Antimicrobial Resistance: The Global and Regional Situation
Outline of Presentation

- Frighten everyone
- Convince everyone that action is possible
  - Individually
  - Professionally
  - Institutionally
  - Nationally
  - Globally

Case Presentations

- 1942 – New Haven, Connecticut year old woman with Streptococcal sepsis – treated with tiny amounts of ‘new’ drug – Penicillin – survived and lived to age 90

- 2008 – San Francisco – 70 year old male with Enterococcal endocarditis – resistant to all antibiotics – patient died
  
  Arias, Murphy – NEJM – Jan 29, 2009
Scope of the Problem

- Global
  - Migratory
- Institutions
- Community

Documented Examples of Drug Resistance by Disease
Global distribution of community-associated meticillin-resistant *Staphylococcus aureus* (CA-MRSA) by multilocus sequence type (ST)

Prevalence of drug-resistant strains of *Shigella*, selected countries in Latin America
AMR surveillance in Europe: proportion of *Escherichia coli* invasive isolates with resistance to fluoroquinolones in 2009


---

Distribution of NDM-1-producing *Enterobacteriaceae* strains in Bangladesh, Indian, Pakistan, and the UK
WHO GASP Regional Report
WPR/SEAR 2009

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the
WHO Western Pacific and South East Asian Regions, 2009.
Communicable Diseases Intelligence 2011;35(1):1-6

- Gonococcal Antimicrobial Surveillance Programme (GASP) since 1992
- Long term surveillance of AMR in *Neisseria gonorrhoeae*
- Lab send AMR data to WHO collaborating centre for STD, Sydney –
data analysis and dissemination
- 8,704 *N. gonorrhoeae* examined for their susceptibility to one or more
  antibiotics used for gonorrhoeae treatment by EQAS controlled
  methods
- 21 countries and jurisdictions - 17 WHO WPR and 4 WHO SEAR
countries

N. *gonorrhoea* antimicrobial resistance pattern in
Western Pacific Region, 2009

- Penicillin Resistance
  - High rate: Brunei (71.9%), Cambodia (100%), Korea (55.7%), Mongolia
    (53.3%), PNG (63%), Philippines (82.5%), Singapore (67.5%)
  - Medium rate: Australia (35.6%), Hong Kong (50.9%), Japan (24.7%), Malaysia
    (50%), New Zealand (24.4%), Viet Nam (38.8%)
  - Low rate: Fiji (8.3%), New Caledonia (0), Tonga (0)

- Quinolone Resistance
  - High rate (> 80%): Brunei, China, the Republic of Korea, Malaysia, Mongolia,
    Philippines, Singapore and Viet Nam
  - High rate (> 70%): Cambodia, Hong Kong, Japan, and (> 45%) Australia
  - Low rate: New Caledonia (1.3%), New Zealand (35); Fiji (0.1%)

- Third Generation Cephalosporins
  - Decreased susceptibility reported on 6 countries on 4,512 strains of
    *N. gonorrhoea*
  - Australia (2%), China (36.9%), Korea (47.5%), Mongolia (34.6%), Tonga (25%)
Drug Resistant TB?

- **Mono-resistant TB**
  - Resistant to 1 anti-TB drug

- **Poly-resistant TB**
  - Resistant to more than 1 anti-TB drugs

- **Multidrug-resistant TB (MDR-TB)**
  - Resistant at least to Isoniazid and rifampicin

- **Extensively drug-resistant TB (XDR-TB)**
  - MDR-TB + resistant to any
    - fluoroquinilones
    - 2nd-line injectable drugs
      - (amikacin, kanamycin, capreomycin)

57 countries have reported at least one XDR-TB case by June 17, 2010

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2009. All rights reserved
27 countries (red) account for 85%+ of the MDR cases in the world

TB disease burden in Asia-Pacific

- **Estimate number of TB (all forms)**: 1.9 million (109 per 100,000)
  - 260,000 (15 per 100,000)
- **Estimated number of deaths due to TB**: 120,000
- **Multidrug-resistant TB**: 45,000
- **HIV-associated TB**:

Malaria

- Chloroquine resistance first appeared in SE Asia – 30-40 years ago and is now almost universal throughout the world

- Artemisinin resistance – may be occurring on the border of Thailand-Cambodia again – but this time – not many weapons in reserve

Consequences

- Mortality/Morbidity

- Financial

<table>
<thead>
<tr>
<th>Time period</th>
<th>DS-TB cases (percent)</th>
<th>MDR-TB (percent)</th>
<th>XDR-TB (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0–5</td>
<td>9</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Month 6–11</td>
<td>10</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Month 12–23</td>
<td>10</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Month 24–35</td>
<td>11</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Month 36+</td>
<td>11</td>
<td>26</td>
<td>35</td>
</tr>
</tbody>
</table>

*Limited to cases alive at diagnosis, initially treated with one or more TB drugs, with both start and end dates reported. The percentage is cumulative mortality.

Source: Shah et al. (2009).

Comparison of first- and second-line anti-TB drug prices

<table>
<thead>
<tr>
<th>Average first-line price (US$)</th>
<th>Average second-line price (US$)</th>
<th>Difference between second-line and first-line prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>$20/course</td>
<td>$3,500/course</td>
<td>175-fold</td>
</tr>
</tbody>
</table>

Source: Data for 2009 Global Drug Facility supplies, Stop TB Partnership.
### Comparison of sample first- and second-line antibiotic procurement prices in Uganda

<table>
<thead>
<tr>
<th>Average first-line price (USS)</th>
<th>Average second-line price (USS)</th>
<th>Difference between second-line and first-line prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0.14 per tab-cap (siprobactin 500 mg.)</td>
<td>$0.26 per tab-cap (amoxicillin/ clavulanic acid 250 mg.)</td>
<td>2- to 80-fold</td>
</tr>
<tr>
<td>$0.01 per tab-cap (penicillin v. 250 mg.)</td>
<td>$0.62 per vial (ceftriaxone 1 g.)</td>
<td></td>
</tr>
</tbody>
</table>

Note: The final price to the patient is composed of the manufacturer’s selling price plus taxes, tariffs, markups, and other supply chain costs. See [http://www.haiweb.org/medicines/presforc](http://www.haiweb.org/medicines/presforc) for discussion of what retail medicine prices include.


---

### Comparison of earlier-generation and current antimalarial prices

<table>
<thead>
<tr>
<th>Average early-generation and monotherapy prices (USS)</th>
<th>Average recommended treatment price (USS)</th>
<th>Difference between second-line and first-line prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0.05–$0.25/adult course (chloroquine/SP)</td>
<td>Private: $5–$10/adult course (ACT) Donor-funded: $0.20–$0.50</td>
<td>Private: 3- to 500-fold Public: rough equivalence</td>
</tr>
<tr>
<td>$1.50/adult course for artemisinin monotherapy</td>
<td>in private settings, free or $0.05 in public settings</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of first- and second-line ARV prices

<table>
<thead>
<tr>
<th>Average first-line price (USD)</th>
<th>Average second-line price (USD)</th>
<th>Difference between second-line and first-line prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>$90/patient/year</td>
<td>$1,214/patient/year</td>
<td>Average: 14-fold</td>
</tr>
<tr>
<td>Third-party negotiated: $425/patient/year</td>
<td>Donor-negotiated: 5-fold</td>
<td></td>
</tr>
</tbody>
</table>

Note: Median prices of first- and second-line highly active antiretroviral therapy in low-income countries in 2007. Higher prices prevail in middle-income countries. Lower price shown is available in a defined set of developing countries through agreements with the Clinton Health Access Initiative.

Alternatives to first line are expensive

- TB – up to 195 fold
- Malaria – 3 fold to 500 fold
- Common antibiotics – 2 fold to 60 fold
- ARVs – 5 fold to 14 fold
Causes

• Darwin – survival of the fittest – this is an ongoing battle and there is no certainty that humans will win out over microbes

but

• Human behaviour has hastened the demise of effective antimicrobial treatment

Human activities that exacerbate resistance

Selective pressure

• Inappropriate antimicrobial use in chemotherapy
• Use of a narrow repertoire of antimicrobials on most patients
• Antimicrobial misuse and abuse in human beings
• Agricultural antimicrobial use and misuse
• Use of poor quality antimicrobials

Dissemination of resistant organisms

• Inadequate infection control in health-care institutions
• Shortfalls in hygiene, sanitation, and public health
• Lack of surveillance and consequent late detection
Where antibiotics are used

<table>
<thead>
<tr>
<th>Where antibiotics are used</th>
<th>Types of use</th>
<th>Questionable use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human use (50%)</td>
<td>20% Hospital</td>
<td>20-50% Unnecessary</td>
</tr>
<tr>
<td></td>
<td>80% Community</td>
<td></td>
</tr>
<tr>
<td>Agricultural use (50%)</td>
<td>20% Therapeutic</td>
<td>40-80% Highly questionable</td>
</tr>
<tr>
<td></td>
<td>80% Prophylactic/growth promotion</td>
<td></td>
</tr>
</tbody>
</table>


Inappropriate/Substandard Use

- 68% of Americans with URI seeing a doctor are given antibiotics - CDC USA estimates that 80% of these are prescribed inappropriately

- One study in SE Asia – 38% of antimalarials were fake or substandard – the same is true of other antibiotics
Antibiotic Use Increases Resistance

- Use of antibiotics previously increases the risk of infection with a resistant organism four fold
- The increased risk of resistant infection after antibiotic treatment persists for at least one year

Relationship between penicillin resistant *S. pneumoniae* and total antibiotic use by country

Note: ddd is defined daily dose.
Source: Albrich, Mennet, and Harbarth (2004)
HIVDR surveillance and Prevention in WPR Countries

- Surveillance of transmitted HIVDR among recently infected individuals:
  - 10 paper reviewed: Cambodia 1; China 7; Viet Nam: 2
  - All transmitted HIVDR low or <10%

- Monitoring of HIVDR emerging in populations on ART:
  - 11 studies/surveys reviewed: Cambodia: 2; China: 9
  - Satisfactory viral suppression in areas with good adherence support;
  - High % of treatment failure if poor adherence, and high HIVDR among the treatment failure in 4 studies

Quinolone-resistant MDR Salmonella Typhimurium
DT104 United Kingdom, 1992-1997

- November 93 – Enrofloxacin licensed for animal use

- Percent of isolates:
  - 92: 0
  - 93: 0
  - 94: 0
  - 95: 0
  - 96: 0
  - 97: 0

- Chickens, Cattle, Pigs, Humans
Consumption of antimicrobial agents for growth promotion and occurrence of antimicrobial resistance in *Enterococcus faecium* and *E. faecalis* isolated from Danish pigs or broilers from 1995 to 2003

**Erythromycin resistance**

<table>
<thead>
<tr>
<th>% resistance</th>
<th>Consumption (tons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>100</td>
</tr>
<tr>
<td>1996</td>
<td>80</td>
</tr>
<tr>
<td>1997</td>
<td>60</td>
</tr>
<tr>
<td>1998</td>
<td>40</td>
</tr>
<tr>
<td>1999</td>
<td>20</td>
</tr>
<tr>
<td>2000</td>
<td>10</td>
</tr>
<tr>
<td>2001</td>
<td>0</td>
</tr>
<tr>
<td>2002</td>
<td>0</td>
</tr>
<tr>
<td>2003</td>
<td>0</td>
</tr>
</tbody>
</table>

- **E. faecium** from pigs
- **E. faecalis** from pigs
- Tylosin use

Trends in the prevalence of fluoroquinolone resistance in clinical isolates of *Campylobacter jejuni*, in Spain, examined for resistance from 1987 to 1996

**Fluoroquinolones licensed for poultry and livestock in 1990**

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>(n = 100)</td>
</tr>
<tr>
<td>1988</td>
<td>(n = 198)</td>
</tr>
<tr>
<td>1989</td>
<td>(n = 408)</td>
</tr>
<tr>
<td>1990</td>
<td>(n = 344)</td>
</tr>
<tr>
<td>1991</td>
<td>(n = 569)</td>
</tr>
<tr>
<td>1992</td>
<td>(n = 738)</td>
</tr>
<tr>
<td>1993</td>
<td>(n = 734)</td>
</tr>
<tr>
<td>1994</td>
<td>(n = 526)</td>
</tr>
<tr>
<td>1995</td>
<td>(n = 535)</td>
</tr>
<tr>
<td>1996</td>
<td>(n = 605)</td>
</tr>
</tbody>
</table>
“It is difficult to get a man to understand something when his salary depends on not understanding it.” - Upton Sinclair

Can we just get a new generation of drugs?

• Probably not – very few in the pipeline

• Big pharma research focus has moved away from antibiotics – the diseases of the rich countries get preference
Probabilities of success in the drug development pipeline

Estimated cost and duration of phase

- Discovery: ~$380 million, 4 years
- Preclinical: 1–2 years
- Phase I: 2–3 years
- Phase II: 2–3 years
- Phase III: 1–1.5 years
- New drug application approval

Number of candidates

- 100
- 10
- 7
- 4
- 2
- 1

Note: II and III refer to Phase II and Phase III stages of product development.

Source: Adams and Bransner (2003); DiMasi, Hansen, and Grabowski (2003); Lowell and Earl (2009).

What can be done?
Individuals

- Don’t demand antibiotics

- Infection control – good hygiene – household and personal

- Infection control in community settings – e.g. wrestlers
(A) Antimicrobial resistance patterns among *S. typhi* isolates from children presenting at the Aga Khan University Hospital, Pakistan (1988–2001)

(B) Antimicrobial sales data for Karachi (units/10,000 population) in the same period


Box plots indicate range of infection prevalence and cumulative incidence for first and third quartile. Medians are indicated as a black line. Whiskers indicate lower and upper end of distribution. Infection proportions are shown as infections per 100 patients (Inf/100 pts) and infected patients per 100 patients (Inf pts/100 pts).