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Use of Antimicrobials in Food-producing Animals in Switzerland and the European Union (EU)

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A new era in human medicine began in the 1930's with the discovery of antimicrobial agents. Sulfonamides were the first antibiotics introduced into the hospital. Although penicillin was first discovered in 1929, this drug has only been deployed for therapy of bacterial diseases in humans since 1940. In the following decades, a wide variety of antibiotics such as streptomycin, chloramphenicol, tetracycline, erythromycin and quinolones have been developed. Soon after their introduction in human medicine, antibiotics were also used in veterinary medicine to treat and to prevent infectious diseases in animals. Additionally, subtherapeutic doses of antibiotics were used as feed additives to improve growth rate in animals. However, infectiology soon became confronted with bacteria that developed antibiotic resistances, which since the 1980's led to severe problems in antibiotics therapy (1). Moreover, since that time, the development of antibiotics consisted solely of modifications and improvements of existing drugs, but not of the discovery of a new class of antibiotics. Important pathogenic bacteria such as *Salmonella, Escherichia coli, Campylobacter, Mycobacterium tuberculosis,* staphylococci, enterococci and *Pseudomonas* species are today resistant to many antibiotics. Bacteria possess several mechanisms to fight back at antibiotics thereby developing resistances. This results from either specific DNA mutations that modify targets or from the acquisition of antibiotic resistance genes that specify for enzymes that can inactivate antibiotics, prevent their access to their targets or generate their removal out of the cell. Such genes can be found on transmissible genetic elements like plasmids, transposons or integrons that can be exchanged between bacteria (2).

In Europe, many antibiotics that have been used as growth promoters have belonged to the same classes as important antibiotics used in human medicine. Thereby, antibiotic resistant bacteria from animal origin were selected for and turned out to show cross resistance against antibiotics currently used in human med-

icine (3, 4). The use of these antibiotics as feed additives represents a threat to the effectiveness of antibiotic therapy particularly if antibiotic resistance genes are transmitted to pathogenic bacteria that cause human and animal diseases (5). The multidrug resistant *Salmonella* Typhimurium DT104 originally isolated from cattle, has spread worldwide and represents a significant hazard to humans (6, 7, 8). Isolates of *Salmonella* Typhimurium DT104 that are resistant to up to nine different antibiotics are currently encountered (9). Furthermore, vancomycin resistant enterococci from animal origin harbouring transferable *vanA* genes can potentially transfer the vancomycin resistance gene to multidrug resistant *Staphylococcus aureus* (10).

To face the increasing amount of antibiotic resistant bacteria and to limit the potential transfer of antibiotic resistance genes of resistant bacteria from animals to human pathogens, the Swann Committee of the United Kingdom recommended in 1969 that antibiotics used for therapeutic purposes or generating cross-resistances to therapeutically used antibiotics should not be used as growth promoters (11). In response to the Swann Committee, some antibiotics such as penicillin, streptomycin and tetracyclines have been restricted to therapeutic use only. However, eleven other antimicrobial substances were still allowed to be used as growth promoters until their withdrawal in the late 1990's (see below). The authorized drugs included avoparcin, bacitracin, flavomycin, spiramycin, tylosin, virginiamycin, carbadox, olaquindox, monensin, salinomycin and avilamycin.

Regulation of antibiotic use in food-producing animals in the EU and in Switzerland

In the European Union, the use of antibiotics in feeding stuff and in veterinary medicine are regulated separately: the decisions for antimicrobial growth promoting feed additives are made through the European Commission, after consultation with the Scientific Committee on Animal Nutrition and after hearing the member states. The regulations of growth promoting antimicrobial feed additives are based on the 1970 Council directive (70/524/EEC) including its amendments (especially 96/51/EC). The individual EU countries regulate the authorization of antibiotics for animal therapy. This led to the situation whereby certain antibiotics authorized in some countries are forbidden in others. To obtain an EU wide authorization for sales, drug companies must get first the approval from The European Agency for the Evaluation of Medicinal Products (EMEA) (http://www.emea.eu.int) (12) and then from the European Commission.

In Switzerland, the regulations concerning the use of antibiotics as growth promoters are listed in the Federal Law for Agriculture (LAgr SR 910.1). The Federal Law on Medicinal Products and Medicinal Devices [Law on Therapeutic Products SR 812.21 (January 1st, 2002)] regulates the use of antibiotics in veterinary medicine. Antibiotics can only be used under the control of a veterinarian and the animal owners must register the antibiotic use in a treatment book. The Federal Laws can be found in French, German or Italian under the link http://www.admin.ch/ch/f/ rs/rs.html.

Ban of antimicrobial growth promoters in the EU and in Switzerland

In 1986 Sweden, not yet a member of the EU, accomplished pioneering work by banning antibiotic use in animals for non-therapeutic purposes, whereas the antimicrobial feed additives listed above were still in use in the other countries of the EU. A significant turn-around occurred when glycopeptide resistant enterococci from animal origin sounded the alarm (13, 14). *Enterococcus* strains isolated from pigs and chickens were found to harbour the vancomycin resistance gene *vanA* on a transferable element (15, 16). Avoparcin, a glycopeptide antibiotic like vancomycin, had been used as a feed additive for more than 20 years, while at the same time vancomycin was reserved in human medicine as the last weapon to treat infections caused by methicillin resistant *Staphylococcus aureus* (MRSA). The authorization for avoparcin was then withdrawn in Denmark in May 1995, in Germany in January 1996 and in December 1996 in all other EU countries as a preventive measure to avoid the spread of vancomycin resistance to important pathogens (Commission directive 97/6/EC amending Directive 70/524/EEC). It was also decided in January 1998, not to renew the authorization of ardacin, another glycopeptide antibiotic used in feeding stuff (Commission Directive 97/72/EC). Similarly, the Council of Agriculture Ministers decided in December 1998 to withdraw the authorization to use the macrolide antibiotics tylosin and spiramycin as well as the streptogramin antibiotics virginiamycin and bacitracin as growth promoting feed additives beginning July 1st 1999 (Council regulation (EC) No. 2788/98). Macrolides used as growth-promoting feed additives were considered to contribute to the selection of resistant bacteria such as enterococci with the possibility that macrolide resistant *Enterococcus* strains and *erm*-genes (gene conferring cross-resistance to macrolides, lincosamides and streptogramins) could become a threat to human medicine. Macrolides are currently important antibiotics in human medicine, used to treat among others, important respiratory tract infections. The streptogramin antibiotic virginiamycin is suspected to select for the streptrogramin resistance gene *(satA)* that has been shown to be widespread in *Enterococcus* species from pig and poultry origin (17, 18). Two streptogramin antibiotics, namely pristinamycin and the combination dalfopristin/quinupristin are clinically important in human medicine as a last-resort treatment of infections with vancomycin resistant enterococci and staphylococci. In view of their possible adverse effect on human health (genotoxicity), the authorizations for the growth promoters olaquindox and carbadox were withdrawn from the directive 70/524/EEC in December 1998 entering into force August 31st 1999 (Commission Regulation (EC) No 2788/98). By the end of 1999, four antibiotics were still authorized: avilamycin, flavophospholipol (bambermycin), monensin and salinomycin. In March 2002, the European Commission presented new proposals to prohibit any antibiotic for use as growth-promoting feed additives. Under these proposals, the four remaining authorized antibiotics would have to be phased out by January 1st 2006. The EU Council directives and amendments are available on the EurLex website (http://europa.eu.int/eur-lex).

In Switzerland, the use of all growth-promoting antibiotics was banned by January 1st 1999. The regulation is to be found in Article 160, Paragraph 8 of the Federal Law for Agriculture (LAgr SR 910.1) revised in April 1998 and entered into force January 1st 1999.

Amount of antibiotics used for animals in Europe and Switzerland

A study conducted by the European Federation of Animal Health (FEDESA) (http://www.fedesa.be) estimated that in Europe, human consumption represented 65 % of the total volume of antibiotics prescribed in 1999 (8528 tons) while animals consumed 35 % (4688 tons). Due to the ban, the consumption of antibiotics used as growth promoters dropped by 50 % from 1997 (1599 t) to 1999 (786 t). However, the amount of therapeutic antibiotics used in the EU for animals increased 11 % in the same period: 3494 t in 1997 and 3902 t in 1999. In Switzerland, the amount of antibiotics used in animal husbandry is based on the volume of antibiotics imported. The import of antibiotics used as growth-promoting feed additives decreased by 99.8 % between 1995 and 2001. The import of antibiotics used in therapeutic feed was reduced by one half from the same period. However, the amount of antibiotics used for medical treatment of single animals increased by 23 % from 1995 to 2001. In general, the import of antibiotics for animal use has dropped by 50 % in Switzerland over the past six years, going from 80.1 t in 1995 to 34.1 t in 2001 (data obtained from the Federal Office for Agriculture, Berne, Switzerland). The amount of antibiotics imported into the country gives only an indication of the quantity of antibiotics used in animals, as no detailed data are available on the effective volume of antibiotics consumed by animals. To determine the effective amount of antibiotics consumed by pigs, the quantity of active ingredients prescribed yearly by veterinarians for medicated feed was reported for one Swiss canton from 1996 to 2001. This study conducted by Swissmedic (http://www.swissmedic.ch) showed that the amount of antimicrobials effectively consumed by pigs decreased from 1200 kg of active ingredients in 1996 to 935 kg in 2001 (19).

Effect of the ban of antimicrobial growth promoters on the resistances of bacteria

The resistance profile of *Enterococcus* species isolated from faecal samples of pigs receiving the macrolide antibiotic tylosin as an antimicrobial growth promoter before the ban was compared with that of *Enterococcus* species isolated in the same farms six month after the ban. A clear decrease in resistance to the macrolides erythromycin and spiramycin and to the lincosamide clindamycin was observed (20). In enterococci, the resistance to macrolides, lincosamides and streptogramins are most likely due to the presence of one single gene *erm(B)*, which seems to be vanishing in enterococci of porcine origin since the ban of antimicrobial growth promoters in Switzerland.

Use of antibiotics as therapeutics in food-producing animals

Antibiotics authorized for therapy in food-producing animals in the EU and in Switzerland are the same or are structurally related to those used in human medicine. Animals are either treated individually by injection or by oral administration of antibiotics. Entire herds are often treated with antibiotics mixed in with the feed (medicated feed) to prevent or cure bacterial diseases. The oral administration of antibiotics through medicated feed for herd treatment constitutes a stronger selective pressure on the surrounding microflora than administration by injection and thus selects for antibiotic resistant bacteria. In Switzerland, chlortetracycline, sulfadimidine and the combination sulfonamide/trimethoprim are the most prescribed antibiotics for medicated feed in pig production (19). *Escherichia coli* isolated from pigs suffering from diarrhea and oedema diseases were screened for antibiotic resistance (21). Resistance to sulfonamide (81 %), tetracycline (54 %), streptomycin (37 %), spectinomycin and the combination sulfonamide/trimethoprim (20 %) were the most frequent, indicating that a correlation exists between the antibiotics commonly used in pig breeding and the frequency of resistance found in *E. coli*. Resistance data have been compared with those from Sweden (22). Sweden has not used any antibiotics as growth promoters since 1986 and uses mainly tetracycline, the combination sulfonamide/trimethoprim and streptomycin as therapeutics in pig production. Additionally, it has a vaccination program to prevent neonatal piglet diarrhea. In Sweden like in Switzerland, the resistance levels are correlated with the type of antibiotics used. Indeed in Sweden, pathogenic *E. coli* from pigs showed mainly resistance to tetracycline (35 %), streptomycin (27 %) and the combination sulfonamide/trimethoprim (20 %). However, the frequency of antibiotic resistant bacteria is significantly higher in Switzerland than in Sweden.

Pigs in Switzerland as a reservoir of new antibiotic resistance genes

In Switzerland, the sulfonamide resistance of pathogenic *E. coli* from pigs was shown in 70 % of the cases to be due to *sul1* or *sul2* genes (21). The mechanism of sulfonamide resistance for the remaining 30 % of the isolates could be explained by the presence of the new sulfonamide resistance gene *sul3* (23). The *sul3* gene, flanked by two mobile insertion sequences and located on a conjugative plasmid has a strong potential for dissemination within the bacterial population.

Monitoring of antibiotic resistance and surveillance of antibiotic use

The European Commission has responded to the emerging problem of antibiotics resistance by funding the European Antimicrobial Resistance Surveillance System (EARSS; http://www.earss.rivm.nl) that collects comparable and validated antimicrobial susceptibility data of clinical isolates from more than 600 laboratories in 27 countries. The data are published in their annual report (EARSS Annual Report 2001). Monitoring systems and surveillance of antimicrobial resistance in bacteria from food animals have been in place for some years and are published by

the Scandinavian countries Denmark (DANMAP 2001 (24)), Sweden (SVARM 2001 (22)) and Norway (NORM VET 2000 (25)). In Switzerland, a systematic surveillance program of resistance has yet to be established. Additionally, the surveillance of antibiotic resistance should definitely be correlated with a surveillance of antimicrobial usage to develop a prescription system (appropriate use and amount of antibiotics) to avoid the selection of new or existing antibiotic resistance and to optimize the therapy.

In Europe, an effort has been made to reduce the use of antimicrobials in food-producing animals. Current data show that antibiotic resistance in bacteria from animal origin has significantly decreased since the ban of antibiotics as growth promoters. In Sweden in particular, where the use of antimicrobial feed additives was abolished in 1986 and where good surveillance programs have been applied, we observe a very low level of antibiotic resistant pathogens isolated from animals.

A prudent and appropriate use of antibiotics in food-producing animals (e.g. single animal treatment) has to be correlated with good manufacturing practices, good hygiene and vaccination programs. This will keep the level of resistances in bacteria low and avoid the emergence of incurable bacterial diseases.

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Summary

The intensive and inappropriate use of antibiotics in both medicine and agriculture has selected for antibiotic resistant bacteria that cause severe problems in

antibiotic therapy. In animal husbandry, antibiotics are used for therapeutic and preventive treatments of infectious diseases and as growth promoters. In Europe, many antibiotics used as growth promoters were of the same classes as important antibiotics used in human medicine. The European Union withdrew the authorization for the use of the major antimicrobial growth promoters between 1996 and 1999. In 1999 Switzerland decided to ban the use of all antimicrobials as growth-promoting feed additives. The regulations concerning antibiotic use in animal husbandry and the chronological reasons for the ban of antimicrobial growth promoters are described. This ban led to a decrease of the antibiotic volume deployed in agriculture. This measure helps to reduce the amount of antibiotic resistant bacteria in food-producing animals. However, the use of medicated feed is still a common practice to prevent and to remedy bacterial infections and thus still leads to resistant pathogens. Surveillance programs, single animal treatment, good manufacturing practices and vaccinations are additional measures to be taken to keep the level of resistances in bacteria low.

Zusammenfassung

Durch den intensiven und nicht gezielten Einsatz von Antibiotika in der Medizin und in der Landwirtschaft haben pathogene Keime Resistenzen gegen eine Vielzahl von Antibiotika entwickelt. Das Auftreten multiresistenter Krankheitserreger führt heute zu grossen Schwierigkeiten bei Antibiotika-Behandlungen. Antibiotika werden bei Tieren zu prophylaktischen und therapeutischen Zwecken sowie als Wachstumsförderer eingesetzt. Viele, als Wachstumsförderer eingesetzte Antibiotika, waren mit Antibiotika eng verwandt, welche in der Humanmedizin eingesetzt werden. Die Europäische Union hat zwischen 1996 und 1999 die Bewilligungen für gewisse antimikrobielle Wirkstoffe als Leistungsförderer zurückgezogen. In der Schweiz sind alle antimikrobiellen Leistungsförderer seit 1999 verboten. Seitdem wurde die in der Landwirtschaft eingesetzte Menge von Antibiotika reduziert. Dadurch wird der Selektivdruck reduziert, und die Anzahl resistenter Bakterien nimmt ab. Die Anwendung von Antibiotika im Futtermittel ist jedoch weiterhin eine gewöhnliche Praxis zur Verhinderung und Behandlung von Infektionskrankheiten. Dies führt immer noch zur Erzeugung von Antibiotika-resistenten Krankheitserreger. Aus diesem Grund sind Überwachungsprogramme, die Praxis der Einzeltier-Behandlung, gute Merkblätter der Antibiotikahersteller sowie eine rigorose Hygiene notwendig um eine weitere Verminderung von Antibiotika-resistenten Keimen zu erreichen.

Résumé

L'utilisation intensive et inappropriée d'antibiotiques en médecine et dans l'agriculture a eu pour effet de sélectionner des bactéries de plus en plus résistantes aux antibiotiques. Certaines infections bactériennes sont aujourd'hui devenues difficiles à traiter par les antibiotiques. Chez les animaux d'élevage, les antibiotiques sont utilisés

pour traiter et prévenir les maladies infectieuses, mais aussi comme stimulateur de croissance. En Europe, de nombreux antibiotiques utilisés comme stimulateur de croissance étaient de la même famille que ceux utilisés en médecine humaine. Ainsi entre 1996 et 1999, l'Union Européenne a retiré les autorisations pour l'utilisation de la plupart des antibiotiques comme stimulateur de croissance. En Suisse, toute substance antibiotique a été interdite comme stimulateur de croissance dès 1999. Depuis ces interdictions, le volume d'antibiotiques utilisés en agriculture a considérablement diminué. En l'absence de pressions sélectives, le nombre de bactéries résistantes aux antibiotiques diminue aussi. Pourtant, l'utilisation d'antibiotiques directement mélangés au fourrage reste une pratique prophylactique et thérapeutique courante contre les infections bactériennes. Cette pratique présente également le risque d'induire des résistances chez des bactéries pathogènes. Des programmes de surveillance des résistances, un traitement individuel des animaux, de bonnes pratiques d'élevage et d'hygiène pourront permettre de limiter le nombre de résistances chez les bactéries.

Key words

Antibiotics, Resistance, Regulation, Growth promoters, Ban, Animals

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