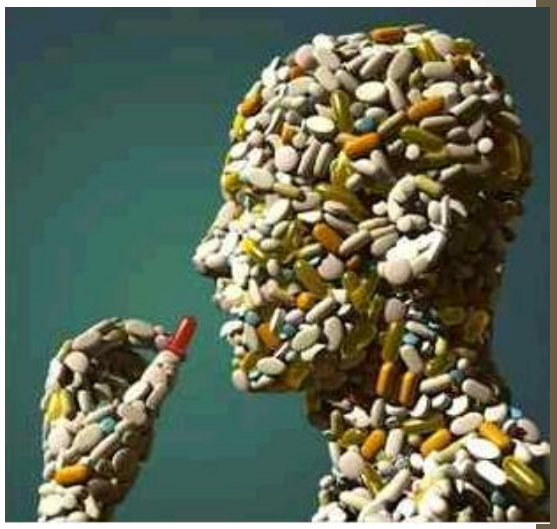
NSW GOVERNMENT Health
Hunter New England Local Health District

Antimicrobial Resistance and Prescribing



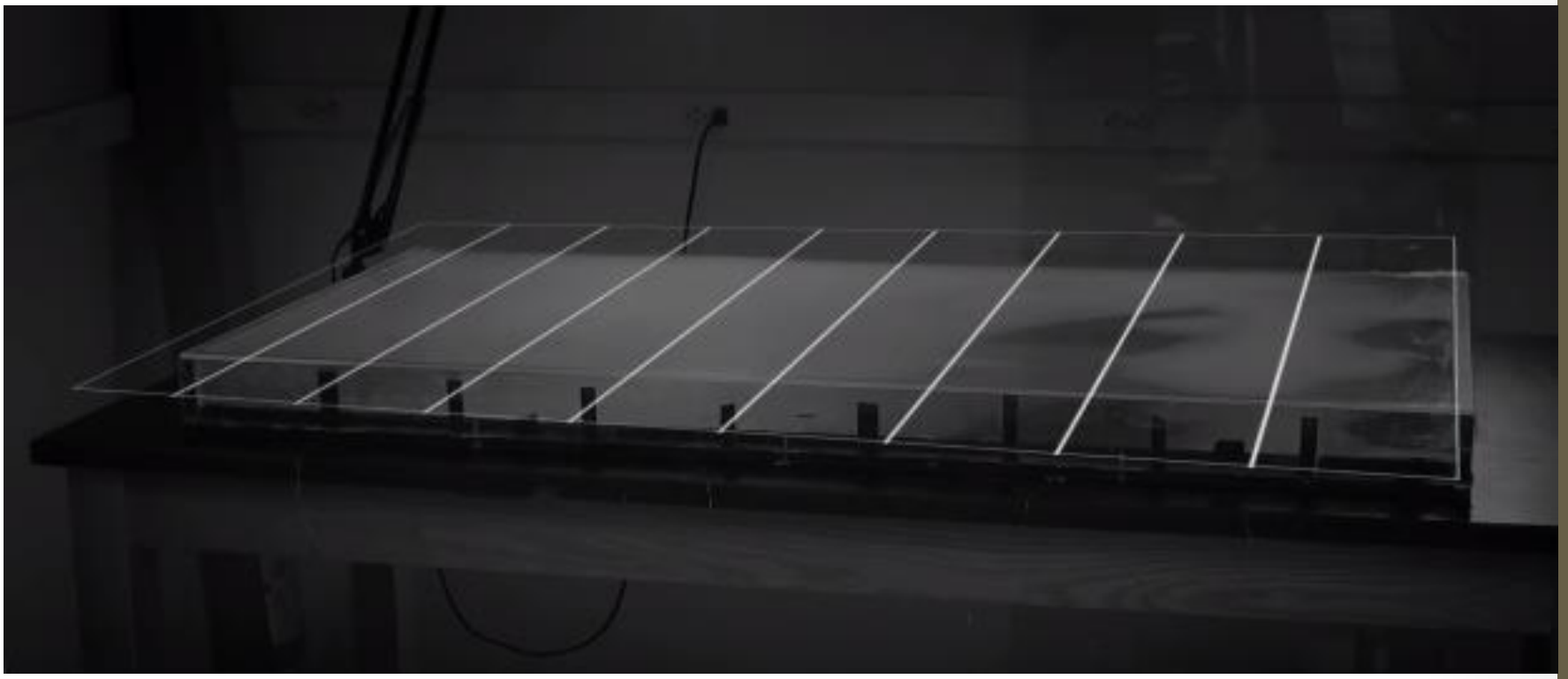
John Ferguson, Microbiology & Infectious Diseases, John Hunter Hospital, University of Newcastle, NSW, Australia

M Med Part 1 updates

UPNG 2017

Tw @mdjkf http://idmic.net

Watching antibiotic resistance evolve…



https://www.youtube.com/watch?v=yybsSqcB7mE

What is Antimicrobial Resistance (AMR)?

Medicines for treating infections lose effect because the microbes change;

1. mutate
2. acquire genetic information from other microbes to develop resistance

Types of AMR

1. **Antibacterial resistance** (e.g. to antibiotics and other antibacterial drugs)
2. **Antiviral resistance** (e.g. to anti-HIV medicines)
3. **Antiparasitic resistance** (e.g. to anti-malaria medicines)
4. **Antifungal resistance** (e.g. to medicines used to treat *Candidiasis*)

AMR is a natural phenomenon accelerated by use of antimicrobial medicines. Resistant strains survive and aggregate.

What is antimicrobial resistance?

- Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.
- Resistant microorganisms are able to withstand attack by antimicrobial drugs, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.
- This phenomenon is nearly as old as the discovery of antimicrobials themselves, having been described by pioneers like Ehrlich for trypanosomes and Fleming for staphylococci.

5 reasons why AMR matters:

1. Antimicrobial resistance kills

Antimicrobial resistant infections often fail to respond to standard treatment, resulting in *prolonged illness, higher health care expenditures, and a greater risk of death.*

Increase in sepsis due to multi-resistant enteric gram-negative bacilli in Papua New Guinea

THE LANCET • Vol 353 • June 26, 1999

Trevor Duke, Audrey Michael

Between April 1998 and March 2000, multi-resistant enteric gram negative sepsis occurred in 106 of 5331 paediatric admissions (2%), but caused 87 (25%) of 353 deaths

Bacteria	Nosocomial	Community acquired	Chloramphenicol sensitivity	Gentamicin sensitivity
Klebsiella sp*	12	2	0	3
*Pseudomonas aeruginosa**	7	4	0	2
*Escherichia coli**	1	7	1	5
Citrobacter freundii	1	2	1	0
Enterobacter sp	3	4	0	3
Morganella morganii	0	2	2	2
Burkholderia capacia	2	1	1	0
Proteus mirabilis	2	1	0	2
Acinetobacter sp	1	0	0	1
Serratia sp	0	2	0	1
Providentia sp	0	1	1	1
Aeromonas sp	0	1	0	1
Alcaligenes sp	0	1	0	1

*We could not be certain of the origin of one additional isolate of each of these three bacteria.

Sensitivity of bacterial isolates and place of acquisition

Risk of Death is Higher in Patients Infected with Resistant Strains

		Deaths (%)		
	Outcome (number of studies included)	**Resistant**	**Not resistant**	**RR (95% CI)**
***Escherichia coli* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	23.6	12.6	2.02 (1.41 to 2.90)
Fluoroquinolones	Bacterium attributable mortality (n=1)	0	0	
***Klebsiella pneumoniae* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	20	10.1	1.93 (1.13 to 3.31)
Carbapenems	Bacterium attributable mortality (n=1)	27	13.6	1.98 (0.61 to 6.43)
***Staphylococcus aureus* resistant to:**				
Methicillin (MRSA)	Bacterium attributable mortality (n=46)	26.3	16.9	1.64 (1.43 to 1.87)

Risk of Death is Higher in Patients Infected with Resistant Strains

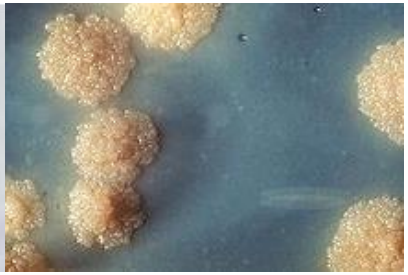
		Deaths (%)		
	Outcome (number of studies included)	Resistant	Not resistant	RR (95% CI)
***Escherichia coli* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	23.6	12.6	2.02 (1.41 to 2.90)
Fluoroquinolones				
Klebsiella pneumo				
3rd gen. cephalospori			.1	1.93 (1.13 to 3.31)
Carbapenems	Bacterium attributable mortality (n=1)	27	13.6	1.98 (0.61 to 6.43)
***Staphylococcus aureus* resistant to:**				
Methicillin (MRSA)	Bacterium attributable mortality (n=46)	26.3	16.9	1.64 (1.43 to 1.87)

Resistant organisms - Up to twice the risk of dying

2. AMR hampers the control of infectious diseases

AMR reduces the effectiveness of treatment; thus *patients remain infectious for a longer time, increasing the risk of spreading* resistant microorganisms to others.

Catherina Abraham



Aged 20 years, flew to Cairns from Torres Strait, 2012 diagnosed with XDR-TB.

After almost a year in an isolation ward at Cairns Base Hospital, she died on 8 March 2013.

Secondary case, aged 32 also died.

Tony Kirby Med J Aust 2013; 198 (7): 355.

3. AMR increases the costs of health care

Resistant infections require more expensive therapies and longer duration of treatment

Catherina's treatment cost Queensland Health about $500 000 and would have cost $1 million had she lived to complete it.

4. The achievements of modern medicine are put at risk by AMR

- organ transplantation
- cancer chemotherapy
- major surgery

5. AMR threatens health security, damages trade and economies

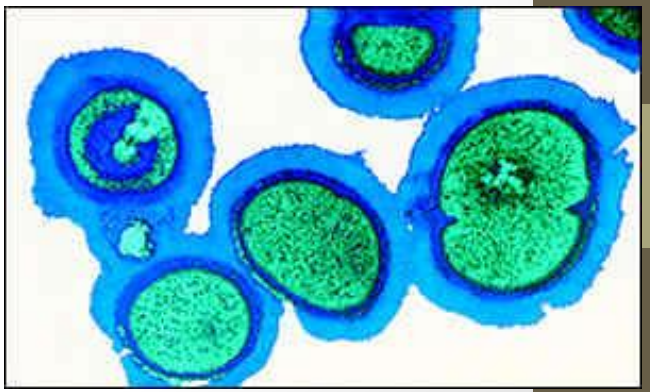
WHO 2014

AMR in PNG

1. WHY is it an important problem?
2. **HOW has the problem arisen?**
3. WHAT do we have to do?

Bacterial perspective

- 3.5 billion years of evolutionary diversification
- Estimated 10^{21} bacteria; one billion progeny/ day
- Adapted to innumerable niches
- Sense their environment, exhibit cooperative behaviours and adaptive stress responses
- Antibiotic resistance genes are ancient
- Humans carry 2-3 kg of bacterial biomass acquired from diverse sources



Intrinsic Resistance

- **Intrinsic resistance** is that type of resistance which is naturally coded and expressed by all (or almost all) strains of that particular bacterial species.
- "Insensitivity" since it occurs in organisms that have never been exposed to that particular drug.

Such natural insensitivity can be due to:

- lack of affinity of the drug for the bacterial target
- inaccessibility of the drug into the bacterial cell
- extrusion of the drug by chromosomally encoded active exporters
- Innate (chromosomal) production of enzymes that inactivate the drug

ORGANISMS	NATURAL 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 (a beta-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 spp.	Ampicillin (a beta-lactam)	Production of enzymes (beta-lactamases) that destroy ampicillin before the drug can reach the PBP targets
Stenotrophomonas. maltophila	Imipenem (a beta-lactam)	Production of enzymes (beta lactamases) that destroy imipenem before the drug can reach the PBP targets.

Advanced topic slide- Pathology M Meds only!

ORGANISMS	NATURAL RESISTANCE AGAINST:	MECHANISM
Lactobacilli and *Leuconostoc*	Vancomycin	Lack of appropriate cell wall precursor target to allow vancomycin to bind and inhibit cell wall synthesis
Pseudomonas 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

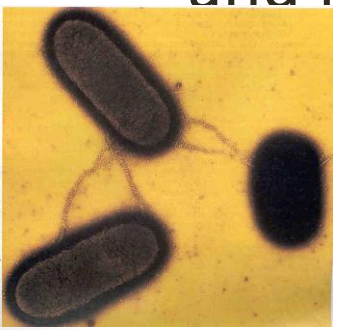
Advanced topic slide- Pathology M Meds only!

How does acquired resistance arise?

1. mutational change in bacterial chromosome with clonal expansion of a resistant subpopulation

AND/OR

2. horizontal transfer of new resistance gene(s) from another bacterial species by direct transfer and recombination



Antibiotic exposure increases the rate of both processes

Antibiotics select and promote growth of resistant subpopulations

Bacterial genetics and resistance

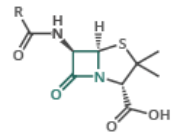
Mechanism	Species	Antibiotic resistance
Mutation	*M. tuberculosis* *E. Coli*	INH or rifampicin resistance Ceftriaxone resistance (ESBL)
Horizontal transfer Plasmid transfer (multiple resistance genes usually):	*Staphylococcus aureus* *E. coli*	Betalactamase Carbapenemase , ESBL, many other resistance genes
Transformation (uptake of native DNA from dead bacilli):	*Strep. pneumoniae*	Partial resistance to penicillin due to acquisition of penicillin binding protein gene from related streptococcus species
Transduction (virus that infects bacteria):	*C. diphtheriae*	Toxin production gene is introduced by bacteriophage
Other tricks Transposition:	Widespread mechanism for genes to move between plasmids and chromosomal locations and vice versa	
Conjugation	Process that allows sex tubes to form between bacterial cells – chromosomal or plasmid DNA may transfer and then integrate into the recipient cell's chromosome	

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



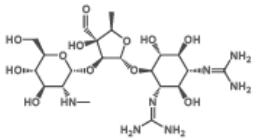
All contain a beta-lactam ring

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



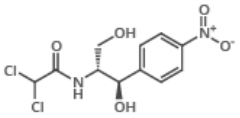
All contain aminosugar substructures

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



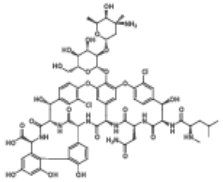
Distinct individual compound

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'



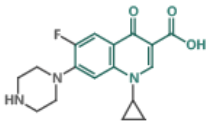
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



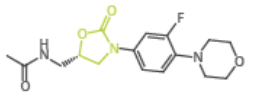
All contain fused aromatic rings with a carboxylic acid group attached

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

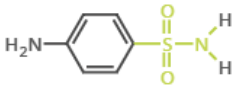
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

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

DISCOVERY 1930 1940 1950 1960 1970 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



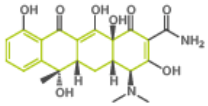
All contain the sulfonamide group

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



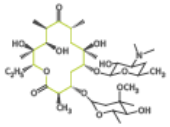
All contain 4 adjacent cyclic hydrocarbon rings

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



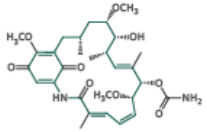
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

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

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



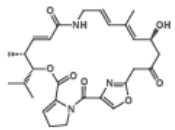
All contain an aromatic ring bridged by an aliphatic chain.

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



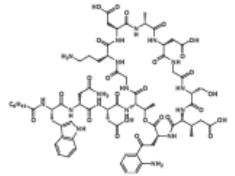
Combination of two structurally differing compounds, from groups denoted A & B

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



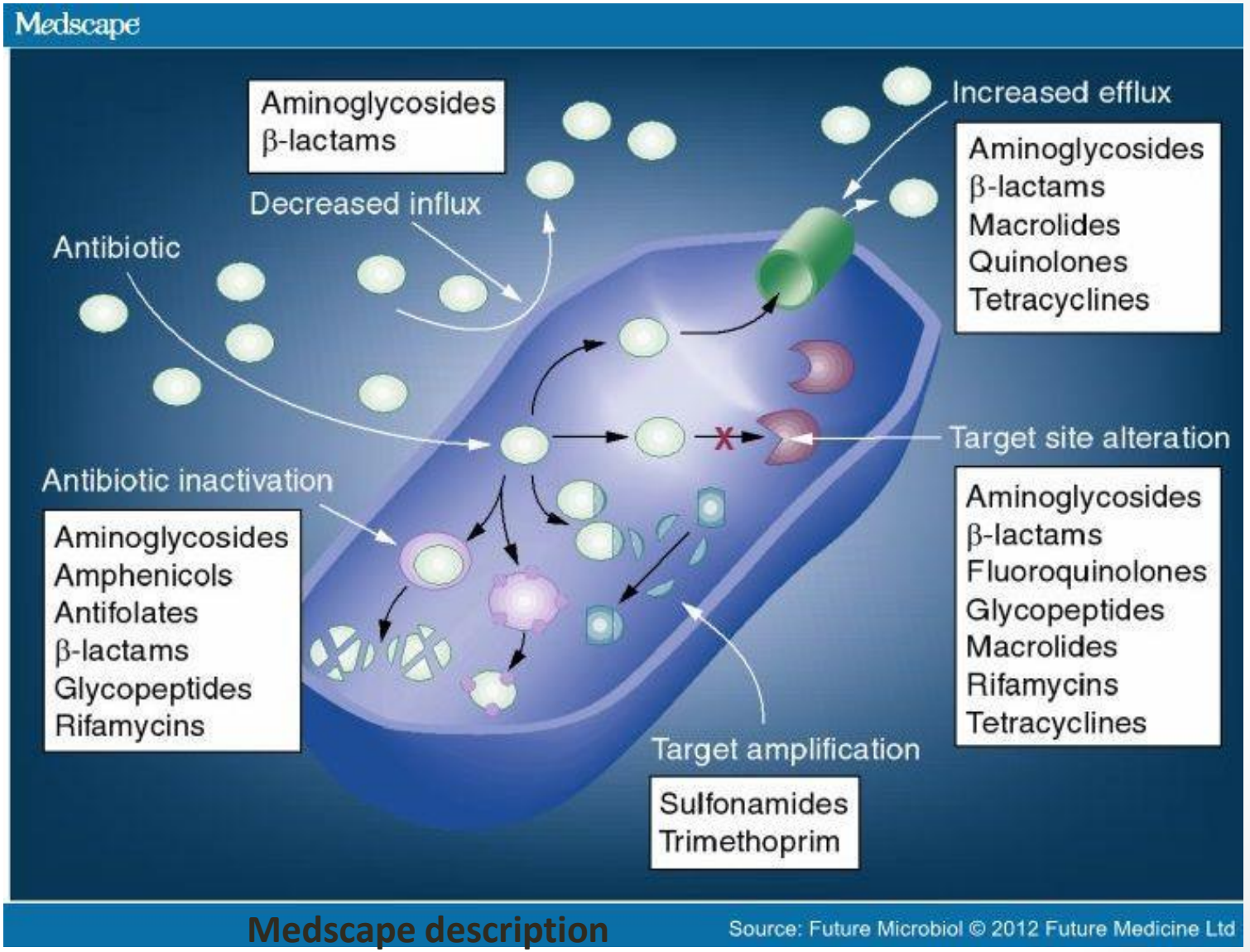
All contain a lipid bonded to a peptide

EXAMPLES
Daptomycin (shown), surfactin.

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

https://aimed.net.au/2017/02/01/antibiotic-classes-why-so-important-to-know-about-them/

Resistance mechanisms



Medscape description

http://www.medscape.com/viewarticle/756378_2

Gram positive resistance:

Staph. aureus, Enterococci and TB are the problem

Genera	Antibiotic	Mechanism
Staphylococci	Penicillin Flucloxacillin Glycopeptide (vancomycin)	Betalactamase *mecA* gene acquisition *vanA* resistance operon acquisition
	Erythromycin/clindamycin Tetracycline Cotrimoxazole	Various mechanisms
Streptococci	Penicillin Vancomycin	Transformation (*Strep. pneumoniae*) NO betalactamases No vanc resistance described
	Erythromycin/clindamycin Tetracycline Cotrimoxazole	Various mechanisms

Gram positive resistance

Genera	Antibiotic	Mechanism
Enterococci (group D strep) Large range of intrinsic resistances	Penicillin Glycopeptide (vancomycin)	Intrinsic penicillin resistance – *E. faecium* Betalactamase (rare) *vanA* and *vanB* resistance operons (groups of genes)
Anaerobic Gram positives - Peptostreptococci - Clostridium - Listeria - Actinomyces	Penicillin Vancomycin	NO betalactamases No resistance described

Gram negative resistance: the problem customers include:

Genera	Antibiotic	Mechanism
Enterobacteriaceae (*E. coli, Klebsiella* and other coliform species)	Ampicillin Ceftriaxone Meropenem (carbapenem) Colistin Pan-resistance increasing	Penicillinase ESBL Carbapenemase = CPE Plasmid borne gene – mechanism not known
Pseudomonas aeruginosa and Acinetobacter baumannii Many intrinsic resistance characters	Aminoglycosides Ciprofloxacin Meropenem Colistin Pan-resistance increasing	Multiple mechanisms - influx, efflux - Carbapenemases - MCR1 - Target modification
Neisseria gonorrhoeae	Prospects of untreatable pan resistance	Multiple mechanisms

CPE= **Carbapenemase Producing Enterobacteriaceae**

2016-17 DRAFT PNG NATIONAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

Antimicrobial resistance now a priority agenda for the Ministry of Health. Country situation analysis Sept 2016

January 2017: National AMR multi-sector symposium took place

Recommendations drafted against the WHO policy package on AMR under these headings:

1. National coordination mechanisms (governance)
2. Access to, and quality of, essential medicines
3. Surveillance and laboratory capacity
4. Rational use of medicines in humans and animals
5. Infection prevention and control
6. Research and development

Country Situation Analysis

- “In general, the analysis revealed that the current level of activities addressing AMR in PNG across these six elements is low.
- The most significant challenge relates to rational use of medicines in humans and animals. This challenge is driven by patients and providers alike. Patients typically self-prescribed before seeking care services, and providers over-prescribe at the point of care.
- Similarly, there is no regulation to restrict the use of critically important medicines for human use in animals, and there is no regulation to restrict the use of antimicrobials as growth promoters.”