Colistin use in animals- can it be banned?

April 25, ECCMID 2017

Dik Mevius
Conflicts of interests?

- None
Can colistin be banned in animal medicine?

- **Of course it can be banned**
  - This would be a risk manager’s, political choice

- The question is should it be banned??
  - Would a ban have adverse effects on animal health and welfare?
  - Would a ban support human health care?
  - Would a ban prevent emergence of colistin resistance in isolates involved in nosocomial infections?

**Risks versus Benefits**

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Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health
For what indications was colistin used?

- Infections by Enterobacteriaceae (E. coli, Salmonella)
  - Pigs, poultry, cattle, sheep, goats and rabbits
  - Predominantly orally administered
    - Combinations with a.o. amoxicillin, neomycin
    - Products for parenteral and intramammary administration
      - Cattle and horses: endotoxaemia
    - Eye and eardrops (dogs, cats)

---

Colistin has never been licenced by the FDA for oral use in livestock
Combination products

<table>
<thead>
<tr>
<th>Combination*</th>
<th>Route of administration</th>
<th>Indications</th>
<th>Withdrawal time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin-Ampicillin</td>
<td>IM</td>
<td>Septicemia, gastrointestinal, respiratory and genitourinary infections</td>
<td>21</td>
</tr>
<tr>
<td>Colistin-Amoxicillin</td>
<td>IM</td>
<td>Septicemia, gastrointestinal, respiratory infections</td>
<td>10</td>
</tr>
<tr>
<td>Colistin-Erythromycin</td>
<td>Oral</td>
<td>Intestinal infections</td>
<td>21</td>
</tr>
<tr>
<td>Colistin-Neomycin</td>
<td>Oral</td>
<td>Intestinal infections</td>
<td>14</td>
</tr>
<tr>
<td>Colistin-Oxytetracycline</td>
<td>Oral</td>
<td>Intestinal infections</td>
<td>7</td>
</tr>
<tr>
<td>Colistin-Spiramycin</td>
<td>Oral</td>
<td>Intestinal infections</td>
<td>10</td>
</tr>
<tr>
<td>Colistin-Trimethoprim</td>
<td>Oral</td>
<td>Intestinal infections</td>
<td>7</td>
</tr>
<tr>
<td>Colistin-Amoxicillin-Dexamethasone</td>
<td>IM</td>
<td>Septicemia, gastrointestinal, respiratory infections</td>
<td>21</td>
</tr>
</tbody>
</table>

*Colistin is always used as colistin sulfate. IM, intramuscular.

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Total sales of antibiotics mg/PCU

Figure 8. Sales for food-producing species, in mg/PCU, of the various veterinary antimicrobial classes, for 29 European countries, in 2014.

* Amphenicols, cephalosporins, other quinolones and other antibacterials (classified as such in the ATCvet system).

1 Differences between countries can be partly explained by differences in animal demographics, in the selection of antimicrobial agents, in dosage regimes, in type of data sources, and veterinarians prescribing habits and prices.

Sales of veterinary antimicrobial agents in 29 European countries in 2014
Sixth ESVAC report
Total sales in 2014 in 29 European countries

- 9009.5 tons
- Polymyxins sales: 595 tons
Most important indications for use since 1950 in the EU were

- Pigs: treatment and prevention of neonatal and weaning diarrhoea
- (Veal)calves: E. coli infections, “start treatment”
- Poultry: colibacillosis (invasive infection)
  - Preventive use at risk moments
  - E.g. start of laying period

Control of Salmonella
Polymyxin use in animals (mg/PCU)

Figure 5. Spatial distribution of sales of polymyxins in veterinary medicine, in mg/kg biomass, in 26 EU/EEA countries, for 2013. No sales reported in Finland, Iceland and Norway. (EMA/ESVAC, 2015)

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Polymyxin use as bar graph.

Figure 2. Consumption estimates based upon sales for food-producing animals (including horses) of polymyxins, adjusted for biomass under exposure (in mg/PCU), by country, for 2011-2013 (EMA/ESVAC, 2015). No sales reported in Finland, Iceland and Norway.
Major routes of administration in animals

Figure 3 Distribution of veterinary sales for polymyxins by pharmaceutical form, adjusted for biomass under exposure (in mg/PCU), by country for 2013. No sales in Finland, Iceland and Norway. In addition, negligible amounts were sold as bolus, oral paste, intramammarys and/or intrauterine preparations in some countries (EMA/ESVAC, 2015).

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### Polymixin use in human medicine (ECDC)

#### Table 1. Trends in consumption of polymyxins in EU/EEA countries, 2010-2014 (expressed in DDD per 1,000 inhabitants and per day)

<table>
<thead>
<tr>
<th>Country</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>Average annual change 2010-2014</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland (s)</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lithuania (s)</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Norway</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Poland (s)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Latvia</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
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<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
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<tr>
<td>Romania</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
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<tr>
<td>Denmark</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Slovenia</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>United Kingdom (s)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hungary</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>France</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Malta</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>EU/EEA</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ireland</td>
<td>0.009</td>
<td>0.009</td>
<td>0.009</td>
<td>0.009</td>
<td>0.009</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Portugal (s)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Croatia</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Slovakia (s)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Italy</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Greece (s)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Belgium</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

The number for EU/EEA refers to the corresponding population-weighted mean consumption, calculated by summing the products of each country's consumption in DDD per 1,000 inhabitants per day x country population as in Eurostat, and then dividing this sum by the total EU/EEA population.

- **a)** These countries did not report data for all years during the period 2010-2014.
- **b)** Finland: data include consumption in rural primary healthcare centres and nursing homes.
- **c)** Portugal: data relate to public hospitals only.
- **d)** United Kingdom: data do not include consumption from UK-Wales (2012) or UK-Northern Ireland (2014).
- **n.a.** not applicable; linear regression was not applied due to missing data.
- **n.s.** not significant.

*Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health EMA/231573/2016*
TABLE 1

Observed BSI caused by *K. pneumoniae* during the study period\(^a\)

<table>
<thead>
<tr>
<th>Yr</th>
<th>No. of <em>K. pneumoniae</em> BSI</th>
<th>No. (% of <em>K. pneumoniae</em>) isolates that were:</th>
<th>Colistin consumption(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Carbapenemase sensitive</td>
<td>Carbapenemase resistant(^b)</td>
</tr>
<tr>
<td>2009</td>
<td>29</td>
<td>28 (97)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>2010</td>
<td>49</td>
<td>38 (78)</td>
<td>11 (22)*</td>
</tr>
<tr>
<td>2011</td>
<td>76</td>
<td>44 (58)</td>
<td>42 (42)*</td>
</tr>
<tr>
<td>2012</td>
<td>128</td>
<td>46 (36)</td>
<td>82 (64)*</td>
</tr>
<tr>
<td>2013</td>
<td>93</td>
<td>32 (34)</td>
<td>61 (66)</td>
</tr>
<tr>
<td>Total</td>
<td>375</td>
<td>188 (50)</td>
<td>187 (50)</td>
</tr>
</tbody>
</table>

\(^a\)Numbers and proportions of BSI cases caused by carbapenem-susceptible, carbapenem-resistant, and carbapenem- and colistin-resistant (COL\(^e\) CRKP) strains. For patients with recurrent BSI episodes, only the first episode was considered.

\(^b\)An asterisk indicates that the difference in the proportion of resistant isolates was statistically significantly different (\(P < 0.05\)) from that for the previous year. For statistical analysis, the chi-squared test with Yates' correction or Fisher's exact test (as appropriate) was used.

\(^c\)Proportions are reported in relation to both *K. pneumoniae* BSI and CRKP BSI. (Values are shown in parentheses and separated by semicolons.) COL\(^e\) *K. pneumoniae* was only observed among CRKP cases.

\(^d\)Data on colistin consumption in the hospital during the study period, expressed as the defined daily dose per 1,000 inhabitants per day, are also reported.
<table>
<thead>
<tr>
<th>Yr</th>
<th>No. of K. pneumoniae BSI</th>
<th>Carbapenem sensitive</th>
<th>Carbapenem resistant</th>
<th>COL&lt;sup&gt;r&lt;/sup&gt; CRKP&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>19</td>
<td>19 (100)</td>
<td>0 (0)</td>
<td>0 (0;0)</td>
</tr>
<tr>
<td>2010</td>
<td>25</td>
<td>25 (100)</td>
<td>0 (0)</td>
<td>0 (0;0)</td>
</tr>
<tr>
<td>2011</td>
<td>29</td>
<td>29 (100)</td>
<td>0 (0)</td>
<td>0 (0;0)</td>
</tr>
<tr>
<td>2012</td>
<td>28</td>
<td>28 (100)</td>
<td>0 (0)</td>
<td>0 (0;0)</td>
</tr>
<tr>
<td>2013</td>
<td>18</td>
<td>18 (100)</td>
<td>0 (0)</td>
<td>0 (0;0)</td>
</tr>
<tr>
<td>2014</td>
<td>21</td>
<td>20 (95%)</td>
<td>1 (5%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0 (0;0)</td>
</tr>
<tr>
<td>2015&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45</td>
<td>44 (98%)</td>
<td>1 (2%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (2;100)</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>183</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Numbers and proportions of BSI cases caused by carbapenem-susceptible, carbapenem-resistant, and carbapenem- and colistin-resistant (COL<sup>r</sup> CRKP) strains. For patients with recurrent BSI episodes, only the first episode was considered.

<sup>b</sup> Proportions are reported in relation to both K. pneumoniae BSI and CRKP BSI. (Values are shown in parentheses and separated by semicolons.)

<sup>c</sup> Until December 3, 2015

<sup>d</sup> OXA-48 carbapenemase producer.

<sup>e</sup> Meropenem MIC 3 mg/L. Fenotypically and genotypically no carbapenemase detection.

Courtesy of Marc Bonten, UMCU, NL
Discovery of a gene encoding for plasmid mediated colistin resistance

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
The “obvious” pathway of antibiotic resistance

1. Antibiotic use in animals
2. Antibiotic resistance in animals
3. Antibiotic resistance in healthy humans
4. Infections

Livestock-Associated MRSA
ESBL
CRE/CPE

ESCMID eLibrary
© by author
Contribution from animals is an evolutionary risk
Antibiotic use in animals and humans
Antibiotic sales for animal use in NL (Source FIDIN)

90% oral administration by group/flock mediation
Animal versus human use in kg

van Geijlswijk, et al, TvD, 2009
Figure 2. Developments in sales of antimicrobial agents between 1999 and 2015, in number of kilograms of active substances sold (x1,000) (source: FIDIN), by main pharmacotherapeutic group.
Sales by antibiotic class

Figure ABuse02: Antimicrobial veterinary medicinal product sales by pharmacotherapeutic class from 2011-2015 in kg (thousands).
Current *mcr-1* prevalence in livestock

- *mcr-1* was found frequently until 2010.
- In 2011 reduction measure were implemented.
- In 2016: prevalence of *mcr-1* *E. coli* was 0.5% in Dutch livestock.
Public health risks??

- Very limited data on mcr-1 in human clinical isolates
  - In Europe!
  - This in spite of decades of colistin use in animals and the occurrence of mcr-1 since the 1980s (in China)
Control of colistin use in animals!

- Precaution of ongoing evolution!!
  - Prevention of transfer of mcr-1 to nosocomial Klebsiella’s (incl KPC-producers)

- Direct effect of a ban on health care will be very limited!
Bacterial infections in animals

Problem

Overuse of antibiotics → Development of resistance

Solution sets

Prophylactic vaccines

Prevention strategies

Frontline diagnostics

Treatment strategies

New antibiotics (Human medicine)

Alternative therapeutics
Negative effects of ban on animal health?

- Pigs (diarrhoea often multifactorial):
  - Neonatal diarrhoea well controllable by vaccine
  - Shiga toxin producing E. coli vaccine provides protection until after weaning
  - Weaning diarrhoea: no effective vaccines available
    - Alternatives:
      - Auto-vaccines
      - ZnO
      - Improved hygiene and infection control
        - No mixing of litters
      - Other antibiotics
        - Neomycin, Trim/Sulfa, Amoxicillin??
Zink-Oxide for prevention of weaning diarrhoea

- Licenced in the EU since 2015:
  - Used in DK, S, F, N, It, P, Pl, UK, Ir
  - Max 14 days after weaning
  - 2500 ppm Zn in the feed
  - Positive effect on digestion, immunomodulatory, antibacterial effects
  - Heavy metal >>> environmental pollution
  - Selection for Zn resistance (eg LA-MRSA, R-plasmids)
Use in veal calves

- Starting “treatment” to prevent infections in vulnerable animals
  - Not a rational for prudent use
    - Stopped in 2011 (in NL)
  - Alternative?
    - Doxycycline, neomycin, enrofloxacin
  - Consequences:
    - Increase in Salmonella infections
    - Alternative: Improved hygiene and infection control
Use in poultry

- To control colibacillosis
  - Colistin is not absorbed from the GI-tract
    - Used as spray/aerosol
    - Preventive use
  - Alternatives?
    - Fluoroquinolones?
    - (Auto)vaccine
Is a ban necessary?

- NO, but....
  - Use should be much more restricted solely to infection with non invasive *E. coli*
  - No preventive use
  - No use as growth promoter
  - Group treatments limited
    - Based on antibiogram
- Make use data transparent and target future intervention at remaining high using countries..
Targets defined by EMA

Figure 4. Sales of colistin in for use in animals in mg/PCU in 2013 (ESVAC data), including the 5 and 1 mg/PCU levels. No sales reported in Finland, Iceland and Norway.

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EMA/231573/2016
Acknowledgements

My group at WBVR

Marc Bonten