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Do clinical microbiology laboratory data distort the picture of antibiotic resistance in humans and domestic animals?

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2 June 2018
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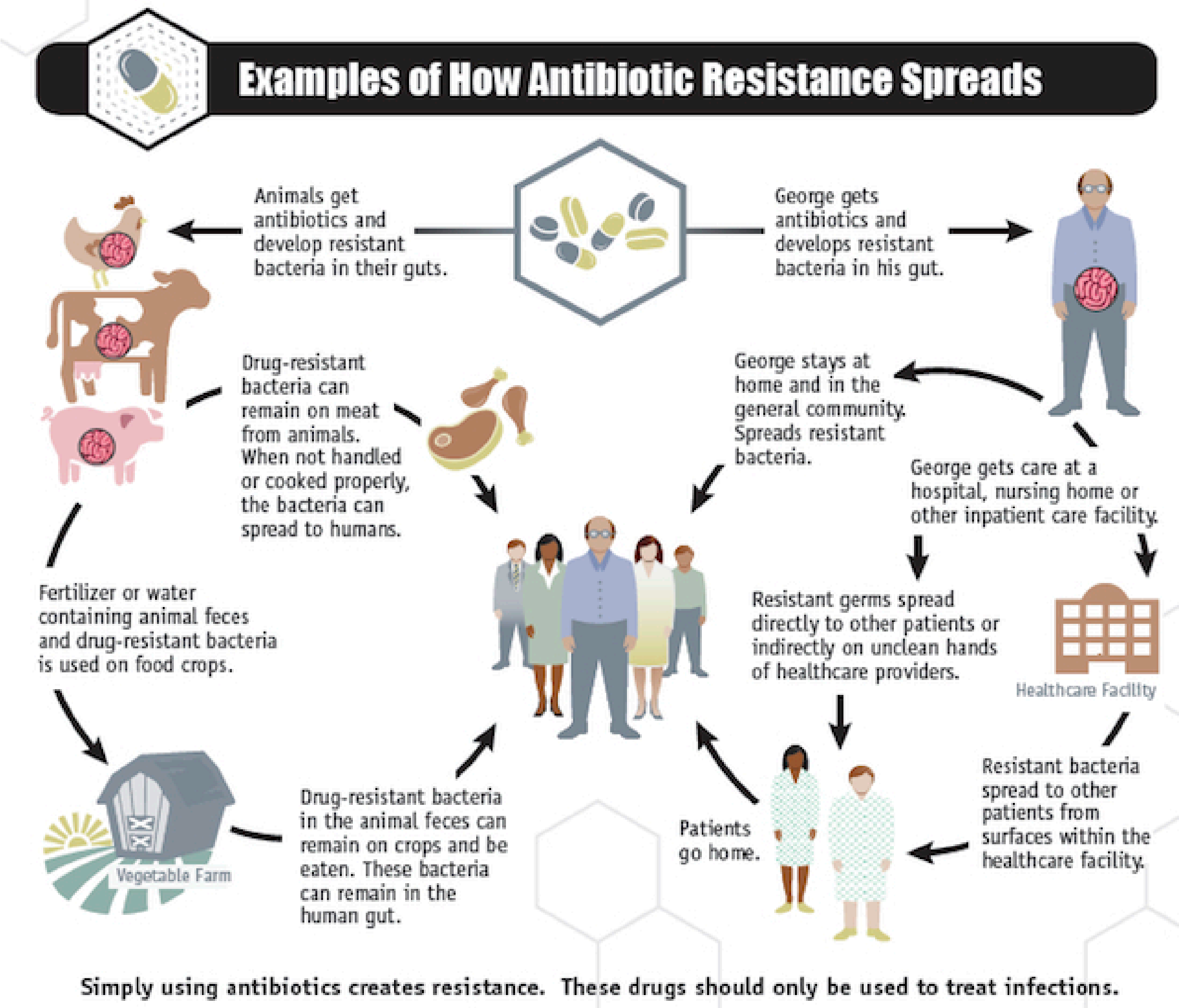
Disclosures

I have no financial conflicts of interest to disclose

Vive la resistance.



The goals of the *National Action Plan* include:

1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections.
2. Strengthen National One-Health Surveillance Efforts to Combat Resistance.
3. Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria.
4. Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines.
5. Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development.

MARCH 2015

THE WHITE HOUSE
WASHINGTON

An integrated human, animal and environmental health approach to antimicrobial resistance

One Health concept endorsed by:
WHO
CDC
USDA
National Academy of Medicine

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Integrated?

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Washington State One Health Committee

WA Department of Fish and Wildlife

WA Department of Health

WA Department of Agriculture

UW Center for One Health Research

WSU Colleges of Veterinary Med and Ag

Office of the Governor

UW Dept. of Allergy & Infectious Diseases

Washington State Veterinary Medical Association

Washington State Medical Association

One Health Working Groups

Antimicrobial Stewardship WG

Data Integration WG

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Data Integration Working Group

How do we look regionally at antimicrobial resistance in a One Health way?

Partying like it's 1999

results displayed as <u>% resistant</u>

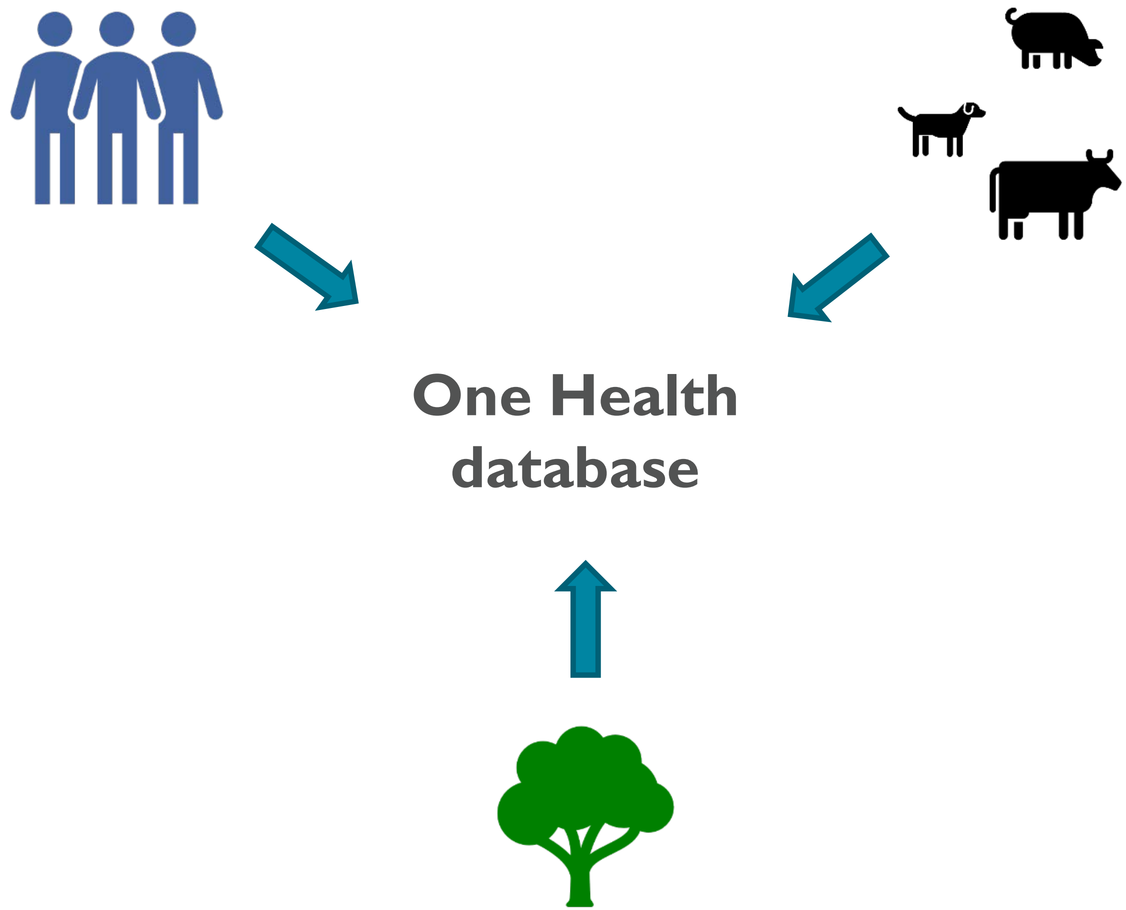
GRAM POSITIVE ISOLATES	Number Tested	Ampicillin	Carbenicillin	Cefamandole	Cephalothin	Chloramphenicol	Clindamycin	Erythromycin	Gentamicin	Methicillin	Penicillin	Sulfisoxazole	Tetracycline	Tobramycin	Trimethoprim-sulfamethoxazole	Vancomycin
Enterococcus	75	0				1		25		100			72			0
Staph. aureus	627	87		0	0	0	2	6	3	0	87		8			0
Staph. epidermidis	61	48		2	2	2	39	39	28	20	48		33			0
Strept. grp. B	14	0		0	0	0	0	0	14	0	0		86			0
Strept. pneumoniae	26					0		0			0					
GRAM NEGATIVE ISOLATES																
Acinetobacter	17	94	12	100	100	50			18			6	60	18	20	
Citrobacter freundii	11	54	18	18	54	0			0			36	44	0	30	
Enterobacter cloacae	21	90	14	24	90	0			0			14	18	0	18	
Escherichia coli	421	32	32	0	10	17			0			30	25	0	3	
Haemophilus influenzae B	76	15				0										
Klebsiella oxytoca	35	98	100	1	1	0			0			1	4	0	9	
Klebsiella pneumoniae	60	92	92	0	1	1			0			18	10	0	5	
Morganella morganii	5	100	0	20	100				0			40	20	0	20	
Neisseria meningitidis	9					0					0	0				
Proteus mirabilis	29	0	0	0	3	0			0			24	96	0	10	
Proteus vulgaris	7	100	0	52	100	0			0			29	80	0	0	
Pseudomonas aeruginosa	258	96	23	96	100	84			12			85	85	0	94	
Pseudomonas maltophilia	12	100	92	100	100	9			58			17		42		
Salmonella sp.	28	14	14	0	0	11			0			26		0		
Serratia marcescens	16	100	6	100	100				6			50	77	6	11	
Shigella sp.	10	0	0	0	0				0			80	40	0	0	
Yersinia enterocolitica	4	75	75	0	75	0			0			0		0	0	

Limitations of the annual institutional antibiogram

- Static
  - Once a year
  - Trends tell stories!
- Presented as a flat file (eg, pdf format)
  - Severed from back-end data where richness resides
  - Back-end data may have limited clinical information
- Aggregated by species
  - Assumes source patients are equivalent
    - Overestimates resistance in healthier patients
    - Underestimates resistance in sicker patients
- Time-intensive if done by hand or by homegrown electronic method
- Not transparent
  - Especially with regard to de-duplication methodology
- Implies to caregivers that the infectious threat is primarily bacterial

One Health Data Integration Working Group

How do we look regionally at antimicrobial resistance in a One Health way?



Washington Integrated Surveillance for Antibiotic Resistance (WISAR)

Purpose: Offer a cross-sector look at antibiotic resistance by combining human, animal and environmental data in common database

- Goal 1: Integrates data on antimicrobial resistance across human, animal and environmental health sectors
- Goal 2: Build capacity to detect and prevent emergence of antibiotic resistance
- Goal 3: Support stewardship efforts across human, animal, and environmental sectors

Isolate datasets enrolled to date

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Human Medicine:	0	0	0	0	0	0	0	0	7066	11024	11490	11196	11566	12237	13058	0	77637
NARMS Public Health Laboratory Surveillance (Human Clinical):	0	0	0	0	0	0	0	0	102	95	149	161	156	182	0	0	845
Veterinary Medicine:	806	16	0	272	770	935	971	896	927	950	754	711	5650	11561	9566	285	35070
NARMS Public Health Laboratory Surveillance (Non-human):	3015	3691	4133	3996	3944	3172	3371	3414	3773	3735	0	3904	4650	114	0	0	44912
																Total	158464

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Canine Antibiogram

WISAR Database Canine Antibiogram for All Isolates, 2002-2017

Gram-Negative Bacteria	# Isolates (Max tested)	Ampicillin	Amoxicillin-Clavulanate	Cefovecin	Cefpodoxime	Ceftiofur	Ticarcillin	Ticarcillin-clavulanic acid	Enrofloxacin	Marbofloxacin	Amikacin	Gentamicin	Trimethoprim-sulfamethoxazole	Chloramphenicol		Doxycycline	Tetracycline
		% Susceptible														
Acinetobacter	143	2%	40%	18%	20%	18%	89%	94%	47%	30%	99%	92%	92%	3%		98%	
Bordetella	49						86%	92%	59%	98%	61%	59%	94%	98%		100%	
Enterobacter	266	1%	0%	31%	36%	24%	4%	80%	89%	92%	100%	96%	94%	85%		88%	50%
Escherichia coli	5178	69%	81%	70%	77%	83%	64%	77%	91%	84%	100%	92%	91%	90%		83%	93%
Klebsiella	203	1%	14%	85%	84%	81%	1%	91%	93%	93%	100%	96%	93%	90%		88%	50%
Proteus mirabilis	900	88%	94%	88%	93%	95%	91%	100%	97%	97%	99%	92%	91%	87%		0%	0%
Pseudomonas aeruginosa	1232	1%	0%	0%	0%	1%	90%	92%	58%	66%	98%	81%	17%	1%		1%	0%
Serratia marcescens	136	4%	2%	40%	41%	44%	16%	95%	55%	87%	97%	89%	93%	70%		5%	
Pasteurella	341	100%	100%	99%	100%	100%	100%	100%	100%	94%	100%	100%	99%	100%		100%	

Gram-Positive Bacteria	# Isolates (Max tested)	Ampicillin	Amoxicillin-Clavulanate	Cefovecin	Cefpodoxime	Ceftiofur	Ticarcillin	Ticarcillin-clavulanic acid	Enrofloxacin	Marbofloxacin	Amikacin	Gentamicin	Trimethoprim-sulfamethoxazole	Chloramphenicol	Clindamycin	Erythromycin	Doxycycline	Tetracycline
		% Susceptible																
Enterococcus sp.	1915	86%	87%	1%	3%	5%	12%		42%	24%	47%	8%	42%	91%	7%	28%	73%	56%
Staphylococcus sp.	5261	30%	76%	76%	75%	76%	45%	76%	71%	77%	100%	76%	80%	87%	70%	70%	71%	82%
Streptococcus sp.	1185	95%	100%	97%	99%	99%	98%	100%	65%	72%	73%	83%	87%	97%	90%	7%	78%	59%

Bug-drug combinations with <30 isolates are not shown in antibiogram

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Feline Antibiogram

WISAR Database Feline Antibiogram for All Isolates, 2002-2017																	
Gram-Negative Bacteria	**# Isolates (Max tested)**	**Ampicillin**	**Amoxicillin-Clavulanate**	**Cefovecin**	**Cefpodoxime**	**Ceftiofur**	**Ticarcillin**	**Ticarcillin-clavulanic acid**	**Enrofloxacin**	**Marbofloxacin**	**Amikacin**	**Gentamicin**	**Trimethoprim-sulfamethoxazole**	**Chloramphenicol**		**Doxycycline**	**Tetracycline**
		% Susceptible															
Enterobacter	46	**0%**	**0%**	**38%**	**63%**	**17%**	**3%**	**87%**	**95%**	**95%**	**98%**	**95%**	**98%**	**90%**		**92%**	
Escherichia coli	1751	**71%**	**87%**	**86%**	**89%**	**91%**	**69%**	**85%**	**95%**	**90%**	**99%**	**94%**	**96%**	**94%**		**85%**	**96%**
Proteus mirabilis	32	**83%**	**88%**			**90%**							**100%**				
Pseudomonas aeruginosa	123						**83%**	**85%**	**71%**	**90%**	**98%**	**93%**					
Pasteurella	199	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**96%**	**98%**	**98%**	**100%**			**100%**
Gram-Positive Bacteria	**# Isolates (Max tested)**	**Ampicillin**	**Amoxicillin-Clavulanate**	**Cefovecin**	**Cefpodoxime**	**Ceftiofur**	**Ticarcillin**	**Ticarcillin-clavulanic acid**	**Enrofloxacin**	**Marbofloxacin**	**Amikacin**	**Gentamicin**	**Trimethoprim-sulfamethoxazole**	**Chloramphenicol**	**Clindamycin**	**Erythromycin**	**Doxycycline**	**Tetracycline**
		% Susceptible															
Enterococcus sp.	822	**92%**	**93%**	**0%**	**0%**	**2%**	**10%**	**30%**	**45%**	**28%**	**5%**	**6%**	**38%**	**92%**	**4%**	**32%**	**74%**	**60%**
Staphylococcus sp.	679	**58%**	**82%**	**81%**	**79%**	**82%**	**62%**	**81%**	**85%**	**86%**	**93%**	**91%**	**89%**	**95%**	**76%**	**76%**	**93%**	**100%**
Streptococcus sp.	152	**96%**	**99%**	**98%**	**98%**	**99%**	**99%**	**100%**	**69%**	**71%**	**48%**	**60%**	**66%**	**94%**	**86%**	**25%**	**72%**	**73%**
Bug-drug combinations with <30 isolates are not shown in antibiogram																	

Bovine Antibiogram

WISAR Database Bovine Antibiogram for All Isolates, 2002-2017

Gram-Negative Bacteria	# Isolates (Max tested)	Ampicillin	Amoxicillin-Clavulanate	Ceftiofur	Ticarcillin	Enrofloxacin	Amikacin	Gentamicin	Trimethoprim-sulfamethoxazole	Chloramphenicol		
		% Susceptible										
Escherichia coli	3572	92%	98%	98%	68%	95%	100%	98%	97%	96%		
Pasteurella	44	80%		98%		84%		82%	81%			
Salmonella	322	63%	81%	74%		98%	100%	92%	98%	82%		
Gram-Positive Bacteria	**# Isolates (Max tested)**	**Ampicillin**	**Amoxicillin-Clavulanate**	**Ceftiofur**	**Ticarcillin**	**Enrofloxacin**	**Amikacin**	**Gentamicin**	**Trimethoprim-sulfamethoxazol**	**Chloramphenicol**	**Clindamycin**	**Erythromycin**
		% Susceptible										
Enterococcus sp.	4187	84%	91%	14%		30%		99%	87%	99%		32%
Staphylococcus sp.	113	53%	72%	89%	29%	92%	100%	82%	86%	98%	90%	77%

Bug-drug combinations with <30 isolates not shown in antibiogram

Poultry Antibiogram

WISAR Database Poultry Antibiogram for All Isolates, 2002-2017									
Gram-Negative Bacteria	# Isolates (Maximum Tested)	Ampicillin	Amoxicillin-Clavulanic acid	Ceftiofur	Amikacin	Gentamicin	Trimethoprim-sulfamethoxazole	Chloramphanical	
		% Susceptible							
Escherichia coli	8398	66%	85%	93%	99%	66%	95%	97%	
Salmonella	3817	65%	75%	84%	100%	84%	99%	97%	
Enterococcus sp.	9534					80%		98%	

Gram-Positive Bacteria	# Isolates (Max tested)	Ampicillin	Amoxicillin-Clavulanate	Ceftiofur	Amikacin	Gentamicin	Trimethoprim-sulfamethoxazole	Chloramphenicol	Erythromycin
		% Susceptible							
Enterococcus sp.	9534					80%		98%	28%
Bug-drug combinations with <30 isolates are not shown in antibiogram									

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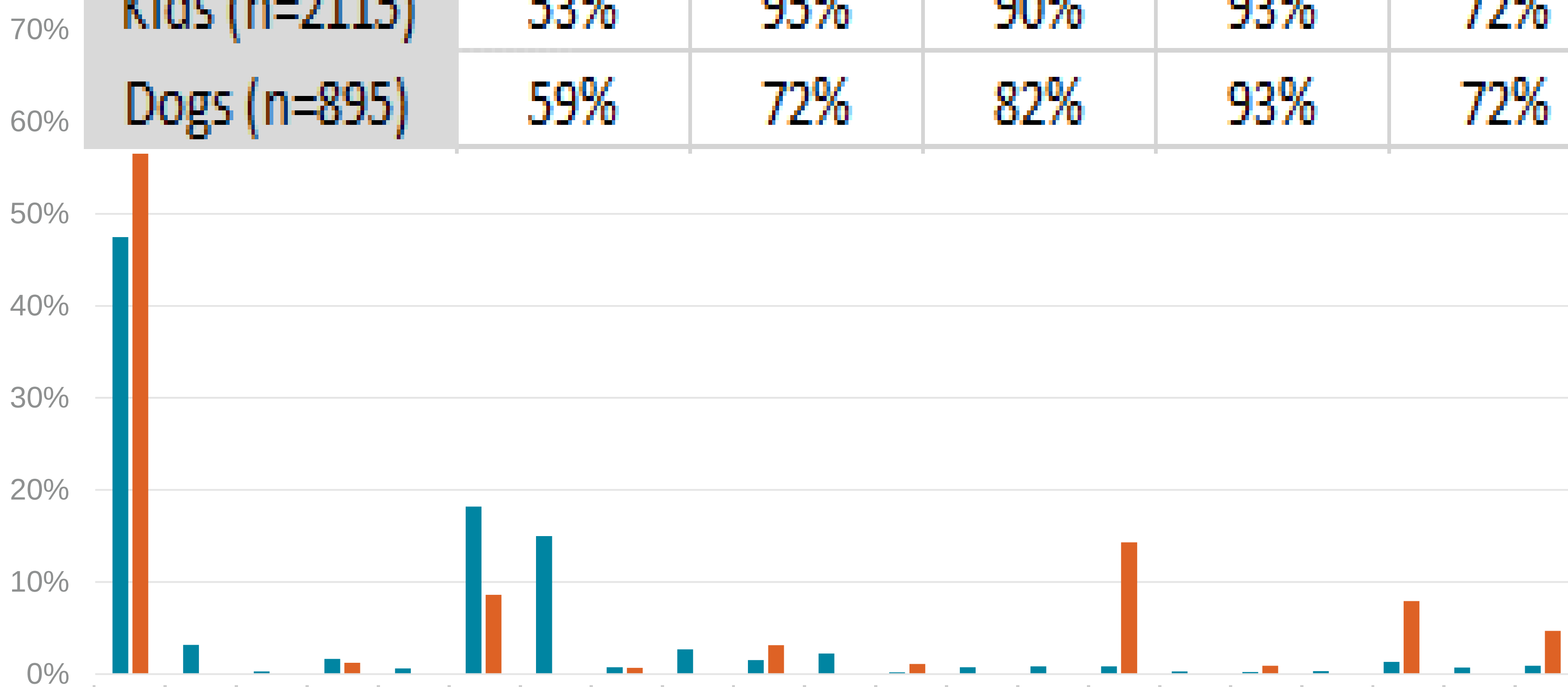
Susceptibility rates of deduplicated urinary *E. coli* from kids and dogs, 2014-2016

	AMP	3GC	FQ	GM	TS
Kids (n=2115)	53%	95%	90%	93%	72%
Dogs (n=895)	59%	72%	82%	93%	72%



AMP	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3GC	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
FQ	0	0	0	1	1	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
GM	0	0	1	0	0	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1	1
TS	0	1	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1

Susceptibility rates of deduplicated urinary *E. coli* from kids and dogs, 2014-2016

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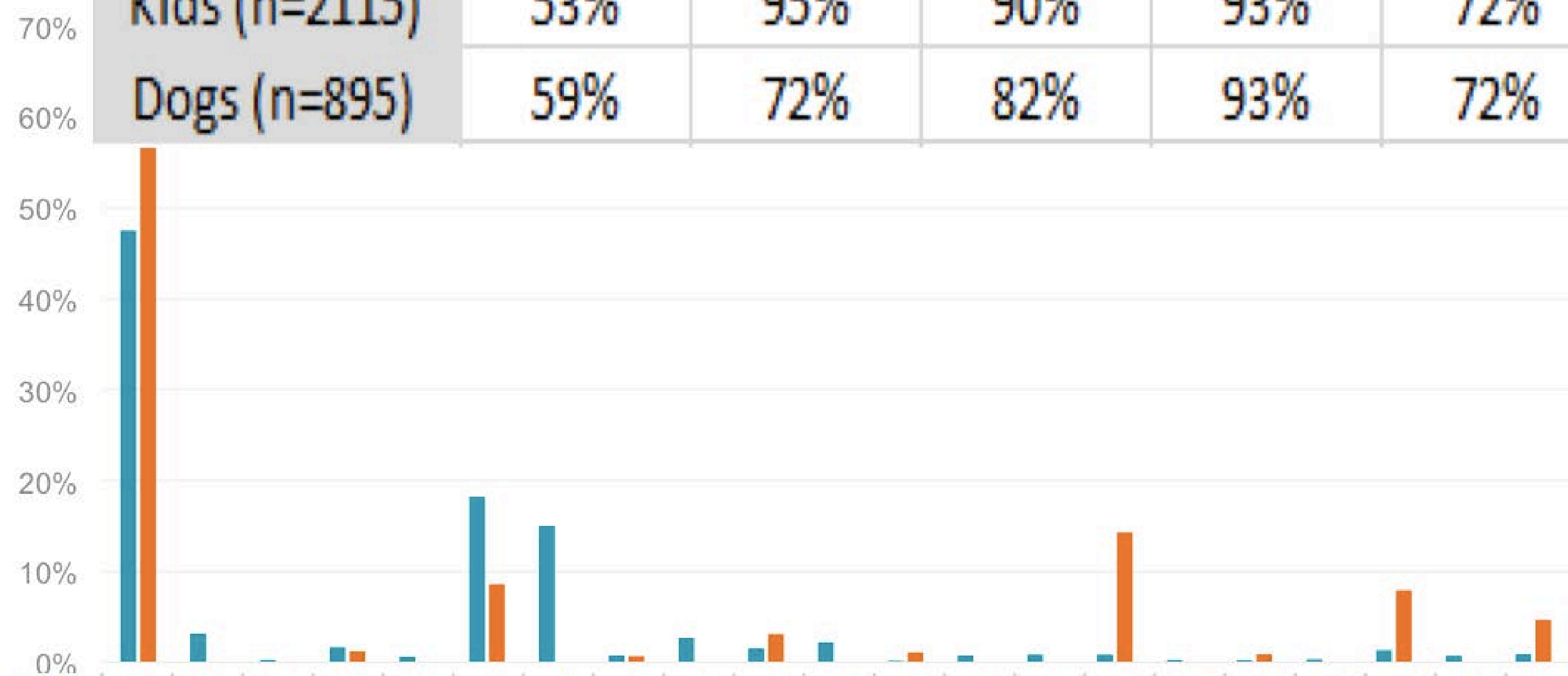
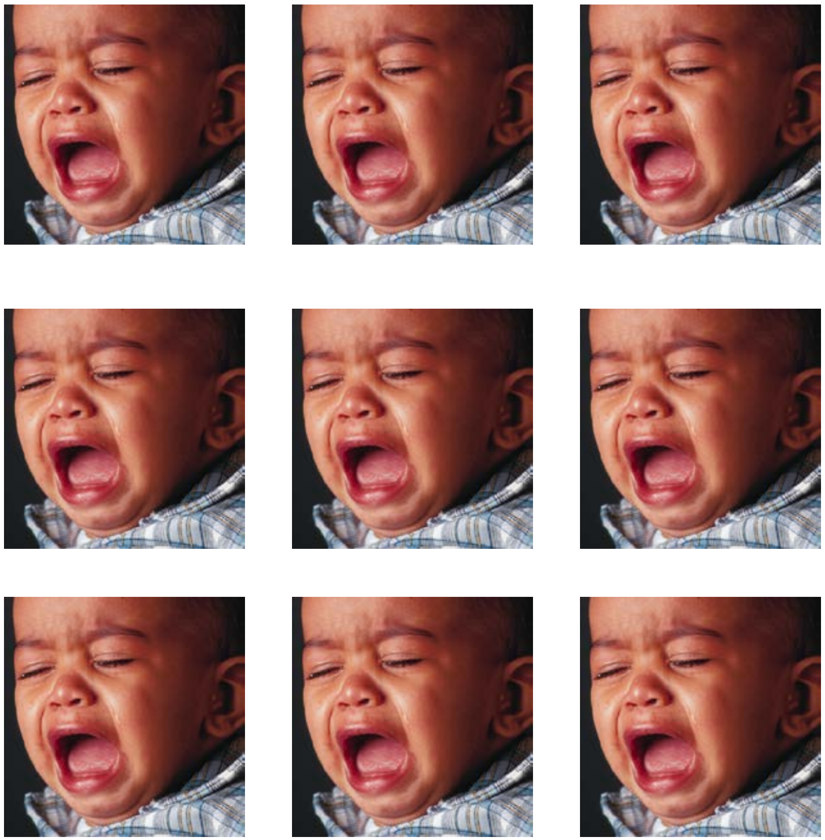


AMP	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3GC	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1
FQ	0	0	0	1	1	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
GM	0	0	1	0	0	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1	1
TS	0	1	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1

How to measure the unmeasured?



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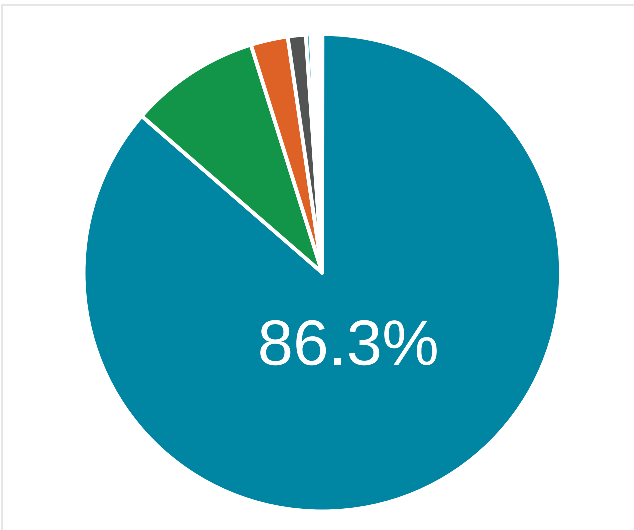
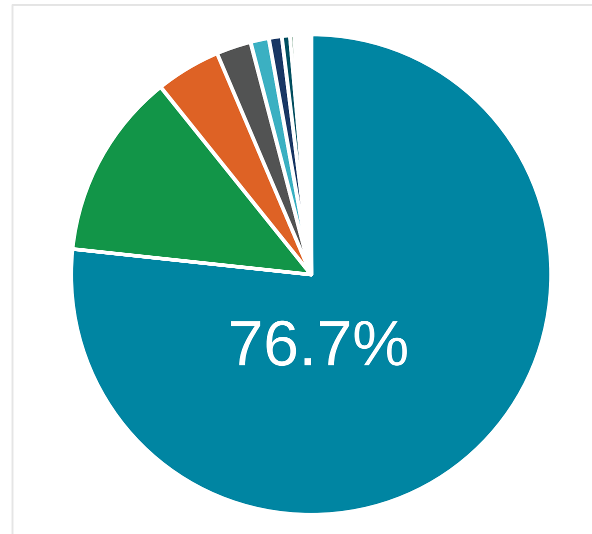
Proportion of culture-naïve patients falls with a longer time horizon (Seattle Children's data)

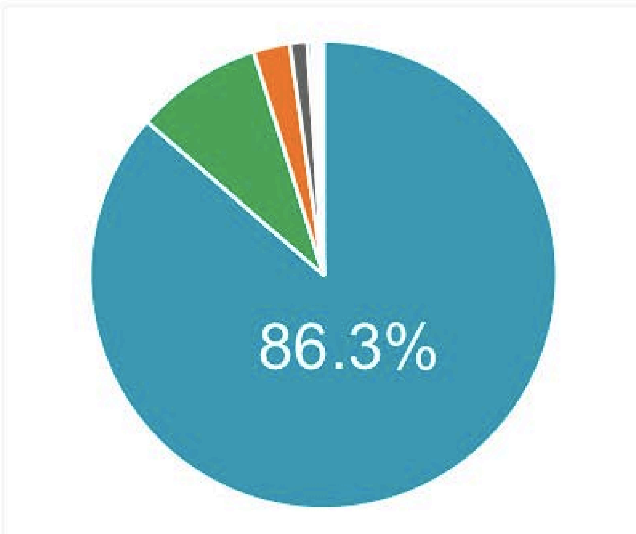




2016 only

2010-2016

Proportion of culture-naïve patients falls with a longer time horizon (Seattle Children's data)



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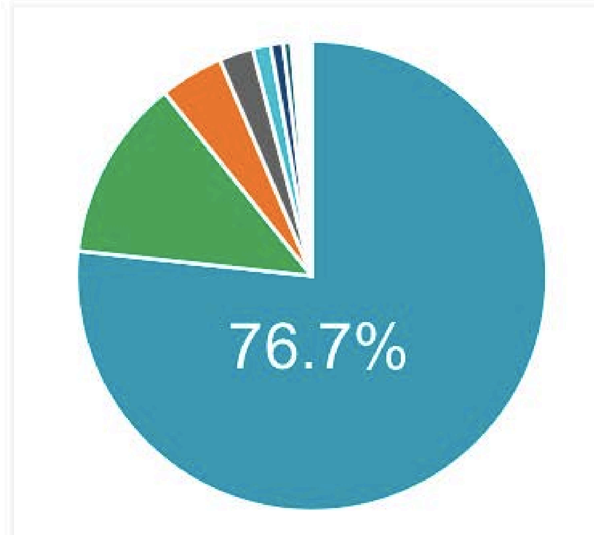

2010-2016

Antibiogram as artifact …
molded by what? by whom?

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A picture is coming into focus…

https://binocularshub.com/%EF%BB%BFtop-5-binoculars-for-birding/

Summary

- Participating facility/lab enrollment remains limited
  - Barriers identified in human health care facility engagement
  - Lagging engagement for environmental health samples
- Sampling, testing & reporting methods vary across sectors
- Comparisons between host species and sectors must be done with caution, if at all
- But is it possible to stratify clinical microbiology data for better comparability? or leverage knowledge of population sampling patterns to characterize clinical practice habits better?

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Acknowledgments

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- Marisa D’Angeli & Kelly Kauber (WA Department of Health)
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  - CDC Epidemiology and Laboratory Capacity Grant
- Faye Sturtevant, Cheryl Adler (Phoenix Laboratories, Mukilteo, WA)
- Tim Bazler, Claire Burbick (WA Animal Disease Diagnostic Lab)

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Center for One Health Research

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Limitations of the cumulative antibiogram

- Static
  - Once a year
  - Trends tell stories!
- Presented as a flat file (eg, pdf format)
  - Severed from back-end data where richness resides
  - Back-end data may have limited clinical information
- Aggregated by species
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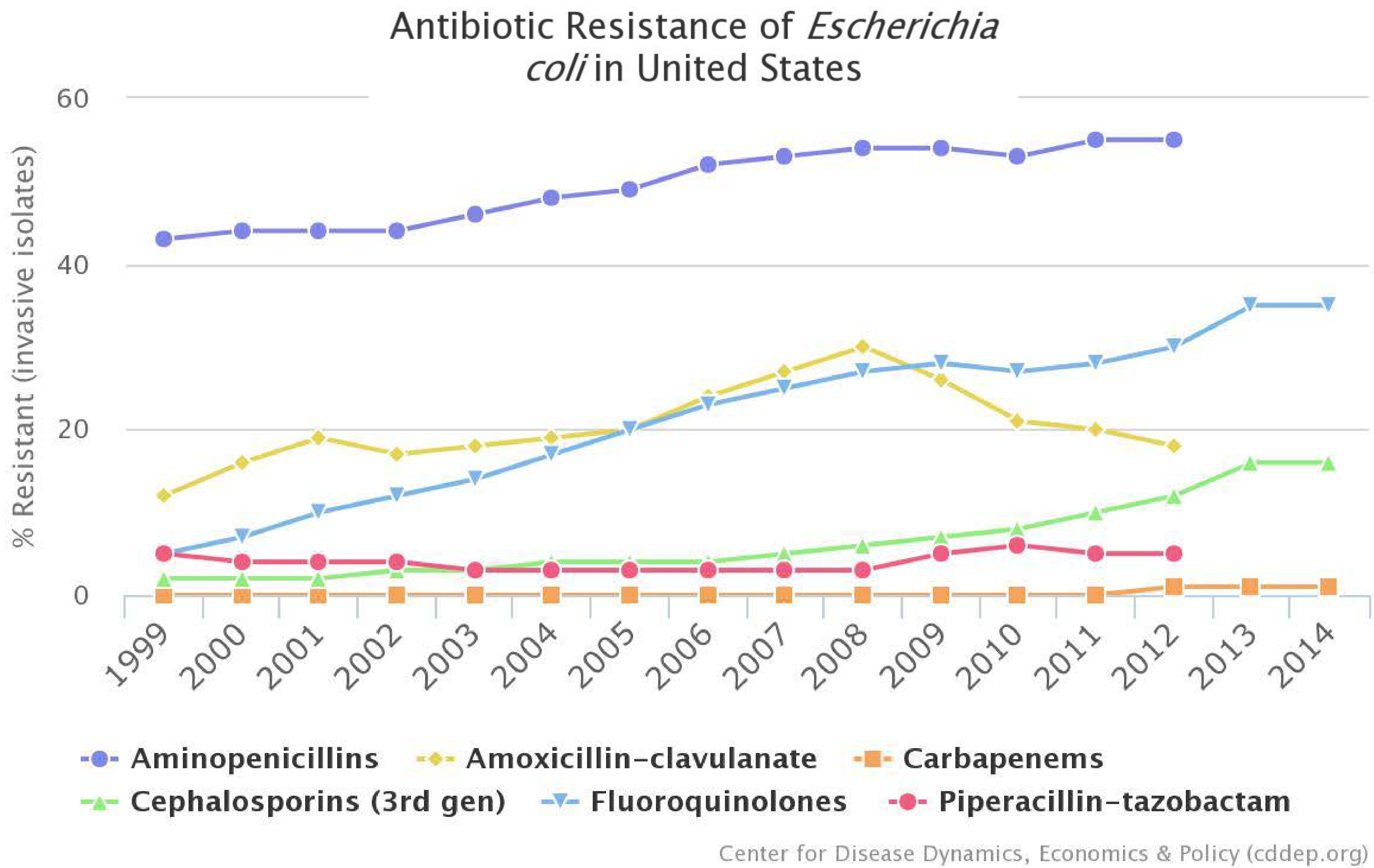
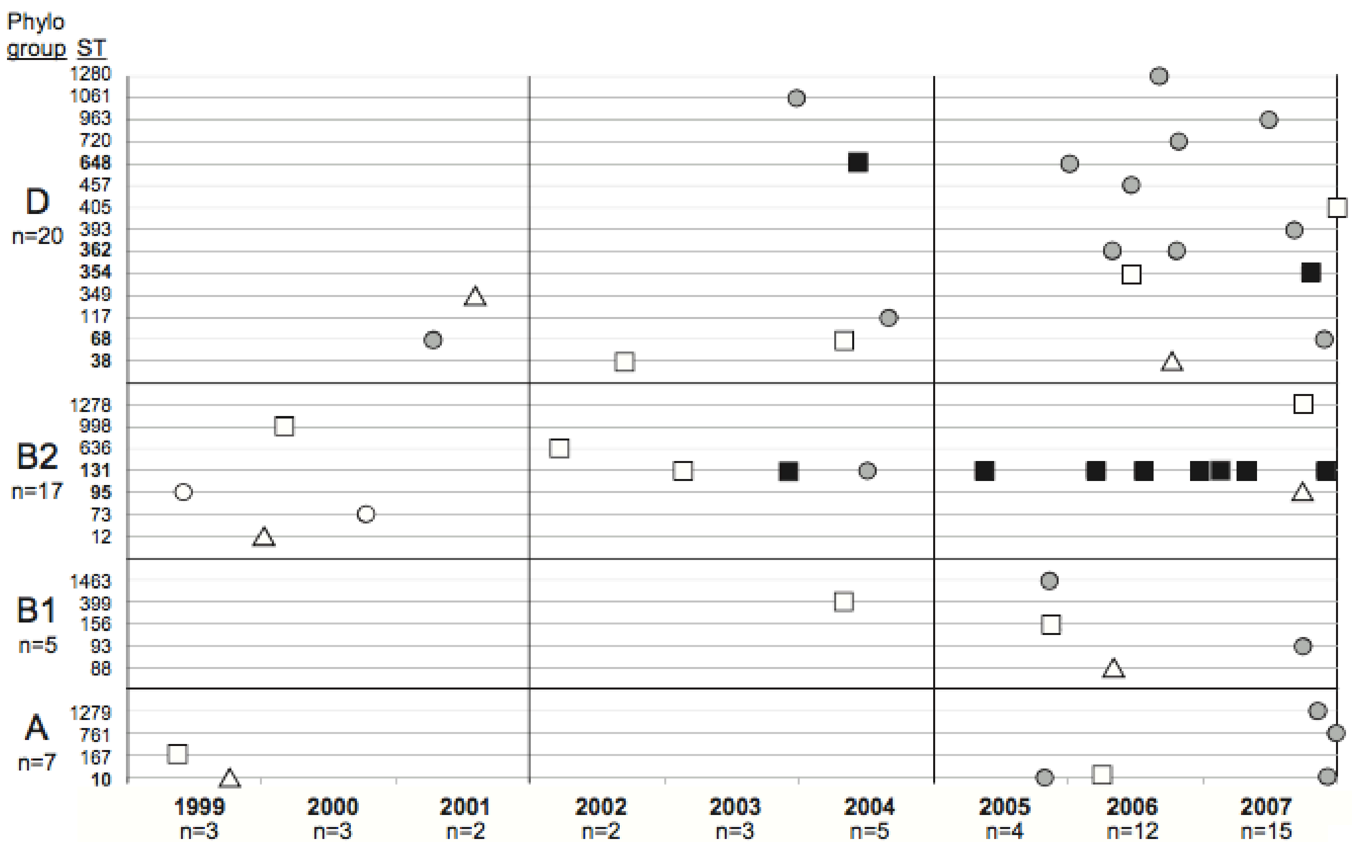
- Not transparent
  - Especially with regard to de-duplication methodology
- Implies that the threat is primarily bacterial

Trends tell stories



Trends tell stories



Key: Bold STs have more than 1 representative. Squares: Isolates carrying Class A enzymes. Black squares: Isolates carrying CTX-M-15. Circles: Isolates carrying Class C enzymes. Grey circles: Isolates carrying CMY-2. Triangles: Isolates with no enzyme identified.

Fig. 1. Phylogenetic and temporal distribution of 49 *Escherichia coli* isolates resistant to extended-spectrum cephalosporins at Seattle Children's Hospital (Seattle, WA) during 1999–2007. *ST*, sequence type.

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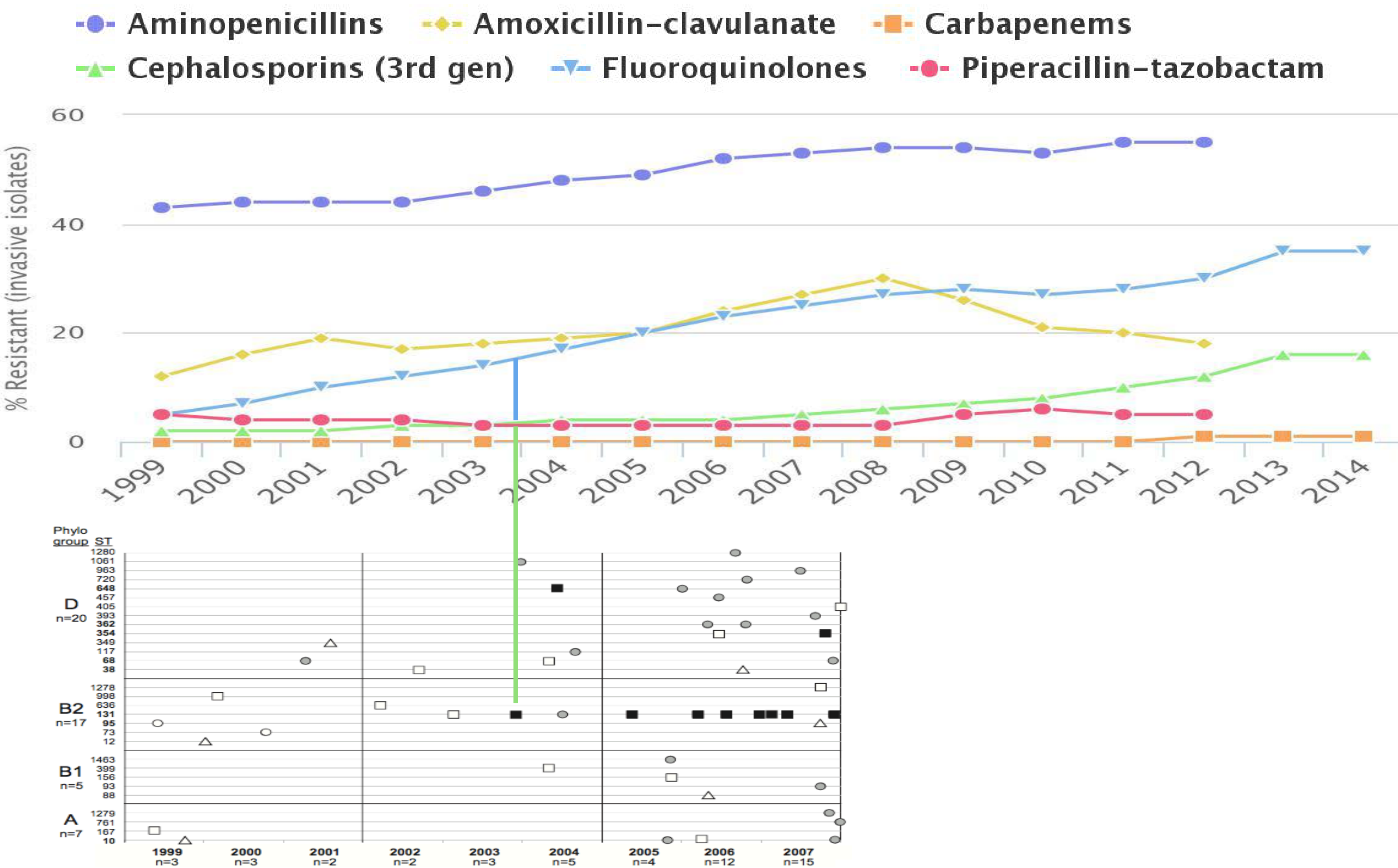
S.J. Weissman et al. / International Journal of Antimicrobial Agents 41 (2013) 414–420



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Late 2007

Journal of Antimicrobial Chemotherapy (2008) **61**, 273–281
doi:10.1093/jac/dkm464
Advance Access publication 11 December 2007

JAC

Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15

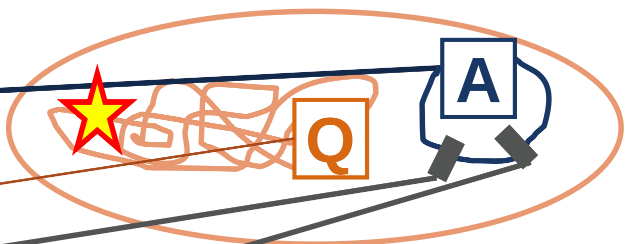
Marie-Hélène Nicolas-Chanoine[1,2]*, Jorge Blanco[3], Véronique Leflon-Guibout[1], Raphael Demarty[1], Maria Pilar Alonso[4], Maria Manuela Caniça[5], Yeon-Joon Park[6], Jean-Philippe Lavigne[7], Johann Pitout[8] and James R. Johnson[9]

[1]Service de Microbiologie, Hôpital AP-HP Beaujon, 92110 Clichy, France; [2]Inserm, U-773, Faculté de Médecine D. Diderot, Université Paris 7, Paris, France; [3]E. coli Reference Laboratory, Department of Microbiology and Parasitology, Faculty of Veterinary Science, University of Santiago de Compostela, Lugo, Spain; [4]Laboratory of Clinical Microbiology, Complejo Hospitalario Xeral-Calde, Lugo, Spain; [5]Antibiotic Resistance Unit, National Institute of Health Dr Ricardo Jorge, Lisbon, Portugal; [6]Department of Clinical Pathology, College of Medicine, The Catholic University of Korea, Kangnam St Mary's Hospital, Seoul, South Korea; [7]Laboratoire de Bactériologie, Virologie et Parasitologie, CHU de Nîmes, Nîmes, France; [8]Calgary Laboratory Services and Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, Alberta, Canada; [9]Veterans Affairs Medical Center and University of Minnesota, Minneapolis, MN, USA

Building a better superbug: Sequence Type 131

	Escherichia coli
Drug	zzzInterp
Ampicillin	Resist
Augmentin	Resist
Cefazolin/Cephalexin	Resist
Ceftazidime	Resist (c)
Ceftriaxone	Resist
Cefuroxime	Resist
Ciprofloxacin	Resist
Gentamicin	Resist
Meropenem	Suscept
Trimethoprim/Sulfamethoxazole	Resist

ESBL-bearing resistance plasmid



chromosomal mutation conferring quinolone resistance

plasmid borne multidrug resistance genes

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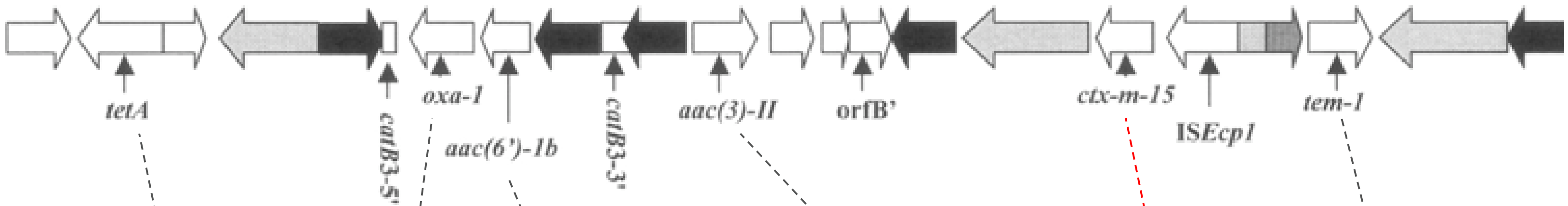
Resistance plasmids – genetic basis for linkage of multiple resistance genes

A



OXA-1
Oxacillinase

***aac*(3)-II**
Aminoglycoside modifying enzyme

TEM-1
Narrow-spectrum beta-lactamase

tetA
Tetracycline efflux pump

CTX-M-15 Extended spectrum beta-lactamase

Lavollay et al (2006) *AAC* 50:2433.