CRE

Carbapenem-resistant enterobacterales

Antibiotic Awareness Week

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Karen Bush is not an employee of, nor is she affiliated with, the Indiana Department of Health.

The views expressed are the speaker's own and may not reflect the view(s) of the Indiana Department of Health.

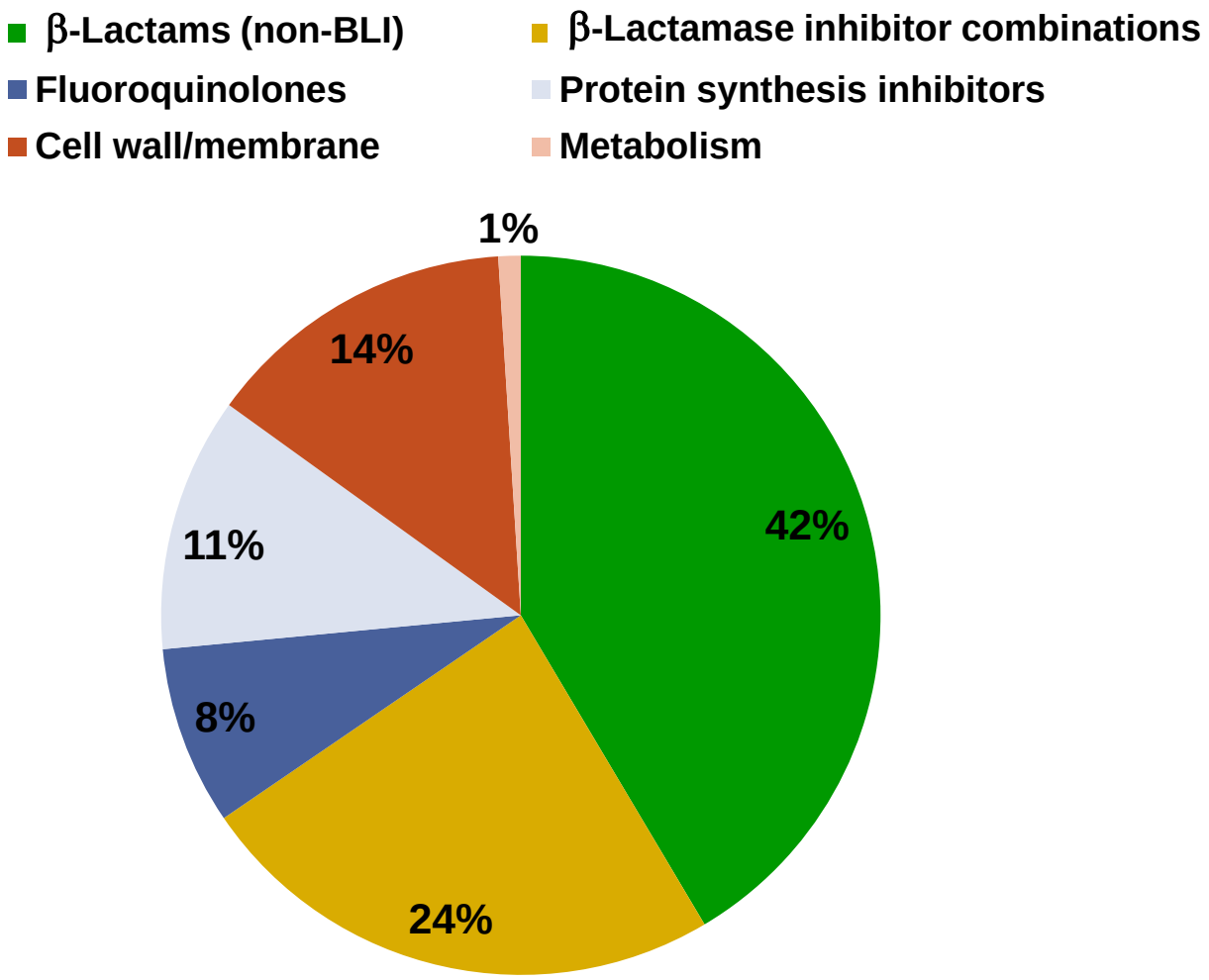
Disclosures

- ***Retiree compensation:***
  - 35 years in antibacterial R&D (1973–2009):
  - Bristol-Myers Squibb, Johnson & Johnson (shareholder), Pfizer (Wyeth)
- ***Consultant or scientific advisory board:***
  - Achaogen, Allecra, Allergan, Eli Lilly, Entasis, Fedora (shareholder), Melinta, Qiagen, Roche, Shionogi, Sumitovant, Tetraphase, WarpDrive
- ***Research support:***
  - Achaogen, Actavis-Allergan, Fedora, Merck, Shionogi, Tetraphase

Presentation overview

- Definitions
- CRE distributions
- CRE emergence in Indiana
- Therapeutic options

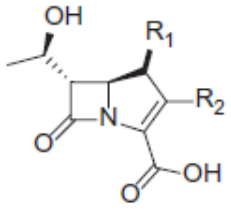
β-lactam antibiotics represent the largest proportion of prescriptions in US hospitals by antibiotic class (2004-2014)

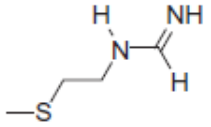
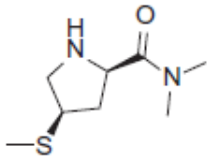
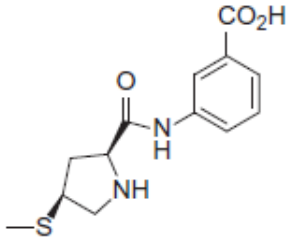
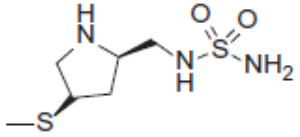
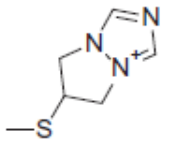
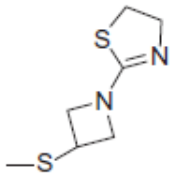


Modified from Bush and Bradford, Cold Spr. Harbor, 2016

Carbapenems – "last resort antibiotics"

- Imipenem introduced in 1985.
- Stable to all the clinically relevant β-lactamases at the time
  - The only β-lactam that was stable to the ESBLs (extended spectrum β-lactamases) that emerged in the late 1980s
  - Used extensively to treat infections caused by ESBL-producing gram-negative pathogens
- By the time meropenem was available, carbapenem resistance was widespread



Name	R_1	R_2	Approval date[a,b]	Status
Imipenem	H		1985	Widely available
Meropenem	CH_3		1996	Widely available
Ertapenem	CH_3		2001	Widely available
Doripenem	CH_3		2007	Widely available
Biapenem	CH_3		2001 (Japan)	Available in Japan
Tebipenem[c]	CH_3		2009 (Japan)	Available in Japan

[a]FDA approved unless otherwise noted.
[b]Dates were updated from Medeiros (1997) (www.accessdata.fda.gov/scripts/cder/drugsatfda; www.drugs.com; adisinsight.springer.com/drugs/800010812).
[c]Formulated as the pivoxil ester.

Bush & Bradford. Cold Spring Harb Perspect Med
doi: 10.1101/cshperspect.a025247

What is CRE (CPE)?

- CRE
  - Initially: Carbapenem-resistant *Enterobacteriaceae* (a family within the order of Enterobacterales)
  - Currently: Carbapenem-resistant Enterobacterales
  - Organisms in the order Enterobacterales that are resistant to carbapenems
- The order Enterobacterales includes the following families:
    - *[Budviciaceae]*
    - *Enterobacteriaceae**
    - *[Erwiniaceae]*
    - *Hafniaceae**
    - *Morganellaceae**
    - *[Pectobacteriaceae]*
    - *Yersiniaceae**
- Two major causes for CRE:
  - CPE: Carbapenemase-producing Enterobacterales (*Enterobacteriaceae*), most often due to transferable carbapenem-hydrolyzing β-lactamases
  - Chromosomal mutations related to efflux or porin defects

From CDC site:

Name Change

In 2020, a taxonomy change was adopted to use "Enterobacterales" as the name of a new scientific order. "*Enterobacteriaceae*" are now a family within the "Enterobacterales" order, along with *Erwinaceae, Pectobacteriaceae, Yersiniaceae, Hafniaceae, Morganellaceae*, and *Budvicaceae*.

Why is CRE important?

- **According to the Centers for Disease Control and Prevention (CDC) in 2019**
  - More than 2.7 million people in the United States are infected with antibiotic-resistant bacteria
  - At least 35,000 deaths due to hospital-acquired resistant bacteria
  - Multidrug-resistant *Enterobacteriaceae*, *Acinetobacter* and *Pseudomonas aeruginosa* are some of our most serious and urgent medical threats
- **Notable antibiotic resistance threats in Gram-negative pathogens**
  - **Carbapenem resistance (carbapenemases)**
  - Plasmid-mediated colistin resistance (*mcr*-1)
  - Cephalosporin resistance in *Neisseria gonorrhoeae*

CDC, Antibiotic Resistance Threats, 2013 and 2019

CDC: threats of antibiotic resistance, 2013 and 2019

2013

Urgent threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

- **Serious threats**
  - Multidrug-resistant *Acinetobacter*
  - Drug-resistant *Campylobacter*
  - Extended spectrum β-lactamase-producing *Enterobacteriaceae* (ESBLs)
  - Vancomycin-resistant *Enterococcus* (VRE)
  - Multidrug-resistant *Pseudomonas aeruginosa*
  - Drug-resistant nontyphoidal *Salmonella*
  - Drug-resistant *Salmonella typhi*
  - Drug-resistant *Shigella*
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Drug-resistant *Streptococcus pneumoniae*

2019

Urgent threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

- **Serious threats**
  - Drug-resistant *Campylobacter*
  - Drug-resistant *Candida*
  - ESBL-producing *Enterobacteriaceae*
  - Vancomycin-resistant *Enterococcus* (VRE)
  - Multidrug-resistant *Pseudomonas aeruginosa*
  - Drug-resistant nontyphoidal *Salmonella*
  - Drug-resistant *Salmonella* serotype Typhi
  - Drug-resistant *Shigella*
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Drug-resistant *Streptococcus pneumoniae*
  - Drug-resistant Tuberculosis

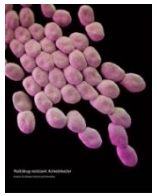
CDC
Centers for Disease Control and Prevention

CDC, Antibiotic Resistance Threats, 2013; CDC Antibiotic Resistance Threats, 2019

WHO critical and high priority pathogens, 2021

CDC Threat Level (2019)

- ***Acinetobacter baumannii***
  - Carbapenem-resistant



Urgent

- ***Pseudomonas aeruginosa***
  - Carbapenem-resistant

Serious

- ***Enterobacteriaceae***
  - **Carbapenem-resistant**, ESBL/"3rd generation" cephalosporin-resistant

Urgent/Serious

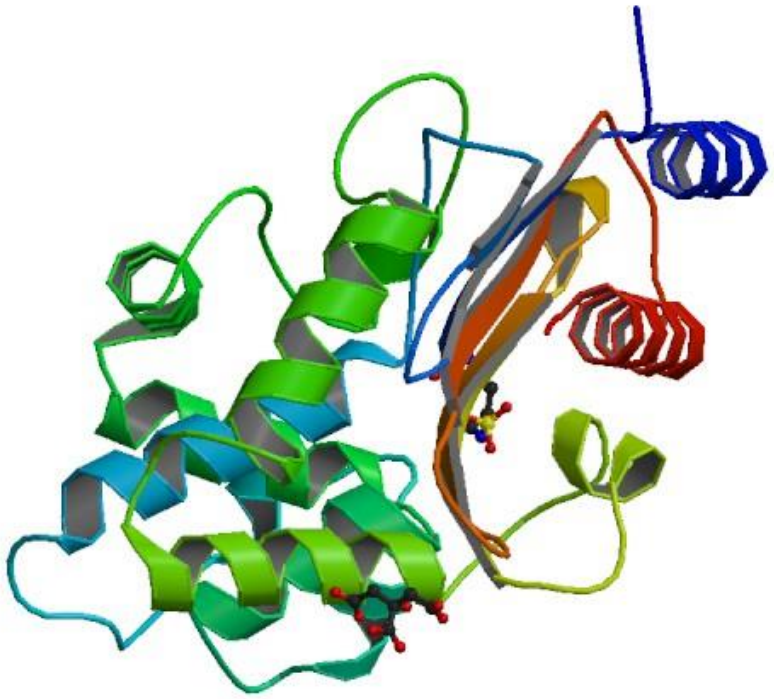
- ***Staphylococcus aureus***
  - Methicillin-resistant, vancomycin-nonsusceptible

Serious

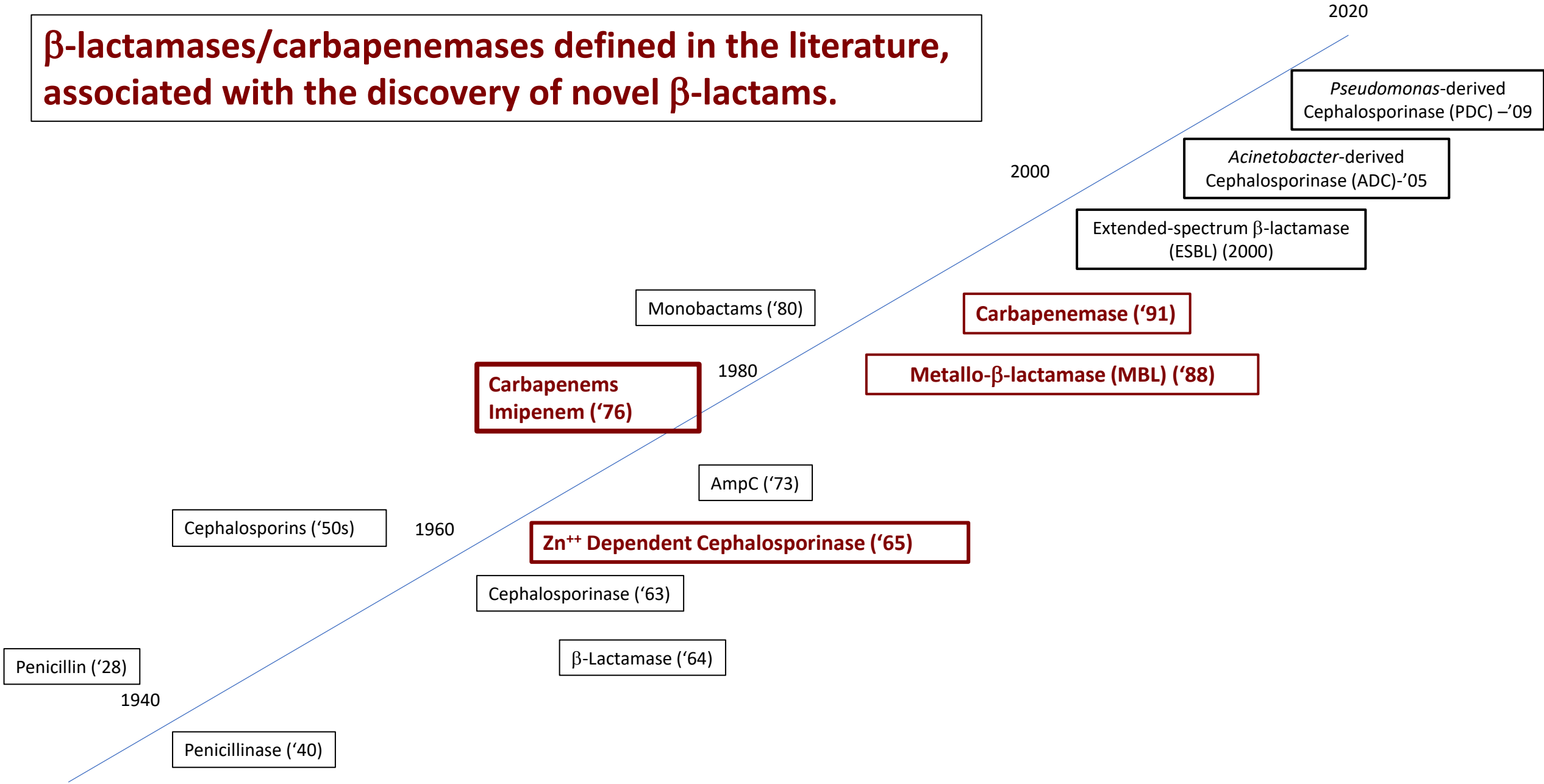
https://www.testtargettreat.com/en/home/news-events/who_published_list_bacteria.html (2021)

CDC, Antibiotic Resistance Threats, 2013; CDC Antibiotic Resistance Threats, 2019

β-lactamases: the most prevalent resistance mechanism for β-lactam antibiotics



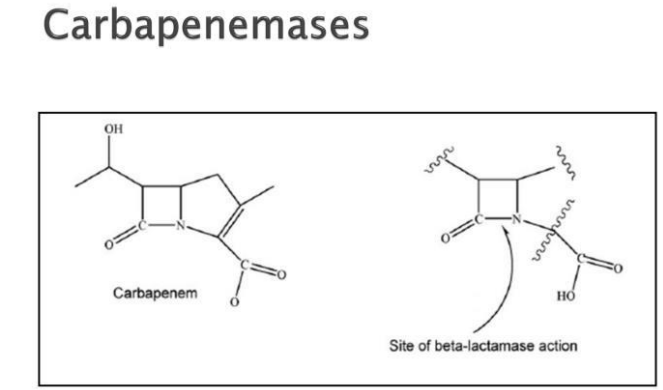
β-lactamases/carbapenemases defined in the literature, associated with the discovery of novel β-lactams.

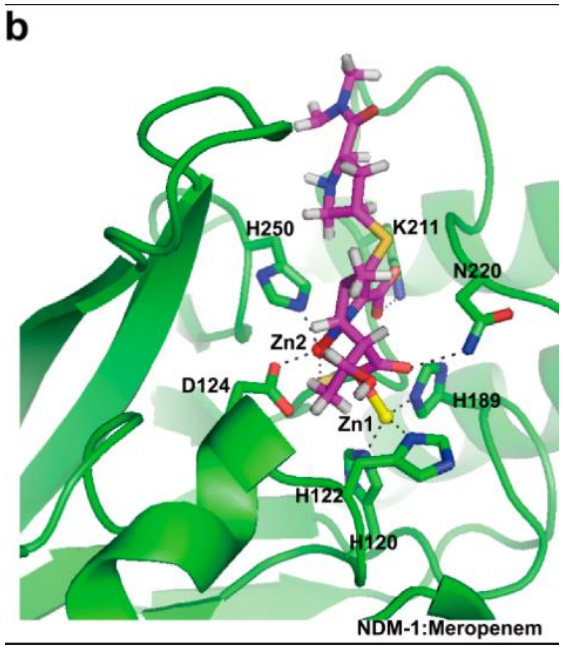


Adapted from Bush, 2023.
EXP REV ANTI-INFECT THER. https://doi.org/10.1080/14787210.2023.2194633

What is a carbapenemase?

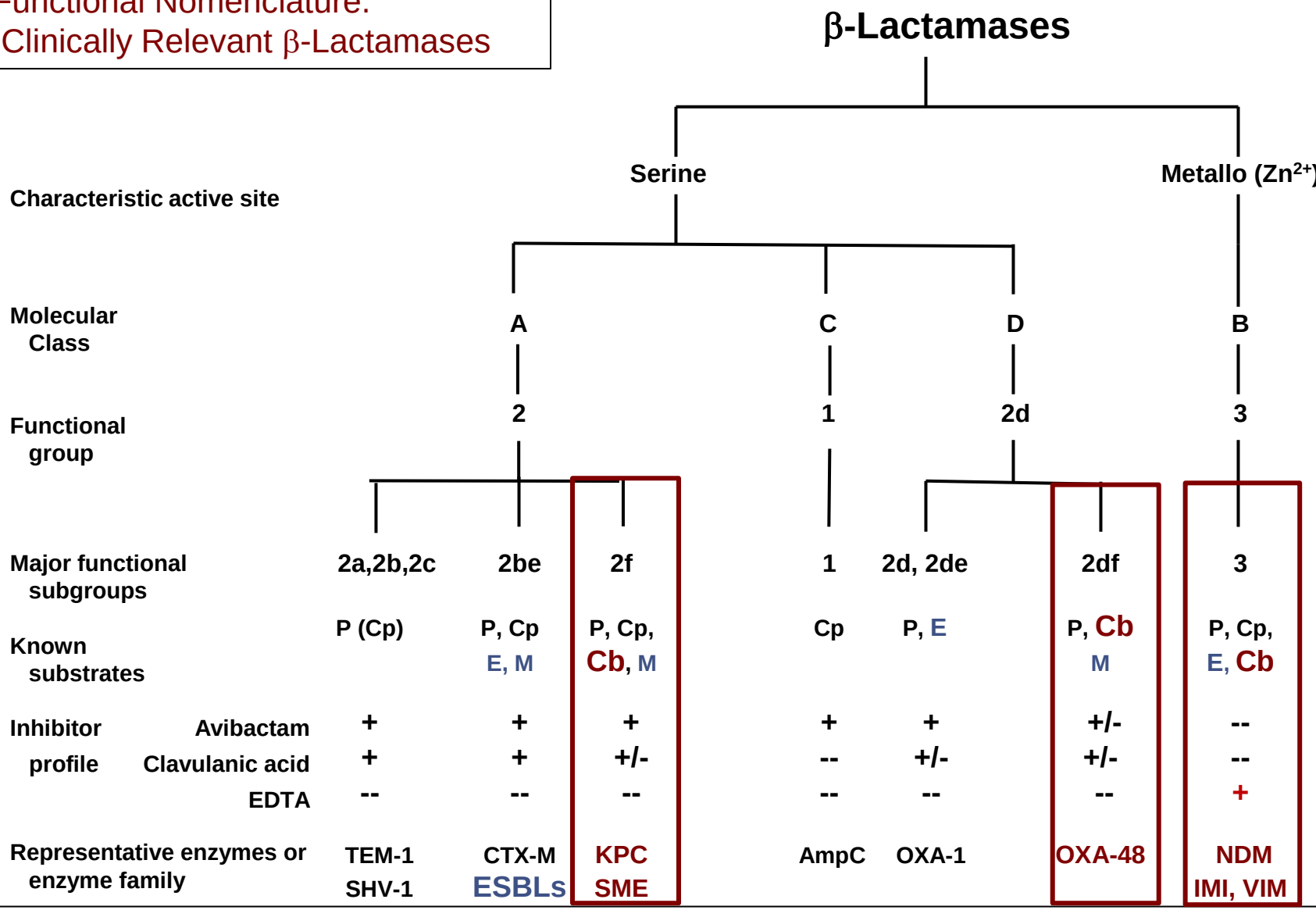
- An enzyme that hydrolyzes/inactivates a carbapenem
  - Also hydrolyzes most other classes of β-lactams
- Two major types that hydrolyze almost all β-lactam antibiotics
  - Those that utilize the amino acid serine to perform hydrolysis
    - Serine β-lactamase, or SB
    - Some cephalosporins (cefepime, cefotaxime) are not easily hydrolyzed by some SBLs
  - Those that require a zinc atom to perform hydrolysis
    - Metallo-β-lactamase, or MBL
    - Aztreonam (a monobactam) is not hydrolyzed
- Two sources for β-lactamase genes
  - Chromosomal
  - Plasmid-encoded – mobile, transferable





Simplified Correlation Between Molecular and Functional Nomenclature. Focus on Most Clinically Relevant β-Lactamases

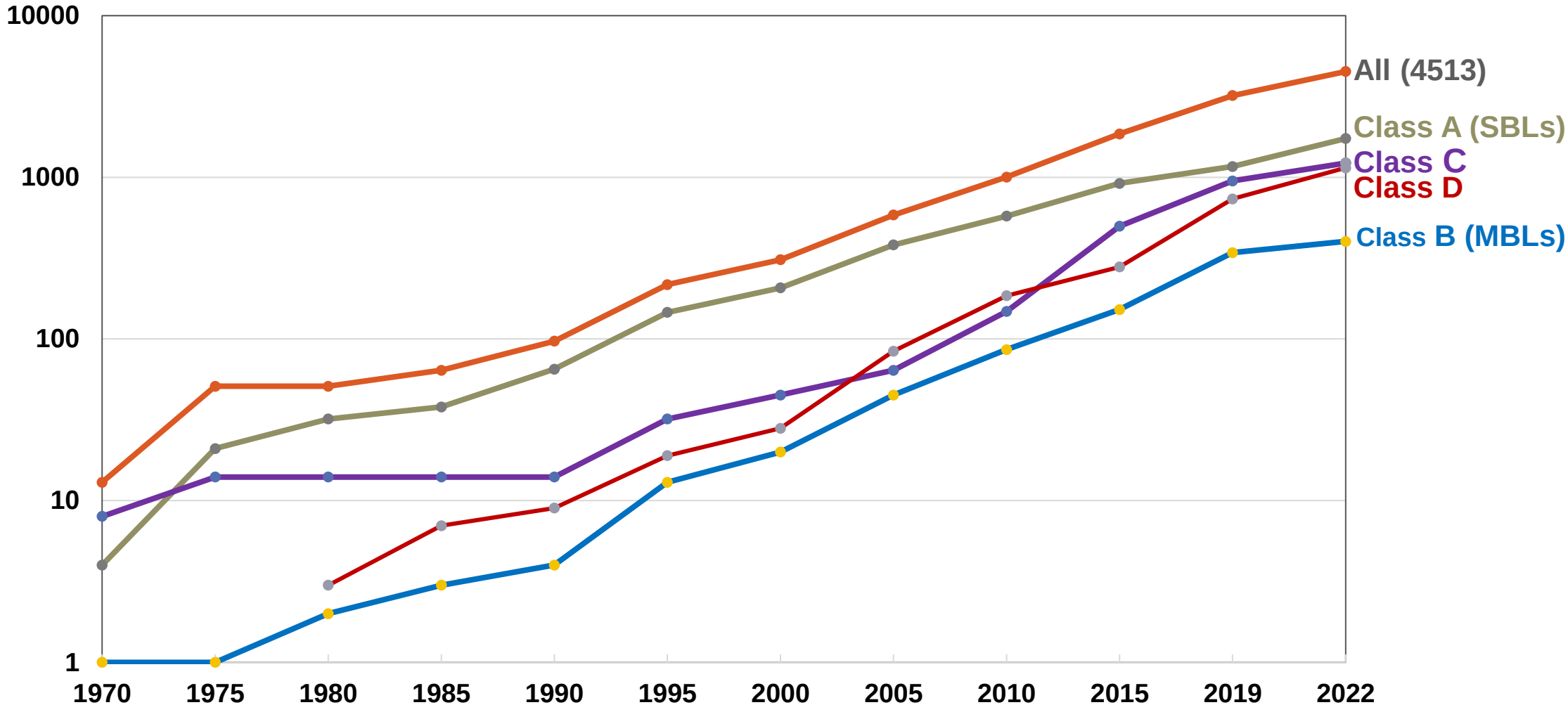
Adapted from Bush, K. 2018. Antimicrob Agents Chemother 62:e01076-18



Carbapenemases are in Groups 2f, 2df (SBLs) and Group 3 (MBLs)

Abbreviations:
Cb, carbapenem; Cp, cephalosporin; **E, expanded-spectrum cephalosporin; M, monobactam, P, penicillin**
Representative enzymes are color-coded to correspond to their most important substrates.

Exponential Increase In Numbers of Discrete β-Lactamases
2022 Update



Data compiled by Bush from http://www.lahey.org/Studies/ and https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047

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:**
  - Hospitals: up to $66,000;
  - Third party payers: up to $31,000;
  - Society: up to $83,500

Bartsch et al. Clin. Microbiol. Infect. 23:p48.e9 (2016)

Plasmid-encoded 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
- NDM-1, originating in India and Pakistan, is becoming widespread – including Indiana
- KPC now often in Italy and Greece, together with MBLs

Unusual to find both kinds of enzymes in one organism, but IU students found isolates like these.

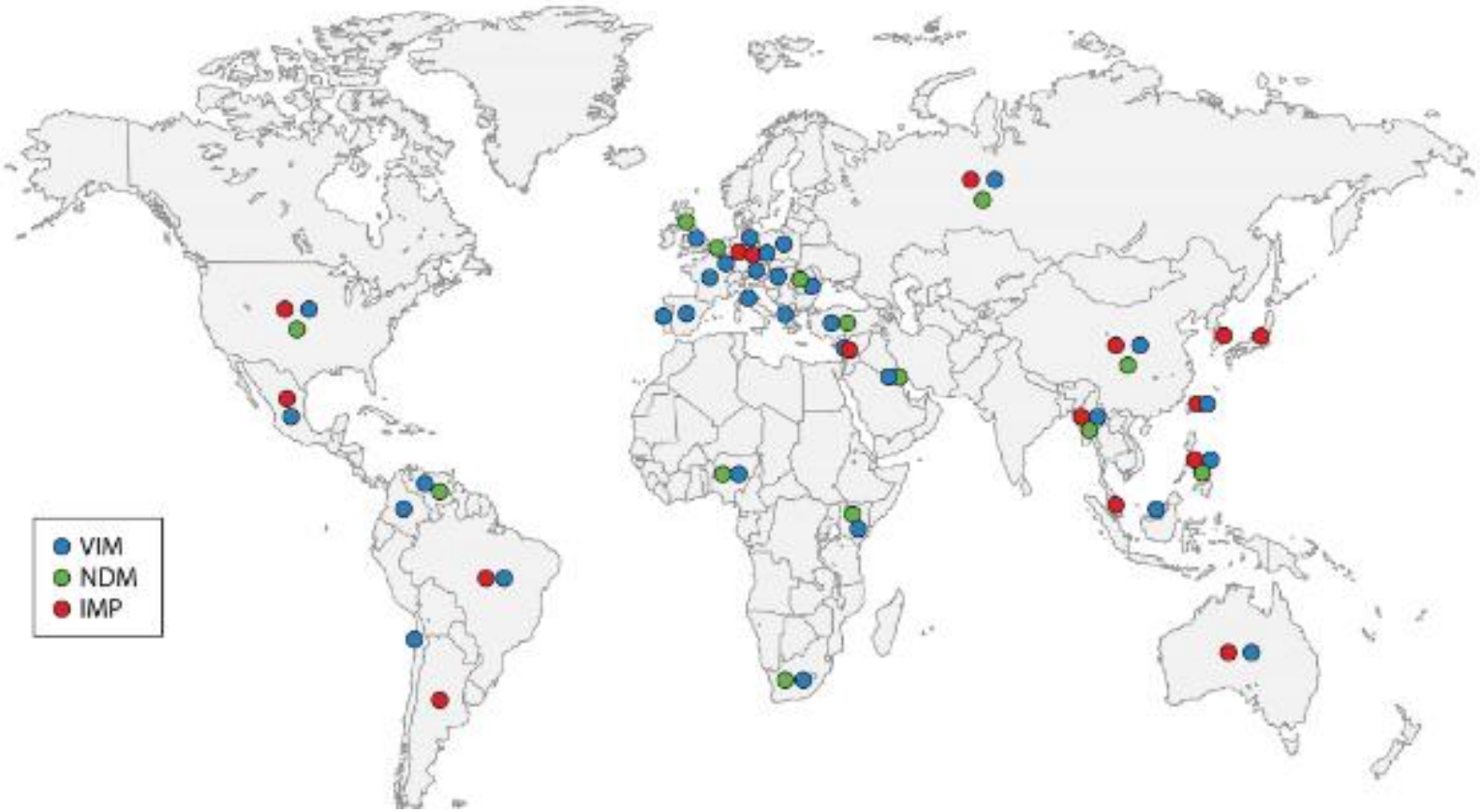
CRE are more frequently accumulating resistance determinants leading to isolates that are pan-resistant to all antibiotics tested.

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

Distribution of KPC-producing (SBL) isolates from 2012-2014 surveillance

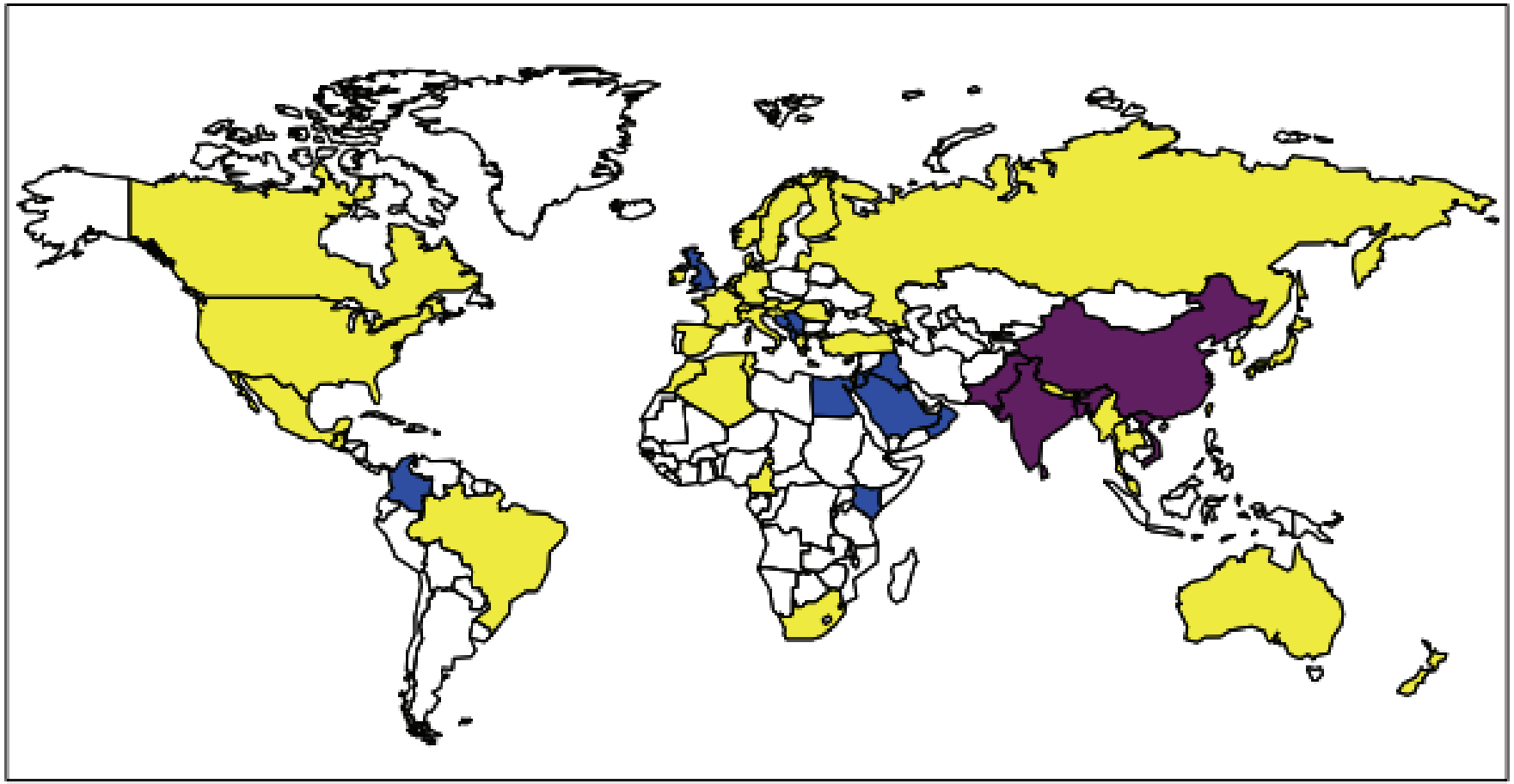
Bush K, Bradford PA. 2020. Clin Microbiol Rev 33:e00047-19.https://doi.org/10.1128/CMR.00047-19.

Distribution of MBL-producing isolates from 2012-2014 surveillance



Bush K, Bradford PA. 2020. Clin Microbiol Rev 33:e00047-19.https://doi.org/10.1128/CMR.00047-19

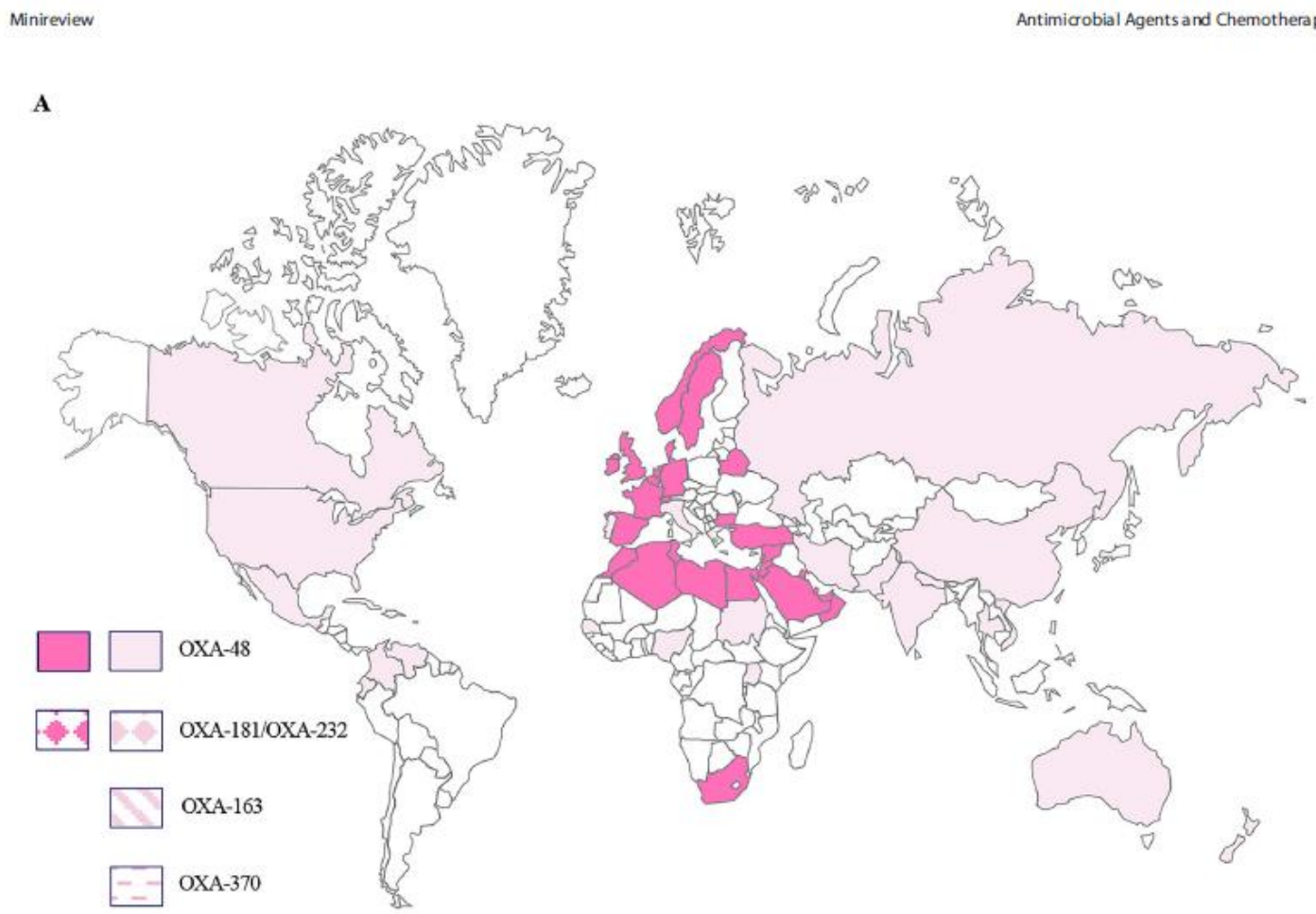
Global distribution of NDM (MBL) producers



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

Dortet et al. BioMed Research International Volume 2014, Article ID 249856, 12 pages http://dx.doi.org/10.1155/2014/249856

Class D: OXA-48 Carbapenemase (SBL) and its relatives

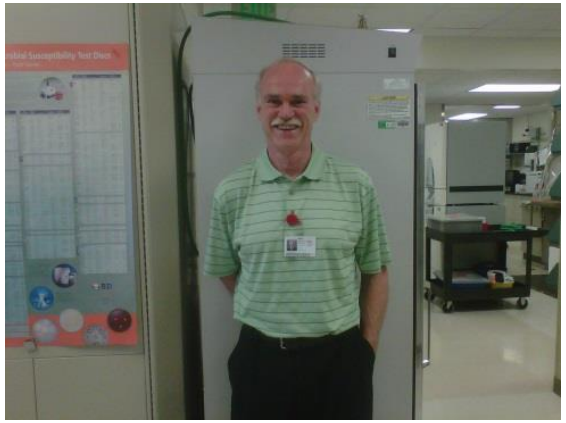


Darker colors indicate that OXA is the prevalent carbapenemase.

Boyd et al. Antimicrob Agents Chemother. Aug.2022 Vol. 66 (8) 10.1128/aac.00216-22

CRE In Indiana – IU collaboration

- Carbapenem resistance was rare in Indianapolis before 2009.
- Surveillance began in July 2009 at a central laboratory at the IU Pathology laboratory (IU Medical School) serving
  - Two large Indianapolis hospitals (increased to five by 2019)
  - Twelve smaller Health Care Centers (HCCs) (increased to 14 by 2019)
- CRE identified based on CDC guidelines (Gerald Denys at IU Medical School)
- Molecular characterization of CRE isolates
  - IU Biotechnology students of K. Bush, R. Lee, R. Sultana
  - PCR conducted for
    - Serine and metallo-carbapenemases
    - Other β-lactamases
  - Gene sequencing was conducted on enzymes of interest

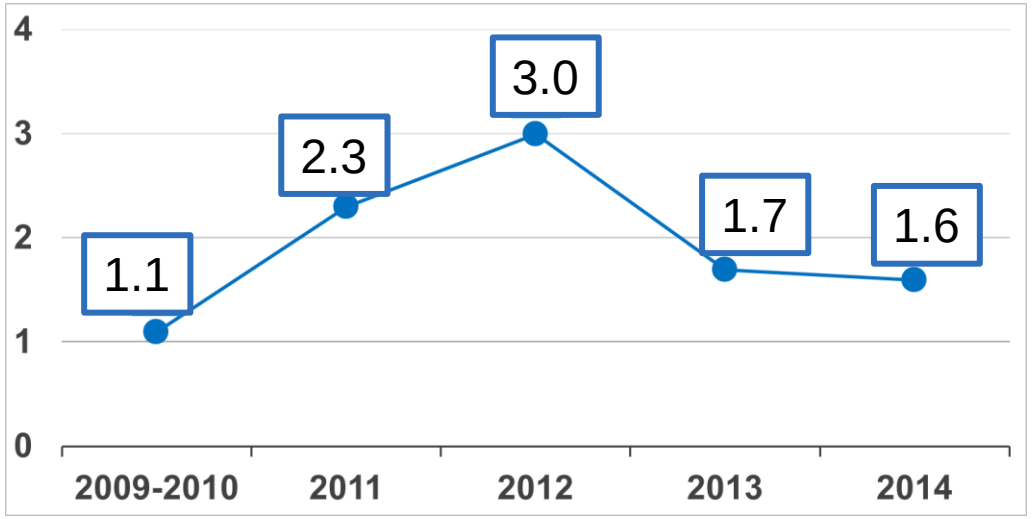


Gerald Denys

Emergence of CRE in Indianapolis health care centers

- Beginning in July 2009, surveillance of CRE in patient isolates was initiated.
  - Two to five large urban hospitals in Indianapolis
  - 12 to 14 central Indiana health care centers (HCCs)
  - Gerald Denys (IU Health) provided isolates; IU Biotechnology students did molecular characterization

Percentage CRE identified per year



Results:

- Stricter infection control practices were instituted after 2011
- CRE incidence plateaued in 2013-2014

Kashikar et al. ICAAC 2015

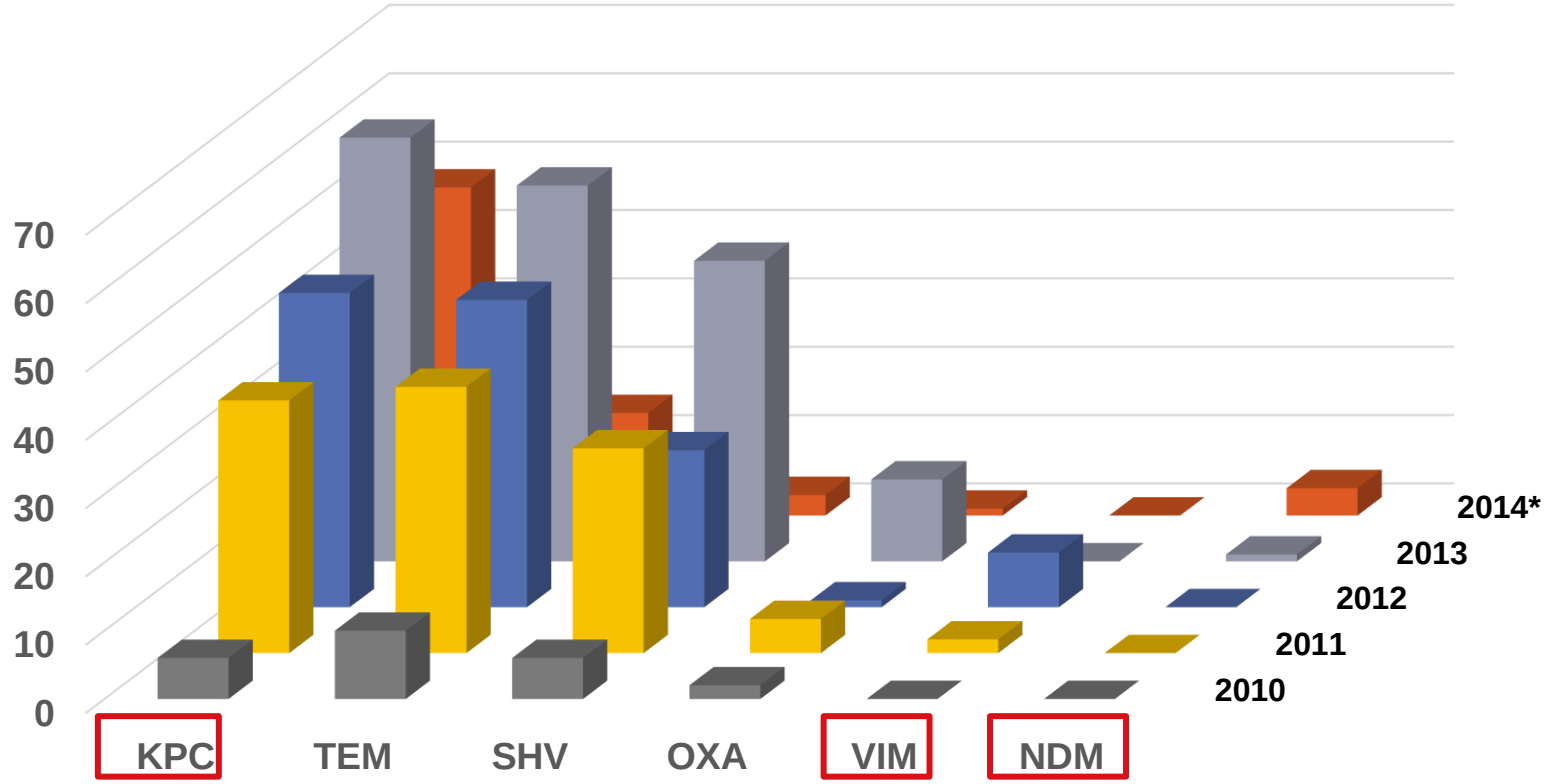
Co-production of carbapenemases with other β-lactamases

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

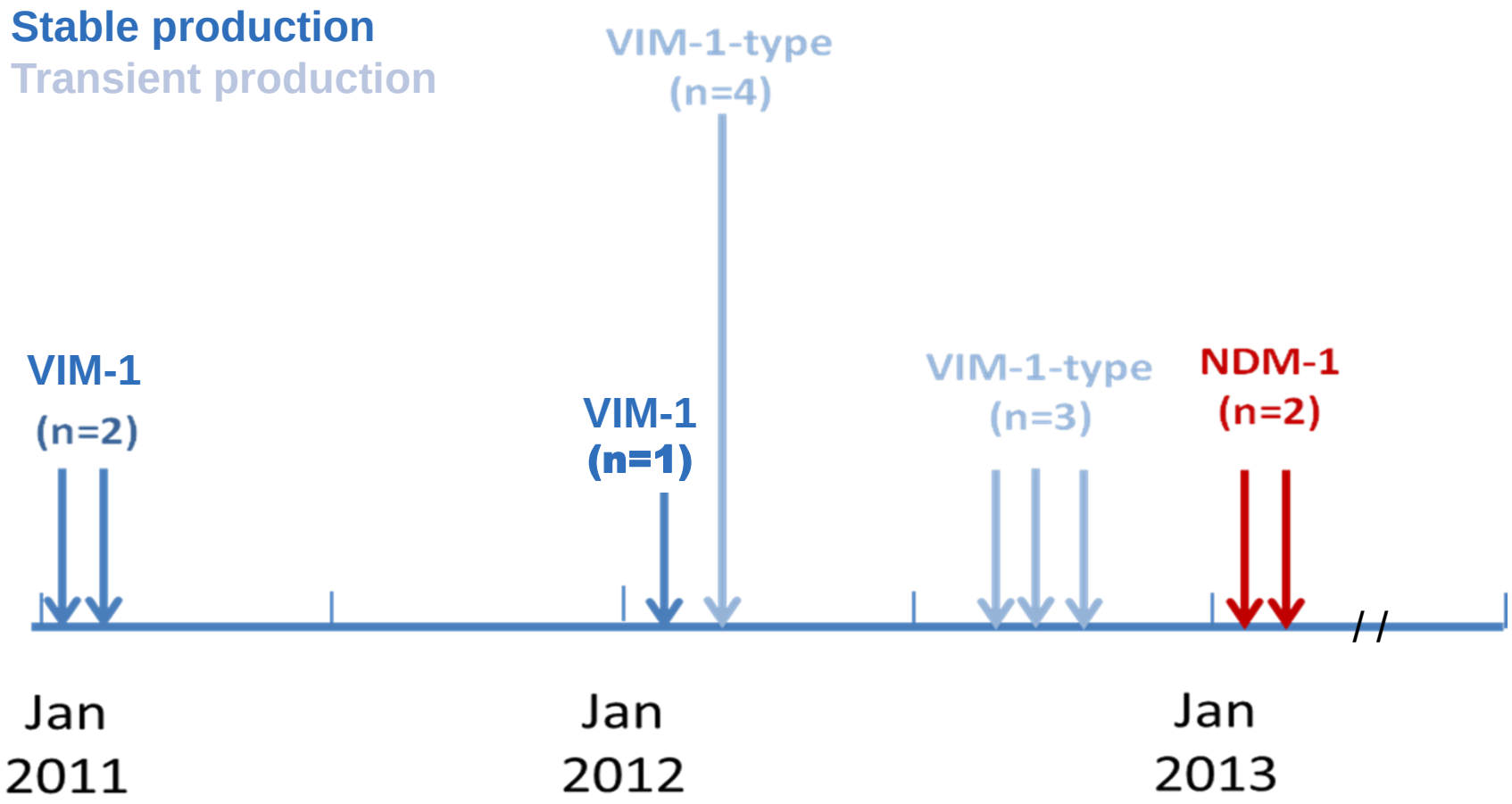
Distribution of β-lactamases in Central Indiana analysis by IU biotech students



- Among carbapenemases, KPC is the predominant
- TEM and/or SHV enzymes were major accompanying enzymes, with minor contributions of OXA and CTX-M enzymes
- KPC always occurred with other β-lactamases

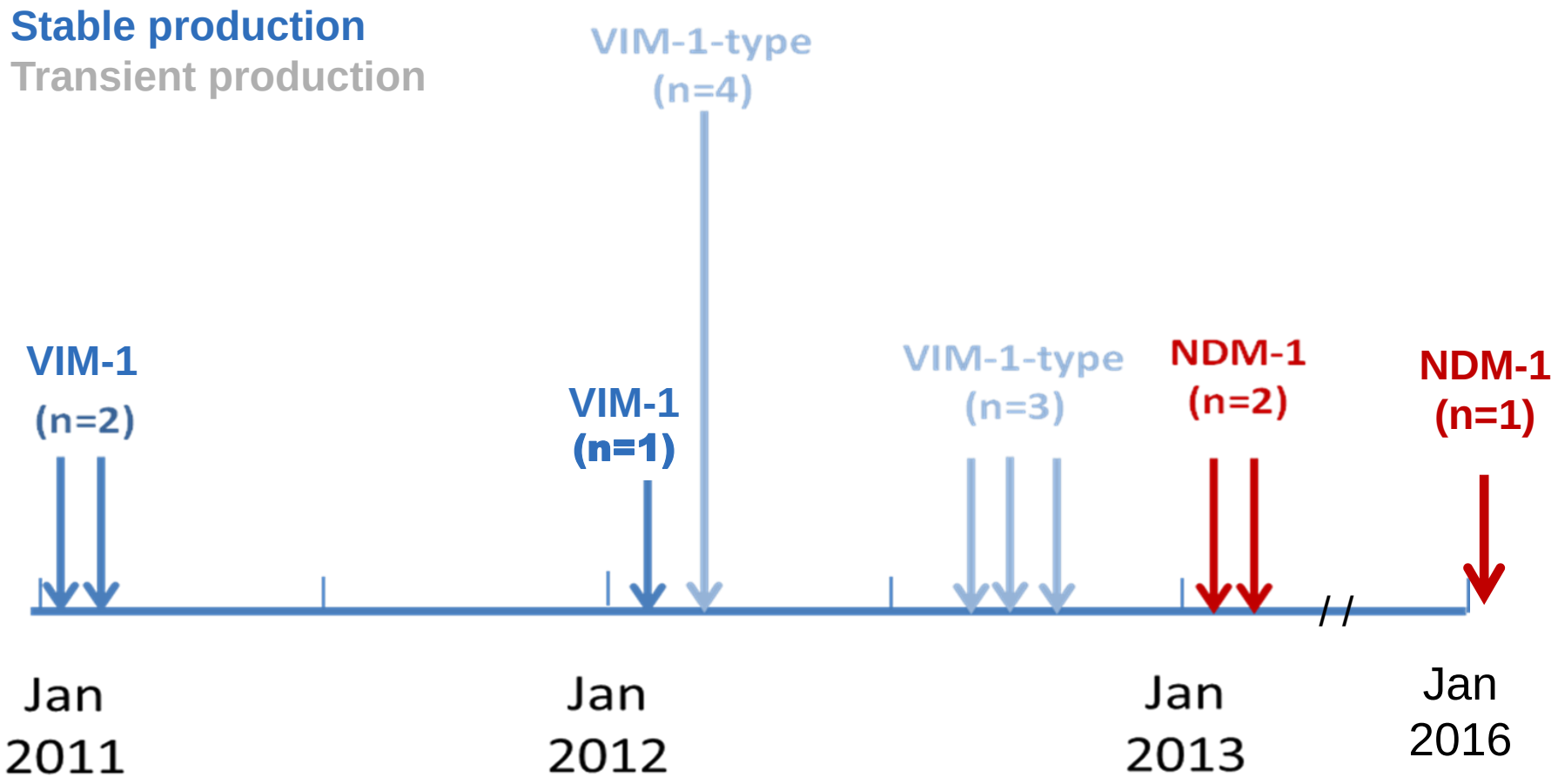
Kashikar et al. ICAAC 2015; Tulpule ASM General Meeting 2016

Timeline for MBLs in Indianapolis



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

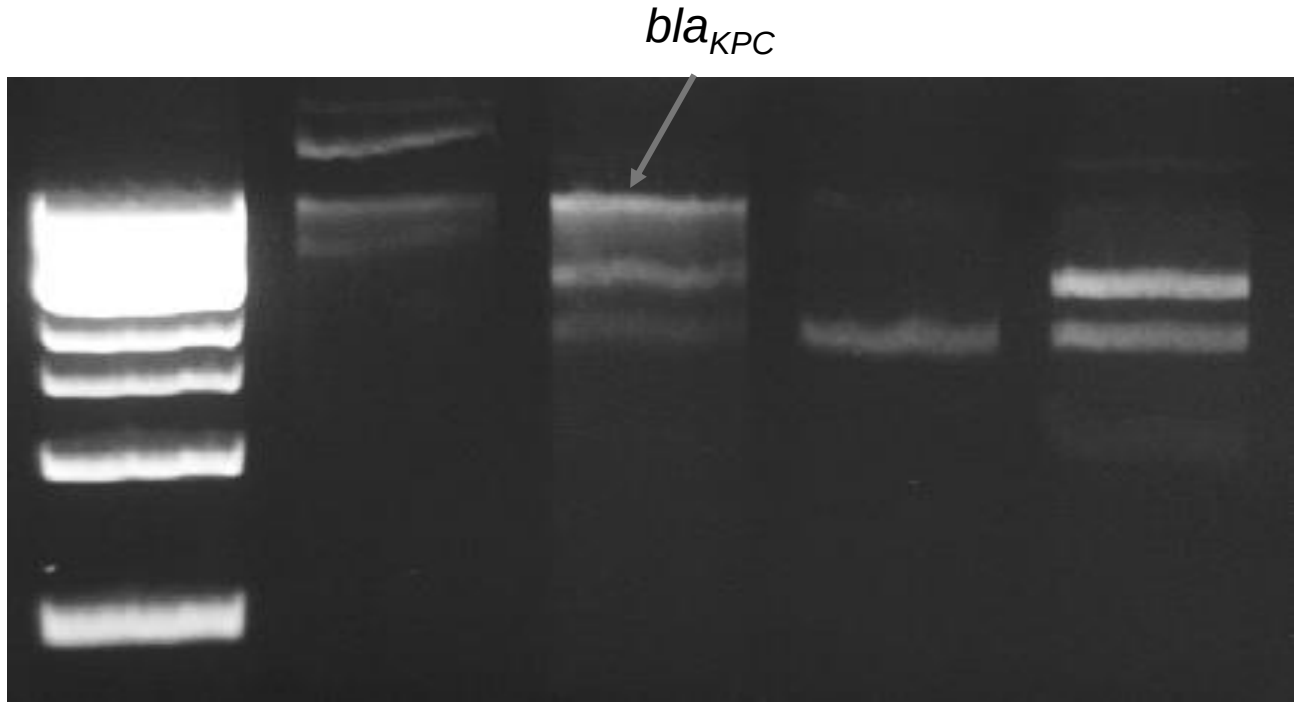
Timeline for MBLs in Indianapolis



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

Variable plasmid content from subcultures of KPC/VIM-producing isolates

PCR results



Markers	EC-1A	ECL-4A	EC-1B	ECL-4B	
	+	+	--	--	KPC
	--	+	+	+	VIM

Li et al. ASM Abstract # 1543 (2013)

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, ASM 2016

Changes in CRE incidence in Enterobacteriaceae also observed after strict infection control in New York City

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*

- **14 hospitals in New York City**
  - 2006 compared to 2009
  - KPC in *K. pneumoniae* decreased from 38% to 29%
  - Imipenem resistance:

	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)

Are there viable therapeutic options to treat infections caused by CRE?

Systemic antibacterial drugs for MDR gram-negative pathogens: FDA approvals, 2014 to present

Date	Generic Name	Brand Name	Activity Against Carbapenemases?	
			SBLs	MBLs
2014	Ceftolozane-tazobactam	Zerbaxa®	--	--
2015	Ceftazidime-avibactam	Avycaz®	Yes	--
2017	Delafloxacin	Baxdela®	--	--
2017	Meropenem-vaborbactam	Vabomere®	--	--
2018	Plazomicin	Zemdri®	Yes	Yes
2018	Eravacycline	Xerava®	Yes	Yes
2018	Omadacycline	Nuzyra®	Yes	Yes
2019	Imipenem-relebactam	Recarbrio®	Yes	--
2019	Cefiderocol	Fetroja®	Yes	(Yes)
2023	Sulbactam-durlobactam[#]	Xacduro®	Yes	--

[#] FDA approval for bacterial pneumonia caused by *Acinetobacter baumannii-calcoaceticus* complex

Theuretzbacher et al. *Nature Rev. Microbiol.* 2020. https://dx.doi.org/10.1038/s41579-020-0340-0

Investigational antibacterial drugs for MDR gram-negative pathogens

Generic Name	Activity Against Carbapenemases?	
	SBLs	MBLs
Aztreonam-avibactam	Yes	Yes
Cefepime-taniborbactam	Yes	Yes*
Cefiderocol-xeruborbactam	Yes	Yes*
Cefepime-zidebactam	Yes	Yes

*Occasional resistance to NDM-producing isolates

Le Terrier et al. *Lancet* 2023. https://doi.org/10.1016/ S1473-3099(23)00069-5
Theuretzbacher et al. *Nature Rev. Microbiol.* 2020. https://dx.doi.org/10.1038/s41579-020-0340-0

Summary

- Carbapenem antibiotics are potent agents whose effectiveness has been compromised by the emergence of carbapenemases
- In the United States, and in Indiana, the KPC-3 carbapenemase is most prevalent
- MBL-producing isolates were less frequent in Indiana and generally produced multiple β-lactamases
  - Many of these isolates lost the plasmid that encoded the MBL gene after multiple passages in the absence of drug, suggesting that these plasmids may be unstable
- Many of the newly approved systemic antibiotics demonstrated in vitro susceptibility and clinical efficacy against KPC-producing Enterobacterales
- Several investigational β-lactamase inhibitor combinations have promising in vitro activity against both SBL- and MBL- producing CRE isolates

New antimicrobial agents

RESISTANCE

Thank you!

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