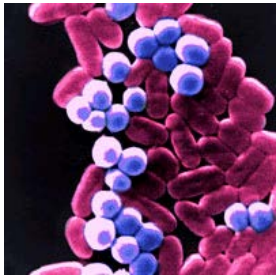
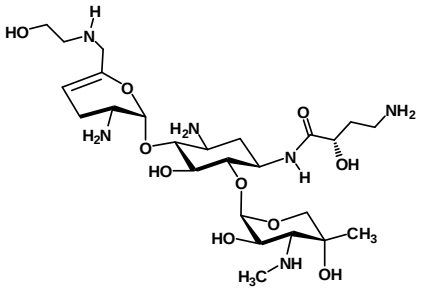
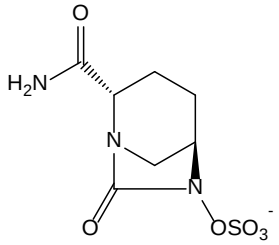


Antibacterial Drugs in the Pipeline



Karen Bush

Indiana University Bloomington



CLSI Education Workshop

Arlington, Virginia

June 13, 2015

INDIANA UNIVERSITY

Conflicts of Interest (2014–2015)

Retiree Compensation:

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

Consultant or Scientific Advisory Board:

Achaogen, Allecra, Cubist, Fedora, Medivir, Merck, The Medicines Company, Rempex, Roche, Vertex, WarpDrive

Research Support:

AstraZeneca, Forest, Tetraphase

Outline of Presentation

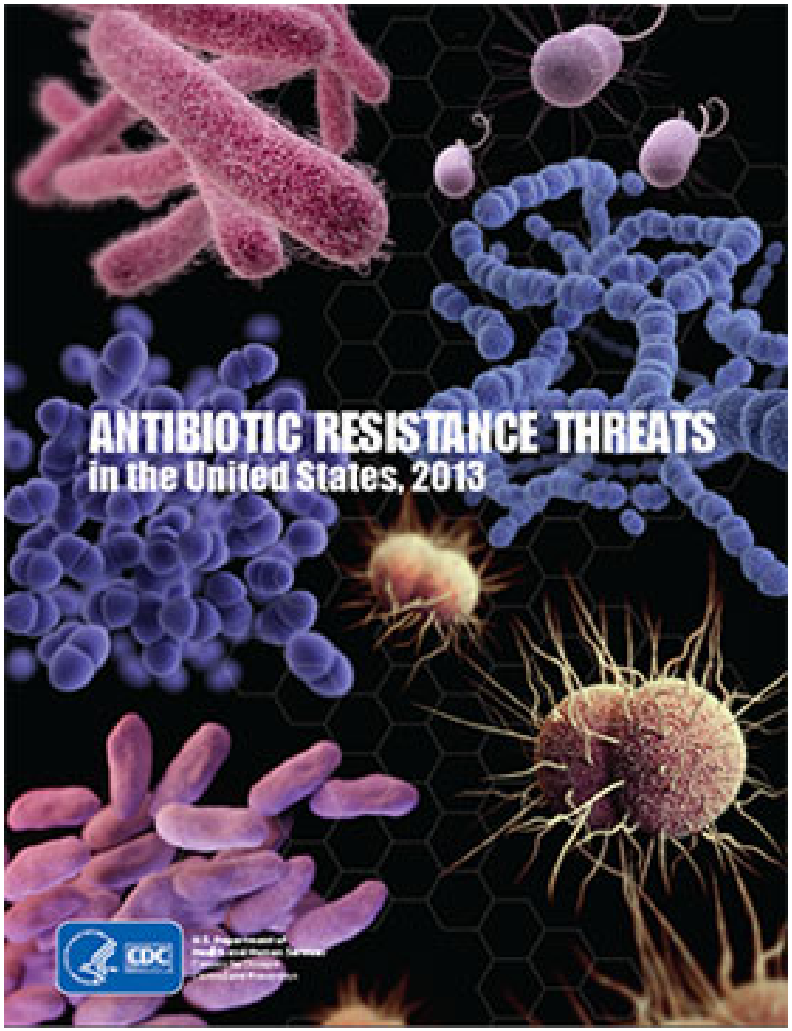
- Medical need (historical)
- Current pipeline of antibiotics for systemic use in hospital infections
  - Development status
  - Profiles

Alarms Sounded by IDSA

- Aimed at the general public and legislators
- Resistance continues to increase
- Beginning in 2002 campaigns to address
  - Need for new agents
  - Need for new investment in antibacterial drug development
- Campaign in 2004
  - "Bad Bugs, No Drugs"

Boucher et al. *CID.* 2013;56:1685

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



CDC, Threat Report, September 16, 2013

CDC Evaluation of Medical Needs September 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*

CDC, Threat Report, September 16, 2013

CDC Medical Needs September 2013 Combined With "ESKAPE" Pathogens

- **Urgent Threats**
  - *Clostridium difficile*
  - **CRE**
  - **Drug-resistant *Neisseria gonorrhoeae***
- **Serious Threats**
  - **Multidrug-resistant *Acinetobacter***
  - **Drug-resistant *Campylobacter***
  - **ESBLs**
  - **VRE**
  - **Multidrug-resistant *Pseudomonas aeruginosa***
  - **Drug-resistant nontyphoidal *Salmonella***
  - **Drug-resistant *Salmonella typhi***
  - **Drug-resistant *Shigella***
  - **MRSA**
  - Drug-resistant *Streptococcus pneumoniae*

CDC, Threat Report, September 16, 2013

IDSA Concerned About the Decrease in Pharmaceutical Activity to Create a Pipeline to Treat Gram-Negative Infections

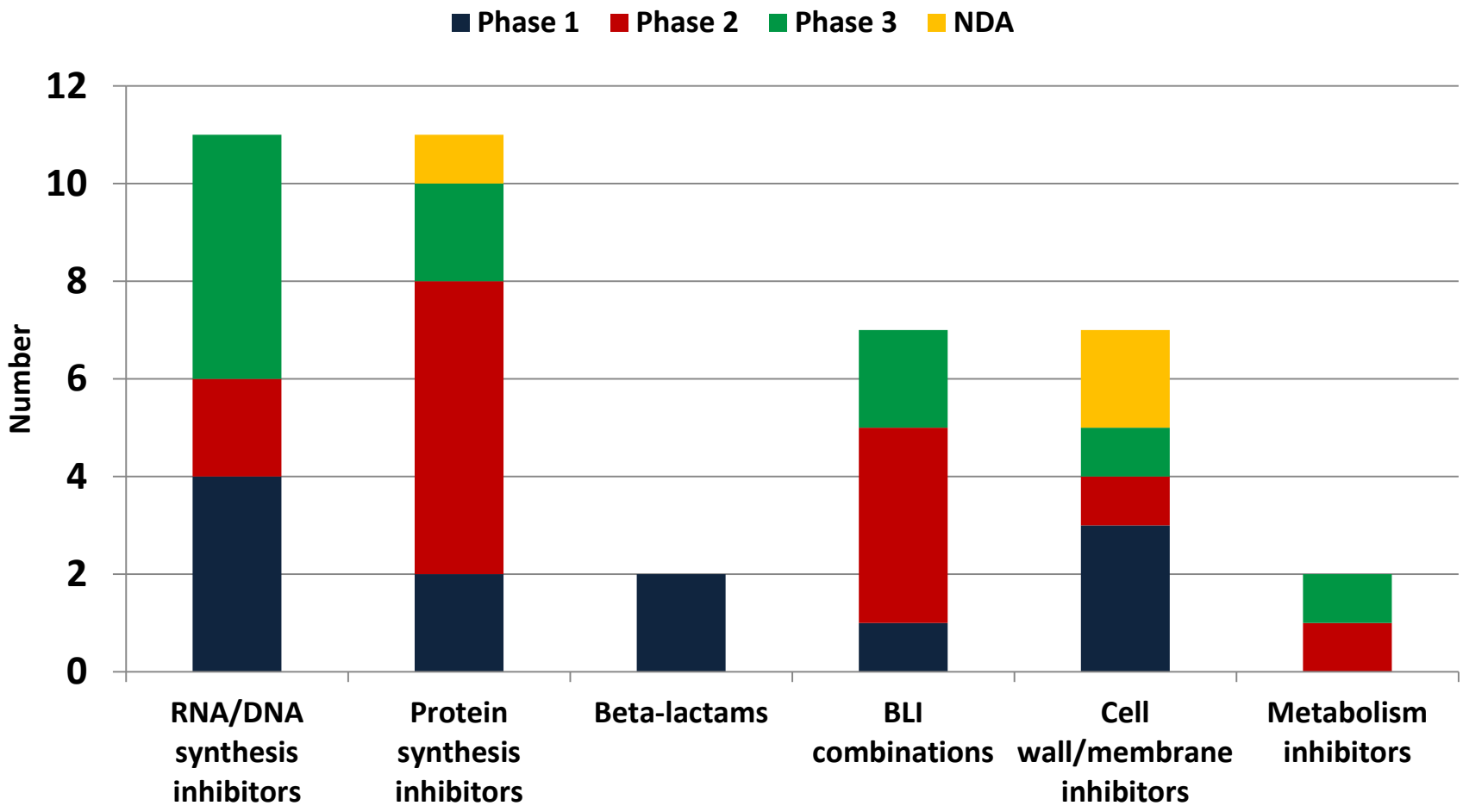
In 2010: “10 by 20” campaign

Development and regulatory approval of 10 novel, efficacious, and safe systemically administered antibiotics by 2020

The Pipeline as Viewed by Pucci, Page, and Bush (2014)

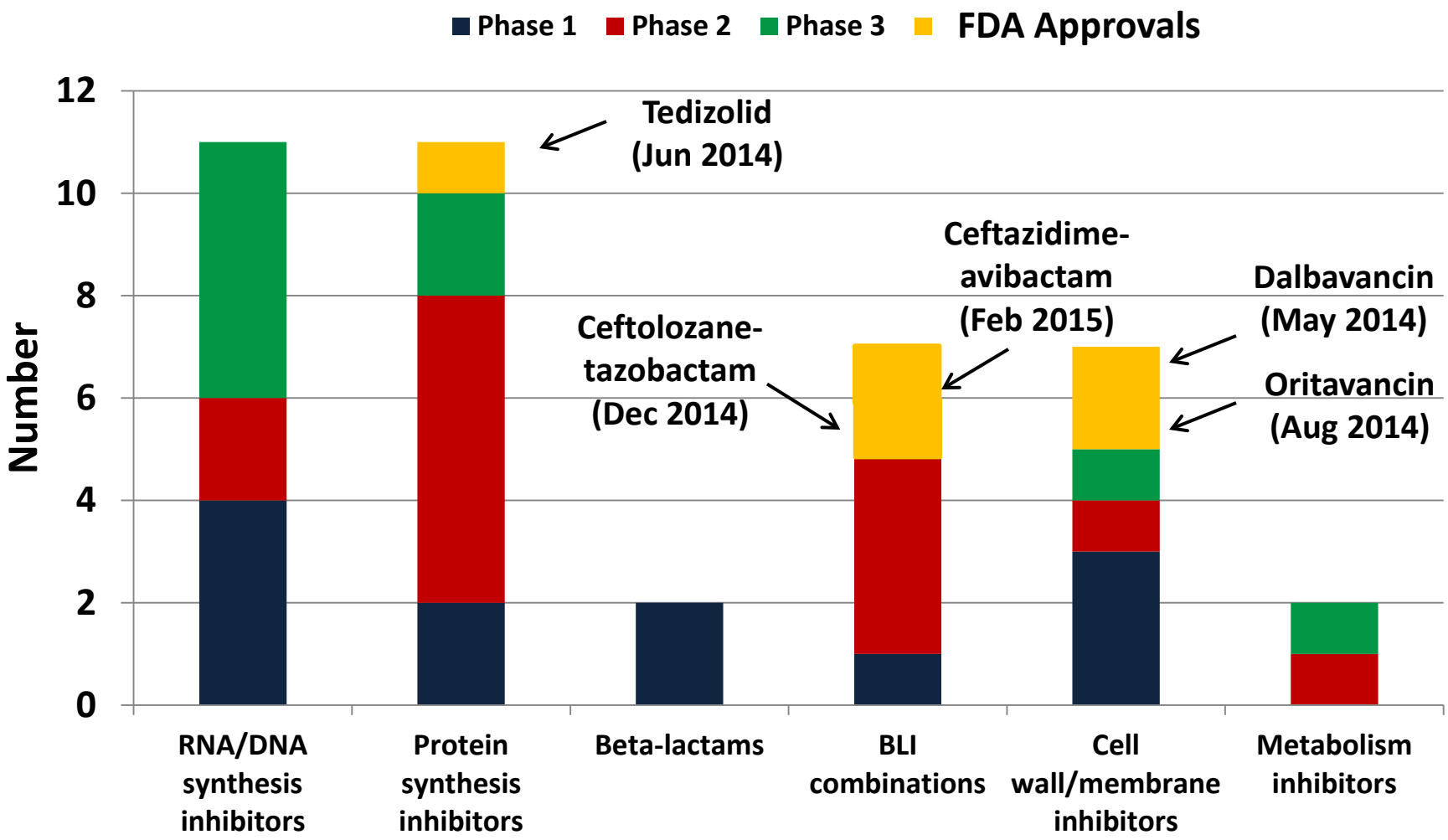
Pucci et al. *Microbe.* Apr 2014; Page and Bush, *Curr Opin Pharmacol.* 2014;18:91

Investigational Antibacterial Agents in Clinical Development in **March 2014**



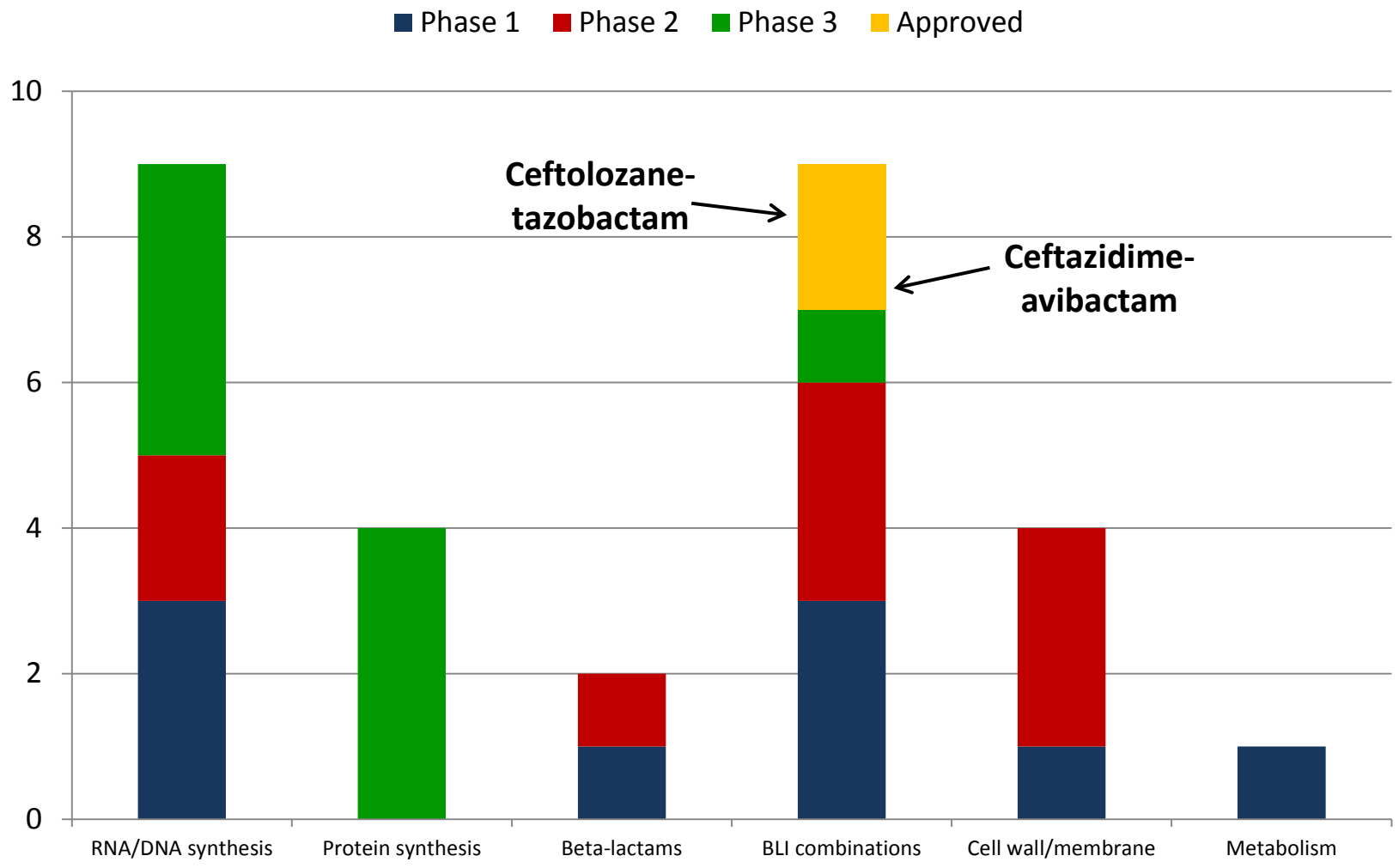
Pucci et al. *Microbe.* Apr 2014

Investigational and Recently Approved Antibacterial Agents in **February 2015**



Pucci et al. *Microbe.* Apr 2014 (updated)

Investigational and Recently Approved Antibacterial Agents in **June 2015**



Pucci et al. *Microbe.* Apr 2014; Page and Bush, *Curr Opin Pharmacol.* 2014 (updated with https://clinicaltrials.gov)

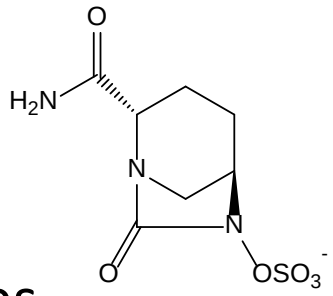
Recently Approved β-Lactamase Inhibitor Combinations

Name	Company	β-Lactam Class	Staph/ Strep	Gram-negatives
Ceftolozane + tazobactam (Dec 2014)	(Astellas/Calixa) Cubist	Cephalosporin + penicillanic acid sulfone	+ / +	++ ESBLs (some) +++ *Pseudomonas*
Ceftazidime + avibactam* (Feb 2015)	(Novexel) Forest/Actavis AstraZeneca (Europe)	Cephalosporin + diazabicyclo-octane (DBO)	+ / ++	+++ ESBLs +++ KPCs ++ *Pseudomonas*

***Approved based ONLY on Phase 2 clinical data. New FDA Guidance allowed approval due to the urgent unmet medical need for KPC-related infections. Phase 3 studies are ongoing in nosocomial pneumonia and complicated intra-abdominal infections.**

Clinicaltrials.gov, March 2015

Avibactam Could Be a "Game Changer"



- Novel structure: diazabicyclooctane (DBO)
- First β-lactamase inhibitor to show efficacy against organisms with **class A ESBLs**, **class A carbapenemases**, class C cephalosporinases, and some class D oxacillinases
- At least four DBO combinations are in clinical development
- Avibactam in combination with aztreonam; synergy is demonstrated against pathogens with **class B MBLs**
- Novel mechanism of action
  - Reversible covalent binding except for KPC-2
  - Slow hydrolysis by KPC-2 followed by fragmentation
  - If multiple β-lactamases are present, avibactam preferentially binds to enzyme(s) with the highest affinity

Li et al. *AAC.* 2015;59:1789; Ehmann et al. *J Biol Chem.* 2012;288:27960

What's Left in the Pipeline?

Investigational Antibacterial Agents
β-Lactamase Inhibitor Combinations

Name (Phase)	Company	β-Lactam Class	Staph/ Strep	Gram-negatives
Imipenem + relobactam (MK7655) (Ph 2/3)	Merck	Carbapenem + DBO	++ / ++	+++ ESBLs +++ KPCs +++ *(Pseudomonas)**
Ceftaroline + avibactam (Ph 2)	Forest/Actavis (AstraZeneca)	Cephalosporin + DBO	+ ++ (MRSA) / +++	+++ ESBLs +++ KPCs
Aztreonam + avibactam (Ph 2)	AstraZeneca (IMI in Europe)	Monobactam + DBO	– / –	+++ ESBLs +++ KPCs + *(Pseudomonas)** ++ MBLs
Carbavance (Meropenem + RPX7009) (Ph 3)	(Rempex) The Medicines Company	Carbapenem + boronic acid inhibitor	++ / ++	+++ ESBLs +++ KPCs +++ *(Pseudomonas)**

***No enhanced activity from BLI**

Summarized in: Pucci and Bush. *Clin Micro Rev.* 2013; updated with https://clinicaltrials.gov

Investigational Antibacterial Agents β-Lactamase Inhibitor Combinations

Name (Phase)	Company	β-Lactam Class (Phase)	Staph/ Strep	Gram-negatives
RG6080 (OP0595, FPI-1459) (Ph 1)	Fedora/Meiji/ Roche	DBO (BLI) + ?	?	+++ ESBLs +++ KPCs ++ MBLs +++ (*Pseudomonas*)
Cefepime + AAI101 (Ph 1)	Allecra	Unpublished	?	(Some MDR-gram-negatives)
CB-618 (Ph 1-?)*	Cubist/Merck	Unknown BLI	?	+++ ESBLs +++ KPCs

* ADISInsight lists it as in Phase 1 trials in the US (Feb 2015), but not listed on clinicaltrials.gov or in the Merck pipeline.

Company websites; Crandon and Nicolau, AAC online, Feb 2015; http://adisinsight.springer.com/drugs/800042003; http://www.merck.com/research/pipeline/home.html

Investigational Antibacterial Agents
β-Lactams

Name (Phase)	Company	β-Lactam Class (Phase)	Staph/ Strep	Gram-negatives
S2696266 (Ph 2)	Shionogi	Siderophore Cephalosporin	?	++ MDR Enterics
BAL30072 (Ph 1)	Basilea	Siderophore Monosulfactam Possibly combined with meropenem	None	++ MDR Enterics +++ Acinetobacter

http://www.shionogi.co.jp/en/company/news/2014/e141010.html

http://www.basilea.com/Portfolio/BAL30072/

Investigational β-Lactam-Containing Agents

Agents in Preclinical Development

Name	Company	β-Lactam Class	Staph/ Strep	Gram-negatives
AIC499	AICuris (with IMI - ND4BB program in Europe)	Not defined	?	"With a BLI: **MDR Gram-negatives *Pseudomonas*, Acinetobacter"**
S200	Sopharmia	Cephalosporin	?	**+++ ESBLs** **+++ KPCs** **++ MBLs (?)**

Summarized in: Page and Bush. *Curr Opin Pharmacol.* 2014;
http://www.aicuris.com/29/Research-Development/R-D-Pipeline.htm

Investigational Antibacterial Agents
DNA/RNA Inhibitors

Name (Phase)	Company	Class	Spectrum
Delafloxacin (Ph 3)	(Wakunaga)/Rib-X	Chloro-fluoroquinolone (Gyrase and Topo IV inhibitor)	+++ **MRSA** +++ MDR-strep ++ Enteric bacteria* +++ ***N. gonorrheae***
Nemonoxacin (Ph 3)	(Procter & Gamble)/TaiGen	Nonfluorinated quinolone	+++ **MRSA** +++ MDR-strep ++ Enteric bacteria*
Zabofloxacin (Ph 3)	(Dong Wha)/Pacific Beach Biosciences	Fluoroquinolone	+++ **MRSA** +++ MDR-strep ++ Enteric bacteria* +++ ***N. gonorrhoeae***
Finafloxacin**	MerLion	Fluoroquinolone	++ **MRSA** ***Helicobacter pylori*** ***Acinetobacter* spp.**

*Activity against *Enterobacteriaceae* similar to moxifloxacin
*Approved by FDA for topical ophthalmic use

Summarized in: Pucci and Bush. *Clin Micro Rev.* 2013; updated with https://clinicaltrials.gov

Investigational Antibacterial Agents DNA/RNA Inhibitors

Name	Company	Class	Staph/ Strep	Gram-negatives
Avarofloxacin (JNJ-Q2) (Ph 2 completed)	(JNJ)/Furiex	Fluoroquinolone	+++ MRSA +++ **MDR-strep**	++ Enteric bacteria
AZD0914 (Ph2)	Entasis Therapeutics	Spiropyrimidine-trione	+++ MRSA +++ **MDR-strep**	+++ ***N. gonorrhoeae*** ++ Atypicals
GSK 2140944 (Ph2)	GlaxoSmith Kline	Topoisomerase II inhibitor	[+++ MRSA +++ **MDR-strep]**	+++ ***N. gonorrhoeae***
Nadifloxacin WCK771 and prodrug WCK2349 (Ph 2/1)	Wockhardt	Tricyclic fluoroquinolone	+++ MRSA +++ **MDR-strep**	? Enteric bacteria
KRP-AM1977 (Ph1)	Kyorin	Nonfluorinated quinolone	+++ MRSA +++ **MDR-strep**	? Enteric bacteria

Based on: Pucci and Bush. *Clin Micro Rev.* 2013; Huband et al. Antimicrob Agents Chemother. 59:467 (2015) ; https://clinicaltrials.gov/ct2/show/NCT02257918?term=AZD0914&rank=1; http://www.entasistx.com/; http://newdrugapprovals.org/2015/05/18/lascufloxacin-krp-am1977-by-kyorin/

Investigational Antibacterial Agents
Protein Synthesis Inhibitors

Name (Phase)	Company	Class	Staph/ Strep	Gram-negatives	Dosing
Eravacycline (Ph 3)	Tetraphase	Tetracycline	+++ (MRSA)/++	+++ ESBLs +++ KPCs ++ *Acinetobacter*	IV and oral
Omadacycline (Ph 3)	Paratek	Tetracycline (Glycylcycline)	+++ (MRSA)/++	+++ ESBLs +++ KPCs	IV and oral
Plazomicin (Ph 3)	Achaogen	Aminoglycoside	+++ (MRSA)	+++ ESBLs +++ KPCs ++ *Acinetobacter*	IV
Solithromycin (Ph 3)	Cempra	Fluoroketolide	+++ MDR-strep	+++ *N. gonorrhoeae* +++ Atypicals +++ *M. avium*	IV and oral

Summarized in: Pucci and Bush. *Clin Micro Rev.* 2013; updated with https://clinicaltrials.gov/; http://www.cempra.com/products/Solithromycin-cem-101/

Investigational Membrane-Active Antibacterial Agents

Name	Company	Class	Gram-positives	Gram-negatives
Lefamulin (BC-3781) (Ph 2)	Nabriva	Pleuromutilin	+++ MRSA +++ MDR strep +++ VRE	++ Enterics ++ Atypicals
RG7929 (POL7080) (Ph 2)	Roche/ Polyphor	Peptidomimetic; LptD (LPS) inhibitor	None	+++ *P. aeruginosa*
ACHN-975*	Achaogen	LPS biosynthesis inhibitor	None	++ *E. coli* +++ *P. aeruginosa*

*Clinical trials were terminated due to irritation at the infusion site.

http://www.nabriva.com/programs/pleuromutilins/; http://www.polyphor.com/products/ ; http://www.achaogen.com/pipeline-overview/ ; Reyes et al. ICAAC 2013., Abstract F-1229

Other Investigational Antibacterial Agents

Name	Company	Class or Target	Gram-positives	Gram-negatives
TD-1792 (Ph 2)	Theravance	Glycopeptide-cephalosporin	+++	None
TD-1607 (Ph 1)	Theravance	Glycopeptide-cephalosporin	+++	None
Debio 1450 (Prodrug of AFN-1252) (Ph 1)	Affiniium/ Debiopharm	FabI inhibitor	+++ MRSA	None
GSK1322322 * (Ph 3)	GSK	PDF inhibitor	+++ MRSA +++ MDR strep	None
AN3365* (Ph 2)	Anacor/GSK	Leu-tRNA synthase inhibitor	None	++ Enterics ++ *P. aeruginosa*

*Clinical trials were terminated.

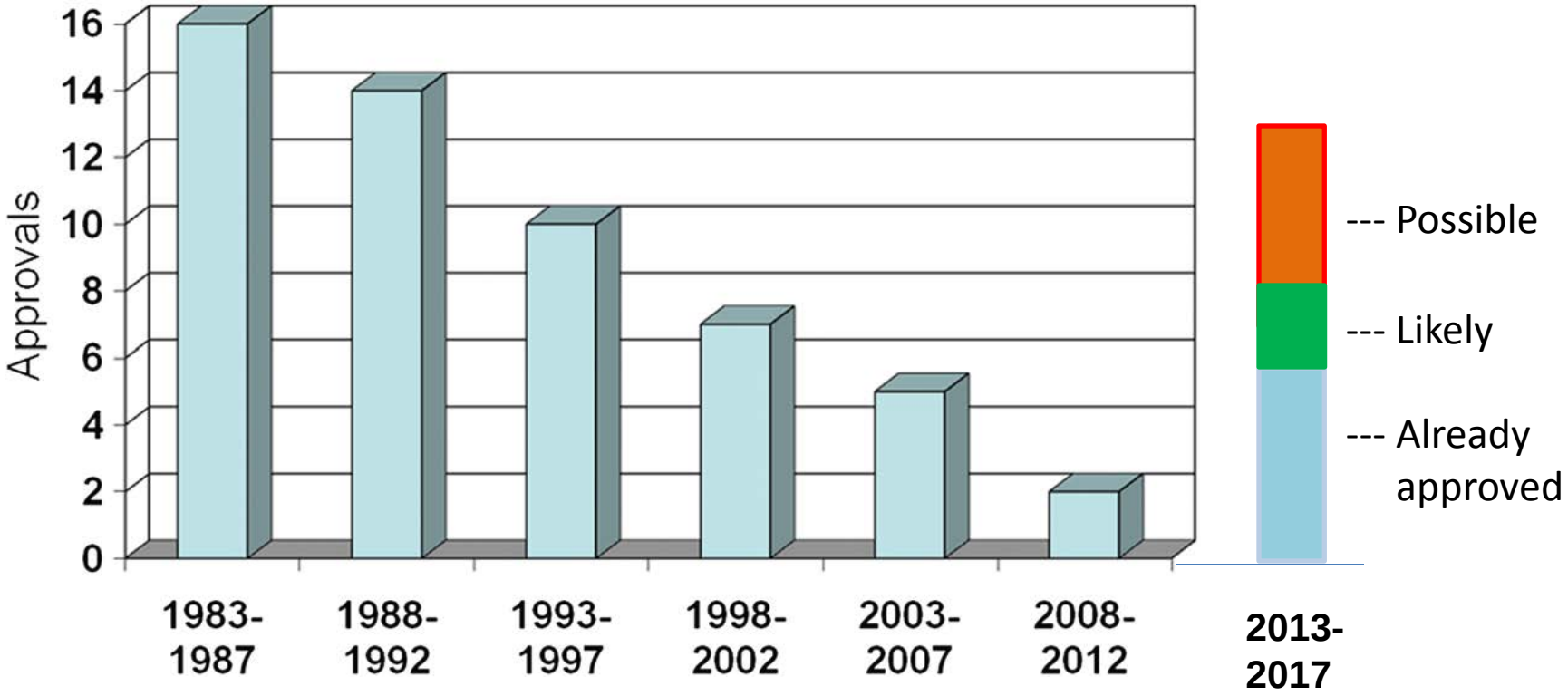
Summarized in: Page and Bush. *Curr Opin Pharmacol.* 2014. Updated with http://clinicaltrials.gov

Non-Small Molecule Approaches

- Prophylactic and therapeutic antibodies
- MedImmune
  - MEDI3902
    - Prevention of *Pseudomonas* pneumonia
    - Phase 1 (US)
  - MEDI4893
    - Prevention of *Staphylococcus aureus* pneumonia
    - Phase 2 (US and Europe/Innovative Medicines Initiative)

https://clinicaltrials.gov/; https://www.medimmune.com/research/pipeline

Bush Update to IDSA Accounting



Boucher et al. *CID.* 2013;56:1685. Modified by Bush, 2015

Do We Have Drugs in the Pipeline to Address CDC and IDSA Priorities?

- **Urgent Threats**
  - ✓ Y *Clostridium difficile*
  - ✓ Y **CRE**
  - ✓ Y Drug-resistant *Neisseria gonorrhoeae*
- **Serious Threats**
  - (Y) **Multidrug-resistant *Acinetobacter***
  - ✓ Y Drug-resistant *Campylobacter*
  - ✓ Y **ESBL-producing *Enterobacteriaceae***
  - ✓ Y **VRE**
  - ✓ (Y) **Multidrug-resistant *Pseudomonas aeruginosa***
  - ✓ Y Drug-resistant nontyphoidal *Salmonella*
  - ✓ Y Drug-resistant *Salmonella typhi*
  - ✓ Y Drug-resistant *Shigella*
  - ✓ Y **MRSA**
  - ✓ Y Drug-resistant *Streptococcus pneumoniae*

CDC, Threat Report, September 16, 2013; L. Rice, J *Infect Dis.* 2008;197:1079

Closing Thoughts

- In spite of the alarms set by IDSA and the CDC, viable new antibacterial agents are in late-stage development.
- New agents with novel structures from established chemical classes will compete with new agents with novel targets for the same sets of organisms.
- Successful new agents with novel targets are represented less frequently in late-stage development.
- Every new drug will have a slightly different safety or dosing profile, or resistance selection, so there may be a place for multiple, similar agents.


New Antimicrobial Agents
RESISTANCE