Antibiotic Resistance
Mutations or Creations?

How We Squander a Miracle

Ben Harris  Med Lab Scientist  Infection Prevention & Control
Important Dates

Years Ago

• 4.5 Billion Origin of the Earth
• 3.5 Billion Prokaryote Bacteria
• 2.5 Billion Oxygen in Atmosphere
• 1.5 Billion Eukaryote cells with nucleus
  (animal, plant cell precursors)
• 0.5 Billion Cambrian explosion
  multicellular Eukaryote organisms, plants & animals
Human Infections (1)

Used to be mainly **epidemics**: Smallpox, plague, cholera, diphtheria, TB, syphilis, influenza, measles, etc

i.e. **exogenous source** “All Bugs Are Bad”

Public Health, Sanitation, Vaccinations have largely contained or eliminated these
`All Bugs are Bad`

Deadliest pandemics including:

- 14th-century Black Death 75 to 200 million plague deaths in Europe
- 1492 Post Colombus South America 37 million population was reduced by 90%
- 1900-1977 smallpox deaths 300-500 million
- 1918–1919 Spanish influenza pandemic at least 50 to 100 million deaths
- ongoing HIV/AIDS pandemic, more than 35 million deaths
Emerging Infectious Diseases
‘All Bugs are Bad’

335 infectious diseases emerged globally in humans between 1940 and 2004, nearly two-thirds originated in wildlife.

Infectious Diseases cause nearly 1 in 5 deaths worldwide.
Pre-vaccine era estimated annual morbidity in the U.S.

% Decrease

Diphtheria: 100%
H. Influenza: 99%
Hepatitis A: 91%
Hepatitis B: 83%
Measles: 99%
Mumps: 99%
Pertussis: 93%
Pneumococcal Disease: 74%
Polio: 100%
Rubella: 99%
Congenital Rubella: 99%
Smallpox: 100%
Tetanus: 98%
Varicella: 89%

Most recent reports of cases in the U.S.

- Diphtheria: 0 cases
- H. Influenza: 243 cases
- Hepatitis A: 11,049 cases
- Hepatitis B: 11,269 cases
- Measles: 61 cases
- Mumps: 982 cases
- Pertussis: 13,506 cases
- Pneumococcal Disease: 4,167 cases
- Polio: 0 cases
- Rubella: 4 cases
- Congenital Rubella: 1 case
- Smallpox: 0 cases
- Tetanus: 14 cases
- Varicella: 449,363 cases
Human Infections (2)

Now mainly

Emerge from our own microbiome

i.e. endogenous source

Who, me?

No way!
“…. the microbes are educated to resist penicillin ...
the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism

I hope this evil can be averted ”

-Sir Alexander Fleming, June 1945
Antibiotic Resistance Sharing

HUMANS

Hospital  Community

Rest  Homes
300 antibiotic free chickens in 6 cages.
Barn Chickens Fed Tetracycline

- 300 antibiotic free chickens in cages
- Tetracycline feed additive in 2 cages at one end of barn only
- Farming family of 11 (2 adults + 9)
- Gut flora: E. coli, P. mirabilis, enterococci
  + Kleb. pneumoniae, Ps. aeruginosa, Acinetobacter
Chickens Fed Tetracycline

Within one week most chicken intestinal flora resistant to tetracycline

(E coli, Pr mirabilis, enterococci)
Chickens Fed Tetracycline (contd)

After **Tetra** use for $\geq 10$ weeks in chickens

$>50\%$ E coli **also resistant to**

- Streptomycin
- Ampicillin
- Carbenicillin
- Sulphonamides
Chickens Fed Tetracycline

Farm workers then developed increased intestinal resistance

Within six months 31.3% weekly faecal samples from farm dwellers had >80% tetracycline resistant bacteria
Key Point

Ongoing use of a **single** antibiotic selects resistance for **multiple** structurally unrelated ABs via linkage genes, plasmids, transposons
Antibiotic Dispersion Effect in Populations of People or Animals
Antibiotic Dispersion Effect in Populations of People or Animals
Emerging Antibiotic Resistance

Worldwide Antibiotic Usage

20% Human

80% Agriculture
Horticulture
Aquaculture

100% Tx

80% Increase growth
(i.e. profit)
Prophylaxis
‘Then we eat the resistance genes’

80% Community

20% Hospital

20% Tx
NZ non medical AB use

2009-2011

Horticulture/Agriculture use ↓ 19%

From 70,343 kg
to 57,043 kg !

But ↑ macrolides
↑ aminoglycosides
↑ cephalosporins including 3rd generation cephalosporins ↑ 26%

Sub therapeutic use to be phased out by 2030 !
NZ Antibiotic Use 2012

Assoc Prof Mark Thomas, University of Auckland

Annually:

- 180 AB courses per 100 children <5y !!!
- 60 AB courses per 100 25-29yrs old

the lowest prescribing rate age group! !
IBD & Number Antibiotic courses in children correlation

TROUBLING CORRELATION
The risk of inflammatory bowel diseases in children rises with the number of courses of antibiotics taken.

<table>
<thead>
<tr>
<th>Number of courses</th>
<th>Rate ratio (relative to 0 courses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-2</td>
<td>1.5</td>
</tr>
<tr>
<td>3-4</td>
<td>2.0</td>
</tr>
<tr>
<td>5-6</td>
<td>2.5</td>
</tr>
<tr>
<td>7+</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Dosed up: could excessive prescription of antibiotics be hampering children’s ability to fight disease?

Stop the killing of beneficial bacteria
Aust & NZ
Non Human Antibiotic Use

Aust
• 500 tons for animal production (in 1999)
• 300 tons human therapeutic

NZ
• 56 tons for animal production (in 2009)

+ Horticulture
+ Aquaculture
Increasing Frequency of Resistance

Chart 1: Resistant Strains Spread Rapidly

MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = Vancomycin-resistant *enterococci*
FQR = Fluoroquinolone-resistant *Pseudomonas aeruginosa*

*Source: Centers for Disease Control and Prevention*
**E. coli in Midstream Urine**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>- resistant</td>
</tr>
<tr>
<td>Augmentin</td>
<td>- resistant</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>- intermediate</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>- resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>- resistant</td>
</tr>
<tr>
<td>Co-Trimoxazole</td>
<td>- resistant</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>- resistant</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>- resistant</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>- intermediate</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>- resistant</td>
</tr>
<tr>
<td>Imipenem</td>
<td>- sensitive BUT how much longer ?</td>
</tr>
</tbody>
</table>
Post Antibiotic Signs - CRE

And one only of the carbapenem groups (New Delhi metallo-beta lactamase 1):

http://eurosurveillance.org/ViewArticle.aspx?ArticleId=20809

Note India 52.3%

Figure 3
The worldwide distribution of New Delhi Metallo-beta-lactamase-1-producing bacteria 1 December 2009–31 December 2012 (n=950)

A. Worldwide distribution of autochthonous published isolates carrying the \textit{bla}_{NDM-1} gene
And carbapenemase resistance in Acinetobacter species, usually more ICU associated infections:

Figure 7. Occurrence of carbapenem-resistant *A. baumannii* in European countries based on self-assessment by the national experts, March 2013

The stage designations for CRAb should be taken with caution for all 38 participating countries. Most NEs highlighted that the exact epidemiology of CRAb remains uncertain in their country, because at the time of the survey, surveillance and reporting of
Only 2.8% were ESBL positive on screening pre travel, but 69.4% post travel, 86.6% ESBL positive post travel to India. A particular risk factor was eating ice cream or pastry (Odds Ratio increased 3.90)

<table>
<thead>
<tr>
<th>Table 4 Prospective studies on travel-associated colonization with ESBL-producing Enterobacteriaceae – rates and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travellers (n) overall</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Current study</td>
</tr>
<tr>
<td>Tängden et al. [8]</td>
</tr>
<tr>
<td>Kennedy et al. [9]</td>
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<tr>
<td>Weisenberg et al. [10]</td>
</tr>
<tr>
<td>Paltansing et al. [11]</td>
</tr>
<tr>
<td>Östholm-Balkhed et al. [12]</td>
</tr>
</tbody>
</table>

*Risk factors: Travel Destination, Length of Stay, Visiting Friends and Relatives, Consumption of Ice Cream & Pastry, Travelling to India, Gastroenteritis during Trip, Antibiotics while Travelling, not done, Travelling to South and East Asia, Travelling to Indian subcontinent, Asia, Africa north of equator.
500 People with skin infection endogenous, from themselves
5% of 500 Staph aureus infection MRSA positive, which ones ???
5% MRSA + and 5% ESBL + of 500 People
3 of this 500 have swab taken should the MRSA be isolated? Benefits vs Risks of isolating??
MDRO Approach
Silo or Horizontal Required?

Staph. aureus  E. coli  Klebsiella  Enterococcus

- Subset MRSA
- Subset ESBL, Carba
- Subset ESBL, Carba
- Subset VRE
Chlorhexidine Exposure Selects Antibiotic Resistance (MIC’s)


<table>
<thead>
<tr>
<th>Hours Drying with Chlorhexidine</th>
<th>AMP</th>
<th>CTX</th>
<th>VAN</th>
<th>GEN</th>
<th>CIP</th>
<th>CEF</th>
<th>TET</th>
<th>OXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>control (no exposure)</td>
<td>0.06</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
<td>0.25</td>
<td>4</td>
<td>0.5</td>
<td>0.12</td>
</tr>
<tr>
<td>2</td>
<td>0.06</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.25</td>
<td>1</td>
<td>0.25</td>
<td>0.12</td>
</tr>
<tr>
<td>24</td>
<td>0.002</td>
<td>1</td>
<td>0.002</td>
<td>0.25</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>48</td>
<td>128</td>
<td>32</td>
<td>&gt;128</td>
<td>2</td>
<td>2</td>
<td>64</td>
<td>1</td>
<td>128</td>
</tr>
</tbody>
</table>

MSSA (susceptible *Staph. aureus*)
Chlorhexidine Exposure Selects Antibiotic Resistance (MIC’s)


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<th>VAN</th>
<th>GEN</th>
<th>CIP</th>
<th>CEF</th>
<th>TET</th>
<th>OXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA (EMRSA 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (no exposure)</td>
<td>&gt;128</td>
<td>8</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>&gt;128</td>
<td>8</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>8</td>
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<tr>
<td>24</td>
<td>&gt;128</td>
<td>8</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>&gt;128</td>
<td>16</td>
<td>128</td>
<td>2</td>
<td>2</td>
<td>64</td>
<td>2</td>
<td>128</td>
</tr>
</tbody>
</table>
Antibiotic usage/resistance correlation

Antibiotic use and AMR from 1990–2000 in selected countries

PDD: Defined Daily Doses
Total antibiotic use in outpatients versus prevalence of penicillin-nonsusceptible Streptococcus pneumoniae in 20 industrialized countries.

New Antibiotics each 5 years
1983-2011
Lifespan of Each Antibiotic

### Antibiotic Categories
- **β-lactams**
  - Penicillin
  - Methicillin
  - Ampicillin
  - Augmentin
- **Amphenicols**
  - Chloramphenicol
- **Tetracyclines**
  - Tetracycline
- **Aminoglycosides**
  - Streptomycin
  - Kanamycin
- **Macrolides**
  - Erythromycin
- **Glycopeptides**
  - Vancomycin
- **Quinolones**
  - Nalidixic acid
  - Norfloxacin
- **Streptogramins**
  - Synercid
- **Oxazolidinones**
  - Linezolid
- **Lipopeptides**
  - Daptomycin

### Lifespan
- 8 years average

### Years from Introduction to Clinical Resistance

**Source:** Future Microbiol © 2012 Future Medicine Ltd
Seeing the Future

Resistant bacteria on the rise

Antibiotics on the fall
Tragedy of the Commons

Refers to depletion and collapse of a common but limited resource when individuals act selfishly to maximise personal gains.
Imagine a World Without Antibiotics

- You know how you are FEELING better than anyone else.
- Your medical practitioner knows what the CAUSE is, bacterial, viral or other and what to treat you with better than anyone else.

Listen, do not ask for or demand antibiotics – they may well cause you and others significant harm.

<table>
<thead>
<tr>
<th>Illness</th>
<th>Usual Cause</th>
<th>Antibiotic Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold/Runny Nose</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>Bronchitis/Chest Cold</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>Whooping Cough</td>
<td>✓</td>
<td>Yes</td>
</tr>
<tr>
<td>Flu</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>Strep Throat</td>
<td>✓</td>
<td>Yes</td>
</tr>
<tr>
<td>Sore Throat (except strep)</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>Fluid in the Middle Ear</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>✓</td>
<td>Yes</td>
</tr>
</tbody>
</table>

http://www.cdc.gov/getsmart/community/for-patients/common-illnesses/
Simply

• Bacteria do not become resistant

we selectively breed resistance with every antimicrobial use

• Then we share our large bacterial microbiome mainly by our hands, coughing & environment
What’s the Microbiome?
Microbiome
Our Microbial Garden

Emerging realisation of importance of resident microbes to our health and well-being

particularly with respect to roles played in:

- our immune system
- food digestion
- acting as first line of defense against ‘pathogens’

Many diseases are the result of disturbed microbiomes - ‘dysbiosis’
Sharing my microbiome

This vast microbiome is routinely shared with others + animals and environment
Inverse Relation Incidence (1950-2000)
Infectious Diseases ↓ and Immune Disorders ↑

Microbiome Lifetime Dynamics
Influences on microbiome during infant development

Diet, Womb, Mode of delivery, Gestational age, Genetics, Environment, Antibiotics → Microbiome → Healthy development or Disease

Efrem S. Lim et al
http://www.cell.com/trends/microbiology/fulltext/S0966-842X(16)30064-6
# Caesarian Delivery vs Vaginal Delivery

## Associated Childhood Diseases


<table>
<thead>
<tr>
<th>Caesarian Delivery</th>
<th>Odds Ratio 95% CI versus vaginal delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic Rhinitis</strong></td>
<td></td>
</tr>
<tr>
<td>All Caesarians</td>
<td>1.37 (1.14 – 1.63)</td>
</tr>
<tr>
<td>Repeat Caesarians only no Rupt.Mem</td>
<td>1.78 (1.34 - 2.37)</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
</tr>
<tr>
<td>All Caesarians</td>
<td>1.24 (1.01 – 1.53)</td>
</tr>
<tr>
<td>Female</td>
<td>1.53 (1.10 – 2.10)</td>
</tr>
<tr>
<td>Female &amp; Repeat Caesarians no RM</td>
<td>1.83 (1.13 – 2.97)</td>
</tr>
<tr>
<td>Caesarian Delivery</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Coeliac Disease</td>
<td>1.80</td>
</tr>
<tr>
<td>Diabetes Mellitus (Type 1)</td>
<td>1.19</td>
</tr>
<tr>
<td>Gastroenteritis requiring hospitalisation</td>
<td>1.31</td>
</tr>
<tr>
<td>Gastroenteritis &amp; Asthma</td>
<td>1.74</td>
</tr>
</tbody>
</table>
Staph aureus infection
single species ‘microbes are bad’
eliminate them
Newer Concepts in SSI

- **Blood Sugar** regulation important
- **Body Temperature** regulation intra op outside 1-1.5°C core increases SSI x2
- **Oxygenation** - ↑ periop inspiration ↓ SSI
Future Strategies

• **Surveillance** ↑
  - ID epidemics by common & uncommon isolates
  - Correct AB prophylaxis (AB, timing, dose, duration)
  - Document costs, risk factors, readmission rates
  - Monitor post disch infections, $2^0$ consequences
  - Typing all isolates (?? + staff) for cross infection

• **Preventing Emerging Resistance**
  - AB necessary ?, choice, route, time, evidence??
  - Hand + Environmental Hygiene
Wound Infection Risk Balance

Relative Infection Risk:
- β Strep (grp A)
- Staph. aureus
- Pseudomonas
- Coliforms
- Anaerobes
- Skin commensals

≥ 10^5 bacteria/gram

Host Immunity:
- Tissue perfusion
- WBC
- Oxygen

Wound depth, site, type contamination
Sweet Tooth Diet Emerged
Re/De mineralization Vs. pH

- pH Drop after a diet
- Reduction of Demineralization area with Fluoride inclusion
- Remineralization Area
  - pH Threshold without Fluoride
  - pH Threshold with Fluoride
- Demineralization Area
World Infection Trends (1)

“All Microbes are Bad”

‘Old’ diseases return or increase from endemic areas

e.g. malaria, measles, dengue, foodborne illnesses
World Infection Trends (2)  
"All Microbes are Bad"

‘New’ diseases keep emerging  
e.g. HIV/AIDS, SARS,  
MERS, Ebola, Zika

H5N1 (bird flu), H7, H9

2009 H1N1 (swine)
World Infection Trends (3)
Antibiotic Use Creates These:
New forms of old diseases - endogenous

MDRO’s including:
- MRSA
- ESBL
- VRE
- C. difficile
- CRE carbapenemases

From our own shared microbiome
World Infection Trends
Summary

Today’s emerging infectious diseases become

tomorrows endemics
Bug Sharing
Our Actions Now Are Our Future
ben.harris@sclabs.co.nz

www.canterburyscl.co.nz
Key Points

Every antimicrobial use either

- Selects for resistant strains already present e.g. in low numbers and/or
- Induces microbial genetic memory resistance which was not apparent or expressed prior

these resistances are then cumulatively shared by all in any healthcare facility, community, region, country, ultimately worldwide (tourism, food, immigration, etc)

“My Bugs are Your Bugs”
Key Points

• Any **individual** known to be a carrier of a resistant microbe (MDRO e.g. MRSA, ESBL) **is not the problem** but an **indicator** of a much **much larger issue** (however if that individual happens to develop an infection there will be fewer treatment options for them)

• We catch most infections from ourselves i.e. endogenous e.g. *Staph aureus*

• Routine community swab isolates
  - **South Island** 5% all Staph MRSA positive
  - **Wellington community** 8% MRSA positive
  - **AKL community** 13% MRSA positive
  - **SE Asia community** 24% MRSA positive
Key Points

Any individual that happens to be a carrier of MDRO (e.g. MRSA, ESBL, CRE) spontaneously loses that carriage in 1-12 months 90% of the time (often 1-3 months) so long as they do not use any antimicrobials (e.g. antibiotics or antiseptic body washes) within that time, which both reselect for and/or induce antibiotic resistances.

Anyone that is or has been on recent past antimicrobials also has less normal flora to help hold back unwanted strains.
Key Points

• Antibiotic resistance is a very real shared emerging concern that we are creating

• The damage every antibiotic use does to our normal vast microbial microbiome which is integral for many health parameters (including obesity, moods, depression, autoimmune illnesses – Crohns, IBD, MS, arthritis, etc) may well be an even larger medium term outcome concern