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Report on the sales of antibiotics for veterinary use and

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SUMMARY

Use of antibiotics in veterinary medicine

In 2013, a total of 57,157 kg of antibiotics were sold for veterinary medicine, which constitutes a decrease of 8.3% in comparison with the previous year. Compared with the peak year to date – 2008 – this even represents a decrease in the total quantities of 21.1% (15,335 kg). In terms of quantity, and as for the previous year, sulfonamides were most widely used, followed by penicillins and tetracyclines. The proportion of medicated foodstuffs in the total quantities constituted around two-thirds, as was the case for previous years. In contrast to the trend towards an increase in cepalosphorins over many years, a decrease was observed for the first time in 2012. Whether this will become a long-term trend remains to be seen.

The PCU method developed by the ESVAC was also used in Switzerland. It shows that standardising sales data on antibiotics by animal population (milligrams of active pharmaceutical ingredient per PCU) has led to a constant decrease since 2008. This indicates that the decreasing use of antibiotics cannot be attributed to the decline in the number of animals alone.

Antibiotic resistance in livestock

Since 2006 various standardized tests have been carried out in Switzerland as part of a national surveillance programme to assess the situation regarding antibiotic resistance in broilers, fattening pigs and cattle.

The development and spread of antimicrobial resistance has become a growing problem in human and veterinary medicine over the last few years. It is difficult to estimate to what extent the resistance seen in bacteria that are transmitted through animal-based food impacts on human medicine. Equally the role of food in the transfer of resistance genes has not yet been sufficiently studied (EFSA 2008, EFSA & ECDC 2013). Nevertheless, continuous monitoring of the development of resistance in zoonotic pathogens and indicator bacteria in livestock is a basic requirement for gaining a better understanding of how resistance spreads by this route, and it is thus also a basis for evaluating measures for an improvement in the situation.

Zoonotic pathogens

In *C. jejuni* from broilers the resistance to ciprofloxacin has increased significantly since 2006. It rose from 15% in 2006 to more than 40% in 2011. In the latest study from 2012 the resistance rate is still 33.3%.

In pigs, the rate of *C. coli* strains resistant to streptomycin is very high at around 70.8%. In 2006, however, it was over 90% and has since fallen significantly. High rates of resistance to tetracycline and ciprofloxacin have also been found, and in the case of ciprofloxacin a statistically significant upward trend has been discernible since 2006.

Both *C. jejuni* and *C. coli* from bovine isolates show medium to high proportions of strains resistant to (fluoro)quinolones (ciprofloxacin and nalidixic acid). *C. jejuni* in particular shows a high proportion of strains resistant to tetracycline. Compared with 2006, the rate of resistance to ciprofloxacin has increased (14.3% vs 36.8%), while the rate of resistance to streptomycin has fallen (35.7% vs 5.3%).

Table 1: Antibiotic resistance monitoring programme 2012

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cloacal swab - broilers	564	*Campylobacter* spp.	185
Cloacal swab - broilers	218	*E. coli*	185
Cloacal swab - broilers	249	Enterococci	190
Cloacal swab - broilers	168	ESBL	61
Faecal swab - fattening pigs	305	*Campylobacter* spp.	145
Faecal swab - fattening pigs	208	*E. coli*	185
Faecal swab - fattening pigs	398	Entercocci	147
Faecal swab - fattening pigs	171	ESBL	20
Nasal swab – fattening pigs	397	MRSA	72
Faecal swab - slaughter cattle	373	*Campylobacter* spp	48
Faecal swab - slaughter cattle	202	*E. coli*	187
Faecal swab - slaughter cattle	393	Enterococci	114
Faecal swab - slaughter cattle	170	ESBL	7
Clinical material / all animal species	-	*Salmonella* spp.	120
Clinical material / all animal species	-	*S.* Typhimurium incl. monophasic variant	55
Clinical material / all animal species	-	*S.* Enteritidis	11

On the other hand, the occurrence of MRSA in Switzerland has increased significantly with a prevalence of 18.1%. In 2009 and 2011, prevalence was very much lower at 2% and 5.6%, respectively. The results show that one clonal MRSA line in particular (CC398-t034) is spreading widely in Switzerland's population of slaughter pigs. This MRSA type is also frequently found in the livestock of other European countries and is a so-called livestock-associated MRSA. In a case-control study carried out on the pig holdings sampled in 2012, no common source of the MRSA could be established.

Overall, only a few salmonella isolates were available from clinical material. As in previous years, S. Typhimurium isolates from birds and bovine animals show higher rates of resistance than S. Enteritidis isolates. The forms of resistance found most frequently were to ampicillin, streptomycin and sulfamethoxazole.

Indicator bacteria

In *E. coli* isolates, medium to high rates of resistance to ampicillin, streptomycin, sulfamethoxazole, tetracycline and trimethoprim are found in all animal species. Broilers also frequently show resistance to ciprofloxacin and nalidixic acid. The resistance of *E. coli* to both antibiotics and also to ampicillin has significantly increased in broilers over the last few years. In pigs, the resistance situation has not significantly changed compared with previous years. In bovine animals, *E. coli* isolates resistant to tetracycline, sulfamethoxazole, streptomycin and ampicillin have significantly increased in the last few years.

Testes on the enterococcal species *E. faecalis* and *E. faecium* showed some extremely high rates of resistance to neomycin in all three animal species. In *E. faecalis* high to very high rates of resistance to tetracycline and erythromycin were likewise seen in all three animal species, the resistance to these two antibiotics having significantly decreased in broilers over the last year. *E. faecium* isolates from poultry and pigs also show high to very high rates of resistance to quinupristin/dalfopristin, but low resistance to ampicillin. In the last 3 years, no further resistance to vancomycin has been found in enterococcocci.

The results of studies on ESBL/pAmpC-producing *E. coli* did not significantly differ from those in 2011. Using selective methods, ESBL/pAmpC-producing *E. coli* were found in 38.1% of broiler flocks, in 11.7% of fattening pigs and in 4.1% of cattle. Besides resistance to beta-lactam antibiotics, the isolates showed very high to extremely high rates of resistance to (fluoro)quinolones, sulfonamides and tetracycline in all 3 species. The rates of resistance were likewise extremely high with regard to streptomycin and trimethoprim in pigs and cattle and also to gentamicin and kanamycin in cattle. No resistance to carbapenem was found. To gain a better understanding of the extent to which the resistance found impact human medicine, the findings are currently undergoing further characterization in a study by the Institute of Veterinary Bacteriology at the University of Bern and being compared with isolates from humans.

Conclusion

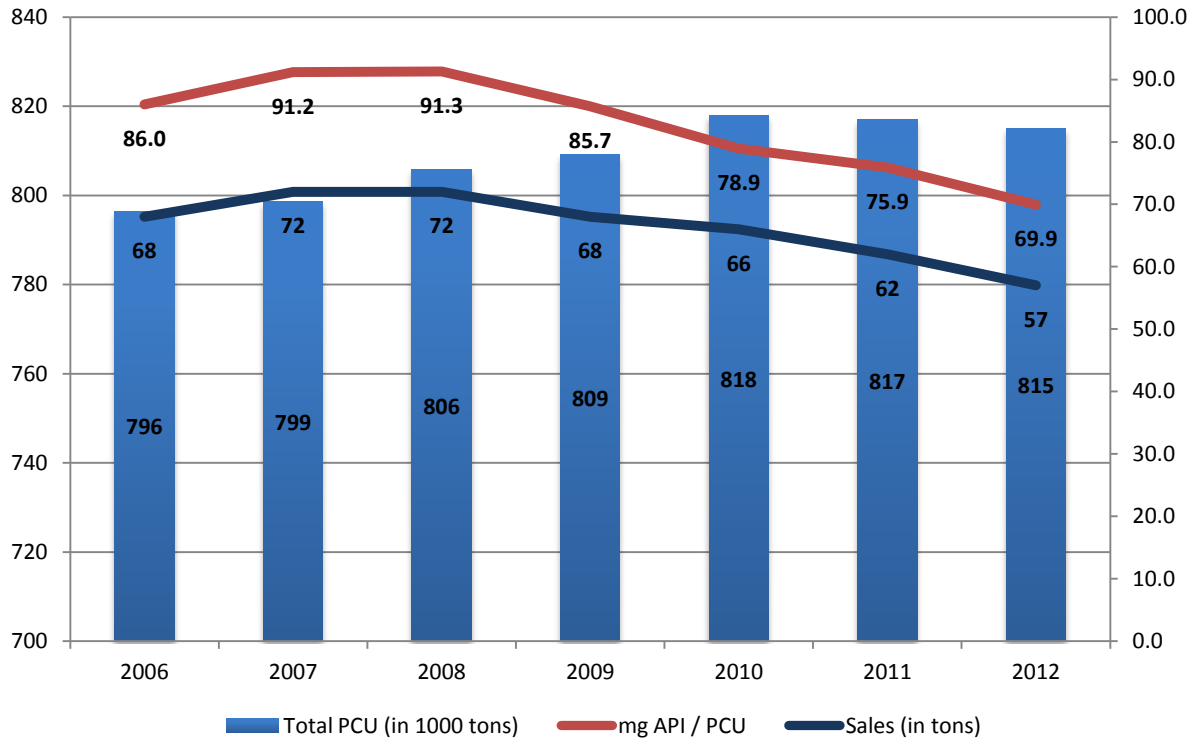
Resistance is frequently found in Switzerland both in zoonotic pathogens and also in indicator bacteria of healthy livestock. MRSA is spreading in Switzerland's pig population and resistance to important antibiotics is continuing to grow in some cases. This shows that measures must be urgently developed and introduced to reduce the problem.

In focus

Introduction of the standardisation of sales data on antibiotics by animal population (PCU method)

The quantity of antibiotics sold is to a large extent dependent on the number of animals treated. Within the framework of the EU ESVAC project, a standardisation method was therefore developed making it possible to link overall sales to the overall population (EMA, 2011). Since the population of domestic animals is not known in many countries, only livestock was taken into consideration. For this purpose, the "PCU" (Population Correction Unit) was developed: 1 PCU = 1 kg, calculated using the number of live animals (dairy cows, sheep, sows, horses) and slaughtering animals (veal / bovines, pigs, lambs, poultry, turkeys). These figures are then multiplied by the theoretical weight at the time of processing. The import and export of live animals is also taken into account.

The PCU method was applied to standardise the overall sales in Switzerland. The graph below shows the sales figures, the population biomass (total PCU) and the milligrams of antimicrobial active pharmaceutical ingredients (API) / PCU for the years 2006 to 2012.



This graph demonstrates that the population biomass grew between 2006 and 2010 and then dropped slightly until 2012. Sales, however, increased until 2008 and then decreased. Since the sales of antibiotics decreased more sharply than the population biomass, the result is a net decrease of the milligram of active pharmaceutical substance per PCU. This indicates that the decreasing use of antibiotics is not the result of the decline in the number of animals alone.

Significant increase in MRSA among fattening pigs in Switzerland

Staphylococcus (S.) aureus is a bacterium that colonizes the skin and mucous membrane of humans and animals without inducing disease (den Heijer et al., 2013). But in some cases, these *S. aureus* bacteria are also isolated as pathogens of wound infections and inflammation of the airways. Such infections can normally be treated without any complications using antibiotics. But if infections occur with methicillin-resistant *S. aureus* (MRSA), which are resistant to all beta-lactam antibiotics (penicillins and cephalosporins) and often also to other classes of antibiotics, treatment is difficult and the infection can run a severe course.

MRSA is also found in livestock and in food of animal origin. Europe has seen the substantial spread of a specific type of MRSA in recent years. It belongs to the clonal complex CC389, where above all the spa types t034 and t011 occur particularly often in pigs. This type of MRSA is described as livestock-associated MRSA (LA-MRSA).

In 2008, a Europe-wide baseline survey on the occurrence of MRSA in holdings with breeding pigs was carried out in dust samples (EFSA; 2009). In the context of this study no MRSA was detected in Switzerland. Since 2009 the occurrence of MRSA has been surveyed in slaughter pigs based on nasal swabs taken as part of the national resistance monitoring programme. In the first few years of these studies, only a few isolated pigs were found to be carriers of MRSA. But even then there was an increase from 2% in 2009 to 5.6% in 2011 (Overesch, 2011; 2012). But these values were low by international standards until 2011 (ARCH-Vet, 2009, 2010;ARCH-Vet 2010, 2011; ARCH-Vet 2011, 2012).

In 2012, a marked increase has now been seen in the occurrence of MRSA in slaughter pigs. Overall, 18.1% of the 397 pigs tested were carriers of MRSA. The results of typing show that the increase was mainly attributable to the spread of a particular clone of LA-MRSA (CC398). Besides resistance to beta-lactams, all MRSA isolates were also resistant to tetracycline. Extremely high rates of resistance of 85 – 90% were also seen with regard to macrolide/lincosamide antibiotics (erythromycin/clindamycin) and to quinupristin/dalfopristin, tiamulin and trimethoprim.

To establish whether a common source could be found for the colonization of slaughter pigs with MRSA, a survey was carried out among the pig keepers whose animals tested positive in the 2012 study and among the same number of keepers with pigs that tested negative. Preliminary results show that the fattening pigs which tested positive came from all over Switzerland and no high risk establishments were found even among piglet producers (Bangeter, Overesch; personal communication). Further studies are needed to gain a better epidemiological understanding of the way MRSA spreads within the pig population in Switzerland and to come up with proposals for targeted measures to stem the spread.

Whether or not MRSA occurs in an animal holding is primarily determined by whether the bacterium is introduced to the herd and spread by people, animals or contaminated material. For the persistence and dynamics of MRSA in the livestock population, however, the use of antibiotics appears to play only a subordinate role (Broens et al., 2012; Weese et al., 2011). Nevertheless, caution in the use of antibiotics is important for reducing selection pressure in favour of resistant pathogens. In addition, however, biosafety measures, such as thoroughly cleaning and disinfecting the housing facilities between fattening cycles and preventing introduction of the microorganism, are important for reducing the risk of colonization with MRSA. Since transmission of LA-MRSA between pigs is very easy, it has to be expected that LA-MRSA will remain in a population for a long time even if no antibiotics are used (Broens et al., 2012, Crombe et al., 2012).

With regard to the impact of MRSA from livestock on human medicine, a risk assessment by EFSA (EFSA, 2009) comes to the conclusion that most MRSA infections in humans are caused by hospital or population-associated MRSA, which comes about through direct or indirect contact with infected humans.

Colonization with LA-MRSA is possible, however, through direct contact with infected animals. Those most at risk are animal keepers, veterinarians and slaughterhouse workers. Colonization with LA-MRSA has been found more frequently in these groups than in the normal population (Cuny et al., 2009). Human-to-human transmission of LA-MRSA has been found to be much rarer than with other strains of MRSA, which are better adapted to humans, so relatives of veterinarians and family members of animal owners without direct contact with animals are only rarely colonized with LA-MRSA and the spread of this strain in the hospital setting is less common (Cuny et al., 2009, Wassenberg et al., 2011). Nevertheless, more recent studies from Holland, a country in which the occurrence of LA-MRSA in the animal population is very high, show that humans without direct contact with livestock are also increasingly colonized with LA-MRSA (Price et al., 2012). A study in hospitals in Holland and Germany, where admitted patients are tested for MRSA, also show that a total of 29% of the MRSA detected was LA-MRSA and that this LA-MRSA was also found in 8% of cases of septicaemia and 14% of respiratory infections caused by staphylococci (Kock et al., 2013).

In Switzerland, the number of isolated MRSA in hospitals has remained constant since 2004, but the number of MRSA isolations in outpatient clinics has increased significantly over this period (Anresis, 2013). There are no national typing data for Switzerland from human medicine, so it cannot be assessed at present whether the increase in LA-MRSA in the pig population is also accompanied by a greater occurrence of these strains in humans.

There appears to be hardly any transmission of MRSA through food, according to current knowledge. While MRSA has been found in meat from livestock (EFSA & ECDC, 2012), no transmission of such bacteria to humans has been detected to date. In Switzerland, as far as we know, food of animal origin has only once been tested for MSRA on a major scale, and no positive samples were found (Huber et al., 2010).

To protect against colonization with MRSA, the usual hygiene measures have to be observed when handling food and animals. It is particularly important here to wash the hands thoroughly with soap and water after contact with animals and also before and after the preparation of raw meat.

Further monitoring of the occurrence and also research into the correlations and spread of MRSA in humans and animals are necessary to ensure a better assessment of the risk and to facilitate the development of concrete measures. A joint approach by all the sectors involved will be crucially important in order to assess the situation properly. It is to be hoped that the National Strategy on antibiotic resistance, which has been commissioned by Federal Councillors Alain Berset and Johann Schneider-Ammann and is being elaborated under the aegis of the Federal Office of Public Health together with the Federal Veterinary Office and the Federal Offices for Agriculture and the Environment, as well as other stakeholders within and outside the federal administration, will be the starting point for further interdisciplinary cooperation.

Literature

ANRESIS: Antibiotic Resistance Data in Switzerland, University of Bern, www.anresis.ch, last accessed 12 July 2013

ARCH-Vet 2009, 2010: Bericht über den Vertrieb von Antibiotika in der Veterinärmedizin und das Antibiotikaresistenzmonitoring bei Nutztieren in der Schweiz. Swissmedic / BVET; 59 pp.

ARCH-Vet 2010, 2011: Bericht über den Vertrieb von Antibiotika in der Veterinärmedizin und das Antibiotikaresistenzmonitoring bei Nutztieren in der Schweiz. Swissmedic / BVET; 65 pp.

ARCH-Vet 2011, 2012: Bericht über den Vertrieb von Antibiotika in der Veterinärmedizin und das Antibiotikaresistenzmonitoring bei Nutztieren in der Schweiz. Swissmedic / BVET; 76 pp.

Broens, E. M., E. A. Graat, A. W. van de Giessen, M. J. Broekhuizen-Stins and M. C. de Jong 2012: Quantification of transmission of livestock-associated methicillin resistant Staphylococcus aureus in pigs. Vet Microbiol 155(2-4): 381-388.

Crombe, F., W. Vanderhaeghen, J. Dewulf, K. Hermans, F. Haesebrouck and P. Butay: 2012. Colonization and transmission of methicillin-resistant Staphylococcus aureus ST398 in nursery piglets. Appl Environ Microbiol 78(5): 1631-1634.

Cuny, C., R. Nathaus, F. Layer, B. Strommenger, D. Altmann and W. Witte 2009: Nasal colonization of humans with methicillin-resistant Staphylococcus aureus (MRSA) CC398 with and without exposure to pigs. PLoS One 4(8): e6800.

den Heijer, C., E. van Bijnen, W. Paget, M. Pringle, H. Goossens, C. Bruggeman, F. Schellevis, E. Stobberingh and A. S. Team 2013: Prevalence and resistance of commensal Staphylococcus aureus, including methicillin-resistant S aureus, in nine European countries: a cross-sectional study. Lancet Infect Dis 13(5): 409-415.

EFSA, 2008: Report from the Task Force on Zoonoses Data Collection including guidance for harmonized monitoring and reporting of antimicrobial resistance in commensal Escherichia coli and Enterococcus spp. from food animals. The EFSA Journal, 141, 1-44. Available online: www.efsa.europa.eu/efsajournal.

EFSA, 2009: Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Assessment of the Public Health significance of methicillin resistant Staphylococcus aureus (MRSA) in animals and foods. The EFSA Journal, 993, 1-73. Available online: www.efsa.europa.eu/efsajournal.

EFSA& ECDC, 2012: The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union in 2010. EFSA Journal 10, 233. Available online: www.efsa.europa.eu/efsajournal.

EMA (European Medicines Agency), 2011. Trends in the sales of veterinary antimicrobial agents in nine European countries (2005-2009). (EMA/238630/2011).

Huber, H., S. Koller, N. Giezendanner, R. Stephan and C. Zweifel 2010: Prevalence and characteristics of methicillin-resistant Staphylococcus aureus in humans in contact with farm animals, in livestock, and in food of animal origin, Switzerland, 2009. Euro Surveill 15(16).

Kock, R., F. Schaumburg, A. Mellmann, M. Koksal, A. Jurke, K. Becker and A. W. Friedrich 2013: Livestock-associated methicillin-resistant Staphylococcus aureus (MRSA) as causes of human infection and colonization in Germany. PLoS One 8(2): e55040.

Overesch, G., S. Büttner, A. Rossano, V. Perreten, 2011: The increase of methicillin-resistant Staphylococcus aureus (MRSA) and the presence of an unusual sequence type ST49 in slaughter pigs in Switzerland. BMC Veterinary Research 7:30.

Overesch, G., S. Büttner, V. Perreten, 2012: Entwicklung der Prävalenz von MRSA des Sequenztyps ST49. Fleischwirtschaft 92 (12): 95-97.

Price, L. B., M. Stegger, H. Hasman, M. Aziz, J. Larsen, P. S. Andersen, T. Pearson, A. E. Waters, J. T. Foster, J. Schupp, J. Gillece, E. Driebe, C. M. Liu, B. Springer, I. Zdovc, A. Battisti, A. Franco, J. Zmudzki, S. Schwarz, P. Butaye, E. Jouy, C. Pomba, M. C. Porrero, R. Ruimy, T. C. Smith, D. A. Robinson, J. S. Weese, C. S. Arriola, F. Yu, F. Laurent, P. Keim, R. Skov and F. M. Aarestrup 2012: Staphylococcus aureus CC398: host adaptation and emergence of methicillin resistance in livestock. MBio 3(1).

Wassenberg, M. W., M. C. Bootsma, A. Troelstra, J. A. Kluytmans and M. J. Bonten, 2011: Transmissibility of livestock-associated methicillin-resistant Staphylococcus aureus (ST398) in Dutch hospitals. Clin Microbiol Infect 17(2): 316-319.

Weese, J. S., A. Zwambag, T. Rosendal, R. Reid-Smith and R. Friendship 2011: Longitudinal investigation of methicillin-resistant Staphylococcus aureus in piglets. Zoonoses Public Health 58(4): 238-243.