

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

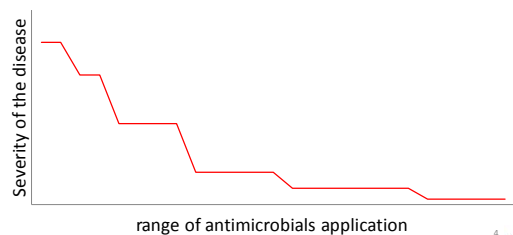


The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products



Introduction

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



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

5 

Antimicrobials-related surveillance areas experiences in Poland

6 

ANTIMICROBIAL MARKETING AUTHORISATION

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

LEGAL BASIS:
Directive 2001/82/EC; Regulation (EC) No 726/2004
Pharmaceutical law (2008)

7 

Antimicrobials marketing authorisation

Procedures:

- centralised
- **‘European’:**
 - mutual recognition,
 - decentralised
- national

8 

Antimicrobials marketing authorisation

Application dossier

- Part 1: Summary of the dossier
 - Part 1.B: Summary of Product Characteristics
- 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 in the EU: epidemiology and control options for human and animal health
- Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

9 

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)

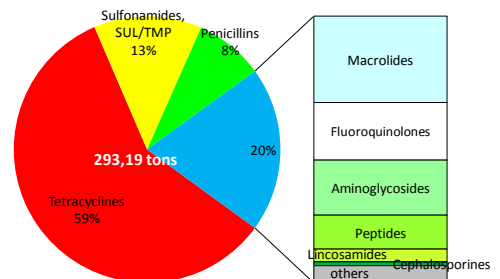
10 

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

11 

Consumption of antimicrobials in 2010



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

12 

Consumption of antimicrobials in 2010

ATCvet codes:

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

13 

PREFERENCES in ANTIMICROBIAL USAGE in ANIMALS

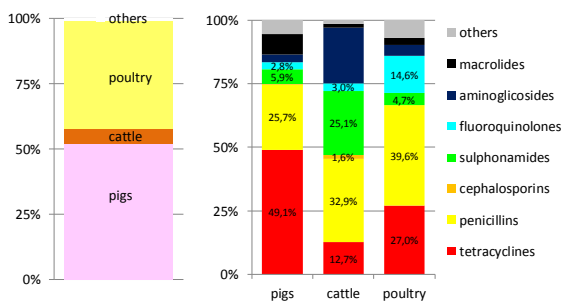
Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE

LEGAL BASIS:
Government Res. 244/2008

country-wide questionnaire study on representative group of veterinary practitioners on usage of antimicrobials in food producing animals

14 

Preferences in antimicrobial usage



15 

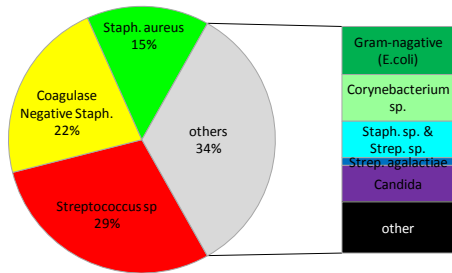
ANTIBIOTIC RESISTANCE in ANIMAL PATHOGENS

Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE

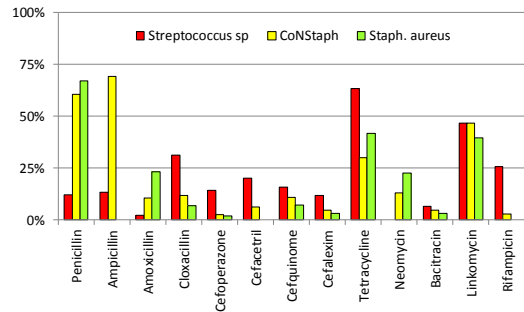
LEGAL BASIS:
Act on control of infectious diseases in animals (2004/2010)
Government Res. 244/2008

16 

Mastitis: poliethiological infections



Mastitis: variable resistance of ethiological agents



Mastitis: treatment recommendations

Empirical treatment:

- high risk of failure due to poliethiological background (different resistance patterns)

Diagnosis: isolation and susceptibility testing of casuative agent

Treatment: usually combined preparations

- tetracycline/neomycin/bacitracin
- amoxicillin/clavulanic acid,
- cefalexin/kanamycin,
- neomycin/penicillin/novobiocin/streptomycin
- cefquinom

Respiratory tract infections in pigs

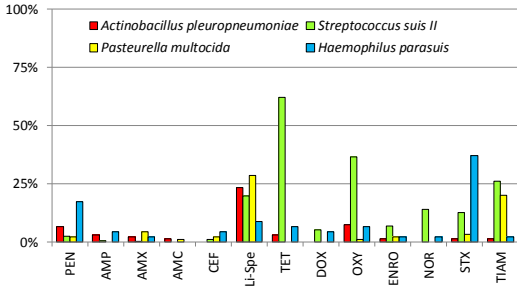
Upper respiratory disorders (nasal swabs):

- 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



21

Respiratory infections: treatment recommendations

Empirical treatment:

- low risk of therapeutic failure
 - betalactams
 - fluoroquinolones
- Linco-spectin, Tiamulin (popular broad-spectrum antimicrobials often used in pigs)
 - based on bacteriological examinations and susceptibility testing

22

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

Responsibility: NATIONAL VETERINARY RESEARCH INSTITUTE

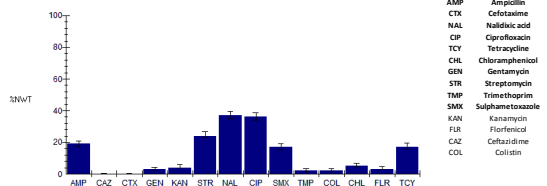
LEGAL BASIS:
Directive 2003/99/EC
Commission Decision 2007/407/EC

23

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

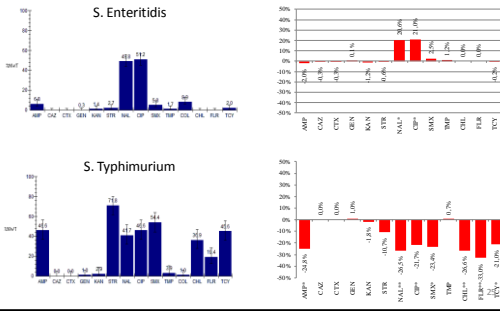
Salmonella 2008-2010



24

Serovar-related resistance in *Salmonella*

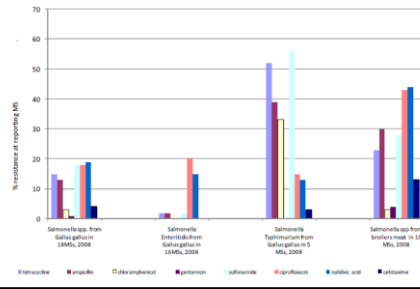
Microbial drug resistance in 2010 and its trends compared to 2008/9



Quinolone resistance in Poland from EU perspective (2008)

EFSA Journal 2010, 8, 1-261

Figure SA29: Antimicrobial resistance to tetracycline, ampicillin, chloramphenicol, gentamicin, sulfonamide, ciprofloxacin, nalidixic acid and cefotaxime in *Salmonella* spp., *S. Enteritidis* and *S. Typhimurium*, from *Gallus gallus* and broiler meat at reporting MS group level in 2008

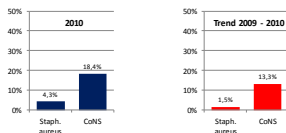


Animals as a source of MRSA

Meticillin-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

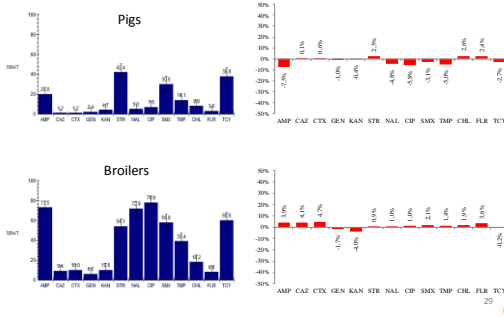
LEGAL BASIS:

EFSA recommendations [EFSA Journal (2008) 141: 1-44]

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:
 - betalactams, 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:
 Regulation 2004/882/EC; Directive 96/23/EC; Commission Decisions 97/747/EC; 98/179/EC; 2002/657/EC
 Act on Veterinary Inspection (2004); Animal products (2005) Food Safety and Nutrition (2006); Government Res. 244/2008

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

Year	Samples tested		Samples (%) positive (non-compliant)			
	residues (all)	antimicrobials	residues (all)		antimicrobials	
2008	29717	12821	160	0,54%	10	0,08%
2009	29509	12053	145	0,49%	10	0,08%
2010	28999	11834	91	0,31%***	9	0,08% n.i.

EFFECTS of ANTIBIOTIC USAGE CROSS-SECTIONAL OVERVIEW



33



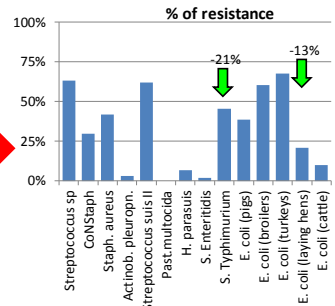
Tetracyclines

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

high resistance →

Residues (2008 - 2010)

	Doxy	Oxy
cattle-kidney		1
cattle-muscles		1
pigs-kidney	5	4
pigs-muscles	5	1
poultry-liver	2	
poultry-muscles	1	
table eggs	1	



34

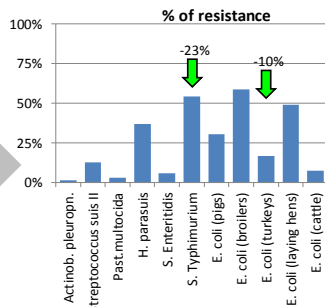


Sulphonamides

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

moderate clinical significance →

Residues (2008 - 2010)
Not detected in food-producing animals



35

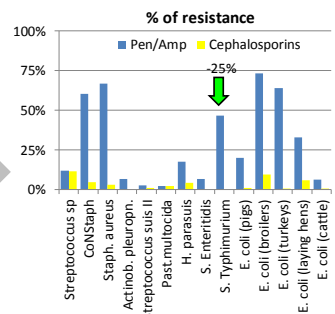


Penicillins and cephalosporins

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

penicillins resistance may occur in clinical settings →

Residues (2008 - 2010)
pigs-kidney 2



36

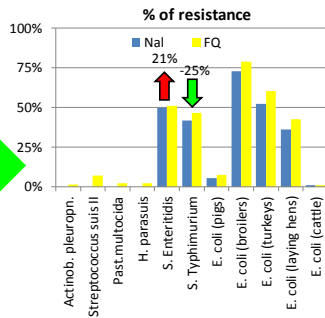


Quinolones and fluoroquinolones

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

high clinical efficacy →

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



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

Area	Name, affiliation, e-mail
Marketing authorisation	Dr. Katarzyna Krzyżarska, The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, katarzyna.krzyzarska@urpl.gov.pl
Antimicrobial consumption	Dr. Dorota Waliszewska-Dysińska, Department of Food Safety and Veterinary Matters, dorota.waliszewska@minrol.gov.pl
Usage preferences	Prof. Wojciech Cybulski, NVRI, Department of Veterinary Pharmacy, wojciech.cybulski@piwet.pulawy.pl
Antibiotic resistance (mastitis)	Prof. Edward Malinowski, NVRI, Department of Pathophysiology of Reproduction and Mammary Gland, vetri@logonet.com.pl
Antibiotic resistance (respiratory infections in pigs)	Dr. Jacek Zmudzki, NVRI, Department of Swine Diseases, jaca@piwet.pulawy.pl
Antibiotic resistance (Salmonella and E. coli)	Dr. Dariusz Wasyl, NVRI, Department of Microbiology, wasyd@piwet.pulawy.pl
Antibiotic residues	Prof. Andrzej Posyniak, NVRI, Department of Pharmacology and Toxicology, aposyn@piwet.pulawy.pl