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## Report

**on sales of antibiotics for veterinary use**

**and antibiotic resistance monitoring in livestock in Switzerland**

# 2009

**Short Version**

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# EXECUTIVE SUMMARY

## Use of antibiotics in veterinary medicine

In 2009 a total of 70,789 kg of antibiotics were placed on the market. After a 7.1% increase from 2006 to 2008, the total for 2009 dropped again by 3.2%. As in previous years, the sulphonamides accounted for the largest proportion with 42%, followed by tetracyclines (23%) and penicillins (19%). The reduction in comparison with the previous year is mainly attributable to tetracyclines (–1,140 kg) and penicillins (–715 kg). If we take into account the relative trend in other classes of antibiotics, it can be seen that in comparison with 2006, significantly more cephalosporines and fluoroquinolones were sold in the last year under review.

The majority of antibiotic substances (53,284 kg) were sold in preparations for oral administration to farm animals. Most preparations were pharmaceutical premixes that are mixed into the animal feed or drinking water before administration. These were 68% (48,176 kg) of the total.

5,190 kg of the active substance was sold in preparations for intramammary application in farm animals. In this category the cephalosporin group showed the largest increase, i.e. 105% since 2006, and the newer ($3^{rd}$ and $4^{th}$) generations as much as 169%. Part of this growth is attributable to the launch of newly licensed preparations.

In all as much as 1,175 kg of antibiotics in preparations for topical use (ointments, drops, sprays or preparations for intrauterine application) was placed on the market, of which 934 kg was in preparations for farm animals. Of these 23% were tetracycline derivates in sprays.

Among preparations for small animals, the 709 kg of beta-lactams represented 74% of the total amount of antibiotics placed on the market. The proportion in preparations for oral application in small animals was even greater, 80%. Penicillins (58% of the beta-lactams) and cephalosporins (42%) contributed comparable proportions.

If we compare these quantities with the farm animal population the quantity of antibiotics sold in Switzerland per kilo of body weight (approx. 90 mg/kg) is comparable with that sold in Germany, Great Britain and the Czech Republic (Grave, 2010).

## Antibiotic resistance in farm animals

In 2009 samples of broilers, fattening pigs and cattle were taken to monitor antibiotic resistance in the slaughterhouse and then examined in the ZOBA (centre for zoonoses, bacterial animal diseases and antibiotic resistance).

As *Salmonella* is only rarely found in Swiss livestock, there is no active monitoring for this bacterium. However, all *Salmonella* isolated from clinical material sent to the ZOBA as part of its reference role is investigated for antibiotic resistance. The results for *S.* Typhimurium and *S.* Enteritidis have also been compiled in this report for the first time.

**Table 1: Antibiotic resistance monitoring programme 2009**

| Type of test | Number of samples | Bacterium tested | Number of resistance tests |
|---|---|---|---|
| Broiler caecum | 442 (groups of 5) | *Campylobacter* | 185 |
| Broiler caecum | 238 (groups of 5) | *E. coli* | 136 |
| Broiler caecum | 206 (groups of 5) | *Enterococcus* | 183 |
| Faecal swab – pigs | 350 | *Campylobacter* | 191 |
| Faecal swab – pigs | 202 | *E. coli* | 181 |
| Faecal swab – pigs | 392 | *Enterococcus* | 141 |
| Nose swab – pigs | 393 | MRSA | 9 |
| Faecal swab – cattle | 188 | *E. coli* | 132 |
| Faecal swab – cattle | 188 | *Enterococcus* | 38 |
| Clinical material | not applicable | *S.* Typhimurium | 46 |
| Clinical material | not applicable | *S.* Enteritidis | 22 |

## Resistance in zoonotic agents from healthy animals

High resistance rates of 31–41% to (fluoro-)quinolones and 20–32% to tetracycline were found in *Campylobacter* from broilers. Even higher values were found in *C. coli* to streptomycin, of which 48% of the isolates demonstrated resistance. The high rates of resistance to (fluoro-)quinolones can be explained by the therapeutic use of enrofloxacin, which belongs to this class of substances. A comparison of the resistance rates of *C. jejuni* and *C. coli* from broilers in recent years also shows that there is increasing resistance to these substances. This is a worrying development, because (fluoro-)quinolones belong to the most important classes of antibiotics in both veterinarian and human medicine.

In fattening pigs the *C. coli* isolates showed a very high resistance of 73% to streptomycin. With rates of 35%, there was also a high rate of resistance to (fluoro-)quinolones. 24% of isolates were resistant to tetracycline. Resistance rates to tetracycline and streptomycin have been decreasing in recent years.

Nine meticillin-resistant *Staphylococcus aureus* (MRSA) strains were found in the nose swab samples from pigs. In addition to resistance to the beta-lactam antibiotics, six MRSA isolates also demonstrated resistance to macrolide antibiotics. This means that the prevalence of MRSA in Swiss pigs is still small in comparison with other countries.

## Resistance in indicator bacteria from healthy animals

In comparison with previous years, the antibiotic resistance of *E. coli* in broilers, pigs and cattle has not changed significantly. The proportion of resistant *E. coli* isolates is considerably higher in broilers and pigs than in cattle. On the other hand, high to very high rates of resistance to sulfamethoxazole, streptomycin, tetracycline and ampicillin were found, as they are in widespread use in livestock in Switzerland.

Frequent examples of resistance were found in *enterococci*. *E. faecalis* isolates were very often resistant to neomycin, with 87–94% resistance rates. Resistance to tetracycline (52–69%) and bacitracin (32–50%) was also very high. Two vancomycin-resistant strains of *E. faecalis* were isolated from pigs. A high to very high proportion of the *E. faecium* isolates was resistant to bacitracin and quinupristin/dalfopristin.

## Resistance in *Salmonella* from clinical material

In comparison to last year, the antibiotic resistance in *Salmonella* isolates from clinical material has not changed. *S.* Typhimurium strains showed greater rates of resistance than *S.*

Enteritidis strains, with resistance to ampicillin, streptomycin, sulfamethoxazole and tetracycline the most common.

## Conclusion

Although the situation in Switzerland is still much better than in other countries, the situation has worsened in respect of some bacteria-antibiotic combinations. All sectors affected by this problem must therefore make greater efforts to minimize the danger of antibiotic resistance developing. Hence, changes in the prevalence of antibiotic resistance will be of particular interest in the continuous monitoring programme on antimicrobial resistance in Swiss livestock over the coming years.

# OVERVIEW

The joint publication of data on sales of antibiotics in veterinary medicine and antibiotic resistance in livestock allows the association of the respectively recorded values and developments. However, conclusions are only possible to a limited extent, with sales figures not allowing an exact estimate of the actual use of antibiotics in the various types of animals, and due to the fact that resistance development is partly monitored on the basis of few isolates only or over a short observation period.

However, below we have attempted to discuss some of the notable results from both reports attached.

## Fluoroquinolones and *Campylobacter* in broilers

Resistance rates to fluoroquinolones (FQ) are on the increase in both *C. jejuni* and *C. coli*.

An increase in resistance to this antibiotic group is worrying because fluoroquinolones are considered to be particularly important in human and veterinary medicine and resistant bacteria can make it difficult to treat *Campylobacter* infections in humans (FAO/WHO/OIE, 2008).

In Switzerland only a few antibiotic preparations are specifically licensed for use as pharmaceutical premixes and in poultry: besides enrofloxacin, there are amoxicillin, colistin, tylosin, tiamulin and tilmicosin. Colonization with *Campylobacter* does not cause illness in chickens, so none of the preparations mentioned is licensed to treat *Campylobacter* infections in poultry. The resistance issue therefore is likely an undesirable consequence of the use of antibiotics against other pathogens.

Countries where fluoroquinolones has never been licensed for use in poultry only have a low prevalence resistance to FQ, or even no FQ resistant *Campylobacter jejuni* were found (Miflin, 2007). Resistance to fluoroquinolones can develop relatively quickly in *Campylobacter* as it is primarily acquired by a point mutation in the gyrA gene (Zhang, 2003). This simple mechanism leads us to suspect that a reduction in FQ use would enable us to achieve a reduction in the resistant population. Various studies have indeed shown a certain reduction. For example, one year after the ban on the use of fluoroquinolones in poultry in the USA (FDA, 2005) 8.5% FQ resistant bacteria was isolated in Louisiana (Han, 2009). In comparison with that, the prevalence for the whole USA prior to the ban was an average of 19%. On the other hand, other studies have shown that despite a ban, the prevalence of FQ resistant *Campylobacter* does not drop, or only slowly (Price, 2007). This could be attributable to the fact that resistant bacteria have a better chance of survival even without the use of antibiotics and can form a reservoir in the environment. It was actually shown for *C. jejuni* in vivo that FQ resistant strains could multiply better than non-resistant strains (Luo, 2003).

The quantities of fluoroquinolones actually used in poultry production cannot be deduced from the sales statistics, since most preparations (including those containing FQ) are also licensed for other livestock animals. In 2009 a total of 40 kg of FQ was placed on the market in pharmaceutical premixes. Had the total amount been used to treat broilers, at the recommended dose of 10 mg/kg this would correspond to the treatment of approximately 2 million broilers, or approximately 4% of chickens slaughtered in Switzerland (Proviande, 2010). An estimation based on research in slaughterhouses revealed that 6.3% (95% CI 4.3–9%) of the broiler flocks raised in Switzerland were treated with fluoroquinolones. These figures indicate that additional factors, such as the above-mentioned bacterial fitness, may play an important role in developing resistance and it must be assumed that the spread of FQ resistance in *Campylobacter* does not decrease even without the selection pressure from FQ antibiotics.

## Resistant bacteria in milk

Since 2006 no more milk products have been investigated for resistance as part of our antibiotic resistance monitoring. However, the sales figures published for intramammary preparations in this sector reveal a considerable increase for classes that are defined as critical by the WHO (FAO/WHO/OIE, 2008). Sales of cephalosporins of the newer 3rd and 4th generations for intramammary application in particular have shown a sharp increase of 169% since 2006. As mentioned, this can partly be attributed to the licensing and subsequent launch of new preparations.

The use of the newer cephalosporines can lead to the selection of gram-negative bacteria with extended-spectrum beta-lactamases (ESBLs). So far this connection has only been demonstrated in a few isolated cases. It was established in pigs that the use of cephalosporins of the 3rd and 4th generations leads to higher levels of persistence of ESBLs in gut bacteria such as *E. coli* (Cavaco, 2008). Studies from human medicine also reveal an influence from the use of this antimicrobial on the selection of ESBL-producing bacteria (Medeiros, 1997; Gniadkowski, 2001). It was shown in a simulation that up to 75% of the monthly variations in the incidence of ESBLs can be attributed to the use of this group of antimicrobials, but that this could occur with a latency of up to three months (Kaier, 2009). The principle of selection pressure should therefore be applicable to use in animals (SAGAM, 2008). However, there is currently no proof of transmission of such resistant bacteria from animals to people (Carattoli, 2008). More recent studies from Holland show, however, that 10% of the resistance genes from human ESBL-producing *E. coli* were identical to those of *E. coli* in chickens (Mevius, 2010).

The systematic application of dry cow therapy can also affect the resistance pattern of the gut flora in the treated cows (Mollenkopf, 2010). One study showed, for example, that the prevalence of resistant coliform bacteria in herds is significantly higher if these have been treated with cephalothin-containing dry cow therapy (first generation). On the other hand there was no proof of selection pressure when a combination of penicillin and streptomycin was used. The authors attribute the resistance observed in the gut flora either to the spread of resistant bacteria or to the contamination of the surrounding area with drops of antibiotic-containing milk.

The greatest problem with gram-positive bacteria is meticillin-resistant *Staphylococcus aureus* (MRSA). There are countless reports about their prevalence in milk (Huber, 2010; Fessler, 2010; Vanderhaeghen, 2010; Türkyilmaz, 2010), and in some of these cases the bacteria show resistance to up to six different classes of antibiotics (Fessler, 2010; Türkyilmaz, 2010). The prevalence of *S. aureus* in biofilms can make the problem even worse (Melchior, 2006a). It was shown that the minimum inhibitory concentration (MIC) in biofilm bacteria was three times higher for cloxacillin, and between one and three times higher for cephalothin, cefoperazone and cefquinome (Melchior, 2006b) than in the bacteria that did not form any biofilm.

The milk of treated cows can be fed to calves during the waiting period under Article 24 par. 2 of the Veterinary Medicines Ordinance (TAMV). Feeding milk with subinhibitory antibiotic concentrations to calves contributes to the selection of resistance in gut bacteria. This is shown by the example of the increase in resistant *enterococci* after feeding with milk containing spiramycin (Würgler-Aebi, 2004).

As with every use of antibiotics, intramammary application also leads to the development of resistance. Current resistance monitoring focuses on observing the resistance situation in gut bacteria in cows and calves. Considering the above-mentioned risks with the intramammary use of antibiotics, it would make sense to monitor the development of resistance in bacteria isolated from milk more systematically over the next few years. In this way the changes in sales figures could be better associated with the prevalence of resistance and any trends identified.

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