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Report on the sale of antibiotics for veterinary use

and antibiotic resistance monitoring of livestock in Switzerland

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SUMMARY

Use of antibiotics in veterinary medicine

Once again there has been a decrease in overall quantities: compared with the previous year, the quantity of active substances sold fell by 3.9%. In relation to the previous maximum of 2008, there has thus been a decline of 9.4% (6894 kg) in total quantities. This year, too, the ranking of antibiotics according to quantities sold remains unchanged. The substances that were sold the most were sulphonamides, followed by tetracyclines and penicillins. At 67.4%, medicated premixes (MPs) accounted for approximately the same proportion of total quantities in 2010 as in previous years.

In the case of products approved solely for use in pets, the quantity of fluoroquinolones sold rose 12% in 2010 and also compared with the previous year, having remained stable in the previous years.

The steady increase in cephalosporins, which was already observed last year, has also continued this year. This is especially noticeable with the products for the treatment of mastitis during lactation, for which 60% more cephalosporins were sold in 2010 than in 2006. Although cephalosporins only account for 1.6% of the quantities of all active ingredients sold in this product group, they account for 16% of all potential treatments.

Antibiotic resistance in livestock

In 2010 samples were taken from broilers, fattening pigs and calves in the slaughterhouse for resistance monitoring and then analysed in the Centre for Zoonoses, Bacterial Animal Diseases and Antibiotic Resistance (ZOBA).

Table 1: Antibiotic resistance monitoring programme 2010

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cloacal swab - broilers	398 (groups of 5)	*Campylobacter* spp.	126
Cloacal swab - broilers	200 (groups of 5)	*E. coli*	183
Cloacal swab - broilers	219 (groups of 5)	Enterococci	185
Cloacal swab - broilers	398 (groups of 5)	MRSA	0
Faecal swab - broilers	296	*Campylobacter* spp.	192
Faecal swab - broilers	201	*E. coli*	179
Faecal swab - broilers	381	Enterococci	138
Nasal swab - broilers	392	MRSA	23
Faecal swab - slaughter calves	245	*Campylobacter* spp.	37
Faecal swab -slaughter calves	204	*E. coli*	184
Faecal swab - slaughter calves	249	Enterococci	134
Nasal swab - slaughter calves	240	MRSA	5
Clinical material / all animal species	not applicable	*Salmonella* spp.	105
Clinical material / all animal species	not applicable	*S.* Typhimurium incl. monophasic variant	47
Clinical material / all animal species	not applicable	*S.* Enteritidis	14

Since *Salmonellae* only very rarely occur in Swiss livestock, this bacterial species was not included in the active monitoring programme. But all Salmonellae from clinical material sent to the ZOBA in its function as a reference laboratory underwent resistance testing. The relevant results for Salmonellae from birds, bovine animals and pigs have likewise been compiled in this report.

Resistance in zoonotic agents from healthy animals

In the case of *Campylobacter* spp., high rates of resistance to (fluoro)quinolones and to tetracycline were found in all three animal species tested. *C. coli* isolates from pigs and calves also showed resistance to streptomycin in an extremely high percentage. A comparison of the resistance situation of *C. jejuni* and *C. coli* from broilers over the last few years shows that resistance to these substances has increased. This is a worrying development, since fluoroquinolones are among the most important antibiotic classes both for veterinary and for human medicine.

In 23 of 392 nasal swabs from fattening pigs methicillin-resistant staphylococci (MRSA) were discovered. The occurrence of MRSA in fattening pigs in Switzerland has thus increased significantly from 2.2% to 5.9% compared with the previous year. Further molecular testing showed that the increase was due to a further spread of two clonal lines, one of which is a widespread line in Europe and the other a line specific to the Swiss swine population (Overesch, 2011). The prevalence of MRSA in calves was very low at 2.1%, while no MRSA-positive samples were discovered in broilers. Compared with other European countries, MRSA prevalence in Swiss livestock thus remains very low and the risk of transmission from animals to humans can be regarded as minimal. But the situation should continue to be monitored, especially in fattening pigs.

Resistance in indicator bacteria from healthy animals

Resistance in non-pathogenic *E. coli* from Swiss farm animals is widespread. Compared with previous years, the resistance situation has not significantly changed. High to very high rates of resistance to sulphamethoxazole, streptomycin, tetracycline and ampicillin have been observed. Sulphonamides, tetracyclines and penicillins are antibiotics that are often used in veterinary medicine. In broilers, resistance to fluoroquinolones was also often found. If broilers are treated for bacterial diseases, fluoroquinolones are used in more than 70% of cases (ARCH-Vet, 2009). For the first time, in the course of resistance monitoring, two *E. coli* from broilers were isolated that produce an extended-spectrum β-lactamase (ESBL) and are thus resistant to all penicillins and cephalosporins. Since this resistance could prove to be of major significance for human medicine, its occurrence must continue to be monitored in the future and molecular genetic studies must be conducted to explore more closely the correlation with ESBL resistance genes that have been found in humans.

Resistance has also often been observed in enterococci. Both *E. faecalis* and *E. faecium* from all three animal species showed very high to extremely high rates of resistance to neomycin and bacitracin. Rates of resistance to tetracycline were also very high in *E. faecalis* as was resistance to quinupristin/dalfopristin in *E. faecium*. Both bacterial species of all three animal species also showed high rates of resistance to erythromycin. No vancomycin-resistant enterococci were found in the year under review.

Resistance in Salmonellae from clinical material

As in the last few years, *S*. Typhimurium strains showed more resistance than *S.* Enteritidis strains. The high rates of resistance in *S*. Typhimurium compared with previous years are due to the fact that the monophasic strain 4,12:i:- is now also regarded as a *S.* Typhimurium strain and this strain often shows multi-resistance.

In focus

The joint publication of data on the sale of antibiotics in veterinary medicine and resistance to antibiotics in livestock allows a correlation of the values and trends that are observed. Yet conclusions are only possible to a limited extent, because statistics on the sale of antibiotics do not allow a precise estimate of the active substances that are actually used in the various animal species, and the development of resistance is assessed to some extent only on the basis of fewer isolates or over a short observation period. In the following some of the notable results from both reports are discussed jointly.

Development of resistance in zoonotic agents:

The resistance situation in zoonotic agents and indicator bacteria from Swiss livestock has not substantially changed for most antibiotics. However, there has been a slight increase in resistance to (fluoro)quinolones. Fluoroquinolones are considered important reserve antibiotics both in veterinary and in human medicine.

Last year also saw an increase in MRSA prevalence in the Swiss pig population (Overesch, 2011). These strains are resistant to all beta-lactam antibiotics and often also to several other active substance groups, for example tetracyclines. In humans, the MRSA strains that are important in veterinary medicine primarily play a role in people who work with farm animals. In this case, people may also act as MRSA carriers and facilitate a (re)infection of the animals. Antibiotic control strategies are often counterproductive in such situations, because these bacteria are often multiresistant. Good standards of hygiene must therefore be established and favoured, because the use of antibiotics can lead directly to a selection of resistant bacteria.

Cephalosporins and ESBL

Over the period 2006-2010, cephalosporins are the only group of substances that showed a steady increase. This is especially marked in the third and fourth-generation cephalosporins. Some substances in these groups have high Maximum Residue Levels (MRLs), which results in very short withdrawal periods, especially for the milk of treated cows. This plays an important part in the selection of a product (Pokludova, 2009). Third and fourth-generation cephalosporins are among the most important substance groups both in human and in veterinary medicine. Against this background, Collignon and Aarestup criticized the high level of permitted MRLs back in 2007. They voiced their suspicion that these products were being used instead of other substances because of their short withdrawal periods.

Cephalosporins belong to the beta-lactam antibiotics, and thus are involved in the selection of extended-spectrum β-lactamases (ESBLs). While all beta-lactam antibiotics can exert a selection pressure, the potential is greater with newer-generation cephalosporins (Cavaco, 2008). The same authors also showed that the selection effect is preserved beyond the planned withdrawal period.

In the last few years, ESBL-producing bacteria have increasingly led to problems in human medicine. In Switzerland, ESBL-producing *E. coli* were detected for the first time in broilers during routine *E. coli* assays for resistance monitoring. A study in pigs and calves at slaughter also showed in selective assays that 15% and 17% of faecal samples contain ESBL-producing bacteria (Geser, 2011). Yet the prevalence of resistance is only of limited significance, because resistant strains or their mobile genetic elements can be transmitted to other individuals. The risk of selection thus increases if antibiotics are used. Horton et al. pointed out this situation in the case of ESBLs that were detected in livestock (Horton, 2011). While they detected low median values for the prevalence of ESBL-expressing *E. coli* in

bovine animals (0.013%), poultry (0.0197%) and pigs (0.121%) in their study, the authors pointed out at the same time that greater consideration has to be given to the absolute figures of ESBL-positive bacteria when evaluating the risk of resistance spreading.

The role of livestock as a reservoir for ESBL-producing bacteria has not yet been unequivocally clarified. A direct transmission of resistance from poultry to humans via meat was suspected, for example, in the Netherlands on the basis of genotyping of plasmids (Leverstein-van Hall, 2011). The horizontal transmission of ESBL genes between *E. coli* isolates of poultry and humans has been demonstrated *in vitro* in treatment with cefotaxim, a third-generation cephalosporin (Smet, 2010).

Since this resistance is of major significance in human medicine, this development must continue to be observed through both resistance monitoring and checks on the sale of antibiotics.

Cephalosporins are also increasingly being marketed in products for intramammary administration. This, too, marks the continuation of a trend over the last few years. As already mentioned in the last report (ARCH-Vet, 2009), no milk samples have so far been studied for resistance as part of the antibiotic resistance monitoring programme. The resistance situation with mastitis pathogens is also not routinely studied, so it is not known whether this development is associated with an increase in resistance among mastitis pathogens or other microorganisms that are not primarily pathogenic. In a study from Italy, however, 9 of 140 Klebsiella isolates from clinical cases of mastitis were resistant to ceftiofur (Locatelli, 2010). Only one of these isolates was unequivocally identified as a producer of ESBLs. A correlation between the use of newer (3rd and 4th) generation cephalosporins and the prevalence of ESBLs was demonstrated in a study from the Czech Republic (Dolejska, 2011). Once again it must be pointed out that a systematic monitoring of resistance development in bacteria isolated from milk is important in order to correlate this with the development of sales figures. In 2011, as part of a pilot study, the resistance situation will be analysed for the first time in selected microorganisms from tank milk.

Literature

ARCH-Vet 2009: Bericht über den Vertrieb von Antibiotika in der Veterinärmedizin und das Antibiotikaresistenzmonitoring bei Nutztieren in der Schweiz. Swissmedic / BVET, 2010.

Cavaco LM, Abatih E, Aarestrup FM, Guardabassi L. Selection and persistence of CTX-M-producing Escherichia coli in the intestinal flora of pigs treated with amoxicillin, ceftiofur, or cefquinome. Antimicrob Agents Chemother. 2008, 52: 3612–3616.

Collignon P, Aarestrup, FM. Extended-spectrum beta-lactamases, food, and cephalosporin use in food animals. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007, 44: 1391-2. doi: 10.1086/516612.

Dolejska M, Jurcickova Z, Literak I, Pokludova L, Bures J, Hera A, Kohoutova L, Smola J, Cizek A. IncN plasmids carrying bla CTX-M-1 in Escherichia coli isolates on a dairy farm. Vet Microbiol. 2011, 149: 513–516.

Geser N, Stephan R, Kuhnert P, Zbinden R, Kaeppeli U., Cernela N, Haechler H. Fecal carriage of extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* in swine and cattle at slaughter in Switzerland. Journal of Food Protection, 2011, 74, 446-449.

Horton RA, Randall LP, Snary EL, Cockrem H, Lotz S, Wearing H, Duncan D, Rabie A, McLaren I, Watson E, La Ragione RM, Coldham NG. Fecal Carriage and Shedding Density of CTX-M Extended-Spectrum {beta}-Lactamase-Producing Escherichia coli in Cattle, Chickens, and Pigs: Implications for Environmental Contamination and Food Production. 2011, Appl Environ Microbiol 77: 3715-3719.

Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, Voets GM, van den Munckhof MP, van Essen-Zandbergen A, Platteel T, Fluit AC, van de Sande-Bruinsma N, Scharinga J, Bonten MJM, Mevius DJ, and National ESBL surveillance group. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin Microbiol Infect. 2011, 17: 873–880.

Locatelli C, Scaccabarozzi L, Pisoni G, Moroni P. CTX-M1 ESBL-producing Klebsiella pneumoniae subsp. pneumoniae isolated from cases of bovine mastitis. J Clin Microbiol. 2010, 48: 3822–3823.

Overesch G, Büttner S, Rossano A, Perreten V. The increase of methicillin-resistant *Staphylococcus aureus* (MRSA) and the presence of an unusual sequence type ST49 in slaughter pigs in Switzerland, 2011. BMC Veterinary Research (in press).

Pokludova L, Bures J, Hera A. Evaluation of the sales data of “prudent use” antimicrobials contained in veterinary medicinal products in the Czech Republic, trends and perspectives. 2009, J. vet. Pharmacol. Therap. 32 (Suppl. 1): 1340

Smet A, Rasschaert G, Martel A, Persoons D, Dewulf J, Butaye P, Catry B, Haesebrouck F, Herman L, Heyndrickx M: In situ ESBL conjugation from avian to human Escherichia coli during cefotaxime administration. Journal of Applied Microbiology. 2010, 110: 541–549.