Antimicrobials use in the UE from veterinary perspective – general trends and experience in Poland

Dariusz Wasyl, DVM, PhD
National Veterinary Research Institute
National Reference Laboratory for Salmonellosis & Antibiotic Resistance in Salmonella and E. coli

Contributors

National Veterinary Research Institute (NVRI)
- scientific unit of the Ministry of Agriculture and Rural Development
- National Reference Laboratory
  - infectious diseases in animals and zoonoses
  - food and feed hygiene

Contributors

Ministry of Agriculture and Rural Development
General Veterinary Inspectorate
The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

Introduction

ANTIMICROBIALS – milestone in health protection
from life-threatening infection to common use

Severity of the disease

range of antimicrobials application
Introduction

ADVERSE EFFECTS

• intoxication: overdosing - rare
• antimicrobial resistance
  – bacterial pathogens – therapeutic failures
  – „ancient“ phenomenon:
    • β-lactam, tetracycline and glycopeptide (VanA) resistance genes in 30,000-year-old Beringian permafrost sediments (D’Costa et al. Nature 2011 (477): 457–461)
  – selective pressure: untargeted action – resistant bacteria take over depopulated ecological niche
  – spread of resistance genes
• residues
  – toxicity, allergies, carcinogenicity
  – food processing disturbance

Antimicrobials-related surveillance areas

experiences in Poland

Antimicrobials marketing authorisation

Procedures:
• centralised
• ‘European’:
  • mutual recognition,
  • decentralised
• national

ANTIMICROBIAL MARKETING AUTHORISATION

Responsibility: THE OFFICE FOR REGISTRATION OF MEDICINAL PRODUCTS, MEDICAL DEVICES AND BIOCIDAL PRODUCTS

LEGAL BASIS:
Pharmaceutical law (2008)
Antimicrobials marketing authorisation

Application dossier
• Part 1: Summary of the dossier
• Part 2: Chemical, Pharmaceutical and Biological
• Part 3: Safety and Residues
  — Part 3.B: Residue documentation
• Part 4: Pre-clinical and Clinical
  — Part 4.1.C: Resistance documentation

Guidance documents (examples)
• Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial products
• Revised guideline on the SPC for antimicrobial products
• Reflection paper on the use of fluoroquinolones in food-producing animals – Precautions for use in the SPC regarding prudent use guidance
• Revised reflection paper on the use of 3rd and 4th generation cephalosporins in food producing animals in the EU – development of resistance and impact on human and animal health
• Reflection paper on MRSA in food producing and companion animals: The EU epidemiology and control options for human and animal health
• Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

CONSUMPTION of ANTIMICROBIALS

Responsibility: MINISTRY OF AGRICULTURE AND RURAL DEVELOPMENT

LEGAL BASIS:
Directive 2001/82/EC; Regulation 726/2004
Pharmaceutical law (2008)
Regulation on monitoring of trade of medicinal products for veterinary use (2011)

Consumption of antimicrobials - monitoring scheme

• national monitoring of veterinary pharmaceuticals consumption on wholesalers’ level
• quarterly reports
• in compliance with trade confidentiality
• launched in 2010: 38% of wholesalers reporting
• progress in 2011 (Jan-Jun): 88% of wholesalers reporting

Consumption of antimicrobials in 2010

- Sulfonamides, SUL/TMP 13%
- Tetracyclines 59%
- Fluoroquinolones 20%
- Macrolides
- Aminoglycosides
- Peptides
- Other antimicrobials

European Medicines Agency: first report on sales of veterinary antimicrobial agents (2011)
tetracyclines, penicillins, and sulfonamides: the top three antimicrobial classes sold in tonnes, accounting for more than 80% of total sales
Consumption of antimicrobials in 2010

ATCvet codes:
QA: Alimentary track and metabolism
QG: Genito-urinary system and sex hormones
QJ: Antiinfectives for systemic use

PREFERENCES in ANTIMICROBIAL USAGE in ANIMALS

Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE
LEGAL BASIS:
Government Res. 244/2008
country-wide questionnaire study on representative group of veterinary practitioners on usage of antimicrobials in food producing animals

ANTIBIOTIC RESISTANCE in ANIMAL PATHOGENS

Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE
LEGAL BASIS:
Act on control of infectious diseases in animals (2004/2010)
Government Res. 244/2008
Mastitis: poliethiological infections

- **Streptococcus sp.**: 29%
- **Coagulase Negative Staph.**: 22%
- **Staph. aureus**: 15%
- **Gram negative (E.coli)**
- **Corynebacterium sp.**
- **Staph. sp. & Str. sp.**
- **Candida**
- **others**: 34%

Mastitis: variable resistance of ethiological agents

- **Penicillin**
- **Ampicillin**
- **Amoxicillin**
- **Cloxacillin**
- **Cefoperazone**
- **Cefacetril**
- **Cefquinome**
- **Cefalexim**
- **Tetracycline**
- **Neomycin**
- **Bacitracin**
- **Linkomycin**
- **Rifampicin**

Mastitis: treatment recommendations

**Empirical treatment:**
- high risk of failure due to poliethiological background (different resistance patterns)

**Diagnosis:** isolation and susceptibility testing of causative agent

**Treatment:** usually combined preparations
- tetracycline/neomycin/bacitracin
- amoxicillin/clavulanic acid
- cefalexin/kanamycin
- neomycin/penicillin/novobiocin/streptomycin
- cefquinom

Respiratory tract infections in pigs

**Upper respiratory disorders (nasal swabs):**
- multi-aethiological syndrom - mixed bacterial (ubiquitous) flora
  - Streptococcus suis serotype II
  - Haemophilus parasuis
  - Streptococcus suis & Haemophilus parasuis
  - Pasteurella multocida

**Pleuropneumonia (lung sections):**
- *Actinobacillus pleuropneumoniae*
Antimicrobial resistance in pig’s respiratory bacteria

Respiratory infections: treatment recommendations

Empirical treatment:
- Low risk of therapeutic failure
  - β-lactams
  - Fluoroquinolones
- Linco-spectin, Tiamulin (popular broad-spectrum antimicrobials often used in pigs)
  - Based on bacteriological examinations and susceptibility testing

ANTIBIOTIC RESISTANCE in ZOONOTIC BACTERIA of PUBLIC HEALTH RELEVANCE (Salmonella sp.)

Antibiotic resistance in Salmonella spp.

- Salmonella control programmes in laying hen, broiler, and turkey flocks
- Interpretation criteria: epidemiological cut-off values – identification or resistance mechanisms
Serovar-related resistance in *Salmonella*

Microbial drug resistance in 2010 and its trends compared to 2008/9

- **S. Enteritidis**
- **S. Typhimurium**

Quinolone resistance in Poland from EU perspective (2008) EFSA Journal 2010, 8, 1-261

Animals as a source of MRSA

Methicillin-resistant *Staph. aureus* – human pathogen
- resistant to all beta-lactams (chromosomally located *mecA* gene)
- nosocomial infections
- community-acquired MRSA
- animal-associated MRSA
  - EU baseline survey in pigs (2008): PL prevalence < 5%
  - other sources

Methicillin resistance in staphylococci isolated from mastitis

ANTIBIOTIC RESISTANCE in COMMENSAL BACTERIA of PUBLIC HEALTH RELEVANCE

(E. coli from animals at slaughter)

Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE

LEGAL BASIS:
Government Res. 244/2008
Antibiotic resistance in commensal E. coli

Microbial drug resistance in 2010 and its trends compared to 2009

Commensal E. coli resistance

- reflects selective pressure of antimicrobials used in animal husbandry
- proves animals as a possible reservoir of resistant bacteria or resistance genes (horizontal spread)
- "Critically or highly important antimicrobials for human medicine"; WHO:
  - beta-lactams, including cephalosporins
  - fluoroquinolones (transferable low-level resistance)
  - amphenicols
  - aminoglycosides
- Need for prudent use
  - always follow SPC
  - feedback on adverse effect and lack of efficacy

ANTIBIOTIC RESIDUES in FOOD of ANIMAL ORIGIN

Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE

LEGAL BASIS:

National Monitoring Programme for the Presence of Prohibited Substances and Chemical, Biological and Medical Residues in Animals and Food of Animal Origin

Methods:
- screening: microbiological methods
- confirmation & identification: chemical analysis (LC-MS)

Antimicrobials:
- group A: prohibited substances (chloramphenicol)
- group B: veterinary compounds, including antimicrobials

<table>
<thead>
<tr>
<th>Year</th>
<th>Samples tested</th>
<th>Samples (%) positive (non-compliant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>residues (all)</td>
<td>antimicrobials</td>
</tr>
<tr>
<td>2008</td>
<td>29717</td>
<td>160 0.54%</td>
</tr>
<tr>
<td>2009</td>
<td>29509</td>
<td>145 0.49%</td>
</tr>
<tr>
<td>2010</td>
<td>18999</td>
<td>91 0.31%***</td>
</tr>
</tbody>
</table>
**Effects of Antibiotic Usage**

CROSS-SECTIONAL OVERVIEW

**Tetracyclines**

- Consumption:
  - 1st (59%)
- Usage preferences:
  - 1st: pigs
  - 2nd: poultry

**Residues (2008 - 2010)**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Organ</th>
<th>Number of Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>Cattle-kidney</td>
<td>1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Cattle-muscles</td>
<td>1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Pigs-kidney</td>
<td>5</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Pigs-muscles</td>
<td>5</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Poultry-liver</td>
<td>2</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Poultry-muscles</td>
<td>1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Table eggs</td>
<td>1</td>
</tr>
</tbody>
</table>

**Sulphonamides**

- Consumption:
  - 2nd (13%)
- Usage preferences:
  - 2nd: cattle
  - 3rd: pigs

**Residues (2008 - 2010)**

- Not detected in food-producing animals

**Penicillins and Cephalosporins**

- Consumption:
  - 3rd (8%)
- Usage preferences:
  - 1st: poultry, cattle
  - 2nd: pigs

**Penicillin/Ampicillin vs Cephalosporins**

- Penicillin resistance may occur in clinical settings
Quinolones and fluoroquinolones

- Consumption: 6th (4%)
- Usage preferences:
  - 3rd: poultry
  - 4th: pigs, cattle

Residues (2008 - 2010)
- pigs-muscles: 2%
- table eggs: 2%

% of resistance

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Nal</th>
<th>FQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. parainfluenzae</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>H. parasuis</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>Streptococcus suis II</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Past multocida</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Actinob. pleuropn.</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Perspectives
Continuing monitoring:
- antimicrobial consumption and usage preferences
- antimicrobial resistance in animal pathogens and indicator bacteria
- antimicrobial residues in food of animal origin

Feedback on the monitoring results to:
- pharmaceutical industry
- public health
- veterinary practitioners
Feedback from practitioners on pharmacovigilance

Conclusions
- Building up capacity to gather reliable data
- Compliance with EU legislation
- Risk communication and management
- Aim: to reduce antimicrobial usage
  - recommendations for animal treatment
  - critically important for human health
  - animal welfare and better, safer food

Contributing experts

<table>
<thead>
<tr>
<th>Area</th>
<th>Name, affiliation, e-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorisation</td>
<td>Dr. Katarzyna Kryszewska, The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, <a href="mailto:katarzyna.kryszewska@urpl.gov.pl">katarzyna.kryszewska@urpl.gov.pl</a></td>
</tr>
<tr>
<td>Antimicrobial consumption</td>
<td>Dr. Dorota Waliszewska-Dysińska, Department of Food Safety and Veterinary Matters, <a href="mailto:dorota.waliszewska@minrol.gov.pl">dorota.waliszewska@minrol.gov.pl</a></td>
</tr>
<tr>
<td>Usage preferences</td>
<td>Prof. Władysław Cypuński, NVRI, Department of Veterinary Pharmacy, <a href="mailto:wladyslaw.cypunski@piwet.pulawy.pl">wladyslaw.cypunski@piwet.pulawy.pl</a></td>
</tr>
<tr>
<td>Antibiotic resistance (mastitis)</td>
<td>Prof. Edward Malinowski, NVRI, Department of Pathophysiology of Reproduction and Mammary Gland, <a href="mailto:etm@kipvet.com.pl">etm@kipvet.com.pl</a></td>
</tr>
<tr>
<td>Antibiotic resistance (respiratory infections in pigs)</td>
<td>Dr. Jakub Żmudzki, NVRI, Department of Swine Diseases, <a href="mailto:jaca@piwet.pulawy.pl">jaca@piwet.pulawy.pl</a></td>
</tr>
<tr>
<td>Antibiotic resistance (Salmonella and E. coli)</td>
<td>Prof. Dariusz Wasyl, NVRI, Department of Microbiology, <a href="mailto:wasyl@piwet.pulawy.pl">wasyl@piwet.pulawy.pl</a></td>
</tr>
<tr>
<td>Antibiotic residues</td>
<td>Prof. Andrzej Posyniak, NVRI, Department of Pharmacology and Toxicology, <a href="mailto:aposyn@piwet.pulawy.pl">aposyn@piwet.pulawy.pl</a></td>
</tr>
</tbody>
</table>