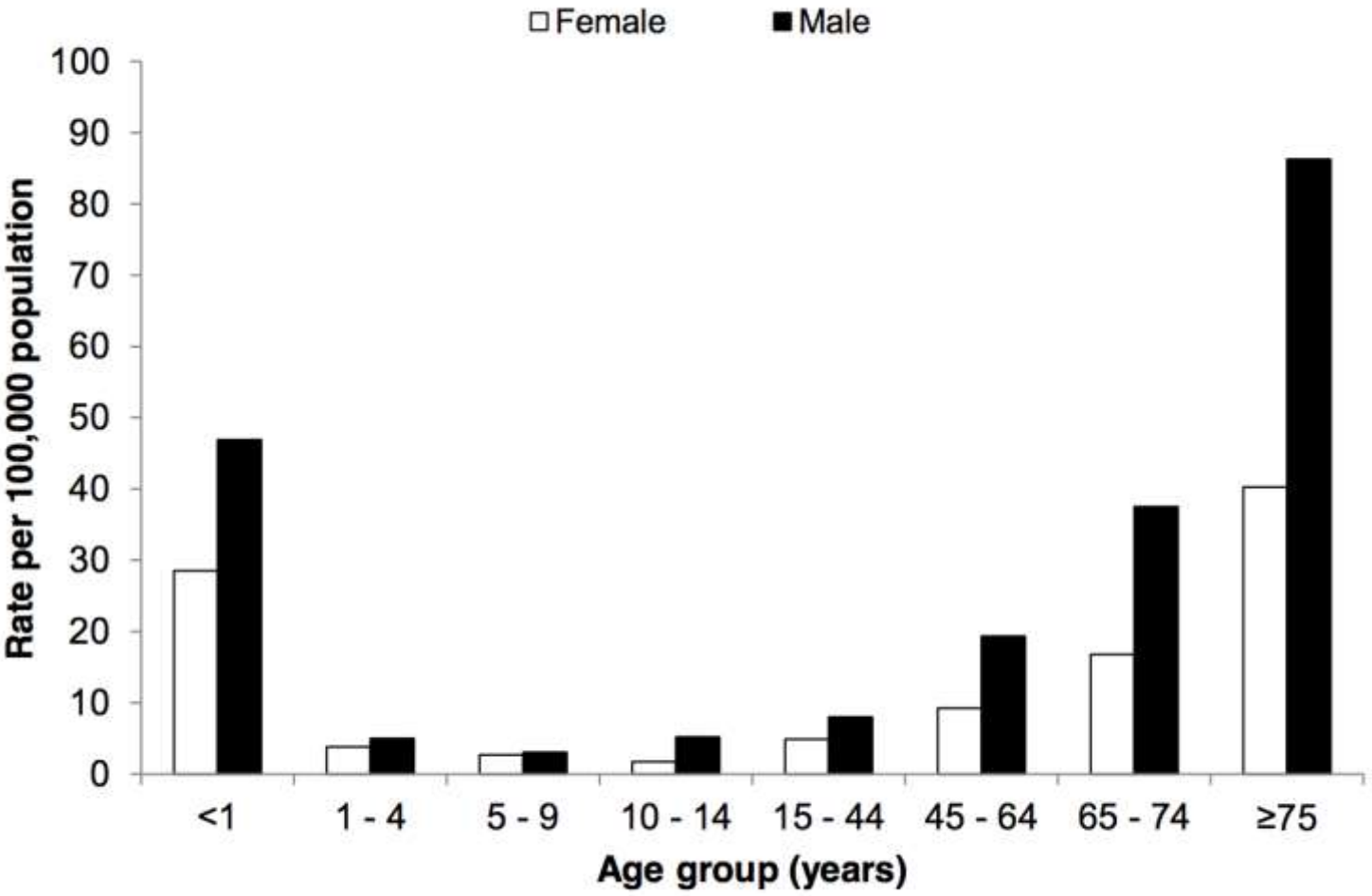
61% decrease MRSA

14% increase MSSA

37% increase in Staph not reported with sens

*similar across both mandatory and voluntary reporting systems

Age and sex difference - MSSA bacteraemia



Example 1

Specimen : 3514 *Staphylococcus aureus* Your report : *Staphylococcus aureus* Referral : not referred

Reference Lab	ISO MIC mg/L 1	2	Result EUCAST	CLSI	Breakpoints EUCAST	CLSI
Cefoxitin	4	4	S	S	S≤4 R>4	S≤4 R≥8
Clindamycin	0.12	0.12	S	S	S≤0.25 R>0.5	S≤0.5 R≥4
Daptomycin	0.25	0.25	S	S	S≤1 R>1	S≤1
Erythromycin	0.5	0.25	S	S	S≤1 R>2	S≤0.5 R≥8
Fusidic acid	>64	>64	R	-	S≤1 R>1	
Gentamicin	0.5	0.5	S	S	S≤1 R>1	S≤4 R≥16
Linezolid	2	4	S	S	S≤4 R>4	S≤4 R≥8
Oxacillin	2	4	S/R	S/R	S≤2 R>2	S≤2 R≥4
Rifampicin	0.015	0.015	S	S	S≤0.06 R>0.5	S≤1 R≥4
Teicoplanin	0.5	0.5	S	S	S≤2 R>2	S≤8 R≥32
Tetracycline	0.5	1	S	S	S≤1 R>2	S≤4 R≥16
Vancomycin	1	1	S	S	S≤2 R>2	S≤2 R≥16

- This specimen contained a meticillin-sensitive *Staphylococcus aureus*.
- WGS - indicated the presence of the blaZ gene encoding the typical *S. aureus* penicillinase.
- The isolate did not contain mecA or mecC. The isolate was susceptible to meticillin (mecA negative), although phenotypic tests gave borderline results.

- 80.1% of users reported a correct result for cefoxitin.
  - EUCAST - 93.9% using disk diffusion methods reported a susceptible result, whereas only 64.0% using automated systems reported a susceptible result.
  - CLSI - 69.8% overall, and only 57.1% of those using automated systems reported a correct result

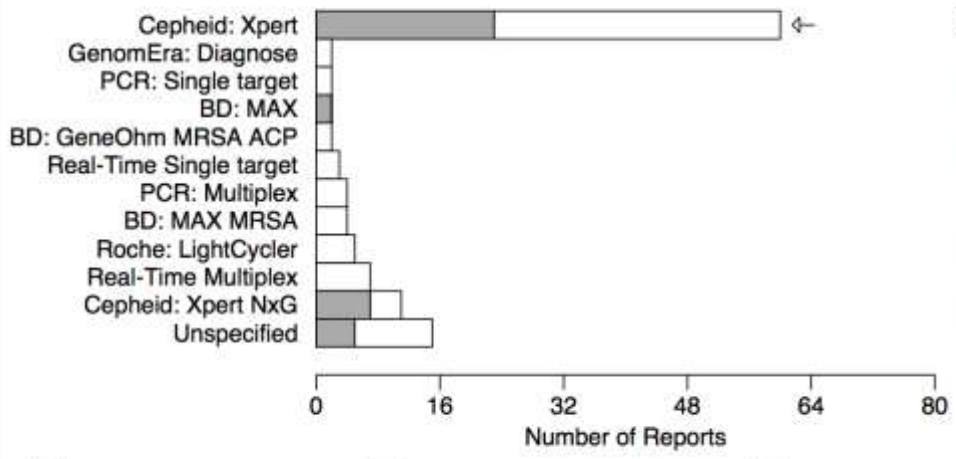
- 411 participants reporting oxacillin
  - 36.2% susceptible
  - 63.3% resistant

- This reflects the borderline findings on reference testing, and the poor performance of oxacillin testing for identification of meticillin susceptibility in this isolate.

Example 2

Specimen : 3796

Molecular result: MRSA detected



	UK	(%)	All	(%)
Cepheid: Xpert	23	(57.5)	60	(50.8)
GenomEra: Diagnose	0	(0.0)	2	(1.7)
PCR: Single target	1	(2.5)	2	(1.7)
BD: MAX	0	(0.0)	2	(1.7)
BD: GeneOhm MRSA ACP	1	(2.5)	2	(1.7)
Real-Time Single target	1	(2.5)	3	(2.5)
PCR: Multiplex	0	(0.0)	4	(3.4)
BD: MAX MRSA	3	(7.5)	4	(3.4)
Roche: LightCycler	1	(2.5)	5	(4.2)
Real-Time Multiplex	0	(0.0)	7	(5.9)
Cepheid: Xpert NxG	1	(2.5)	11	(9.3)
Unspecified	9	(22.5)	15	(12.7)

MRSA detected (molecular) MRSA not detected (molecular) Invalid: request repeat (molecular)

Your Score : **Not scored**

Overall Results	UK	All	Score
Detected	27	82	NS
Not detected	14	37	NS
Invalid	0	0	NS
Total	41	119	
% Correct	65.9	68.9	

Example 3

- Specimen 3679 contained *Staphylococcus aureus* with methicillin resistance mediated by mecC
- There was a high concordance of participants reporting the correct result with the antimicrobial agents tested
- However a lower concordance of 77.3% was shown for reports of susceptibility to oxacillin

mecC MRSA

- Usually MRSA conferred by *mecA* gene
  - Mobile genetic element
  - Staphylococcal cassette chromosome (SCC*mec*) carrying *mecA* gene
  - Encodes altered PBP – PBP2a/PBP2'
- 2007 an isolate isolated from bulk tank milk sample phenotypically MRSA
  - Significant because first detection MRSA in dairy herd so further work..

Paterson GK, Harrison EM, Holmes MA. The emergence of mecC methicillin-resistant Staphylococcus aureus. Trends Microbiol. 2014 Jan;22(1):42-7

- *mecA* negative
- Genome sequencing at Wellcome Trust Sanger
  - Novel *mecA* – termed $mecA_{LGA251}$
  - 69% identical to conventional *mecA* at DNA level
  - Encoded PBP2a was 63% identical at amino acid level
- Retrospective search of isolates in UK and Denmark found 65 positives
  - Earliest from Danish human blood in 1975

- In 2009 designated type XI SCC*mec*
- Renamed *mecC* in 2012
  - *mecB* already taken by *Macrococcus caseolyticus*
- Cefoxitin more reliable than oxacillin in disc diffusion, broth microdilution and agar dilution assays.
- Beware of the oxacillin sensitive/cefoxitin resistant phenotypes

Clinical management of *Staphylococcus aureus* bacteraemia

Guy E Thwaites, Jonathan D Edgeworth, Effrossyni Gkrania-Klotsas, Andrew Kirby, Robert Tilley, M Estée Török, Sarah Walker, Heiman F L Wertheim, Peter Wilson, Martin J Llewelyn, for the UK Clinical Infection Research Group*

Lancet Infect Dis 2011; 11: 208–22

Panel: Key clinical questions concerning the management of SAB

1 How should SAB be defined?
2 Is identification and removal of the focus of infection important?
3 Should all patients with SAB have echocardiography?
4 Are glycopeptides equivalent to β-lactams for the treatment of SAB?
5 Are cephalosporins as effective as penicillins for the treatment of SAB?
6 Is teicoplanin as effective as vancomycin?
7 What is the optimum duration of therapy for SAB?
8 Is oral therapy as effective as intravenous therapy?
9 Is combination antimicrobial therapy better than monotherapy?
10 What is the role of the newer antimicrobials in the treatment of SAB?

6 years on….

YES
YES
NO
DEPENDS
?
Min 2 weeks
YES
?
Not gent, levo, rif
?
Dapto? Dalba? Ceftaroline?

Comparative Effectiveness of Cefazolin Versus Nafcillin or Oxacillin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Infections Complicated by Bacteremia: A Nationwide Cohort Study

Jennifer S. McDanel,[1,2,3] Mary-Claire Roghmann,[4,5] Eli N. Perencevich,[1,2,3] Michael E. Ohl,[1,2] Michihiko Goto,[1,2] Daniel J. Livorsi,[1,2] Makoto Jones,[6,7] Justin P. Albertson,[2] Rajeshwari Nair,[1,2] Amy M. J. O'Shea,[1,2] and Marin L. Schweizer[1,2,3]

Clinical Infectious Diseases® 2017;65(1):100–6

'cefazolin had a lower risk of mortality and similar odds of recurrent infections compared with nafcillin or oxacillin ….. Physicians might consider definitive therapy with cefazolin for these infections'

Narrative review

Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia: a narrative review

P. Loubet [1,2], C. Burdet [1,3], W. Vindrios [2], N. Grall [1,4], M. Wolff [1,5], Y. Yazdanpanah [1,2], A. Andremont [1,4], X. Duval [1,6], F.-X. Lescure [1,2,*]

Clinical Microbiology and Infection xxx (2017) 1–8

'Based on currently available studies, there are no data that enable a choice to be made of one antibiotic over the other except in patients with allergy or renal impairment.'

September 5, 2017

Association of Evidence-Based Care Processes With Mortality in *Staphylococcus aureus* Bacteremia at Veterans Health Administration Hospitals, 2003-2014

Michihiko Goto, MD, MSCI[1,2]; Marin L. Schweizer, PhD[1,2]; Mary S. Vaughan-Sarrazin, PhD[1,2]; et al

- Retrospective observational cohort study
- 36 868 patients – 52% MRSA
- 30 day mort (23.5% in 2003 to 18.2% in 2014)

- Care processes associated with lower mortality
  - Appropriate antibiotics – OR 0.74 (95% CI, 0.68-0.79)
  - ECHO – OR 0.73 (95% CI, 0.68-0.78)
  - ID Consultation – OR 0.61 (95% CI, 0.56-0.65)

- Conclusion: Increasing application of evidenced based care may improve survival from SAB.

PLOS ONE

RESEARCH ARTICLE

The Impact of Reporting a Prior Penicillin Allergy on the Treatment of Methicillin-Sensitive *Staphylococcus aureus* Bacteremia

Kimberly G. Blumenthal[1,2,3,4]*, Erica S. Shenoy[2,3,5,6], Mingshu Huang[2,7], James L. Kuhlen[8], Winston A. Ware[4], Robert A. Parker[2,3,7], Rochelle P. Walensky[2,3,5]

Table 3. Multivariable log-binomial regression model of optimal therapy trial among inpatients with MSSA bacteremia (n = 456).

	Relative Risk [95% CI]	P Value*
Factors Associated with *Decreased* Likelihood of Receipt of Optimal Therapy		
Penicillin Allergy	0.64 [0.49, 0.83]	0.001
End-Stage Renal Disease	0.75 [0.60, 0.94]	0.01
Factors Associated with *Increased* Likelihood of Receipt of Optimal Therapy		
Infectious Disease Consultation	1.34 [1.14 1.57]	<0.001
Endocarditis	1.11 [1.03 1.19]	0.004
Later year of hospitalization	1.04 [1.01, 1.07]	0.02

Point-of-Care β-Lactam Allergy Skin Testing by Antimicrobial Stewardship Programs: A Pragmatic Multicenter Prospective Evaluation

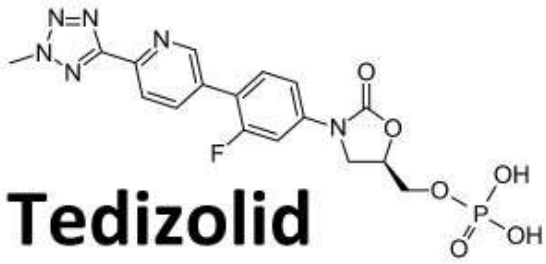
Jerome A. Leis,[1,2,3] Lesley Palmay,[4] Grace Ho,[5] Sumit Raybardhan,[6] Suzanne Gill,[5] Tiffany Kan,[6] Jackie Campbell,[4,7] Alex Kiss,[2] Janine B. McCready,[1,5] Pavani Das,[1,6] Brian Minnema,[1,6] Jeff E. Powis,[1,3,5] Sandra A. N. Walker,[4] Heather Ferguson,[7] Benny Wong,[6,8] and Elizabeth Weber[7,8]

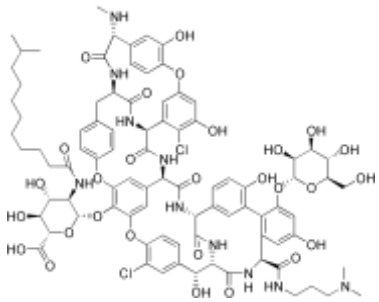
Clinical Infectious Diseases® 2017;XX(00):1–7

- Pragmatic multicenter prospective evaluation of BLAST
  - Pharmacists and physicians received training by allergist
- 827 patients over 15 months reported allergy
  - 50% received preferred beta-lactam based on history
  - 81% received preferred beta-lactam with BLAST
- 4.5 fold greater odds of receiving preferred beta-lactam therapy with BLAST

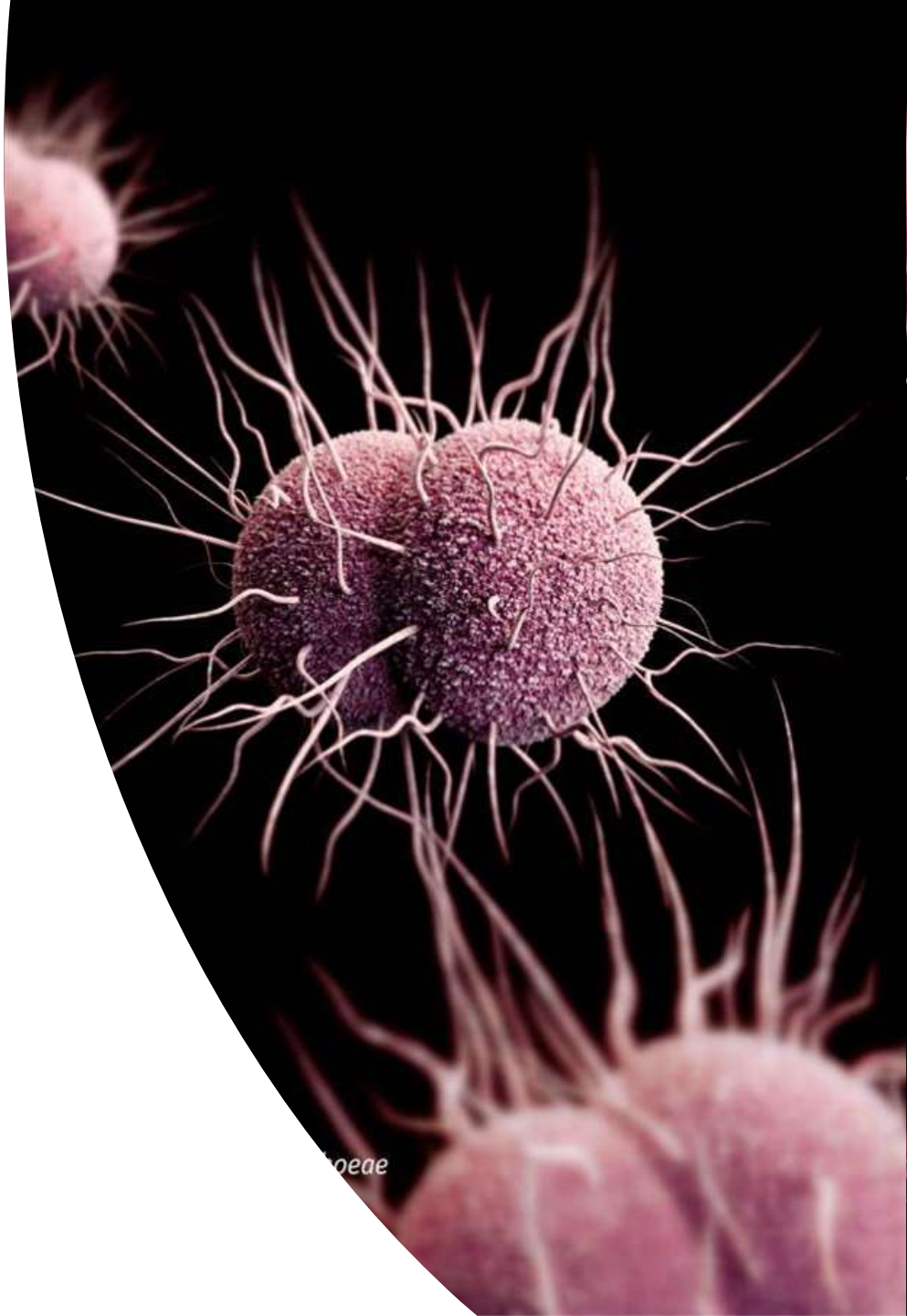
NOPAT

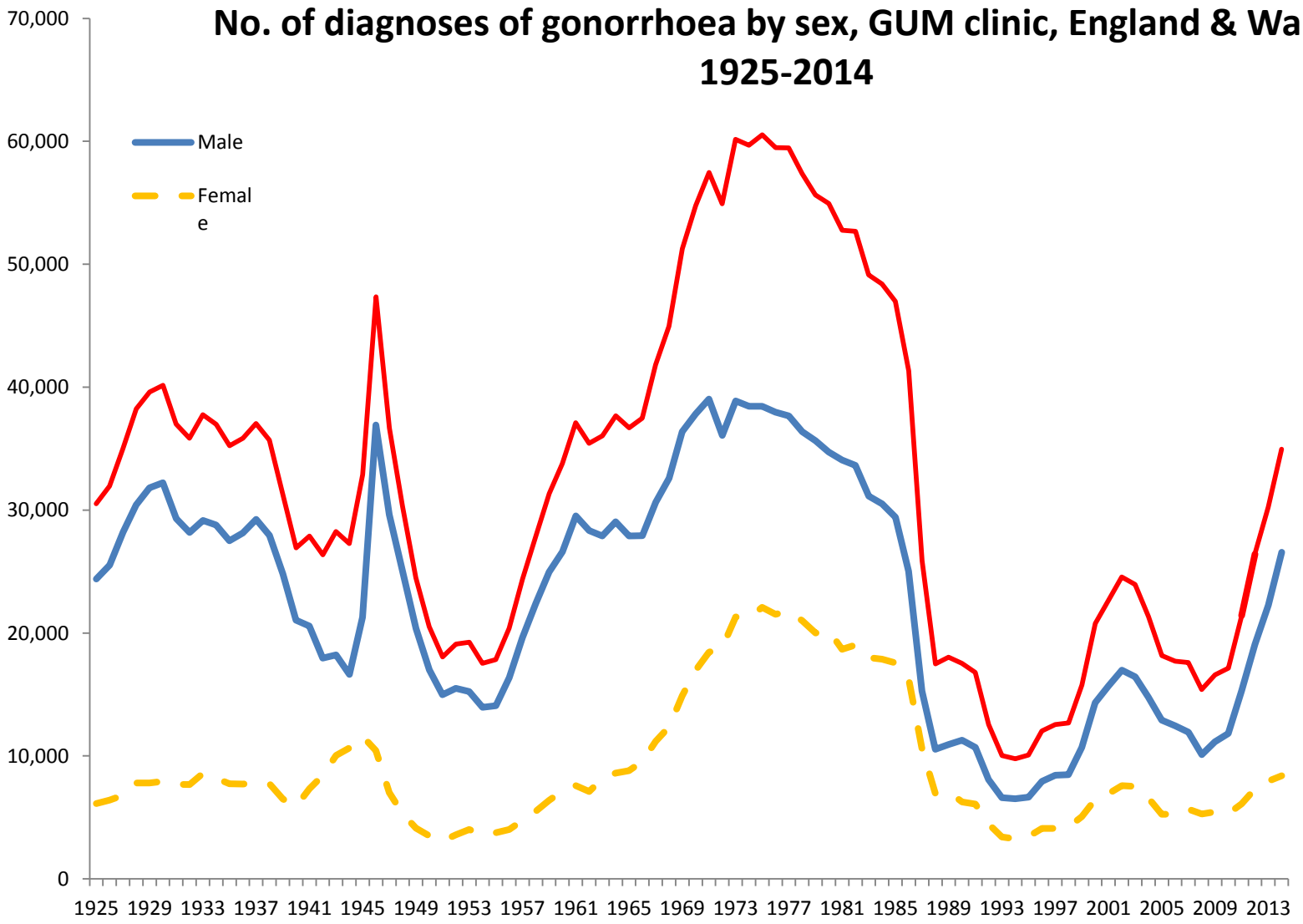
OVIVA

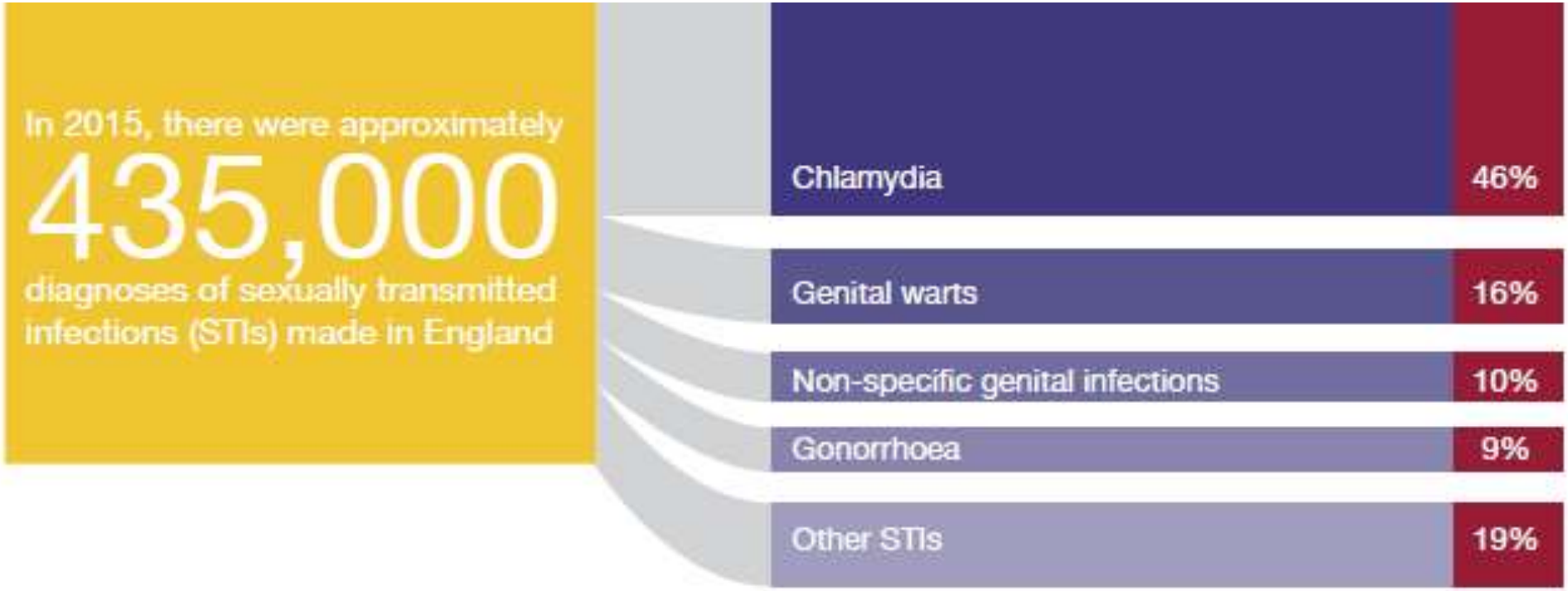




Neisseria gonorrhoeae




No. of diagnoses of gonorrhoea by sex, GUM clinic, England & Wales: 1925-2014
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
Male
Female
1925 1929 1933 1937 1941 1945 1949 1953 1957 1961 1965 1969 1973 1977 1981 1985 1989 1993 1997 2001 2005 2009 2013

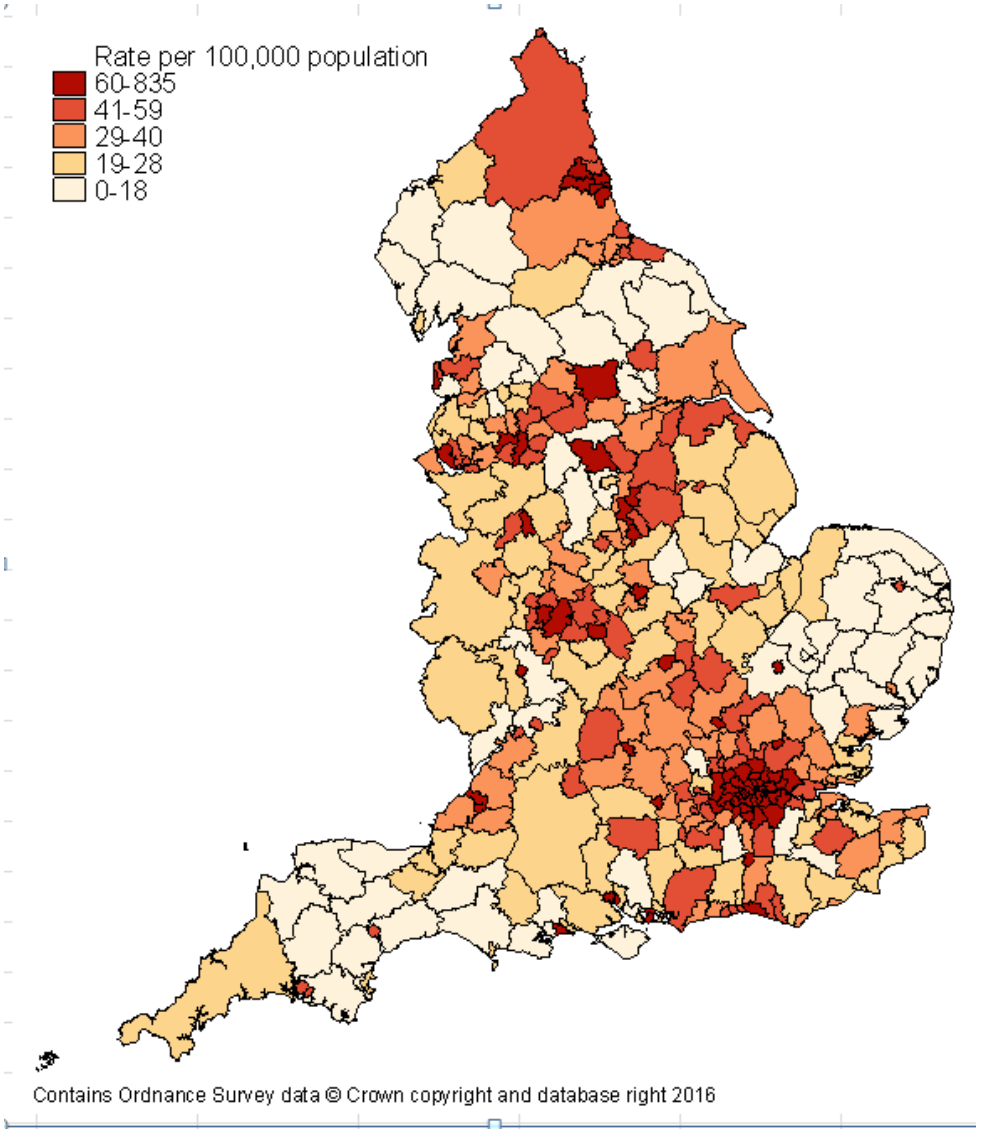


2016: 12% decrease in gonorrhoea diagnoses
41,262 to 36,244

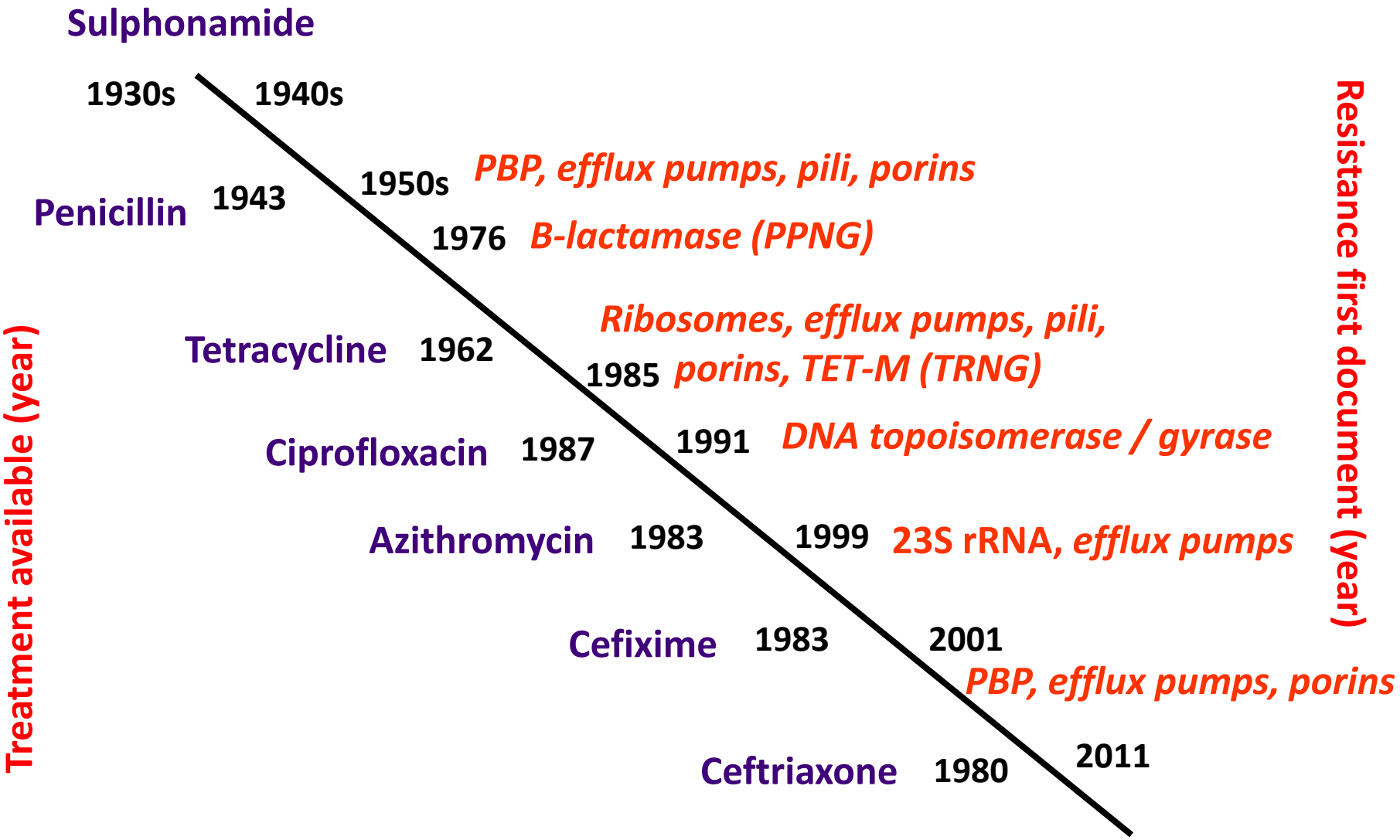
Rates of gonorrhoea diagnosis by LA of residence: England 2015

Highly geographically concentrated

Highest rates in London



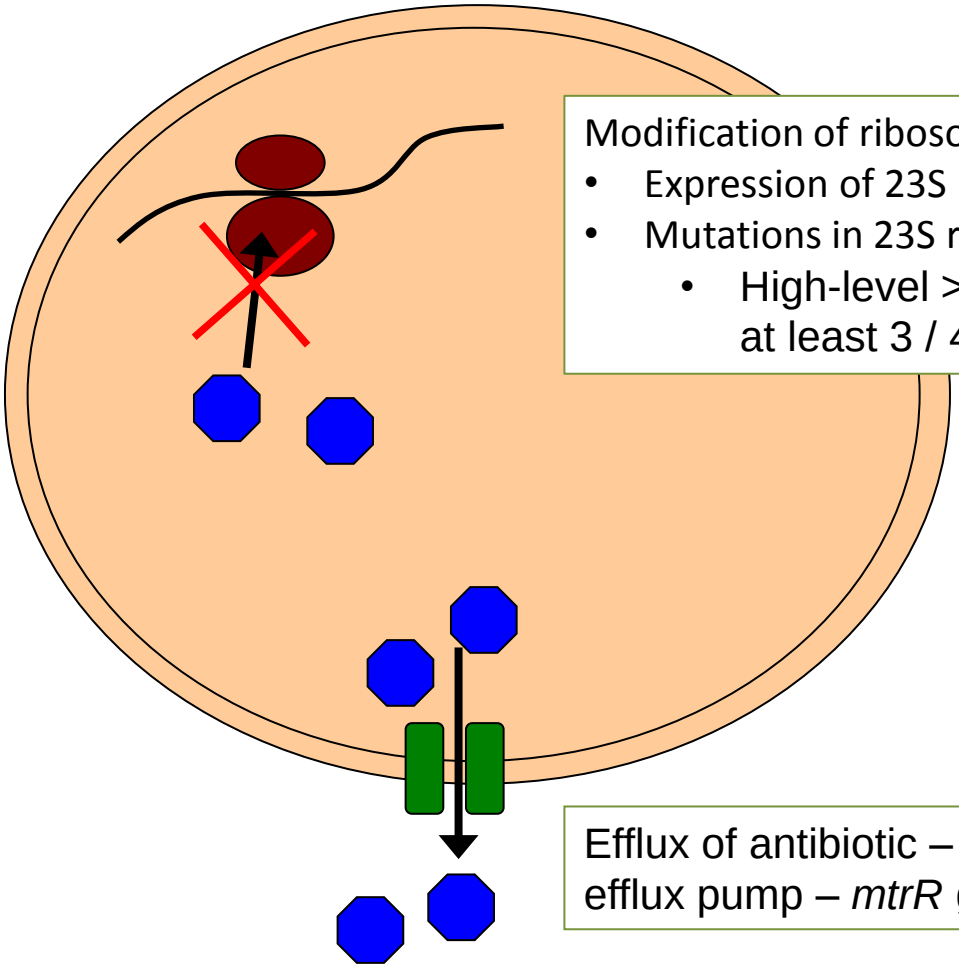
N. gonorrhoeae treatments & resistance timeline



Adapted from: Unemo & Shafer, Ann. N. Y. Acad. Sci. 1230 (2011) E19-E28

Azithromycin - mechanisms of resistance

(EUCAST >0.5 mg/L)



Modification of ribosomal target

- Expression of 23S RNA methylases
- Mutations in 23S rRNA alleles
  - High-level >256 mg/L from mutations in at least 3 / 4 alleles.

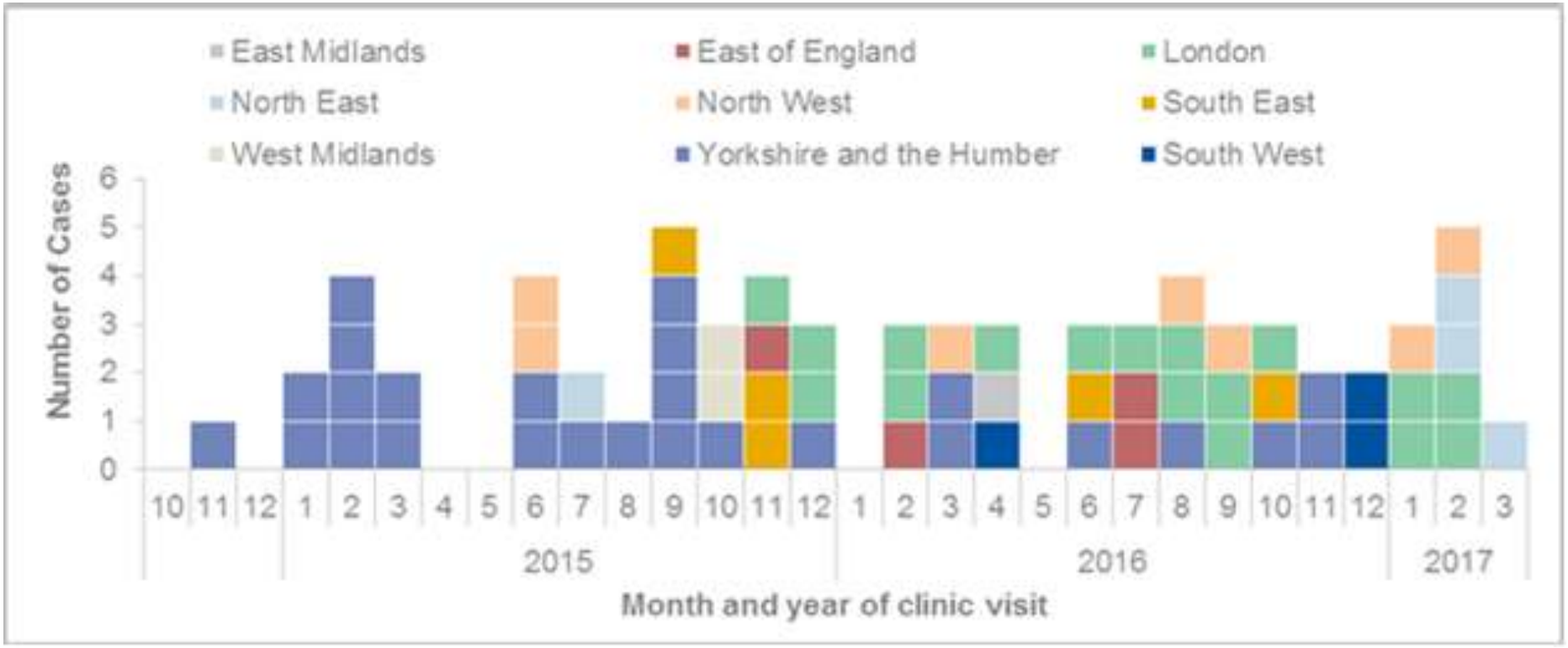
Efflux of antibiotic – Up regulation of efflux pump – *mtrR* gene mutations

High-level azithromycin resistance (HL-AziR) *Neisseria gonorrhoeae* (NG) outbreak

- HL-AziR = MIC >256 mg/L (AzR EUCAST >0.5 mg/L)
  - » 3/4 mutated alleles in 23S rRNA A2059G
- Azithromycin resistance renders the azithromycin component of dual therapy (CRO/AZ) ineffective
- Dual therapy aims to delay the accumulation of resistance and extend the useful life of ceftriaxone
- HL-AziR NG reported sporadically worldwide – clusters in Scotland/England 2007 and in Hawaii 2016

Outbreak of High-level Azithromycin Resistant (>256 mg/L) *Neisseria gonorrhoeae* in England

Cases of HL-AziR gonorrhoeae Nov 2014 to March 2017 by area of residence (n=72)



Initially young heterosexuals; detected MSM since late 2015

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 countries.[1-3] We describe treatment failure with dual therapy in a patient with gonorrhea.

In December 2014, a heterosexual man presented to a sexual health clinic in the United Kingdom with a 2-week history of urogenital

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 orally.[3] At the test of cure on day 112, the pharyngeal specimen was negative (according to the nucleic acid amplification test). Initial pretreatment specimens were unavailable for further analysis.

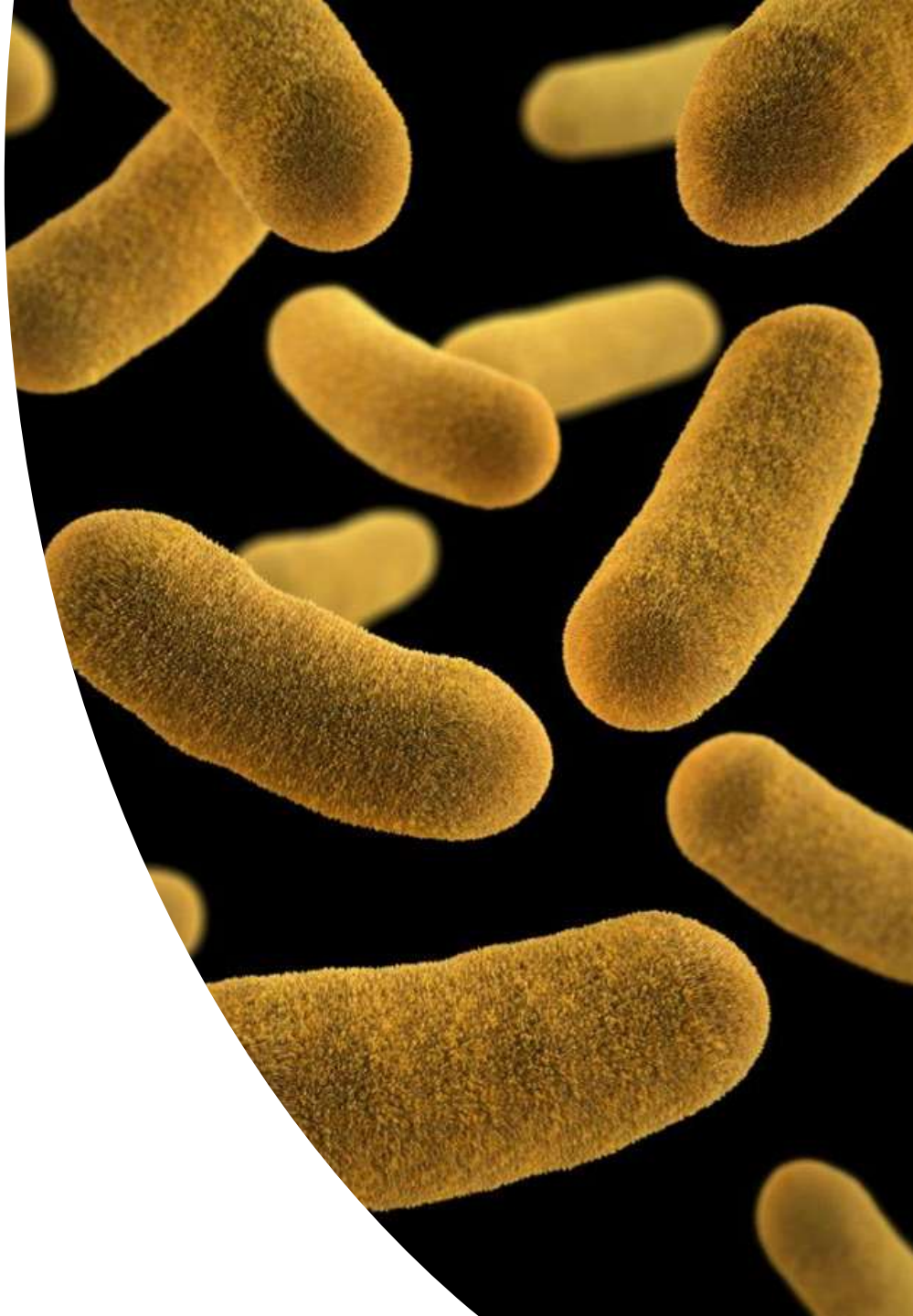
Resistance determinant	Affect
Mosaic PBP2x	decreases ceftriaxone target affinity
Deletion of adenine in mtrR promoter	Increases efflux ceftriaxone and azithromycin
penB	Decreases PorB influx ceftriaxone and azithromycin

Fifer et al. N Eng J Med. 2016 Jun 23;374(25)

Current situation

- Low overall resistance to ceftriaxone and cefixime
- Azithromycin resistance is easily selected and increasing worldwide
- HLAziR reported from increasing number of countries
- First dual treatment failure reported but true level of treatment failure unknown
- Dual therapy may not be an effective long-term solution
- Limited alternative options

Carbapenem resistant Enterobacteriaceae



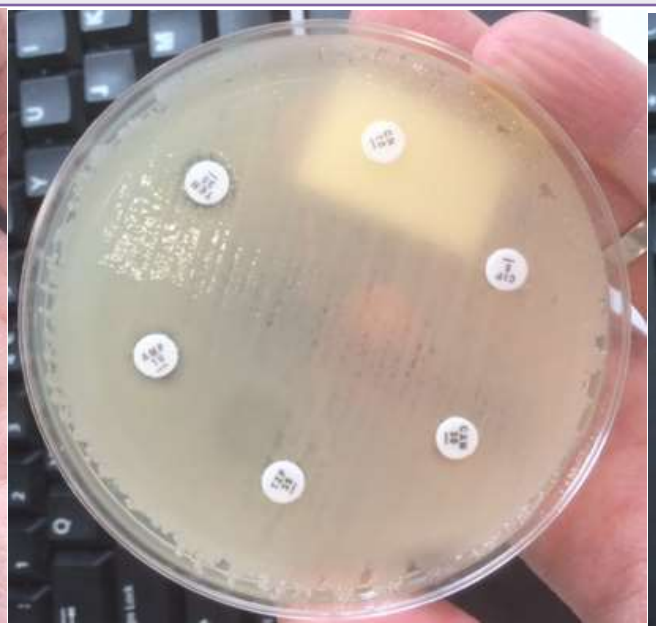
30 day old neonate

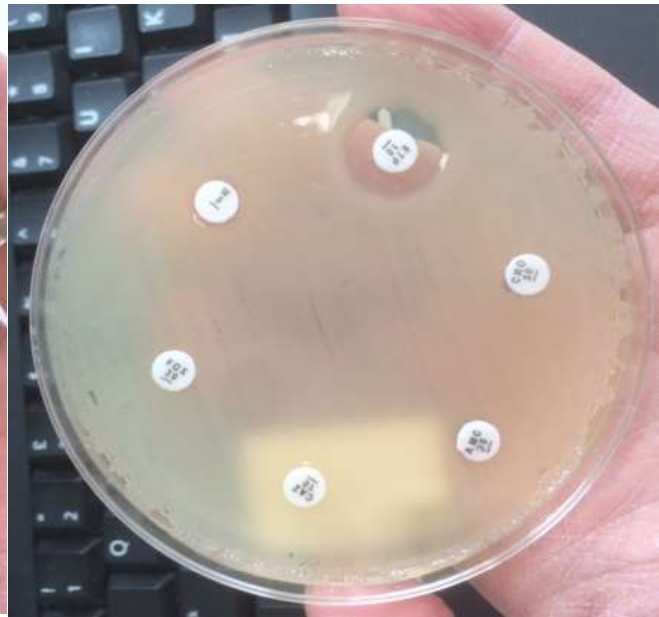
Colonised *Citrobacter freundii* rectal swab

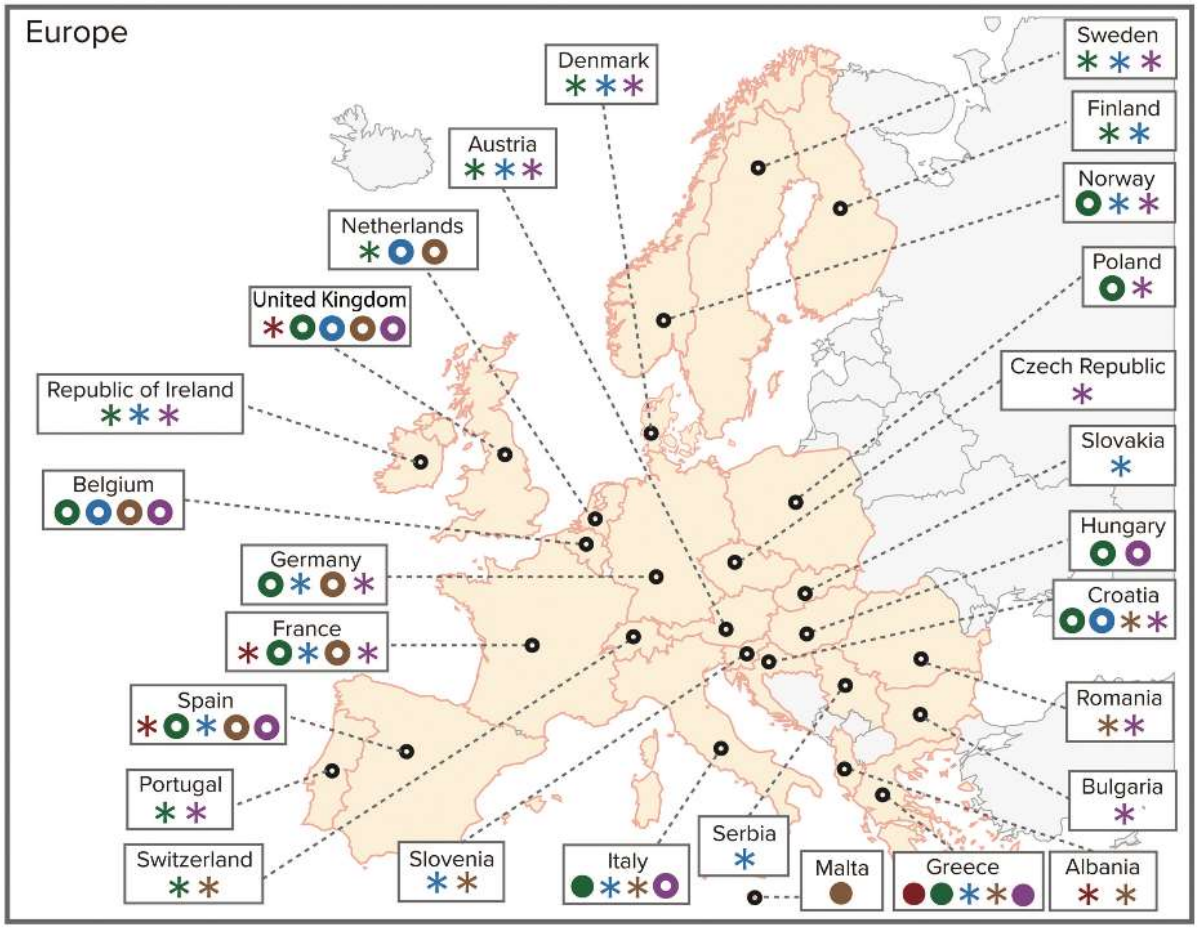
Desaturations and bradycardia

Needs intubation
?sepsis

Antibiotic	Susceptibility	Antibiotic	Susceptibility
Amoxicillin	Resistant	Ciprofloxacin	Resistant
Co-amoxiclav	Resistant	Gentamicin	Resistant
Cefuroxime	Resistant	Amikacin	Resistant
Ceftriaxone	Resistant	Tobramycin	Resistant
Ceftazidime	Resistant	Ertapenem	Resistant
Cefoxitin	Resistant	Meropenem	Resistant
Temocillin	Resistant	Tigecycline	Sensitive
Pip-taz	Resistant	Aztreonam	Resistant
Colistin	Zone present	Trimethoprim	Resistant

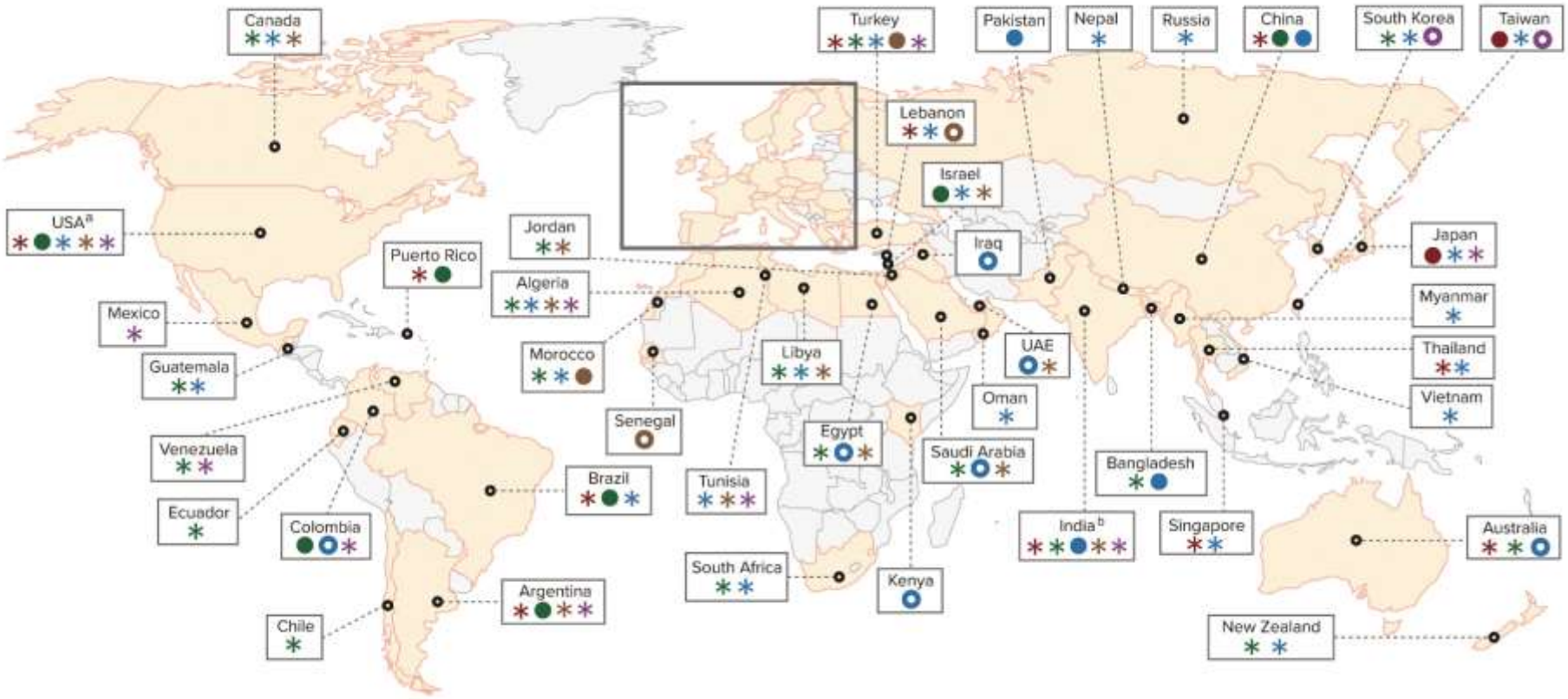






	IMP	KPC	NDM	OXA	VIM
Endemic/nationwide distribution	●	●	●	●	●
Significant outbreaks/ regional spread	○	○	○	○	○
Sporadic outbreak/ occurences	*	*	*	*	*

Logan et al. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J Infect Dis 2017



	IMP	KPC	NDM	OXA	VIM
Endemic/nationwide distribution	●	●	●	●	●
Significant outbreaks/ regional spread	○	○	○	○	○
Sporadic outbreak/ occurences	*	*	*	*	*

Logan et al. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace.
J Infect Dis 2017

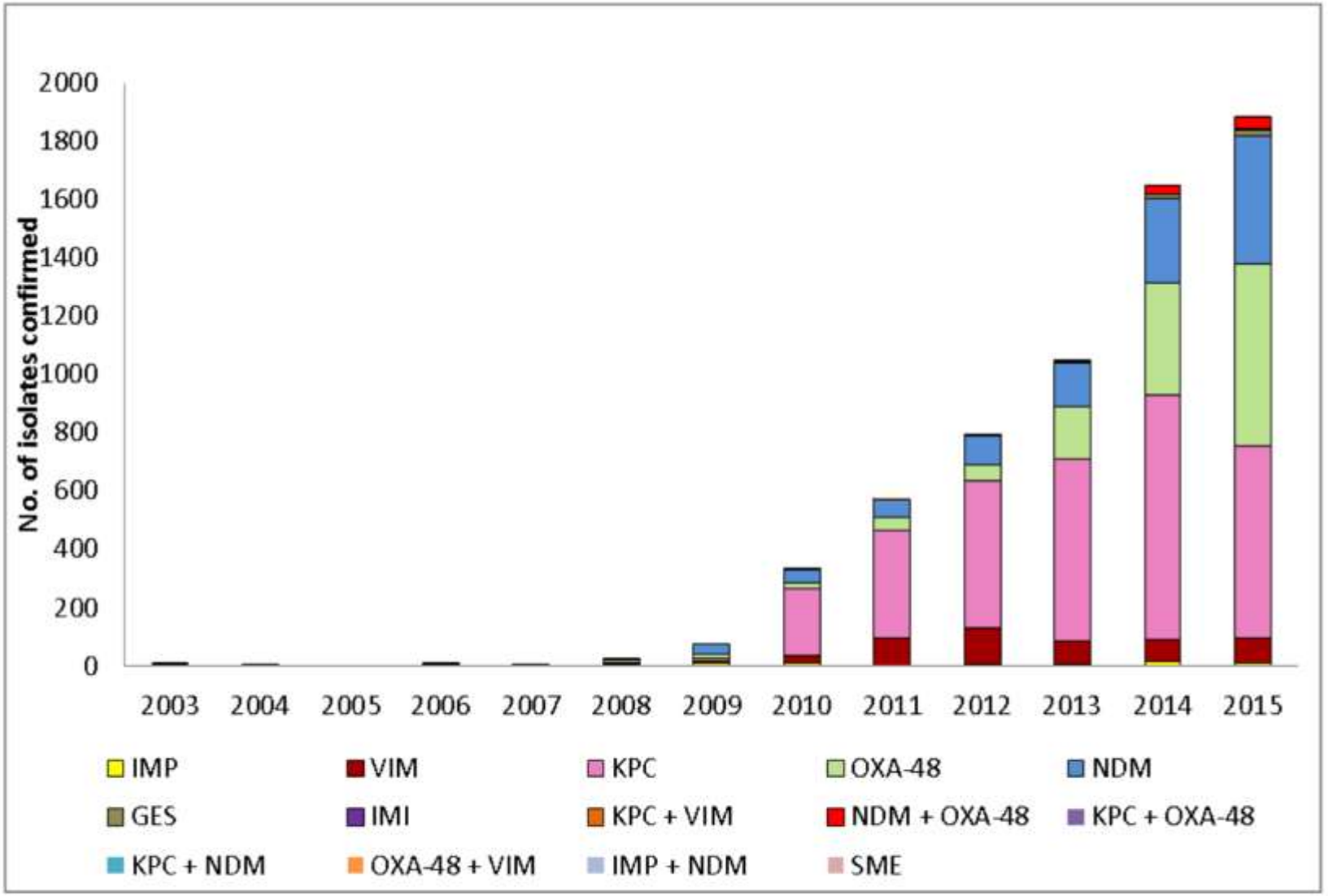
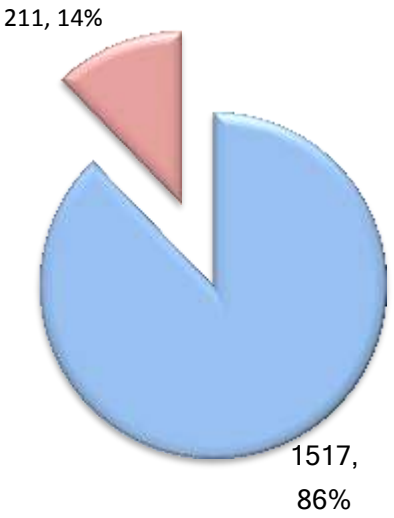


Figure 2.17 Number of isolates referred from UK hospital microbiology laboratories confirmed as carbapenemase-producing Enterobacteriaceae by AMRHAI, 2003-2015

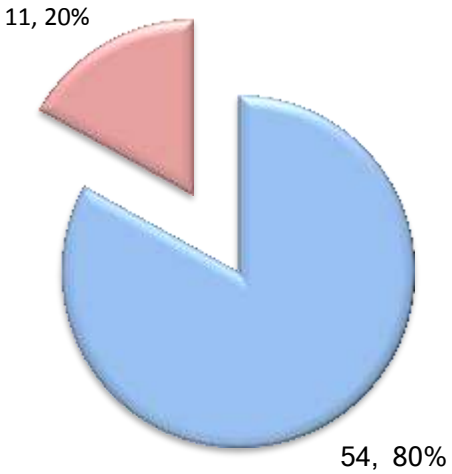
PHE.

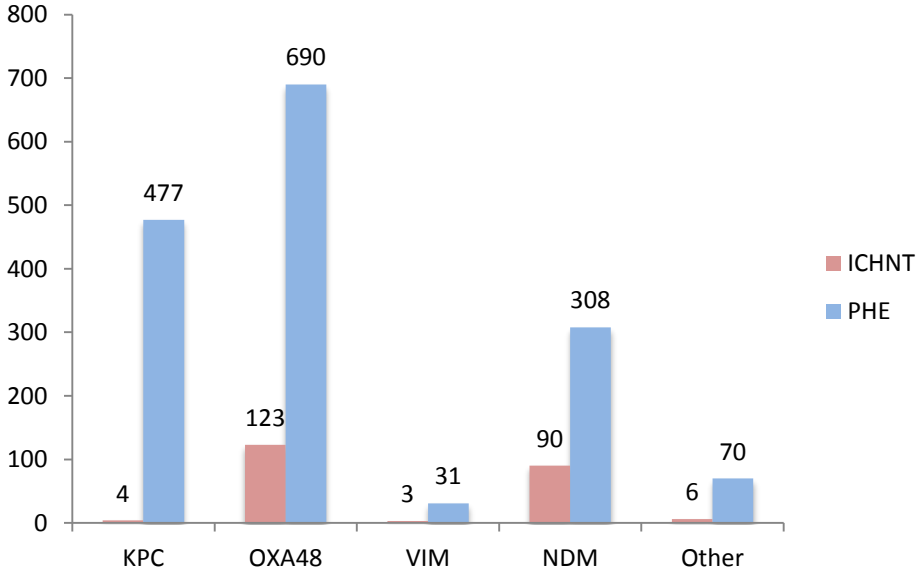
Enterobacteriaceae

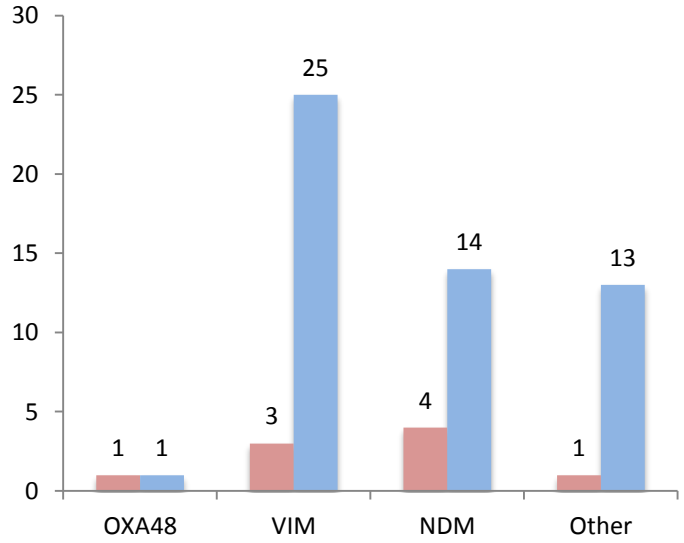


2016-2017

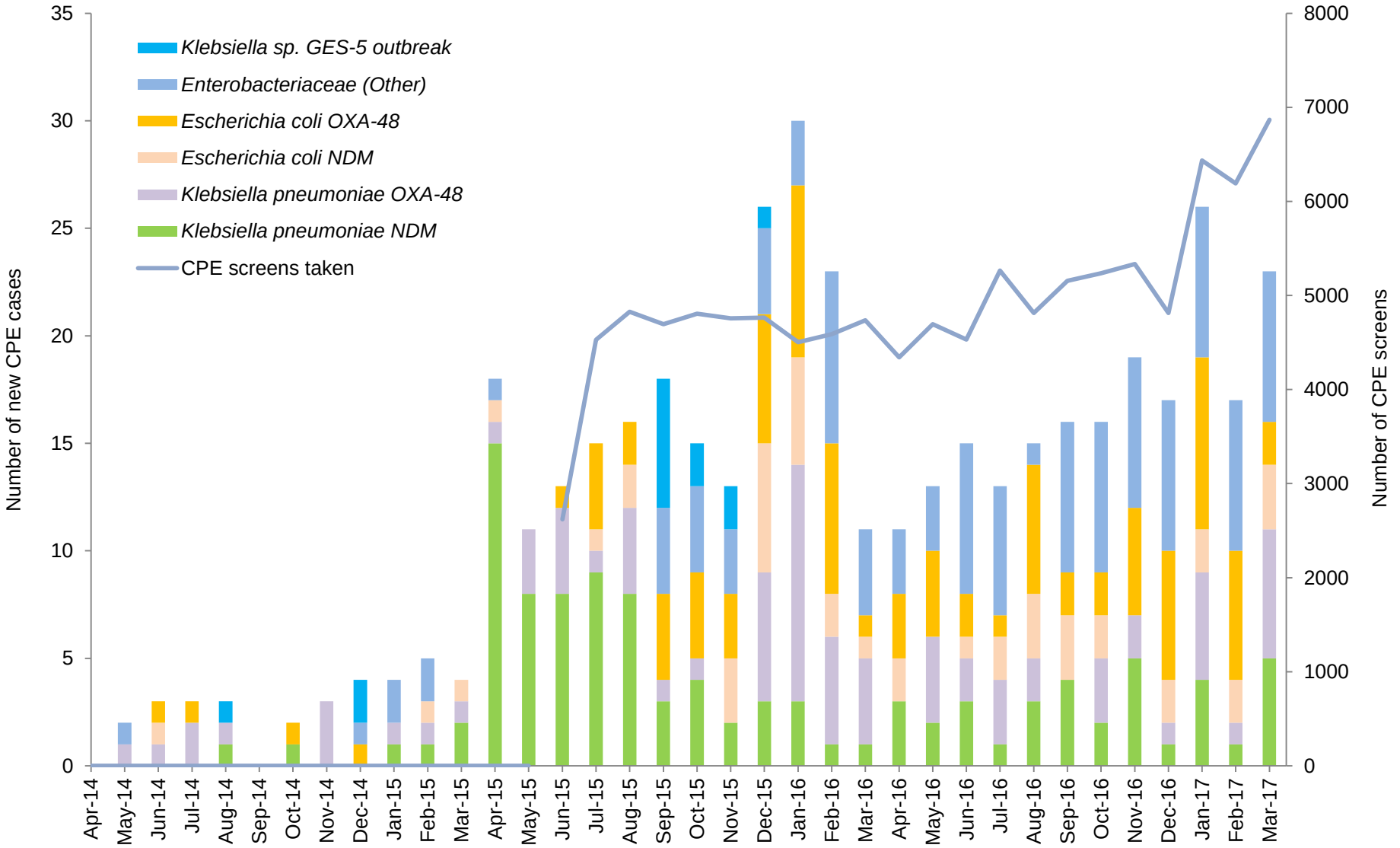
Non-Enterobacteriaceae







Detection of new CPE cases at ICHT by month



Organism	VIM	NDM	OXA48	KPC	IMP	GES
Klebsiella pneumoniae	✓	✓	✓	✓	✓	
Klebsiella oxytoca		✓	✓			✓
Klebsiella variicola		✓				
Escherichia coli		✓	✓			✓
Citrobacter freundii	✓	✓	✓	✓	✓	
Citrobacter amalonaticus		✓	✓			
Enterobacter cloacae	✓	✓	✓		✓	
Enterobacter aerogenes		✓	✓			
Enterobacter asburiae					✓	
Enterobacter ludwigii			✓			
Moraanella moraanii		✓	✓			
Raoutella spp			✓			
Acinetobacter baumanii		✓				
Pseudomonas aeruginosa	✓	✓	✓		✓	

How do we find them? - screening

- Which patient group to screen?
- Which anatomical site to screen?
- How to sample patients?
- Is serial admission screening useful?
- Is pre-emptive isolation feasible?
- Should we de-isolate known carriers?
- How much does screening cost?
- Which lab method is best?

Which patient group to screen?

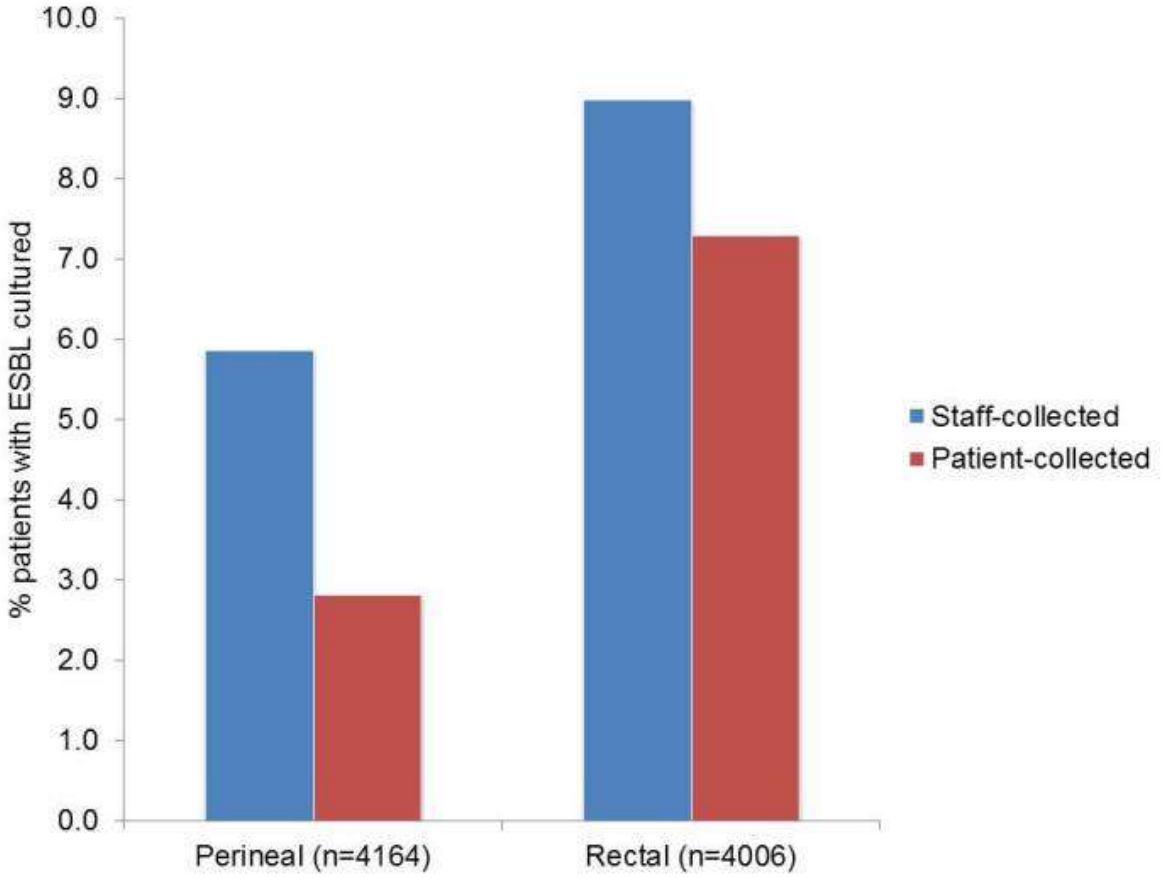
UK PHE CPE Toolkit screening triggers:

1. An inpatient in a hospital abroad
2. An inpatient in a UK hospital which has had problems with CPE if known
3. Previously positive cases

Also consider screening admissions to high-risk units such as ICU, and patients who live overseas.

Which anatomical site to screen?

Paired rectal and perineal swabs from the same individuals yielded ESBL-E in 7.8% of rectal swabs vs. 3.8% of perineal swabs, p<0.001

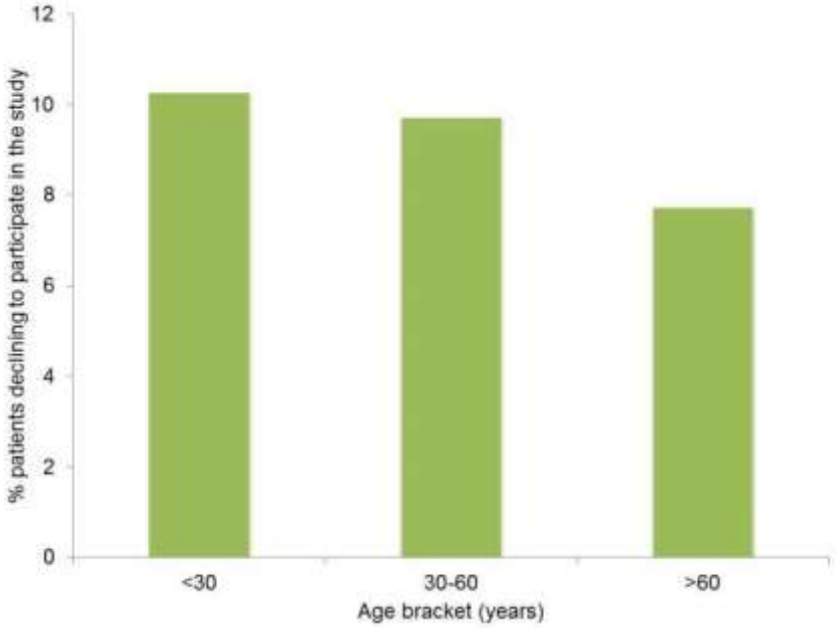


Dyakova *et al*. Efficacy and acceptability of rectal and perineal sampling for identifying gastrointestinal colonization with ESBL Enterobacteriaceae. *Clin Microbiol Infect* 2017

How do I screen?

- Rectal swab is the best sample
  - Insert no more than 2cm into rectum
  - Twist gently and withdraw
  - Ideally want to see faeces on swab.
- Patient and staff education as to why this is needed in order to overcome taboos
- Alternate specimen is stool sample, but have to wait for the patient to ‘go’

Can I swab your rectum please?

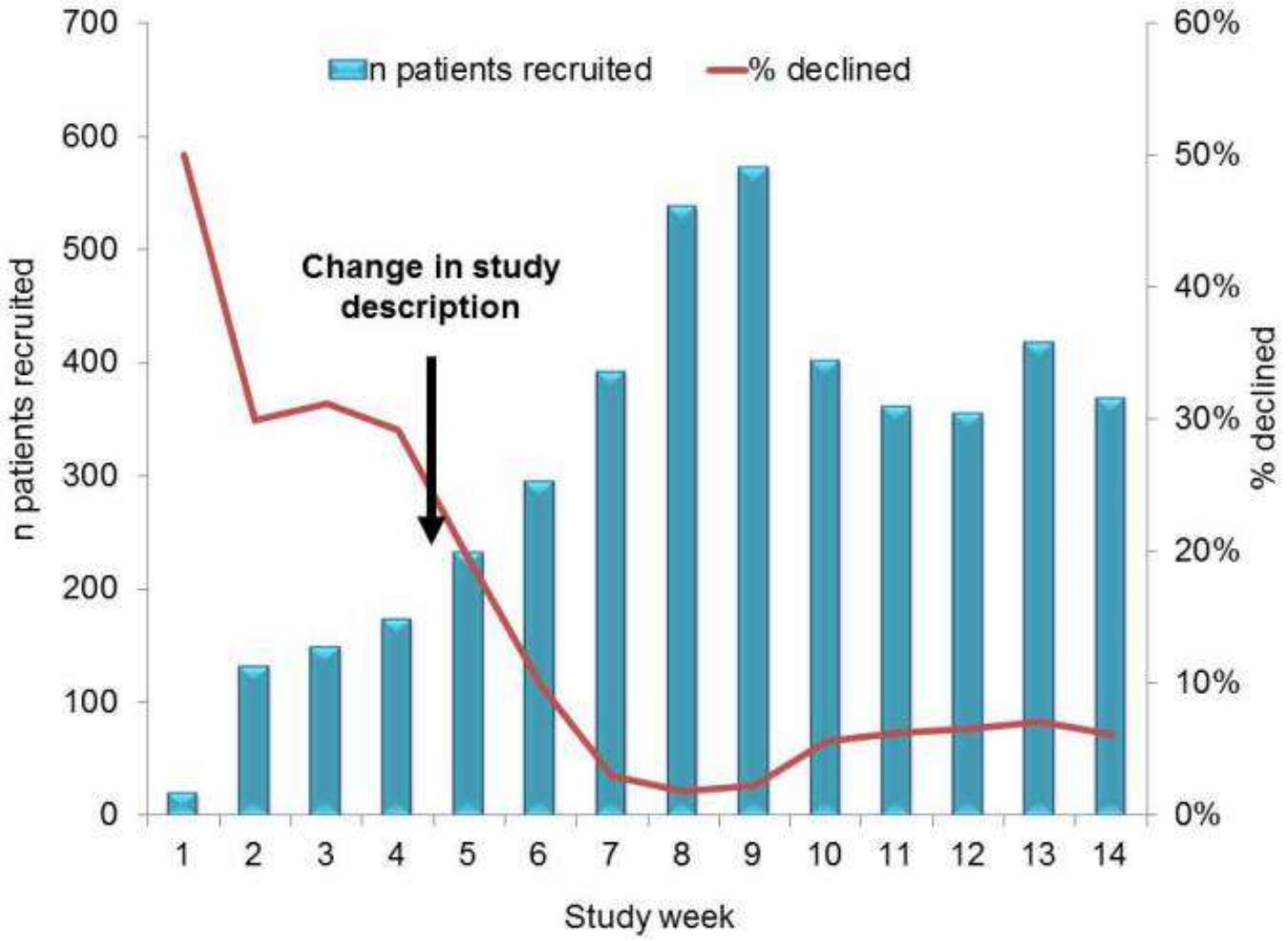


Factors associated with patients declining to provide a rectal swab were:

- younger age (odds ratio (OR) 0.99, 95% confidence interval (CI) 0.99-1.00) female gender (OR 1.26, CI 1.04-1.52),
- admission before the change in study description (OR 0.39, CI 0.31-0.48)
- the staff member who consented the patient ($p<0.001$);
- ethnicity was not a significant factor.

Dyakova *et al*. Efficacy and acceptability of rectal and perineal sampling for identifying gastrointestinal colonization with ESBL Enterobacteriaceae. *Clin Microbiol Infect* 2017

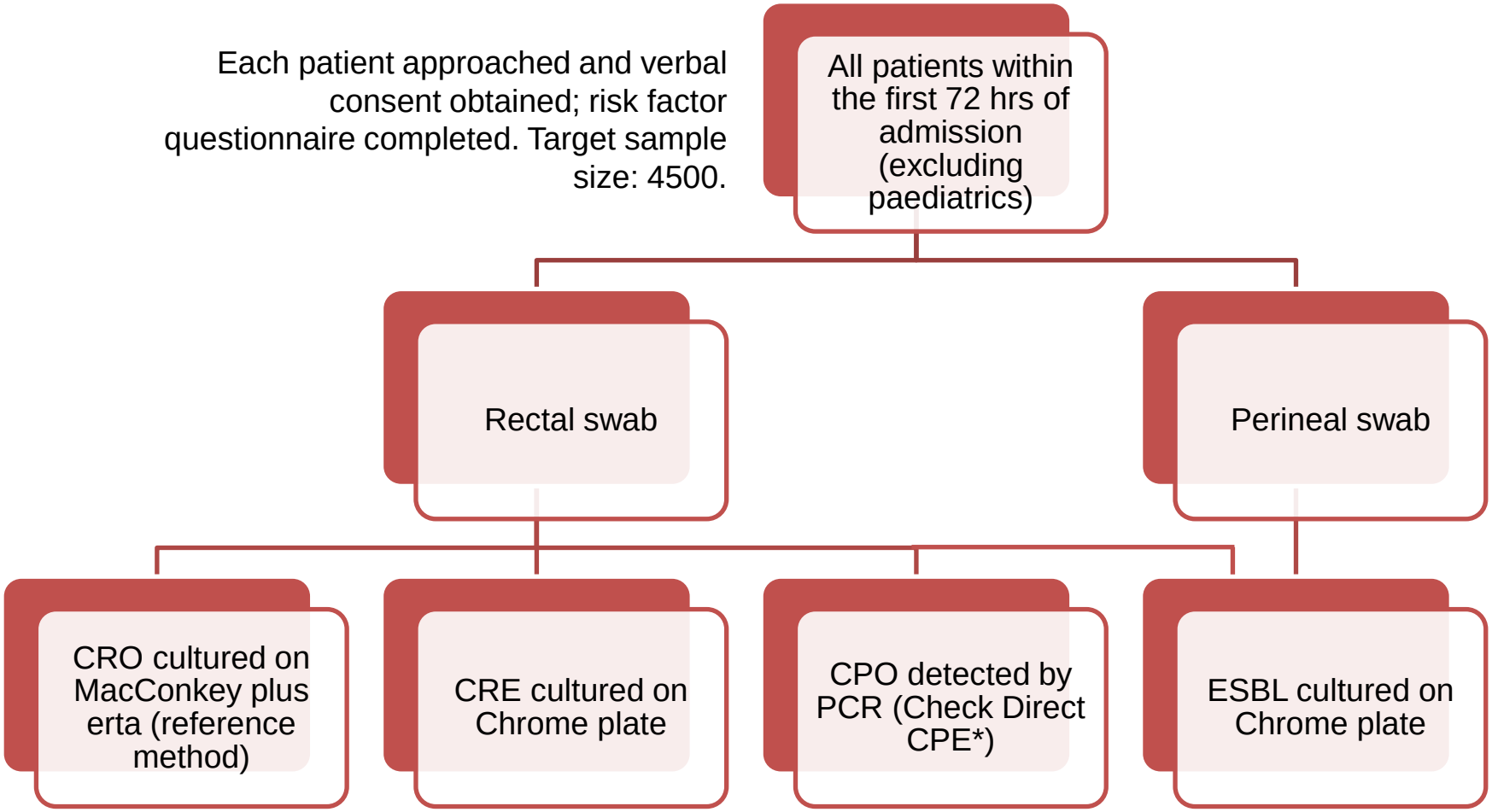
Improving screening compliance



Dyakova *et al*. Efficacy and acceptability of rectal and perineal sampling for identifying gastrointestinal colonization with ESBL Enterobacteriaceae. *Clin Microbiol Infect* 2017

Universal admission screening in London

Each patient approached and verbal consent obtained; risk factor questionnaire completed. Target sample size: 4500.



* PCR+ samples repeated on Cepheid PCR.

The study was approved by the NHS Research Ethics Committee.

Otter *et al*. *J Antimicrob Chemother* 2016;71:3556-3561.

Universal admission screening in London

- 4843 patients enrolled.
- Rectal swabs collected from 4207 patients.

- **CPE cultured from 5 (0.1%) patients.**
  - Risk factors were overseas hospitalisation anywhere, or in a PHE risk country.

- Samples from 2 patients were PCR+/culture negative by both PCR systems (Cepheid and CheckDirect).
  - **CPE identified in 7 (0.2%) patients.**

Otter *et al*. *J Antimicrob Chemother* 2016;71:3556-3561.

Risk factor prevalence

Risk factor	n pts	% pts
Non-UK residents	55	1.2%
Overseas travel in the past 12 months	1524	32.4%
Overnight hospital stay in the past 12 months - GSTT	1658	35.3%
Overnight hospital stay in the past 12 months - within M25	1964	41.8%
Overnight hospital stay in the past 12 months - North West	8	0.2%
Overnight hospital stay in the past 12 months - any UK hospital (including London)	2187	46.5%
Overnight hospital stay in the past 12 months - overseas hospital (PHE risk countries)	20	0.4%
Overnight hospital stay in the past 12 months - overseas hospital (any country)	49	1.0%
Antibiotics in the past 6 months - any	2628	55.9%
Antibiotics in the past 6 months - one course	1399	29.8%
Antibiotics in the past 6 months - more than one course	1229	26.1%
At least one risk factor	3618	77.0%
At least one risk factor (excluding antibiotics)	2961	63.0%

n=4701.

Otter *et al*. *J Antimicrob Chemother* 2016.

Simple, stark, sobering sums

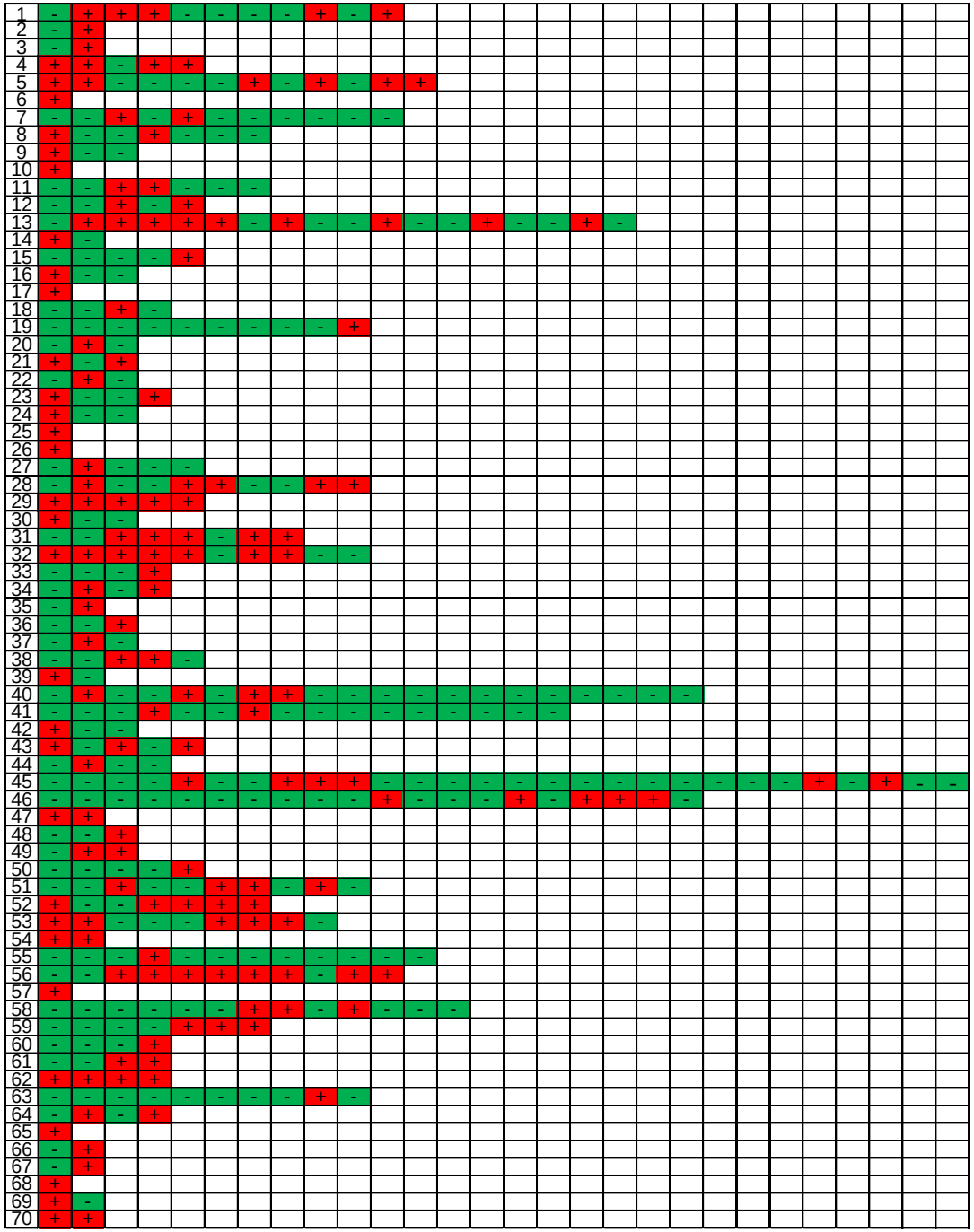
$0.5\%^{1} \times 186{,}393 = 932$ (!)

$0.1\%^{2} \times 186{,}393 = 186$

$0.1\% \times 15.892\text{m}^{*} = 15{,}892$

* Admissions to NHS acute hospitals, Financial Year 14/15. NHS Confederation, Key Statistics on the NHS,

1. Mookerjee *et al.* ECCMID 2016.
2. Otter *et al*. *J Antimicrob Chemother* 2016;71:3556-3561

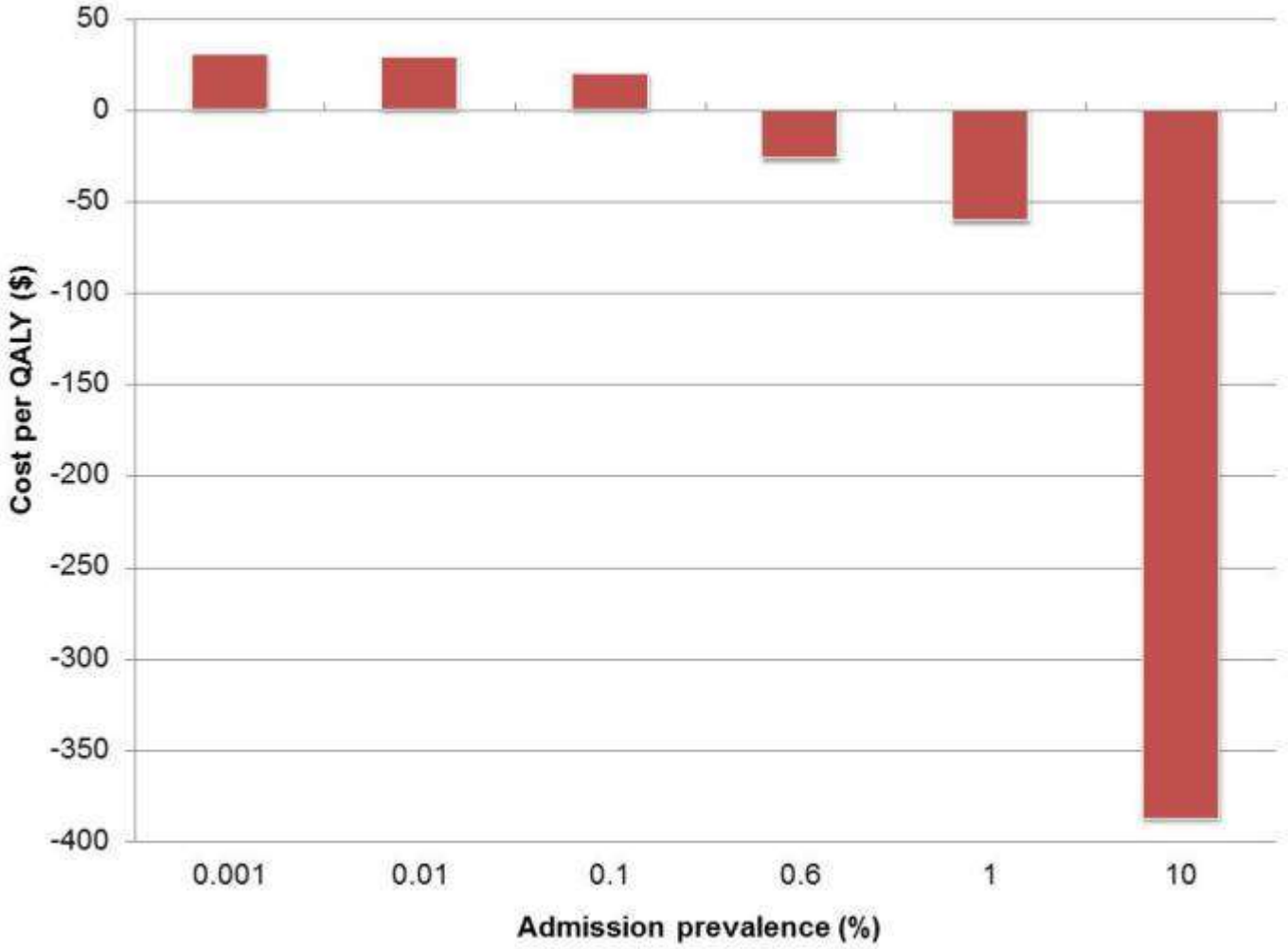


Once positive, always positive?

- Of 51 that had least three screens, 24 (47.1%) had a ‘+-+’ pattern.
- 60 / 64 (93.8%) patients had at least one negative surveillance culture during their hospital stay (excluding 6 patients with a single positive screen).

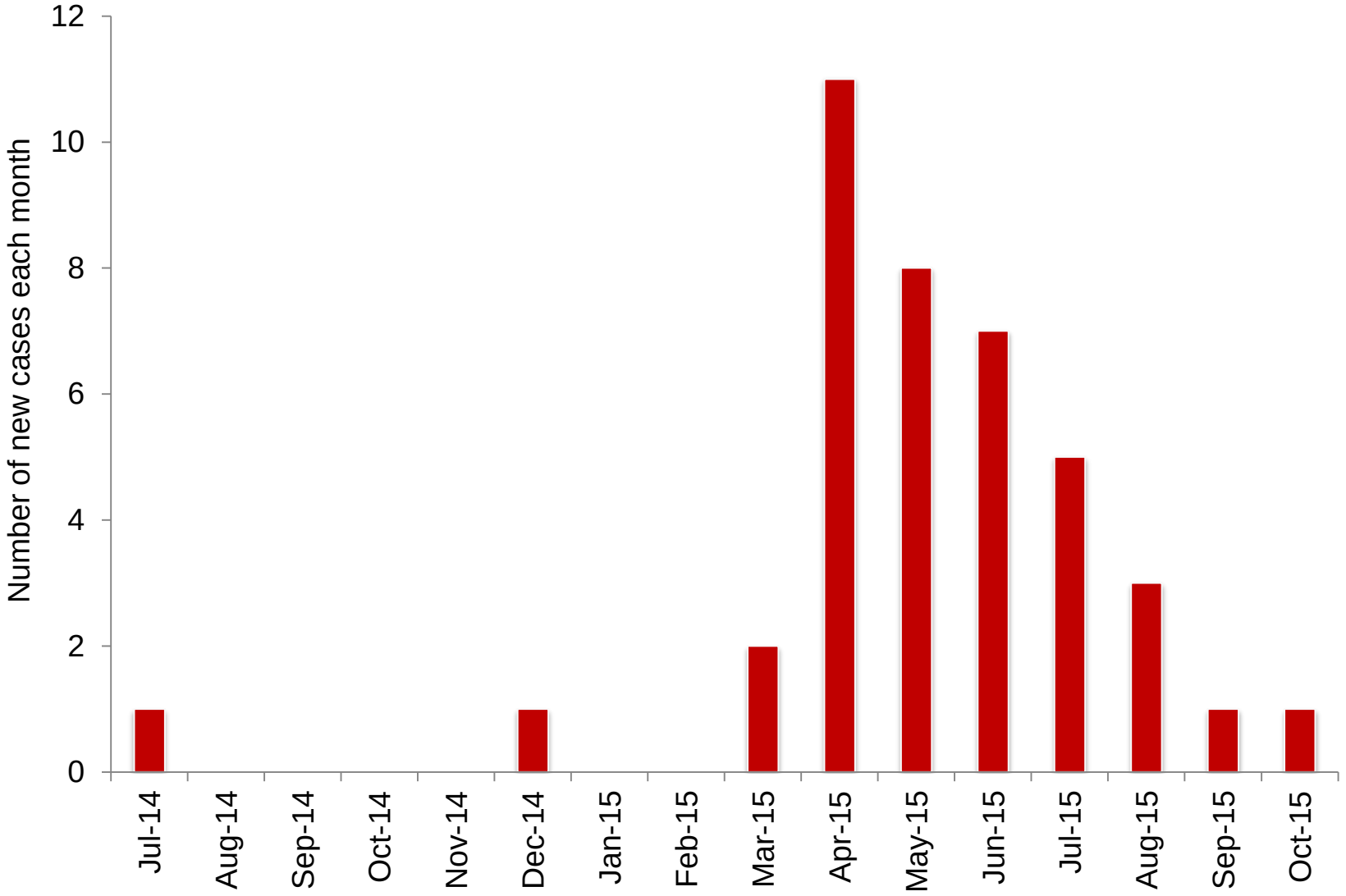
Serial CPE screens from 70 patients who were found to be CPE positive by screening cultures during June – December 2015. Red = positive. Green = negative.

Screening cost-effectiveness



Lapointe-Shaw *et al. Eur J Clin Microbiol Infect Dis* 2017;36:1047-55.

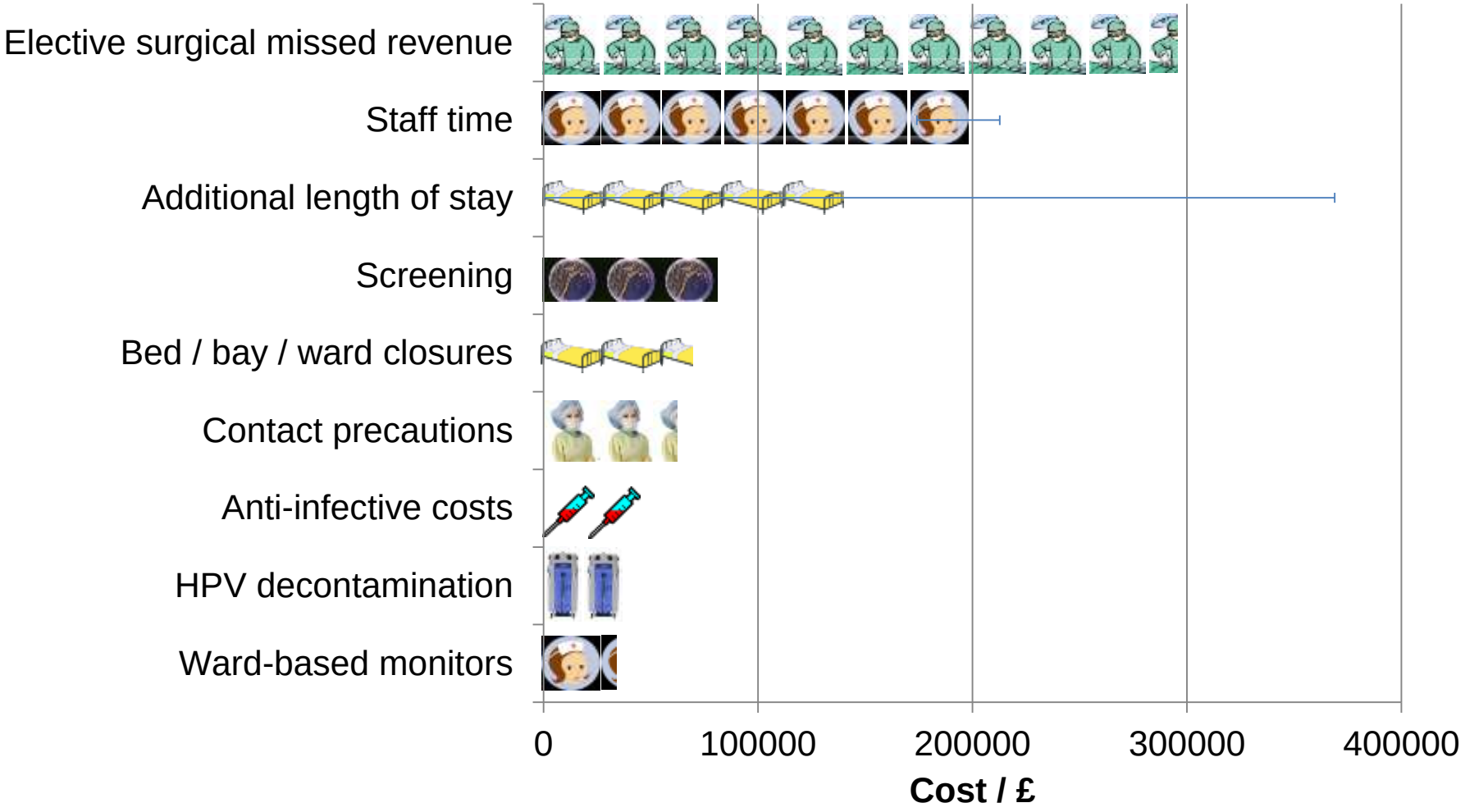
K. pneumoniae NDM outbreak; total number of cases



8 cases first identified by clinical culture, 32 by screening culture; of these 32, 14 had a subsequent positive clinical culture

Cost hierarchy

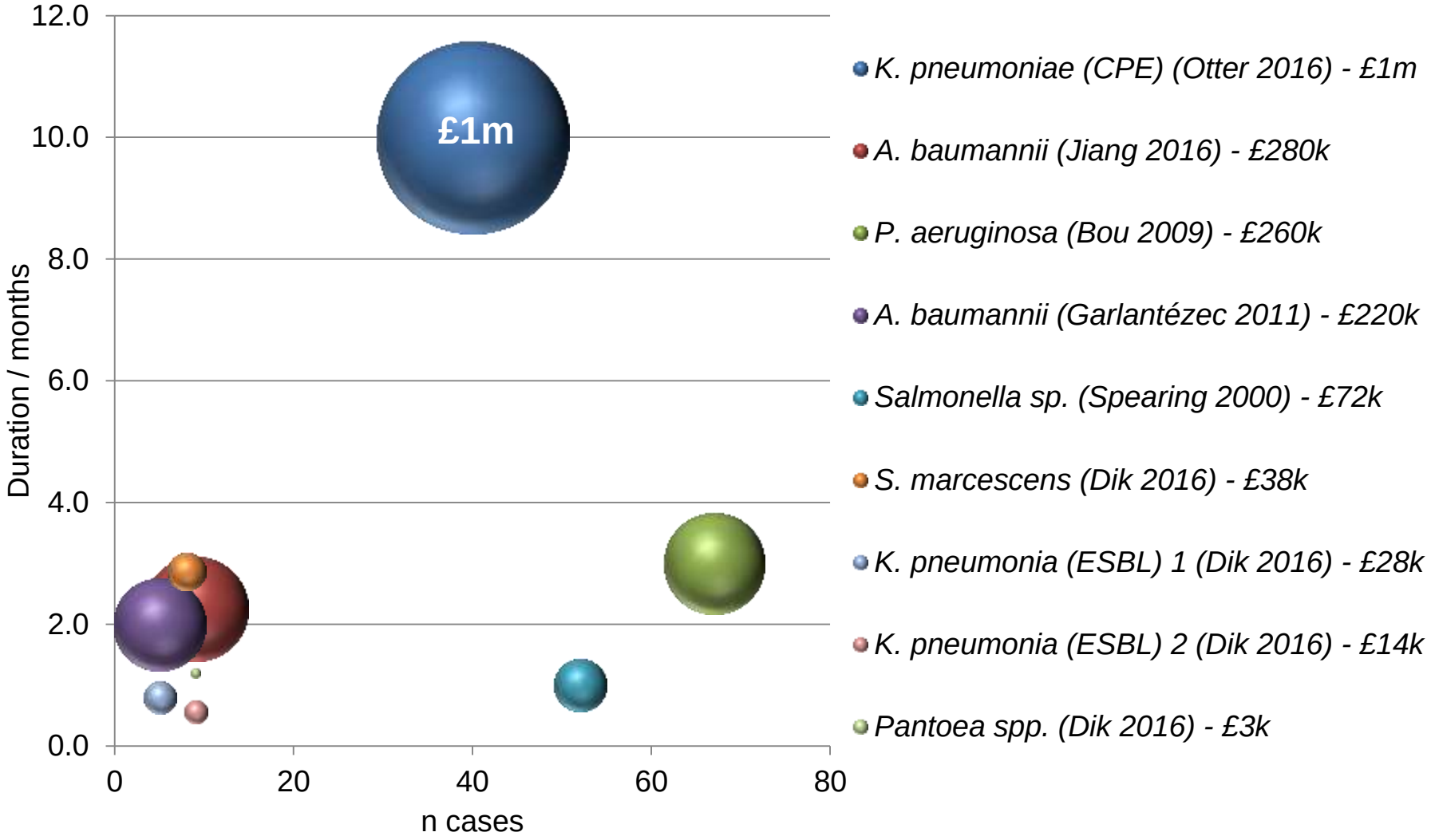
Economic evaluation of a 40 case outbreak of CPE. Error bars represent range



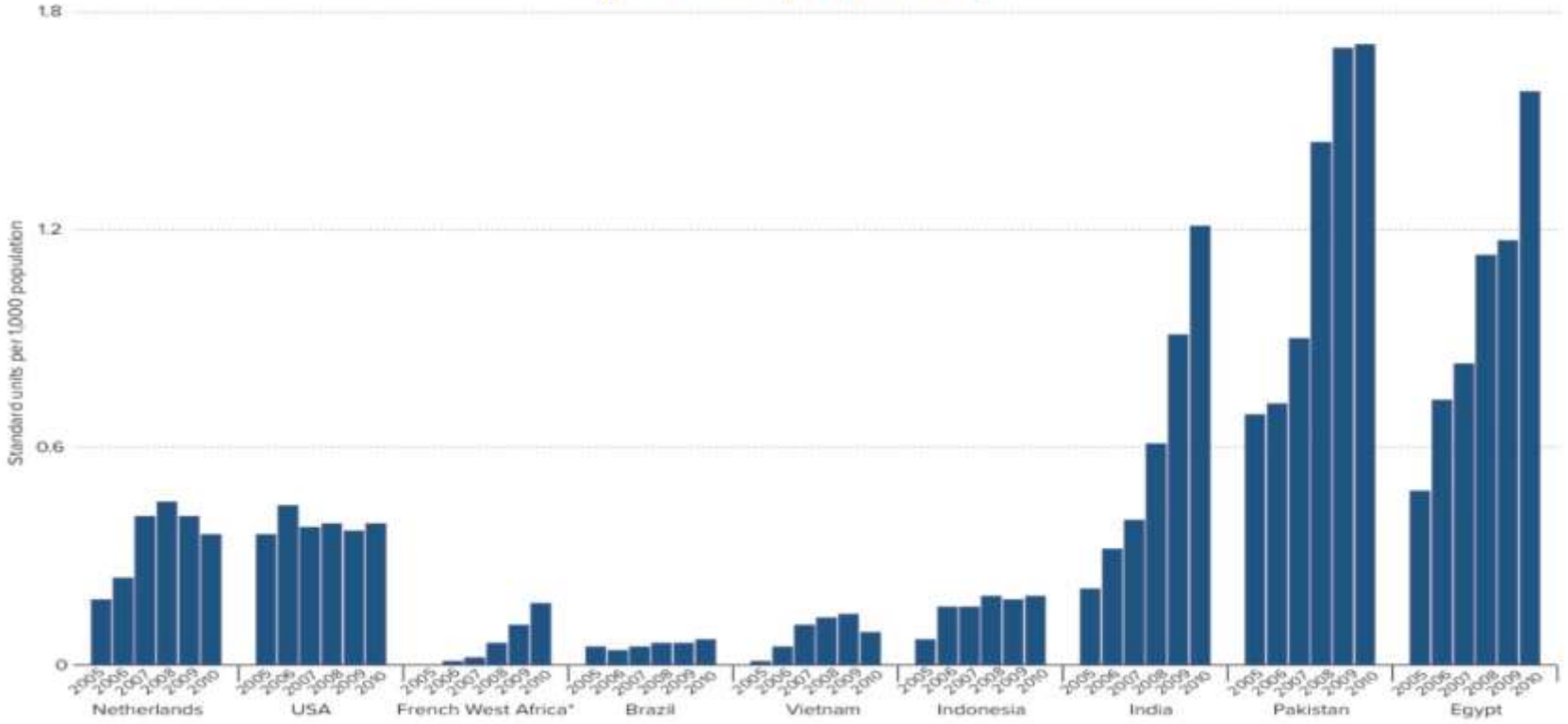
Otter *et al.* Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. *Clin Microbiol Infect* 2017.

Costs in context

Bubble size represents the total cost of the outbreak

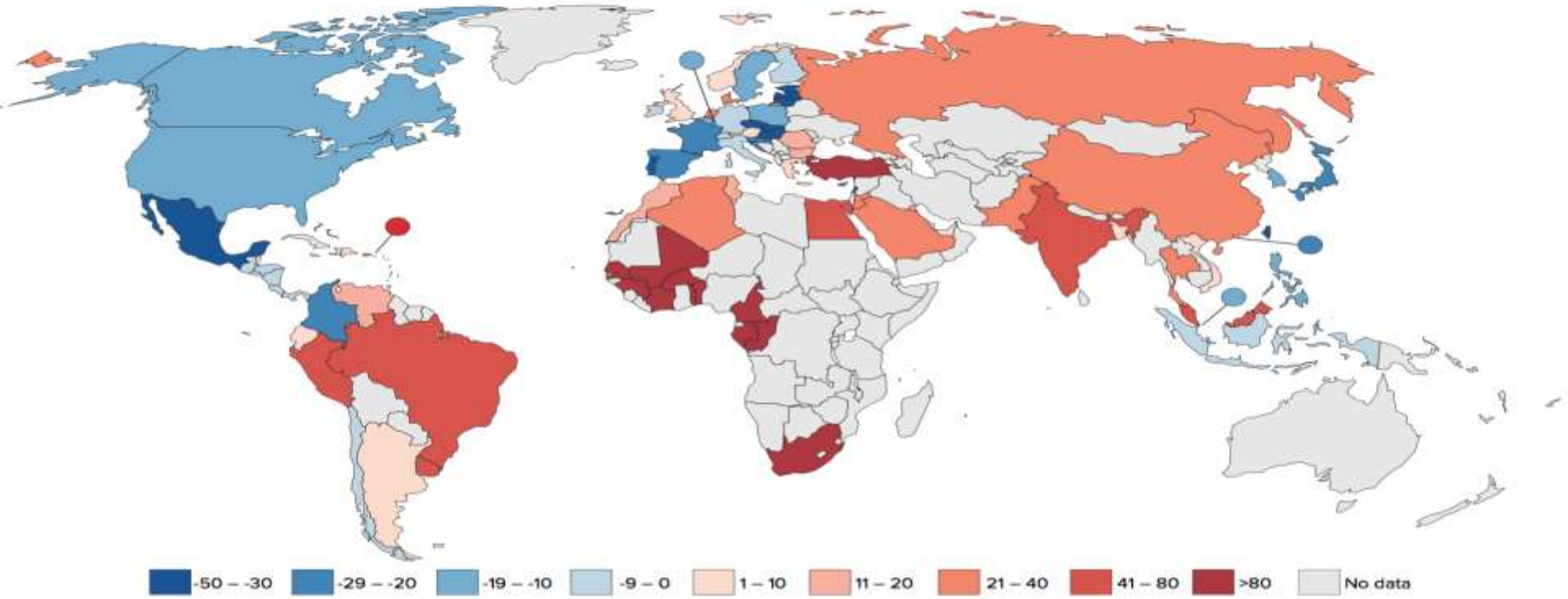


Carbapenem retail sales in selected countries, 2005–2010 (per 1,000 population)



CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

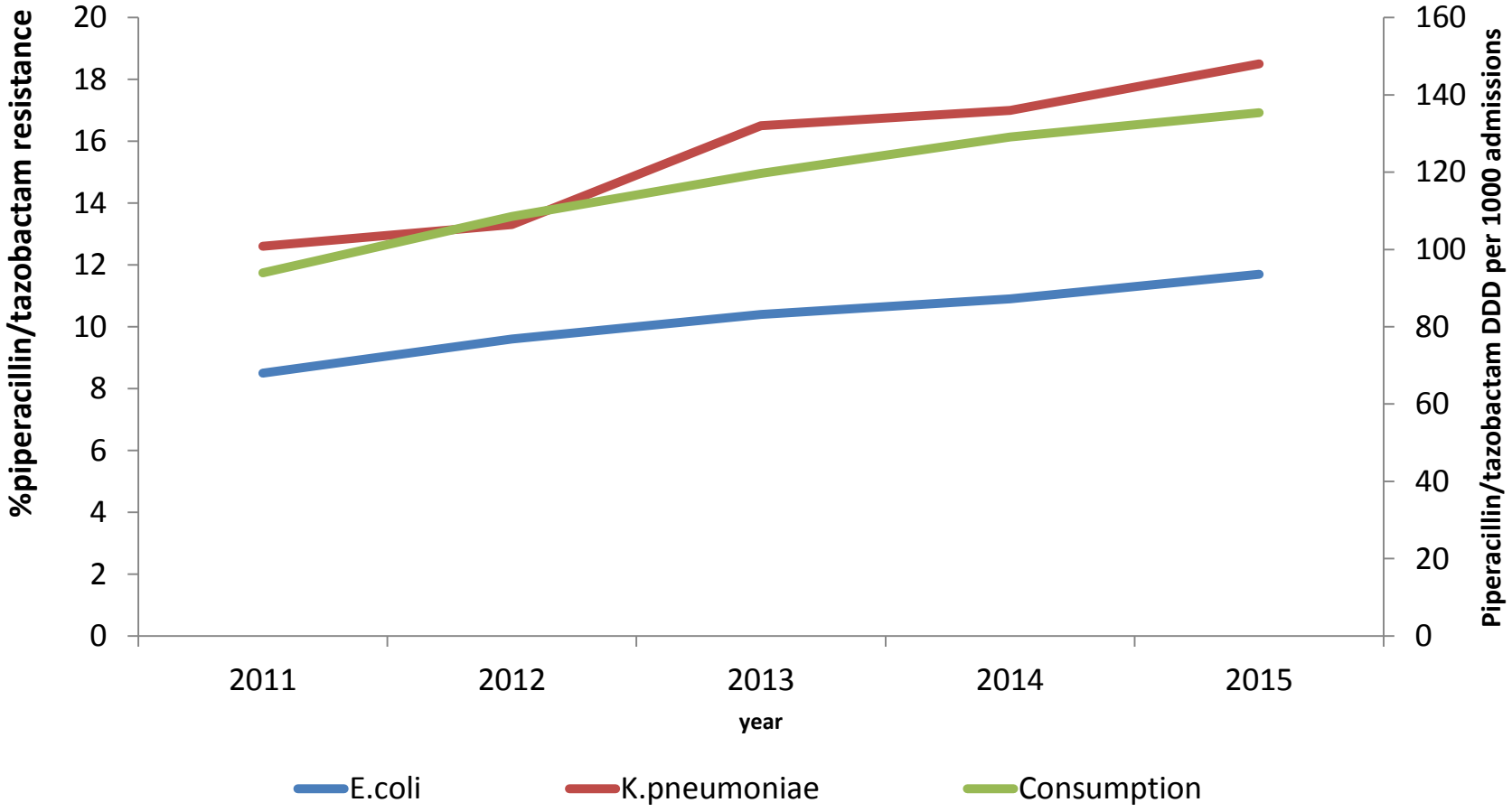
Percentage change in antibiotic consumption per capita 2000–2010*, by country



Source: Van Boeckel et al. 2015 (adapted; based on IMS MIDAS)

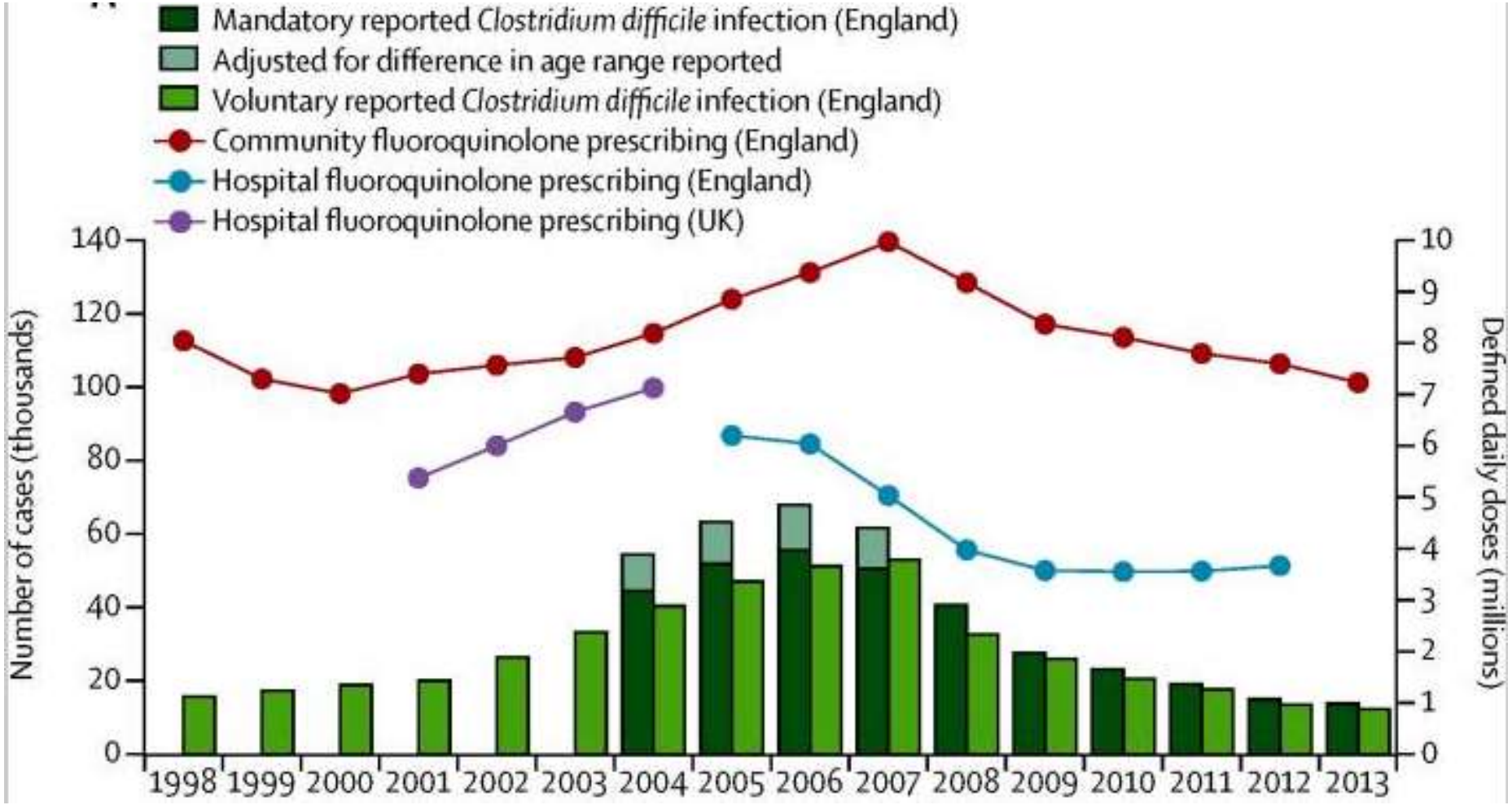
CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

Relationship between Antibiotic resistance and use



ESPAUR, PHE 2016

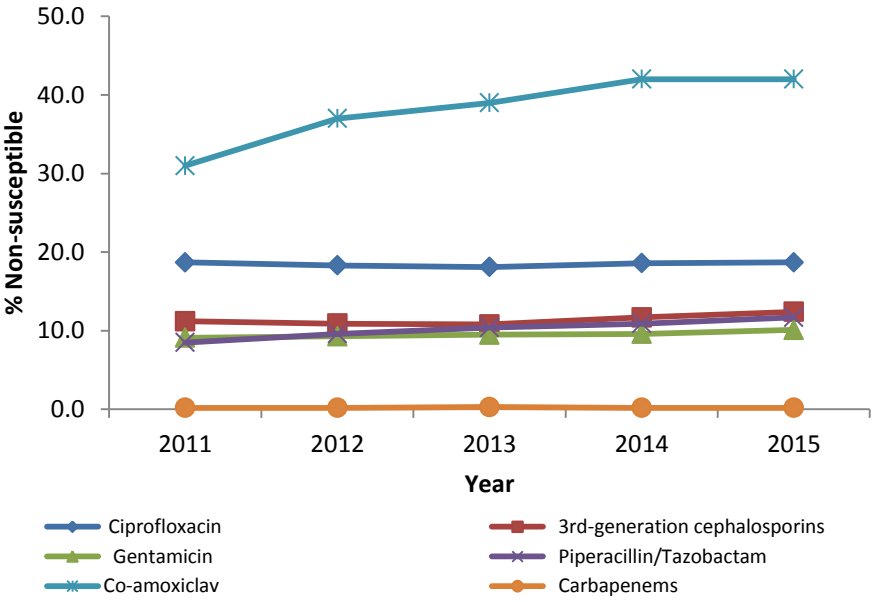
Relationship between Antibiotic resistance and use



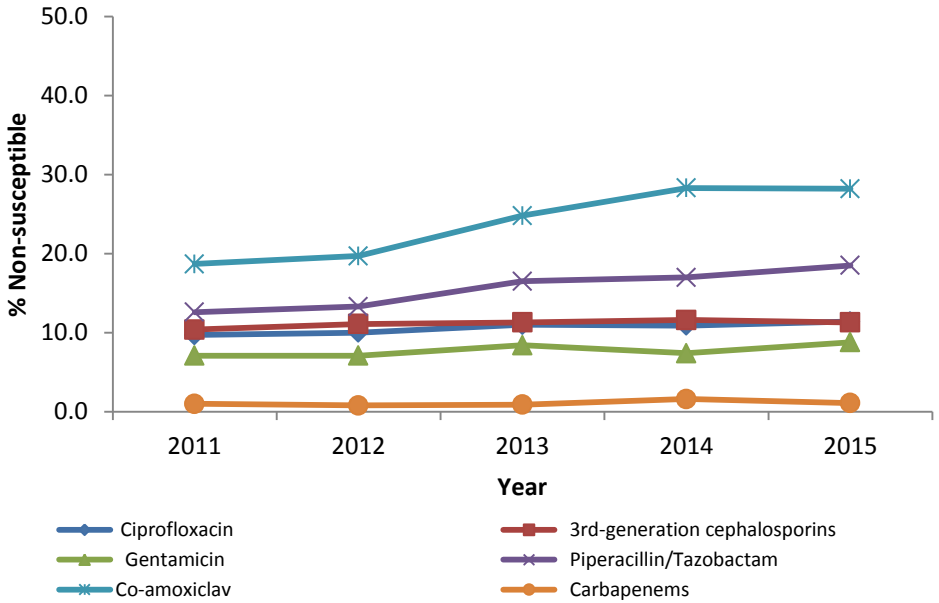
Dingle et al. Effects of control interventions on Clostridium difficile infection in England: an observational study. *Lancet Infect Dis*. 2017 Apr; 17(4): 411–421.

Resistance in key Gram-negatives

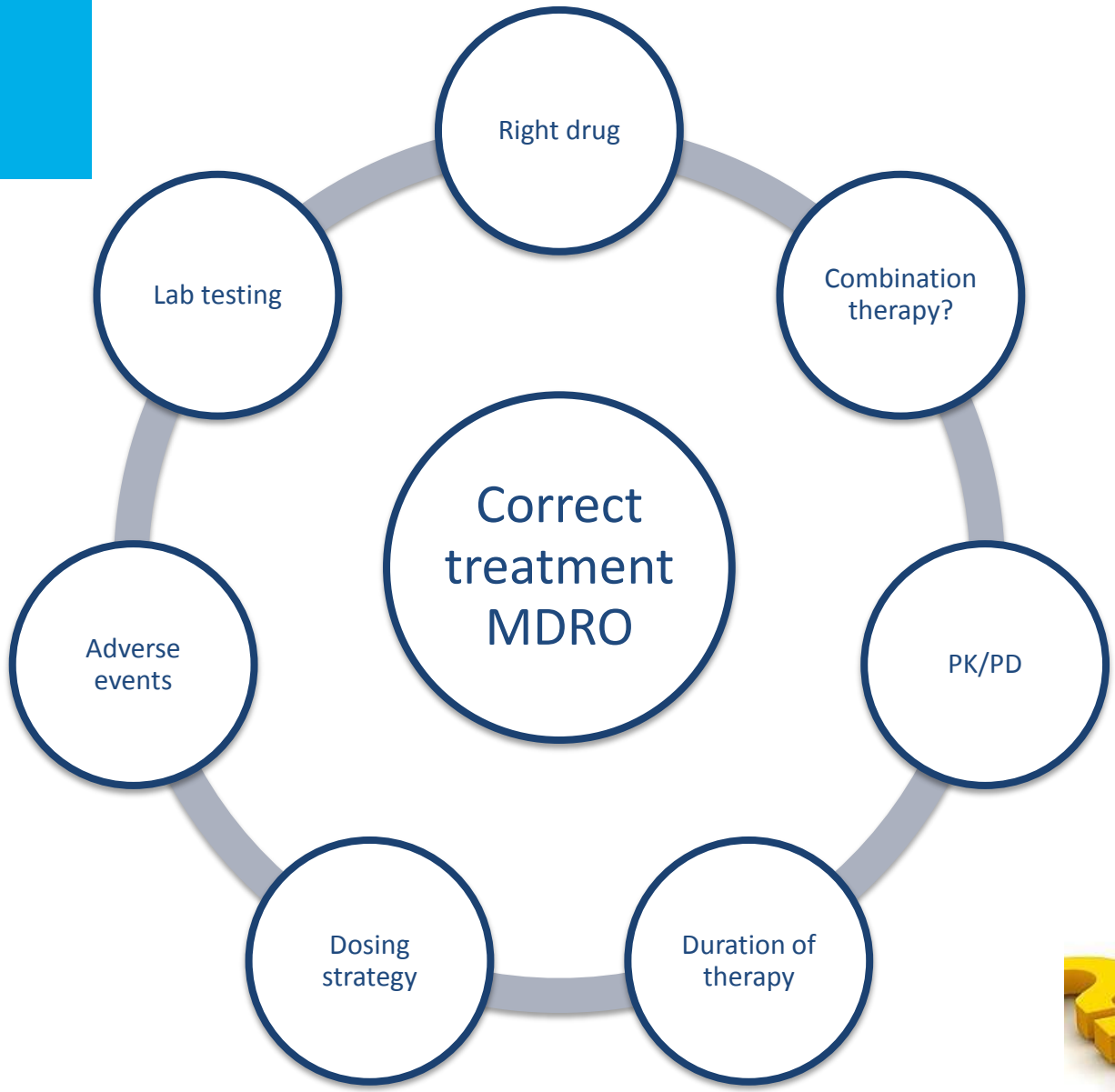
E. coli



Klebsiella pneumoniae



ESPAUR, PHE 2016

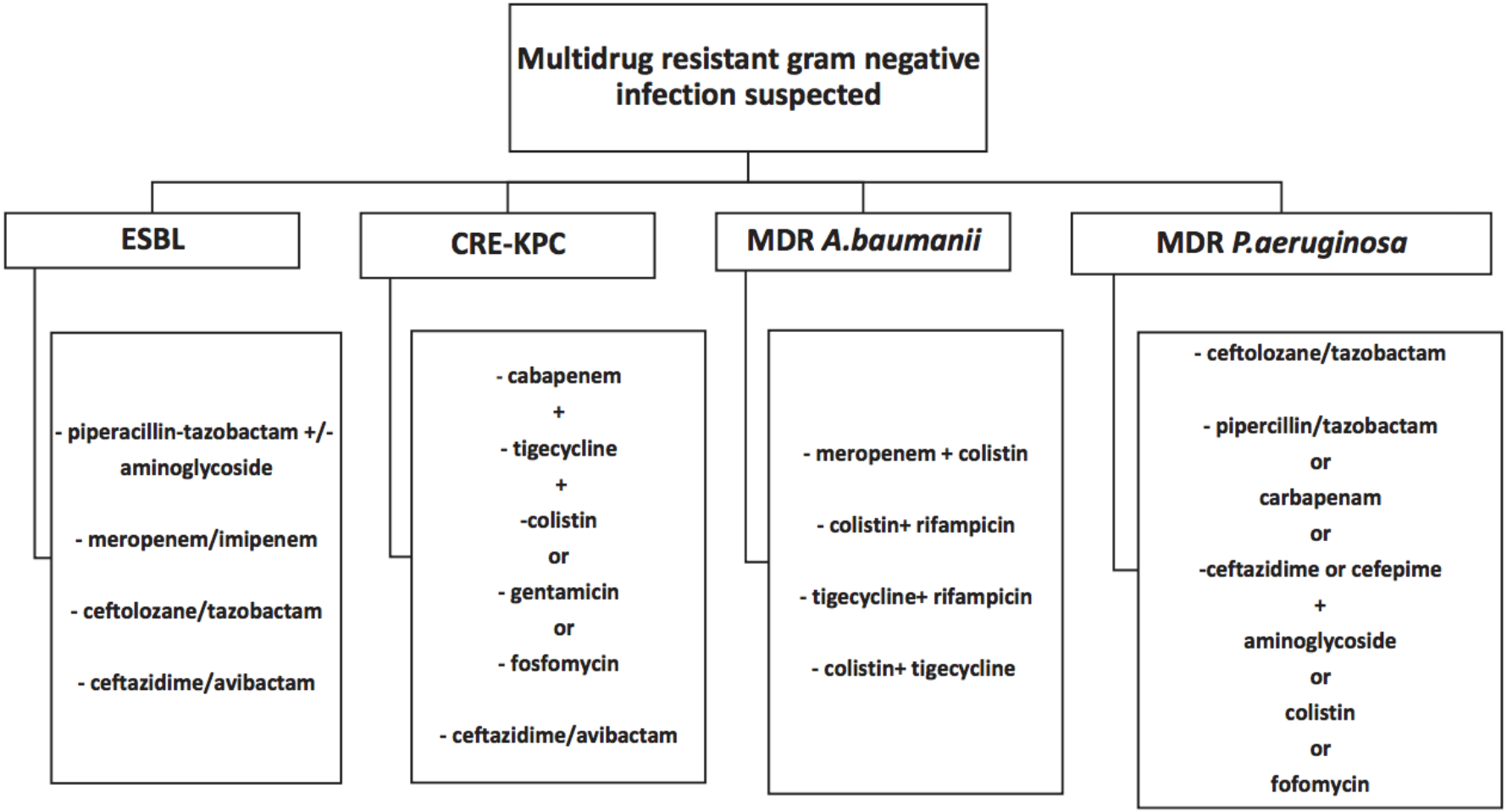

Right drug
Combination therapy?
PK/PD
Duration of therapy
Dosing strategy
Adverse events
Lab testing
Correct treatment MDRO

Public Health England

Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae

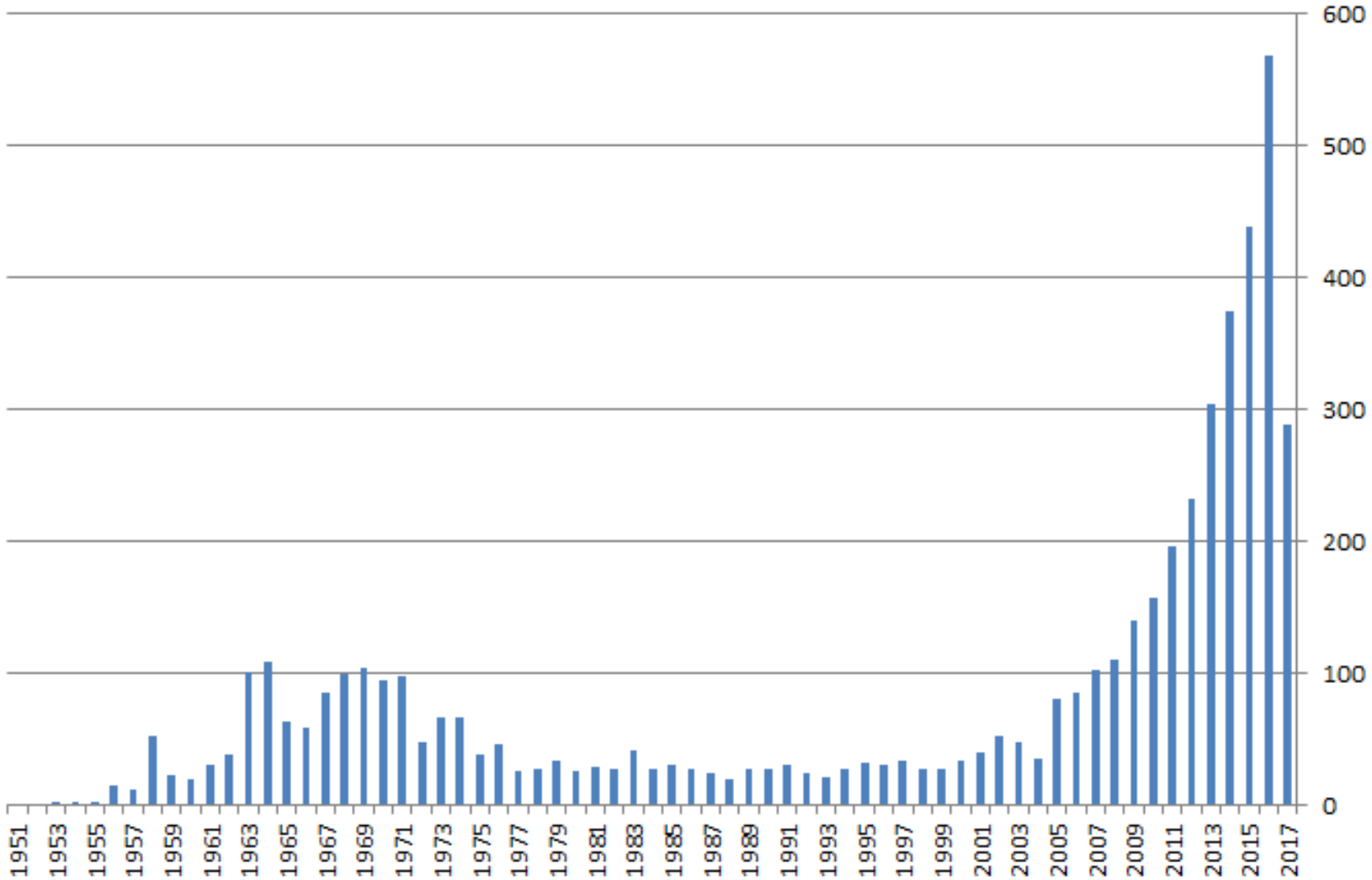
A.5 Effective treatment – antibiotics and a view on decolonisation

KEY MESSAGE: Treatment[13] of the patient with an infection caused by carbapenemase-producing Enterobacteriaceae should be undertaken under the advice of the microbiologist
Firstly, establish whether the patient has an infection or is colonised with carbapenemase-producing Enterobacteriaceae as confirmed on laboratory testing:
If the patient has an infection, *under the advice of the microbiologist*, consider: Monotherapy (not recommended for treatment of severe infection): • Polymyxins (eg colistin) • Tigecycline • Fosfomycin[14] (i.v. or, for lower UTI only, oral), is active against most carbapenemase-positive *E. coli,* but variable against other genera • Aminoglycosides (less consistent) Combination therapy (supported by outcome analyses for treatment of severe infections): • Polymyxin + carbapenem • Polymyxin + tigecycline • Polymyxin + aminoglycoside



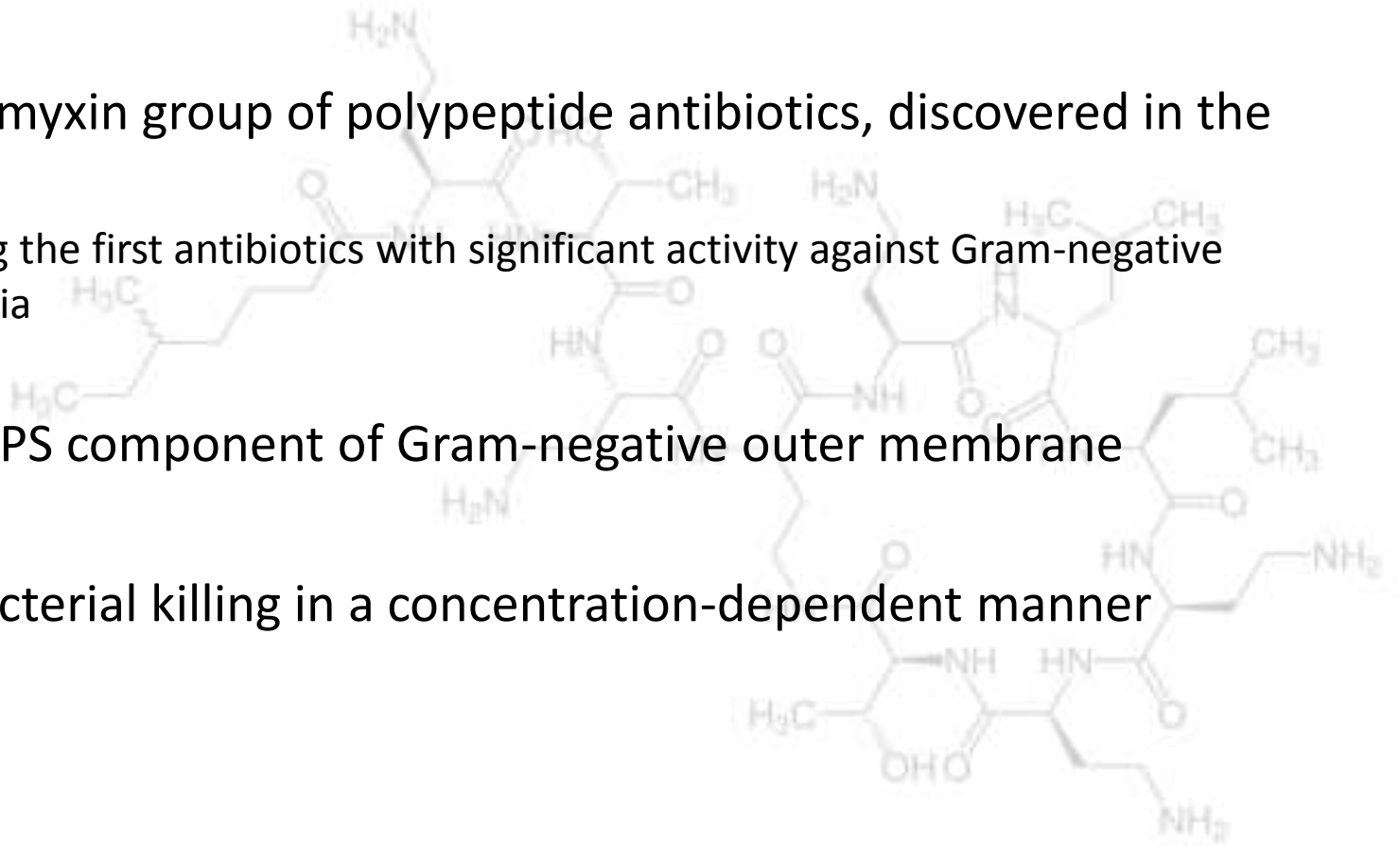
Bassetti et al. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. Expert Review of Anti-Infective Therapy. 2017.

PubMed Article on Colistin



“The” treatment option: Colistin

- Colistin is a cationic polypeptide antibiotic of the polymyxin family
- The polymyxin group of polypeptide antibiotics, discovered in the 1940s
  - among the first antibiotics with significant activity against Gram-negative bacteria
- Targets LPS component of Gram-negative outer membrane
- Rapid bacterial killing in a concentration-dependent manner



Clinical Microbiology and Infection, Volume 18 Number 1, January 2012

TISSUE PENETRATION

- Blood–brain barrier to the CNS is poor - estimated 5%
- Enhancement of penetration during meningitis and inflammation has been reported to range between 0 to 67%
- Distribution to the biliary tract, pleural fluid and joint fluid is considered to be similarly poor

TOXICITY

- Nephrotoxicity is the main adverse effect of colistin
  - older age, pre-existing renal insufficiency, hypo-albuminaemia, and concomitant use of NSAIDs or vancomycin
- In the last decade, neurologic side-effects of these antimicrobials have not been reported

Clinical Microbiology and Infection, Volume 18 Number 1, January 2012

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2014
EMA/785229/2014 corr1

European Medicines Agency completes review of polymyxin-based medicines

Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics

On 23 October 2014 the European Medicines Agency (EMA) completed a review of the safety and effectiveness of products containing the antibiotics colistin or colistimethate sodium (known as polymyxins) and recommended changes to their product information to ensure safe use in the treatment of serious infections that are resistant to standard antibiotics.

Polymyxin-based products have been available since the 1960s, but their use quickly decreased due to the availability of antibiotics with fewer potential side effects. Due in part to this limited use, colistimethate sodium has retained activity against a number of bacteria which have become resistant to commonly used antibiotics. This has led to a resurgence in recent years in the use of polymyxins in patients with few other options. However, current experience has raised concerns that the existing product information, in particular relating to dosing and the way the medicine is handled in the body (pharmacokinetics), might need updating. The European Commission therefore requested the EMA to

Loading 9MU
then
4.5 MU BD
OR
3MU TDS

? Filtration/
Haemodialysis
optimal dose

Paediatric / Neonatal
optimal dose

Al-lawama et al. Ann Clin Microbiol Antimicrob (2016) 15:8
DOI 10.1186/s12941-016-0126-4

Karli et al. Annals of Clinical Microbiology and Antimicrobials 2013, 12:32
http://www.ann-clinmicrob.com/content/12/1/32

ANNALS OF CLINICAL MICROBIOLOGY AND ANTIMICROBIALS

RESEARCH

Intravenous of multidru in neonates

Manar Al-lawama[1*], Hayth

Abstract

Background: Neonatal se parts of the world. It is a m the treatment of choice, fe

Methods: A retrospective and were treated with Coli

Results: During the study culture and clinical signs of (700–3600), respectively. N Nineteen (91 %) newborns our patients had elevated counts ± standard deviatic with a p value of less than

Conclusion: Our study sh bacter neonatal sepsis. This might affect the response

Keywords: Colistin, Sepsis

RESEARCH **Open Access**

Colistin use in pediatric intensive care unit for severe nosocomial infections: experience of an university hospital

Arzu Karli[1], Muhammet Sukru Paksu[2,6*], Adil Karadag[3], Nursen Belet[1], Sule Paksu[4], Akif Koray Guney[5], Muhammet Akgun[1], Nazik Yener[2] and Sema Gulnar Sensoy[1]

Abstract

Background: The aim of this study was to investigate the efficacy and safety of colistin therapy in pediatric patients with severe nosocomial infections in pediatric intensive care unit.

Methods: The medical records of patients treated with colistin at a 200-bed university children hospital were reviewed.

Result: Thirty-one patients (male/female = 22/9; median age, 3 years; range, 3 months-17 years) received forty-one courses of colistin. The average dose of colistin was 4.9 ± 0.5 mg/kg/day and average treatment duration was 19.8 ± 10.3 days. Three patients who received concomitant nephrotoxic agent with colistin developed nephrotoxicity. Colistin treatment was well tolerated in other patients, and neurotoxicity was not seen in any patient. Favourable outcome was achieved in 28 (68.3%) episodes. Twelve patients died during the colistin therapy. Six of these patients died because of primary underlying disease. The infection-related mortality rate was found 14.6% in this study.

Conclusion: In our study, colistin therapy was found to be acceptable treatment option for the severe pediatric nosocomial infections caused by multi-drug resistant bacteria. However, the use of concomitant nephrotoxic drugs with colistin must be avoided and renal function test should be closely monitored.

Keywords: Colistin, Child, Multi-drug resistant bacteria, Nosocomial infection, Nephrotoxicity

High Dose Intravenous Colistimethate Sodium (Colistin) Guideline for the treatment of multi drug resistant Gram-negative organisms

NEONATAL Dosing

The data supporting the dose regimen in neonates is very limited. The regimen below is seen very much as an initial dosing schedule based on a paper from the Indian Neonatal experience.

50,000 units – 75,000 units per kilogram per day in 3 divided doses

A multi-disciplinary discussion should take place regarding on-going management including infection specialists with experience of using the drug in adults. Obtaining colistin levels is critical in the management and subsequent dosing in this population.

The full paper is available from pharmacy.

PAEDIATRIC Dosing

The data supporting the dose regimen in paediatric patients are very limited. Renal function should be taken into consideration when selecting the dose. The dose should be based on lean body weight (calculate using a centile chart for height).

Children ≤ 40kg: 150,000 units per kilogram per day in 3 divided doses.

For children with a body weight above 40 kg, use of the dosing recommendation for adults should be considered.

The use of doses >150,000 units per kilogram per day has been reported in children with cystic fibrosis.

There are no data regarding the use or magnitude of a loading dose in critically ill children.

No dose recommendations have been established in children with impaired renal function.

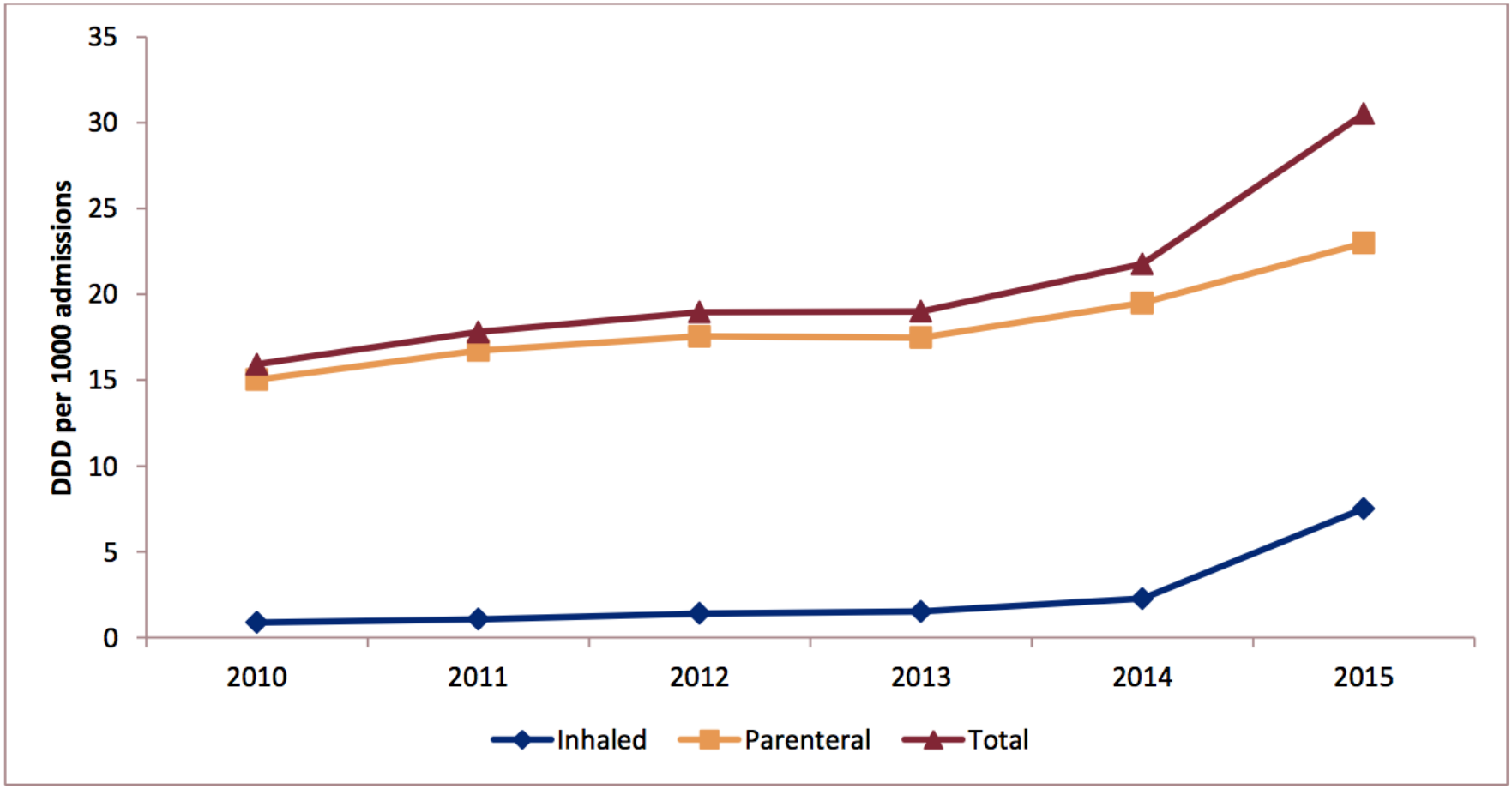


Figure 3.27 Colistin consumption in all trusts, expressed as DDD per 1000 admissions, England, 2010-2015

ESPAUR 2016, PHE

Emergence of plasmid-mediated colistin resistance

Lancet Infect Dis 2016;

Hospital outbreak of MCR-1 Klebsiella reported in China

Filed Under: Antimicrobial Stewardship; MCR-1

Chris Dall | News Reporter | CIDRAP News | May 25, 2017

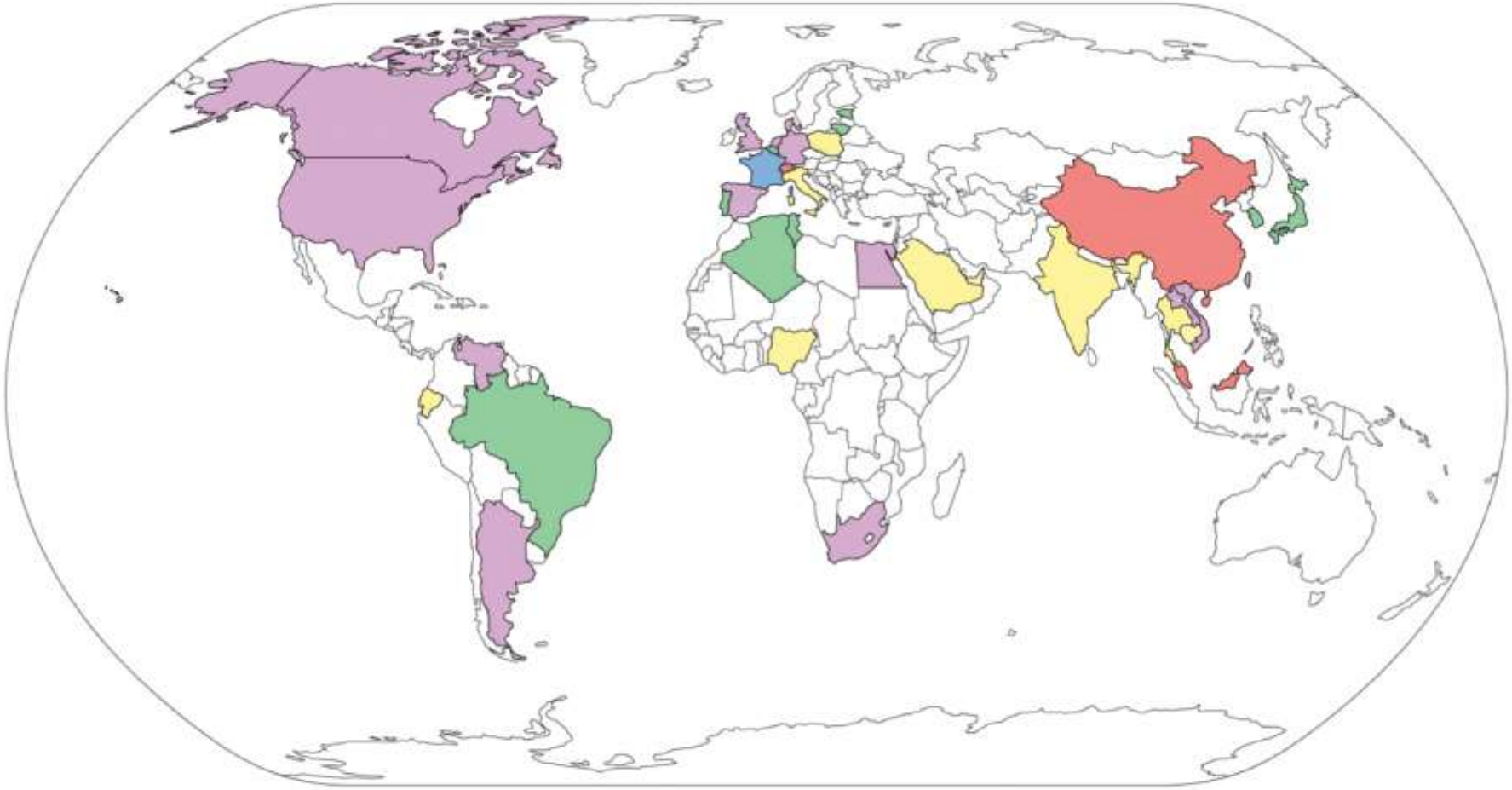
kdshutterman / iStock

Chinese scientists are reporting a deadly outbreak of MCR-1-producing *Klebsiella pneumoniae* among pediatric leukemia patients in China, apparently the first reported hospital outbreak involving the colistin-resistance gene.

In a letter published in *The Lancet Infectious Diseases*, researchers say clinical isolates—including one *Escherichia coli* and five *K pneumoniae*—from six patients with pneumonia admitted to a pediatric leukemia ward in Guangzhou, China, were found to harbor the colistin-resistance gene. The isolates were collected from January 2015 through January 2016.

In addition to colistin, which is considered a last-resort antibiotic, the six isolates were resistant to several other antibiotics, including polymixin B, cefotaxime, and gentamicin. The five *K pneumoniae* isolates were additionally resistant to ceftazidime, cefepime, amikacin, fosfomycin, and ciprofloxacin.

Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*



Isolate source(s):

- Animals
- Humans
- Animals and humans
- Animals and environment
- Animals, humans and environment

Data source: Al-Tawfiq, J. A., Laxminarayan, R. & Mendelson, M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? Int. J. Infect. Dis. (2016). doi:10.1016/j.ijid.2016.11.415

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

World Health Organization

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

WHO Secretariat: N. Magrini, L. Mojs, M. Sl-Mehand and Marie-Paule Kieny

subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.

	FDA Approv	EUCAST Brkpt	Enterobacteriaceae					MDR Pseudo monas	MDR Acineto bacter
			ESBL	AmpC	OXA48	KPC	MBL		
Ceftolozane-tazobactam	Yes	Yes							
Ceftazidime-avibactam	Yes	Yes							
Imipenem-relebactam	No	No			If carba sen				
Meropenem-vaborbactam	Yes	No			If carba sen				
Aztreonam-avibactam	No	No							
Cefiderocol	No	No							
Eravacycline	No	No							
Plazomicin	No	No							

Active	Variable	Not active

Adapted from Wright et al. New agents for the treatment of infections with Gram-negative bacteria: Restoring the miracle or false dawn. CMI Sept 2017

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne bla_{KPC-3} Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ceftolozane-Tazobactam

- Licensed in 2016
  - Intra-abdominal (ASPECT-cIAI CID, 2015)
  - Urinary tract (ASPECT-cUTI Lancet ID 2015)
- Off licensed indications for MDR Pseudomonas
  - high affinity for PSA PBPs
- Questions over trial dosing structure
  - 3g TDS currently in phase 3
  - Stability data re: prolonged infusion
- Learn lessons of history (dose reduction)

http://www.medicines.org.uk/emc/medicine/31132 accessed June 17

ACCEPTED MANUSCRIPT

Colistin vs. Ceftazidime-avibactam in the Treatment of Infections due to Carbapenem-Resistant Enterobacteriaceae

David van Duin, M.D., Ph.D. ✉, Judith J Lok, Ph.D., Michelle Earley, M.S.,

Clinical Infectious Diseases, cix783,
Published: 04 September 2017

- Prospective, multicenter, observational study.
- KPC-producing *Klebsiella pneumoniae*
- Patients selected by consortium
- 38 with CTZ/AVI and 99 colistin
  - Most received additional anti-CRE agents.
- All cause hosp mortality at 30 days
  - 9% ceftaz/avi
  - 32% colistin
  - Difference 23% (95% bootstrap CI:9-35%) p=0.0012
- Indicated uniform superiority but need RCT

- Decreased efficacy in poorer renal function
- Development of resistance in short courses of concern

Meropenem-Vaborbactam

- FDA approved Sept 2017
- TANGO-1
  - Phase 3 trial in cUTI
- TANGO-2
  - Multi-center, randomised, open label phase 3 trial mero-vabor Vs best available therapy for blood, cUTI, HAP/VAP, IAI for CRE
  - Discontinued randomisation as improved clinical cure rates compared to comparator
    - Also clear difference in renal toxicity
  - Continued single arm recruitment
  - Metallos and OXAs excluded

ClinicalTrials.gov: NCT021689946

Relebactam with Imipenem

- Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial
- To estimate efficacy and safety of Imipenem/ Relebactam Versus Colistin + Imipenem in Imipenem-Resistant Bacterial Infection (RESTORE-IMI 1)
- Phase 3 ongoing – est completion 29 Sept 2017
- HAP/ VAP/ cIAI/ cUTI
- Not UK

https://clinicaltrials.gov/ct2/show/NCT02452047

Plazomicin

- Novel aminogylcoside
- MDR Enterobacteriaceae, including CRE
  - EPIC (Evaluating Plazomicin in cUTI)
    - Plazomicin successfully met the objective of non-inferiority compared to meropenem
  - CARE (Combating Antibiotic Resistant Enterobacteriaceae)
    - In the Phase 3 CARE trial, a lower rate of mortality or serious disease-related complications was observed for plazomicin compared to colistin therapy.
- FDA Q3 2017 & EMA 2018
- Weakness against 16S rRNA methylases
- Likely TDM will be required
- ?good combination with ceftaz/avi

Cefiderocol

- Siderophore cephalosporin
  - Active transport of drug over outer membrane
- Active against ESBL, KPC, MBL and OXAs
- APEKS-cUTI trial
  - Met non-inferiority to imipenem for cUTI
- CREDIBLE-CR trial
  - Best available for severe infections caused by CRE
  - Phase 3 RCT currently recruiting.

Eravacycline

- Novel, synthetic fluorocycline tetracycline
- Similar to tigecycline
- Active against KPC, OXAs, NDM
- Not active against Pseudo or Burkholderia
- Trials
  - cIAI and cUTI compared with ertapenem. Similar clinical cures but low severity and low level resistance
  - cUTI compared to levo did not reach non-inferiority
- ?similar issue to tigecycline and higher mortality rates in severe infection

MDT approach

Take home points

- If the MSSA bacteraemia not improving
  - ?diagnostic
  - ?management
- Don't have as much fun as the 70s as we now don't have the drugs to help you
- Screen at your peril…

(My prediction = inevitable)

Acknowledgements

- Imperial College Healthcare NHS Trust
- Mark Gilchrist
- Jon Otter
- Hugo Donaldson
- Frances Davies
- Helen Fifer
- Michelle (PHE)