“Supermobile Superbugs”

*International travel and antibiotic resistance*

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Deaths attributable to AMR every year compared to other major causes of death

AMR in 2050
10 million

- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Cancer: 8.2 million
- Measles: 130,000
- Cholera: 100,000 - 120,000
- Diarrhoeal disease: 1.4 million
- Diabetes: 1.5 million

Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations

The Review on Antimicrobial Resistance
Chaired by Jim O’Neill
December 2014
AMR's impact on World GDP in trillions of USD

Deaths attributable to AMR every year by 2050

More than 2 billion people travel long distances each year

~300 million / year travel to areas highly endemic for antibiotic resistance
Global movement of people

- **IATA**: ~1.45 billion international air travel passengers estimated for 2016
  - ~35% of all international air travel in Asia-Pacific region, set to expand rapidly

- **UN Tourism**: 348 million international tourists Jan-April 2016
  - ~18 million more than the same period in 2015 (+5.3%)
  - 2016: will be the 7th consecutive year of above-average growth in tourism

http://www.iata.org; http://www2.unwto.org
World at war

Global Refugee Trends

Countries of Origin

Countries of Destination

Map created by Tina Gotthardt & Benjamin Hennig

www.unhcr.org
Gram-negatives possess multiple mechanisms to resist antibiotics

- Mutation in lipopolysaccharide (polymixin resistance)
- Hydrolysis by β-lactamase (plasmid acquired or over-expressed chromosomal genes)
- Overexpression of efflux pumps (multidrug resistance)
- Modified drug target (e.g., Quinolones)
- Antibiotic modification (e.g., Aminoglycosides)
- Antibiotic

Zowawi, Harris et al. Nat Urol Rev 2015
Plasmids and resistance

- ~25% of bacterial genome acquired by Lateral Gene Transfer
- Allows phenomenal diversity and rapid adaptation
- >18,000 potential genes in the E. coli “pan-genome” despite there being only ~2000 genes in each cell
“Lateral gene transfer potentially makes all genes in the microbial biosphere a single, common and shared resource. In the same way that wars can be won by nations with the greatest industrial capacity, so it is that bacteria can draw on a global resource that .... can rapidly mobilize and transfer useful genes across physical and phylogenetic distances.”

**CTX-M: A true global traveller**

- “Cefotaximase-Munich” ESBL
- Origins from chromosomal *klu* beta-lactamase of *Kluyvera*
  - plasmid uptake in common pathogens e.g. *E. coli*, *Salmonella spp*
  - *May have occurred multiple times*
- Once CTX-M penetrates a specific geographic area it tends to displace TEM / SHV ESBLs
- Frequently seen in successful pandemic clones e.g. ST131 uropathogenic *E. coli*

Davies, 2010;74:417-433
MERINO Trial: 3GC-R *E. coli / K. pneumoniae* in BCs

33% $bla_{CTX-M-15}$
23% $bla_{CTX-M-27}$
9% $bla_{CTX-M-14}$
(all belong to CTX-M-9 lineage)

Dominance of ST-131 *E. coli* carrying CTX-M-type ESBLs
3rd generation cephalosporin resistant Enterobacteriaceae – urinary isolates
Carbapenem retail sales in selected countries, 2005–2010
(per 1,000 population)

Source: Leoministoury et al. 2013 (based on IMS MIDAS)

* An IMS grouping of Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Guinea, Mali, Republic of the Congo, Senegal, and Togo.
Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014

18,695 isolates, 47.5% Gram-negative bacilli
~60% of *K. pneumoniae* resistant to carbapenems!
Antimicrobials Increase Travelers’ Risk of Colonization by Extended-Spectrum Betalactamase-Producing Enterobacteriaceae

Kantele et al, Clinical Infectious Diseases, January 2015

Overall 21% of Finnish travellers acquired ESBLs; 37% if had diarrhoea and antibiotics

TD-AB= 12%
TD+AB= 8%
TD+AB+ 28%

TD-AB= 23%
TD+AB= 47%
TD+AB+ 80%

TD-AB= 14%
TD+AB= 32%
TD+AB+ 69%
THE RESISTANCE MOVEMENT
Carbapenem-resistant Enterobacteriaceae have been on the move since at least 1996.


2. 2003: KPC-positive bacteria are found spreading rapidly through hospitals across New York City. By 2007, 21% of Klebsiella in the city carry the resistance gene.

3. 2005: KPC-positive bacteria make their way from New York to several other countries, including Israel. From Israel, the bacteria travel to Italy, Colombia, the United Kingdom and Sweden.

4. 2008: Doctors in Sweden find a new carbapenem-resistance gene, NDM. Traced back to India, NDM-positive bacteria have moved quickly.
What is happening in Australia?
Resistance in community-onset infections

### Escherichia coli

<table>
<thead>
<tr>
<th>Year</th>
<th>Ampicillin %I</th>
<th>Ampicillin %R</th>
<th>Cefazolin %R</th>
<th>Ceftriaxone %NS</th>
<th>Ciprofloxacin %NS</th>
<th>Gentamicin %R</th>
<th>Meropenem %NS</th>
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### Klebsiella species

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<th>Ciprofloxacin %NS</th>
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<td>5.0</td>
<td>2.8</td>
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Mainly driven by IMP-4 carbapenemase in Enterobacter
May 2016: retrieval from an overseas hospital

- Severe burns – day 4 of admission (under contact precautions from admission)

Polymicrobial bloodstream infection, including carbapenem-resistant *A. baumannii* (CRAB): susceptible only to colistin (MIC 0.125), tigecycline (MIC=2) and doxycycline (MIC=2)
CRAB
ESBL-K. pneumoniae
Mero-R Pseudomonas
IMP-4 +ve Enterobacter cloacae
• Each circle = one patient
• Size of circle = number of isolates
• Solid line = identical core genome SNP profile
• Arrow = direction of transmission from SNP profile

Diagram courtesy of Leah Roberts
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