ANTIBIOTIC RESISTANCE AND NEW ANTIBIOTICS

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Disclosures

- None

Goals

1. Understand the impact and causes of antibiotic resistance

2. Recognize the role of antimicrobial stewardship

3. Become familiar with new antibiotics approved for the treatment of three common infectious syndromes
   - *Complicated UTI (cUTI)*
   - *Acute bacterial skin and skin structure infection (ABSSSI)*
   - *Community acquired bacterial pneumonia (CABP)*

Mentimeter – Word cloud

- “What are the most common infection syndromes that you manage?”

Mentimeter – word cloud

- “What infectious syndromes to you find the most difficult to treat?”

Mentimeter – word cloud

- “What resistant pathogens are the most commonly encountered in your practice?”

Antimicrobials and modern medicine

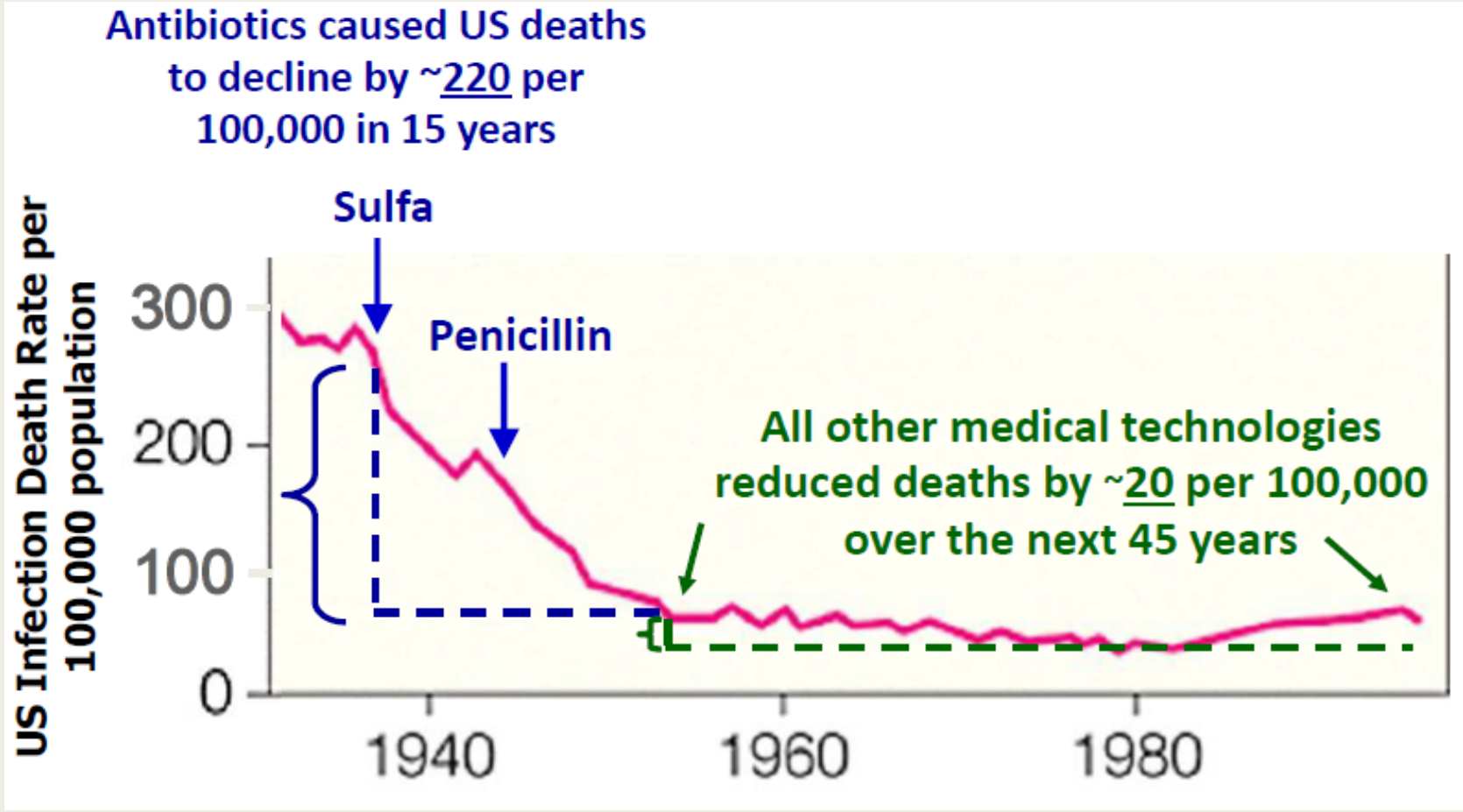
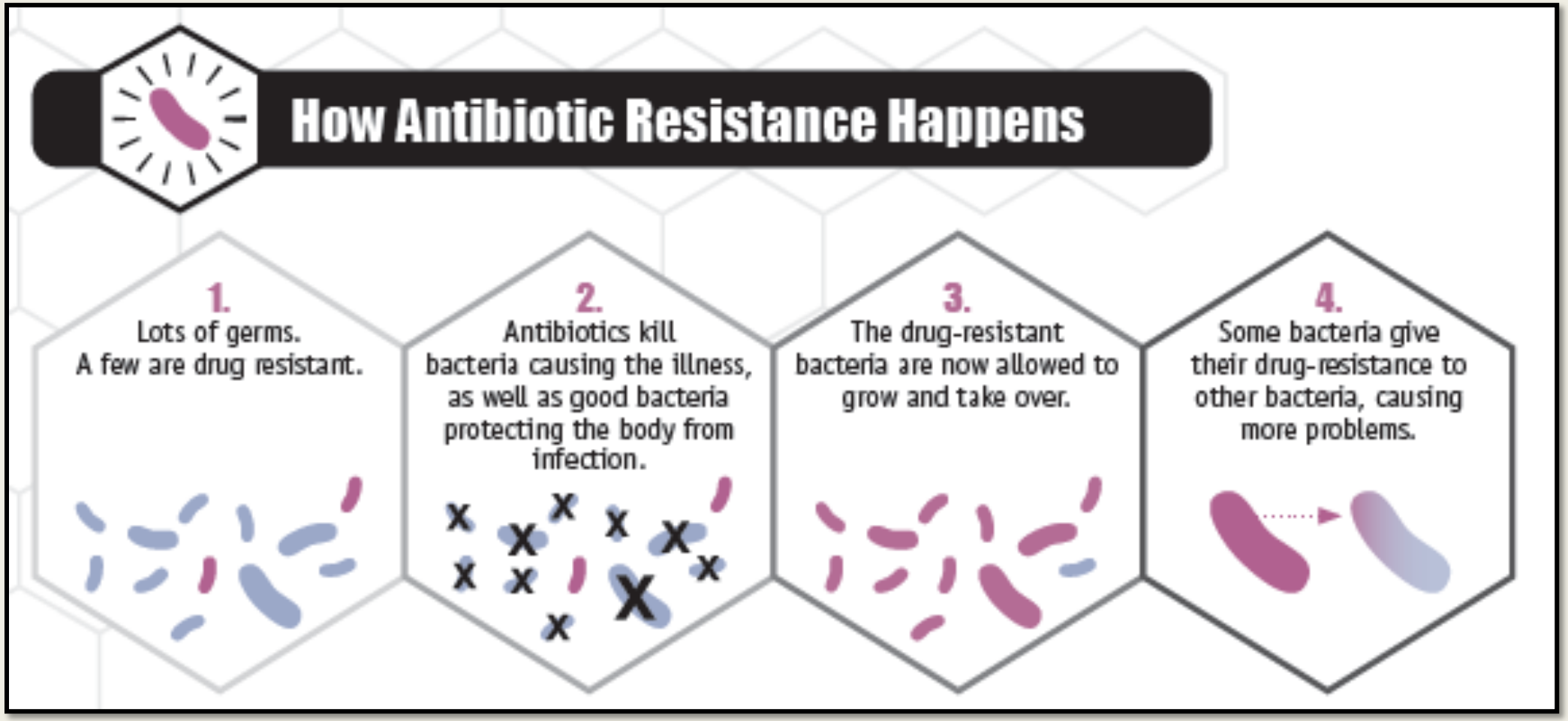
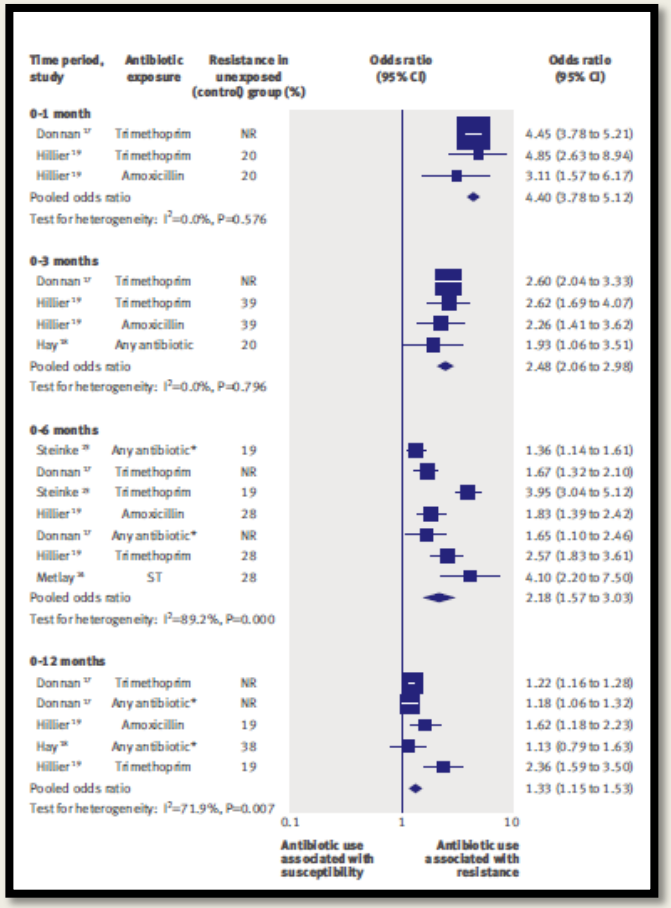


Figure from C. Sears presentation to US Congress. 2013
Armstrong GL, et al. JAMA 1999; 281:61-66

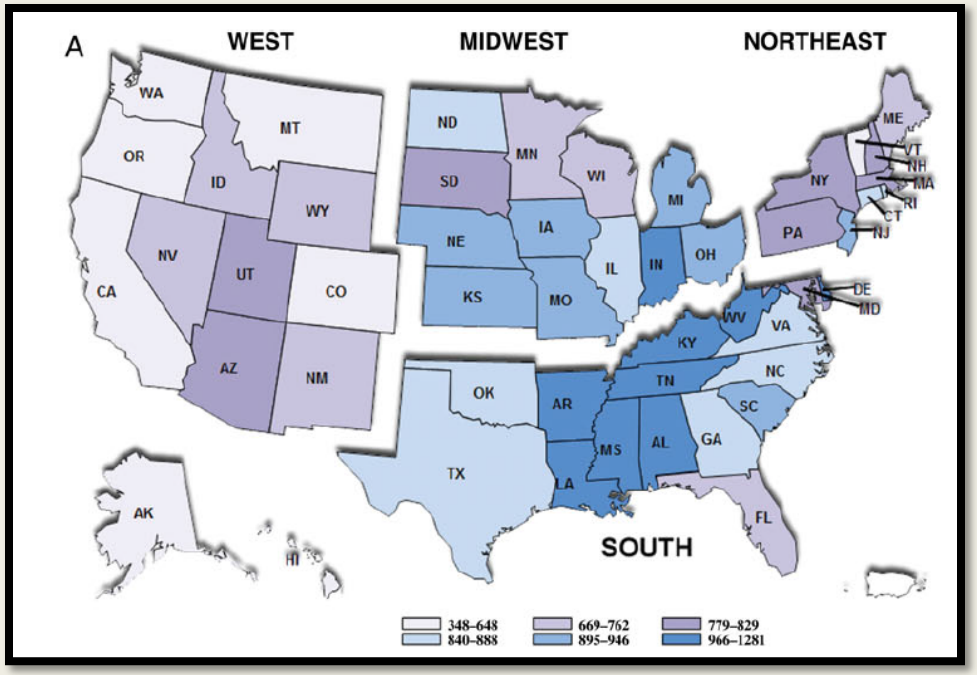


Antimicrobial resistance threats in the US, 2013.
CDC

Correlation between antibiotic use and resistance

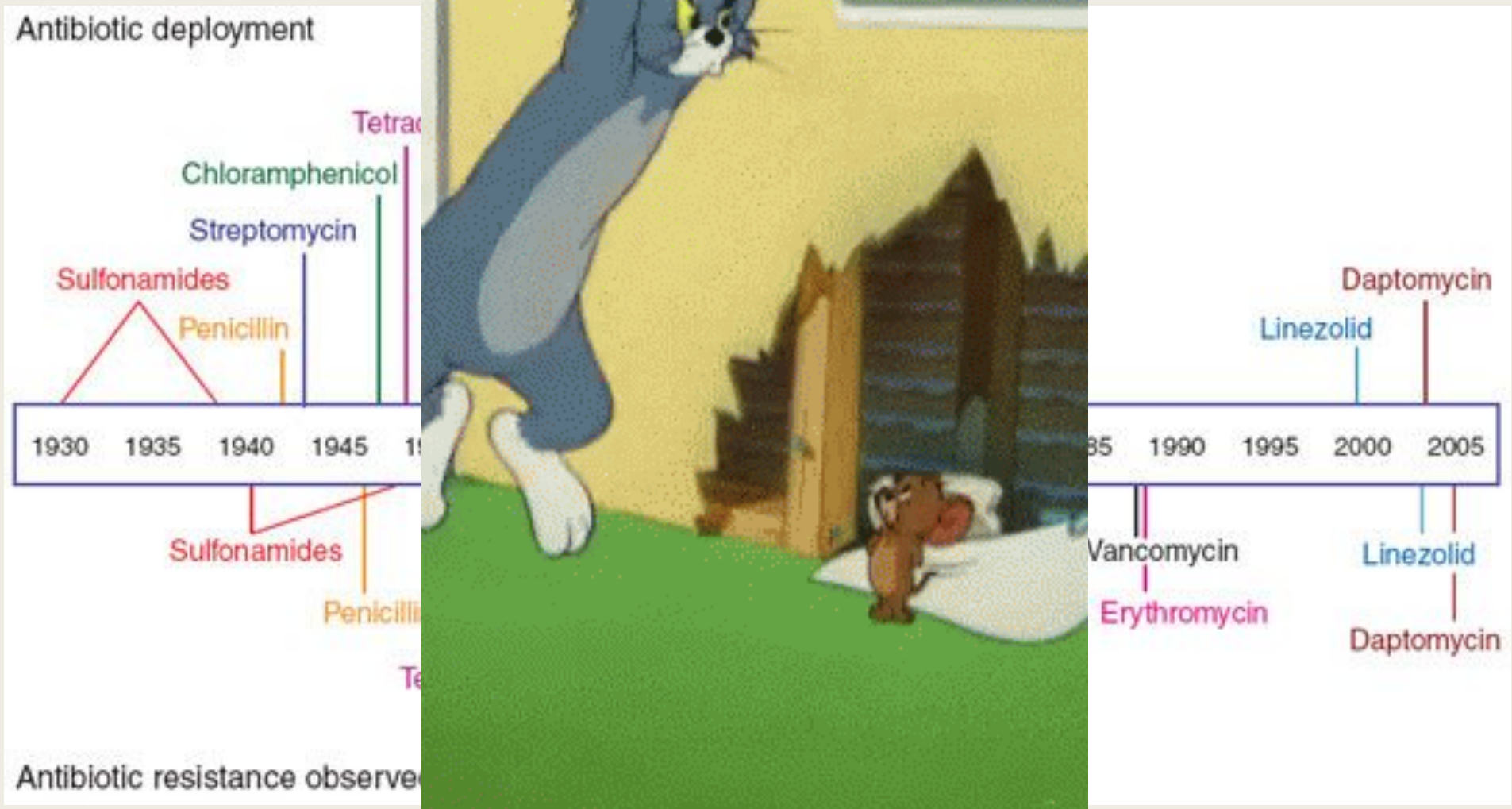


Costelloe C et al. BMJ 2010; 340

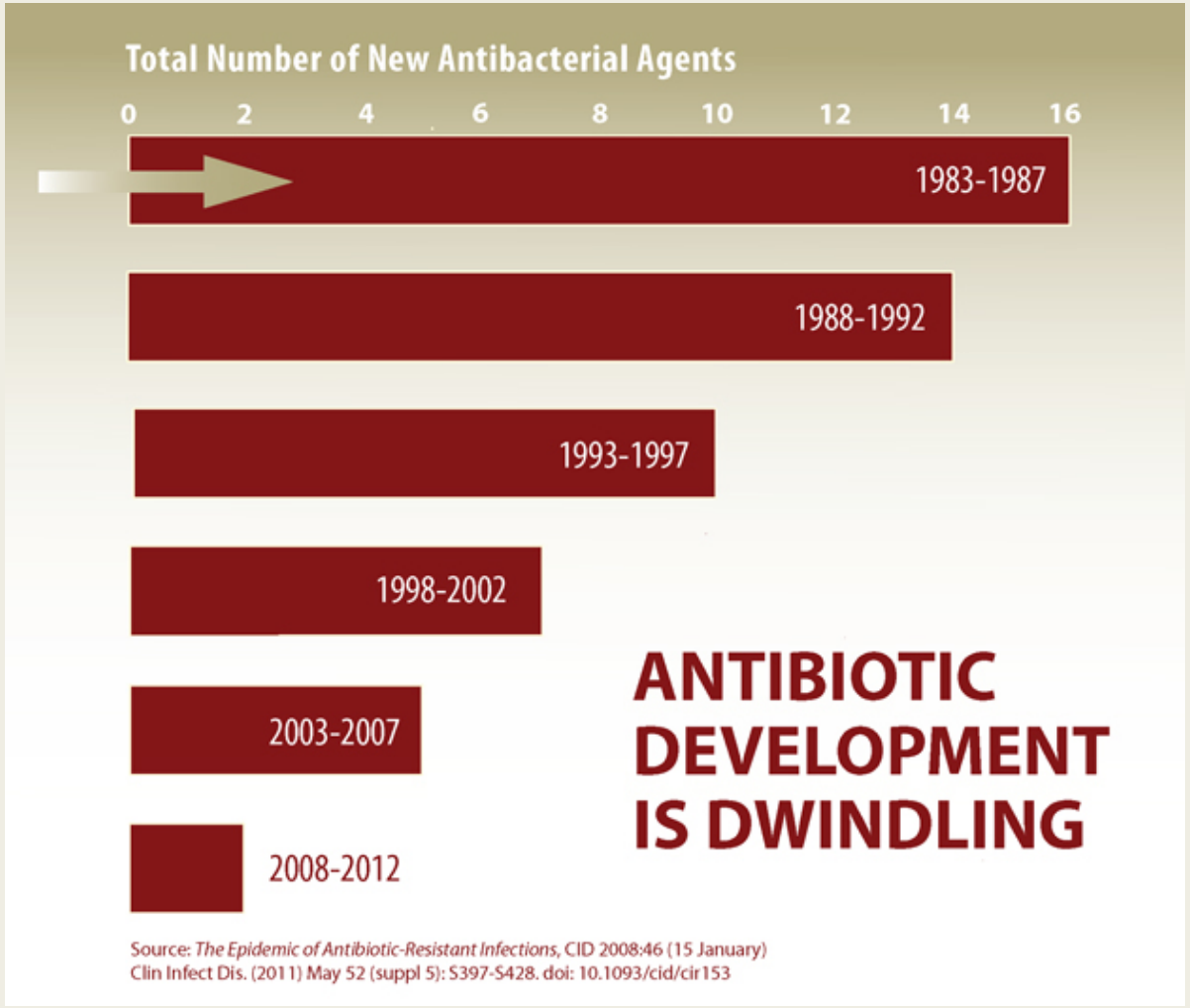


Hicks LA, et al. Clinical Infectious Diseases. 2015;60(9):1308–16

Resistance timeline

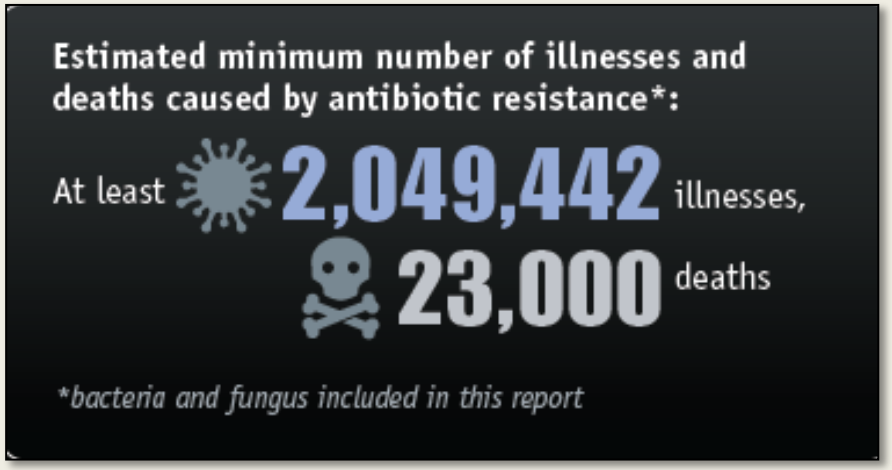


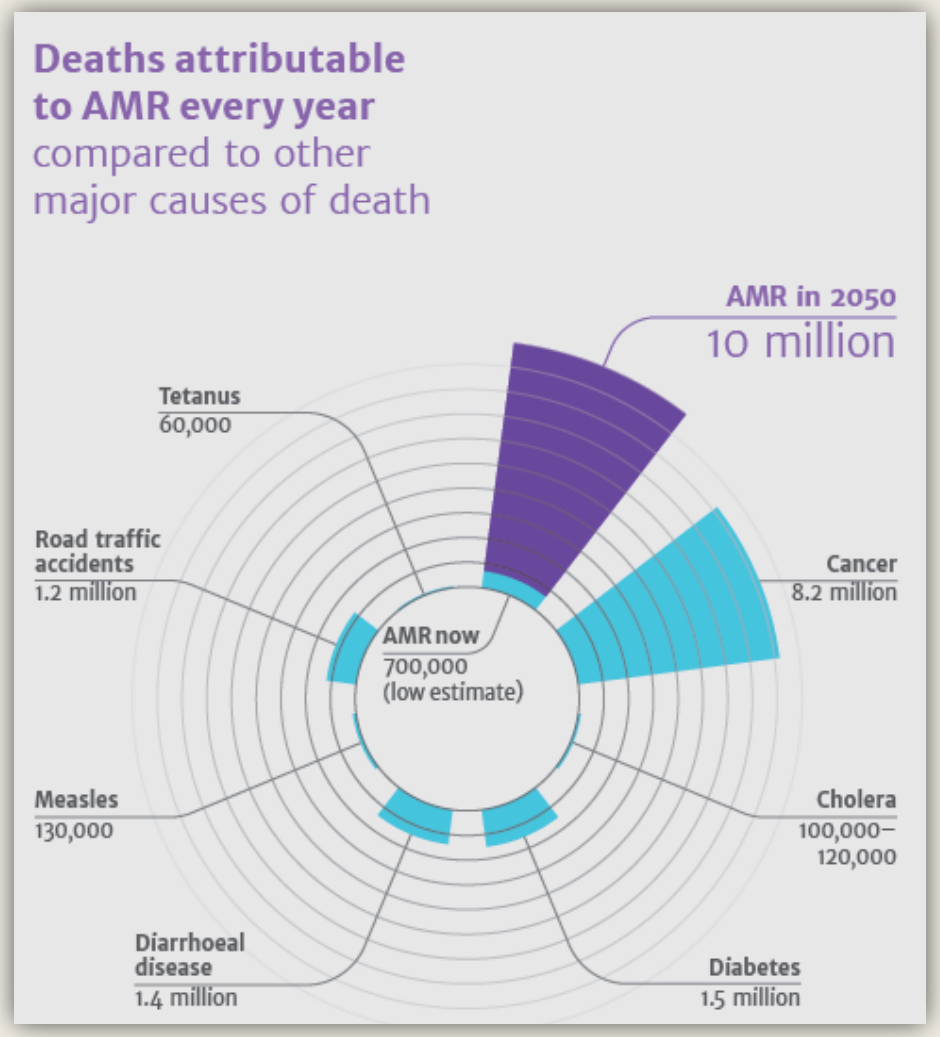
The antibiotic pipeline



Spellburg B, et al. *Clinical Infectious Diseases*. 2011

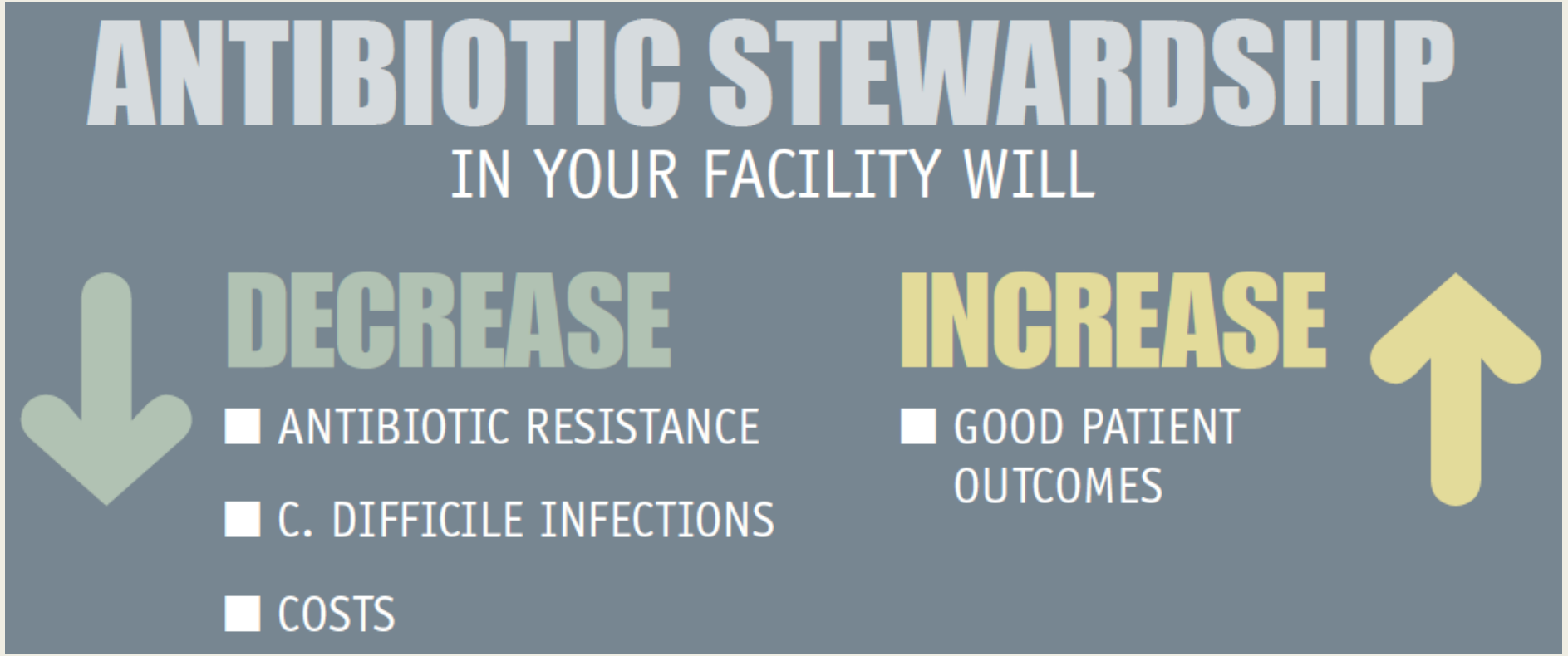
Impact of antimicrobial resistance





Antimicrobial resistance threats in the US, 2013. CDC
The Review on Antimicrobial Resistance. Oneil J, 12/2014

What is Antimicrobial Stewardship?



CDC. Antibiotic Resistance Solutions Initiative

Mentimeter – Poll Question Clinical Case

A 75-year-old female with dementia, T2DM, and CKD 3 is brought in from the nursing home where she resides for evaluation of a positive urine culture. A urinalysis was sent 2 days prior in the setting of increased somnolence and notable for 2+ squamous epithelial cells, 110 WBC, 0 RBC, positive LE, negative nitrite, and 2+ bacterial. The urine culture has grown >100cfu ESBL E. coli that is sensitive to Bactrim and Carbapenems. In clinic she is afebrile, hemodynamically stable, and denies dysuria or increased urgency/frequency. What is the most appropriate management?

- A. Bactrim for 14 days
- B. Ertapenem for 5 days
- C. Plazomicin for 5 days
- D. No need for antibiotic therapy

NEW ANTIBIOTICS: COMPLICATED URINARY TRACT INFECTIONS (cUTI)

Plazomicin (Zemdri)

Mechanism and Spectrum

- Novel aminoglycoside, interferes with protein synthesis at 30s ribosomal subunit
- Enterobacteriacae, variable against pseudomonas

Indications

- cUTI, including pyelonephritis (FDA approved 6/2018)

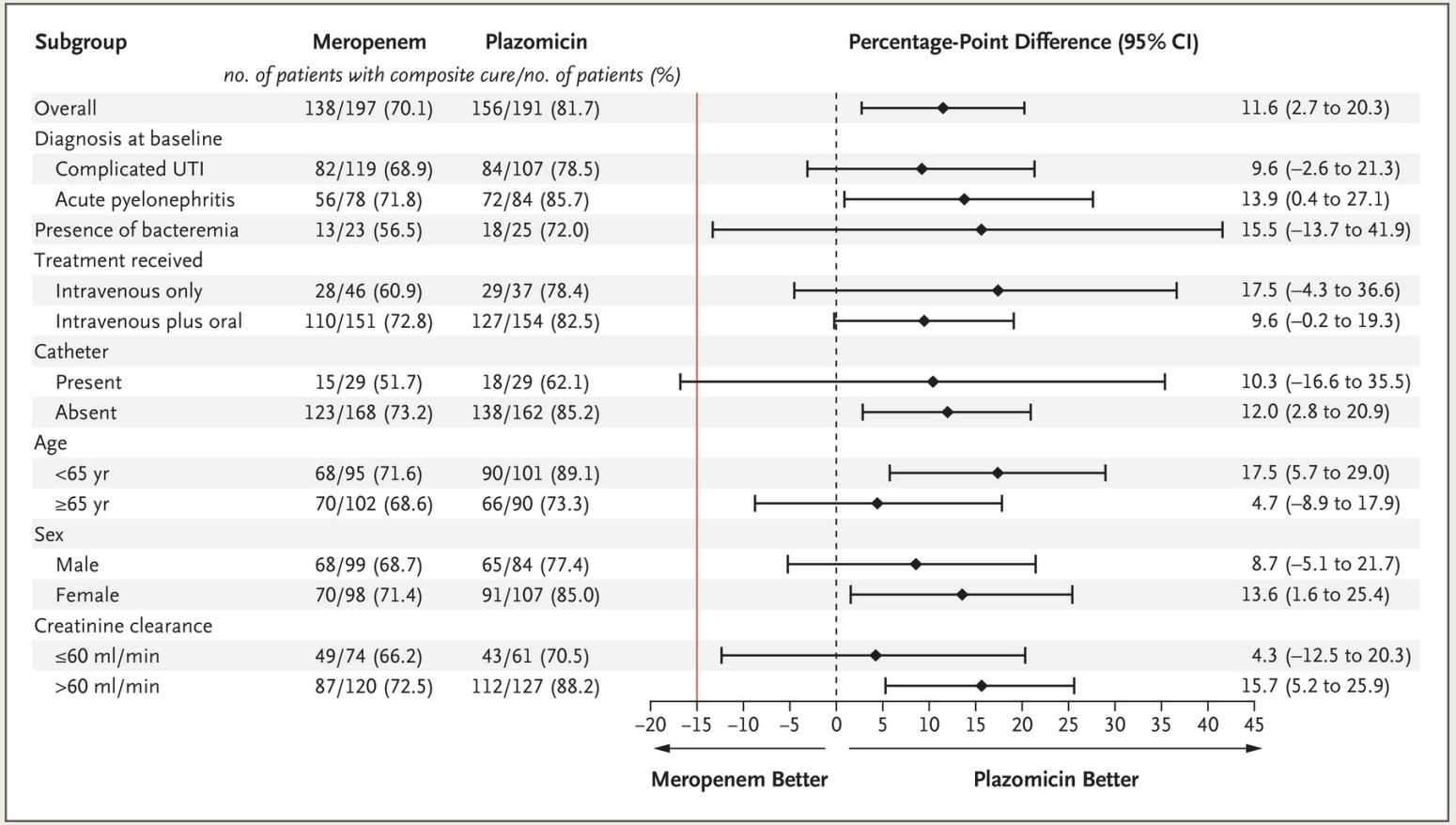
Formulations

- IV once daily (~$74 per dose)

Special Considerations

- Ototoxicity and nephrotoxicity documented

Evaluating Plazomycin in cUTI (EPIC) Trial



Subgroup	Meropenem	Plazomicin	Percentage-Point Difference (95% CI)
	no. of patients with composite cure/no. of patients (%)		
Overall	138/197 (70.1)	156/191 (81.7)	11.6 (2.7 to 20.3)
Diagnosis at baseline			
Complicated UTI	82/119 (68.9)	84/107 (78.5)	9.6 (–2.6 to 21.3)
Acute pyelonephritis	56/78 (71.8)	72/84 (85.7)	13.9 (0.4 to 27.1)
Presence of bacteremia	13/23 (56.5)	18/25 (72.0)	15.5 (–13.7 to 41.9)
Treatment received			
Intravenous only	28/46 (60.9)	29/37 (78.4)	17.5 (–4.3 to 36.6)
Intravenous plus oral	110/151 (72.8)	127/154 (82.5)	9.6 (–0.2 to 19.3)
Catheter			
Present	15/29 (51.7)	18/29 (62.1)	10.3 (–16.6 to 35.5)
Absent	123/168 (73.2)	138/162 (85.2)	12.0 (2.8 to 20.9)
Age			
<65 yr	68/95 (71.6)	90/101 (89.1)	17.5 (5.7 to 29.0)
≥65 yr	70/102 (68.6)	66/90 (73.3)	4.7 (–8.9 to 17.9)
Sex			
Male	68/99 (68.7)	65/84 (77.4)	8.7 (–5.1 to 21.7)
Female	70/98 (71.4)	91/107 (85.0)	13.6 (1.6 to 25.4)
Creatinine clearance			
≤60 ml/min	49/74 (66.2)	43/61 (70.5)	4.3 (–12.5 to 20.3)
>60 ml/min	87/120 (72.5)	112/127 (88.2)	15.7 (5.2 to 25.9)

Florian ME, et al. NEJM. 2019; 380: 729-740

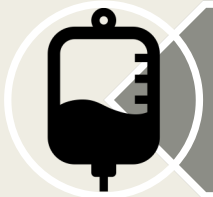
Meropenem-vaborbactam (Vabomere)

Mechanism and spectrum

- Combination carbapenem with novel beta-lactamase (including KPC) inhibitor
- *Enterobacteriacae*, including P*seudomonas*

Indications

- cUTI, including pyelonephritis (FDA approved 7/2019)



Formulations

- IV every 8h ($198/dose)

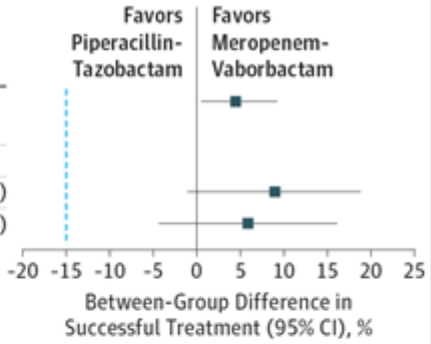
Special Considerations

- Does not enhance clinical activity of meropenem against carbapenem-resistant pseudomonas or acinetobacter

TANGO 1 Trial: Meropenem-vaborbactam vs Zosyn in cUTI

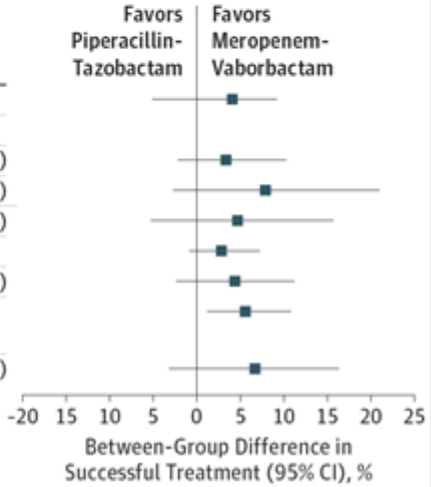
A Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



B Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure[a]	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment[a]			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source[c]	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment[d]	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



Kaye KS, et al. *JAMA*. 2018; 319(8): 788-799

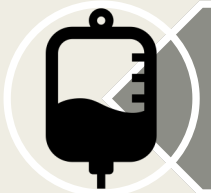
Imipenem/cilastin and relabactam (Recarbrio)

Mechanism and spectrum

- Combination carbapenem with beta lactamase inhibitor
- *Enterobacteriacae*, including P*seudomonas*

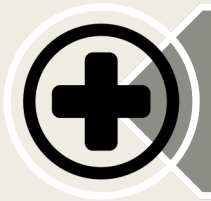
Indications

- cUTI, including pyelonephritis and cIAI (FDA approved 7/2019)



Formulations

- IV every 6h



Special Considerations

- Received FDA's qualified infectious disease product (QIDP) designation, awaiting phase 3 trial results

Mentimeter – Poll Question Clinical Case

A 28-year-old uninsured man with a history of IVDU and medical non-compliance is seen in the ED for L upper extremity cellulitis at a recent injection site. He is afebrile, hemodynamically stable, labs show normal renal function, and an ultrasound of the L upper extremity shows soft tissue edema without fluid collection. Of note, he has a documented prior MRSA infection that was resistant to Clindamycin as well as sulfa allergy. What antibiotic treatment would you recommend?

A. Bactrim DS PO BID for 7 days

B. Linezolid 600mg PO BID for 7 days

C. Dalbavancin 1500mg IV x 1

D. Cephalexin 500mg PO q6h for 7 days

NEW ANTIBIOTICS: ACUTE BACTERIAL SKIN AND SOFT STRUCTURE INFECTIONS (ABSSSI)

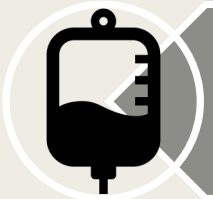
Dalbavancin (Dalvance)

Mechanism and spectrum

- Lipoglycopeptide, interfere with cell wall synthesis
- Gram positive (including MRSA)

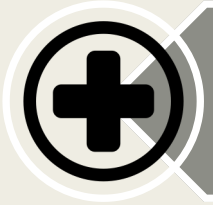
Indications

- ABSSSIs (FDA approved 1/2016)



Formulations

- IV weekly ($1,814/dose)



Special Considerations

- Can be used in ESRD
- Infusion reactions that resemble “Red-man syndrome” documented

DISCOVER 1 and 2

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	–1.0 (–5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (–3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (–2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	–1.5 (–4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	–1.4 (–4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	–0.7 (–3.0 to 1.5)

* The primary end point was the success rate at 48 to 72 hours after the initiation of therapy (i.e., early clinical response) in the intention-to-treat population. The sensitivity analysis of the primary end point was the success rate, defined as a reduction in the infection area of at least 20% at 48 to 72 hours after the initiation of therapy, in the intention-to-treat population. The secondary end points were evaluated in a pooled analysis and included success rates at the end of therapy in the clinical per-protocol population. For the pooled analysis, the weighted difference in success rates was calculated.
† The degree of fluctuance or localized heat or warmth had to be improved from baseline.

Boucher HW, et al. *NEJM*. 2014; 370: 2169-2179

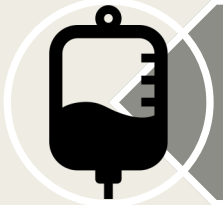
Delafloxacin (Bexdela)

Mechanism and spectrum

- Fluoroquinolone, inhibits bacterial DNA replication
- Gram positive (including MRSA) and gram negative (including *Pseudmonas*)

Indications

- ABSSSIs (FDA approved 7/2017)



Formulations

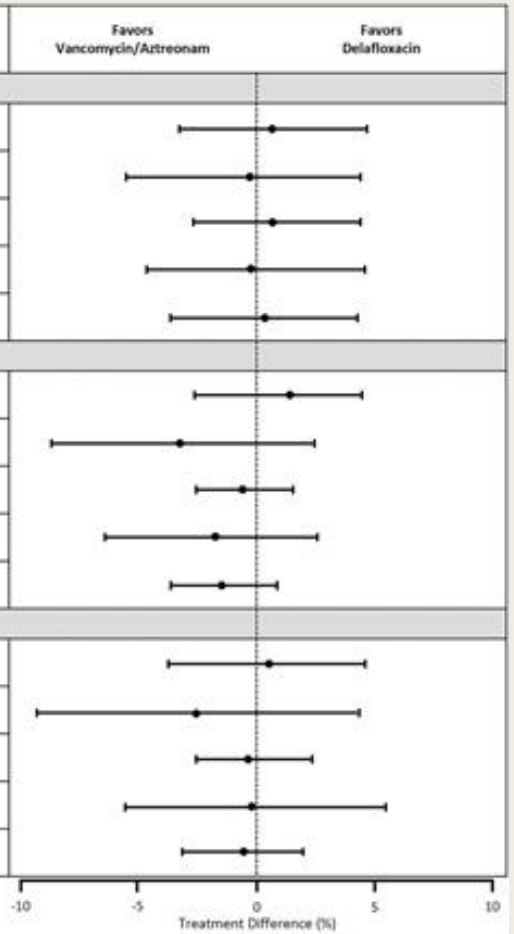
- IV ($159/dose) or PO ($85/tablet) every 12h

Special Considerations

- Similar to other fluoroquinolones, risk of tendon rupture and aortic dissection
- Unlike other fluoroquinolones, not associated with QT-prolongation

Delafloxacin vs Vancomycin/Aztreonam for ABSSSI: Phase 3 Trial

Study Population	Delafloxacin (% [n/N])	Vancomycin/ Aztreonam (% [n/N])	Treatment Difference (95% CI)
Intent-to-treat Population Analysis Set (ITT)			
Objective Response at 48-72 hours*	81.3 (613/754)	80.7 (610/756)	0.8 (-3.2, 4.7)
Investigator Assessed Cure at FU**	55.2 (416/754)	55.7 (421/756)	-0.5 (-5.5, 4.5)
Investigator Assessed Success at FU**	84.7 (639/754)	84.1 (636/756)	0.8 (-2.8, 4.5)
Investigator Assessed Cure at LFU	69.0 (520/754)	69.0 (522/756)	-0.1 (-4.8, 4.6)
Investigator Assessed Success at LFU	82.0 (618/754)	81.7 (618/756)	0.3 (-3.6, 4.2)
Clinically Evaluable Analysis Set (CE)			
Objective Response at 48-72 hours	86.5 (596/689)	85.4 (584/684)	1.2 (-2.6, 4.9)
Investigator Assessed Cure at FU	61.0 (362/593)	63.9 (366/573)	-3.1 (-8.6, 2.5)
Investigator Assessed Success at FU	96.6 (573/593)	97.2 (557/573	-0.6 (-2.7, 1.6)
Investigator Assessed Cure at LFU	80.2 (467/582)	82.5 (468/567)	-1.9 (-6.4, 2.6)
Investigator Assessed Success at LFU	96.0 (559/582)	97.2 (551/567)	-1.4 (-3.6, 0.8)
Microbiologically Evaluable Analysis Set (ME)			
Objective Response at 48-72 hours	87.8 (425/484)	87.4 (415/475)	0.5 (-3.8, 4.7)
Investigator Assessed Cure at FU	59.8 (245/410)	61.9 (245/396)	-2.5 (-9.2, 4.2)
Investigator Assessed Success at FU	97.8 (401/410)	98.0 (388/396)	-0.2 (-2.5, 2.2)
Investigator Assessed Cure at LFU	81.0 (332/410)	81.1 (321/396)	0.1 (-5.3, 5.5)
Investigator Assessed Success at LFU	97.1 (398/410)	97.5 (386/396)	-0.5 (-3.1, 2.0)



* Primary endpoint. ** The primary efficacy endpoint for the EMA submission, and a secondary efficacy endpoint for the FDA submission
Cure = no remaining signs and symptoms; Improved = some remaining signs and symptoms but no further antibiotics required; Success = Cure + Improved
Intent-to-treat (ITT; all patients randomized) ; Clinically evaluable (CE; patients who completed activities as defined in the protocol) ; Microbiologically evaluable (ME; CE patients with eligible pathogen)
MRSA, Methicillin Resistant *Staphylococcus aureus*.
Confidence intervals are calculated using Miettinen and Nurminen method without stratification for individual studies and stratified by studies for Pool 1 analysis.

Giordano PA, et al. *Clinical Infectious Diseases*. 2019; 68(3): 223-232

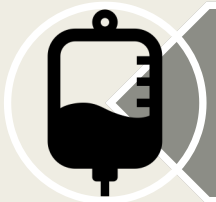
Omadacycline (Nuzyra)

Mechanism and spectrum

- Aminomethylcycline tetracycline, inhibits protein synthesis
- Typical/atypical respiratory pathgens and gram positive (including MRSA)

Indications

- ABSSSIs and CABP (FDA approved 10/2018)



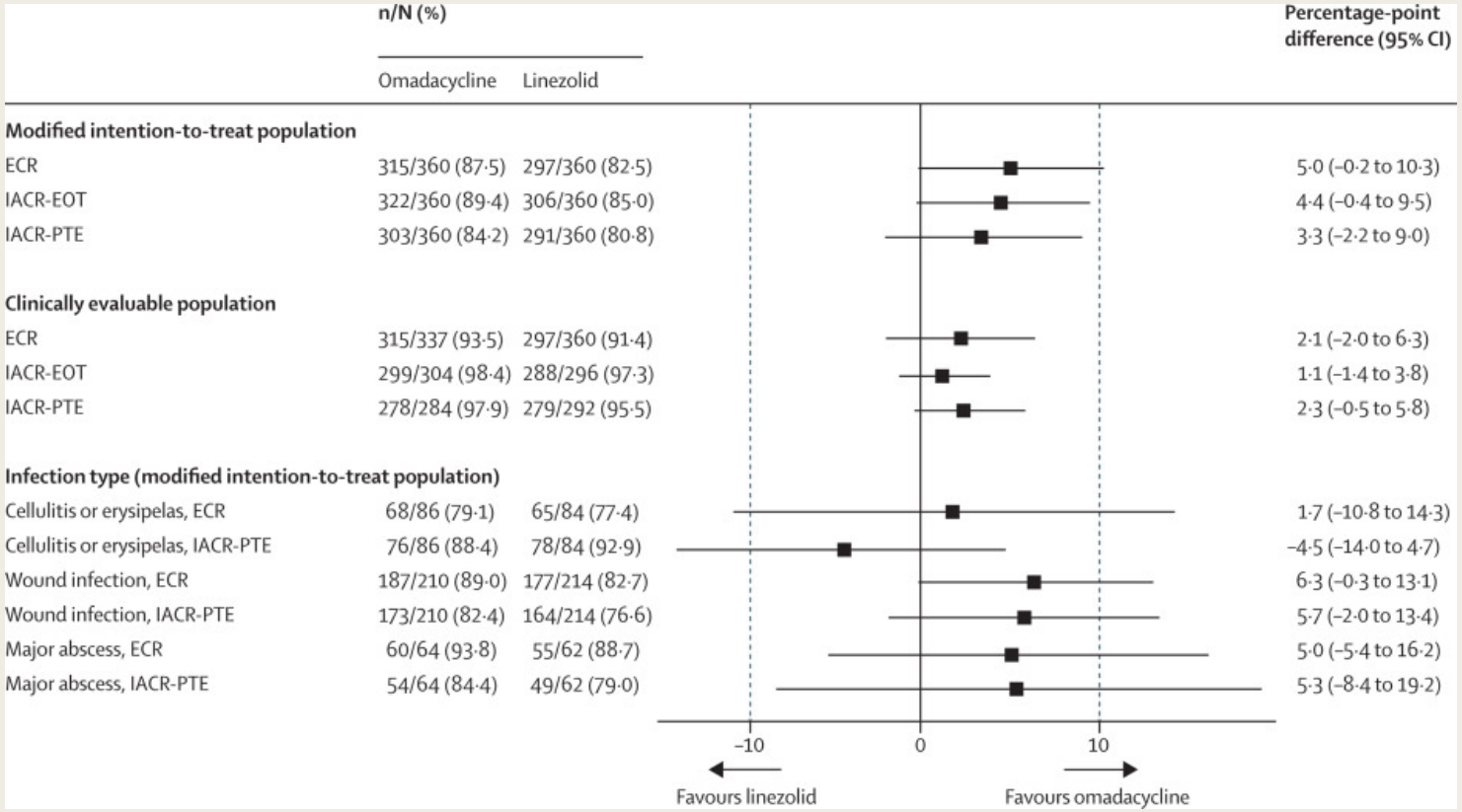
Formulations

- IV daily ($414/dose) or oral daily ($237/tablet)

Special Considerations:

- Similar side effect profile as other tetracyclines

OASIS-2 Study: Omadacycline vs Linezolid for ABSSSIs



	n/N (%)		Percentage-point difference (95% CI)
	Omadacycline	Linezolid	
Modified intention-to-treat population			
ECR	315/360 (87·5)	297/360 (82·5)	5·0 (–0·2 to 10·3)
IACR-EOT	322/360 (89·4)	306/360 (85·0)	4·4 (–0·4 to 9·5)
IACR-PTE	303/360 (84·2)	291/360 (80·8)	3·3 (–2·2 to 9·0)
Clinically evaluable population			
ECR	315/337 (93·5)	297/360 (91·4)	2·1 (–2·0 to 6·3)
IACR-EOT	299/304 (98·4)	288/296 (97·3)	1·1 (–1·4 to 3·8)
IACR-PTE	278/284 (97·9)	279/292 (95·5)	2·3 (–0·5 to 5·8)
Infection type (modified intention-to-treat population)			
Cellulitis or erysipelas, ECR	68/86 (79·1)	65/84 (77·4)	1·7 (–10·8 to 14·3)
Cellulitis or erysipelas, IACR-PTE	76/86 (88·4)	78/84 (92·9)	–4·5 (–14·0 to 4·7)
Wound infection, ECR	187/210 (89·0)	177/214 (82·7)	6·3 (–0·3 to 13·1)
Wound infection, IACR-PTE	173/210 (82·4)	164/214 (76·6)	5·7 (–2·0 to 13·4)
Major abscess, ECR	60/64 (93·8)	55/62 (88·7)	5·0 (–5·4 to 16·2)
Major abscess, IACR-PTE	54/64 (84·4)	49/62 (79·0)	5·3 (–8·4 to 19·2)

O'riordan WO, et al. *The Lancet Infectious Diseases*. 2019; online

Mentimeter – Poll Question
Clinical case

A 64-year-old woman with COPD is seen in an urgent care clinic with sinus drainage and increased productive cough for 3 days. She is afebrile, oxygen saturation is 97% on room air, and her lungs are clear to auscultation. She helps care for her 3-year-old grandson two days a week when he is not in daycare. She requests a prescription for an antibiotic for her symptoms. What is the most appropriate management?

A. Azithromycin 500mg PO x1 followed by 250mg PO daily x 4 days

B. Levofloxacin 500mg PO daily for 5 days

C. Lefamulin 600mg PO BID for 5 days

D. Offer education that no antibiotic therapy is indicated at this time

NEW ANTIBIOTICS: COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP)

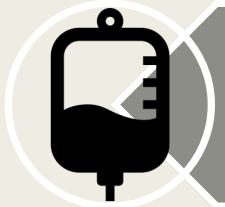
Lefamulin (Xenlata)

Mechanism and spectrum

- First-in-class pleuromutilin, inhibits bacterial protein synthesis
- Typical/atypical resp pathogens, *S. aureus* (including MRSA), *Enterococcus* (including VRE)

Indications

- Pneumonia, community-acquired (FDA approved 8/2019)



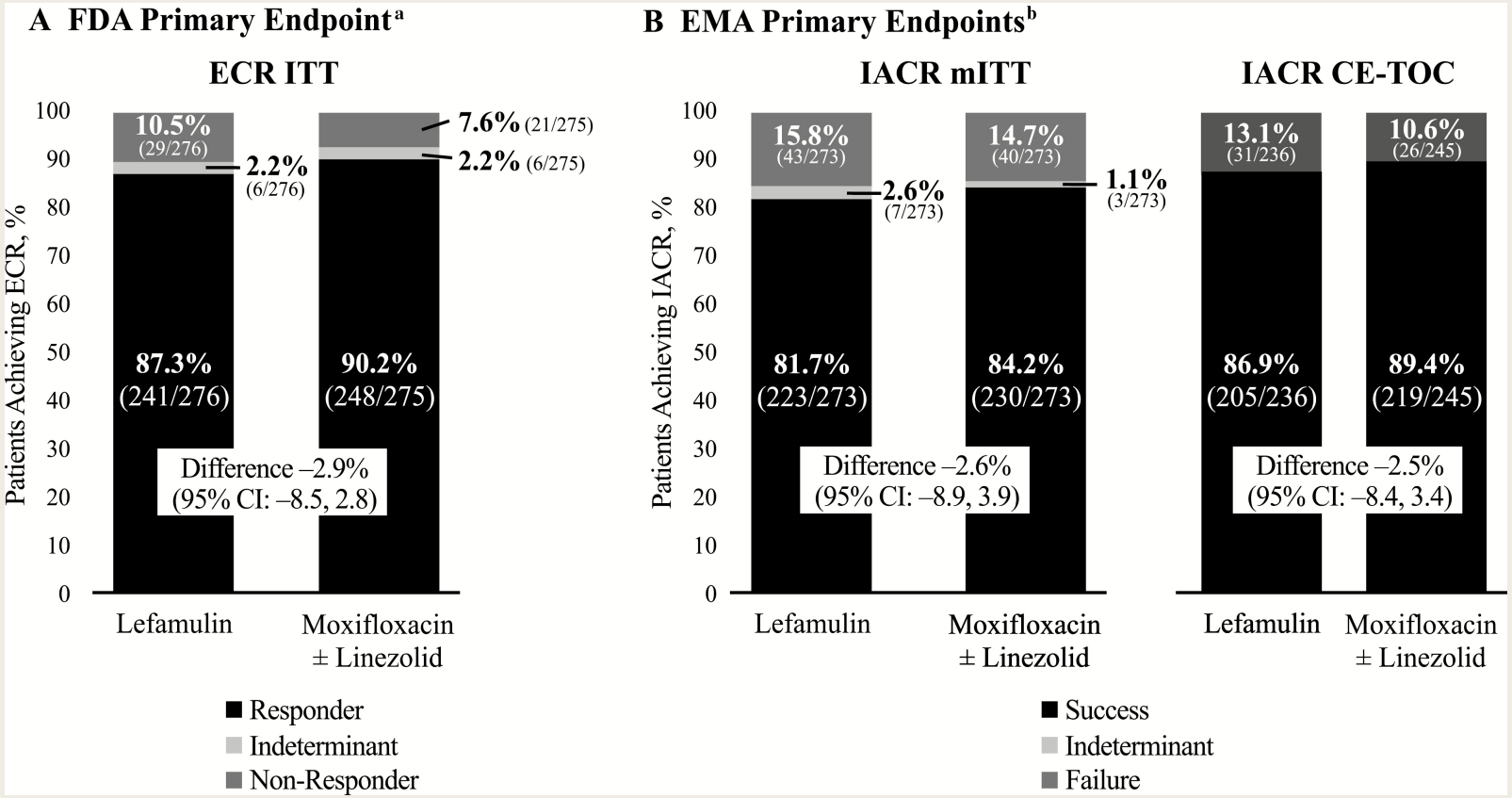
Formulations

- IV or PO every 12h

Special Considerations

- Associated with QT-prolongation
- Substrate of CYP3A4 (inhibits), multitude of drug-drug interactions

LEAP I and II Trials



File TM, et al. *Clinical Infectious Diseases*. 2019

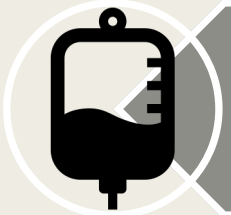
Omadacycline

Mechanism and spectrum

- Aminomethylcycline tetracycline, inhibits protein synthesis
- Typical/atypical respiratory pathgens and gram positive (including MRSA)

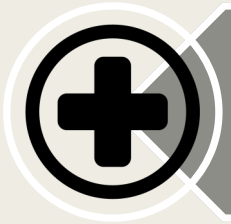
Indications

- ABSSSIs and CABP (FDA approved 10/2018)



Formulations

- IV daily ($414/dose) or oral daily ($237/tablet)

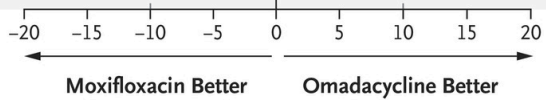


Special Considerations

- Lower success rates in treatment of CABP in patients >65yo

OPTIC Trial: Omadacycline vs Moxifloxacin

Subgroup	Omadacycline	Moxifloxacin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
ITT population			
Early clinical response	313/386 (81.1)	321/388 (82.7)	−1.6 (−7.1 to 3.8)
Investigator-assessed clinical response at EOT	349/386 (90.4)	341/388 (87.9)	2.5 (−1.9 to 7.0)
Investigator-assessed clinical response at PTE	338/386 (87.6)	330/388 (85.1)	2.5 (−2.4 to 7.4)
Clinical per-protocol population			
Early clinical response	308/356 (86.5)	314/360 (87.2)	−0.7 (−5.7 to 4.3)
Investigator-assessed clinical response at EOT	336/357 (87.0)	329/357 (84.8)	2.0 (−1.8 to 5.8)
Investigator-assessed clinical response at PTE	316/340 (92.9)	312/345 (90.4)	2.5 (−1.7 to 6.8)
Patients with PSI risk class II in the ITT population			
Early clinical response	43/57 (75.4)	41/56 (73.2)	2.2 (−14.0 to 18.4)
Investigator-assessed clinical response at PTE	47/57 (82.5)	47/56 (83.9)	−1.5 (−15.7 to 12.8)
Patients with PSI risk class III in the ITT population			
Early clinical response	191/227 (84.1)	187/216 (86.6)	−2.4 (−9.1 to 4.2)
Investigator-assessed clinical response at PTE	206/227 (90.7)	190/216 (88.0)	2.8 (−3.0 to 8.7)
Patients with PSI risk class IV in the ITT population			
Early clinical response	79/102 (77.5)	93/116 (80.2)	−2.7 (−13.8 to 8.1)
Investigator-assessed clinical response at PTE	85/102 (83.3)	93/116 (80.2)	3.2 (−7.4 to 13.4)



Stets R, et al. *NEJM*. 2019; 380: 517-527

Key points

- Antibiotic resistance is a global health emergency
- Resistance mechanisms exist for all current antibiotics and few new drugs are in development
  - *New antimicrobials should be considered a limited resource*
- Antimicrobial stewardship aims to minimize unintended consequences of antibiotic use
- Recently approved antibiotics include (by infectious syndrome):

cUTI	ABSSSI	CABP
Plazomicin	Delafloxacin	Lefamulin
Meropenem/vaborbactam	Dalbavancin	Omadacycline
Imipenem/relabactam	Omadacycline	*Delafloxacin*

Questions?

Thank you!
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