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Gram Negative Bacteria in Clinical Medicine

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Gram Negative Bacteria

in clinical medicine

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USAID PEER/Liberia ID Lecture Series

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Objectives

Define the molecular structure of Gram-negative organisms

Highlight differences between Gram-negatives and Gram-positives

Discuss the most important clinically-relevant Gram-negative bacteria

Review treatments for Gram-negatives

Illustrate clinical scenarios involving Gram-negative infection

(*Won't* discuss much about laboratory classification, eg oxidase test, lactose fermentation, etc. If you run a lab, you will need to know this!)

You can approach thinking about causes of infections in two different ways

One way is by organ system, e.g. pneumonia:

Streptococcus pneumoniae, Klebsiella pneumoniae, Chlamydophila pneumoniae, Mycoplasma, Moraxella, E. coli, Staph aureus, etc.

Advantage is that you can memorize various causes in a way that makes sense and not have to review every single organism in your head when you think about an infection, as there are dozens

But…could you *miss* an organism this way?

You can approach thinking about causes of infections in two different ways

The second way is by organism, via categories, e.g.:

*"*Gut Gram-negatives, including *E. Coli, Klebsiella, Salmonella, Shigella, Enterobacter, Citrobacter, Serratia"*

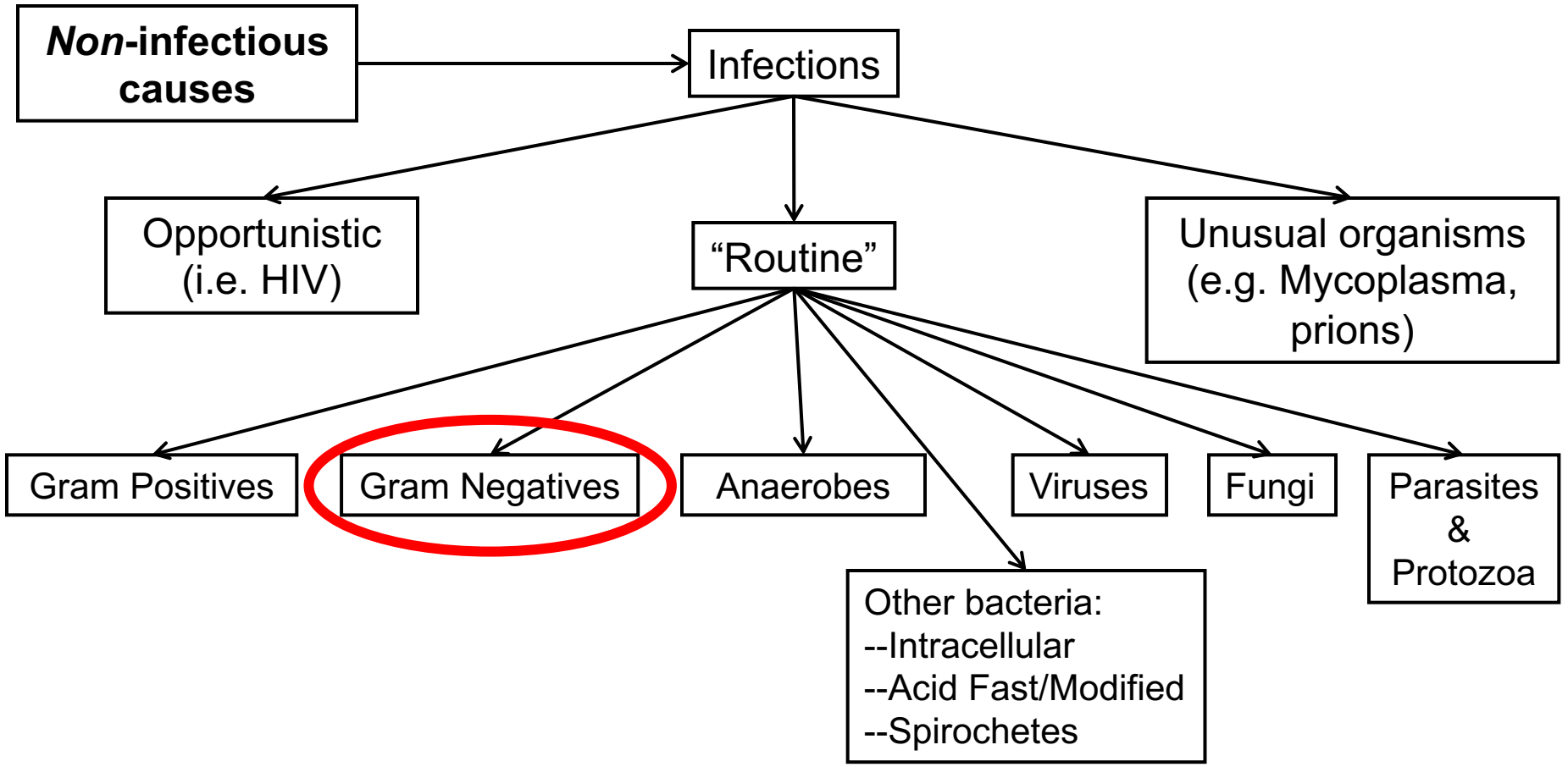
Advantage here is that you can review in your head the major infectious organisms and *not miss an important microbe*

The point is you need to use *both* ways of thinking about infections in order to make sure your differential is complete

Only a computer can list all the manifestations of disease by organism, or all the infectious causes of a focal infection

But a human brain can do pretty well if you switch back and forth

The "ID Differential"



What *is* a Gram stain?

Named after Dr. Gram (1884 paper)

Some bacteria take up crystal violet dye; some don't

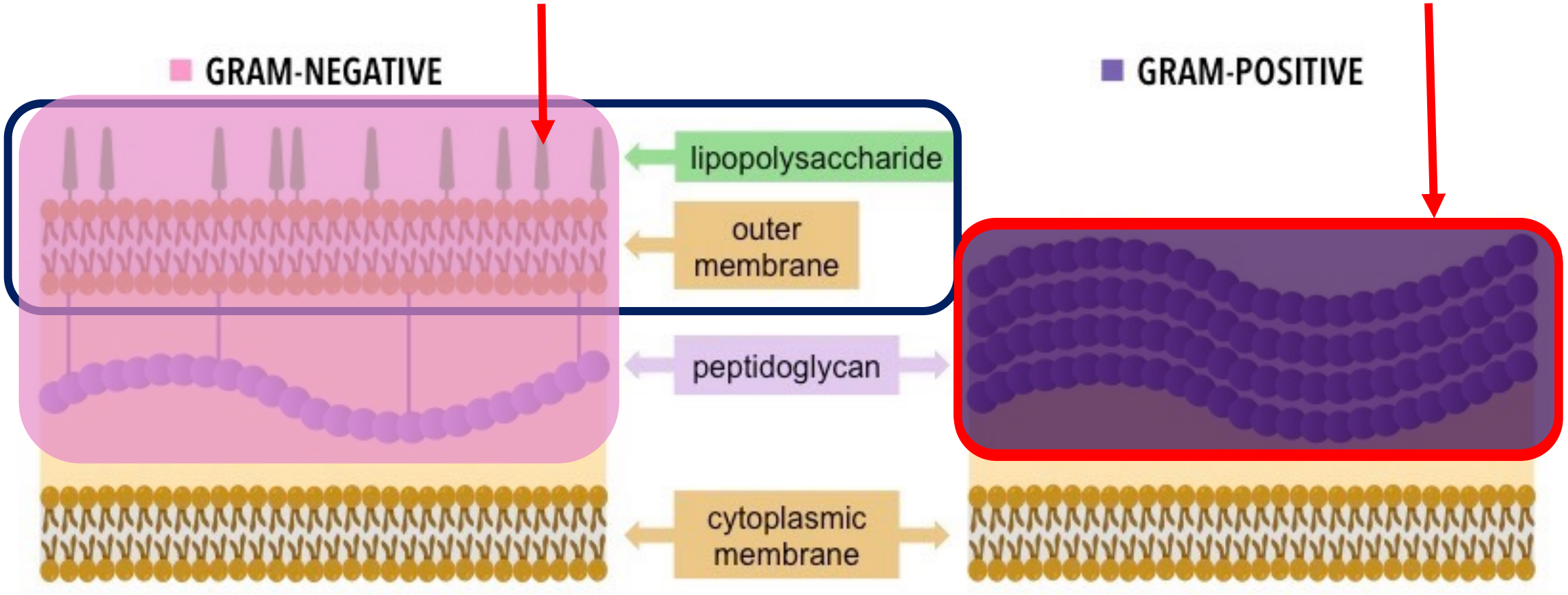
Some take up a counter-stain (safranin), *but some don't*

That is, not *all* bacteria can be seen by Gram stain (e.g. Mycobacteria)

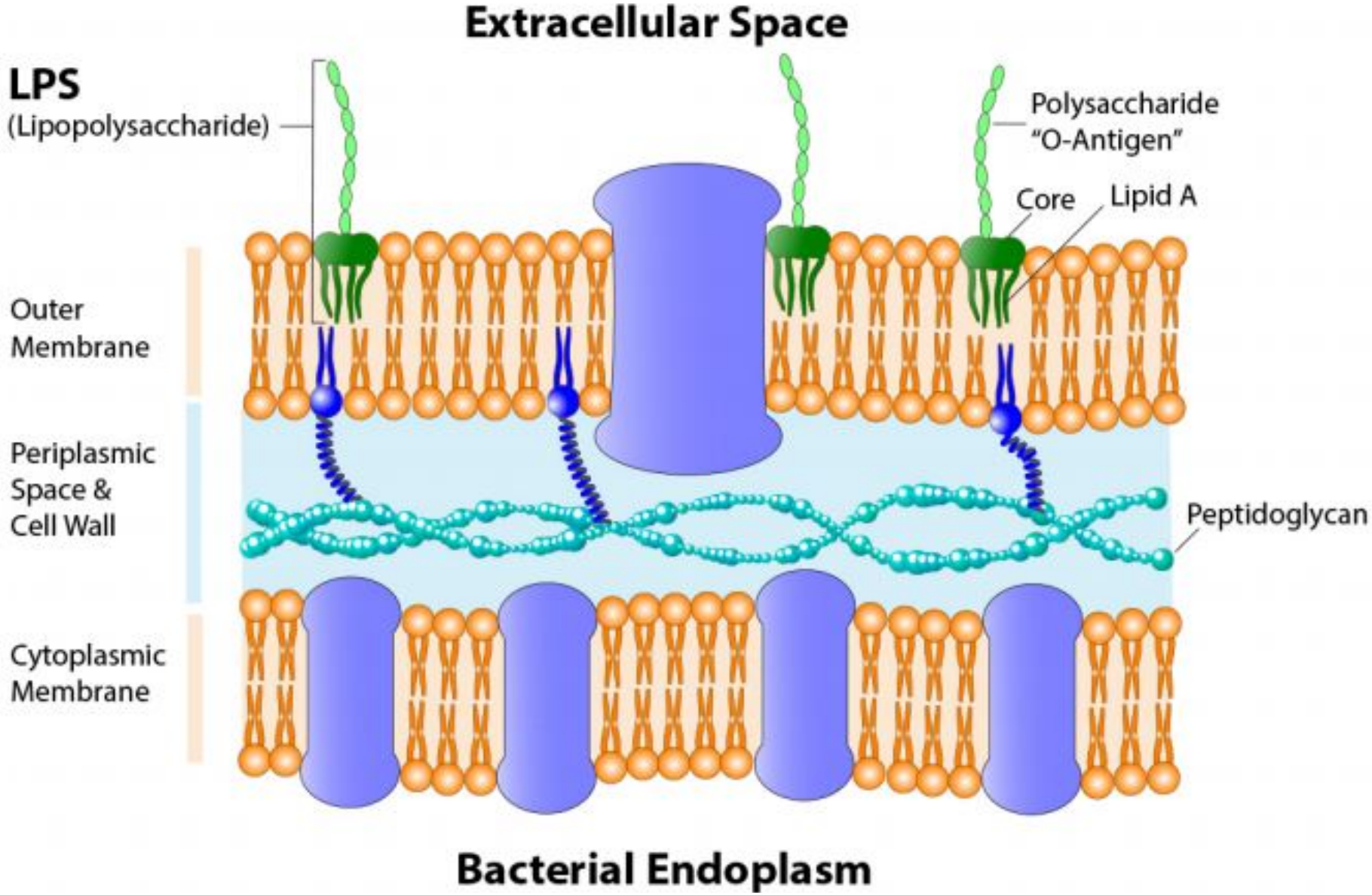
Structural differences

Virulence factor(s)

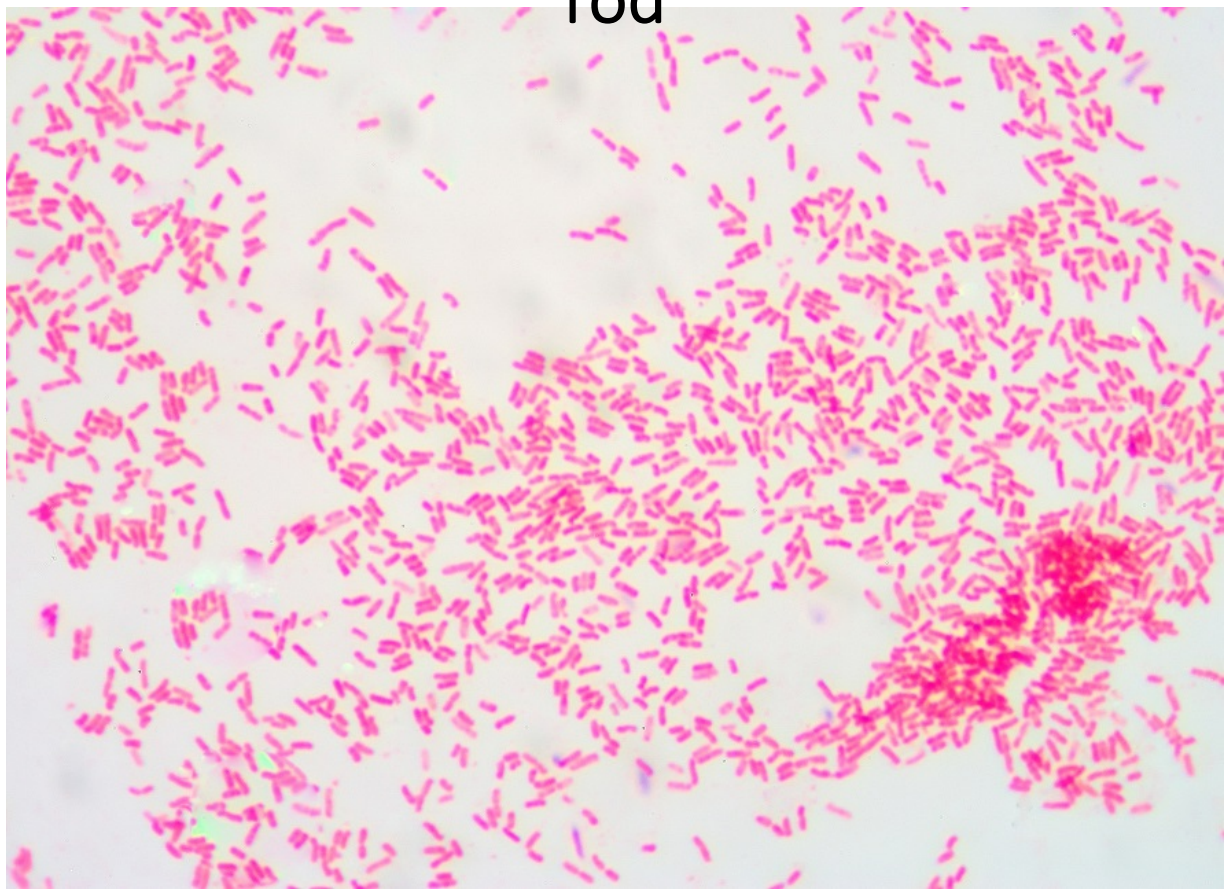
Crystal violet binds the peptidoglycan layer



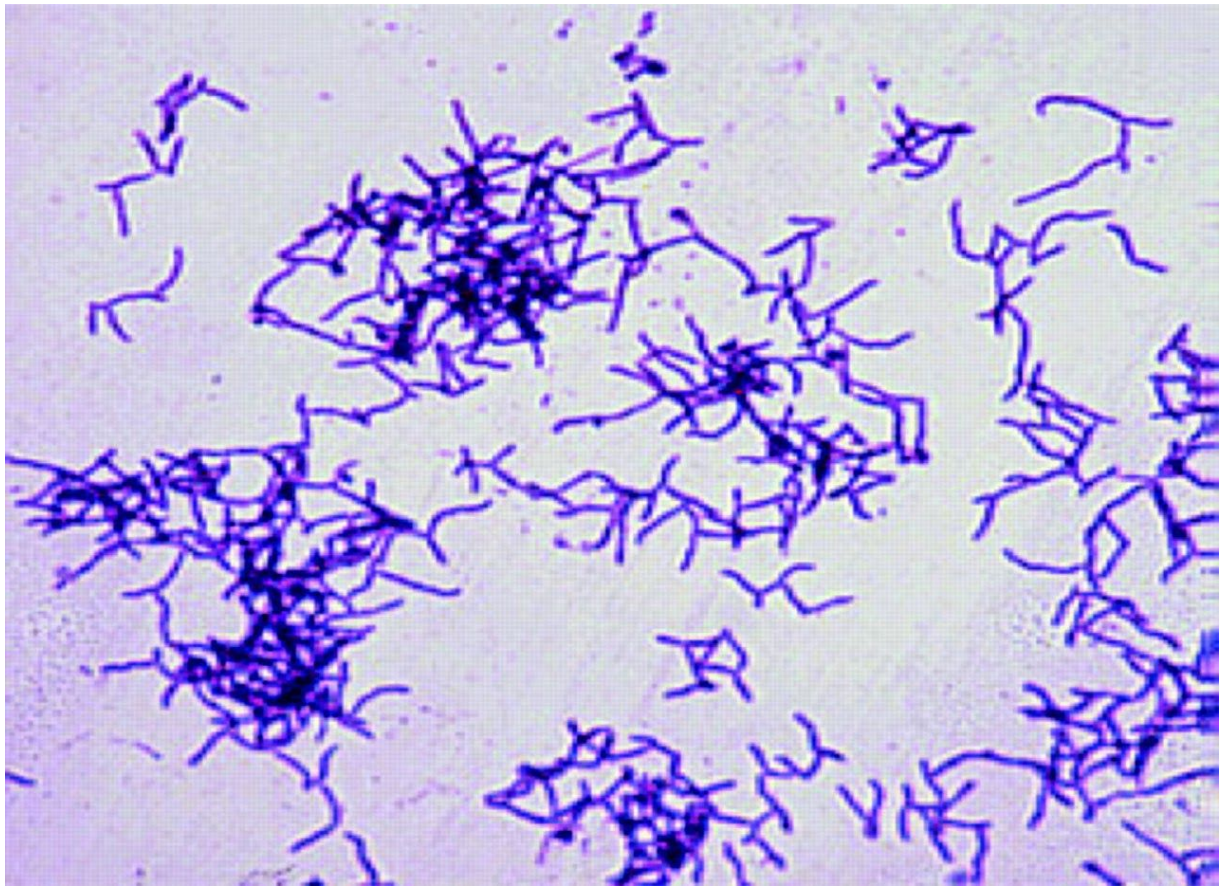
The differences in the cell wall lead to differing pathogenesis, as well as different targets for antimicrobial (and other) therapy

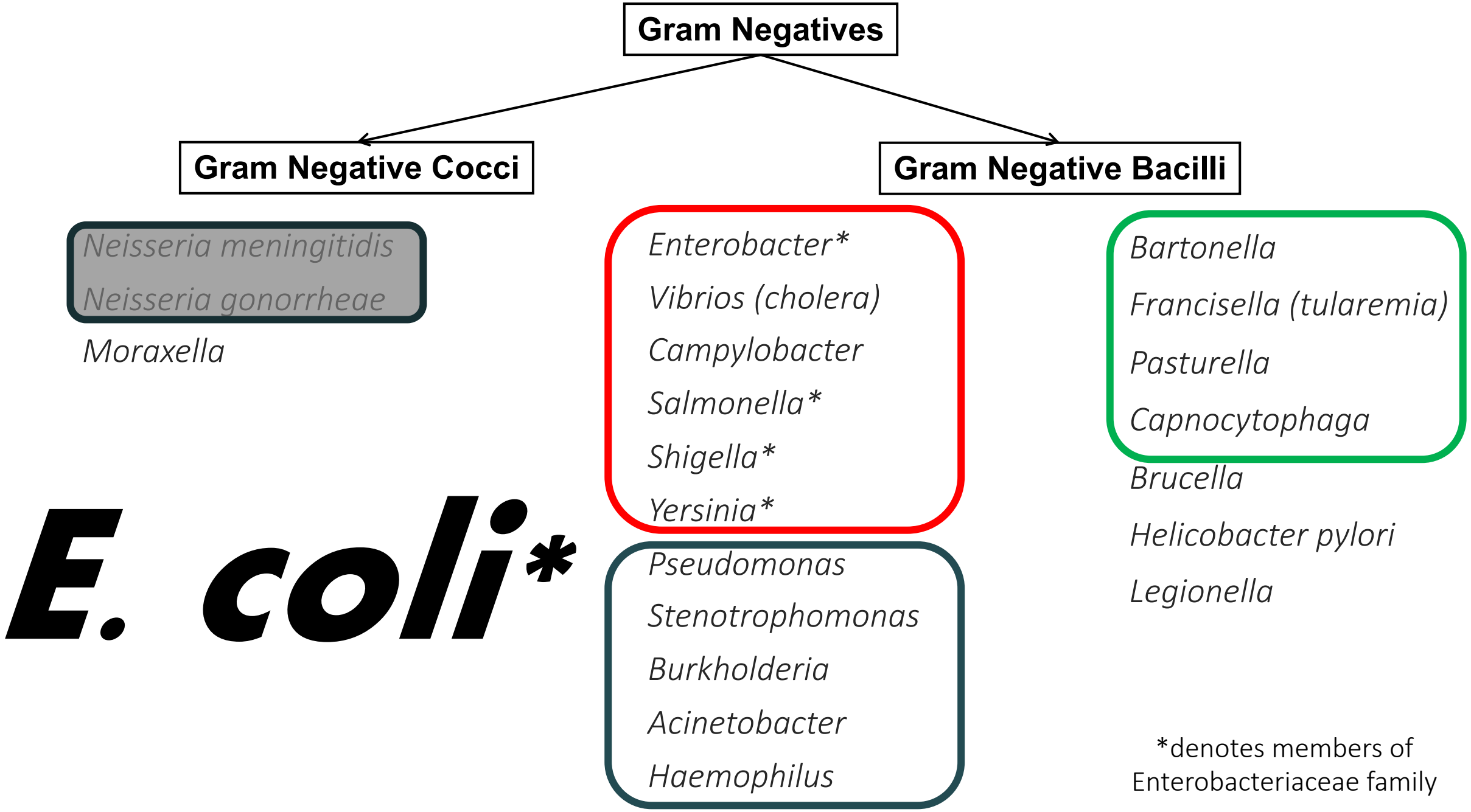

Extracellular Space
LPS
(Lipopolysaccharide)
Polysaccharide
"O-Antigen"
Core
Lipid A
Outer
Membrane
Periplasmic
Space &
Cell Wall
Peptidoglycan
Cytoplasmic
Membrane
Bacterial Endoplasm

Gram-negative rod



Gram-positive rod




Gram Negatives
Gram Negative Cocci
Gram Negative Bacilli
Neisseria meningitidis
Neisseria gonorrheae
Moraxella
Enterobacter*
Vibrios (cholera)
Campylobacter
Salmonella*
Shigella*
Yersinia*
Pseudomonas
Stenotrophomonas
Burkholderia
Acinetobacter
Haemophilus
Bartonella
Francisella (tularemia)
Pasturella
Capnocytophaga
Brucella
Helicobacter pylori
Legionella
E. coli*
*denotes members of Enterobacteriaceae family

Enterobacteriaceae: GI/GU organisms

Citrobacter

Enterobacter

Eschericia (eg *E. coli*)

Klebsiella

Morganella

Proteus

Providencia

Salmonella

Shigella

Yersinia

Cholecystitis/cholangitis

Diverticulitis

Abdominal perforation

Appendicitis (perforation)

Gut translocation

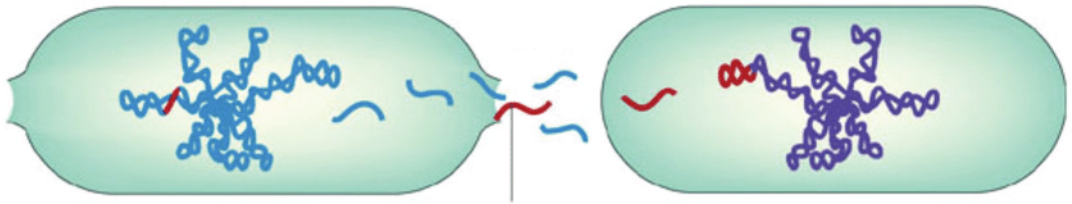
Diarrhea

UTIs, esp *E. coli*, *Morganella*, *Proteus*, *Providencia*

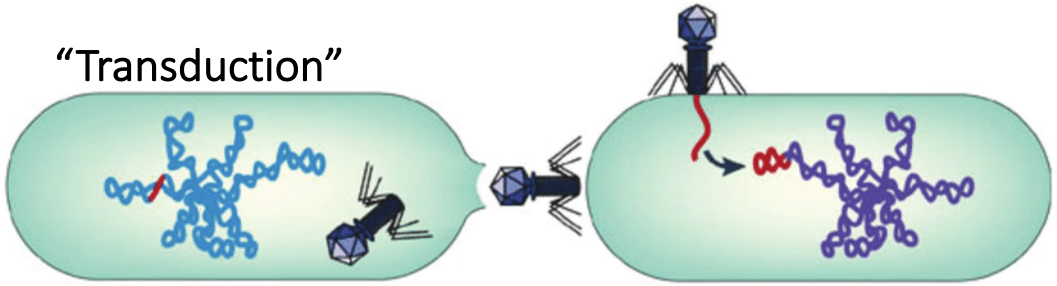
Bacteremia

Gram-negatives are exceptionally good at developing drug resistance

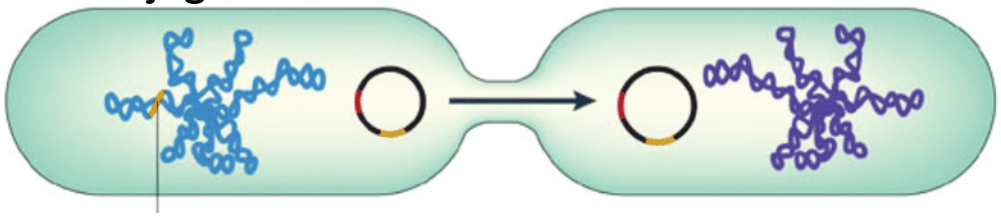
"Transformation"

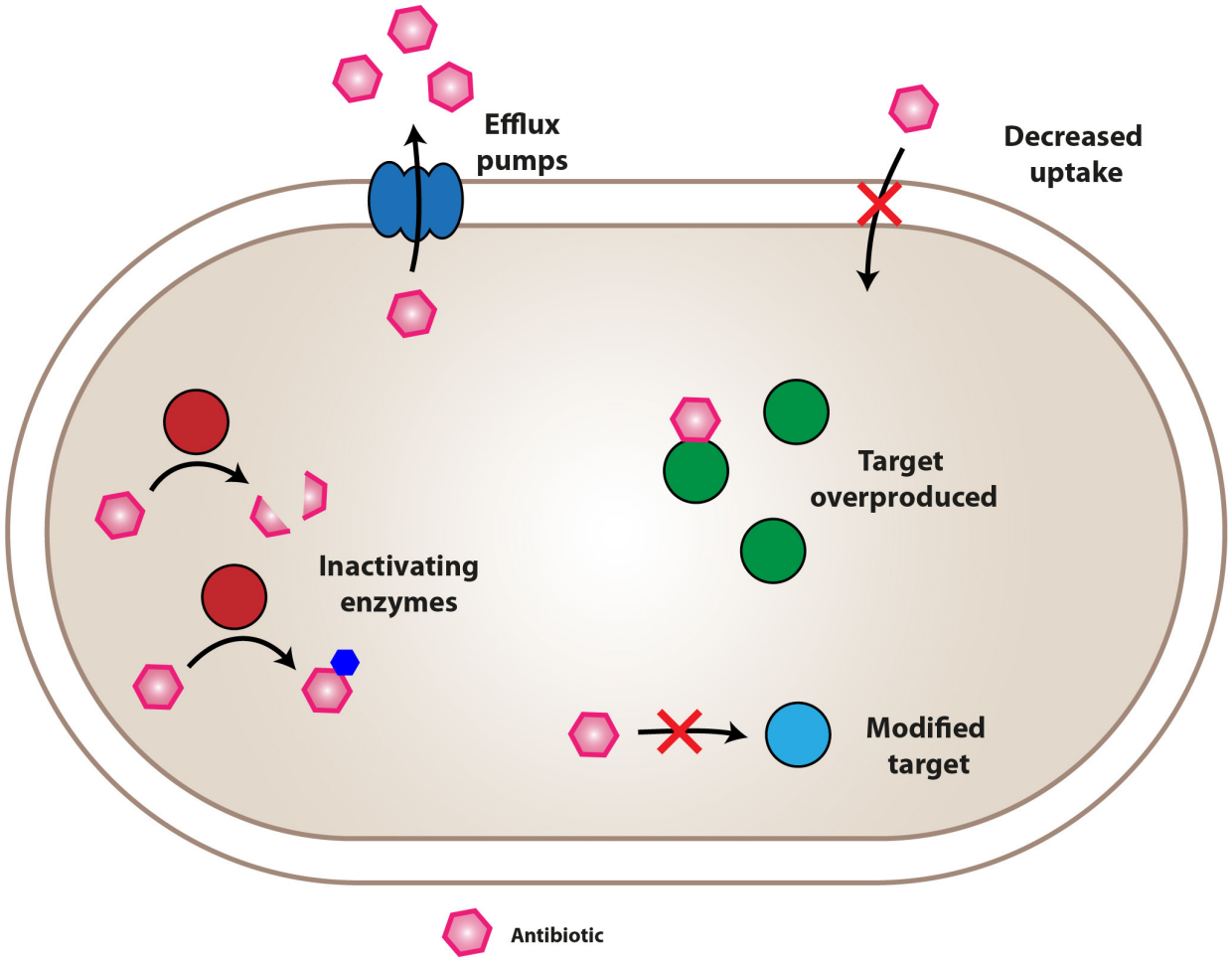


"Transduction"



"Conjugation"





Options for treatment of Gram Negatives

PCNs (often not effective)

PCNs with beta-lactamases (Augmentin, ie amox-clav)

Piperacillin (ureidopenicillins)

$3^{rd}/4^{th}$ gen cephalosporins (ceftriaxone, ceftazidime)

Carbapenems (meropenem)

Fluoroquinolones (ciprofloxacin)

Aminoglycosides (gentamicin)

Tetracyclines

Chloramphenicol

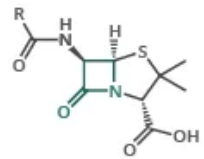
Sulfonamides (Septrin)

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key: COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION — COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

ß-LACTAMS

MOST WIDELY USED ANTIBIOTICS IN THE NHS



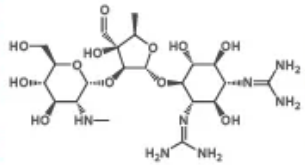
All contain a beta-lactam ring

EXAMPLES
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES

FAMILY OF OVER 20 ANTIBIOTICS



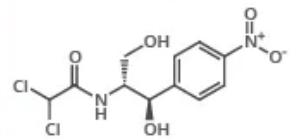
All contain aminosugar substructures

EXAMPLES
Streptomycin (shown), neomycin, kanamycin, paromomycin.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL

COMMONLY USED IN LOW INCOME COUNTRIES



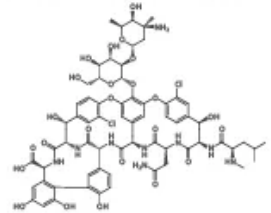
Distinct individual compound

MODE OF ACTION
Inhibits synthesis of proteins, preventing growth.

No longer a first line drug in any developed nation (except for conjunctivitis) due to increased resistance and worries about safety.

GLYCOPEPTIDES

COMMON 'DRUGS OF LAST RESORT'



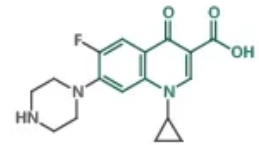
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



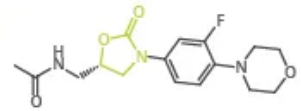
All contain fused aromatic rings with a carboxylic acid group attached

EXAMPLES
Ciprofloxacin (shown), levofloxacin, trovafloxacin.

MODE OF ACTION
Interfere with bacteria DNA replication and transcription.

OXAZOLIDINONES

POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'



All contain 2-oxazolidone somewhere in their structure

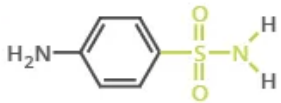
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

DISCOVERY — 1930 — 1940 — 1950 — 1960 — 1970 — 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



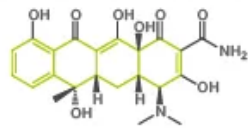
All contain the sulfonamide group

EXAMPLES
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.

MODE OF ACTION
Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES

BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE



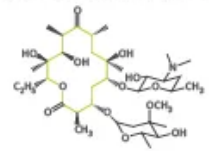
All contain 4 adjacent cyclic hydrocarbon rings

EXAMPLES
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES

SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS



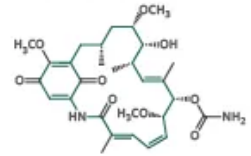
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

MODE OF ACTION
Inhibit protein synthesis by bacteria, occasionally leading to cell death.

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



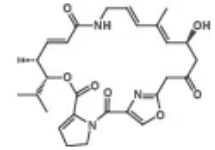
All contain an aromatic ring bridged by an aliphatic chain.

EXAMPLES
Geldanamycin (shown), rifamycin, naphthomycin.

MODE OF ACTION
Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS

TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY



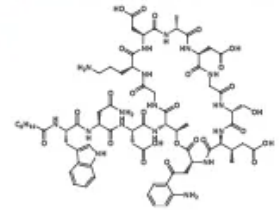
Combination of two structurally differing compounds, from groups denoted A & B

EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

LIPOPEPTIDES

INSTANCES OF RESISTANCE RARE

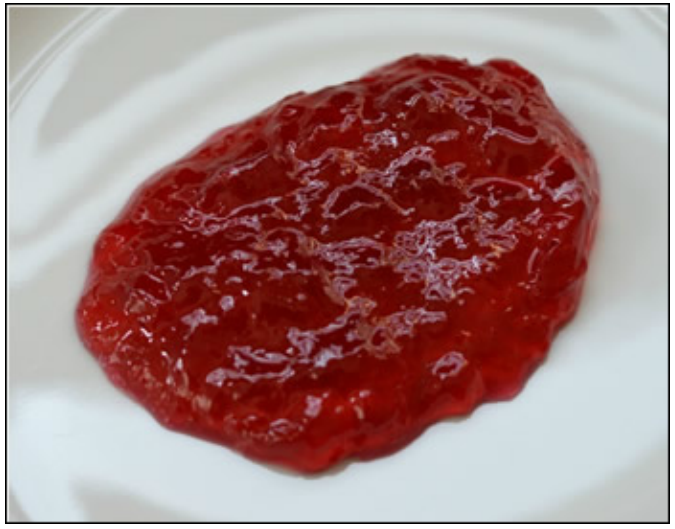


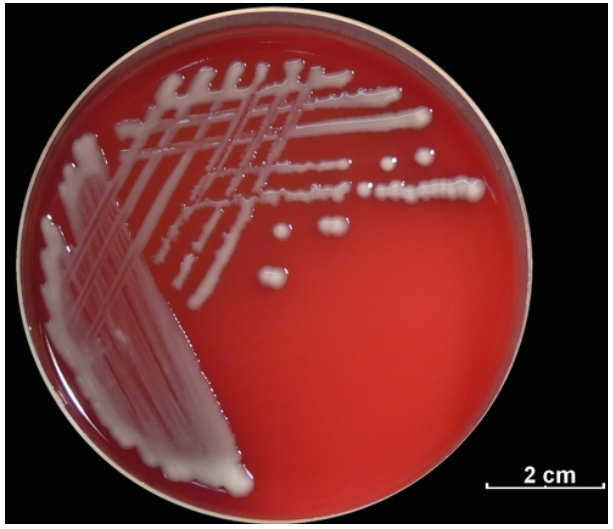
All contain a lipid bonded to a peptide

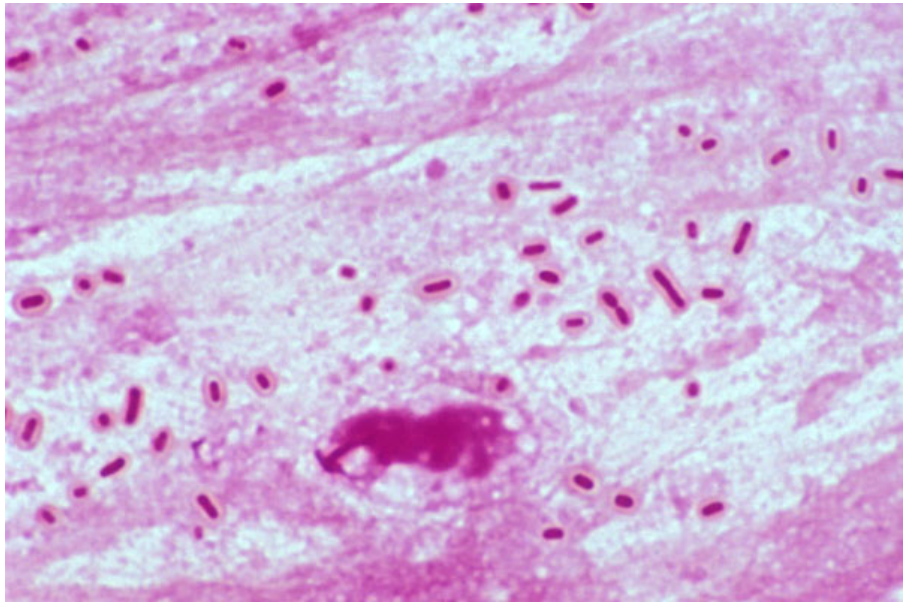
EXAMPLES
Daptomycin (shown), surfactin.

MODE OF ACTION
Disrupt multiple cell membrane functions, leading to cell death.

A 58 year-old man presents with acute cough, fever, and chills. The cough produces a thick, red sputum. Gram stain is shown.







Which is the *most likely* organism?

A. *Streptococcus pneumoniae*

B. Providencia stuartii

C. Mycobacterium avium

D. Klebsiella pneumoniae

E. Mycoplasma pneumoniae

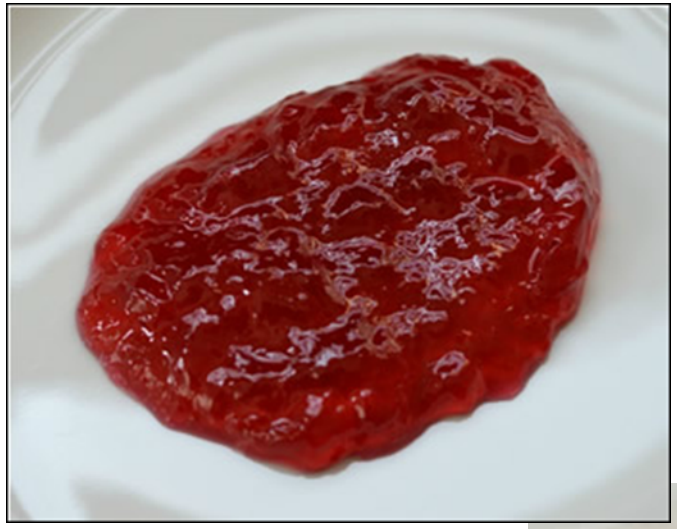
Answer: *Klebsiella pneumoniae*

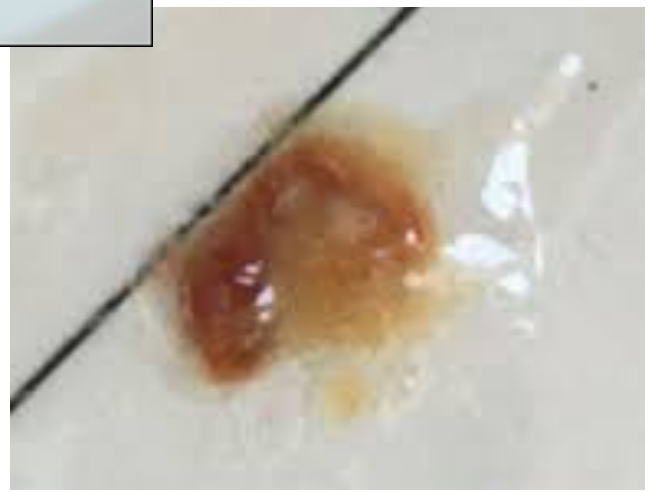
- Gram negative encapsulated organism

- “Currant jelly” sputum: localized tissue necrosis & tissue inflammation

- contrast with pneumococcus “rust colored” sputum

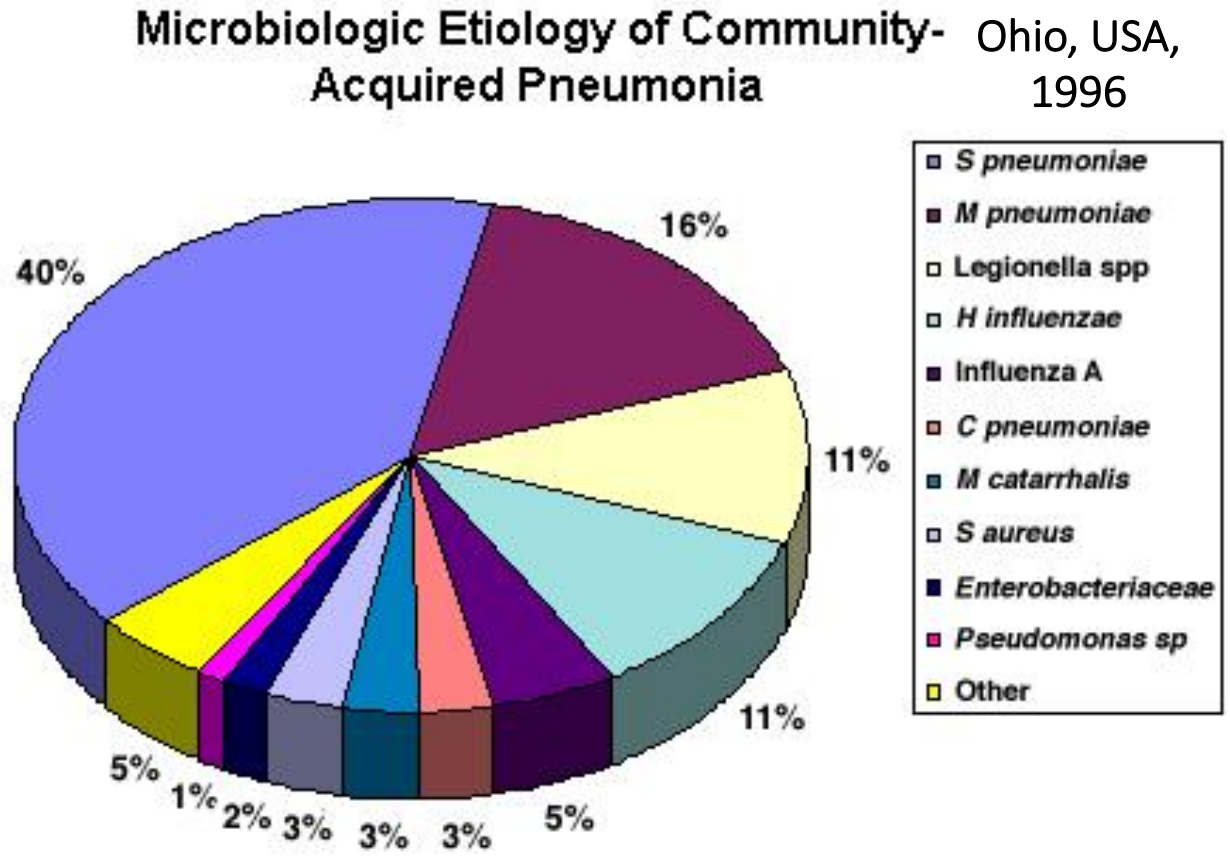
- ? May be more common in Africa than in Europe or US



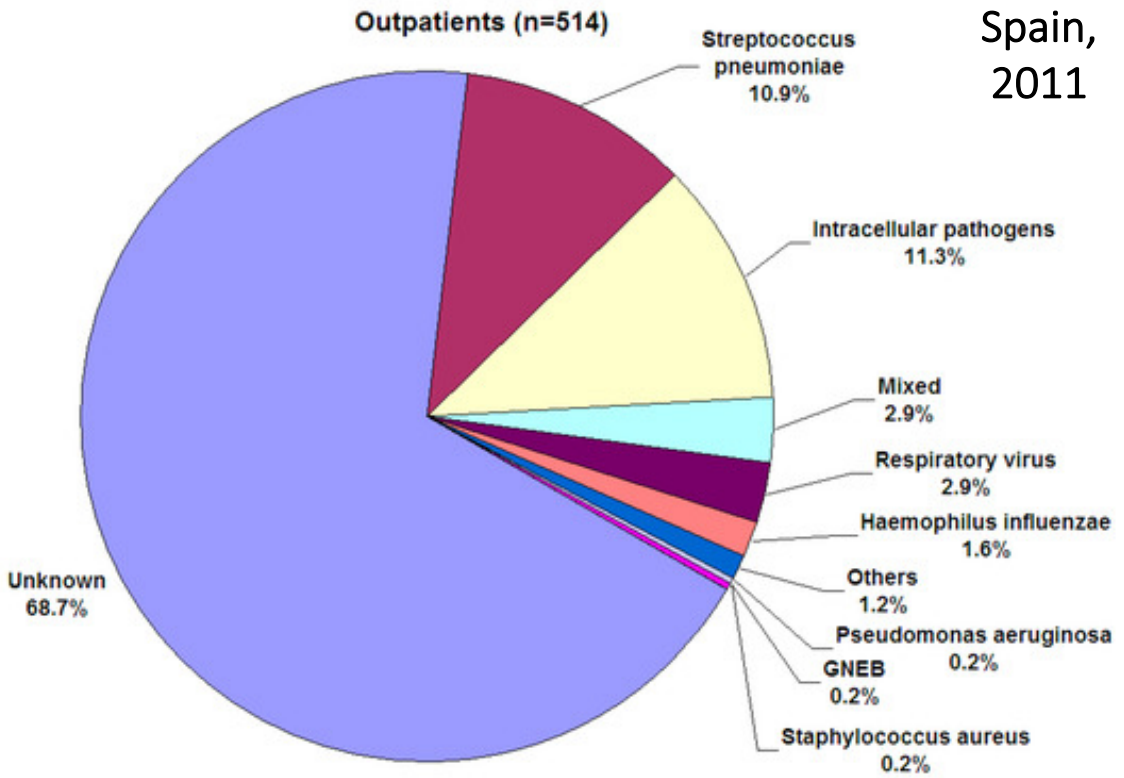


CAP is most often ***pneumococcus***, followed by everything else with lots of Gram-negatives (African epidemiology/distribution may be different)

https://www.ncbi.nlm.nih.gov/books/NBK519004/



Ohio, USA, 1996



Spain, 2011

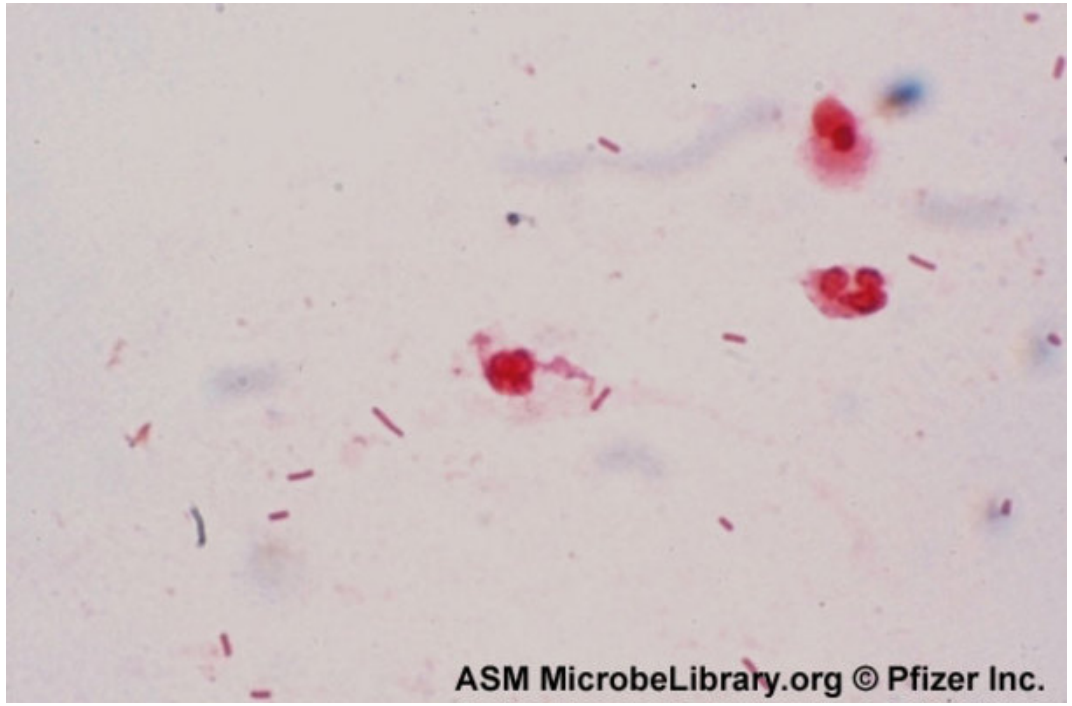
(A): abbreviations: GNEB = Gram-negative enteric bacilli.

A 22 year-old woman presents with dysuria, foul-smelling urine, chills, and pelvic pain x 48 hours.

Treated for UTIs at least six times over past 1-2 years. Can't remember which abx given, been to different clinics & pharmacies.

Temp 100.7 F, HR 110, BP 120/78. Exam notable for mild/moderate tenderness on CVA percussion.

UA: 1.030, >100 WBCs, Leuk Est pos, nitrite pos, microscopy shown



Which of the following organisms are likely causes of her presentation?

A. *Staphylococcus saprophyticus*

B. *E. coli*

C. *Moraxella catarrhalis*

D. *Enterococcus faecium*

E. *Pasturella multocida*

Which of the following statements are **true**?

A. She requires short-course (ie, 3-day) treatment for UTI.

B. She is at low risk for sepsis secondary to bacteremia.

C. A fluoroquinolone such as cipro is the best choice to treat her.

D. Septrin would be contraindicated since it does not treat Gram-negatives.

E. This is a person for whom a urine culture with antibiotic susceptibilities would be very helpful in establishing proper treatment.

Recurrent UTIs

- *E. coli* accounts for ~80% of UTIs in women, ~70% in men

- Much more common in women however

- This patient has *pyelonephritis*, no cystitis (CVA tenderness)

- Will require prolonged abx as consequence

- At high risk of having drug resistance, most likely to FQs or Septrin since they are the most commonly prescribed UTI abx

- May require hospitalization

- *Minimum* five days therapy required, possibly longer

Am Fam Physician. 2011 Sep 1;84(5):519-526.

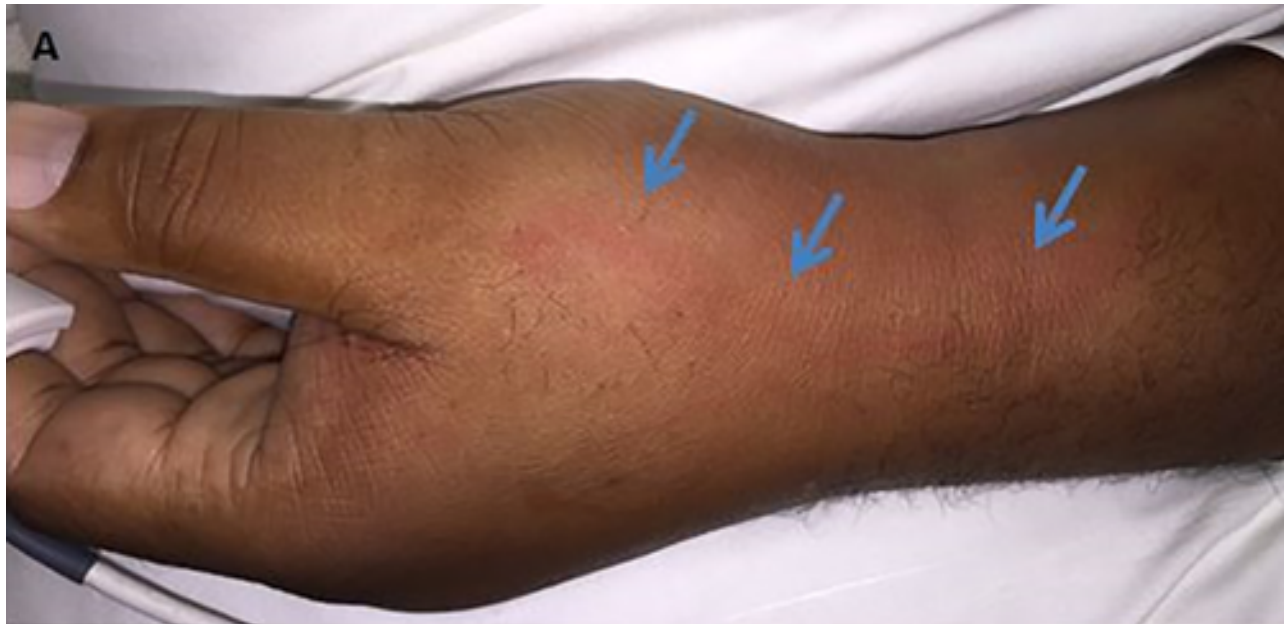
A 16 year-old male presents with sore L arm.

Onset early this morning. Woke out of sleep with pain; has gotten worse since then, now severe.

Noted playing with a dog who bit him yesterday.

Exam: HR 126, T 102.2, BP 110/68

Tremulous, diaphoretic, hand & forearm exquisitely tender, minimally swollen; streaking erythema across wrist & forearm



What is the *next* step in the patient's management?

A. Consult surgery immediately.

B. Obtain echocardiogram to evaluate endocarditis.

C. Order CT of L upper extremity to evaluate for fluid collection.

D. Provide pain relief, await abx pending CBC.

E. Start empiric abx and admit for observation.

The following antibiotics are likely to be effective ***except***:

A. Penicillin VK

B. Ampicillin

C. Clindamycin

D. Ciprofloxacin

E. Doxycycline

Animal bites and Gram-negatives

- Commonly associated with cat & dog bites

- *Pasturella multocida* seen in both

- Cat tooth = natural syringe

- *Bartonella* infections

- *Capnocytophaga* in dogs; encapsulated organism, issues with dogs & pts without spleens or partial spleens (eg Sickle Cell pts)

Bites are forms of injections—they move faster than "typical" cellulitis

Pain out of proportion to exam signals a surgical emergency

Immediate abx

PCNs most effective with Pasturella; most β-lactams

Clindamycin and erythromycin *not* likely to be effective

Don't forget about rabies!

An 18 yo male presents with abdominal pain, fever and constipation x 72 hours

- Dry cough, non-productive
- Brought in by family
- Exam: HR 120, BP 116/68, T 103F
- Diffuse abd tenderness, mild, no rebound
- Neck supple

You consider typhoid fever in your differential. Which of the following is **true**?

A. A fluoroquinolone such as ciprofloxacin may be adequate tx

B. Ceftriaxone is always ineffective

C. Typhoid is unlikely because there is not a pulse-pressure dissociation

D. Hepatitis is not a complication

E. Typhoid is unlikely if there is not a “rose spot” rash

Typhoid fever

Salmonella typhi & *S. paratyphi*

Fecal-oral spread infection

HIV pts at 20- to 100-fold higher risk (all *Salmonella* spp. incl non-typhoidal)

Extra-intestinal manifestations (CNS, hepato- & splenomegaly, bone/joint)

Widal test: good not great, have index of suspicion

Treat empirically while awaiting BCx

FQ resistance *may* be a problem in Liberia? (Research project!)

Cipro, chloramphenicol, ampicillin or amoxicillin, TMP/SMX, ceftriaxone, azithro all good empiric choices