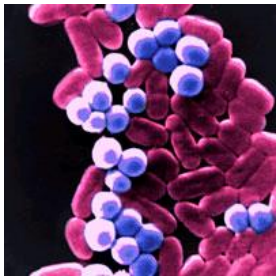


Antibiotic Resistance: Past, Present and Future

Karen Bush, PhD

Professor of Practice in Biotechnology

Indiana University Bloomington

Great Plains Emerging Infectious Diseases Conference

University of Iowa

April 7, 2017

INDIANA UNIVERSITY

Conflicts of Interest (2016-2017)

Retiree Compensation:

35 Years in Antibacterial R&D (1973–2009):
Bristol-Myers Squibb, Johnson & Johnson, Pfizer (Wyeth)

Consultant or Scientific Advisory Board:

Achaogen, Allecra, Fedora, Gladius, Melinta, Merck, Roche, WarpDrive

Research Support:

Achaogen, Allergan/Actavis, Merck, Tetraphase

Shareholder:

Fedora, Johnson & Johnson

Outline of Presentation

- Antibiotic resistance
  - Historical perspectives
  - Current situation
  - Future trends

FAQs Related to Antibiotic Resistance

- What is an antibiotic/antimicrobial agent?
  - An antibiotic is generally defined as a drug that kills bacteria, or prevents them from growing
  - An antimicrobial agent is a drug that fight infections caused by bacteria, viruses or fungi/yeast

- What is antimicrobial resistance?
  - The ability of a microbe (bacteria, virus, fungus) to evade the action of an antibiotic or antimicrobial agent
  - Resistance occurs when microbes have genetic mutations that allow them to grow in the presence of a previously effective drug

https://www.cdc.gov/drugresistance/about.html ; http://www.clipartkid.com/tell-us-cliparts/

Antibiotic Resistance is a Fact of Life.

The CDC and WHO on Antibiotic Resistance

- "Antibiotic resistance has been called one of the world's most pressing public health problems." (http://www.cdc.gov/getsmart/antibiotic-use/anitbiotic-resistance-faqs.html)
- "Resistance anywhere is resistance everywhere" (http://www.cdc.gov/getsmart/campaignmaterials/week/downloads/factsheet)

- "…it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country." (WHO's first global report on antimicrobial resistance/2014) (http://www.who.int/mediacentre/news/releases/2014/amr-report/en/)

Antibacterial Resistance Today

- According to the Centers for Disease Control and Prevention (CDC) report in 2013
  - More than 2 million people in the United States are infected with antibiotic-resistant bacteria
  - At least 23,000 deaths due to hospital-acquired resistant bacteria
- According to the UN report (2016)
  - An estimated 700,000 people die each year from drug-resistant strains of common bacterial infections, HIV, tuberculosis, and malaria.
  - A 2014 report from the Review on Antimicrobial Resistance projected that if rising AMR is not addressed, the annual death toll could reach 10 million by the year 2050

CDC, Antibiotic Resistance Threats, 2013; http://www.cidrap.umn.edu/news-perspective/2016/09/un-leaders-pledge-fight-antimicrobial-resistance

United Nations General Assembly and Antimicrobial Resistance (Sept. 21, 2016)

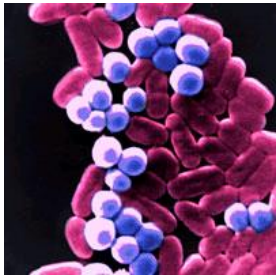
- “Antimicrobial resistance (AMR) poses a fundamental, long-term threat to human health, sustainable food production and development," (UN Secretary-General Ban Ki-moon)
- All UN member states signed a declaration to fight drug-resistant superbugs estimated to kill more than 700,000 people each year.
- A blueprint for combating AMR was put forward by the World Health Organization (WHO) in 2015
- The declaration allowed for formation of a group to address AMR representing the WHO, the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE)

http://www.cidrap.umn.edu/news-perspective/2016/09/after-un-declaration-amr-what-comes-next

PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA

- March 2015
  - The U.S. Department of Health and Human Services (HHS) authorized establishment of the *Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria*.
- September 15, 2015
  - HHS, the U.S. Department of Agriculture (USDA), and the U.S. Department of Defense (DoD) announced appointment of nationally recognized experts to the Advisory Council
- Role of the Advisory Council
  - Provide advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy) and the National Action Plan for Combating Antibiotic-Resistant Bacteria (Action Plan) on these topics:
    - Detect, prevent, and control illness and death related to antibiotic-resistant infections
    - Reduce the emergence and spread of antibiotic-resistant bacteria
    - Ensure the continued availability of effective therapeutics for the treatment of bacterial infections
- Meets quarterly to discuss antibiotic resistance and issue reports

http://www.hhs.gov/ash/carb/



Antibiotic Resistance: Past, Present and Future

We Have a Classical Evolutionary Battle

Naturally-occurring antibiotics are produced by microorganisms in complex environmental sources to conserve resources for their own growth

+ Antibiotics

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We Have a Classical Evolutionary Battle

Antibiotics are produced by microorganisms in complex environmental sources to conserve resources for their own growth

+ Antibiotics

+ Resistance Factors

Other microorganisms produce resistance determinants such as inactivating enzymes that allow their own survival

Antibiotic Resistance Genes are Ancient !

- β-lactam-inactivating enzymes are estimated to have originated over 2 billion years ago
  - A little less than half the estimated geological age of the earth

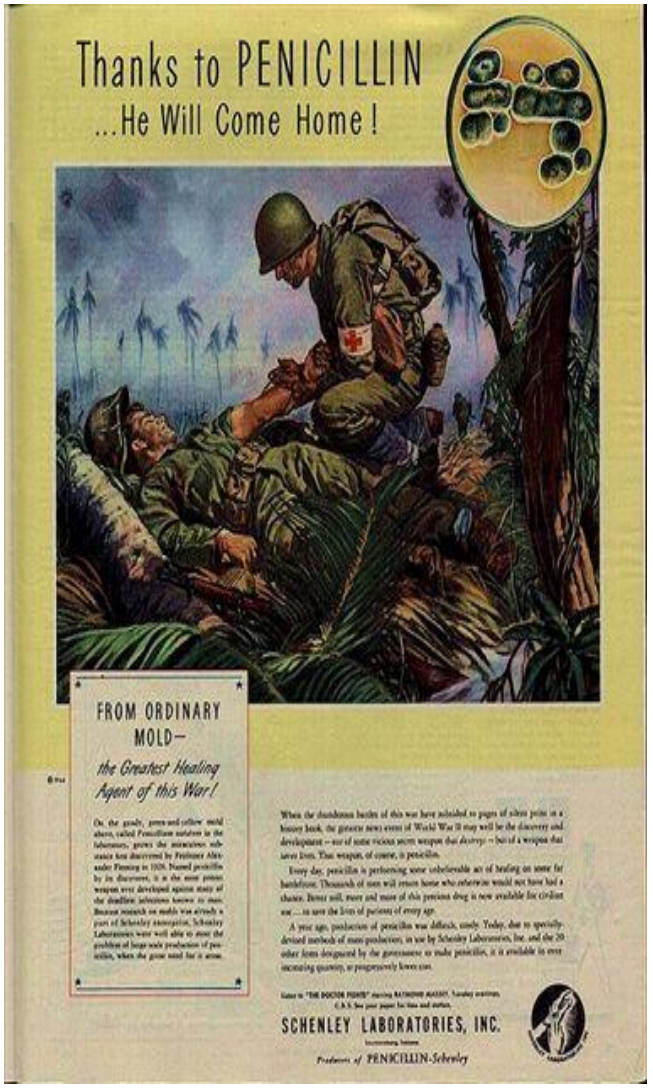
Img.geocaching.com

- A variety of resistance genes have been identified in
  - A region of the Lechuguilla Cave, New Mexico that had been isolated for over 4 million years
  - 30,000-year-old permafrost sediments east of Dawson City, Yukon

Hall & Barlow, Drug Resistance Updates. 7:111 (2004); D'Costa. Nature 2011:10388; Bhullar, PLoS One, 7:e34953 (2012)

Fast facts about penicillin

- Identified by Alexander Fleming in 1928
- Human use of penicillin:
  - First patient dosed in 1940 improved but died
  - First patient cured by penicillin in 1942
- Outbreak of World War II was the impetus for a collaborative effort to produce larger quantities of penicillin.
  - Consortium **of the USDA Northern Regional Research Laboratory in Peoria** and five pharmaceutical companies: Abbott Laboratories, Lederle Laboratories, Merck, Pfizer and E.R. Squibb & Sons
  - Highest titer of penicillin was produced from a cantaloupe from a **Peoria fruit market.**
- Sufficient quantities eventually produced during WW II to treat the Allied soldiers

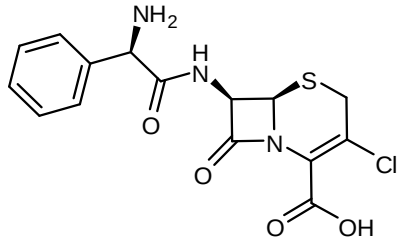


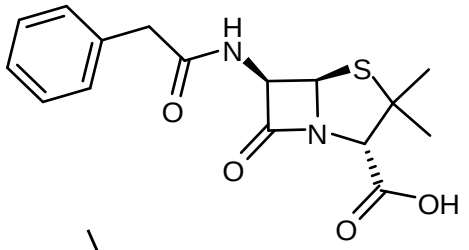
Life magazine, August 14 1944

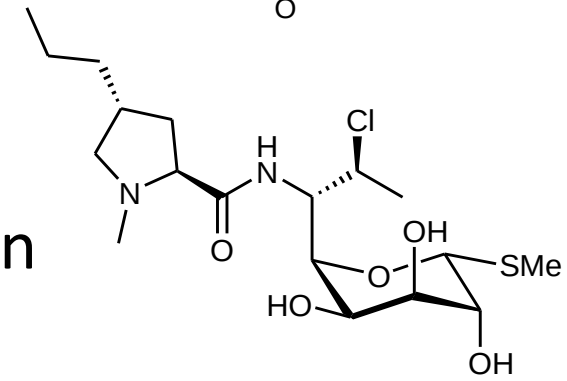
http://www.pbs.org/newshour/rundown/the-real-story-behind-the-worlds-first-antibiotic/
http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html#increasing-penicillin-yield

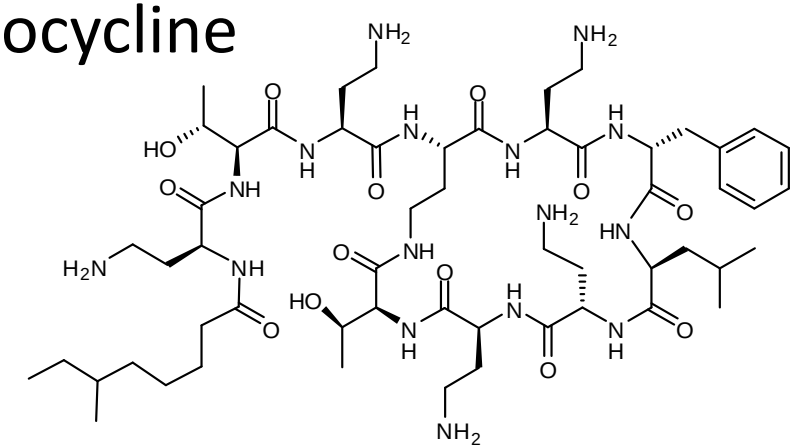
Following WW II, Many Pharmaceutical Companies Responded to the Call for New Antibiotics -- with Diversity

- Multiple β-lactam antibiotics
  - Penicillins
  - Cephalosporins
- Erythromycin
- Clindamycin
- Streptomycin, gentamicin, tobramycin
- Sulfamethoxazole with trimethoprim
- Tetracycline, doxycycline, minocycline
- Rifampicin
- Polymyxin



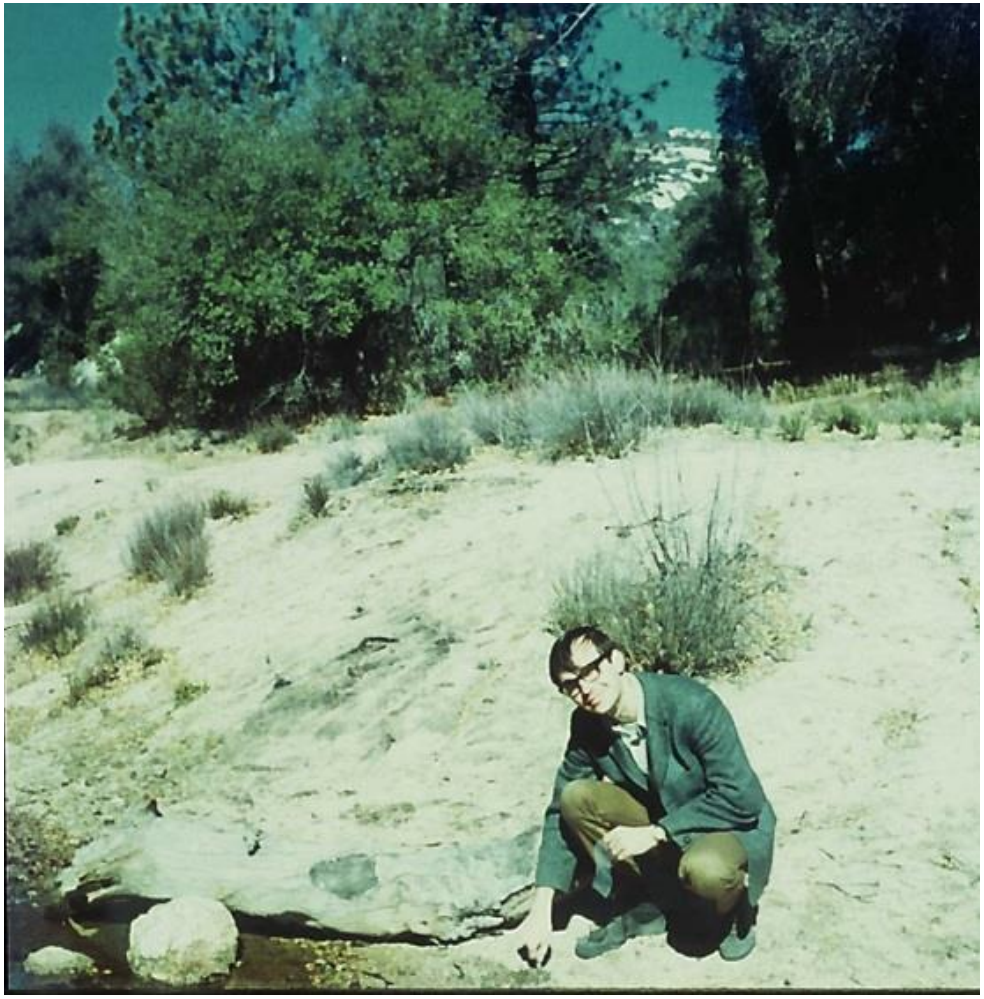




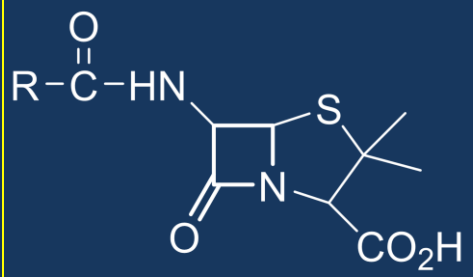


Time period: ~1943 - 1975

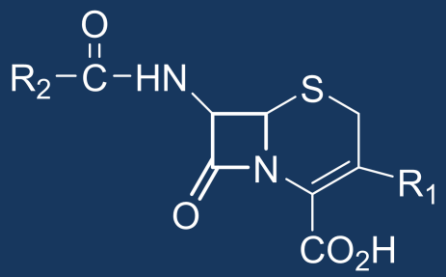
Most were Isolated from Natural Products, Especially Soil Samples



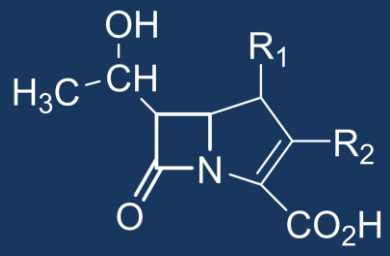
β-Lactam-Containing Antimicrobial Agents, Like Most Antibiotics, Originated from Natural Sources



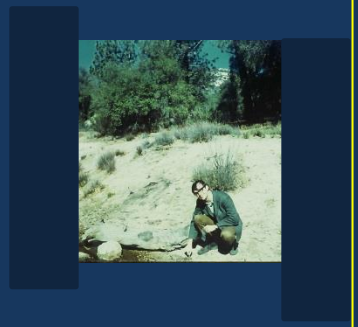
Penicillin (1928)
(mold)

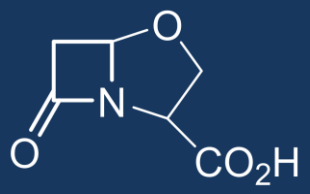


Cephalosporin (1955)
(fungus in sewage sludge)

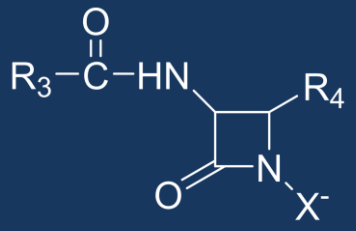


Carbapenem (1976)
(soil samples)





Oxapenam (Clavam)
(1976)
(soil sample)



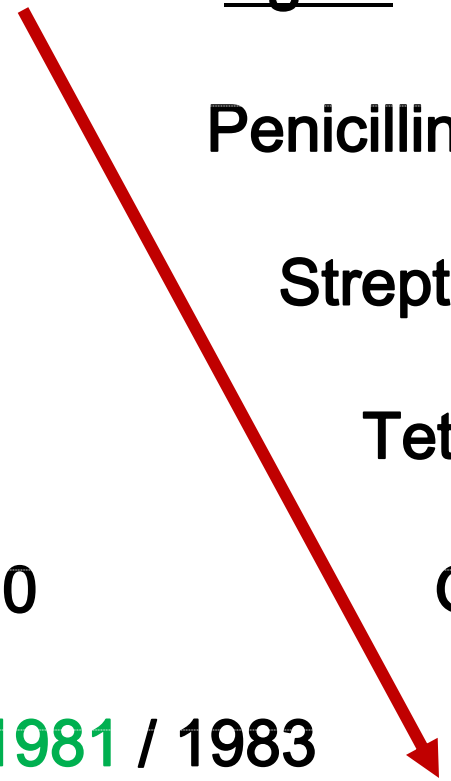
Monobactam (1979)
(soil, bog, water
samples)

But, Resistance To Our Known Antibiotics Became a

BIG

Issue

Rapid Reports of Resistance Associated With Introduction of New Agents

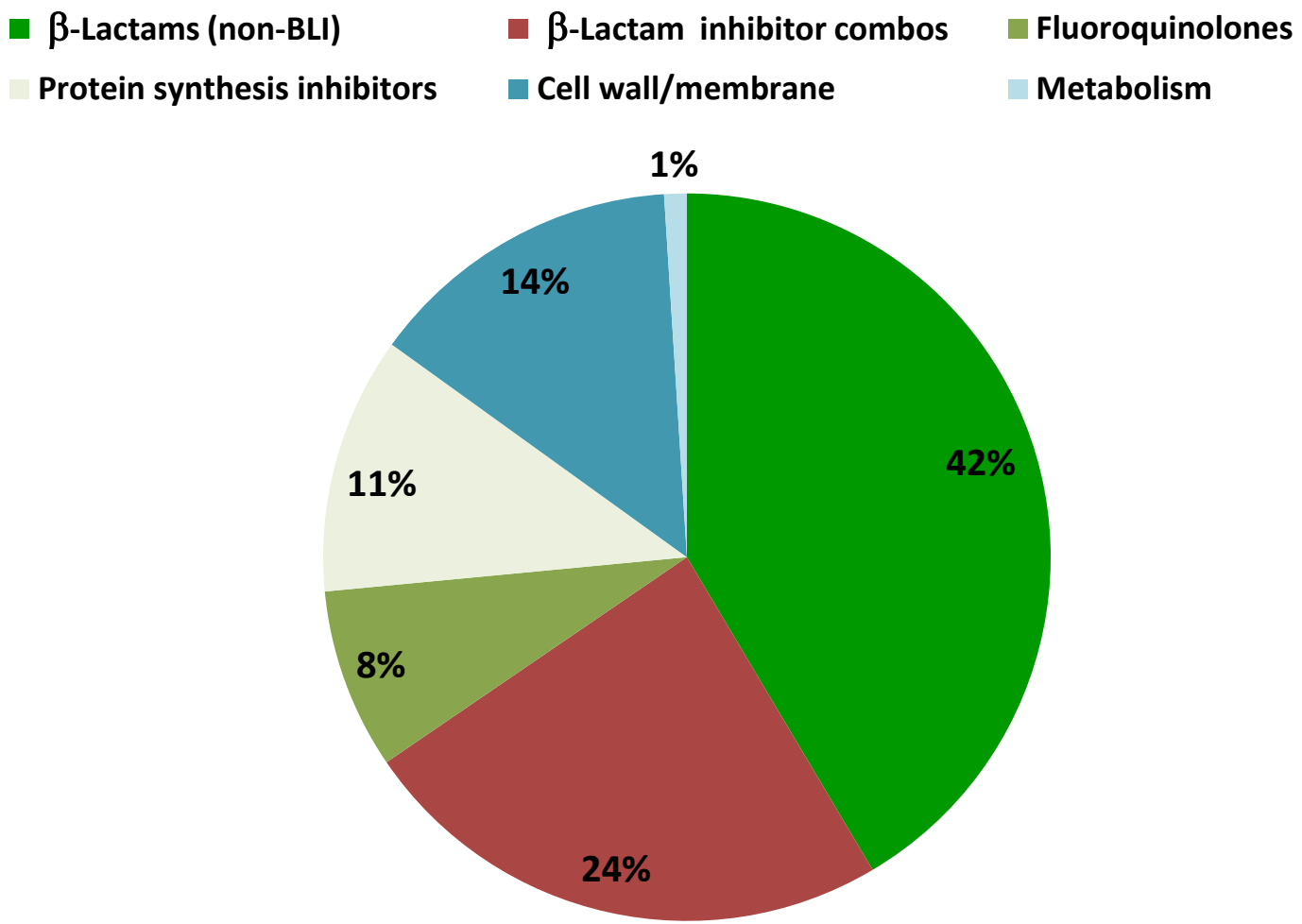


Resistance	Agent	FDA Approval
1940	Penicillin	1943
1947	Streptomycin	1947
1956	Tetracycline	1952
1970	Gentamicin	1967
1981 / 1983	Cefotaxime	1981

Resistance to β-Lactams -- Important

- β-Lactam resistance is often used as a marker for other plasmid-encoded resistances
  - Co-resistance is common
- Focus for the rest of the talk

Proportion of Prescriptions in US Hospitals by Antibiotic Class (2004-2014)



Modified from Bush and Bradford, Cold Spr. Harbor, 2016

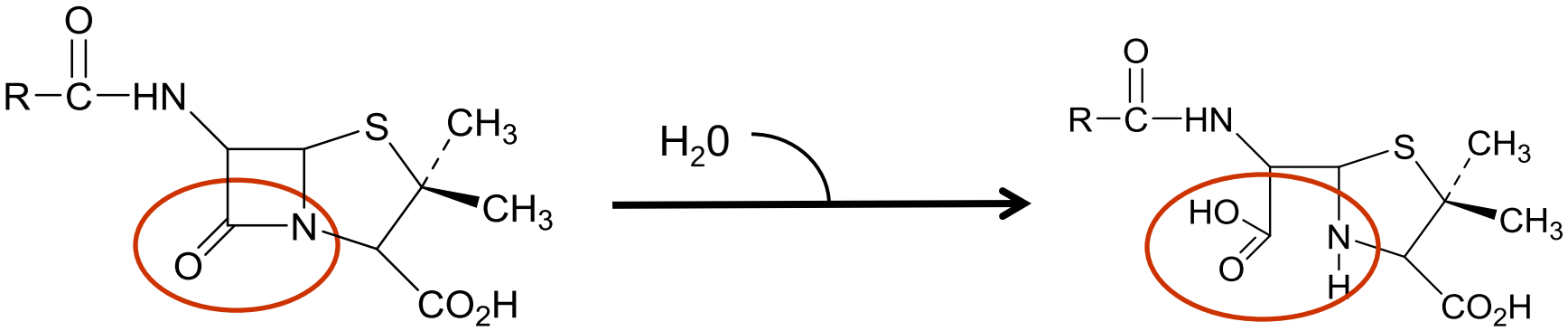
Resistance to β-Lactams

- Gram-positive bacteria
  - Altered Penicillin-Binding Proteins (PBPs/cell wall synthesizing enzymes)
  - Staphylococcal penicillinases
- Gram-negative bacteria
  - Efflux
  - Decreased permeability
  - β-Lactamase production
    - With or without efflux or porin defects
  - Altered PBPs

β-LACTAMASES: THE MOST PREVALENT RESISTANCE MECHANISM FOR β-LACTAM ANTIBIOTICS

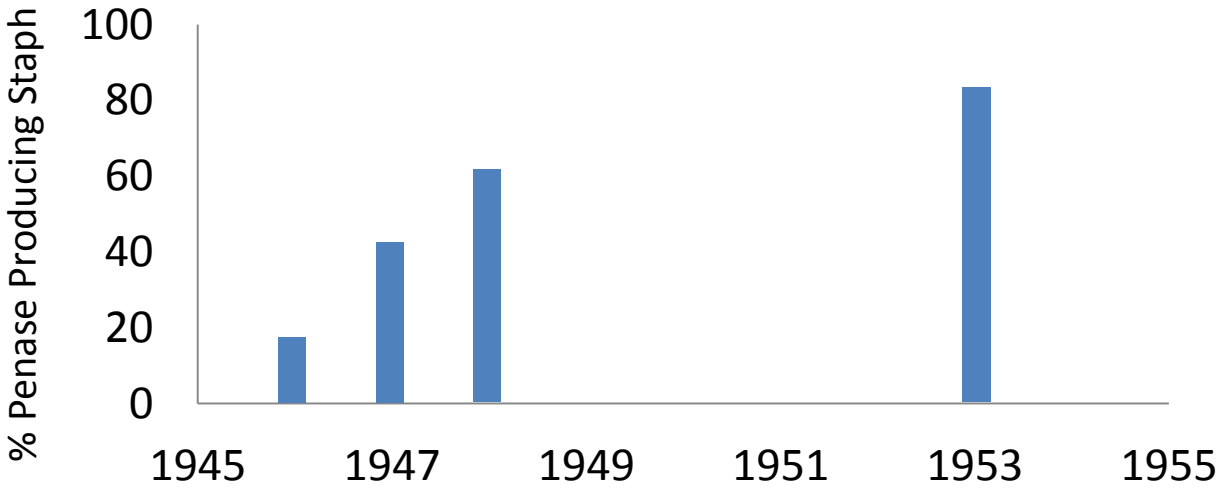
β-Lactamases

- Enzymes that can hydrolyze penicillins, or carbapenems, or cephalosporins, or monobactams, or any other β-lactam
- The primary resistance mechanism operative for β-lactam antibiotics in Gram-negative bacteria



Rapid Resistance to Penicillin After Its Introduction During WW II

- Initial use of penicillin to treat streptococcal infections
- Penicillin-resistant *Staphylococcus aureus* soon reported
  - United States
    - 1942: 4 patients receiving penicillin
    - 1944: 7 patients not receiving penicillin
  - England
    - Penicillinase (St. Thomas Medical School)



Barber, Br. Med. J. 2:565 (1949); Medeiros, Clin. Inf. Dis. 24 (Suppl 1):S19 (1997)

Early Compilations of Unique Natural β-Lactamases in Gram-Negative Bacteria

Classification	Year	Discrete Enzymes
Jack and Richmond	1970	13
Richmond and Sykes	1973	27
Sykes and Matthew	1976	57

Jack & Richmond. FEBS Lett 12:30 (1970); Richmond & Sykes In *Advances in Microbial Physiology. Volume* 9:31 (1973); Sykes & Matthew JAC 2:115 (1976)

Recognition of Transferable β-Lactamases in Gram-Negatives

- Earliest reported β-lactamases were chromosomal
- In the mid-1960s "R-factors" conferring resistance to β-lactams were described in Gram-negative bacteria
  - Plasmids encoding β-lactamases
  - Japan, England, Greece
- Substrate profiles for many of these enzymes included new penicillins and cephalosporins that had been introduced following the identification of cephalosporin C in the 1950s
- By the 1970s RTEM (TEM-1) became the most prevalent plasmid-encoded β-lactamase in surveillance collections

Mitsuhashi et al. J. Bacteriol. 84:9 (1962); Datta & Kontimichalou, Nature 208:239 (1965); Tanaka et al. J. Bacteriol. 21:591 (1966)

The Promiscuous Spread of TEM-1 into *Neisseria gonorrhoeae* in 1976

- Plasmid-encoded "RTEM" entered *Neisseria gonorrhoeae* and traveled around the world
  - Two strains circulating with penicillin – and tetracycline -- resistance
    - Asia (Philippines, especially among prostitutes)
    - West Africa (Ghana)
- Dissemination assisted by sailors who imported strains to Ghana and, the UK, and elsewhere
- Great concern among the military & CDC
  - Single dose of penicillin was no longer effective
- Panic ensued from the pharmaceutical world
  - How can we contain this RTEM enzyme?

Phillips, Lancet 2:656 (1976); Ashford et al. Lancet 2:657 (1976); Perine et al. Lancet **2:**993 (1977)

The Pharmaceutical World and β-Lactamases in 1977

- TEM-1 appeared in *Neisseria*, and then in *Haemophilus influenzae*
- Increased urgency to find new β-lactams
- European companies were trying to counteract TEM-1 and chromosomal cephalosporinases
  - β-lactams stable to hydrolysis
  - Inhibitors of enzymatic activity

Hoechst

Roche

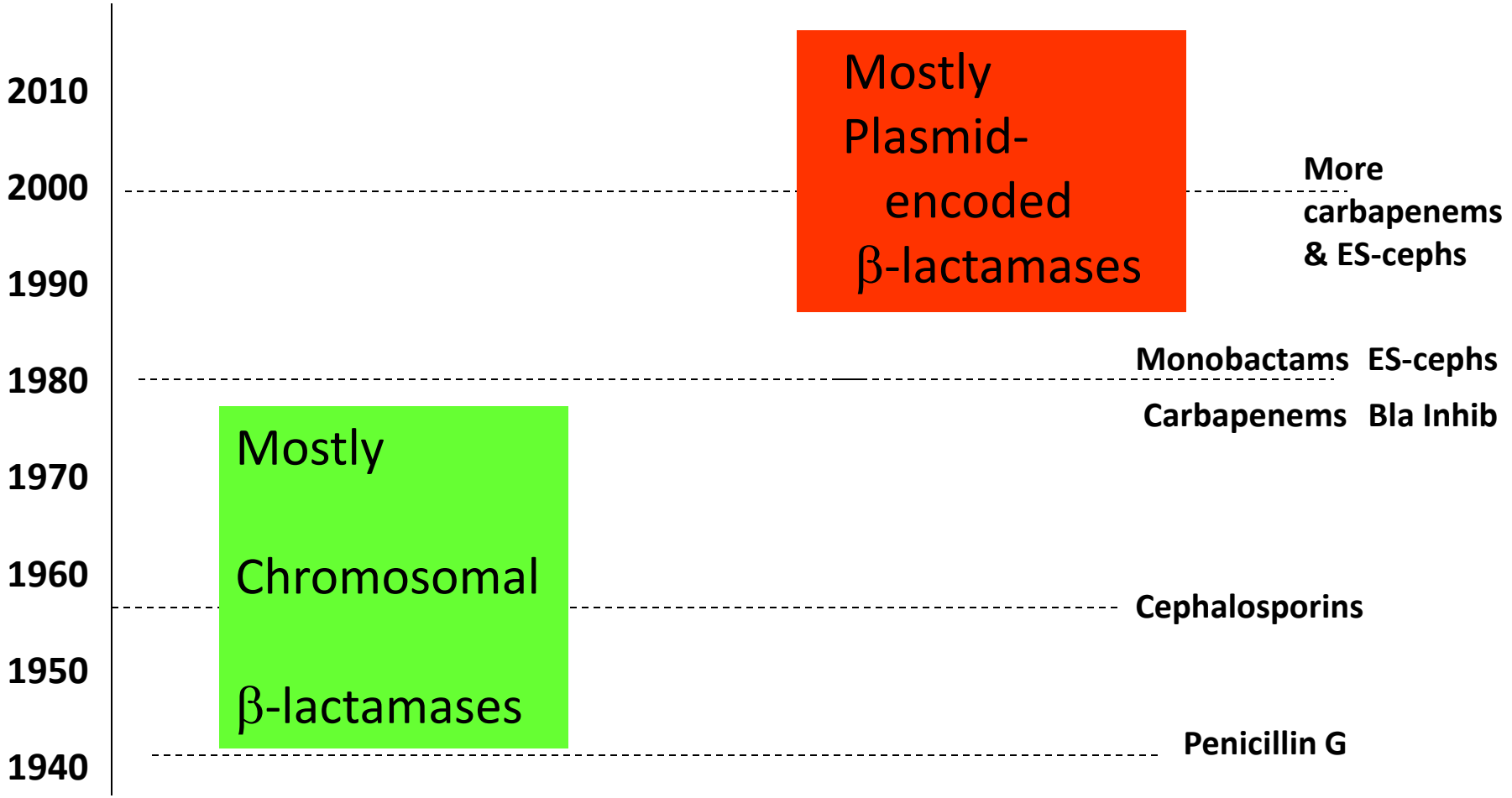
Glaxo

Gunn … Thornsberry, Lancet 2:845 (1974); Percival et al. Lancet 2:1379 (1976);

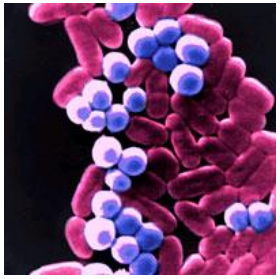
My Entry Into the World of β-Lactamases at Squibb in 1977

- Like other companies, E. R. Squibb implemented β-lactam-focused antibiotic discovery programs
  - Directed by Miguel Ondetti and Richard Sykes
  - Biochemists screened for novel β-lactamase inhibitors based on mechanistic and medicinal chemistry approaches
  - Microbiologists conducted targeted screening of natural products for novel β-lactams
- Results
  - Identification of 6-β-bromopenicillanic acid sulfone and non-druggable natural product inhibitors
  - Discovery of the monobactams
  - Development of aztreonam
    - Activity only against Gram-negative bacteria

Introduction of New β-Lactams and Emergence of New β-Lactamases



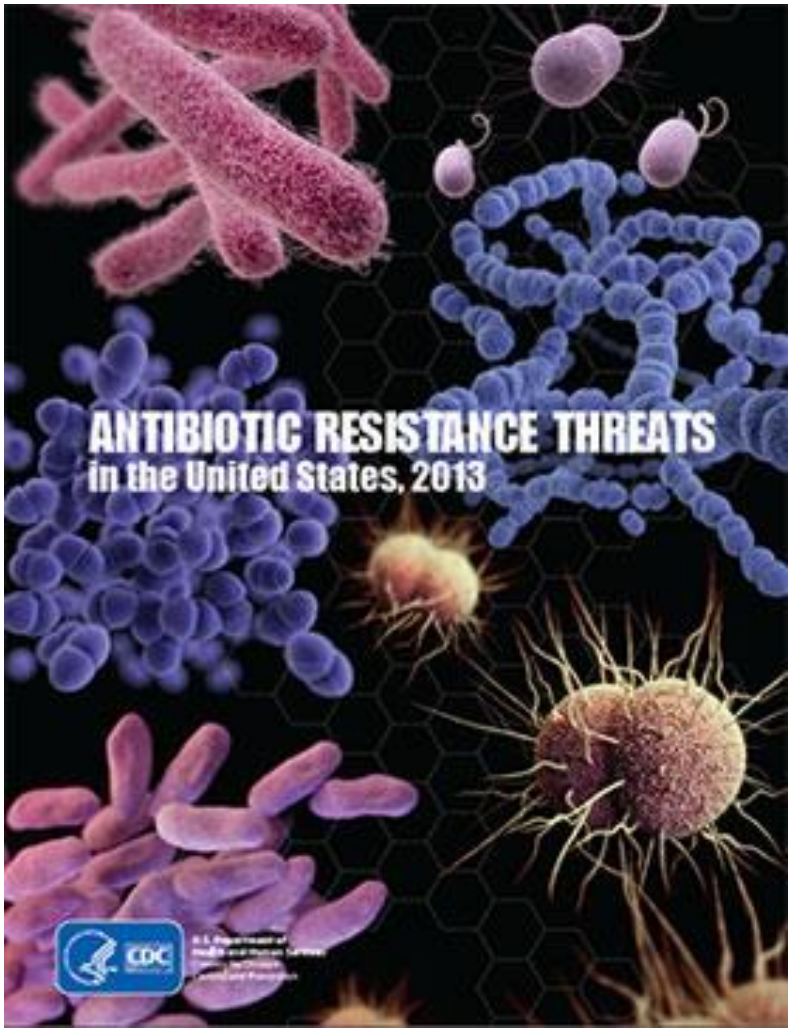
Bush, Personal Communication. 50 Years of ICAAC, ASM Press (2010)



Antibiotic Resistance:

*Past, **Present** and Future*

Centers for Disease Control and Prevention (CDC) Antibiotic Threat Report – 2013



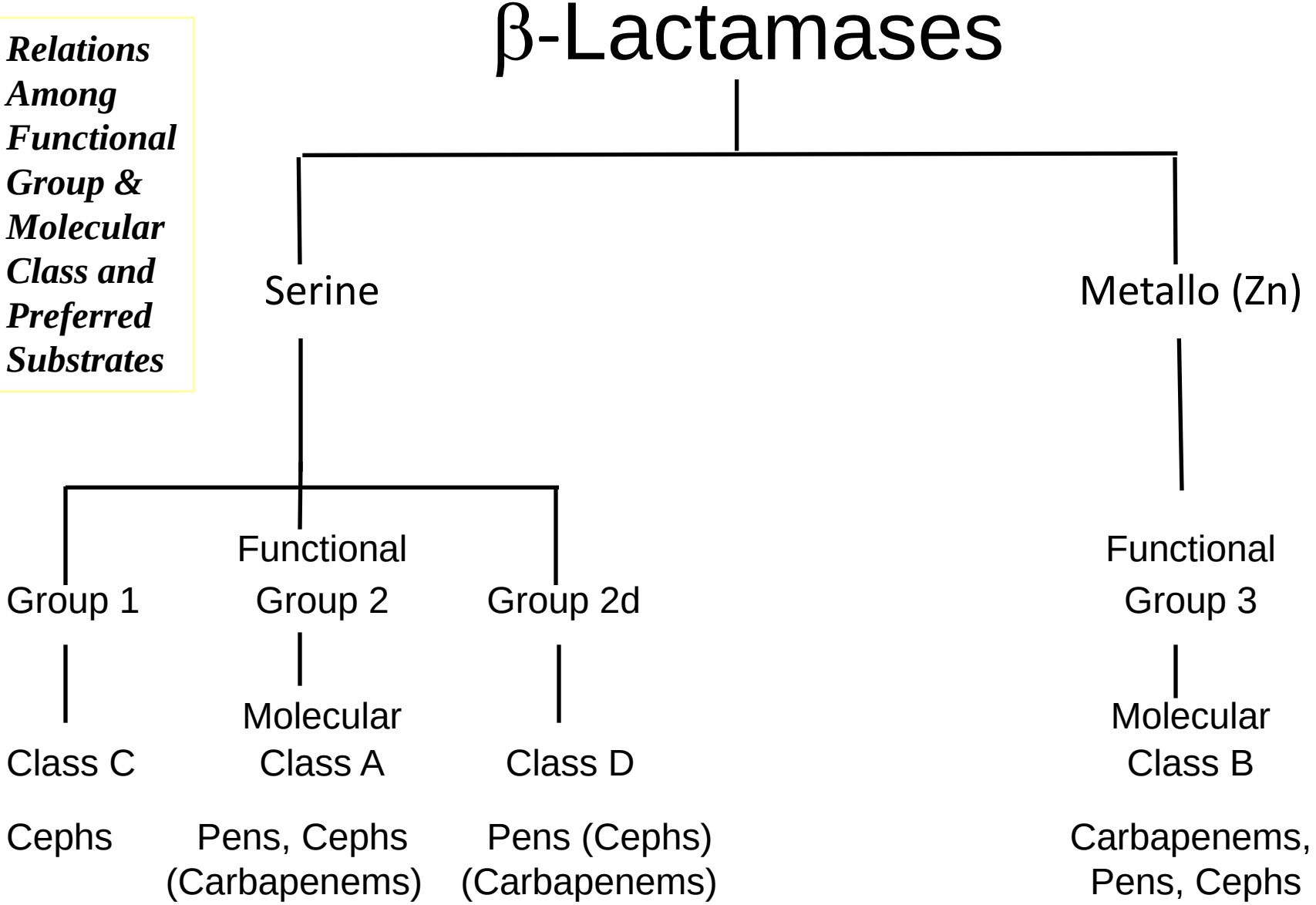
CDC, Threat Report, September 16, 2013

2014 ICAAC Symposium

"Multidrug-Resistant (MDR) Gram-Negatives:

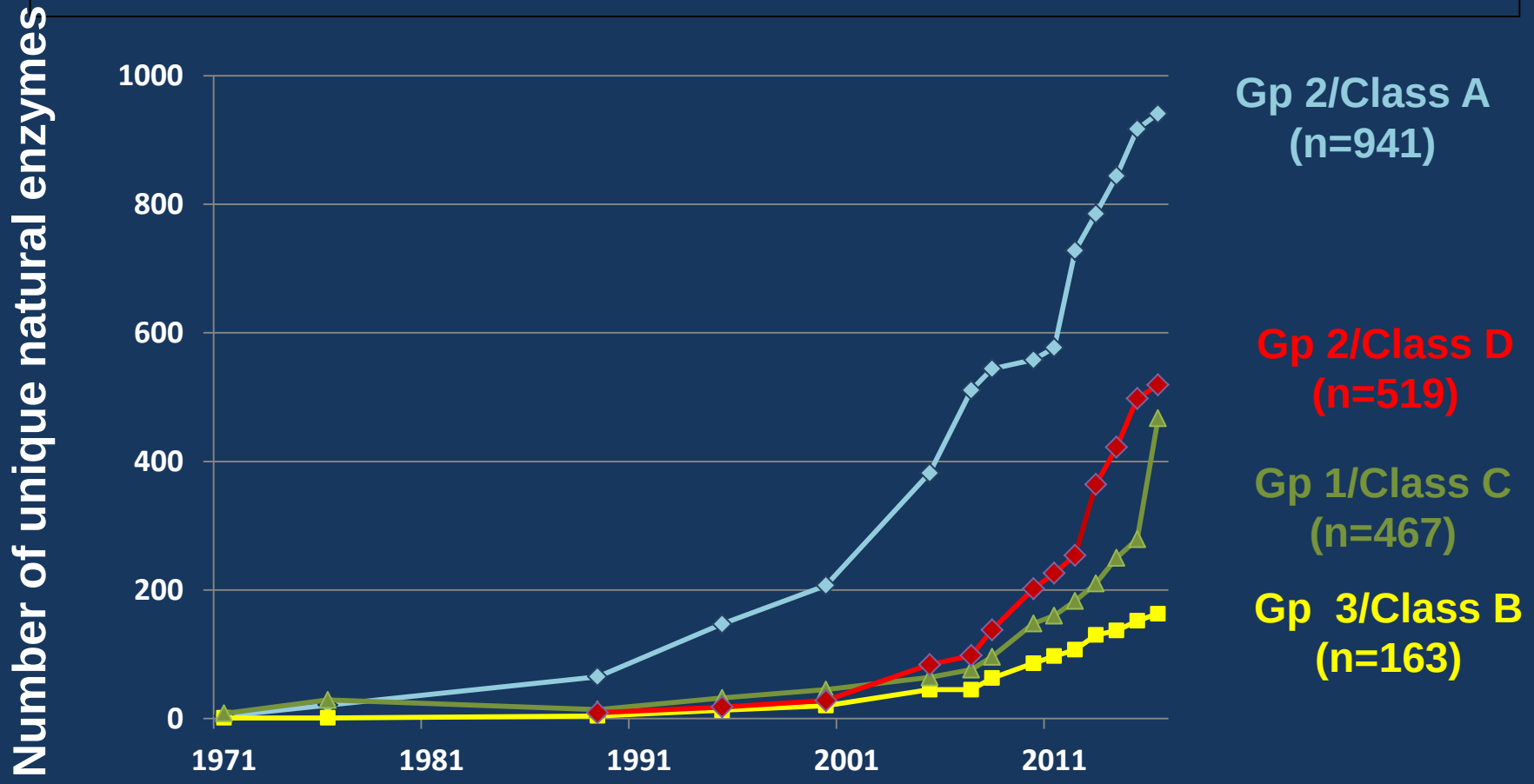
On the Highway to Hell"

Relations Among Functional Group & Molecular Class and Preferred Substrates



Based on Bush, Jacoby & Medeiros AAC:39:1211 (1995)

Increasing Numbers of β-Lactamases (N = 2106)



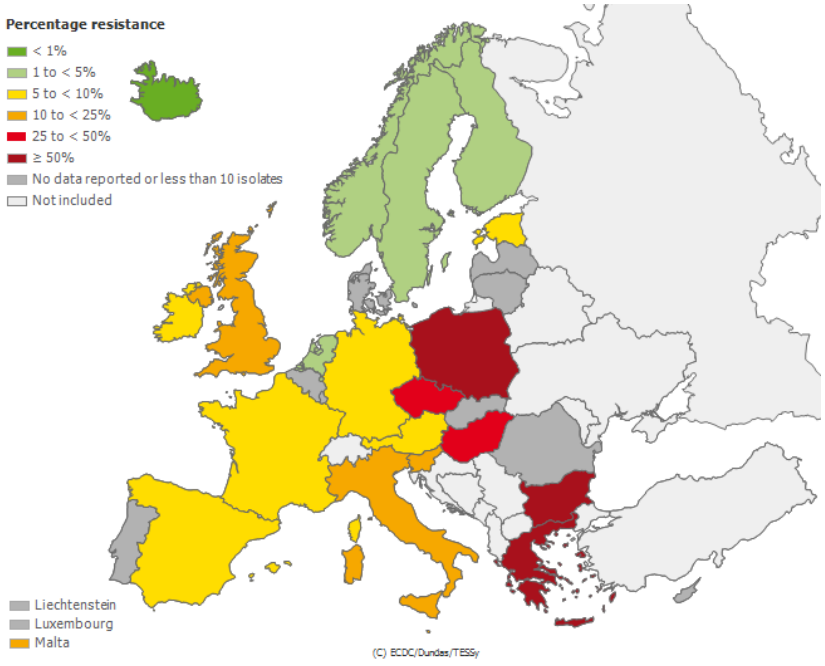
Compilation of Unique β-Lactamase Sequences from Natural Isolates

Based on Bush , Jacoby & Medeiros, AAC 39:1211 (1995). Updates based : http://www.lahey.org/Studies/ and http://bigsdb.web.pasteur.fr/klebsiella/klebsiella.html (Oct. 2016)

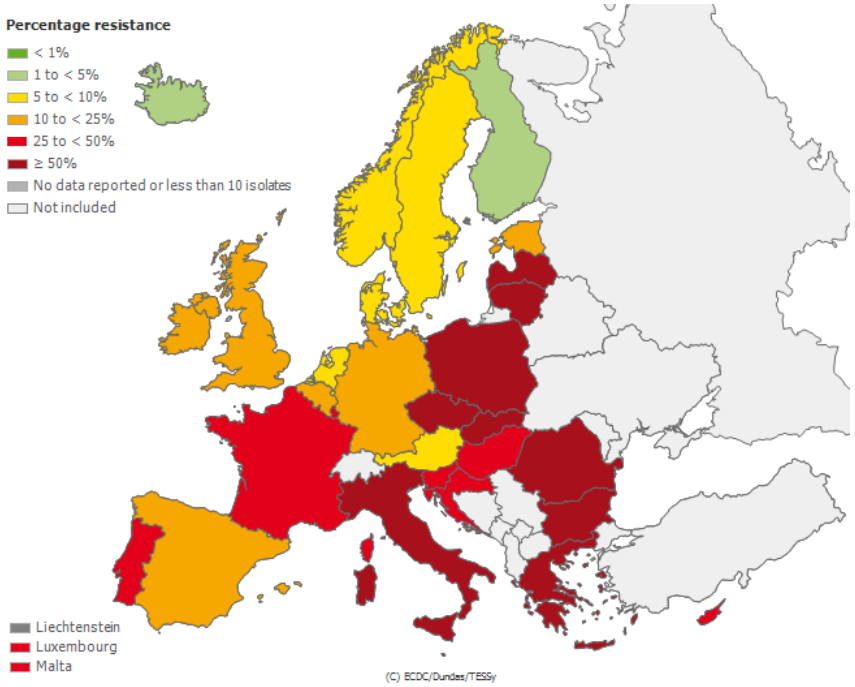
CEPHALOSPORIN RESISTANCE DUE TO EXTENDED-SPECTRUM β-LACTAMASES (ESBLs)

Cephalosporin-Nonsusceptibility in European *Klebsiella pneumoniae* [EARSS/EARS-Net data 2005 - 2014]

K. pneumoniae 2005



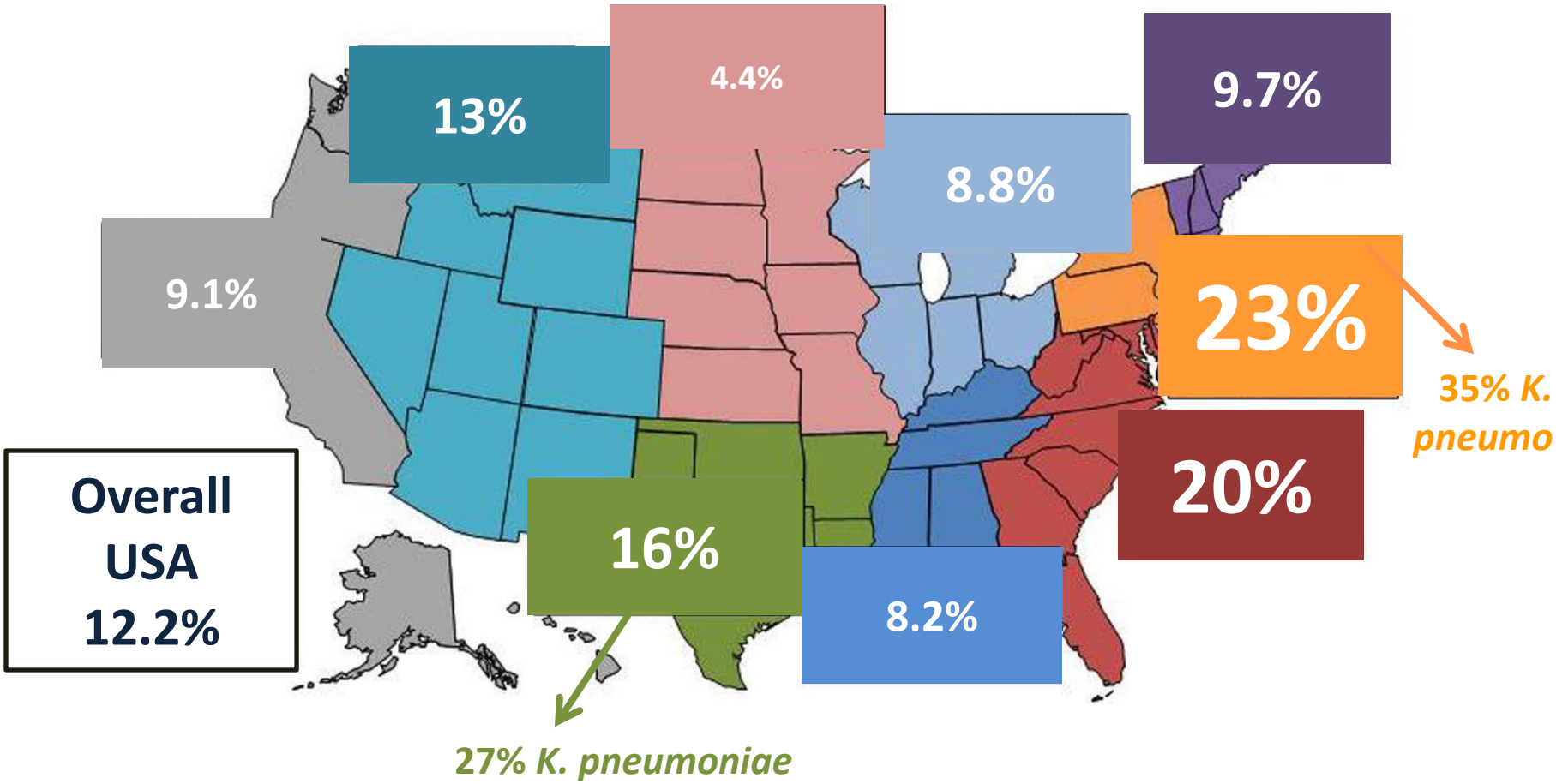
K. pneumoniae 2014



≥50% 25 - <50% 10 - <25% 5 - <10%

Data from EARSS website: http://www.rivm.nl/earss/database/;
http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

ESBL Prevalence among *Enterobacteriaceae* Isolates from 72 U.S. Hospitals in 2012



Castanheira M et al. Antimicrob. Agents Chemother. 58:833-838 (2014)
Antimicrobial Agents and Chemotherapy

CARBAPENEM RESISTANCE DUE TO CARBAPENEMASES

Carbapenem-Resistant *Enterobacteriaceae* (CRE)

- Carbapenems are the antibiotics with the greatest potency against the largest number of bacterial species
  - Carbapenems are often reserved in hospitals for the most critical patients
- Carbapenem-Resistant *Enterobacteriaceae* (CRE) are on the "Urgent Threat" list from the CDC
- Organisms are resistant to many, or all, antibiotics
- If carbapenems are not effective, most other antibiotics will not work either.
  - Resistance genes for other antibiotics are transferred together with carbapenemase genes
- Mortality in some hospitals can be as high as 70%
- High costs for a single CRE infection : up to $66,000

Bartsch et al. Clin. Microbiol. Infect. 2016 (in press)

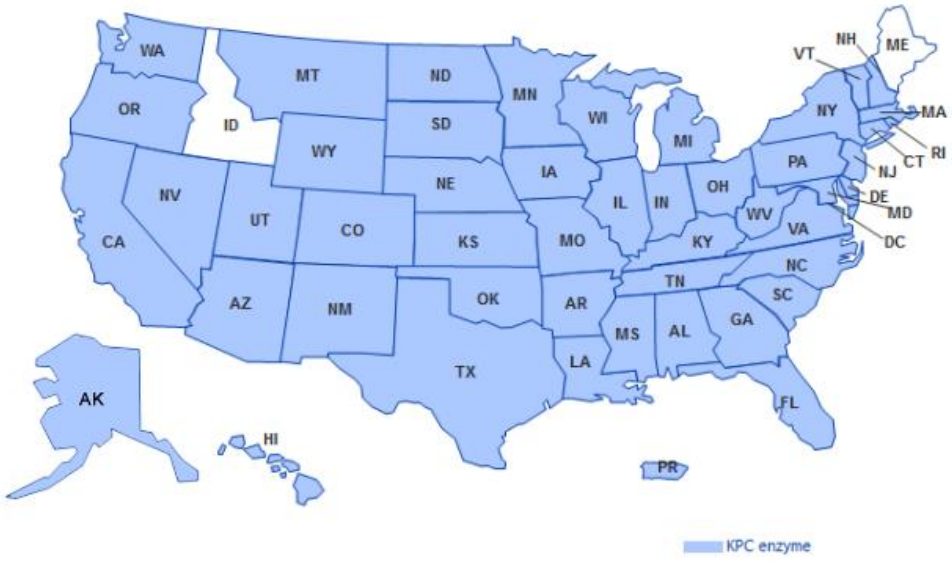
Carbapenemases – Main Cause for CRE

- β-Lactamases that are found on mobile elements (plasmids, integrons) that can be transferred freely among bacteria
- Class A carbapenemases with serine at active site (KPC)
  - Hydrolyze virtually all β-lactams
  - Most frequently found in the USA, Western Europe, China
- Metallo-β-lactamases (MBLs) contain at least one active zinc (VIM, NDM)
  - Hydrolyze all β-lactams except monobactams
  - MBLs more frequent in Asia-Pacific region and Mediterranean, but KPC now often in Italy and Greece
  - NDM-1, originating in India and Pakistan, is becoming widespread – including Indiana
- Unusual to find both kinds of enzymes in one organism, but IU students found isolates like these.

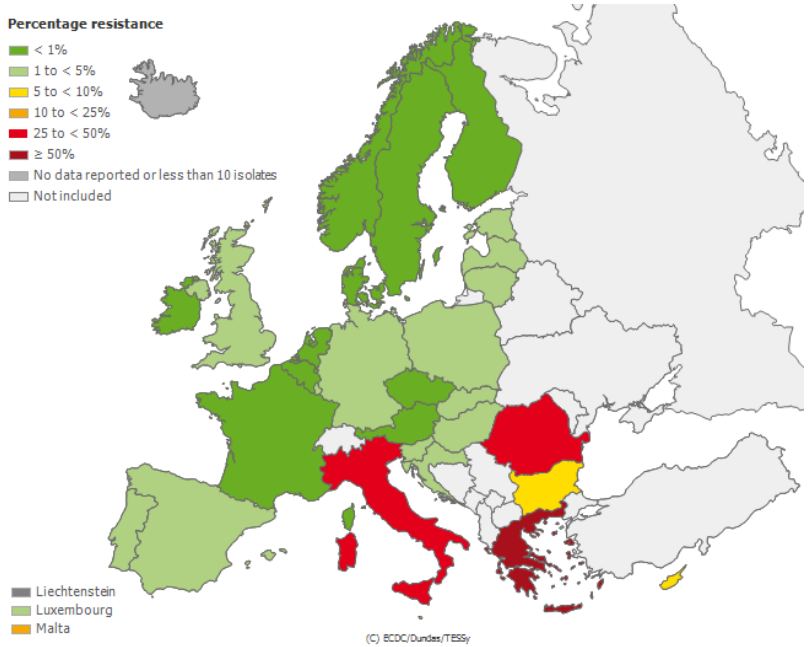
Bush, J. Global Antimicrob. Resistance 1 (2013) 7-13.

Prevalence of Carbapenem Resistance

KPC carbapenemases reported in the United States



Carbapenem Resistance in *K. pneumoniae* in Europe (2014)

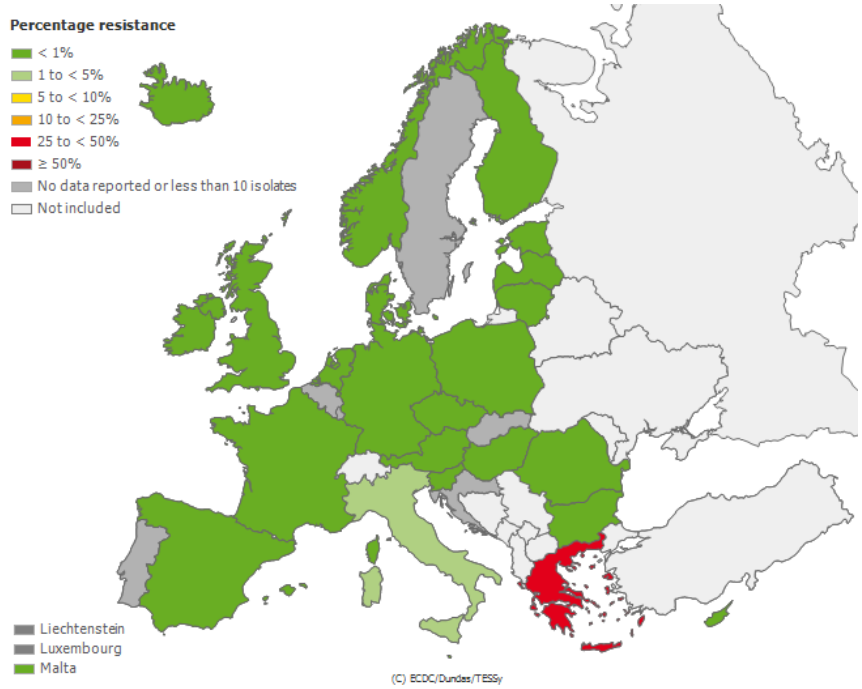


Map was updated in April 2017

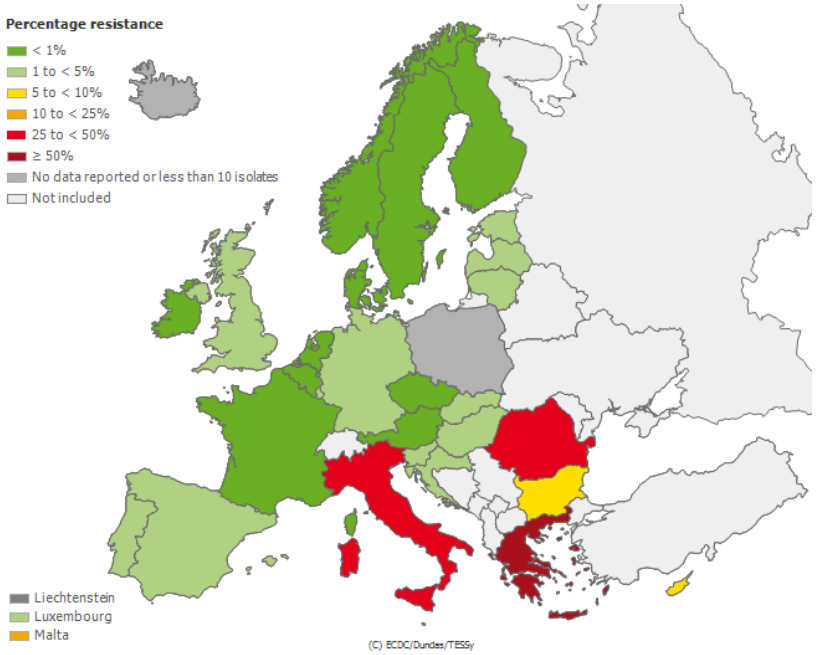
http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html; http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial_resistance/database/Pages/map_reports.aspx

Carbapenem- Non-Susceptibility in European *Klebsiella pneumoniae* [EARSS data 2006 - 2014]

K. pneumoniae 2006



K. pneumoniae 2014



≥50% 25 - <50% 10 - <25% 5 - <10%

Data from EARSS website: http://www.rivm.nl/earss/database/

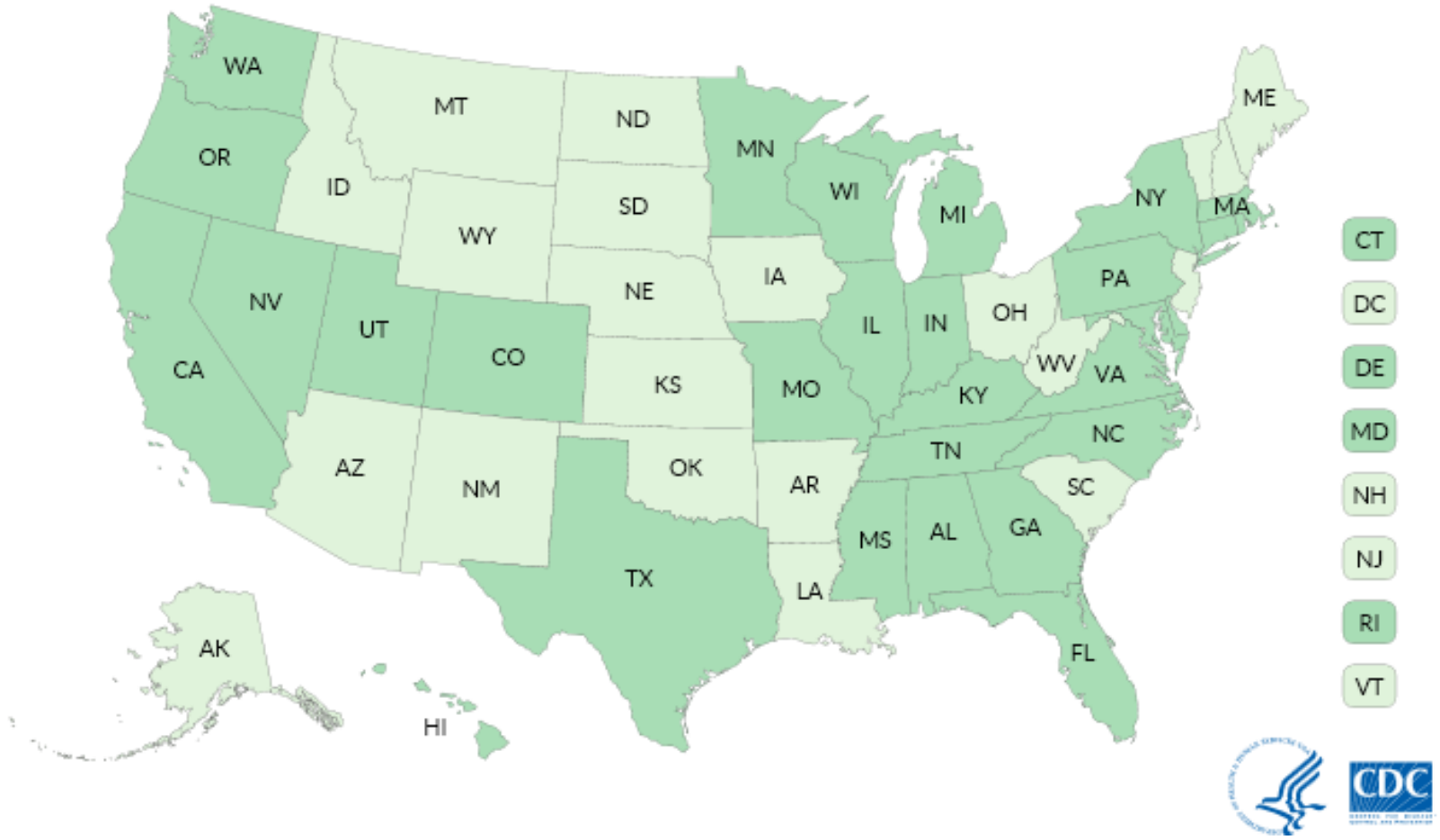
NDM (New Delhi Metallo-β-Lactamase)

- First identified in 2009 from patients with connections to India and Pakistan
- Isolates are highly resistant to almost all antibiotics

- Great outrage from the Indian government because this "superbug" was associated with medical treatment in India
- But, many public health issues in that area of the world
  - Counterfeit antibiotics available in incomplete doses on the street
  - Some hospitals used for medical tourism had poor infection control practices
  - Poor public sanitation throughout the country
- Now NDM enzymes are found globally (including USA) in bacteria that respond to few, if any, antibiotics

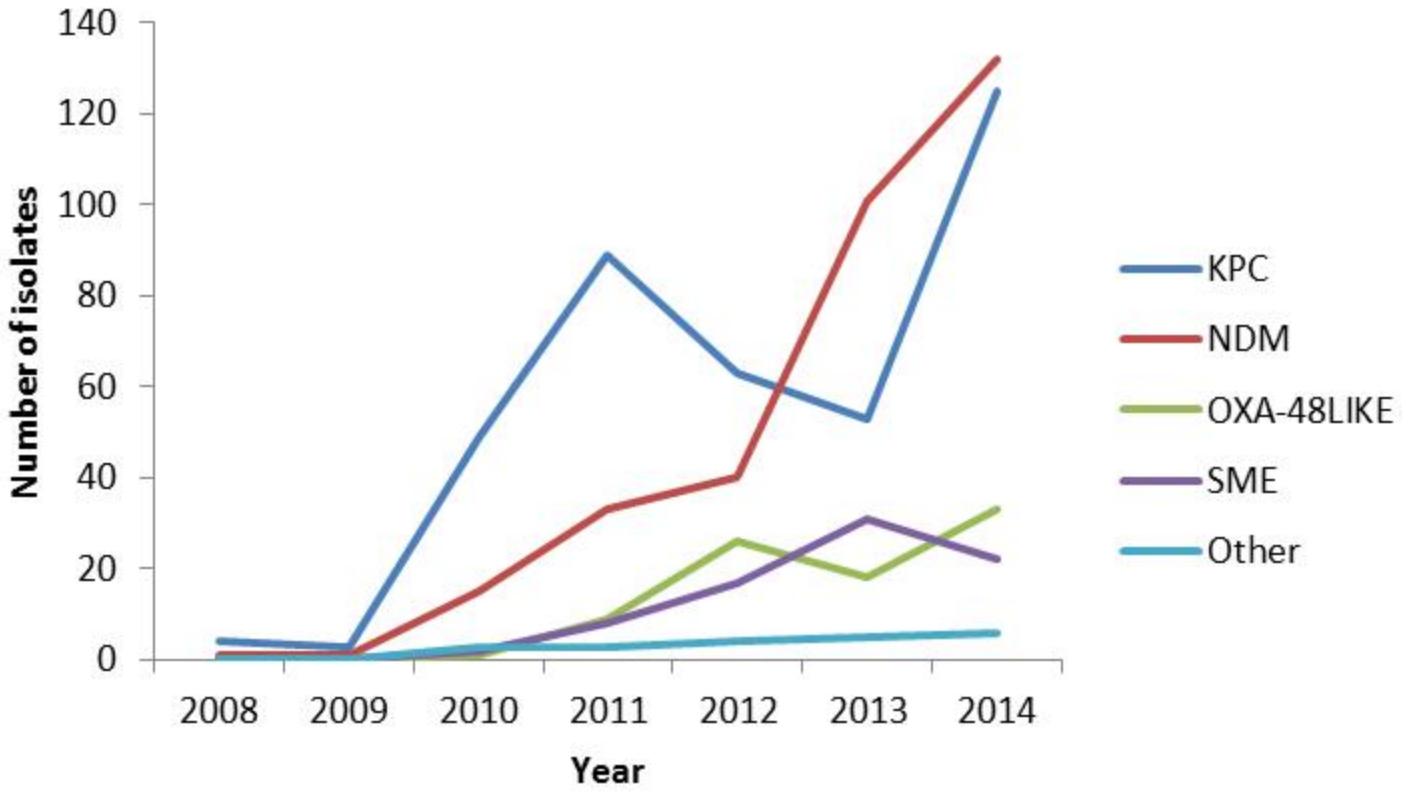
http://articles.timesofindia.indiatimes.com/2011-01-12/india/28360252_1_drug-resistant-superbug-ndm-1-new-superbug

NDM-1 Metallo-β-Lactamases (MBLs) in the USA (Jan. 6, 2017)



https://www.cdc.gov/hai/organisms/cre/trackingcre.html

Carbapenemase-producing Enterobacteriaceae (CPE) in Canada: the Canadian Public Health Laboratory Network (CPHLN) data, 2008 to 2014



http://healthycanadians.gc.ca/publications/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/antimicrobial-surveillance-antimicrobioresistance-eng.php#a4-2-2

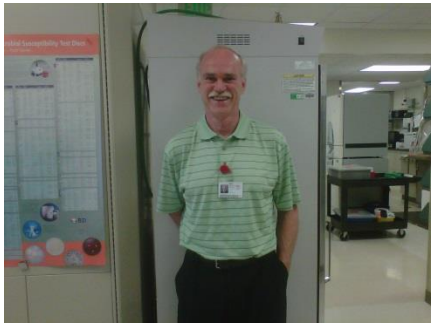
NDM Raised Issues with Antibiotic Usage and Public Health Issues in India

- Survey from Sept 26 to Oct 10, 2010
  - 171 seepage samples and 50 tap water samples from New Delhi
  - Controls: 70 sewage effluent samples from Wales
- *bla*$_{\text{NDM-1}}$ and NDM-1-producing organisms
  - 2 drinking-water samples
  - 51 seepage samples from New Delhi
  - Eleven "new" species including *Shigella boydii* and *Vibrio cholerae*
- As a result of this "public shaming" the Indian government instituted stricter controls on the sales of antibiotics
- Public sanitation is still an issue
  - Less that 31 % of India's 1.2 billion population has access to sanitation facilities.

Walsh et al. *Lancet Infect Dis* 2011;11: 355; http://www.zdnet.com/article/in-india-a-high-tech-toilet-that-generates-revenue/

CRE In Indiana – IU Collaboration

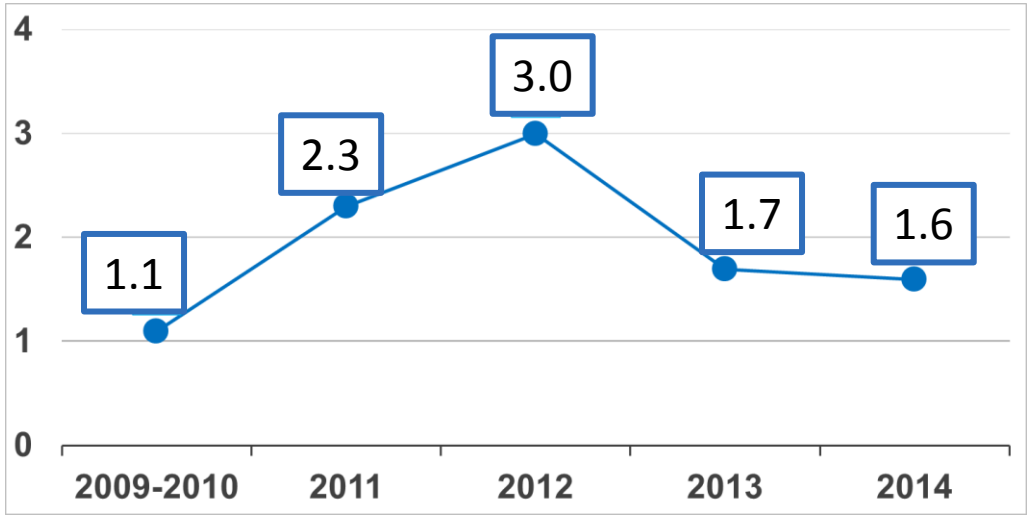
- Carbapenem resistance was rare in Indianapolis before 2009
- Surveillance begun in July 2009 at a central laboratory at the IU Pathology laboratory (G. Denys, IU Medical School) serving
  - Two large Indianapolis hospitals
  - Twelve smaller Health Care Centers (HCCs)
- CRE identified based on CDC guidelines
- Molecular characterization of CRE isolates
  - IU Biotechnology students
  - PCR conducted for
    - Serine and metallo-carbapenemases
    - Other β-lactamases
  - Gene sequencing conducted on enzymes of interest



Our IU Lab Began to Track CRE in Indianapolis Health Care Centers

- Beginning in July 2009, surveillance of CRE in patient isolates was initiated.
  - 2 to 5 large urban hospitals in Indianapolis
  - 12 to 14 central Indiana health care centers (HCCs).

% CRE Identified per year



Results:
- Stricter infection control practices were instituted approx. 2011-2012.
- CRE incidence has plateaued

Kashikar et al. ICAAC 2015

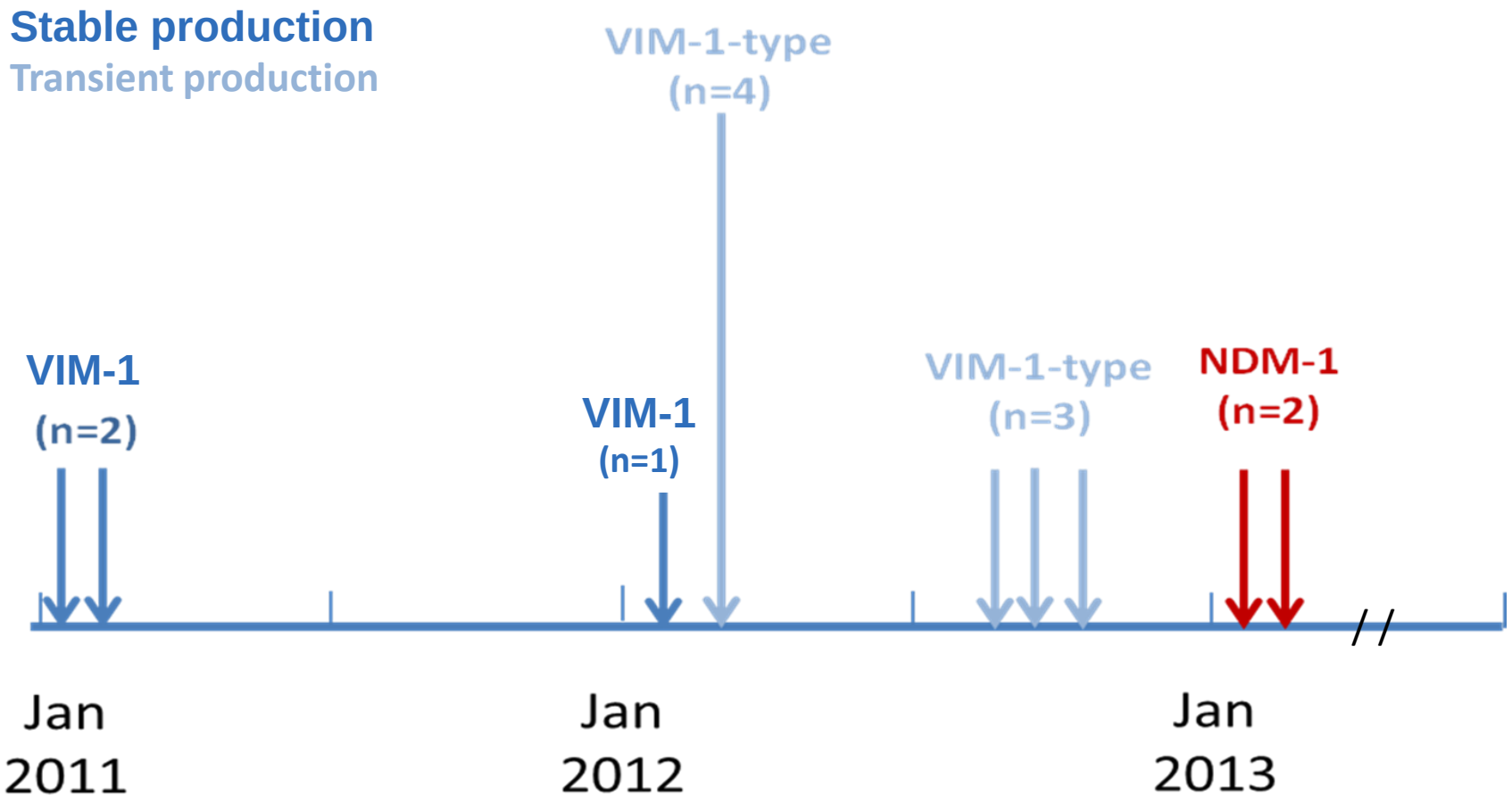
Co-Production of Carbapenemases with Other β-Lactamases

β-Lactamase	*E.. cloacae* (n=3)	*E. coli* (n=5)	*K. pneumoniae* (n=96)	*S. marcescens* (n=6)
KPC-2	0	1	15	0
KPC-3	3	4	80	3
KPC-3 + VIM-1	3	0	(4)*	0
KPC-3 + NDM-1	0	0	2	0
SME-1	0	0	0	3
KPC + SHV	2	4	70	2
KPC + TEM	3	5	90	3
KPC + CTX-M-15	0	4	5	0
KPC + TEM + SHV + CTX-M-15	0	4	2	0
KPC + TEM + SHV + OXA	3	4	21	0

*VIM-encoding plasmids lost on storage

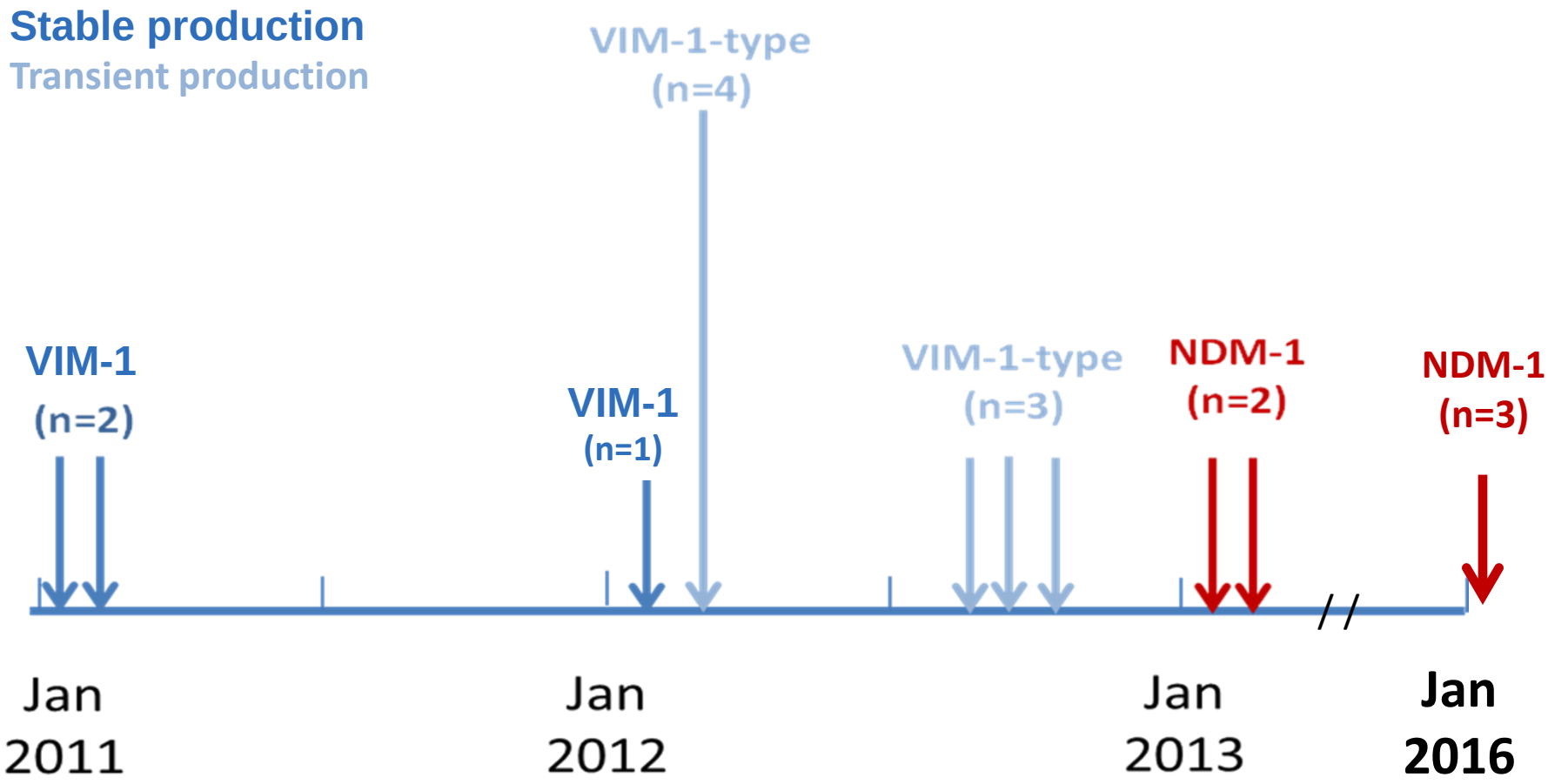
Zhang et al., ASM 2016

Timeline for MBLs in Indianapolis



Bush lab, compiled from 2010 through 2013; Kashikar et al. ICAAC 2015

Timeline for MBLs in Indianapolis



Bush lab, compiled from 2010 through 2013; Kashikar et al. ICAAC 2015; Tulpule 2016

Molecular Relationships Among Isolates that Originally Produced both KPC and an MBL

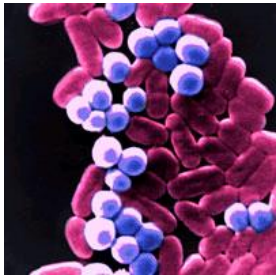
- Sequence typing for *K. pneumoniae*
  - Analyze the nucleotide sequences of 7 housekeeping genes
  - Compare to STs in international database at the Pasteur Institute
- Determine the "pulsotype" of each strain based on the gel electrophoresis profile of an enzymatic digest of whole genomic DNA

A. Tulpule, Microbe 2017

Molecular Relatedness of *K. pneumoniae* Isolates that Originally Produced both a KPC and MBL

KPC-3 producing isolate	MBL	Sequence Type	Pulsotype	Health Care Center
KP-88	NDM	ST674	KpA	1
KP-49	VIM	ST258	KpA	2
KP-83	VIM	ST258	KpA	3
KP-84	VIM	ST258	KpA	4
KP-80	VIM	ST258	KpB	5
KP-85	VIM	ST258	KpB	6
KP-86	VIM	ST258	KpB	6

A. Tulpule, Microbe 2017



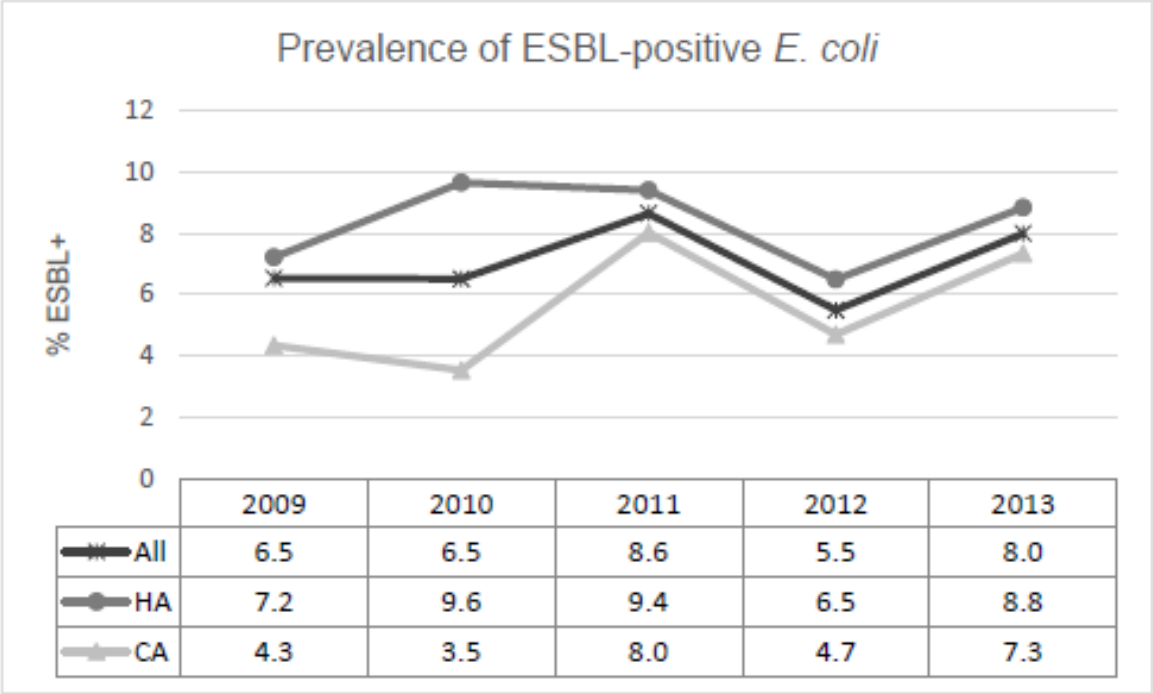
Antibiotic Resistance:

Past, Present and ***Future***

Stabilization of Resistance?

ESBLs in Intraabdominal Infections
SMART Study for 2009-2013 (USA)

Trends in prevalence of phenotypically ESBL-positive *E. coli* isolates from IAI in the USA (2009-2013)
29 hospitals, n=2897

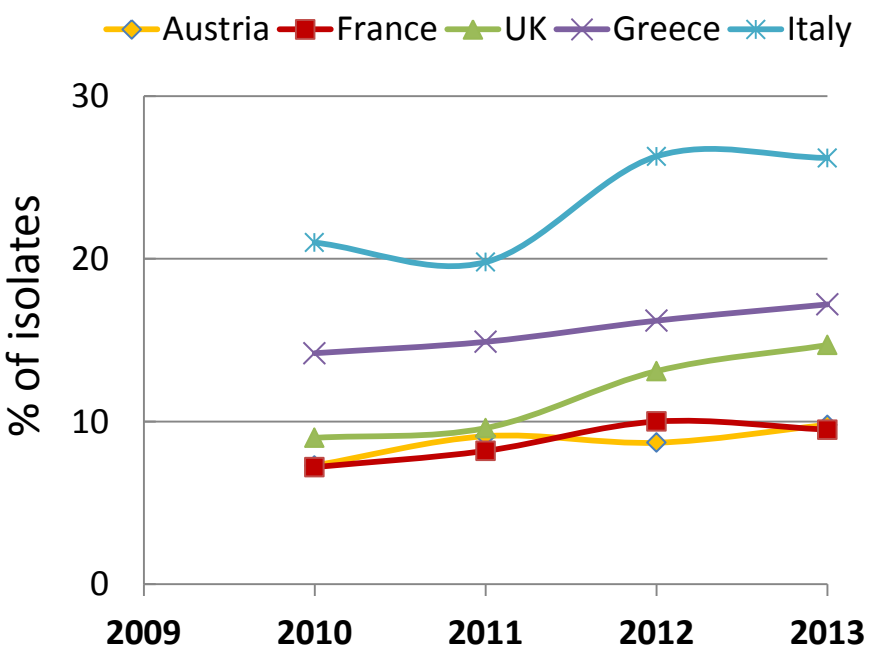


	2009	2010	2011	2012	2013
All	6.5	6.5	8.6	5.5	8.0
HA	7.2	9.6	9.4	6.5	8.8
CA	4.3	3.5	8.0	4.7	7.3

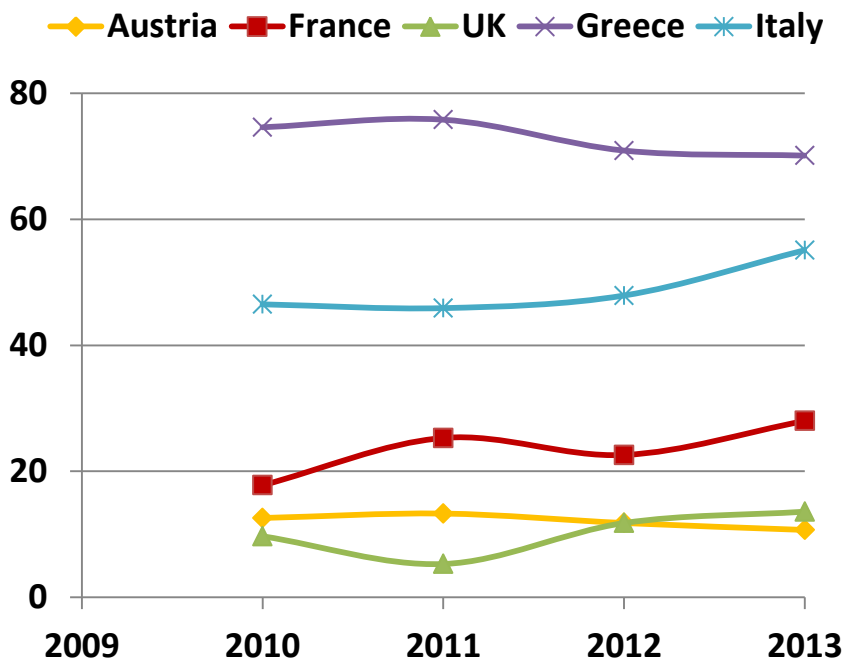
Lob et al. AAC 59:3606 (2015)

"3rd Generation" Cephalosporin Resistance in European Invasive Isolates

E. coli



K. pneumoniae



EARS-Net Report. Antibiotic Resistance Surveillance in Europe 2013

Changes in CRE Incidence in Enterobacteriaceae After Strict Infection Control in NYC

1. Infection control program initiated in a 10-bed medical and surgical ICU in New York City (2006)
   - Mean number of new patients per 1,000 patient-days per quarter with cultures yielding carbapenem-resistant *K. pneumoniae*
   - Decreased from 9.7 before the intervention to 3.7 after the intervention ($P < 0.001$).
   - No change in carbapenem-R in *Acinetobacter* or *Pseudomonas*
2. 14 hospitals in NYC
   - 2009 compared to 2006
   - KPC in *K. pneumoniae* decreased from 38% to 29%
   - But Imipenem resistance increased:

	2006	2009
Acinetobacter	63%	82%
Pseudomonas	31%	39%

Kochar et al. *Infect Control Hosp Epidemiol*. 30:447-452 (2009); Landman et al. JAC 67(6):1427 (2012)

Appearance of the Transferable Colistin Resistance gene *mcr* in the Asia-Pacific Region

- Transferable colistin resistance due to *mcr*-1 gene
  - Phosphoethanolamine transferase enzyme family
  - Expression in *E. coli* results in addition of phosphoethanolamine to lipid A
- First reported in a Chinese pig isolate in 2015. From 2011 to 2014 (in China)
  - 78 (15%) of 523 samples of raw meat
  - 166 (21%) of 804 animals (chickens and pork)
  - 16 (1%) of 1322 samples from inpatients with infection
- Two 2015 *K. pneumoniae* (n=2 with NDM-5 and *mcr-1*) patient isolates resistant to carbapenems, not resistant to quinolones
- Appearance of *mcr*-1 in *E. coli* in first United States patient (May, 2016)
- At least two more variants have been identified.

Liu et al., Lancet Infect Dis 2016; 16: 161–68; Du et al. Lancet Infect. Dis. 2016; 16:287; http://www.cdc.gov/media/releases/2016/s0531-mcr-1.html

What Can We Do to Prevent and Treat these "Superbugs"?

- New antibiotics?
  - Limited number of new antibacterial drug discovery programs
  - Decreasing numbers of companies working on these drugs

Potential New Agents to Control Carbapenem Resistance?

- β-lactamase inhibitor (BLI) combinations
  - Two approved in 2014-2015
    - Ceftolozane-tazobactam* (especially *Pseudomonas*)
    - Ceftazidime-avibactam* (covers many CRE)
  - Other BLI combinations in development to treat CRE
    - Phase 1/2/3 clinical development = 9, including imipenem-relebactam*
    - At least 2 others in late preclinical evaluation
    - Not all will be successful, commercially or medically
- New aminoglycoside in Phase 3 – plazomicin*
- New tetracycline in Phase 3 – omadacycline and eravacycline*
- New antimicrobial peptides (Discovery work at IU)*

*New agents that have been tested against clinical isolates at IU

Estabrook et al. J. Clin. Micro. 52:4049 (2014); Li et al., ICAAC 2014; Zhang et al., ICAAC 2016; Zhang et al. , J. Antibiotics 69:600 (2016); Kao et al. mBio (2016) *doi:10.1128/mBio.01418-16*

Antimicrobial Activities of New Agents Against 110 Indiana CRE Isolates

	Minimum Inhibitory Concentration in μg/ml							
Antibiotic	**≤0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**≥32**
Imipenem*	--	--	--	2	10	58	17	23
Plazomicin	27	65	8	6	2	1	--	1
Eravacycline		2	68	36	4	--	--	--
Ceftazidime*	--	--	1	2	--	--	--	108
Ceftazidime-Avibactam*	3	12	46	43	2	1	--	--
Aztreonam*	--	--	--	--	--	1	2	107
Aztreonam-Avibactam	84	21	--	1	3	1	--	--

*FDA approved

Li et al., ICAAC 2014; Zhang et al., ICAAC 2016; Zhang et al. , J. Antibiotics 69:600 (2016)

Resistance to New Agents

- Resistance to plazomicin
  - 16S rRNA methyl transferases
  - Transferred on many naturally-occurring plasmids encoding NDM-1
- Resistance to ceftazidime-avibactam
  - Multiple mutations in KPC-3 carbapenemase conferring resistance to avibactam but restoring susceptibility to meropenem – in patients treated with ceftazidime-avibactam
  - Insertion sequences in *E. coli* PBP3 conferring resistance to cephalosporins and aztreonam but not meropenem

Livermore, et al. JAC **66:**48 (2011); Shields et al., AAC (2017); Alm et al. JAC **70:**1420 (2015)

What Can We Do to Prevent and Treat these "Superbugs"?

- New antibiotics?
  - Limited number of new antibacterial drug discovery programs
  - Decreasing numbers of companies working on these drugs
- New incentives to entice companies back into the business?

Generating Antibiotic Incentives Now (GAIN) Act
FDA Safety and Innovation Act (signed into law July 9, 2012)

- Limited only to antibacterial and antifungal products for human use that treat serious or life-threatening infections
- HHS developed and will update a list of qualifying pathogens
  - Includes MRSA, *Bacillus anthracis,* CRE
- 5 additional years of Hatch/Waxman patent exclusivity for new antibiotics and antifungals
- Qualified infectious disease products eligible for Fast Track and Priority Review
- Provides advice for the rapid development of antibacterial drugs that target a limited spectrum of pathogens

http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20/Letters/To_Congress/IDSA%20Summary%20of%20Antibiotic%20Incentives%20in%20FDASIA.pdf

21st Century Cures Act
(Bipartisan Support, Dec. 2016)

- 94 to 5 Senate vote followed a 392 to 26 House vote
  - Supported by the pharmaceutical industry
  - Criticized by the FDA
- $6.3 billion in funding, mostly for the NIH
- $4.8 billion to NIH for precision medicine and biomedical research
- Expedite the process by which new drugs and devices are approved using “real world” data in addition to controlled clinical trial data

CARB-X

- Combatting Antibiotic Resistance Bacteria – Biopharmaceutical Accelerator established July 2016
- Global public-private partnership launched by HHS, NIAID and BARDA (Biomedical Advanced Research and Development Agency)
- Stimulate development of promising new antibacterial therapies over 5 years with $480 M in funding
  - BARDA
  - Wellcome Trust – London-based global charitable trust
- Announcement on March 30, 2017
  - $48 M for 11 early stage projects from 168 proposals
  - Goal is to fund up to a total of 20 projects

https://www.phe.gov/about/barda/CARB-X/Pages/default.aspx

European Responses

- The **European Union**
  - "Innovative Medicines Initiative" (IMI), the world's largest public-private partnership in the life sciences;
  - **€3.3 billion** budget for the period 2014-2024. Much of the funding is focused on antibacterial drugs.
- England's **Chief Medical Officer, Professor Dame Sally Davies**
  - Stark warnings about the catastrophes if we do not immediately address the threat of antimicrobial resistance (2015 annual report).
- Members of the **European Parliament** (MEPs)
  - Action plan for 'safer healthcare in Europe: improving patient safety and fighting antimicrobial resistance' (2011-2016)
  - Second AMR Action Plan to be launched in 2017

IMI Newsletter, 02Jun2015; http://bsac.org.uk/news/antimicrobial-resistance-poses-catastrophic-threat-says-chief-medical-officer/#sthash.vqmUvWZG.dpuf

What Can We Do to Prevent and Treat these "Superbugs"?

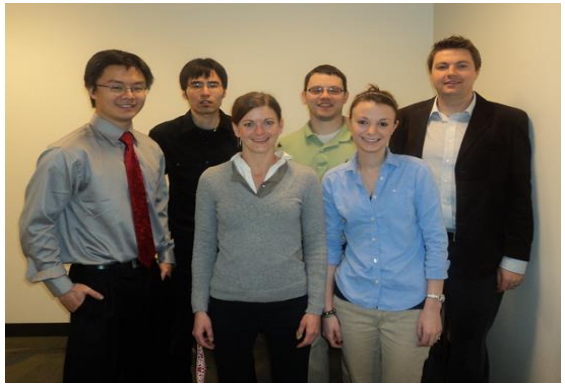
- New antibiotics?
  - Limited number of new antibacterial drug discovery programs
  - Decreasing numbers of companies working on these drugs
- New incentives to entice companies back into the business?
- Practice Antibiotic Stewardship
  - Use antibiotics wisely
  - Limit use in feed animals
  - Take antibiotics only when needed and for only as long as they are needed

Closing Thoughts

- Resistance is increasing -- globally
  - Resistance to β-lactams most worrisome because they travel on mobile elements, together with resistance genes that can confer resistance to most antibacterial agents
- Resistance in Indiana isolates is similar to what is being seen in other parts of the United States
- Carbapenem-resistant pathogens can be reduced in number, but never disappear completely
- Some progress has been made in developing new drugs to treat CRE infections, but resistance has already emerged.


New Antimicrobial Agents
RESISTANCE

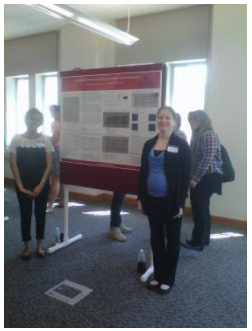
Biotechnology Antibiotic Resistance Teams at IU



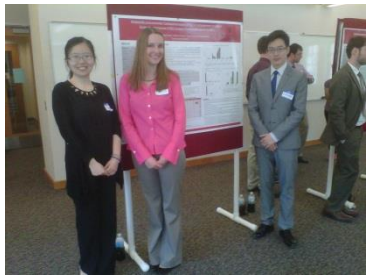
2010-2011

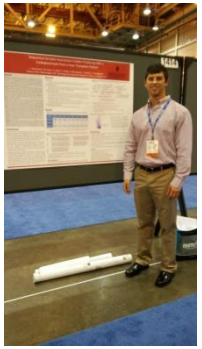
2011-2012

2012-2013



2013-2014





2014-2015

2015-2016

2016-2017

Funding:
Cubist, AstraZeneca, Achaogen, Tetraphase, Forest/ Allergan, Merck

Thank you!

INDIANA UNIVERSITY

Back-Ups

Very Few Large US and European Pharmaceutical Companies Are Still Conducting Antibacterial Research - 2017

1980 (N = 36)

- Abbott
- Astra
- Ayerst
- Bayer
- Beecham
- Bristol-Myers
- Burroughs
- Ciba-Geigy
- Dow
- DuPont
- Glaxo
- Hoechst
- ICI
- Lederle
- Lilly
- Marion
- Merck
- Merrell
- Miles
- Parke Davis
- Pfizer
- Pharmacia
- Proctor & Gamble
- Rhone-Poulenc
- Rorer
- Roche
- Roussel
- Sandoz
- Sanofi
- Schering
- SmithKline
- Squibb
- Upjohn
- Warner-Lambert
- Wellcome
- Wyeth

1998 (N = 20)

- Abbott
- Astra
- Bayer
- Bristol-Myers Squibb
- Glaxo Wellcome
- Hoechst Marion Roussel
- Johnson & Johnson
- Lilly
- Merck
- Novartis
- Parke Davis
- Pfizer
- Pharmacia & Upjohn
- Rhone-Poulenc Rorer
- Roche
- Sanofi
- Schering
- SmithKline Beecham
- Wyeth-Ayerst
- Zeneca

2017 (N = 5-6)

- Glaxo SmithKline
- [Johnson & Johnson]
- Merck-ScheringPlough
- [Pfizer]
- Novartis
- Sanofi-Aventis
- The Medicines Co.**

**Medium-sized company with anti-infective R&D