The Roller Coaster of Antibacterial Drug Discovery and Development in an Era of Multi-Drug Resistance

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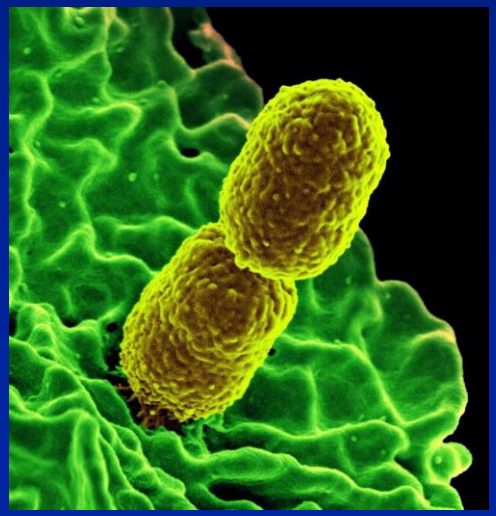
April 21, 2018

Santa Ana, CA



New Affiliation

Spero Therapeutics, Cambridge, MA

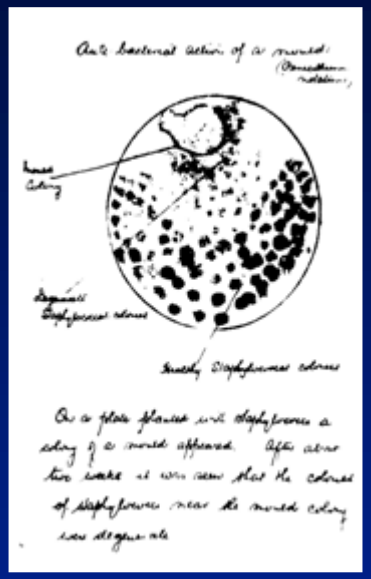
Agenda

Introduction

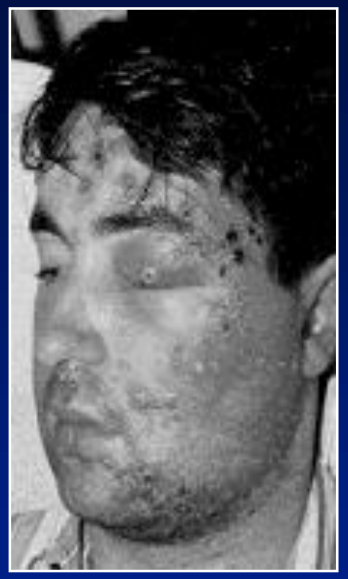
History	- Discovery of penicillin - Traditional Antibiotic R&D - The "Golden Era"
Challenges	- Lots of drugs *vs*. few targets - Resistance mechanisms - Difficult to discover new drugs - Genomics and HTS
New Discoveries	- Approvals in 21st Century
What's in the Pipeline?	- Development Candidates
Acceleration of Antibiotic R&D	- GAIN/Tiered Approaches

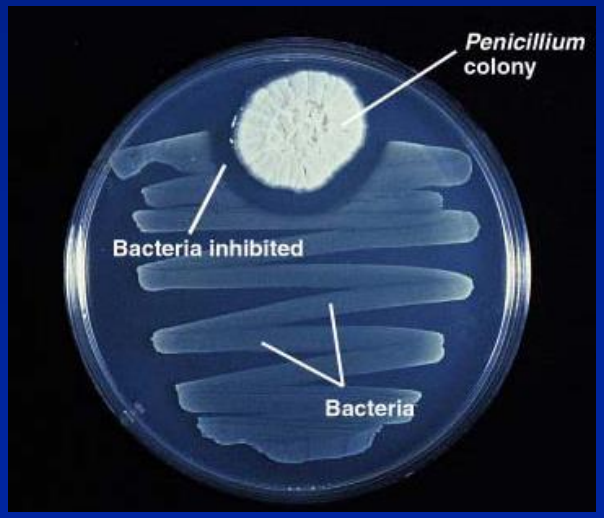
Impact of Fleming's Accidental Discovery of Penicillin

Fleming, 1928



Florey and Chain, 1940





Traditional Antibiotic R&D

- Nearly all antibiotics used today belong to classes discovered before 1970
  - Derivatives of naturally produced antibiotics from soil streptomycetes and fungi
- Only new classes to reach market since 1970
  - Oxazolidinones (discovered 1978, launched 2000)
  - Lipopeptides (discovered 1986, launched 2003
- Advances from improvements within antibiotic classes yielding analogs with:
  - increased potency
  - broader spectrum of activity
  - activity against resistant phenotypes

The First in Class Antibiotics: 1940-1969

Decade	Year	Agent	First in Class
1940's	1942	Benzyl penicillin	Penicillin
		Gramicidin S	Peptide
	1944	Streptomycin	Aminoglycoside
	1948	Chlortetracycline	Tetracycline
1950's	1952	Erythromycin	Macrolide
	1955	Vancomycin	Glycopeptide
	1958	Colistin	Polymyxin
1960's	1960	Methicillin	Penicillin active vs Staph β-lactamase
		Metronidazole	Nitroimidazole
	1961	Trimethoprim	Dihydrofolate reductase inhibitor
	1964	Cefalothin	Cephalosporin
	1967	Nalidixic acid	Quinolone

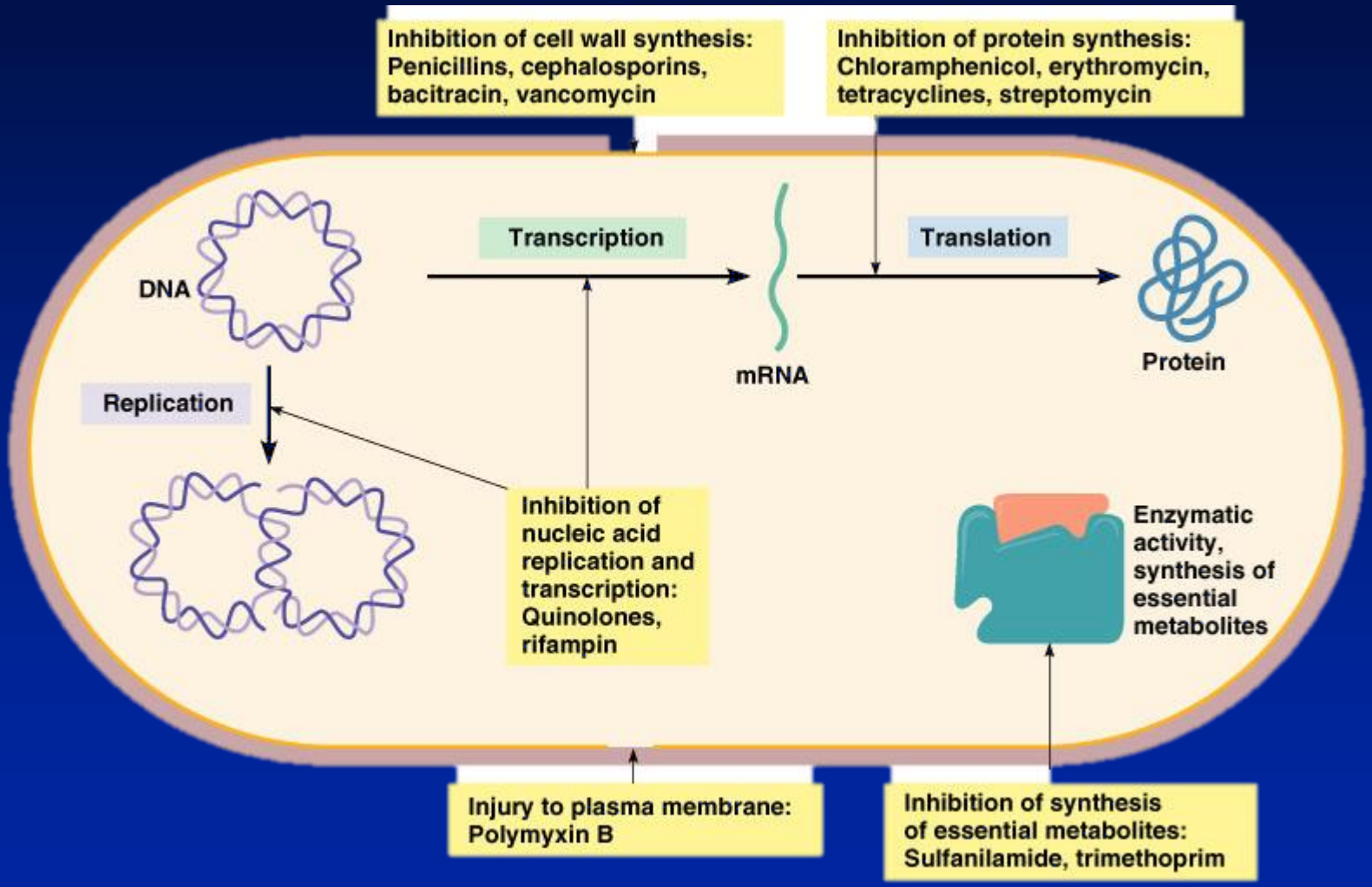
Many Antibiotics Developed in the Golden Era

Decade	Year	Agent	
1970's		Cephalexin, pivampicillin, amoxicillin, cefradine, minocycline, pristinamycin, fosfomycin, tobramycin, becampicillin, ticarcillin, amikacin, azlocillin, cefadroxil, cefamandole, cefoxitin, cefuroxime, mezlocillin, pivmecillinam, cefaclor, cefmetazole	
1980's		Cefotaxime, cefsulodin, piperacillin, amoxicillin/clavulanate, cefoperazone, cefotiam, latamoxef, netilmicin, apalcillin, ceftriaxone, ceftazidime, ceftizoxime, norfloxacin, cefonicid, cefotetan, temocillin, cefpiramide, oxfloxacin, ampicillin/sulbactam, cefixime, roxithromycin, sultamicillin	
	1985	Imipenem/cilastatin	Carbapenem
	1986	Mupirocin	Monoxycarbolic acid
	1987	Ciprofloxacin	2nd generation quinolone
		Rifaximin	Ansamycin
1990's		Arbekacin, clarithromycin, cefdinir, cefetamet, cefpirome, cefprozil, ceftibuten, fleroxacin, loracarbef, piperacillin/tazobactam, rufloxacin, brodimoprim, dirithromycin, levofloxacin, nadifloxacin, panipenem/betamipron, sparfloxacin, cefepime, quinupristin/dalfopristin	

Fewer Antibiotics Approved in the 21st Century

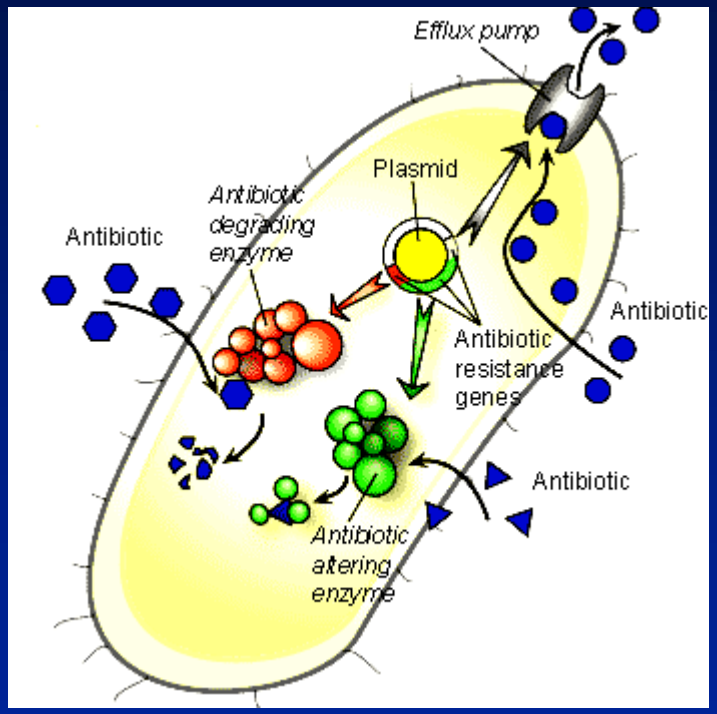
Decade	Year	Agent	First in Class
2000's	2000	Linezolid	Oxazolidinone
	2001	Telithromycin	Ketolide
	2003	Daptomycin	Lipoglycopeptide
	2005	Tigecycline	Glycylcycline
	2005	Doripenem	
	2009	Telavancin	
2010's	2010	Ceftaroline	Cephalosporin with activity against MRSA
	2011	Fidaxomycin	Macrocyclic
	2014	Dalbavancin, Oritavancin	
	2014	Tedizolid	
	2014	Ceftolozane-tazobactam	BL/BLI
	2015	Ceftazidime-avibactam	Avibactam (DABCO) - BLI
	2017	Meropenem-vaborbactam	Vaborbactam (Boronic) - BLI

Most Antibiotics Directed against a Few Well Known Targets

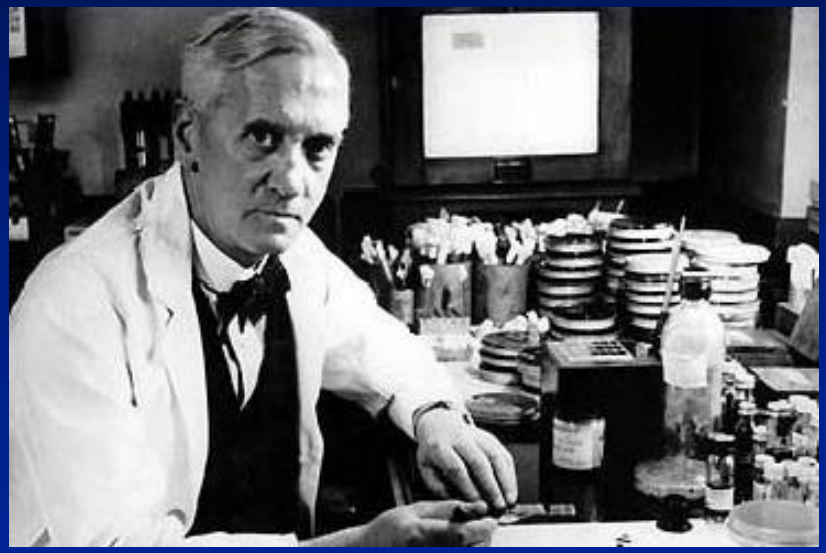


Common Pathways of Resistance

- Enzymatic degradation of the antibiotic
- Decreased uptake or accumulation of the drug
- Altered antimicrobial target



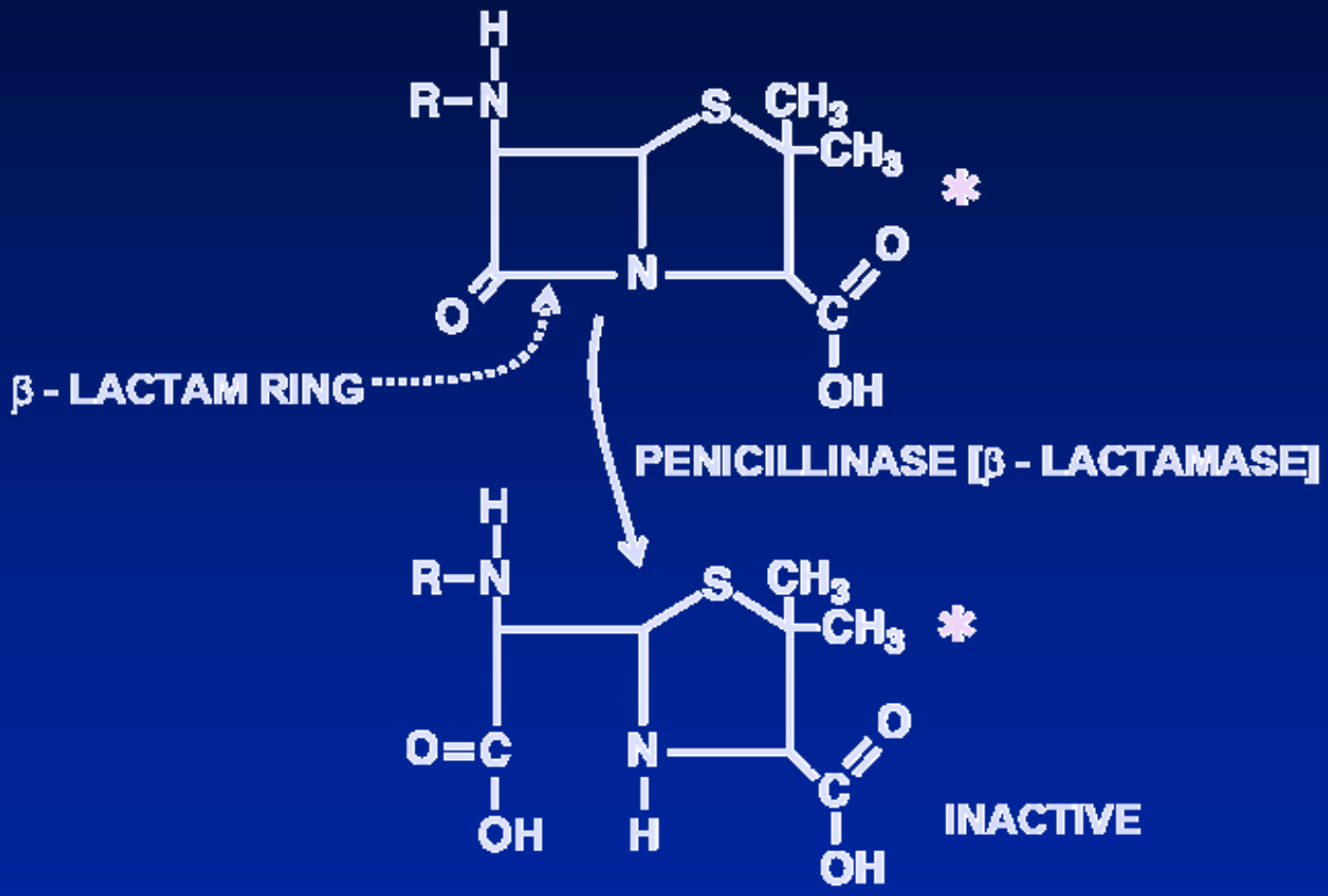
Emergence of Resistance



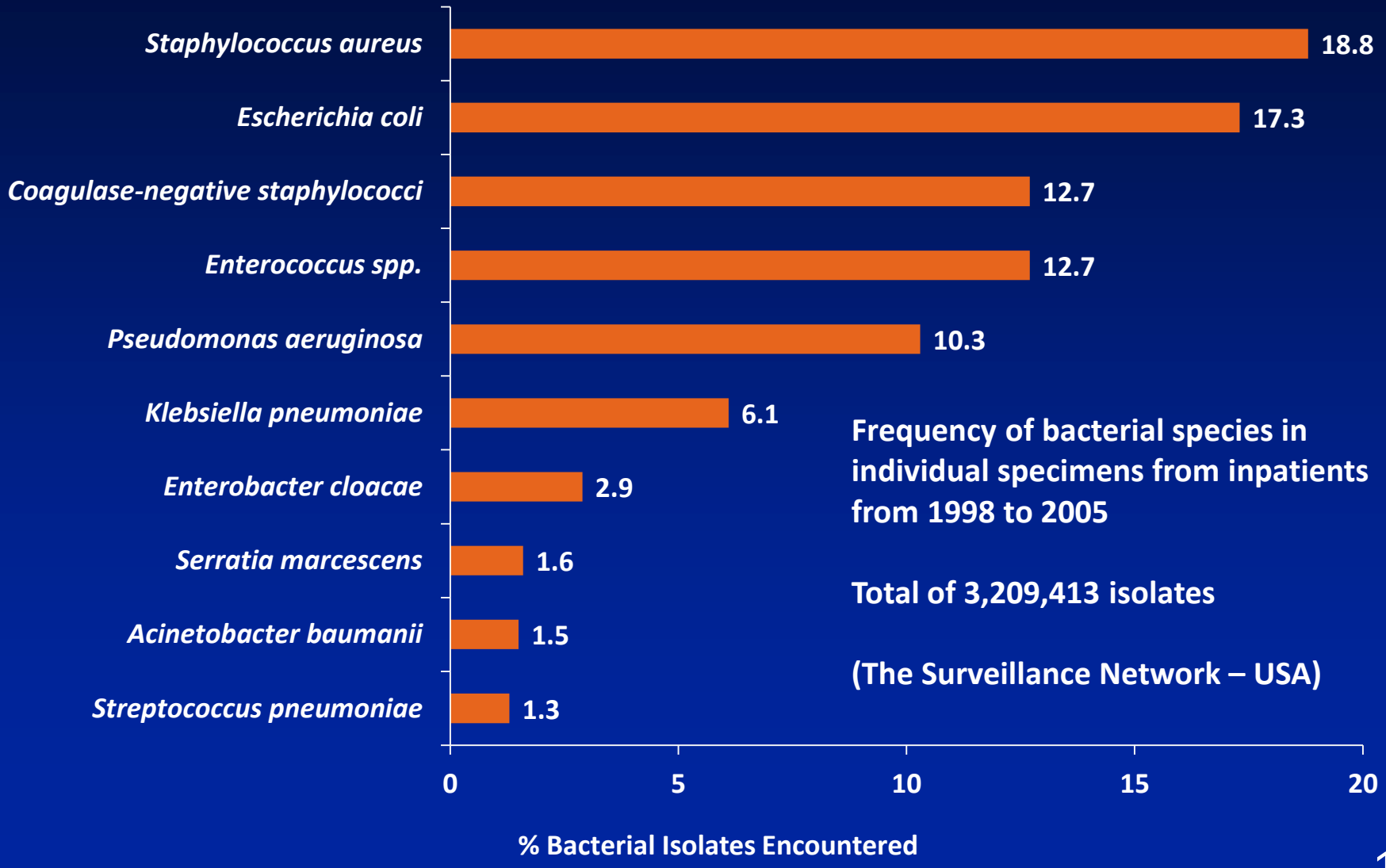
"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them and the same thing has happened in the body"

- Alexander Fleming, 1945

β-Lactamase Hydrolysis of Penicillin



Top Ten Problem Pathogens Encountered in the Hospital



Frequency of bacterial species in individual specimens from inpatients from 1998 to 2005

Total of 3,209,413 isolates

(The Surveillance Network – USA)

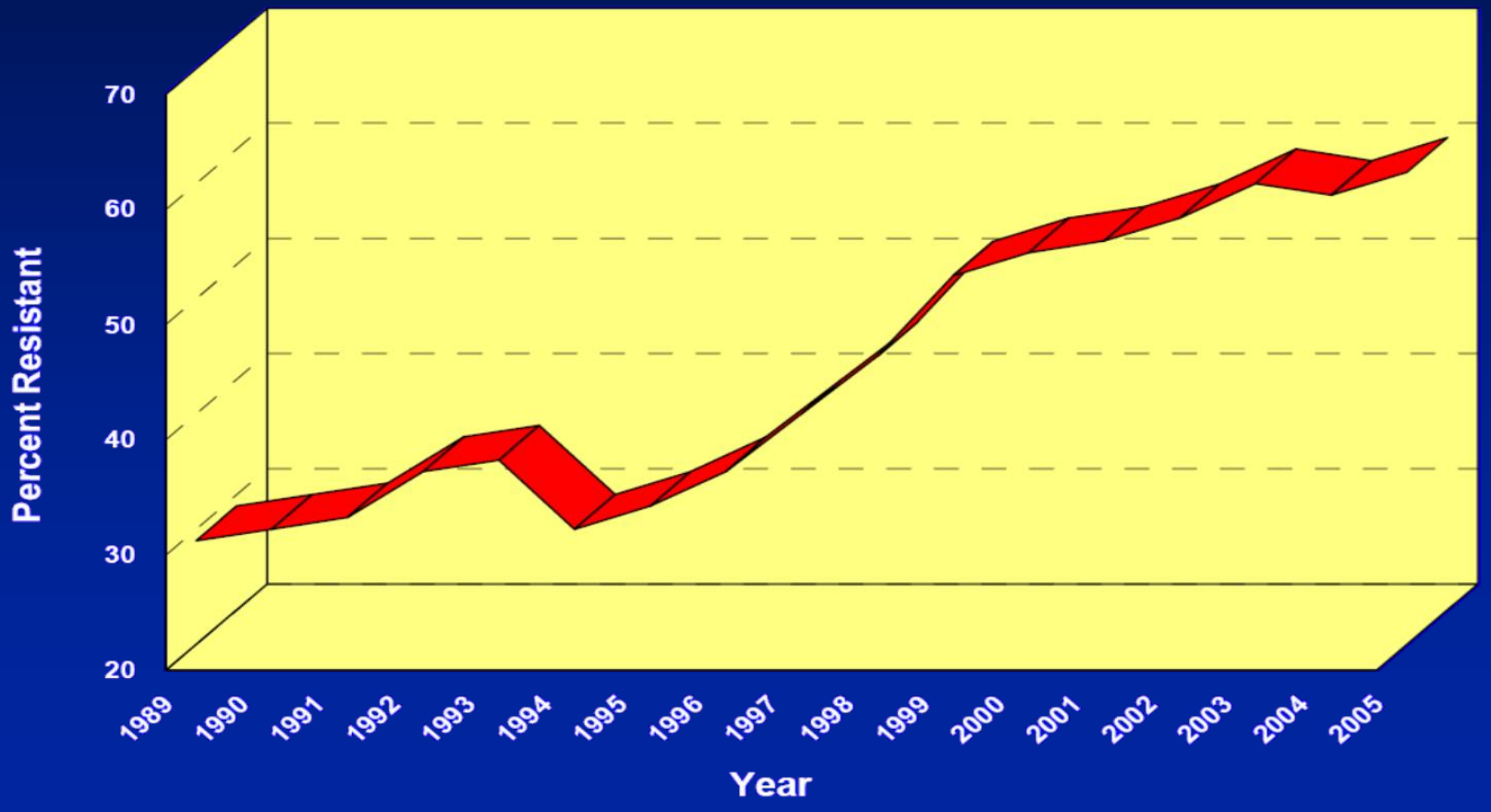
History of Methicillin-Resistant *Staphylococcus aureus*

- 1959 - Methicillin introduced
- 1960 - Methicillin-resistant *S. aureus* identified with *mec*A gene and altered PBP2a
- 1968 - First documented MRSA outbreak in U.S. at Boston City Hospital
- >1968 - Progressive increase in prevalence and reports of nosocomial outbreaks
- 1980-82 - Community-acquired outbreak in Detroit
- 1990-96 - "Community-acquired" strains in Australia, Canada
- 1998-99 - Community strain outbreaks in U.S
- 1996-2000 - VISA
- 2002 - VRSA

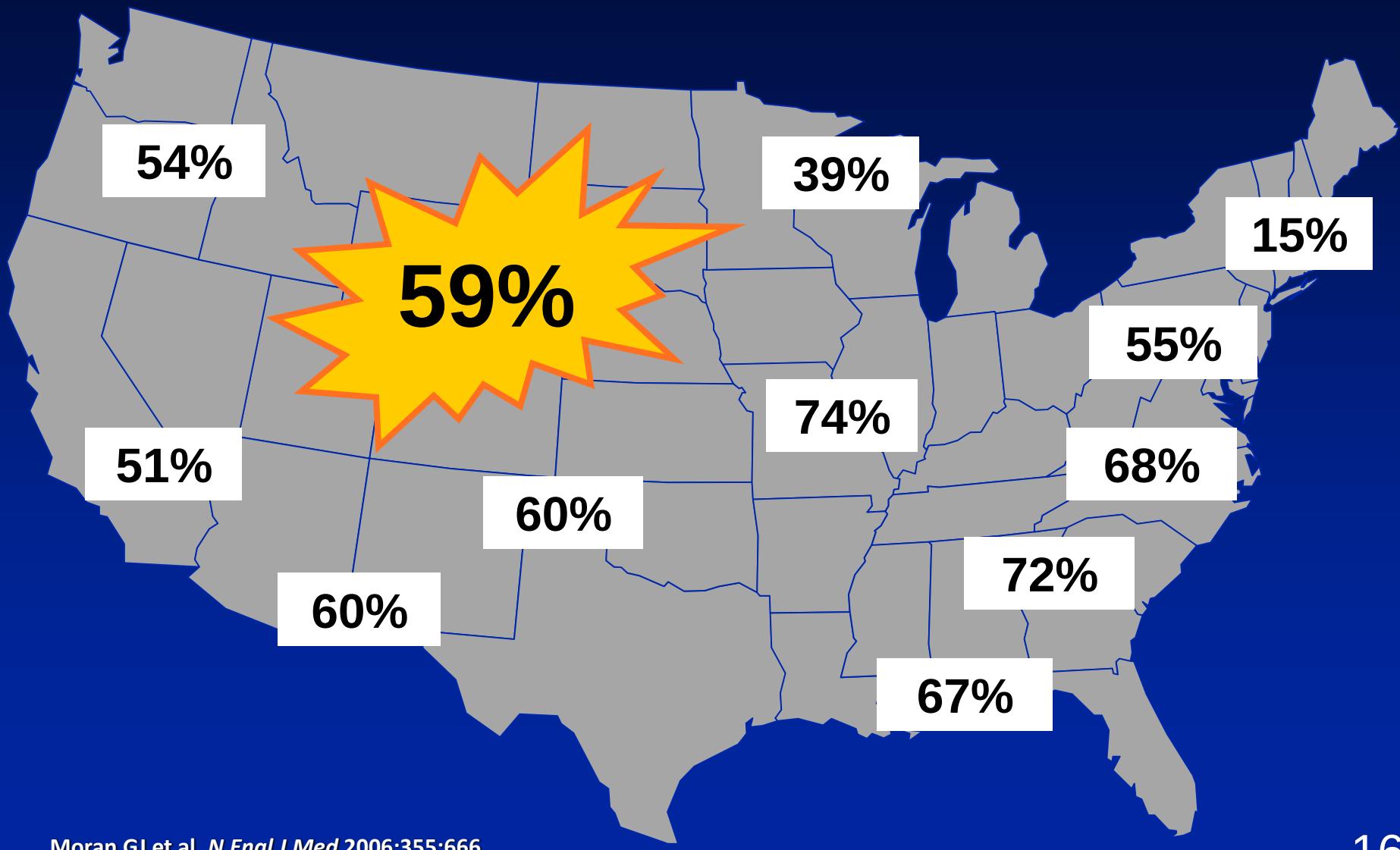
Methicillin-resistant *S. aureus* (MRSA)

- Lethal targets for β-lactam antibiotics are penicillin-binding proteins (PBPs)
  - –Transpeptidases that catalyze the formation of peptide cross-links between adjacent glycan strands during the final stages of peptidoglycan synthesis in bacteria
  - –Peptidoglycan envelopes the bacterial cell wall and is essential for growth, division and cell shape
- MRSA acquired a modified PBP encoded by *mec*A gene (PBP2a)
  - –Low affinity for most β-lactams permitting cell wall biosynthesis in presence of antibiotic

Proportion of *S. aureus* Nosocomial Infections Resistant to Oxacillin (Methicillin) Among ICU Patients



MRSA among 422 ED Patients with Skin Infections



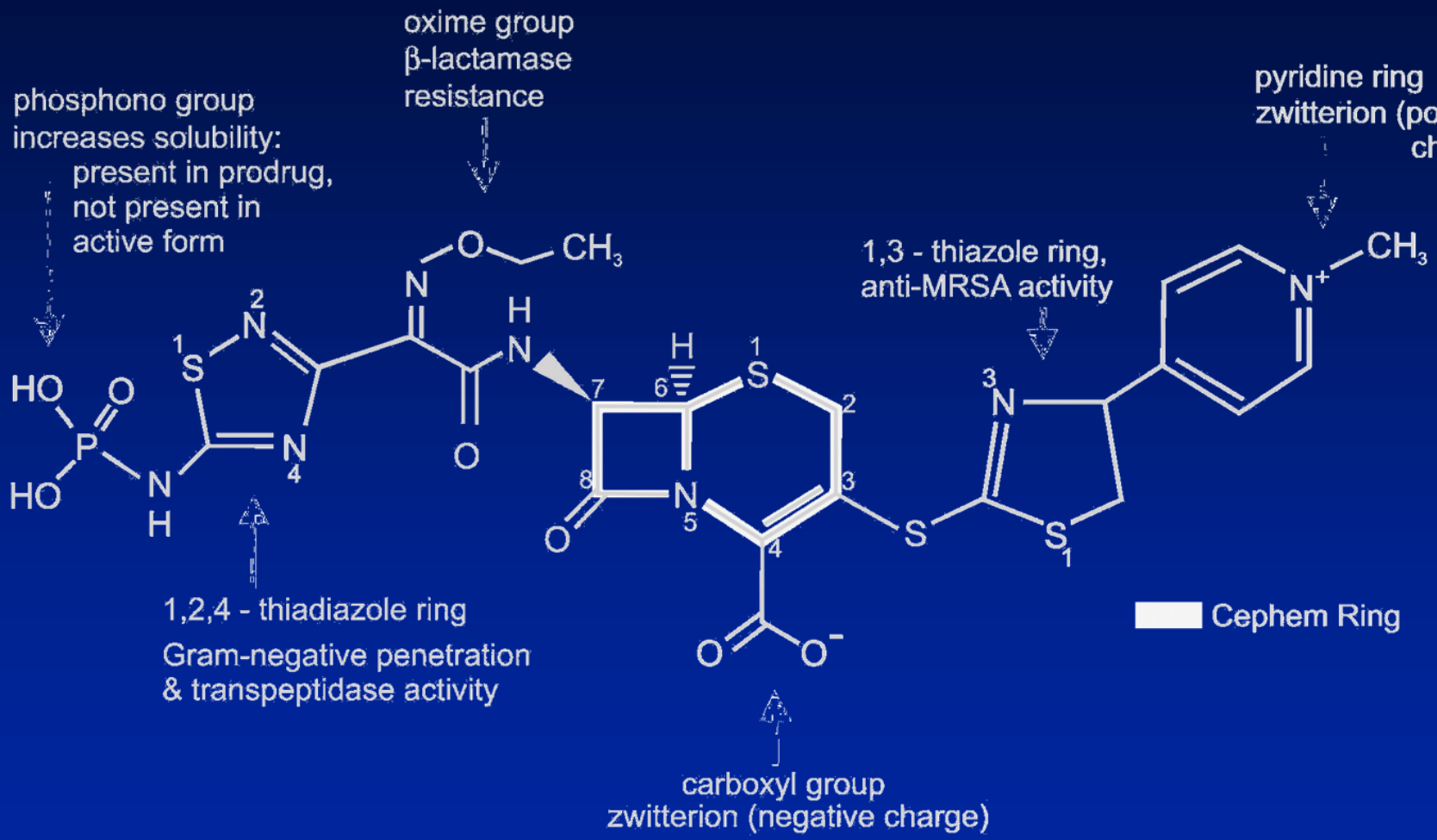
Moran GJ et al. *N Engl J Med* 2006;355:666.

The Response to the MRSA Challenge

Approved Agents with activity against MRSA

- Vancomycin
- Linezolid, Tedizolid
- Daptomycin
- Tigecycline
- Telavancincin, Dalbavancin, Oritavancin
- Ceftaroline (first anti-MRSA cephalosporin approved in US and EU)
- Delafloxacin (first fluoroquinolone with anti-MRSA activity)

Structure Activity Relationships for Ceftaroline



Affinity for Modified PBPs in PRSP and MRSA

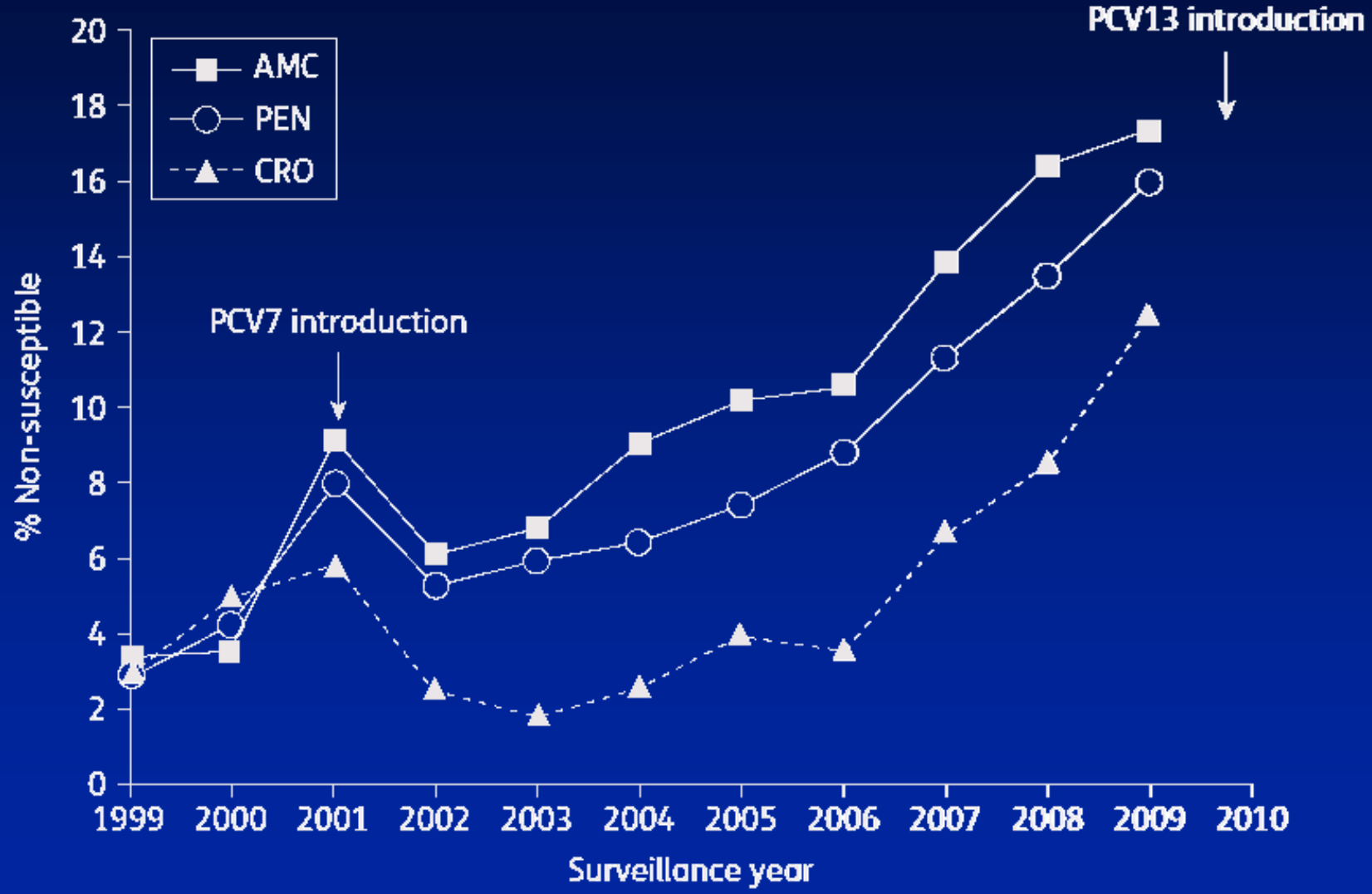
Correlation between affinity for modified PBPs and MICs

	PRSP *S. pneumoniae* 2039	
Antibiotic	MIC (µg/mL)	PBP2x IC_{50} (µg/mL)
Ceftaroline	0.12	0.17
Ceftriaxone	1 – 2	0.64
Penicillin	1 – 2	0.79

	MRSA Strain 67-0	
Antibiotic	MIC (µg/mL)	PBP2a IC_{50} (µg/mL)
Ceftaroline	0.5 – 1	0.16
Ceftriaxone	> 128	677
Oxacillin	128	408

Moisan H et al. *J Antimicrob Chemother* 2010 65(4):713-6.

β-Lactam Resistance in *S. pneumoniae*



Jones et al., 2011. JAC 66 Suppl 3:iii69-iii80

What About Gram-negative Pathogens?

- Quinolones – last antibiotic new class to treat Gram-negative bacilli first discovered over 40 years ago
- "For Gram-positives, we need better drugs. For Gram-negatives, we need ANY drugs" *John Bartlett, MD*

ESKAPE BACTERIA

*E**nterococcus faecium*** (VRE)

*S**taphylococcus aureus*** (MRSA)

*K**lebsiella pneumoniae***

*A**cinetobacter baumannii***

*P**seudomonas aeruginosa***

*E**nterobacter*** species

Gram-negative Unmet Need

Gram-Negative Resistance: Four Major Areas of Need

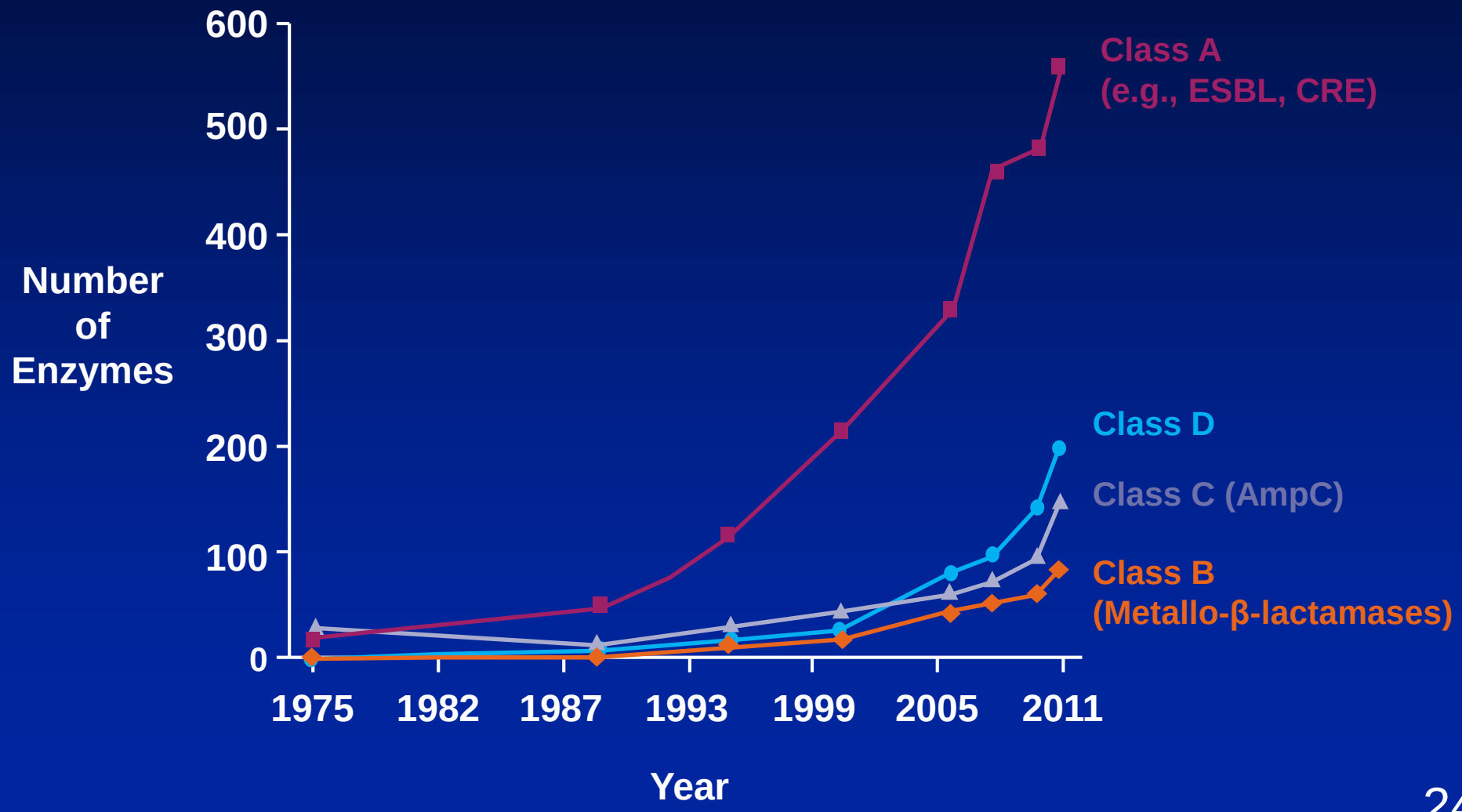
Resistant Gram-negative Phenotype	CDC Threat Level	Estimated Cases & Attributable Deaths in US per Year
ESBL-producing *Enterobacteriaceae*	Serious	26,000 cases 1,700 deaths
MDR *P. aeruginosa*	Serious	6,000 cases 400 deaths
Carbapenem-resistant *Enterobacteriaceae* (e.g., KPC)	Urgent	9,300 cases 610 deaths
Metallo-β-lactamase-producers	N/A	Very rare

CDC, Antibiotic Resistance Threats in the US, 2013

Cephalosporins and Gram-negative Coverage

- Second and third generation cephalosporins developed to extend coverage of Gram-negative pathogens including Pseudomonas
  - Extended spectrum β-lactamases (ESBLs) and AmpC (cephalosporinases) threaten empiric utility
  - Increased use of carbapenems (stable to ESBL and AmpC β-lactamase)
  - Emergence of KPC carbapenemase-producing organisms

Dramatic Increase in β-Lactamases



Shlaes et al., 2013

Outbreak of Carbapenem-resistant *Klebsiella pneumoniae*

RESEARCH ARTICLE

NOSOCOMIAL INFECTION

Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing

Evan S. Snitkin,[1] Adrian M. Zelazny,[2] Pamela J. Thomas,[1] Frida Stock,[2] NISC Comparative Sequencing Program,[3] David K. Henderson,[2] Tara N. Palmore,[2]* Julia A. Segre[1]*

The Gram-negative bacteria *Klebsiella pneumoniae* is a major cause of nosocomial infections, primarily among immunocompromised patients. The emergence of strains resistant to carbapenems has left few treatment options, making infection containment critical. In 2011, the U.S. National Institutes of Health Clinical Center experienced an outbreak of carbapenem-resistant *K. pneumoniae* that affected 18 patients, 11 of whom died. Whole-genome sequencing was performed on *K. pneumoniae* isolates to gain insight into why the outbreak progressed despite early implementation of infection control procedures. Integrated genomic and epidemiological analysis traced the outbreak to three independent transmissions from a single patient who was discharged 3 weeks before the next case became clinically apparent. Additional genomic comparisons provided evidence for unexpected transmission routes, with subsequent mining of epidemiological data pointing to possible explanations for these transmissions. Our analysis demonstrates that integration of genomic and epidemiological data can yield actionable insights and facilitate the control of nosocomial transmission.

Wednesday, August 22, 2012

Scary KPC outbreak at the NIH

Today's Washington Post contains an article that will send chills down the spine of every hospital epidemiologist and infection preventionist in the world. It describes an outbreak of carbapenem-resistant Klebsiella pneumoniae (KPC) at the hospital of the National Institutes of Health in Bethesda. Over a 6-month period last year, 17 patients became colonized or infected with KPC; of these 8 developed bloodstream infections. A total of 11 patients died; 6 of these deaths were attributed to the infection.

The outbreak was terminated using typical interventions (cohorting of patients and staff, active surveillance cultures, contact precautions, and enhanced cleaning protocols). Further details can be found in a report in Science Translational Medicine (abstract here, full text requires subscription). This report outlines how the outbreak was able to be tracked using whole genome sequencing, which allowed the epidemiologists to determine that the entire outbreak could be traced to a single patient. Traditional molecular typing with PFGE would not have provided enough discriminatory power to do this.

KPC Kills 7th Person At NIH

09/15/12 04:48 PM ET AP

BETHESDA, Md. -- A deadly germ untreatable by most antibiotics has killed a seventh person at the National Institutes of Health Clinical Center in Maryland.

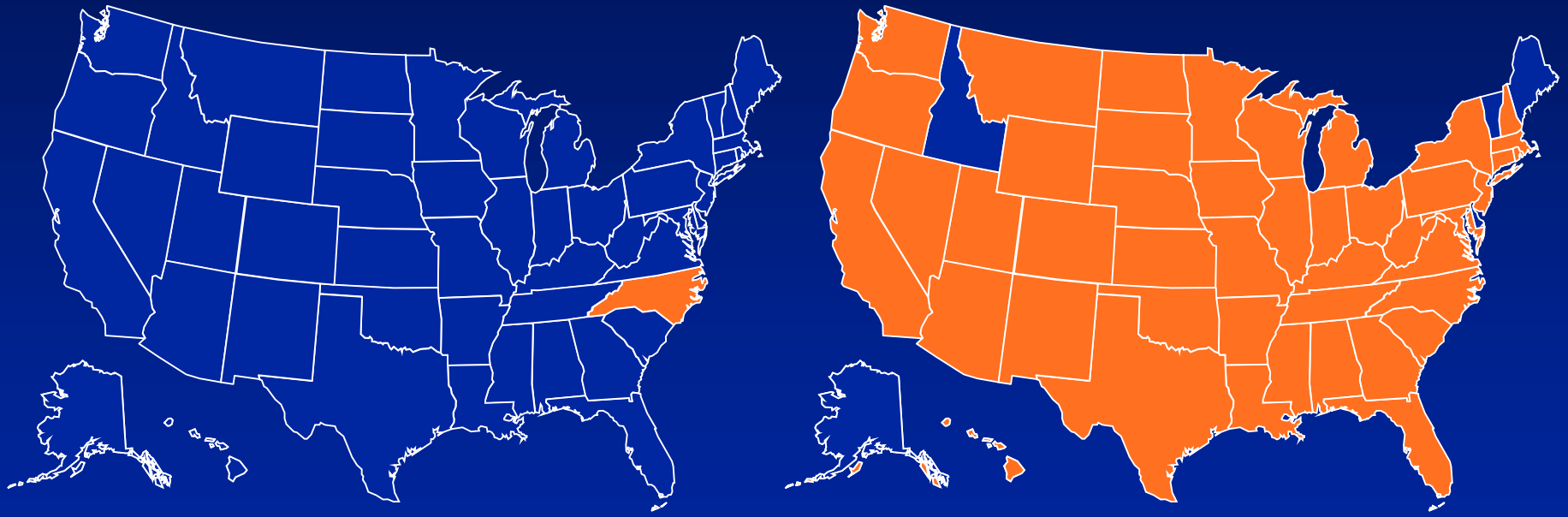
He was the 19th patient at the hospital to contract an antibiotic-resistant strain of KPC, or Klebsiella pneumoniae. The outbreak stemmed from a single patient carrying the superbug who arrived at the hospital last summer.

The paper reported the Minnesota boy's case marked the first new infection of this superbug at NIH since January.

Spread of CRE Across US - US Hospital Reports to CDC

2001

2014



CRE cases reported to CDC

Centers for Disease Control and Prevention, 2013, 2014

Combination of cephalosporin with a β-lactamase inhibitor to protect the activity of the antibiotic

- A well proven and successful strategy with the penicillins
  - Amoxicillin-clavulanate
  - Ticarcillin-clavulanate
  - Piperacillin-tazobactam
  - Ampicillin-sulbactam

- Early β-lactamase inhibitors lack inhibitory activity against contemporary β-lactamases (KPC, AmpC) and metallo-β-lactamases such as NDM-1

β-Lactam-β-Lactamase Inhibitors

BL/BLI Combination	Company	Development
Ceftazidime-avibactam	Allergan/Pfizer	Approved
Ceftolozane-tazobactam	Merck	Approved
Meropenem-vaborbactam	Melinta	Approved
Imipenem-relebactam	Merck	Phase 3

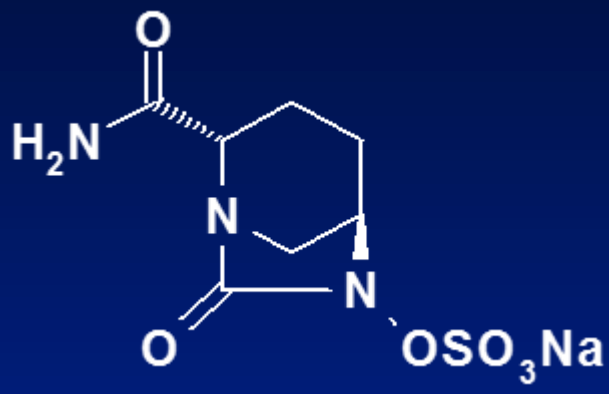
Avibactam: A new inhibitor for Class A and C β-lactamases

Formerly known as AVE1330A or NXL104

Physicochemistry:

- Molecular weight: 287.23
- Chemical formula: $C_7H_{10}N_3O_6SNa$
- Sodium salt
- Soluble compound
- Stability in solution at room temperature

Parenteral administration



Avibactam (active enantiomer) 1,6-diazabicyclo[3.2.1]octane-2-carboxamide, 7-oxo-6-(sulfooxy), monosodium salt, (1R,2S,5R)

Spectrum of Activity of Avibactam

β-Lactamase		Clavulanate	Tazobactam	Avibactam
Class A	TEM, SHV and ESBLs	√	√	√
	CTX-M and ESBLs	√	√	√
	PER, VEB, GES	√	√	√
	KPC	X	X	√
Class B	IMP, VIM, NDM	X	X	X
Class C	Chromosomal *Enterobacteriaceae* AmpC	X	X	√
	Chromosomal *Pseudomonas* AmpC	X	X	√
	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	X	X	√
Class D	Penicillinase-type OXA-1, -31, -10, -13	Variable OXA-1, -10	Variable	Variable OXA-1, 31
	Carbapenemase-type OXA-23, -40, -48,-58	Variable	Variable OXA-23, -48	Variable OXA-48

Expanded Spectrum of Activity Against Contemporary US CAZ-NS Isolates

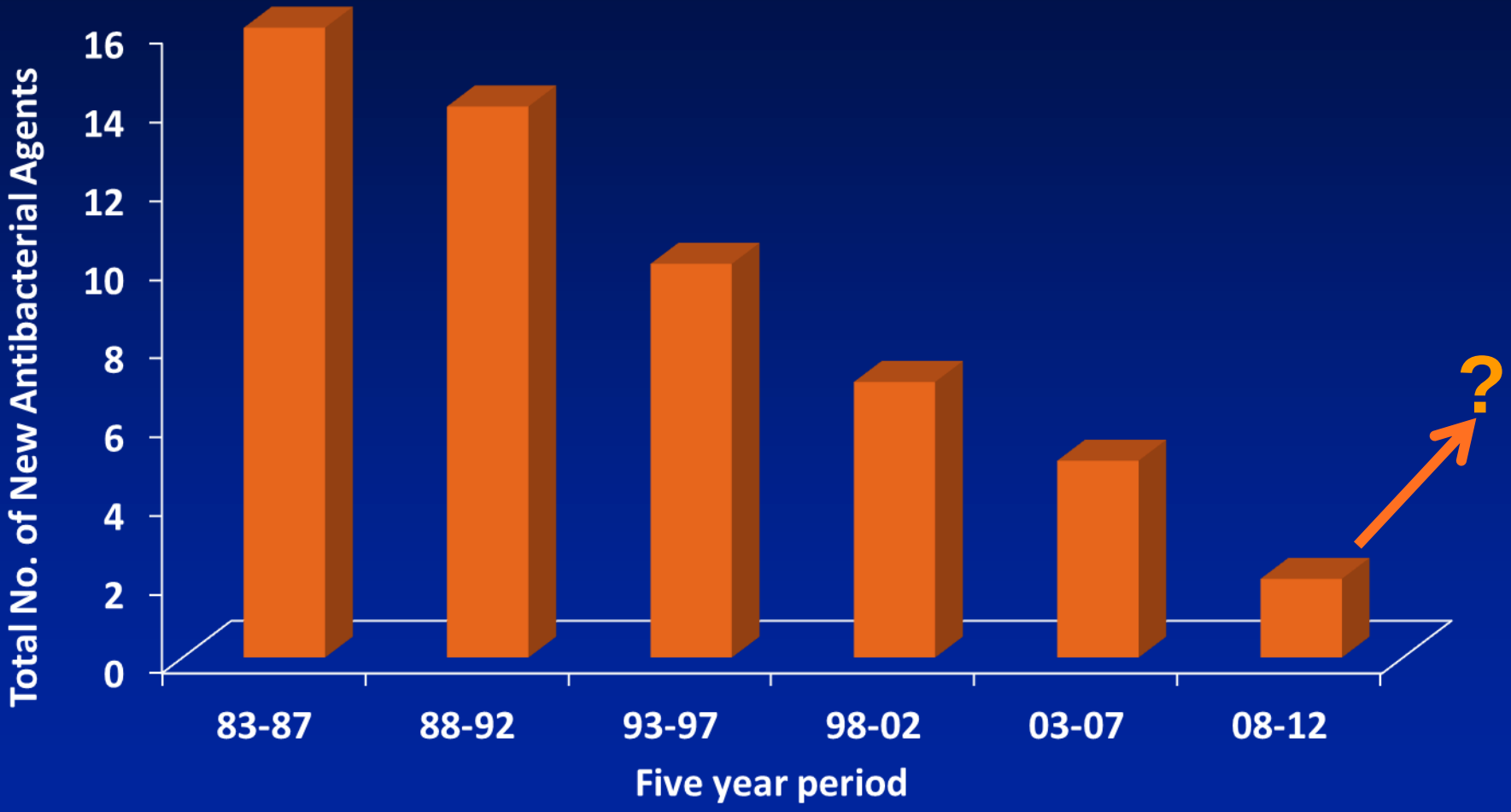
Organism	Phenotype	N	MIC_{90} (mg/L)	
			CAZ-AVI	CAZ
E. coli	All	2,767	0.12	32
	ESBL	328	0.25	>32
K. pneumoniae	All	1,847	0.5	32
	ESBL	296	1	>32
	Meropenem-NS	115	2	>32
E. cloacae	All	951	0.5	>32
	CAZ-NS	200	1	>32
P. aeruginosa	All	1,967	4	32
	CAZ-NS	330	16	>32

*2012 US Surveillance Isolates (Castanheira et al, 2014)

What Else is in the Gram-negative Pipeline?

Agent	Sponsor	Class	Target Pathogens
Eravacycline	Tetraphase	Fluorocyclic tetracycline	MDR Enterobacteriaceae, Acinetobacter
Plazomycin	Achaogen	Neoglycoside derived from sisomycin	MDR Enterobacteriaceae
Cefiderocol	Shionogi	Cephalosporin	MDR Gram-negative

New Antibacterial Drugs Approved in the US per 5 year period (1983 – 2012)



Infectious Diseases Society of America (CID 2011: 52:S397-S428)

Infectious Diseases Society of America

What Factors Have Led to the Decline of Antibiotic Development?

Genomics Based Antibiotic Discovery in the 1990's

- Genomes of multiple pathogens sequenced to identify essential genes that lacked mammalian counterparts
- High throughput screens of existing compound libraries to identify "druggable" molecules that bound to or inhibited the target (enzyme)
- Compound libraries yielded 5-fold fewer hits than for other therapeutic areas
  - Few hits translated into lead candidates
- GSK Experience
  - 300 targets and 67 HTS screens (260,000 – 530,000 compounds)
  - Only 16 screens gave "hits" and 5 lead compounds
- No antibiotic developed by this approach made it to market

Payne et al., 2007 Nat Rev Drug Discov 6 : 29-40

The Challenges of Genomics Based Discovery

- Lack of chemical diversity among compound libraries
  - Biased towards molecules meeting Lipinski's rule of five (chemical algorithm)
- Binding to or inhibiting cell free targets in a screen did not always translate into antibacterial activity (MICs)
  - Efflux and penetration barriers
- Compounds that inhibited single targets very prone to mutational resistance

Antibacterial Drug Development: Other Recent Challenges

- Many bacterial infections becoming increasingly difficult to treat with existing agents
- Low returns on investment
- Restricted use on formularies/antimicrobial stewardship
- AST Device development
- Unpredictable and challenging regulatory pathways resulted in many companies exiting the field

What's Being Done About it?

- Food and Drug Administration (FDA) Safety and Innovation Act
  - Legislation reauthorizing the Prescription Drug User Fee Agreements (PDUFA)
  - Incentives to spur antibacterial and antifungal R&D
  - Provisions modeled after the Generating Antibiotic Incentives Now (GAIN) Act
  - Recognition of the serious problems posed by antibiotic resistance and the dry antibiotic pipeline

GAIN Act

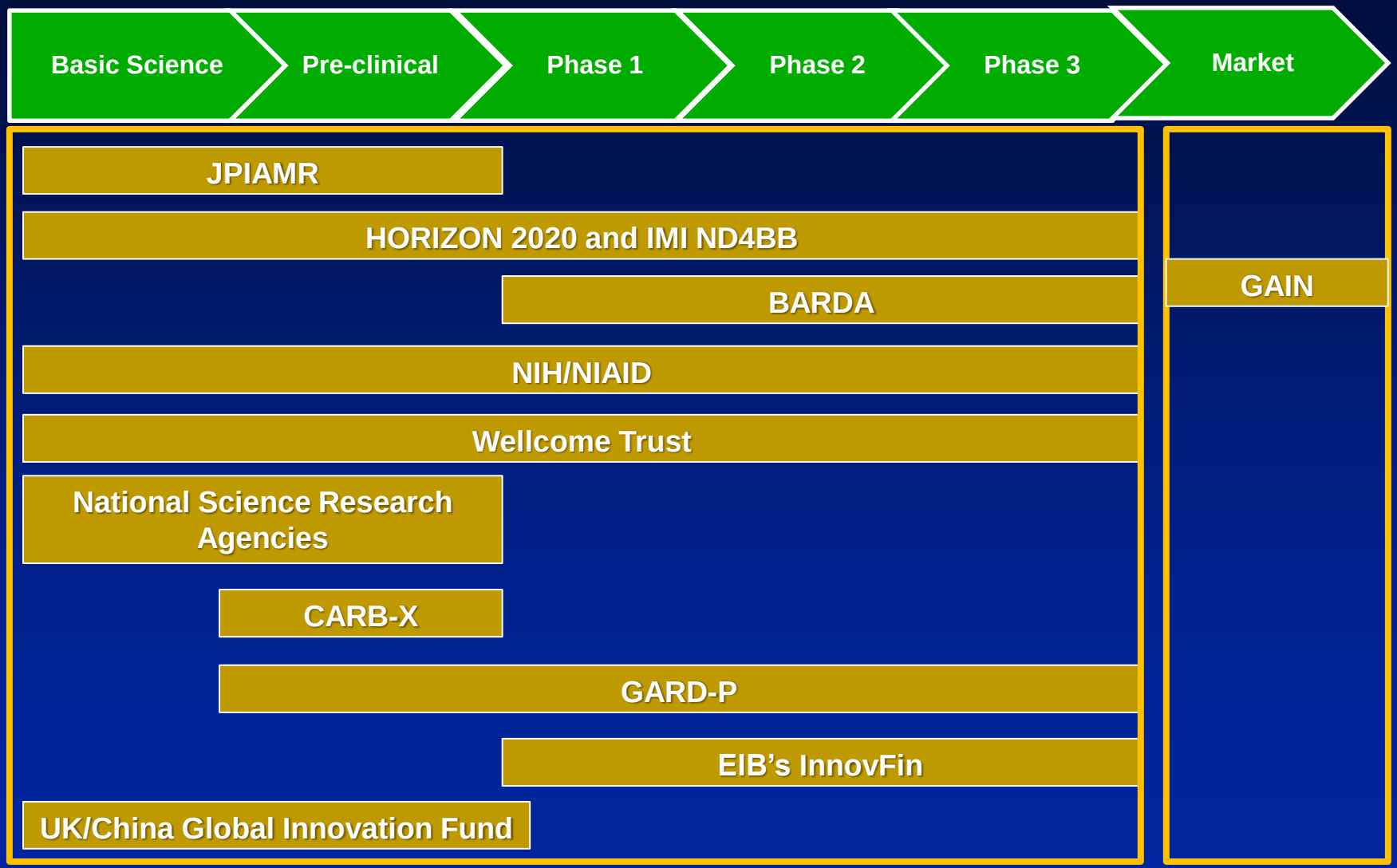
- Title VII (Sections 801-806) of FDASIA provides incentives to develop new treatments for life-threatening infections caused by drug resistant pathogens

- Qualifying pathogens are defined by GAIN to include:
  - Multidrug-resistant Gram-negative bacteria
    - *Pseudomonas aeruginosa*
    - *Acinetobacter*
    - *Klebsiella*
    - *Escherichia coli*
  - Resistant Gram-positive pathogens
    - Methicillin-resistant *S. aureus*
    - Vancomycin-resistant *S. aureus*
    - Vancomycin-resistant Enterococcus
    - *Clostridium difficile*

Qualified Infections Disease Products (QIDP) Benefits

- Advancement of critically needed antibiotics
  - Eligibility for fast track status
  - Priority review
- If approved, a five year extension of Hatch Waxman exclusivity

”Push and Pull” Incentive to Spur Anti-bacterial Drug Development



Summary

- Antibiotics have been miracle drugs and have become victims of their own success
- Bacterial pathogens will continue to adapt and develop new mechanisms to "resist" antibiotics
- Pharma has responded to the MRSA challenge
- Gram-negative pathogens a present and future challenge
  - Several pipelines now include anti gram-negative agents
- Economic/investment challenges remain
- Wider acknowledgement of the challenges spurring initiatives here and in Europe to expedite antibiotic development