Surveillance of Antibiotic Resistance

Prof. Dr. Erlangga Yusuf (and Prof. Dr. Herman Goossens)_ Laboratory of Medical Microbiology UZA ASCID Symposium, November 15th, 2016

CM 2





In the world, at this moment



No. of patients infected with antibiotic-resistant bacteria:

101,061,651









- 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 sucess 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 sucess story of antibiotics (2)

- Morbidity and mortality rate \downarrow
- Modern medicine
 - Immunodeficient and immunocompromised
 - Premature infant care
 - Organ transplants
 - Intensive care
 - Complicated surgeries





• 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





Race that you hardly can win

ANTIBIOTIC RESIS	STANCE NTIFIED	ANTIBIOTIC INTRODUCED	
penicillin-R Staphylococcus	1940 —		
		1943	penicillin
tetracycline-R Shigella	1959 —	1060	mathicillin
methicillin-R Staphylococcus	1962 —	1900	methicillin
		1972	vancomycin
ceftazidime-R Enterobacteriaceae	1987 —	1985	imipenem and ceftazidime
vancomycin-R Enterococcus	1988		
ceftriaxone-R <i>Neisseria gonorrhoeae</i> PDR-Enterobacteriaceae	2009 — _	2010	ceftaroline
ceftaroline-R Staphylococcus	2011		Ξ.

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Race that you hardly can win







Antibiotic consumption, development and spread of resistance





Antibiotics mechanisms of action



Nature Reviews | Drug Discovery



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







Horizontal gene transfer



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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



Chen, et al. *mBio* 5, e1355; 2014

• Plasmid spread: IncL/M plasmid with OXA-48 gene





Clones, plasmids and genes, CPE as example (2)

Gene and plasmid spread: NDM-1 carbapenemase
gene on numerous broad-range plasmids





Hu, et al. PLoSOne; 2011





Scary numbers and the idea of one health





Antibiotic consumption systemic use community







Antibiotic use also in animal



European sales of antimicrobial agents for food-producing animals

EMA, Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011, Third ESVAC report, 2013.





Intimate relation human - animal







One health





UZA'

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







Deaths prediction

Deaths attributable to antimicrobial resistance every year by 2050



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)







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 news drugs and diagnostic tests





Gram positive and negative









- 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 Staphyloccous aureus (MRSA)

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



Global MRSA trends



FIGURE ES-1¹: 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 succes 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 cephamycins (cefoxitin, cefotetan) or carbapenems
- Inhibited by beta- lactamase inhibitors: clavulanic acid, sulbactam, tazobactam





ESBL in Belgium



Surveillance periods







- ↑ 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





Endemic regions



CPE in Belgium, 2012 - 2014



NRC Antibiotica resistente Gram negatieve bacili. 2015





Last.... perhaps really last resort

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.







- 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)



- 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:

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Thank you!



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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



Woerther et al, Clin Microbiol Rev 2013; 26: 744-58





Vancomycin resistant Enterococci (VRE)

Characteristics	vanA	vanB	vanD	vanE/G
Vancomycin MIC (µg/mL)	64 – 1000	4 – 1000	16 – 64	16
Teicoplanin MIC (µg/mL)	15 – 512	0.5 > 32	2 -4	0,5
Species	E. faecium, E. faecalis	<i>E. faecium,</i> <i>E. faecalis</i>	E. faecium,	E. faecalis
Transferable	Yes	Yes	No	No











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.



