
Antibiotic Resistance Surveillance and Public Health

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12/13/2017

The logo for the Oregon Health Authority, featuring the word "Oregon" in a small serif font above the word "Health" in a large serif font, with the word "Authority" in a smaller serif font below "Health".

Oregon
Health
Authority

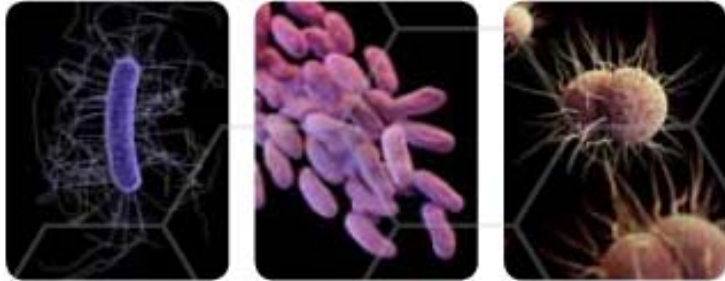
The Telegraph

Resistance to antibiotics could bring "the end of modern medicine as we know it", WHO claim

The world is entering an antibiotic crisis which could make routine operations impossible and a scratched knee potentially fatal, the head of the World Health Organisation has claimed.



Bacteria carried by humans are becoming increasingly resistant to antibiotics Photo: JOHN TAYLOR



THREAT LEVEL
URGENT



These bacteria are immediate public health threats that require urgent and aggressive action.

MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile

Carbapenem-resistant *Enterobacteriaceae*

Drug-resistant *Neisseria gonorrhoeae*

https://www.cdc.gov/drugresistance/biggest_threats.html

Objectives

- How antibiotics work
- Mechanisms of resistance in gram negative bacteria
- Laboratory testing to determine resistance
- Carbapenem-Resistant *Enterobacteriaceae* (CRE)
- CRE special considerations
- New surveillance for other multi-drug resistant organisms (MDRO)

How antibiotics work

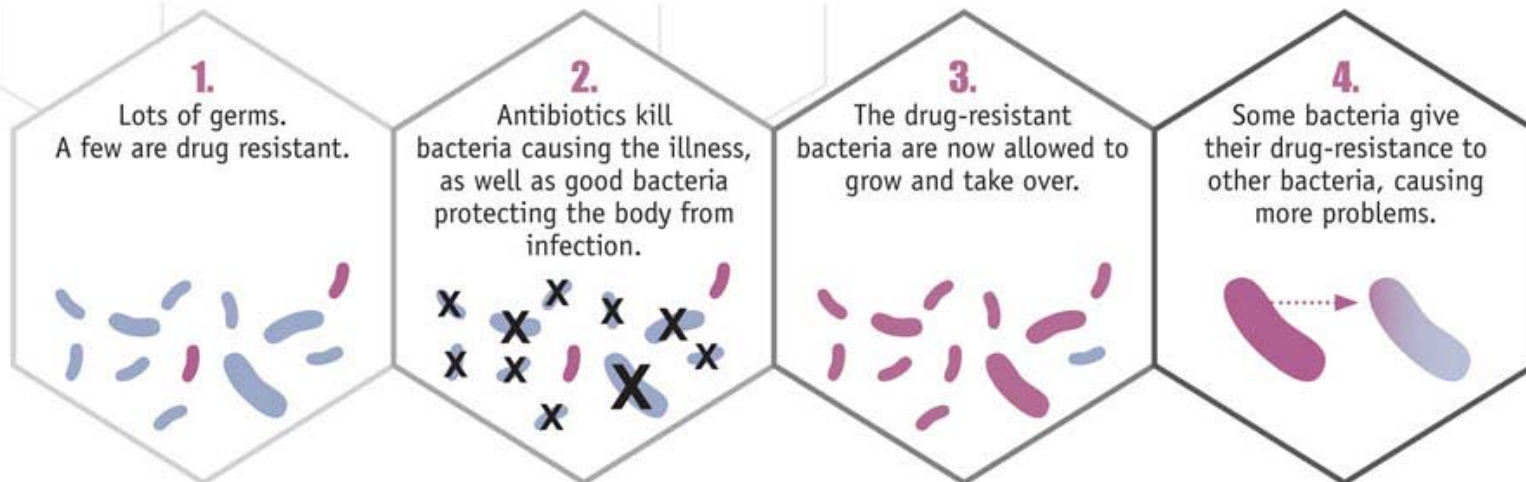
- Interfere with bacterial cell wall synthesis
 - β -lactam antibiotics; penicillin, cephalosporins
- Inhibit protein synthesis
 - aminoglycosides, tetracyclines
- Interfere with nucleic acid synthesis
 - fluoroquinolones
- Inhibit a metabolic pathway
 - Sulfonamides, trimethoprim
- Disorganize the cell membrane
 - Polymyxin, daptomycin

Antibiotic classes and enzymes mediating resistance

Drug Class	Antibiotic Examples	Resistance Mechanism
β -lactams	Penicillin, Amoxicillin	β -lactamases
β -lactam/ β -lactamase inhibitors	Amoxicillin-clavulanic acid (Augmentin)	Extended-spectrum β -lactamases (ESBL)
Cephalosporins	Cephalexin (Keflex) Ceftriaxone (Rocephin) Cefepime (Maxipime)	Extended spectrum cephalosporinases (e.g., AMP C)
Carbapenems	Ertapenem Imipenem Meropenem Doripenem	Carbapenemases

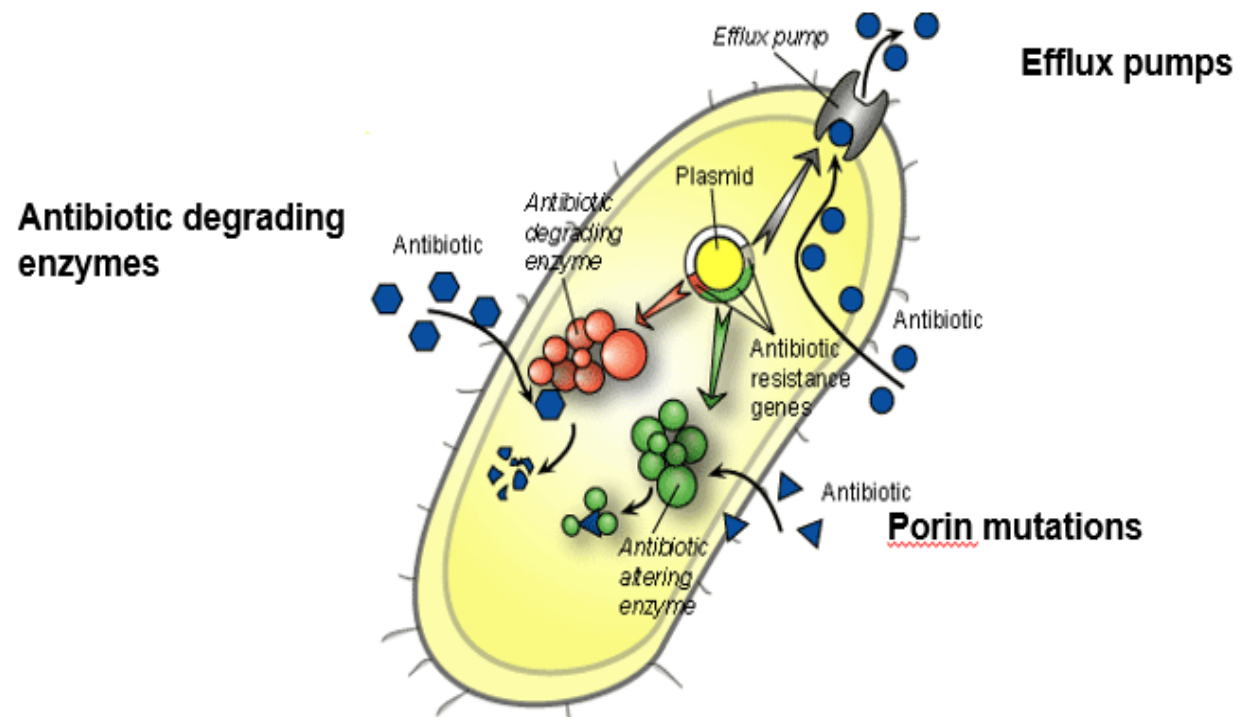


How Antibiotic Resistance Happens



<https://www.cdc.gov/antibiotic-use/community/about/antibiotic-resistance-faqs.html>

Methods of Antibiotic Resistance

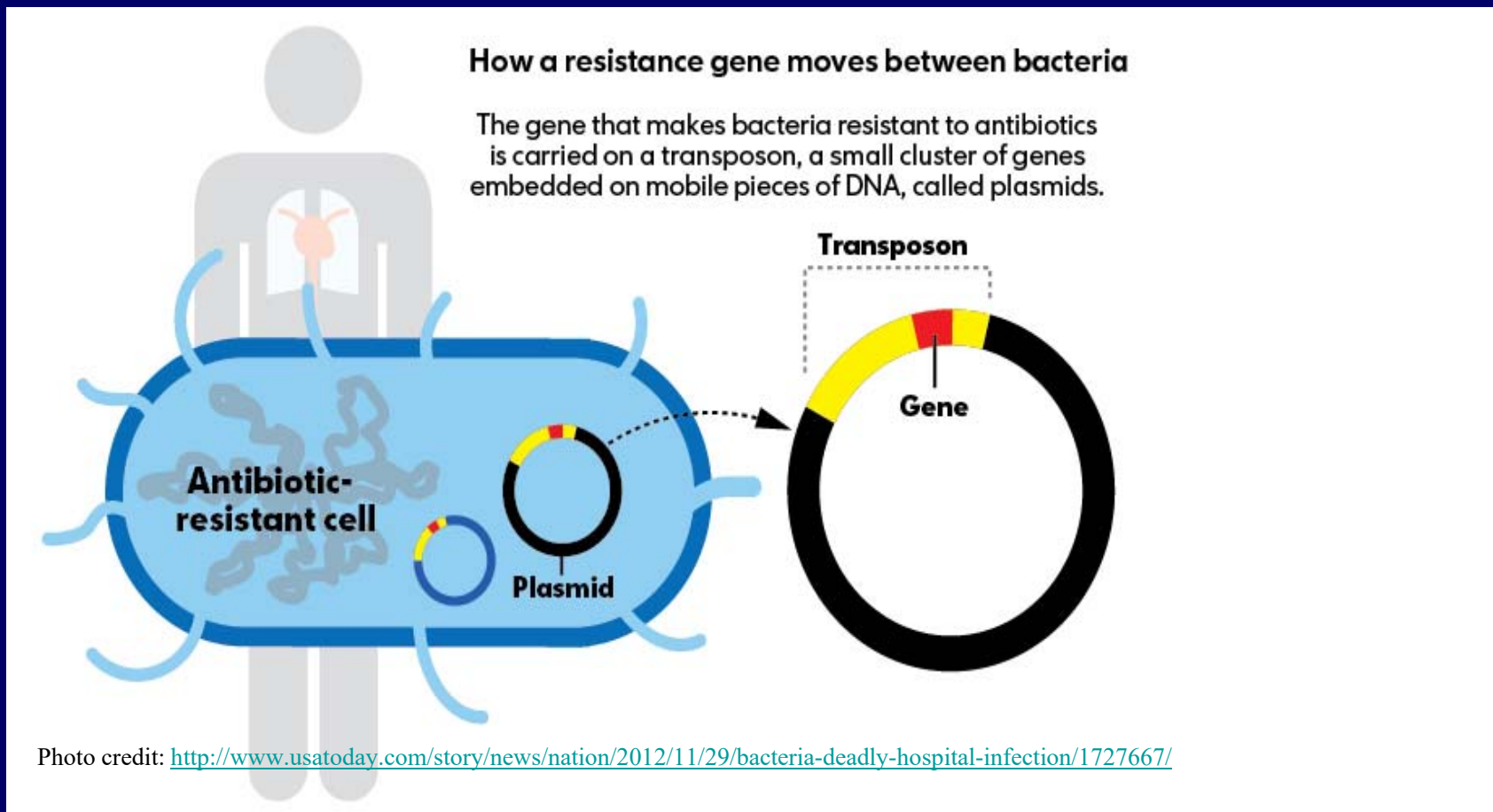


http://textbookofbacteriology.net/resantimicrobial_3.html

Antibiotic resistance continued

- Antibiotic degrading enzymes can be chromosomal or plasmid mediated
- Plasmid mediated enzymes can move easily from one bacteria to another, one species to another
- Plasmids – mobile particles of DNA

Plasmid transfer of resistance #1



Plasmid transfer of resistance #2

How a resistance gene moves between bacteria

Finger-like appendages (pili) on the resistant cell come in contact with an antibiotic-sensitive cell, forming a mating bridge between the two cells.

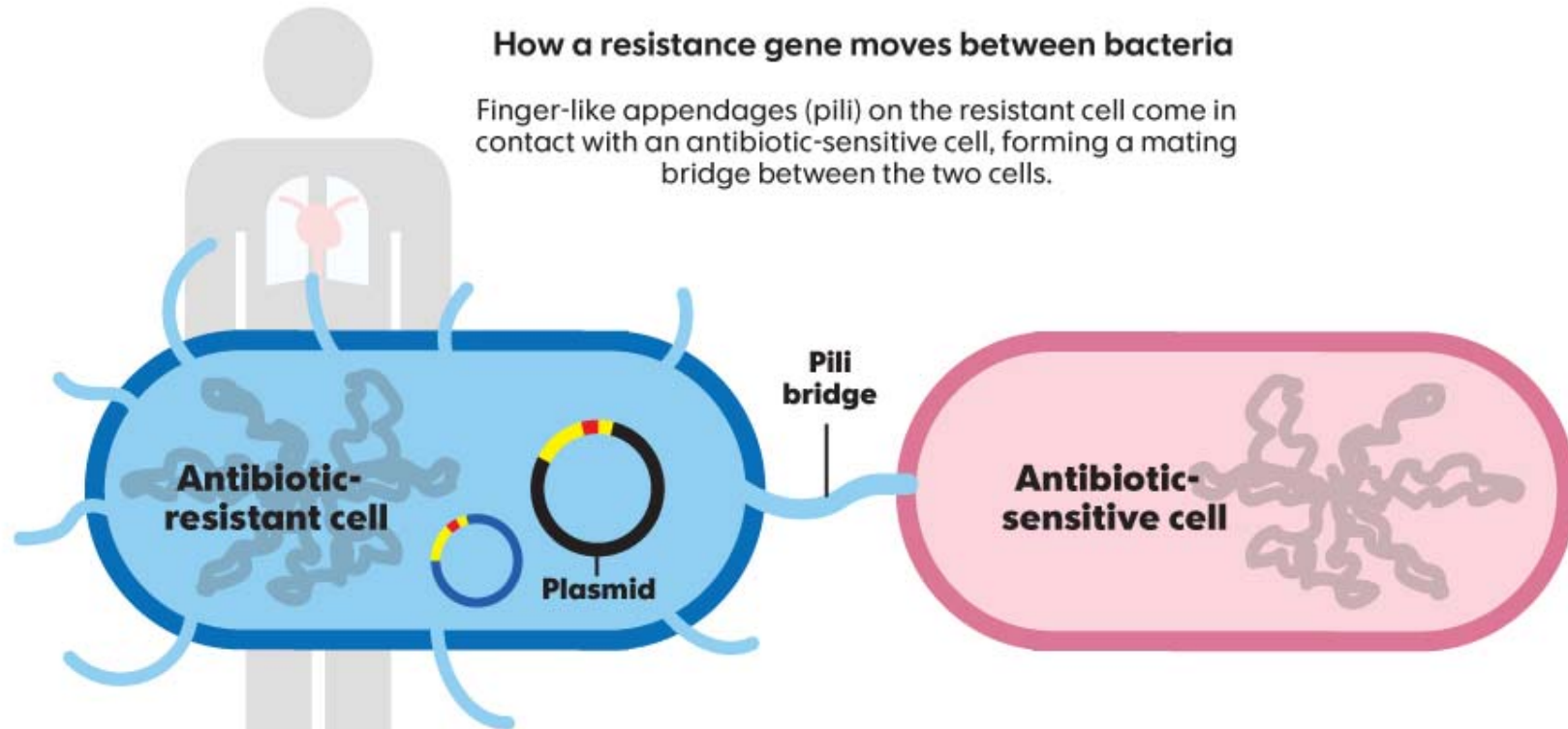


Photo credit: <http://www.usatoday.com/story/news/nation/2012/11/29/bacteria-deadly-hospital-infection/1727667/>

Plasmid transfer of resistance #3

How a resistance gene moves between bacteria

The cells come in contact, a process called conjugation, and the plasmids move from one to another, taking the resistance gene with them and making the new bacterial cell drug-resistant as well.

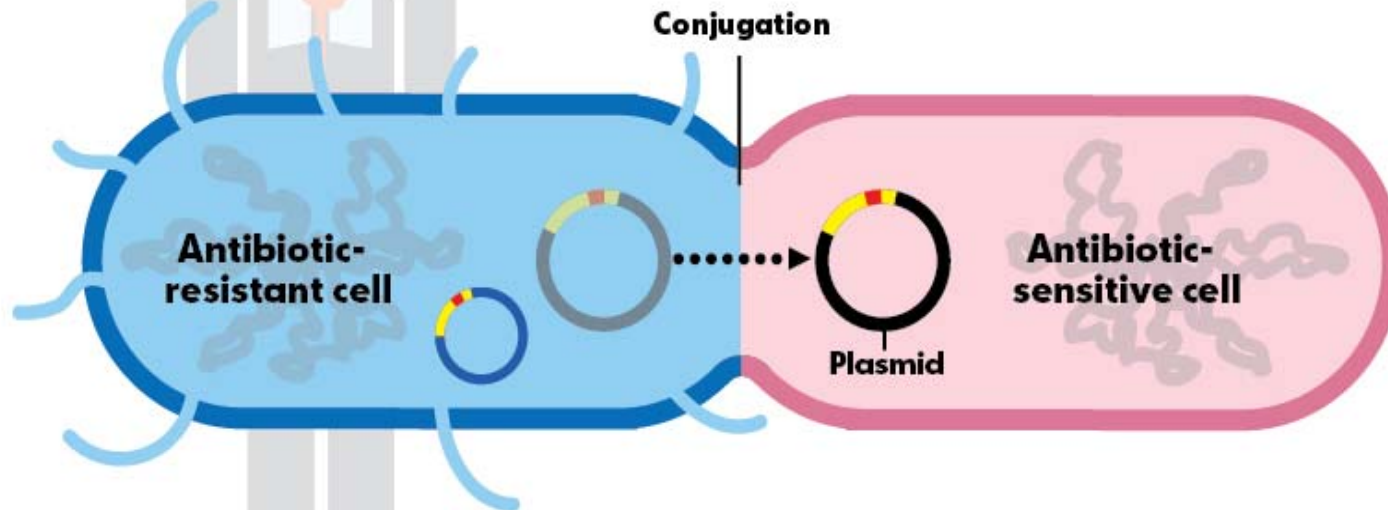


Photo credit: <http://www.usatoday.com/story/news/nation/2012/11/29/bacteria-deadly-hospital-infection/1727667/>

Laboratory testing to determine susceptibility/resistance

- **Minimum inhibitory concentration (MIC):**
Lowest concentration of an antimicrobial drug that inhibits the growth of a microorganism after overnight incubation
- **Breakpoint:**
Level of the antibiotic concentration that determines susceptibility or resistance

Laboratory results

- Automated systems; primarily Vitek

Vitek

Selected Organism: Enterobacter cloacae complex

Susceptibility Information		Card: AST-GN77	Lot Number: 69730620	Expires: May 26, 2015 12:00 GMT-08:00	
Completed: Feb 25, 2014 05:30 GMT-08:00		Status: Final	Analysis Time: 13:50 hours		
Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
Ampicillin			Imipenem	4	R
Ampicillin/Clavulanic Acid	>= 32	R	Amikacin	<= 2	S
Piperacillin/Tazobactam	>= 128	R	Gentamicin	<= 1	S
Ceftazidime	>= 64	R	Tobramycin	<= 1	S
Ceftriaxone	>= 64	R	Ciprofloxacin	<= 0.25	S
Ceftazidime	>= 64	R	Levofloxacin	<= 0.12	S
Cefepime	<= 1	S	Tigecycline	<= 0.5	S
Aztreonam	>= 64	R	Nitrofurantoin	128	R
Ertapenem	>= 64	R	Trimethoprim/Sulfamethoxazole	<= 20	S

== Deduced drug *AES modified == User modified

AES Findings		Last Modified: Jun 28, 2012 10:16 GMT-08:00	Parameter Set: Copy of CLSI-Natural Resistance
Confidence Level:	Consistent		
Phenotype:	BETA-LACTAMS HL CASE + R CARBAPENEMS (MPER)		

Action	Name (User ID)	Date/Time	Comment
Changed by:	[labadmin]	Feb 25, 2014 12:49 GMT-08:00	complex
Reviewed by:	[labadmin]	Feb 28, 2014 12:49 GMT-08:00	

Installed VITEK 2 Systems Version: 05.04
 MIC Interpretation Guidelines: Copy of CLSI M100 S16 (2008)
 Therapeutic Interpretation Guidelines: Copy of NATURAL RESISTANCE
 AES Parameter Set Name: Copy of CLSI-Natural Resistance
 AES Parameter Last Modified: Jun 28, 2012 10:16 GMT-08:00

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Microscan

Current Alerts

Panel Data

Biotype: 7730176

Organism Identification

Organism	% Probability	Pathogens	Species Characteristics
E. cloacae	99.99		

Biochemical Results: (Biochemicals that are bolded and underlined are atypical for the first choice organism)

MIC Results: (Antimicrobials marked with "SP" are suppressed from Long and Short Format Patient Reports)

Alert History

Previous VPC Inappropriate
 ("Unusual resistance", "MICs > 1 to a carbapenem) and (R to 3GCRPM), "No low current CLSI or public health guidelines", "Severe isolate", "Verify isolate results by repeat testing unless patient had isolate previously")

Alert Resolution:

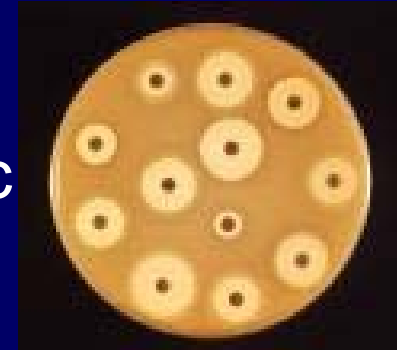
Reported Interpretation Changed
 Printed 12/10/2014 11:07:13 AM

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Other laboratory testing for resistance

- Kirby Bauer disk diffusion

- Disk with concentration of antibiotic
- Correlates with MIC
- Zone sizes

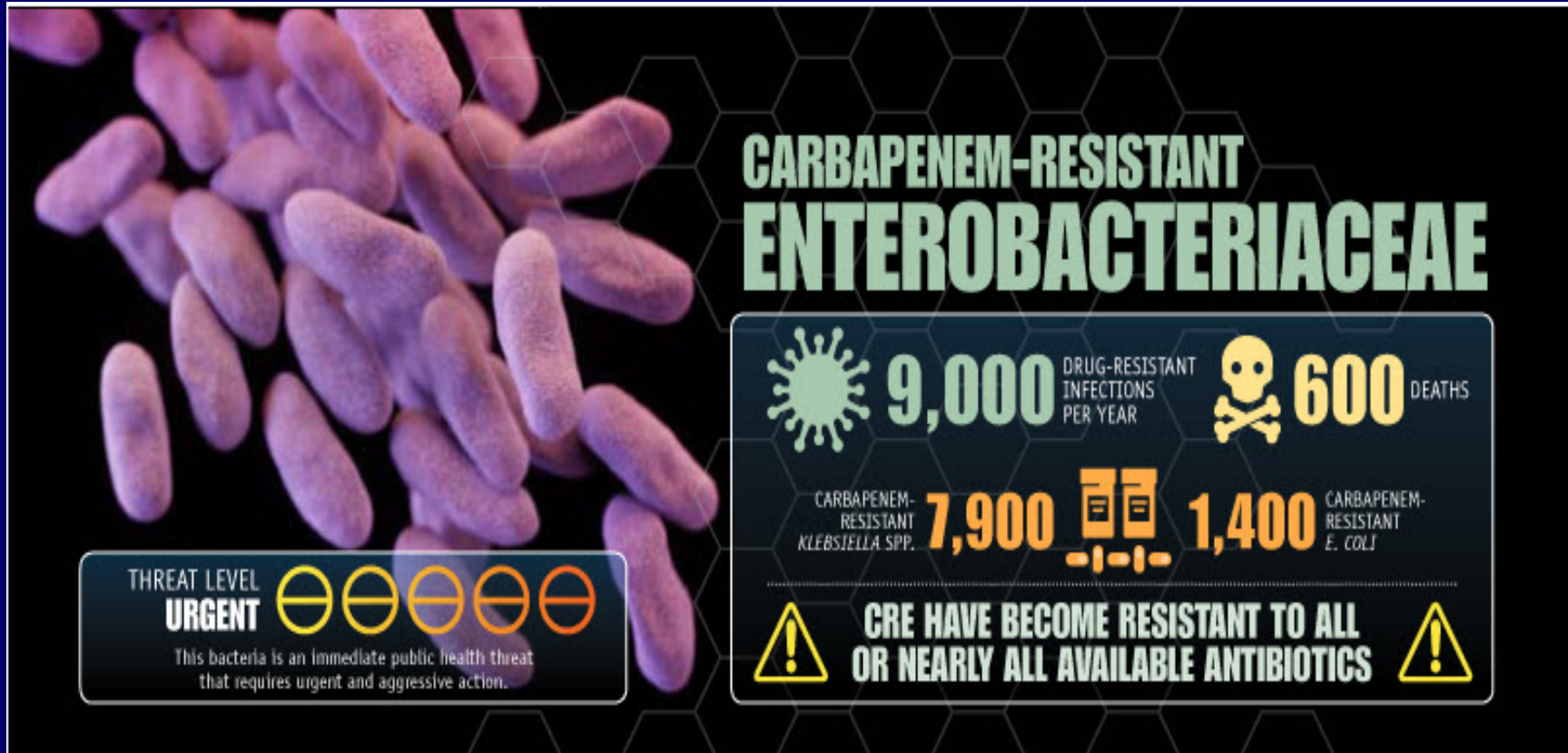


- E-Test

- Gradient of antibiotic on a strip
- Provides MIC



Why we care



Carbapenem-resistant Enterobacteriaceae (CRE)

- **Enterobacteriaceae** – Gram negative bacilli of the gastrointestinal tract
 - *E. coli*, *Klebsiella*, *Enterobacter*
- **Carbapenems** – class of β -lactam antibiotics with a broad spectrum of antibacterial activity
 - Considered antibiotics of last resort



The *Enterobacteriaceae* family of bacteria includes these genera and groups:

<i>Averyella</i>	<i>Leminorella</i>	<i>Tatumella</i>
<i>Budvicia</i>	<i>Morganella</i>	<i>Trabulsiella</i>
<i>Buttiauxella</i>	<i>Moellerella</i>	<i>Xenorhabdus</i>
<i>Cedecea</i>	<i>Pantoea</i>	<i>Yersinia</i>
<i>Citrobacter</i>	<i>Photorhabdus</i>	<i>Yokenella</i>
<i>Cronobacter</i>	<i>Plesiomonas</i>	Enteric Group 58
<i>Edwardsiella</i>	<i>Pragia</i>	Enteric Group 59
<i>Enterobacter</i>	<i>Proteus</i>	Enteric Group 60
<i>Escherichia</i>	<i>Providencia</i>	Enteric Group 63
<i>Ewingella</i>	<i>Rahnella</i>	Enteric Group 64
<i>Hafnia</i>	<i>Raoultella</i>	Enteric Group 68
<i>Klebsiella</i>	<i>Salmonella</i>	Enteric Group 69
<i>Kluyvera</i>	<i>Serratia</i>	Enteric Group 137
<i>Leclercia</i>	<i>Shigella</i>	

1. *Proteus* spp. *Providencia* spp. and *Morganella* spp. are excluded if isolates are resistant only to imipenem and no other carbapenem (e.g., isolate tests ertapenem-susceptible but imipenem-resistant).

CRE definition and breakpoints for resistance

	Current MIC Breakpoints ($\mu\text{g/mL}$) ¹		
	MIC Interpretation ²		
	Susceptible	Intermediate	Resistant
Carbapenems			
Doripenem	≤ 1	2	≥ 4
Ertapenem	≤ 0.5	1	≥ 2
Imipenem	≤ 1	2	≥ 4
Meropenem	≤ 1	2	≥ 4

¹MIC = minimum inhibitory concentration
²CLSI. Performance Standards for Antimicrobial Susceptibility Testing Twenty-Fifth Informational Supplement
 CLSI document M100-S25, Wayne, PA: Clinical and Laboratory Standards Institute: January 2015.

	Current Disk Diffusion Zone Diameters (mm) ³		
	Zone Size Interpretation ²		
	Susceptible	Intermediate	Resistant
Carbapenems			
Doripenem	≥ 23	20–22	≤ 19
Ertapenem	≥ 22	20–21	≤ 18
Imipenem	≥ 23	20–21	≤ 18
Meropenem	≥ 23	20–21	≤ 18

³mm = millimeters
²CLSI. Performance Standards for Antimicrobial Susceptibility Testing Twenty-Fifth Informational Supplement
 CLSI document M100-S25, Wayne, PA: Clinical and Laboratory Standards Institute: January 2015.

Clinical laboratory testing

- Labs may suppress carbapenem values on their lab information system reports
 - Example: a lab may test both ertapenem and imipenem but only imipenem will be reported via ELR
 - LHD may get the report as CRE, not have the ertapenem MICs, imipenem MIC will indicate sensitive
- Automated systems can be set to convert carbapenem interpretations to resistant based on MICs of cephalosporins

Example of MICs in ELR

```

ELR Lab Results
Specimen Date: 11/12/2017 Lag: 4 days
Specimen Type/Site: Urine (Urine Foley Catheter)

Order: Bacteria Ur Cult
-----
Test: Pre
Result: >=100,000 CFU/ml Escherichia coli
WARNING: **INFECTION CONTROL ALERT** MULTI DRUG RESISTANT ISOLATE; SPECIAL PRECAUTIONS APPLY Modified Hodge
Test: NEGATIVE
Test: Bacteria Ur Cult
Result: Escherichia coli (organism)
Test: Bacteria Ur Cult
Result: Escherichia coli (organism)
Test: Ampicillin Islt MIC
Result: >=32
Test: Ampicillin+Sulbac Islt MIC
Result: >=32
Test: Cefazolin Islt MIC
Result: >=64
Test: Ceftriaxone Islt MIC
Result: >=64
Test: Ciprofloxacin Islt MIC
Result: <=0.25
Test: Nitrofurantoin Islt MIC
Result: <=16
Test: Pip+Tazo Islt MIC
Result: >=128
Test: Tobramycin Islt MIC
Result: <=1
Test: TMP SMX Islt MIC
Result: <=20
Test: Ertapenem Islt MIC
Result: 4.0
Test: Meropenem Islt MIC
Result: <=0.25
-----
    
```



```

ELR Lab Results
Specimen Date: 10/17/2017 Lag: 6 days
Specimen Type/Site: Urine Straight Catheter

Order: Bacteria Ur Cult
-----
Test: Bacteria Ur Cult
Carbapenem resistant
Enterobacteriaceae (organism)
-----
Notes: >100,000 cfu/ml Enterobacter cloacae complex , 3,000 cfu/ml Proteus mirabilis
-----
----- Additional Notes -----
>100,000 cfu/ml Enterobacter cloacae complex , 3,000 cfu/ml Proteus mirabilis*****-----
    
```

Order: Bacteria Ur Cult

Test: Bacteria Ur Cult
Result: >100,000 COL/ML
ENTEROBACTER CLOACAE COMPLEX
This isolate is a Carbapenem Resistant Enterobacteriaceae
(CRE) and resistant to all penicillins, cephalosporins,
carbapenems and aztreonam. CONTACT PRECAUTIONS
REQUIRED. Confirmation from OSPHL to follow.
=====

Order: METHOD

Test: Aztreonam Susc Islt
Result: Resistant=4
Resistant (qualifier value)
Test: Pip+Tazo Susc Islt
Result: Resistant<=128
Test: Pip+Tazo Susc Islt
Result: Resistant (qualifier value)
Test: Cefazolin Susc Islt
Result: Resistant<=64
Test: Cefazolin Susc Islt
Result: Resistant (qualifier value)
Test: Ceftriaxone Susc Islt
Result: Resistant=32
Test: Ceftriaxone Susc Islt
Result: Resistant (qualifier value)
Test: Cefepime Susc Islt
Result: Resistant<=1
Test: Cefepime Susc Islt
Result: Resistant (qualifier value)
Test: Meropenem Susc Islt
Result: Resistant=0.5
Test: Meropenem Susc Islt
Result: Resistant (qualifier value)
Test: Amikacin Susc Islt
Result: Susceptible<=2
Test: Amikacin Susc Islt
Result: Sensitive (qualifier value)
Test: Gentamicin Susc Islt
Result: Susceptible<=1
Test: Gentamicin Susc Islt
Result: Sensitive (qualifier value)
Test: Tobramycin Susc Islt
Result: Susceptible<=1
Test: Tobramycin Susc Islt
Result: Sensitive (qualifier value)
Test: Ciprofloxacin Susc Islt
Result: Susceptible<=0.25
Test: Ciprofloxacin Susc Islt
Result: Sensitive (qualifier value)
Test: Nitrofurantoin Susc Islt
Result: Susceptible<=16
Test: Nitrofurantoin Susc Islt
Result: Sensitive (qualifier value)
Test: TMP SMX Susc Islt
Result: Resistant<=320
Test: TMP SMX Susc Islt
Result: Resistant (qualifier value)
Test: Ertapenem Susc Islt
Result: Resistant=4
Test: Ertapenem Susc Islt
Result: Resistant (qualifier value)
Test: Ticarcillin Susc Islt

Order: Bacteria Ur Cult

Test: Bacteria Ur Cult
Result: >100,000 COL/ML
ENTEROBACTER CLOACAE COMPLEX
This isolate is a Carbapenem Resistant Enterobacteriaceae
(CRE) and resistant to all penicillins, cephalosporins,
carbapenems and aztreonam. CONTACT PRECAUTIONS
REQUIRED. Confirmation from OSPHL to follow. ←

Order: METHOD

Test: Aztreonam Susc Islt
Result: Resistant=4
Resistant (qualifier value)
Test: Pip+Tazo Susc Islt
Result: Resistant<=128
Test: Pip+Tazo Susc Islt
Result: Resistant (qualifier value)
Test: Cefazolin Susc Islt
Result: Resistant<=64
Test: Cefazolin Susc Islt
Result: Resistant (qualifier value)
Test: Ceftriaxone Susc Islt
Result: Resistant=32
Test: Ceftriaxone Susc Islt
Result: Resistant (qualifier value)
Test: Cefepime Susc Islt
Result: Resistant<=1
Test: Cefepime Susc Islt
Result: Resistant (qualifier value)
Test: Meropenem Susc Islt
Result: Resistant=0.5 ←

CRE terminology

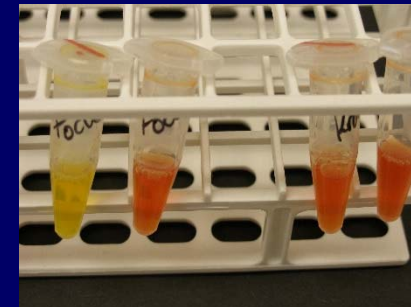
- **Carbapenemase producing (CP-CRE)**
 - Responsible for **rapid global plasmid mediated spread!!**
 - Directly inactivate carbapenems
 - Increased morbidity and mortality
- **Non-carbapenemase-producing (CRE)**
 - Stable/slight increase incidence over time
 - Multiple mechanisms combined for resistance – AmpC, porin changes

Carbapenemases to know

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi metallo- β -lactamase (NDM)
- Verona integron encoded metallo- β -lactamase (VIM)
- Imipenemase metallo- β -lactamase (IMP)
- Oxacillinase – 48 (OXA-48)

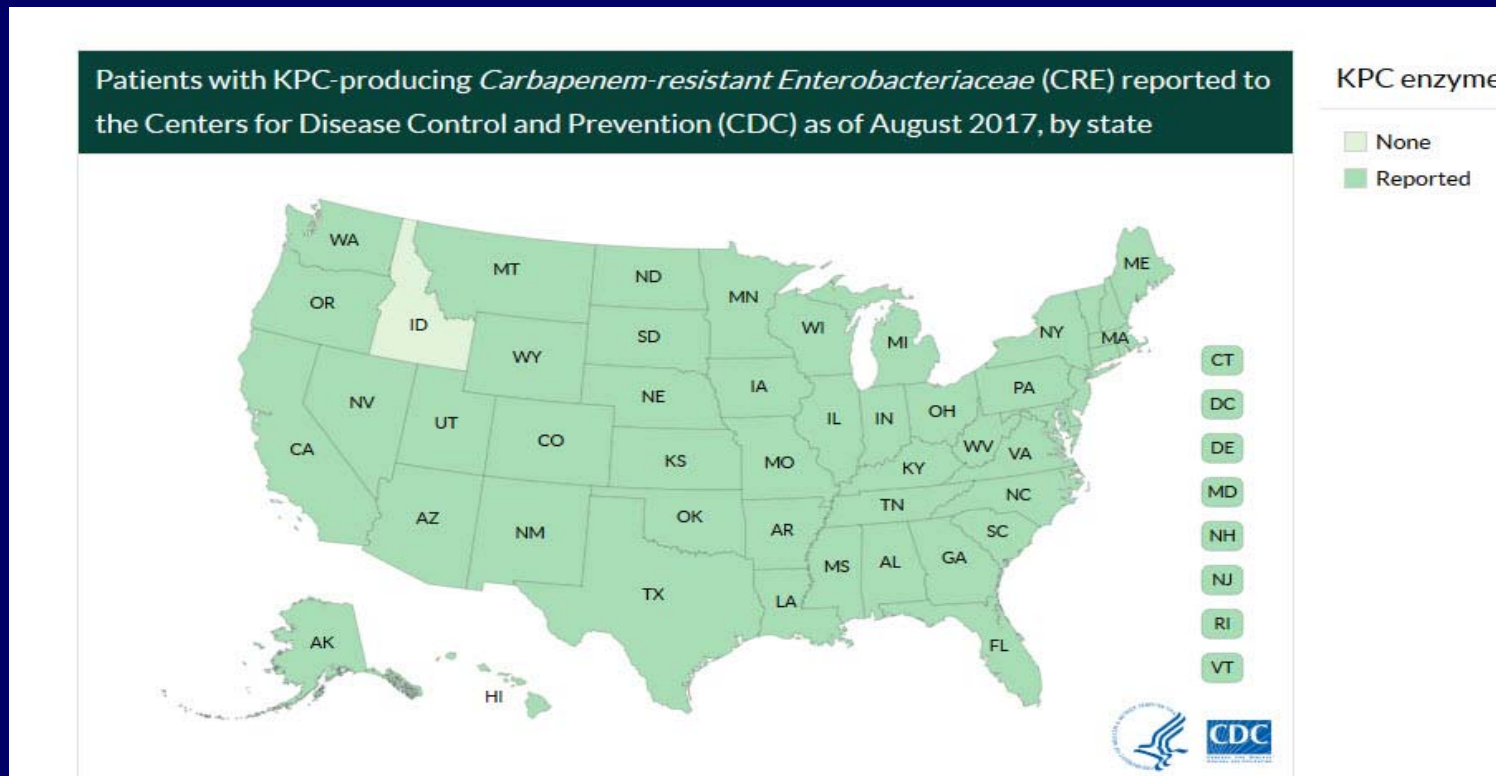
OSPHL Carbapenemase testing

- Labs submit isolates to OSPHL with the automated system print outs
- Print outs are faxed to ACDP
- Carbapenemase testing is done weekly
 - **Carba NP**
 - **Multiplex PCR**
 - OXA-48 only, if Carba NP is negative
 - All 5 carbapenemases if Carba NP positive



Spread of CP CRE in the US

- KPC first discovered in 2000
- Now



CRE prevalence

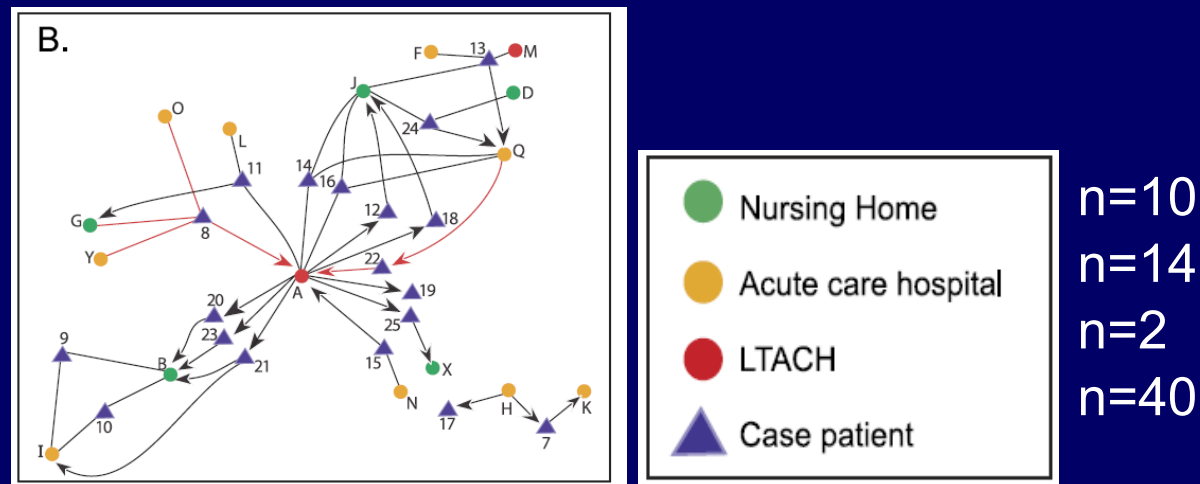
✓ CRE prevalence varies

– Region: Israel \neq Chicago \neq Oregon

✓ Unidentified CRE in inter-facility patient transfer promotes outbreaks

KPC outbreak, Chicago-area, 2008

Figure:
Exposure
Network
Analysis



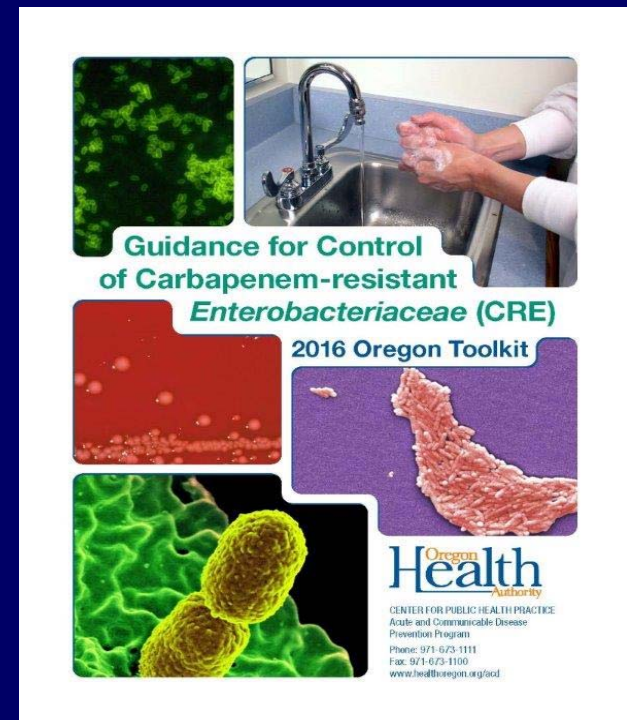
Healthcare out of Oregon and CP-CRE

- Oregon is still a low prevalence state
- 17/496 (3%) of Oregon cases are CP-CRE
- 12/17 (75%) CP-CRE cases had history of healthcare out of state

- Compare to Minnesota - 21% of CRE isolates were KPC, CP-CRE in 2015

Focus of CRE or any MDRO investigation

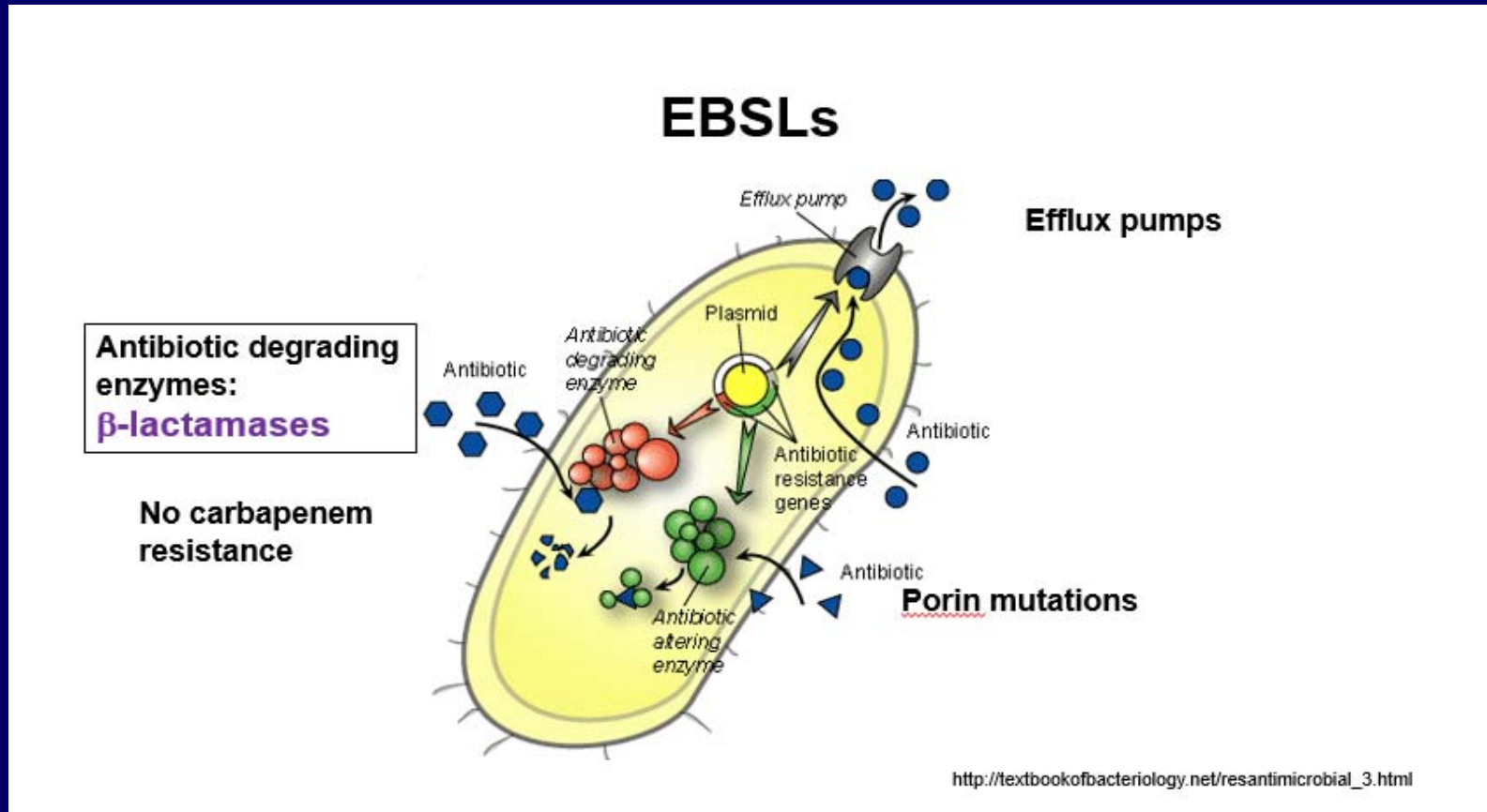
- Prevent spread
 - Identify and confirm
 - Inform facility
 - Verify precautions (contact)
 - Provide education
 - Carrier of resistant organism
 - hand hygiene importance
 - precautions if hospitalized
 - Transfer notification – flagging chart



How does CP-CRE Investigation Differ

- LHD and OHA will work together on screening cultures for high risk contacts
 - Send to OSPHL
 - Recommended site: rectal swabs
- Cohorting of staff is recommended
- LHD should be notified when case transfers

Other MDRO



Other resistant organisms



- Mobilized Colistin Resistance genes (MCRs 1, 2, 3 and
- Plasmid mediated
 - resistance to last line drug - colistin
- Found in China 2 years ago
- Now in >30 countries



Additional surveillance for Multi-Drug-Resistant Organisms (MDROs)

- Multi-site Gram-Negative Surveillance Initiative (MuGSI), Portland tri-county
 - Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
 - Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
- Candidemia surveillance – Emerging Infections Program

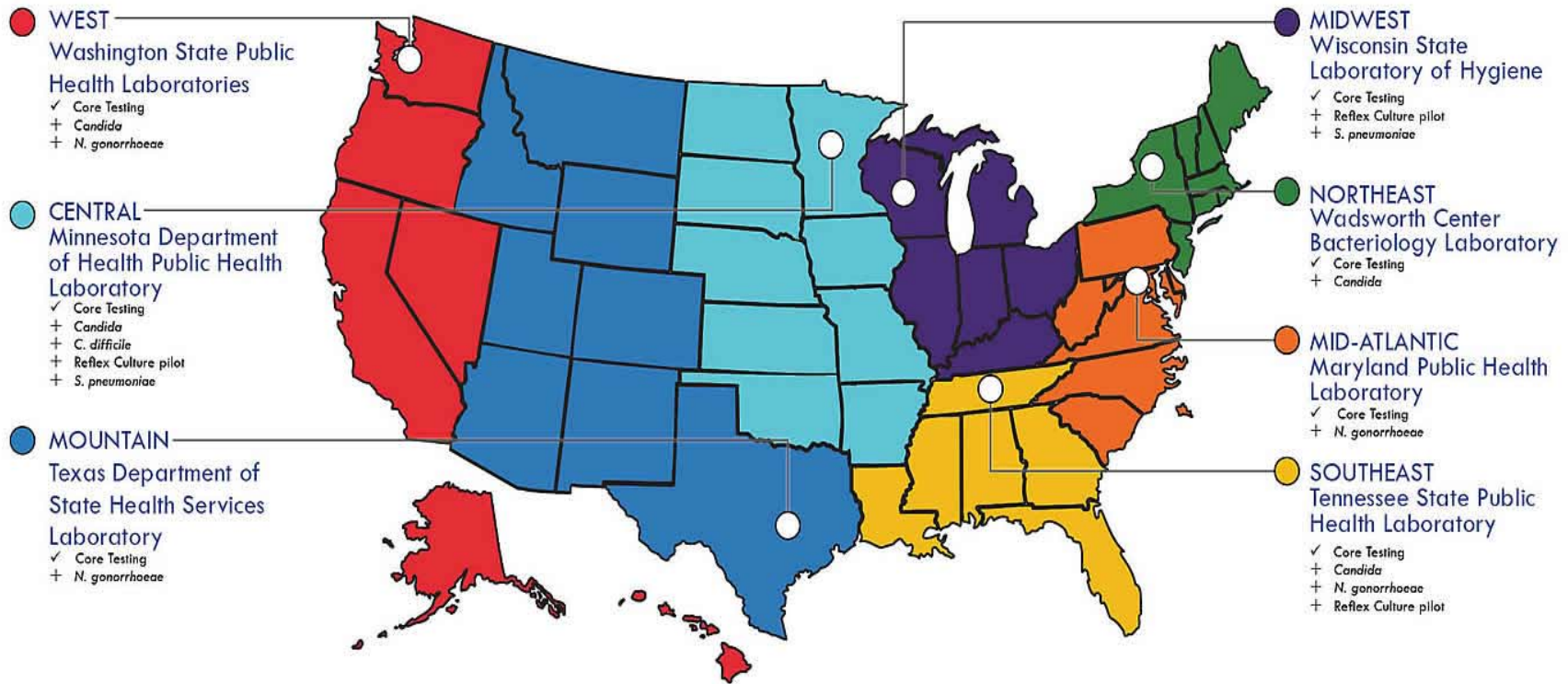
New Surveillance for MDROs

- OSPHL request to clinical labs
- Submit isolates of pan-resistant gram negatives
 - test for carbapenemases
- Submit possible *Candida auris* isolates
 - newly recognized species
 - resistant to antimicrobials
 - cause of outbreaks in other states



New surveillance for MDROs

CDC Antibiotic Resistance Laboratory Network: 7 Regional Labs



New surveillance for MDROs



- Expanding surveillance for
 - Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
 - Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
- Select laboratories statewide will send isolates
- Surveillance for MCRs
 - Test *E.coli* and *Klebsiella spp.* resistant to all 3rd generation cephalosporins

Thanks for contributions to this presentation

- Chris Pfeiffer, MD, MHS
- Ann Thomas, MD
- Rebecca Pierce, PhD, MS, BSN

New CDC project

Combating Antibiotic Resistant Bacteria (CARB)

Julie Hatch, MT, ASCP
Laboratory Surveillance Coordinator

Whole Genome Sequencing (WGS)

- Detect different types of antibiotic resistance
- Detect plasmids
- Certain types of resistance are associated with different parts of the world

2018 Interview Changes

- Salmonella
- Campylobacter

New Interview Questions

- Severity of illness
 - Duration of illness, admission to ICU
- Health conditions
 - Diabetes, cancer, bowel surgery
- Probiotic and antacid use
- Antibiotic use
- Travel

National Antibiotic Resistance Monitoring System (NARMS)

- Tests every 20th Salmonella isolate from all states for antibiotic resistance
- Campylobacter submitted by FoodNet states

Notified by CDC NARMS team

- 2014 case with MCR-3 resistance
- First identified case in US

Salmonella I 4,5,12:i:-

- 29 y F, white, non-Hispanic
- Onset 7/22/14 non-bloody diarrhea
- Stool collected 7/29/14
- No foreign travel during exposure period
- Returned from Cambodia 18 days prior to onset