

# Public Health Surveillance for Multi-Drug-Resistant Organisms in Orange County

Matt Zahn, MD

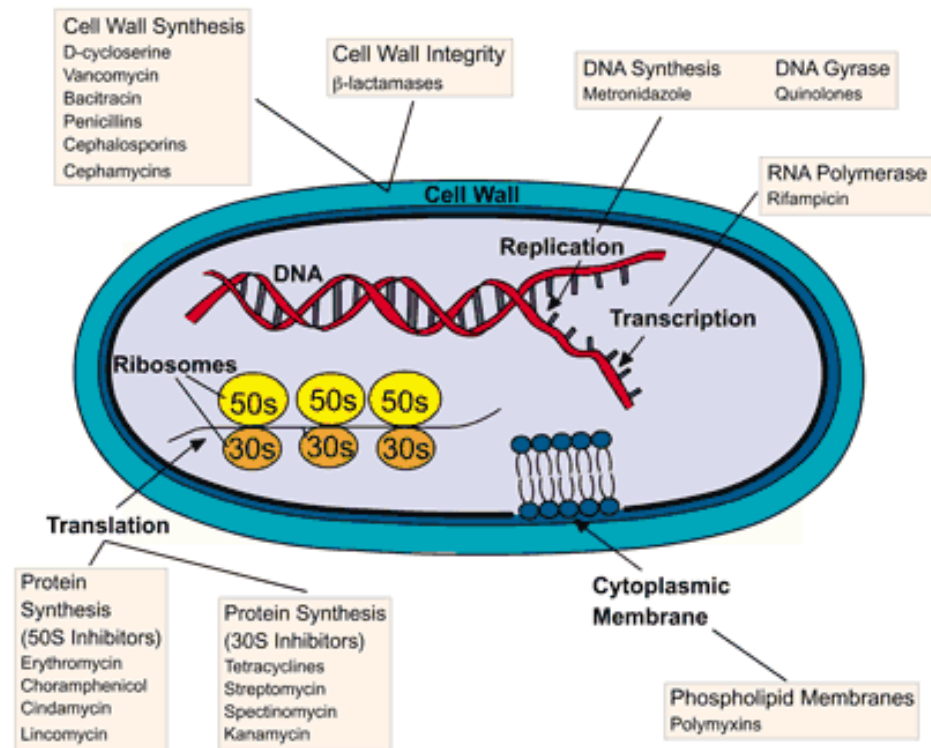
Medical Director

Epidemiology and Assessment

Orange County Public Health



# Antimicrobial Mechanisms of Action

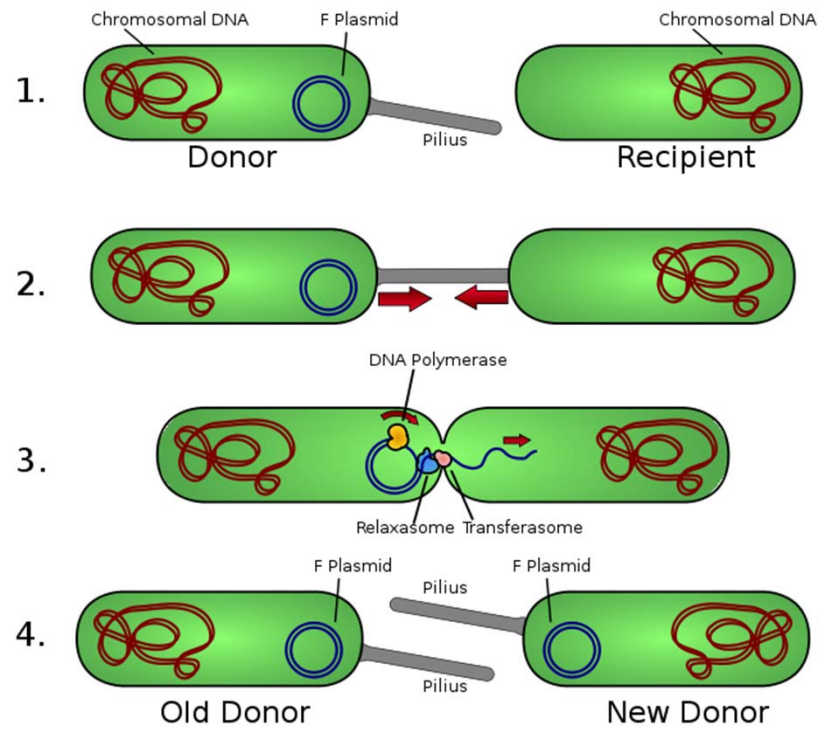




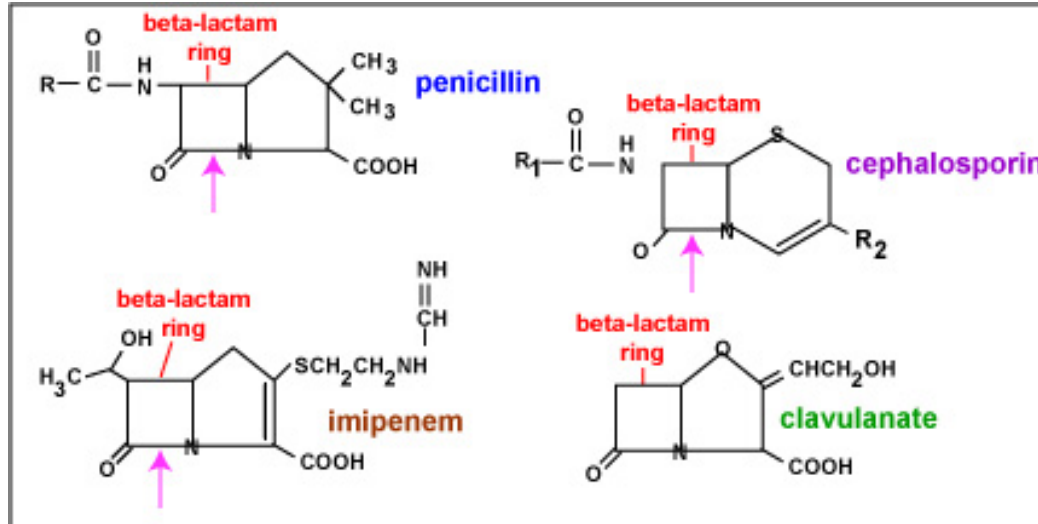
# Intrinsic Resistance

- Occurs due to mutation of chromosomal genes
  - Pseudomonas
  - *Mycobacterium tuberculosis*

# Bacterial Acquired Resistance

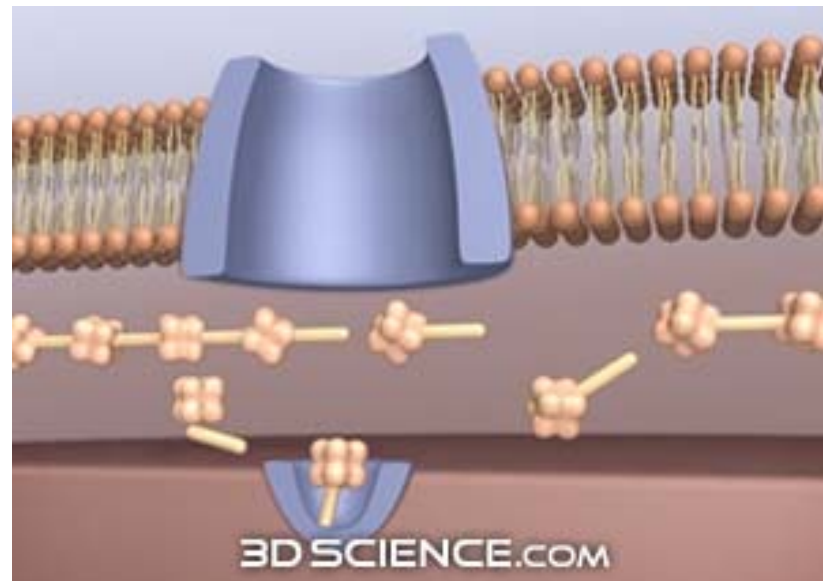


# Beta-Lactam Antibiotics



# Beta-Lactam Antibiotics

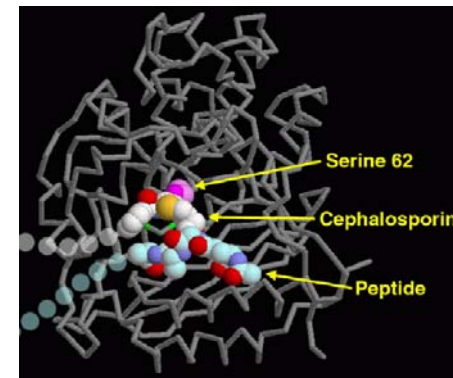
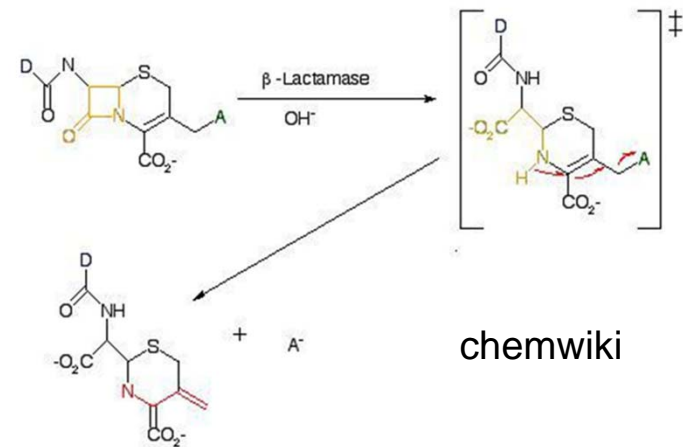
- Penicillins
- Cephalosporins
- Carbapenems



# Beta-Lactam Resistance

Occurs due to:

- Production of beta-lactamase enzymes
- Alteration in penicillin binding proteins



Pdb101.rcsb.org



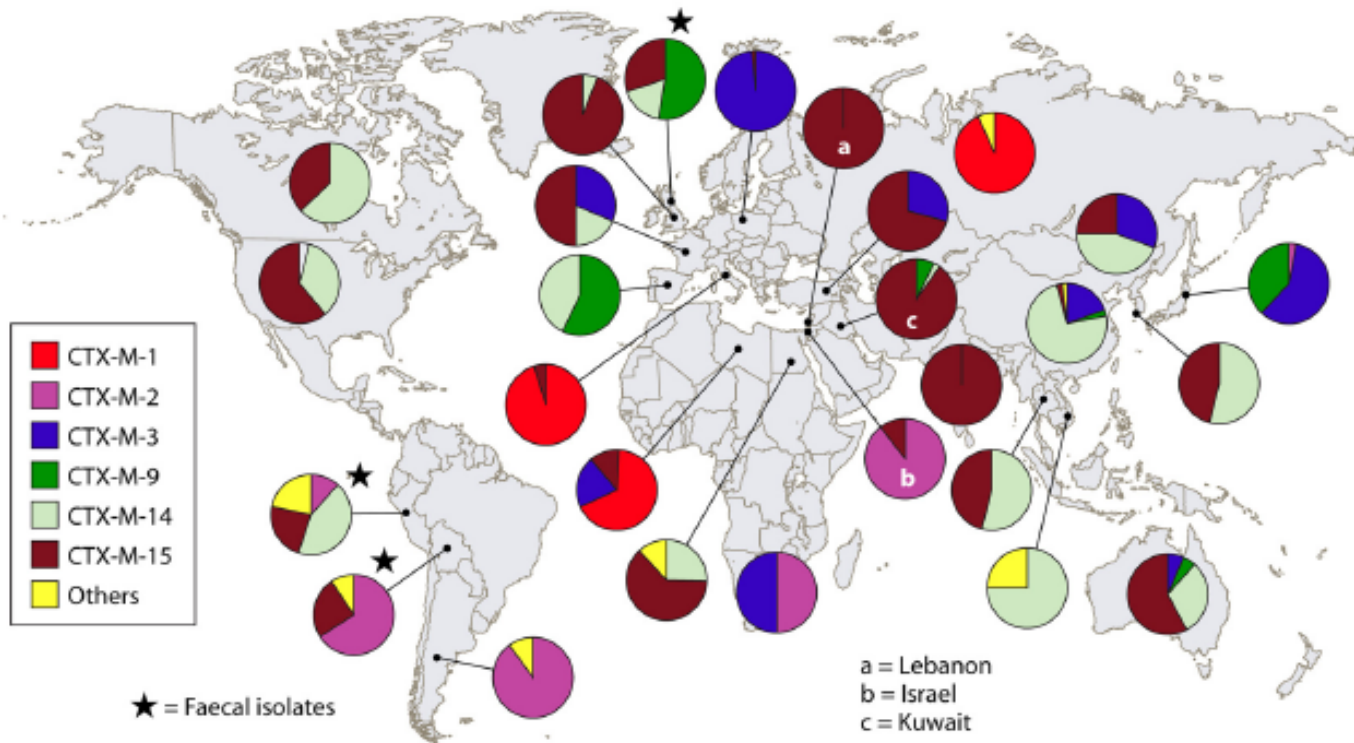
# Initial Beta-Lactamases

- Inhibit penicillin and some cephalosporin activity
- Have been clinically relevant for decades
- Generally do not inhibit third-generation cephalosporins such as ceftriaxone, cefotaxime, and ceftazidime
- Found in:
  - *E. coli*
  - *H. influenzae*
  - *N. gonorrhoeae*

# Extended Spectrum Beta-Lactamases

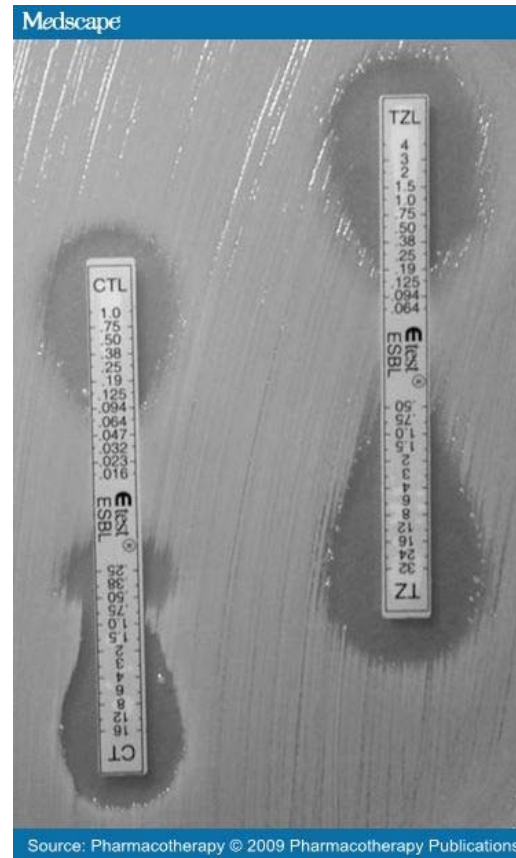
- Beta lactamase enzymes can mutate to expand their spectrum of activity to inhibit more antibiotics, especially cephalosporins
- Common ESBL-producing bacteria include:
  - *E. coli*
  - *Proteus mirabilis*
  - *Klebsiella pneumoniae*
- These bacteria most frequently colonize the intestine
- Respiratory tract and skin can also be sites

**The Trade Routes of the CTX-M Enzymes**



# ESBL Detection

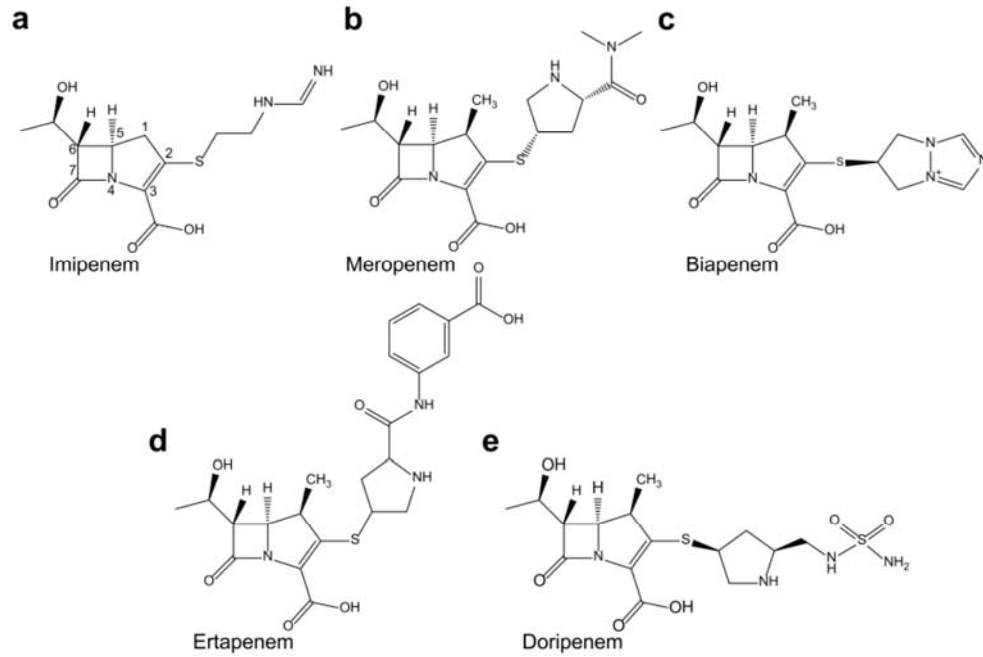
- Methods of detection can include:
  - Phenotypic
  - Molecular
  - Testing for ESBL's can be complex



# ESBL Treatment

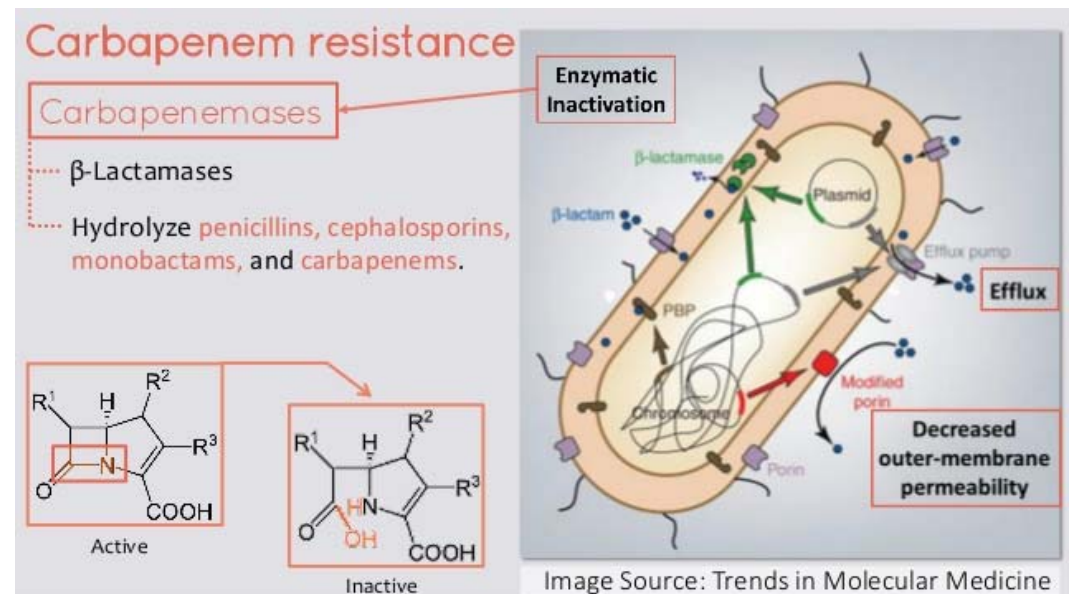
- ESBL-producing organisms may appear susceptible to some extended-spectrum cephalosporins on lab testing
- However, treatment with such antibiotics has been associated with high failure rates
- Carbapenems are often the treatment of choice

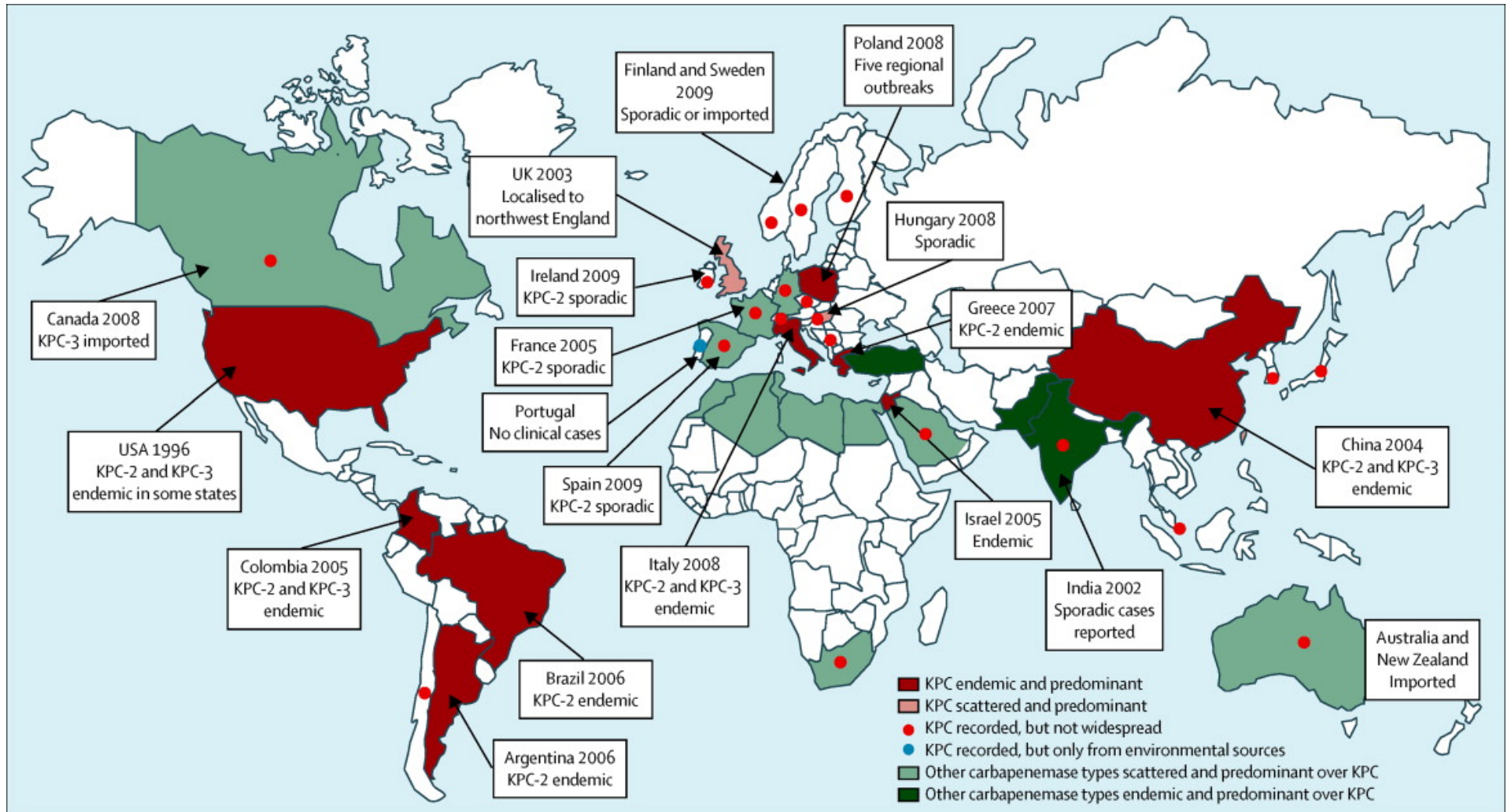
# Carbapenems



# Now We Have Resistance to Carbapenems

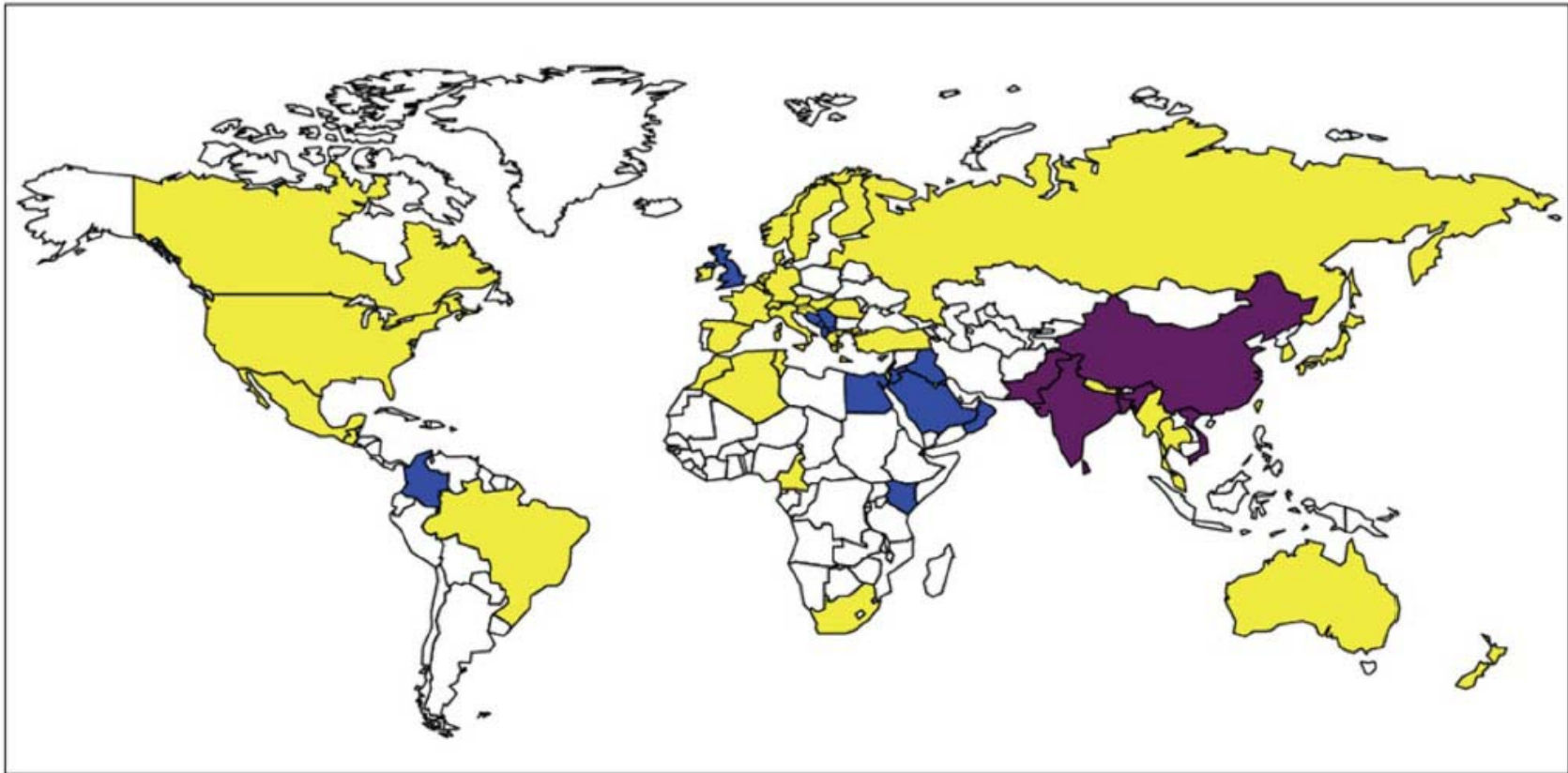
- Carbapenem-Resistant Enterobacteriaceae (CRE)
  - Result from multiple genetic changes in a bacteria that lead to overall resistance
- Carbapenemase-Producing Enterobacteriaceae (CPE)
  - Result from one genetic change
  - Can cause facility and community outbreaks





The Lancet Volume 13(9), P785-796, September 01, 2013





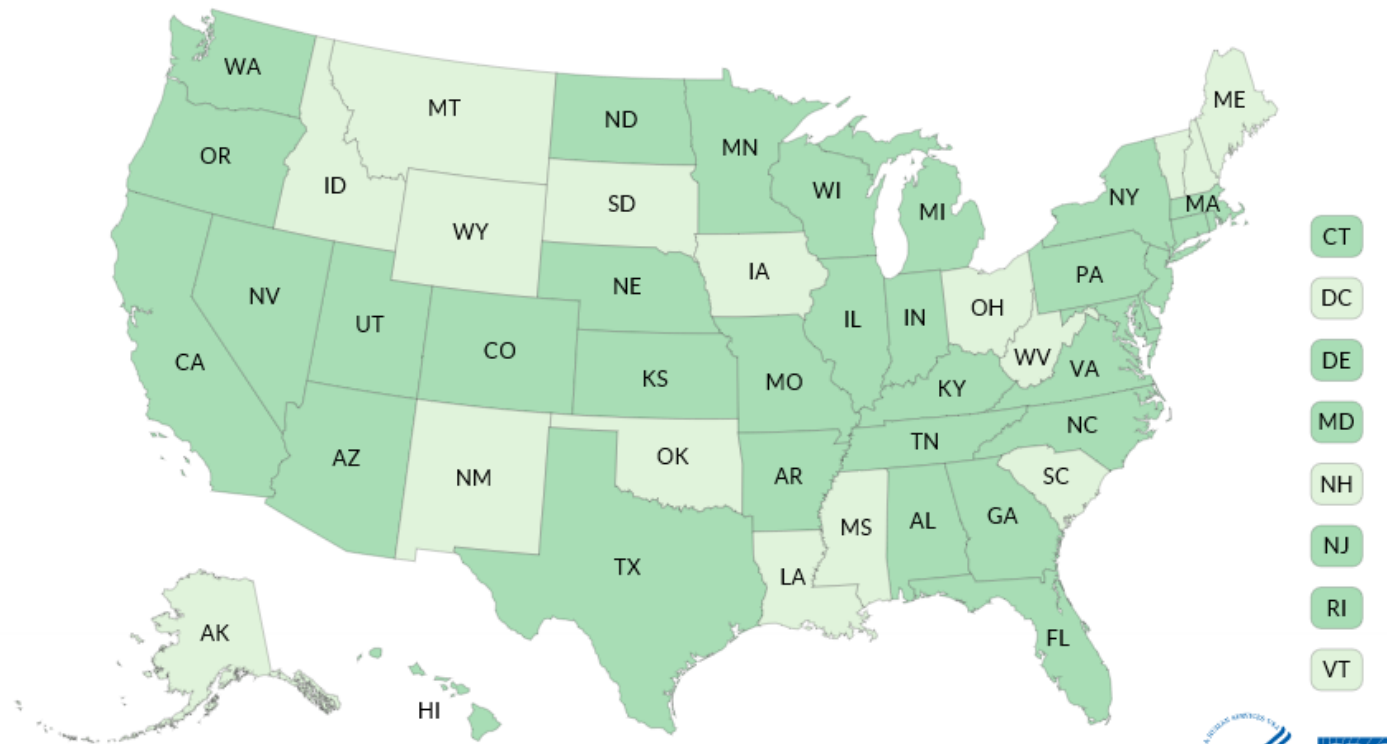
- High prevalence of NDM producers (endemicity)
- Outbreaks and interregional spread of NDM producers
- Sporadic description of NDM producers

Infection and Drug Resistance 2015;8(297-309)

# Orange County Health Care Agency's Journey to Here

- Orange County Health Care Agency has had internal discussions on how to address the problem of multidrug resistance organisms county-wide for years
- We've discussed making CRE (or other MDROs) reportable
  - Is it worth the work?
- Orange County CDI collaborative has been a start to addressing these issues

Patients with NDM-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state

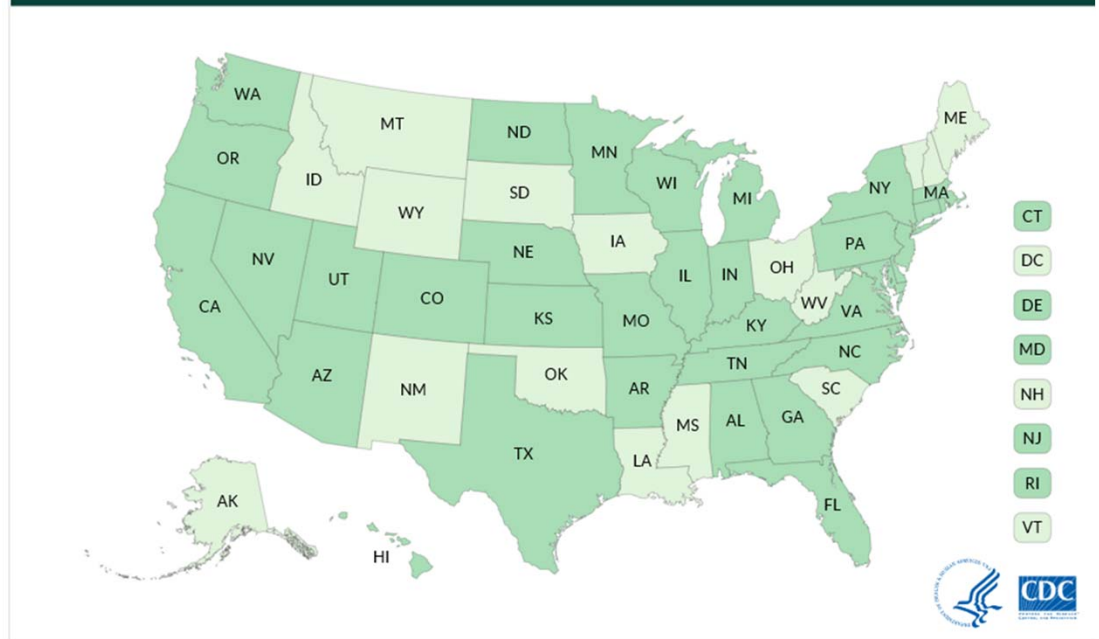


# CRE Surveillance: National reporting from the Centers for Disease Control and Prevention

Total National Counts:

- NDM-producing CRE = 379
- Total OXA-48-producing CRE = 146
- Total VIM-producing CRE = 57
- Total IMP-producing CRE = 36

Patients with NDM-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



# SHIELD OC

Shared Healthcare Intervention  
to Eliminate Life-threatening Dissemination  
of MDROs in Orange County



- Intervention supported by the Centers for Disease Control and Prevention (CDC) and California Department of Public Health
- Carried out by UCI and OCHCA

# SHIELD OC Goals

- Decolonization Strategy in healthcare facilities throughout Orange County
- Goals
  - 1) Reduce clinical disease due to MDROs countywide
  - 2) Assess impact of an infection control intervention in facilities that are participating in SHIELD OC, as well as those that are NOT participating in SHIELD OC

# Decolonization Strategy

- 17 Hospitals

For adult patients on contact precautions:

- Chlorhexidine (CHG) antiseptic soap for daily bathing or showering
- Nasal decolonization with 10% povidone-iodine
- Continue CHG bathing for adult patients in the ICU

- 16 Nursing homes and 3 long-term acute care hospitals (Kindred)

For all residents:

- CHG for routine bathing and showering of all patients
- Nasal decolonization with 10% povidone-iodine on admission and every other week



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July 5, 2016

Dear Laboratory Director:

Antimicrobial resistance is a serious and growing public health problem. In order to better understand this issue and prevent the spread of infectious disease in our County, the Orange County Health Care Agency (OCHCA) is adding laboratory reports of certain antibiotic-resistant bacteria of public health significance to our County's List of Reportable Diseases. Effective July 5, 2016, by authority of the Health Officer under California Health and Safety Code section 120175 and California Code of Regulations, Title 17, Sections 2500 and 2505, hospital laboratories and commercial laboratories receiving specimens from hospitals and skilled nursing facilities are hereby ordered to report all positive laboratory results for the following multidrug resistant organism (MDRO) organisms:

- ✓ All *Enterobacteriaceae* that produce extended spectrum beta-lactamases (ESBLs)
- ✓ All Carbapenem-resistant *Enterobacteriaceae* (CRE)
- ✓ Methicillin-resistant *Staphylococcus aureus* (MRSA) from admitted patients

Laboratory results from specimens sent both for diagnostic and screening surveillance purposes that fit the following criteria are to be reported to the Orange County Health Care Agency:

- 1) MRSA (by culture or PCR)
- 2) *E. coli*, *Klebsiella* spp, and *Enterobacter* spp that are antibiotic-resistant according to ANY of the following criteria:
  - ✓ *E. coli* or *Klebsiella* spp designated as an ESBL-producer by an established testing method
  - ✓ *E. coli*, *Klebsiella* spp, and *Enterobacter* spp, intermediate or resistant to 3<sup>rd</sup> generation cephalosporins according to current CLSI guidance (below):
    - *E. coli* and *Klebsiella* spp. - either disk diffusion  $\leq 22$ mm or MICs  $\geq 2$   $\mu$ g/ml for ceftazidime, aztreonam, cefotaxime or ceftriaxone, or  $\geq 8$   $\mu$ g/ml for cefepodoxime
    - *Enterobacter* spp. isolates with MIC  $\geq 2$  mcg/mL for cefotaxime or ceftriaxone, OR  $\geq 4$  mcg/mL for cefepodoxime OR  $\geq 8$  mcg/mL for ceftazidime or aztreonam
- 3) *E. coli*, *Klebsiella* species, and *Enterobacter* species that are resistant to any carbapenem according to ANY of the following criteria:
  - ✓ MIC of  $\geq 4$   $\mu$ g/ml for doripenem, imipenem or meropenem or  $\geq 2$   $\mu$ g/ml for ertapenem
  - ✓ Production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated using a recognized test (e.g., metallo-beta-lactamase test, modified Hodge test, Carba-NP test, ROSCO discs)
  - ✓ Presence of a carbapenemase gene (e.g. gene encoding KPC, NDM, VIM, IMP, OXA-48) demonstrated using a recognized test (e.g., PCR)

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Health Officer Order  
July 5, 2016  
Page 2 of 2

Facilities are directed to forward a list of the above laboratory results to OCHCA every 2 to 4 weeks. Laboratories are encouraged to contact the Orange County Health Care Agency at 714-834-8180 for questions or for more information on arranging this process.

Eric Handler, MD, MPH

Matt Zahn, MD



# To Be Reported by ALL Orange County Inpatient Facilities and Skilled Nursing Facilities

- Inpatient MRSA
- All CRE
- All ESBL
  - All are at different points of “establishment” in our community
- Notes:
  - All types of positives are reportable
  - Surveillance
  - Disease
  - Includes non-culture methods: PCR, etc.

# Facilities Currently Reporting to OCHCA

- Hospitals
  - 27/27 reporting
  - 17 participating in SHIELD
  - 10 non-participating
- Long-term acute care hospitals (LTACHs)
  - 3/3 reporting
  - All 3 participating
- Skilled Nursing Facilities (SNFs)
  - 67/72 SNFs reporting
  - 16 participating in SHIELD (15 reporting)
  - 7 participating in PROTECT (5 reporting)
  - 49 non-participating (47 reporting)

# MDRO Counts at OC Hospitals

Facility	Organism	2016		2017				2018		Total Cases
		Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	
		BASELINE			PHASE-IN	INTERVENTION				
Hospital Participating in SHIELD**	CRE	34	31	20	28	20	22	29	22	206
	ESBL	726	841	839	833	842	859	919	835	6694
	MRSA	555	542	637	598	556	555	668	540	4651
	Any MDRO	1315	1414	1496	1459	1418	1436	1616	1397	11551
Hospitals Not Participating in SHIELD	CRE	5	6	3	3	5	4	11	8	45
	ESBL	226	202	255	260	262	283	264	208	1960
	MRSA	143	148	169	158	155	175	163	140	1251
	Any MDRO	374	356	427	421	422	462	438	356	3256
Late-Start SHIELD Hospitals*	CRE	2	3	1	3	6	2	5	3	25
	ESBL	96	61	75	66	84	75	77	72	606
	MRSA	58	37	49	55	60	53	67	62	441
	Any MDRO	156	101	125	124	150	130	149	137	1072
Hospital Total	CRE	41	40	24	34	31	28	45	33	276
	ESBL	1048	1104	1169	1159	1188	1217	1260	1115	9260
	MRSA	756	727	855	811	771	783	898	742	6343
	Any MDRO	1845	1871	2048	2004	1990	2028	2203	1890	15879

\*Late-Start Hospitals – started as of 2018 Q2

**MDRO Clinical Culture Counts = Number of 1<sup>st</sup> Clinical LabID Events at facility per patient per month**

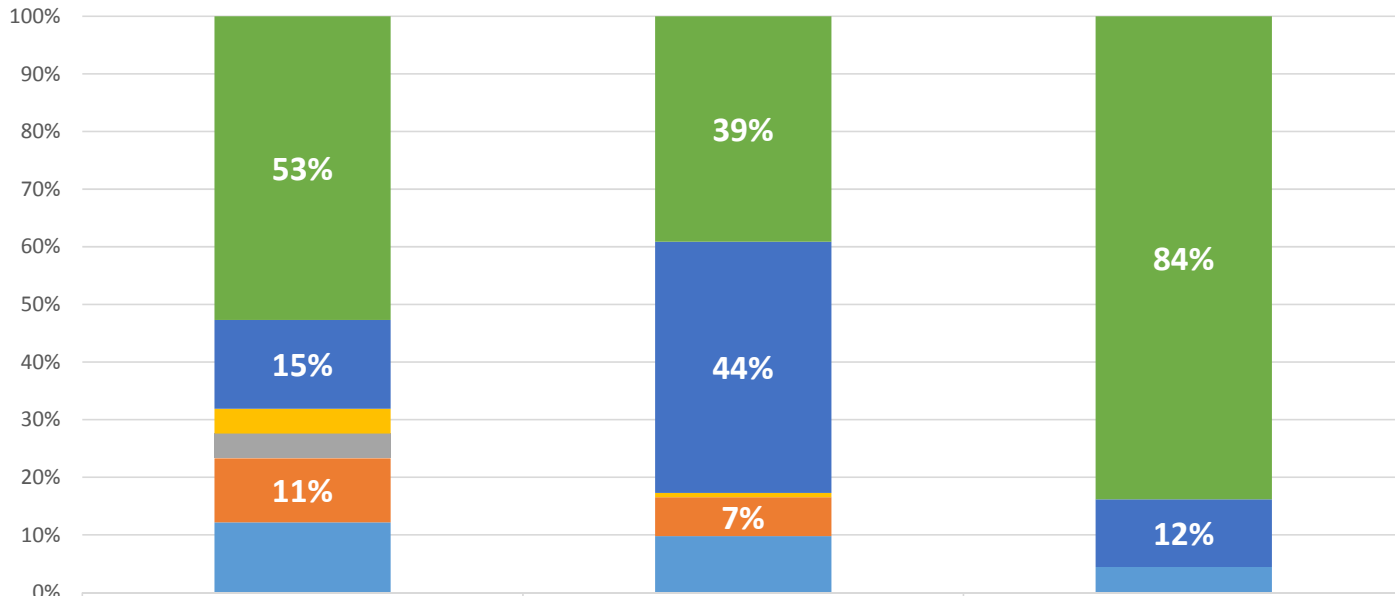
# MDRO Counts at Long-term Acute Care Hospitals

Facility	Organism	2016		2017				2018		Total Cases
		Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	
		BASELINE			PHASE-IN	INTERVENTION				
LTACHs Participating in SHIELD	CRE	25	17	20	7	14	16	13	21	133
	ESBL	47	47	55	37	33	29	41	43	332
	MRSA	49	46	50	35	28	40	42	48	338
	Any MDRO	121	110	125	79	75	85	96	112	803

# Monthly MDRO Counts at Skilled Nursing Facilities

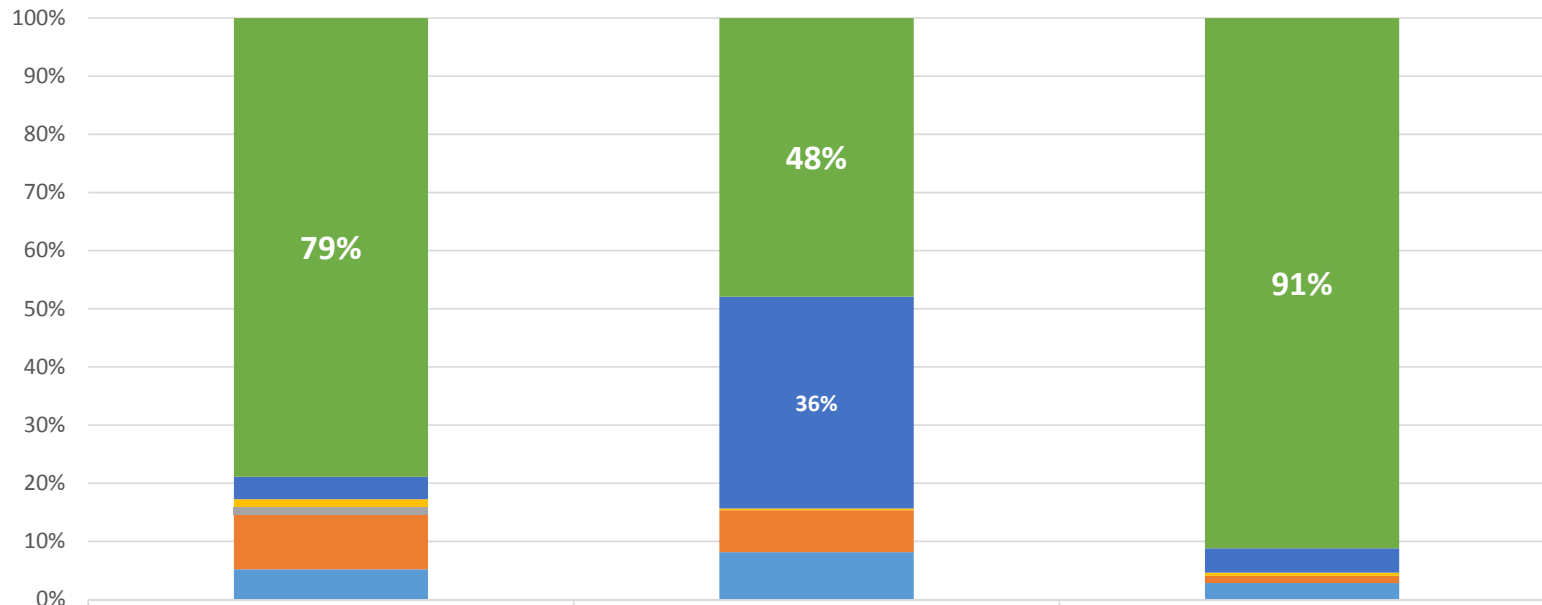
Facility	Organism	2016		2017				2018		Total Cases
		Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	
		BASELINE			PHASE-IN	INTERVENTION				
NHs Participating in SHIELD	CRE	11	6	5	2	1	4	3	5	37
	ESBL	96	79	79	69	81	58	57	45	564
	MRSA	24	18	16	18	12	15	11	14	128
	Any MDRO	131	103	100	89	94	77	71	64	729
SNFs Participating in PROTECT	CRE	0	2	1	0	1	0	0	0	4
	ESBL	9	7	10	14	15	11	5	5	76
	MRSA	1	5	3	2	1	0	2	0	14
	Any MDRO	10	14	14	16	17	11	7	5	94
Non- intervention SNFs	CRE	6	4	2	2	3	1	6	3	27
	ESBL	174	170	156	156	160	133	130	122	1201
	MRSA	42	43	31	29	34	28	30	22	259
	Any MDRO	222	217	189	187	197	162	166	147	1487
SNF Total	CRE	17	12	8	4	5	5	9	8	68
	ESBL	279	256	245	239	256	202	192	172	1841
	MRSA	67	66	50	49	47	43	43	36	401
	Any MDRO	363	334	303	292	308	250	244	216	2310

# Clinical Culture Sites- CRE



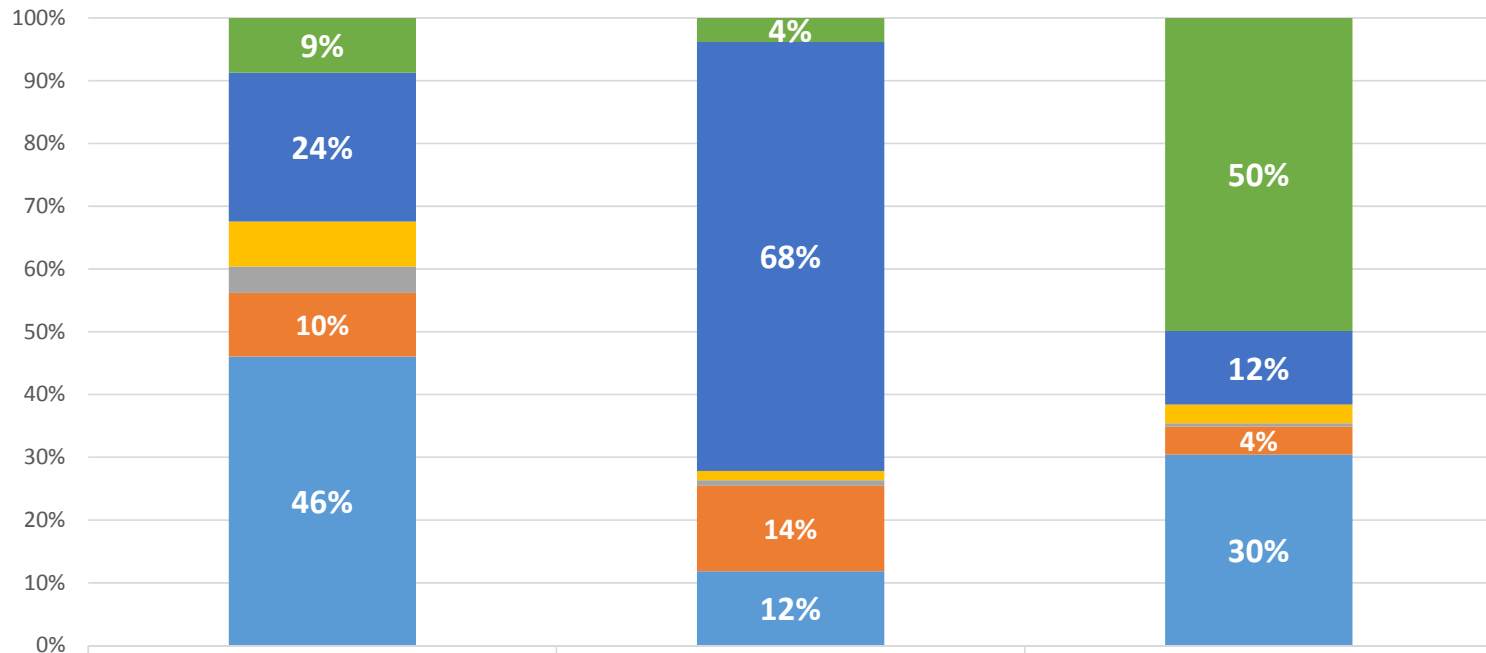
	HOSPITAL	LTAC	SNF
■ Urine	147	52	57
■ Respiratory	43	58	8
■ Other NonsSterile	12	1	0
■ Other Sterile	12	0	0
■ Blood	31	9	0
■ Abscess/Wound	34	13	3

# Clinical Culture Sites- ESBL



	HOSPITAL	LTAC	SNF
■ Urine	7532	159	1679
■ Respiratory	369	121	77
■ Other NonsSterile	128	1	10
■ Other Sterile	124	0	0
■ Blood	897	24	23
■ Abscess/Wound	497	27	52

# Clinical Culture Sites- MRSA



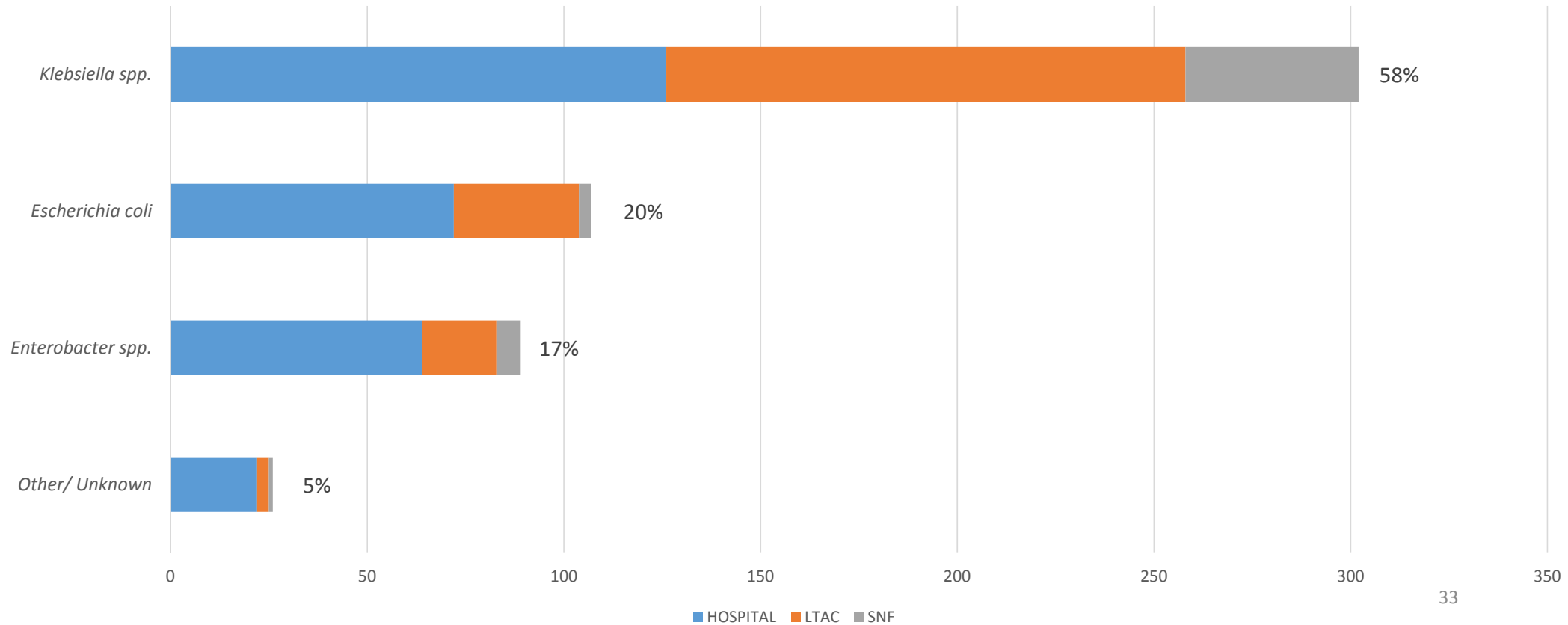
	HOSPITAL	LTAC	SNF
■ Urine	559	13	200
■ Respiratory	1520	231	47
■ Other NonsSterile	458	5	12
■ Other Sterile	269	3	2
■ Blood	650	46	18
■ Abscess/Wound	2951	40	122



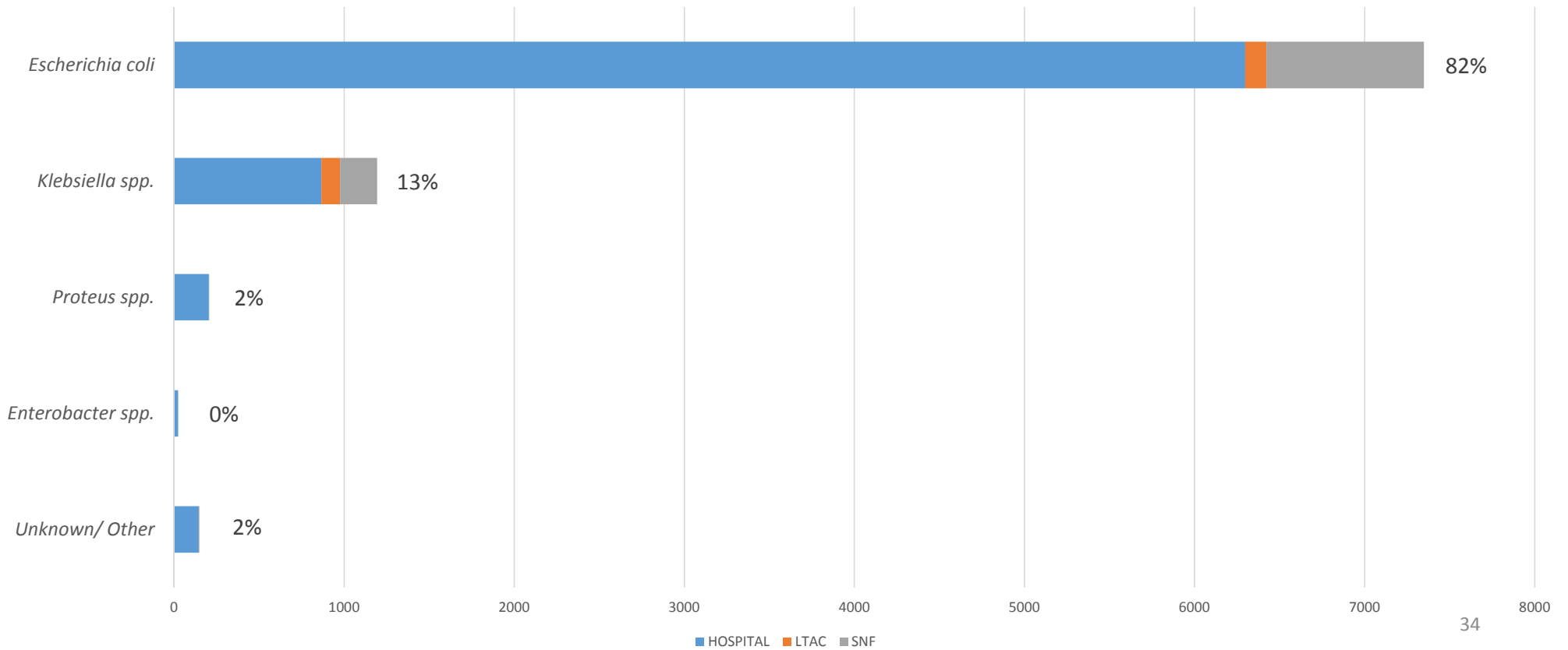
## Regional Carbapenem-resistant *Enterobacteriaceae* Species Breakdown

One count per unique person per species, Clinical and Surveillance Cultures

Hospitals, LTACHs, and SNFs  
7/1/2016-3/31/2018 (N=524)



**Regional ESBL *Enterbacteriaceae* Species Breakdown**  
 One count per unique person, per species, Clinical and Surveillance Cultures  
 Hospitals, LTACHs, and SNFs  
 7/1/2016-3/31/2018 (N=8923)



# ESBL Non-Urine Clinical Isolates

- **Blood cultures:**

- 944 total (23 SNF, 24 LTACH, 897 Hospital)
  - 776 E. coli (82%)
  - 117 Klebsiella (12%)
  - 30 Proteus (3%)
  - 21 Unknown (2%)
- Median age 71 (0\*-100)

- **Wound/Abscess cultures:**

- 576 total (497 Hospital, 27 LTACH, 52 SNF)
  - 412 E. coli (72%)
  - 115 Klebisella (20%)
  - 33 Proteus (6%)
  - 2 Pseudomonas (0%)
  - 9 Unknown (1.5%)
- Median age 61 (0\*-99)

\*24 months: July 1, 2016-June 30, 2018

# Facilities Sharing of Patients with MDROs

Unique patients with (+) MDRO culture from more than one county facility

Sharing patterns amongst county facility types

	<b>MRSA</b> (inpatient only)	<b>E. Coli</b> <b>ESBL</b>	<b>Klebsiella</b> <b>ESBL</b>	<b>Klebsiella</b> <b>CRE</b>
N=	448	770	115	32
Multiple Hospitals Only	57%	44%	30%	13%
Hospitals and LTAC	22%	6%	17%	34%
Hospitals and SNF	18%	48%	47%	38%
Hospitals, LTAC, and SNF	2%	2%	4%	9%
LTAC and SNF	0%	1%	2%	6%
Multiple SNFs Only	0%	1%	1%	0%
Multiple LTACs Only	0%	0%	0%	0%

\*Clinical Cultures Only

# Recurrence of ESBL Infection

## One positive ESBL culture July 1- Dec 31 2016 (n=2309)

### Recurrence of same organism:

- 24.8% (n=585) of patients with one positive culture July 1-Dec 31, 2016 had a second ESBL positive result within the next 12 months
- Klesbiella ESBL= 72/315 (22.9%)
  - 50/72 (69.4%) repeat urinary tract infection \*4 with multiple site infections
- E. coli ESBL= 513/2040 (25.1%)
  - 421/513 (82.1%) repeat urinary tract infection \*36 with multiple site infections

### Recurrence of ESBL infection of any type

- 27.4% (n=632) of patients with one positive culture July 1-Dec 31, 2016 had a second ESBL positive result within the next 12 months (**any organism**)
- 2.0% (n=47) had a positive culture with a different organism

# Voluntary Submission of Isolates to OC

- All facilities are asked to voluntarily forward all CRE isolates to OCHCA
- 4 hospitals are asked to forward 5 ESBL isolates each week to OCHCA
- OCHCA performs antimicrobial resistance testing and modified Carbapenem Inactivation Method (mCIM) testing
- mCIM-positive isolates are forwarded to CDPH for further testing.



COUNTY OF ORANGE  
**HEALTH CARE AGENCY**  
  
PUBLIC HEALTH  
EPIDEMIOLOGY & ASSESSMENT

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TELEPHONE: (714) 834-8180  
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**Enhanced Surveillance for Carbapenem Resistant Enterobacteriaceae (CRE) Disease in Orange County**

May 30, 2017

To: Orange County Hospital Laboratory Directors, Microbiology and Send-Out Staff; Infection  
Preventionists

From: Orange County Public Health Laboratory

Antimicrobial resistance is a serious and growing public health problem. Rates of Carbapenem resistant enterobacteriaceae (CRE) infection in Orange County are some of the highest in California, according to a 2015 laboratory survey conducted by the California Department of Public Health. Infections with CRE are difficult, and in some cases impossible, to treat and have been associated with mortality rates of up to 50%.

In order to better characterize the epidemiology of multidrug resistant organisms in Orange County, on July 5, 2016, Orange County's Health Officer mandated that all positive laboratory results for CRE and extended-spectrum beta lactamase producing (ESBL) and all laboratory positive results for methicillin-resistant staphylococcus aureus (MRSA) from hospital-admitted patients be reported to the Orange County Health Care Agency ([link](#)).

**In addition to reporting the positive result to Epidemiology, we are now requesting all isolates of carbapenem resistant enterobacteriaceae (CRE) recovered from any body site to be submitted to the Orange County Public Health Laboratory (OCPHL).**

Labs are requested to submit actively growing pure culture CRE isolates on a microbiological tubed media that supports the organism's growth. Accompanying each isolate should be an OCPHL requisition form indicating the following required demographic information (submitter name, patient name, birth date, gender), date of collection, and specimen source.

Isolates will be tested by the Centers for Disease Control and Prevention (CDC) by PCR for specific carbapenemases including KPC, NDM and OXA-48 and potentially whole genome sequencing.

# Laboratory Carbapenemase Testing

- Of 14 clinical laboratories interviewed:
  - 8 perform no carbapenemase testing
  - 1 performs mCIM
  - 1 Carba NP
  - 1 CHROMagar test
  - 3 modified Hodge



# OCHCA Laboratory Results from Testing of CREs

- High correlation of OCHCA Lab susceptibility pattern testing with submitter's results: >90%
- Of 153 CRE isolates tested so far:
  - 142 are carbapenemase producing
  - 11 are not carbapenemase producing
- Carbapenemases identified include:
  - 98 KPC
  - 8 NDM
  - 6 OXA-48

# CRE NDM Cluster in Orange County, March, 2017

- Two patients from hospital A were identified to have NDM CRE from urine cultures on February 17 and February 22.
- Upon investigation, it was found that both have been transferred SNF A
  - Both were elderly, both had been in facility for about two weeks before transfer to acute care hospital
  - Stayed in same wing but different rooms
- On outreach to the SNF on March 13:
  - They reported no additional cases of CRE
  - They had not kept patients in isolation precautions (they weren't aware that either had CRE)

# CRE NDM Cluster in Orange County, March, 2017, continued

- OCHCA visited SNF A on March 14
- 59 bed facility
- Residents live two to a room
- 80% of residents stay for rehab for less than 3 weeks, rest are for longer care
- No specific infection control issues identified
- Facility is participating in the PROTECT project
  - All residents get CHG bathing, iodophor if they accept
- Aggressive cleaning of nurses stations, dining room and rehab room all performed

# CRE NDM Cluster in Orange County, March, 2017, continued

- All patients had rectal swab culture for CRE on March 17
- Isolates were sent to public health lab in Seattle, Washington
  - Results from testing back by March 21
- One additional NDM CRE positive case was identified
- Both residents who were still in SNF A remained in contact precautions until discharge
- Follow up testing in two weeks revealed no new cases

Figure 1: CRE reported by Oregon laboratories, by month of culture collection, 2010 – June 2018

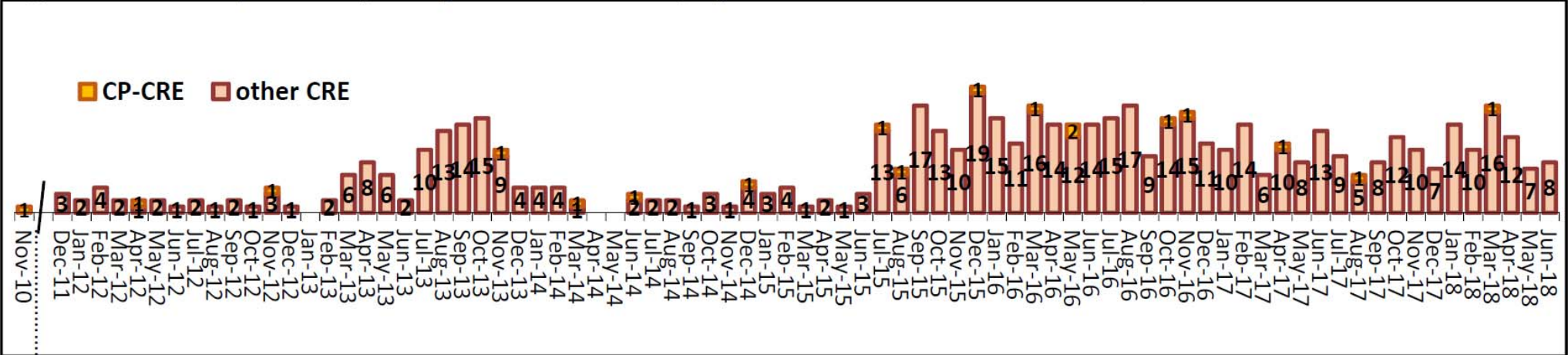
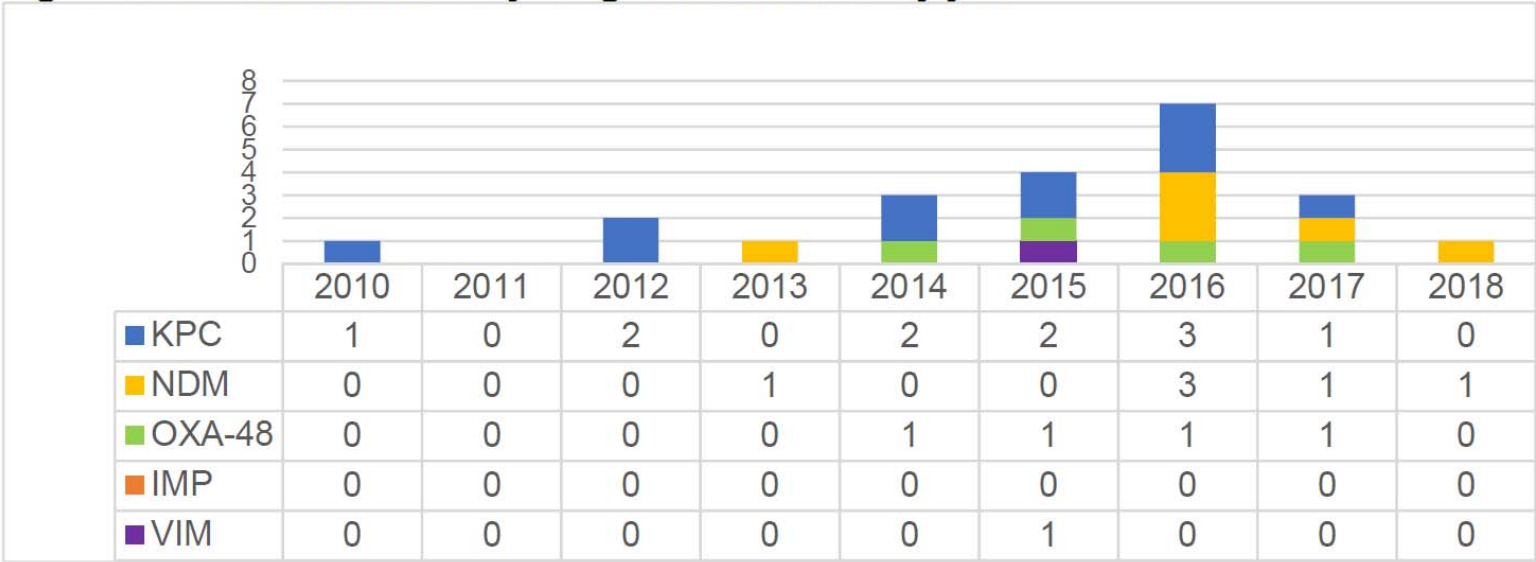


Figure 3. CP-CRE identified by Oregon laboratories by year



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## Los Angeles Area

Regional Prevalence of CRE *Klebsiella* Species  
per 1000 Isolates (95% Confidence Interval)

**64.65 (57.8- 71.8)**



# Antimicrobial Resistance of Different Antibiotics

- Ceftolozane tazobactam
  - Variable effectiveness against KPC-producing isolates
  - Ineffective against NDM and OXA-48 isolates
- Ceftazidime avibactam
  - Effective against most KPC and OXA-48 isolates
  - Ineffective against most NDM

# Where Do We Go from Here?

- Follow up meeting will be held in January or February of 2018 to review SHIELD OC's progress
- Representatives from all OC hospitals and SNFs will be invited
- Goal will be to begin the conversation about next steps



# Where Do We Go from Here?

- The Council of State and Territorial Epidemiologists (CSTE) has made CRE nationally reportable
- CDPH is moving toward making CRE reportable statewide
- Different counties will respond to reports differently
- We need to develop a national strategy in response to CRE and other antimicrobial resistant organisms

# Outreach to Gather Information from Laboratories

- in May, 2018, OCHCA surveyed 15 clinical laboratories to assess how they identified MDROs
  - 4 performed Vitek 2 with a Kirby-Bauer disk diffusion secondary test
  - 4 performed Vitek 2 with a Kirby-Bauer disk diffusion secondary test
  - 1 performed MicroScan
  - 13 used current CLSI breakpoints
  - 2 used pre-2011 CLSI breakpoints