Surveillance of Antibiotic Resistance

Prof. Dr. Erlangga Yusuf (and Prof. Dr. Herman Goossens)
Laboratory of Medical Microbiology UZA
ASCID Symposium, November 15th, 2016
In the world, at this moment

No. of patients infected with antibiotic-resistant bacteria: 1,010,611,651
Outline

• The succes story of antibiotics

• Antibiotic consumption, development and spread of resistance

• Scary numbers and the idea of one health

• Surveillance as one of the ways to fight back
Antibiotic success story and when all good things come to an end
The success story of antibiotics (1)

- Louis Pasteur hypothesis bacteria could kill other bacteria, 1877

- Sir Alexander Fleming discoveries of penicillin 1928

- Sir Alexander Fleming Nobel Prize 1945

- Selman Waksman, Nobel Prize 1952
The success story of antibiotics (2)

- Morbidity and mortality rate ↓

- Modern medicine
  - Immunodeficient and immunocompromised
    - Premature infant care
    - Organ transplants
  - Intensive care
  - Complicated surgeries
But every good things come to an end

- Antibiotic resistance as predicted by Fleming

ALEXANDER FLEMING

Penicillin

Nobel Lecture, December 11, 1945

The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore
<table>
<thead>
<tr>
<th>Antibiotic Resistance Identified</th>
<th>Antibiotic Introduced</th>
</tr>
</thead>
<tbody>
<tr>
<td>penicillin-R <em>Staphylococcus</em></td>
<td>1940</td>
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<tr>
<td></td>
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<tr>
<td>tetracycline-R <em>Shigella</em></td>
<td>1959</td>
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<tr>
<td>methicillin-R <em>Staphylococcus</em></td>
<td>1962</td>
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<td></td>
<td></td>
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<tr>
<td>ceftazidime-R <em>Enterobacteriaceae</em></td>
<td>1987</td>
</tr>
<tr>
<td>vancomycin-R <em>Enterococcus</em></td>
<td>1988</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td>ceftriaxone-R <em>Neisseria gonorrhoeae</em></td>
<td>2009</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
Race that you hardly can win
Antibiotic consumption, development and spread of resistance
Antibiotics mechanisms of action

Lewis, et al. Nature Reviews Microbiology 10, 266-278
Mechanisms of antibiotic resistance

Arias, et al. Nature Reviews Microbiology 10, 266-278
Antibiotic use and resistance

1. Lots of germs. A few are drug resistant.
2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3. The drug-resistant bacteria are now allowed to grow and take over.
4. Some bacteria give their drug-resistance to other bacteria, causing more problems.
Horizontal gene transfer

Furuya, et al. Nature Reviews Microbiology 4, 36-45
Clones, plasmids and genes, CPE as example (1)

• **Clonal spread:** *K. pneumoniae* ST258 with KPC gene


• **Plasmid spread:** IncL/M plasmid with OXA-48 gene
Gene and plasmid spread: NDM-1 carbapenemase gene on numerous broad-range plasmids.
Scary numbers and the idea of one health
Antibiotic consumption systemic use community

ECDC, 2014
Antibiotic use also in animal

European sales of antimicrobial agents for food-producing animals

Sales in milligrams per kilogram of meat stock biomass, 2011, including horses

- Antibiotics are used systematically to combat diseases in factory farms
- Bacteria "defend" themselves by mutating, thus become resistant to the antibiotics
- Resistant bacteria can enter the human body when people eat meat
- Antibiotics used to treat humans are ineffective against the resistant bacteria

Intimate relation human - animal
One health

Centers for Disease Control and Prevention
Antibiotic resistance, somewhere in India

Confidential data, not for sharing
In Europe

Figure 3.1. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2014

- Green: < 1%
- Light green: 1% to < 5%
- Yellow: 5% to < 10%
- Orange: 10% to < 25%
- Red: 25% to < 50%
- Dark red: >= 50%
- Gray: No data reported or less than 10 isolates
- Light gray: Not included

Non-visible countries:
- Liechtenstein
- Luxembourg
- Malta
Deaths attributable to antimicrobial resistance every year by 2050

- Europe: 390,000
- Asia: 4,730,000
- North America: 317,000
- Latin America: 392,000
- Africa: 4,150,000
- Oceania: 22,000

Source: Review on Antimicrobial Resistance 2014
High in the agenda (1)

David Cameron calls for action on antibiotic resistance
2 July 2014 Last updated at 02.14 BST

Prime Minister David Cameron has called for global action to tackle the growing threat of resistance to antibiotics.
High in the agenda (2)

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

Obama battles 'superbugs' with national plan
By Sandee LaMotte, CNN
Updated 5:11 PM ET, Fri March 27, 2015

President Barack Obama announces a five-year plan to fight antibiotic-resistant bacteria.
Fighting back and surveillance
Fighting back: four core actions according to CDC

- Preventing infections and spread of resistance
  - Handwashing
  - Safe food preparation

- Tracking resistance pattern
  - Data on antibiotic resistance
  - Developing specific strategies to prevent infection

- Antibiotic stewardship
  - Cut down antibiotic use

- Developing new drugs and diagnostic tests
Gram positive and negative
Meticillin Resistant *Staphyloccous aureus* (MRSA)

- Gram-positive bacteria
- Skin, nose in many people
- Can cause:
  - Skin and soft tissue infection
  - Surgical site infection
  - Prosthetic joint infection
  - Endocarditis
  - Osteomyelitis
# Meticillin Resistant *Staphylococcus aureus* (MRSA)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HA-MRSA</th>
<th>CA-MRSA</th>
<th>LA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panton-Valentine leukocidin</td>
<td>Absent</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>SCCmec type</td>
<td>Large (type I, II, III)</td>
<td>Small (type IV, V)</td>
<td>Type Iva, V, XI, <em>mecC</em></td>
</tr>
<tr>
<td>Typical clones</td>
<td>ST5, ST8, ST22, ST36, ST45, ST228, ST239</td>
<td>ST1, ST5, ST8 (USA300), ST30, ST80, ST59, ST93</td>
<td>CC398, CC9</td>
</tr>
<tr>
<td>Resistance to non-beta-lactam antibiotics</td>
<td>Common</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Site of infections</td>
<td>Bloodstream and other invasive infections</td>
<td>Skin and soft tissue, pneumonia</td>
<td>SSTIs, endocarditis, pneumonia, necrotising fasciitis</td>
</tr>
<tr>
<td>Population affected</td>
<td>Elderly with co-morbidity</td>
<td>Young, previously healthy, athletes, prisoners, soldiers</td>
<td>Close contact with animals</td>
</tr>
<tr>
<td>Transmission</td>
<td>Within healthcare settings</td>
<td>Families, schools, sport teams, prisons, military camps</td>
<td>Pigs, calves, cattle</td>
</tr>
</tbody>
</table>
Global MRSA trends

**FIGURE ES-1**: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014

*Source: CDDEP 2015*
MRSA trend in Belgium, clinical isolates

B. Jans, National Surveillance WIV – ISP. 2014
Explaining success reduction (HA) MRSA

- Nationwide infection control program
- Dedicated and coordinated infection control networks providing training, surveillance & evaluation
- Screening for MRSA carriage
- Also:
  - “Ecosystem-specific” clonal spread of MRSA and absence of Horizontal Gene Transmission?
  - Regression to the mean?
Extended-Spectrum β-lactamases (ESBL’s)

- Gram-negative bacteria

- Resistance to
  - Oxyimino-cephalosporins (cefotaxime, ceftazidime, ceftriaxone, cefuroxime and cefepime)
  - Monobactams (aztreonam)
  - but not the cephemycins (cefoxitin, cefotetan) or carbapenems

- Inhibited by beta- lactamase inhibitors: clavulanic acid, sulbactam, tazobactam
ESBL in Belgium

WIV-ISP, 2015
Carbapenemase-producing bacteria

- ↑ ESBL → ↑ carbapenems antimicrobial drugs of last resort
- Infections are associated with high morbidity and mortality
- Pandemics of certain clones, plasmids and/or genes in humans, animals and environment:
  - Clonal spread: *K. pneumoniae* ST258 with KPC gene
  - Plasmid spread: IncL/M plasmid with OXA-48 gene
  - Gene and plasmid spread: NDM-1 carbapenemase gene on numerous broad-range plasmids
CPE in Belgium, 2012 - 2014

NRC Antibiotica resistente Gram negatieve bacili. 2015
Antibiotic resistance: World on cusp of 'post-antibiotic era'

By James Gallagher
Health editor, BBC News website

19 November 2015 | Health

The world is on the cusp of a "post-antibiotic era", scientists have warned after finding bacteria resistant to drugs used when all other treatments have failed.

They identified bacteria able to shrug off the drug of last resort - colistin - in patients and livestock in China.
Colistin

• 1959, not in human medicine due to nephrotoxicity and neurotoxicity

• To treat diarrhoea in weaning piglets and calves

• Re-introduced in human medicine to treat infections due to CPE
Structure of mcr-1 harbouring plasmids

Liu et al, LID 2016

Malhotra Kumar et al, LID 2016
More information are available…

Countries (n = 30) reporting presence of *mcr-1* in samples of animal, environmental or human origin (data collected till 27 June 2016)

Xavier BB et al. Euro Surveill. 2016;21(27)
Conclusions

• Antibiotic use and development + spreading of resistance

• Surveillance to understand the burden and transmission (global spread, highly transferable genes and plasmids & bacterial clones)

• One health: animals, food, healthcare settings
30 minutes after starting this presentation

No. of patients infected with antibiotic-resistant bacteria: 101,061,651
Thank you!
Evolution of ESBL’s pandemics

- TEM-1 described
- SHV-1 described
- First ESBL (SHV) described
- First CTX-M described
- CTX-M-15 described
- ST131 described

1960 - 2000

- Pandemic with TEM-1-producing *Escherichia coli*

- Hospital outbreaks with ESBL-producing *Klebsiella* spp. (TEM and SHV types)

- Widespread prevalence in Argentina of CTX-M-producing Enterobactericeae
ESBL’s carriage rate in community

## Vancomycin resistant Enterococci (VRE)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>vanA MIC (µg/mL)</th>
<th>vanB MIC (µg/mL)</th>
<th>vanD MIC (µg/mL)</th>
<th>vanE/G MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>64 – 1000</td>
<td>4 – 1000</td>
<td>16 – 64</td>
<td>16</td>
</tr>
<tr>
<td>MIC (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>15 – 512</td>
<td>0.5 &gt; 32</td>
<td>2 – 4</td>
<td>0.5</td>
</tr>
<tr>
<td>MIC (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Species</td>
<td>E. faecium, E. faecalis</td>
<td>E. faecium, E. faecalis</td>
<td>E. faecium, E. faecalis</td>
<td>E. faecalis</td>
</tr>
<tr>
<td>Transferable</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
% of invasive *K. pneumoniae* R to Carbapenems, 2010 and 2013
Draft Political Declaration of the High-level Meeting of the General Assembly on Antimicrobial Resistance

We, Heads of State and Government and representatives of States and Governments, assembled at the United Nations on 21 September 2016, in accordance with resolution 70/183, which decided to hold a high-level meeting in 2016 on antimicrobial resistance;

15. Request the Secretary-General to establish, in consultation with WHO, FAO and OIE, an ad hoc interagency coordination group, co-chaired by the Executive Office of the Secretary General and WHO, drawing, where necessary, on expertise from relevant stakeholders, to provide practical guidance for approaches needed to ensure sustained effective global action to address AMR; and request the Secretary-General to submit a report for consideration by Member States by the 73rd session of the General Assembly on the implementation of this declaration and further developments and recommendations emanating from the ad hoc interagency group, including on options to improve coordination, taking into account the Global Action Plan.