UW TASP tele-antimicrobial stewardship program | echo

March 28, 2017

Robert Cybulski, PhD
Marisa D'Angeli, MD
Zahra Escobar, PharmD
Natalia Martinez-Paz
Laura Quilter, MD
Yuan Zhou, MD

Agenda

- Didactic: *Drug Resistance in Washington*
- Discussion: *Status of programs and plans for AS interventions*

URL: http://rwpoll.com
Code: uwecho

UW TASP tele-antimicrobial stewardship program | echo

Drug Resistance in Washington: *ESBLs*

John Lynch, MD, MPH
Harborview Medical Center &
The University of Washington

March 27, 2017

URL: http://rwpoll.com
Code: uwecho

This presentation is intended for educational use only, and does not in any way constitute medical consultation or advice related to any specific patient.

Antimicrobial Drug Resistance

What is it?

Non-specific term indicating that a micro-organism is no longer susceptible to the antimicrobials typically used for that infection.

Associated with worse outcomes, longer LOS and increased costs

Examples…

- MRSA, VISA, VRSA
- VRE
- Extended-spectrum beta-lactamases (ESBLs)
- Carbapenem-resistant enterobacteriaceae, such as *E. coli, Salmonella, Klebsiella,* and *Shigella* spp.
- Multi-drug resistant tuberculosis (MDR-TB)
- Drug-resistant *Neisseria gonorrheae*

Definitions of Common Terms Used to Describe Resistant Gram-Negative Bacilli

β-lactam antibiotics	These antibiotics comprise the penicillins , cephalosporins and carbapenems, which share the common basic chemical structure of a 4-member β-lactam ring.
β-lactamases	These enzymes hydrolyze the β-lactam ring and inactivate the β-lactam class of antibiotics.
Ambler classification	This is a classification system for β-lactamases on the basis of their amino acid sequences and their active site residue.
Extended-spectrum β-lactamases (ESBLs)	These are broad-spectrum, Ambler class A β-lactamases, which hydrolyze the penicillins, and first- to fourth-generation cephalosporins, which are cefoxitin susceptible and are inhibited by the β-lactamase inhibitors (eg clavulanate).
Cephalosporinases	ESBLs are technically cephalosporinases but the term cephalosporinase is generally reserved to describe Ambler class C AmpC β-lactamases, which are cefoxitin resistant, hydrolyze the penicillins and first to third-generation cephalosporins, and are not inhibited by the β-lactamase inhibitors, such as clavulanate.
Carbapenemases	These are broad-spectrum β-lactamases (usually Ambler class A, B, or D), which have the ability to hydrolyze carbapenems, in addition to the penicillins and also the first- to fourth-generation cephalosporins, although activity may vary depending on the exact type of carbapenemase.
Carbapenem-resistant gram-negative bacilli and carbapenem-resistant Enterobacteriaceae vs carbapenemase-producing gram-negative bacilli (CPGNB) and carbapenemase-producing Enterobacteriaceae	CPGNB are most often CRGNB (susceptibility testing may yield rare isolates and may have low carbapenem minimum inhibitory concentrations); however, not all CRGNB are carbapenemase producers. Carbapenem resistance may be mediated by ESBL or AmpC production, for example, associated with porin loss.

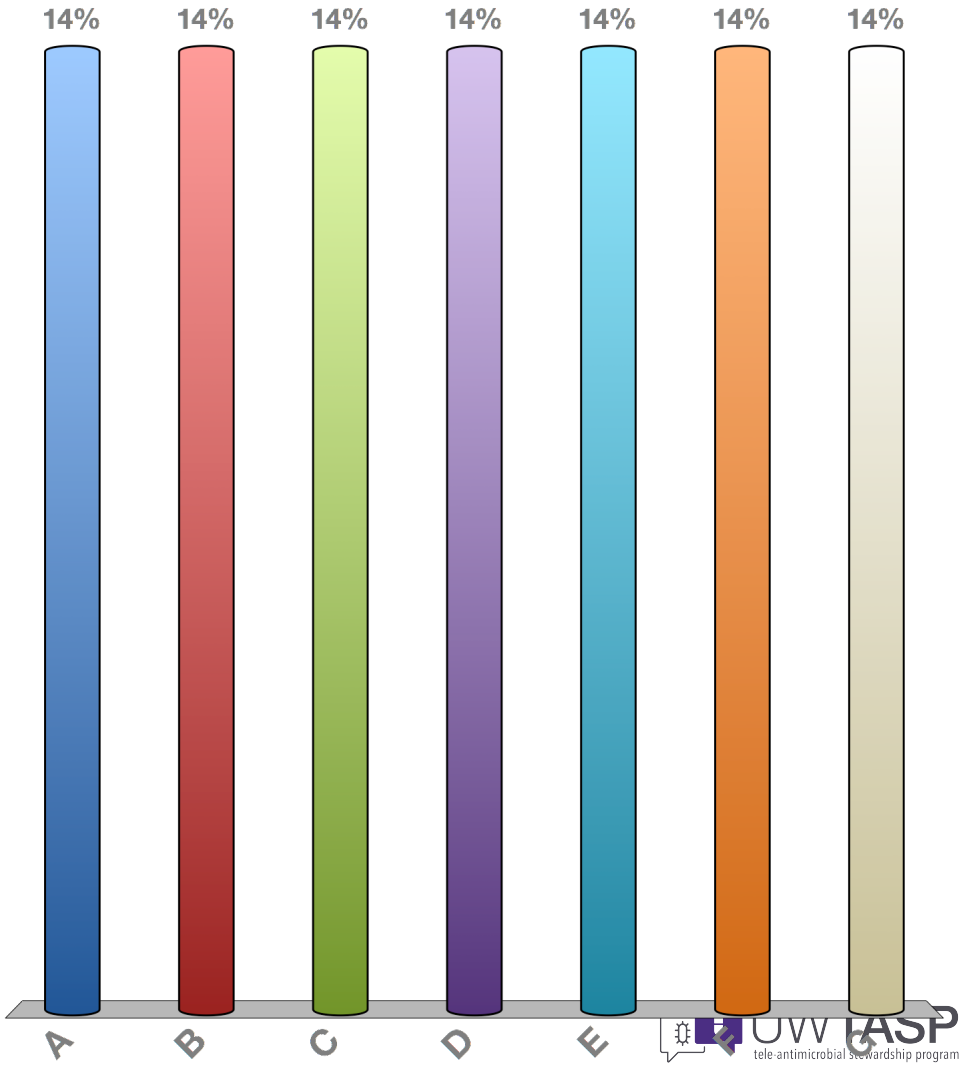
Vasoo, Mayo Clin Proc 2015

ESBLs

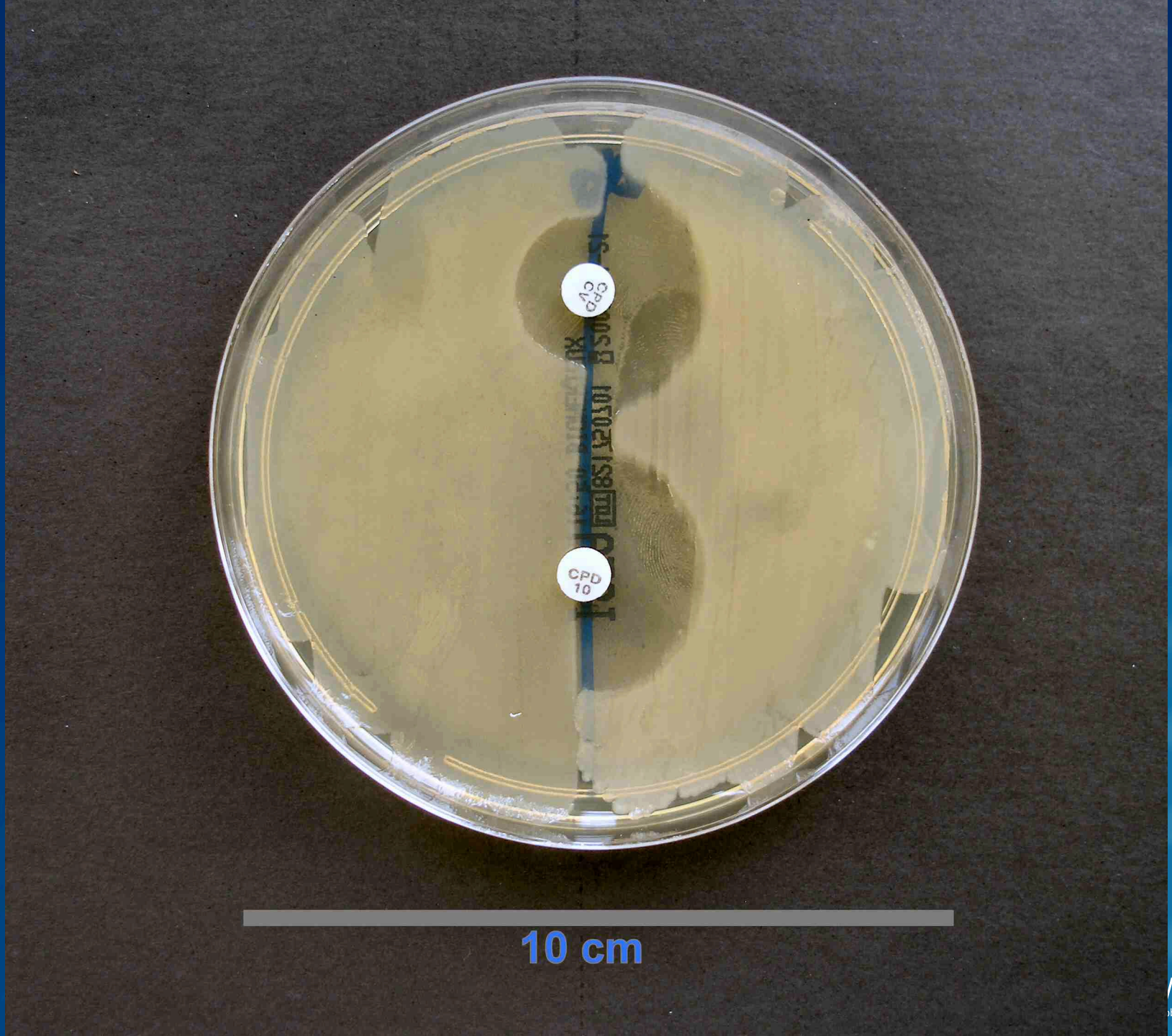
- MOST IMPORTANT mechanism of resistance in GNRs
- First identified in Germany in 1983
- A family of enzymes (often on a plasmid) that degrade the beta-lactam ring of most penicillins and cephalosporins
  - Exceptions: carbapenems, cephamycins (cefoxitin), ceftolozane-tazobactam, ceftazidime-avibactam
- Main mechanism of resistance to 3rd generation cephalosporins like ceftriaxone, ceftazidime and cefotaxime

ARS: Which of the following genes encodes an ESBL?

A. CTX-M
B. SHV
C. TEM
D. OXA
E. AmpC
F. None of the above
G. A through D



URL: http://rwpoll.com
Code: uwecho


CPD 2
CPD 10
10 cm

GNR Resistance Detection: ESBLS

MOA		ESBL	
Location		Plasmid	
Bugs		*E.coli, Klebsiella*	
1 gen Ceph		R	
2 gen Ceph		S	
3 gen Ceph		R	
4 gen Ceph		R / S	
Cefotax + Clav		S	
Carbapenem		S	

ESBLs

- Organisms with ESBL genes often have other mechanisms of resistance (plasmids, transposons, etc)
- Incidence in the U.S. is rising

Rate of ESBL Phenotype in Escherichia coli and Klebsiella Species in 2009 and 2011

	2009	2011
E. coli in United States	11.9%	17.4%
E. coli in Europe	17.8%	20.3%
Klebsiella species in United States	16.2%	18.6%
Klebsiella species in Europe	27.5%	41.8%

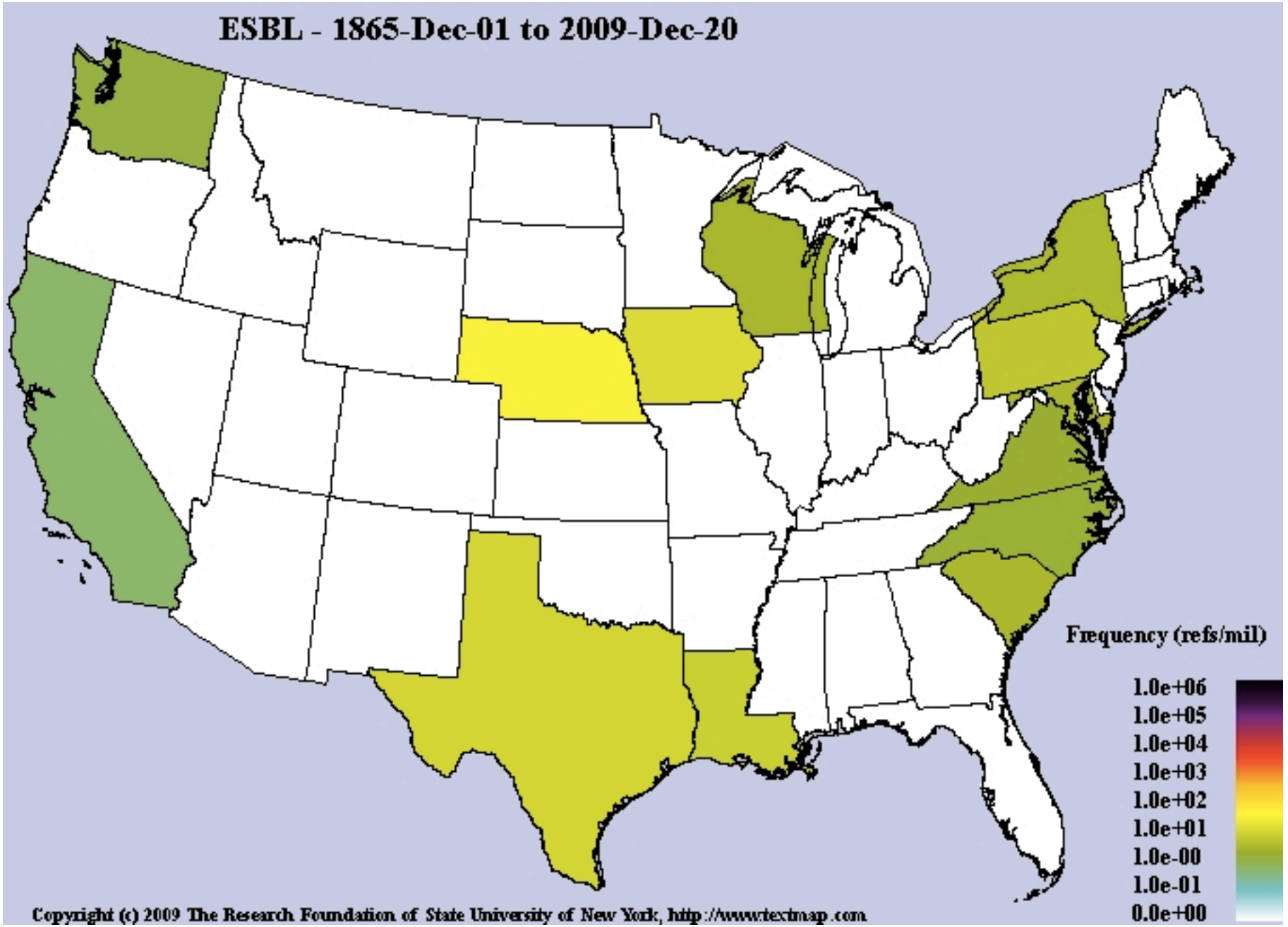
Dynamed, 2016

ESBLs: Epidemiology

- Global epidemic
- Initially all/most were healthcare-acquired
- More recently, infections also coming from community
- Risk factors:
  - recurrent UTI
  - SNF/LTACH residence
  - Exposure to cephalosporins/fluoroquinolones
  - Older age

Comparison of the antimicrobial usage during the last 60 days prior to inclusion in the study population with and without ESBL-producing Enterobacteriaceae infection.

Antimicrobials	ESBL (n = 212)	Non-ESBL (n = 2089)	*p* Value
Aminoglycoside	18 (8.5)	25 (1.2)	<0.0001
Carbapenem	50 (23.6)	239 (11.4)	<0.0001
Cephalosporin			
First generation	11 (5.2)	161 (7.7)	0.184
Second generation	42 (19.8)	120 (5.7)	<0.0001
Third generation	19 (9.0)	200 (9.6)	0.7724
Fourth generation	64 (30.19)	61 (2.9)	<0.0001
Chloramphenicol	9 (4.3)	1 (0.1)	<0.0001
Cyclic lipopeptide	1 (0.5)	11 (0.5)	0.6951
Fosfomycin	5 (2.4)	12 (0.6)	0.0156
Fluoroquinolone	48 (22.6)	160 (7.7)	<0.0001
Glycopeptide	18 (8.5)	112 (5.4)	0.0601
Clindamycin	21 (9.9)	67 (3.2)	<0.0001
Macrolide	1 (0.5)	37 (1.8)	0.1213
Oxazolidinone	30 (14.2)	38 (1.8)	<0.0001
Penicillin	6 (2.8)	224 (10.7)	0.0003
Penem	2 (0.9)	9 (0.4)	0.2691
ST[a]	15 (7.1)	61 (2.9)	0.0013
Tetracycline	43 (20.3)	38 (1.8)	<0.0001
Antifungal agent	25 (11.8)	89 (4.3)	<0.0001


ESBL - 1865-Dec-01 to 2009-Dec-20
Frequency (refs/mil)
1.0e+06
1.0e+05
1.0e+04
1.0e+03
1.0e+02
1.0e+01
1.0e-00
1.0e-01
0.0e+00
Copyright (c) 2009 The Research Foundation of State University of New York, http://www.textmap.com

Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study

Maris S Arcilla, Jarne M van Hattem*, Manon R Haverkate, Martin C J Bootsma, Perry J J van Genderen, Abraham Goorhuis, Martin P Grobusch, Astrid M Oude Lashof, Nicky Molhoek, Constance Schultsz, Ellen E Stobberingh, Henri A Verbrugh, Menno D de Jong, Damian C Melles, John Penders*

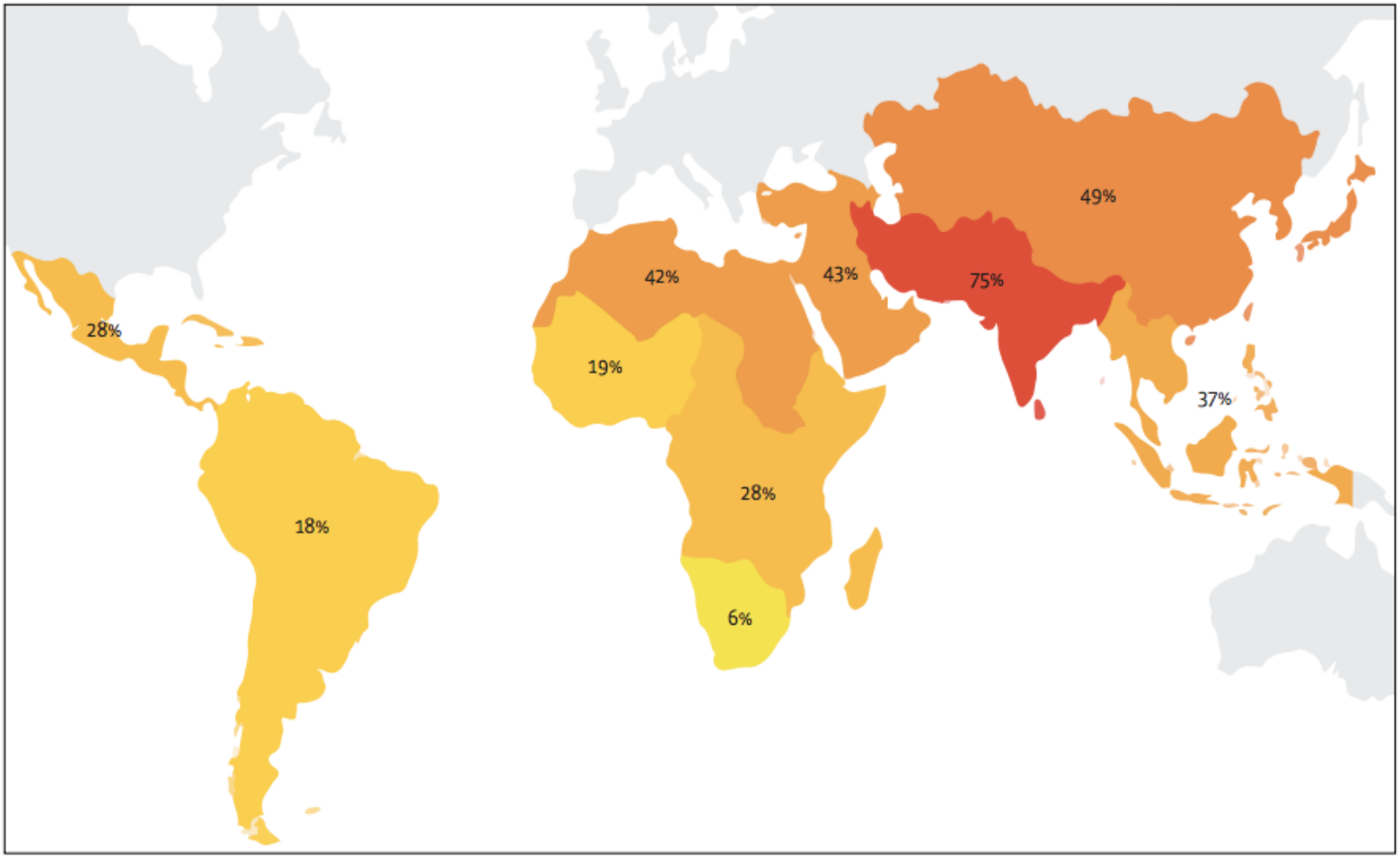
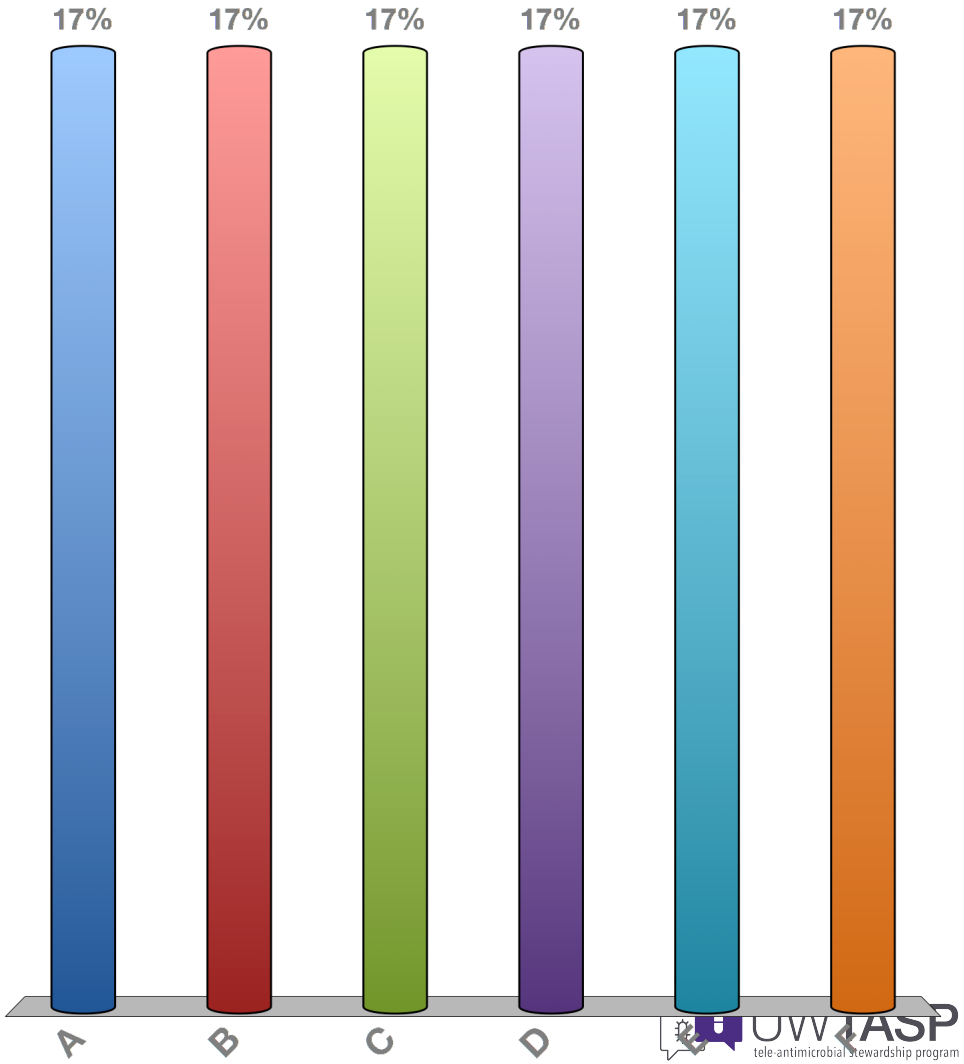


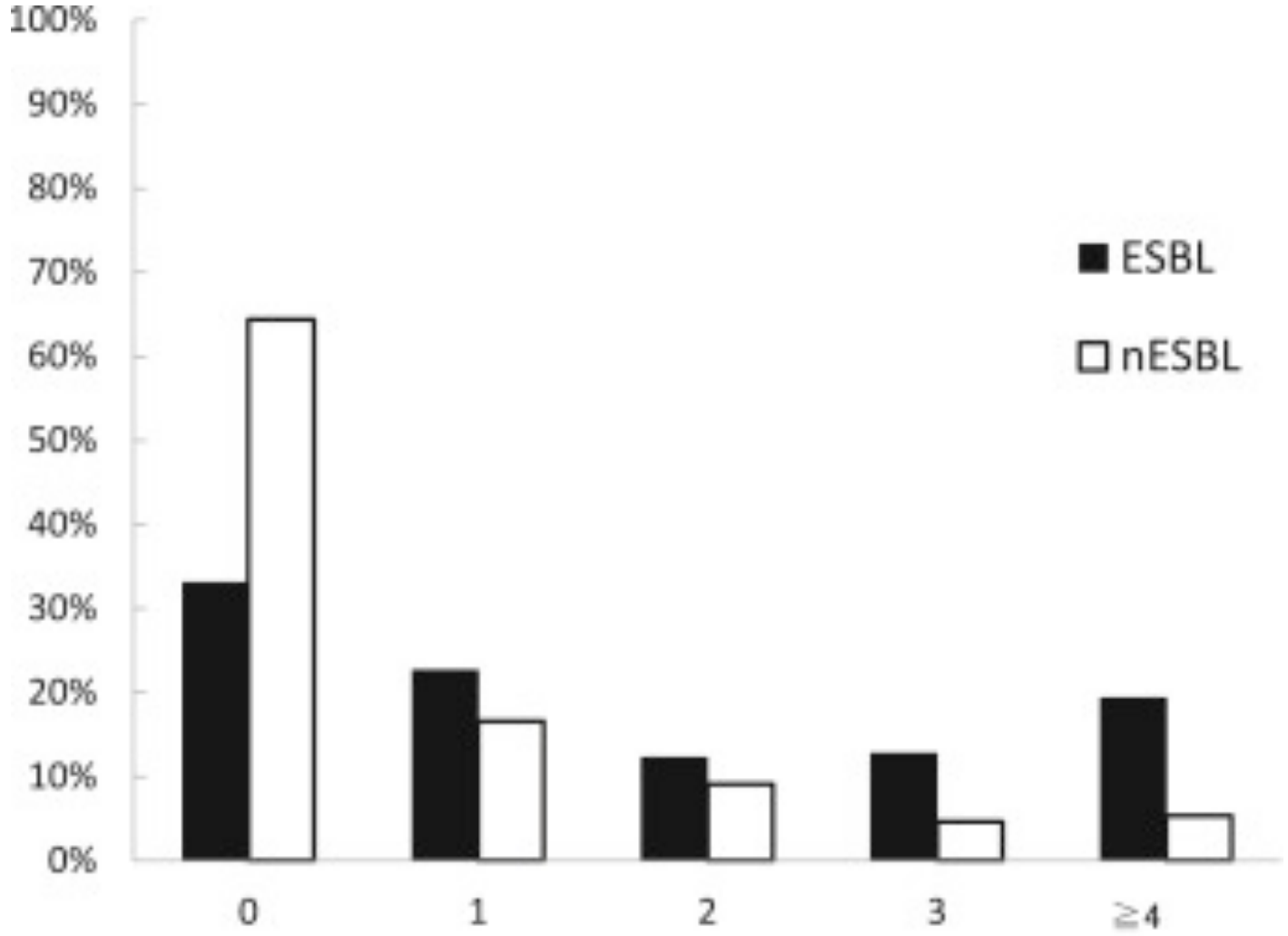
Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

ARS: In the COMBAT Study, how long were ESBLs detectable in the study subjects?

A. 2-3 months
B. 6 months
C. 12 months
D. 16 months
E. 2-3 years
F. Indefinitely



URL: http://rwpoll.com
Code: uwecho



The number of antimicrobial usage between infectious patients with and without- ESBL-producing Enterobacteriaceae proceeding 60 days. The frequency of antimicrobial usage in infectious patients with ESBL-producing Enterobacteriaceae was higher than tha...

Hazuki Nakai, Mao Hagihara, Hideo Kato, Jun Hirai, Naoya Nishiyama, Yusuke Koizumi, Daisuke Sakanashi, Hiroyuki Suematsu, Yuka Yamagishi, Hiroshige Mikamo

Prevalence and risk factors of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae
Journal of Infection and Chemotherapy, Volume 22, Issue 5, 2016, 319–326

Treatment Options

- Carbapenems
- Fosfomycin
- Cetazidime-avibactam or cetolozane-tazobactam
- Nitrofurantoin
- Aminoglycosides
- Tigecycline

References

Tal Jasper, R., Coyle, J. R., Katz, D. E. & Marchaim, D. The complex epidemiology of extended-spectrum β-lactamase-producing Enterobacteriaceae. *Future Microbiol.* **10,** 819–839 (2015).

D'Angelo, R. G., Johnson, J. K., Bork, J. T. & Heil, E. L. Treatment options for extended-spectrum beta-lactamase (ESBL) and AmpC-producing bacteria. *Expert Opin. Pharmacother.* **17,** 953–967 (2016).

Arcilla, M. S. *et al.* Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect. Dis.* **17,** 78–85 (2017).

Nakai, H. *et al.* Prevalence and risk factors of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. *J. Infect. Chemother.* **22,** 319–326 (2016).

UW TASP tele-antimicrobial stewardship program | echo

Thank you!

Topics for next week?

Next session: Tuesday April 4th, 2017