Acknowledgments

TRUE NORTH
VETERINARY DIAGNOSTICS

CVMA ACMV CHAPTER SBCV
CVMA-SBCV Chapter

Antimicrobial

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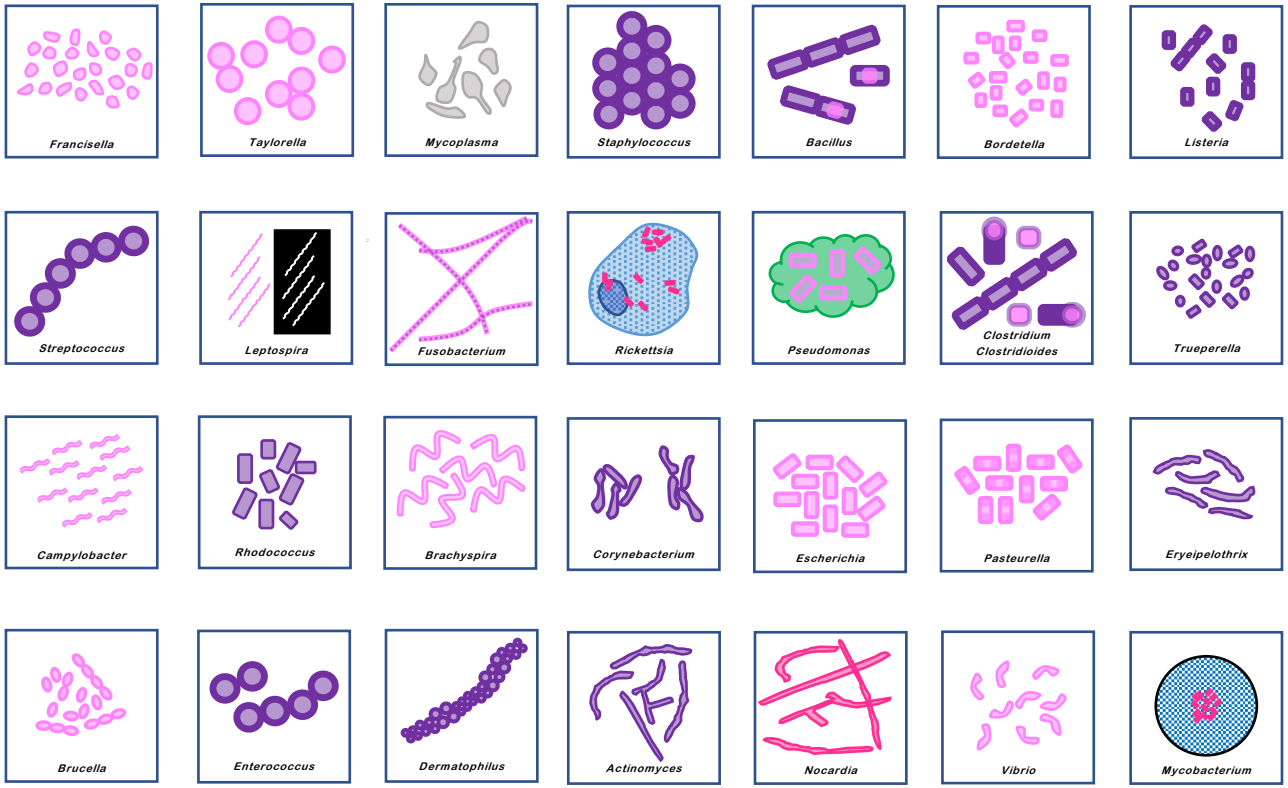
Disclosures

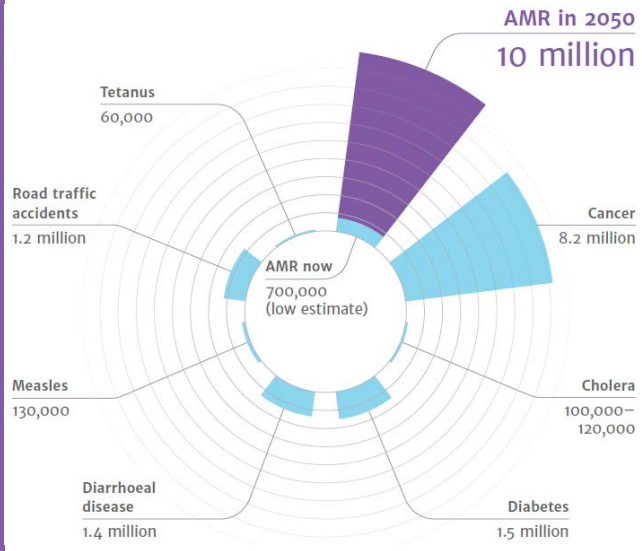
- Received research grants from
  - Zoetis and Elanco/Novartis



Objectives

- To summarize the scope of the problem of AMR
- To inspire the intent to change/reevaluate/improve prescribing practices
- To provide tools to use antimicrobials more effectively
  - Antimicrobial mechanisms of action and resistance
  - Introduction to intrinsic resistance

The Post-Antibiotic Era



Estimated Attributable Deaths in 2050

https://amr-review.org/

Current Threats

Urgent Threats

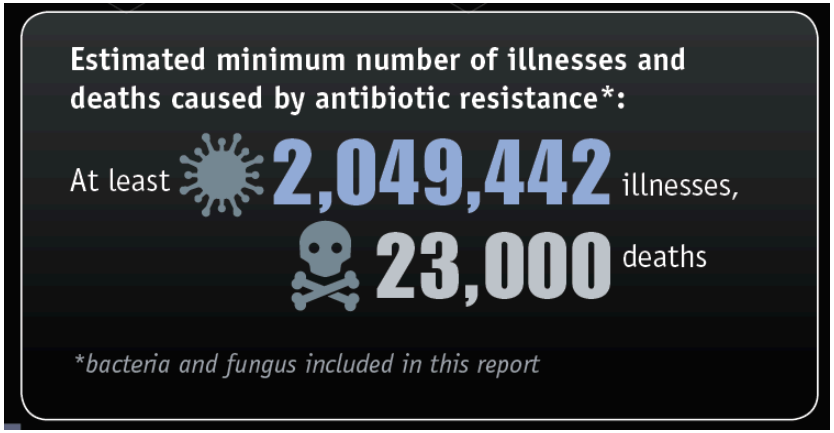
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

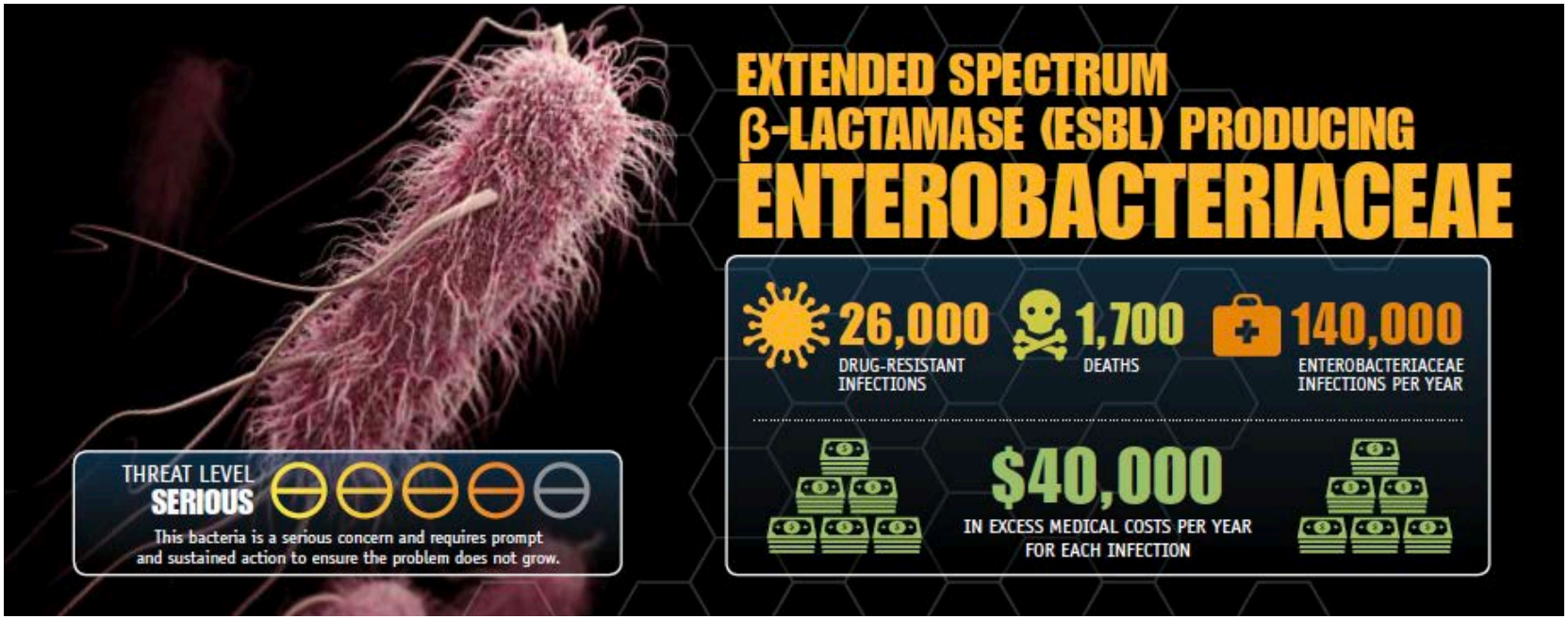
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

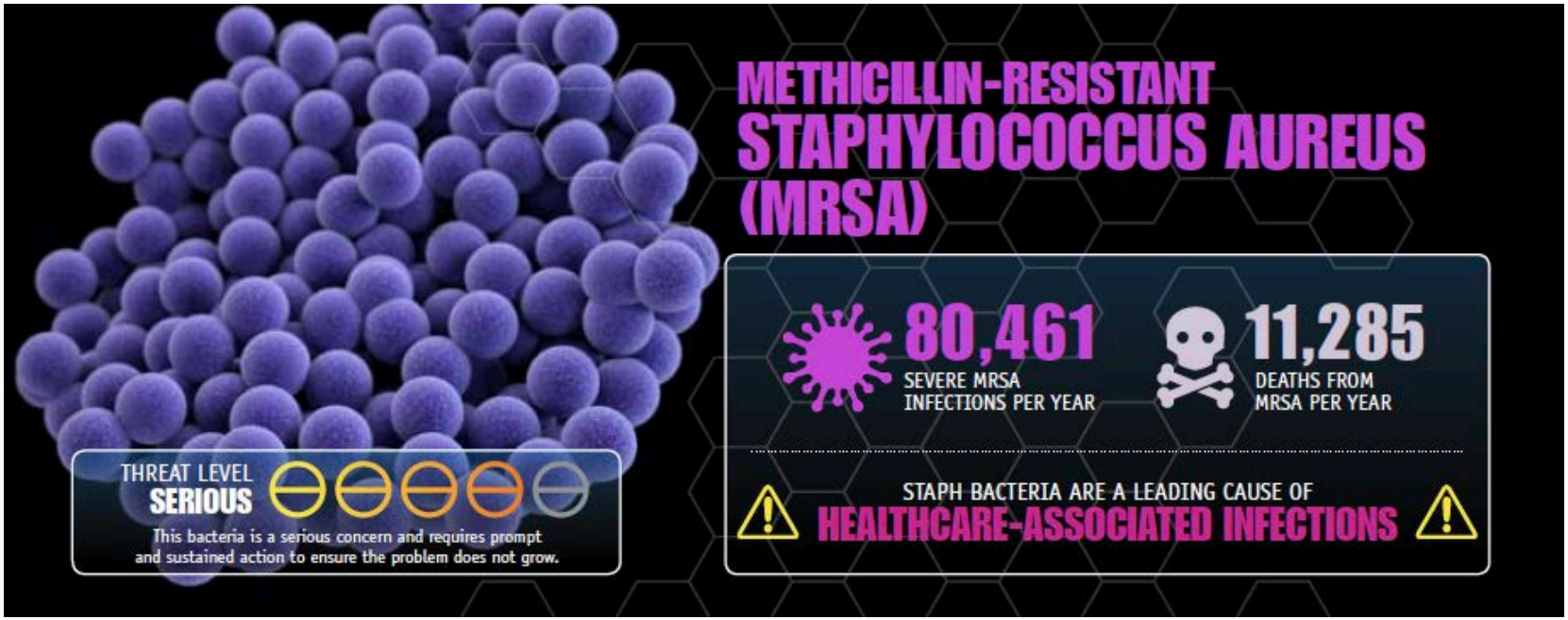


Broad spectrum β-lactamases



ANTIBIOTIC RESISTANCE THREATS in the United States, 2013

Methicillin-resistant *Staph aureus*



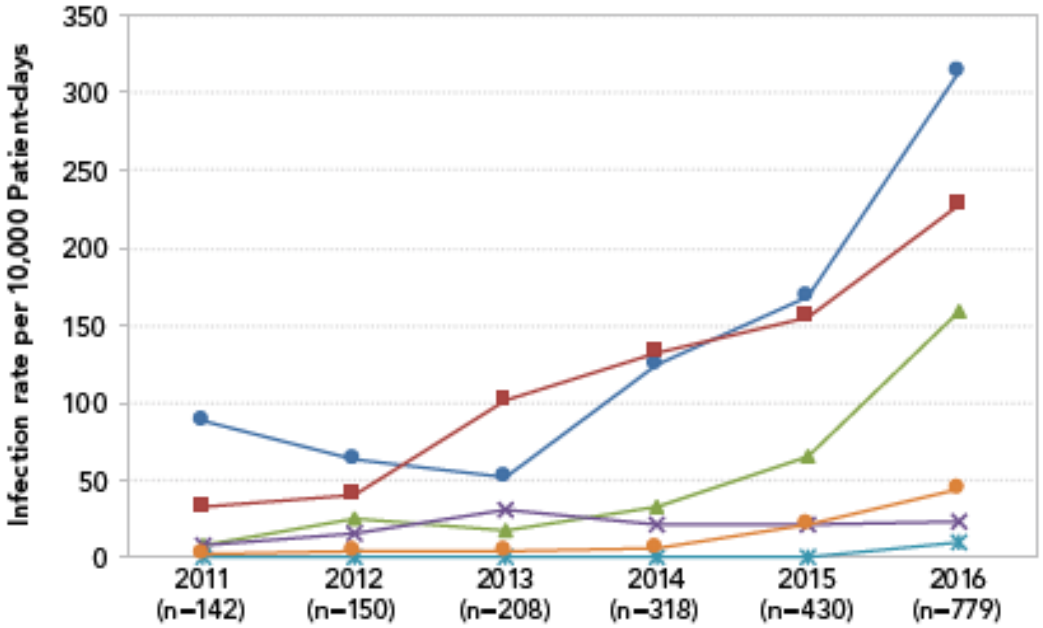
Emerging Resistance Concerns

- ESKAPE organisms
  - *Enterococcus faecium*
    - (VRE, penicillin resistance)
  - *Staphylococcus aureus* (*pseudintermedius*)
    - (MRSA, MDR)
  - *Klebsiella pneumoniae*
    - (ESBL, CPO, aminoglycoside, fluoroquinolone)
  - *Acinetobacter baumannii*
    - (Carbapenems and colistin)
  - *Pseudomonas aeruginosa*
    - (CPO, MDR, PanR)
  - *Enterobacter* spp.
    - (ESBL, CPO, MDR, PanR)

VRE – vancomycin resistant *Enterococcus*, MDR – multidrug resistant, ESBL – extended spectrum β-lactamase, CPO – carbapenemases producing organism, PanR – pan drug resistant.

Emerging Resistance in Canada

FIGURE 15: Count of CPE isolates by resistance gene, 2011-2016



	2011 (n=142)	2012 (n=150)	2013 (n=208)	2014 (n=318)	2015 (n=430)	2016 (n=779)
KPC	89	63	53	125	168	314
NDM	33	40	101	132	155	227
OXA-48-like	9	26	18	33	65	160
SME	8	17	31	22	21	24
OXA-48/NDM	0	0	0	0	0	160
Other	3	4	5	6	21	24

CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM
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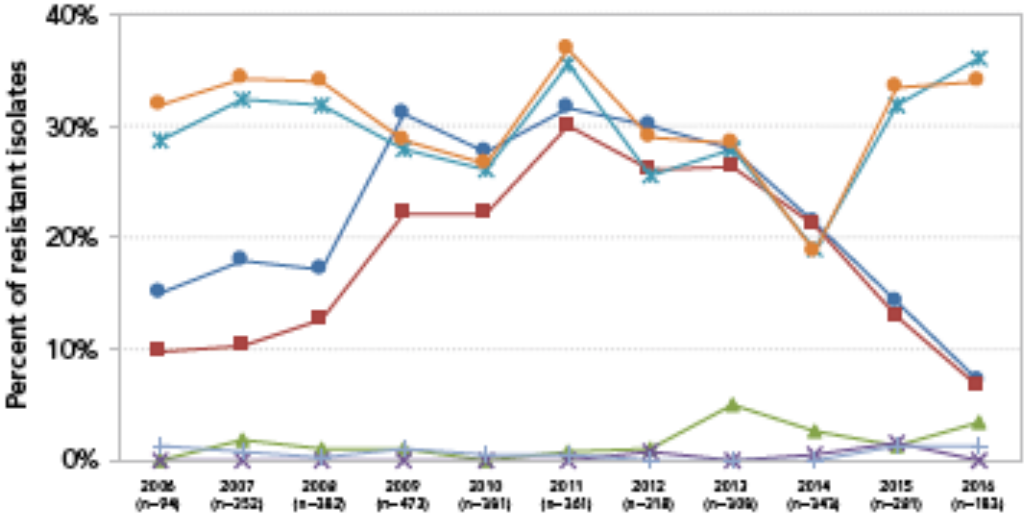
Changing Resistance?

FIGURE 38: Resistance to selected antimicrobials among *Salmonella* isolates from chicken meat samples collected at retail stores, 2006-2016



	2006 (n=94)	2007 (n=252)	2008 (n=382)	2009 (n=472)	2010 (n=291)	2011 (n=261)	2012 (n=218)	2013 (n=309)	2014 (n=342)	2015 (n=297)	2016 (n=183)
Ampicillin	14.9%	17.9%	17.0%	31.1%	27.6%	31.6%	29.9%	27.9%	21.3%	14.2%	7.1%
Ceftriaxone	9.6%	10.2%	12.6%	22.0%	22.0%	29.9%	26.1%	26.3%	21.0%	12.8%	6.6%
Gentamicin	0.0%	1.7%	1.0%	0.8%	0.0%	0.6%	0.9%	4.9%	2.6%	1.1%	3.3%
Nalidixic acid	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.0%	0.3%	1.4%	0.0%
Streptomycin	28.7%	32.4%	31.7%	27.9%	26.0%	35.5%	25.5%	27.9%	19.0%	31.7%	36.1%
Tetracycline	31.9%	34.1%	34.0%	28.8%	26.5%	36.8%	28.9%	28.2%	18.7%	33.5%	33.9%
Trimethoprim-sulfamethoxazole	1.1%	0.6%	0.3%	0.8%	0.5%	0.3%	0.0%	0.0%	0.0%	1.1%	1.1%

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Where Does Resistance Come From?

- Natural phenomenon!
  - Soil organisms survive in an environment that contains antimicrobial compounds
  - Enteric organisms need to survive in the presence of bile acids

LETTER

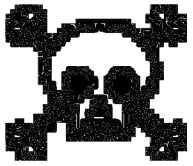
doi:10.1038/nature10388

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics.

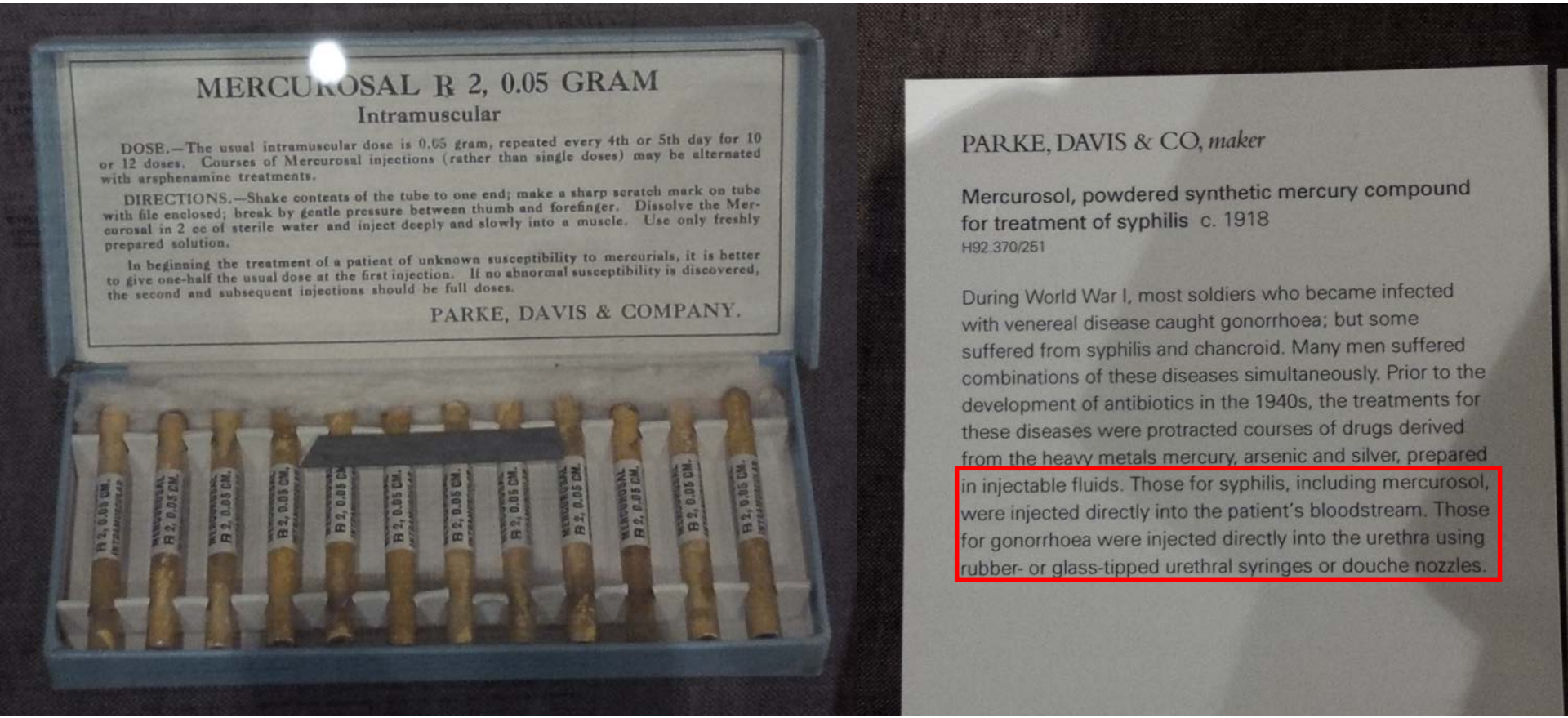
- Resistance to every drug that has, is or will be used in the future already exists
  - Drug resistance is often a byproduct of something else
- ANY/ALL drug use (appropriate or inappropriate) results in selection pressure
  - If you use a drug it better be worth it!

The Pre-Antibiotic Era 

- Largely powerless to stop invasive infections
- Interesting accounts of infectious disease in conflict settings (WW1)
  - Infected wounds progressed
    - Cut = infection = sepsis = death
  - Quiescent tubercles ubiquitous in urban areas
  - Sexually transmitted infections were ‘moral’ rather than medical issues
    - Occurred at a rate of 272/1,000 soldiers in US army in WW1

Importance of antibiotics cannot be overstated… estimate to have led to 10 year increase in life expectancy!

The Dark Ages



Mercury based preparations for the treatment of venereal disease. Specimen photographed at the State Library of Victoria, Melbourne Australia.

Fleming's Observation

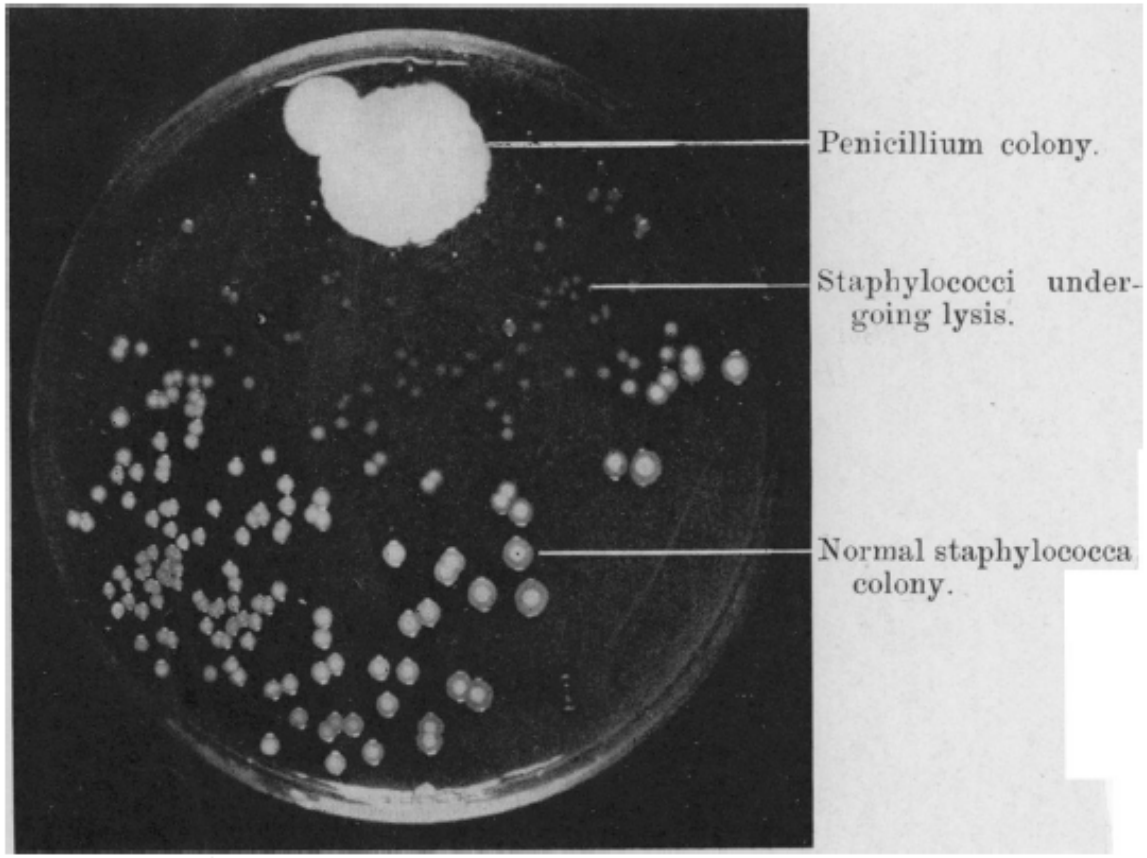


FIG. 1.—Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.

The Finding that Changed it All

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ*.

ALEXANDER FLEMING, F.R.C.S.

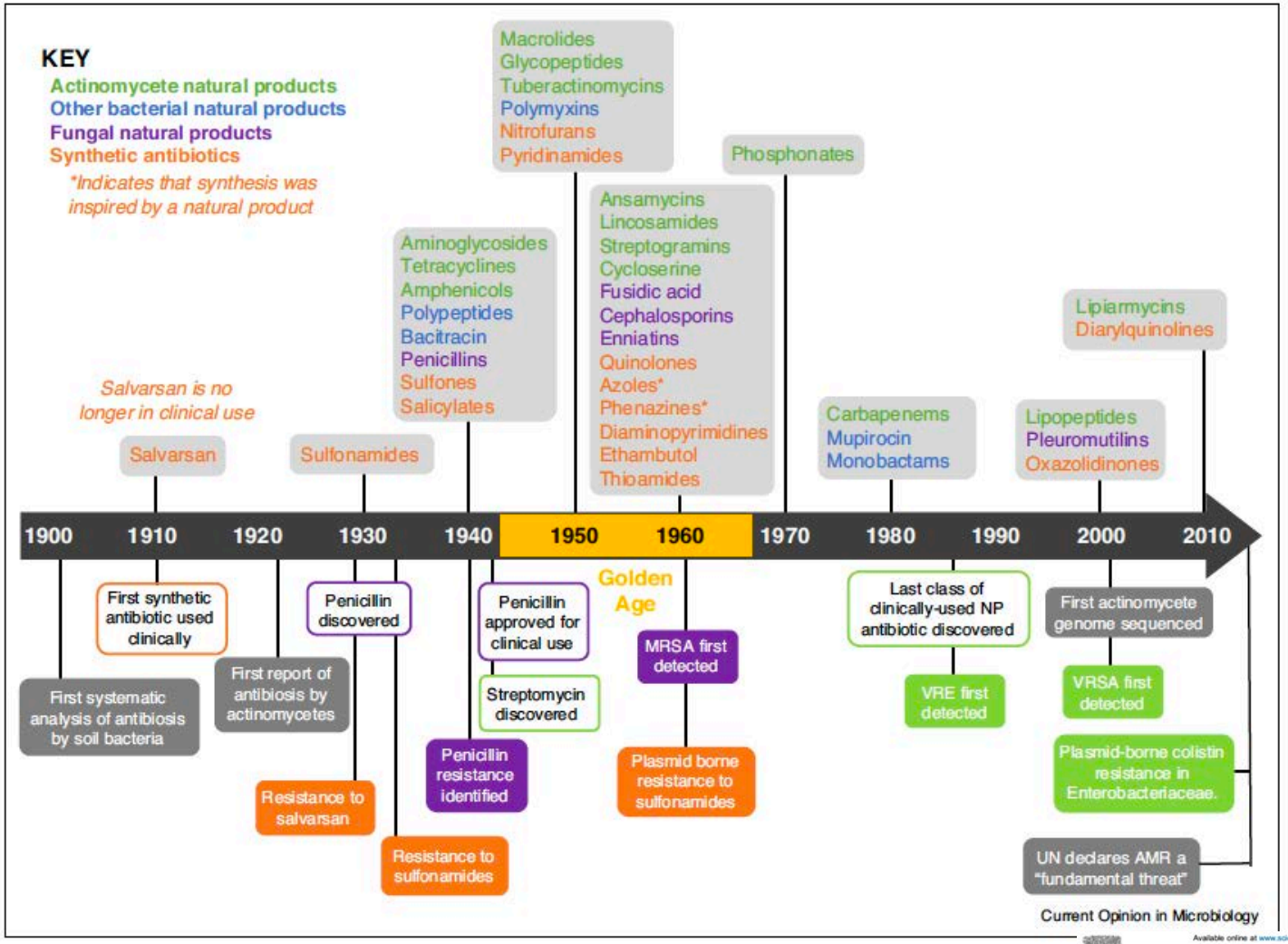
From the Laboratories of the Inoculation Department, St Mary's Hospital, London.

Received for publication May 10th, 1929.

Ernst Boris Chain

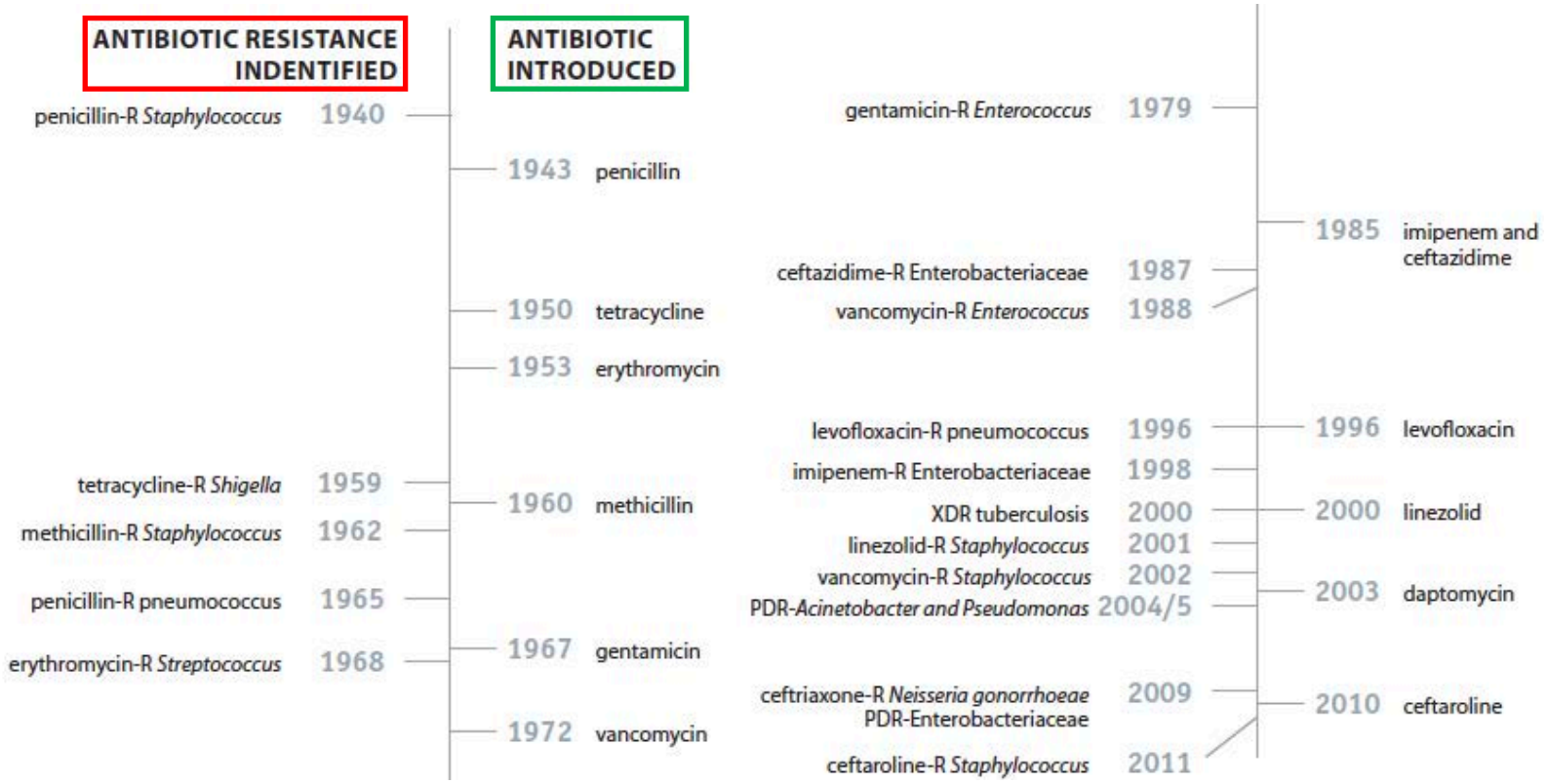
Sir Howard Florey

History of Drug Discovery



Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Microbiology
Antibiotics: past, present and future
Matthew I Hutchings[1], Andrew W Truman[2] and Barrie Wilkinson[2]

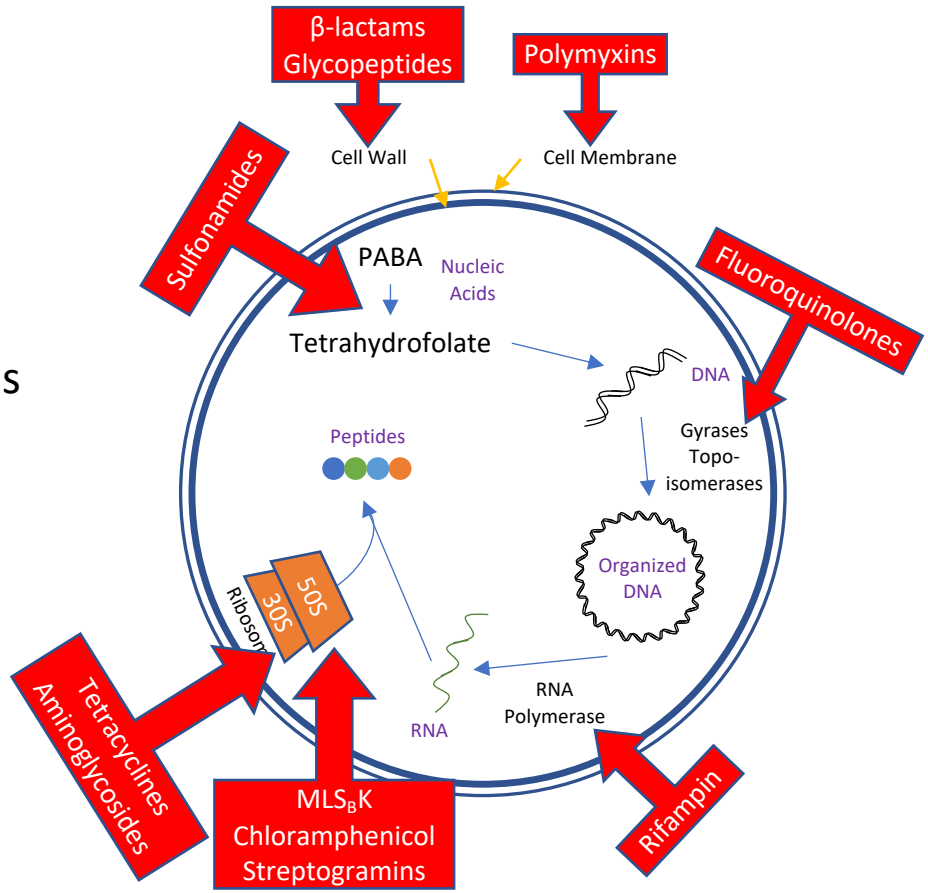
Resistance Follows Usage



https://www.cdc.gov/drugresistance/about.html

How Antibiotics Work

- Attack physiological processes unique to bacteria
  - Inside/Outside
    - Cell wall
    - Cell membrane
  - Central Dogma
    - Nucleic acids
      - Nucleic acid synthesis
      - DNA metabolism
      - RNA polymerase
    - Protein synthesis



How Bacteria Resist

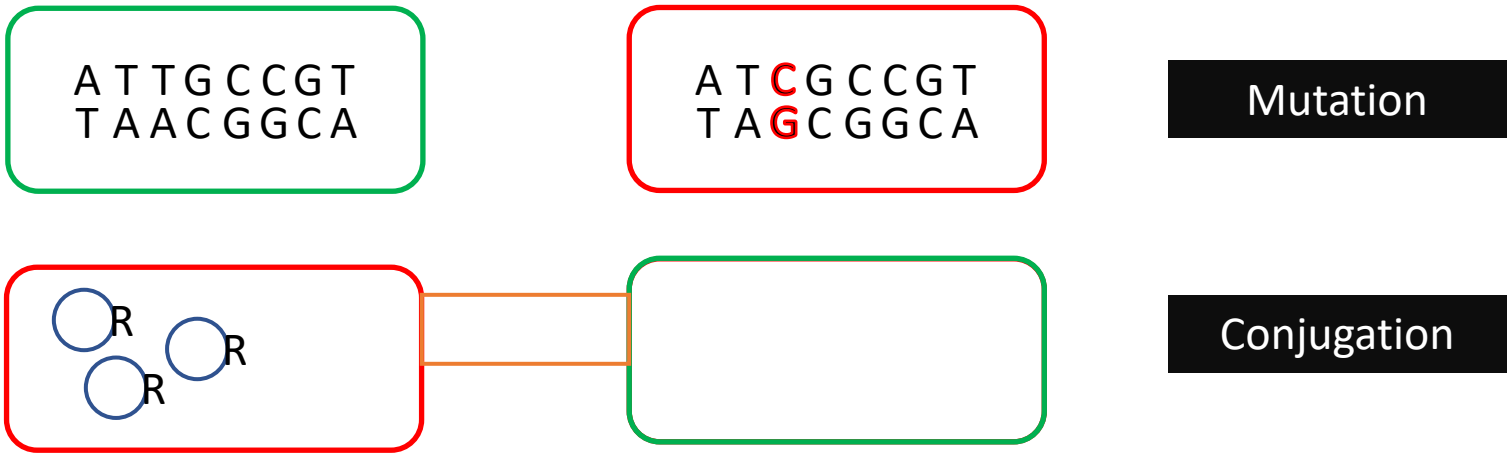
• Decreased permeability	Prevent entry
• Active Efflux	Pump out
• Enzymatic Degradation/Alteration	Destroy
• Target Modification	Disguise
• Alternate Pathways	Do something else
• Resistance by Absence	Lacking target

Bacteria can deploy these strategies intrinsically or after gaining genetic competence

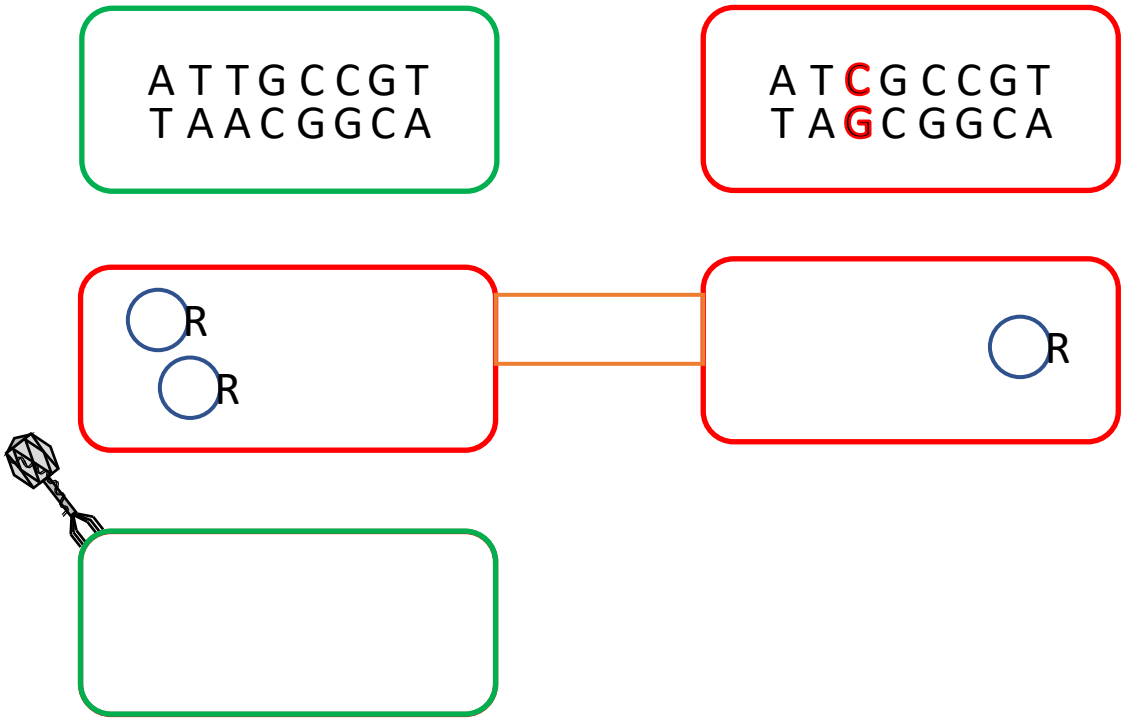
Where Resistance Comes From

Mutation

Where Resistance Comes From



Where Resistance Comes From

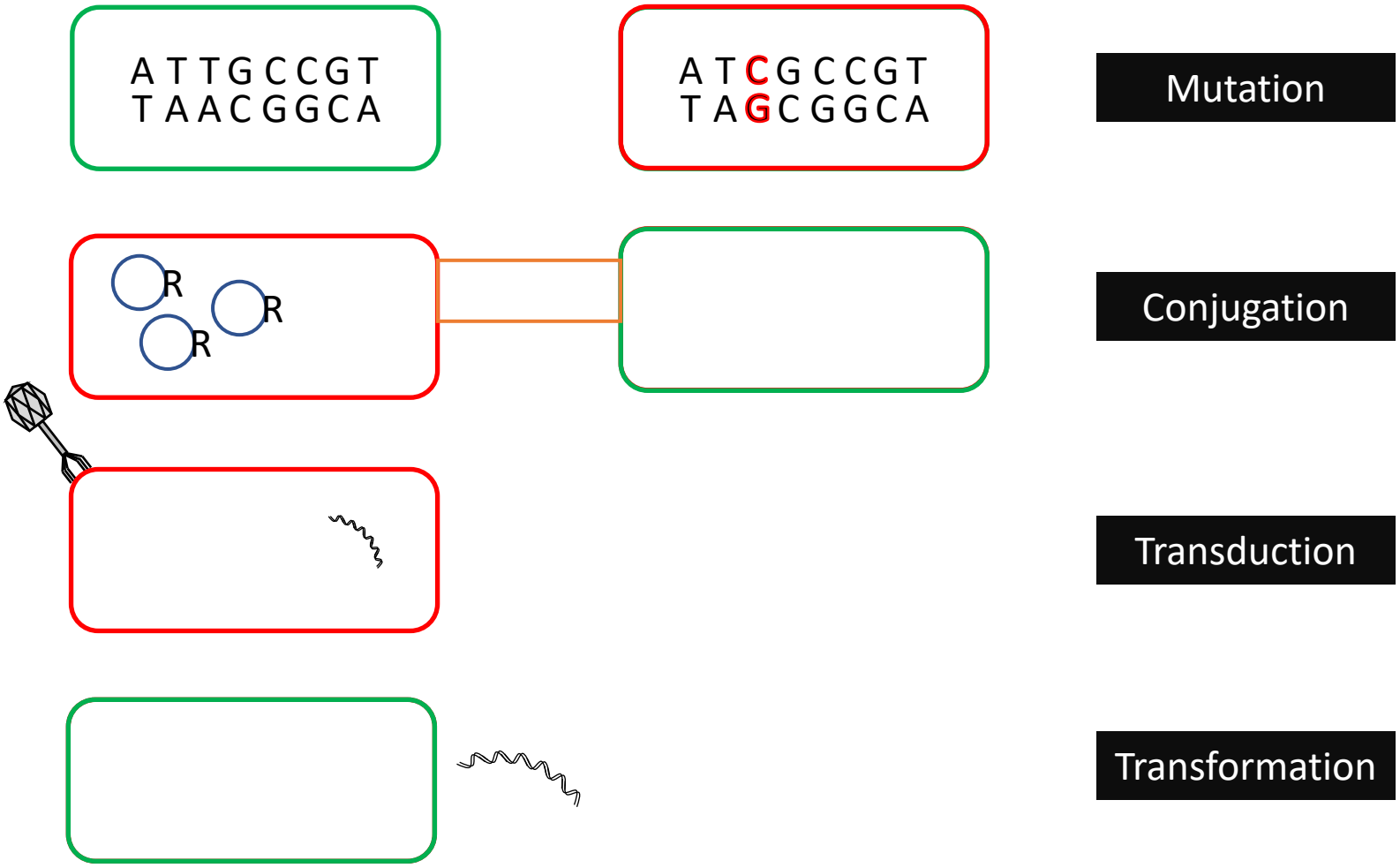


Mutation

Conjugation

Transduction

Where Resistance Comes From



Words of Wisdom for New Tools

"It is a neck-and-neck race in which many of us tend to underestimate the opponent. Staphylococci will not be defeated by the haphazard use of each new antibiotic. As new antibacterial agents are discovered, let us use them with discrimination."

Dr. Mary Barber - 1955

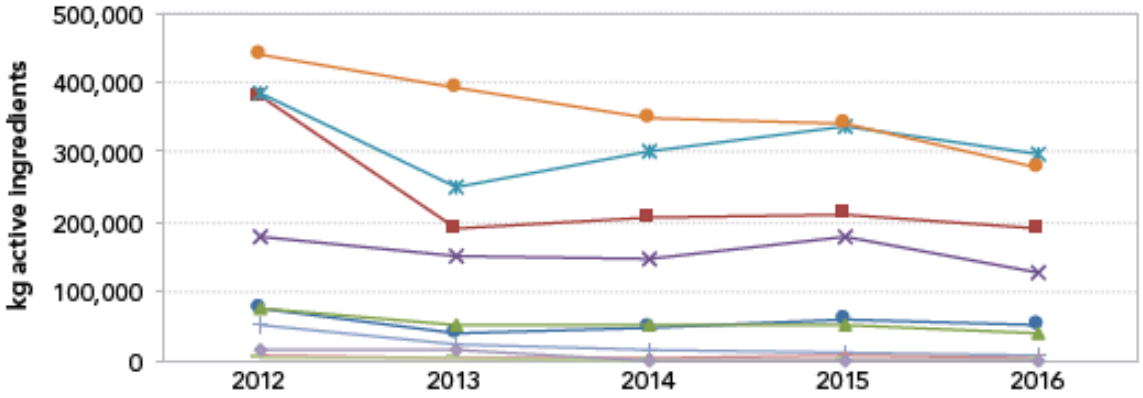
https://www.youtube.com/watch?v=plVk4NVIUh8

Evolutionary Power

	Human Generations Since Species Origin	Bacterial Generations in Antimicrobial Era
Time		
Generation Length		
Generations		

Antimicrobial Use Animals

FIGURE 51: Quantity of medically important antimicrobials (kilograms) distributed for sale for use in animals, by province, 2012-2016



	2012	2013	2014	2015	2016
BC	74,376	38,680	47,351	60,067	52,738
AB	381,193	189,245	206,573	210,475	189,870
SK	77,971	50,961	50,333	50,708	39,976
MB	178,577	151,675	147,088	179,660	128,715
ON	386,917	249,621	303,240	336,049	296,916
QC	440,364	392,312	348,387	343,544	276,971
NB	50,797	23,850	14,696	11,092	8,066
NS	7,959	6,172	5,782	6,780	4,463
PE	3,781	4,164	1,134	1,147	1,378
NL	17,322	15,023	1,883	1,740	1,357

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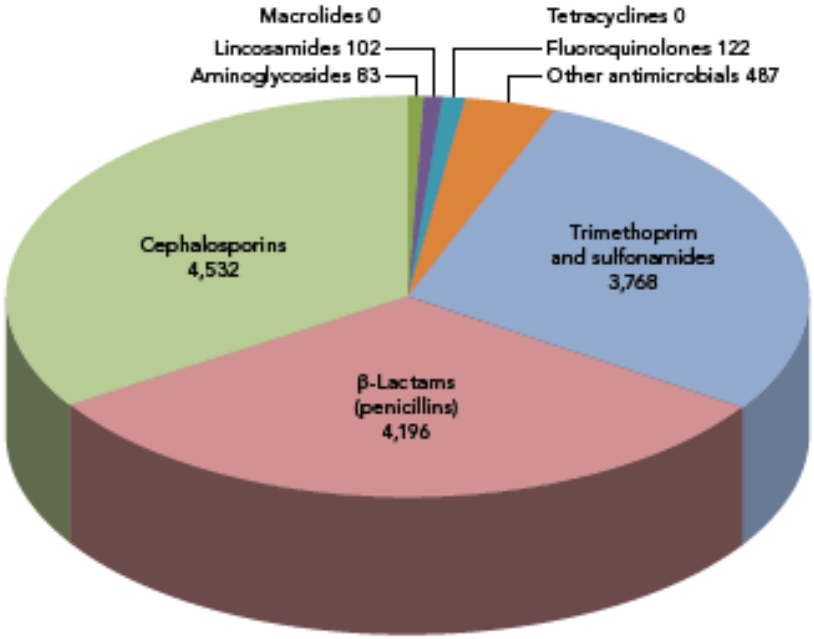
Antimicrobial Use Dogs and Cats

Antimicrobial use in companion animals

In 2016, the predominant classes of antimicrobials used in companion animals were cephalosporins, β-lactams, and trimethoprim-sulfas (Figure 54). All three of these classes are antimicrobials of high importance to humans according to the classification system of the Veterinary Drugs Directorate, Health Canada[15].

FIGURE 54: Relative quantities of antimicrobial classes distributed for use in companion animals (percentages based on kg active ingredient), 2016.



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Antimicrobial Use Dogs and Cats

- Large study out of UK
  - 216 practices
    - >400,000 dogs
    - >200,000 cats

The Veterinary Journal 224 (2017) 18–24

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Original article

Patterns of antimicrobial agent prescription in a sentinel population of canine and feline veterinary practices in the United Kingdom

D.A. Singleton[a,*,1], F. Sánchez-Vizcaíno[a,b], S. Dawson[c], P.H. Jones[a], P.J.M. Noble[c], G.L. Pinchbeck[a], N.J. Williams[a], A.D. Radford[a]

Table 3
Percentage breakdown of canine antimicrobial agent prescriptions by antimicrobial agent class prescribed for total, systemic and topical prescriptions from a network of United Kingdom small animal veterinary premises.

Antimicrobial agent class	Total		Systemic		Topical	
	%	95% CI[a]	%	95% CI[a]	%	95% CI[a]
Aminoglycoside	12.0	11.4–12.6	0.1	0.0–0.2	29.1	28.0–30.2
Amphenicol	1.9	1.6–2.1	0.0	<0.00	4.5	3.9–5.2
Other antimicrobial agent[b]	7.2	6.6–7.8	0.0	<0.00	17.4	16.1–18.8
β-lactam	43.6	42.3–44.8	73.8	72.2–75.4	0.1	0.0–0.2
Fluoroquinolone	4.4	3.6–5.1	4.1	3.1–5.2	4.6	4.0–5.2
Fusidic acid	18.2	17.4–19.0	0.0	<0.00	44.3	43.1–45.4
Lincosamide	4.7	4.2–5.2	7.9	7.0–8.8	0.0	<0.00
Macrolide	0.2	0.0–0.3	0.3	0.0–0.6	0.0	<0.00
Nitroimidazole	4.7	4.0–5.4	8.0	6.7–9.2	0.0	<0.00
Nitroimidazole-macrolide	0.8	0.5–1.0	1.3	0.8–1.7	0.0	<0.00
Rifamycin	0.0	<0.00	0.0	<0.00	0.0	<0.00
Sulphonamide	1.5	1.1–1.9	2.5	1.9–3.2	0.0	<0.00
Tetracycline	1.2	1.0–1.3	2.0	1.7–2.2	0.0	0.00–0.01

Table 5
Percentage breakdown of β-lactam antimicrobial agent prescription by species and β-lactam sub-categories as a percentage of total and systemic antimicrobial agent prescriptions from a network of small animal veterinary premises in the United Kingdom.

Class of antimicrobial agent	Total prescription				Systemic prescription			
	Dog		Cat		Dog		Cat	
	%	95% CI[a]	%	CI[a]	%	CI[a]	%	CI[a]
Amoxicillin	5.3	4.1–6.5	12.5	10.0–15.0	9.0	7.1–10.9	15.3	12.2–18.3
Other β-lactams[b]	0.4	0.0–0.8	0.07	0.01–0.13	0.5	0.0–1.3	0.02	0.00–0.05
First generation cephalosporin	8.4	7.8–9.0	0.4	0.3–0.5	14.2	13.2–15.3	0.5	0.4–0.6
Second generation cephalosporin	0.04	0.01–0.07	0.01	0.00–0.02	0.07	0.02–0.12	0.02	0.00–0.03
Third generation cephalosporin	0.9	0.7–1.0	36.2	33.9–38.5	1.5	1.3–1.8	45.1	42.1–48.2
Clavulanic acid potentiated amoxicillin	28.6	27.4–29.8	21.6	19.6–23.6	48.5	46.0–50.9	26.9	24.5–29.3
Penicillin	0.03	0.01–0.05	0.03	0.01–0.05	0.04	0.01–0.07	0.04	0.01–0.06
Total	43.6		70.8		73.8		87.9	

How Canada's AMU Compares

FIGURE 57: J01 Antimicrobial consumption (DDDs per 1,000 inhabitant-days), Canada (CA) and Europe (EU)

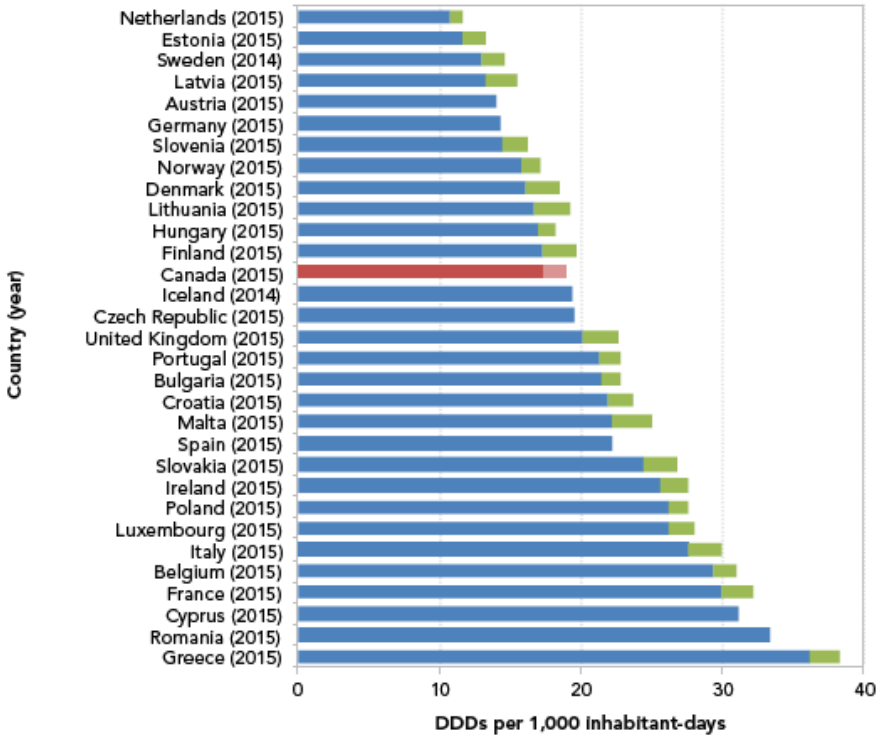
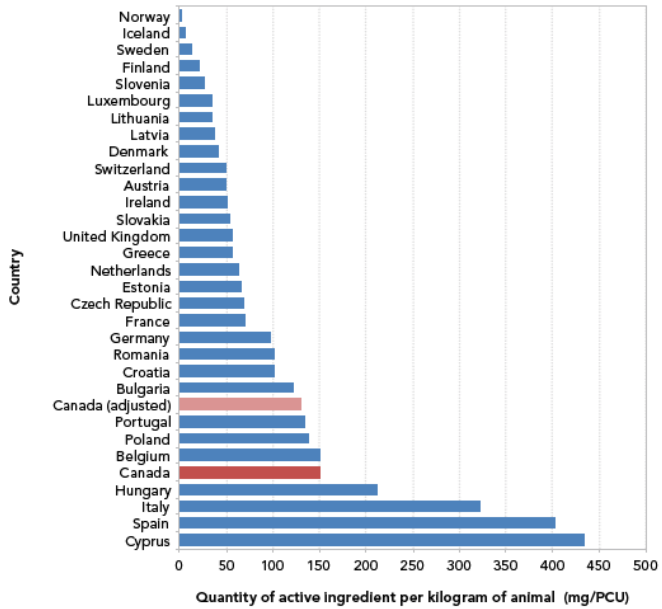


FIGURE 58: Sales of antimicrobials (adjusted by populations and weights) for Canada (2016) and countries participating in the European Surveillance of Veterinary Antimicrobial Consumption (2015)



NOTE: Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-Food Canada, Equine Canada, European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). PCU = population correction unit. The Canadian data used for live horses were from 2010 and fish from 2015; more recent data were unavailable. For the Canadian data, values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. The PCU denominator was harmonized to the greatest extent possible with ESVAC[a]. ESVAC denominator does not include beef cows, whereas in Canada beef cows are a significant population and are included. The ESVAC approach excludes companion animal data.

We're somewhere in the middle, so there's probably room to improve

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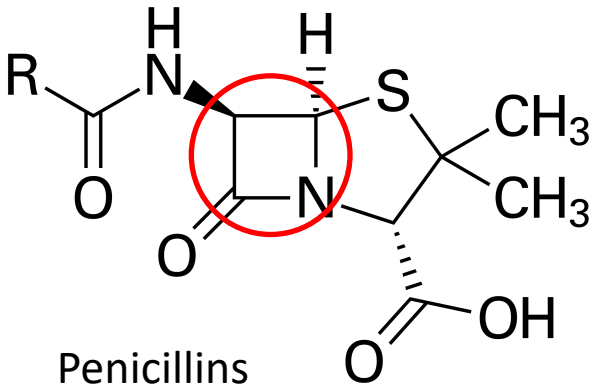
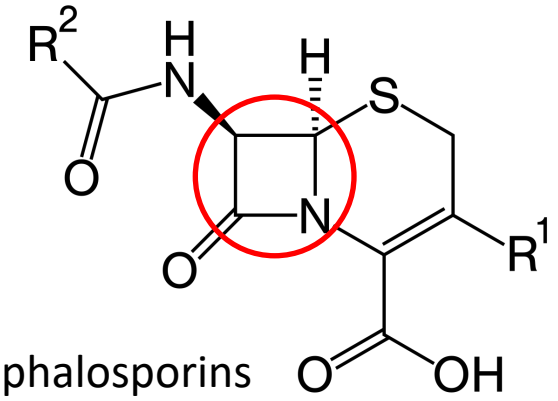
β-lactams

- Inhibit cell wall synthesis
  - Bind to penicillin binding proteins
    - Transpeptidases and carboxypeptidases
  - Prevent final stage of peptidoglycan synthesis
- Super family of antimicrobials
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - β-lactamase inhibitors

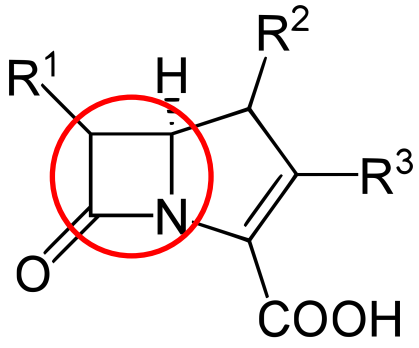
β-lactam Basic Structure



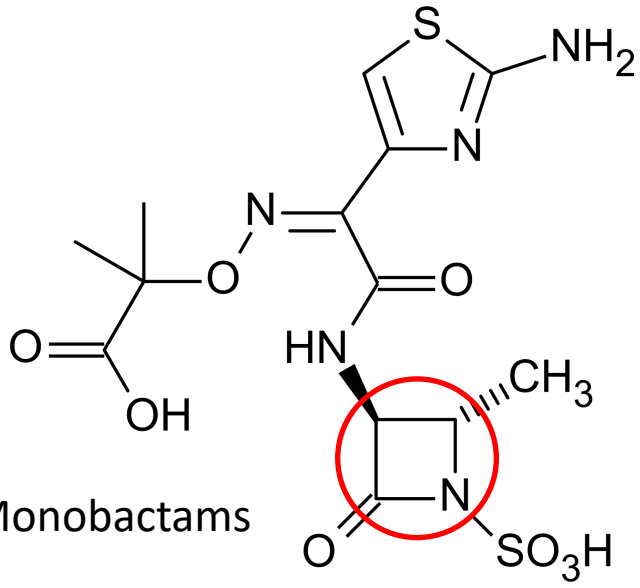
Penicillins



Cephalosporins



Carbapenems



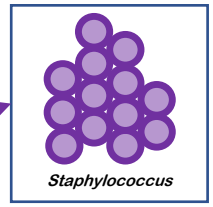
Monobactams

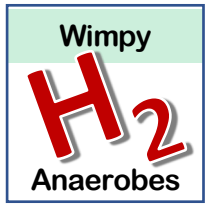
β-lactams - Penicillins

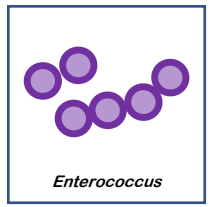
Penicillinase-stable penicillin

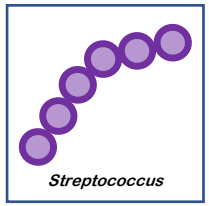
oxacillin, methicillin, cloxacillin, flucloxacillin

No Gram-negative, anaerobic or enterococcal coverage









β-lactams - Penicillins

Penicillinase-stable penicillin

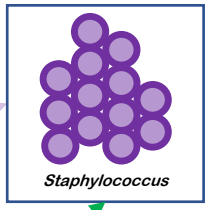
oxacillin, methicillin, cloxacillin, flucloxacillin

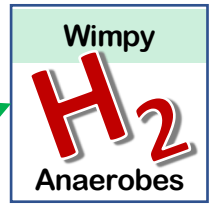
No Gram-negative, anaerobic or enterococcal coverage

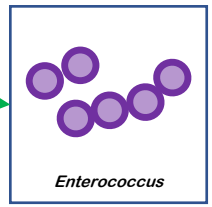
Penicillin

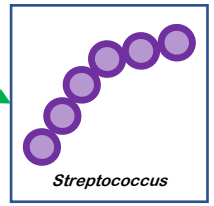
penicillin G, penicillin V, procaine penicillin

Gram-positives aerobes, wimpy Gram-positive and negative anaerobes

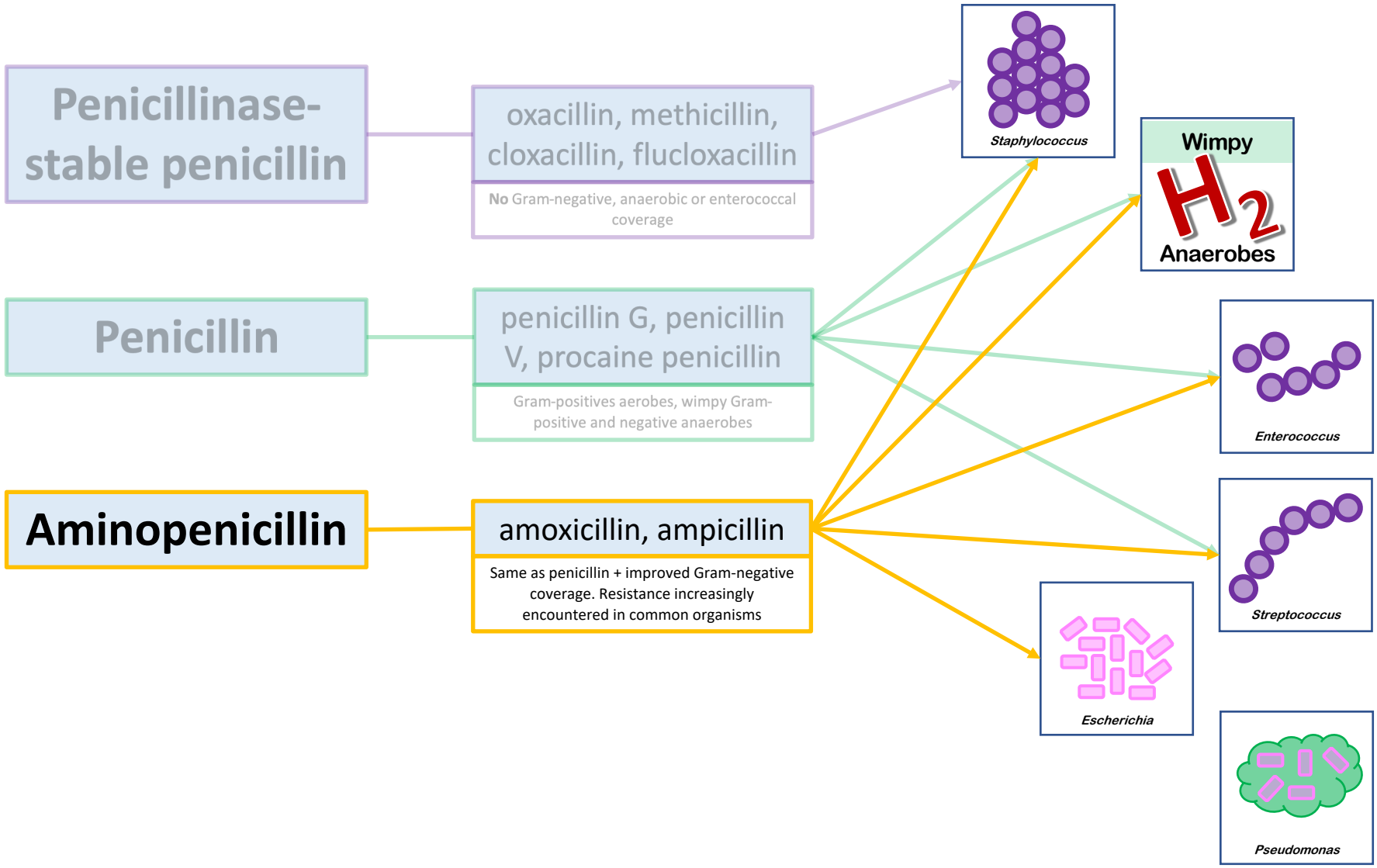




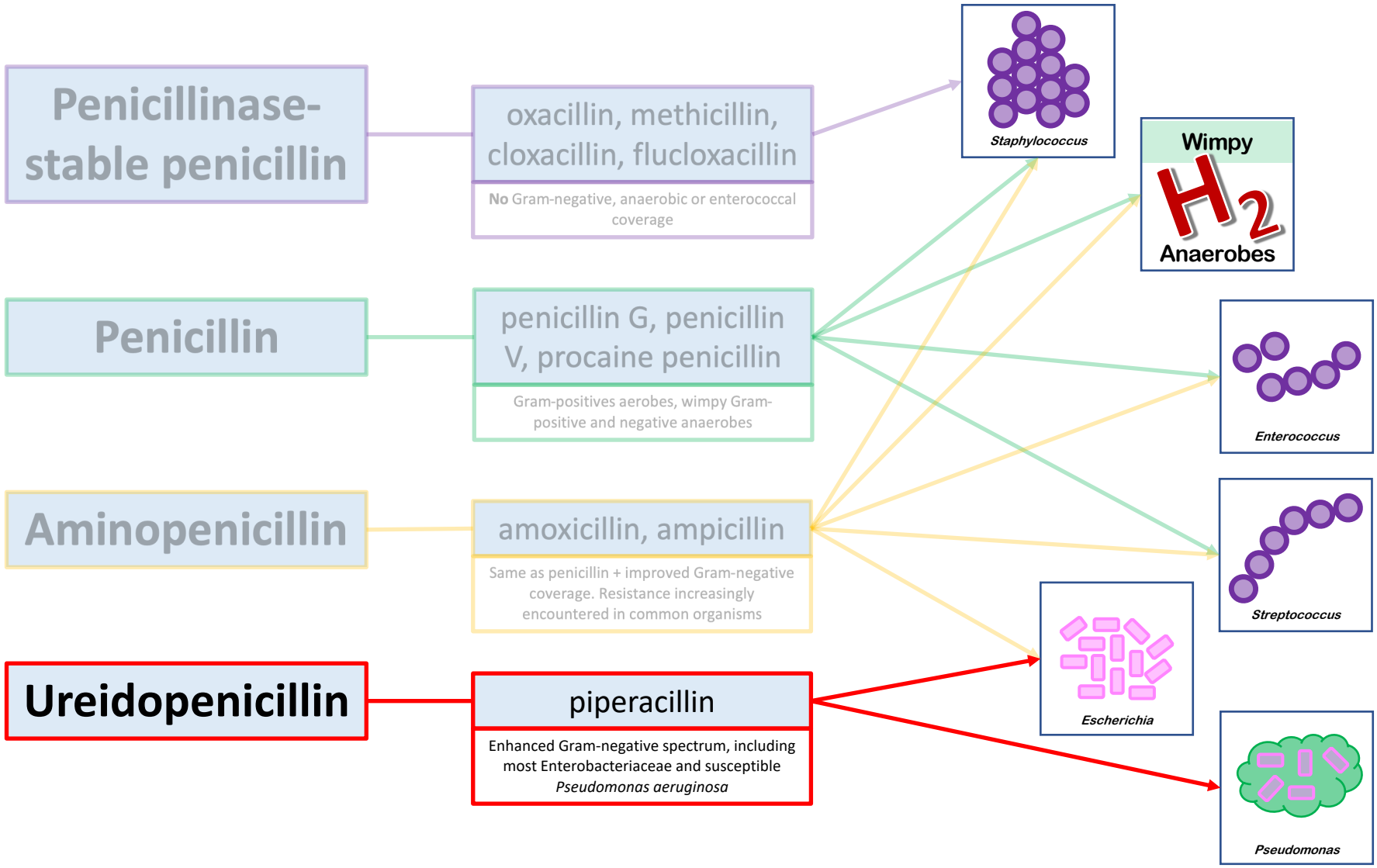




β-lactams - Penicillins



β-lactams - Penicillins



β-Lactams/Inhibitor Combinations

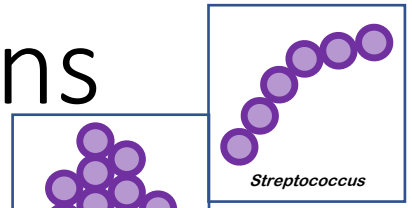
- Currently available:
  - Clavulanic acid (amoxicillin + clavulanic acid)
  - Sulbactam (ampicillin + sulbactam)
  - Tazobactam (piperacillin + tazobactam)
- Act by irreversibly binding to the serine catalytic site of certain bacterial β-lactamases
  - Only active against Class A enzymes
  - NOT ALL β-LACTAMASES can be inhibited

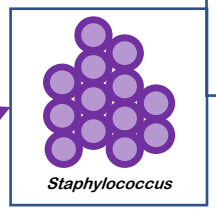
β-lactams - Cephalosporins

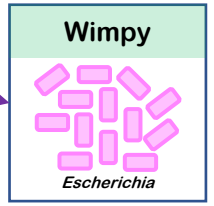
1st Generation

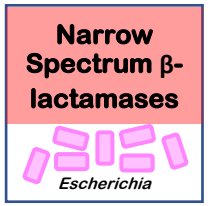
cefazolin, cephalexin, cefadroxil

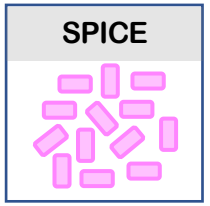
Primarily active against Gram-positives, moderate Gram-negative activity if susceptible

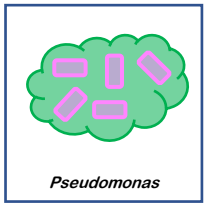




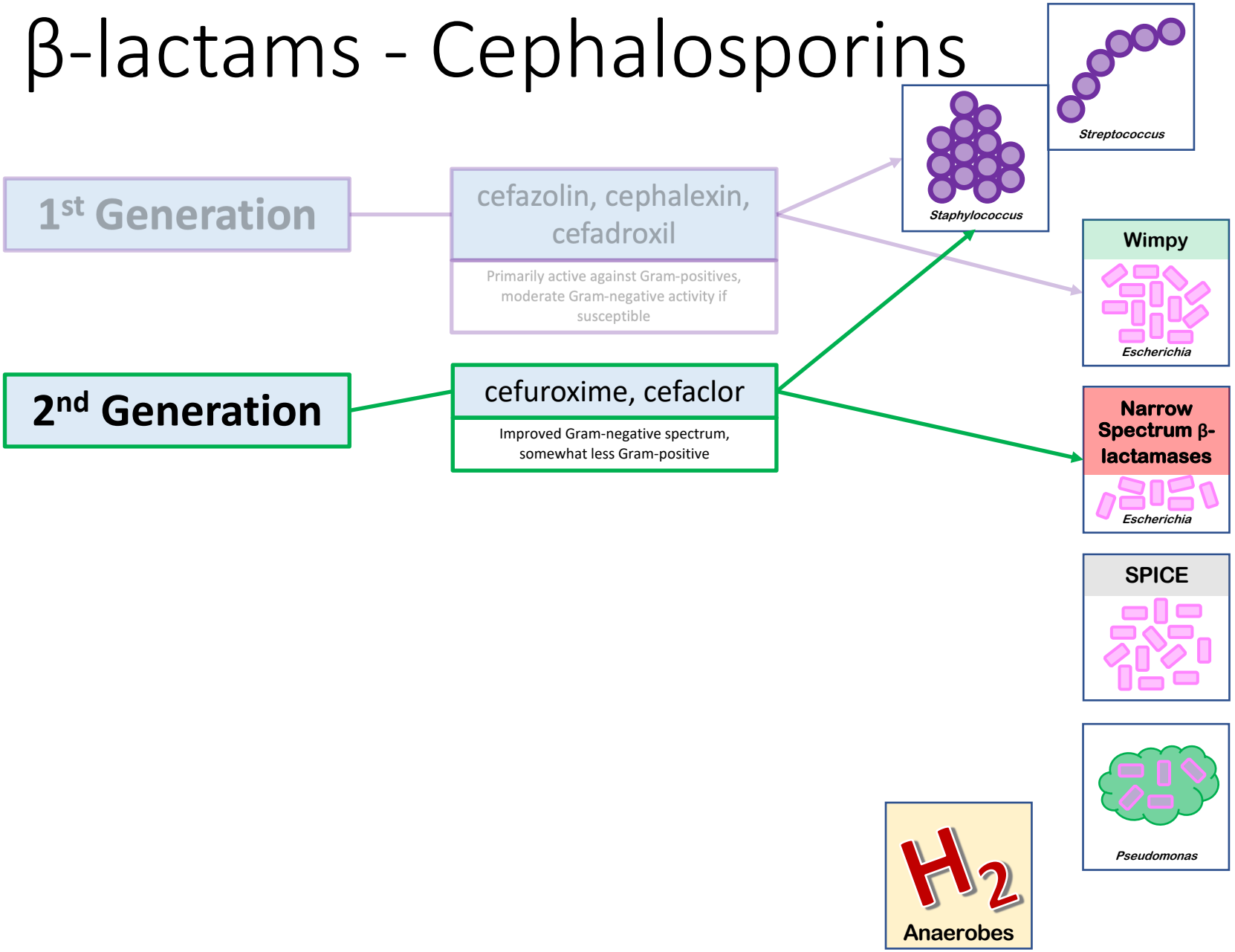




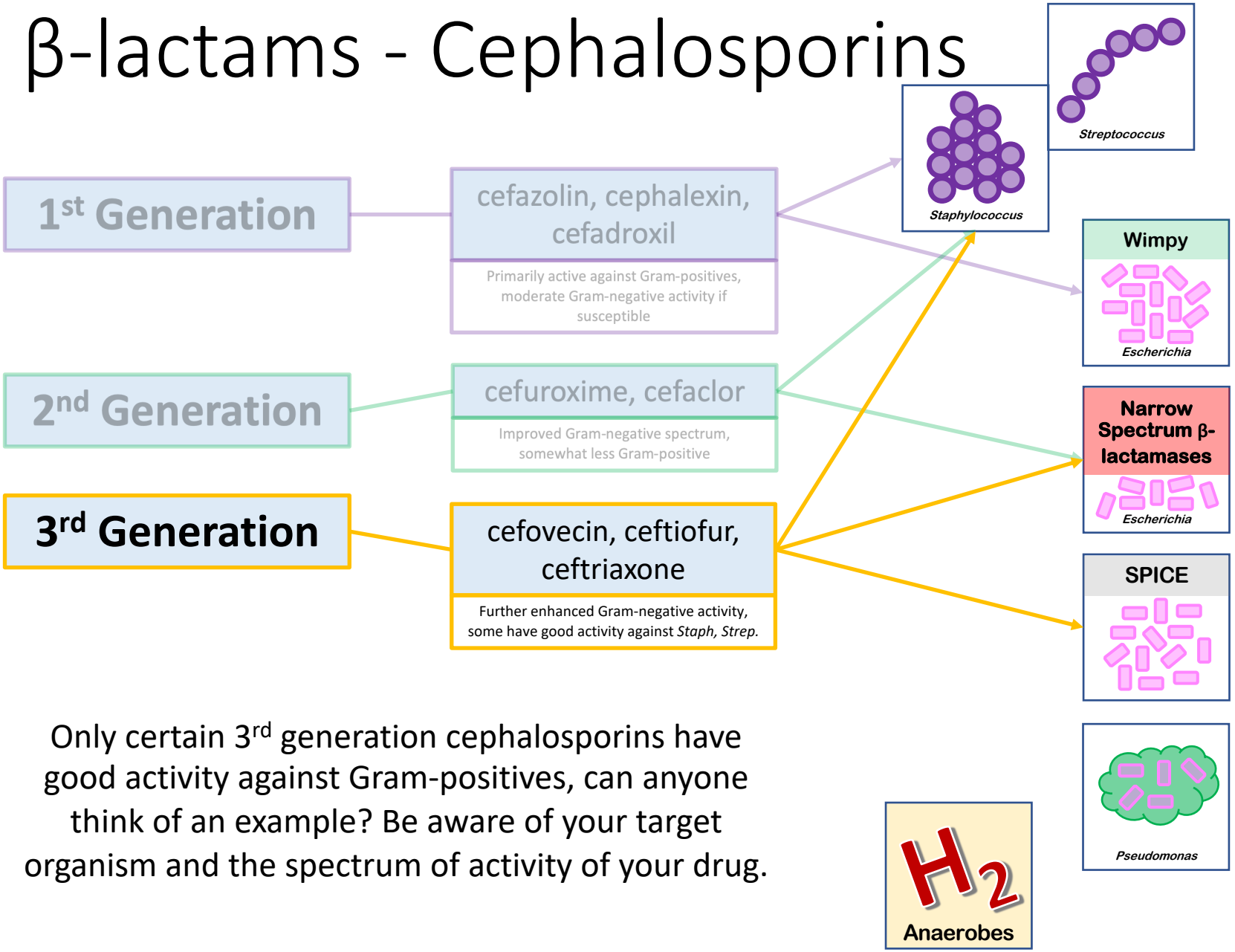




β-lactams - Cephalosporins

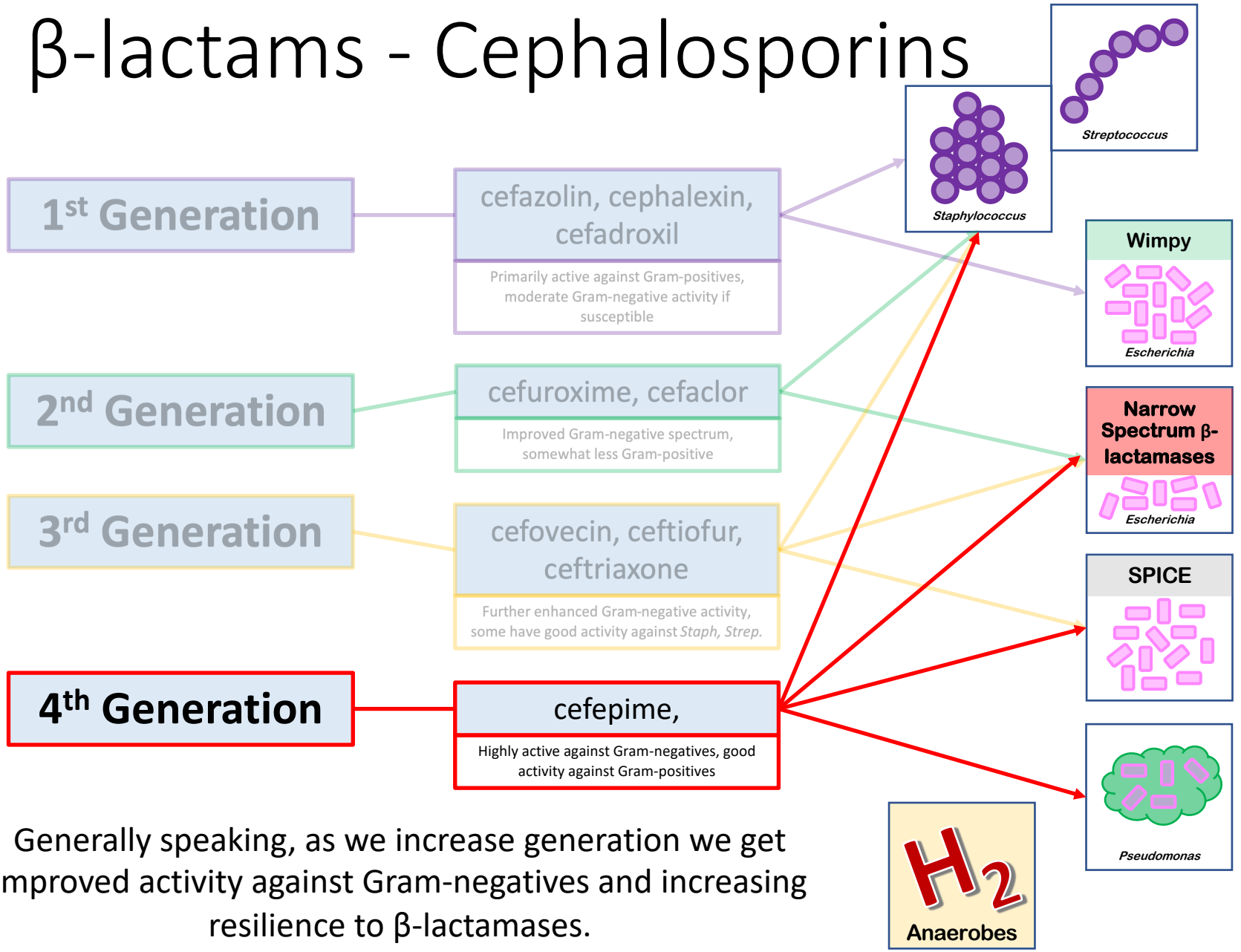


β-lactams - Cephalosporins



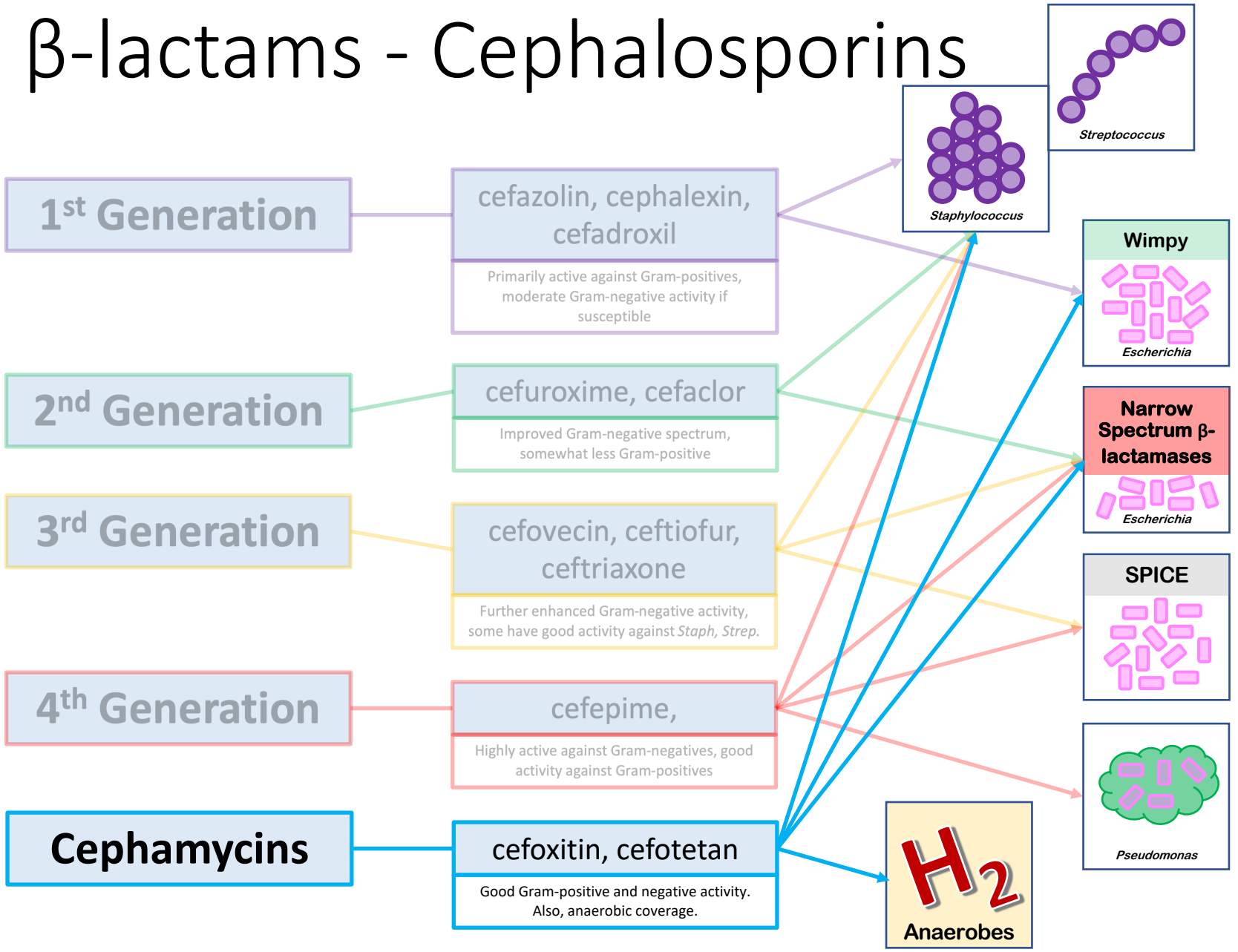
Only certain 3rd generation cephalosporins have good activity against Gram-positives, can anyone think of an example? Be aware of your target organism and the spectrum of activity of your drug.

β-lactams - Cephalosporins



Generally speaking, as we increase generation we get improved activity against Gram-negatives and increasing resilience to β-lactamases.

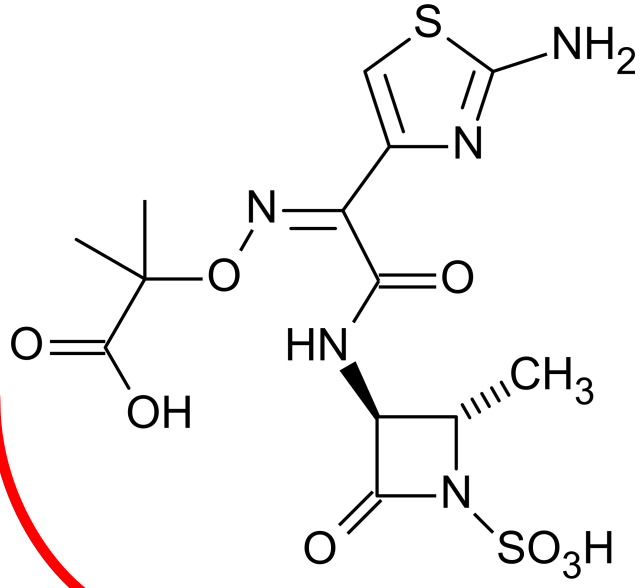
β-lactams - Cephalosporins

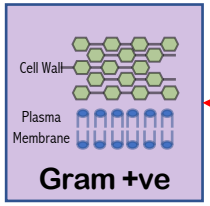


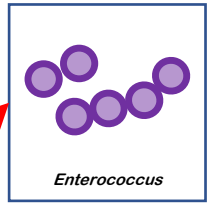
Other β-lactams

Very broad spectrum, most Gram-pos, neg and anaerobes. Ertapenem has no activity against enterococci or *Pseudomonas*

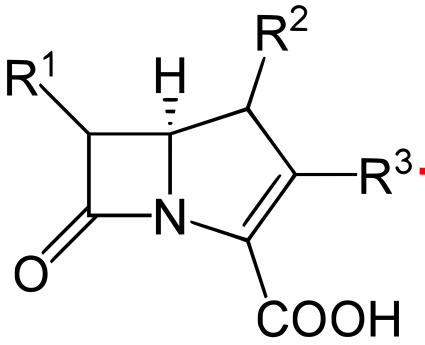
Aztreonam



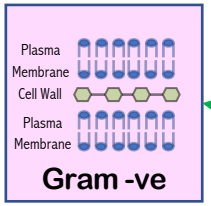




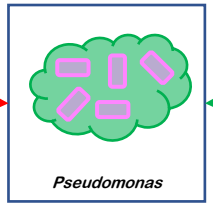
Imipenem, Meropenem



Ertapenem

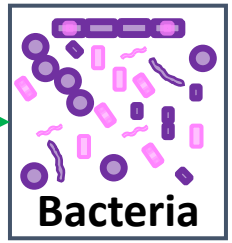


Monobactams



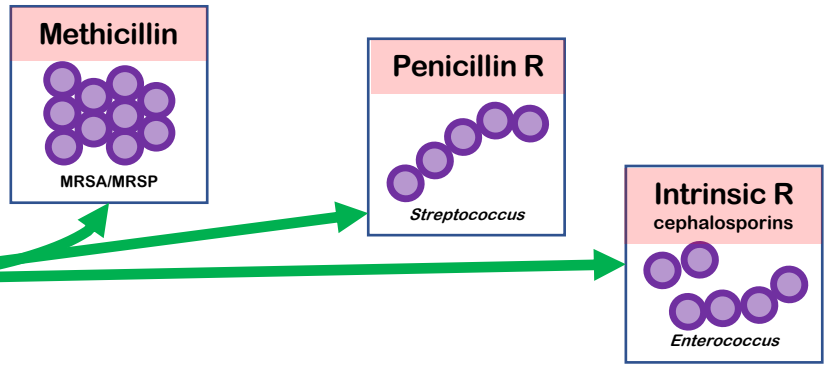
Only Gram-neg activity, including against *Pseudomonas aeruginosa*

Carbapenems



Mechanisms of β-lactam Resistance

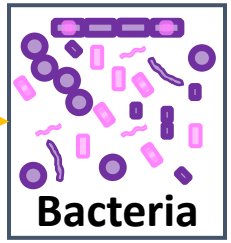
Altered Targets — Altered PBP



Decreased Permeability — Porin Deficiencies

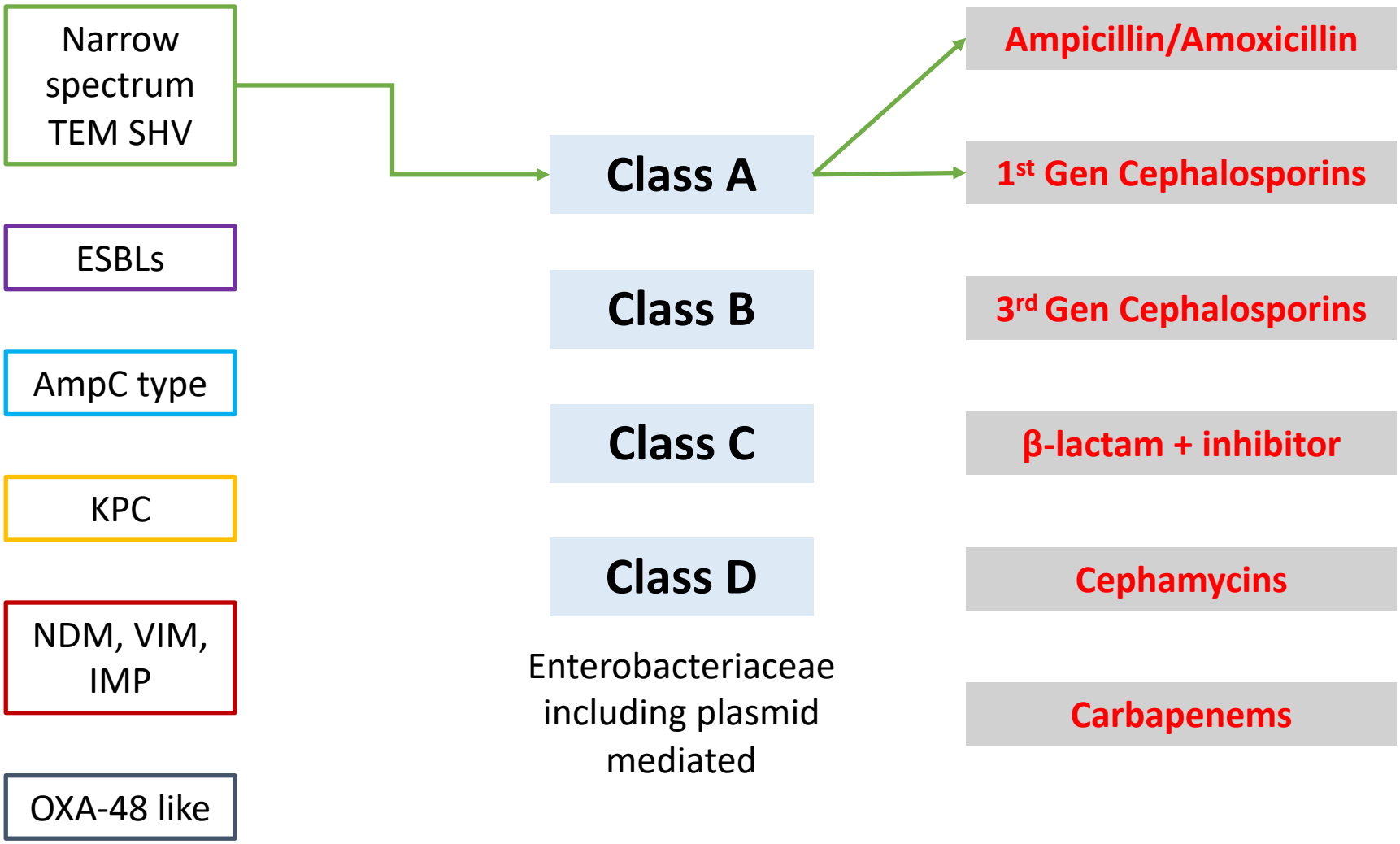
β-lactamases

Enzymatic degradation
VERY common strategy
We'll explore in more detail because it's one where you may be able to do something about it.

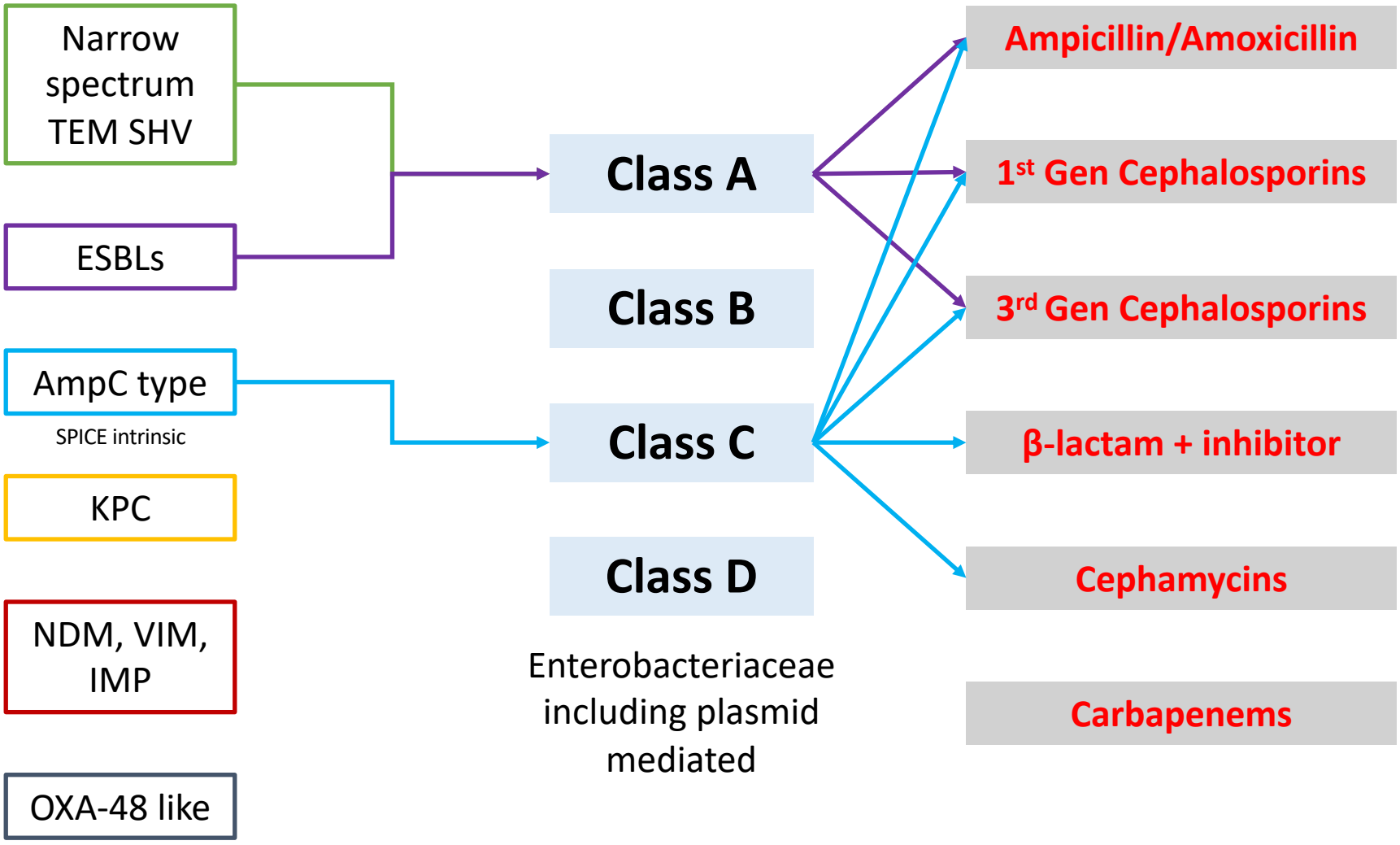


Why is it particularly important for clinicians to understand mechanisms of β-lactam resistance?

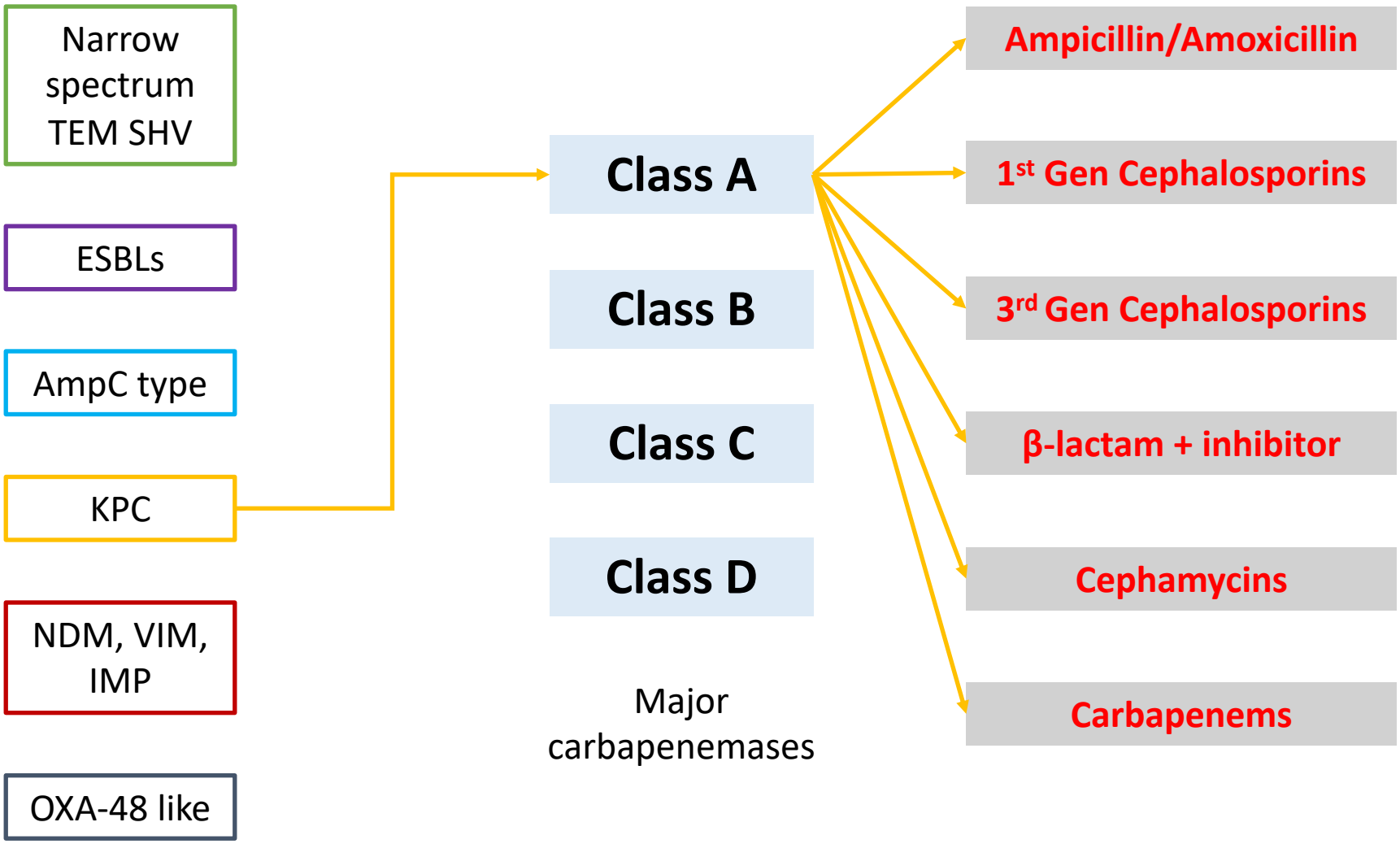
β-lactamase Diversity



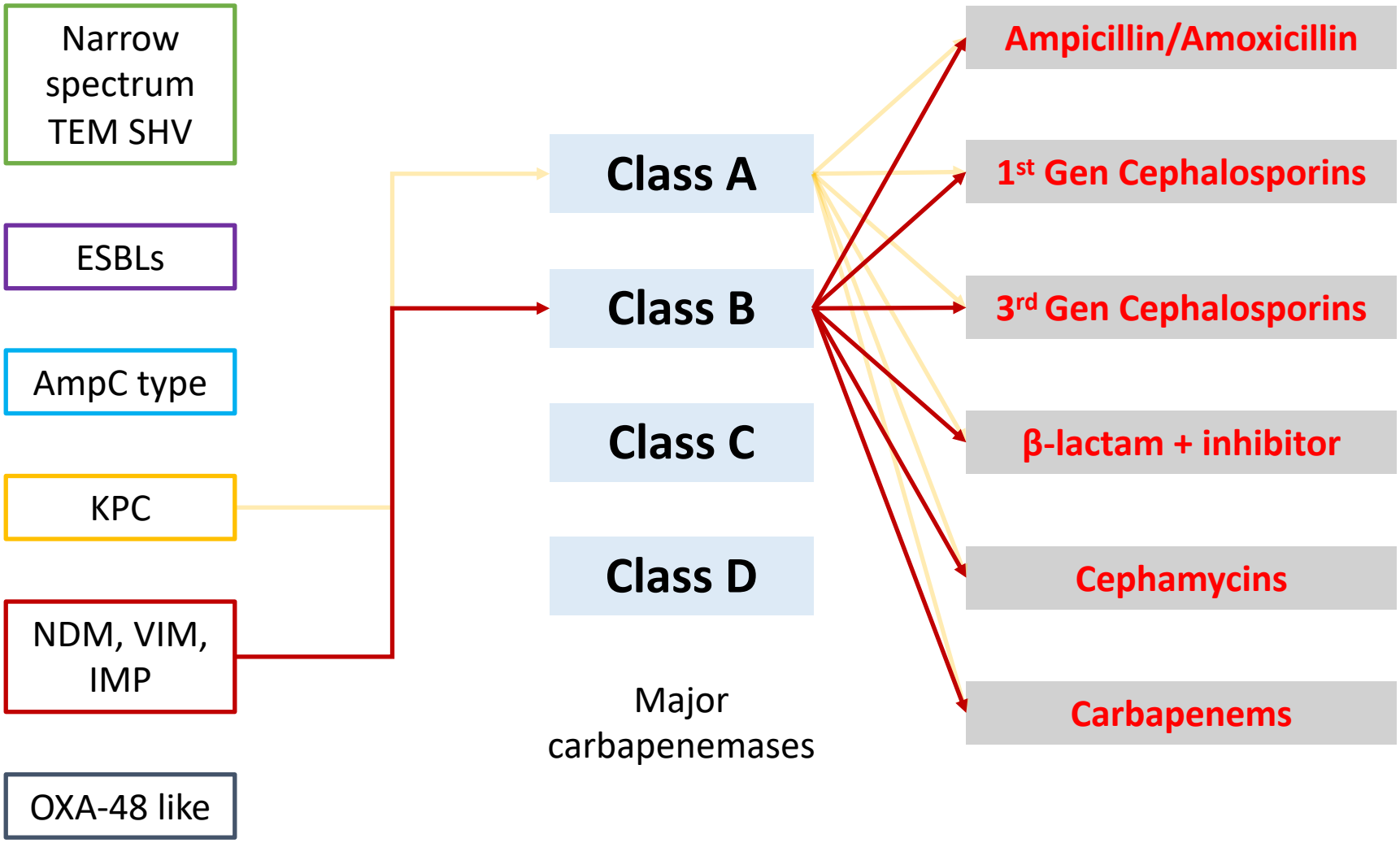
β-lactamase Diversity



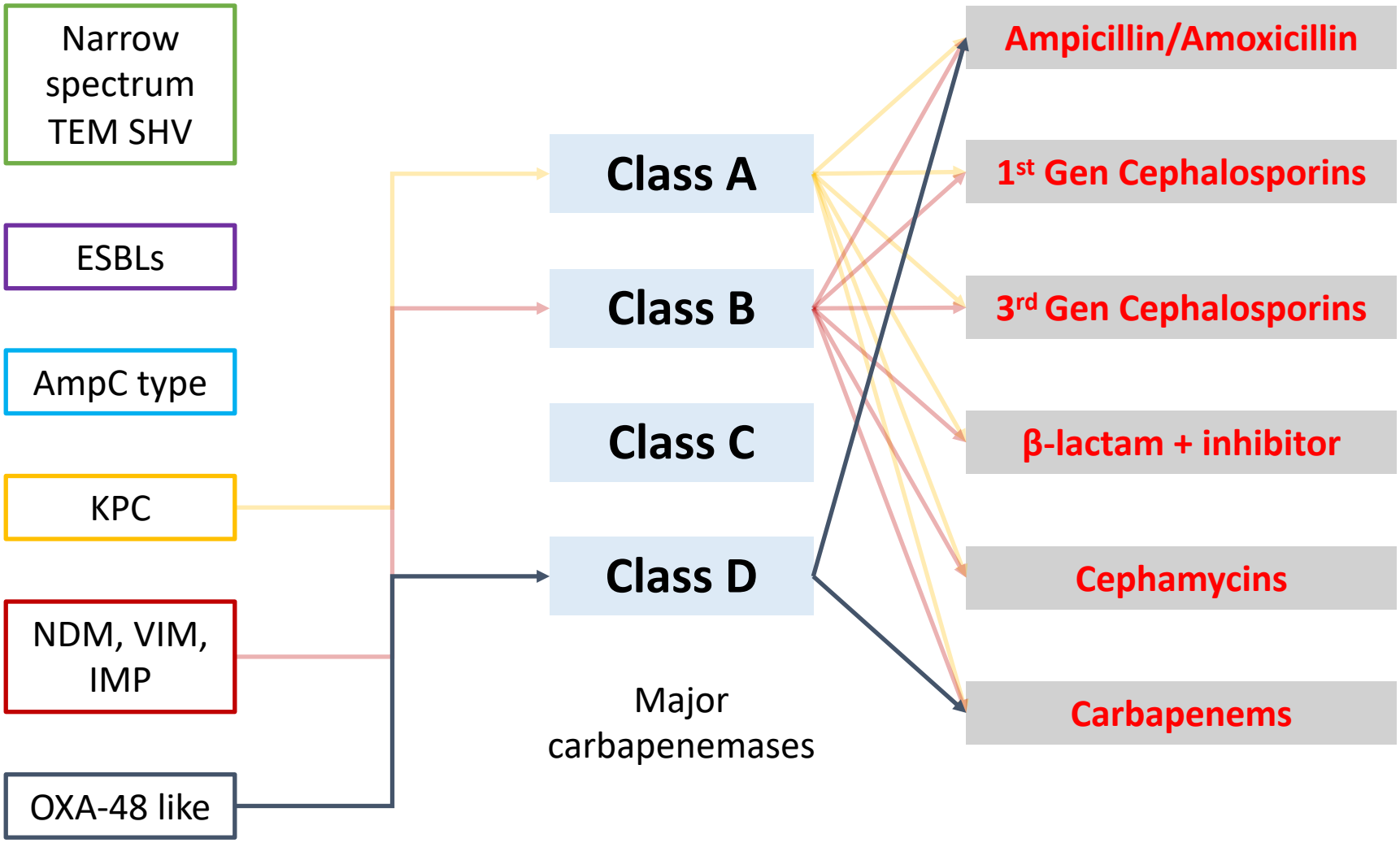
β-lactamase Diversity



β-lactamase Diversity

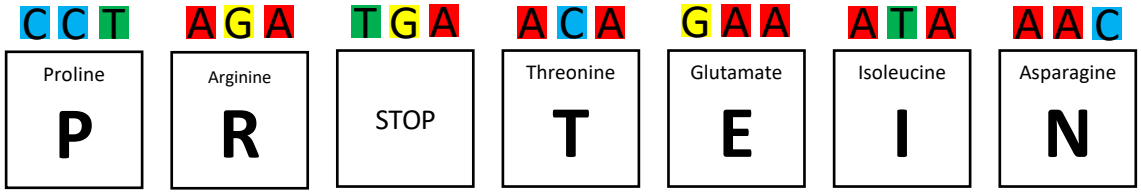


β-lactamase Diversity



Protein synthesis inhibitors

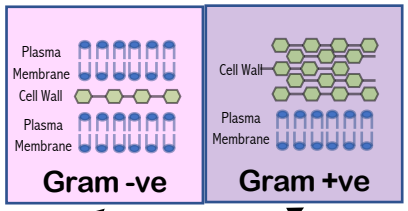
- Bacteria a 30S and 50S ribosomal subunits
  - Distinct from Eukaryotes – 40S and 60S
- Targets for many drug classes
  - Tetracyclines
  - Aminoglycosides
  - MLS_BK
  - Phenicols
  - Streptogramins

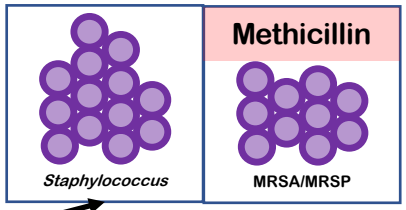


Tetracyclines

Broad spectrum agents. Gram positive activity more limited than Gram negative Resistance is common, so susceptibility testing essential

Binds to 30S ribosomal subunit reversibly - bacteriostatic





Increasing Lipophilicity

Tetracycline

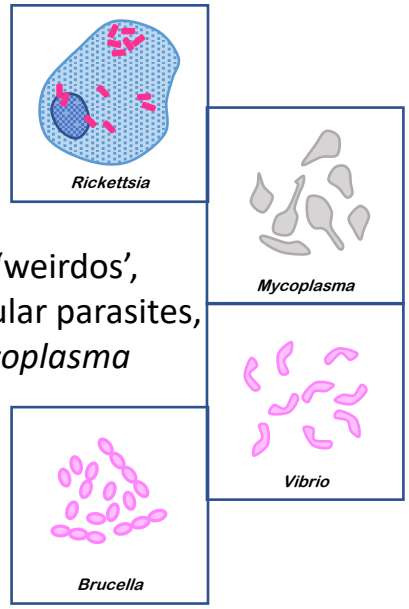
Doxycycline

Minocycline

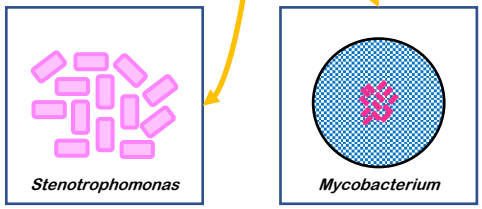
Increasingly important as MRSP becomes more common

What does increasing lipophilicity mean for you as a clinician?

The 'weirdos', intracellular parasites, *Mycoplasma*



Minocycline has activity against *Stenotrophomonas* and *Mycobacterium marinum*



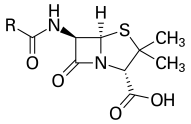
Mechanisms of Tetracycline Resistance

- Efflux
  - Common in Gram positive and negative
    - Resistance not necessarily across class...
      - If you want to use a drug test it!
- Ribosomal protection
  - Very common
    - *S. pseudintermedius* (tetM)
  - Conformational change in tetracycline binding site on 30S subunit of ribosome
- Ribosomal mutations, enzymatic inactivation also occur

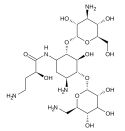
Aminoglycosides

Binds to 30S ribosomal subunit but also effects electron transport chain, DNA metabolism and cell membrane - bactericidal

ONLY AEROBIC BACTERIA!


β-lactam

\+


Amikacin

= synergy

Streptomycin

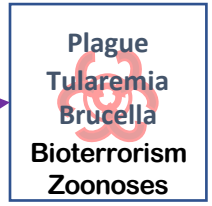
Gentamicin

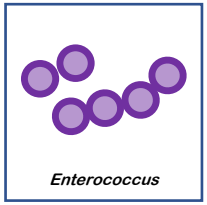
Amikacin

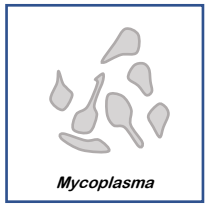
Neomycin

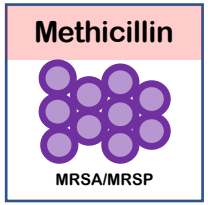
Spectinomycin*

*Aminocyclitol, related drug class









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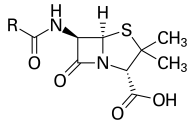
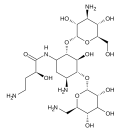

β-lactam

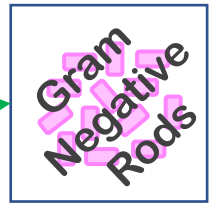
+


Amikacin

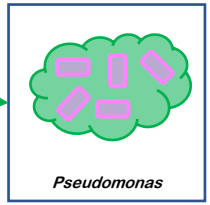
= synergy

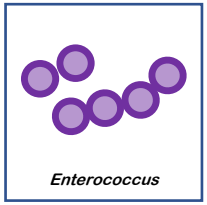
- Streptomycin
- **Gentamicin**
- Amikacin
- Neomycin
- Spectinomycin*

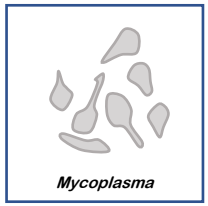
*Aminocyclitol, related drug class

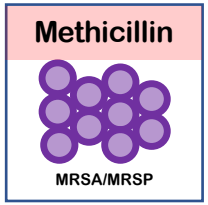


Some of the best anti-pseudomonal activity









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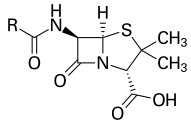
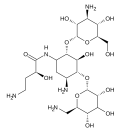
O_2 Aerobes

ONLY AEROBIC BACTERIA!



β-lactam +  Amikacin = synergy

- Streptomycin
- Gentamicin
- **Amikacin**
- Neomycin
- Spectinomycin*

*Aminocyclitol, related drug class

Plague
Tularemia
Brucella
Bioterrorism
Zoonoses

Gram Negative Rods

Some of the best anti-pseudomonal activity

Pseudomonas

+ β-lactam

Enterococcus

Mycoplasma

Nocardia

Methicillin

MRSA/MRSP

Last line of defense against MRSP

Aminoglycosides

Binds to 30S ribosomal subunit but also effects electron transport chain, DNA metabolism and cell membrane - bactericidal

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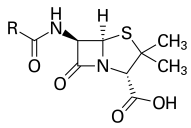
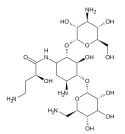


β-lactam +  Amikacin = synergy

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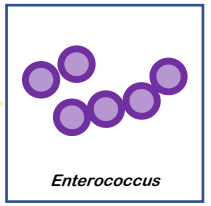
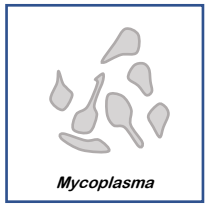
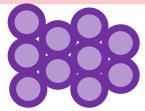




Methicillin



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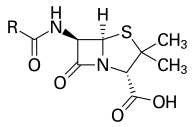
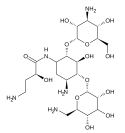


β-lactam +  Amikacin = synergy

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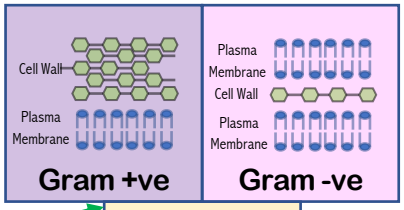
Mechanisms of Resistance Aminoglycosides

- Enzymatic inactivation
  - Aminoglycoside modifying enzymes
  - Most common mechanism of resistance
- Decreased permeability
  - Cross resistance to other antimicrobials

Phenicols

Reversible binding to to 50S ribosomal subunit - bacteriostatic

Broad spectrum agents

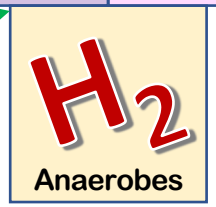


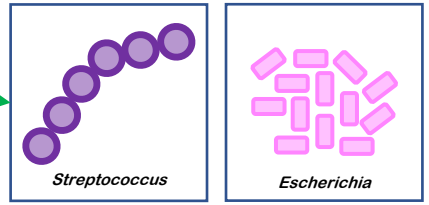
Banned in food animals, rare idiosyncratic aplastic anemia in people (1:20,000-40,000)

Chloramphenicol

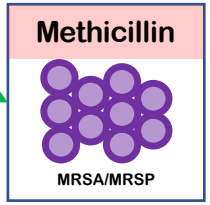
Florfenicol

Aplastic anemia not associated with florfenicol

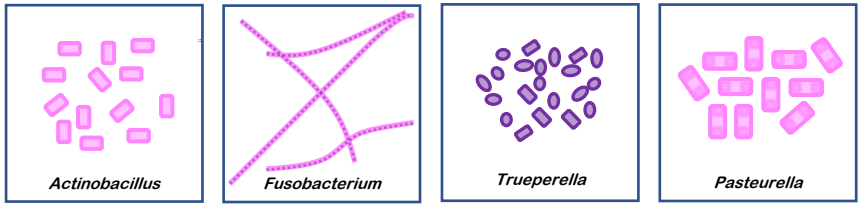




Bacterial conjunctivitis caused by variety of organisms



An option for MRSP



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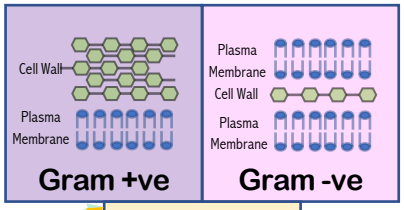

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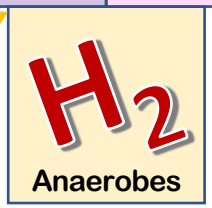

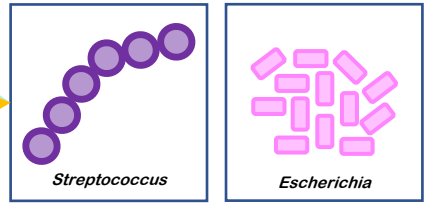

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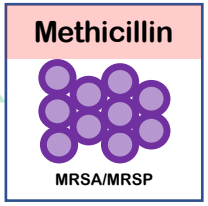

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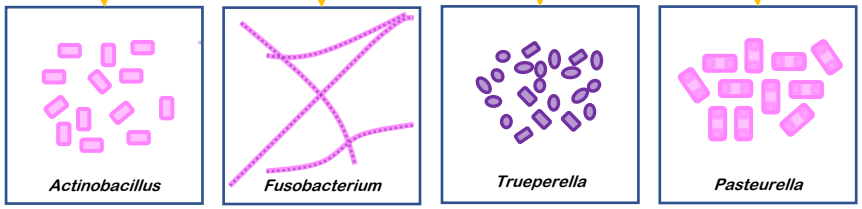

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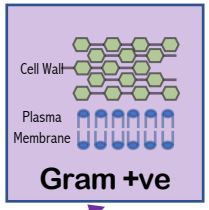

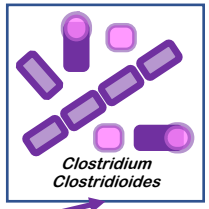

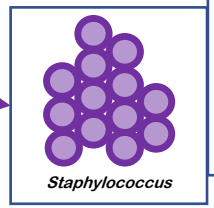

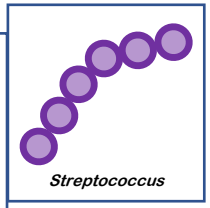

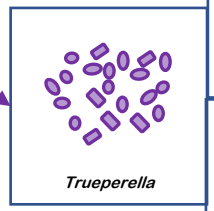

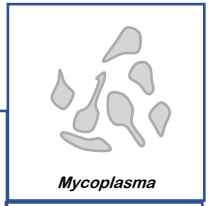

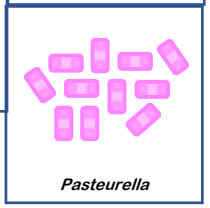

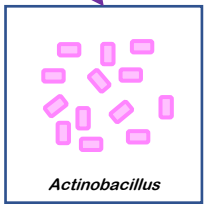

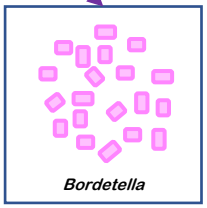

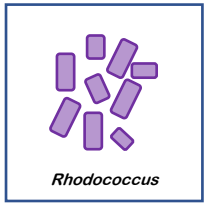

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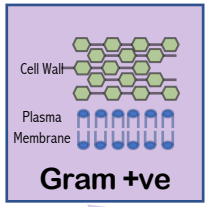

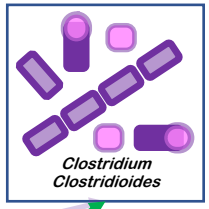

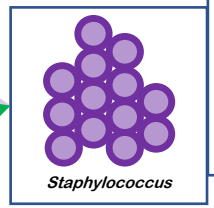

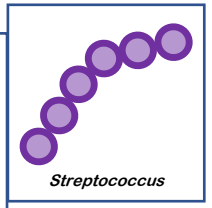

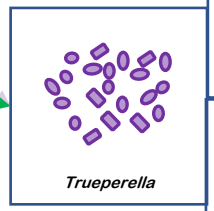

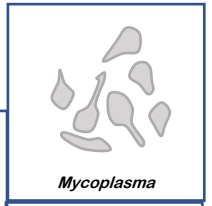

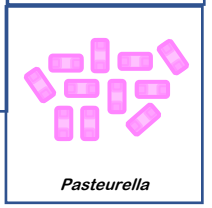

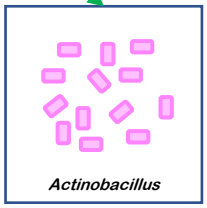

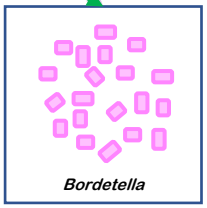

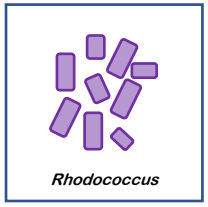

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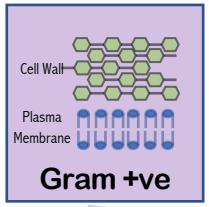

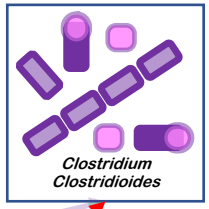

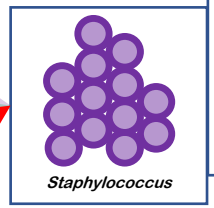

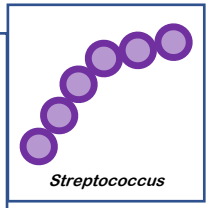

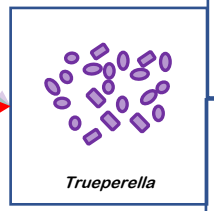

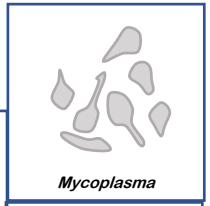

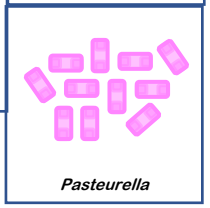

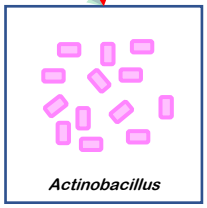

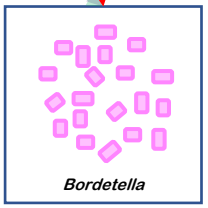

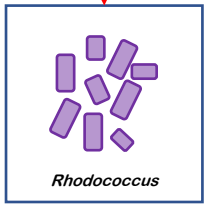

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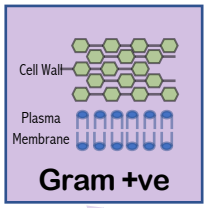
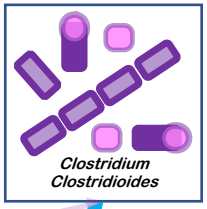
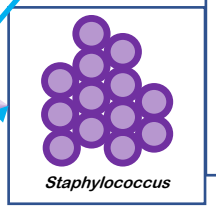
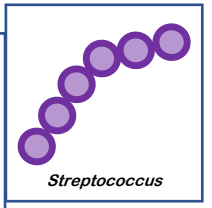
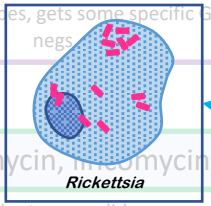
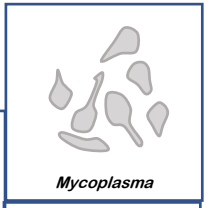


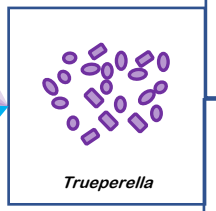


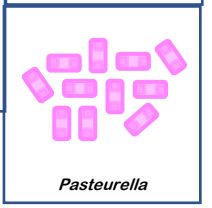


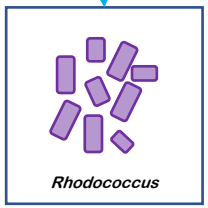


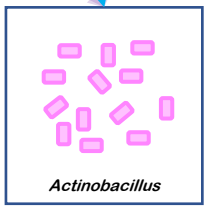


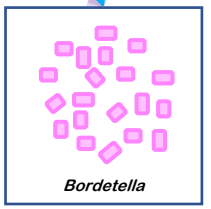












MLS_BK

Resistance increasingly common, susceptibility testing VERY important

Reversible binding to to 50S ribosomal subunit - bacteriostatic

Macrolides

Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin

Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

Lincosamides

Clindamycin, lincomycin

Similar to macrolides

Ketolides

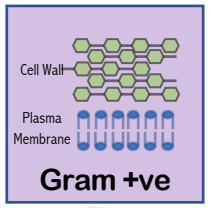
Clarithromycin

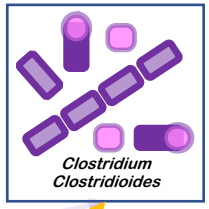
Similar to macrolides with enhanced Gm pos activity

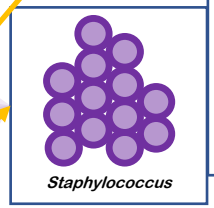
Streptogramins

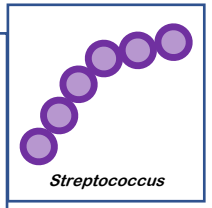
Vinginiamycin

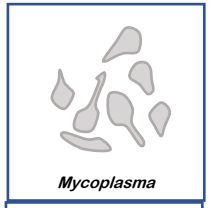
Gm pos cocci and bacilli, Gm neg cocci, anaerobes

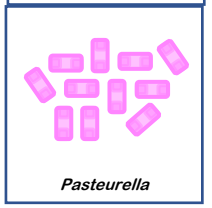


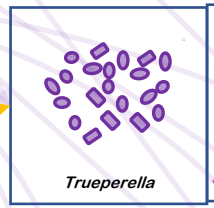


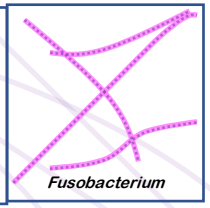


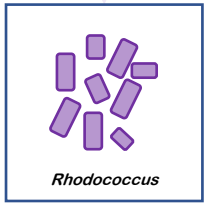


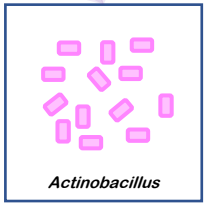


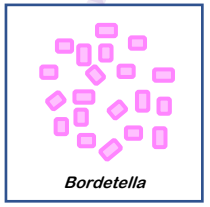






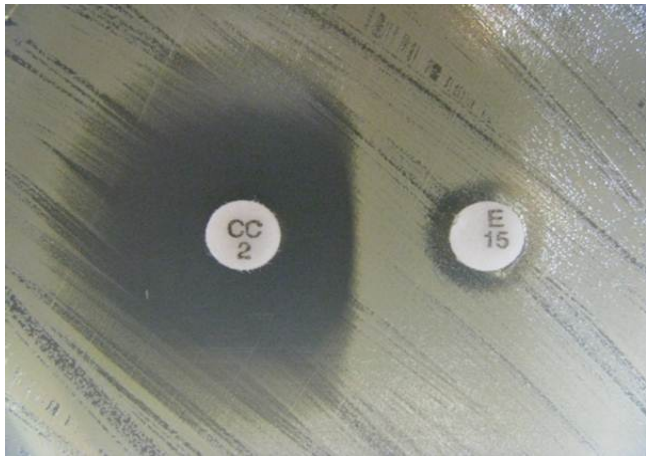






Mechanisms of Resistance MLS_BK

- Target Modification
  - Ribosomal methylases
    - *erm* gene family
  - Be aware of inducible resistance
- Active Efflux
- Enzymatic Inactivation

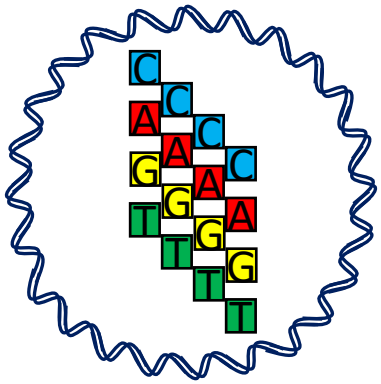


Inducible clindamycin resistance in *S. aureus*

Detection requires specialized laboratory tests

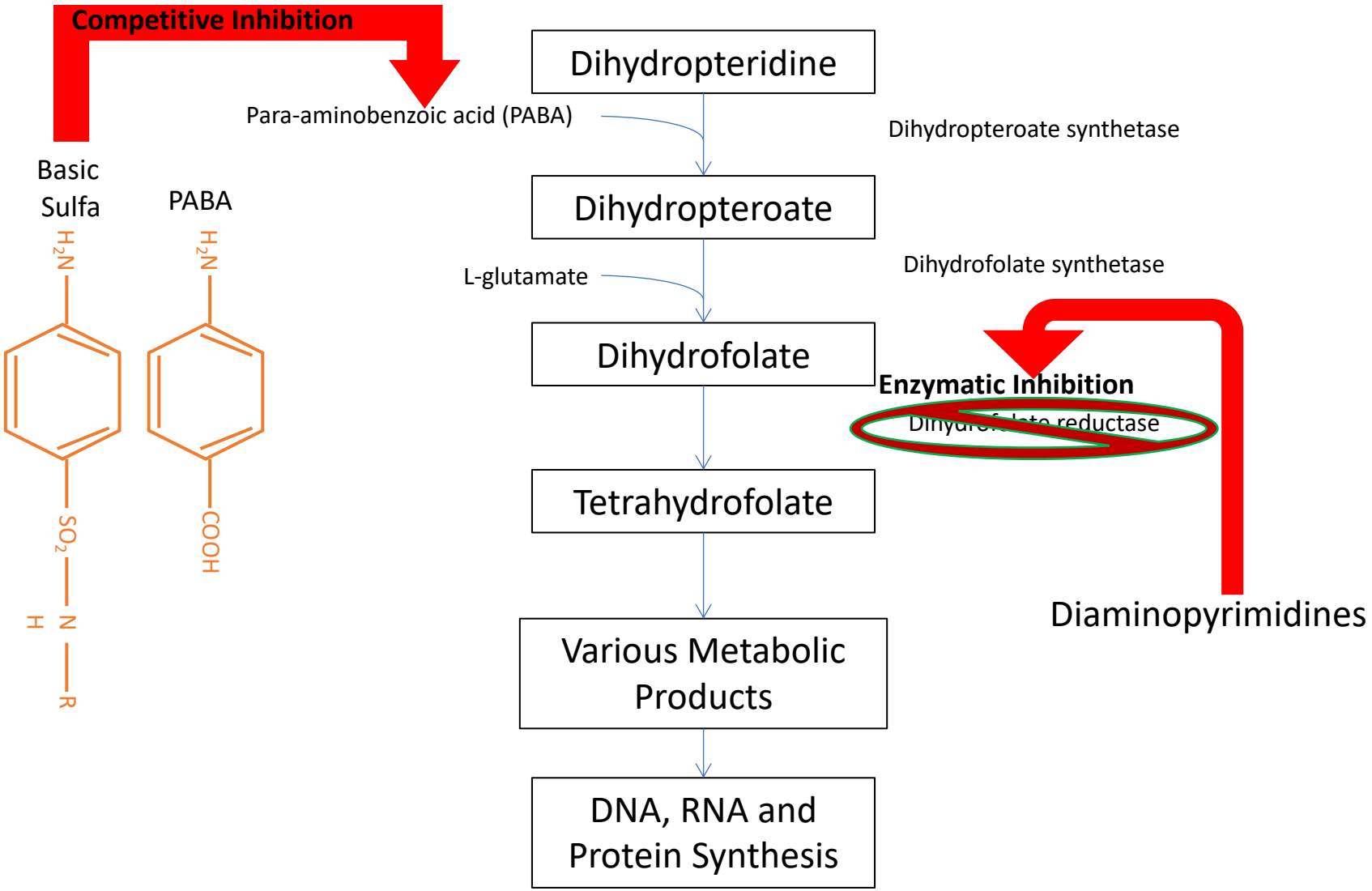
Agents Affecting Nucleic Acids

- Agents act at many steps along the process
  - Folate production
  - Disrupting DNA production
  - DNA organization and replication
  - RNA synthesis



Folate Synthesis Inhibitors

Bacteriostatic

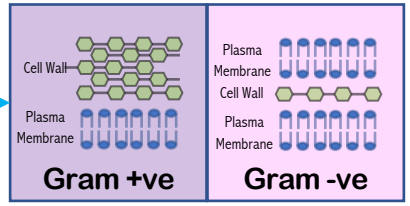


Folate Synthesis Inhibitors

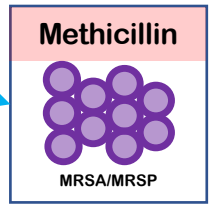
Oldies but goodies!

Trimethoprim + Sulfamethoxazole

Broad bacterial spectrum



Notable Exceptions
Enterococci, *Pseudomonas aeruginosa*
Group A Strep (more human)



Another option for MRSP

Activity against some Protozoans and Toxoplasma

Mechanisms of Resistance

- Altered enzymes
  - *dfr* genes (trimethoprim resistance)
    - Gram positive and negative
  - *sul* genes (sulfa resistance)
    - Gram negative bacteria
    - Often found in multi-resistant bacteria, linkage to other resistance genes
- Hyper-production of PABA

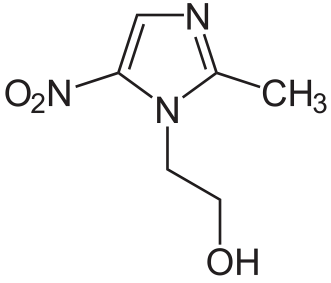
Nitroimidazoles (Metronidazole)

Disrupts DNA production by production of radical anions following intracellular metabolism - bactericidal

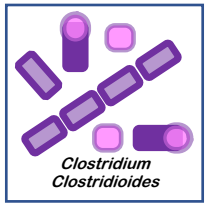
Broad spectrum anaerobic coverage

Activity limited to anaerobes!

Metronidazole



BANNED in food animals



Trichomonas, Giardia, Entamoeba

Shown to reduce colonization resistance for important pathogens (*Salmonella* and *E. coli*) and increase intestinal inflammation

Mechanisms of Resistance:

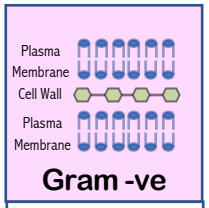
Reduced uptake
Efflux
Reducing the rate of reductive activation
Inactivating enzymes
Increased DNA repair

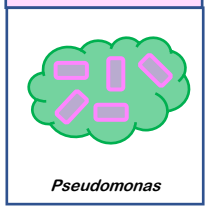
(Fluoro)quinolones

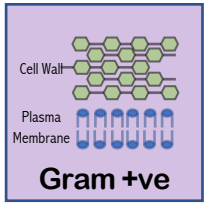
Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal

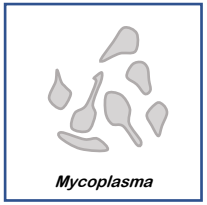
Quinolones

- Nalidixic Acid
  - Only Enterobacteriaceae
- 1st Generation FQ
  - Ofloxacin
    - Gm neg
- 2nd Generation FQ
  - Enrofloxacin, ciprofloxacin
    - Improved Gm neg, and Gm pos spectrum
- 3rd Generation FQ
  - Pradofloxacin
    - Broad spectrum Gm neg, pos, anaerobe









(Fluoro)quinolones

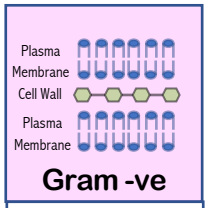
Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal

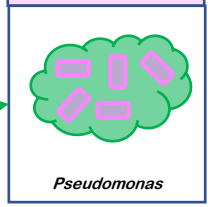
Quinolones — Nalidixic Acid — Only Enterobacteriaceae

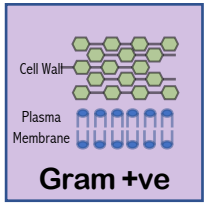
1st Generation FQ — Ofloxacin — Gm neg

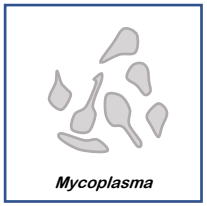
2nd Generation FQ — Enrofloxacin, ciprofloxacin — Improved Gm neg, and Gm pos spectrum

3rd Generation FQ — Pradofloxacin — Broad spectrum Gm neg, pos, anaerobe



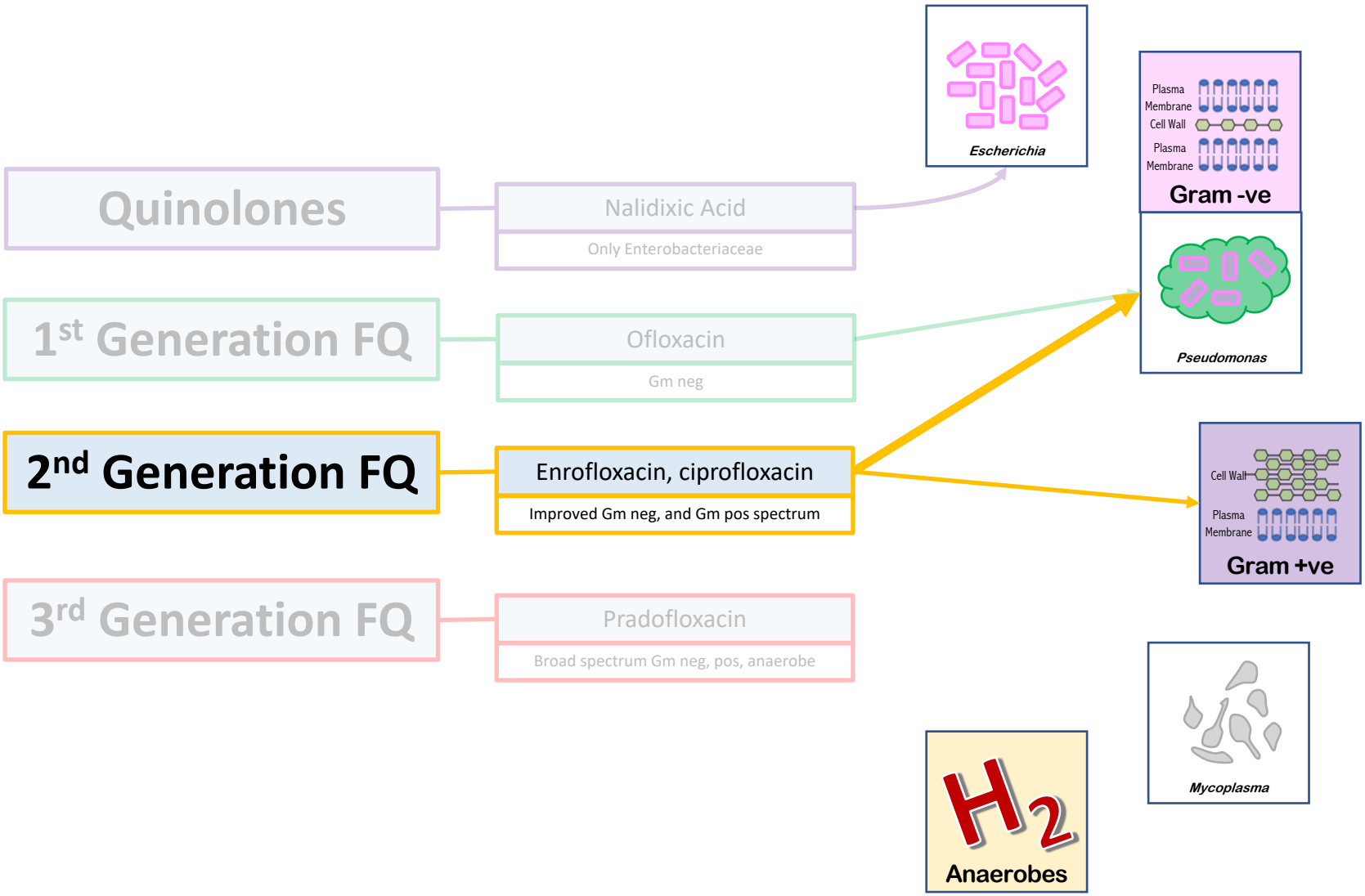






(Fluoro)quinolones

Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal



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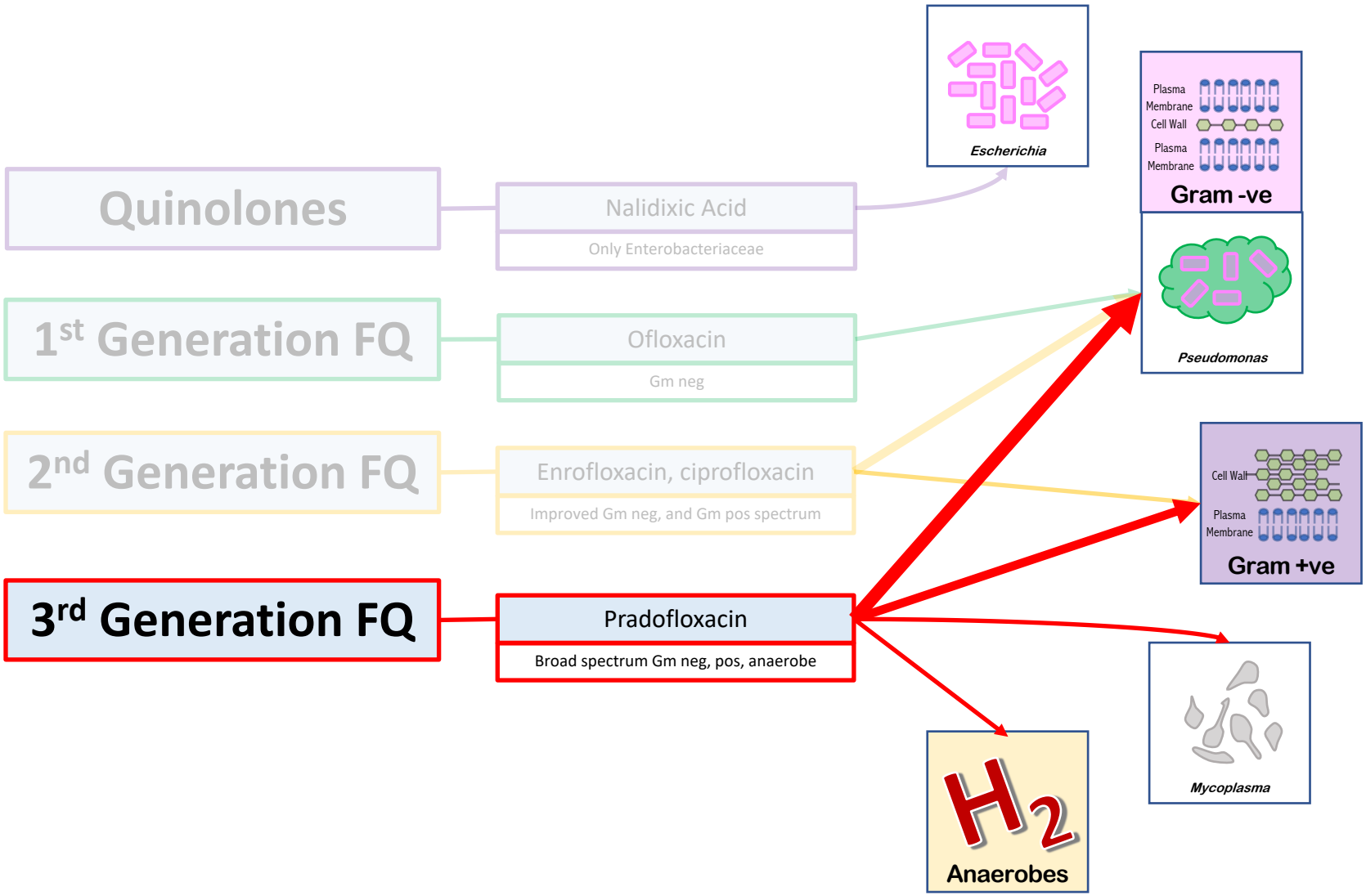
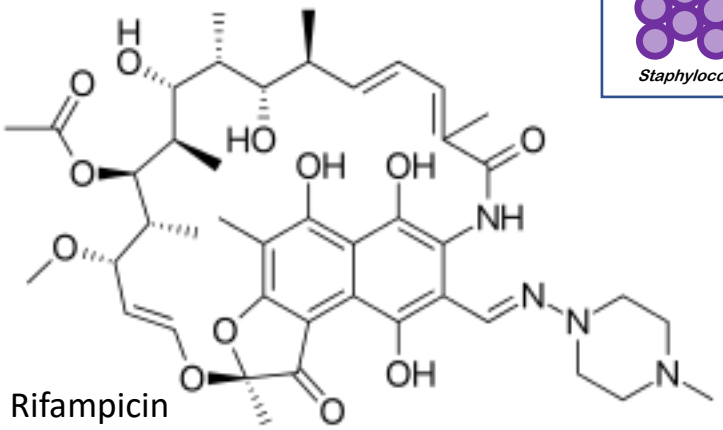


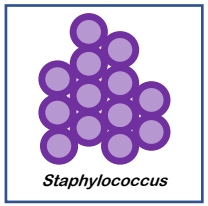
Ansamycins (Rifampin)

Preventing action of DNA-dependent RNA-polymerase, prevents elongation of transcribed RNA.

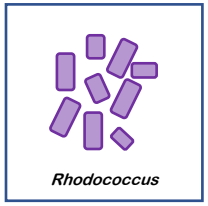
- Primarily for Gram-positives and some *Mycobacteria*



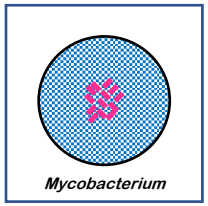
Rifampicin



Never used as a monotherapy - resistance develops quickly.



In people also used for prophylaxis following exposure to *Neisseria meningitidis* or to treat invasive *Haemophilus influenzae* or *Streptococcus pneumoniae infections.*



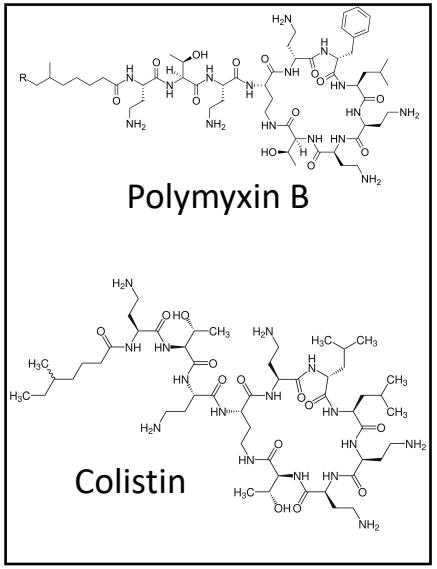
Mechanism of Resistance

1. Through mutations in the genes encoding the machinery for transcription

Polymyxins

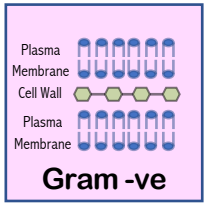
Disrupt outer membrane surrounding Gram negative bacteria

- Only active against Gram-negatives

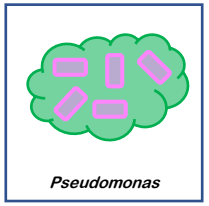


Polymyxin B

Colistin



These are last line of defense drugs against Gram negatives, often the last agents to which MDR organisms remain susceptible



Gram positives and anaerobes intrinsically resistant as they lack LPS containing membrane.

Some Gram negatives are intrinsically resistant, including members of the Enterobacteriaceae (*Edwardsiella* spp., *Morganella morganii, Proteus* spp., *Providentia* spp., *Serratia* spp. Mechanism not known

Mechanisms of Resistance

1. Modification of LPS - chromosomally encoded
2. Plasmid mediated - *mcr*-1 exact mechanism unknown, but this encodes a protein homologous to one in *Paenibacillus* spp. which product polymyxins

Key Definitions

- MIC (minimum inhibitory concentration)
  - The lowest antimicrobial concentration inhibits growth
  - By convention, a doubling dilution series
    - e.g. 0.12µg/ml, 0.25µg/ml, 0.5µg/ml, 1µg/ml, 2µg/ml, 4µg/ml

Susceptible

When a patient has an infection with a susceptible organism, there is a high likelihood of clinical success when treated with a drug according to the drug label indication

Resistant

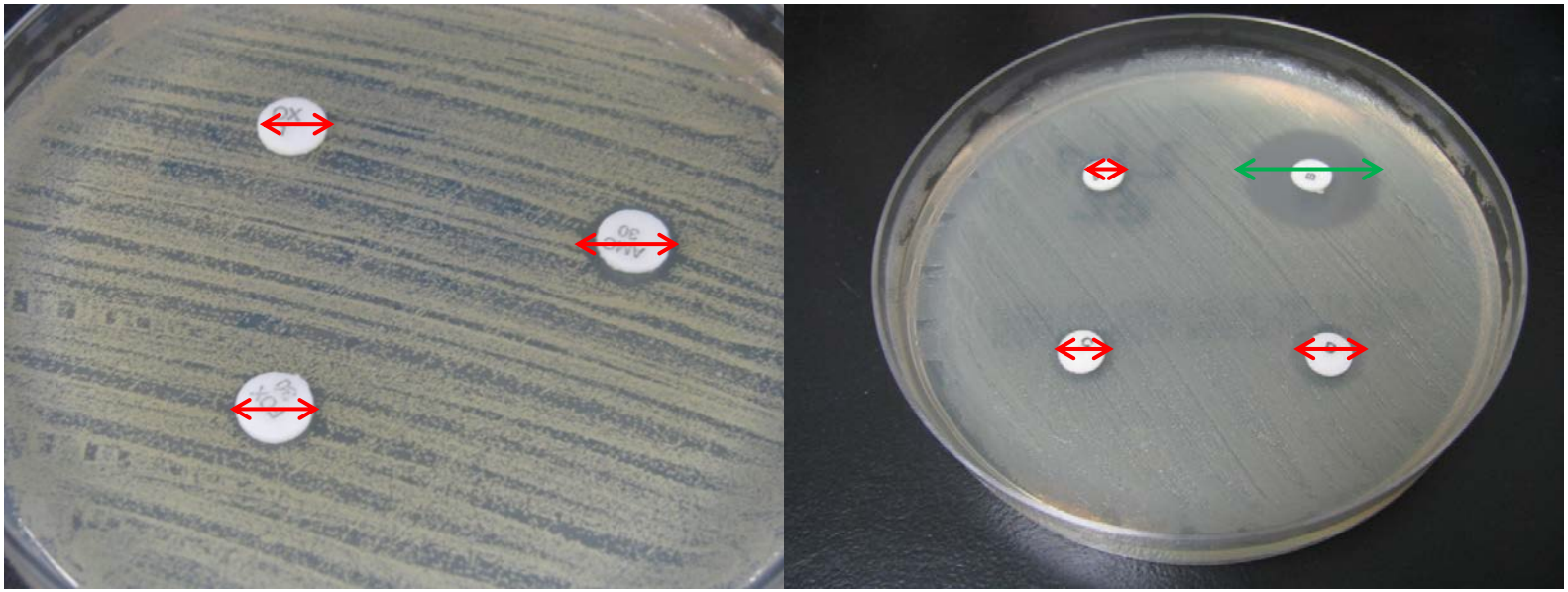
When a patient has an infection with a resistant organism, clinical failure is predicted when treated with a drug according to the label indication

Susceptibility Test Methods

- Categorical methods
  - Only tell you whether the organism is susceptible or resistant
- Quantitative methods
  - Yield an MIC which describes exactly *how* susceptible or resistant the isolate is
  - An MIC can be translated into a categorical result

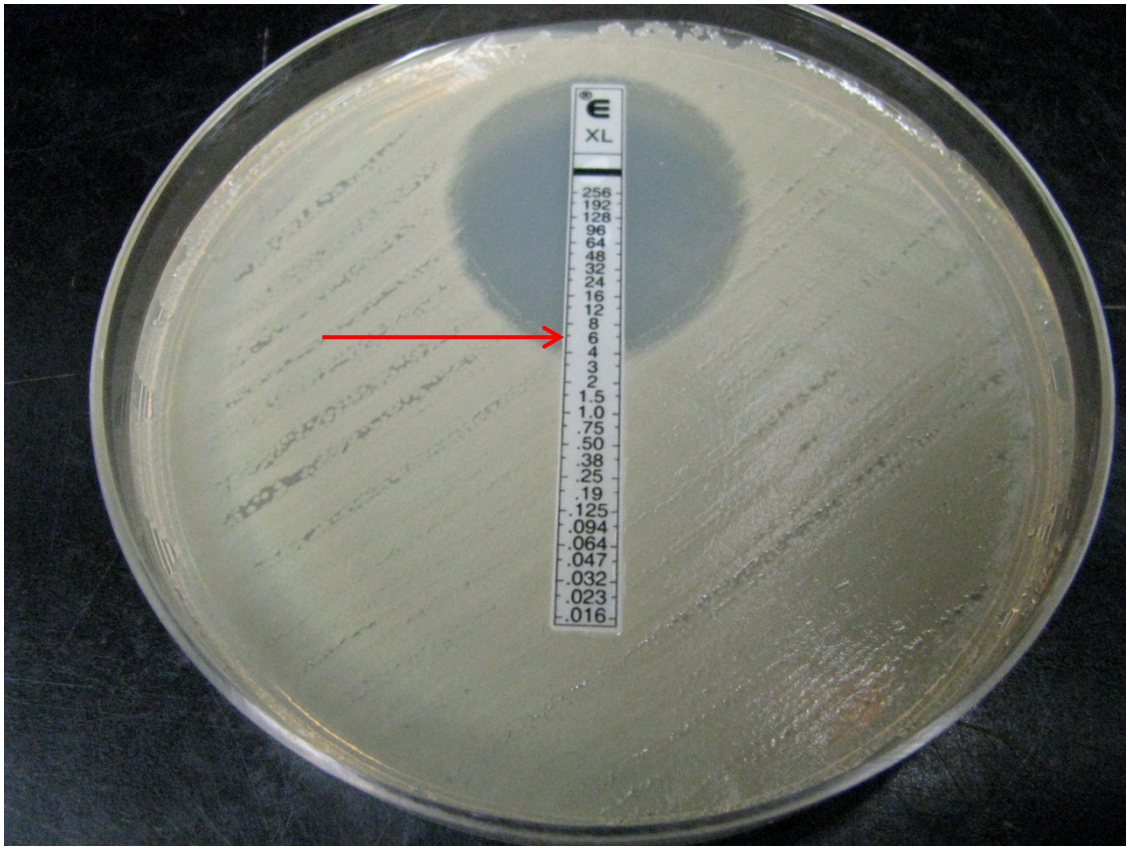
	Diffusion Methods	**Dilution Methods**
Categorical	Kirby-Bauer (Disks)	
Quantitative	Gradient strips (E-tests)	Agar dilution Broth micro/macro dilution

Kirby-Bauer Disk Testing



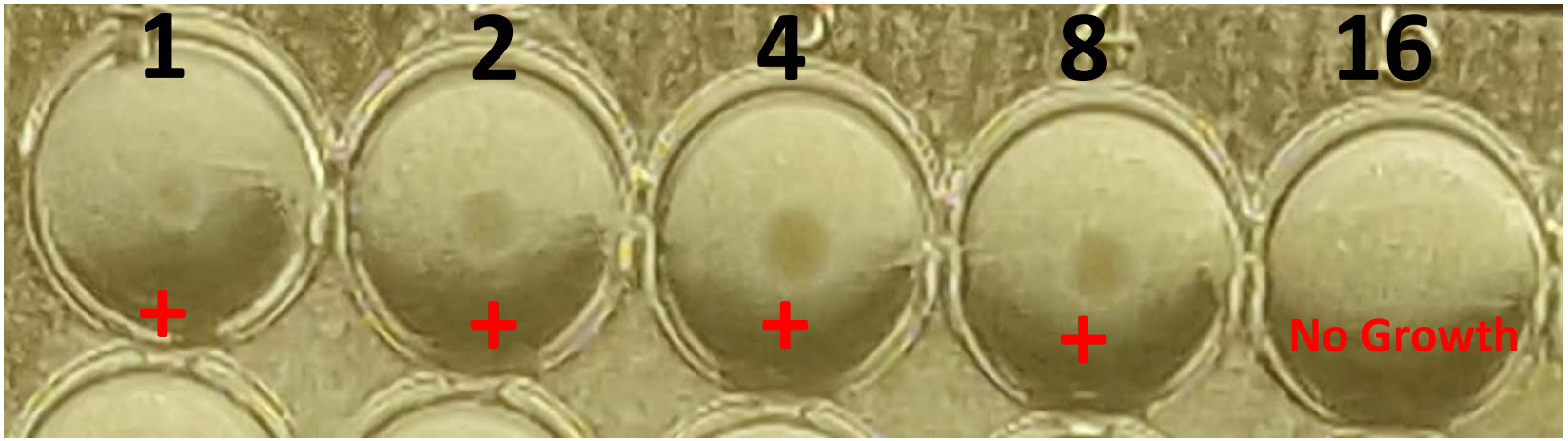
Gradient Strips

MIC = 6
By convention, this is rounded to 8



Broth Micro-Dilution

Tetracycline



Interpretation of Tests

- Standardized interpretive criteria critical
  - Clinical and Laboratory Standards Institute (CLSI) – USA
  - European Committee on Antimicrobial Susceptibility Testing (EUCAST) – Europe

Interpretation of Tests

Enterobacteriaceae

EUCAST Clinical Breakpoint Tables v. 6.0, valid from 2016-01-01

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1ºC, 18±2h
Reading: Read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
Quality control: *Escherichia coli* ATCC 25922. For control of the inhibitor component of beta-lactam inhibitor-combination disks, use either *Escherichia coli* ATCC 35218 or *Klebsiella pneumoniae* ATCC 700603.

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Benzylpenicillin	-	-		-	-	**1/A.** Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 50 mm.
Ampicillin	8[1]	8	10	14[A,B]	14[B]	
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[A,B]	14[B]	**2.** For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
Amoxicillin	8[1]	8	-	Note[C]	Note[C]	**3.** For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
Amoxicillin-clavulanic acid	8[1,3]	8[3]	20-10	19[A,B]	19[B]	**4.** For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32[1,3]	32[3]	20-10	16[A,B]	16[B]	~~**5/D.** Mecillinam (pivmecillinam) breakpoints relate to *E. coli*, *Klebsiella* spp. and *P. mirabilis* only.~~
Piperacillin	8	16	30	20	17	
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17	**B.** Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agars.
Ticarcillin	8	16	75	23	23	**C.** Susceptibility inferred from ampicillin.
Ticarcillin-clavulanic acid	8[3]	16[3]	75-10	23	23	**D.** Ignore isolated colonies within the inhibition zone for *E. coli*.
Phenoxymethylpenicillin	-	-		-	-	
Oxacillin	-	-		-	-	
Cloxacillin	-	-		-	-	
Dicloxacillin	-	-		-	-	
Flucloxacillin	-	-		-	-	
Mecillinam (uncomplicated UTI only) *E. coli*, *Klebsiella* spp. and *P. mirabilis*	8	8	10	15[D]	15[D]	

WHAT is definition based on?

Species | Indication | Drug | Dosing Regimen | Breakpoint

								S	I	R	
Dogs											
A	Skin, soft tissue	Amoxicillin-clavulanate	*E. coli*	–	–	–	–	≤0.25/0.12	0.5/0.25	≥1/0.5	**(19)** Amoxicillin-clavulanate breakpoints were determined from an examination of MIC distribution data, efficacy data, and PK-PD analysis of amoxicillin in dogs. The dosage regimen used for PK-PD analysis of amoxicillin was 11 mg/kg administered every 12 hours orally. **(20) With the exception of isolates from UTIs, *E. coli* and other *Enterobacteriaceae* should be reported as resistant to ampicillin, amoxicillin, and amoxicillin-clavulanate because the drug concentrations achieved according to the labeled dosing regimen are not high enough to reach the therapeutic target. For uncomplicated UTIs, see comment (21).**
A	UTI	Amoxicillin-clavulanate	*E. coli*	–	≥18	–	–	≤8/4	–	–	**(21)** This breakpoint was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg were administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs >300 µg/mL. **See comment (20).**
Cats											
A	Skin, soft tissue, UTI	Amoxicillin-clavulanate	*E. coli*	–	–	–	–	≤0.25/0.12	0.5/0.25	≥1/0.5	**(23)** Amoxicillin-clavulanate breakpoints were determined from an examination of MIC distribution **data**, efficacy data, and PK-PD analysis of amoxicillin in cats at a dosage of 12.5 mg/kg (amoxicillin) administered every 12 hours orally.

Dogs											
A	Skin, soft tissue	Ampicillin	*E. coli*	–	–	–	–	≤0.25	0.5	≥1.0	**(12) Systemic breakpoints were derived from microbiological and PK-PD data. The dosage regimen used for PK-PD analysis of amoxicillin was 22 mg/kg every 12 hours orally.** **(13) Except for lower UTI, *E. coli* and other *Enterobacteriaceae* will test resistant to ampicillin and amoxicillin.**
A	UTI	Ampicillin	*E. coli*	–	–	–	–	≤8	–	–	**(14)** This breakpoint for UTIs was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs >300 µg/mL.
Cats											
A	**Skin, soft tissue, UTI**	**Ampicillin**	***E. coli***	**–**	**–**	**–**	**–**	**≤0.25**	**0.5**	**≥1.0**	**(15) Ampicillin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of amoxicillin in cats. The dosage regimen used for PK-PD analysis of amoxicillin was 12.5 mg/kg administered every 12 hours orally.**
Cattle											
A	**Metritis**	**Ampicillin**	***E. coli***	**–**	**–**	**–**	**–**	**≤0.25**	**0.5**	**≥1.0**	**(16) Breakpoints were derived from microbiological and PK-PD data. The dose of ampicillin trihydrate used to derive this breakpoint was 11 mg/kg every 24 hours IM.**

22 mg/kg q12 hours

11 mg/kg q8 hours

12.5 mg/kg q8 hours

11 mg/kg q24 hours

Human EC

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
PENICILLINS											
A	Ampicillin	10 µg	≥ 17	-	14-16	≤ 13	≤ 8	-	16	≥ 32	**(4)** Results of ampicillin testing can be used to predict results for amoxicillin. See general comment (2).

Table 2H. ***Pasteurella multocida*** **(Continued)**

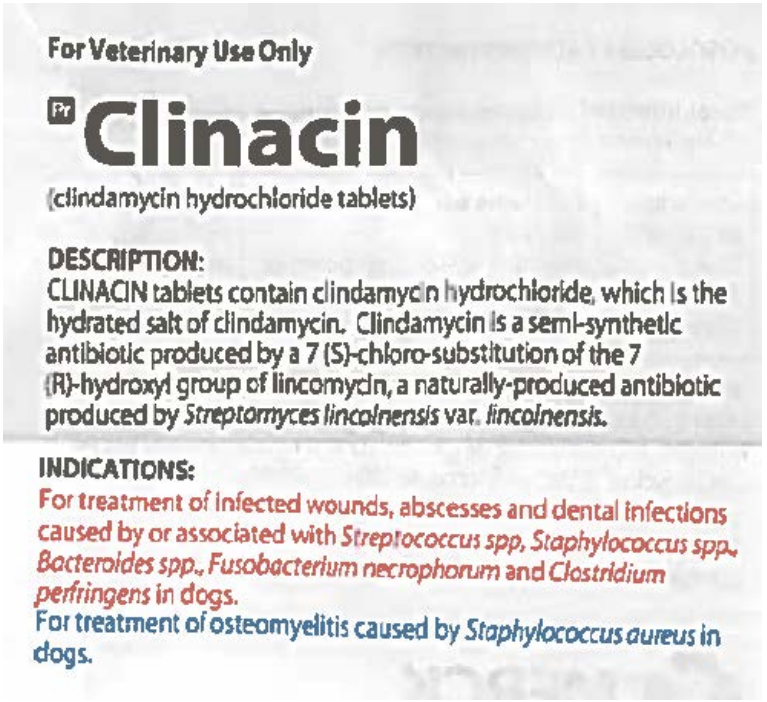
Test/ Report Group	Body Site	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
				S	I	R	S	I	R	
Penicillins										
Cats										
A	**Skin, soft tissue, UTI**	**Ampicillin**	–	–	–	–	**≤0.25**	**0.5**	**≥1**	**(3) Ampicillin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of amoxicillin in cats. The dosage regimen used for PK-PD analysis of amoxicillin was 12.5 mg/kg administered every 12 hours orally.**
Swine										
A	Respiratory	Ampicillin	–	–	–	–	≤0.5	1	≥2	**(4) Ampicillin is the class representative for the aminopenicillins and should be tested.** **(5)** Breakpoints were derived from microbiological data using ampicillin, PK data from a dose of 15 mg/kg IM of amoxicillin once daily, and PD data.[1]
A		Penicillin G	–	–	–	–	≤0.25	0.5	≥1	**(6)** Breakpoints were derived from microbiological, PK data (using accepted clinical but extra-label doses), and PD data. The dose of procaine penicillin G modeled was 33 000 U/kg every 24 hours IM by needle in the neck.
Cattle										
A	**Respiratory**	**Ampicillin**	–	–	–	–	**≤0.03**	**0.06–0.12**	**≥0.25**	**(7) Breakpoints were derived from microbiological and PK-PD data. The dose of ampicillin trihydrate used to derive this breakpoint was 11 mg/kg every 24 hours IM.**
A	Respiratory	Penicillin G	–	–	–	–	≤0.25	0.5	≥1	**(8)** Breakpoints were derived from microbiological, PK data (using accepted clinical but extra-label doses), and PD data. The dose of procaine penicillin G modeled was 22 000 U/kg every 24 hours IM.

12.5 mg/kg q12 hours

15 mg/kg q24 hours

11 mg/kg q24 hours

Read the Monograph!!!!



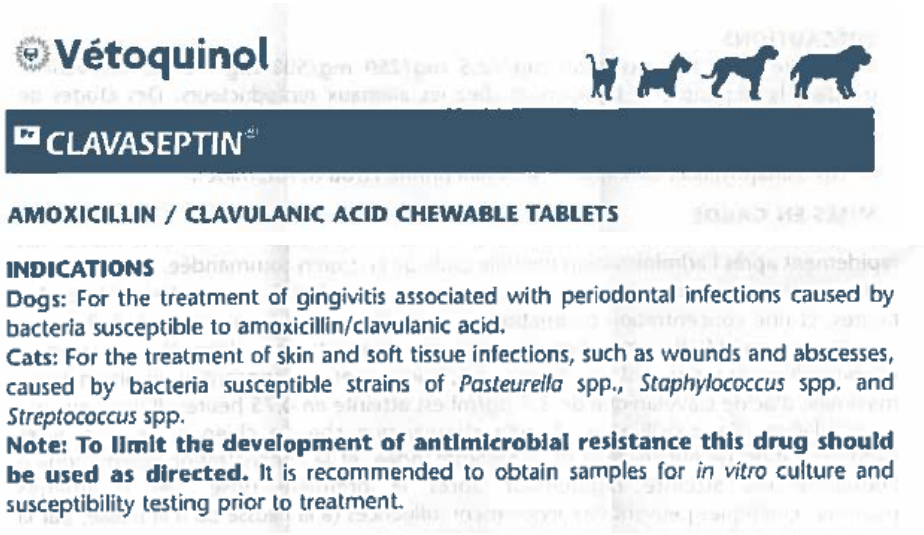
For Veterinary Use Only

Pr **Clinacin**

(clindamycin hydrochloride tablets)

DESCRIPTION:
CLINACIN tablets contain clindamycin hydrochloride, which is the hydrated salt of clindamycin. Clindamycin is a semi-synthetic antibiotic produced by a 7 (S)-chloro-substitution of the 7 (R)-hydroxyl group of lincomycin, a naturally-produced antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis*.

INDICATIONS:
For treatment of infected wounds, abscesses and dental infections caused by or associated with *Streptococcus spp, Staphylococcus spp., Bacteroides spp., Fusobacterium necrophorum* and *Clostridium perfringens* in dogs.
For treatment of osteomyelitis caused by *Staphylococcus aureus* in dogs.



Vétoquinol

Pr CLAVASEPTIN

AMOXICILLIN / CLAVULANIC ACID CHEWABLE TABLETS

INDICATIONS
Dogs: For the treatment of gingivitis associated with periodontal infections caused by bacteria susceptible to amoxicillin/clavulanic acid.
Cats: For the treatment of skin and soft tissue infections, such as wounds and abscesses, caused by bacteria susceptible strains of *Pasteurella* spp., *Staphylococcus* spp. and *Streptococcus* spp.
Note: To limit the development of antimicrobial resistance this drug should be used as directed. It is recommended to obtain samples for *in vitro* culture and susceptibility testing prior to treatment.

Off label use of a product, reduces the predictive power of a susceptibility test.

ex. higher dose might result in clinical success despite resistance

ex. treating a different type of infection may result in clinical failure despite susceptibility

Resistance Defined

- Resistance can be sub-divided into intrinsic and acquired
- Intrinsic resistance is constitutive for an organism
  - Natural “superbugs”, it’s just part of what they are

Pseudomonas aeruginosa

Basic Definition – What is Resistance?

- Resistance can be sub-divided into intrinsic and acquired
- Intrinsic resistance is constitutive for an organism
- Acquired resistance is not inherent to the organism, these bugs have something that makes them "super"

Staphylococcus aureus

versus

(MRSA)

Intrinsic resistance

- A good grasp of normal allows lab data to be interpreted
  - What do all of those “R’s” really mean?
- Intrinsic resistance is independent of antibiotic exposure
- “Wild-type” phenotype
- *Mycoplasma* spp. intrinsically resistant to penicillin
  - They lack a cell wall and therefore don’t have the drug target

Intrinsic Resistance Enterobacteriaceae

Table 1. Intrinsic resistance in Enterobacteriaceae. Enterobacteriaceae are also intrinsically resistant to benzylpenicillin, glycopeptides, fusidic acid, macrolides (with some exceptions[1]), lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

Rule no.	Organisms	Ampicillin	Amoxicilin-Clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Cefazolin, Cefalotin Cefalexin, Cefadroxil	Cefoxitin[2]	Cefuroxime	Tetracyclines	Tigecycline	Polymyxin B, Colistin	Nitrofurantoin
1.1	*Citrobacter koseri,Citrobacter amalonaticus*[3]	R			R							
1.2	*Citrobacter freundii*[4]	R	R	R		R	R					
1.3	*Enterobacter cloacae* complex	R	R	R		R	R					
1.4	*Enterobacter aerogenes*	R	R	R		R	R					
1.5	*Escherichia hermannii*	R			R							
1.6	*Hafnia alvei*	R	R	R		R	R					
1.7	*Klebsiella pneumoniae*	R			R							
1.8	*Klebsiella oxytoca*	R			R							
1.9	*Morganella morganii*	R	R	R		R			R		R	R
1.10	*Proteus mirabilis*								R	R	R	R
1.11	*Proteus penneri*	R				R		R	R	R	R	R
1.12	*Proteus vulgaris*	R				R		R	R	R	R	R
1.13	*Providencia rettgeri*	R	R	R		R		R	R	R	R	R
1.14	*Providencia stuartii*	R	R	R		R		R	R	R	R	R
1.15	*Raoultella* spp.	R			R							
1.16	*Serratia marcescens*	R	R	R		R	R	R	R[5]		R	R
1.17	*Yersinia enterocolitica*	R	R	R	R	R	R					
1.18	*Yersinia pseudotuberculosis*										R	

R = resistant

[1] Azithromycin is effective *in vivo* for the treatment of typhoid fever and erythromycin may be used to treat travellers' diarrhoea.

ALL Enterobacteriaceae intrinsically Resistant to:

- Benzylpenicillin (original penicillin)
- Macrolides
- Lincosamides

A group to remember

- SPICE organisms
  - *Serratia*
  - *Providentia*
  - Indole positive Proteae*
  - *Citrobacter*
  - *Enterobacter*
- Produce AmpC β-lactamases
  - Can become de-repressed (over-produced) with therapy
- Intrinsic 3rd generation cephalosporin resistance
- In a veterinary context I would recommend avoiding all β-lactams

*Includes *Proteus vulgaris* and *Morganella* spp.

Intrinsic Resistance Non-Fermenters

Table 2. Intrinsic resistance in non-fermentative Gram-negative bacteria. Non-fermentative Gram-negative bacteria are also generally intrinsically resistant to benzylpenicillin, first and second generation cephalosporins, glycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin, daptomycin and linezolid

Rule no.	Organisms	Ampicillin	Amoxicillin-Clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Ticarcillin-clavulanic acid	Piperacillin	Piperacillin-tazobactam	Cefazolin, Cefalothin Cefalexin, Cefadroxil	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomycin	Tetracyclines	Tigecycline	Polymyxin B/Colistin
2.1	*Acinetobacter baumannii, Acinetobacter pittii, Acinetobacter nosocomialis* and *Acinetobacter calcoaceticus* complex	R	R	Note[1]					R	R	R			R	R						R	R	R[2]	Note[2]	
2.2	*Achromobacter xylosoxydans*	R							R	R	R				R											
2.3	*Burkholderia cepacia* complex[3]	R	R	R	R	R	R	R	R	R	R			R	R			R	R	R[4]	R	R			R
2.4	*Elizabethkingia meningoseptica*	R	R	R	R	R	R		R	R	R	R	R	R	R	R	R								R
2.5	*Ochrobactrum anthropi*	R	R	R	R	R	R	R	R	R	R	R	R	R	R										
2.6	*Pseudomonas aeruginosa*	R	R	R					R	R	R				R				R	Note[5]	R		R	R	
2.7	*Stenotrophomonas maltophilia*	R	R	R	R		R	R	R	R	R			R	R	R	R			R[4]	R[6]	R	R[7]		

R = resistant

Intrinsic Resistance Gram-Positives

Table 4. Intrinsic resistance in Gram-positive bacteria. Gram-positive bacteria are also intrinsically resistant to aztreonam, temocillin, polymyxin B/colistin and nalidixic acid

Rule no.	Organisms	Fusidic acid	Ceftazidime	Cephalosporins (except ceftazidime)	Aminoglycosides	Macrolides	Clindamycin	Quinupristin-dalfopristin	Vancomycin	Teicoplanin	Fosfomycin	Novobiocin	Sulfonamides
4.1	*Staphylococcus saprophyticus*	R	R								R	R	
4.2	*Staphylococcus cohnii,*		R									R	
4.3	*Staphylococcus xylosus*		R									R	
4.4	*Staphylococcus capitis*		R								R		
4.5	Other coagulase-negative staphylococci and *Staphylococcus aureus*		R										
4.6	*Streptococcus* spp.	R	R		R[1]								
4.7	*Enterococcus faecalis*	R	R	R	R[1]	R	R	R					R
4.8	*Enterococcus gallinarum, Enterococcus casseliflavus*	R	R	R	R[1]	R	R	R	R				R
4.9	*Enterococcus faecium*	R	R	R	R[1,2]	R							R
4.10	*Corynebacterium* spp.										R		
4.11	*Listeria monocytogenes*		R	R									
4.12	*Leuconostoc* spp., *Pediococcus* spp.								R	R			
4.13	*Lactobacillus* spp. (*L. casei, L. casei* var. *rhamnosus*)								R	R			
4.14	*Clostridium ramosum, Clostridium innocuum*								R				

R = resistant

[1] Low-level resistance (LLR) to aminoglycosides. Combinations of aminoglycosides with cell wall inhibitors (penicillins and glycopeptides) are synergistic and bactericidal against isolates that are susceptible to cell wall inhibitors and do not display high-level resistance to aminoglycosides.

[2] In addition to LLR to aminoglycosides, *Enterococcus faecium* produces a chromosomal AAC(6')-Ii enzyme that is responsible for the loss of synergism between aminoglycosides (except gentamicin, amikacin and streptomycin) and penicillins or glycopeptides.

What is Stewardship?

"The term "antimicrobial stewardship" is used to describe the multifaceted and dynamic approaches required to sustain the clinical efficacy of antimicrobials by optimizing drug use, choice, dosing, duration, and route of administration, while minimizing the emergence of resistance and other adverse effects."

Antimicrobial Stewardship in Small Animal Veterinary Practice: From Theory to Practice

Luca Guardabassi, DVM, PhD[a,*], John F. Prescott, VetMB, DVM, PhD[b]
Vet Clin Small Anim 45 (2015) 361–376
http://dx.doi.org/10.1016/j.cvsm.2014.11.005 vetsmall.theclinics.com
0195-5616/15/$ – see front matter

What is Stewardship?

"…a coherent set of actions which promote using antimicrobials responsibly… translated into context-specific and time-specific actions."

Clinical Microbiology and Infection 23 (2017) 793–798

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

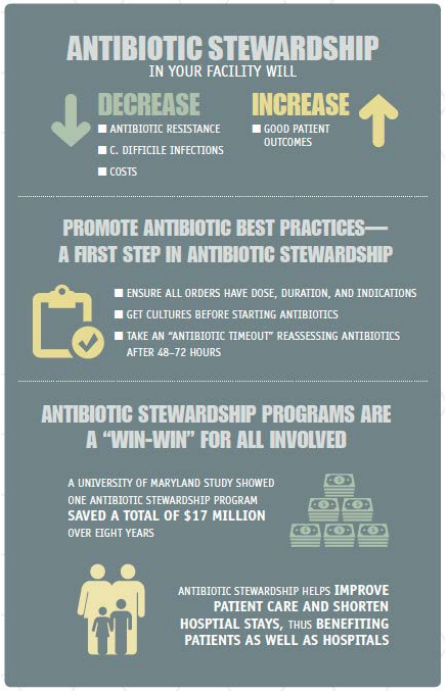
Review

What is antimicrobial stewardship?

O.J. Dyar [1,*], B. Huttner [2], J. Schouten [3], C. Pulcini [4], on behalf of ESGAP (ESCMID Study Group for Antimicrobial stewardshiP)

What is Stewardship?

- Active stewardship – changing behaviors
- Greatest impact on antimicrobial use
  - Specialist consultation on patient management (ID specialists, pharmacists)
  - Laboratory reports
    - Nudging
    - Suppressing
    - Framing
  - Active monitoring of antimicrobial usage (institutional level)
  - Audit and feedback



What is Stewardship?

- Passive stewardship – providing knowledge
- Less effective
  - Prudent use guidelines
  - Continuing education

The Veterinary Journal 247 (2019) 8–25

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats

J. Scott Weese[a,*], Joseph Blondeau[b,c], Dawn Boothe[d], Luca G. Guardabassi[e,f], Nigel Gumley[g], Mark Papich[h], Lisbeth Rem Jessen[i], Michael Lappin[j], Shelley Rankin[k], Jodi L. Westropp[l], Jane Sykes[l]

Principles of Rational AMU

Box 3
General principles of rational antimicrobial use

- Antimicrobials should be used only when there is evidence or at least a well-founded clinical suspicion of bacterial infection
- Antimicrobials should not be used for treatment of self-limiting infections
- Antimicrobial, pathogen, infection site, and patient factors should be considered when choosing an appropriate treatment
- Cytology should be used as a point-of-care test to guide antimicrobial choice for relevant disease conditions (eg, otitis and urinary tract infections)
- Antimicrobial susceptibility testing should be performed if
  - There is suspicion of a complicated or life-threatening infection
  - The patient does not respond to initial treatment
  - The patient has a recurring or refractory infection
  - The patient is immunosuppressed
  - There is a need to monitor the outcome of therapy (eg, long treatment period)
  - The patient is at risk of infection with multidrug-resistant bacteria

Antimicrobial Stewardship in Small Animal Veterinary Practice: From Theory to Practice

Luca Guardabassi, DVM, PhD[a,*], John F. Prescott, VetMB, DVM, PhD[b]
Vet Clin Small Anim 45 (2015) 361–376
http://dx.doi.org/10.1016/j.cvsm.2014.11.005 vetsmall.theclinics.com

Principles of Rational AMU

- As narrow a spectrum therapy as possible should be used
- Topical therapy should be preferred over systemic therapy for treatment of superficial skin infections
- Antimicrobials should be used for as short a time as possible
- Extra-label use should be avoided when on-label options are reasonable
- Use of critically important antimicrobials not authorized for veterinary use should at least be restricted to rare and severe patient conditions (eg, diagnosed, life-threatening bacterial infections that cannot be treated by any other available antimicrobials, provided that treatment has a realistic chance of eliminating infection)
- Antimicrobial therapy should never be used as a substitute for good infection control, and good medical and surgical practices
- Perioperative prophylaxis should be used only when indicated, and follow standard guidelines
- Clients should be educated to ensure compliance

Antimicrobial Stewardship in Small Animal Veterinary Practice: From Theory to Practice

Luca Guardabassi, DVM, PhD[a,*], John F. Prescott, VetMB, DVM, PhD[b]
Vet Clin Small Anim 45 (2015) 361–376
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Prescribing Decisions

- Pathogen identified (or likely pathogen)
- Susceptibility of organism
  - Knowledge of local resistance epidemiology
- Animal species
- Signalment
- Site/type of infection
- Co-morbidities
- Route of administration

- Cost
- Client compliance
- Label indication
- Withdrawal time

Prescribing Decisions


King et al. BMC Veterinary Research (2018) 14:332
https://doi.org/10.1186/s12917-018-1646-2

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Exploring the behavioural drivers of veterinary surgeon antibiotic prescribing: a qualitative study of companion animal veterinary surgeons in the UK

C. King[1*], M. Smith[1], K. Currie[1], A. Dickson[1], F. Smith[1], M. Davis[2] and P. Flowers[1]

- Business factors

Business factors

Veterinary surgeons talked about the tensions, which they experienced, between maintaining a viable business, client satisfaction and appropriate antibiotic prescribing:

... people are our customers and they are what keeps the business going, so if we annoy them and there is another veterinary surgeon practice they can go to where they may just be handed out antibiotics [they will potentially do that] (Veterinary surgeon 1)

Prescribing Decisions


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- Business factors
- Fear factors

Fear factors

The fear of missing an infection, and potential professional consequences, were also magnified for veterinary surgeons with the forever present possibility of client complaint or disciplinary action through their professional bodies:

... vets are completely paranoid the Royal Veterinary College [sic Royal College of Veterinary Surgeons] is going to cause them damage or get them struck off (Veterinary surgeon 5)

Prescribing Decisions


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- Business factors
- Fear factors
- Habitual practice factors

Habitual practice factors

Many of the veterinary surgeons talked about prescribing patterns which had been established over time and which influenced clients' expectations of when their pet would receive an antibiotic. The examples of kennel cough and the treatment of cat abscesses were often used by veterinary surgeons to illustrate this point:

> *There is some kind of pattern generated ... this is what I've always treated this with, a jag (Scottish version of the word injection) of penicillin for a cat bite abscess. It's a hard habit to get out of.*
> *(Veterinary surgeon 2)*

Prescribing Decisions


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- Business factors
- Fear factors
- Habitual practice factors

Peer influence was viewed to be a powerful factor in shaping prescribing behaviours within veterinary surgeon practice:

... the new grads are initially more prone to not give antibiotics because they were taught, well actually it's bad, and they stand their ground more. But then as they get in to practice and get more experience and maybe they just get worn down or maybe the daily life ... then they start giving antibiotics more loosely. (Veterinary surgeon 4)

Prescribing Decisions


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- Business factors
- Fear factors
- Habitual practice factors
- Pharmaceutical factors

Pharmaceutical factors

Veterinary surgeons also identified that pharmaceutical companies influenced antibiotic prescribing. This opportunity to influence prescribing was created by the marketing of products to address challenges around the administration of antibiotics, such as, difficulties in getting cats to consume tablets.

> *... we do use [antibiotic injections] in cats and we know the problems with it, but we do it when we feel that the owners will not be able to give tablets ... we prescribe it quite often to be honest. ... I am not aware of much evidence that it contributes to specific antimicrobial resistance, but it is a third generation Cephalosporin ... (Veterinary surgeon 11)*

Drugs vs. Brands

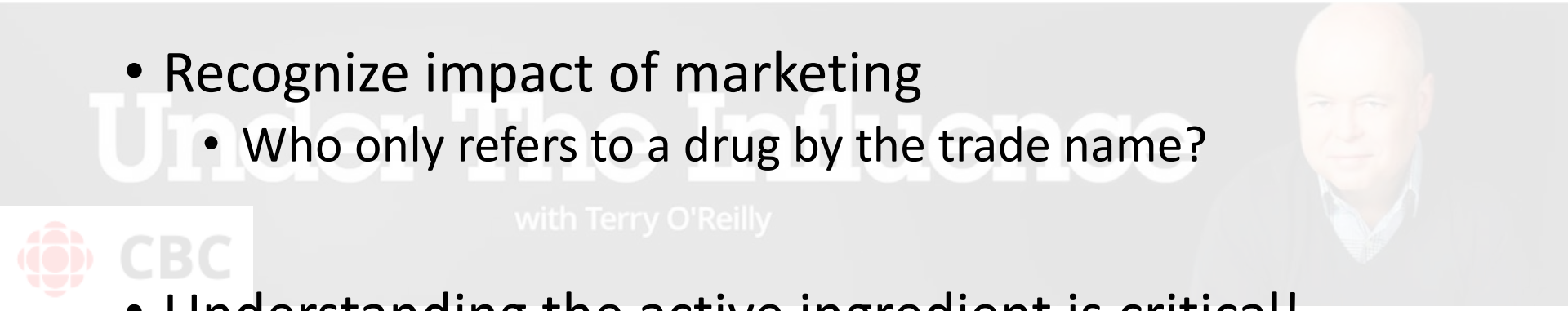
Baytril®

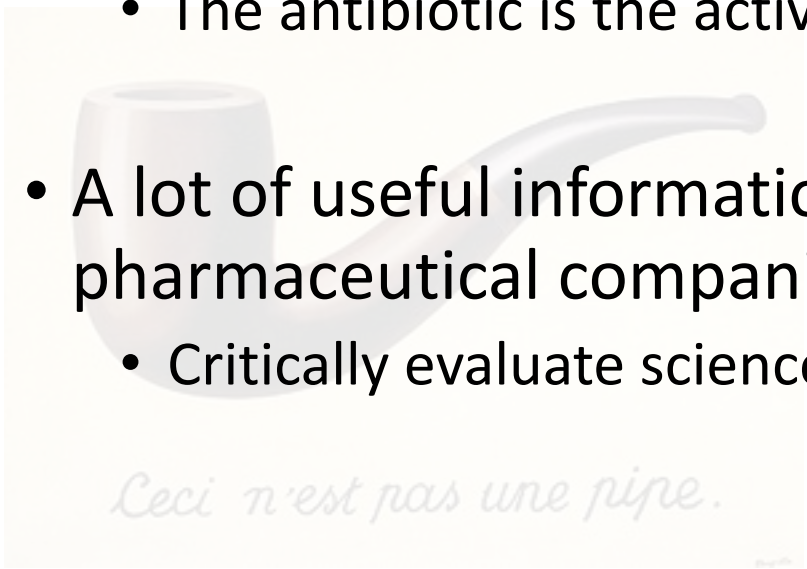
Ce n'est pas un antibiotique

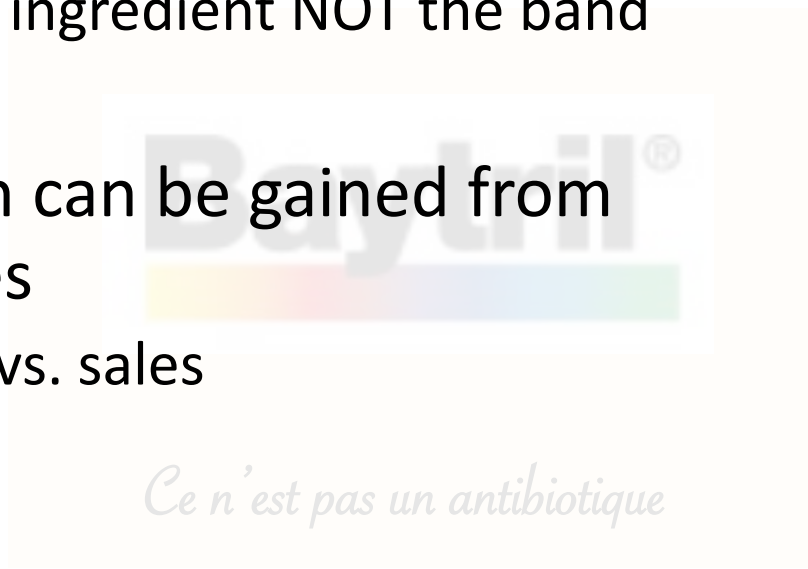
René Magritte

Drugs vs. Brands

- Recognize impact of marketing
  - Who only refers to a drug by the trade name?
- Understanding the active ingredient is critical!
  - The antibiotic is the active ingredient NOT the band
- A lot of useful information can be gained from pharmaceutical companies
  - Critically evaluate science vs. sales

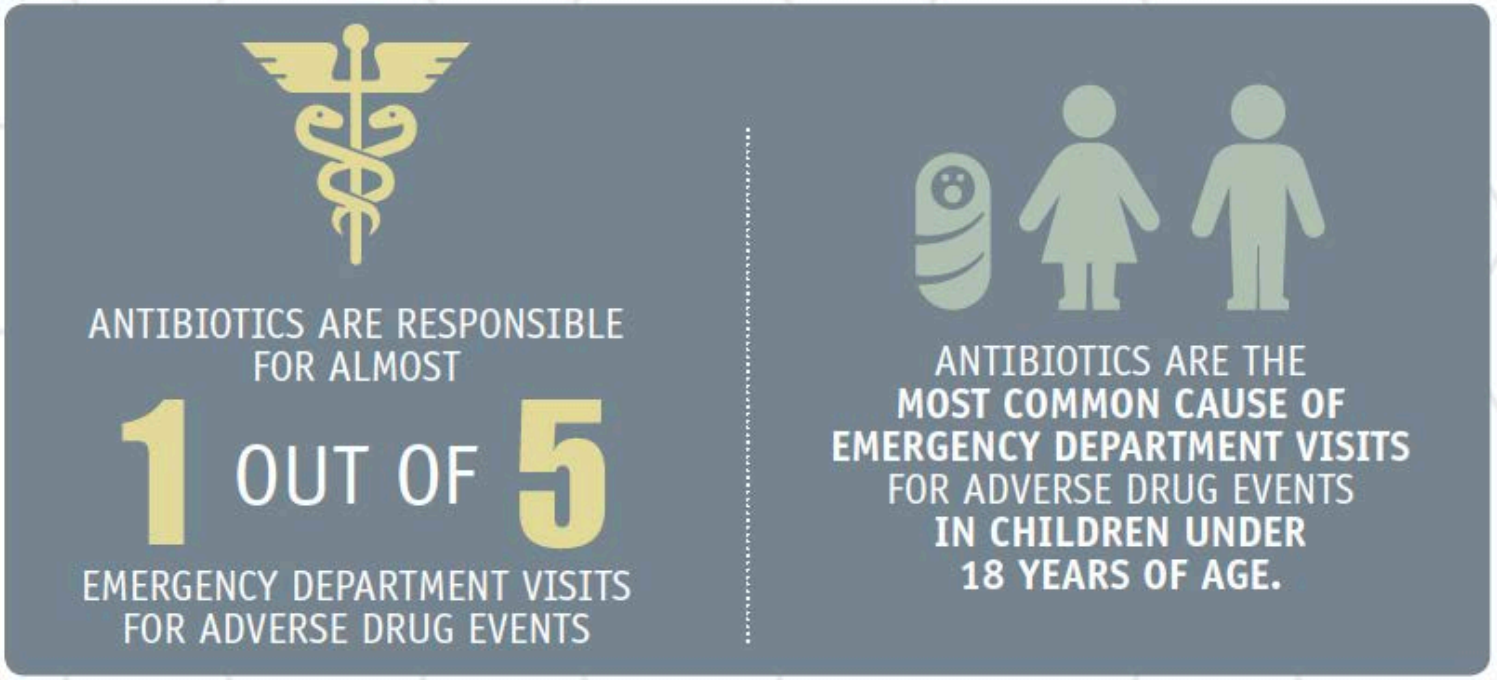






Proximate Risks of AMU

Adverse Drug Events



Adverse Drug Events

- 20% of hospitalized patients given antimicrobials had ADE
  - 19% of ADE occurred in patients not needing antimicrobials

JAMA Internal Medicine | Original Investigation

Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Pranita D. Tamma, MD, MHS; Edina Avdic, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS

JAMA Intern Med. 2017;177(9):1308-1315. doi:10.1001/jamainternmed.2017.1938
Published online June 12, 2017.

Adverse Drug Events

"… ADEs are common among inpatients receiving antibiotics, some of which may be avoidable with more judicious use of antibiotics."

"…antibiotic-associated ADEs may not be recognized by clinicians because ADEs have varied manifestations…"

JAMA Internal Medicine | Original Investigation

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Adverse Drug Events

- >140,000 annual emergency department visits in the United States for antibiotic associated ADE

Although the risk of an ED visit for an antibiotic-associated adverse event is small for an individual patient, when antibiotics are commonly prescribed for indications for which they have no benefit, the burden of preventable adverse events in the population is great.

Emergency Department Visits for Antibiotic-Associated Adverse Events

Nadine Shehab, Priti R. Patel, Arjun Srinivasan, and Daniel S. Budnitz

Division of Healthcare Quality Promotion, National Center for Detection, Preparedness, and Control of Infectious Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Clinical Infectious Diseases 2008; 47:735–43

What Stewardship Means to Me

- Treating a diagnosis rather than a syndrome
- Concatenating laboratory evidence and your clinical exam into a diagnosis
  - Asking questions when you need more information
- Using evidence based empiric therapy
  - Likely pathogens, local resistance epidemiology
- Applying your knowledge of
  - Intrinsic resistance
  - Drug mechanisms of action and spectrum of activity
  - Mechanisms of resistance

What Stewardship Means to Me

- Recognizing the evolving world of infectious diseases
  - Resistance is emerging
  - Be nimble enough to adapt
- Lifelong learning - sounds cliché but:
  - Professional duty
  - If you're not up to date you're out of date
- Utilizing recognized therapeutic guidelines

https://www.canadianveterinarians.net/AMU-UAM

Applying Guidelines

- Canine urinary tract infection (sporadic cystitis)
- We'll assume that a diagnosis has been made

Canine	Urinary	Sporadic cystitis	**RECOMMENDED TREATMENT:** 1. Amoxicillin: 11-15 mg/kg PO q12h 2. Amoxicillin/clavulanic acid: 12.5-25 mg/kg PO q12h 3. Trimethoprim-sulfonamide (TMS): 15-30 mg/kg PO q12h Duration: 3-5d **ALTERNATIVE TREATMENT:** 4. Enrofloxacin: 10-20 mg/kg PO q24h 5. Marbofloxacin: 2.7-5.5 mg/kg PO q24h 6. Orbifloxacin: 2.5-7.5 mg/kg PO q24h 7. Pradofloxacin: 3-5 mg/kg PO q24h 8. Cefpodoxime: 3-5 mg/kg PO q24h 9. Cephalexin: 3-5 mg/kg PO q24h 10. Cefovecin: 3-5 mg/kg PO q24h	1. II 2. I 3. II 4. I 5. I 6. I 7. I 8. I 9. II 10. I	Benefit of amoxicillin/clavulanic acid over amoxicillin is unclear. NSAIDs should be considered to control cystitis, when appropriate for that patient (e.g. consider renal function). An initial course of NSAIDs without antimicrobials can be considered.

CVMA GUIDELINES FOR VETERINARY ANTIMICROBIAL USE

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Short-course Antibiotic Therapy—Replacing Constantine Units With "Shorter Is Better"

Noah Wald-Dickler[1,2] and Brad Spellberg[1,2]

[1]Los Angeles County and University of Southern California (LAC+USC) Medical Center, and [2]Division of Infectious Diseases, Keck School of Medicine at University of Southern California, Los Angeles

Table 1. Diseases for Which Short-course Antibiotic Therapy Has Been Found to Be Equally Effective to Longer Traditional Courses of Therapy (With References)

Diagnosis	Short (d)	Long (d)	Result
Community-acquired pneumonia [6–14]	3 or 5	7, 8, or 10	Equal
Hospital-acquired/ventilator-associated pneumonia [15, 16]	7–8	14–15	Equal
Complicated urinary tract infections/pyelonephritis [17–22]	5 or 7	10 or 14	Equal
Complicated/postoperative intraabdominal infections [23, 24]	4 or 8	10 or 15	Equal
Gram-negative bacteremia [25]	7	14	Equal
Acute exacerbation of chronic bronchitis/chronic obstructive pulmonary disease (meta-analysis of 21 trials [26])	≤5	≥7	Equal
Acute bacterial skin and skin structure infections (cellulitis/major abscess) [27–29]	5–6	10	Equal
Chronic osteomyelitis [30]	42	84	Equal
Empiric neutropenic fever [31]	Afebrile and stable × 72 h	Afebrile and stable × 72 h and with absolute neutrophil count > 500 cells/μL	Equal

Clinical Infectious Diseases

MAJOR ARTICLE

Late-career Physicians Prescribe Longer Courses of Antibiotics

Cesar I. Fernandez-Lazaro,[1,2] Kevin A. Brown,[1,3] Bradley J. Langford,[1] Nick Daneman,[1,4,5] Gary Garber,[1,6] and Kevin L. Schwartz[1,3,7]

[1]Infection Prevention and Control, Public Health Ontario, Toronto, Canada; [2]Department of Biomedical and Diagnostic Sciences, University of Salamanca, Spain; and [3]Dalla Lana School of Public Health, University of Toronto, and [4]Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Canada; [5]Institute of Health Policy, Management and Evaluation, University of Toronto, Canada [6]Department of Medicine, Ottawa Hospital Research Institute, Canada; and [7]Department of Medicine, St. Joseph's Health Centre, Toronto, Canada

CONCLUSIONS

The use of prolonged antibiotic treatments in outpatient settings is common, particularly among those family physicians in late-career stages. Moreover, there is meaningful interphysician variability in the selection of prolonged antibiotic durations, highlighting the need for multifaceted antimicrobial stewardship interventions. Future research should evaluate the optimal community-based interventions to improve prescribing behaviors.

EDITORIAL

Annals of Internal Medicine

Duration of Antibiotic Therapy: Shorter Is Better

Vaughn and colleagues' findings add to the considerable body of evidence supporting the antibiotic mantra "shorter is better" (2, 3, 9). The cumulative evidence indicates that each day of antibiotic therapy beyond the first confers a decreasing additional benefit to clinical cure while increasing the burden of harm in the form of adverse effects, superinfections, and selection of antibiotic resistance. The question is, where do those 2 competing trends cross, such that continuing tilts the balance to harm over benefit? For community-acquired pneumonia, the data indicate net harm somewhere around 3 to 5 days of therapy for most patients.

When indicated, the benefits of shorter therapy include:

1. Decreased rate of adverse effects
2. Decreased super-infections
3. Decreased antimicrobial resistance

In a veterinary context, additional benefits conceivably include:

- Increased client compliance
- Decreased cost to client

What About Feline Dentistry?

Are prophylactic drugs used?

What drugs are used?

What patients would be treated?

The Guidelines Say…

- Dental abscesses
  - No antimicrobials
  - Unless evidence of cellulitis or bone involvement
- Dental prophylaxis
  - No antimicrobials
  - Unless history of infective endocarditis, unrepaired cyanotic congenital heart disease, PDA, subaortic or aortic stenosis, imbedded pacemaker leads.
- Dental extractions
  - No antimicrobials
  - Unless same indications as above or **MARKED** involvement of local soft tissue or concurrent involvement of bone

The use of antimicrobials is infrequently indicated – should be the exception NOT the rule

My Take on Guidelines

- They’re a great starting point following diagnosis
- Summary of up-to-date recommendations
  - Whether empiric therapy is warranted
  - First line therapies
  - Treatment duration
- BUT… can’t be algorithmic
  - Must have a diagnosis to apply the guidelines
  - Clinical skills required to integrate signalment, history, physical exam findings and lab results into diagnosis

When Test Result ≠ Outcome

POSSIBLE EXPLANATIONS FOR TEST/OUTCOME DISAGREEMENT*

VARIABLE	UNEXPECTED POSITIVE CLINICAL OUTCOME	UNEXPECTED NEGATIVE CLINICAL OUTCOME
PHARMACOKINETIC	High urine drug concentrations	Failure of drugs to penetrate protected sites Drug interactions decreasing absorption or activation or increasing elimination
PHARMACODYNAMIC		Failure of aminoglycosides in acidic or anaerobic environments Failure of sulfonamides in purulent environments
DISEASE/PATHOLOGY	No infection Self-limiting infection	Failure to address underlying pathology or primary disease Indwelling device
THERAPEUTIC	Utilizing localized therapy, high concentrations overcoming low level resistance Off label use (dose, dosing frequency, route of administration)	Poor owner compliance Off label use (dose, dosing frequency, route of administration)
RESISTANCE		Development of resistance *in vivo*
ORGANISM LIFESTYLE		Biofilm formation Intracellular infections
ORGANISM IDENTIFICATION	Mis-identified organism False positive culture (ex. contamination)	Mis-identified organism Mixed infection
SUSCEPTIBILITY TEST	Incorrectly performed or reported test	Incorrectly performed or reported test Inducible resistance

*Disagreement: clinical cure despite laboratory determined resistance OR failure to cure despite laboratory determined susceptibility

Take Home Messages

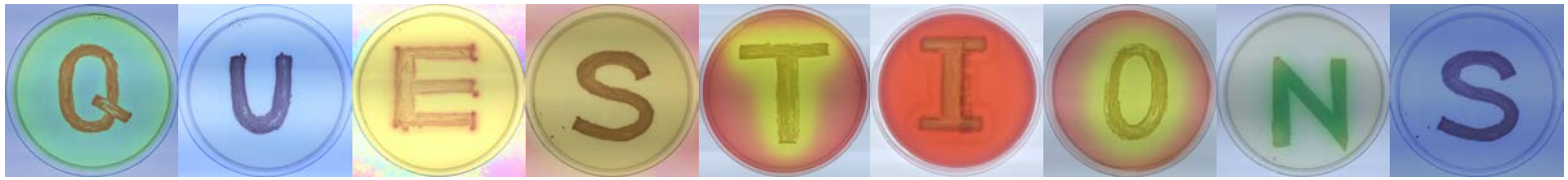
THE EASY AND OBVIOUS

- Antimicrobial resistance is increasing
  - The post-antibiotic era is on it's way
- Treat documented (or at least infections w/ evidence!)
- Next time you think "… just in case" your next thought should be "…but what if?"
- Optimize drug/dose to infection
- Familiarize yourself with relevant guidelines (CVMA, ISCAID, industry recommendations)
- Susceptibility profiles are highly variable, laboratory guidance is **VERY** important for aiding therapeutic selection

Take Home Messages

THE HARDER ONES

- Be aware of local susceptibility profiles
  - Ask your lab about what's going on locally
  - Keep track of test results your clinic receives
    - ex. how often do you see MRSP?
  - Use them to guide empiric therapy
- Don't forget about intrinsic resistance
- Reflect on outcomes
  - Why did that patient recover/not recover?


QUESTIONS