Colistin Resistance Global concern

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Background

- Colistin is antibacterial agent of the polymyxin class (polymyxin E)
- Introduced in 1950's for human use – toxicity limited use to topical applications
- Since the 1950's Colistin has been used for growth promotion, treatment and prevention of disease in animal production (pigs, poultry, cattle, sheep, goats, rabbits, and in aquaculture)
- Now used as drug of last resort for MDR gram negative infections (Pseudomonas, Klebsiella pneumoniae, Acinetobacter, E.coli etc)
- Spread originally thought to be chromosomal, then discovery in China of a mobile gene MCR-01 raised concern of potential global spread (Lui et al. 2015)
- MCR-01 often together with ESBLs and carbapenemases.
- Use in animals can select for colistin-resistant enterobacteriaceae which have the potential to be transmitted to humans (EMA/231573/2016)

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

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

www.thelancet.com/infection **Published online November 18, 2015** **http://dx.doi.org/10.1016/S1473-3099(15)00424-7**

mcr-1 Global Identification

Over 32 countries

- Found in *Salmonella, E. coli, Klebsiella pneumoniae, Enterobacter* spp., and *Pseudomonas aeruginosa* (experimental conjugation)

- Found in many plasmid types: IncI2, IncX4, IncIH1B, IncHI2, IncIH2A, IncFII, and IncIFB

- Initial Canadian report of *E. coli mcr-1* from retail beef (n=2; ground beef) and a human case also OXA-48 positive
  Mulvey et al. Lancet Infect Dis 2016. 16:289-90.

- *mcr-1* identified from *E. coli* isolates from the 1980s in China Shen et al. Lancet Infect Dis 2016. 16:293.

- *MCR-01, MCR-02, MCR-03, MCR-04, MCR-05…..MCR-08*

Retrospective isolate sampling to screen for MCR at the NML

- CANWARD; 2008-16; 10-15 hospital sites (>6,000 isolates)
  Walkty *et al.* CMAJ. 2016. 4:641-645.

- CNISP Carbapenemase Surveillance; 2007-16 (>500 isolates)

- CIPARS in 2016 and screened all human (n=4200) and agri-food *Salmonella* (n=3271) and *E. coli* (n=4507)

- Reference Services

- PulseNet WGS Analysis of existing *E. coli and Salmonella* (>5000)

- Toronto area sewage/recreational beach

Methods

- Developed screen plate for colistin-R for all animal, food, and human isolates from CIPARS since 2016, retrospective analyses of isolates from humans since 2010, and animals/food since 2013
  - Mueller Hinton, 2 mg/L colistin;
  - 1/10 dilution of 0.5 MacFarland dilution
  - Spot 2 ul on plate
  - validated on 100 *Enterobacteriaceae*

- Multiplex PCR
  - TEM, SHV, CTX, CMY, OXA-1
  - *mcr-1* and *mcr-2*

Canadian *mcr-1 (thousands of isolates screened)*

- Human cases (6 cases; 8 isolates)
  - *E. coli* Toronto, Ontario (2010); blood isolate from ER; **CANWARD**
  - *E. coli* Vancouver, British Columbia (2010); blood isolate from ER; **CANWARD**
  - *E. coli* Ottawa, Ontario (2011); OXA-48 positive, pan-drug resistant; Lived in Egypt for previous 5 years; **Reference Service**
  - *S*. Typhimurium Ontario (2012); **CIPARS**
  - *E. coli* isolated in (2016) in BC; obtained health care in China; **Reference Service**
  - *E. coli* isolated in (2017) in BC; NDM-01 positive, colonization, recent travel to China; **Reference Service**
    - 2 additional cases from this patient MCR-1 positive (N17-00575, N17-00576)
- Food/Animal (8 isolates)
  - 2 *E. coli* retail ground beef (2010) Ontario; different retail locations; **CIPARS**
  - *E. coli* from retail veal (2012) Ontario; **CIPARS**
  - *E. coli* from soft shell turtle, (2015) purchased Vancouver, BC; origin Thailand; **U of Sask study (J. Rubin)**
  - *E. coli* from frozen Abalone (2016) purchased Toronto; origin China; **CIPARS**
  - *Salmonella* 4,[5],12:i:- isolated in 2016 from bovine (Ontario); **CIPARS**
  - 2 *E. coli* isolated in 2016 from bovine (Quebec); U of Montreal (FMV)/CIPARS
- Environment (3 isolates)
  - 3 *E. coli* from sewage, Toronto, ON, 2012. **WGS GRDI funded study**

Mulvey et al. 2016 Lancet Infect Dis 289-90

MCR – summary in Canada

- Mobile colistin resistance remains rare in Canada, but present since at least 2010
- Widely distributed (environment, animal, food, and human)
- *E. coli* isolates not closely related using except for two isolates from a single patient
  - No outbreaks or patient to patient transmission observed
  - No linkage between human and agri-food isolates
- Multiple plasmid backbone associated with spread of *mcr-1*

Food Animal Perspectives

- Extensive use of colistin in food animals is deemed a major driving force for the emergence and transmission of mcr-1
  - Thousands of KG of colistin still produced and exported
- Spread among humans, between humans and animals and the environment is considered likely in countries where colistin still used.
- Limiting colistin use in animal production may still not effectively mitigate colistin resistance due to an overlooked non-colistin usage factor(s)
- MCR-1 confers cross-resistance to bacitracin, a popular in-feed antibiotic used in food animals. Thus, imprudent and extensive usage of bacitracin in food animals may serve as a non-colistin usage risk factor for the transmissible colistin resistance (Xu F, Zeng X, Hinenoya A, Lin J. 2018. MCR-1 Confers Cross-Resistance to Bacitracin, a Widely Used In-Feed Antibiotic. - PubMed - NCBI. mSphere 3:161)
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China, Brasil - Banned use in feed (2017)

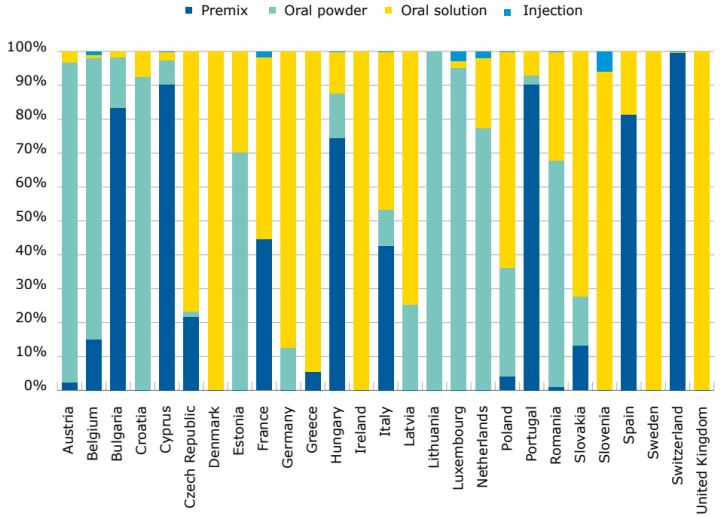
EU – 2016 targeted reduction of Consumption (sales) of colistin to < 5mg/PCU (kg livestock) over 3-4 years.

Canada – no approved use

US – no approved Use

[1] No sales in Finland, Iceland and Norway.

Figure 38. Distribution of sales by pharmaceutical form for polymyxins, in mg/PCU, by country, for 2015[1,2]



Antimicrobial Agents Used for AGP (OIE, 2016)

Three countries provided antimicrobial classes rather than active ingredients used for growth promotion, and so were not included in the analysis for Figure 5. Analysis at a regional level by antimicrobial class is presented in the annexes by OIE Region (Annexes 1-5).

Figure 5. Antimicrobial Agents Used for Growth Promotion in Animals in 33 Countries in 2016