Connecting resistance data in the animal and human sector

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The Antimicrobial Crisis

AMR – Why food-producing animals are a hot spot?

Data connecting AMR in food animals-humans: main concerns

Final Remarks
The Antimicrobial Resistance (AMR) Crisis
The Antimicrobial Resistance (AMR) Crisis

25 000 EU
23 000 USA
700 000
Worldwide

millions?
10 millions Worldwide/ 2050*

The Antimicrobial Resistance (AMR) Crisis

- Reduce efficacy of related AM
- Increase broaden spectrum/recent AM use
- Increase likelihood for infections (e.g. Salmonella)
- Morbidity
- Increased Human healthcare costs*

*1.5 billions euros of healthcare and productivity losses
AMR – Why food-producing animals are a hot spot?

- > 50% in animals
  - USA: up to 80% of total antimicrobial sales

Global quantities for livestock unknown

High amounts of Antimicrobials

Relevant Antibiotics
  - identical or belonging to the same classes of important to humans

Dose Imprecision
  - Antibiotics in Feed additives
  - [Antibiotic] < MIC

Resistome availability

Few exceptions

E.g. Linezolid only humans

Emergence and Amplification of AMR

Grave et al., JAC 2014
AMR Dissemination
More than 50 years of highly used antibiotics

Danger from the Stall
How antibiotic resistant bacteria spread

Antibiotics -> Humans travel
Trade of animals & food

Humans travel
Trade of animals & food

Air, Dust

Waste water, Water

Plants

feed

nourishment

nourishment

Humans infect each other with bacteria

Antibiotics

fecal matter

fecal matter

Graphic Adapted from (Danger from the Stall) withdrawn from the newspaper "Der Spiegel" Original URL: http://www.spiegel.de/international/world/bild-811560-309342.html
Antimicrobial consumption & AMR data

AMR emergence and success is a complex process

IS

Bacterial Host

Variable ability to acquire & maintain R

Plasmid
(Host-range; Toxin/Anti-toxin systems; restriction enzymes; Vir./conj.)

R Plasmid (co & cross R)

ICE/cTn

Transmission across the food chain is often complex

Host Adaptation

IS - insertion sequence; ICE - integrative conjugative element; Tn - conjugative transposon; M – mutation
Antimicrobial consumption & AMR data correlation

- Antibiotic use correlates with AMR emergence, but ...

- Difficulties in the prediction and quantification of specific AMR risks for Humans

Contributed to continuing controversy about the use of antimicrobial agents in veterinary medicine
AMR in animals-humans: main evidences

**European Union, 2015**

- **FQ resistance**: High-levels (C. coli 80-100%; most countries)
  - **Humans**
    - EU: 13.3%
    - Asia: 15-48%

**Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline-Supplemented Feed on a Farm**

Stuart B. Levy, M.D., George B. FitzGerald, Ph.D., and Ann B. Macone, B.S.

**Quinolone use & Quinolone-resistant Campylobacter**

**MDR Salmonella**

**Gram- bacteria resistant to Cefotaxime &/or Ceftazime in foods and animals**

European Union, 2015

Resistance to Extended-Spectrum Cephalosporins (ESC)

Ceftiofur & cefquinome – widely used in food producing animals

Cross resistance with all extended-spectrum cephalosporins

Mechanism of Resistance

Cephalosporinases

- **ESBLs** (TEM, SHV and CTX-M)
- **AmpC-type** beta-lactamase more frequent: CMY-2
- **OXA-type**: OXA-1

Carbapenemases
Cephalosporinases in non-typhoid *Salmonella*

**Cefotaxime**
- Humans - 1.1%
- Broiler meat - 0.6%
- Broiler - 2.3% (0.4-27.3%)

-27.3%:
  - mostly CTX-M-1 clone - *S. Infantis*, Italy
  - CMY-2 - *S. Heidelberg*, The Netherlands

**SHV-12**
- *S. Enteritidis*
- *S. Kentucky*
- *S. Virchow*
- *S. Typhimurium*

**CMY-2**
- *S. Infantis*
- *S. Virchow*
- *S. Typhimurium*

**TEM-52**
- *S. Typhimurium*

**CMY-2**
- *S. Kentucky*
- *S. Heidelberg*

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Cephalosporinases in non-typhoid *Salmonella*

**Humans: ~ 2 %**

**Humans: Asia 38%**

- **CTXM-2**
  - *S. Typhimurium*
  - *S. Infantis*
  - *S. Enteritidis*
  - *S. Heidelberg*

- **CTXM-8**
  - *S. Typhimurium*

- **CTXM-14**
  - *S. Heidelberg*
  - *S. Typhimurium*
  - *S. Enteritidis*

- **CTXM-15**
  - *S. Enteritidis*
  - *S. Virchow*

- **TEM-20**
  - *S. Infantis*

- **TEM-52**
  - *S. Infantis*

- **SHV-2**
  - *S. Heidelberg*

- **CMY-2**
  - *S. Typhimurium*
  - *S. 4,[5],12:i:-*
  - *S. Kentucky*
  - *S. Heidelberg*
  - *S. Infantis*

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Resistance to Extended-Spectrum Cephalosporins (ESC)

Worldwide increase of Resistance to ESC in *Escherichia coli* over the past decade

Different animal species, mainly in poultry

via whole bacterium transmission?
via mobile genetic elements (MGE)?

Humans infections

Madec et al., CMI. 2017; Lazarus et al., CID. 2015
Main settings of main cephalosporinase-producing *E. coli*

- **IncI1/2**
- **IncA/C**
- **A-CC10, A-CC23, D-ST117**
- **D-ST38**
- **IncA/C**
- **Incl1/2**
- **InclK InclN Incl1**
- **A-CC10, A-CC23**
- **D-ST69, D-ST393, B2-ST131**
- **IncFLI**
- **Incl1 InclN InclX3**
- **D-ST405**
- **IncFLI**
- **B2-ST131**
- **Incl1 InclN InclX3**
- **D-ST405**
- **IncFLI**
- **B2-ST131**

**Animals**

- **Humans**
- **Community**

- **Top cephalosporinases**
  - **CMY-2**
  - **TEM-52**
  - **CTX-M-1**
  - **CTX-M-14/27**
  - **SHV-12**
  - **CTX-M-15**

- **Quantitative and geographical extent of the problem is unclear and requires further investigation**

- **Transmission through direct contact (few evidences). Food product types? Strain or MGE?**

- **A proportion of human extraintestinal ESCR-EC infections originates in food-producing animals.**

- **Broader sampling and higher-resolution molecular comparisons required.**
Carbapenemases in non-typhoid *Salmonella*

Carbapenems not used in animal setting

**OXA-48** (From North Africa)
- S. Kentucky
- S. Saintpaul
- S. Typhimurium

**NDM-1**
- S. Senftenberg
- S. Westhampton
- S. Corvallis
- S. Westhampton

**VIM-1**
- S. Typhimurium
- S. Infantis (2011-2016) (1 positive of 145 tested in 2015)

Co-selection events

Carbapenemase-producing *Salmonella* are still rarely described in humans & animals

Carbapenemases in non-typhoid Salmonella

- **KPC-2**
  - S. Cubana
  - S. Typhimurium
  - S. Schwarzengrund

- **NDM-1**
  - S. Senftenberg
  - S. Agona
  - S. Stanley

- **VIM-2**
  - S. Kentucky

- **OXA-204**
  - S. Kentucky

- **IMP-1**
  - S. Agona

- **IMP-4**
  - S. Typhimurium

Borowiak M et al. JAC 2017; Madec JY et al. CMI 2017; Sotillo A et al. JMM 2015; Guerra B et al. VM 2014.
Carbapenemases in livestock

Carbapenemase-producing Gram- rarely described;
EU surveillance – voluntary;
No systematic analysis in different countries;

Belgium
OXA-23 (Acinetobacter)

France
OXA-23 (Acinetobacter)

Germany
OXA-23 (Acinetobacter)
VIM-1 (E. coli)

USA
IMP-27 (multiple Enterobacteriaceae species)

Algeria
NDM-1 (Acinetobacter)
OXA-23 (Acinetobacter)

Lebanon
OXA-23, OXA-58 (Acinetobacter)
VIM-2 (Pseudomonas)

China
NDM-1 (Acinetobacter, E. coli); NDM-5 K. pneumoniae

Carbapenemases in poultry, China

Comprehensive resistome analysis reveals the prevalence of NDM and MCR-1 in Chinese poultry production

Yang Wang, Rongmin Zhang, Jiuyun Li, Zuowei Wu, Wenjuan Yin, Stefan Schwarz, Jonathan M. Tyrrell, Yongjun Zheng, Shaojin Wang, Zhangqi Shen, Zhihai Liu, Jianye Liu, Lei Lei, Mei Li, Qidi Zhang, Congming Wu, Qijing Zhang, Yongming Wu, Timothy R. Walsh and Jianzhong Shen

NATURE MICROBIOLOGY 2, 16260 (2017)

- 739 non-duplicate samples
- 2 two hatchery farms
- 4 commercial farms (chicken; nests of swallows or sparrows; farmer; dog; flies; sewage
- 1 slaughterhouse (chicken, sewage)
- 16 supermarkets (chicken legs and breast)

Possible transmission routes of blaNDM

161 NDM producers: NDM- 5, 9, 1 and 7
23% also carried mcr-1
E. coli, K. pneumoniae & Enterobacter
AMR in animals-humans: main evidences


- Tetracycline resistant *Escherichia coli*
- Quinolone use & Quinolone-resistant *Campylobacter*
- Quinolone use & Quinolone-resistant *Salmonella*
- 3rd Generation Cephalosporin Resistant

**Prevalence EU:**
- Mainly pigs
- Mainly ST398
- % of human cases: Variable
- Direct contact. Food?

**Human infection with LA-MRSA**

**MRSA**

**OptrA**

**Linezolid and Phenicol resistant bacteria in humans**

OptrA and Linezolid resistance in Enterococcus

- Oxazolidinones (linezolid/tedizolid) important in the treatment of human infections caused by *Staphylococcus* (MRSA included) and *Enterococcus*

**OptrA** - Oxazolidinone phenicol transferable resistance

- Highest protein similarity with ABC transporter Sal(A) from *Staphylococcus sciuri*

- Use of phenicols in animals
- Use of oxazolidinones in hospitals

Wang et al. JAC 2015
OptrA and Linezolid resistance in *Enterococcus*

- Since at least 2005

Wang et al. JAC 2015; Mendes et al. JAC 2016; Gawryszewska et al. EJCMID 2017; Huang et al. JAC 2017; Tamang et al. VM 2017; Freitas et al. ECCMID 2017; Fleige et al. ECCMID 2017
High variability of:

- optrA gene clusters
- platforms/transferability
- hosts and settings
- clonal types (epidemic vs. non-epidemic)
- Linezolid resistance phenotypes (2-32 mg/L)

ECOFF = 4 mg/L --- from susceptible to clinically resistant

- All tedizolid resistant (1 - >32 mg/L)
AMR in animals-humans: main evidences

- Tetracycline resistant *Escherichia coli*
- Quinolone use & Quinolone-resistant *Campylobacter*
- Quinolone use & Quinolone-resistant *Salmonella*
- 3rd Generation Cephalosporin Resistance
- Human infection with LA-MRSA
- Linezolid and Phenicol resistant bacteria in humans
- Optra
- MCR-1 & colistin resistance

**MCR-1 & animal use of colistin**

**Paenibacillus polymyxa. Ex: Bacillus polymyxa**

**Human medicine:**
- Introduction in 1950s
- Last-resort antibiotic for MDR Gram negative infections in different countries.
- Not used in China

**Veterinary medicine:**
- Extensive use for decades worldwide
  - EU: 5th sales list (600 x in food animals than humans)
  - Different animal species, mostly in swine.
  - Growth promotion (not EU) & Inf. treatment (gastrointestinal infections)
MCR-1 & animal use of colistin

November 2015

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Zhangqin Shen, Yang Wang, Yingbo Shen, Jianzhong Shen, Congming Wu


MCR-1:
- Phosphoethanolamine transferase
- Addition of phosphoethanolamine to lipid A
- Often mobilization by ISAp1-mcr1-ISAp1
- Important reservoirs: Moraxella

March 2016

Early emergence of mcr-1 in Escherichia coli from food-producing animals - chicken

Kiefer et al., AAC.2017; Poirel et al., AAC 2017; Wang et al., Nat. Microbiol. 2017

Mostly in food-producing animals
(Pigs at slaughter and Retail meat-chicken and pork)
Colistin resistance: Worldwide dissemination of mcr-1 gene

mcr-1
Gene

mcr-1.2
E. coli

K. pneumoniae (KPC-3)

Low incidences in human infections
mcr-1 gene is on a rising trend

Mostly E. coli.
Also Salmonella, K. pneumoniae

Colistin resistance: Worldwide dissemination of \textit{mcr-1} gene

Mostly \textit{E. coli} (ST10 & several other)


Plasmids: IncX4, I2, HI2, F, Y P, FI, FIB

With/without other R genes (e.g. NDM, KPC, CTX-M)

Lei et al., EID. 2017; Miriam et al., AAC. 2017; Wang et al., Nat. Microbiol., 2017; Kuo et al., Jac 2016
Why animal setting is a likely source for mcr-1?

- *mcr*-1 & 2, other associated resistance genes or genetic elements are common in animal bacterial species (e.g. floR and ISAp1, IncX4)
- *mcr*-1 largely disseminated in China where colistin have been only used in the farming sector
- The predominance of *mcr*-1 in farms and in livestock of China, compared with normal human flora and hospital infections
Concluding Remarks

**AMR is a global challenge** and the use of antimicrobials in animals is part of the problem, contributing for:

- **Old antibiotic resistance problems** (*tet, erm, dhfr, sul, oqxAB, qnR, van genes, mecA/C* .....
  ESBL/AmpC) persist in the animal setting
- **Emerging problems** (carbapenemases, *optrA, mcr*) rising

What can be done to **reduce** the use of **antibiotics** in animals?

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