Antimicrobial resistance – an example of evolution in action

Professor Mary Barton
University of South Australia

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 gonorrhoeae and Shigella: becoming increasingly resistant to drugs

Recent papers reporting microbial resistance in Indonesia


Recent papers reporting microbial resistance in Indonesia


## Resistant mechanisms against the major classes of antibiotics

<table>
<thead>
<tr>
<th>Major resistance mechanisms</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactams</strong></td>
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<tr>
<td>• <strong>β-lactamases</strong></td>
<td></td>
</tr>
<tr>
<td>• Target site modification - Low affinity PBPs – staphylococci, enterococci</td>
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<tr>
<td>• Decreased transport – porins in Gram-negative bacteria</td>
<td></td>
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<tr>
<td>• Many <em>bla</em> genes</td>
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<tr>
<td>Eg mecA (staphs)</td>
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<tr>
<td><strong>Glycopeptides</strong></td>
<td></td>
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<tr>
<td>• Target site modification - Modification of terminal dipeptide on pentapeptide precursor</td>
<td><em>van</em> genes - multiple</td>
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<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
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<tr>
<td>• Modifying enzymes (phosphoryltranferases, acetyltransferases, nucleotidyl transferases)</td>
<td>30 different genes - <em>aad, ant, aph</em></td>
</tr>
<tr>
<td><strong>Sulphonamides</strong></td>
<td></td>
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<tr>
<td>• Overproduction of PABA (para-aminobenzoic acid)</td>
<td><em>sul</em> genes - 3</td>
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<tr>
<td>• Lowered affinity for PABA</td>
<td></td>
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<tr>
<td>• By-pass – use preformed folic acid</td>
<td><em>folP</em> gene (DHPS)</td>
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Resistant mechanisms against the major classes of antibiotics

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<td>Macrolides</td>
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<tr>
<td>• <strong>Target site modification</strong> - methylation of mRNA; site-specific mutations in 23S rRNA gene</td>
<td>20 classes <em>erm</em> genes</td>
</tr>
<tr>
<td>• <strong>Efflux pumps</strong></td>
<td>• Gram+ve – <em>mef</em> genes; Gram-ve multi-drug efflux pumps</td>
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<td></td>
<td>• <em>ereA</em> and <em>ereB</em> (erythromycin)</td>
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<td></td>
<td></td>
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<tr>
<td>• Modifying enzymes (esterases, phosphotransferases)</td>
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<tr>
<td>Quinolones</td>
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<tr>
<td>• <strong>Altered target</strong> – DNA gyrase, topoisomerase IV</td>
<td>• <em>gyrA, parE</em></td>
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<tr>
<td>• <strong>Efflux pumps</strong></td>
<td>• <em>norA, pmrA</em></td>
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<tr>
<td>Tetracyclines</td>
<td></td>
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<tr>
<td>• <strong>Efflux pumps</strong></td>
<td>• many <em>tet</em> genes</td>
</tr>
<tr>
<td>• <strong>Target modification</strong></td>
<td>• many <em>tet</em> genes</td>
</tr>
<tr>
<td>• <strong>Enzyme modification</strong></td>
<td>• <em>tetX</em></td>
</tr>
<tr>
<td>Phenicols</td>
<td>Several <em>cat</em> genes</td>
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<tr>
<td>• <strong>Modifying enzymes</strong> (acetyltransferase)</td>
<td><em>floR, cmlA, craA</em></td>
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<tr>
<td>• <strong>Efflux pumps – MFS</strong></td>
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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
Horizontal transfer of genes in bacteria
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.”

**A PERFECT STORM**

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.

*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus; FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa.*
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


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/
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)