NEW ANTIBACTERIAL DRUGS

Drug pipeline

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These slides were used for preparing a **video** which was broadcasted to the registered participants through Internet

Disclosures

Research grants for work on investigational compounds discussed in this presentation from

- Cempra Pharmaceuticals
- Cerexa
- GSK
- Bayer
- Melinta therapeutics
- The Medicine Company (antitibiotic franchise acquired by Melinta)
- MerLion Pharmaceuticals
- Theravance
- Trius (now part of Merck)
- Merck
- Debiopharm

Speaker's and consultant's fees: Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, Merck, Trius

Institutional and non profit organizations

- Fonds de la Recherche Scientifique (F.R.S.-FNRS)
- Université catholique de Louvain

Decision-making and consultation bodies

- European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
- European Medicines Agency (external ad-hoc expert)
- US National Institutes of Health (grant reviewing)
- Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*] (governance)

What do we do ?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - kétolides (solithromycin…)
  - oxazolidinones (tedizolid …)

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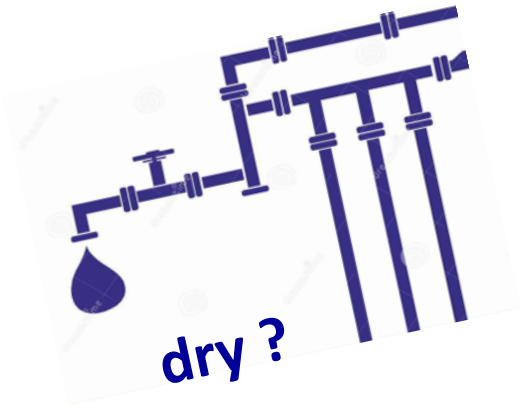
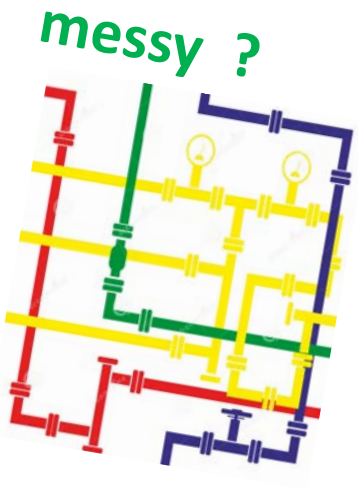
- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

ISAP

www.isap.org

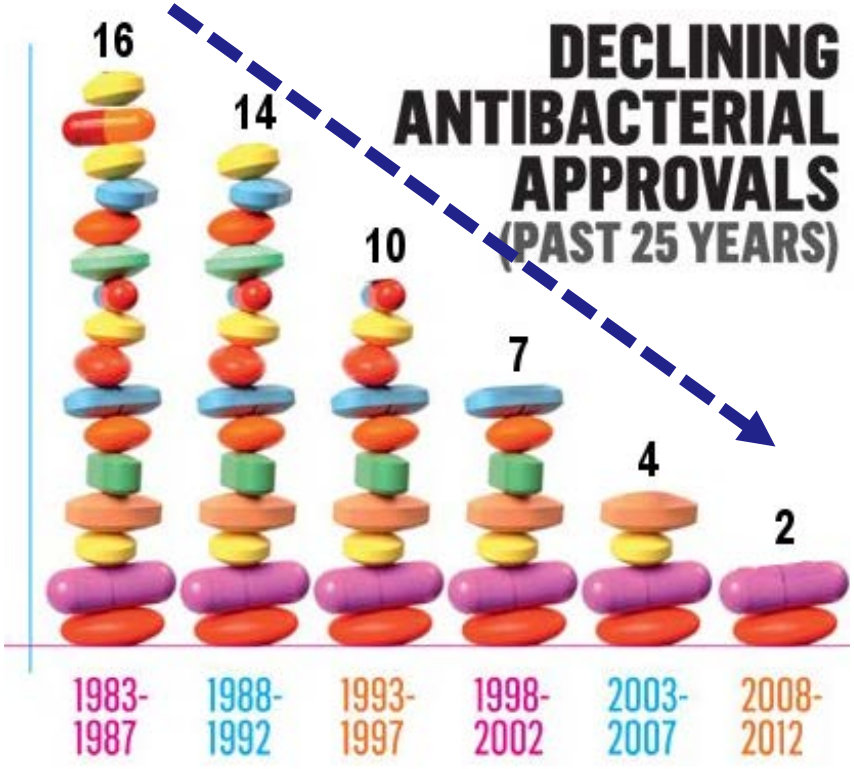
New antibiotics: what is your own view of the pipeline ?





New antibiotics: where are we ?

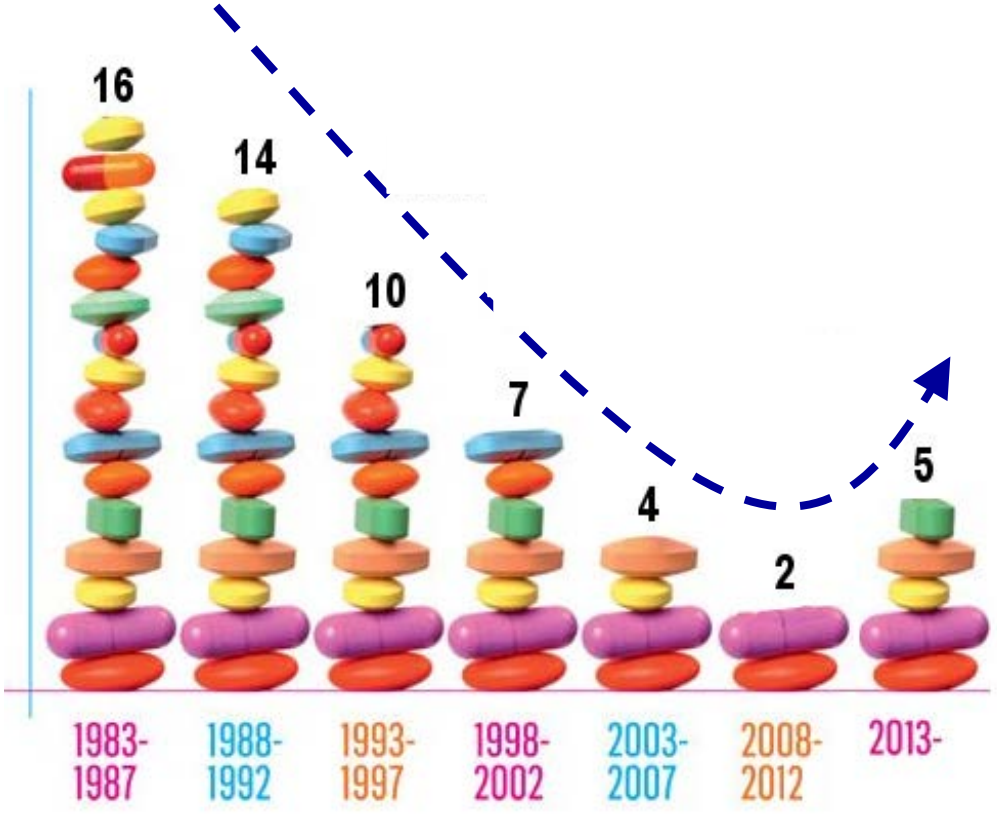
Approvals by FDA/EMA – systemic antibiotics



telavancin

New antibiotics: where are we ?

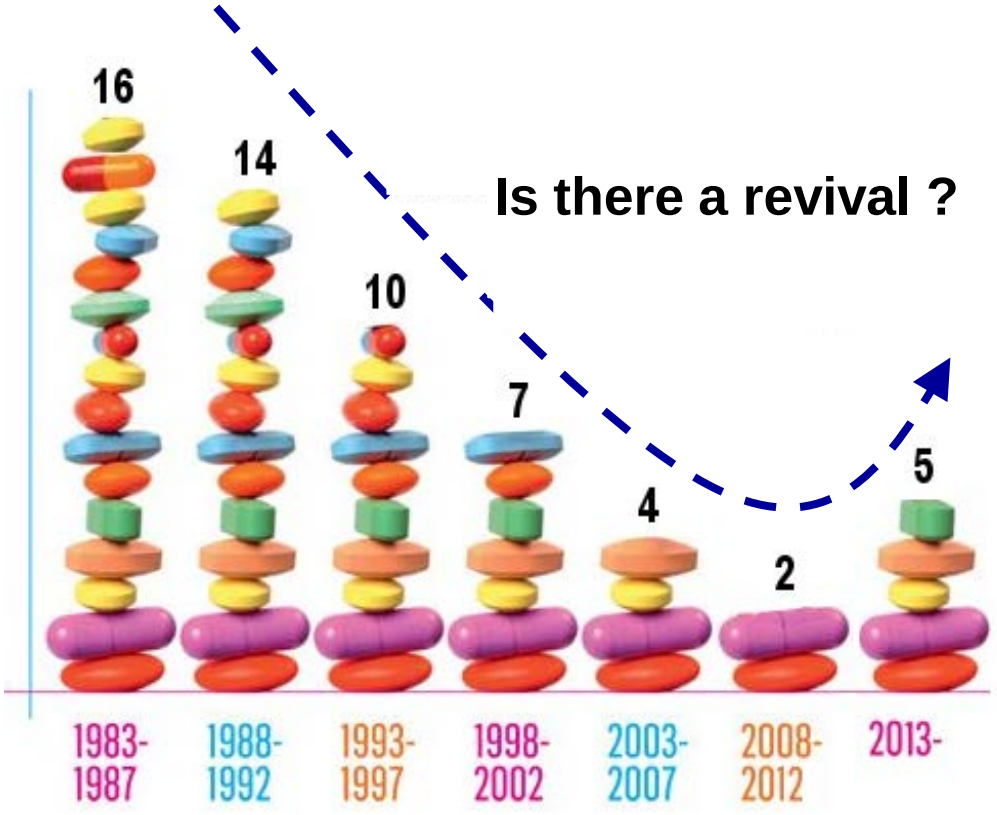
Approvals by FDA/EMA – systemic antibiotics



- dalbavancin, oritavancin
- tedizolid ...
- ceftaroline
- delafloxcin
- avibactam

- telavancin
- ceftaroline

New antibiotics: where are we ?



- PK improvements (long acting)
- Modications to ↘ resistance
- restoring activity (add on)
- better target exploitation
- new mode of action

Possible areas of interest for discovery and development of novel antibiotics
(not an exhaustive list...)

New antibiotics: where are we ?

Shall we succeed ?

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Chair: E. Tacconelli (Infectious Diseases, DZIF Center, Tübingen University, Germany) and N. Magrini (WHO, EMP Department)

Coordinating group: Y. Carmeli, Tel Aviv University, Israel; S. Harbarth, University of Geneva, Switzerland; G. Kahlmeter, University of Uppsala, Sweden; J. Kluytmans, University Medical Center Utrecht, Netherlands; M. Mendelson, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa; C. Pulcini, University of Lorraine and Nancy University Hospital, France; N. Singh, George Washington University, USA; U. Theuretzbacher, Center for Anti-infective Agents, Austria

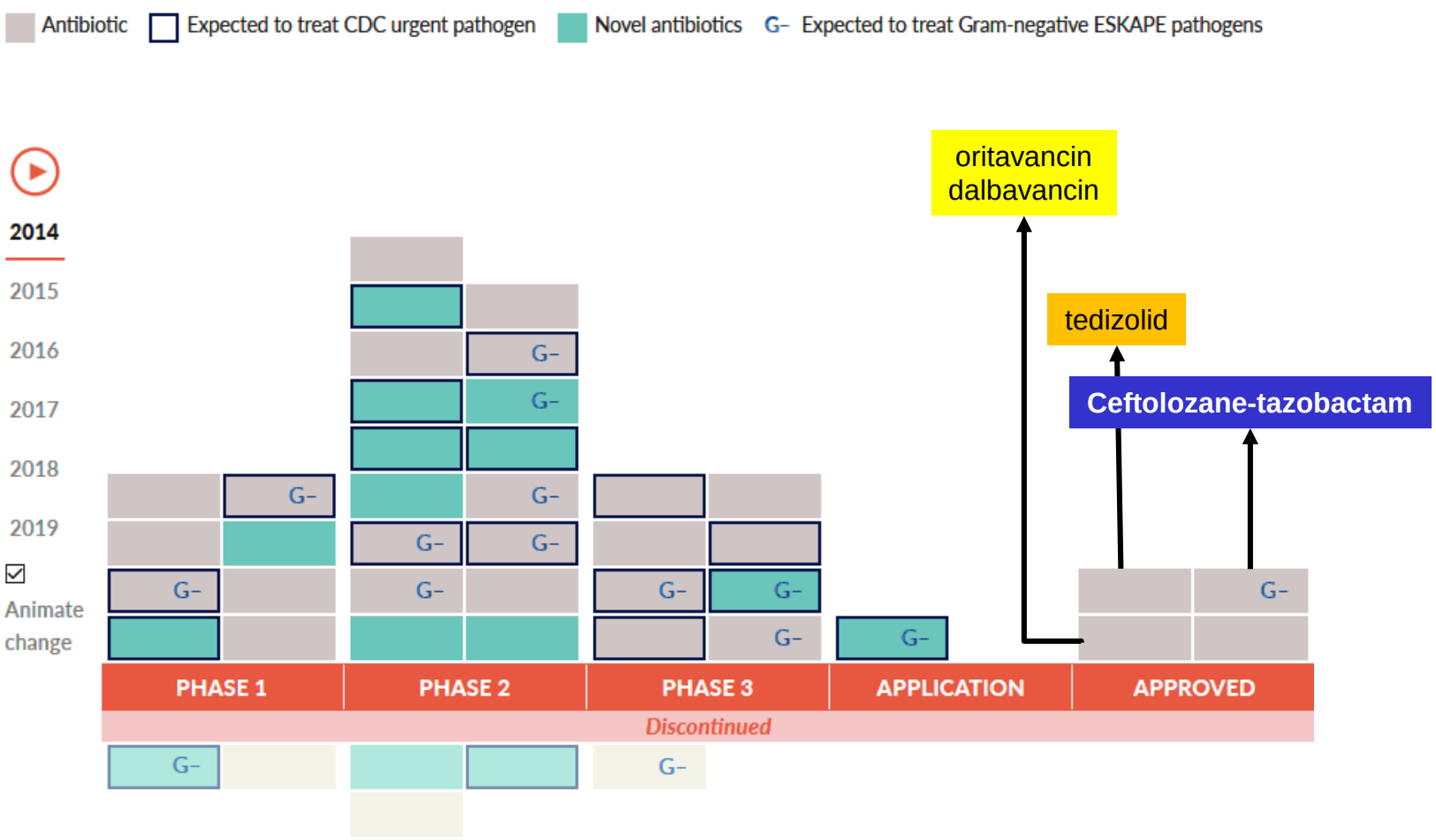
Challenging pathogens

Approvals by FDA/EMA – systemic antibiotics

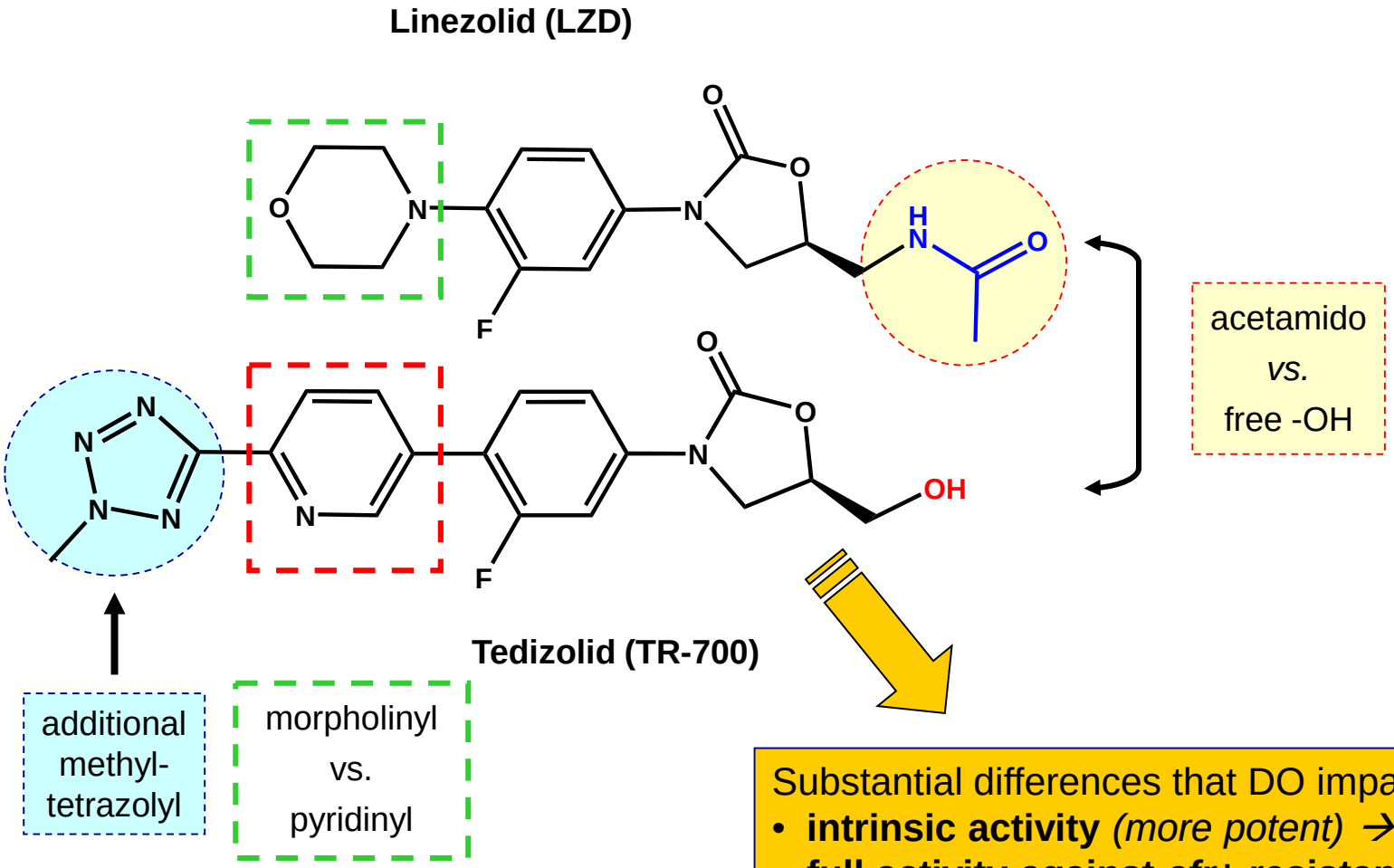
What did we gain (or loose) since 2014 ?

New antibiotics: where are we ?

Gains in 2014 ...



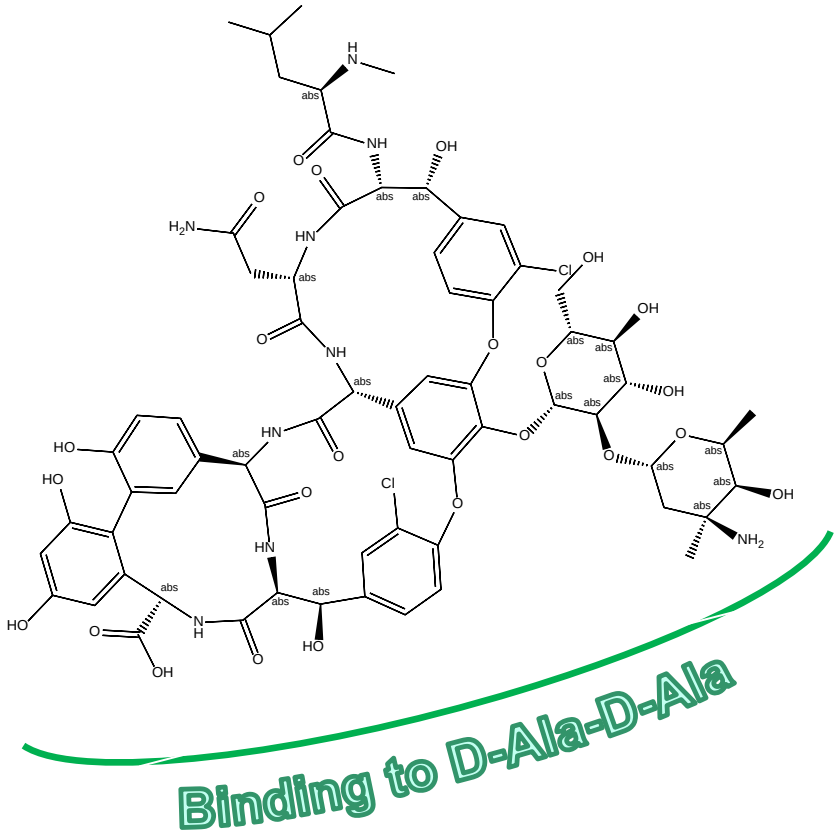
Tedizolid



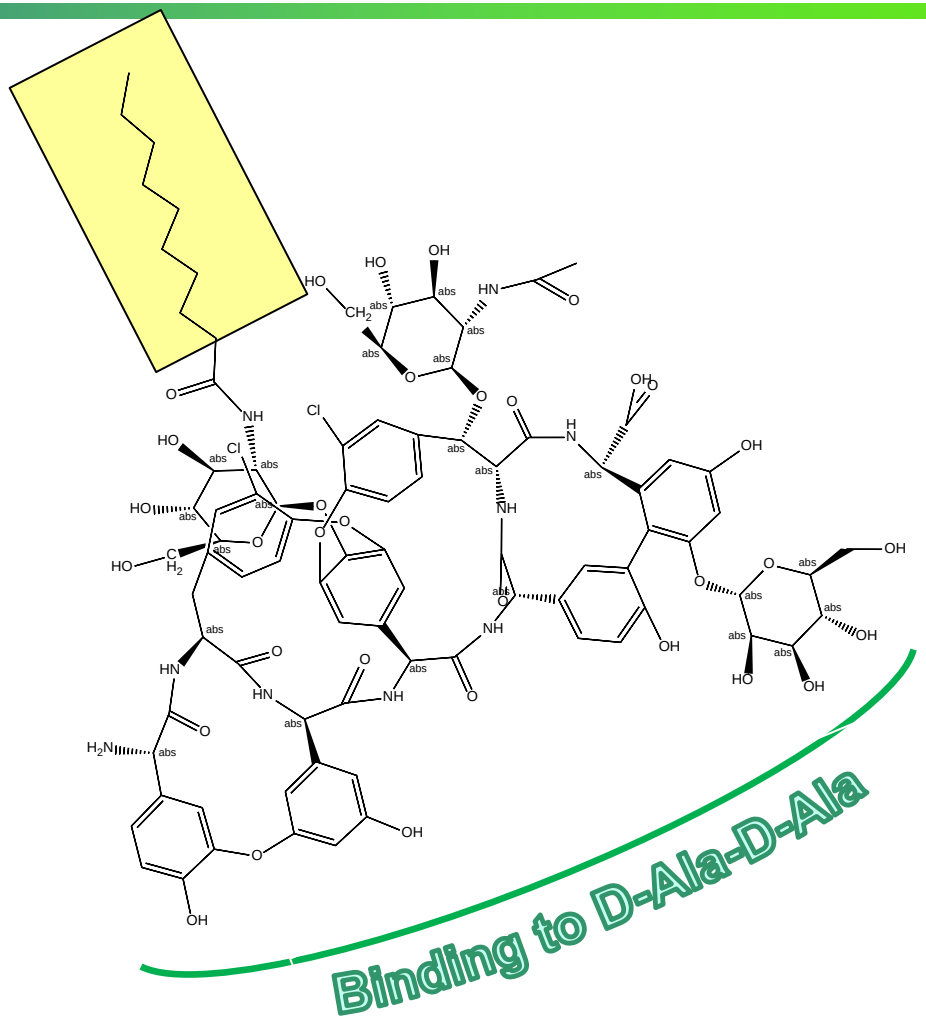
Substantial differences that DO impact on

- **intrinsic activity** *(more potent)* → *200 mg/day*
- **full activity against *cfr*+ resistant strains**
- ***Longer half-life*** → *once daily dosing*
- *Lower toxicity (dosage/schedule)*

From vancomycin to long-acting glycopeptides

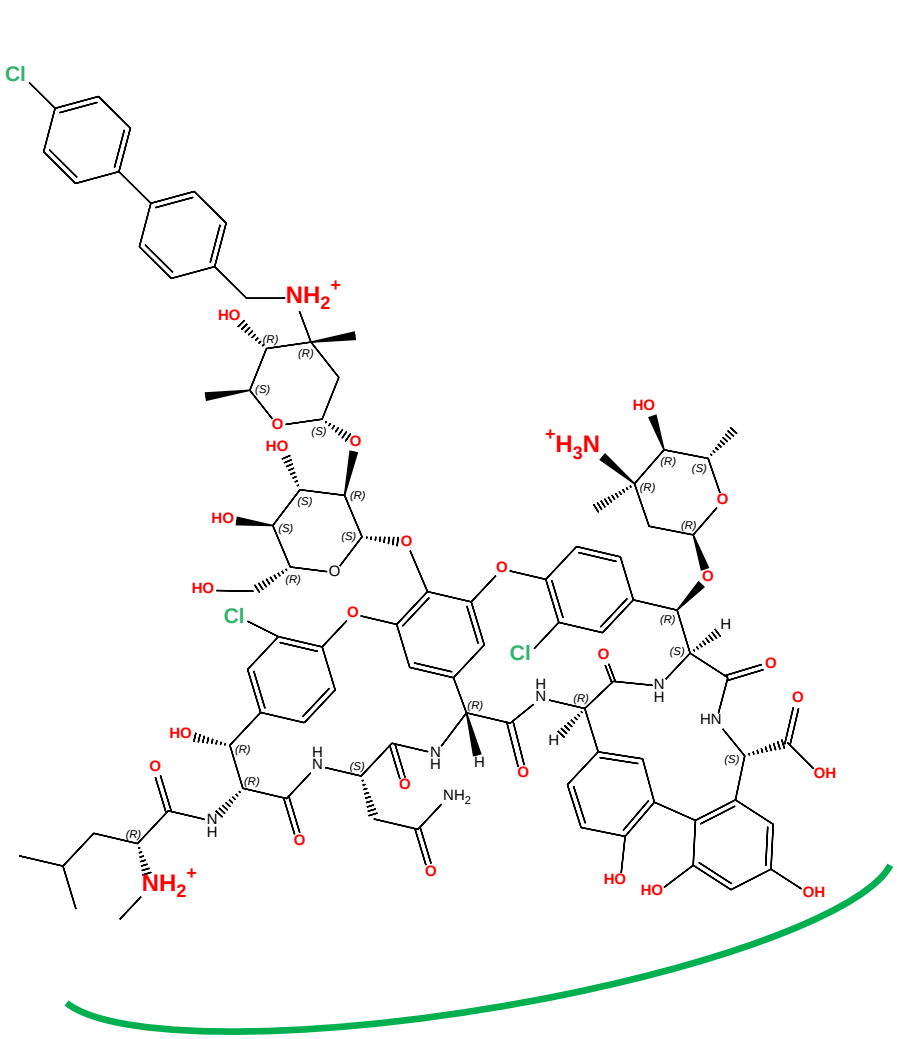


vancomycin

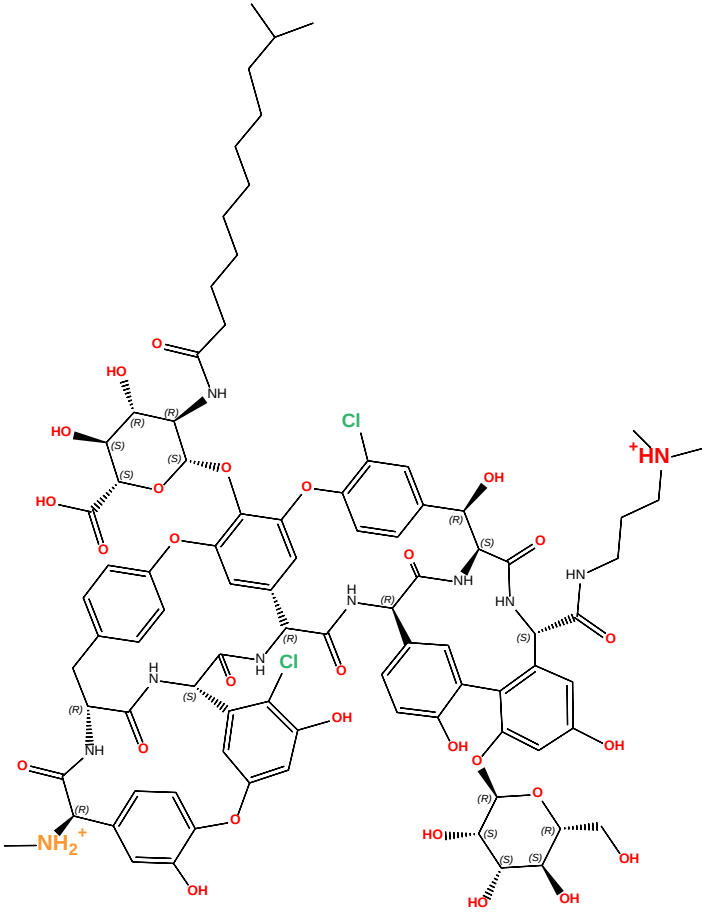


teicoplanin

Oritavancin - Dalbavancin

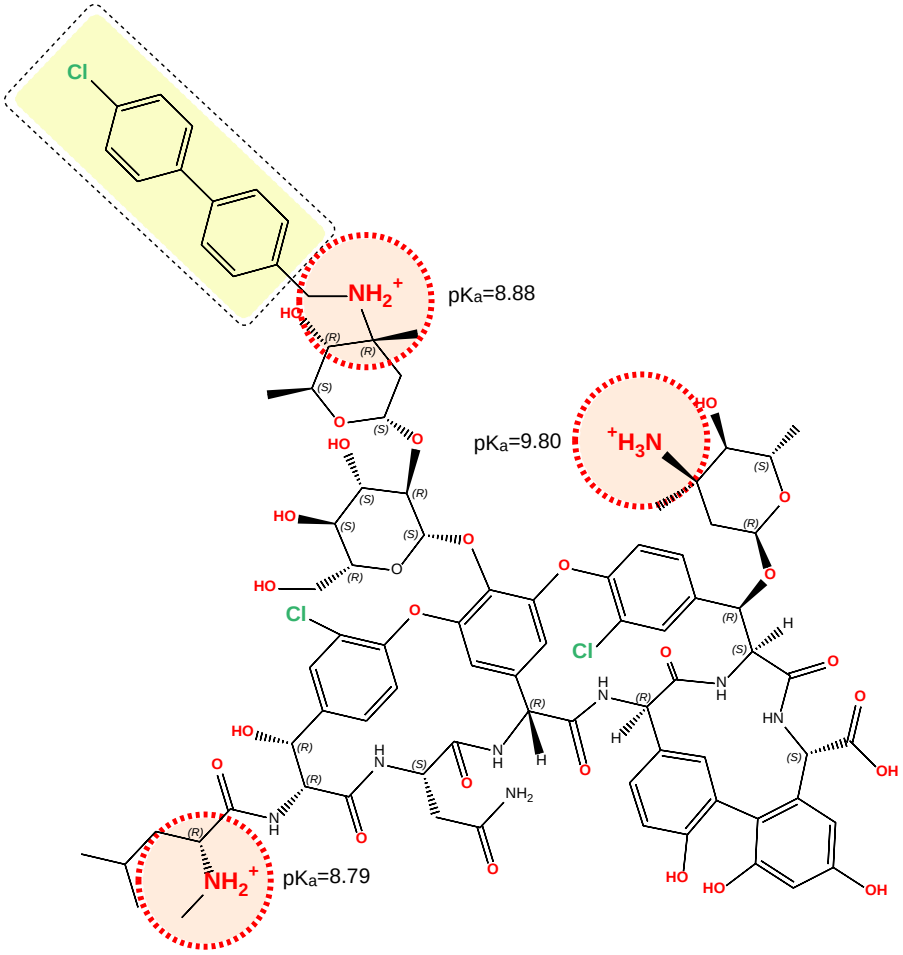


oritavancin

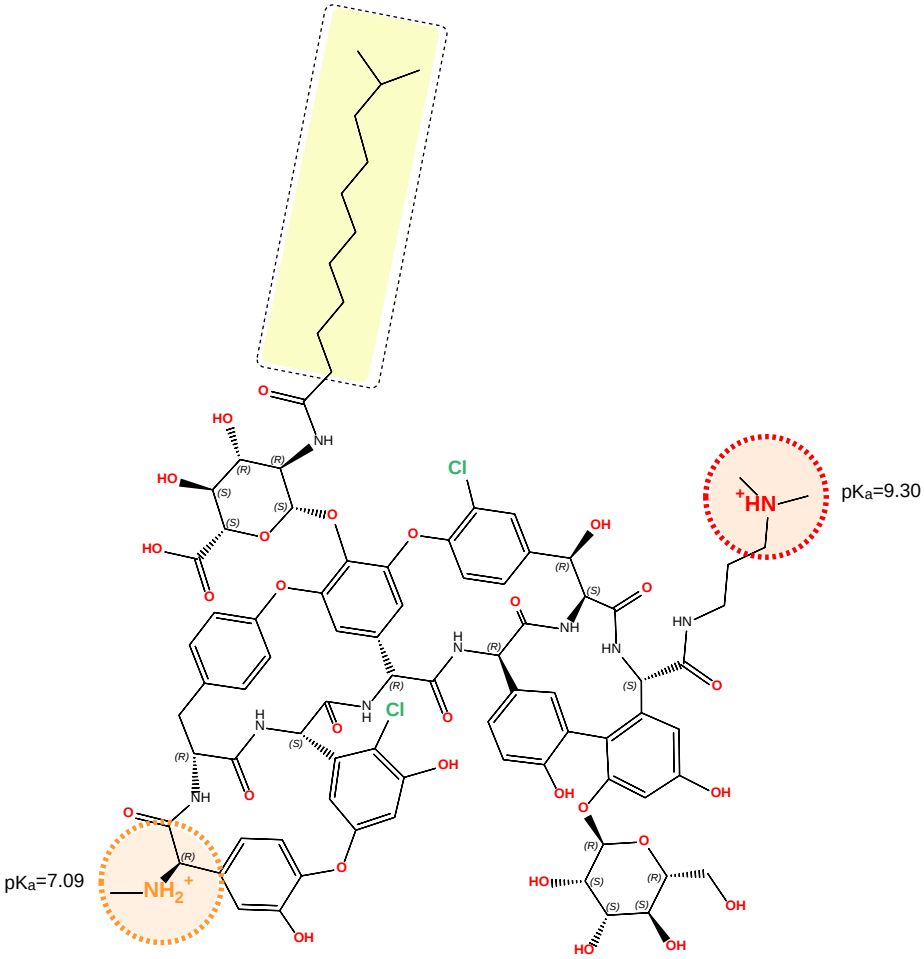


dalbavancin

Oritavancin – Dalbavancin: charges and hydrophobicity

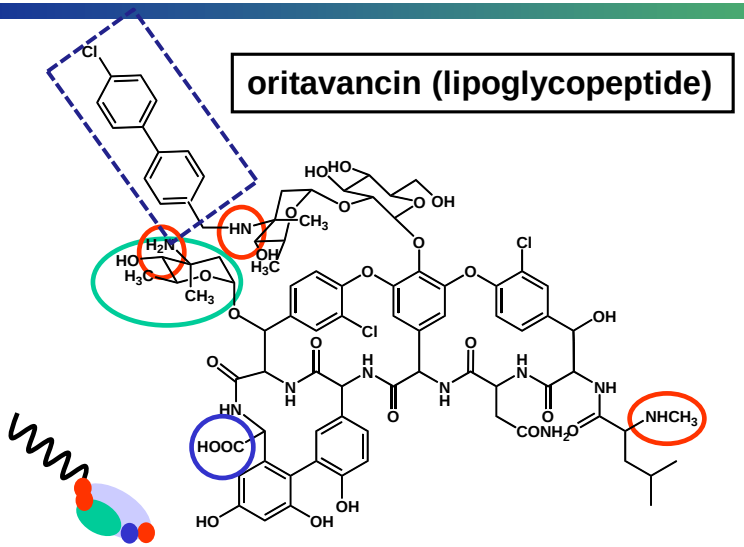


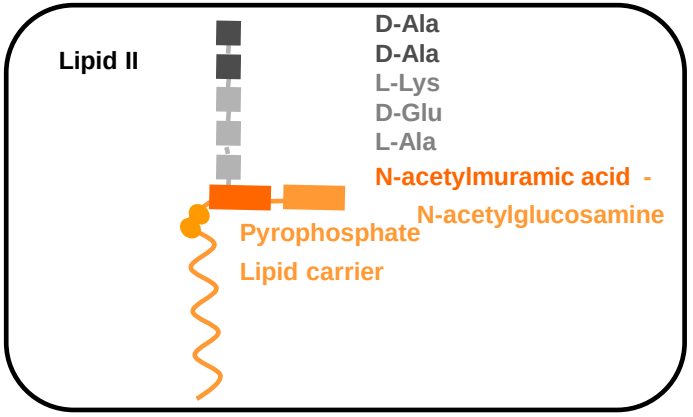
oritavancin



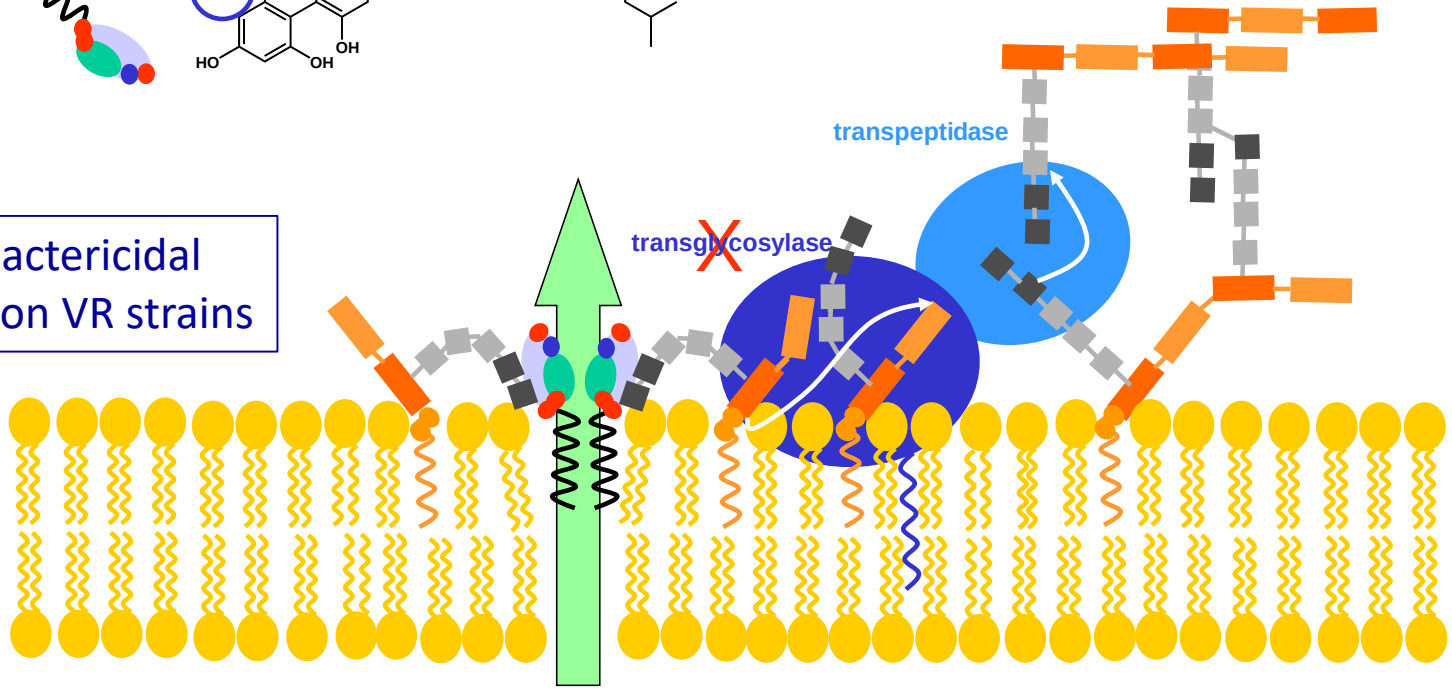
dalbavancin

Oritavancin: double mode of action





- highly bactericidal
- activity on VR strains



Van Bambeke et al, TIPS 2008, 29:124-134

(Lipo)glycopeptides pharmacokinetics

parameter	VAN	TEC	TLV	DAL	ORI
Dosage	15 mg/kg	6 mg/kg	10 mg/kg	1000 mg	1200 mg
C_{max} (mg/L)	20-50	43	93	287	138
AUC (mg.h/L)	260	600	668	3185 (24h) 23443 (tot)	1110 (24h) 2800 (tot)
(%) prot. binding	55	88-94	95	99	85
T ½ (h)	1 (β) 3-9 (γ)	10 (β) 168 (γ)	8	**346** (γ)	14 (β) **245** (γ)

twice daily | every 2 days | once daily | once-a-week | once !

(Lipo)glycopeptides: pro and cons

Pros

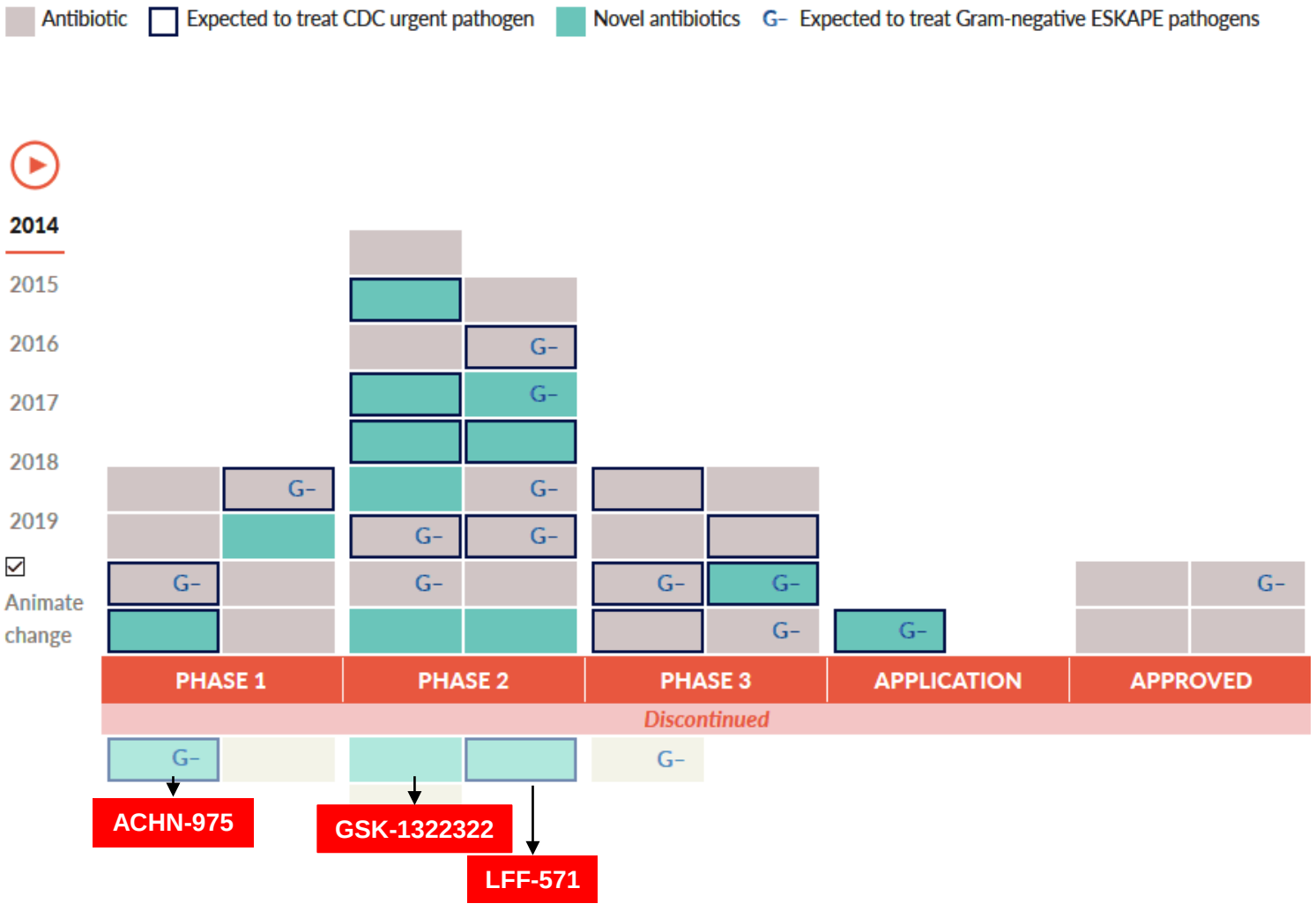
- Patient with MRSA or *Enterococcus faecalis* with reduced susceptibility to vancomycin
  (MIC ≥ 2 mg/L [MRSA] or ≥ 4 mg/L [Enterococci])
  → documented therapy)
- Preference for **once daily** (telavancin), **once a week** (dalbavancin), or **once** (oritavancin) *vs* **twice daily for 7 to 14 days** (vancomycin)
- No need (or provision) for monitoring (so far…)

Cons

- Limited indications (at present) → **off label use !**
- Insufficient knowledge about toxicity risks (but low so far)
- Price (but low burden than vancomycin) → **pharmacoeconomics**

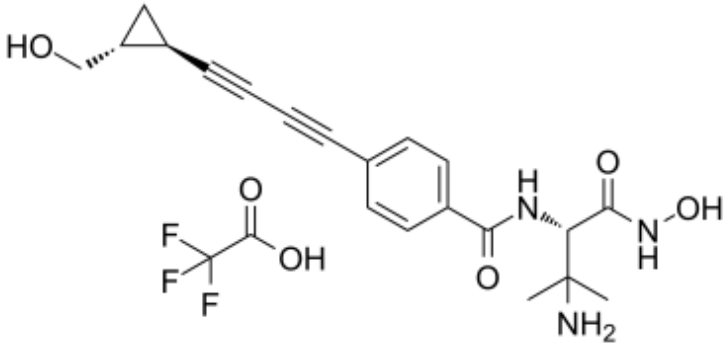
New antibiotics: where are we ?

Lost in 2014 …



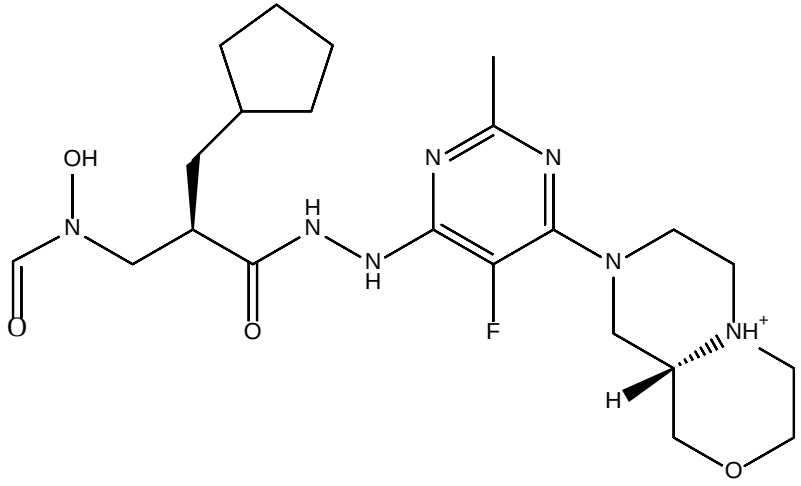
Lost in 2014 ...

- ACHN-975:
  - a selective LpxC inhibitor with subnanomolar LpxC inhibitory activity.
  - active against a wide range of gram-negative bacterias with low MIC values (≤1 µg/mL).



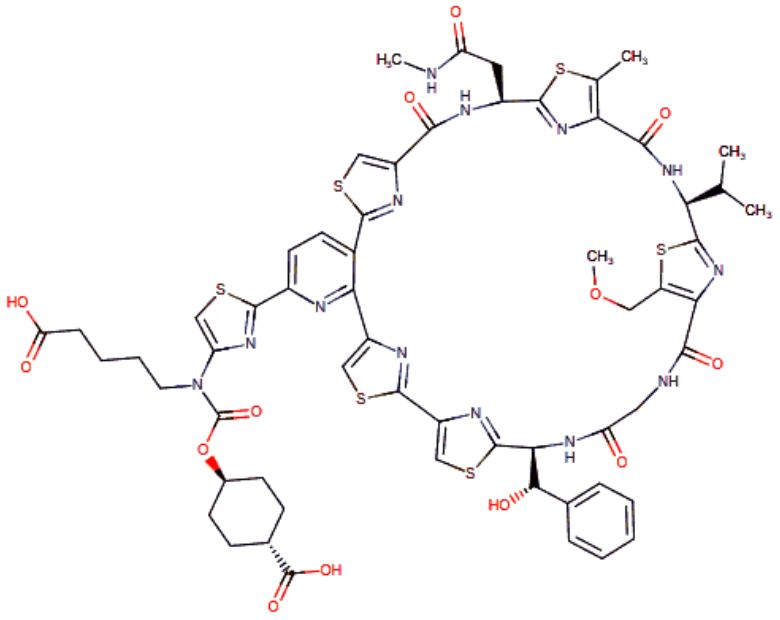
Lost in 2014 ...

- GSK 1322322
  - peptide deformylase inhibitor with very low MIC's against methicillin-resistant *Staphylococcus aureus* and penicllin-resistant *Streptococcus pneumoniae*

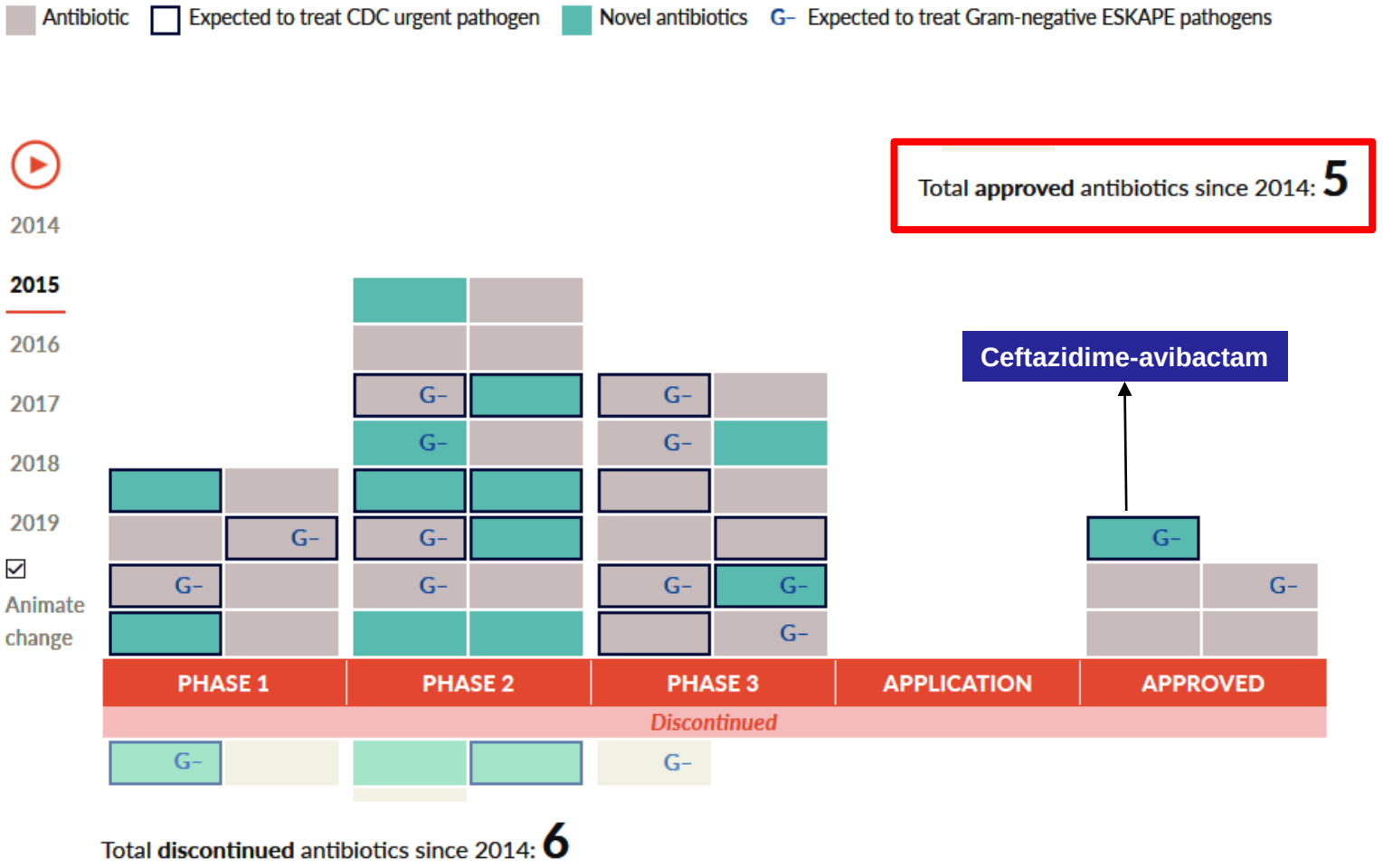


Lost in 2014 ...

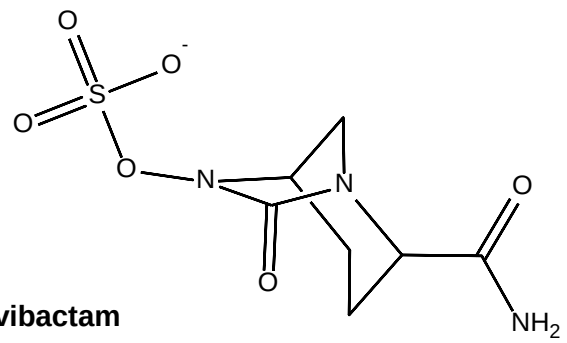
- LFF571
  - novel thiopeptide (macrolactam) antibacterial that shows in vitro potencies against *C. difficile* comparable to or greater than other clinically-used antibiotics ...
  - The parent compound is a translational inhibitor that binds elongation factor Tu (EF-Tu) and blocks its function.



2015: what we gained ...



Avibactam

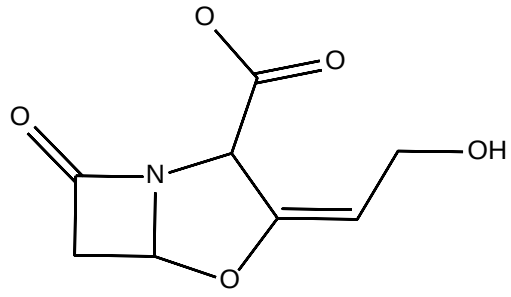


avibactam

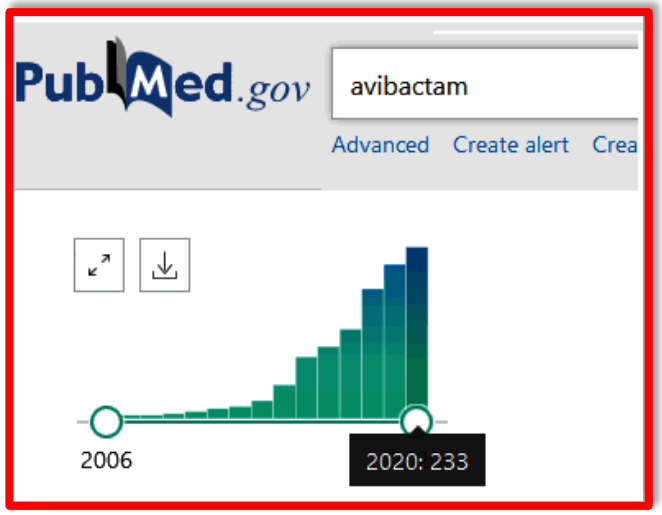
Ceftazidime-avibactam is the combination of third-generation cephalosporin ceftazidime and the novel, non-β-lactam β-lactamase inhibitor avibactam. I

Ceftazidime-avibactam has excellent in vitro activity against many important Gram-negative pathogens, including many **extended-spectrum β-lactamase**-, **AmpC**-, ***Klebsiella pneumoniae* carbapenemase**- and **OXA-48**-producing Enterobacteriaceae and **drug-resistant *Pseudomonas aeruginosa*** isolates/

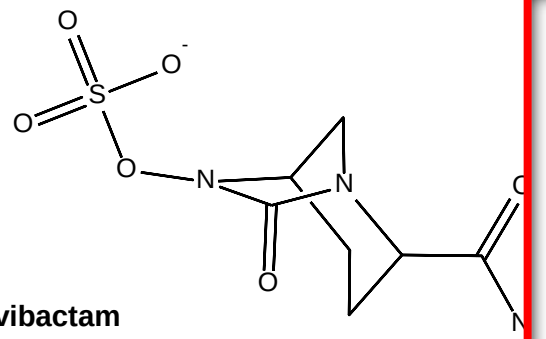
It is not active against metallo-β-lactamase-producing strains.



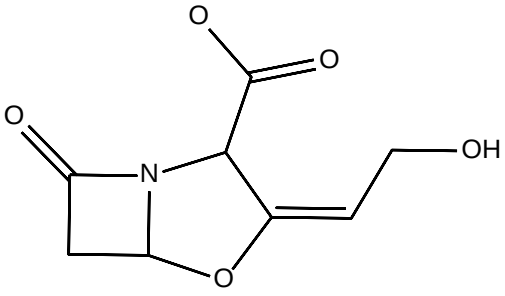
clavulanic acid



Avibactam: the down side



avibactam



clavulanic acid

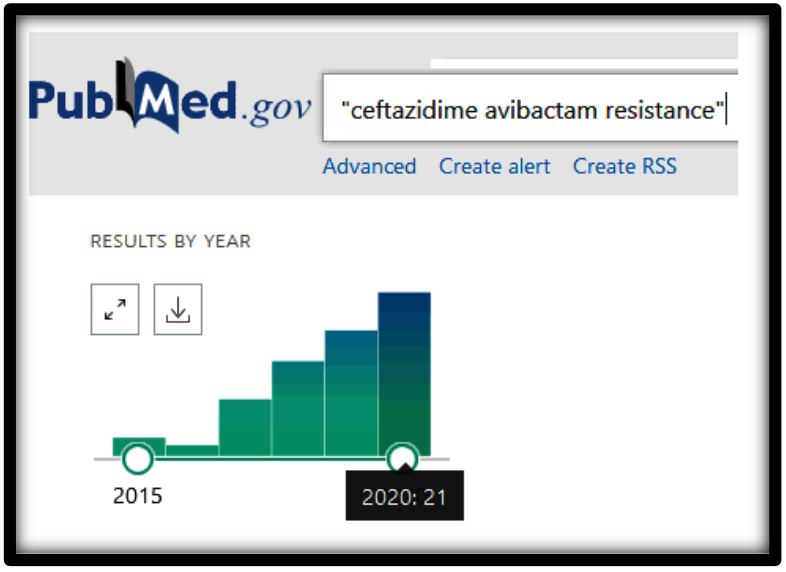
Antimicrob Agents Chemother. **2015** Oct; 59(10): 6605–6607.

First Report of Ceftazidime-Avibactam Resistance in a KPC-3-Expressing *Klebsiella pneumoniae* Isolate

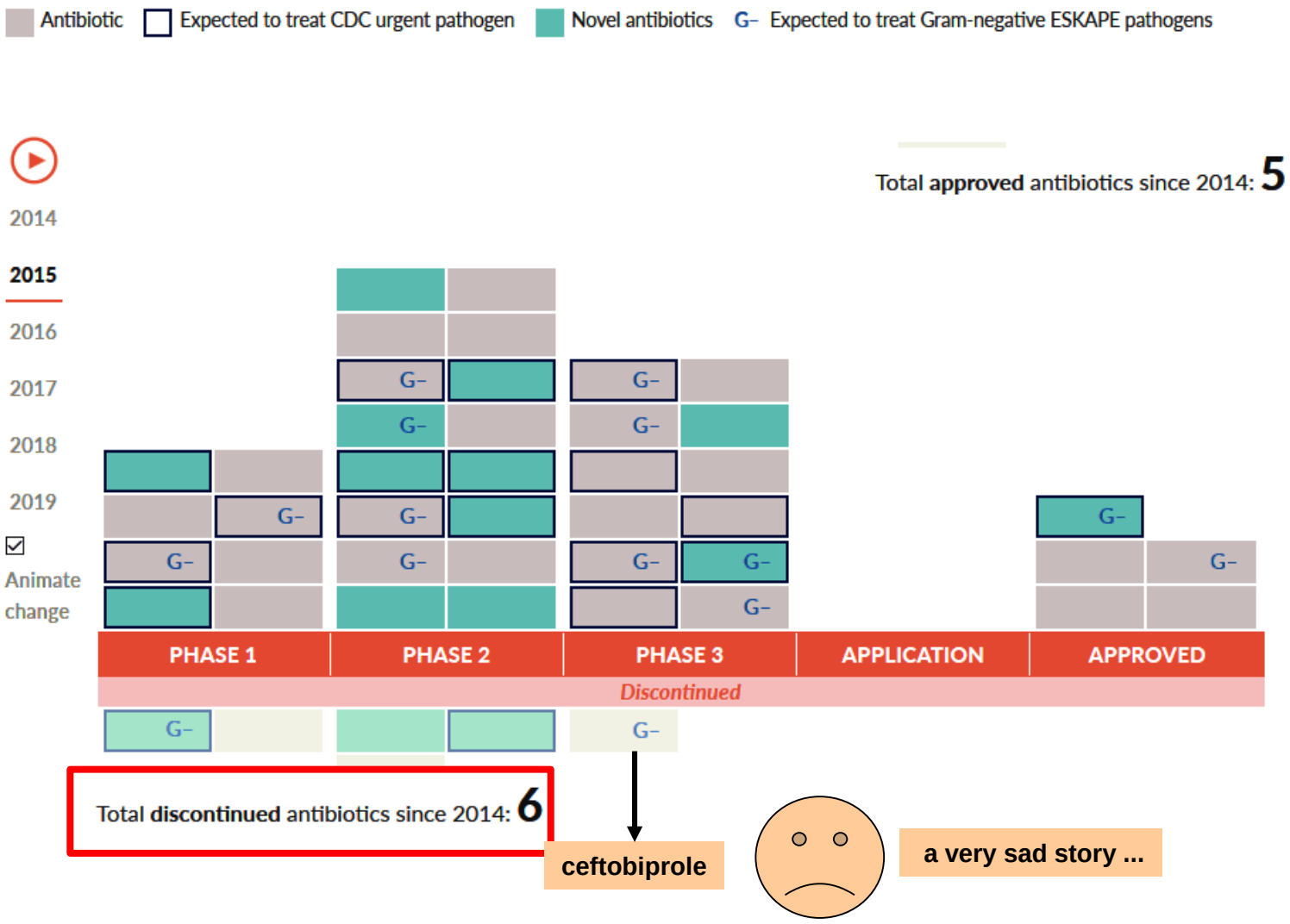
Romney M. Humphries,[a] Shangxin Yang,[a] Peera Hemarajata,[a] Kevin W. Ward,[a] Janet A. Hindler,[a] Shelley A. Miller,[a] Aric Gregson[b]

Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, California, USA[a]; Department of Medicine, Division of Infectious Diseases, University of California, Los Angeles, Los Angeles, California, USA[b]

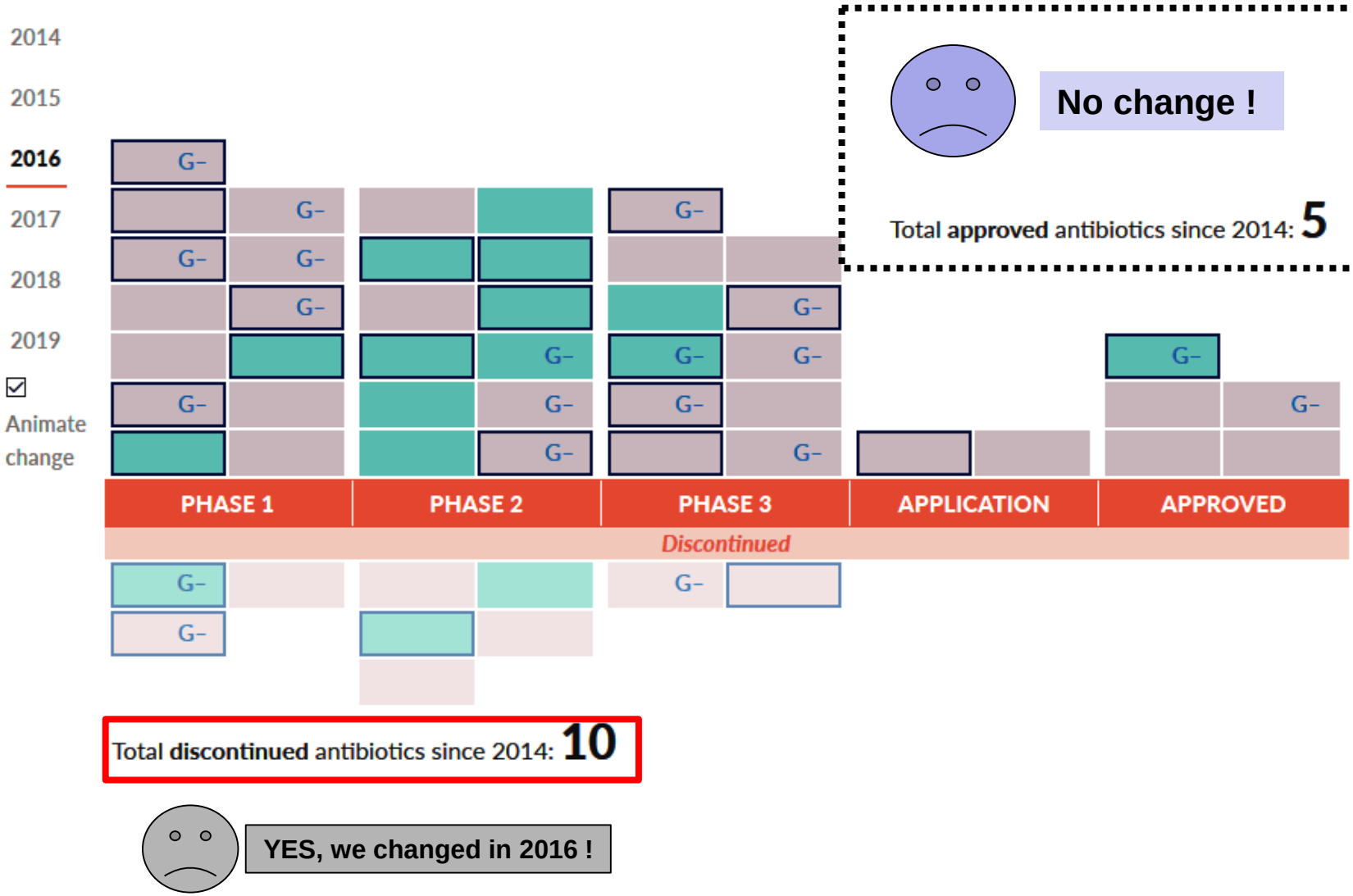
Ceftazidime-avibactam is the first antimicrobial approved by the U.S. FDA for the treatment of carbapenem-resistant *Enterobacteriaceae*. Avibactam, a non-β-lactam β-lactamase inhibitor, inactivates class A serine carbapenemases, including *Klebsiella pneumoniae* carbapenemase (KPC). We report a KPC-producing *K. pneumoniae* isolate resistant to ceftazidime-avibactam (MIC, 32/4 μg/ml) from a patient with no prior treatment with ceftazidime-avibactam.



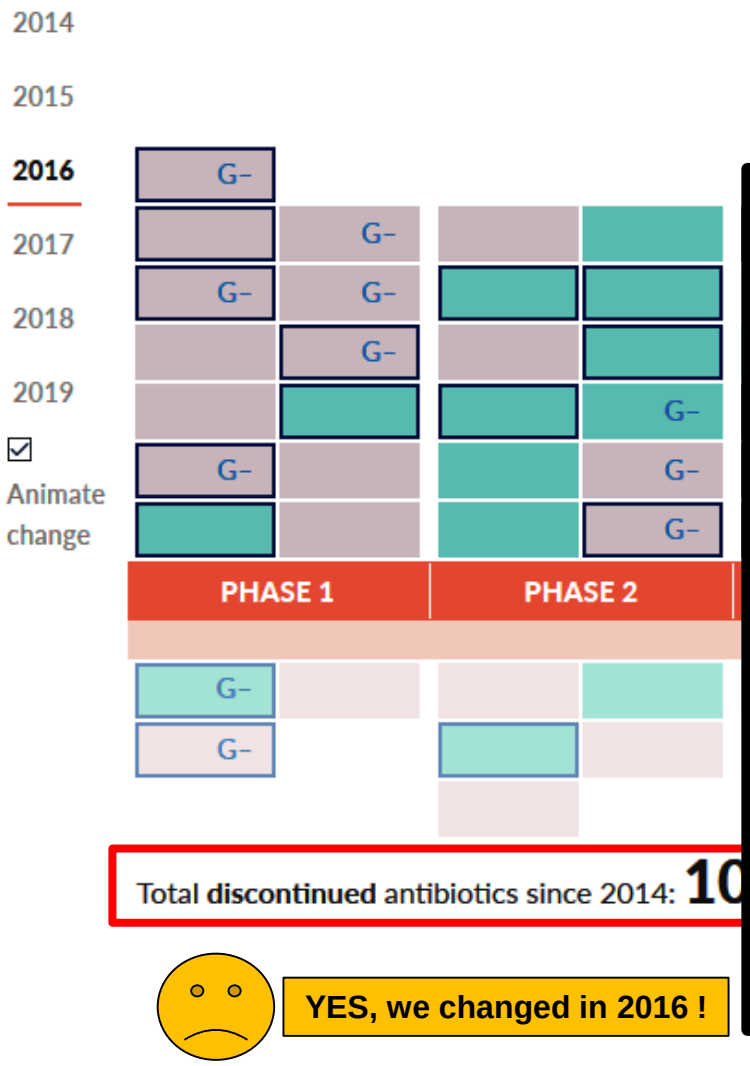
2015: what we lost ...



2016: no gain but 4 loss...



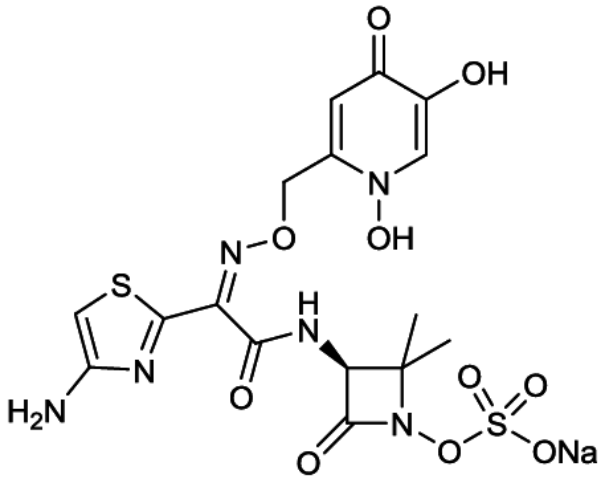
2016 : the loss

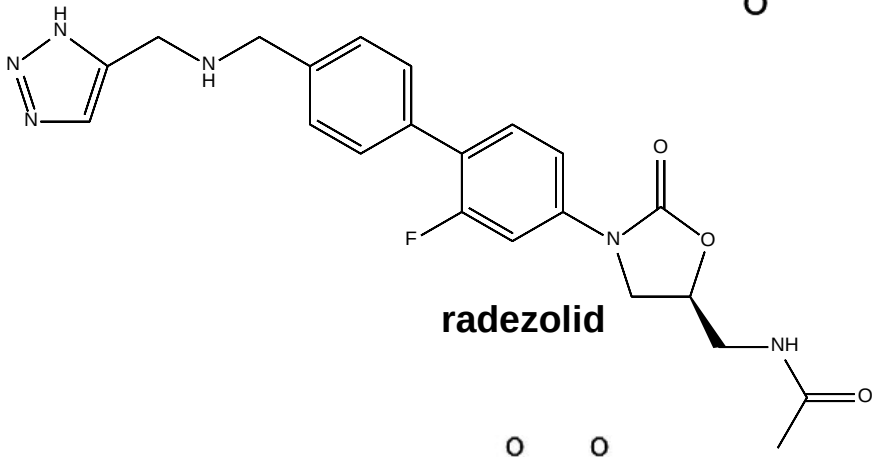


- **BAL30075:** a monosulfactam antibiotic using iron trasporters (supported by the EU Innovative Medicines Initiative [€50.7 million])
- **Radezolid:** 2d-generation oxazolidinone base on analysis of the ribosomal binding region of oxazolidinones
- **Avarofloxacin:** an aminoethylidenylpiperidine fluoroquinolone with low MICs against Gram-positive bacteria fluoroquinolones.
- **Surotomycine:** developped by Cubists for C. difficile diarrhea (no intestinal resorbtion but stopped by Merck & Co (who acquired Cubist Pharmaceuticals) due to its non-superiority to current therapies

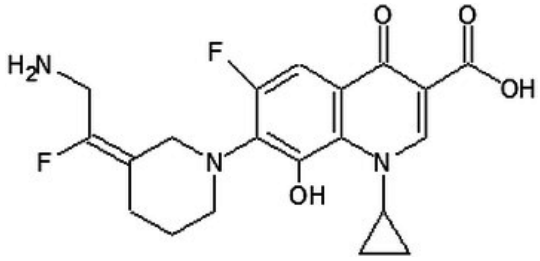
BAL 30072 – radezolid – avrofloxacin - Surotomycin

BAL 30072

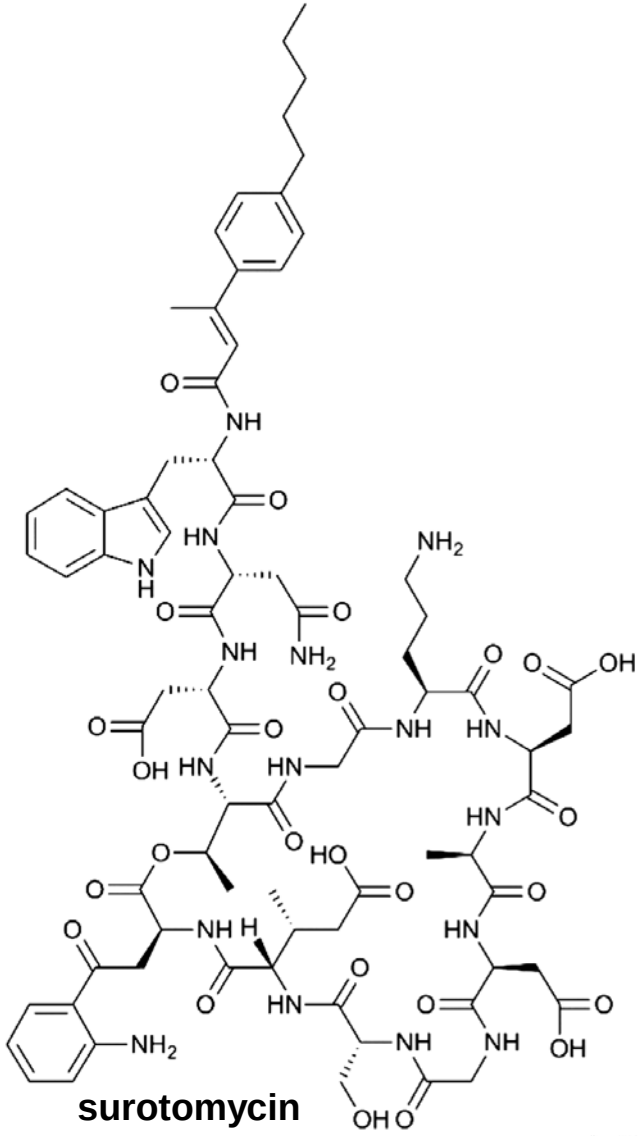




radezolid

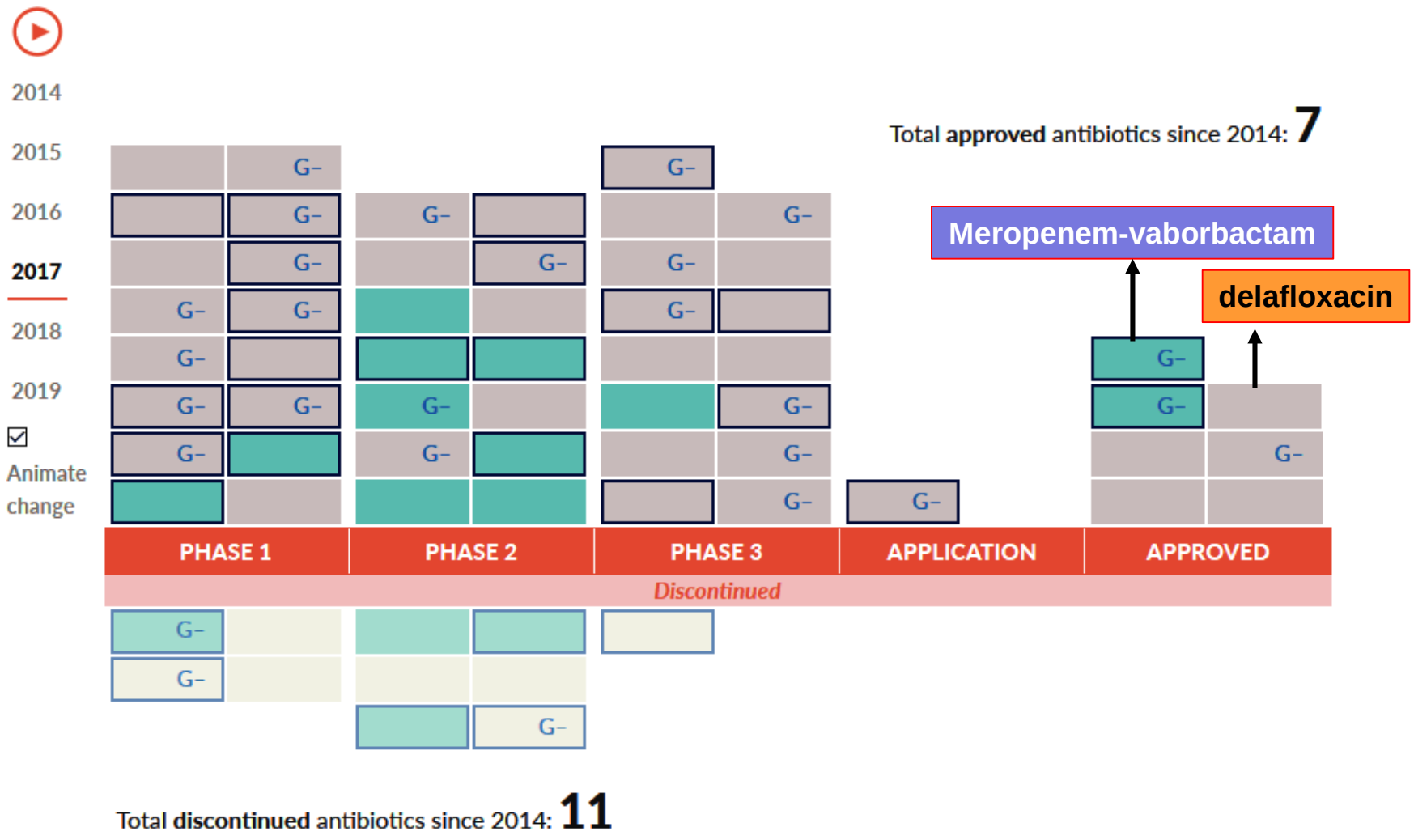


avrofloxacin

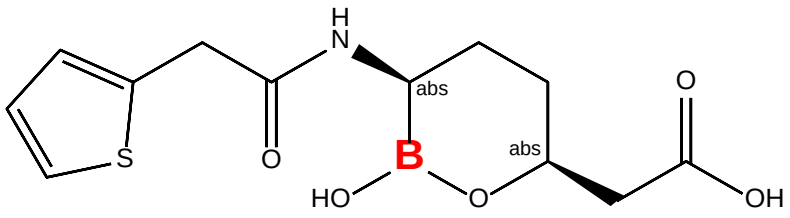


surotomycin

2017 : what we gained ...



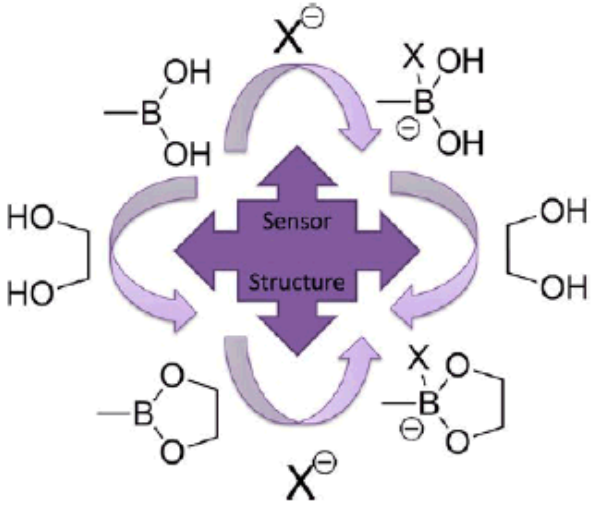
Vaborbactam



Vaborbactam inhibits a variety of β-lactamases, including KPC-2 carbapenemase, CTX-M-15 and SHV-12.

Boronic acids reversibly form covalent bonds with the active site serine in serine carbapenemases.

Meropenem-vaborbactam has emerged as treatment option for Enterobacterales producing ESBL, KPC, or AmpC,



Boronic acids can interact with Lewis bases to generate boronate anions, and they can also bind with diol units to form cyclic boronate esters.

Boronic acid based receptor designs originated when Lorand and Edwards used the pH drop observed upon the addition of saccharides to boronic acids to determine their association constants.

Accounts of Chemical Research 2013;46:312–326.

β-lactamase inhibitors

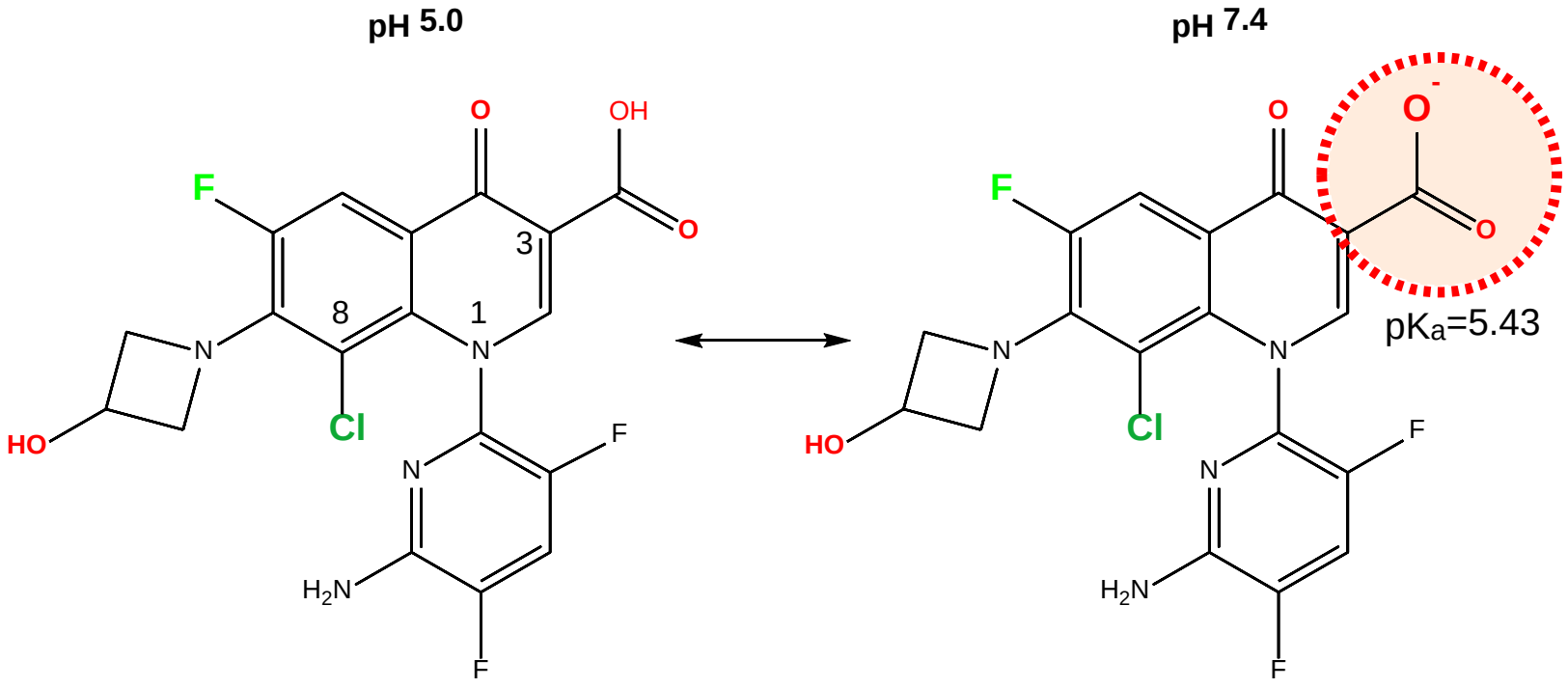
TABLE 1 Reported activity of various β-lactamase inhibitors from the BLBLIs against β-lactamase enzymes

Enzyme	Inhibited by: Avibactam	Tazobactam	Vaborbactam	Relebactam
Class A				
KPC	Yes	No	Yes	Yes
SHV	Yes	Yes	Yes	Yes
TEM	Yes	Yes	Yes	Yes
CTX-M	Yes	Yes	Yes	Yes
Class B				
MBL	No	No	No	No
Class C				
AmpC	Yes	No	Yes	Yes
Class D				
OXA	VD[a]	No	No	VD

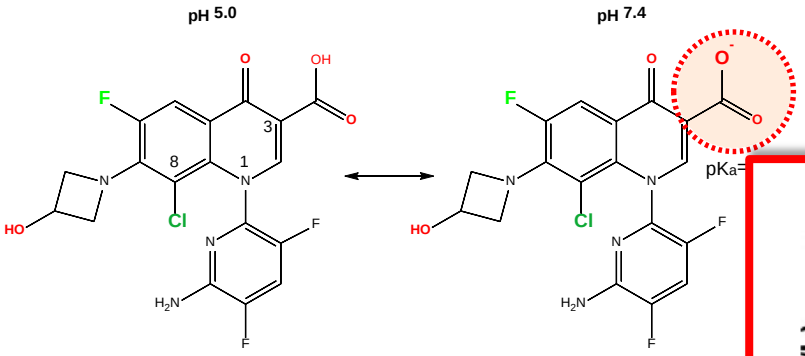
[a]VD, variable data.

Yahav et al. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin Microbiol Rev. 2020 Nov 11;34(1):e00115-20. doi: 10.1128/CMR.00115-20. PMID: 33177185

Delafloxacin



Delafloxacin



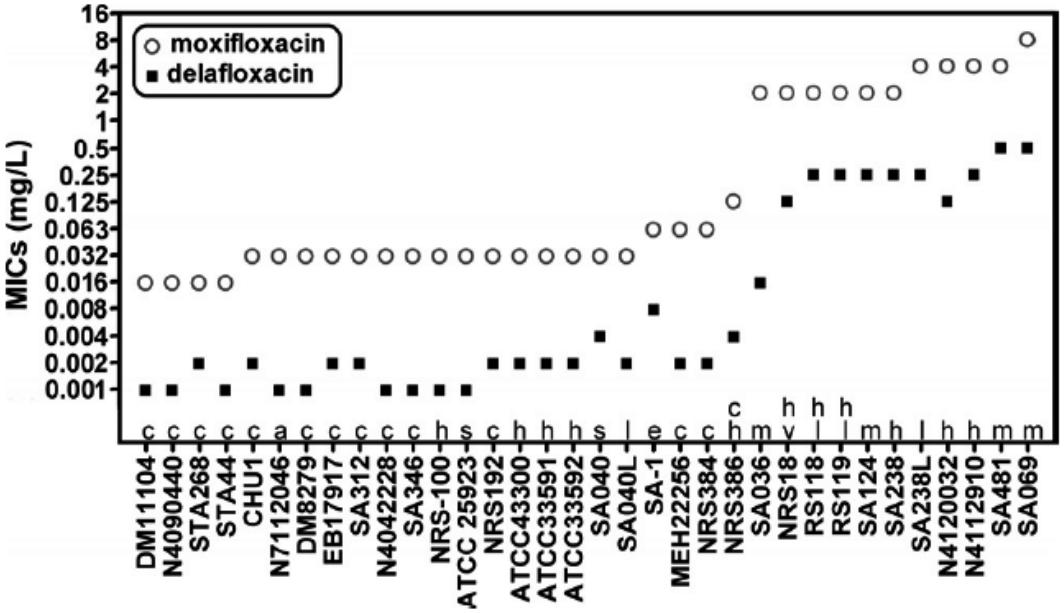


FIG. 2. Comparative susceptibilities of various *S. aureus* isolates to moxifloxacin (circles) or delafloxacin (squares). MICs were measured at pH 7.4, and strains are ranked based on their susceptibility to moxifloxacin. Resistance phenotypes and/or strain source are designated by lowercase letters along the *x* axis: a, animal MRSA; c, CA-MRSA; e, efflux (NorA); h, HA-MRSA; l, linezolid-resistant; m, characterized mutations in fluoroquinolone targets; s, MSSA.

Lemaire *et al*. Antimicrob Agents Chemother 2011;55:649-58 – PMID: 21135179

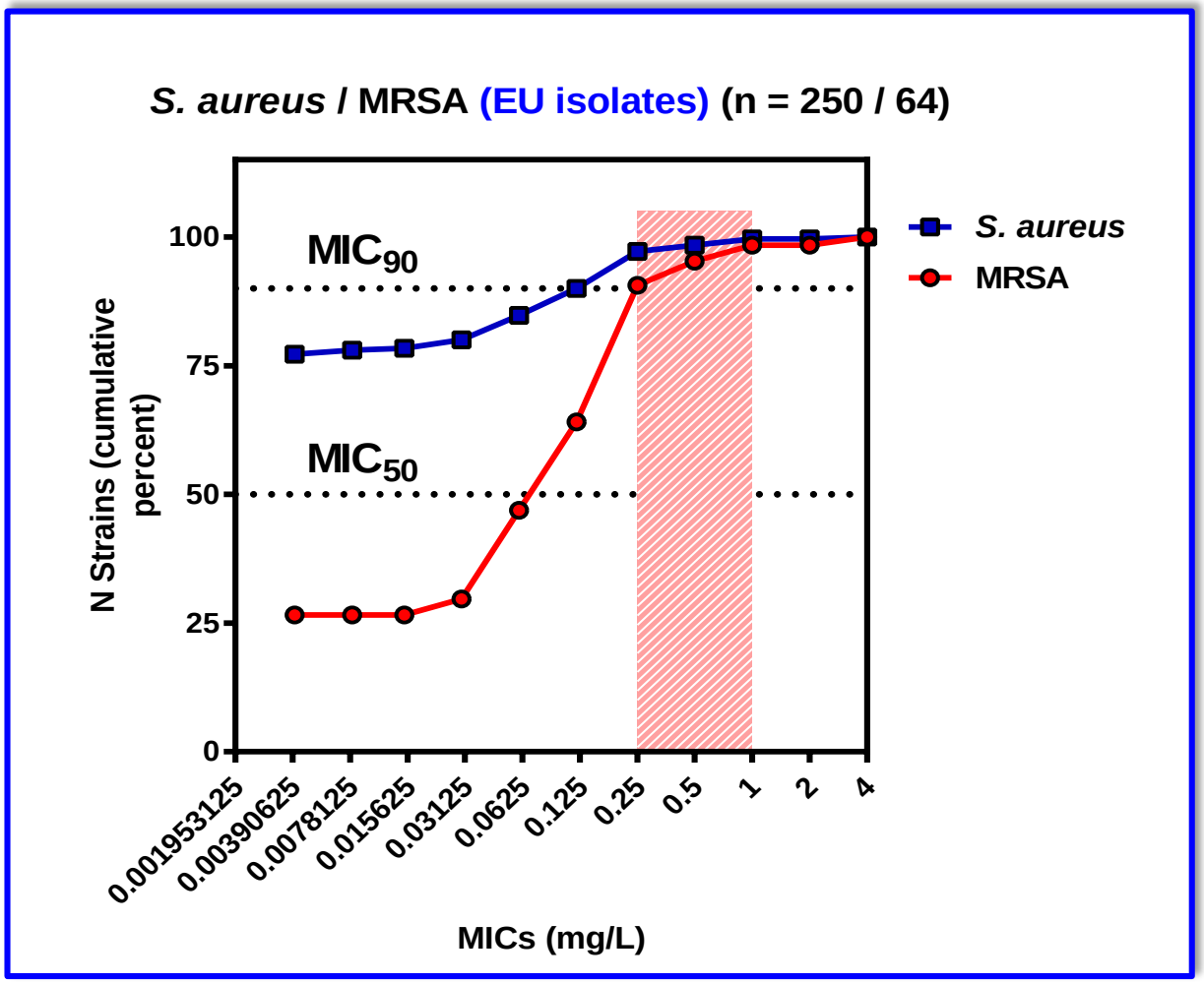
Delafloxacin

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

***In Vitro* Activity of Delafloxacin against Contemporary Bacterial Pathogens from the United States and Europe, 2014**

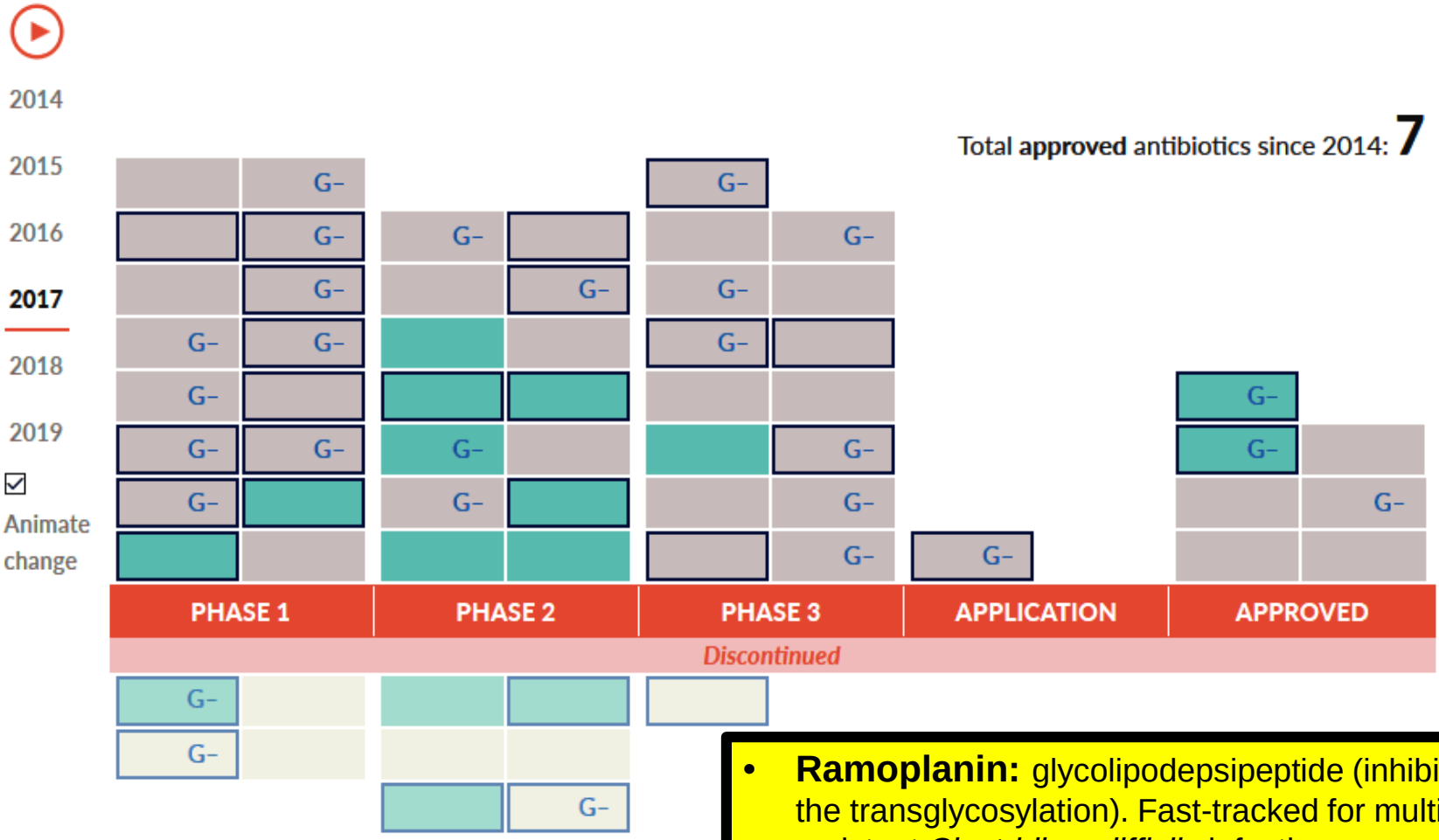
M. A. Pfaller,[a,b] H. S. Sader,[a] P. R. Rhomberg,[a] R. K. Flamm[a]
JMI Laboratories, North Liberty, Iowa, USA[a]; University of Iowa, Iowa City, Iowa, USA[b]

Pfaller et al. Antimicrob Agents Chemother 2017;61:pii: e02609-16 - PMID: 28167542



Pfaller et al. Antimicrob Agents Chemother 2017;61:pii: e02609-16 - PMID: 28167542
* see original paper for data from the US and additional data in Mogle *et al.* J Antimicrob Chemother. 2018 – Epub ahead of print - PMID: 29425340

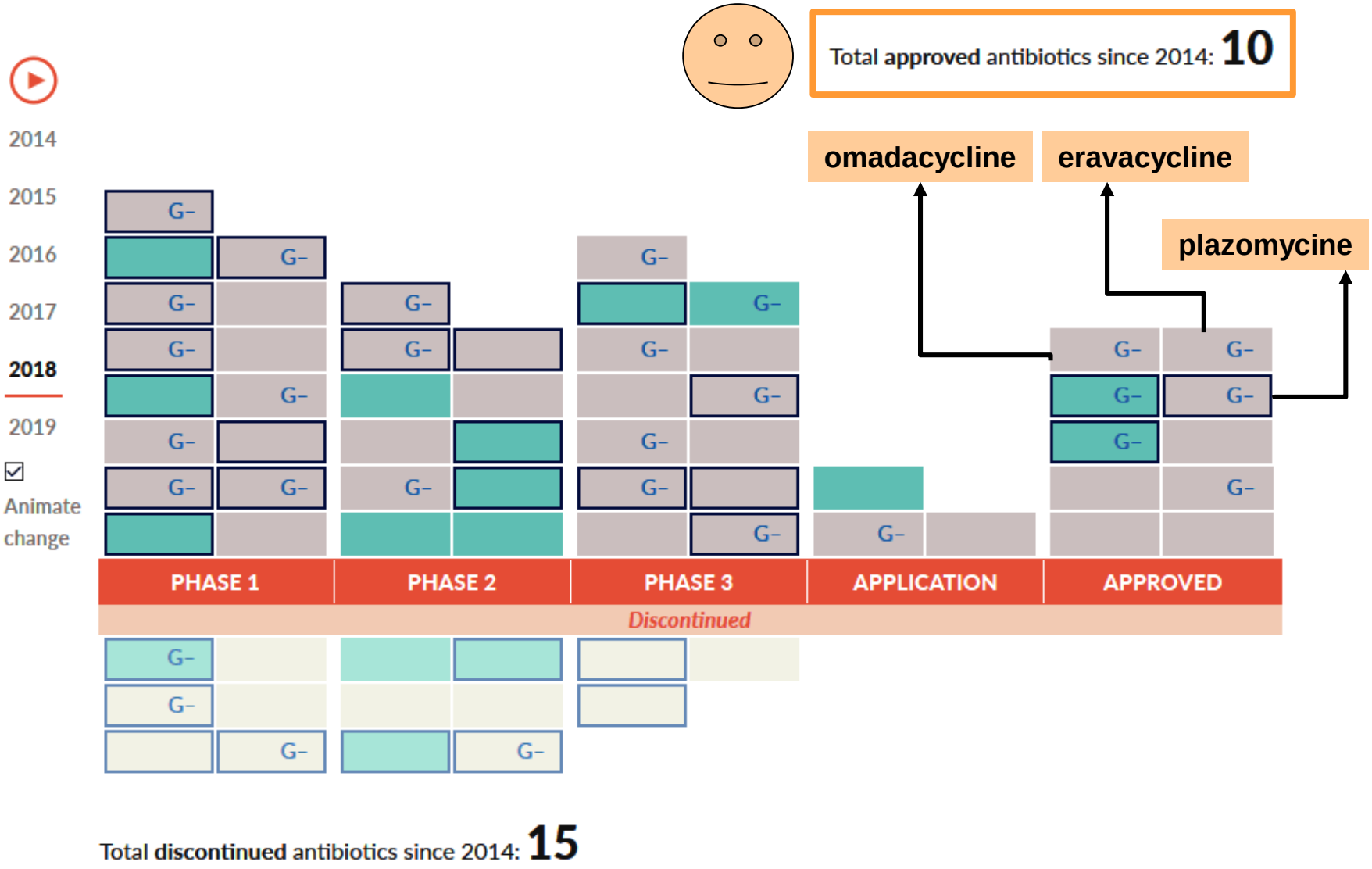
2017: the loss ...



Total **discontinued** antibiotics since 2014: **11**

- **Ramoplanin:** glycolipodepsipeptide (inhibiting the transglycosylation). Fast-tracked for multi-resistant *Clostridium difficile* infections...
- **Ceftaroline-avibactam:** approved for clinical use but dropped (marketing reasons ?)

2018: what we gained



Plazomycin : a new aminoglycoside ...

Do you know who was Selman Waksman ?

Waksman and Fleming …

streptomyces grisaeus

From the point of view of human benefit, never was a Nobel prize so justifiably awarded as was the award to Selman Waksman for the discovery of streptomycin. Waksman and his talented team developed the concept of **systematic screening** of microbial culture products for biological activity

J. Davies: In Praise of Antibiotics, ASM News
http://www.asm.org/memonly/asmnews/may99/feature6.html

Aminglycosides : the resistance challenge

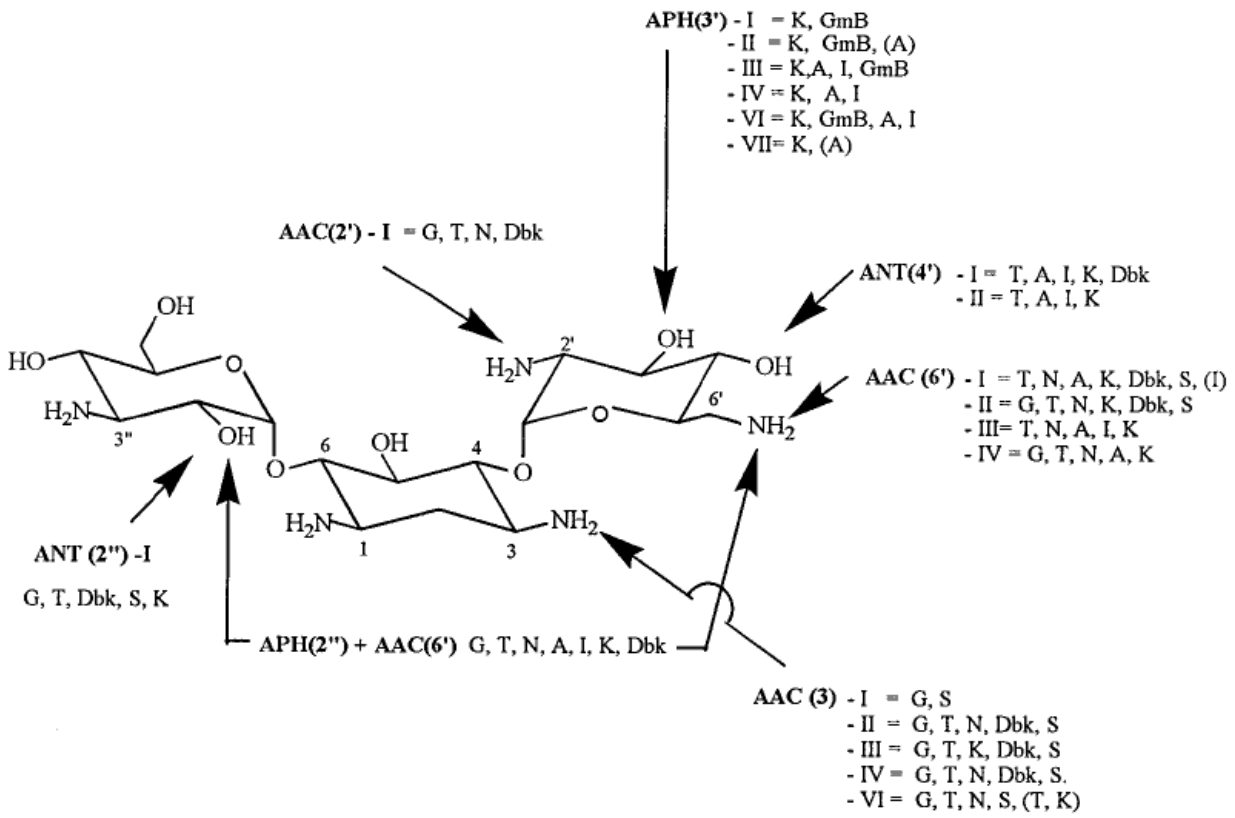
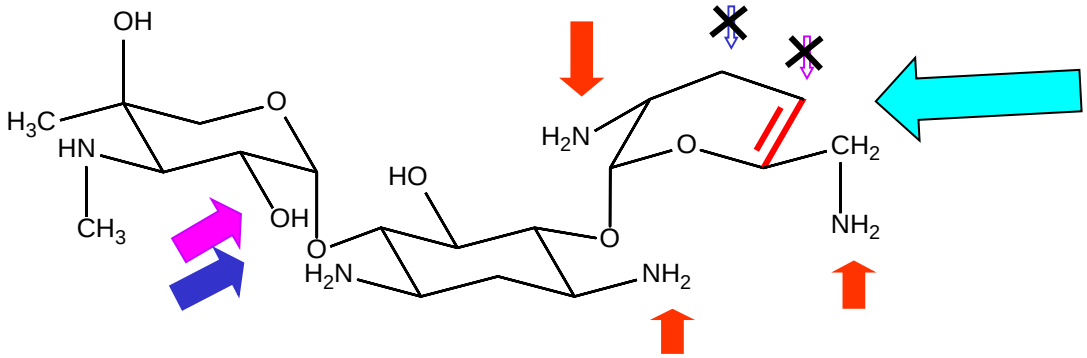


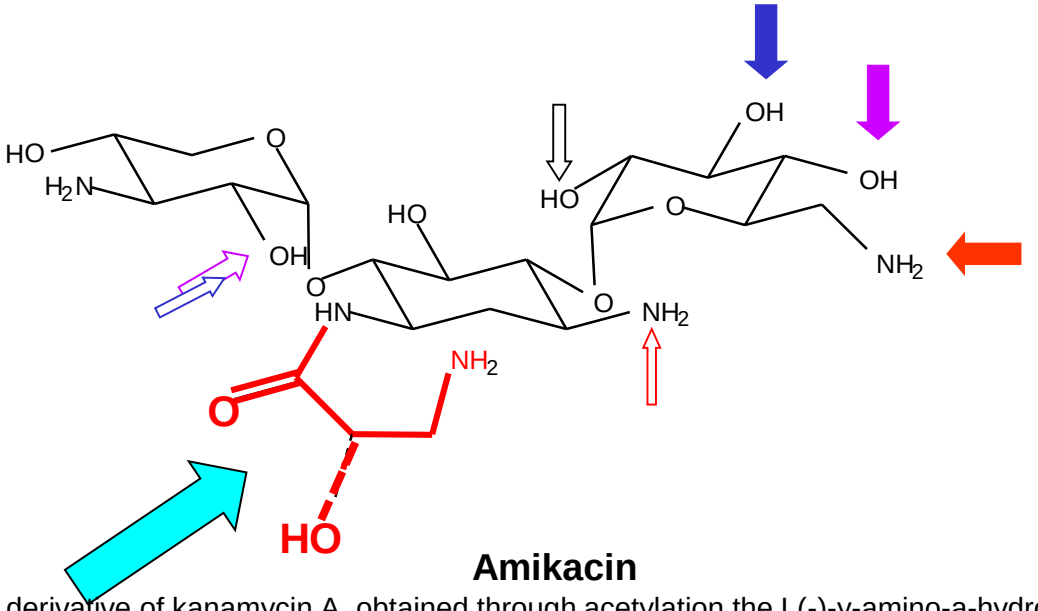
FIG. 3. Major aminoglycoside-modifying enzymes acting on kanamycin B (this aminoglycoside is susceptible to the largest number of enzymes). Each group of enzymes inactivates specific sites, but each of these sites can be acted upon by distinct isoenzymes (roman numerals) with different substrate specificities (phenotypic classification; each phenotype comprises several distinct gene products [denoted by lowercase letters after the roman numeral in the text]); at least one enzyme is bifunctional and affects both positions 2″ (*O*-phosphorylation) and 6′ (*N*-acetylation)). The main clinically used aminoglycosides on which these enzymes act are as follows: amikacin (A), dibekacin (Dbk), commercial gentamicin (G) (see text), gentamicin B (GmB), kanamycin A (K), isepamicin (I), netilmicin (N), sisomicin (S), and tobramycin (T) (see text for discussion of arbekacin, sagamicin, and dactimicin). The drug abbreviations which appear in parentheses are those for which resistance was detectable in vitro even though clinical resistance was not conferred. Based on the data of Shaw et al. (89).

Aminoglycosides and resistance: two early answers



Sisomicin

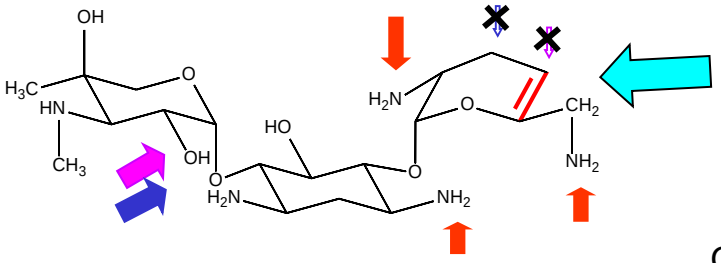
isolated from the fermentation broth of a new species of the genus Micromonospora (Weinstein et al. 1970)



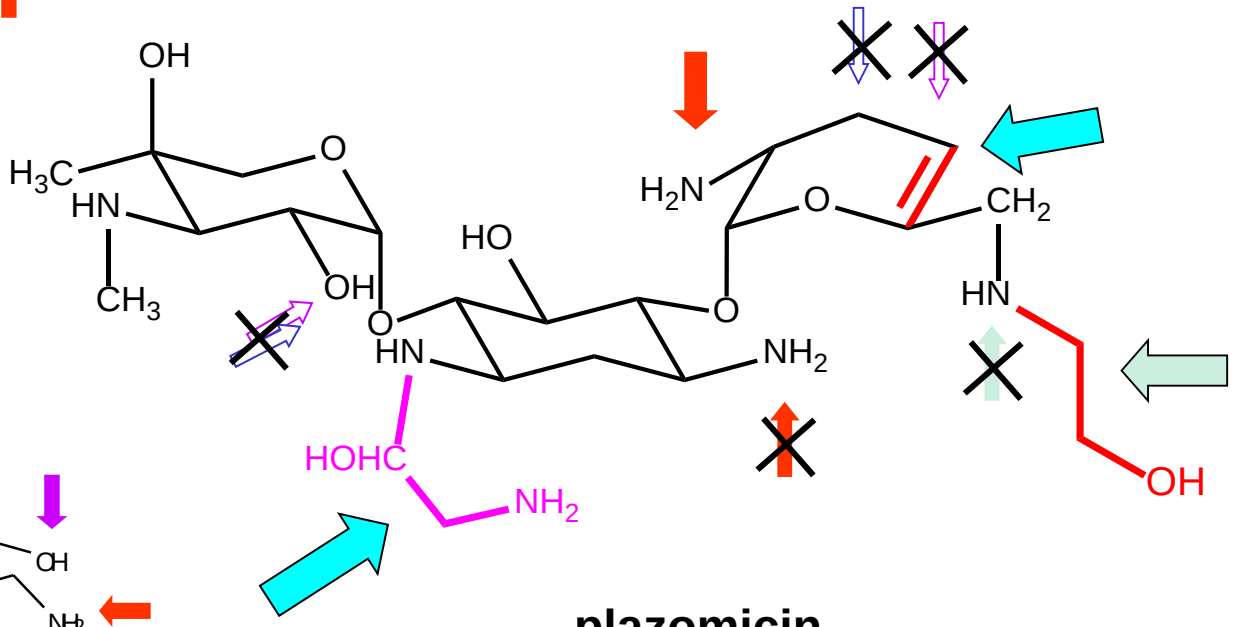
Amikacin

a derivative of kanamycin A, obtained through acetylation the L(-)-y-amino-a-hydroxybutyryl side chain at the C-l1 amino group of the streptaminemoiety (Kawaguchi et al.1972

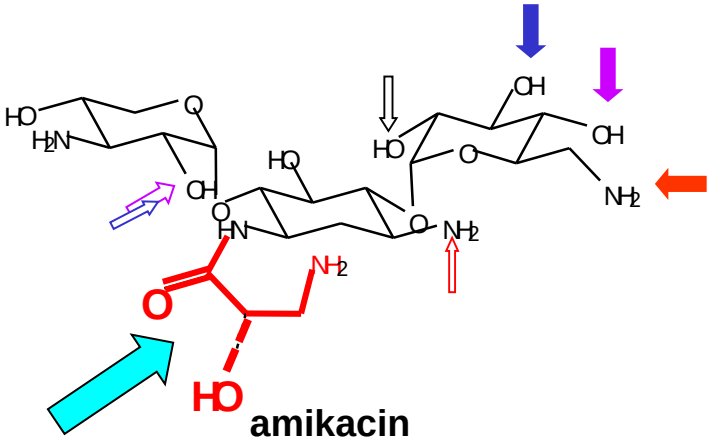
Aminoglycosides and resistance: two answers



sisomicin



plazomicin



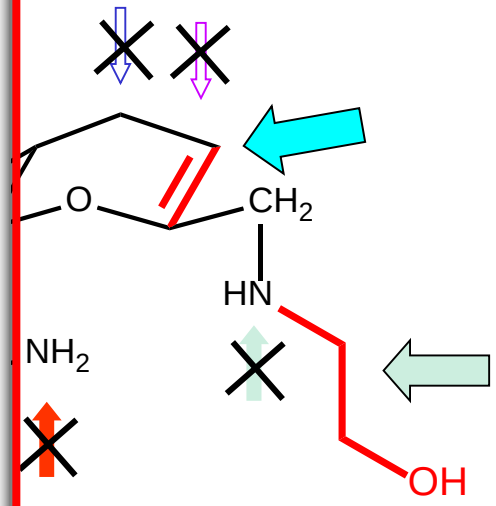
amikacin

Plazomycin: the answer of the market

BRIEF

Achaogen files for bankruptcy protection, seeks asset sale

Flickr: Images Money



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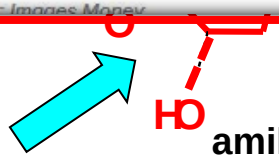


amikacin

Plazomycin: the answer of the market

BRIEF

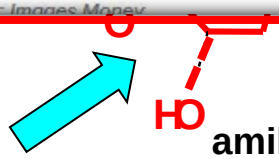
Achaogen files fo
protection, seeks

Flickr: Images Money

Achaogen's steady stock erosion since 2017

Andrew Dunn / BioPharma Dive, market data

Even Zemdri's approval brought challenges, as the FDA only approved the drug for certain complicated urinary tract infections, knocking back the company's bid to win an OK in bloodstream infections.



amikacin

Plazomycin: the answer of the market

BRIEF

Achaoge… files f…
protectio…

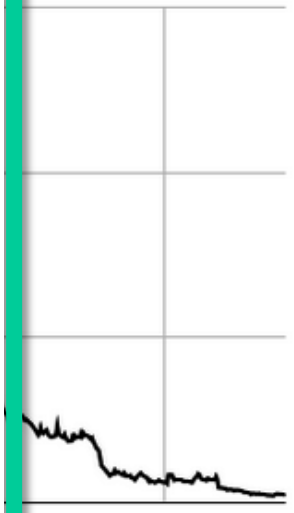
Flickr: Images Money

MOST POPULAR

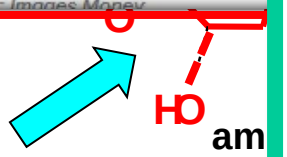
1.

Trump administration pushes last-ditch plans to lower drug prices

2. Stem cell therapy for ALS fails a large clinical trial

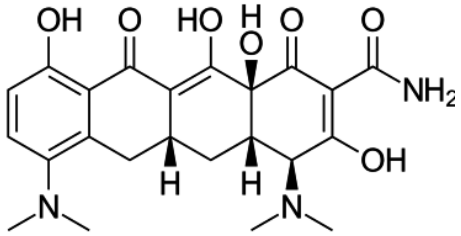


…A only approved the
…nocking back the



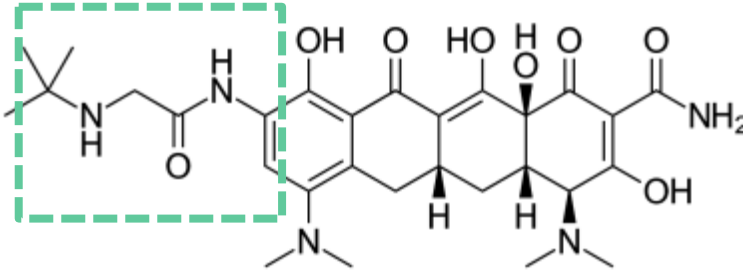
The twins ... Later than tigecycline...

minocycline



Limited by resistance

tigecycline



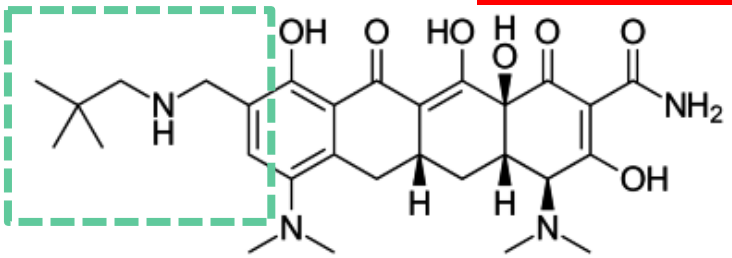
Active against many tetracycline-resistant strains

No pseudomonal activity
IV only
Limited by toxicity

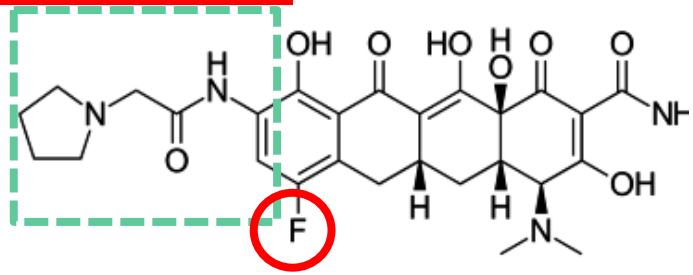
omadacycline

Oral
active on tetracycliines resistant strains

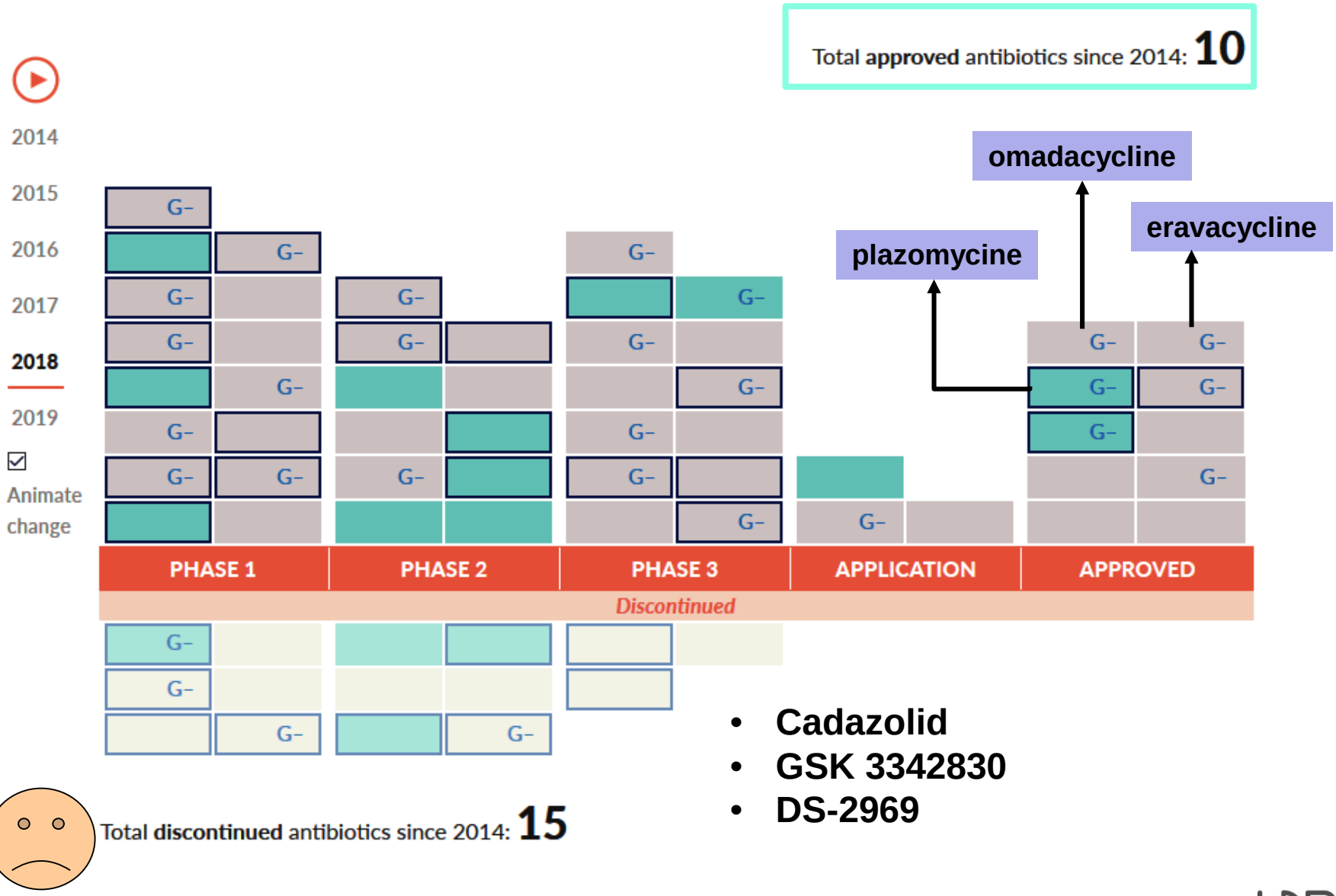
No useful activity against Pseudomonas



eravacycline

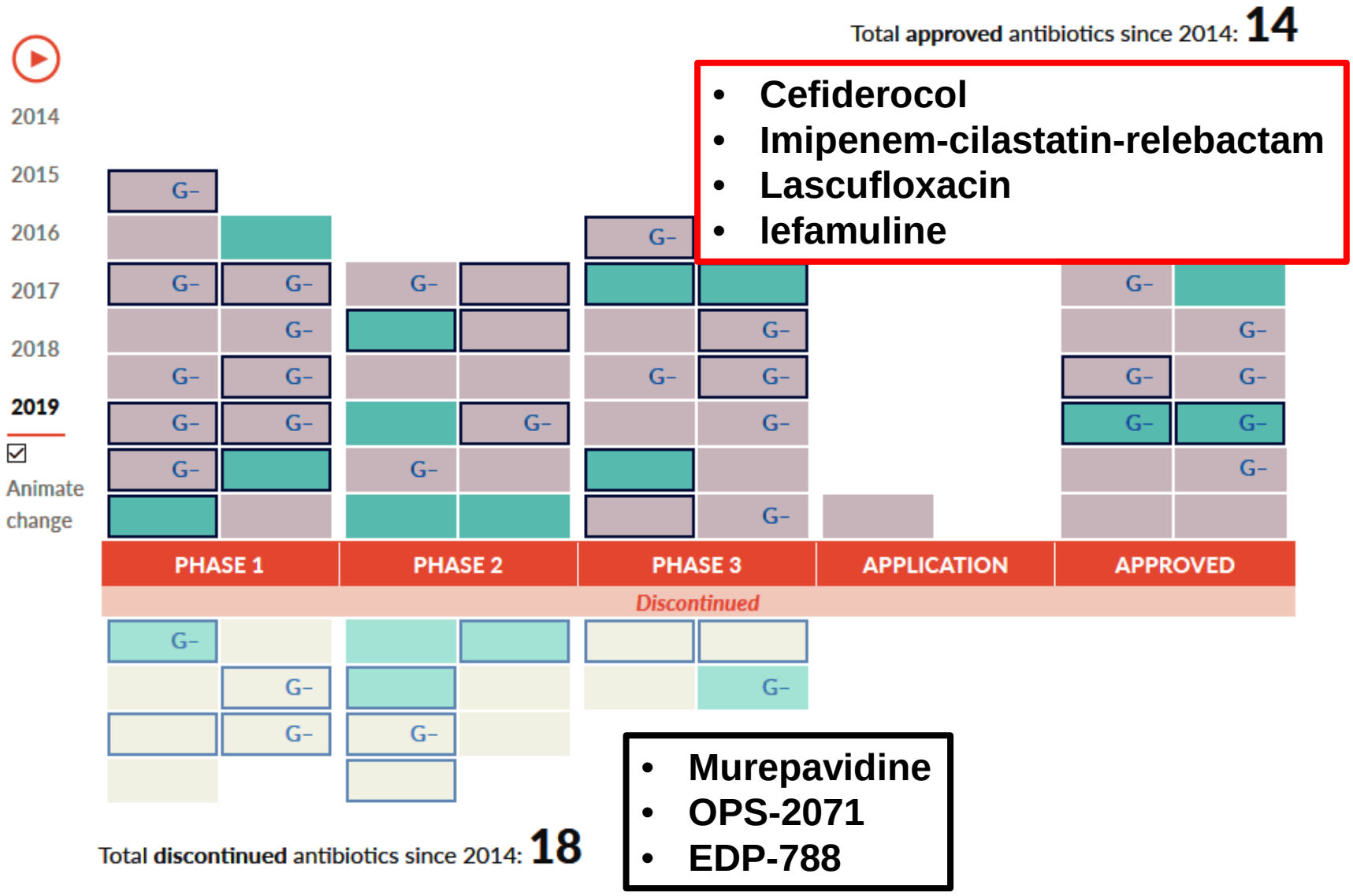


2018: what we lost ...



- **Cadazolid**
- **GSK 3342830**
- **DS-2969**

2019...

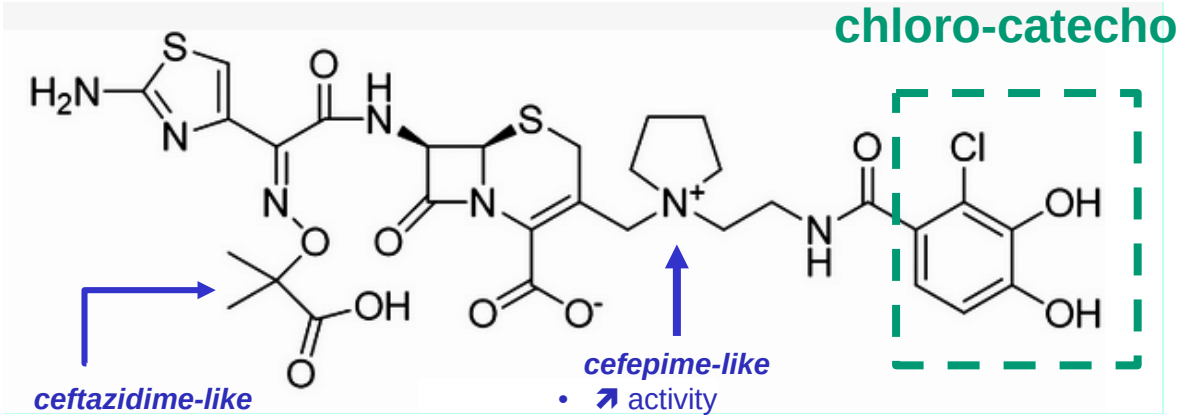


- Cefiderocol
- Imipenem-cilastatin-relebactam
- Lascufloxacin
- lefamuline

- Murepavidine
- OPS-2071
- EDP-788

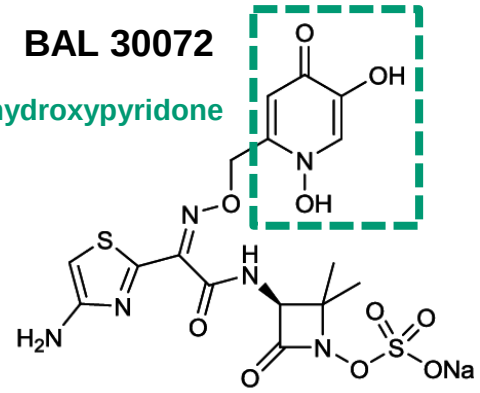
Cefiderocol – Relebactam - Lascufloxacin

cefiderocol

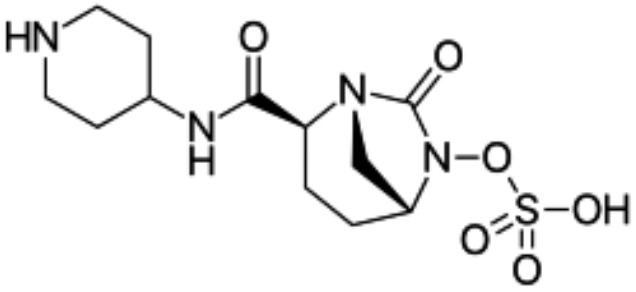


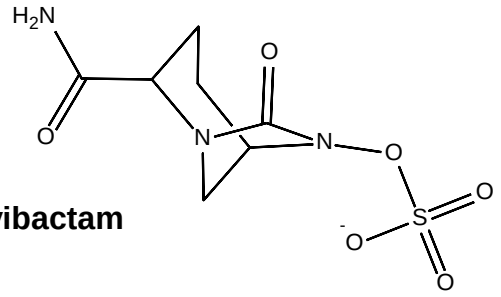
BAL 30072

hydroxypyridone



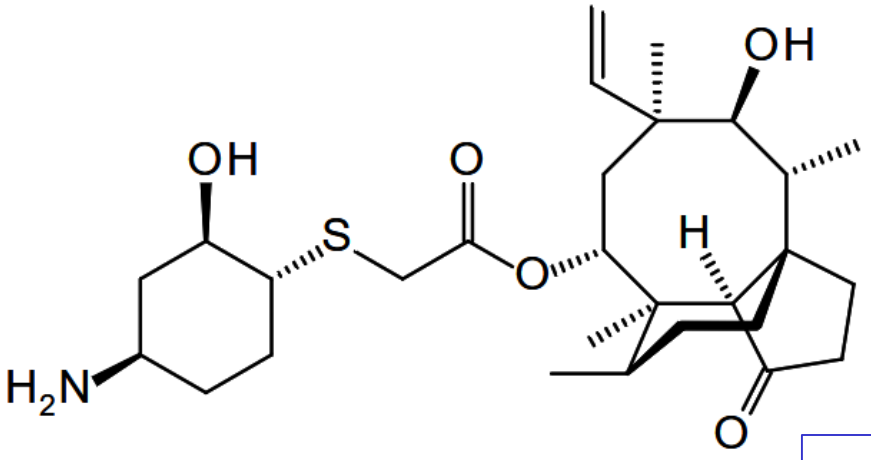
relebactam





avibactam

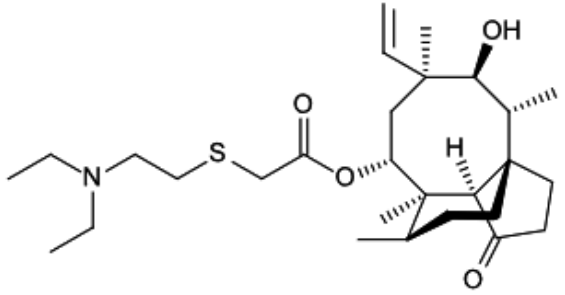
Lefamuline



Lefamulin has *in vitro* activity against *Streptococcus viridans*, *Moraxella catarrhalis*, *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), among other bacteria.

History

It was developed by Nabriva Therapeutics and approved in the United States in 2019.[3] It was granted fast track status by the US Food and Drug Administration (FDA) in 2014. Although pleuromutilin antibiotics were first developed in the 1950s, lefamulin is the first to be used for systemic treatment of bacterial infections in humans.



Tiamulin (previously thiamutilin) is a pleuromutilin antibiotic drug that is used in veterinary medicine particularly for pigs and poultry. **Tiamulin** is a diterpene antimicrobial with a pleuromutilin chemical **structure** similar to that of valnemulin.

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics

?

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics

Update from WHO and

Pew

urg

acc

dev

?

Recent assessments from both organizations find that there are not enough antibacterial treatments in development to keep up with growing resistance

New antibiotics: do we have enough ?

Is this enough ?

We may need a real revolution ...

New antibiotics: do we have enough ?

Is this enough ?

We may need a real revolution ...


Van Eyck 1432

A real revolution ?

It was shown to the public in 1436 ...

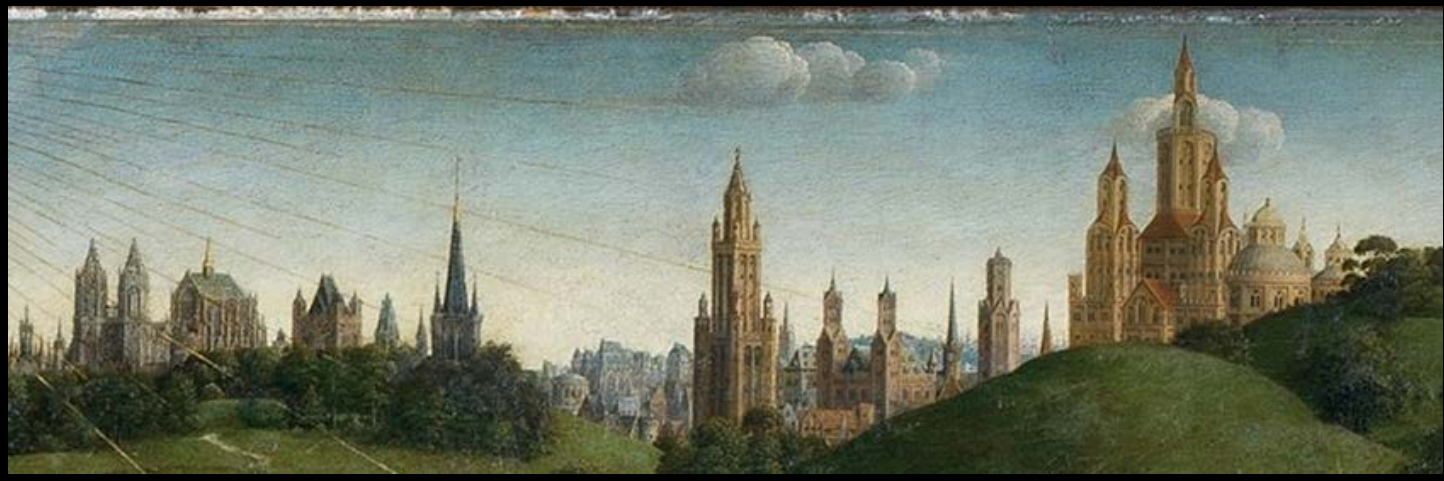
When most if not all paintings were like this:

Fra Angelico
Virgin's corronation

Francesco d'Antonio,
St Jerome's Dream (1433)

A real revolution ?

With a fantastic opening to details and decors



A real revolution ?

With a fantastic opening to details and decors

A real revolution ?

With a fantastic opening to details and decors

A real revolution ?

Adressing major points of thinking

A real revolution ?

But also being close of the daily life...

A real revolution ?

Being new but not hesitating to restore and revisit old places

Antibiotic pipeline: did you change your mind ?

- Large number of molecules in clinical development
  … much more in preclinical development

- More advanced molecules (Phase III) are new derivatives in existing classes with improved properties
  (MIC – resistance – PK- safety)

Antibiotic pipeline: can we do better ?

- Equivalence to current options in comparative clinical trials

  ⇨ This will raise issues for reimbursement,
  especially against the generics of the comparators
  used in these studies

  ⇨ Need to design superiority trials and
  to focus pricing and reimbursement
  for documented cases of infection by resistant organisms

Non-inferiority vs superiority trials ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NON-INFERIORITY if NO evidence of spontaneous resolution rate (more effective than placebo)

Indications (and delta):

- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than ≤ -12.5%)
- Skin and soft tissue infections (-10%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)

→ DRUG/comparator trial

SUPERIORITY if spontaneous resolution (placebo effective)

- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Acute otitis media
- Superficial skin infections (such as impetigo and minor wounds)
- Inhaled antibacterial agents (excl. CF)

→ Placebo/ DRUG/comparator trial

LIMITED TRIALS

- Rare MDR organisms
- Few patients

→ DRUG non comparative trial