ORGANISM	INTRINSIC RESISTANCE AGAINST:	MECHANISM
Anaerobic bacteria	Aminoglycosides	Lack of oxidative metabolism to drive uptake of aminoglycosides
Aerobic bacteria	Metronidazole	Inability to anaerobically reduce drug to its active form
Gram-positive bacteria	Aztreonam (β-lactam)	Lack of penicillin binding proteins (PBPs) that bind and are inhibited by this beta lactam antibiotic
Gram-negative bacteria	Vancomycin	Lack of uptake resulting from inability of vancomycin to penetrate outer membrane
Klebsiella sp.	Ampicillin (β-lactam)	Production of enzymes (beta-lactamases) that destroy ampicillin before the drug can reach the PBP targets
Stenotrophomonas maltophila	Imipenem (β-lactam)	Production of enzymes (beta lactamases) that destroy imipenem before the drug can reach the PBP targets.
Lactobacilli and *Leuconostoc*	Vancomycin	Lack of appropriate cell wall precursor target to allow vancomycin to bind and inhibit cell wall synthesis
P. aeruginosa	Sulfonamides, trimethoprim, tetracycline, or chloramphenicol	Lack of uptake resulting from inability of antibiotics to achieve effective intracellular concentrations
Enterococci	Aminoglycosides	Lack of sufficient oxidative metabolism to drive uptake of aminoglycosides
	All cephalosporins	Lack of PBPs that effectively bind and are inhibited by these beta lactam antibiotics

Acquired resistance

Resistance of *S. aureus* to penicillin was 1% in 1941, now it's around 90%. Not all resistances are acquired at the same rate. *S. pyogenes* is still largely susceptible to penicillin. No clear explanation for the rate or the extensiveness that the resistance is in a bacterial population. Can be caused by mutation or transfer.

ACQUIRED RESISTANCE VIA:	RESISTANCE OBSERVED	MECHANISM INVOLVED
Mutation	*Mycobacterium tuberculosis* resistance to rifamycins	Point mutations in the rifampicin-binding region of *rpoB*
	Resistance in many clinical isolates to fluoroquinolones	Predominantly mutation of the quinolone-resistance-determining-region (QRDR) of *gyrA* and *parC/grlA*
	E. coli, *Hemophilius influenzae* resistance to trimethoprim	Mutations in the chromosomal gene specifying dihydrofolate reductase
Horizontal gene transfer	*Staphylococcus aureus* resistance to methicillin (MRSA)	Via acquisition of *mecA* genes which are on a mobile genetic element called "staphylococcal cassette chromosome" (SCCmec) which codes for penicillin binding proteins (PBPs) that are not sensitive to ß-lactam inhibition
	Resistance of many pathogenic bacteria against sulfonamides	Mediated by the horizontal transfer of foreign *folP* genes or parts of it
	Enterococcus faecium and *E. faecalis* resistance to vancomycin	Via acquisition of one of two related gene clusters *vanA* and *van B,* which code for enzymes that modify peptidoglycan precursor, reducing affinity to vancomycin.

Extended spectrum B-lactamases include TEM-1, 2, CTX-M and SHV-1
Affect cephalosporins

- CTX-M over 80 versions found in Klebsiella, e. coli and salmonella. Hydrolyses cefotaxime.
- SHV-1 over 50 versions in Klebsiella
- OXA poorly inhibited by clavulonic acid
- PSE *Pseudomonas* carried, hydrolyse carbapenems as fast as penicillin

These are serine based b-lactamases, some require Zinc

- Metallo-B-lactamases
- Inhibited by the metal chelator EDTA
- Found in a diverse range of organisms such as Acinetobactor, P. aeruginosa and Bacteriodes.
- Hydrolyses almost all B-lactams including carbapenems.

There are hundreds of B-lactamases but very few B-lactams:

- Penams: Narrow, broad and extended spectrum types
- Cephems: 1 – 5th generation
- Monobactams

This is because the enzymes are ancient being 2 – 3 billion years old

4 – Target change by mutagenesis
Fluoroquinolones target the gryA (DNA Gryase), which is essential for bacteria and absent in higher eukaryotes. Upon exposure salmonella make point mutations in gryA. Does not affect the activity of the enzyme but give resistance to fluoroquinolones. So must be used in combinationaxa with other drugs.
Altering the target examples:
Beta-lactams: PBP is modified in MSRA, S. pneumoniae and N. gonorrhoeae
Glycopeptides: Vancomycin, after 30 years of use in enterococci D-alanyl-D-Alanine has been replaces with D-Alanyl-D-Lactate of D-alanyl-D-Serine, Stpah with overproduce peptidoglycan precursors to soak up vancomycin. Staph has acquired vanA from enterococci but very rare (a two component system to confer resistance to vancomycin).
Metabolic Bypass – Sulphonamides
Hyper-production of PABA or mutation in Dihydropteroate Synthase (DHPS, chromosomal) or the duplication of DHPS (plasmids)
MB – Trimethoprim
Duplication of the Dihydrofolate reductase plasmid

Global Perspective

Antimicrobial resistance reduced the overall effectiveness of a treatment, infections last longer and the rate of death increases along with chance of spread.
MRSA patients are 64% more likely to die than people with a non-resistant infection.
Plasmodium falciparum becoming resistant to artemisinin, one of the strongest drugs used against the pathogen.
Multi-drug resistant TB is a growing concern and largely under-reported which compromises the safety of those who don't have it by ruining control procedures.

Res to first line drugs means more expensive therapies must be used, stay in hospital longer, increase healthcare costs, increases the economic burden on families and society.
Means all modern medicines are put at risk, those who require chemo, transplants or major surgery are at risk.
Res spread rapidly due to global trade and travel due to both humans and food.
Res causes loss in GDP, indirect cost may be more than 3 times the cost of direct health care spending.
Affects developing economies proportionally more than developed ones.

Example: Gonorrhoea
Treatment failure to the drug of last resort (3rd gen cepha) has been confirmed in several countries.
Untreated gonococcal infections increase rate of illness and complications, will reverse to step made to control the spread of the STD.

Cr-Kp
res to Carbapenems caused by common intestinal bacteria has spread world wide.
Since 1996 incidence of carba res K. pneumoniae infections has dramatically increased. Currently available penicillin, cepha, and carbs are not active.
Very few treatment options remain with CR-Kp septicaemia. Tigecycline and colistin are still active but one is concentrated low in the plasma whilst the other is toxic.

Tissue tropism not just adherence…but where disease is caused

- Not all pathogens cause disease at the same locations
- E.g *Staphylococcus aureus*..no disease in the nasal area until skin breached then infection, inflammation.
- *Clostridium tetani*..in wounds causes local tissue death..but paralysis only if the secreted toxin reaches nerve cells..
- Whereas the food pathogen *Shigella* causes diseases of the GI tract yet would not cause severe wound infections.
- Pathogens have specific tropisms ..cause disease under the right conditions and locations.
- This includes host immune status
- Mycoses, *Pseudomonas aeruginosa*

Example of Tissue tropism and disease according to site of infection: Tuberculosis

- If droplets are breathed in tuberculosis of the lungs.
- Macrophages infected with the bacteria are walled off by fibroblasts
- Granuloma's ..latent..not dead.
- In 10% of cases these walled off areas burst and release bacteria throughout the tissue
- CNS—meningitis
- Lymphatics system -Scrofula

Pott disease (1-2% of TB cases) reported in 1779
Fusion of vertebrae and damage to the spine
Ancient Egypt, Iron age remains
Skin ….cadaver wart

Nutrition

Dealt with elsewhere but
Iron…siderophores
Amino acids.. Proteases
Lipids lipases
carbohydrates., amylases
Parasitic organisms, obligate intracellular growth, Chlamydia, Rickettsia, Legionella all have fascinating ways of stealing nutrition, within the cell
Where they are – of course hidden from the host response ….

For nutrient acquisition rickettsia prowazekii has enzymes which steal Tri-phosphates via dihydroxyacetone phosphate transport system working with a Glycerol – 3- phosphate dehydrogenase.

Chlamydia does this by re-routing transport vesicles and hi-jacking organelles. Proteolytic fragmentation of the Golgi body and recruitments of Rab GTPases and SNARE proteins. Has a nucleotide transport system which imports ATP whilst exporting ADP.

Some species, eg *Mycobacterium tuberculosis,* are able to invade cells (macrophages)
Avoid humoral host defences…..antibodies
Survival in phagocytes
Niche rich in nutrients
No competition from other bacteria
Then can spread from cell to cell
Mechanism of invasion ..

Anthrax is the first gram positive to have been found to secrete hemophores (which bind to heme groups), which is required to alter gene expression of intimin and invasion of host cells.
← Salmonella, listeria

Cholera
G-ve, bacilli, oxidase positive, Single polar flagella, tolerant to alkali – growth range pH 6.8 – 10.2 over 130 serotypes, V. cholera 01 – major cause of epidemics, Non-01 v. cholera is milder. Two serotypes 01 and 0139. New 01 variant strains believed to be emerging and cause a more severe form of cholera. Non 01 or 0139 variants do not cause epidemics.
Resevoirs are people and brackish water which are often associated with algal blooms, global warming may be beneficial for the bacteria.
Causes an acute intestinal disease caused by the ingestion of contaminated food or water. Short incubation time and produced the enterotoxin called cholera toxin (CTX, choleragen) which copious watery diarrhoea which can quickly lead to dehydration, vomiting can also occur. Death will occur if the patient is not treated. The majority of people effected by the organism are asymptomatic, although bacteria is present for 7 – 14 days afterwards. When illness does occur, 90% are mild. The rest get the typical severe cholera. EST of those effected are 3 – 5 million per annum, and 110, 000 deaths.
01 split into 2 biotypes Classical and El Tor, both have coregulated pilus and the CTX, El Tor produces a haemolysin and is resistant to polymixin B.

7 Pandemics with many more epidemics.
Organism multiplies in the alkaline small intestine. Organisms migrate and adhere to the epithelial cells (Toxin co-reg pilus) and produce toxin, map that fucking!!

Symptoms are sudden vomiting, profuse watery diarrhoea which can lead to rapid dehydration and shock – fatal in a day. Rice water stools, muscle cramps, lethargy, low blood pressure, absent or weak pulse.
Treatment is oral rehydration, IV in serious cases.
Antibiotic treatment can reduce the volume of water lost. Children under 12 given a 3 das course of erythromycin
Under 5 should be given zinc for ten days.
Teens and adults, 3 days of tetracycline or a single doxycycline dose.
Tissue culture, toxin testing, serotyping and genetic typing.
Dip stick test in stool.

Active immunisation is prophylactic. Whole pathogen – inactivated or attenuated.
Passive are passed from one to another (Ab).
Can also have subunit vaccines which require a adjuvant. These will be toxoids such as DPT
A vaccine needs to have a long shelf life, be safe (minimal number of side effects).

Vaccines need to target critical Ag's that the organism can't do without. Vaccines against these can cause a protective immunity against pathogens or their products such as the DPT vaccines.
Some may need a adjuvant such as aluminium which acts as a depot vaccine, keeping the Ag in one place to create a strong immune system targeting one location. This makes it look more like a organism to the immune system. The more similar the vaccine is to the real thing the more immunogenic.