Antimicrobial resistance – an example of evolution in action

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WHO AMR World Health Day 7 April, 2011 - http://www.who.int/world-health-day/2011/en/index.html

AMR: a major challenge – WHO perspective

- Tuberculosis (TB): 440,000 new multidrug resistance (MDR) TB cases annually; extensively drug resistance (XDR) TB cases reported in 64 countries so far
- Malaria: Emergence of Artemisinin resistance linked to ongoing use of monotherapies
- HIV: With expanded use of antiretrovirals (ARVs), resistance is a concern
- Methicillin-resistant *Staphylococcus aureus*: lethal infections in hospital settings becoming increasingly frequent
- Multi-drug resistant *E.coli, K.pneumoniae* and *Enterobacter* sp.: infections are on the rise and a new beta-lactamase, NDM-1, is causing alarm
- *Neisseria gonorrheae* and *Shigella*: becoming increasingly resistant to drugs

Recent papers reporting microbial resistance in Indonesia

Massi MN, et al. Drug resistance among tuberculosis patients attending diagnostic and treatment centres in Makassar, Indonesia. Int J Tuberc Lung Dis. 2011 Apr;15(4):489-95

Nishibori T, et al. Phenotypic and genotypic characterisation of *Vibrio cholerae* clinically isolated in Surabaya, Indonesia. Jpn J Infect Dis. 2011;64(1):7-12.

Lestari ES eta l; Group Antimicrobial Resistance in Indonesia Prevalence and Prevention. Determinants of resistance of *Staphylococcus aureus* in *S aureus* carriers in the Indonesian population inside and outside hospitals. Trop Med Int Health. 2010 Oct;15(10):1235-43

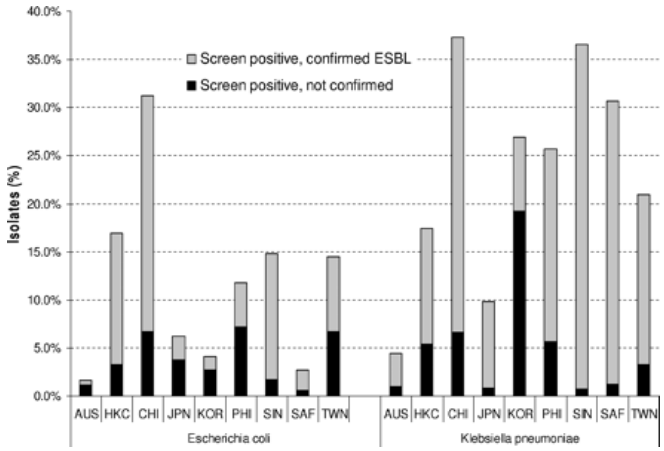
Herwana E et al. Shigella-associated diarrhoea in children in South Jakarta, Indonesia. Southeast Asian J Trop Med Public Health. 2010 Mar;41(2):418-25.

Yanagi D et al. Emergence of fluoroquinolone-resistant *Salmonella enterica* in Surabaya, Indonesia. Diagn Microbiol Infect Dis. 2009 Aug;64(4):422-6.

Recent papers reporting microbial resistance in Indonesia

Duerink DO, et al; Study Group Antimicrobial Resistance in Indonesia: Prevalence and Prevention (AMRIN). Determinants of carriage of resistant *Escherichia coli* in the Indonesian population inside and outside hospitals. J Antimicrob Chemother. 2007 Aug;60(2):377-84.

Sutrisna A, et al. Increasing resistance to ciprofloxacin and other antibiotics in *Neisseria gonorrhoea* from East Java and Papua, Indonesia in 2004. Int J STD AIDS. 2006 Dec;17(12):810-2.



Bell et al (2007) J Clin Micro 45:1478

Resistant mechanisms against the major classes of antibiotics

	Major resistance mechanisms	Genes
β-lactams	• **β-lactamases** • **Target site modification - Low affinity PBPs – staphylococci, enterococci** • Decreased transport – porins in Gram-negative bacteria	many *bla* genes *Eg mec*A (staphs)
Glycopeptides	• Target site modification - Modification of terminal dipeptide on pentapeptide precursor	*van* genes - multiple
Aminoglycosides	• Modifying enzymes (phosphoryltranferases, acetyltransferases, nucleotidyl transferases)	30 different genes - *aad, ant*, *aph*
Sulphonamides	• **Overproduction of PABA (para-aminobenzoic acid)** • **Lowered affinity for PABA** • By-pass – use preformed folic acid	*sul* genes - 3 *fol*P gene (DHPS)

6

Resistant mechanisms against the major classes of antibiotics

	Major resistance mechanisms	Genes
Macrolides	• **Target site modification-** methylation of mRNA; site-specific mutations in 23S rRNA gene • **Efflux pumps** • Modifying enzymes (esterases, phosphotransferases)	20 classes *erm* genes • Gram+ve – *mef* genes; Gram-ve multi-drug efflux pumps • *ere*A and *ere*B (erythtomycin)
Quinolones	• **Altered target – DNA gyrase, topoisomerase IV** • **Efflux pumps**	• *gyr*A, *par*E • *nor*A, *pmr*A
Tetracyclines	• **Efflux pumps** • **Target modification** • Enzyme modification	• many *tet* genes • many *tet* genes • *tet*X
Phenicols	• **Modifying enzymes (acetyltransferase**) • Efflux pumps – MFS	Several *cat* genes *flo*R, *cml*A, *cra*A

Microbial evolution

- Random mutation + natural selection = evolution
- Multiplication rate of bacteria very rapid
- Mutation rate of 1 in 10^9 cell divisions
- Antibiotics are just another “natural selection” mechanism for bacteria

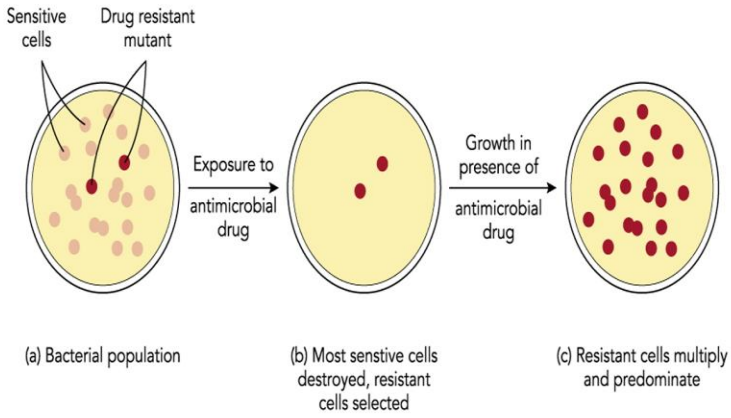


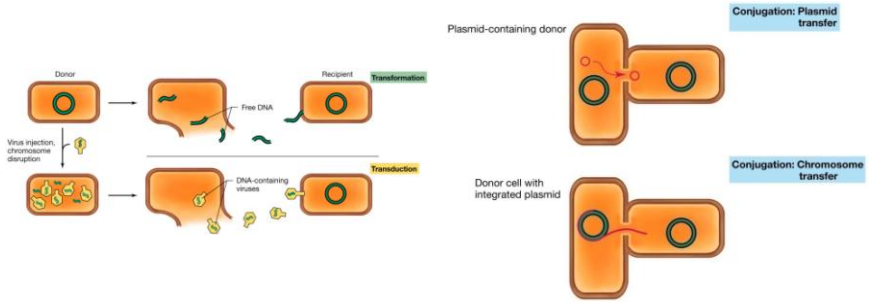
Figure 12.13

Effect of exposure to antimicrobial drugs

If the concentration of drug is not sufficient to kill *all* cells, the resistant mutant cells are selected and can multiply.

9

Horizontal transfer of genes in bacteria



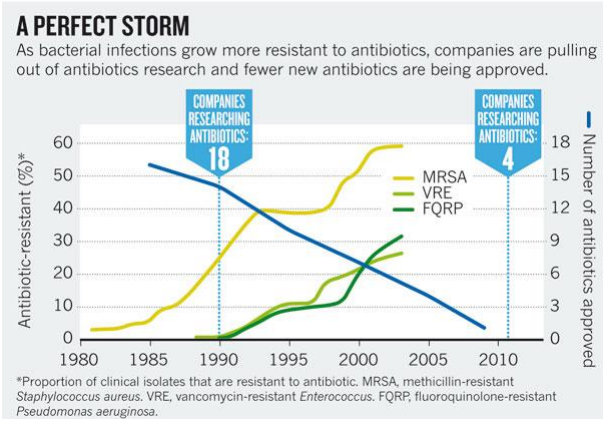
10

We are running out of new classes of antimicrobials

Antimicrobial class	*Year of launch*
• Sulphonamides	1936
• Penicillins	1940
• Tetracyclines	1949
• Chloramphenicol	1949
• Aminoglycosides	1950
• Macrolides	1952
• Glycopeptides	1958
• Streptogramins	1962
• Quinolones	1962
• Oxazolidinones	2001
• Cyclic lipopeptides	2003
• Glycylcyclines	2005

1969 – US Surgeon General said "It is time to close the book on infectious diseases."

11



History of Medicine

2000 BC – here, eat this root
1000 AD – the root is heathen; here say this prayer
1850 AD- that prayer is superstitious; here drink this potion
1920 AD – that potion is snake oil; here swallow this pill
1945 AD – that pill is ineffective; here take this penicillin
1955 AD – oops …bugs mutated; here take this tetracycline
1960 AD – 39 more "oops" …; here take this more powerful antibiotic
2000 AD – the bugs have won! Here eat this root

Anonymous - Quoted in "Overcoming Antimicrobial Resistance" - World Health 2000.

13

Are there any solutions?

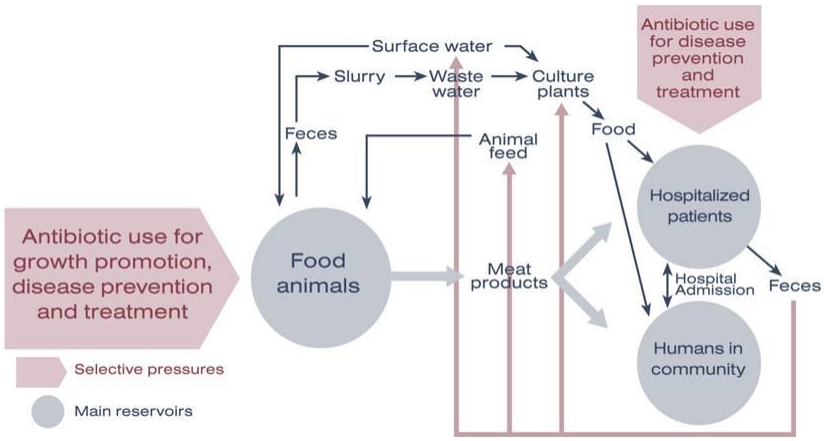
- Reduce prevalence of infectious disease
  - Improved public health
    - Clean water, clean food
    - Good hygiene in homes and food outlets
  - Improved infection control in hospitals
  - Cheap and effective vaccines
    - Note pneumococcus, *Haemophilus influenzae* B (HiB), meningococcus
    - tuberculosis, typhoid, non-typhoidal salmonella, shigella, gonorrhoea, cholera, MRSA…..

Are there any solutions?

- Improve antimicrobial stewardship – protect the antibiotics we have
  - Antibiotic use and control policies in hospitals and the community
    - Hold critical antimicrobials in reserve – eg fluoroquinolones, 3rd/4th generation cephalosporins
    - Use effective older antimicrobials where possible
    - Use narrow spectrum rather than broad spectrum antimicrobials
    - Stop over the counter supply of antimicrobials
    - Only prescribe/use antimicrobials when they are needed
  - Control use of antimicrobials in animals
    - Ban non-therapeutic growth promotant use
    - Ban use of antimicrobials of critical importance in human medicine
  - Monitoring and surveillance of antimicrobial resistance and antibiotic use

Links between animals & humans –

spread of antimicrobial resistant bacteria & genes



http://www.oznet.ksu.edu/

16

Are there any solutions?

- Find new classes of antimicrobial agents
  - Traditional bioprospecting – various habitats
  - Natural products – eucalyptus, tea-tree oils
  - Genomics and computational chemistry
- Probiotics, prebiotics & competitive exclusion organisms
  - Reduce pathogenic microorganisms in animal GIT
- Bacteriophages

Conclusions

- Microbes will continue to evolve
- Simply producing new antimicrobials is not going to solve the antimicrobial resistance problem
- Reducing the need to use antimicrobials is important
- We need to preserve the antimicrobials we have (and any new classes developed)