Usage of Antibiotics and Occurrence of Antibiotic Resistance in Bacteria from Humans and Animals in Switzerland

Joint report 2013

ARCH-Vet
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Foreword

1 Foreword

Antibiotic resistance is an emerging global public health threat. The use of antibiotics contributes to the selection of resistant bacteria leading to treatment failure of bacterial diseases in humans and animals. Resistant bacteria can spread between humans in the community and healthcare. On the other hand, resistant bacteria from animals and the environment can be transmitted to humans either through direct contact or through ingestion of contaminated food or other contaminated vehicles. Increasing global trade and travel favor additionally the spread of antimicrobial resistance between countries and continents. Regarding the complexity of the epidemiology of antimicrobial resistance, it is important to monitor trends in antibiotic resistance in a holistic approach ("One Health approach") including data on usage and resistance in human and veterinary medicine as well as in food production.

In response to the growing concern about antibiotic resistance, the Ministries of home and economic affairs assigned the Federal Office of Public Health (FOPH), the Food Safety and Veterinary Office (FSVO), the Federal Office for Agriculture (FOAG) and the Federal Office for the Environment (FOEN) to develop and implement a national strategy to combat antibiotic resistance ("Strategie Antibiotikaresistenzen, StAR"). The approval by the Federal Council is planned for the end of 2015. The strategy will encompass all the action fields of the different sectors (regulatory, prudent use, surveillance, research, control in hospitals etc.). The global goal of the strategy is to ensure the long-term efficacy of antibiotics in preserving human and animal health. It emphasizes the importance of monitoring antimicrobial drug usage and resistance in both human and veterinary medicine.

The first National Research "Antibiotic Resistance" (NRP 49) in Switzerland was approved in 1999 and ran between 2001 and 2006. A very important achievement of this program was the establishment of a surveillance system for human medicine (anresis.ch). Since 2004, anresis.ch has been collecting routine antibiotic resistance data from human microbiology laboratories. The system has been further developed and at present, it also monitors data on human antibiotic consumption (hospitals and outpatient).

The NRP 49 also provided the basis for a monitoring program in veterinary medicine. In 2006, the FSVO introduced a system to enable the continuous monitoring of resistance in farm animals, meat and dairy products in Switzerland. Additionally it compiles data on sales of antimicrobial agents for veterinary medicine. Since 2009 data on sales of veterinary antimicrobials and results of the monitoring of resistance in farm animals are published yearly in the ARCH-Vet report.

The present report, which is the first joint report from anresis.ch and ARCH-Vet, presents Swiss data for 2013. In addition to resistance data it includes data on the consumption of antibiotics in humans and sales of antimicrobials in veterinary medicine. It is the basis for the detection, interpretation and evaluation of trends regarding usage of antibiotics and occurrence of resistance. Although the data for human and veterinary medicine are presented in one report, it is important to be aware that differences between the monitoring systems for collection, interpretation and reporting hamper direct comparisons of the results. Cooperation and coordination between the different monitoring-networks have to be strengthened and refined to improve comparability and fill the gaps, as it is foreseen in the national strategy on antimicrobial resistance (StAR).

The editors would like to thank all those who contributed to data collection and the writing of this report for their excellent work.

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1 Vorwort

Antibiotikaresistenzen sind ein globales Problem und bedrohen die öffentliche Gesundheit weltweit. Die Verwendung von Antibiotika trägt zur Selektion resistenter Bakterien bei, was zu Behandlungsversagen bei bakteriellen Erkrankungen von Mensch und Tier führt. Resistente Bakterien können sich einerseits zwischen Menschen in der Bevölkerung und in Gesundheitseinrichtungen ausbreiten. Andererseits können resistente Bakterien von Tieren und aus der Umwelt entweder durch direkten Kontakt oder durch kontaminierte Lebensmittel oder andere Trägerstoffe auf Menschen übertragen werden. Zunehmender globaler Handel und Reiseaktivitäten fördern zusätzlich die Verbreitung von Antibiotikaresistenzen über Länder und Kontinente hinweg. Angesichts der komplexen Epidemiologie von Antibiotikaresistenzen ist es wichtig, Trends bei resistenten Bakterien nach einem ganzheitlichen Ansatz («One Health Approach») zu überwachen und Daten zur Antibiotikaverwendung und Resistenzlage aus der Human- und Veterinärmedizin sowie der Lebensmittelproduktion einzubeziehen.

Als Reaktion auf die wachsende Besorgnis bezüglich Antibiotikaresistenzen erteilten die Eidgenössischen Departemente des Innern (EDI) und für Wirtschaft, Bildung und Forschung (WBF) den Bundesämtern für Gesundheit (BAG), für Lebensmittelsicherheit und Veterinärwesen (BLV), für Landwirtschaft (BLW) und für Umwelt (BAFU) den Auftrag, eine nationale Strategie zur Bekämpfung von Antibiotikaresistenzen (StAR) zu entwickeln und umzusetzen. Die Verabschiedung durch den Bundesrat ist für Ende 2015 vorgesehen. Die Strategie wird alle Handlungsfelder der verschiedenen Sektoren (Regulierung, umsichtige Verwendung, Überwachung, Forschung, Kontrollen in Spitälern usw.) umfassen. Oberstes Ziel ist, die Wirksamkeit der Antibiotika zur Erhaltung der menschlichen und tierischen Gesundheit langfristig sicherzustellen. Zentral dabei ist die Überwachung von Antibiotikaverwendung und -Resistenzlage in der Human- wie auch in der Veterinärmedizin.

Das erste nationale Forschungsprogramm «Antibiotikaresistenz» (NFP 49) in der Schweiz lief von 2001 bis 2006. Eine sehr wichtige Errungenschaft dieses Programms war die Implementierung eines Monitoringsystems für die Humanmedizin (anresis.ch). Seit 2004 sammelt anresis.ch Routinedaten zur Antibiotikaresistenzlage aus humanmikrobiologischen Laboratorien. Das System wurde dann weiterentwickelt und überwacht nun auch die Daten zum menschlichen Antibiotikakonsum (Spitäler und ambulanter Bereich). Das NFP 49 bildete auch die Grundlage für ein Monitoringprogramm in der Veterinärmedizin. 2006 führte das BLV ein System ein, um in der Schweiz ein kontinuierliches Antibiotikaresistenzmonitoring bei Nutztieren, Fleisch und Milchprodukten zu ermöglichen. Zusätzlich trägt es Daten zum Vertrieb von Antibiotika in der Veterinärmedizin zusammen. Seit 2009 werden die Daten zum Vertrieb von Veterinärantibiotika und die Ergebnisse des Antibiotikaresistenzmonitorings bei Nutztieren jährlich im ARCH-Vet Bericht veröffentlicht.

Das vorliegende Dokument, bei dem es sich um den ersten gemeinsamen Bericht von anresis.ch und ARCH-Vet handelt, präsentiert Schweizer Daten für das Jahr 2013. Zusätzlich zu den Resistenzdaten umfasst er Daten zum menschlichen Verbrauch antibiotischer Wirkstoffe und zum Vertrieb von Antibiotika in der Veterinärmedizin. Er bildet die Grundlage für die Erkennung, Interpretation und Evaluation von Trends bezüglich Verwendung antibiotischer Wirkstoffe und Auftreten von Resistenzen. Obwohl die Daten der Human- und der Veterinärmedizin in einem Bericht erscheinen, gilt es zu beachten, dass die Überwachungssysteme Unterschiede betreffend Datensammlung, Interpretation und Berichterstattung aufweisen, was einen direkten Vergleich der Ergebnisse erschwert. Zusammenarbeit und Koordination zwischen den verschiedenen Überwachungsnetzwerken müssen verstärkt und verfeinert werden, um die Vergleichbarkeit der Daten zu verbessern und Lücken zu schliessen, wie es in der nationalen Strategie Antibiotikaresistenzen (StAR) vorgesehen ist.

Die Verfasser des Berichts möchten all jenen, die zur Datenerhebung und zur Erstellung dieses Berichts beigetragen haben, für ihre ausgezeichnete Arbeit danken.

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1 Avant-propos

L'émergence de la résistance aux antibiotiques constitue un enjeu mondial de santé publique : l'administration d'antibiotiques favorise l'apparition de souches résistantes de bactéries, qui tiennent en échec le traitement de certaines maladies bactériennes chez l'homme et l'animal. Les bactéries résistantes peuvent se propager d'une personne à l'autre, au sein du système sanitaire comme en dehors. L'être humain peut aussi bien être infecté par des bactéries présentes chez l'animal ou dans l'environnement, la transmission s'effectuant soit par contact direct, soit par ingestion d'aliments ou d'autres vecteurs contaminés. Par ailleurs, le développement des échanges mondiaux (circulation des personnes et des marchandises) favorise davantage encore la propagation des résistances d'un pays et d'un continent à l'autre. L'épidémiologie de la résistance aux antibiotiques s'avérant d'une grande complexité, la surveillance doit procéder d'une approche holistique (concept « One Health ») et recenser des données sur l'utilisation d'antibiotiques et sur le développement des résistances non seulement en médecine humaine et vétérinaire, mais encore dans l'industrie alimentaire.

En réponse à la préoccupation croissante que suscite la résistance aux antibiotiques, le Département fédéral de l'intérieur (DFI) et le Département fédéral de l'économie, de la formation et de la recherche (DEFR) ont chargé l'Office fédéral de la santé publique (OFSP), l'Office fédéral de la sécurité alimentaire et des affaires vétérinaires (OSAV), l'Office fédéral de l'agriculture (OFAG) et l'Office fédéral de l'environnement (OFEV) d'élaborer et d'appliquer une stratégie nationale contre la résistance aux antibiotiques (Strategie Antibiotikaresistenzen, StAR). Cette stratégie, que le Conseil fédéral devrait adopter d'ici fin 2015, tirera parti de tous les domaines d'action des différents secteurs (réglementation, utilisation rationnelle des antibiotiques, surveillance, recherche, contrôles dans les hôpitaux, etc.). L'objectif premier de la stratégie est de garantir l'efficacité des antibiotiques à long terme pour le maintien de la santé humaine et animale. Elle accorde une place importante à la surveillance de leur utilisation et de l'évolution des résistances en médecine humaine et vétérinaire.

Le Programme national de recherche « La résistance aux antibiotiques » (PNR 49), approuvé en 1999 et mené de 2001 à 2006, a été le premier à traiter de cette question en Suisse. Il a notamment débouché sur la création d'un système de surveillance en médecine humaine (anresis.ch) : depuis 2004, des laboratoires de microbiologie envoient à anresis.ch les résultats de tests de résistance effectués dans le cadre de diagnostics de routine. À présent, le système recueille également des données sur la consommation d'antibiotiques en médecine humaine, en milieu hospitalier et ambulatoire.

Le PNR 49 a aussi donné lieu à un programme comparable en médecine vétérinaire : c'est ainsi que l'OSAV a institué en 2006 un système de surveillance continue de la résistance chez les animaux de rente et dans la viande et les produits laitiers en Suisse. Il recense également des données sur les ventes d'antibiotiques en médecine vétérinaire. Publié chaque année depuis 2009, le rapport ARCH-Vet présente ces données sur les ventes d'antibiotiques et la résistance chez les animaux de rente.

Le présent rapport rassemble pour la première fois les résultats d'anresis.ch et d'ARCH-Vet, pour l'année 2013. Il livre des données sur l'antibiorésistance, mais aussi sur la consommation d'antibiotiques en médecine humaine et sur les ventes d'antibiotiques en médecine vétérinaire, informations indispensables pour identifier, interpréter et évaluer les tendances en matière d'utilisation d'antibiotiques et d'apparition des résistances. Bien que ces données de médecine humaine et vétérinaire fassent ici l'objet d'un rapport commun, il convient de garder à l'esprit que leurs modalités de collecte, d'analyse et de présentation diffèrent d'un système de surveillance à l'autre, invalidant toute tentative de comparaison directe. Améliorer la comparabilité de ces données et en combler les lacunes impliquent de renforcer et d'affiner la coopération et la coordination des différents réseaux de surveillance : c'est là l'un des objectifs de la stratégie nationale contre la résistance aux antibiotiques (StAR).

Les éditeurs remercient pour leur excellent travail tous ceux qui ont contribué à la collecte des données et à la rédaction du présent rapport.

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1 Prefazione

Il fenomeno della resistenza agli antibiotici è una minaccia emergente per la salute pubblica globale. L'uso indiscriminato di antibiotici contribuisce alla selezione e diffusione di batteri resistenti che possono portare al fallimento delle cure di malattie batteriche sia nell'essere umano che negli animali. I batteri resistenti si possono diffondere da persona a persona all'interno della comunità e delle istituzioni sanitarie. Inoltre, possono essere trasmessi all'essere umano dagli animali e dall'ambiente per contatto diretto, per ingestione di alimenti contaminati o tramite altri veicoli contaminati. L'aumento dei commerci e dei viaggi a livello globale favorisce ulteriormente la diffusione della resistenza antimicrobica tra Paesi e continenti. Dato la complessità dell'epidemiologia di questo fenomeno, è fondamentale adottare un approccio olistico (approccio «One Health») per monitorare le tendenze nello sviluppo della resistenza agli antibiotici, includendo dati sull'uso e sulla resistenza nella medicina umana e in quella veterinaria, oltre che nella produzione di alimenti.
In risposta alla crescente preoccupazione riguardo alla resistenza antibiotici, i Dipartimenti federali dell'interno e dell'economia hanno affidato all'Ufficio federale della sanità pubblica (UFSP), all'Ufficio federale della sicurezza alimentare e di veterinaria (USAV), all'Ufficio federale dell'agricoltura (UFAG) e all'Ufficio federale dell'ambiente (UFAM) il compito di sviluppare e realizzare una strategia nazionale per combattere la resistenza agli antibiotici («Strategia nazionale contro le resistenze agli antibiotici, StAR»). Per la fine del 2015 è prevista la sua approvazione da parte del Consiglio federale. La strategia comprenderà tutte le aree d'intervento (disciplinamento, utilizzo prudente, sorveglianza, ricerca, controllo negli ospedali, ecc.) dei diversi settori coinvolti. La Strategia nazionale contro le resistenze agli antibiotici mira principalmente a garantire a lungo termine l'efficacia degli antibiotici per preservare la salute dell'essere umano e degli animali. L'importanza del monitoraggio dell'utilizzo di antibiotici e della resistenza sia nella medicina umana che in quella veterinaria è pure fortemente sottolineata.
Il primo programma nazionale di ricerca «Resistenza agli antibiotici» (PNR 49) in Svizzera è stato approvato nel 1999 e condotto tra il 2001 e il 2006. Un risultato molto importante ottenuto nell'ambito di questo programma è stato la realizzazione di un sistema di sorveglianza in medicina umana (anresis.ch). Dal 2004, anresis.ch continua a raccogliere dati di routine sulla resistenza agli antibiotici provenienti dai laboratori di microbiologia umana. Il sistema è stato ulteriormente sviluppato e attualmente monitora anche i dati sul consumo di antibiotici nel settore della medicina umana (negli ospedali e nell'ambito delle cure ambulatoriali).
Il PNR 49 ha fornito anche le basi per un programma di monitoraggio in medicina veterinaria. Nel 2006, l'USAV ha introdotto un sistema che consente un monitoraggio continuo della resistenza negli animali da reddito, nella carne e nei prodotti di latte in Svizzera. Inoltre, elabora dati sulla vendita degli agenti antimicrobici in medicina veterinaria. Dal 2009, i dati relativi alla vendita di antimicrobici veterinari e i risultati derivanti dal monitoraggio della resistenza negli animali da reddito sono pubblicati annualmente nel rapporto ARCH-Vet. Il presente rapporto, il primo congiunto tra anresis.ch e ARCH-Vet, illustra i dati del 2013 per la Svizzera. Oltre ai dati sulla resistenza, include anche quelli sul consumo di agenti antimicrobici nell'uomo e sulla vendita di antimicrobici in medicina veterinaria. Rappresenta la base per l'individuazione, l'interpretazione e la valutazione delle tendenze riguardo all'uso di agenti antimicrobici e all'insorgenza di fenomeni di resistenza. Sebbene i dati riguardanti la medicina umana e veterinaria siano riportati in un unico rapporto, è importante tenere in considerazione il fatto che le differenze nei sistemi di monitoraggio per quanto riguarda la raccolta, l'interpretazione e la segnalazione impediscono un confronto diretto dei risultati. La cooperazione e la coordinazione tra le diverse reti di monitoraggio devono essere rafforzate e perfezionate per migliorare la comparabilità e colmare le lacune, come previsto nella Strategia nazionale contro le resistenze agli antibiotici (StAR).

Gli editori ringraziano tutti coloro che hanno contribuito alla raccolta dei dati e alla stesura di questo rapporto per l'eccellente lavoro svolto.

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2

Summary

2 Summary

Antibiotic consumption in human medicine

In Swiss acute care hospitals, consumption of antibiotics for systemic use (Anatomical Therapeutic Chemicals (ATC) group J01, see Annex I) increased by 36% to 62.7 DDD per 100 bed-days between 2004 and 2013, whereas it was relatively stable when expressed in DDD per 100 admissions. This discrepancy can be explained by an increasing number of admissions and a decreasing number of bed-days in hospitals due to shorter length of hospital stay. The most commonly used class of antibiotics was the penicillins (ATC Code J01C), followed by the other beta-lactam antibacterials, including cephalosporins (ATC group J01D) and by the quinolones (ATC group J01M). The relative consumption of fluoroquinolones and penicillins including beta-lactamase inhibitors was relatively high in comparison with countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), however the total consumption of antibiotics in the inpatient setting was close to the median.

In 2013 (no previous data available for comparison), in the outpatient care, the most commonly used class of antibiotics was the penicillins (ATC group J01C), followed by the quinolones (ATC Code J01M) and the macrolides, lincosamides and streptogramines (ATC group J01F).Total consumption of antibacterials for systemic use (ATC group J01) was relatively low in the outpatient setting compared with the countries participating to ESAC-Net.

Sales of antibiotics in veterinary medicine

A steady decrease in the volume of antibiotics sold, has been apparent since 2009. In 2013, a total of 53,384 kg of antibiotics were sold for veterinary purposes. This represents a decrease of 6.7% compared with 2012 and 26% (or 18,920 kg) compared with the peak year 2008. The proportion of medicated pre-mixes was about two thirds of the total volume (approx. 33 tonnes). The proportion of active ingredients licensed only for pets amounted 1.5% of the total volume.

Sulfonamides, penicillins and tetracyclines represented 82% of the total antibacterial sales. Of the critically important antibacterial classes with highest priority for human medicine, macrolides decreased since 2008 and cephalosporines since 2011. However, there has been an increase in sales of long-acting macrolide injection preparations. The reduction of cephalosporines in 2013 is mainly due to a drop in sales of first-generation cephalosporins. Sales of third and fourth generation cephalosporins on the other hand increased slightly.

Sales of fluoroquinolones increased 15% in 2013 compared with the previous year.

Resistance in bacteria of human clinical isolates

Since 2004, different trends were observed in gram-positive and gram-negative bacteria. Methicillin resistant *Staphylococcus aureus* (MRSA) rates decreased significantly since 2004, mainly in the Western part of Switzerland. This trend was observed also in a couple of other European countries, including the neighbouring France. Penicillin-resistance in *Streptococcus pneumoniae* also decreased over time, probably driven by the introduction of pneumococcal vaccines, which led to a decrease of the more resistant serotypes. Vancomycin-resistance in enterococci is very low, and remained stable over the last 10 years.

In contrast we observed a steady increase in quinolone-resistance and 3rd generation cephalosporin resistance in *Escherichia coli* and *Klebsiella pneumoniae.* This increase is observed in most European countries and is consistent with the wide distribution of extended-spectrum-beta-lactamase (ESBL-) producing isolates. In *Pseudomonas aeruginosa* and *Acinetobacter* spp. resistance rates were rather stable during the last 10 years.

Resistance in zoonotic bacteria

In *Campylobacter jejuni* from broilers, microbiological resistance to ciprofloxacin has increased significantly since 2006, rising from 15% in 2006 to more than 41.3% in 2013. Microbiological resistance to erythromycin was observed only rarely in *C. jejuni* from broilers. In the reporting year, only two such isolates were found (1.3%); however, both were also microbiologically resistant to ciprofloxacin. Fluoroquinolones, which include ciprofloxacin, and macrolides, which include erythromycin, are classed as highest-priority critically important antibiotics (WHO/OIE/FAO), because these substance groups represent the treatment of choice for serious forms of campylobacteriosis or salmonellosis in humans.

In pigs, the rate of *Campylobacter coli* strains microbiologically resistant to streptomycin is very high, at around 74.3%. However, it was over 90% in 2006 and has fallen significantly since then. High rates of resistance to tetracycline and ciprofloxacin have also been found; in the case of ciprofloxacin, a statistically significant upward trend has been discernible since 2006. Eight isolates (3%) showed microbiological resistance to both ciprofloxacin and erythromycin. Overall, only a few *Salmonella* isolates were available from clinical material. Resistance was found especially in monophasic *S.* Typhimurium strains, which were consistently resistant to ampicillin, streptomycin, sulfamethoxazole and tetracycline. Microbiological resistance is then frequently found in Switzerland in zoonotic pathogens and in isolates from livestock, the levels are similar to or below the average levels in the EU.

Resistance in indicator bacteria in animals

In *E. coli* isolates, medium to high rates of microbiological resistance to ampicillin, streptomycin, sulfamethoxazole, tetracycline and trimethoprim were found in all animal species. In *E. coli* isolates from broilers, microbiological resistance to ciprofloxacin and nalidixic acid was also observed frequently. In veal calves, 14% of *E. coli* isolates were microbiologically resistant to kanamycin. In pigs, the resistance situation has not changed significantly compared with previous years. In fattening calves, microbiological resistance to ampicillin, streptomycin, sulfamethoxazole and tetracycline has declined significantly since 2006.

Tests on the enterococcal species *Enterococcus faecalis* and *Enterococcus faecium* showed high rates of microbiological resistance in both broilers and veal calves. In recent years, rates of resistance to bacitracin, tetracycline and erythromycin in *E. faecalis* from broilers and to bacitracin in *E. faecalis* from veal calves have declined significantly. One microbiologically vancomycin-resistant *E. faecalis* isolate from a veal calf was found in this reporting year.

The results of studies on ESBL (type pAmpC)-producing *E. coli* did not differ significantly from those in 2012. Using selective methods, ESBL (type pAmpC)-producing *E. coli* were found in 27.7% of broiler flocks, in 9.4% of fattening pigs and in 16.6% of veal calves. Besides resistance to beta-lactam antibiotics, the isolates showed very high to extremely high rates of microbiological resistance to (fluoro) quinolones, sulfonamides, tetracycline and trimethoprim in all three species. The rates of microbiological resistance were likewise high to extremely high with regard to chloramphenicol, gentamicin and kanamycin in pigs and cattle. No resistance to carbapenem was found.

The occurrence MRSA in pigs has remained constant compared with the previous year, at 20.8%. Prevalence was much lower in 2009 and 2011, 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 slaughterhouse pigs. This MRSA type is also frequently found in the livestock of other European countries and is a so called livestock-associated MRSA.

In veal calves, the prevalence of MRSA is still low (at 4%) and has not risen significantly since 2010. In addition to type CC398-t011 MRSA, type CC398-t034 MRSA was found in veal calves for the first time in this reporting year. Its spread will be monitored over the coming years.

MRSA has spread in Switzerland's pig population in recent years and microbiological resistance to certain important antibiotic groups continues to grow or remains unchanged at a high level

Resistance levels in indicator bacteria are over the years often significantly higher in Switzerland than in Nordic countries but significantly lower than in Southern countries of the EU.

Resistance in diagnostic submissions from animals

Up to now, in Switzerland exists neither a monitoring of antibacterial resistance in relevant pathogens from livestock nor such a monitoring from companion animals. As these data are important for the risk assessment of resistance in the future, national and international organizations focused on these topics recently. The Center for Zoonoses, Bacterial Animal Diseases and Antibiotic Resistance (ZOBA) exemplified such data of staphylococci from dogs, cats and horses for the first time within this report. High detection rates of methicillin-resistant *Staphylococcus pseudintermedius* in dogs as well as methicillin-resistant *S. aureus* in horses from clinics, exhibit not only a challenge for veterinarians but are also a risk for humans because of their zoonotic potential. Moreover, the detection of multidrug-resistant isolates underlines the necessity for the prudent use of antimicrobials in veterinary medicine. It will be important to fill up these data with more isolates from other laboratories as well with other relevant gram positive and gram-negative pathogens to provide an insight into future trends and risks.

Conclusions

These results provide the most comprehensive picture as is presently possible of the antibiotic resistance and antibiotic consumption trends in Switzerland. Further monitoring of the development of resistance, and research into the connections between spreading of resistance in humans and animals, is necessary in order to gain a better assessment of the risk. With the aim of ensuring the effectiveness of antibiotics in preserving human and animal health in the long term, coordinated measures are currently being developed in the National Strategy on Antibiotic Resistance (StAR) in partnership with all sectors involved.

2 Zusammenfassung

Antibiotikaverbrauch in der Humanmedizin

In Schweizer Akutspitälern stieg der Verbrauch von Antibiotika zur systemischen Anwendung (Kategorie J01 der anatomisch-therapeutisch-chemischen Klassifikation (ATC), siehe Anhang I) zwischen 2004 und 2013 um 36% auf 62,7 DDD (Defined Daily Doses, definierte Tagesdosen) pro 100 Bettentage. In DDD pro 100 Einweisungen berechnet, blieb er relativ stabil. Diese Diskrepanz lässt sich mit einer steigenden Anzahl Einweisungen und einer sinkenden Anzahl Bettentage aufgrund kürzerer Spitalaufenthalte erklären. Die am häufigsten verwendete Antibiotikagruppe waren die Penicilline (ATC-J01C), gefolgt von den anderen Beta-Laktam-Antibiotika, inkl. Cephalosporine (ATC-J01D), und von den Quinolonen (ATC-J01M). Der relative Verbrauch von Fluoroquinolonen und Penicillinen inkl. Beta-Lactamase-Inhibitoren war im Vergleich mit Ländern, die sich am European Surveillance of Antimicrobial Consumption Network (ESAC-Net) beteiligen, relativ hoch, doch lag der gesamte Antibiotikaverbrauch im stationären Bereich nahe am Median.

2013 (es bestehen keine früheren Daten zum Vergleich) waren die Penicilline (ATC-J01C) in der ambulanten Versorgung die am häufigsten verwendete Antibiotikagruppe, dann die Quinolone (ATC-J01M) sowie die Makrolide, Lincosamide und Streptogramine (ATC-J01F). Der gesamte Antibiotikaverbrauch zur systemischen Anwendung (ATC-J01) bewegte sich im Vergleich mit den am ESAC-Net beteiligten Ländern im ambulanten Bereich auf einem relativ tiefen Niveau.

Vertrieb von Antibiotika in der Veterinärmedizin

Seit 2009 ist eine stetige Abnahme der verkauften Antibiotikamenge festzustellen. Im Jahr 2013 wurden insgesamt 53384 kg Antibiotika für die Veterinärmedizin verkauft. Im Vergleich zum Vorjahr entspricht dies einem Minus von 6,7%. Verglichen mit dem Spitzenjahr 2008 beträgt der Rückgang sogar 26% (oder 18920 kg). Der Anteil der Arzneimittelvormischungen betrug etwa zwei Drittel der Gesamtmenge (ca. 33 Tonnen). Der Anteil der Menge Wirkstoffe, die nur für Haustiere zugelassen sind, umfasste 1,5% der Gesamtmenge. Sulfonamide, Penicilline und Tetracycline machten 82% des gesamten Antibiotikavertriebs aus. Von den kritischen Antibiotika mit höchster Priorität für die Humanmedizin verzeichneten die Makrolide seit 2008 und die Cephalosporine seit 2011 einen Rückgang. Eine Zunahme erfolgte allerdings bei den Verkäufen von langwirksamen, einmalig applizierten Injektionspräparaten. Der Rückgang der Cephalosporine im Jahr 2013 ist primär auf einen Rückgang der Verkaufszahlen der Cephalosporine der ersten Generation zurückzuführen. Im Unterschied dazu sind die Verkäufe von Cephalosporinen der dritten und vierten Generationen leicht angestiegen.

Die Verkäufe von Fluoroquinolonen haben 2013 im Vergleich zum Vorjahr um 15% zugenommen.

Resistenz bei Bakterien aus klinischen Isolaten vom Menschen

Seit 2004 wurden verschiedene Tendenzen bei grampositiven und gramnegativen Bakterien beobachtet. Die Raten methicillinresistenter *Staphylococcus aureus*-Bakterien (MRSA) nahmen seit 2004 bedeutend ab, vor allem in der Westschweiz. Dieser Trend liess sich auch in einigen anderen europäischen Ländern, einschliesslich des benachbarten Frankreichs, feststellen. Die Penicillin-Resistenz bei *Streptococcus pneumoniae* ging im Laufe der Zeit ebenfalls zurück, wahrscheinlich aufgrund der Einführung von Pneumokokken-Impfstoffen, die zu einer Abnahme der resistenteren Serotypen führte. Die Vancomycin-Resistenz bei Enterokokken ist sehr tief und blieb über die letzten zehn Jahre stabil.

Im Gegensatz dazu nahmen die Resistenzen gegen Quinolone und Cephalosporine der dritten Generation bei *Escherichia coli* und *Klebsiella pneumoniae* stetig zu. Dies ist in den meisten europäischen Ländern zu beobachten und passt zur weiten Verbreitung von Extended-Spectrum-Beta-Lactamase (ESBL) produzierenden Isolaten. Bei *Pseudomonas aeruginosa* und *Acinetobacter* spp. waren die Resistenzraten in den letzten zehn Jahren ziemlich stabil.

Resistenzen bei Zoonoseerregern

Bei *Campylobacter jejuni* in Mastpoulets hat die mikrobiologische Resistenz gegenüber Ciprofloxacin seit 2006 signifikant zugenommen. Sie stieg von 15% im Jahr 2006 auf über 41,3% im Jahr 2013. Mikrobiologische Resistenzen gegenüber Erythromycin werden bei *C. jejuni* in Mastpoulets selten festgestellt. Im Berichtsjahr wurden lediglich zwei solcher Isolate gefunden (1,3%), die jedoch beide zusätzlich auch gegenüber Ciprofloxacin mikrobiologisch resistent waren. Fluoroquinolone, zu denen das Ciprofloxacin gehört, und Makrolide, zu denen das Erythromycin gehört, gelten als kritische Antibiotika höchster Priorität (WHO/OIE/FAO), weil diese Wirkstoffgruppen bei schweren Verlaufsformen der Campylobacteriose oder der Salmonellose beim Menschen bevorzugt zum Einsatz kommen.

Bei den Schweinen ist die Resistenzrate der *Campylobacter coli*-Stämme gegenüber Streptomycin mit rund 74,3% sehr hoch. Sie lag jedoch 2006 noch bei über 90% und ist seither signifikant gesunken. Hohe Resistenzraten gab es ebenfalls gegenüber Tetracyclin und Ciprofloxacin, wobei bei Ciprofloxacin seit 2006 ein statistisch signifikant zunehmender Trend zu sehen ist. Acht Isolate (3%) zeigten sowohl eine mikrobiologische Resistenz gegenüber Ciprofloxacin als auch gegenüber Erythromycin.

Insgesamt standen nur wenige Salmonellen-Isolate aus klinischem Material zur Verfügung. Resistenzen wurden insbesondere in monophasichen *S.* Typhimurium-Stämmen gefunden, die durchwegs gegenüber Ampicillin, Streptomycin, Sulfamethoxazol und Tetracyclin mikrobiologisch resistent waren. Antibiotikaresistenzen sind demnach in der Schweiz häufig bei Zoonoseerregern und Isolaten von Nutztieren zu finden, wobei das Ausmass dem EU-Durchschnitt ähnelt oder darunter liegt.

Resistenzen bei Indikatorkeimen in Tieren

In *Escherichia coli*-Isolaten wurden bei allen Tierarten mittlere bis hohe Resistenzraten gegenüber Ampicillin, Streptomycin, Sulfamethoxazol, Tetracyclin und Trimethoprim gefunden. Zudem liessen sich bei *E. coli*-Isolaten von Mastpoulets häufig mikrobiologische Resistenzen gegenüber Ciprofloxacin und Nalidixinsäure nachweisen, und bei Mastkälbern waren 14% der *E. coli*-Isolate mikrobiologisch resistent gegenüber Kanamycin. Bei den Schweinen hat sich die Resistenzsituation im Vergleich zu den Vorjahren nicht signifikant verändert. Bezüglich Mastkälber haben mikrobiologische Resistenzen gegenüber Ampicillin, Streptomycin, Sulfamethoxazol und Tetracyclin seit 2006 signifikant abgenommen.

Die Untersuchungen der Enterokokkenspezies *E. faecalis* und *E. faecium* zeigten, dass mikrobiologische Resistenzen sowohl bei Mastpoulets als auch bei Mastkälbern häufig vorkommen. In den letzten Jahren sind die Resistenzraten gegenüber Bacitracin, Tetracyclin und Erythromycin von *E. faecalis* in Mastpoulets und gegenüber Bacitracin von *E. faecalis* in Mastkälbern signifikant zurück gegangen. Wie bereits im Jahr 2010 hat man auch im Berichtsjahr wieder ein mikrobiologisch vancomycinresistentes *E. faecalis*-Isolat bei einem Mastkalb isoliert.

Die Resultate der Untersuchungen betreffend ESBL/pAmpC produzierenden *E. coli* unterschieden sich nicht signifikant von jenen im Jahr 2012. Mit selektiven Methoden wurden bei 27,7% der Mastpouletherden, 9,4% der Mastschweine und 16,6% der Mastkälber ESBL/pAmpC produzierende *E. coli* gefunden. Die Isolate ergaben bei allen drei Spezies neben der Resistenz gegenüber Beta-Laktam-Antibiotika sehr hohe bis extrem hohe Resistenzraten gegenüber (Fluoro)Quinolonen, Sulfonamiden, Tetracyclin und Trimethoprim. Die Resistenzraten bei Schweinen und Rindern gegenüber Chloramphenicol, Gentamicin und Kanamycin waren ebenfalls hoch bis extrem hoch. Es wurden keine Carbapenem-Resistenzen festgestellt.

Das Auftreten von MRSA bei Schweinen blieb im Vergleich zum Vorjahr mit einer Prävalenz von 20,8% konstant. 2009 war die Prävalenz mit 2% und 2011 mit 5,6% noch deutlich geringer. Die Resultate zeigten, dass sich in der Schweizer Schlachtschweine-Population insbesondere eine klonale MRSA-Linie stark ausbreitet (CC398-t034). Dieser MRSA-Typ wird auch bei Nutztieren anderer europäischer Länder häufig gefunden und gehört zu den sogenannten Nutztier-assoziierten MRSA.

Bei Mastkälbern fällt die MRSA-Prävalenz mit 4% noch gering aus; sie ist seit 2010 nicht signifikant angestiegen. Neben MRSA vom Typ CC398-t011 wurden bei den Mastkälbern im Berichtsjahr erstmals MRSA vom Typ CC398-t034 gefunden, deren Ausbreitung in den nächsten Jahren weiterverfolgt werden sollte.

MRSA hat sich in den letzten Jahren im Schweizer Schweinebestand ausgebreitet, und die mikrobiologische Resistenz gegenüber gewissen bedeutenden Antibiotikagruppen nimmt weiter zu oder bleibt unverändert hoch.

Das Resistenzniveau bei Indikatorkeimen lag in der Schweiz über die Jahre oft bedeutend höher als in nordischen Ländern, aber auch bedeutend tiefer als in südlichen EU-Ländern.

Resistenz bei klinischen Isolaten von Tieren

Bis heute gibt es in der Schweiz kein Antibiotikaresistenzmonitoring bei relevanten Krankheitserregern von Nutz- oder Heimtieren. Da solche Daten für die Risikobewertung von Resistenzen wichtig sind, fokussierten sich nationale und internationale Organisationen in letzter Zeit auf diese Themen. Das Zentrum für Zoonosen, bakterielle Tierkrankheiten und Antibiotikaresistenz (ZOBA) erläutert im vorliegenden Bericht erstmals entsprechende Daten von Staphylokokken aus Hunden, Katzen und Pferden. Hohe Nachweisraten methicillinresistenter *Staphylococcus pseudintermedius* bei Hunden wie auch methicillinresistenter *S. aureus* bei Pferden aus Kliniken zeigen nicht nur eine Herausforderung für die Tierärztinnen und -ärzte auf, sondern aufgrund des zoonotischen Potenzials auch ein Risiko für den Menschen. Ausserdem unterstreicht der Nachweis von multiresistenten Isolaten die Notwendigkeit einer umsichtigen Verwendung von Antibiotika in der Veterinärmedizin. Es ist wichtig, diese Daten mit weiteren Isolaten aus anderen Laboratorien sowie mit weiteren relevanten grampositiven und gramnegativen Erregern zu ergänzen, um künftige Trends und Risiken vorherzusehen.

Fazit

Die vorliegenden Resultate vermitteln das derzeit bestmögliche Bild zu den Trends beim Antibiotikaverbrauch und bei den Antibiotikaresistenzen in der Schweiz. Um das Risiko künftig noch besser einzuschätzen zu können, müssen die Entstehung und Ausbreitung von Resistenzen bei Mensch und Tier weiter überwacht und mögliche Zusammenhänge erforscht werden. Mit dem Ziel, die Wirksamkeit der Antibiotika zur Erhaltung der menschlichen und tierischen Gesundheit langfristig sicherzustellen, ist die Nationale Strategie Antibiotikaresistenzen (StAR) mit allen beteiligten Sektoren entwickelt worden.

2 Synthèse

Consommation d'antibiotiques en médecine humaine

Dans les hôpitaux suisses de soins aigus, la consommation d'antibactériens à usage systémique (classe J01 de la classification ATC [Anatomique Thérapeutique Chimique], cf. annexe I) exprimée en doses définies journalières (DDD, defined daily doses) pour 100 journées d'hospitalisation a crû de 36% entre 2004 et 2013 pour s'établir à 62,7. Elle est en revanche restée relativement stable lorsqu'exprimée en DDD pour 100 admissions : cette différence résulte d'une augmentation du nombre d'admissions, accompagnée d'une diminution du nombre de journées d'hospitalisation due à une réduction de la durée des séjours à l'hôpital. La classe d'antibiotiques les plus fréquemment utilisés était les pénicillines (classe ATC J01C), suivie des autres bêtalactamines (classe ATC J01D), qui comprennent notamment les céphalosporines, et des quinolones (classe ATC J01M). Si la consommation relative de fluoroquinolones et de pénicillines incluant des inhibiteurs de bêtalactamases était élevée par rapport aux pays membres du réseau européen de surveillance de la consommation d'antimicrobiens (ESAC-Net), la consommation totale d'antibiotiques en milieu hospitalier était en revanche proche de la médiane.

En milieu ambulatoire, la classe d'antibiotiques les plus fréquemment utilisés en 2013 (aucune donnée antérieure n'est disponible pour comparaison) était les pénicillines (classe ATC J01C), suivie des quinolones (classe ATC J01M) et des macrolides, des lincosamides et des streptogramines (classe ATC J01F). La consommation totale d'antibactériens à usage systémique (classe ATC J01) en milieu ambulatoire s'est avérée relativement faible en comparaison avec les autres pays participant à ESAC-Net.

Ventes d'antibiotiques utilisés en médecine vétérinaire

Les ventes d'antibiotiques à usage vétérinaire décroissent régulièrement depuis 2009. En 2013, 53 384 kg de médicaments de ce type ont été vendus : cela correspond à une baisse de 6,7% par rapport à l'année précédente, baisse qui atteint même 26% (soit une réduction de 18 920 kg) si l'on compare ce chiffre à celui de 2008, qui fut une année record. Près des deux tiers de la quantité totale ont été vendus sous la forme de prémélanges pour aliments médicamenteux (environ 33 tonnes). La part de principes actifs autorisés uniquement pour les animaux de compagnie se montait quant à elle à 1,5% de la quantité totale.

Les sulfonamides, les pénicillines et les tétracyclines représentaient 82% des ventes totales d'antibactériens. Pour ce qui est des antimicrobiens critiques de première priorité en médecine humaine, on constate un recul des ventes de macrolides depuis 2008 et de céphalosporines depuis 2011. A noter toutefois que les ventes de préparations de macrolides injectables à action prolongée ont augmenté, et que le recul des ventes de céphalosporines en 2013 était essentiellement imputable aux céphalosporines de première génération, les ventes de céphalosporines de troisième et de quatrième génération ayant pour leur part légèrement augmenté.

Enfin, en 2013, les ventes de fluoroquinolones ont crû de 15% par rapport à l'année précédente.

Résistance des bactéries dans les isolats cliniques chez l'être humain

Depuis 2004, des tendances différentes se dessinent chez les bactéries à Gram positif et chez les bactéries à Gram négatif : les taux de résistance à la méticilline de *Staphylococcus aureus* (SARM) ont nettement reculé depuis 2004, en particulier en Suisse romande. Cette tendance a également pu être observée dans quelques autres pays européens, dont la France. La résistance à la pénicilline de *Streptococcus pneumoniae* a également diminué au fil du temps, probablement grâce à l'introduction de vaccins contre les infections invasives à pneumocoques, qui ont pu provoquer un recul des sérotypes les plus résistants. Chez les entérocoques, les taux de résistance à la vancomycine, très faibles, sont restés stables au cours de la décennie écoulée.

En revanche, la résistance aux quinolones et aux céphalosporines de troisième génération croît de façon régulière chez *Escherichia coli* et *Klebsiella pneumoniae*. Cette évolution a également pu être observée dans la plupart des pays européens et coïncide avec la large distribution des isolats producteurs de bêtalactamases à spectre élargi (BLSE). Chez *Pseudomonas aeruginosa* et *Acinetobacter* spp., les taux de résistance sont restés relativement stables au cours de la décennie écoulée.

Résistance des bactéries zoonotiques

Chez les poulets de chair, la résistance microbiologique de *Campylobacter jejuni* à la ciprofloxacine a augmenté de manière significative depuis 2006, passant de 15% à plus de 41,3% en 2013. En revanche, les bactéries *C. jejuni* identifiées chez les poulets de chair sont rarement microbiologiquement résistantes à l'érythromycine : durant l'année sous revue, seuls deux isolats (1,3%) résistants à l'érythromycine ont été trouvés. Tous deux étaient toutefois également microbiologiquement résistants à la ciprofloxacine. Or les fluo-

roquinolones, dont fait partie la ciprofloxacine, et les macrolides, dont fait partie l'érythromycine, sont classés dans la catégorie des antimicrobiens critiques de première priorité (OMS/OIE/FAO), ces groupes de principes actifs constituant le traitement de choix en cas de forme sévère de campylobactériose ou de salmonellose chez l'homme.
Chez les porcs, le taux de résistance microbiologique à la streptomycine des souches de *Campylobacter coli* est très élevé (74,3%). Il était toutefois supérieur à 90% en 2006, ce qui dénote une baisse significative. Des taux de résistance importants ont également été trouvés envers la tétracycline et la ciprofloxacine : on enregistre depuis 2006 une tendance à la hausse statistiquement significative des résistances à la ciprofloxacine. Par ailleurs, huit isolats (3%) présentaient une résistance microbiologique à la fois envers la ciprofloxacine et l'érythromycine. Peu d'isolats de salmonelles provenant d'échantillons cliniques étaient disponibles. Les résistances ont été observées principalement chez les variants monophasiques de *Salmonella* Typhimurium, qui étaient toujours résistants à l'ampicilline, à la streptomycine, au sulfaméthoxazole et à la tétracycline. En Suisse, des résistances microbiologiques sont ainsi fréquemment constatées tant chez les agents zoonotiques que les isolats issus d'animaux de rente, mais les taux relevés sont similaires ou inférieurs aux moyennes européennes.

Résistance des germes indicateurs chez les animaux

Les isolats d'*E. coli* présentent des taux de résistance microbiologique moyens à élevés à l'ampicilline, à la streptomycine, au sulfaméthoxazole, à la tétracycline et au triméthoprime chez les trois espèces animales considérées. En outre, les isolats d'*E. coli* chez les poulets de chair se sont fréquemment avérés microbiologiquement résistants à la ciprofloxacine et à l'acide nalidixique, tandis que chez les veaux d'engraissement, 14% des isolats d'*E. coli* présentaient une résistance microbiologique à la kanamycine. Si le taux de résistance d'*E. coli* n'a pas évolué de manière significative chez les porcs par rapport aux années précédentes, chez les veaux d'engraissement, les résistances microbiologiques à l'ampicilline, à la streptomycine, au sulfaméthoxazole et à la tétracycline ont significativement diminué depuis 2006.
L'analyse des entérocoques *Enterococcus faecalis* et *Enterococcus faecium* révèle de fortes résistances microbiologiques tant chez les poulets de chair que chez les veaux d'engraissement. Ces dernières années, les taux de résistance d'*E. faecalis* à la bacitracine, à la tétracycline et à l'érythromycine chez les poulets de chair et à la bacitracine chez les veaux d'engraissement ont diminué de manière significative. Un isolat d'*E. faecalis* microbiologiquement résistant à la vancomycine a été découvert chez un veau d'engraissement.
Les résultats des analyses concernant *E. coli* producteurs de BLSE/AmpC ne présentent pas de différences significatives avec ceux de 2012. Des méthodes sélectives ont permis d'identifier des *E. coli* producteurs de BLSE/pAmpC dans 27,7% des cheptels de poulets de chair, chez 9,4% des porcs d'engraissement et chez 16,6% des veaux d'engraissement. Outre des résistances aux bêtalactamines, les isolats ont révélé des taux très élevés à extrêmement élevés de résistance microbiologique aux (fluoro)quinolones, aux sulfonamides, à la tétracycline et au triméthoprime chez ces trois espèces animales. Chez les porcs et les bovins, les taux de résistance microbiologique au chloramphénicol, à la gentamicine et à la kanamycine se sont également avérés élevés à extrêmement élevés. Aucune résistance aux carbapénèmes n'a en revanche été identifiée.
La prévalence des *Staphylococcus aureus* résistants à la méticilline (SARM) chez les porcs est restée constante (20,8%) par rapport à l'année précédente. Elle était nettement plus faible en 2009 et en 2011, où elle s'élevait respectivement à 2% et à 5,6%. Les résultats montrent qu'un certain complexe clonal (CC398-t034) s'est fortement répandu dans le cheptel suisse des porcs d'engraissement. Ces SARM, typiquement associés aux animaux de rente (livestock-associated MRSA), ont également souvent été identifiés dans les cheptels d'autres pays européens.
La prévalence des SARM chez les veaux d'engraissement est encore faible (4%) et n'a pas augmenté de manière significative depuis 2010. Outre des SARM de type CC398-t011, des SARM de type CC398-t034 ont été trouvés pour la première fois chez des veaux d'engraissement durant l'année sous revue : il y a lieu de suivre leur propagation au cours des prochaines années.
Ces dernières années, les SARM se sont propagés dans le cheptel suisse de porcs et la résistance microbiologique à certains groupes importants d'antibiotiques continue de croître ou stagne à un niveau élevé.
Les taux de résistance des germes indicateurs sont, année après année, nettement plus élevés en Suisse que dans les pays scandinaves. Mais ils restent significativement plus faibles qu'en Europe méridionale.

Résistance détectée dans les résultats des analyses à visée diagnostique chez l'animal

Actuellement, la Suisse ne dispose de monitorage de l'antibiorésistance des agents pathogènes d'importance clinique ni pour le cheptel vif ni pour les animaux de compagnie. Comme ces données sont importantes pour évaluer le risque que des résistances se développent, des organisations nationales et internationales se sont récemment saisies de la question. Dans le présent rapport, le Centre des zoonoses, des maladies animales bactériennes et de l'antibiorésistance (ZOBA) livre pour la première fois des données relatives à l'antibiorésistance des staphylocoques chez les chiens, les chats et les chevaux. Elles révèlent un taux élevé de résistance à la méticilline de *Staphylococcus pseudintermedius* chez le chien et de *S. aureus* chez le cheval dans les cliniques vétérinaires, mettant ainsi en évidence non seulement le défi qui se pose aux vétérinaires, mais aussi le risque que ces bactéries présentent pour l'homme du fait de leur potentiel zoonotique. Par ailleurs, la mise en évidence d'isolats multirésistants souligne la nécessité de faire preuve de prudence dans l'emploi d'antimicrobiens en

médecine vétérinaire. Il sera important à l'avenir de consolider ces données avec des isolats soumis par d'autres laboratoires ainsi qu'avec d'autres agents pathogènes d'importance clinique à Gram positif et à Gram négatif, afin d'en tirer une vision plus complète des tendances et des risques susceptibles de se profiler.

Conclusion

Ces résultats constituent le panorama le plus complet qu'il soit actuellement permis de dresser concernant les tendances de consommation d'antibiotiques et d'antibiorésistance en Suisse. Il importe de continuer à surveiller l'évolution des résistances et d'étudier les liens de cause à effet dans la propagation des résistances chez l'homme et chez l'animal pour permettre une meilleure évaluation du risque. Dans le cadre de la stratégie nationale contre la résistance aux antibiotiques (StAR), les secteurs concernés sont en train de développer des mesures coordonnées visant à garantir sur le long terme la capacité des antibiotiques à préserver la santé humaine et animale.

2 Sintesi

Consumo di antibiotici in medicina umana

Negli ospedali svizzeri per cure acute, il consumo di antibiotici per uso sistemico (appartenenti al gruppo J01 del Sistema di classificazione anatomico, terapeutico e chimico ATC, vedi Allegato I) tra il 2004 e il 2013 è aumentato del 36% a 62,7 dosi definite giornaliere (DDD) per 100 giorni di degenza mentre, se espresso in DDD per 100 ricoveri, risulta essere rimasto relativamente stabile. Questa discrepanza può essere spiegata dal fatto che, sebbene il numero di ricoveri sia aumentato, la loro durata più breve ha comportato una diminuzione del numero di giorni di degenza. La classe di antibiotici più frequentemente usata è stata quella delle penicilline (codice ATC: J01C), seguita dagli altri antibatterici beta-lattamici, cefalosporine incluse (gruppo ATC: J01D), e dai chinoloni (gruppo ATC: J01M). Il consumo relativo di fluorochinoloni e penicilline, inclusi gli inibitori delle beta-lattamasi, è stato piuttosto alto se paragonato ai livelli dei Paesi che partecipano alla Rete di sorveglianza europea sul consumo di antibiotici (ESAC-Net). Tuttavia, il consumo totale di antibiotici nei reparti ospedalieri si situa in prossimità del valore mediano.

A livello ambulatoriale, nel 2013 (non sono disponibili dati precedenti per un confronto), la classe di antibiotici più frequentemente usata è stata quella delle penicilline (gruppo ATC: J01C), seguita da chinoloni (codice ATC: J01M) e macrolidi, lincosamidi e streptogramine (gruppo ATC: J01F). Il consumo totale di antibatterici per uso sistemico (gruppo ATC: J01) nel settore ambulatoriale è stato relativamente basso in confronto a quello dei Paesi che partecipano all'ESAC-Net.

Vendita di antibiotici in medicina veterinaria

Dal 2009 si registra una costante diminuzione delle quantità di antibiotici venduti. Nel 2013 sono stati venduti complessivamente 53.384 kg di antibiotici per la medicina veterinaria, ossia il 6,7% in meno rispetto all'anno precedente. Se si comparano le vendite nel 2013 all'anno record 2008, la riduzione è addirittura del 26% (ossia di 18.920 kg). La proporzione di premiscele di medicamenti rimane di circa due terzi della quantità complessiva (ca. 33 tonnellate). La quantità di principi attivi omologati unicamente per l'utilizzo su animali da compagnia rappresenta l'1,5% della quantità complessiva.

L'82% delle vendite totali di antibatterici è stato rappresentato da sulfonamidi, penicilline e tetracicline. Per quanto riguarda le classi di antibatterici critici di massima priorità per la medicina umana (i cosiddetti critically important antibacterial classes), il consumo di macrolidi è in diminuzione dal 2008 e quello delle cefalosporine dal 2011. Per contro nei macrolidi a lunga emivita c'è stato un aumento nelle vendite di preparati iniettabili. La diminuzione delle cefalosporine nel 2013 è dovuta principalmente ad un calo nelle vendite di cefalosporine di prima generazione. Le vendite di cefalosporine di terza e quarta generazione, invece, sono leggermente aumentate.

Nel 2013 le vendite di fluorochinoloni sono aumentate del 15% rispetto all'anno precedente.

Resistenza nei batteri presenti negli isolati clinici umani

Dal 2004 nei batteri gram-positivi e gram-negativi sono state osservate tendenze opposte. I tassi relativi allo *Staphylococcus aureus* resistente alla meticillina (MRSA) sono diminuiti in maniera significativa dal 2004, per lo più nella parte occidentale della Svizzera. Questa tendenza è stata osservata anche in un paio di altri Paesi europei, inclusa la vicina Francia. È diminuita nel corso del tempo anche la resistenza alla penicillina osservata in *Streptococcus pneumoniae,* probabilmente come conseguenza dell'introduzione dei vaccini contro gli pneumococchi che hanno portato ad una diminuzione dei sierotipi più resistenti. La resistenza alla vancomicina negli enterococchi è molto bassa ed è rimasta stabile nel corso degli ultimi 10 anni.

Al contrario, abbiamo osservato un aumento costante della resistenza ai chinoloni e alle cefalosporine di terza generazione in *Escherichia coli* e *Klebsiella pneumoniae.* Questo aumento si osserva nella maggior parte dei Paesi europei ed è in linea con l'ampia distribuzione di isolati che producono beta-lattamasi a spettro esteso (ESBL). In *Pseudomonas aeruginosa* e in *Acinetobacter* spp. i tassi di resistenza sono rimasti relativamente stabili negli ultimi 10 anni.

Resistenza nei batteri zoonotici

Per quanto concerne il *Campylobacter jejuni* presente nel pollame da ingrasso, il tasso di resistenza microbiologica alla ciprofloxacina è aumentato significativamente dal 2006, passando dal 15% del 2006 a più del 41,3% del 2013. Nel *C. jejuni* presente nel pollame da ingrasso vengono invece rilevate raramente resistenze microbiologiche all'eritromicina. Nel 2013, sono stati trovati solo due isolati con questa resistenza (1,3%), entrambi però resistenti anche alla ciprofloxacina. I fluorochinoloni, dei quali fa parte anche la ciprofloxacina, e i macrolidi, dei quali fa parte l'eritromicina, sono classificati come antibiotici critici di massima priorità (OMS/OIE/FAO), poiché questi gruppi di principi attivi rappresentano la terapia di prima scelta in caso di gravi forme di campilobatteriosi o salmonellosi nell'uomo.

Nei suini, il tasso di resistenza alla streptomicina nei ceppi di *Campylobacter coli* è molto elevato e si aggira attorno al 74,3%. Nel 2006 era però ancora superiore al 90% ed è da allora diminuito significativamente. Si osservano tassi di resistenza elevati anche alla tetraciclina e alla ciprofloxacina.

Dal 2006, nel caso della ciprofloxacina è possibile osservare una tendenza all'aumento statisticamente significativa. In 8 isolati (3%) è stata riscontrata una resistenza microbiologica sia alla ciprofloxacina sia all'eritromicina. Nel complesso si sono avuti solo pochi isolati di salmonella provenienti da materiale clinico. Sono state riscontrate resistenze soprattutto in ceppi monofasici di *S.* Typhimurium che erano, senza eccezione, resistenti ad ampicillina, streptomicina, sulfametoxazolo e tetraciclina. In Svizzera, si riscontra frequentemente una resistenza microbiologica nei patogeni zoonotici e negli isolati prelevati dal bestiame. I livelli sono simili o inferiori ai livelli medi nell'UE.

Resistenza nei batteri indicatori negli animali

Negli isolati di *E. coli* di tutte le specie animali sono stati riscontrati tassi di resistenza da medi ad elevati nei confronti di ampicillina, streptomicina, sulfametoxazolo, tetraciclina e trimetoprim. Negli isolati di *E. coli* provenienti da pollame da ingrasso si osservano inoltre spesso resistenze microbiologiche a ciprofloxacina e acido nalidixico. Nei vitelli da ingrasso il 14% degli isolati di *E. coli* erano resistenti alla kanamicina. Nei suini, l'evoluzione delle resistenze è rimasta pressoché invariata rispetto agli anni precedenti. Dal 2006 ad oggi, nei vitelli da ingrasso le resistenze nei confronti di ampicillina, streptomicina, sulfametoxazolo e tetraciclina sono diminuite significativamente.

Le analisi effettuate sulle specie di enterococchi *Enterococcus faecalis* ed *Enterococcus faecium* hanno dimostrato che le resistenze microbiologiche sono elevate sia nel pollame da ingrasso, sia nei vitelli da ingrasso. Negli ultimi anni sono diminuiti sensibilmente i tassi di resistenza nei confronti di bacitracina, tetraciclina ed eritromicina negli *E. faecalis* provenienti da pollame da ingrasso e il tasso di resistenza alla bacitracina negli *E. faecalis* provenienti da vitelli da ingrasso. Come nel 2010, anche nel 2013 è stato riscontrato un isolato di *E. faecalis* proveniente da un vitello da ingrasso resistente alla vancomicina.

I risultati delle analisi riguardanti *E. coli* produttrici di ESBL/pAmpC non si discostano significativamente da quelli del 2012. Dalle analisi selettive emerge che nel 27,7% del pollame da ingrasso, nel 9,4% dei suini da ingrasso e nel 16,6% dei vitelli da ingrasso sono presenti *E. coli* produttrici di ESBL/pAmpC. In tutte e tre le specie gli isolati mostrano, oltre alla resistenza agli antibiotici beta-lattamici, tassi di resistenza da molto elevati ad estremamente elevati a (fluoro) chinoloni, sulfonamidi, tetracicline e trimetoprim. Nei suini e nei bovini anche i tassi di resistenza nei confronti di cloramfenicolo, gentamicina e kanamicina sono da elevati ad estremamente elevati. Non sono state riscontrate resistenze al carbapenem.

Con una prevalenza del 20,8% la presenza di MRSA nei suini è rimasta costante rispetto all'anno precedente. Nel 2009 e nel 2011 la prevalenza era molto inferiore, con valori rispettivamente del 2% e del 5,6%. I risultati dimostrano che in Svizzera, nella popolazione di suini da macello, è molto diffusa soprattutto una linea clonale di MRSA (CC398-t034). Questo tipo di MRSA viene spesso riscontrato anche negli animali da reddito di altri Paesi europei e rientra nella categoria dei cosiddetti MRSA associati agli animali da reddito.

Nei vitelli da ingrasso, la prevalenza di MRSA è ancora bassa (al 4%) e, dal 2010, non è aumentata in modo significativo. Nel 2013, oltre a MRSA del tipo CC398- t011, nei vitelli da ingrasso sono stati rilevati per la prima volta MRSA del tipo CC398- t034, la cui diffusione dovrà essere seguita nei prossimi anni.

In Svizzera, gli MRSA si sono diffusi negli ultimi anni all'interno della popolazione di suini e la resistenza microbiologica a determinati gruppi di antibiotici importanti continua a crescere o rimane invariata, ma ad un livello elevato.

I livelli di resistenza nei batteri indicatori nel corso degli anni in Svizzera si situano spesso a livelli significativamente più alti rispetto a quelli dei Paesi nordici, ma significativamente più bassi rispetto a quelli dei Paesi del Sud dell'UE.

Resistenza nei campioni diagnostici su animali

Fino ad oggi, in Svizzera non esiste un monitoraggio della resistenza antibiotica di patogeni importanti né nel bestiame né negli animali da compagnia. Vista l'importanza di questi dati nella valutazione del rischio d'insorgenza di resistenze in futuro, organizzazioni nazionali e internazionali hanno recentemente affrontato questo tema. Il Centro per le zoonosi, le malattie animali di origine batterica e la resistenza agli antibiotici (ZOBA) ha illustrato per la prima volta nel presente rapporto questi dati con particolare riguardo agli stafilococchi in cani, gatti e cavalli. Gli alti tassi di resistenze alla meticillina riportati sia per *Staphylococcus pseudintermedius* nei cani che per *S. aureus* nei cavalli a livello clinico costituiscono non solo una sfida per i veterinari, ma anche un rischio per l'uomo a causa del loro potenziale zoonosico. Inoltre, il rilevamento di isolati multifarmaco-resistenti evidenzia la necessità di un uso prudente degli antimicrobici in medicina veterinaria. Per avere indicazioni su tendenze e rischi futuri, sarà fondamentale integrare questi dati con quelli derivanti da più isolati provenienti da altri laboratori nonché con dati relativi ad altri patogeni gram-positivi e gram-negativi.

Conclusioni

Questi risultati forniscono il quadro d'insieme il più completo possibile al momento sulle tendenze relative all'antibiotico-resistenza e al consumo di antibiotici in Svizzera. Al fine di poter meglio valutare i rischi, è necessario sorvegliare ulteriormente l'evoluzione delle resistenze microbiologiche ed esaminare a fondo le relazioni che intercorrono tra la loro diffusione nell'uomo e negli animali. Nell'ambito della Strategia nazionale contro le resistenze agli antibiotici (StAR), tutti i settori coinvolti sviluppano attualmente misure coordinate tra loro con l'obiettivo di garantire l'efficacia degli antibiotici a lungo termine al fine di preservare la salute dell'essere umano e degli animali.

3

Introduction

3 Introduction

3.1 Antibiotic resistance

Antibiotic resistance is responsible for increased morbidity and mortality and adds significant health care costs. Alternative treatments may have more serious side effects, need longer treatments and hospitals stays, with increased risk of suffering and death. Physicians in hospitals must increasingly rely on the so-called last-line antibiotics (e.g. carbapenems). Increasing antibiotic resistance, also to this last-line antibiotics, raises a serious concern. Surveillance of antibiotic use and resistance is considered to be the backbone of action plans developed by the different countries in order to determine the extent of the problem and the effectiveness of the measures taken.

3.2 About anresis.ch

In 2001, Prof. Kathrin Mühlemann from the Institute for Infectious Diseases Bern, started to build up the Swiss Centre for Antibiotic Resistance 'anresis.ch' (formerly called SEARCH) in the frame of the national research program 49 'Antibiotic Resistance' (NRP49, see also Chapter 1). After termination of the NRP49, end of 2006, financing was further guaranteed by the Swiss Federal Office of Public Health, the Swiss Conference of the Cantonal Ministers of Public Health and the University Bern. The project is supported by the Swiss Society of Infectious Diseases (SSI), the Swiss Society for Microbiology (SSM), the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) and PharmaSuisse, the Swiss Society of Pharmacists.

The first microbiology laboratories participated in anresis.ch in 2004. The surveillance system expanded continuously during the following years; it now includes the National Reference Center for Antibiotic Resistance of human clinical isolates (NARC), the bacteremia database (since 2006) and the antibiotic consumption database (since 2006 for inpatients, and since 2015 for outpatients). Data on antibiotic resistance in clinical veterinary isolates are also collected in the anresis.ch database since 2014. The open data structure still allows further developments.

The steering committee of anresis.ch is composed of specialists from microbiology laboratories, infectious disease, hospital epidemiology, veterinary medicine, the Swiss Federal Office of Public Health, the Swiss Conference of the Cantonal Ministers of Public Health and the University Bern (Annex IV).

3.2.1 Monitoring of antibiotic consumption in human medicine

For the inpatient setting, the consumption of antibiotics has been monitored since 2006 through a sentinel network of hospital pharmacies. Yearly, data of about 60 hospitals are collected on a voluntary basis. These hospitals are distributed all over the geographic territory and representing 54% of the total number of acute somatic care hospitals (excluding psychiatric and rehabilitation centers) and 47% of all beds in this category in Switzerland (33% of all beds) (see chapter 11.1). The participating hospitals receive a benchmarking report, allowing them to compare their results with those of similar-size hospitals.
Data for the outpatient setting were provided by PharmaSuisse. They are based on the prescriptions at individual level and obtained from the privately run pharmacies. The coverage is about 65% of all pharmacies in Switzerland.

3.2.2 Monitoring of resistance in human medicine

Anresis.ch collects and analyses anonymous antibiotic resistance data provided by the participating clinical microbiology laboratories (Annex IV). These laboratories are homogeneously distributed all over the geographic territory. They include university laboratories, representing isolates mainly from tertiary-care hospitals, as well as cantonal and private laboratories, representing data from smaller hospitals and ambulatories. They send antimicrobial susceptibility test results (AST) of all routinely performed analysis including isolates from non-sterile sites. Collected data represent at least 60% of annual hospitalization days and about 30% of the practitioners in Switzerland. The epidemiological data provided, allow for stratification of resistance results according to hospital versus outpatients, age groups, and anatomical location of the infection.

The proportion of the following multi-resistance bacteria in invasive isolates, is reported and updated monthly in the weekly Bulletin of the federal office of public health (http://www.bag.admin.ch/dokumentation/publikationen): fluoroquinolone-resistant *Escherichia coli,* extended-spectrum cephalosporin-resistant (ESCR) *E. coli,* ESCR *Klebsiella pneumoniae,* methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant Enterococci.
More detailed data from anresis.ch are published now for the first time in this report.

3.3 About ARCH-Vet

The use of antibiotics in livestock is often the subject of public concern, as resistant germs may be selected and can enter the food chain and eventually infect people. Hence, a system to enable the continuous monitoring of resistance in farm animals, meat and dairy products in Switzerland was introduced in 2006 on the basis of article 291d of the Epizootic Diseases Ordinance (EzDO; SR 916.401). Additionally it compiles data on sales of antimicrobial agents for veterinary medicine in accordance with article 36 of the former Federal Ordinance on Veterinary Medicines (FOVM; SR 812.212.27) Since 2009 data on sales of veterinary antimicrobials and results of the monitoring of resistance are published yearly in the ARCH-Vet report. For the first time the ARCH-Vet data are reported jointly with the anresis.ch data.

3.3.1 Sales of antibiotics in veterinary medicine

Sales data are used to estimate the consumption of antimicrobial agents in veterinary medicine. Marketing-authorisation holders have to report their sales of antimicrobial agents to Swissmedic (Swiss Agency for Therapeutic Products). These data are transmitted to the Food Safety and Veterinary Office (FSVO), where they are processed and analysed. Coverage of the data is 100% for the sales of authorised antimicrobial agents.

Sales of veterinary antimicrobials are published yearly in the ARCH-Vet report. The data are additionally transmitted to the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) database and published in the Annex of the ESVAC report on sales of veterinary antimicrobial agents in 26 EU/EEA countries.

3.3.2 Monitoring of resistance in zoonotic and indicator bacteria from animals

The main goals of the standardized monitoring of resistance to antibiotics in zoonotic and indicator (commensal) bacteria, isolated from healthy food animals, are to estimate resistance prevalence, to detect trends over years and to produce data for risk assessment. This information provides the basis for policy recommendations to combat the spread of resistance and also allows to evaluate the impact of measures taken.

Species examined
Cattle, pigs and broilers are monitored because of their importance in food production.
Fecal and nasal swab samples are taken by official meat inspectors at the slaughterhouse. Meat and dairy products from shops are also examined at specific intervals.
Resistance tests are performed for the zoonotic pathogens *Campylobacter jejuni* and *C. coli* and for the indicator germs *Escherichia coli, Enterococcus faecalis* and *E. faecium.* Since 2009, nasal swab samples from fattening pigs and cattle have also been tested for methicillin-resistant *Staphylococcus aureus* (MRSA). Since 2011, tests have been carried out to detect ESBL (extended-spectrum beta-lactamase)-producing *E. coli* in broilers, pigs and cattle using a selective enrichment procedure. *Salmonella* isolates available from clinical material from various animal species from the national control program for *Salmonella* in poultry, are also included.

Sampling
Slaughterhouse testing is organized in a way, that at least 80% of the slaughtered animals of the concerned species may potentially form part of the sample. Every slaughterhouse taking part in the program has to collect a number of samples proportional to the number of animals of the species slaughtered per year. In addition, sampling is spread evenly throughout the year.
The number of samples tested should allow:
- to estimate the proportion of resistant isolates within +/–8% of an actual resistance prevalence of 50%
- to detect a change of 15% in the proportion of resistant isolates if resistance is widespread (50% resistant isolates)
- to detect a rise of 5% in the proportion of resistant isolates if resistance was previously low (0.1% resistant isolates)

Resistance testing needs to be carried out on 170 isolates in order to achieve this accuracy. The sample size must be adjusted to reflect prevalence in previous years for the concerning animal species in order to obtain this number of isolates. As the prevalence of particular pathogens in some animal species is very low in Switzerland, it is not always possible to obtain 170 isolates. 170 isolates is the target for *C. jejuni, E. coli* and *Enterococcus* spp. in broilers, *C. coli* and *E. coli* for fattening pigs and for *E. coli* in cattle.

3.4 Guidance for readers

The present anresis.ch – ARCH-Vet report is the result of a cooperation between the Federal Office of Public Health (FOPH), the Food Safety and Veterinary Office (FSVO), anresis.ch and the Center for Zoonotic Diseases, Bacterial Diseases and Antibiotic Resistance in Animals (ZOBA). We are glad to present the Swiss data on the consumption of antimicrobials and antimicrobial resistance, both in humans and in animals.

Though these data are presented in one report, it is important to be aware, that differences between the monitoring systems for collection, interpretation and reporting hamper direct comparisons of the results.

Antibiotic consumption data
Antimicrobial consumption data from humans are reported as defined daily doses (DDD) per 1000 inhabitants and per day, or as DDD per 100 occupied bed-days or as DDD per 100 admissions.

In veterinary medicine, sales data on antimicrobials are used to estimate the consumption of these products. They are

reported by weight (kg) of active substance per year or by weight of active substance per population correction unit (PCU) and per year. A comparable unit of measurement like the DDD in human medicine is not yet available.

Antibiotic resistance data
The main issues when comparing antimicrobial resistance data originating from humans and food-producing animals are the different sampling strategies, the use of different laboratory methods and different interpretative criteria of resistance.

Sampling strategies:
Resistance in bacteria from humans is determined in isolates from clinical submissions, whereas for animals, bacteria originate from samples taken of healthy food-producing animals in the framework of an active monitoring.

Laboratory methods:
Susceptibility testing in human isolates is done in different laboratories using different methods (diffusion and microdilution methods). Animal isolates are tested at the Swiss national reference laboratory for antimicrobial resistance (the Centre for Zoonoses, Bacterial Diseases and Antibiotic Resistance in Animals (ZOBA), Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern) using a microdilution method.

Criteria of resistance:
Human clinical isolates are classified as 'susceptible', 'intermediate' or 'resistant' applying clinical breakpoints and quantitative resistance data are not available for most isolates. This interpretation indicates the likelihood of a therapeutic success with a certain antibiotic and thus helps the attending physician to select the best possible treatment. Clinical breakpoints are defined against a background of clinically relevant data such as dosing, method and route of administration, pharmacokinetic and pharmacodynamics. The use of different clinical breakpoints (e.g. EUCAST vs. CLSI) or changing breakpoints over time may therefore influence the results.
The resistance monitoring in animals uses epidemiological cut-off values (ECOFFs) to separate the natural, susceptible wild-type bacterial populations from isolates that have developed reduced susceptibility to a given antimicrobial agent. So called 'non-wild-type' organisms are assumed to exhibit acquired or mutational resistance mechanisms and are referred as 'microbiologically resistant'. ECOFF-values allow no statement on the potential therapeutic success of an antimicrobial, but as they are able to indicate resistance mechanisms at an early stage, they are used for epidemiological monitoring programs that measure resistance development over time.

Clinical breakpoints and ECOFFs may be the same, although it is often the case that the ECOFF is lower than the clinical breakpoint. That means although the bacteria can be "microbiologically resistant", therapeutically the antimicrobial can still be effective.

Cooperation and coordination between the different monitoring-networks has to be strengthened and systems have to be refined, to improve comparability, as it is foreseen in the National Strategy against Antibiotic Resistance (StAR).

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4

Abbreviations

4 Abbreviations

AFSSA	French Food Safety Agency
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical
CAESAR	Central Asian and Eastern European Surveillance on Antimicrobial Resistance
CI	Confidence interval
CC	Clonal complex
CLSI	Clinical Laboratory Standards Institute
DD	Disc diffusion
DDD	Defined daily doses
EARSS	European Antimicrobial Resistance Surveillance System
ECDC	European Centre for Disease Prevention and Control
ECOFF	epidemiological cut-off value
EEA	European Economic Area
EFSA	European food Safety Authority
EMA	European Medicines Agency
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	Extended spectrum beta-lactamase
ESC-R	Extended spectrum cephalosporin resistance
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
EUCAST	European Committee on Antimicrobial Resistance Testing
EzDO	Epizootic Diseases Ordinance
FAO	Food and Agriculture Organization
FOAG	Federal Office for Agriculture
FOEN	Federal Office for the Environment
FOPH	Federal Office of Public Health
FSVO	Food Safety and Veterinary Office
GSASA	Swiss association of public health administration and hospital pharmacists
GP	General practitioner
ICU	Intensive care units
MALDI TOF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy
mCCDA	modified charcoal cefoperazone deoxychelate agar
MDR	Multi drug resistant
MIC	Minimal inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin susceptible *Staphylococcus aureus*
MRSP	Methicillin resistant *Staphylococcus pseudintermedius*
MSM	Men who have sex with men
NRP	National research project
OFAC	professional cooperative of the Swiss pharmacists
OIE	World organization for animal health
pAmpC	plasmid-mediated AmpC-beta-lactamase
PBP	Penicilline binding proteine
PCU	Population correction unit
PNSP	Penicillin non-susceptible *Streptococcus pneumoniae*
PSSP	Penicillin susceptible *Streptococcus pneumonia*
SFOPH	Swiss Federal Office of Public Health
SIR	Susceptible – Intermediate – Resistant
SNF	Swiss National Foundation
SSM	Swiss society for microbiology
SSP	Swiss society of pharmacists, Pharma-Suisse
spp.	species
t	spa type
VetCAST	EUCAST Veterinary Subcommittee on Antimicrobial Susceptibility Testing
VMD	Veterinary Medicines Directorate
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization
ZOBA	Center for Zoonosis, Bacterial Animal Diseases and Antimicrobial Resistance

5

Antibacterial consumption in human medicine

5 Antibacterial consumption in human medicine

5.1 Hospital care

5.1.1 Total antibiotic consumption in hospitals participating to anresis.ch

Considering the hospitals that have participated each year since 2004 to the surveillance system anresis.ch (n = 27), the number of DDD was relatively stable over the 10-year period (+9%). The number of admissions increased (+15%), while the number of bed-days decreased (–15%).
The total consumption of systemic antibiotics in DDD per 100 bed-days increased by 36% from 46.2 (weighted mean, range: 21.0–97.4) in 2004 to 62.7 (range: 42.5–86.6) in 2013 (Figure 5. a).

This increasing trend was observed in the three categories of hospital sizes and the total consumption was slightly higher in the large-size hospitals. Whereas the total antibiotic consumption in DDD per 100 admissions remained stable from 2004 to 2013 (–2%) (Figure 5. a).
The total consumption of antibacterial agents for systemic use (ATC group J01) was approximated at 1.9 DDD per 1000 inhabitants per day in 2013. In comparison, the median consumption was 2.0 DDD per 1000 inhabitants per day (range 1.4–2.8) in 2012 in the countries participating to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1].

5.1.2 Antibiotic consumption in hospitals participating to anresis.ch by antibiotic class and by specific antibiotic

In 2013, penicillins consumption (ATC group J01C) ranked first among antibiotic classes, representing 46% of the total consumption (Figure 5. b). It was followed by the consumption of cephalosporins (ATC group J01D) and quinolones (ATC group J01M) (24% and 10%, respectively).

Table 5. a shows the consumption of antibiotic classes expressed in DDD per 100 bed-days in sentinel hospitals over the period 2004–2013. Out of the 20 antibiotic classes, the use of three of them decreased between 2004 and 2013 (fourth-generation cephalosporins, aminoglycosides and tetracyclines). The most important progression (more than 100%) in consumption between 2004 and 2013 was observed for the polymyxins, the nitrofuran derivates, the penicillins including beta-lactamase inhibitors (anti-pseudomonal), the carbapenems, the glycopeptides, the betalactamase sensitive penicillins and the third-generation cephalosporins.

Figure 5. a: Total antibiotic consumption expressed in DDD per 100 bed-days (in blue) and in DDD per 100 admissions (in black) in the hospitals participating to anresis.ch over the period 2004–2013.

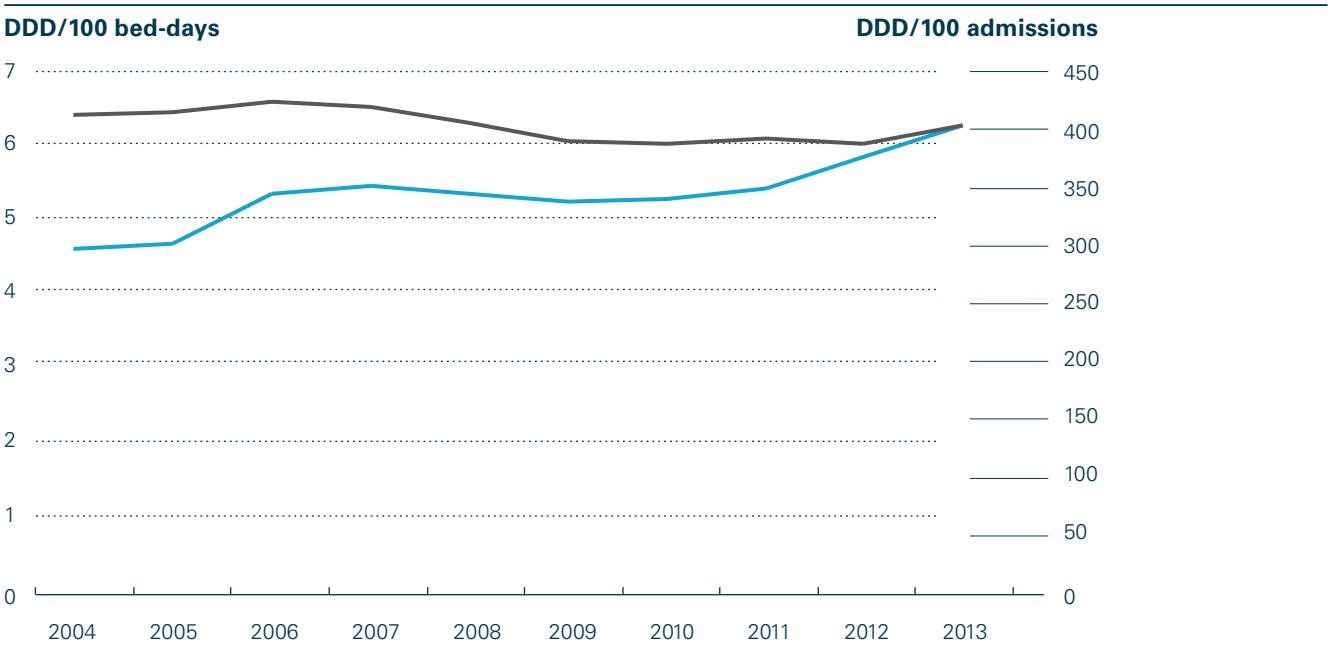


Figure 5. b: Antibiotic classes consumption (Antibacterials for systemic use code ATC J01) in proportion of the total antibiotic consumption by the different hospital size categories or by the overall hospitals participating to anresis.ch (2009–2013).

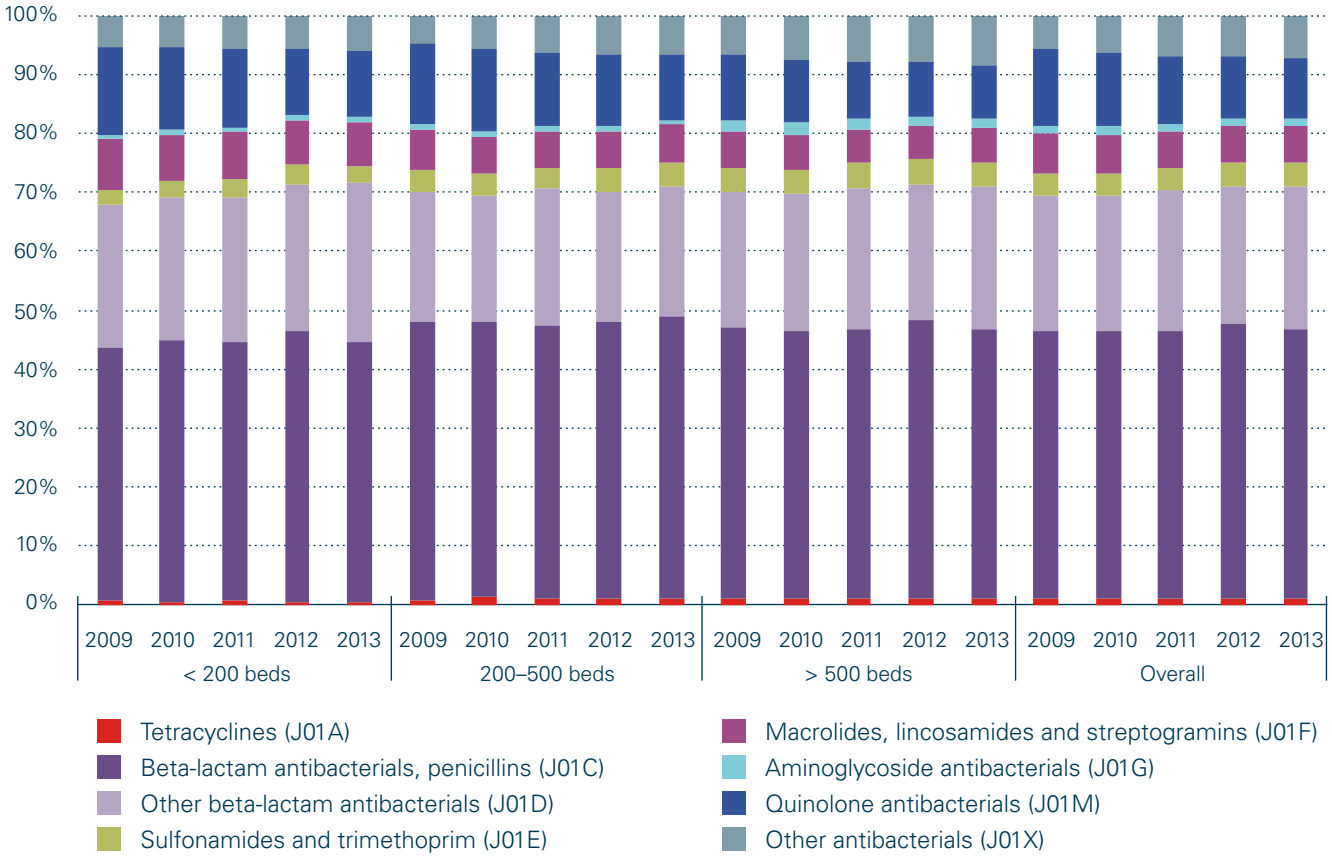


Table 5. a: Consumption of antibiotic classes expressed in DDD per 100 bed-days in hospitals participating to anresis.ch (2004–2013).

ATC Group	Antibiotic class	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
J01G	Aminoglycosides	0.8	0.6	0.9	0.8	0.7	0.7	0.8	0.7	0.7	0.7
J01CF	Beta-lactamase resistant penicillins	1.8	1.7	1.9	1.7	1.6	1.7	1.8	1.9	2.1	2.1
J01CE	Beta-lactamase sensitive penicillins	0.6	0.7	0.8	0.9	0.9	1.1	1.1	1.3	1.5	1.3
J01DH	Carbapenems	1.4	1.4	1.7	2.2	2.2	2.4	2.4	2.6	2.8	3.2
J01DB	Cephalosporins – first generation	0.9	0.9	1.1	1.2	1.3	1.2	1.1	1.1	1	1
J01DC	Cephalosporins – second generation	3.0	3.0	3.6	3.9	3.8	3.6	3.6	3.6	3.8	4.3
J01DD	Cephalosporins – third generation	2.4	2.6	3.2	3.7	3.7	3.7	3.8	4.0	4.2	4.9
J01DE	Cephalosporins – fourth generation	2.4	2.1	1.8	0.7	1.1	1.0	1.1	1.3	1.5	1.6
J01MA	Fluoroquinolones	6.1	6.9	7.8	7.9	7.3	6.7	6.5	6.1	6.1	6.4
J01XA	Glycopeptides	0.6	0.5	0.7	0.8	0.9	0.9	1.0	1.1	1.1	1.2
J01FF	Lincosamides	0.8	0.7	0.9	0.9	0.9	0.9	0.8	0.8	0.9	1.0
J01FA	Macrolides	2.5	2.6	2.7	3.1	2.9	2.7	2.6	2.5	2.7	3.0
J01XE	Nitrofuran derivates (nitrofurantoin)	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.3	0.4
J01CR02	Penicillins & beta-lactamase inhibitor (amoxicillin & clavulanic acid)	15.0	15.0	16.9	16.8	16.0	16.7	16.3	16.5	18.2	18.8
J01CR03-05	Penicillins & beta-lact. inhibitor (anti-pseudomonal)	0.6	0.6	1.1	1.3	1.5	1.6	1.8	1.9	2.3	2.7
J01CA	Penicillins with extended spectrum (amoxicillin)	2.1	2.1	2.5	2.5	2.7	2.5	2.5	2.7	2.9	3.4
J01XB	Polymyxins (colistin)	0.0	0.0	0.1	0.1	0.2	0.0	0.1	0.1	0.1	0.2
J04AB	Rifamycins	0.8	0.8	0.9	1.0	1.0	0.9	1.0	0.9	0.8	0.8
J01E	Sulfonamides & trimethoprim	1.9	1.9	1.9	2.1	2.1	1.9	1.9	2.0	2.3	2.3
J01A	Tetracyclines	0.7	0.9	0.7	0.7	0.7	0.5	0.6	0.5	0.6	0.6
	Others	1.7	1.8	2.2	2.3	2.3	1.8	2.1	2.4	2.6	2.9

Figure 5. c: Consumption of penicillins (ATC group J01C) expressed in DDD per 100 bed-days in hospitals participating to anresis.ch (2004–2013).

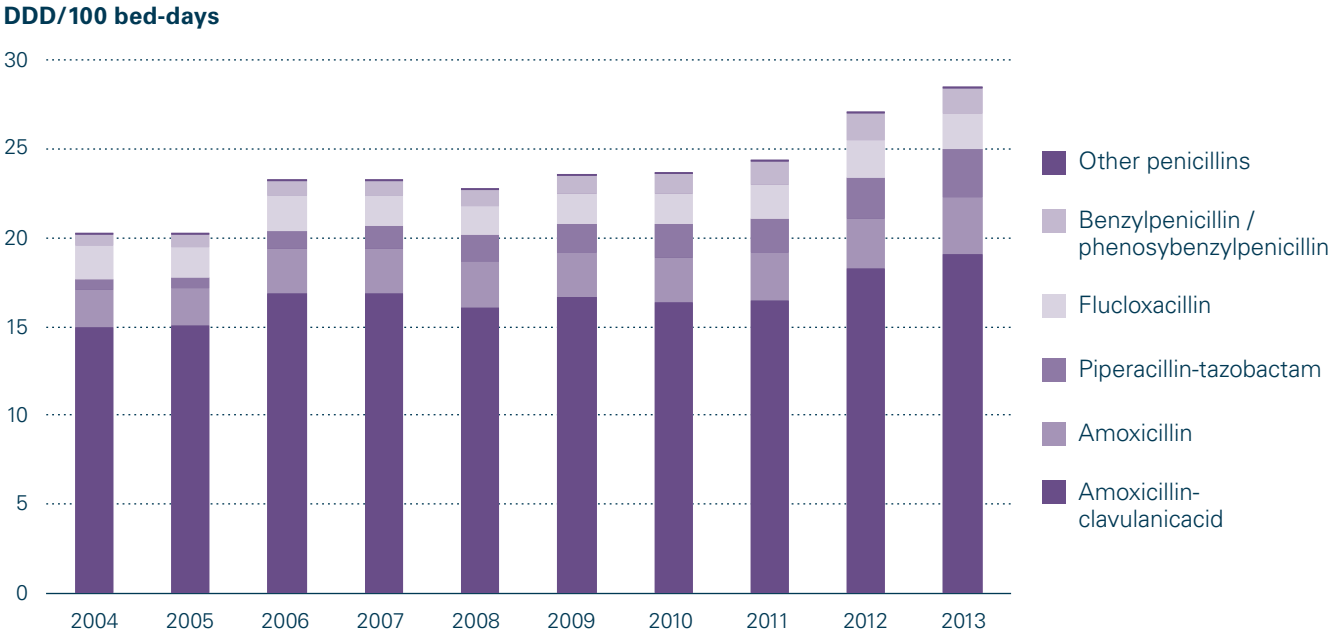
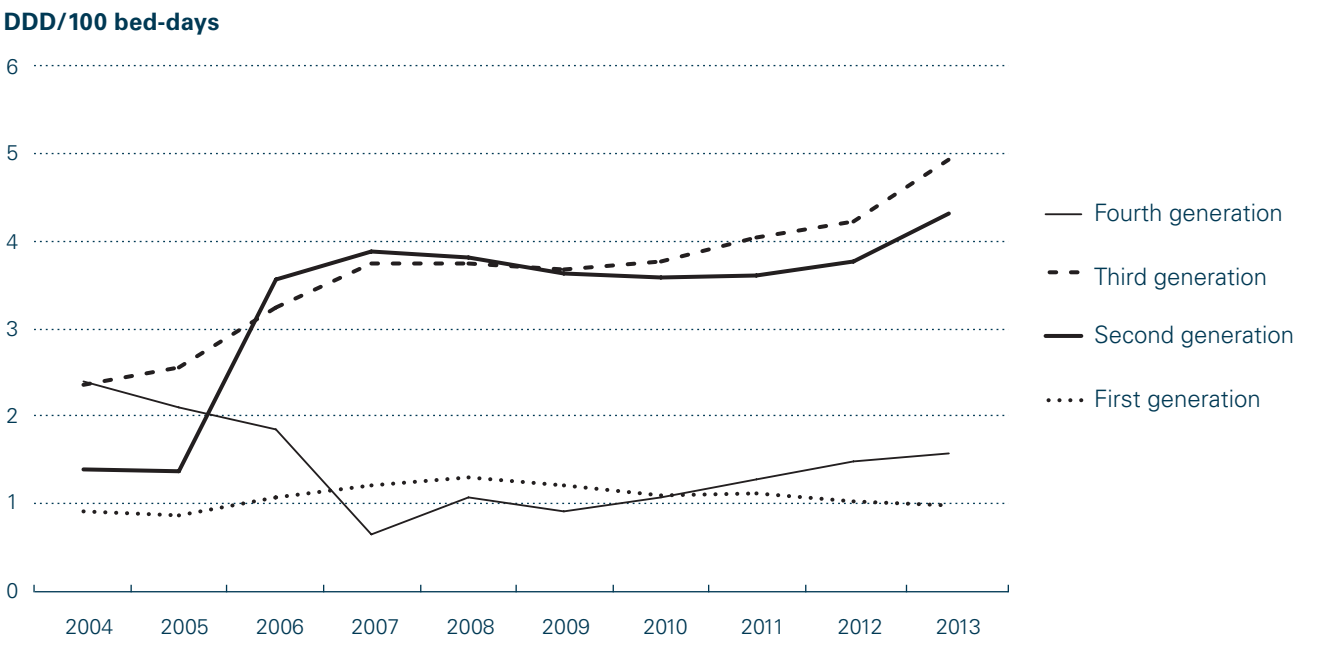


Figure 5. d: Consumption of cephalosporins (first, second, third and fourth generation; ATC group J01DB-DC-DD-DE) expressed in DDD per 100 bed-days in hospitals participating to anresis.ch (2004–2013).



Among penicillins, the association of amoxicillin and clavulanic acid was the most frequently prescribed antibiotic and ranged from 15.0 in 2004 to 16.9 DDD per 100 bed-days in 2013. The association piperacillin and tazobactam increased by 316% between 2004 and 2013 (Figure 5. c).

The use of second- and third- generation cephalosporins increased markedly from 2004 to 2013 (Figure 5. d). In 2013 cefuroxim (second generation) and ceftriaxon (third generation) were the most used cephalosporins in the three hospital size categories. Cefepime (fourth generation) decreased in 2007 due to drug shortage.

Figure 5. e: Consumption of carbapenems (ATC group J01DH) expressed in DDD per 100 bed-days by hospital size category (2004–2013).

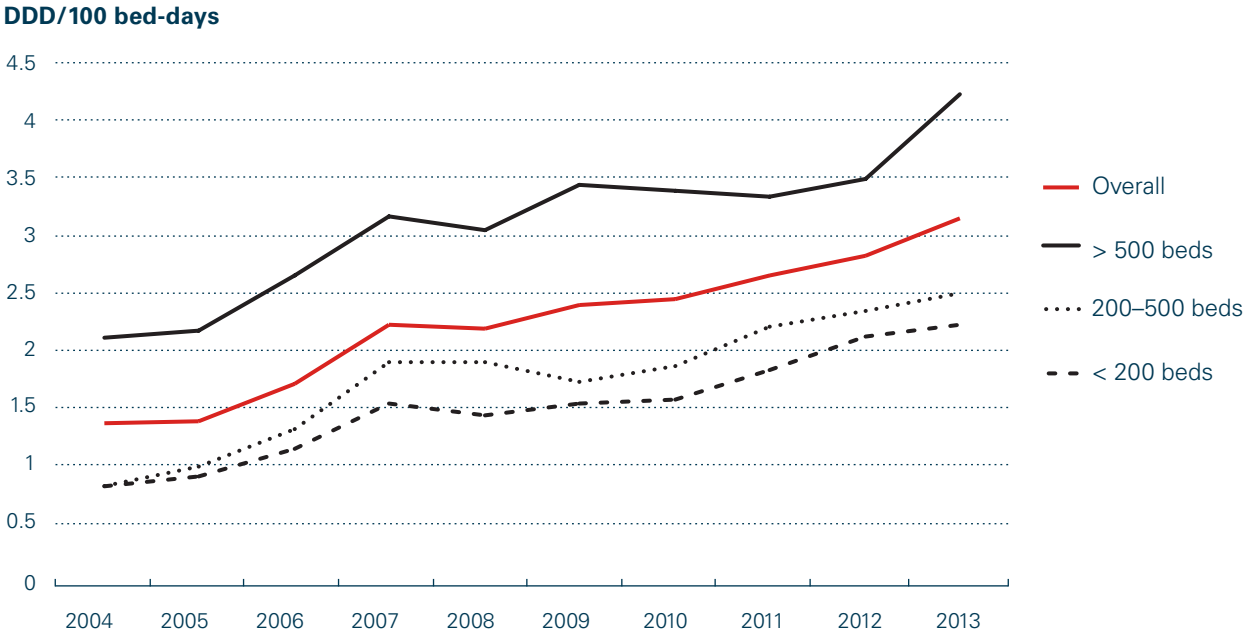
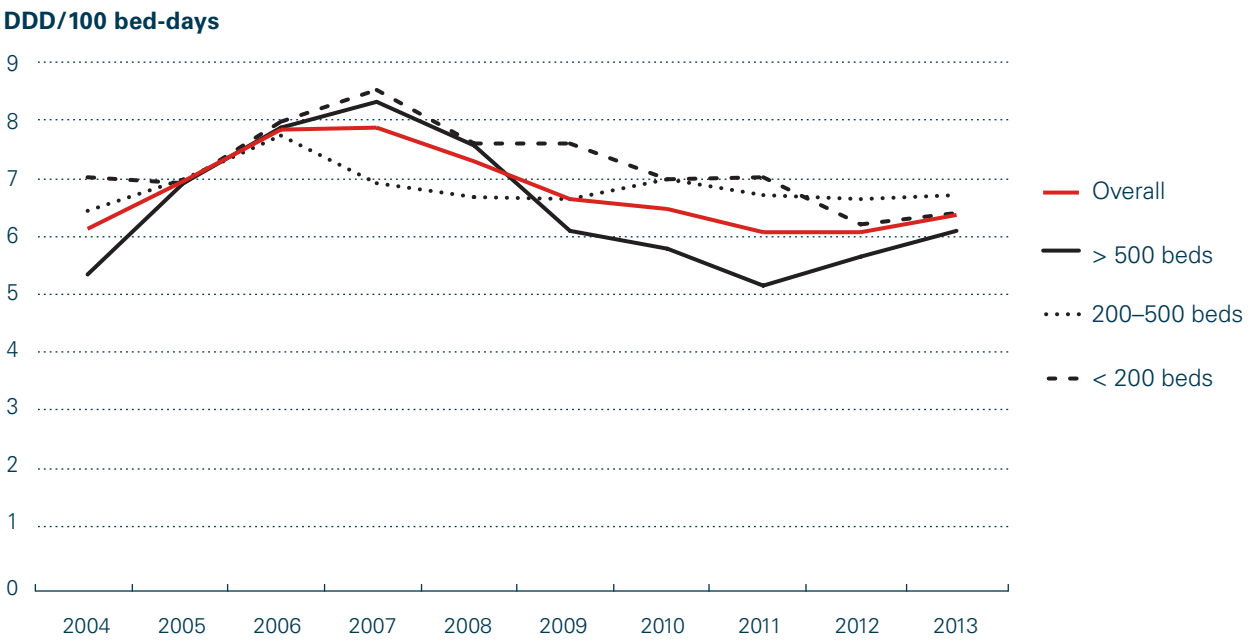


Figure 5. f: Consumption of fluoroquinolones (ATC group J01MA) expressed in DDD per 100 bed-days by hospital size categories (2004–2013).



Since 2004, the consumption of carbapenems has increased in the 3 categories of hospital size (Figure 5. e). Overall, the consumption has increased by 132% from 1.4 to 3.2 DDD per 100 bed-days over the last 10 years. We observed a marked progression in consumption for meropenem (+143%) between 2004 and 2013.

Fluoroquinolone consumption decreased over the years 2007–2012 and was stable in 2013 compared to 2012 (Figure 5. f). Ciprofloxacin (oral) is the most used fluoroquinolone in the three hospital size categories: 64% of fluoroquinolone use in the small-size, 67% in the medium-size and 62% in the large-size hospitals. The consumption of levofloxacin and moxifloxacin was relatively stable over the years 2004–2013 accounting for 1.1 and 0.2 DDD per 100 bed-days respectively in 2013. Norfloxacin and ofloxacin use decreased in the three hospital size categories over the 10-year period.

Macrolide consumption remained stable over the period 2004–2013. Clarithromycin was the most used macrolide (80% of macrolide use in 2013), followed by azithromycin (11%) and erythromycin (9%).

Figure 5. g: Consumption of vancomycin, linezolid, daptomycin and teicoplanin expressed in DDD per 100 bed-days in hospitals participating to anresis.ch (2004–2013).

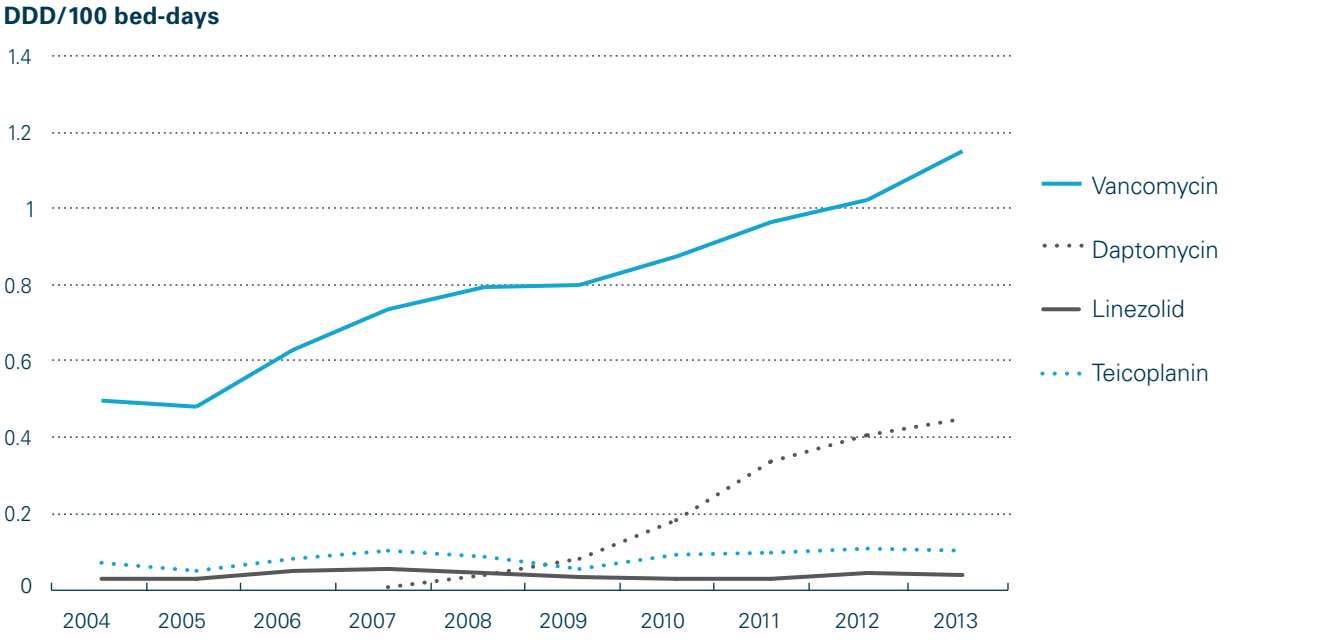
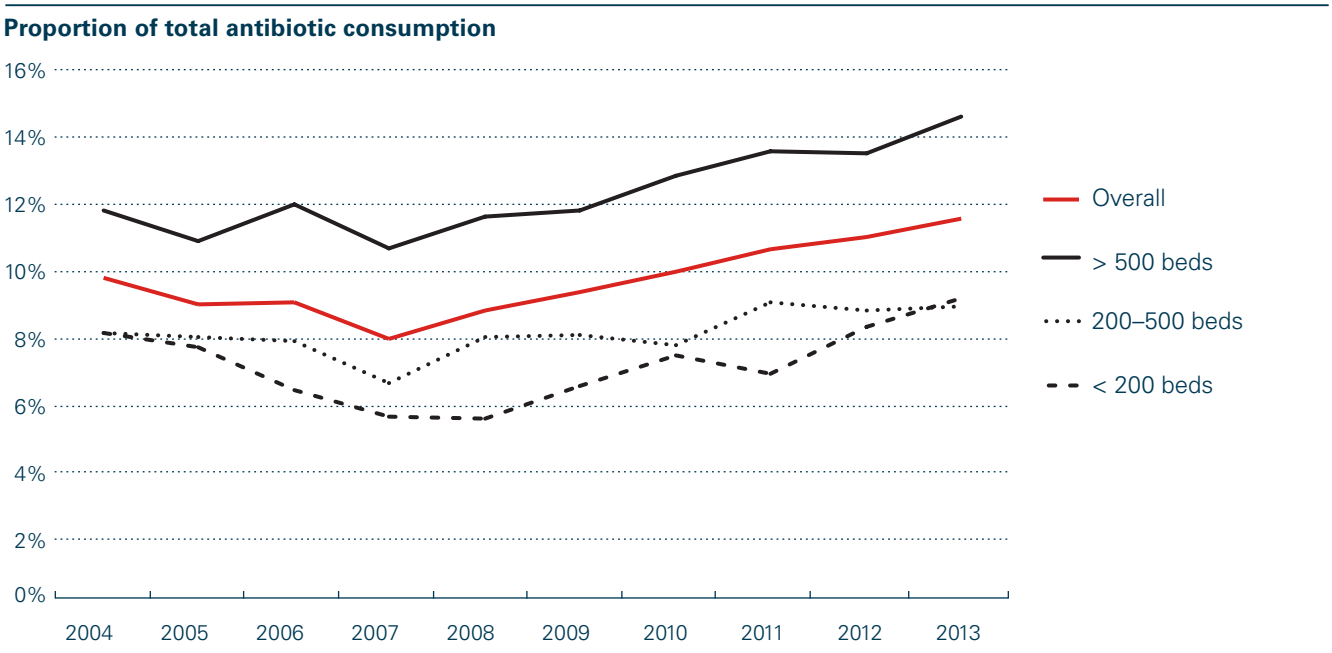


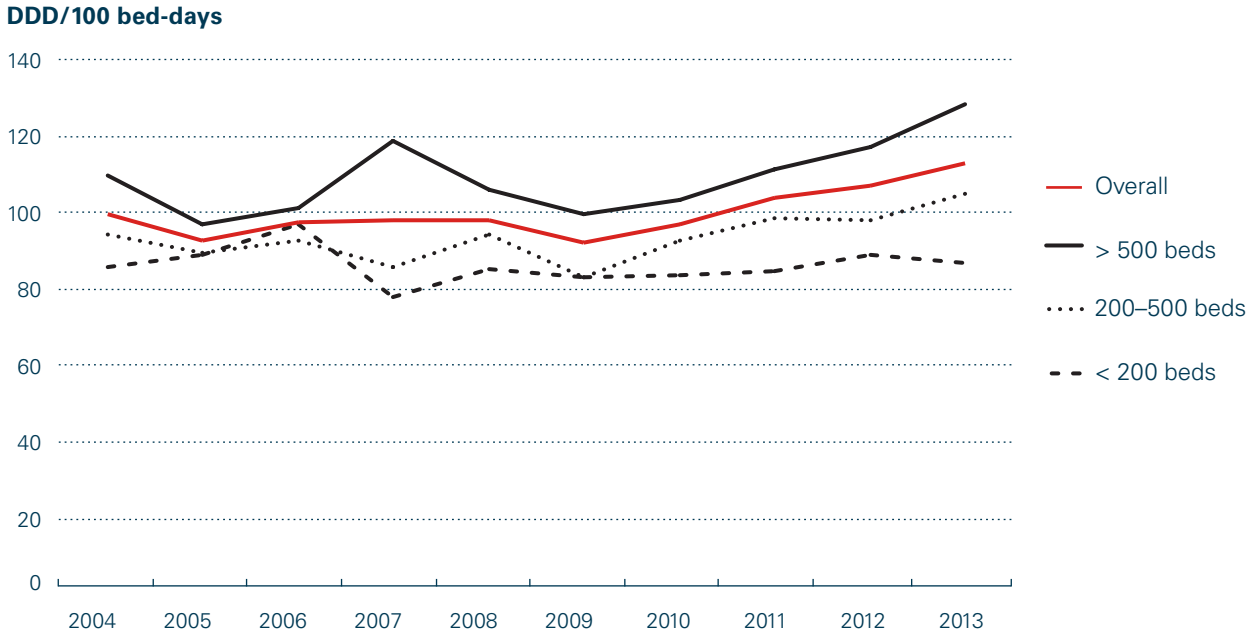
Figure 5. h: Proportion of the broadest-spectrum antibiotics by hospital size categories (2004–2013). The broadest-spectrum antibiotics include: aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin, piperacillin-tazobactam, ticarcillin and ticarcillin-tazobactam.



Among antibiotics active against resistant gram-positive bacteria, we observed an increase by 133% in consumption of vancomycin between 2004 and 2013 (Figure 5. g). Consumption of daptomycin was higher in the large-size hospitals (0.64 DDD per 100 bed-days) than in the medium-size and the small-size hospitals (0.37 and 0.23 DDD per 100 bed-days, respectively). Linezolid and teicoplanin remained stable over the years 2004–2013.

The proportion of the broadest-spectrum antibiotics increased in the three hospital sizes categories over the years 2004–2013 (Figure 5. h). In the present report, aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin, piperacillin-tazobactam, ticarcillin and ticarcillin – tazobactam were considered as the broadest-spectrum antibiotics. In 2013, piperacillin-tazobactam was the most used of them in the sentinel hospitals (37% of the broadest-spectrum antibiotic use), followed by meropenem (24%), cefepime (22%) and imipenem (14%).

Figure 5. i: Total antibiotic consumption expressed in DDD per 100 bed-days in intensive care units of hospitals participating to anresis.ch over the period 2004–2013.



5.1.3 Total antibiotic consumption in intensive care units of hospitals participating to anresis.ch

Global use of systemic antibiotics remained relatively stable from 99.4 in 2004 to 113.1 DDD per 100 bed-days in 2013. Total antibiotic consumption was higher in the intensive care units of large-size hospitals (109.9 and 128.6 DDD per 100 bed-days in 2004 and 2013, respectively), compared with the ones of medium-size (94.2 and 105.1) and small-size (99.4 and 113.1) hospitals (Figure 5. i).

5.2 Outpatient care

5.2.1 Total antibiotic consumption in the outpatient setting

In 2013, the total consumption of antibacterial agents for systemic use (ATC code J01) was approximated at 6 DDD per 1000 inhabitants per day and 0.7 packages per 1000 inhabitants per day (see Chapter 5.3 discussion). In comparison, the mean consumption was 21.5 DDD per 1000 inhabitants per day (range 11.3–31.9) and 3.1 packages per 1000 inhabitants per day (range 1.1–4.9) in 2012 in the countries participating to European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1].

5.2.2 Antibiotic consumption in the outpatient setting by antibiotic class and by specific antibiotic

Consumption of penicillins (ATC Code J01C) ranked first among antibiotic classes, corresponding to 42% of the total antibiotic consumption in 2013 (Figure 5. j). It was followed by the consumption of quinolones (ATC Code J01M) and macrolides, lincosamides and streptogramins (ATC Code J01F) (14% and 13%, respectively).

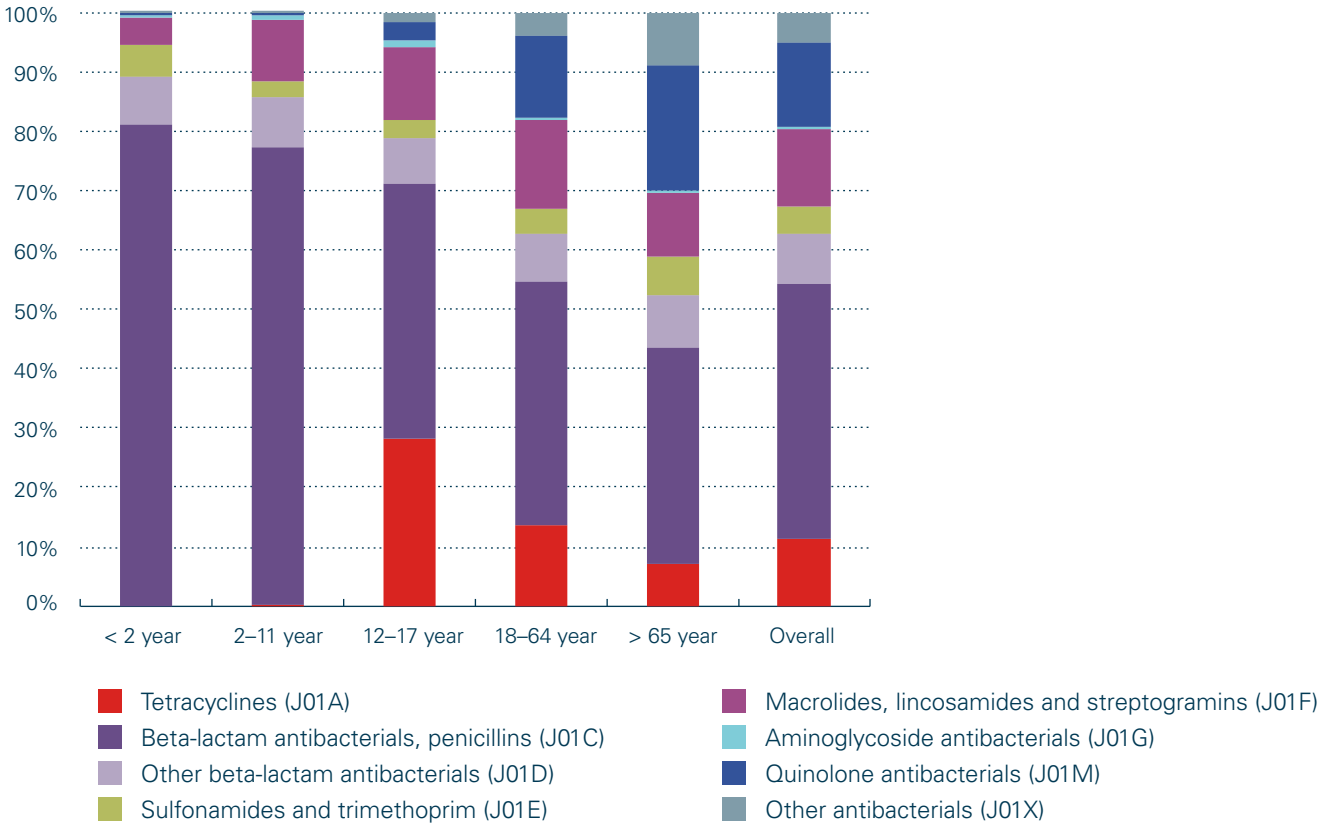
Penicillins with extended spectrum (ATC Code J01CA), namely amoxicillin, were the most used penicillins in children aged less than 2 years (65% of penicillin use), whereas combinations of penicillins including beta-lactamase inhibitors were the most used penicillins in the other age groups (2–11 years: 53%, 12–17: 70%, 18–64: 79%; >65: 83% of penicillin use). The relative consumption of beta-lactamase-sensitive penicillins (ATC Code J01CE) was 1% of the total antibiotic consumption (ATC Code J01). This indicator ranged from <0.1% to 27.9% in countries participating to ESAC-Net [1]. The relative consumption of combinations of penicillins including beta-lactamase inhibitors (ATC Code J01CR) was 32% of the total antibiotic consumption (ATC Code J01). The percentage ranged from <0.1% to 41.1% in countries participating to ESAC-Net [1].

The relative consumption of third- and fourth-generation cephalosporins (ATC code J01DD and J01DE) was 2% in 2013, compared with a range of <0.1% to 6.8% in countries participating to ESAC-Net [1].

Among fluoroquinolones (ATC Code J01MA), ciprofloxacin was the most used in all age groups (12–17 years: 74%, 18–64: 61%; >65: 59%; overall: 60% of fluoroquinolone consumption). Consumption of norfloxacin, levofloxacin, moxifloxacin and ofloxacin accounted for 15%, 13%, 9% and 2% of the quinolones, respectively. Seniors aged 65 and more were relatively high consumers of fluoroquinolones (21% of their total antibiotic consumption). The relative consumption of fluoroquinolones (ATC code J01MA) was 14% in 2013, compared with a range of 2.1% to 13.7% in countries participating to ESAC-Net [1].

Considering the macrolides, lincosamides and streptogramins (ATC Code J01F), clarithromycin and azithromycin

Figure 5. j: Antibiotic classes (Antibacterials for systemic use code ATC J01) per age group and overall in proportion of the total consumption in primary health care in 2013.



were the most commonly used antibiotics in all age groups. Clindamycin accounted for more than 10% of the total J01F class consumption in adults (over 18 years old).
Tetracyclines were the second most prescribed antibiotic class (after the penicilines) in the age group between 12 and 17 years old. Lymecycline was the most used tetracycline in this age group (40% of the tetracycline consumption in patients between 12–17 years old), whereas doxycycline was more often used in the age groups 2–11, 18–64 and >65 years (82%, 72%, 85%, respectively).
Among aminoglycosides, inhaled tobramycin corresponded to the most used antibiotic from this class in most age groups.

5.3 Discussion

In Swiss acute care hospitals, total antibiotic consumption increased from 46.2 to 62.7 DDD per 100 bed-days between 2004 and 2013, whereas it was relatively stable when expressed in DDD per 100 admissions. This discrepancy can be explained by an increasing number of admissions and a decreasing number of bed-days in hospitals due to shorter length of hospital stay. Expressed in DDD per 1000 inhabitants per day, the total antibiotic consumption (1.9) was close to the median (2.1) obtained in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1]. The most commonly used class of antibiotics was the penicillins (ATC Code J01C), followed by the other beta-lactam antibacterials, including cephalosporins (ATC Code J01D) and quinolones (ATC Code J01M).

In the outpatient setting, the total consumption of antibacterial agents for systemic use (ATC code J01) was approximated at 6 DDD per 1000 inhabitants per day and 0.7 packages per 1000 inhabitants per day in 2013, which was lower than observed in countries participating to European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1]. However, comparisons with other countries have to be done with caution as consumption may have been underestimated in Switzerland (see limitations). The most commonly used class of antibiotics was the penicillins (ATC Code J01C), followed by the quinolones (ATC Code J01M) and the macrolides, lincosamides and streptogramines (ATC Code J01F). The relative consumption of fluoroquinolones and penicillins including beta-lactamase inhibitors was relatively high in comparison with countries participating to ESAC-Net.

Our methodology has several limitations [2]. The DDD methodology allows comparisons between hospitals or countries, but it may inaccurately reflect the dosages chosen in some of them, thus limiting the qualitative appraisal of different prescribers' profiles [3]. Concerning the inpatient setting, a sentinel network like the one of anresis.ch which is based on voluntary participation of hospitals in Switzerland, is a surveillance system comprising a non-exhaustive group of hospitals. Nevertheless, the high proportion of all Swiss

acute care hospitals included in our surveillance suggests that the data are representative. In this report, we expressed the antibiotic consumption mostly in DDD per 100 bed-days rather than per admission for the inpatient setting. The definition of bed-days has been set by the Federal Statistical Office, while the number of admissions is not an official indicator and can be subject to different interpretations among hospitals. Concerning the outpatient setting, the data may be slightly underestimated. Indeed, the data from dispensing physicians and partially from nursing homes are missing in the dataset. Further investigations to analyze the trends of antibiotic consumption by cantons or regions are foreseen.

References

[1] European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014

[2] Plüss-Suard C.et al. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. J Hosp Inf 2011; 79(2): 166–171

[3] de With K et al. Comparison of Defined versus Recommended versus Prescribed Daily Doses for Measuring Hospital Antibiotic Consumption. Infection 2009; 37(4): 349–52.

6

Antibacterial sales in veterinary medicines

6 Antibacterial sales in veterinary medicines

6.1 Total antibacterial sales for use in animals

The total sales of veterinary antibacterials decreased in 2013 (Table 6. a). Compared with 2012, total sales decreased 6.7% (3,829 kg) and compared with the peak year 2008 even 26% (18,920 kg). This was mainly due to reduced sales of sulphonamides and tetracyclines.

Sulfonamides, penicillins and tetracyclines represented 82% of the total antimicrobial sales. Of the critically important antimicrobial classes with highest priority for human medicine [1], macrolides decreased since 2008 and cepha-

Table 6. a: Sales of different antibacterial classes and in total in the years 2006 to 2013.

Sales (in kg)	2006	2007	2008	2009	2010	2011	2012	2013
Sulfonamides	27,069	29,131	29,129	27,261	25,696	23,123	21,556	18,942
Penicillins	12,966	12,990	13,685	13,062	13,413	13,714	13,217	13,083
Tetracyclines	15,025	16,699	16,719	15,559	14,749	13,737	12,043	11,631
Aminoglycosides	3,724	3,722	3,721	3,573	3,222	3,324	3,207	3,124
Macrolides	3,606	4,022	4,287	4,026	3,828	3,481	3,313	3,112
Trimethoprim	2,083	2,018	1,858	1,752	1,704	1,549	1,368	1,148
Polymyxins	1,829	1,666	1,577	1,544	1,489	1,454	1,058	855
Cephalosporins	446	481	501	520	568	565	542	530
Fluoroquinolones	343	385	433	427	415	394	359	413
Others (*)	29	178	42	52	83	407	262	290
Amphenicols	202	232	253	271	258	284	232	202
Lincosamides	104	106	97	83	82	70	57	54
Total	**67,426**	**71,628**	**72,304**	**68,129**	**65,508**	**62,103**	**57,213**	**53,384**

(*) Imidazoles, nitrofurans, pleuromutilins, polypeptides (excluding polymyxins), quinolones, steroidal antibiotics

Table 6. b: Sales of antibiotics by administration route in the years 2006 to 2013.

Administration route	2006	2007	2008	2009	2010	2011	2012	2013
Intramammary	**5,270**	**5,345**	**5,486**	**5,002**	**4,599**	**4,776**	**4,660**	**4,491**
Drying-off products	1,585	1,696	1,601	1,464	1,384	1,510	1,500	1,533
Lactation	3,685	3,649	3,885	3,538	3,214	3,265	3,161	2,958
Oral	**50,881**	**55,040**	**55,132**	**51,993**	**50,143**	**46,476**	**42,005**	**38,756**
Premixes	45,288	48,824	48,794	45,714	44,125	40,606	36,181	33,021
Others	5,592	6,216	6,338	6,279	6,017	5,871	5,824	5,735
Parenteral	**10,131**	**10,091**	**10,479**	**9,973**	**9,555**	**9,643**	**9,415**	**9,075**
Topical / external	**1,144**	**1,152**	**1,207**	**1,161**	**1,211**	**1,207**	**1,133**	**1,062**
Spray	211	227	241	253	280	321	299	278
Others (*)	933	925	966	908	932	886	833	785
Total	**67,426**	**71,628**	**72,304**	**68,129**	**65,508**	**62,103**	**57,213**	**53,384**

(*) Ointments, solutions, intra-uterine oblets

losporines since 2011. However, the reduction of cephalosporines in 2013 is mainly due to a drop in sales of first-generation cephalosporins. Sales of third and fourth generation cephalosporins on the other hand increased slightly (data not shown).
Sales of fluoroquinolones increased 15% in 2013 compared to the previous year.

One third of the products sold for intramammary use are licensed for drying-off of dairy cows and two thirds for treatment during lactation. Sales of drying-off products increased slightly compared with the previous year (Table 6. b).
Of the total sales of active substances licensed for oral administration, 85% were sold as premixes. This proportion has remained relatively constant since recording begun.
After a steady increase from 2006 to 2011, sales of active ingredients sold as sprays decreased since 2012.

6.1.1 Normalisation of total antibacterial sales by animal population (Population Correction Unit, PCU method)

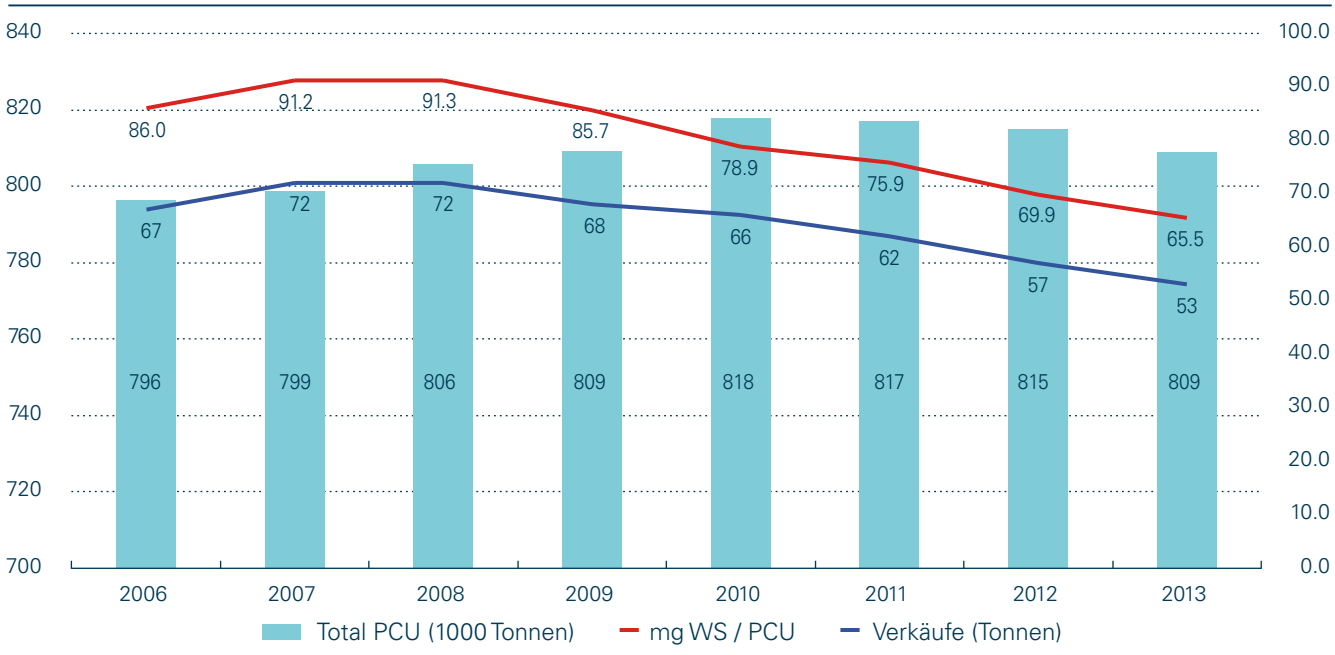
Sales of antibacterials depend on the number of animals treated. To estimate sales corrected by the animal population in individual countries and across countries, a normalisation method was developed as part of the EU project ESVAC (European Surveillance of Veterinary Antimicrobial Consumption). It enables to link total sales to the estimated weight of the food producing population [2]. Pet population is not taken into account by this normalisation method as in many countries the number of pets is unknown. The 'PCU' (Population Correction Unit; 1 PCU = 1 kg) is the number of livestock animals (dairy cows, sheep, sows, horses) and slaughtered animals (cows, calves/beef cattle, pigs, lambs, horses, poultry, turkeys) in the corresponding year multiplied by the estimated weight at the time most likely for treatment. Imports and exports of living animals are also taken into account.
Figure 6. a shows the normalisation of total sales in Switzerland using the PCU method for the years 2006 to 2013. It shows antibiotic sales, population biomass (total PCU) and milligrams of active ingredient/PCU.

This graph shows an increasing population biomass from 2006 to 2010 and a slight decrease from 2010 to 2013. Sales, on the other hand, increased until 2008 and then started to decrease. Because antibiotic sales have fallen more than the population biomass, the result is a net reduction in milligrams of active ingredient per PCU (or kg of food producing animal biomass). This shows that the falling consumption of antimicrobials cannot be attributed solely to the falling numbers of animals.

6.2 Antibacterial sales – pets

The proportion of active ingredients licensed for use in pets was only 1.5% of the total sales The distribution by animal category is based on the product's marketing authorisation. Therefore the actual use is not reflected precisely. Since 2012, products that are licensed for both food producing animals and pets are added to the category 'Food producing animals' in accordance with the guidelines of the ESVAC

Figure 6. a: Veterinary antibiotic sales in Switzerland in the years 2006–2013, compared with population biomass and sales of active ingredients (in mg) per Population Correction Unit (PCU).



Key: Total PCU (1000 Tonnen) = Total PCU (1,000 tonnes)
mg WS/PCU = mg active ingredient/PCU
Verkäufe (Tonnen) = sales (tonnes)

project [3]. This is especially important in the case of active ingredients for parenteral administration, as the bulk of these products (expressed in kg) are licensed for both pets and food producing animals.
In terms of volume, penicillins were the most important active ingredient group among the products that are authorised for use in pets only, followed by cephalosporins, macrolides, licosamides and fluoroquinolones (Table 6. c).
Sales of fluoroquinolones licensed for oral administration in pets increased by 21% in 2013 compared with the previous year.
Only few products with active ingredients from the amphenicol group have remained authorised for use in pets since 2013. For confidentiality reasons, these products are now classed under "Others".

6.3 Antibacterial sales – food producing animals

6.3.1 General

The amount of sales for food producing animals includes products licensed solely for food producing animals and products licensed for food producing animals and pets. This proceeding corresponds to the European report on sales of veterinary antimicrobial agents (ESVAC project, EMA).

Sulfonamides accounted for the bulk of agents sold for the treatment of food producing animals, followed by penicillins and tetracyclines. Sales of cephalosporins have decreased

Table 6. c: Sales of antibacterial classes licensed for use in pets only in the years 2006–2013.

Sales								
(in kg)	2006	2007	2008	2009	2010	2011	2012	2013
Penicillins	334	360	385	412	417	438	415	438
Cephalosporins	315	329	332	317	331	316	304	302
Macrolides + lincosamides	43	46	46	45	46	44	43	41
Fluoroquinolones	24	25	25	24	27	23	24	29
Aminoglycosides	32	33	33	24	7	7	8	9
Amphenicols (*)	95	99	87	95	79	106	64	
Sulfonamides (**)	44	45	41	30	24	5		
Others (***)	52	57	38	34	23	24	22	41
Total	**939**	**995**	**988**	**947**	**954**	**962**	**881**	**860**

(*) From 2013 under others
(**) 2012-2013: No product licensed
(***) Imidazoles, nitrofurans, polymyxins, polypeptides, steroidal antibiotics, tetracyclines, trimethoprim, amphenicols from 2013

Table 6. d: Sales of antibacterial classes licensed for food producing animals in the years 2006–2013.

Sales								
(in kg)	2006	2007	2008	2009	2010	2011	2012	2013
Sulfonamides	27,025	29,086	29,088	27,231	25,672	23,118	21,556	18,942
Penicillins	12,632	12,630	13,300	12,650	12,996	13,277	12,803	12,645
Tetracyclines	14,992	16,664	16,704	15,546	14,746	13,731	12,038	11,626
Macrolides + lincosamides	3,667	4,081	4,338	4,063	3,864	3,508	3,326	3,125
Aminoglycosides	3,692	3,688	3,688	3,549	3,215	3,317	3,199	3,115
Trimethoprim	2,079	2,013	1,854	1,749	1,702	1,548	1,368	1,148
Polymyxins	1,829	1,666	1,577	1,543	1,489	1,454	1,057	854
Fluoroquinolones	318	360	408	403	388	371	335	384
Cephalosporins	131	152	169	203	237	249	237	228
Amphenicols								183
Others (*)	122	295	191	211	245	568	413	274
Total	**66,487**	**70,633**	**71,316**	**67,147**	**64,554**	**61,140**	**56,332**	**52,250**

(*) Pleuromutilins, polypeptides, quinolones, amphenicols (until 2012)

Table 6. e: Volumes of antibiotics sold in 2006–2013 as premixes, by active ingredient class.

Sales								
(in kg)	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Sulfonamides	21,410	23,045	23,075	21,412	20,236	17,788	16,319	13,931
Tetracyclines	13,408	15,055	15,008	13,880	12,983	12,006	10,359	9,968
Penicillins	3,490	3,522	3,874	3,836	4,610	4,722	4,309	4,461
Macrolides + lincosamides	3,250	3,569	3,815	3,645	3,444	3,097	2,919	2,762
Polymyxins	1,797	1,636	1,544	1,525	1,472	1,438	1,045	844
Trimethoprim	1,862	1,794	1,399	1,320	1,249	1,124	937	740
Others (*)	71	204	78	96	131	431	293	314
Totals	**45,288**	**48,824**	**48,794**	**45,714**	**44,125**	**40,606**	**36,181**	**33,021**

(*) Aminoglycosides, fluoroquinolones, pleuromutilins, quinolones

Table 6. f: Sales of antibiotics for intramammary use in 2006–2013, by active ingredient class.

Sales								
(in kg)	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Products for drying-off								
Aminoglycosides	295	299	269	252	245	265	261	266
Beta-lactams (*)	1,289	1,395	1,332	1,212	1,139	1,246	1,239	1,267
Others (**)	2	2						
Total	**1,585**	**1,696**	**1,601**	**1,464**	**1,384**	**1,510**	**1,500**	**1,533**
Products for use during lactation								
Penicillins	3,145	3,110	3,333	3,062	2,841	2,917	2,596	2,456
Aminoglycosides	567	558	558	492	445	436	406	376
Cephalosporins	35	38	35	51	56	60	55	52
Others (***)	128	135	147	129	101	102	104	74
Total	**3,875**	**3,841**	**4,073**	**3,734**	**3,443**	**3,514**	**3,161**	**2,958**
Total intramammary preparations	**5,460**	**5,537**	**5,674**	**5,198**	**4,827**	**5,025**	**4,661**	**4,491**

(*) From 2011 only penicillins
(**) Bacitracin
(***) Lincosamides, macrolides, polymyxins

since 2012 (Table 6. d). However, this is based on a reduction in sales of first-generation cephalosporins, while sales of third- and fourth-generation cephalosporins increased slightly.

After sales of fluoroquinolones decreased in the years 2011 and 2012, they increased 15% compared to the previous year.

Sales of macrolides and lincosamides have been decreasing since 2008. Strikingly, however, there has been an increase in sales of long-acting injectable preparations. These preparations are licensed in Switzerland for the treatment of respiratory diseases in cattle and pigs.

The class of amphenicols is shown separately in the statistics for the first time in 2013. Active ingredient groups are listed individually only if at least three different preparations from three different marketing authorisation holders are licensed. Amphenicols met this condition for the first time in 2013.

6.3.2 Premixes

Premixes accounted for 62% of the total sales in 2013, a proportion which was similar to the previous years. A steady decrease in sales of premixes has been determined since 2008 (Table 6. e). Compared with 2012, the total sales increased by 9% and compared with the peak year 2007, the reduction represented 32%. Sulfonamides, tetracyclines and penicillins are the three main classes of active ingredients contained in premixes.

6.3.3 Antibiotics for intramammary use

Products for intramammary use also showed a slight decrease in 2013 (Table 6. f). Penicillins are predominant, accounting for over 80% of all active ingredients administered by the intramammary route. Sales of products containing cephalosporins for the treatment of mastitis during lactation have continued to decrease.

6.4 Discussion

Since 2008, there has been a general decrease in volumes of antibiotics sold for use in veterinary medicine. However, the data should be interpreted cautiously because it is based on sales figures. This means all relevant information about target species (food producing, pet, mixed), route of administration (parenteral, oral, topical/external, intramammary) and galenics are taken from the marketing authorisation (summary of product characteristics). The report contains no data about the effective use. Different dosages between antibiotic classes and target species are not taken into account. Dosages can differ widely, e.g. the dosage for enrofloxacin for oral or parenteral administration is 1 to 5 mg/kg per day, while the dosage for chlortetracycline can vary between 20 to 50 mg/kg 2 to 3 times per day. The dosage for tetracycline is therefore up to 30 times higher than that for enrofloxacin. A unit of enrofloxacin sold could potentially be used to treat up to 30 more animals than the same unit of tetracycline. Only the use of defined daily doses (DDD, analogue human medicine) can correct for this difference. Presently, however, there are no internationally recognised defined daily doses for antibiotics in veterinary medicine.
The decrease in antimicrobial sales in Switzerland is mainly due to a decrease in the sale of the three active ingredients sulfonamides, penicillins and tetracyclines. Compared with antimicrobial classes such as macrolides, fluoroquinolones and third- and fourth-generation cephalosporins, they have to be dosed relatively high and are therefore proportionally more significant. The last three active ingredient groups belong to the critical which have to be used with restraint and caution in view of the problem of antimicrobial resistance in human and veterinary medicine.

Clear information about effective treatment intensities, i.e. the number of animals treated in relation to a given population, can only be provided by consumption data at farm level, which is not available in Switzerland at this point of time.
The recording of usage data is a precondition to introduce reasonable measures in the areas of prevention and prudent use and to follow up their effects. In addition, in connection with the development of antimicrobial resistance, it is not the reduction in total volumes that is relevant but rather the number of treatments per animal or the number of animals treated per unit of time.

References

[1] WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). Critically Important Antimicrobials for Human Medicine. 3rd revision, 2011.

[2] European Medicines Agency. European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011. Third ESVAC report, 2013; (EMA/236501/2013)

[3] Swissmedic/Federal Veterinary Office. ARCH-Vet 2012. Report on sales of antibiotics in veterinary medicine and antibiotic resistance monitoring of livestock in Switzerland, 2013; 75 pp.

7

Resistance in bacteria from human clinical isolates

7 Resistance in bacteria from human clinical isolates

7.1 *Escherichia coli*

Escherichia coli is the most frequent gram-negative microorganism causing bacteremia. It is a colonizer of the intestinal tract and as such the most frequent microorganism causing urinary tract infections. As urinary tract infections are the second most frequent infectious disease in ambulatory care, increasing resistance trends directly affect the hospital as well as the ambulatory setting.

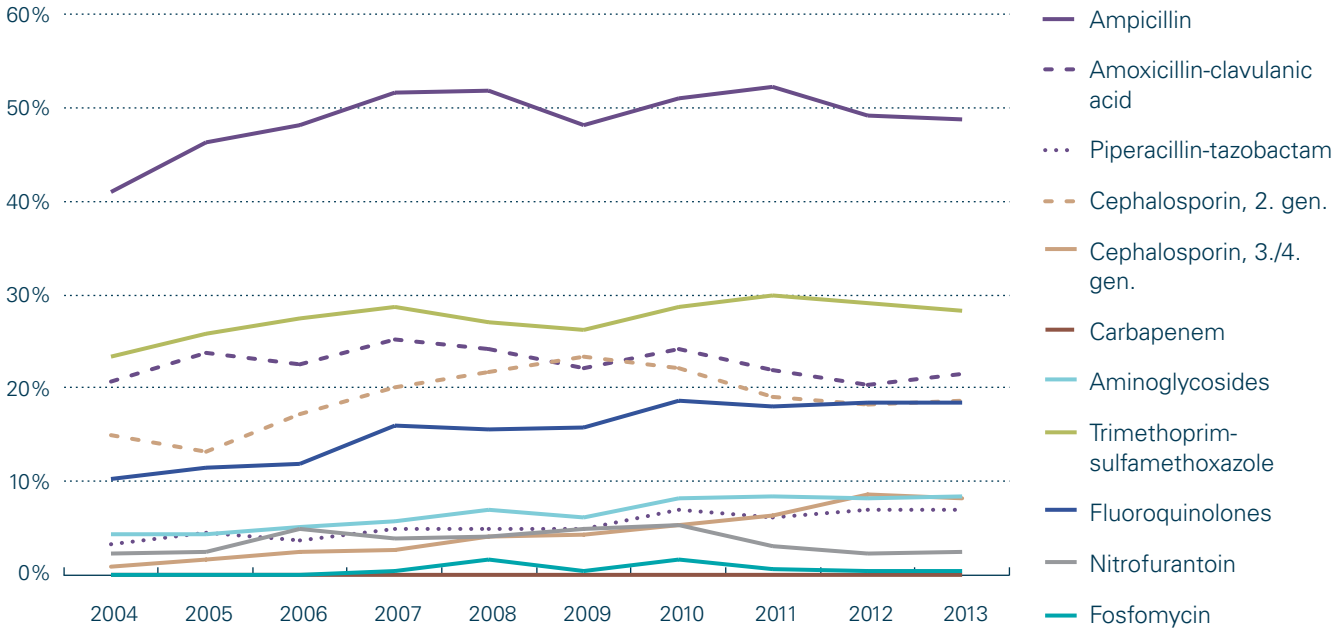
In 2013, resistance to fosfomycin and nitrofurantoin was very low. These antibiotics can only be used for non-invasive urinary tract infections, therefore they represent an important option in ambulatory care. Interestingly only about one quarter of isolates are tested routinely against theses antibiotics. Fluoroquinolone non-susceptibility increased over the last 10 years from 10.3% to 18.4%. This is close to the EU/EEA average of 22.5% in 2013 [1]. Although non-susceptibility to trimethoprim-sulfamethoxazole is even higher (28.4%), this antibiotic still remains a first line option in non-invasive ambulatory urinary tract infections [2]. Non-susceptibility to 3rd/4th generation cephalosporins increased during the last ten years from 0.9% in 2004 to 8.2% in 2013. The EU/EEA average in 2013 was 12.6%. During the last three years, increasing trends were observed in 17/29 EU/EEA states [1]. This increase affected both the hospital and the ambulatory setting (textbox 7. a). The parallel increase in aminoglycoside, quinolone and trimethoprim-sulfamethoxazole resistance is attributable at least in part to cross-resistance. So far, carbapenem-resistance in *E. coli* is very rare, although some isolates are observed and reported (Table 7. a and Figure 7. a). At this time, anresis.ch is not representative for sporadic antibiotic resistance observations. Therefore, a separate active surveillance of carbapenemase producing Enterobacteriaceae is under development. Carbapenems belong to the critically important antimicrobial classes, according to the definition of WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) and are a major last-line class of antibiotics.

Table 7. a: Susceptibility rates of invasive *Escherichia coli* isolates in humans 2013.

Escherichia coli							**2013**
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Ampicillin	2546	1305	51.3%	18	0.7%	1223	48.0%
Amoxicillin-clavulanic acid	4018	3156	78.5%	168	4.2%	694	17.3%
Piperacillin-tazobactam	3890	3621	93.1%	109	2.8%	160	4.1%
Cephalosporin, 2. gen.	3271	2663	81.4%	276	8.4%	332	10.1%
Cephalosporin, 3./4. gen.	4021	3692	91.8%	20	0.5%	309	7.7%
Carbapenems	4026	4025	100.0%	1	0.0%	0	0.0%
Aminoglycosides	4028	3691	91.6%	24	0.6%	313	7.8%
Trimethoprim-sulfamethoxazole	3715	2662	71.7%	10	0.3%	1043	28.1%
Fluoroquinolones[1]	4027	3286	81.6%	46	1.1%	695	17.3%
Nitrofurantoin	1231	1201	97.6%	12	1.0%	18	1.5%
Fosfomycin	744	741	99.6%	0	0.0%	3	0.4%

[1] Fluoroquinolones: Ciprofloxacin, Norfloxacin, Ofloxacin

Figure 7. a: Non-susceptibility rates in invasive *Escherichia coli* isolates in humans 2004–2013.



Textbox 7. a

Detailed antibiotic resistance data allow insights into epidemiological mechanisms

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3rd/4th generation cephalosporin resistance as a surrogate for extended-spectrum cephalosporin resistance (ESC-R) in invasive *E. coli* and *K. pneumoniae* increased during the last 10 years not only in Switzerland but in many European countries. Generally, surveillance systems are focused on monitoring resistance data of invasive isolates, which are mainly collected in hospitalized patients. To understand epidemiological mechanisms, it is important to compare resistance trends in different subpopulations. This became possible with the comprehensive dataset in the anresis.ch-database, including not only blood isolates, but isolates from non-sterile sites (mainly urine) and from outpatients, as well. Herein I summarize some insights into epidemiological mechanisms from a detailed study on temporal trends in ESC-R in *E. coli* and *K. pneumoniae,* published 2013 in Eurosurveillance are summarized[1].

Overall, antibiotic resistance data of 160,010 *E. coli* and 21,290 *K. pneumoniae* isolates were included in this study. Increase in ESC-R *E. coli* from 2004 to 2011 was linear and did not differ between blood and urine isolates (p=0.94). Although increase in ESC-R *E. coli* was significantly lower in outpatients than in inpatients (p=0.03), differences are small, reflecting the broad distribution of ESC-R *E. coli* in the

Figure T 7. a. 1: ESC-R rates in different subsets of *E. coli* isolates 2004–2011.

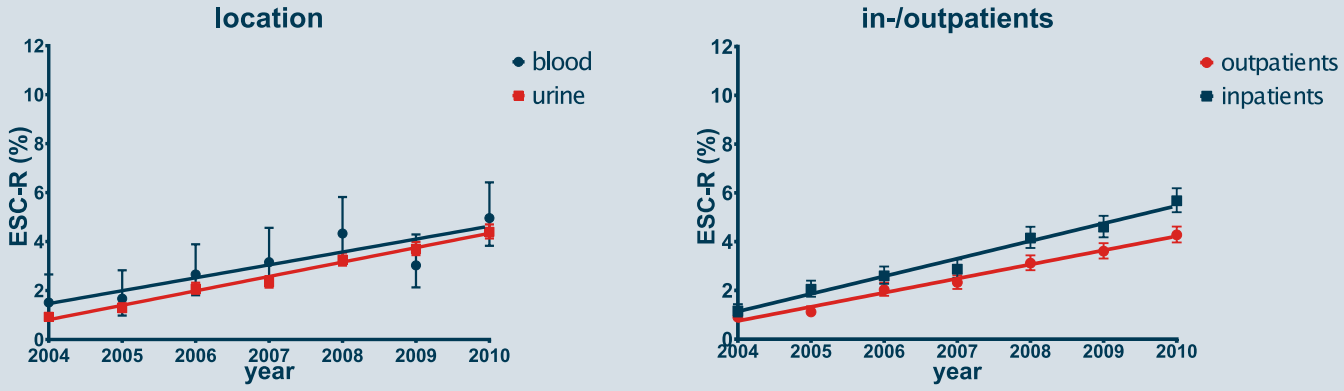
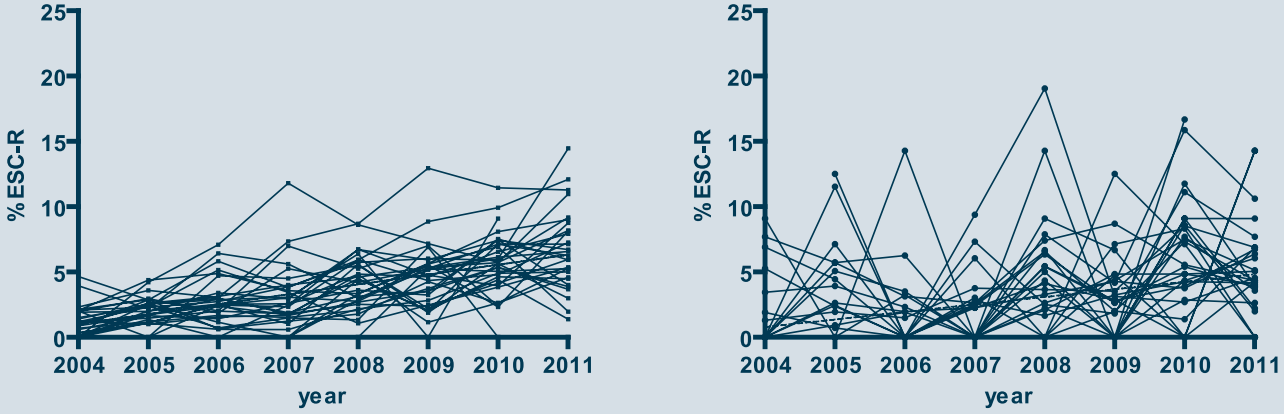


Figure T 7. a. 2: ESC-R rates in different hospitals from 2004–2011 for *E. coli* (left) and *K. pneumoniae* (right).



general human population (Fig. T 7. a. 1). Increase in ESC-R rates did not differ between different subsets of *K. pneumoniae* isolates.

Looking at the ESC-R rates of individual hospitals over time, we found significant differences between ESC-R *E. coli* and ESC-R *K. pneumoniae* (Figure T 7. a. 2). ESC-R *E. coli* increase is steadily and more or less parallel in the individual hospitals, while increase in ESC-R in *K. pneumoniae* is due to the additional effect of individual outbreaks in different hospitals. This picture reflects the different characteristics of these two microorganisms. *E. coli* colonizes the intestinal tract of humans and animals and is a common pathogen in the outpatient setting. ESC resistance is widely distributed in the outpatient sector (and in animals) and patients entering the hospital have been colonized or even infected with ESC-R *E. coli* in the outpatient sector and bringing this resistance into the hospital. On the other side *K. pneumoniae* is mainly acquired in the hospital setting, and ESC-R clones may spread from patient to patient, causing individual outbreaks.

Reference

1 A. Kronenberg, M Hilty, A. Endimiani, K. Mühlemann. Temporal trends of extended-spectrum cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolates in in- and outpatients in Switzerland, 2004 to 2011. Euro Surveill. 2013 May 23;18(21).

7.2 *Klebsiella pneumoniae*

Klebsiella spp. are frequent colonizers of the gastrointestinal tract. Although they may also occur in the outpatient setting, they are more frequently found in the hospital setting, affecting patients with an impaired immune system. Their main focus of infection is urinary tract infections and pneumonia. In contrast to *E. coli,* they are intrinsically resistant to aminopenicillins.

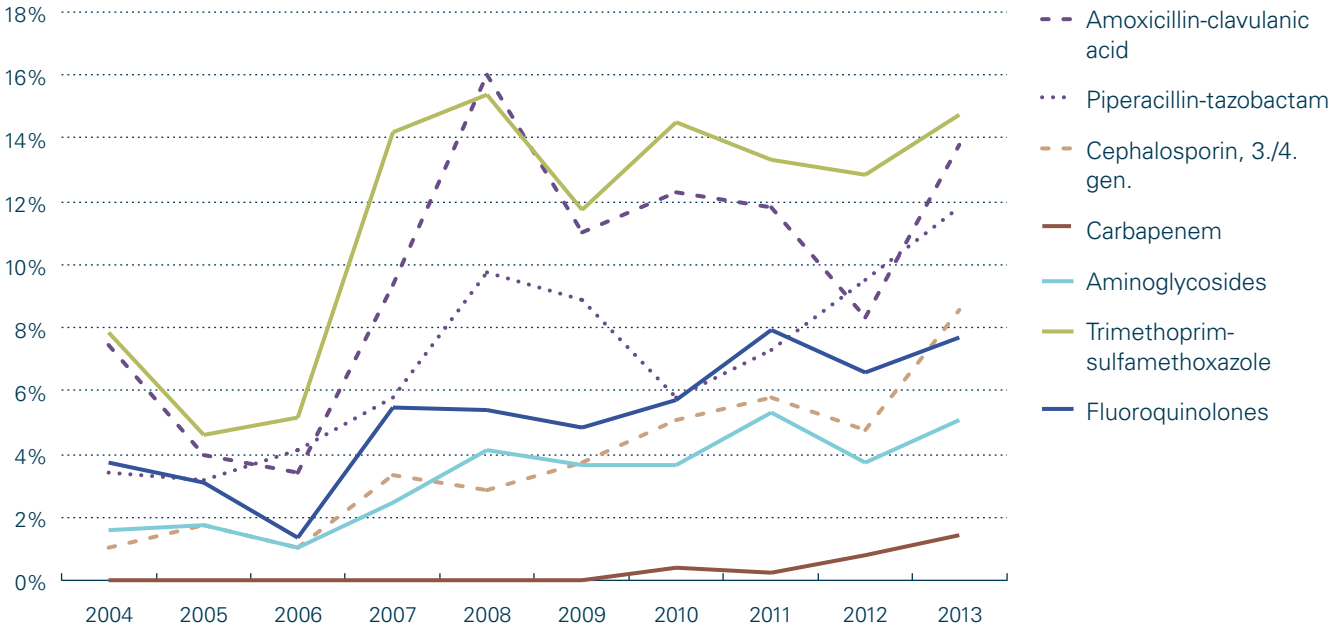
In this report, we only show the data on *K. pneumoniae,* which is the most frequent species of the genus *Klebsiella* isolated in human clinical probes. Like in *E. coli,* increasing resistance to 3rd/4th generation cephalosporins was the main issue during the last 10 years. In Switzerland 3rd/4th generation cephalosporin non-susceptibility increased from 1.3% in 2004 to 8.6% in 2013. These rates are below the EU/EEA average of 30.0% in 2013, but higher than in Scandinavian countries, where resistance rates are below 5% [1]. In contrast to *E. coli,* increasing resistance rates of *K. pneumoniae* were not continuously throughout all hospitals but rather were attributable to several outbreaks in individual hospitals (Textbox 7. a). Besides the increase in 3rd/4th generation cephalosporin resistance, we observed a steadily increase in resistance rates for amoxicillin-clavulanic acid, piperacillin-tazobactam, aminoglycosides, trimepthoprim-sulfamethoxazole and quinolones, which again most probably is at least in part attributable to cross resistance. Carbapenem-resistance in *K. pneumoniae* isolates was almost not present in Switzerland until 2009 but the data available from anresis.ch show an increase during the last 4 years (Figure 7. b and Table 7. b). With an estimate of 1.2% carbapenem non-susceptibility, Switzerland is still low compared to the EU/EEA average of 8.3% in 2013. However, rates differ importantly from one country to the other [1]. For sporadic antibiotic resistance observations, anresis.ch is not representative, therefore a separate active surveillance of carbapenemase producing Enterobacteriaceae is under development. Nevertheless, this increase is worrisome and is associated with increased carbapenem consumption (see Chapter 5.1).

Table 7. b: Susceptibility rates of invasive *Klebsiella pneumoniae* isolates in humans 2013.

Klebsiella pneumoniae							2013
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Amoxicillin-clavulanic acid	719	610	84.8%	22	3.1%	87	12.1%
Piperacillin-tazobactam	698	617	88.4%	34	4.9%	47	6.7%
Cephalosporin, 2. gen.	571	456	79.9%	50	8.8%	65	11.4%
Cephalosporin, 3./4. gen.	719	657	91.4%	8	1.1%	54	7.5%
Carbapenem	718	709	98.7%	1	0.1%	8	1.1%
Aminoglycosides	717	681	95.0%	4	0.6%	32	4.5%
Trimethoprim-sulfamethoxazole	667	566	84.9%	3	0.4%	98	14.7%
Fluoroquinolones	718	660	91.9%	8	1.1%	50	7.0%

[1] Fluoroquinolones: Ciprofloxacin, Norfloxacin, Ofloxacin

Figure 7. b: Non-susceptibility rates of invasive *Klebsiella pneumoniae* isolates in humans 2004–2013.



Textbox 7. b

Extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae in the hospital and the household setting

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Introduction

Since the late 1980s, extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae, mainly *Klebsiella pneumoniae* (ESBL-Kp), have been recognized as a major cause of nosocomial infections and outbreaks. However, during the late 1990s, blaESBL genes have increasingly been identified in the context of urinary tract infections (UTIs) caused by *Escherichia coli* (ESBL-Ec).

An important strategy for controlling the spread of these multidrug-resistant pathogens is the identification of patients with risks for acquisition. In addition, active surveillance and isolation precautions are recommended. Data regarding household spread and risk factors are limited. Thus, a better understanding of the transmission dynamics of ESBL producers is needed in order to guide measures for the control of ESBL producers in the hospital and community.

In the present study[1], transmission rates of ESBL-Ec and ESBL-Kp from hospital index patients to hospital roommates and to household persons were prospectively evaluated.

Study design

Index patients and their hospital contacts were prospectively recruited at the University Hospital of Bern (Bern, Switzerland) from 2008–2010. Index patients are hospitalized or outpatients at the study center presenting with a newly detected carriage or infection with ESBL-Ec or ESBL-Kp. Patients were categorized as inpatients if they required admission to the hospital for >24 hours. Hospital contact patients were defined as roommates who shared the same ward-room, ICU room, or immediate care room for ≥48 hours with an index patient. Household contact persons were defined as persons who shared the same household with the index patient on a regular basis. Transmission was assumed when the index patient and contacts shared a clonally-related (see below) ESBL-Ec or ESBL-Kp isolate with identical blaESBL gene(s).

Stool samples were analyzed with different selective culture media. Phenotypic confirmation of ESBL production was obtained by using the double-disk synergy test with ceftazidime, cefpodoxime, and aztreonam in combination with amoxicillin-clavulanate. Polymerase chain reaction (PCR) for the most common blaESBL genes was performed as was done the molecular typing of the bacterial strains for investigating clonal relatedness.

Results and conclusions

In the hospital, transmission rates were 4.5% (ESBL-Ec) and 8.3% (ESBL-Kp) and the incidences of transmissions were 5.6 (Ec) and 13.9 (Kp) per 1000 exposure days, respectively. Incidence of ESBL-Kp hospital transmission was significantly higher than that of ESBL-Ec ($P < .0001$), despite implementation of infection control measures in 75% of ESBL-Kp index patients but only 22% of ESBL-Ec index patients. Detection of ESBL producers not linked to an index patient was as frequent (ESBL-Ec, 5.7%; ESBL-Kp, 16.7%) as nosocomial transmission events. In households, transmission rates were 23% for ESBL-Ec and 25% for ESBL-Kp. In conclusion, household outweighs nosocomial transmission of ESBL producers. Data furthermore suggest that ESBL-Kp may be more efficiently transmitted within the hospital than ESBL-Ec and may question the effect of infection control measures among different species.

Reference

1 Hilty M, Betsch BY, Bogli-Stuber K, Heiniger N, Stadler M, Kuffer M, Kronenberg A, Rohrer C, Aebi S, Endimiani A, et al: Transmission dynamics of extended-spectrum beta-lactamase-producing Enterobacteriaceae in the tertiary care hospital and the household setting. Clin Infect Dis 2012, 55:967–975.

Textbox 7. c

Transmission rates of extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae without contact precautions in a tertiary academic care center

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[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel

Introduction

The rapid increase of extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae has challenged healthcare facilities worldwide regarding implementation of effective infection control measures to limit further nosocomial spread. We performed active surveillance by screening for ESBL-carriage for all patients who were hospitalized in the same room for >24 hours with a patient colonized or infected with ESBL-producing Enterobacteriaceae before the positive ESBL result was reported and the patient was assigned to contact precautions. The aim of this study[1] was to estimate the rate of spread (R0) for ESBL-producing Enterobacteriaceae in a tertiary academic care center.

Methods

In this observational cohort study performed from June 1999 through April 2011, all patients hospitalized in the same room as a patient infected or colonized with an ESBL-producing Enterobacteriaceae for at least 24 hours, were screened for ESBL-carriage by performance of rectal swabs, samples from open wounds or drainages, and urine samples given the presence of foley catheters. Nosocomial transmission was defined as a positive screening result for ESBL-producing Enterobacteriaceae and confirmation of relatedness with the strain by molecular typing by pulsed-field gel electrophoresis for an index-contact pair.

Results

Screening for ESBL-producing Enterobacteriaceae was performed in 133 consecutive contact patients exposed to patients infected or colonized mainly with ESBL-producing *Escherichia coli* (73.1% of all index cases). After a mean exposure time of 4.3 days, transmission occurred in 1.5% (2/133).

Conclusions

A low number of transmissions of ESBL-producing Enterobacteriaceae was identified in contact patients exposed to patients infected or colonized with ESBL-producing Enterobacteriaceae, mainly *E. coli,* and not yet assigned to isolation precautions while culture results were pending-challenging the routine use of contact precautions in non-epidemic settings.

Reference

1 Tschudin-Sutter S, Frei R, Dangel M, Stranden A, Widmer AF. Rate of transmission of extended-spectrum Beta-lactamase-producing enterobacteriaceae without contact isolation. Clin Infect Dis 2012;55:1505–11.

Textbox 7. d

High colonization rates of ESBL-producing *E.* coli in Swiss travellers to South Asia

Esther Kuenzli[1, 2, 4], Andrea Endimiani[3] and Christoph Hatz[2,4]

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Serious infections due to Gram-negative bacteria are usually treated with extended-spectrum cephalosporins (e.g., ceftriaxone and cefepime). However, the number of bacteria resistant to such antibiotics has risen dramatically over the past 25 years. This is usually due to the production of extended-spectrum beta-lactamase (ESBL) enzymes that are encoded by genes located on plasmids co-carrying other antibiotic resistance genes (e.g., those for aminoglycosides and quinolones). This overall phenomenon makes bacteria multidrug-resistant (MDR), seriously limiting our antibiotic armamentarium[1].

These `difficult to combat` bacteria were originally considered to occur in the hospital setting only. However, since the late 1990s, the importance of ESBL-producing *E. coli* as a major cause for community-acquired infections (e.g., urinary tract infections) has become evident. It is now well-known that previous use of antibiotics, age, presence of co-morbidities, use of indwelling devices, and previous hospitalizations are risk factors for the acquisition of these pathogens[2]. However, food animals, pets, the food chain (e.g., raw meat), wild-life (e.g., fish and birds) and the environment can also serve as reservoirs for MDR bacteria. It should also be noted that while the evidence for direct animal-to-human transmission of MDR bacteria is mainly circumstantial, more robust evidence for transmission via the food chain exists[3,4]. More importantly, recent investigations have shown that international travel is a means of spreading ESBL-producing *E. coli,* from high- to low-prevalence countries through asymptomatic travellers. This is contributing to the importation of non-autochthonous and very resistant bacterial pathogens that are rapidly changing the local epidemiology of countries, such as Switzerland, with low prevalence of MDR bacteria[5,6].

Rates of asymptomatic travel-related intestinal colonization with MDR Gram-negatives vary according to the different travel destination. In particular, travellers returning from the Indian subcontinent show high colonization rates. However, nothing is known about the region-specific risk factors and conducts that can facilitate the colonization of healthy travellers. Therefore, we recently conducted and published an observational prospective multicentre cohort study investigating Swiss travellers to India, Sri Lanka, Bhutan, and Nepal[7]. Before and after travelling, rectal swabs of volunteers were processed to detect possible MDR Gram-negative bacteria in the intestinal tract. Participants also completed several epidemiological questionnaires to identify the hypothetical risk factors for becoming colonized.

During December 2012 to October 2013, 170 adult persons were enrolled in the study, the largest data set on travellers to the Indian subcontinent so far analyzed. These people left Switzerland non-colonized by MDR bacteria at intestinal level (i.e., the rectal swab was negative). However, after returning to our country, the overall acquired colonization rate with ESBL-producing *E. coli* was 69%, being highest in travellers returning from India (87%) and lower in travellers returning from Nepal (80%), Bhutan (79%), and Sri Lanka (35%). The reasons for these variances remain unclear but we speculate that differences in local human prevalence are the most probable reason. Similarly, a difference in the local occurrence of ESBL producers in the environment, animals, and food products might explain the diverse colonization rates in travellers[7].

The analysis of the epidemiological data collected with the questionnaires indicated that the travel destination was a specific risk factor for colonization. Moreover, participants who visited friends and relatives showed a higher risk than participants travelling as tourists only. Consumption of ice cream and pastry were also associated with becoming colonized. Increased length of stay as a risk factor for becoming colonized is self-explanatory. In contrast to previous studies, suffering from gastrointestinal symptoms during the trip and drinking tap water were not recognized as risk factors[7].
Taking into account the high colonization rates in travellers to the Indian subcontinent, the source of colonization is most likely ubiquitous (e.g. environment, food). Therefore, avoidance of colonization while travelling seems impossible. As a consequence, travel-related spread from high to low endemicity areas will probably further increases in the future. As a clinical consequence, recent travel history of patients showing signs of infection should be taken into account when deciding on an empirical antibiotic treatment[7].

References

1 Livermore DM. 2009. Has the era of untreatable infections arrived? J Antimicrob Chemother 64 Suppl 1:i29–36.
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7.3 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a non-fermentative gram-negative rod and the most important human pathogen in this group of bacteria. *P. aeruginosa* is one of the leading causes of nosocomial respiratory tract infections and is also found in hospital acquired urinary tract, wound and blood-stream infections. It is a feared pathogen especially in burn units. Mucoid strains frequently infect cystic fibroses patients and are very difficult to eradicate. The main community acquired infections in immunocompetent hosts caused by *P. aeruginosa* are external otitis (swimmers ear) and sinusitis.

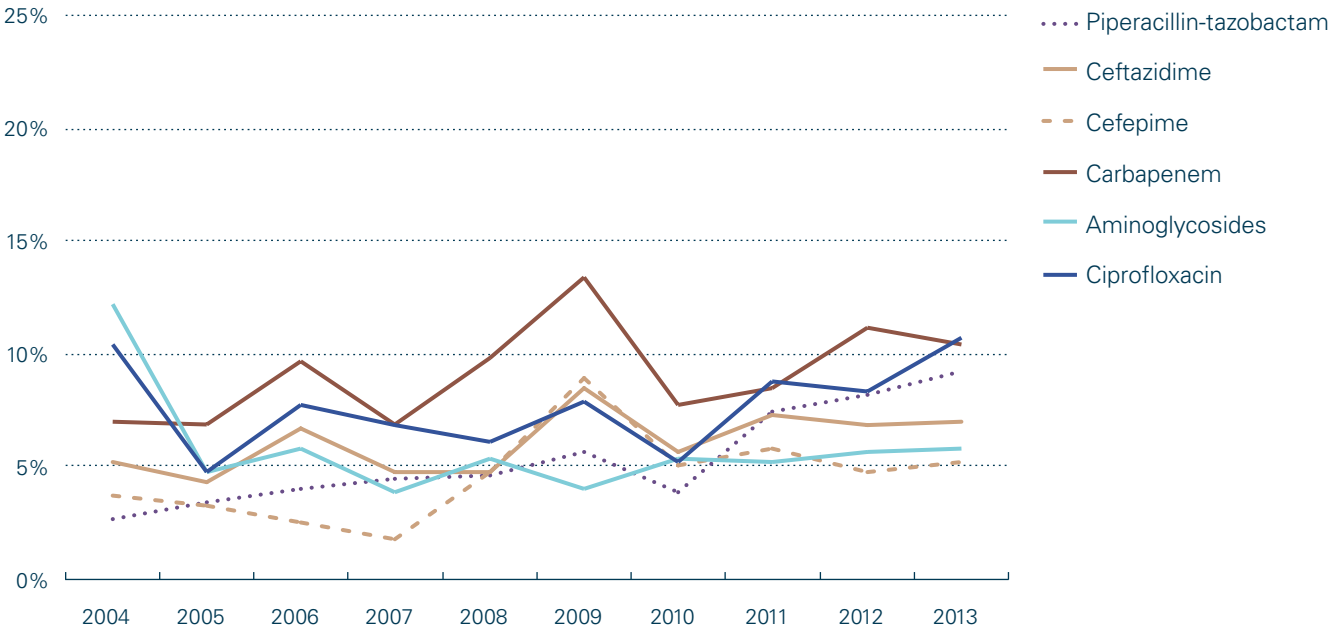
P. aeruginosa is intrinsically resistant to amoxicillin, amoxicillin-clavulanic acid, first and second generation cephalosporins, cefixime, cefpodoxime, ceftriaxone, ertapenem, tetracyclines including tigecycline and trimethoprim sulfamethoxazole. Quinolones are the only orally available antibiotic with activity against *P. aeruginosa*.

Non-susceptibility rates are between 5 and 10% for most antibiotics tested, and slightly above 10% for ciprofloxacin (10.6%) and carbapenems (10.4%) (Table 7. c). Carbapenem-resistance in EU/EEA countries was 17.6% in 2013, with highest rates in southeastern countries as Italy, Greece, Bulgaria, Romania, Hungary and Slovakia [1]. 5.8% of isolates are non-susceptible to aminoglycosides, which compares well with 15.9% in the EU/EEA states [1]. Sticking to tobramycin – which has the lowest epidemiological cut-off for *P. aeruginosa* of all aminoglycosides – we even find a non-susceptibility rate of 3.2% (8 out of 249 isolates). In Switzerland, we did not observe any clear trends over the last 10 years (Figure 7. c).

Table 7. c: Susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans 2013.

Pseudomonas aeruginosa							**2013**
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Piperacillin-tazobactam	368	334	90.8%	9	2.4%	25	6.8%
Ceftazidime	359	334	93.0%	2	0.6%	23	6.4%
Cefepime	365	346	94.8%	2	0.5%	17	4.7%
Carbapenem	374	335	89.6%	5	1.3%	34	9.1%
Aminoglycosides	377	355	94.2%	2	0.5%	20	5.3%
Ciprofloxacin	376	336	89.4%	9	2.4%	31	8.2%

Figure 7. c: Non-susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans 2004–2013.



7.4 *Acinetobacter* spp.

Acinetobacter spp. are gram-negative, strictly aerobic coccobacilli. They can be found in soil and water and are opportunistic pathogens. *Acinetobacter* spp. can roughly be divided into two groups: *Acinetobacter baumannii* group, which are intrinsically resistant to many antibiotic agents and the *Acinetobacter* non-*baumannii* group, including a large number of environmental species with low pathogenicity.

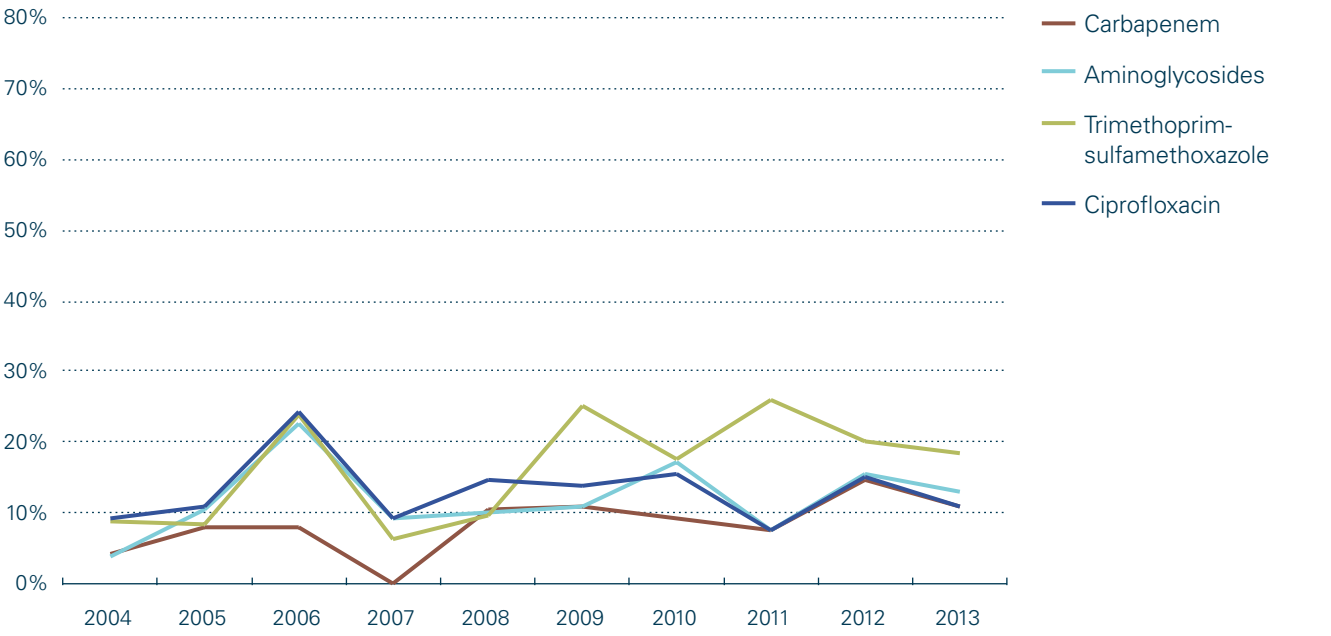
Acinetobacter baumannii infections are a big concern for hospital-acquired infections. They can cause respiratory, urinary, wound infections and septicemia. Meningitis has also been reported. Risk factors for multidrug-resistant *A. baumannii* are severe underlying diseases, prolonged hospital stay especially in ICU with antibiotic administration, mechanical ventilation and surgical procedures. As species identification is difficult, we show aggregated data on genus level as suggested in the ECDC resistance report [1].

Both, ciprofloxacin and carbapenem resistance in 2013 were 11.1% (Table 7. d), which is above the neighboring countries as France, Germany and Austria but well below the very high resistance levels (above 50% for both, ciprofloxacin and carbapenems) in many southern countries of Europe including Italy, Spain, Portugal and Greece [1]. There is no clear trend since 2004 (Figure 7. d).

Table 7. d: Susceptibility rates of invasive *Acinetobacter* spp. isolates in humans 2013.

***Acinetobacter* spp.**							**2013**
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Carbapenem	54	48	88.9%	0	0.0%	6	11.1%
Aminoglycosides	53	46	86.8%	2	3.8%	5	9.4%
Ciprofloxacin	54	48	88.9%	0	0.0%	6	11.1%

Figure 7. d: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans 2004–2013.



Textbox 7. e

Antibacterial resistance in *Neisseria gonorrhoeae* in Switzerland

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Antibacterial resistance to *Neisseria gonorrhoeae* is an increasing problem for both clinical management and control of gonorrhoea, the second most common bacterial sexually transmitted infection in Switzerland.[1] In 2013, 1609 laboratory confirmed cases of gonorrhoea (20 per 100,000 population) were reported to the mandatory surveillance system of the FOPH[1], a fourfold increase since 2000. Of these, 76% were in men and 24% in women. Men who have sex with men (MSM) accounted for 23% of all gonorrhoea cases in 2013.[1]

N. gonorrhoeae evolves rapidly and has developed resistance to all classes of antimicrobials widely used to treat it, through a wide range of mechanisms.[2] The pattern of gonococcal antimicrobial resistance in Switzerland follows that seen in Europe, where a multidrug-resistant clone became the dominant circulating clone,[3] accounting for 29% isolates tested between 2009 and 2012 in Bern.[4] The clone is designated as multilocus sequence type (MSLT) ST 1901 and *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST) ST1407. A subclone (F89) of MLST ST1901/NG-MAST ST1407, first reported from a MSM in France in 2012, resulted in clinical failure of cefixime treatment of a urethral infection. F89 is highly resistant to all extended spectrum cephalosporins (ESC) including cefixime and ceftriaxone, fluoroquinolones, macrolides, tetracycline, trimethoprim-sulfamethoxazole and chloramphenicol.[5] A single novel penA mosaic allele stops the ESC from binding to their site of action on the gonococcal cell wall. Infections from the same clone have caused failures of ESC treatment in urethral, rectal and pharyngeal infections in Austria, Norway, Spain, Slovenia and Sweden.[3]

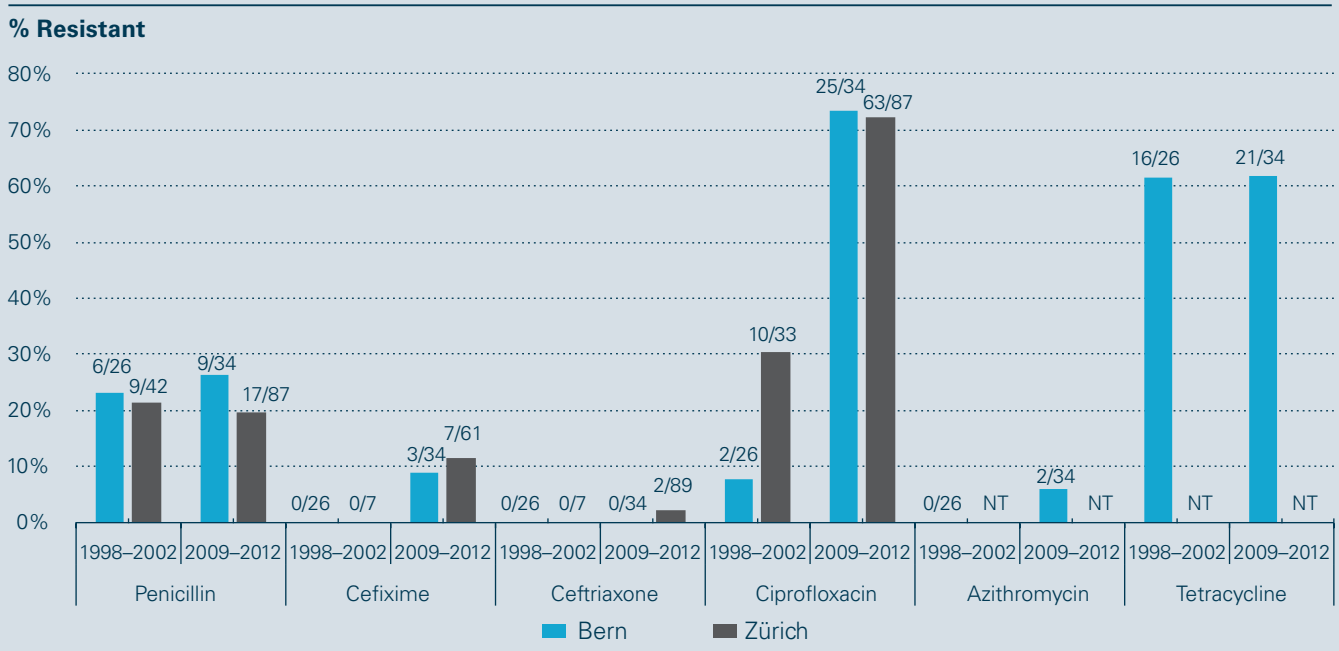
In Switzerland, clinical treatment failure and isolation of the subclone F89 have not been reported yet. But minimum inhibitory concentrations (MIC) of ESC in isolates analysed in Bern[4] and Zurich[6] shifted towards higher values between

1990 and 2012, suggesting emerging resistance.[7] Antimicrobial susceptibility profiles of a limited number of *N. gonorrhoeae* isolates tested in Bern[4] and Zürich[6] show similar patterns over time (Figure T 7. e. 1). Isolates resistant to cefixime or ceftriaxone had MIC values of 0.19–0.25 mg/L (breakpoint for both 0.125 mg/L, European Committee on Antimicrobial Susceptibility, EUCAST, version 4.0). Three in four *N. gonorrhoeae* isolates in both Bern and Zürich are now resistant to ciprofloxacin (breakpoint 0.064 mg/L). Azithromycin resistance (breakpoint 0.5 mg/L) was identified in 2/34 isolates in Bern in 2009–2012. Resistance to penicillin and tetracycline were stable over the two periods studied.

Reports from Switzerland of multidrug-resistant *N. gonorrhoeae* (resistant to at least one oral or injectable ESC or spectinomycin plus two or more of: penicillins, fluoroquinolones, azithromycin, aminoglycosides or carbapenems)[8] are still rare. In Bern from 2009 to 2012, one isolate (ST1407) of 34 tested was resistant to cefixime, azithromycin and ciprofloxacin,[4] with MICs above the EUCAST breakpoints for resistance. The lack of routine surveillance for antimicrobial resistant *N. gonorrhoeae* and scarcity of published data[4,6] are possible reasons for the absence of reported resistance. The anresis network collects data about *N. gonorrhoeae* from about 20 laboratories across Switzerland but these laboratories do not include those serving the clinics that diagnose the largest numbers of gonorrhoea cases and quantitative MIC data are not collected.

There are two main reasons for concern about ESC resistant *N. gonorrhoeae.* First, ceftriaxone is the last antibacterial that can be used for empirical treatment, i.e. without knowledge from antimicrobial susceptibility testing. For all other antibacterials, resistance has been shown for more than 5% of strains; above this level blind treatment is not recommended because of the risk of treatment failure.[9] Second, molecular diagnostic tests have now largely replaced bacterial culture-based methods to detect *N. gonorrhoeae* in Switzerland. These tests do not detect antimicrobial resistance, so resistant strains will not be identified unless they cause clinical treatment failure.[9] In Switzerland, antimicrobial susceptibility testing before treatment with a combination of ceftriaxone 500 mg and azithromycin 1g are now recommended[10]. Improved surveillance and management of gonorrhoea are essential tools to prevent the emergence and

Figure T 7. e. 1: Antibacterial resistance in *N. gonorrhoeae* isolates tested in the microbiology laboratories in Bern and Zürich in 1998–2002 and 2009–2012. Data from Bern published by Endimiani A et al.[4] (data from 1998–2001, 26 isolates; 2009–2012, 34 isolates for all antibacterials using Etest method) and from Zürich by Kovari H et al.[6] (data from 2000–2002, 7 isolates tested with cefixime and ceftriaxone, 33 isolates tested with ciprofloxacin and penicillin; 2009–2012, 26–46 isolates tested with cefixime and ceftriaxone, 43–44 isolates tested with ciprofloxacin and penicillin using Etest method). Zürich Isolates not tested (NT) with azithromycin or tetracycline. Resistance defined as minimum inhibitory concentration (MIC) above the breakpoint for resistance defined by EUCAST version 4.0, except the bars for tetracycline in Bern, which shows the percentage of isolates with MIC ≥ 1 mg/L (data for MIC 1–1.5 mg/L were presented together).[4]



spread of multidrug-resistant *N. gonorrhoeae* in Switzerland.

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7.5 *Streptococcus pneumoniae*

Streptococcus pneumoniae is a common cause of upper respiratory tract infections as sinusitis and otitis media, but is also a common pathogen found in invasive pneumonia, blood-stream infections and meningitis. Since 2002, all invasive isolates of *S. pneumoniae* are sent by the microbiology clinical laboratories to the National Reference Center for invasive *S. pneumoniae,* situated at the Institute for Infectious Diseases, University of Bern. For all isolates, serotyping (to survey the impact of vaccinations on serotype distribution) and antibacterial resistance testing is performed. Results of the latter are then sent to anresis.ch. For this chapter we analyzed the anresis.ch data of *S. pneumoniae* from this reference center, as these data are complete and AMR testing is standardized. E-tests are performed for all penicillin non-susceptible isolates (PNSP). PNSP was defined as MIC >= 0.064 mg/l, resistance was defined as >= 2 mg/l. Ceftriaxone testing was performed only for PNSP, penicillin-susceptible isolates (PSSP) are set to ceftriaxone-susceptible.

In 2013, the PNSP rate was 5.9%. In comparison, PNSP rates in EU/EEA countries ranged from 1.1% to 40.0% during the same time period [1]. However, data between different countries are not comparable, due to differences in the definitions of breakpoints, depending on national guidelines and site of infection. With 9.4%, the macrolide non-susceptibility rate is higher than penicillin non-susceptibility, which holds true for most other European countries, too [1]. Resistance against levofloxacin is still very rare in Switzerland. As shown in figure 7. e resistance in PNSP is higher than in PSSP for trimethoprim-sulfamethoxazole and erythromycin, but not for levofloxacin.

Over the last 10 years, a slight decrease in antibiotic resistance in *S. pneumoniae* for penicillin, trimethoprim-sulfamethoxazole and erythromycin was observed (Figure 7. f). However, as part of the surveillance of *S. pneumoniae* in Switzerland, the National Reference Center for invasive *S. pneumoniae* is currently analyzing these trends in more detail, also taking into account the changing serotype distribution possibly due to the introduction of pneumococcal vaccines.

Table 7. e: Susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans 2013.

Streptococcus pneumoniae							**2013**
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Penicillin[1]	811	763	94.1%	47	5.8%	1	0.1%
Ceftriaxone[2]	811	803	99.0%	8	1.0%	0	0.0%
Trimethoprim-sulfamethoxazole	811	728	89.8%	8	1.0%	75	9.2%
Erythromycin	811	735	90.6%	0	0.0%	76	9.4%
Levofloxacin	811	810	99.9%	0	0.0%	1	0.1%

[1] Penicillin non-susceptible defined as MIC >= 0.064 mg/l, penicillin-resistant defined as MIC >=2 mg/l
[2] Penicillin-susceptible isolates were not tested but set automatically to ceftriaxone-susceptible

Figure 7. e: Susceptibility rates in invasive PSSP (penicillin-susceptible isolates) and PNSP (penicillin non-susceptible isolates) in humans 2013.

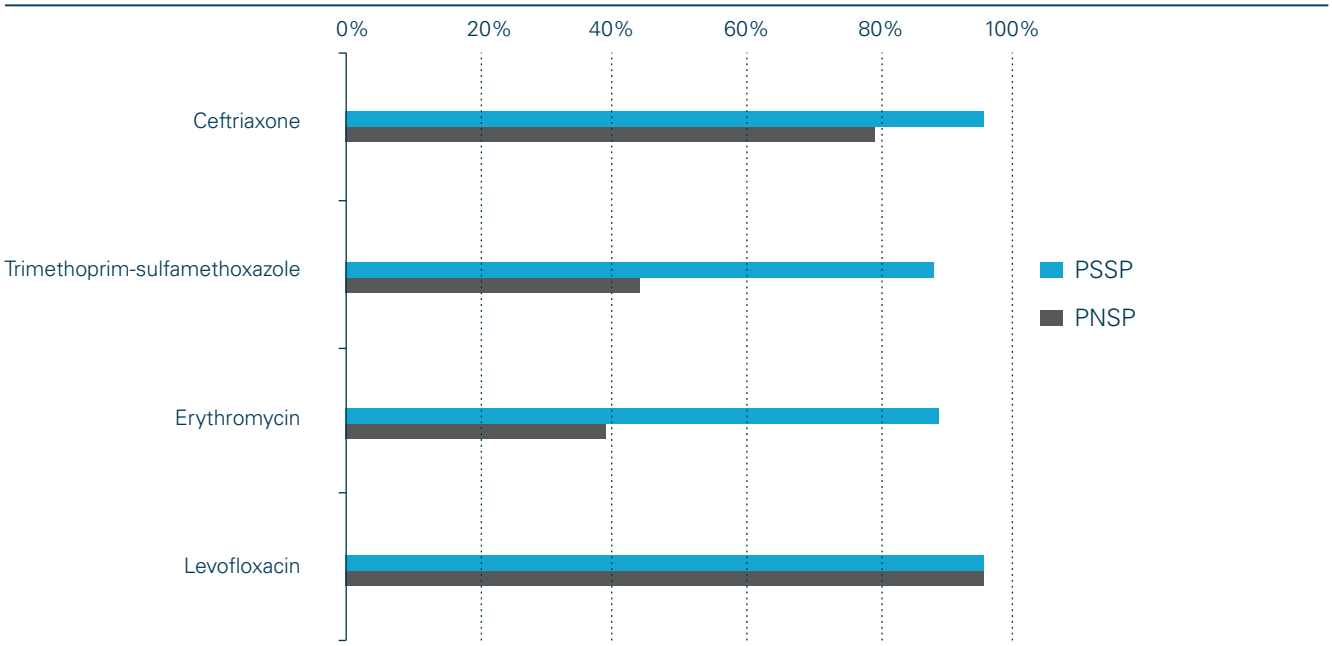
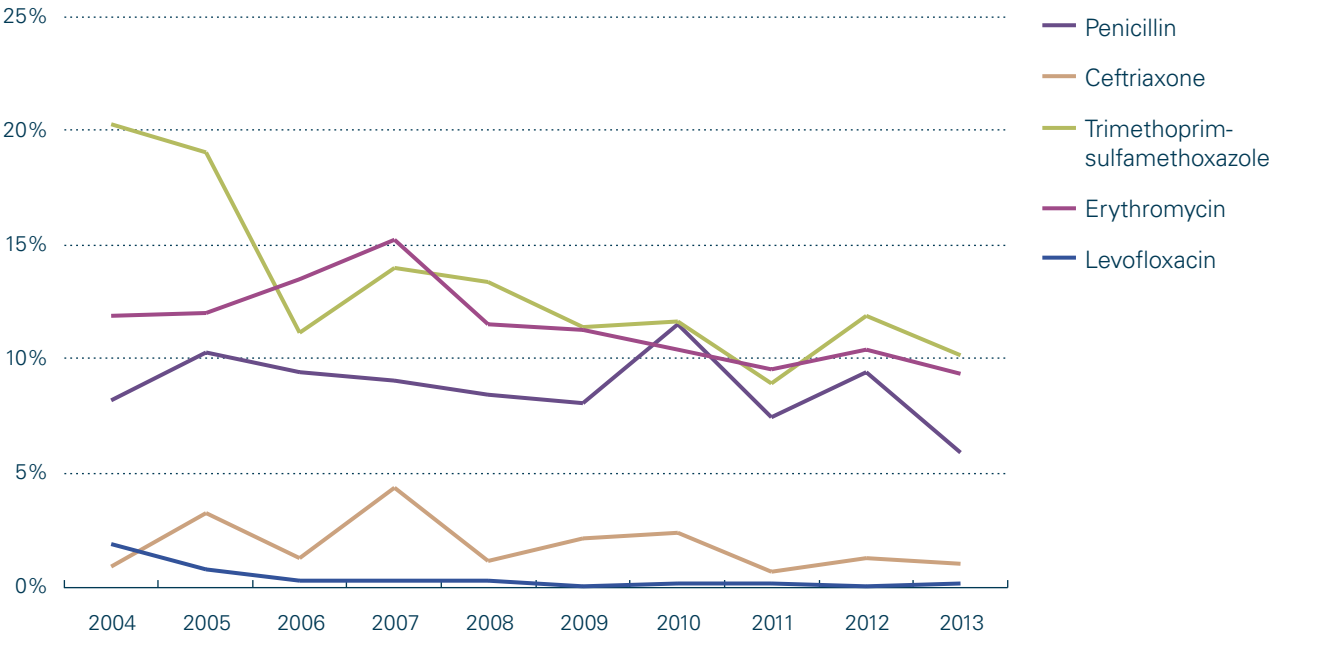


Figure 7. f: Non-susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans 2004–2013.



7.6 Enterococci

Enterococci belong to the normal gastrointestinal flora of humans and animals. As such they often are harmless commensals, however – mainly in the hospital setting – they also can cause serious infections as urinary tract infections, bacteremia, endocarditis, and intraabdominal infections. The vast majority of enterococcal infections are caused by *Enterococcus faecalis* and *E. faecium*. While *E. faecalis* isolates still remain susceptible to many antibiotics, and 98.6% are even susceptible to aminopenicillins, *E.* facium isolates, on the other hand, usually are resistant to aminopenicillin and other beta-lactam agents, including carbapenems. In addition, *E. faecium* shows increased resistance rates to high-level aminoglycosides compared to *E. faecalis* (Table 7. f). In contrast to the Unites States, fortunately vancomycin resistance still is rare in Switzerland and far below the EU/EEA average of 8.9% in 2013 [1].

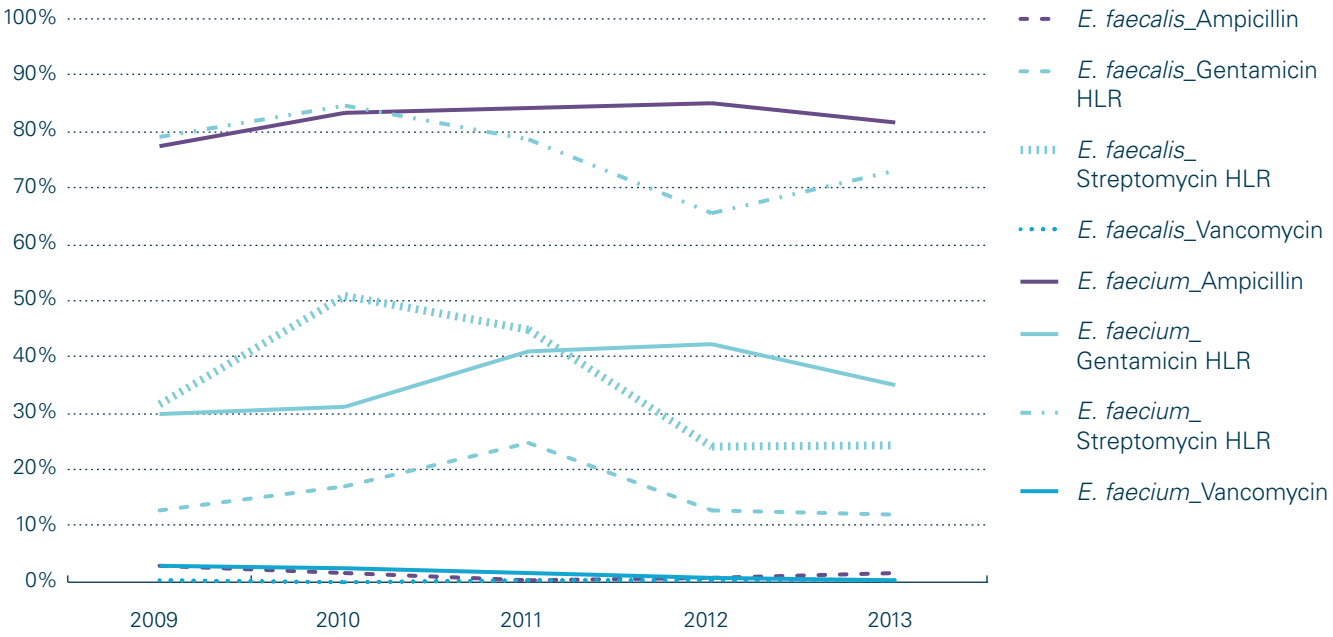
Table 7. f: Susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans 2013.

Enterococcus faecalis							**2013**
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Ampicillin	348	343	98.6%	0	0.0%	5	1.4%
Gentamicin HLR	152	134	88.2%	0	0.0%	18	11.8%
Streptomycin HLR	89	67	75.3%	0	0.0%	22	24.7%
Tetracycline	183	55	30.1%	1	0.5%	127	69.4%
Vancomycin	446	445	99.8%	0	0.0%	1	0.2%
Linezolid	312	309	99.0%	2	0.6%	1	0.3%

Enterococcus faecium							**2013**
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Ampicillin	238	43	18.1%	3	1.3%	192	80.7%
Gentamicin HLR	109	67	61.5%	0	0.0%	42	38.5%
Streptomycin HLR	65	18	27.7%	0	0.0%	47	72.3%
Tetracycline	93	65	69.9%	1	1.1%	27	29.0%
Vancomycin	296	295	99.7%	0	0.0%	1	0.3%
Linezolid	223	222	99.6%	0	0.0%	1	0.4%

Development of resistance between 2009–2013 is shown in figure 7. g. Data before 2008 are not shown due to low numbers of *E.* faecium isolates.

Figure 7. g: Non-susceptibility rates in invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans 2009–2013.



7.7 *Staphylococcus aureus*

Staphylococcus aureus belongs to the most important microorganisms in clinical microbiology. Besides bloodstream infections, *S. aureus* frequently causes soft tissue-infections, osteomyelitis, joint-infections, and – more rarely – endocarditis and pneumonia. Methicillin-resistant *S. aureus* (MRSA) remains one of the most important causes of antimicrobial-resistant infections worldwide. While initially these infections were mainly hospital-acquired, the last years they successfully spread into the community.

There are different methods to detect MRSA, and the methods used for screening changed over time. *Staphylococcus aureus* methicillin/oxacillin resistance can be detected either phenotypically by MIC determination, disk diffusion tests or latex agglutination to detect PBP2a, or genotypically using mecA/mecC detection. Due to poor correlation with the presence of mecA, oxacillin disk testing is discouraged by EUCAST and CLSI guidelines to detect *S. aureus* methicillin/oxacillin resistance (see also Chapter 11). In contrast, cefoxitin susceptibility is a very sensitive and specific marker of mecA/mecC-mediated methicillin resistance and is the agent of choice for disk diffusion testing. *S. aureus* with cefoxitin MIC values >4 mg/l are methicillin-resistant, mostly due to the presence of the mecA gene.

In the anresis.ch database MRSA is defined as non-susceptibility to at least one out of methicillin, oxacillin, flucloxacillin or cefoxitin. Confirmation tests such as PBP2a-agglutination or direct detection of the mecA gene are typically not provided to anresis.ch. MRSA are resistant to all betalactams including combinations with betalactam-inhibitors (e.g. amoxicillin-clavulanic acid). In 2013, MRSA rate in Switzerland was 5.0%. This rate is far below the European average of 18.0%, but above MRSA rates in Northern countries such as Norway (0.7%), Sweden (1.0%), Finland (1.7%), Denmark (1.7%) and the Netherlands (1.2%) in 2013 [1]. Co-resistance in MRSA is frequent and is depicted in figure 7. h.

Development of resistance during the last 10 years is shown in figure 7. i. During the last ten years, we observed a significant decrease in invasive MRSA rates in Switzerland from 12.7% in 2004 to 5% in 2013. Decreasing trends from 2010-2013 were also reported in some neighbouring countries such as France and Germany, as well as Belgium, Hungary, Ireland, Latvia, Luxembourg, Portugal and the United Kingdom [1]. Decrease in invasive MRSA rates was more pronounced in the western part of Switzerland (data not shown). Decrease in MRSA rates run parallel to a decrease in resistance rates (non-susceptibility rates) against ciprofloxacin, macrolides and – to a lesser extend – clindamycin and aminoglycosides in *Staphylococcus aureus* isolates (Figure 7. i). Further detailed analysis of these trends and their interpretation are planned.

Table 7. g: Susceptibility rates of invasive *Staphylococcus aureus* isolates in humans 2013.

Staphylococcus aureus							**2013**
Antibiotikum	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Penicillin	1362	333	24.4%	0	0.0%	1029	75.6%
Aminoglycosides	1403	1350	96.2%	1	0.1%	52	3.7%
Trimethoprim-sulfamethoxazole	1298	1282	98.8%	3	0.2%	13	1.0%
Tetracycline	1116	1075	96.3%	1	0.1%	40	3.6%
Macrolides	1440	1299	90.2%	2	0.1%	139	9.7%
Clindamycin	1444	1336	92.5%	1	0.1%	107	7.4%
Vancomycin	1197	1197	100.0%	0	0.0%	0	0.0%
Ciprofloxacin	1357	1228	90.5%	30	2.2%	99	7.3%
Fusidic acid	1151	1115	96.9%	4	0.3%	32	2.8%
Linezolid	741	741	100.0%	0	0.0%	0	0.0%
Rifampicin	1428	1422	99.6%	1	0.1%	5	0.4%

Figure 7. h: Susceptibility rates of invasive MRSA (Methicillin-resistant *Staphylococcus aureus)* and MSSA (Methicillin-sensitive *Staphylococcus aureus)* isolates in humans 2013.

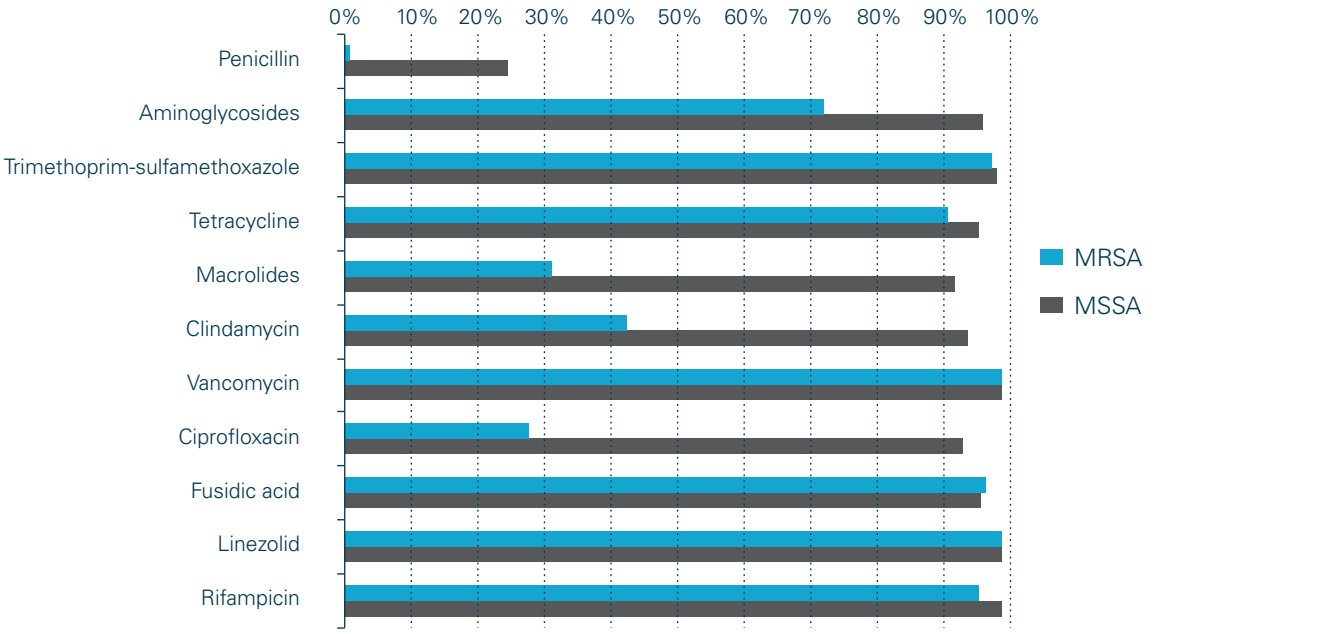
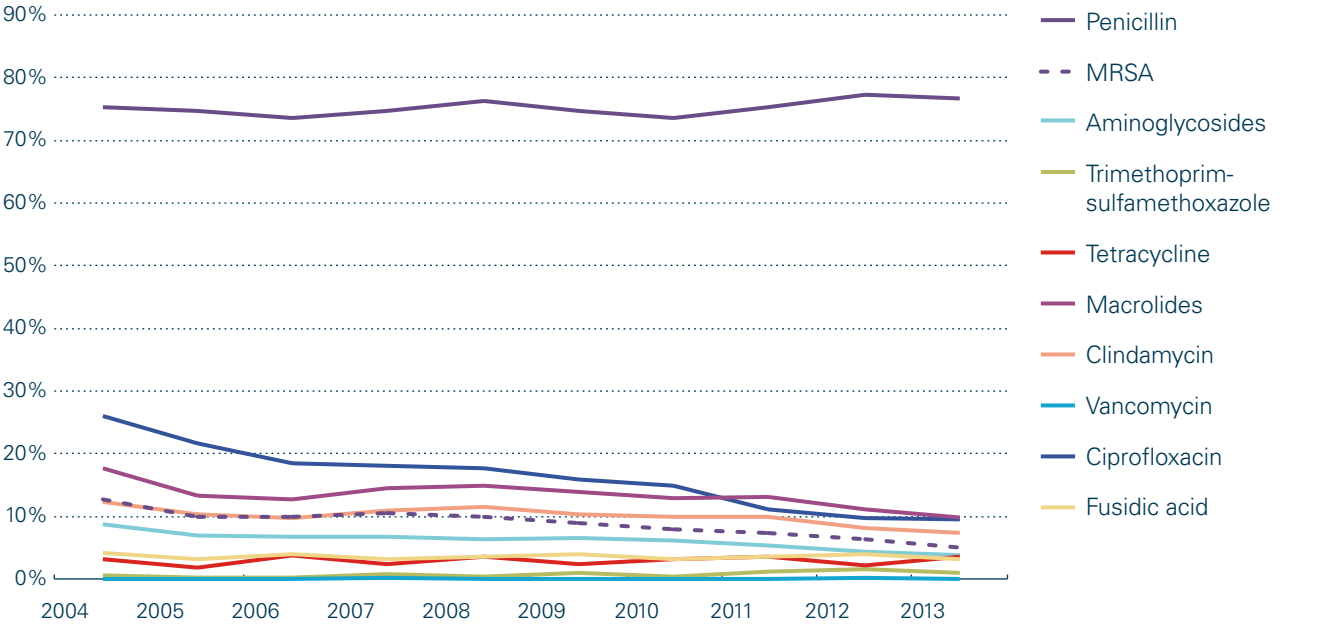


Figure 7. i: Non-susceptibility rates of invasive *Staphylococcus aureus* isolates in humans 2004–2013.



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8

Resistance in zoonotic bacteria

8 Resistance in zoonotic bacteria

Zoonoses are infections and diseases that are transmissible between animals and humans. Infection can be acquired through direct contact with animals or indirectly by contaminated food. The severity of these diseases in humans can vary from mild symptoms to life-threatening conditions. Antimicrobial resistance in zoonotic bacteria from animals is of special concern, since it might compromise the effective treatment of infections in humans.

8.1 *Salmonella* spp.

Salmonella is the second most important zoonotic bacterial pathogen in Switzerland [1]. Salmonellosis in humans has to be notified (ordinance of the SFOPH on laboratory reports), whereas the notification of resistance profile of these findings is not mandatory.

Human salmonellosis does not usually require antimicrobial treatment. In some patients *Salmonella* infection can cause serious illness and sepsis. In these cases effective antimicrobials are essential for treatment and can be lifesaving. The treatment of choice for *Salmonella* infections is fluoroquinolones for adults and third-generation cephalosporins for children.

Information on antimicrobial resistance in anresis.ch was available for more than one-fourth of the reported human *Salmonella* cases. Resistance levels are only generated for aminopenicillins, trimethoprim-sulfamethoxazole and older quinolones (Table 8. c). Serovar typing in human medicine is only done for a minority of isolates. Although this information is interesting for epidemiologic purposes – in contrast to susceptibility testing results – it is irrelevant for treatment decisions. As in veterinary medicine *S.* Typhimurium and *S.* Enteritidis are the most frequent serovars specified and they differ in their antibiotic resistance profile.

Transmission of *Salmonella* from animals to humans usually occurs through food. A wide variety of foodstuffs of animal and plant origin can be contaminated with *Salmonella*. *Salmonella* can also be transmitted through direct contact with colonized animals. In Europe, *S.* Enteritidis and *S.* Typhimurium are the most common serovars in human infections. *S.* Enteritidis cases are mostly associated with the consumption of contaminated eggs and poultry meat, whereas *S.* Typhimurium cases are mostly associated with the consumption of contaminated pig, bovine and poultry meat.

Findings of *Salmonella* in animals have to be notified in Switzerland, and antibacterial susceptibility is tested in one isolate from each animal species involved in an incident. Isolates obtained in the *Salmonella* eradication programme from samples collected from poultry herds are also included.

Table 8. a: Occurrence of resistance in *S.* Typhimurium from poultry, pigs and cattle.

***Salmonella* Typhimurium (N=48)**			**2013**
Antimicrobials	**n**	**%**	**95%CI**
Ampicillin	3	6.3	2.1–16.8
Cefotaxime	0	0.0	0.0–7.4
Ceftazidime	0	0.0	0.0–7.4
Chloramphenicol	3	6.3	2.1–16.8
Ciprofloxacin	0	0.0	0.0–7.4
Colistin	0	0.0	0.0–7.4
Florfenicol	3	6.3	2.1–16.8
Gentamicin	0	0.0	0.0–7.4
Kanamycin	0	0.0	0.0–7.4
Nalidixic acid	0	0.0	0.0–7.4
Streptomycin	4	8.3	3.3–19.6
Sulfamethoxazole	3	6.3	2.1–16.8
Tetracycline	3	6.3	2.1–16.8
Trimethoprim	0	0.0	0.0–7.4

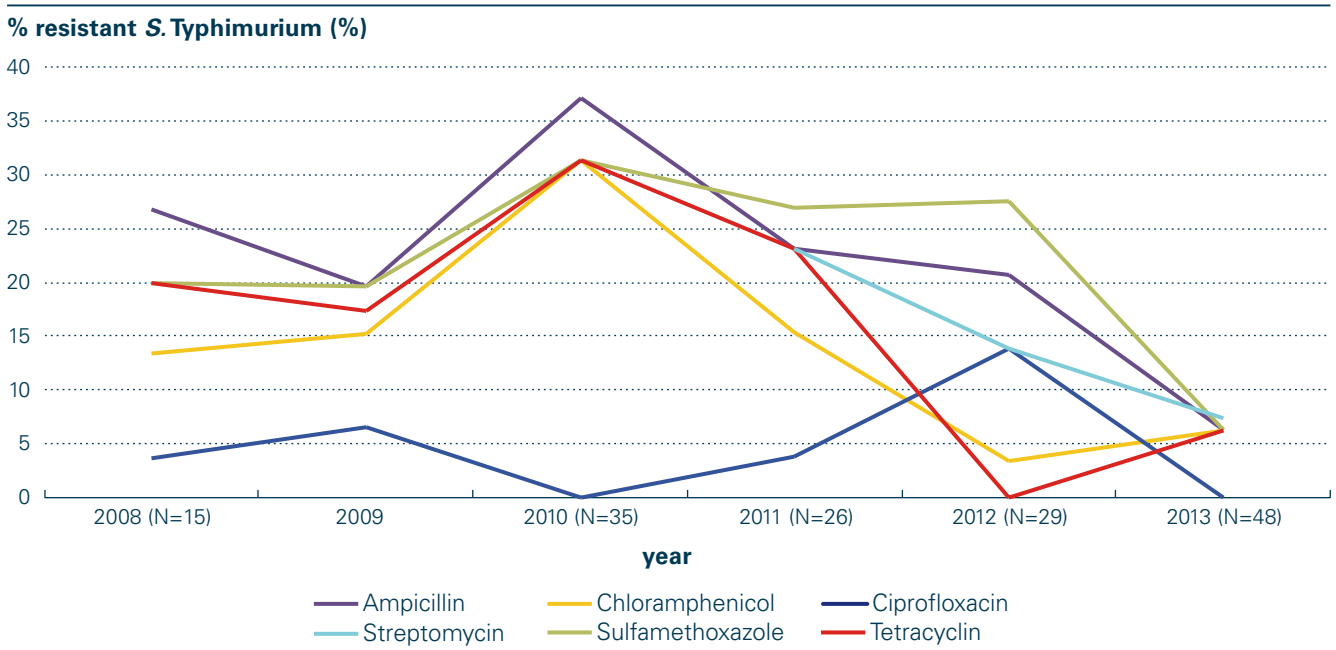
(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Table 8. b: Occurrence of resistance in monophasic *S.* Typhimurium from poultry, pigs and cattle.

Monophasic *Salmonella* Typhimurium (N=17)			2013
Antimicrobials	**n**	**%**	**95%CI**
Ampicillin	17	100.0	81.6–100.0
Cefotaxime	0	0.0	0.0–18.4
Ceftazidime	0	0.0	0.0–18.4
Chloramphenicol	0	0.0	0.0–18.4
Ciprofloxacin	0	0.0	0.0–18.4
Colistin	1	5.9	1.0–27.0
Florfenicol	0	0.0	0.0–18.4
Gentamicin	0	0.0	0.0–18.4
Kanamycin	0	0.0	0.0–18.4
Nalidixic acid	0	0.0	0.0–18.4
Streptomycin	17	100.0	81.6–100.0
Sulfamethoxazole	17	100.0	81.6–100.0
Tetracycline	17	100.0	81.6–100.0
Trimethoprim	0	0.0	0.0–18.4

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Figure 8. a: Trends in ampicillin, chloramphenicol, ciprofloxacin, streptomycin, sulfamethoxazole and tetracycline resistance in *S.* Typhimurium from poultry, pigs and cattle 2008–2013. (N=total number of tested isolates)



8.1.1 *Salmonella* in animals

This report covers only *Salmonella* Enteritidis, *Salmonella* Typhimurium and monophasic *Salmonella* Typhimurium of farm animals (cattle, pigs and poultry).
In 2013, 18 *Salmonella* isolates from poultry of different holdings, 57 *Salmonella* isolates from cattle of different holdings and 7 *Salmonella* isolates from pigs of different holdings were available for susceptibility testing. Of these, 48 isolates were identified as *S.* Typhimurium (8 from poultry, 39 from cattle, 1 from pigs), 17 as monophasic *S.* Typhimurium (14 from cattle, 3 from pigs) and 6 as *S.* Enteritidis (3 from poultry, 2 from cattle, 1 from pigs).

All 6 *S.* Enteritidis isolates were fully susceptible to all tested antimicrobials.

44 *S.* Typhimurium isolates (91.7%) were susceptible to all tested antimicrobials. 1 *S.* Typhimurium isolate from a cow was microbiologically resistant to streptomycin and 3 isolates (2 from cattle, 1 from pigs) (1.4%) were multiresistant and showed microbiological resistance to 6 antimicrobials (ampicillin, chloramphenicol, florfenicol, streptomycin, sulfamethoxazole, tetracycline) (Table 8. a).

All 17 monophasic *S.* Typhimurium isolates were resistant to ampicillin, streptomycin, sulfamethoxazole and tetracycline. One isolate from a cow was also resistant to colistin. None of the tested *Salmonella* isolates showed microbiological resistance to a third-generation cephalosporin (cefotaxime/ceftazidime) nor to a (fluoro)quinolone (ciprofloxacin/nalidixic acid) (Table 8. b).

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.1, II.2 and II.3) and multi-resistance patterns are shown in Annex III (Table III.1, III.2 and III.3)

8.1.2 Non-typhoidal *Salmonella* in human clinical isolates

1271 laboratory confirmed cases in humans were reported in 2013, which represents a notification rate of 15.7 cases per 100,000 inhabitants. The most frequently reported serovars were *S.* Enteritidis (28%), *S.* Typhimurium (16%) and the monophasic strain 4,12:i:- (16%).
Resistance in non-typhoidal human *Salmonella* isolates was high for aminopenicillin (27.2%) and low for ceftriaxone, trimethoprim-sulfamethoxazole and quinolones (2.2%, 8.0% and 6.3%, respectively). In 2013 the most frequent serovars isolated were *Salmonella* Enteritides (n=77) and *Salmonella* Typhimurium (n=54), but 163 isolates have not been speci-

Figure 8. b: Trends in aminopenicillin, ceftriaxone, trimethoprim-sulfamethoxazole and fluoroquinolone – resistance in non-typhoidal *Salmonella* from human clinical isolates 2004–2013.

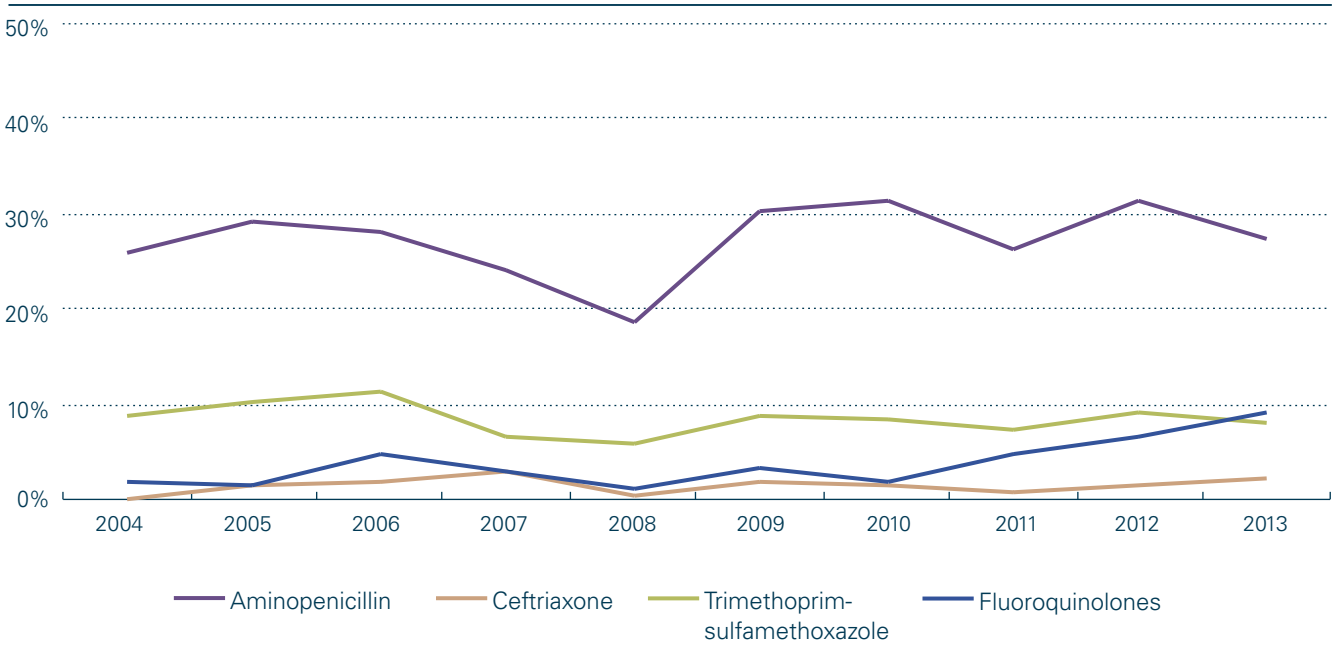


Table 8. c: Occurrence of resistance in non-typhoidal *Salmonella* from human clinical isolates.

***Salmonella ser.* Enteritidis**							2013
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Aminopenicillin	77	77	100.0%	0	0.0%	0	0.0%
Ceftriaxone	54	54	100.0%	0	0.0%	0	0.0%
Trimethoprim-sulfamethoxazole	68	68	100.0%	0	0.0%	0	0.0%
Fluoroquinolones[1]	77	73	94.8%	1	1.3%	3	3.9%

***Salmonella ser.* Typhimurium**							2013
Antibiotic	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Aminopenicillin	52	17	32.7%	0	0.0%	35	67.3%
Ceftriaxone	42	42	100.0%	0	0.0%	0	0.0%
Trimethoprim-sulfamethoxazole	50	43	86.0%	0	0.0%	7	14.0%
Fluoroquinolones[1]	54	51	94.4%	0	0.0%	3	5.6%

(N=Total number of tested isolates, S (n) = number of susceptible isolates, S (%) = percentage of susceptible isolates, I (n) = number of intermediate susceptible isolates, I (%) = percentage of intermediate susceptible isolates, R (n) = number of resistant Isolates, R (%) = percentage of resistant isolates)
[1] Fluoroquinolones: Ciprofloxacin, Norfloxacin, Ofloxacin

fied to serovar level. Non-susceptibility rates were higher in *Salmonella* Typhimurium than in *Salmonella* Enteritidis for aminoopenicillins (67% vs. 0%) and trimethoprim-sulfamethoxazole (14% vs. 0%), but not for fluoroquinolones (5.6 vs. 5.2%). Ceftriaxone-resistance did not occur in any of these isolates (Table 8. c).
Non-susceptibility rates were stable since 2004 for aminopenicillins, ceftriaxone and trimethoprim-sulfamethoxazole but increased for fluoroquinolones since 2010. Indeed in 2013 for the first time non-susceptibility rates for fluoroquinolones were higher than for trimethoprim-sulfamethoxazole (Fig. 8. b).

8.1.3 Discussion

The frequency of resistance to aminopenicillins in human non-typhoidal *Salmonella* spp. isolates in Switzerland was equal to the mean level of resistance to ampicillin in 18 different EU Member States in 2012 [2]. Resistance levels to fluoroquinolones were slightly higher in Switzerland than the mean value for ciprofloxacin resistance in EU Member States (6.3% vs. 5.1%), but variation between Member States was high (0.3–18.5% resistant isolates).
Animals can be carriers of *Salmonella* without showing any clinical signs. In particular poultry, often show no signs of infection. In cattle *Salmonella* infection can cause fever, diarrhoea and abortion. Fever and diarrhoea are less common in pigs.
The situation regarding the occurrence of *Salmonella* spp. in food producing animals in Switzerland is very good. Overall, only a few *Salmonella* isolates from animals were available from clinical material or from *Salmonella* eradication programs over the last 6 years (Figure 8. a).
Microbiological resistance was found especially in monophasic *S.* Typhimurium strains, which were consistently resistant to ampicillin, streptomycin, sulfamethoxazole and tetracycline, but was absent in *S.* Enteritidis and low in *S.* Typhimurium.
A direct comparison of the resistance situation between *Salmonella* in animals and in human clinical isolates is not possible for various reasons. Interpretative criteria (clinical breakpoint in human isolates/ecological cut-off in animal isolates) may differ substantially. If the only information available is qualitative data from human isolates, a reinterpretation of the results using the same cut-off-values is not possible. Regarding the favourable *Salmonella* situation in farm animals in Switzerland, it must be assumed that a substantial part of *Salmonella* infections are acquired from imported food or while abroad. Data on antimicrobial resistance in *Salmonella* from imported food and information about the origin of the infection (domestic/abroad) would be necessary to complete the picture.

8.2 *Campylobacter* spp.

Campylobacter is the most commonly reported cause of human food-borne zoonoses in Switzerland as well as in the European Union [1] [3]. The species most commonly associated with human infections is *C. jejuni,* but other species may also cause infections.
Although most human campylobacteriosis cases are self-limiting and do not require antibacterial treatment, resistance to antibacterials in *Campylobacter* is of concern, because it is crucial in treatment of severe cases. Resistance can lead to therapy failure and longer treatment duration. Fluoroquinolones, such as ciprofloxacin, and macrolides, such as clarithromycin or azithromycin, represent standard therapy for campylobacteriosis and are therefore considered as critically important antimicrobials of highest priority [4].
Incorrect handling of raw poultry meat and the consumption of undercooked contaminated poultry meat and poultry liver are the two main causes for campylobacteriosis cases in humans. Meat from cattle and pigs and contact with pets seem to be less important. Comparison of isolates from humans and animals collected between 2001 and 2012 identified chickens as the main source for human campylobacteriosis (71% of the human cases were attributed to chickens, 19% to cattle, 9% to dogs and 1% to pigs [5]).

8.2.1 *Campylobacter* spp. in broilers

At present, only a few antimicrobial products are licensed for use in poultry in Switzerland. More than half of these products contain antimicrobial substances (mainly enrofloxacin) that belong to the critical antimicrobial classes of highest priority according to WHO/OIE/FAO, which have to be used

Table 8. d: Occurrence of resistance in *Campylobacter jejuni* from broilers.

Broilers: *Campylobacter jejuni* (N=157)			**2013**
Antibacterials	**n**	**%**	**95% CI**
Chloramphenicol	0	0	0.0–2.4
Ciprofloxacin	65	41.4	34.0–49.2
Erythromycin	2	1.3	0.4–4.5
Gentamicin	0	0	0.0–2.4
Nalidixic acid	65	41.4	34.0–49.2
Streptomycin	6	3.8	1.8–8.1
Tetracycline	33	21	15.4–28.0

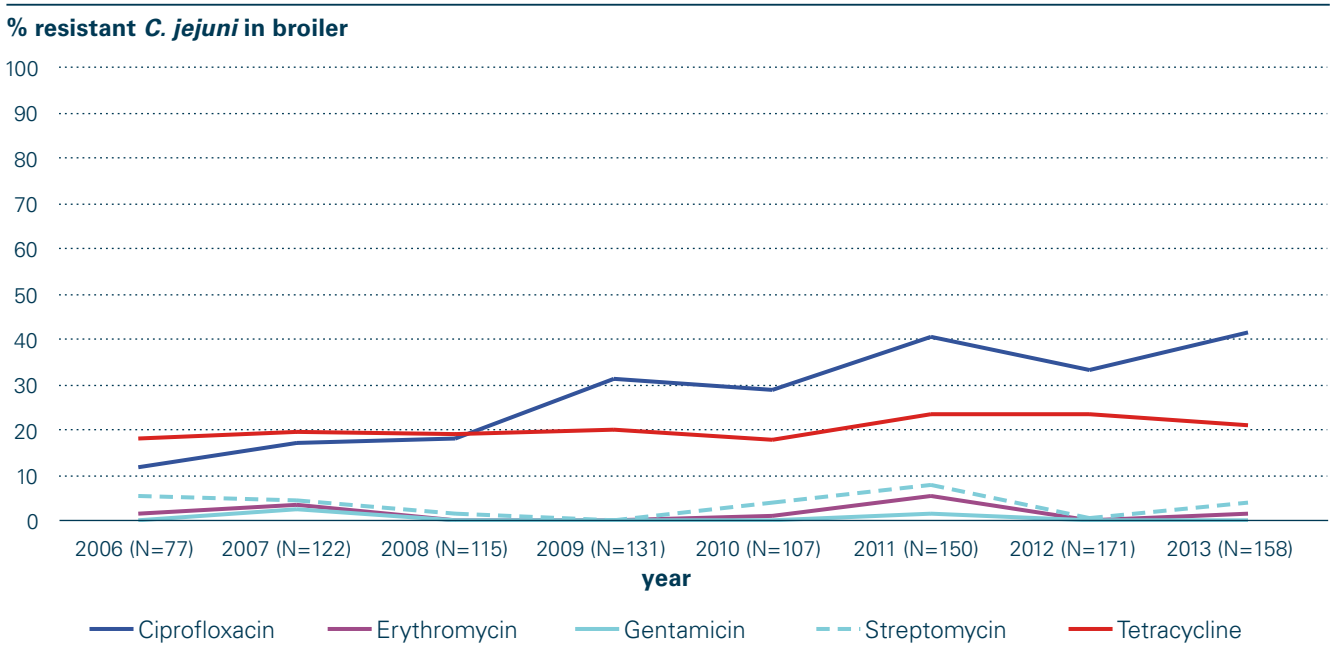
(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Table 8. e: Occurrence of resistance in *Campylobacter coli* from broilers.

Broilers: *Campylobacter coli* (N=11)			**2013**
Antibacterials	**n**	**%**	**95% CI**
Chloramphenicol	1	9.1	1.6–37.7
Ciprofloxacin	6	54.5	28.0–78.7
Erythromycin	1	9.1	1.6–37.7
Gentamicin	0	0	0.0–25.9
Nalidixic acid	6	54.5	28.0–78.7
Streptomycin	6	54.5	28.0–78.7
Tetracycline	3	27.3	9.7–56.6

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval

Figure 8. c: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. jejuni* from broiler 2006–2013. (N=total number of tested isolates)



with caution in view of the problem of antimicrobial resistance in human and veterinary medicine. In the absence of products with less problematic antimicrobials, these substances are often used as first line treatments in broiler production in Switzerland. In Switzerland there are currently no products licensed for use in broilers containing tetracycline or streptomycin. But tetracycline is widely used in other farm animals, especially pigs and cattle.

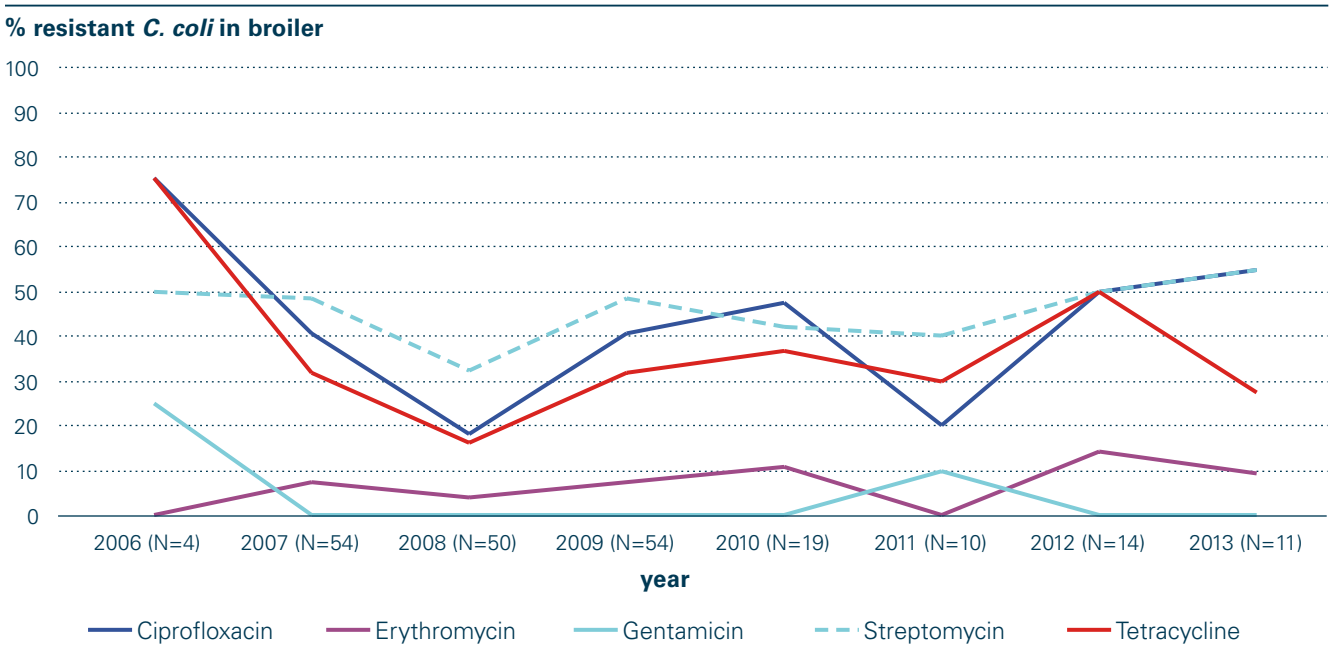
In 2013, a random sample of 448 broiler herds was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using cloacal swabs (5 pooled swabs per herd). 169 of 448 broiler herds (37.7%) were *Campylobacter*-positive *(Campylobacter jejuni* (157×) and *Campylobacter coli* (12×)). All *C. jejuni* and 11 *C. coli* isolates were subjected to susceptibility testing (Tables 8. d–e).

Complete susceptibility to all tested antimicrobials was found in 48% of the *C. jejuni* isolates and in 18% of the *C. coli* isolates. Moderate to high levels of resistance were found in *C. jejuni* as well as in *C. coli* to quinolones (ciprofloxacin: 41.4% and nalidixic acid: 54.5%) and to tetracycline (21% and 27.3% respectively). High microbiological resistance to streptomycin was also found in *C. coli* (54.5%). Two *C. jejuni* isolates (1.3%) and one *C. coli* isolate (9.1%) were microbiologically resistant to both ciprofloxacin and erythromycin.
The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.4 and II.5) and multi-resistance patterns are shown in Annex III (Table III.4 and III.5)

In *C. jejuni* from broilers microbiological resistance to ciprofloxacin showed a statistically significant increasing trend over the last 6 years. It rose from 12% resistant isolates in 2006 to 41.4% (95%CI 33.9 – 42.2%) in 2013. Resistance to the other antibiotics was stable or low (Figure 8. c).

Between 2006 and 2013 few *C. coli* isolates from broilers were available for suceptibility testing (N: from 4 to 54). This small number of isolates does not allow the detection of statistically significant trends over the years (Figure 8. d).

Figure 8. d: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. coli* from broilers 2006–2013. (N=total number of tested isolates)



8.2.2 *Campylobacter* spp. in pigs

In 2013, a random sample of 348 pigs was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using rectal-anal swabs. 226 of the 348 samples (65%) were *Campylobacter*-positive. All 226 isolates were identified as *C. coli* and were subjected to susceptibility testing (Table 8. f).

In *C. coli* from pigs the highest level of microbiological resistance was found to streptomycin (74.3%). High levels of microbiological resistance were also found to ciprofloxacin (38.1%), nalidixic acid (38.5%) and tetracycline (29.2%). 12.4% of the isolates were resistant to erythromycin.
13.3% of the *C. coli* isolates were fully sensitive to all tested antimicrobials, 4% showed resistance to more than four antimicrobials. 8 isolates (3%) showed microbiological resistance to both ciprofloxacin and erythromycin.
The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.6) and multi-resistance patterns are shown in Annex III (Table III.6).

In *C. coli* from pigs, levels of microbiological resistance to streptomycin decreased significantly in the past 7 years but are still extremely high. Microbiological resistance levels to ciprofloxacin in *C. coli* isolates from pigs increased significantly since 2006 despite a slight fall in 2013. The prevalence of resistance to erythromycin has consistently been around 10% since monitoring began in 2006 (Figure 8. e).

Table 8. f: Occurrence of resistance in *Campylobacter coli* from pigs.

Pigs: *Campylobacter coli* (N=226)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Chloramphenicol	0	0	0.0–1.7
Ciprofloxacin	86	38.1	32.0–44.5
Erythromycin	28	12.4	8.7–17.3
Gentamicin	1	0.4	0.1–2.5
Nalidixic acid	87	38.5	32.4–45.0
Streptomycin	168	74.3	68.3–79.6
Tetracycline	66	29.2	23.7–35.4

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Figure 8. e: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. coli* rom pigs 2006–2013. (N=total number of tested isolates)

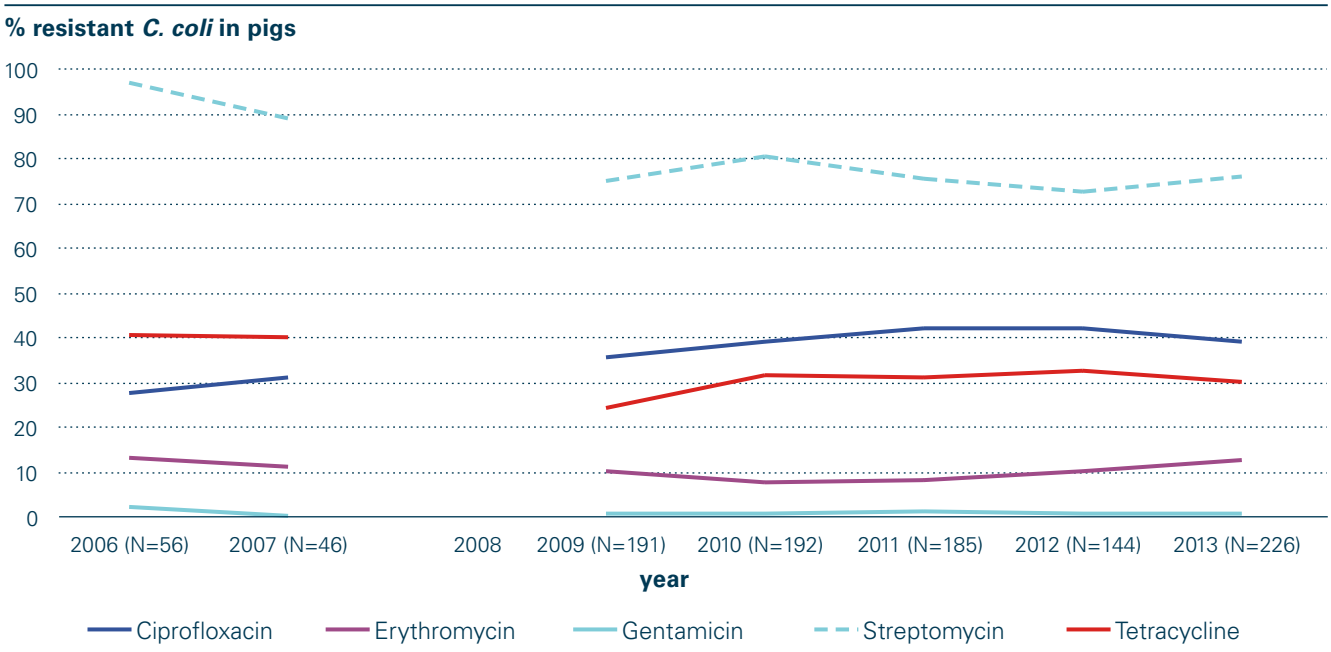


Table 8. g: Occurrence of resistance in *Campylobacter coli* and *Campylobacter jejuni* from human clinical isolates.

Campylobacter coli							**2013**
Antimicrobials	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Macrolides[1]	207	181	87.4%	0	0.0%	26	12.6%
Fluoroquinolones[2]	207	71	34.3%	0	0.0%	136	65.7%

Campylobacter jejuni							**2013**
Antimicrobials	n	S (n)	S (%)	I (n)	I (%)	R (n)	R (%)
Macrolides[1]	2668	2633	98.7%	5	0.2%	30	1.1%
Fluoroquinolones[2]	2666	1337	50.2%	2	0.1%	1327	49.8%

(N=Total number of tested isolates, S (n) = number of susceptible isolates, S (%) = percentage of susceptible isolates, I (n) = number of intermediate susceptible isolates, I (%) = percentage of intermediate susceptible isolates, R (n) = number of resistant Isolates, R (%) = percentage of resistant isolates)

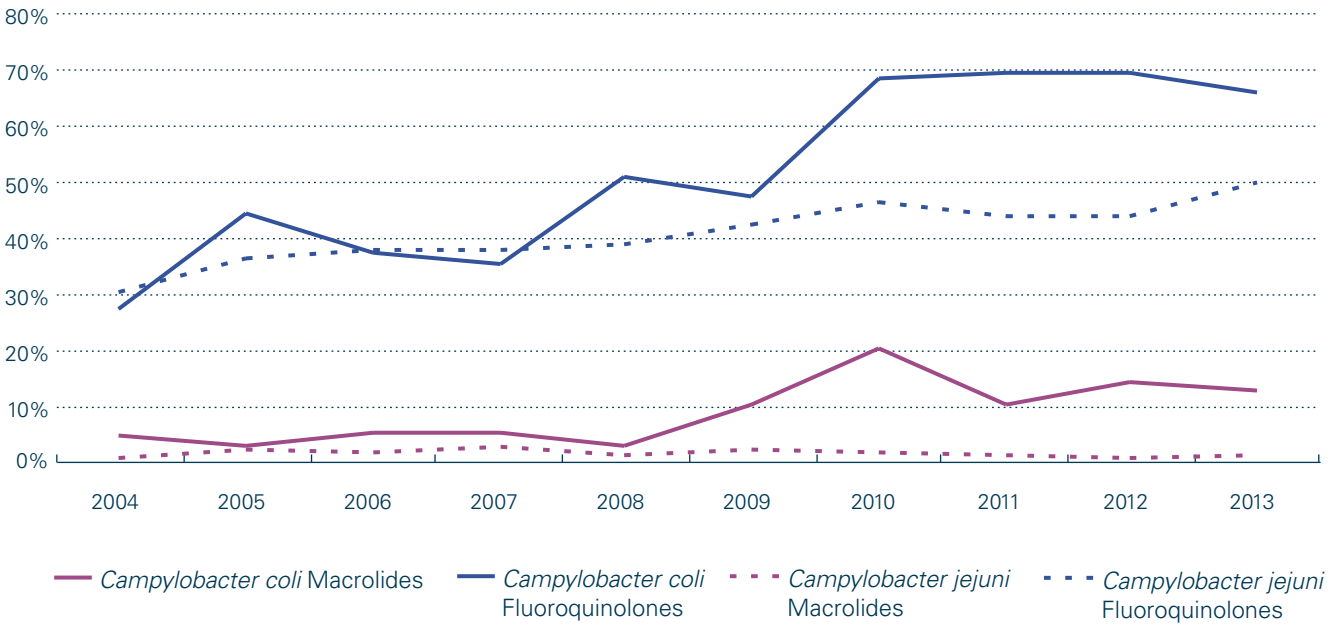
[1] Erythromycin, clarithromycin, azithromycin

[2] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

8.2.3 *Campylobacter* spp. in humans

A total of 7481 laboratory confirmed cases of human campylobacteriosis were reported in 2013 (92.5 per 100,000 inhabitants). 71% of the cases were caused by *C. jejuni,* in 19% of cases no distinction was made between *C. jejuni* and *C. coli.* In anresis.ch resistance data were available for 2907 isolates (39%), 2668 (92%) were identified as *C. jejuni* (92%), 207 (7%) as *C. coli*. Resistance data for 2013 are shown in table 8. g. Over all about half of the isolates were resistant to quinolones but resistance to macrolides was still low (2%). For *C. coli* isolates resistance rates were higher for fluoroquinolones and macrolides. Resistance rates since 2004 were increasing for *C. coli* for macrolides and fluoroquinolones and for *C. jejuni* for fluoroquinolones only (Figure 8. f).

Figure 8. f: Trends in resistance to fluoroquinolones and macrolides in *Campylobacter coli* and *Campylobacter jejuni* from human clinical isolates in Switzerland, 2004–2013.



8.2.4 Discussion

Information on antimicrobial resistance in anresis.ch was available for more than one-third of the reported human *Campylobacter* cases. Resistance levels are reported for fluoroquinolones and macrolides; resistance rates to fluoroquinolones are extremely high (over 50%), and the trend has been rising over the last ten years.
Similar average levels of resistance to ciprofloxacin and nalidixic acid were found in 15 EU countries in 2012 (47.4% and 48.8% respectively), with a high variability in resistance levels in different countries ranging from 31.8% – 85.1% for ciprofloxacin and 44.2% – 96.1% for nalidixic acid (EFSA & ECDC, 2014). As in Switzerland, resistance levels to macrolides (erythromycin) are generally low in EU countries ranging from 0.3% to 26.6% [2].
An increase in resistance to ciprofloxacin in *C. jejuni* from broilers is of special concern, because recent studies estimate that the handling, preparation and consumption of broiler meat may account for 20% – 30% of human campylobacteriosis cases and 50 – 80% of the cases may be attributed to the chicken sector as a whole [6]). Genotyping studies in Switzerland confirmed that chicken must also be considered as the main source for human campylobacteriosis in Switzerland [5] [7] [8].
Levels of microbiological resistance to tetracycline in *C. jejuni* in broilers remained relatively stable from 2006 to 2013. Prevalence of microbiological resistance to gentamicin and erythromycin in *C. jejuni* is constantly low.
For the year 2012, data on microbiological resistance in *C. jejuni* in broilers are available for 10 European countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands and Spain). They showed average levels of resistance of 44.1% to ciprofloxacin, 0.5% to erythromycin, 0.7% to gentamicin, 41.1% to nalidixic acid and 31.1% to tetracycline. As in previous years resistance levels varied greatly among the countries and are generally much lower in Nordic countries compared to other European countries [2].

The average levels of microbiological resistance in *C. coli* isolates from pigs of 5 different EU countries (Denmark, France, Hungary, the Netherlands and Spain) in the year 2012 are 32% for ciprofloxacin, 23.9% for erythromycin, 2.9% for gentamicin, 31.6% for nalidixic acid and 76.8% for tetracycline [2]. Resistance levels for (fluoro)quinolones in Switzerland are therefore similar to the average levels in the EU, but they are significantly higher than in Denmark and the Netherlands (with resistance levels of 12.1% for ciprofloxacin and nalidixic acid) and significantly lower than in Spain (with a resistance level of 96.6% for both substances). Resistance levels for all other tested antimicrobials in Switzerland are below the European average with a decreasing trend by streptomycin and an increasing trend by ciprofloxacin.

The available data do not allow a direct comparison of resistance in *Campylobacter* isolates from humans and animals. The sampling strategy, methodology and breakpoints used for testing of isolates are not the same for animals and humans. Nevertheless it must be assumed, that the increasing trend in fluoroquinolone resistance in *Campylobacter* isolates from humans over the last ten years is due to the increase of resistance in *Campylobacter* from animals. *Campylobacter* infections may be acquired from imported food or while abroad. Studies showed that resistance levels differ substantially for ciprofloxacin in isolates from domestically produced and imported poultry meat, and also depending on

whether patients have been abroad [9]. Therefore more information on resistance levels in *Campylobacter* from meat (domestically produced and imported) and on travel status would be necessary to complete the picture.

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9

Resistance in indicator bacteria in animals

9 Resistance in indicator bacteria in animals

The prevalence of antibacterial resistance among certain bacteria of the normal enteric microflora can be used as an indicator of the selective pressure from use of antibacterial agents in various populations. These bacteria may form a reservoir of transferable resistance genes from which antibiotic resistance can be spread to other bacteria, including those responsible for infections in animals or humans.
Antibiotic resistance in indicator bacteria from healthy animals is monitored in order to provide information about the types of resistance present in intestinal bacteria of animal origin. Resistance can be passed on along the food chain to other types of bacteria, including those with zoonotic potential. All antibiotic use leads to selection pressure for resistant bacteria in the intestinal flora of the animals affected. Monitoring allows a comparison of the effects of this selection pressure in different animal species. It also serves as a valuable early warning system to help identify emerging types of resistance in livestock populations and to monitor their potential spread.

9.1 Enterococci

In antimicrobial resistance monitoring, enterococci are used as 'indicator bacteria' to provide information on the types of resistance present in Gram-positive intestinal bacteria in food producing animals. Resistance can be passed from animals to humans either by the direct transmission of resistant bacterial strains or by horizontal exchange of resistance genes among bacteria [1].
Enterococci occur normally in the gastrointestinal tract of animals and humans. In a hospital setting, however, they can cause diseases such as urinary infections, sepsis and endocarditis in patients with weakened immune systems. Of particular concern in this regard are vancomycin-resistant enterococci (VRE), which can spread rapidly and are difficult to treat. The resistance gene responsible is located on a transposon and can therefore be easily passed on to other bacteria, prompting particular fears that vancomycin resistance might be passed from enterococci to Methicillin-resistant *Staphylococcus aureus* (MRSA).

9.1.1 *Enterococcus* spp. broilers

In 2013, a random sample of 249 broiler herds was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using cloacal swabs (5 pooled swabs per herd).
155 *Enterococcus faecalis* and 58 *Enterococcus faecium* were isolated and subjected to antibiotic susceptibility testing (Tables 9. a and 9. b).

Table 9. a: Occurrence of resistance in *Enterococcus faecalis* from broilers.

Broilers: *Enterococcus faecalis* (N=155)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Amoxicillin/Clavulanic acid 2:1	0	0	0–2.4
Ampicillin	0	0	0–2.4
Bacitracin	29	18.7	13.4–25.6
Chloramphenicol	1	0.6	0.1–3.6
Ciprofloxacin	1	0.6	0.1–3.6
Erythromycin	26	16.8	11.7–23.4
Florfenicol	0	0	0–2.4
Gentamicin	1	0.6	0.1–3.6
Linezolid	0	0	0–2.4
Neomycin	154	99.4	96.4–99.9
Nitrofurantoin	1	0,6	0.1–3.6
Salinomycin	0	0	0–2.4
Streptomycin	5	3.2	1.4–7.3
Tetracycline	59	38.1	30.8–45.9
Vancomycin	0	0	0–2.4

(N=Total number of tested isolates, n= number of resistant Isolates,%= percentage of resistant isolates, 95% CI: 95% Confidence Interval).

Table 9. b: Occurrence of resistance in *Enterococcus faecium* from broilers.

Broilers: *Enterococcus faecium* (N=58)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Amoxicillin/Clavulanic acid 2:1	0	0	0–6.2
Ampicillin	3	5.2	1.8–14.1
Bacitracin	40	69	56.2–79.4
Chloramphenicol	0	0	0–6.2
Ciprofloxacin	1	1.7	0.3–9.1
Erythromycin	16	27.6	17.8–40.2
Florfenicol	0	0	0–6.2
Gentamicin	0	0	0–6.2
Linezolid	0	0	0–6.2
Neomycin	5	8.6	3.7–18.6
Nitrofurantoin	0	0	0–6.2
Quinupristin/Dalfopristin*	36	62.1	48.4–74.5
Salinomycin	0	0	0–6.2
Streptomycin	2	3.4	0–6.2
Tetracycline	18	31	20.6–43.8
Vancomycin	0	0	0–6.2

(N=Total number of tested isolates, n= number of resistant Isolates,%= percentage of resistant isolates, 95% CI: 95% Confidence Interval).

Table 9. c: Occurrence of resistance in *Enterococcus faecalis* from veal calves.

Veal calves: *Enterococcus faecalis* (N=108)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Amoxicillin/Clavulanic acid 2:1	0	0	0–3.4
Ampicillin	0	0	0–3.4
Bacitracin	20	18.5	12.3–26.9
Chloramphenicol	30	27.8	20.2–36.9
Ciprofloxacin	0	0	0–3.4
Erythromycin	46	42.6	33.7–52
Florfenicol	0	0	0–3.4
Gentamicin	15	13.9	8.6–21.7
Linezolid	0	0	0–3.4
Neomycin	101	93.5	87.2–96.8
Nitrofurantoin	7	6.5	3.2–12.8
Salinomycin	0	0	0–3.4
Streptomycin	52	48.1	39–57.7
Tetracycline	84	77.8	69.1–84.6
Vancomycin	1	0.9	0.2–5.1

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval).

Microbiological resistance was commonly found in *E. faecium* and in *E. faecalis* with highest levels to neomycin, tetracycline, bacitracin and erythromycin. Additionally 62.1% of the *E. faecium* isolates were microbiologically resistant to quinupristin/dalfopristin. Only 1 isolate of each enterococcus species was fully susceptible to all tested antimicrobials.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.7 and II.8) and multi-resistance patterns are shown in Annex III (Table III.7 and III.8)

9.1.2 *Enterococcus* spp. in veal calves

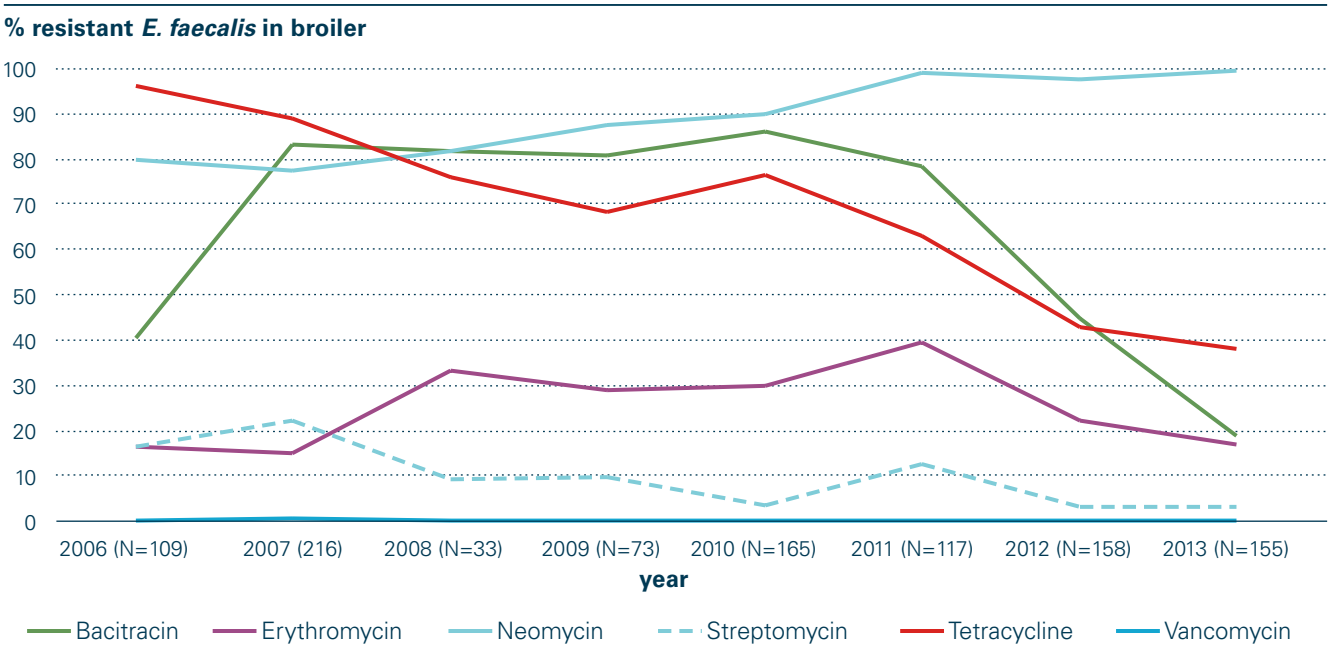
In 2013, a random sample of 253 veal calves was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using rectal swabs.
108 *Enterococcus faecalis* and 68 *Enterococcus faecium* were isolated and subjected to antibiotic susceptibility testing (Tables 9. c and 9. d).

Table 9. d: Occurrence of resistance in *Enterococcus faecium* from veal calves.

Veal calves: *Enterococcus faecium* (N=68)			2013
Antimicrobials	**n**	**%**	**95% CI**
Amoxicillin/Clavulanic acid 2:1	0	0	0–5.3
Ampicillin	0	0	0–5.3
Bacitracin	43	63.2	51.4–73.7
Chloramphenicol	0	0	0–5.3
Ciprofloxacin	2	2.9	0.8–10.1
Erythromycin	8	11.8	6.1–21.5
Florfenicol	0	0	0–5.3
Gentamicin	0	0	0–5.3
Linezolid	0	0	0–5.3
Neomycin	18	26.5	17.04.1938
Nitrofurantoin	0	0	0–5.3
Quinupristin/Dalfopristin*	60	88.2	78.1–94.8
Salinomycin	0	2.9	0.8–10.1
Streptomycin	2	2.9	0.8–10.1
Tetracycline	7	10.3	5.1–19.8
Vancomycin	0	0	0–5.3

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval).

Figure 9. a: Trends in bacitracin, erythromycin, neomycin, streptomycin, tetracycline and vancomycin resistance in *Enterococcus faecalis* from broiler 2006–2013. (N= total number of tested isolates)



Microbiological resistance was commonly found in *E. faecium* and in *E. faecalis* with high to extremely high resistance levels to neomycin and bacitracin. *E. faecalis* isolates additionally showed high to very high levels of resistance to tetracycline, erythromycin, streptomycin and chloramphenicol, whereas 88.2% of the *E. faecium* isolates were microbiologically resistant to quinupristin/dalfopristin. One *E. faecalis* isolate from aveal calvs showed resistance against vancomycin. No resistance to linezolid was observed.
Only 2.8% of *E. faecium* and 5.9% of *E. faecalis* were fully susceptible to all tested antimicrobials.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.9 and II.10) and multi-resistance patterns are shown in Annex III (Table III.9 and III.10).

9.1.3 Discussion

Microbiological resistance to antibiotics is widespread in enterococci from food producing animals in Switzerland.

Figure 9. b: Trends in bacitracin, erythromycin, neomycin, streptomycin, tetracycline and vancomycin resistance in *Enterococcus faecalis* from veal calves 2006/2010/2013. (N= total number of tested isolates)

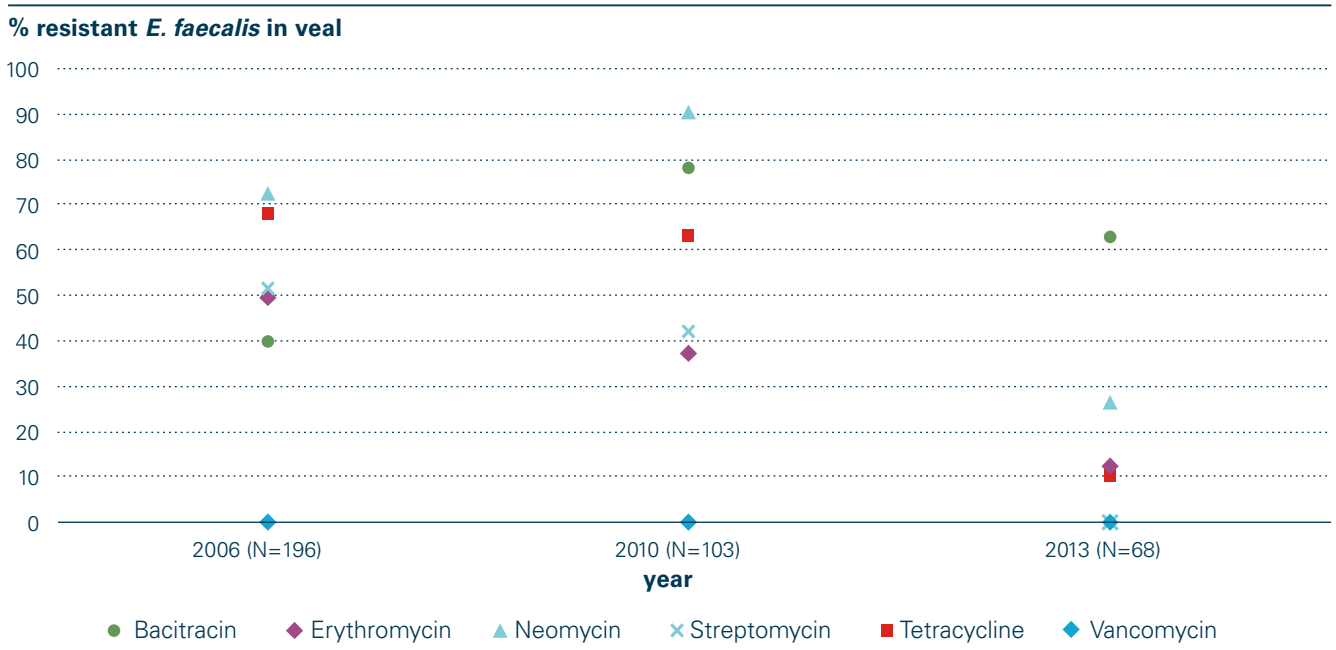
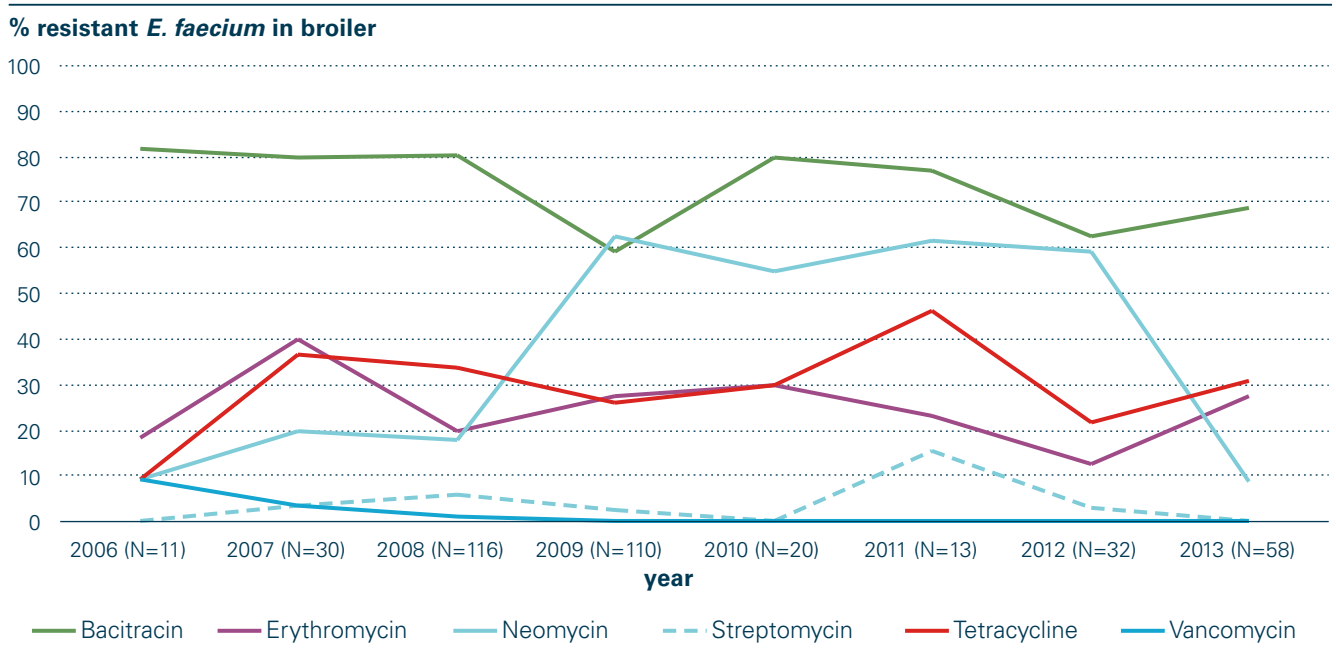


Figure 9. c: Trends in bacitracin, erythromycin, neomycin, streptomycin, tetracycline and vancomycin resistance in *Enterococcus faecium* from broiler 2006–2013. (N= total number of tested isolates)

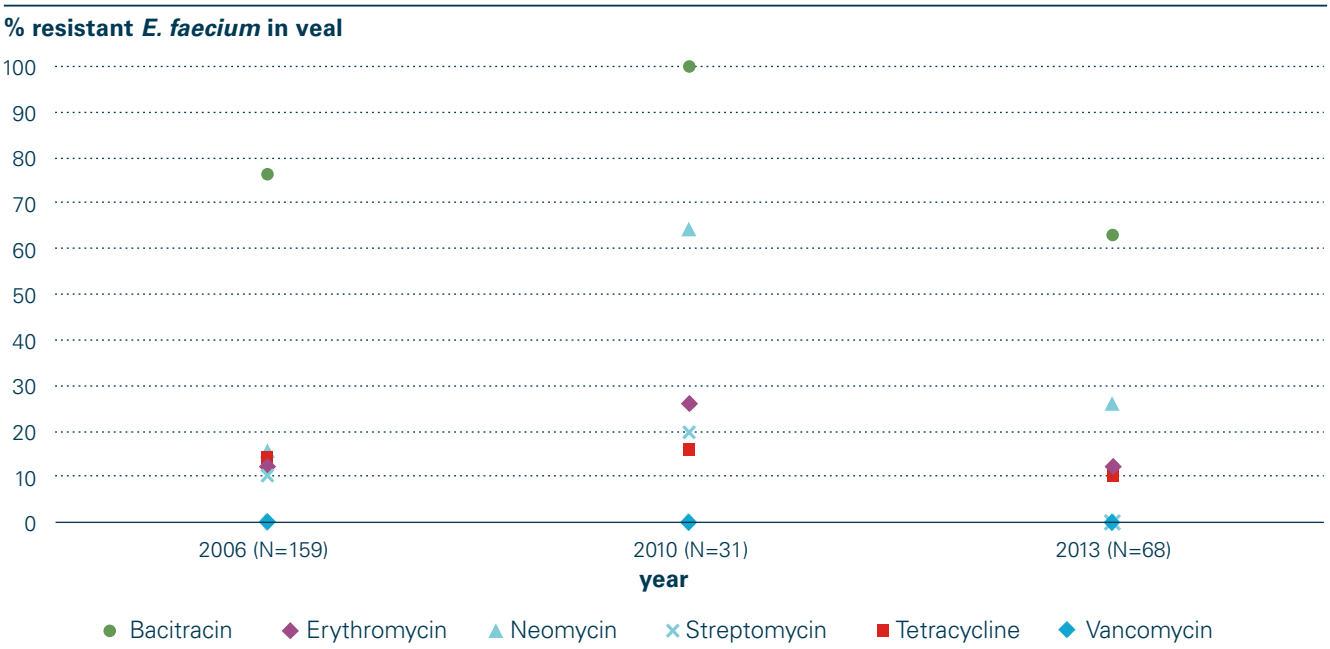


In *E. faecalis*, extremely high rates of neomycin resistance were found in both broiler chickens and veal calves; however, resistance rates in the *E. faecium* strains tested have fallen significantly since 2010 in both animal species (Figures 9. a–d). In the case of *E. faecalis* strains, high proportions of isolates with microbiological resistance to tetracycline were additionally detected in both species.

E. faecium strains from broilers and calves showed very high rates of microbiological resistance to quinupristin/dalfopristin and bacitracin. Compared with the previous year, rates of neomycin resistance in *E. faecium* strains from broilers have decreased significantly.

Moderate to high rates of erythromycin resistance were detected in *E. faecalis* and *E. faecium* from both animal species. No microbiological resistance to ampicillin was detected in *E. faecalis;* in *E. faecium,* only low rates of resistance were found. One of the *E. faecalis* isolates obtained from fattening calves showed microbiological resistance to vancomycin. No microbiological resistance to linezolid was detected. Compared with the previous year, there has also

Figure 9. d: Trends in bacitracin, erythromycin, neomycin, streptomycin, tetracycline and vancomycin resistance in *Enterococcus faecium* from veal calves 2006/2010/2013. (N=total number of tested isolates)



been a significant decrease in bacitracin resistance in *E. faecalis.*

Microbiological resistance to quinupristin/dalfopristin in *E. faecium* from broilers and pigs remains widespread. This drug combination was originally recommended as an alternative for the treatment of vancomycin-resistant enterococci in humans. It is not used in veterinary medicine but other streptogramins (e.g. virginiamycin) have been used prophylactically (although not in Switzerland). This use has been prohibited throughout Europe since the late 1990s.

In human medicine, the drug of choice for enterococcal infections is ampicillin, in severe cases combined with gentamicin. In 2012, no microbiological resistance to ampicillin was detected in *E. faecalis* isolates from broilers, pigs or cattle (data not shown). Similarly, in 2013, no ampicillin resistance was detected in *E. faecalis* isolated from broilers or calves. Low rates of ampicillin resistance were found in *E. faecium* isolated from broilers; no ampicillin resistance was detected in *E. faecium* isolated from fattening calves. None of the *E. faecium* isolates tested showed microbiological resistance to gentamicin.

In combination therapy, the glycopeptide antibiotic vancomycin is used instead of ampicillin in the presence of ampicillin resistance. The emergence of vancomycin resistance in bacteria from food producing animals is linked to the use of avoparcin as a growth promoter. This use was consequently banned in Europe in 1997. After the ban, a decline was shown to have occurred not only in the incidence of VRE in the livestock population but also in the proportion of people in the normal population with VRE gut colonisation [2]. Today, resistance rates are low to very low in all European countries in which the incidence of vancomycin resistance in enterococci is studied [3]. Resistance monitoring in food producing animals in Switzerland has not detected any microbiological vancomycin resistance in enterococci in recent years. In 2013, however, resistance was again detected in one *E. faecalis* isolate (0.9%) from fattening calves.

Anresis.ch monitoring on antibiotic resistance in humans shows that the proportion of clinically vancomycin-resistant *E. faecium* and *E. faecalis* is very low and with a decreasing trend (see Chapter 7.2)[4]. VRE remains a widely feared hospital pathogen. However, transmission to humans via animals or foods of animal origin plays a minor role due to its low prevalence in animals.

9.2 *Escherichia coli*

9.2.1 *Escherichia coli* in broilers

In 2013, a random sample of 201 broiler herds was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using cloacal swabs (5 pooled swabs per herd).198 *E. coli* were isolated and were subjected to susceptibility testing.

33.3% of the *E. coli* isolates were susceptible to all tested antimicrobials. Highest levels of resistance were found to ampicillin, ciprofloxacin, nalidixic acid, sulfamethoxazole and tetracycline, with resistance levels between 23.8% and 35.4% (Table 9. e). One isolate (0.5%) was resistant to third generation cephalosporins (cefotaxime, ceftazidime) and is therefore suspected of being an ESBL/AmpC producer.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.11) and multi-resistance patterns are shown in Annex III (Table III.13)

Table 9. e: Occurrence of resistance in *Escherichia coli* from broilers.

Broilers: *Escherichia coli* (N=189)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	48	25.4	19.7–32.0
Cefotaxime	1	0.5	0.1–2.9
Ceftazidime	1	0.5	0.1–2.9
Chloramphenicol	2	1.1	0.3–3.8
Ciprofloxacin	67	35.4	29–42.5
Colistin	0	0	0.0–2.0
Florfenicol	0	0	0.0–2.0
Gentamicin	1	0.5	0.1–2.9
Kanamycin	5	2.6	1.1–6.0
Nalidixic acid	65	34.4	28.0–41.1
Streptomycin	29	15.3	10.9–21.2
Sulfamethoxazole	51	27	21.2–33.7
Tetracycline	45	23.8	18.3–30.4
Trimethoprim	27	14.3	10.0–20.0

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval).

Table 9. f: Occurrence of resistance in *Escherichia coli* from pigs.

Pigs: *Escherichia coli* (N=183)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	33	18	13.1–24.2
Cefotaxime	2	1.1	0.3–3.9
Ceftazidime	2	1.1	0.3–3.9
Chloramphenicol	12	6.6	3.8–11.1
Ciprofloxacin	9	4.9	2.6–9.1
Colistin	0	0	0.0–2.1
Florfenicol	0	0	0.0–2.1
Gentamicin	4	2.2	0.9–5.5
Kanamycin	7	3.8	1.9–7.7
Nalidixic acid	8	4.4	2.2–8.4
Streptomycin	86	47	39.9–54.2
Sulfamethoxazole	71	38.8	32.0–46.0
Tetracycline	62	33.9	27.4–41.0
Trimethoprim	36	19.7	14.6–26.0

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

9.2.2 *Escherichia coli* in pigs

In 2013, a random sample of 200 pigs was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using rectal-anal swabs. 183 *E. coli* were isolated and subjected to susceptibility testing.

41.5% of the isolates were susceptible to all tested antimicrobials.

Highest levels of resistance were found to ampicillin, streptomycin, sulfamethoxazole, trimethoprim and tetracycline, with resistance levels between 18.0% and 47% (Table 9. f). Two isolates (1.1%) were resistant to third generation cephalosporins (cefotaxime, ceftazidime) and are therefore suspected of being ESBL/AmpC producers.

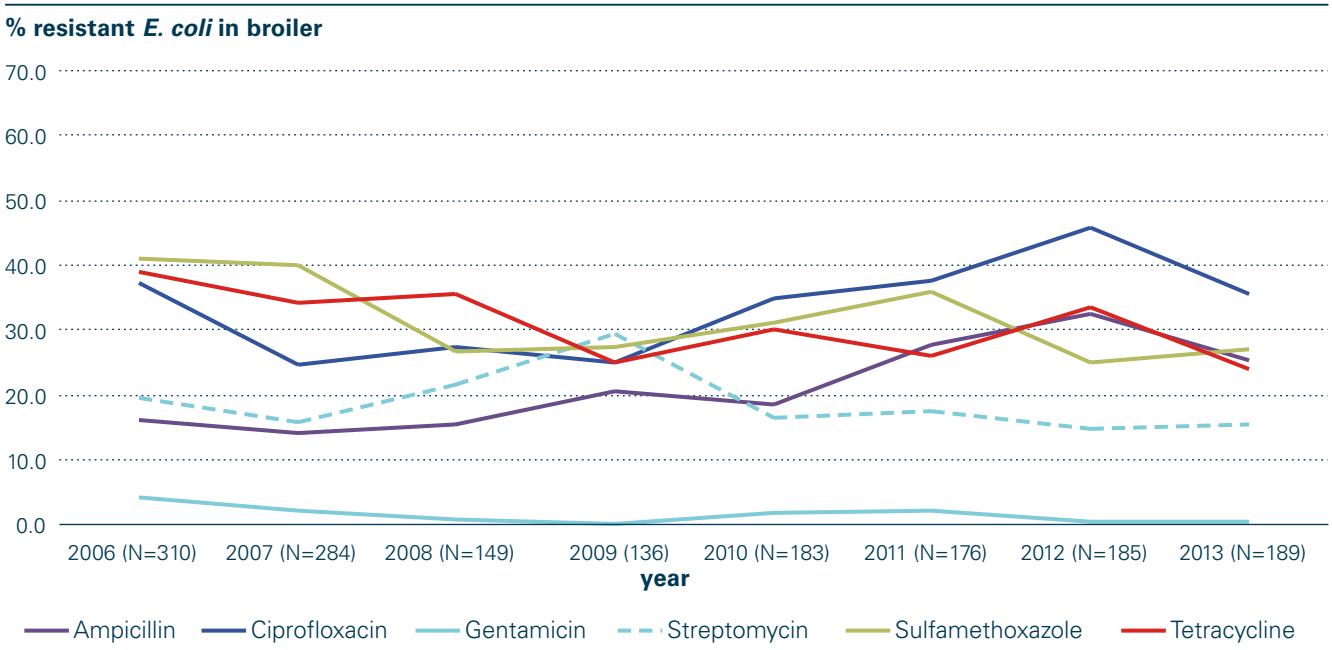
The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.12) and multi-resistance patterns are shown in Annex III (Table III.12).

Table 9. g: Occurrence of resistance in *Escherichia coli* from veal calves.

Veal calves: *Escherichia coli* (N=176)			2013
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	48	27.3	21.2–34.3
Cefotaxime	0	0	0.0–21
Ceftazidime	0	0	0.0–21
Chloramphenicol	17	9.7	6.1–14.9
Ciprofloxacin	13	7.4	4.4–12.2
Colistin	0	0	0.0–21
Florfenicol	5	2.8	1.2–6.5
Gentamicin	6	3.4	1.6–7.2
Kanamycin	25	14.2	9.8–20.1
Nalidixic acid	13	7.4	4.4–12.2
Streptomycin	72	40.9	33.9–48.3
Sulfamethoxazole	81	46	38.8–53.4
Tetracycline	67	38.1	31.2–45.4
Trimethoprim	39	22.2	16.7–28.9

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Figure 9. e: Trends in ampicillin, ciprofloxacin, gentamicin, streptomycin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from broilers 2006–2013. (N= total number of tested isolates)



9.2.3 *Escherichia coli* in veal calves

In 2013, a random sample of 208 veal calves was investigated at slaughter in the framework of the antimicrobial resistance monitoring programme using rectal swabs.176 *E. coli* were isolated and subjected to susceptibility testing.

44.9% of the isolates were susceptible to all tested antimicrobials.
Highest levels of resistance were found to streptomycin, sulfamethoxazole and tetracycline, with resistance levels between 38.1% and 46% (Table 9. g).

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.13) and multi-resistance patterns are shown in Annex III (Table III.13).

9.2.4 Discussion

Microbiological resistance is widespread in *E. coli* from food producing animals in Switzerland. Medium to high rates of microbiological resistance to ampicillin, streptomycin, sulfamethoxazole, tetracycline and trimethoprim were found in all animal species (Figures 9. e–g). In addition, high rates of

Figure 9. f: Trends in ampicillin, ciprofloxacin, gentamicin, streptomycin, sulfamethoxazole and tetracycline resistance in *E. coli* from pigs 2006–2013. (N= total number of tested isolates)

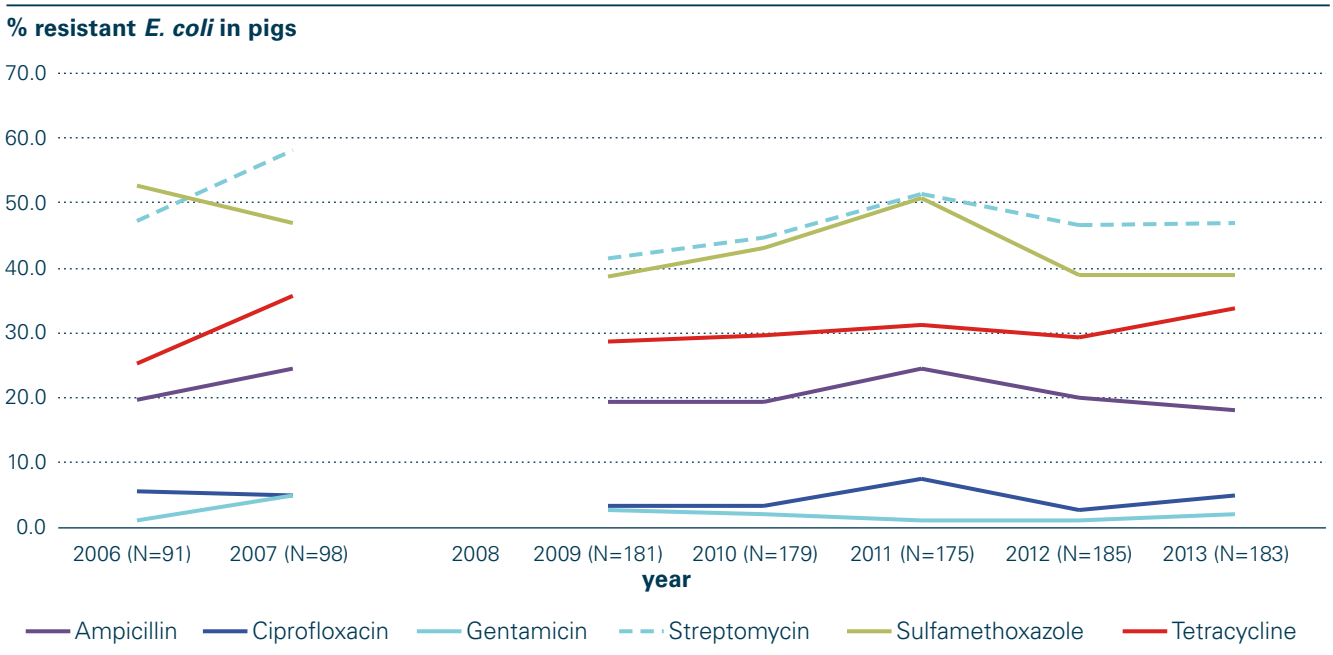
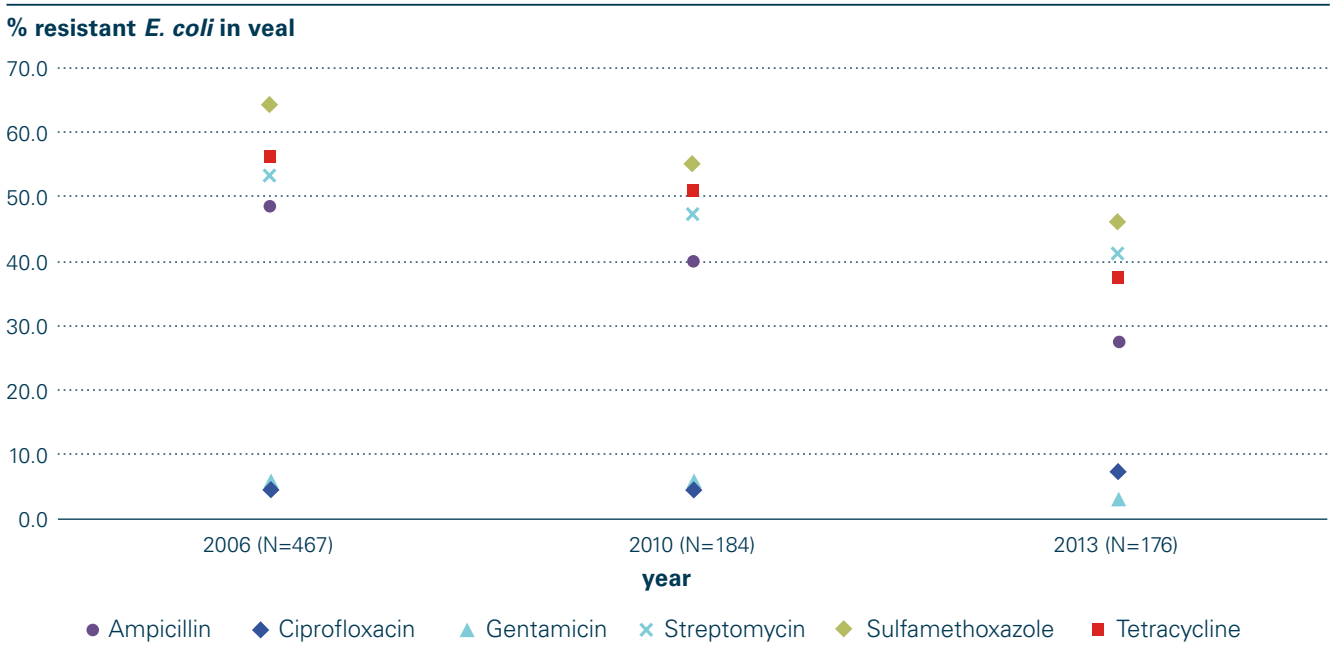


Figure 9. g: Trends in ampicillin, ciprofloxacin, gentamicin, streptomycin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from veal calves 2006/2010/2013. (N= total number of tested isolates)



microbiological resistance to ciprofloxacin and nalidixic acid were found in broilers (35.5% and 34.4%); microbiological resistance to both of these antibiotics has declined by 10% compared with the previous year. There has also been a significant fall in the proportion of *E. coli* with resistance to ampicillin and tetracycline.

In *E. coli* in pigs, the resistance situation has remained stable in recent years, whereas rates of microbiological resistance to ampicillin, sulfamethoxazole, streptomycin, tetracycline and chloramphenicol in *E. coli* in fattening calves have fallen significantly compared with 2007. In addition, moderate rates of kanamycin resistance (14.2%) were found in *E. coli* in fattening calves.

The detection of *E. coli* which are microbiological resistant to ampicillin, cefotaxime and ceftazidime is recommended by the EFSA as a non-selective method for the detection of ESBL-producing isolates [5]. In 2013 one such isolate was found in broiler flocks, two in fattening pigs and none in fattening calves.

In addition, levels of chloramphenicol, gentamycin and kanamycin resistance were high to very high in pigs and calves. *E. coli* showed high proportions of isolates with microbiological resistance to antibiotics that have been used for sev-

eral years to treat food producing animals, for example trimethoprim/sulfonamide, tetracycline and ampicillin.
Sulfonamides, tetracyclines and penicillins are the antibiotic classes most widely used in the Swiss livestock population. In broilers, where the most-used antibiotics are fluoroquinolones, ciprofloxacin resistance is frequently observed in *E. coli*. This indicates that the resistance situation in non-pathogenic *E. coli* from the gastrointestinal tract actually reflects the selection pressure to which the bacteria are exposed as a result of antibiotic use in the animal species concerned.
The high prevalence of microbiological resistance to ciprofloxacin and nalidixic acid in *E. coli* from broilers could potentially lead to problems in human medicine as well.

9.3 ESBL / pAmpC-producing *Escherichia coli*

Recent years have seen an increase in the detection of broad-spectrum beta-lactamase-producing intestinal bacteria in food producing animals in various countries, which show increasing resistance to the antibiotic group of aminopenicillins and cephalosporins. Bacteria producing both extended-spectrum beta-lactamase (ESBL) and plasmid-encoded AmpC (pAmpC) have been found. If these types of resistance are passed on to humans via zoonotic pathogens, there may be significant consequences for human medicine. In addition, they can form a reservoir in indicator organisms, from where resistance can be passed to pathogenic organisms via mobile genetic elements such as plasmids, integrons or transposons.
ESBL and pAmpC are produced by a variety of intestinal bacteria. Most of these live harmlessly in the gut without causing disease. However, resistance can also occur in disease-causing (pathogenic) bacteria (e.g. *Salmonella* or enterohaemorrhagic *E. coli).* These diseases do not usually require treatment with antibiotics. In certain vulnerable patients, however, such as young children, the elderly or patients with weakened immune systems, they can take a severe course which renders antibiotic treatment necessary. Pathogenic bacteria with ESBL or pAmpC resistance are difficult to treat, which can prolong and worsen the course of the disease.
For this reason *Escherichia coli* isolates from animal are also used to gauge the spread of bacteria that produce ESBL. We correlated the distribution of the MICs for *E. coli* with the

Table 9. h: Occurrence of resistance in ESBL/AmpC producing *Escherichia coli* from broilers.

Broilers: ESBL / pAmpC – producing *Escherichia coli* (N=47)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	47	100	92.4–100
Cefotaxime	47	100	92.4–100
Cefotaxime/Clavulanic acid	2	4.3	1.2–14.2
Ceftazidime	44	93.6	82.5–98.7
Ceftazidime/Clavulanic acid	6	12.8	6–25.2
Cefazolin	47	100	92.4–100
Cefepime	16	34	22.2–48.3
Cefoxitin	7	14.9	7.4–27.7
Cefpodoxime	47	100	92.4–100
Ceftriaxone	47	100	92.4–100
Cefalotin	47	100	92.4–100
Chloramphenicol	1	2.1	0.4–11.1
Ciprofloxacin	19	40.4	27.6–54.7
Colistin	0	0	0–7.6
Florfenicol	0	0	0–7.6
Gentamicin	3	6.4	2.2–17.2
Imipenem	0	0	0–7.6
Kanamycin	3	6.4	2.2–17.2
Meropenem	0	0	0–7.6
Nalidixic acid	18	38.3	25.8–52.6
Piperacillin/Tazobactam	0	0	0–7.6
Streptomycin	16	34	22.2–48.3
Sulfamethoxazole	36	76.6	62.8–86.4
Tetracycline	23	48.9	35.3–62.8
Trimethoprim	33	70.2	56–81.3

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

presence of extended-spectrum beta-lactamase (ESBL) and plasmid-mediated AmpC beta-lactamase (pAmpC) genes.

9.3.1 ESBL / pAmpC-producing *Escherichia coli* in broilers

In 2013, 47 ESBL/pAmpC-producing *E. coli* were isolated with selective enrichment methods from a random sample of 170 broiler herds (5 pooled cloacal swabs per herd). This corresponds to a herd prevalence of 27.7% (95% CI 11.1–35.0%). All isolates were subjected to testing (Table 9. h).

All isolates showed microbiological resistance to beta-lactame antimicrobials. Additionally extremely high levels of microbiological resistance were found to sulfonamides and trimethoprim as well as high levels to (fluoro)quinolones and tetracycline. 34% of the isolates were resistant to cefepime, a fourth generation cephalosporin, which is more stable against certain beta-lactamases than other cephalosporins. None of the isolates was resistant to colistin nor to carbapenems (imipenem, meropenem) nor to piperacillin/tazobactam and only 6.4% of the isolates were microbiologically resistant to aminoglycosides (gentamicin/kanamycin). The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.14) and multi-resistance patterns are shown in Annex III (Table III.14)

9.3.2 ESBL / pAmpC-producing *Escherichia coli* in pigs

In 2013, 16 ESBL/pAmpC-producing *E. coli* were isolated with selective enrichment methods from a random sample of 171 rectal swabs from pigs. This corresponds to a prevalence 9.4% (95% CI 5.4–14.8%). All isolates were subjected to susceptibility testing (Table 9. i).

All isolates showed microbiological resistance to beta-lactame antimicrobials and tetracycline. Additionally high to extremely high levels of microbiological resistance were found to ciprofloxacin, gentamicin, kanamycin, streptomycin, sulfamethoxazole and trimethoprim. 9 isolates (56.3%) showed a microbiological resistance to cefepime, a fourth generation cephalosporin, which is more stable against certain beta-lactamases than other cephalosporins. 2 isolates were resistant to piperacillin/tazobactam. None of the isolates was resistant to colistin nor to carbapenems (imipenem, meropenem).

Table 9. i: Occurrence of resistance in ESBL/AmpC producing *Escherichia coli* from pigs.

Pigs: ESBL / pAmpC – producing *Escherichia coli* (N=16)			**2013**
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	16	100	80.6–100
Cefotaxime	16	100	80.6–100
Cefotaxime/Clavulanic acid	2	12.5	3.5–36
Ceftazidime	16	100	80.6–100
Ceftazidime/Clavulanic acid	1	6.3	1.1–28.3
Cefazolin	16	100	80.6–100
Cefepime	9	56.3	33.2–76.9
Cefoxitin	2	12.5	3.5–36
Cefpodoxime	16	100	80.6–100
Ceftriaxone	16	100	80.6–100
Cefalotin	16	100	80.6–100
Chloramphenicol	4	25	10.2–49.5
Ciprofloxacin	10	62.5	38.6–81.5
Colistin	0	0	0–19.4
Florfenicol	1	6.3	1.1–28.3
Gentamicin	5	31.3	14.2–55.6
Imipenem	0	0	0–19.4
Kanamycin	8	50	28–72
Meropenem	0	0	0–19.4
Nalidixic acid	8	50	28–72
Piperacillin/Tazobactam	2	12.5	3.5–36
Streptomycin	12	75	50.5–89.8
Sulfamethoxazole	12	75	50.5–89.8
Tetracycline	12	75	50.5–89.8
Trimethoprim	6	37.5	18.5–61.4

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Table 9. j: Occurrence of resistance in ESBL/AmpC producing *Escherichia coli* from veal calves.

Veal calves: ESBL/pAmpC – producing *Escherichia coli* (N=30)			2013
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	30	100	89–100
Cefotaxime	30	100	89–100
Cefotaxime/Clavulanic acid	1	3.3	0.6–16.7
Ceftazidime	30	100	89–100
Ceftazidime/Clavulanic acid	2	6.7	1.8–21.3
Cefazolin	30	100	88.6–100
Cefepime	16	53.3	36.1–69.8
Cefoxitin	3	10	3.5–25.6
Cefpodoxime	30	100	88.6–100
Ceftriaxone	30	100	88.6–100
Cefalotin	30	100	88.6–100
Chloramphenicol	12	40	24.6–57.7
Ciprofloxacin	22	73.3	55.6–85.8
Colistin	0	0	0–11.4
Florfenicol	3	10	3.5–25.6
Gentamicin	21	70	52.1–83.3
Imipenem	0	0	0–11.4
Kanamycin	22	73.3	55.6–85.8
Meropenem	0	0	0–11.4
Nalidixic acid	20	66.7	48.8–80.8
Piperacillin/Tazobactam	2	6.7	1.8–21.3
Streptomycin	20	66.7	48.8–80.8
Sulfamethoxazole	25	83.3	66.4–92.7
Tetracycline	30	100	88.6–100
Trimethoprim	20	66.7	48.8–80.8

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

The distribution of the minimal inhibitory concentrations (MICs) are shown in Annex II (Table II.15) and multi-resistance patterns are shown in Annex III (Table III.15).

9.3.3 ESBL / pAmpC-producing *Escherichia coli* in veal calves

In 2013, 30 ESBL/pAmpC-producing *E. coli* were isolated with selective enrichment methods from a random sample of 181 rectal swabs from veal calves. This corresponds a prevalence 16.6% (95% CI 11.5–22.8%). All isolates were subjected to susceptibility testing (Table 9. j).

All isolates showed microbiological resistance to beta-lactame antimicrobials and tetracycline. Additionally extremely high levels of microbiological resistance were found to ciprofloxacin, gentamicin, kanamycin, streptomycin, sulfamethoxazole and trimethoprim. 16 isolates (53.3%) showed a microbiological resistance to cefepime, a fourth generation cephalosporin, which is more stable against certain beta-lactamases than other cephalosporins. 2 isolates were resistant to piperacillin/tazobactam. None of the isolates was resistant to colistin nor to carbapenems (imipenem, meropenem).
The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.16) and multi-resistance patterns are shown in Annex III (Table III.16).

9.3.4 Discussion

Using non-selective methods, ESBL/pAmpC-producing *E. coli* were detected in only 0.5% of Swiss broiler flocks and 1.1% of fattening pigs; using selective methods, however, ESBL/pAmpC-producing *E. coli* were found in 27.7% of broiler flocks, 9.4% of fattening pigs and 16.6% of calves. These results for pigs and broilers are not significantly different from the previous year's results.
Besides microbiological resistance to beta-lactam antibiotics, the isolates showed very high to extremely high rates of microbiological resistance to (fluoro)quinolones, sulfonamides and tetracycline in all three animal species. In fattening pigs, there were also extremely high rates of gentamicin and kanamycin resistance; similarly, fattening pigs and calves showed high resistance to streptomycin and trimethoprim.

No microbiological resistance to carbapenems was found.
Using the selective method, comparatively lower rates of ESBL/AmpC-producing *E. coli* were found in Switzerland than in other European countries. For a more accurate assessment of their importance in human medicine, these types of resistance are currently being studied at the Institute of Veterinary Bacteriology of the University of Bern. The aim is to characterise them further and compare them with isolates from humans.
Until a few years ago, ESBL/pAmpC-producing bacteria were mainly a problem in hospitals. However, for some time now, they have increasingly been found in the normal population as well. Here, they either occur harmlessly in the guts of healthy individuals or cause diseases such as bladder inflammation. The incidence of these types of resistance has increased in Switzerland in recent years, both in hospitals and in outpatients (see Chapter 7.1) [6].

A study carried out in Switzerland in healthy staff of meat-processing plants found ESBL-producing intestinal bacteria in 5.8% of those tested [7]. Another study, which tested 291 faecal swab samples from patients of GP practices, found ESBL-producing bacteria in 5.2% of the samples [8].
Tests conducted on packaged Swiss meat from March 2013 to February 2014 showed that the extent of resistance to third-generation cephalosporins is also increasing in ready-prepared foods: 73.3% of the *E. coli* isolated from poultry meat showed resistance to third-generation cephalosporins; in beef, 2% of the *E. coli* tested were resistant [9]. The prevalence of these types of resistance in poultry meat is much higher than the prevalence in poultry flocks (27.7%). This might indicate that resistant bacteria are spreading and multiplying during the slaughter process and/or the subsequent meat processing.

Textbox 9. a

The ESBL issue in Switzerland from a One Health perspective

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Despite prompt awareness about antibiotic resistance in Switzerland – as in Northern neighbouring countries – and despite high standard of knowledge of all stakeholders as well as good compliance to strict guidelines for drug use, Switzerland receives only medium ranking concerning prevalence of resistance, while Scandinavian countries score top. The reasons are diverse and are partly due to Switzerland's more-than-average international exchange. This can be seen e.g. in the region around Geneva, an exceptionally international city, which shows a stronger tendency towards a higher burden of resistance than average regions.

Whereas the situation with MRSA has largely stabilized on a relatively moderate level in Switzerland due to successful counter measures[1], the situation concerning another important mechanism of resistance – the production of extended-spectrum beta-lactamases (ESBL) – has gone more and more out of control in recent years. Counter measures are called for urgently to stabilize or preferentially decrease the burden of ESBLs. This is an important goal in order to prevent increased therapeutic use of carbapenems, the last reserve option from the indispensable beta-lactam class of antibiotics.

ESBLs are minor mutational derivatives of the so-called broad-spectrum beta-lactamases (BSBL) such as TEM-1 or SHV-1, which had been detected in Gram-negative rods as early as in the 1960-ties – predominantly in Enterobacteriaceae. Instead of hydrolyzing only penicillins and 1st-generation cephalosporins as the BSBLs, ESBLs confer resistance to all penicillins, all 4 generations of cephalosporins as well as to monobactams. The first ESBL, SHV-2, found in 1982 was followed by a plethora of over 700 micro-evolutionary ESBL variants from 1987 until today. Meanwhile, they fall into four main families of beta-lactamases, TEM, SHV, OXA, and CTX-M. While TEM and SHV-ESBLs had disseminated world-wide in hospitals by the end of the century, they were overtaken by the extremely successful CTX-M-ESBLs starting from around 2001. Since around 2005 ESBL-producers have alarmingly begun to be detected in healthy humans and in the environment.

Because of insufficient knowledge on ESBL prevalence in Switzerland until 2009, an appropriate research program was initiated at the Institute for Food Safety and Hygiene of the Vetsuisse Faculty, University of Zürich. From 2009 to 2014 some 20 studies were performed and published yielding data on prevalence, isolate-characterization, ESBL-gene determination as well as characterization and transferability of the involved resistance plasmids. The most important findings derived from these studies are described and referenced in the following. The general conclusions draw a worrisome situation.

Since ESBLs are usually expressed by Gram-negative rods of the normal intestinal flora the main route of dissemination was hypothesized to be food. Consequently, the food chain was the primary subject of analysis – with milk and meat products being considered of highest priority due to the well-known use of therapeutic antibiotics in animal husbandry. Second in line were healthy humans. ESBL-producers were detected in 13.7%, 15.3%, 8.6% und 63.4% of faecal samples of cattle/calfs, pigs, sheep, and chicken flocks, respectively. A total of 267 milk- and 104 ground meat sam-

ples produced from the first three kinds of animals remained negative[2,3]. In contrast, CTX-M-1-producing *Escherichia coli* were found on a high percentage of raw poultry meat[4]. Moreover, 5.8% of healthy humans turned out to be faecally colonized with *E. coli*-ESBL[5]. Interestingly, the ESBL CTX-M-1 was most abundant (>65%) in food animals, whereas CTX-M-15 was predominant (42%) in humans with CTX-M-1 ranking second[3]. Nevertheless, an association seems plausible between the high rate of contaminating CTX-M-1-producers on poultry on the one hand, and in healthy humans on the other, even though the exact origin of CTX-M-1-producers in the latter is not known. It is important, however, to realize that contaminating CTX-M-1-producers on poultry meat are thoroughly eliminated by proper handling and cooking procedures and can therefore enter the consumer only via cross-contamination through a lack of sufficient kitchen hygiene.

Follow-up studies on wild animals and surface water bodies yielded additional worrisome results: one of 298 pigeons from the City of Zürich was found to carry mit *E. coli*-CTX-M-15, and one each among 30 great cormorants hunted in the Canton of Zürich were colonized with producers of CTX-M-15 or CTX-M-27, respectively[6]. One roe deer originating from the lowlands among a total 235 hunted wild animals, including ibex, chamois, red deer and roe deer, was a proven carrier of *E. coli*-CTX-M-1[7]. Among 139 fish belonging to eight species and caught in the lakes of Zürich and Thun, respectively, 18.7% were colonized with ESBL-producers, 23% of which even with several distinct strains. The most frequently encountered ESBL was CTX-M-15[8]. The important and final study for the time being on water bodies yielded the most intriguing results. Samples of 500ml were taken from 40 lakes and 18 rivers from the German part of Switzerland and from heights between 286 and >2000 meters above sea level. ESBL producing Enterobacteriaceae were found in 36.2% of the samples. From the 21 positive samples, a total of 73 ESBL producers were isolated. One strain alarmingly expressed even a carbapenemase, VIM. CTX-M-15 was the most frequent ESBL (62%)[9]. This, and the fact that exclusively urban water bodies of the lowlands were concerned led to the conclusion that contaminations with ESBL-producers of surface water are by and large caused by incoming waste water of human origin. It has to be assumed that waste water treatment plants are unable to eliminate *E. coli*-ESBL sufficiently. In contrast to the lowlands, none of the probed water bodies above 1000 meters above sea level yielded *E. coli*-ESBL in spite of the sampling being carried out during July, hence during the alpine summer farming season[9].

In conclusion, it is important to realize that dissemination of ESBL-producing Enterobacteriaceae is far advanced and worrisome in Switzerland: aside from hospital patients, at least healthy humans, food animals, the food chain, wild animals and surface water bodies are concerned. Although ESBL-producers are most usually representatives of the normal flora, they can quickly become opportunistic pathogens as soon as they are transferred into normally sterile compartments, where they then cause e.g. wound or urinary tract infections or even sepsis, all of which are then difficult to treat or not all. Aside from increased morbidity, this causes prolonged hospital stays and massively increased costs.

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9.4 Methicillin resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus is a bacterium that colonises the skin and mucous membranes of humans and animals without inducing disease [10]. But, in some cases, these *S. aureus* bacteria are also isolated as pathogens of wound infections and inflammations of the airways. Such infections can normally be treated without any complications using antibiotics.

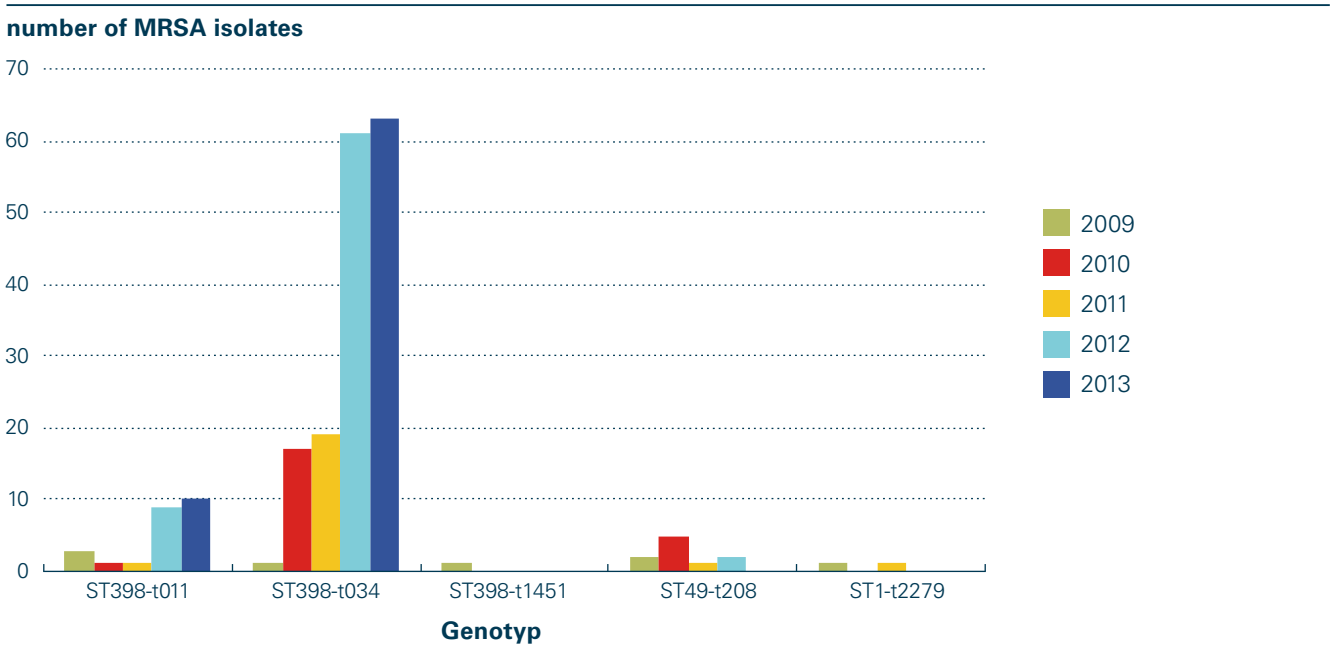
But if infections occur with methicillin-resistant *S. aureus* (MRSA), which are resistant to all beta-lactam antibiotics (penicillins and cephalosporins) and often to other classes of antibiotic as well, treatment is difficult and the infection may take a severe course.

Table 9. k: Occurrence of resistance in MRSA from pigs.

Pigs: Methicillin-resistant *Staphylococcus aureus* (N=73)			**2013**
Antimicrobials	**n**	**%**	**95%CI**
Cefoxitin	73	100.0	95–100
Chloramphenicol	0	0.0	0–5
Ciprofloxacin	4	5.5	2.2–13.3
Clindamycin	63	86.3	76.6–92.4
Erythromycin	60	82.2	71.9–89.3
Fusidic acid	2	2.7	0.8–9.5
Gentamicin	6	8.2	3.8–16.8
Kanamycin	6	8.2	3.8–16.8
Linezolid	0	0.0	0–5
Mupirocin	2	2.7	0.8–9.5
Penicillin	73	100.0	95–100
Quinupristin/Dalfopristin	63	86.3	76.6–92.4
Rifampin	1	1.4	0.2–7.4
Streptomycin	46	63	51.5–73.2
Sulfamethoxazole	2	2.7	0.8–9.5
Tetracycline	73	100	95–100
Tiamulin	63	86.3	76.6–92.4
Trimethoprim	69	94.5	86.7–97.8
Vancomycin	0	0	0–5

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

Figure 9. h: Number of MRSA genotypes from pigs 2009–2013.



9.4.1 MRSA in pigs

In 2013, 73 methicillin resistant *Staphylococcus aureus* (MRSA) were isolated with selective enrichment methods from a random sample of 351 nasal swabs from pigs. This corresponds to a prevalence of 20.8% 9.4% (95%CI 16.7-25.45). 63 isolates were spa-typed as ST389-t034 and 10 isolates as ST398-t011. All isolates were subjected to susceptibility testing (Table 9. k).

All isolates were resistant to beta-lactames and tetracycline. Very high to extremely high microbiological resistance levels were also found to macrolides and lincosamides (erythromycin 82.23%/clindamycin 86.3%) and to quinupristin/dalfopristin (86.3%), tiamulin (86.3%), trimethoprim (94.5%) and streptomycin (63%). 6 isolates (6.8%) were additionally resistant to kanamycin and gentamicin, 4 (5.5%) to ciprofloxacin und two (2.7%) to mupirocin. One isolate was microbiologically resistant to rifampin.
36 isolates belonging to the most commonly detected spa type CC 398-t034 shared an identical resistance profile. They showed resistance to beta-lactames, tetracycline, macrolides, lincosamides, trimethoprim, pleuromutilins, streptomycin and quinupristin/dalfopristin. 21 isolates were also resistant to all these antimicrobials except streptomycin, whereas two isolates were also resistant to all tested aminoglycosides. Two isolates (one t-011/one t-034) were also resistant to fusidic-acid, mupirocin and sulfamethoxazole, while the t-034 isolate was also resistant to rifampin and ciprofloxacin.

At 20.8% (95% CI 16.7-25.4), the prevalence of MRSA in Switzerland has remained stable compared with the previous year (18.1%, 95% CI 14.66-22.23). It was formerly much lower, at 2.0% in 2009 (95% CI 0.9-3.9) and 5.6% in 2011 (95% CI 3.6-8.4) [11] [12].
The largest increase has been in genotype CC398-t034, which was found most often (with 63 isolates). Genotype CC398-t011 was detected 10 times.

In 2013, all MRSA isolates were resistant to penicillin and cefoxitin; in fattening pigs, tetracycline resistance was also found in all MRSA isolates.

In the reporting year, multiple microbiological resistance to 15 antibiotics was found in one isolate of spa type t034 from a fattening pig; the only antibiotic tested that was still effective in this isolate was erythromycin (Annex III, Table III.17).

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.17) and multi-resistance patterns are shown in Annex III (Table III.17).

9.4.2 MRSA in veal calves

In 2013, 10 methicillin resistant *S. aureus* (MRSA) were isolated with selective enrichment methods from a random sample of 253 nasal swabs from veal calves. This corresponds to a prevalence of 4.0% (95%CI 1.9-7.1%). 3 isolates belonged to the spa-type CC398-t034, 5 to the spa-type

Table 9. I: Occurrence of resistance in MRSA from veal calves.

Veal calves: Methicillin-resistant *Staphylococcus aureus* (N=10)			**2013**
Antimicrobials	**n**	**%**	**95%CI**
Cefoxitin	10	100.0	72–100
Chloramphenicol	0	0.0	0–28
Ciprofloxacin	2	20.0	6–51
Clindamycin	8	80.0	49–94
Erythromycin	8	80.0	49–94
Fusidic acid	0	0.0	0–28
Gentamicin	2	20.0	6–51
Kanamycin	2	20.0	6–51
Linezolid	0	0.0	0–28
Mupirocin	0	0.0	0–28
Penicillin	10	100.0	72–100
Quinupristin/Dalfopristin	4	40.0	17–69
Rifampin	0	0.0	0–28
Streptomycin	3	30	11–60
Sulfamethoxazole	0	0	0–28
Tetracycline	9	90	60–98
Tiamulin	3	30	11–60
Trimethoprim	4	40	17–69
Vancomycin	0	0	0–28

(N=Total number of tested isolates, n= number of resistant Isolates, %= percentage of resistant isolates, 95% CI: 95% Confidence Interval)

CC398-t011, and one to the spa-type CC398-t1255 and t-032, respectively. All isolates were subjected to susceptibility testing (Table 9. I).

All isolates were resistant to beta-lactames and only one isolate (t-032) was susceptible to tetracycline. Extremely high microbiological resistance levels were found to macrolides and lincosamides (erythromycin/clindamycin 80%, each). Microbiological resistance levels to ciprofloxacin, gentamicin, kanamycin, quinupristin/dalfopristin, streptomycin, tiamulin and trimethoprim were between 20 and 40%.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table II.18) and multi-resistance patterns are shown in Annex III (Table III.18).

9.4.3 Discussion

The reported results confirm that MRSA of spa type t034 in particular (and to a lesser extent of spa type t011) is becoming widespread in Switzerland's population of slaughterhouse pigs. These are also the spa types most often found in livestock in other European countries, and belong to the group of "livestock-associated" MRSA. To observe the continuing spread of MRSA in pigs in Switzerland, its prevalence will be established again in the 2014 and 2015 resistance monitoring. In a 2012 case-control study [12] based on a survey of farms with pigs testing positive and an equal number of farms with pigs testing negative, no common source of MRSA was identified. The fattening pigs that tested positive came from finishing units all over Switzerland. No high-risk units were found among the piglet producers either.

In calves, the MRSA prevalence in 2013 was 4.0% (95% CI 1.9–7.1%). Three isolates matched genotype CC398-t034, five genotype CC398-t011, one genotype CC398-t1255 and one genotype CC398-t032. Two isolates of genotype CC398-t034 showed microbiological resistance to beta-lactams, aminoglycosides, tetracyclines, macrolides, lincosamides, trimethoprim, pleuromutilin and quinupristin/dalfopristin. Only one MRSA isolate (t032) was sensitive to tetracycline (Annex II, Table II.18).

In 2010 the prevalence of MRSA in calves was 2.1% (95% CI 0.7–4.8) and all isolates tested belonged to genotype CC398-t011. This was also the most common genotype in 2013. In the context of resistance monitoring, genotype CC398-t034 was isolated for the first time in Swiss fattening calves in 2013. It remains to be seen whether this strain too will spread rapidly within the Swiss fattening calf population. The prevalence of MRSA in Swiss fattening calves is relatively low compared with that in pigs, but MRSA monitoring in fattening calves will be continued nevertheless.

In 2012, Belgium, Germany, Finland, the Netherlands and Switzerland tested their livestock and/or the animals' surroundings for the presence of MRSA. Because different methods were used, the data have only limited comparability. No MRSA was detected in the pigs tested in Finland; in the Netherlands, 99% of samples were positive. In Switzerland, 18.1% of the fattening pigs tested in 2012 contained MRSA, around the same proportion as in 2013 (20.8%) [3]. The spa type t032 isolated in a calf is one of the MRSA genotypes most often found in humans. In a 2009 study [13], no MRSA was detected in foods of animal origin from Switzerland. However, people in close contact with animals ran an increased risk of being MRSA carriers.

Colonisation with MRSA does not generally induce disease in healthy individuals. However, if resistant *S. aureus* is introduced into a hospital setting, it can cause wound infections which are difficult to treat. The EFSA therefore recommends that, in countries with a high prevalence of MRSA in livestock, persons at particular risk (e.g. veterinarians, pig farmers, veal producers) should be tested for MRSA before entering hospitals and decolonised if found positive [13].

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10

Resistance in diagnostic submissions from animals

10 Resistance in diagnostic submissions from animals

In Switzerland, monitoring of antimicrobial resistance exists neither for relevant pathogens from diseased livestock nor for companion animals. As these data may also be important for the assessment of future trends in antimicrobial resistance, international organizations focused on these topics recently [1]. This is also seen with the establishment of a European Veterinarian Committee on Antimicrobial Susceptibility Testing (VetCAST) in 2015. As Swiss national reference laboratory for antibacterial resistance, ZOBA provided for the first time data of staphylococci of dogs, cats and horses within this report. The relative low number of isolates is due to the fact that only data from the diagnostic unit of the ZOBA were implemented. In the future, additional data from other Swiss veterinary diagnostic laboratories will also be included and other relevant bacterial species, i. e. *Acinetobacter* spp., Enterobacteriacae and Streptococci will also be reported.

10.1 *Staphylococcus* spp.

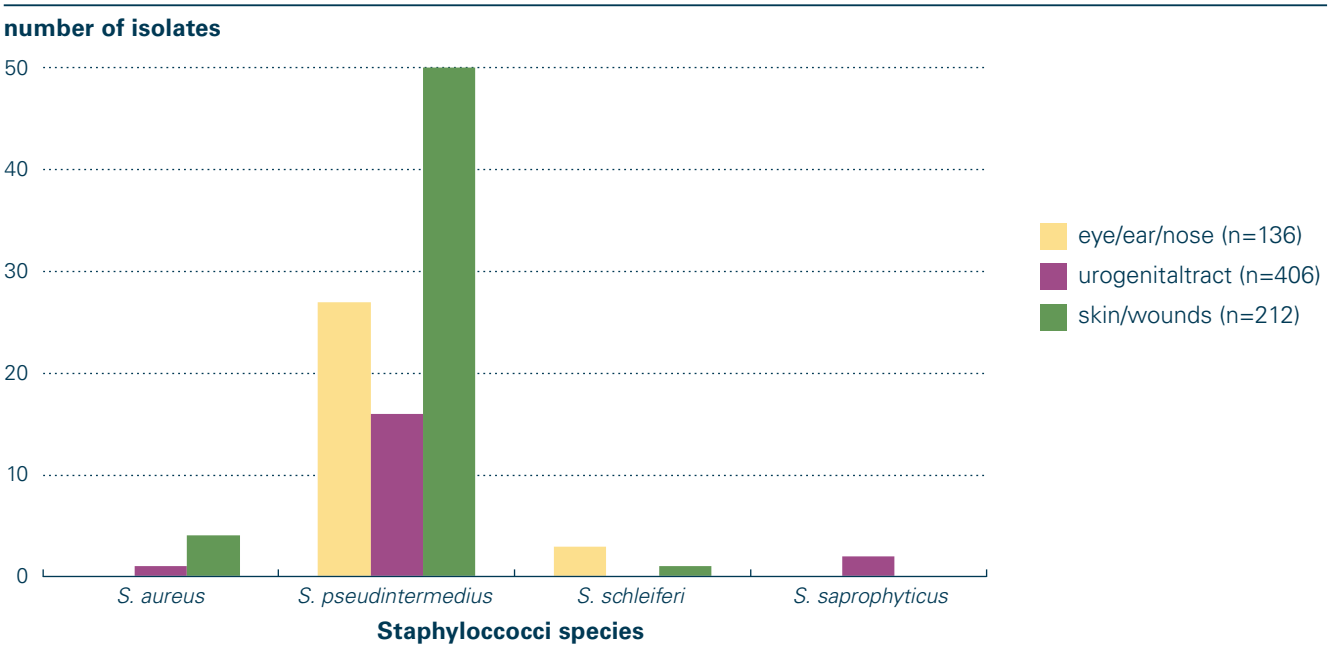
The different *Staphylococcus* species were mainly specifically associated to their hosts as shown for the isolates from 2013 from dogs, cats and horses (Figures 10. a–c).

10.1.1 *Staphylococcus* spp. in dogs

In dogs *Staphylococcus pseudintermedius* was the most relevant staphylococcal species, highly prevalent in affected skin and wounds (24%) (Figure 10. a). In about 20% of clinical cases *S. pseudintermedius* could be isolated from eyes/ears and noses, whereas this species was found only in 4% of urogenital tract complications. *S. pseudintermedius* is a coagulase-positive animal-associated staphylococci, mainly detected in dogs, but can also cause occasionally infections in other animals. Humans with close contact to animals have a higher chance to get colonized with *S. pseudintermedius* [2].

Like other staphylococci, *S. pseudintermedius* is an opportunistic pathogen. First described in 2005 as a novel species, *S. pseudintermedius* gained more in focus of both, human and veterinary medicine, in recent years, because of the emerge of Methicillin-resistant *S. pseudintermedius* (MRSP) [3]. This is not only a therapeutic challenge for the veterinarians treating the infected animals, but also a risk for pet owners to become colonized with MRS*P.* The first case in Switzerland of a human infection associated with a methicillin-resistant *S.* pseudintemedius was described in 2010 [Textbox 10. a].

Figure 10. a: Number of *Staphylococcus* spp. isolates from clinical submissions of dogs 2013. (n= total number of submissions)



Other *Staphylococcus* species, like *S. aureus, S. schleiferi* and *S. saprophyticus* were rarely isolated from clinical cases of dogs (Figure 10. a). While *S. schleiferi* is known as animal-associated staphylococci, *S. saprophyticus* is known as a human-associated staphylococci, but sporadic cases of detection in animals occur.

Antibacterial resistance data from *S. pseudintermedius* isolates from 2013 are presented in Table 10. a. *S. pseudintermedius* isolates have high percentage of resistance to penicillin (81%). Methicillin-resistant *S. pseudintermedius* (MRSP) were detected in 20% of the isolates (n=16). At the beginning of the 21st century, MRSP started to emerge, since then MRSP were detected more frequently worldwide. MRSP is regarded as a nosocomial bacterium in veterinary clinics, comparable to methicillin-resistant *S. aureus* (MRSA) in human settings. The high detection rate of MRSP in our diagnostics is likely due to the disproportionately high rate of submissions from the clinics for small animals at the Vetsuisse Faculty of Bern. Because of the zoonotic potential of MRSP, it is important to include these pathogens in a Swiss monitoring system in the future.

Table 10. a: Susceptibility rates of *Staphylococcus pseudintermedius* isolates in dogs 2013.

Stapylococcus *pseudintermedius*							**2013**
Antimicrobials	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Penicillin	79	15	19%	0	0%	64	81%
Kanamycin	79	48	60%	1	1%	30	39%
Gentamicin	79	69	87%	0	0%	10	13%
Trimethoprim-sulfamethoxazole	79	66	84%	0	0%	13	16%
Tetracycline	79	47	59%	0	0%	32	41%
Erythromycin	79	54	68%	0	0%	25	32%
Clindamycin	79	56	71%	0	0%	23	29%
Vancomycin	79	78	100%	0	0%	0	0%
Mupirocin	79	77	97%	2	3%	0	0%
Fusidic acid	79	77	97%	0	0%	2	3%
Chloramphenicol	79	63	80%	0	0%	16	20%
Enrofloxcacin	79	71	90%	1	1%	7	9%
Marbofloxacin	79	71	90%	1	1%	7	9%
Nitrofurantoin	79	78	99%	0	0%	1	1%
Rifampicin	79	76	96%	0	0%	3	4%

(n: number of isolates, S(n) and S(%): number and percentage of sensitive isolates, I(n) and I(%): number and percentage of intermediate isolates, R(n) and R(%): number and percentage of resistant isolates)

Textbox 10. a

Human infection associated with methicillin-resistant *Staphylococcus pseudintermedius* ST71

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An adult patient developed a post-surgery infection caused by a methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) which belonged to the clonal lineage ST71-spa t02 and contained the SCCmec element II-III. Isolates belonging to this clonal lineage have been disseminating in dogs and cats in Europe over the last years and display resistance to many classes of antimicrobial agents. We report the first case of a human infection associated with this predominant MRSP clone ST71 emphasizing its zoonotic potential and therapeutic challenge.

Reference

Stegmann et al. (2010). Human infection associated with methicillin-resistant *Staphylococcus pseudintermedius* ST71. J. Antimicrob. Chemother. 65:2047–2048.

Resistance percentage to aminoglycosides is high for kanamycin (39%) and moderate for gentamicin (13%). Also resistance to trimethoprim-sulfamethoxazole is moderate (16%). High resistance percentage was also found for tetracycline (41%), erythromycin (32%) and clindamycin (29%), demonstrating the potential therapeutic difficulties in treatment of *S. pseudintermedius* infections in dogs. Chloramphenicol resistance occurred moderately (20%). Low levels of resistance to fluoroquinolones were found (Enrofloxacin, Marbofloxacin, 9% each). No resistance to vancomycin and mupirocin was detected, but two strains were intermediate against the latter. Resistance to rifampicin was found in three isolates (4%), all of them were MRS*P.* Resistance to rifampicin occur very rarely within MRSP up to now, but attention had to be paid to possible emergence of rifampicin resistance in *S. pseudintermedius*, since resistance can develop rapidly during monotherapy. Two isolates were resistant to fusidic acid (3%) and one isolate was resistant to nitrofurantoin (1%).

About 14% of the *S. pseudintermedius* isolates were fully sensitive to all tested antimicrobials. 35% showed resistance to just one antimicrobial, preferable to penicillin. About 23% of the isolates showed resistance to two or three antibacterials. 19% of *S. pseudintermedius* isolates exhibit resistance to more than four and up to nine antibacterrials. Striking is the fact, that 7 isolates (9%) showed antibacterial resistance to nearly all of veterinary therapeutic relevant antibacterials, with nitrofurantion and/or fusidic acid as the only options left. This clearly underlines the necessity for prudent use of antimicrobials and the need of monitoring such data to be aware of the trends in future.

10.1.2 *Staphylococcus* spp. in cats

For cats the situation is quite different from that of the dogs. Although the overall number of samples in general is lower than from dogs, staphylococci species are more rarely isolated from cats than from dogs (Figure 10. b). *S. felis* from skin and wounds and eyes/ears/noses, respectively, was the most prevalent species (6.5%, 1.6%). Only two *S. aureus* and two *S. pseudintermedius* were isolated from feline clinical materials. Antibacterial resistance data are not presented because of the low number of isolates.

10.1.3 *Staphylococcus* spp. in horses

In horses, staphylococci play an important role as pathogen. Particularly *S. aureus* was found in 16% of cases from skin lesions and wound infections (Figure 10. c). In contrast to dogs and cats, no *S. pseudintermedius* was isolated. Other species like *S. epidermidis, S. sciuri* and *S. equorum* were detected only occasionally. Antibacterial resistance data are reported only for the *S. aureus* isolates (Table 10. b).

S. aureus isolates exhibited a high percentage of resistance to penicillin (96%). Methicillin-resistant *S. aureus* (MRSA) were detected in 70% of the isolates (n=16). This worrisome high detection rate of MRSA has to be interpreted carefully. On one hand, the total number of isolates is very small, therefore calculated percentages spread in a wide range and the origin of the samples is limited to a few clinics. A study from Schnellmann et al. (2006) [4] elucidated the rapid change of antimicrobial resistance pattern of staphylococci

Figure 10. b: Number of *Staphylococcus* spp. isolates from clinical submissions of cats 2013. (n= total number of submissions)

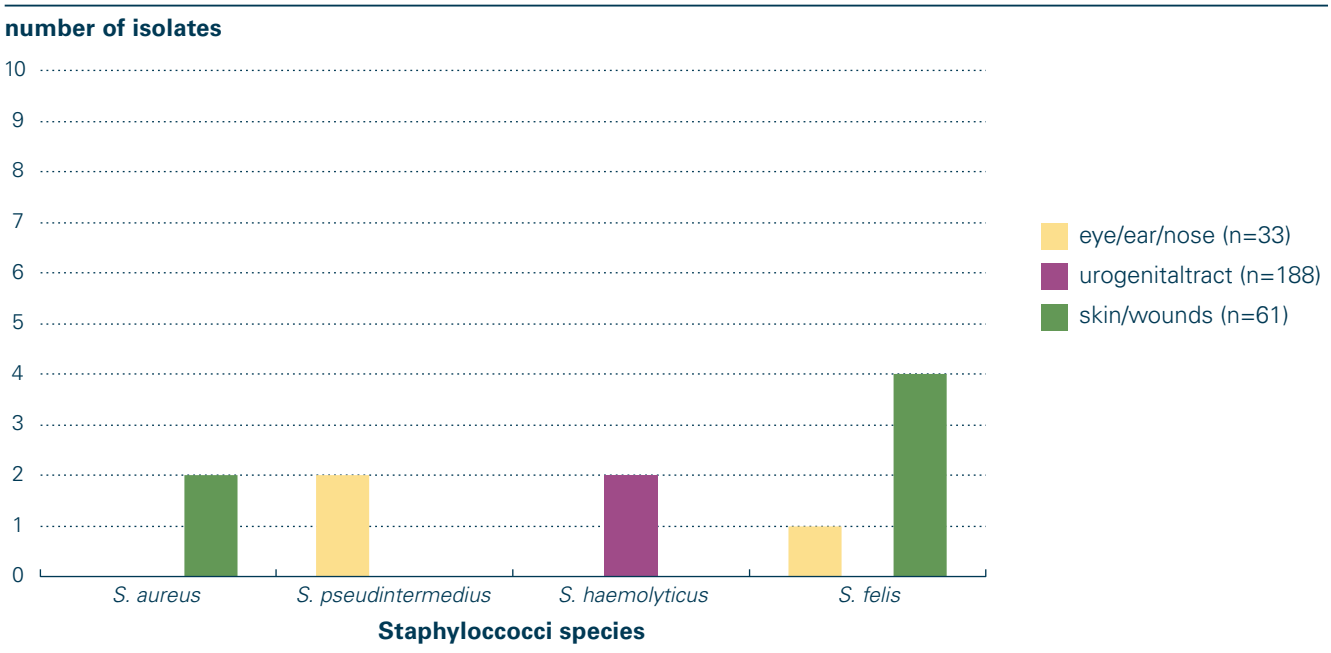

Figure 10. c: Number of *Staphylococcus* spp. isolates from linical submissions of horses 2013. (n= total number of submissions

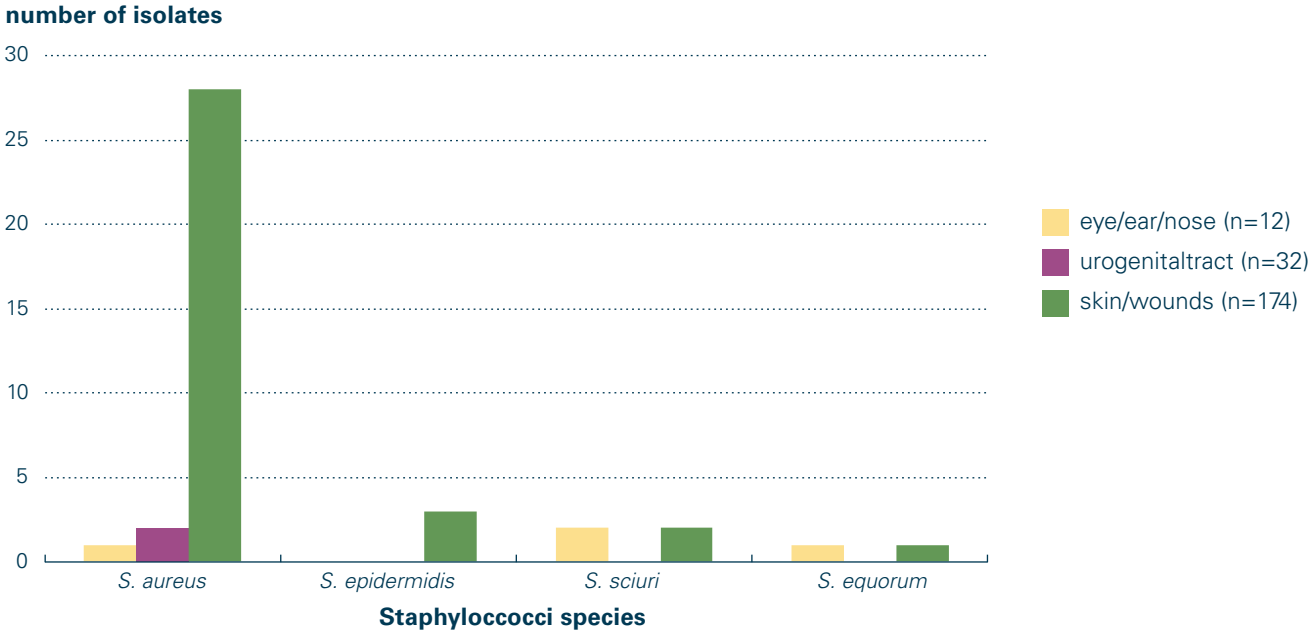

Table 10. b: Susceptibility rates of *Staphylococcus aureus* isolates in horses 2013.

Staphylococcus aureus							**2013**
Antimicrobials	**n**	**S (n)**	**S (%)**	**I (n)**	**I (%)**	**R (n)**	**R (%)**
Penicillin	23	1	4%	0	0%	22	96%
Kanamycin	23	5	22%	0	0%	18	78%
Gentamicin	23	5	22%	0	0%	18	78%
Trimethoprim-sulfamethoxazole	23	6	26%	0	0%	17	74%
Tetracycline	23	5	22%	0	0%	18	78%
Erythromycin	23	22	96%	0	0%	1	4%
Clindamycin	23	22	96%	0	0%	1	4%
Vancomycin	23	23	100%	0	0%	0	0%
Mupirocin	23	23	100%	0	0%	0	0%
Fusidic acid	23	23	100%	0	0%	0	0%
Enrofloxcacin	23	17	78%	1	0%	5	22%
Marbofloxacin	23	17	78%	0	0%	5	22%
Nitrofurantoin	23	22	96%	0	0%	1	4%
Rifampicin	23	23	100%	0	0%	0	0%

(n: number of isolates, S(n) and S(%): number and percentage of sensitive isolates, I(n) and I(%): number and percentage of intermediate isolates, R(n) and R(%): number and percentage of resistant isolates)

isolates from horses undergoing surgery at the clinic. They demonstrated that horses entering the hospital harbor staphylococci containing antibiotic resistance genes, including new variants of mecA and mph(C) genes. Shortly after hospitalization, horses acquire a specific multidrug-resistant skin flora that is presumably selected for and maintained in the hospital by the use of penicillin.

Resistance percentage to aminoglycosides is extremely high for kanamycin (78%) and gentamicin (78%). Also resistance to trimethoprim-sulfamethoxazole and tetracycline is extremely high (74%, 78% respectively). In contrast, low resistance level was found for erythromycin (4%) and clindamycin (4%). Striking are also the high levels of resistance to fluoroquinolones (Enrofloxacin, Marbofloxacin, 22% each). One isolate was resistant to nitrofurantoin (4%). No resistance to vancomycin, mupirocin and rifampicin was detected. Antibacterial resistance pattern of *S. aureus* isolates demonstrated clearly that the use of antibiotics should be limited as far as possible to maintain therapeutic options for the treatment of infections in the future.
None of the *S. aureus* isolates from horses were fully sensitive to all tested antimicrobials. Only 4 strains (17%) showed resistance to just one antimicrobial, not surprisingly to peni-

cillin. All isolated MRSA (70%) exhibited resistance up to eight or more antimicrobials. Three isolates (13%) showed microbiological resistance to nearly all of veterinary therapeutic relevant antibacterials, with nitrofurantion and/or fusidic acid as the only options left, a situation, where treatment with animal approved antibacterial being at the limit.

10.1.4 Perspectives

The presence of extremely high resistance levels to important antibacterials in companion animals highlighted the need for a systematic monitoring of antibacterials resistance in the future. Infections in animals caused by multidrug-resistant staphylococci could be increasingly expected for both *S. pseudintermedius* and *S. aureus*. The presence of multidrug-resistant staphylococci in veterinary medicine does not only constitute a challenge for treatment of the diseased animals, but also represents a risk for humans, because of their zoonotic potential.

In this report, antibacterials resistance data has been presented for a small set of clinical submissions from companion animals. In the future, the number of data should be increased adding isolates from other laboratories to get a more representative overview of the situation in Switzerland. Furthermore, additional bacterial species including other relevant gram-positive and gram-negative pathogens should be reported. Moreover, animal species under observation had to enlarge to livestock, e. g. pigs and calves as well, because these animals receive relevant amounts of antibacterials for prophylactic and/or metaphylactic reasons. This will be the task of the future.

For comparative analysis of the data, the quality and the methodology of the antibacterial resistance from different laboratories have to be harmonized. In this regards, ZOBA as national reference laboratory for antibacterial resistance, started to organize ring trials for harmonization and standardization of antibacterial resistance data from veterinarian diagnostic laboratories in Switzerland.

Our results demonstrated that a significant and sensitive monitoring of antibacterial resistance of bacteria causing diseases in livestock and companion animals is urgently needed. These data will provide an important insight into the occurrence, spread and dynamics of critical antibacterial resistance in animal pathogens in Switzerland.

References

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[3] Clonal spread of methicillin-resistant *Staphylococcus pseudintermedius* in Europe and North America: an international multicentre study (2010). Kristina Kadlec, Stefan Schwarz, Ulrika Grönlund Andersson, Maria Finn, Christina Greko, Arshnee Moodley, Stephen A. Kania, Linda A. Frank, David A. Bemis, Alessia Franco, Manuela Iurescia, Antonio Battisti, Birgitta Duim, Jaap A. Wagenaar, Engeline van Duijkeren, J. Scott Weese, J. Ross Fitzgerald, Alexandra Rossano and Luca Guardabassi, J Antimicrob Chemother. 2010 Jun;65(6):1145–54.

[4] Presence of New mecA and mph(C) Variants Conferring Antibiotic Resistance in *Staphylococcus* spp. Isolated from the Skin of Horses before and after Clinic Admission (2006). Christina Schnellmann, Vinzenz Gerber, Alexandra Rossano, Valentine Jaquier, Yann Panchaud, Marcus G. Doherr, Andreas Thomann, Reto Straub, and Vincent Perreten, J Clin Microbiol. 2006 Dec; 44(12): 4444–4454.

11

Materials and methods

11 Materials and methods

11.1 Data on Antibacterial consumption in human medicine

11.1.1 The Anatomical Therapeutic Chemical (ATC) classification system and defined daily doses (DDD)

Data are collected on antibacterials for systemic consumption (group J01 of the ATC classification). The data of antibiotics for treatment of tuberculosis (ATC group J04AB) and agents against amoebiasis and other protozoal diseases (ATC group P01AB) are not shown in this report. [1]. Antibiotic consumption (in grams or millions of International Units) was converted into defined daily doses (DDD) using the 2014 release of the DDD by the World Health Organization Collaborative Centre for Drug Statistics Methodology (see Annex I).

11.1.2 Data sources in the in- and outpatient settings

For the inpatient setting, a voluntary network of acute care hospitals participating in the surveillance system anresis.ch was set up in 2004. Data were collected from the entire hospitals, and separately from the adult intensive care units (ICUs) when possible. 43 hospitals participated in 2004 and 57 in 2013, of which 36 were small-size hospitals (< 200 beds), 14 medium-size (200–500 beds), and 7 large-size (> 500 beds, which includes the five Swiss university hospitals) (Annex IV, Table IV.1). Initially, the hospital network represented 54% of the total number of acute somatic care hospitals (excluding psychiatric and rehabilitation centers) and 47% of all beds in this category in Switzerland (33% of all beds). Twenty-three hospitals (10 small-, 14 medium- and 5 large-size) also provided data on adult ICUs. Their number increased to 41 (20, 14, 7, respectively) in 2013, representing 56% of the hospitals equipped with ICU-beds in Switzerland. Data on hospital occupied bed-days and admissions were collected, enabling the expression of the consumption density as DDD per 100 occupied bed-days and as DDD per 100 admissions. Of note, the definition of bed-days given by the Swiss Federal Statistical Office (SFSO) included the day of discharge or transfer in the counting days until 2012 and excludes it since then. This means that there is a bias towards a slightly lower number of bed-days in comparison with the previous years and therefore, for a same number of DDD, towards a slightly higher number of DDD/100 bed-days.

Data on sales of antibiotics in the outpatient setting were provided by PharmaSuisse, the Swiss Society of Pharmacists. The updating of the database is entrusted to the professional cooperative of the Swiss pharmacists (OFAC, Genève) that collects the prescriptions orders at individual level from the public pharmacies and produces invoices for health insurance companies on behalf of pharmacies. The coverage is about 65% of all pharmacies in Switzerland. All antibiotics are dispensed with a prescription. The data include the quantities of antibiotics sold to a number of individuals per age group (< 2; 2–11; 12–17; 18–64; > 65 years). Prescriptions from the self-dispensing physicians are not included in the database. The measurement units for reporting antibiotic consumption are DDD per 1000 inhabitants per day, packages per 1000 inhabitants per day, DDD per treated patient and packages per treated patient [1,2]. In this report the sales data of 2013 and 2012 are shown, predate data are not available.

References

[1] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2015. Oslo, 2014.

[2] Bruyndonckx R et al. Measuring trends of outpatient antibiotic use in Europe: jointly modeling longitudinal data in defined daily doses and packages. J Antimicrob Chemother. 2014: 69(7): 1981–6.

11.2 Data on antibacterial sales in veterinary medicine

The list of veterinary products which were granted marketing authorisation in the year under review in this report (2013) was extracted semi-automatically from the internal Swissmedic database on the basis of their ATCvet codes [1] and completed by the products which were withdrawn from the market in the period under review. Marketing authorisation holders were then asked to report sales figures for their products. This excluded products which are authorised only for export, as they cannot be used in Switzerland and so do not contribute to the development of resistance in Switzerland.

The figures obtained were entered for assessment in a Microsoft Access database developed for this purpose. The entry for each product contains a unique identification, the brand name, the ATCvet code, information on the permitted method of application and the target animal group. Pharmaceutical premixtures are indicated separately. The record shows the number of "basic units" sold, such as tablets, vials (with volume), injectors, tubes or pouches/bags (with weight).
The volume of active substance contained in each product and each basic unit is recorded. In the case of antibiotics declared in International Units, conversion factors according to the European Medecines Agency (EMA) [2] or Kroker [3] were used. The methods of application were selected to reflect those referred to in similar reports in other countries (France, AFSSA and United Kingdom, VMD): oral, parenteral, intramammary and topical/external.
As target animal groups are recorded on the basis of marketing authorisations, the only distinction that can be drawn is between "farm animals", "pets" and "mixed group" since there is no specific records of the target animals to which the product is actually administered. Specific animal species or age groups were only recorded if these were clearly mentioned in the marketing authorisation (e.g. intramammary injectors for cows or products to treat piglets).
Total volumes were then calculated by repeatedly multiplying the volume of active substance in each basic unit by the number of basic units sold. Combinable filters (year, ATCvet code, administration route) were used for specific queries.

References

[1] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATCvet classification 2014. Oslo, 2013 http://www.whocc.no/atcvet

[2] European Medicines Agency. Trends in the sales of veterinary antimicrobial agents in nine European countries (2005-2009). EMA/238630/2011; pp. 76

[3] Pharmakotherapie bei Haus und Nutztieren (W Löscher, FR Ungemach & R Kroker, eds) Parey, Berlin (D), 7. Edition, 2006.

11.3 Bacterial isolates from humans (clinical probes)

Currently 20 microbiology laboratories are linked to anresis.ch (Annex IV, Table IV.2). These laboratories send all results from routine testing of all clinical bacteriology cultures on a regular basis (weekly or monthly) to the anresis.ch – database. In contrast to most other surveillance systems all antimicrobial resistance results are sent, not restricting the dataset either to invasive isolates, or to a predefined set of microorganisms only (please note that nevertheless most analysis in chapter 7 are restricted to invasive isolates, due to better comparability with international data). Screening results are labelled specially and do not influence results of this report. Antibiotic resistance test results done as reference laboratory are labelled specially. It is possible to provide epidemiological information like sample location, provider of the sample, patient sex and age. In contrast clinical data as diagnosis, therapy or outcome are not available in anresis.ch. Although we prefer quantitative antibiotic resistance testing results, unfortunately the majority of microbiological laboratories only send qualitative, interpreted resistance data (SIR). Resistance data are not validated by anresis.ch but only by the laboratory sending the data. All laboratories participating in anresis.ch are approved and participating in at least one external quality control program.

11.4 Bacterial isolates from animals (for monitoring: clinical and not clinical probes)

11.4.1 Sampling of healthy animals in the slaughterhouse

Samples were taken from 1 January 2013 to 31 December 2013 (Table 11. a). Sampling was spread throughout the year on the basis of a sampling plan established for meat inspections. Samples were taken at the five largest poultry slaughterhouses, the nine largest pig slaughterhouses and the eight largest calf slaughterhouses in order to ensure that over 80% of the animals slaughtered belonging to the species in question could form part of the sample.
Samples were taken from 448 broiler herds. Cloacal swab sample were taken from 5 chickens selected at random from each herd. These were then sent to the laboratory (ZOBA) and shaken in 1 ml of trypton soya broth to produce a pooled sample per herd.
Faecal swab samples were taken rectally and/or nasal swab samples were taken from deep within the nose. In the case of calves and fattening pigs, the intention was to take samples from one animal selected at random per farm, and to avoid taking two samples a year from any particular farm. All samples were taken on Monday or Tuesday for logistical reasons. The results discussed in this report are illustrating the data from 2006 to 2013, sampling procedures in the previous years were done in a similar way.

11.4.2 Samples clinical isolates animals

For *Salmonella* isolates no special monitoring at slaughter was feasible, because of the very low prevalence of *Salmonella* spp. in Swiss livestock. Therefore *Salmonella* isolates which were sent to ZOBA in 2013 in connection with its reference function or which were isolated during the course of its own diagnostic activities were also included in the assessment (Table 11. a). Most of these were isolates from clinical material from various animal species, but there were also a small number of isolates derived from samples isolated as part of *Salmonella* monitoring in accordance with articles 257 and 258 of the Epizootic Diseases Ordinance of

27 June 1995 (EzDO; SR 916.401). The results discussed in this report are illustrating the data from 2006 to 2013, sampling procedures in the previous years were done in a similar way.
All staphylococci strains were isolated from clinical submissions of canine, feline and equine origin, which were sent from veterinarian practitioners and clinics to the diagnostic unit of the ZOBA in 2013.

11.5 Susceptibility testing, breakpoints, processing antibiotic resistance data from human isolates

There are no mandatory Swiss guidelines for antibiotic resistance testing. Most laboratories initially based on CLSI guidelines and changed to EUCAST guidelines between 2011 and 2013. In general use of automated systems increased over years. The Swiss Society of Microbiology encourages the use of EUCAST breakpoints and provides recommendations on their website (http://www.swissmicrobiology.ch). Nevertheless individual laboratories are free to use other guidelines than EUCAST.
Therefore identification methods used, may differ between the different laboratories. In most laboratories validated automated systems – generally based on CLSI guidelines – were introduced during the last couple of years. There is no formal validation of species identification by anresis.ch and no systematic collection of multiresistant isolates.
The antibiotic resistance data presented in this report were extracted from the database using the analysis tool SAGENT, which is provided to all participating laboratories. For data selection we used the identical methodology like the antibiotic surveillance systems of the ECDC (EARS) and of the WHO-Europe (CASEAR), restricting the isolates analyzed to invasive isolates from blood cultures or cerebrospinal fluid. Isolates from foreign countries were excluded. Doubles were defined as identical microorganism from the same patient during the same calendar year and were, therefore, excluded (only first isolate per calendar year analyzed). As patient identifiers are specific for individual laboratories only, it was not possible, to exclude doubles, if isolates from the same patient originated from different laboratories. For *Salmonella* spp. and *Campylobacter* spp. we analyzed isolates from all materials (e.g. stool), doubles were excluded as described above.

For this analysis we used the interpreted, qualitative data (SIR) as delivered form the participating laboratories. An isolate was considered resistant (R) to an antimicrobial agent, when tested and interpreted as resistant in accordance with the breakpoint used by the local laboratory. Quantitative resistance data are not provided in most cases and are not used in this analysis (except for *S. pneumoniae).* An isolate was considered non-susceptible to an antimicrobial agent, when tested and found resistant or intermediate susceptible to this antibiotic. An isolate was considered resistant/intermediate to an antibiotic group, if it was tested resistant/intermediate to at least one antibiotic of this group.

Changing breakpoints over time may influence resistance data. This especially comes true for *S. pneumoniae,* where in addition to changing breakpoints over time different breakpoints are used for different kind of infections. Therefore we decided, to use the dataset from the Swiss National Reference Center for invasive Pneumococci, which collects all invasive *S. pneumoniae* isolates, and – besides serotyp-

Table 11. a: Antimicrobial resistance monitoring programme 2013.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cloacal swab – broilers	448	*Campylobacter* spp.	168
Cloacal swab – broilers	201	*E. coli*	189
Cloacal swab – broilers	249	Enterococci	213
Cloacal swab – broilers	170	ESBL	47
Faecal swab – fattening pigs	348	*Campylobacter* spp.	266
Faecal swab – fattening pigs	200	*E. coli*	183
Faecal swab – fattening pigs	171	ESBL	16
Nasal swab – fattening pigs	351	MRSA	73
Faecal swab – veal calves	253	Enterococci	176
Faecal swab – veal calves	208	*E. coli*	176
Faecal swab – veal calves	181	ESBL	30
Nasal swab – veal calves	253	ESBL	10
Clinical material/all species	–	*Salmonella* spp.	85
Clinical material/all species	–	*S.* Typhimurium	48
Clinical material/all species		Monophasic *S.* Typhimurium	17
Clinical material/all species	–	*S.* Enteritidis	6

ing – repeats antibiotic resistance testing on a standardized manner. This means that all isolates are tested for erythromycin, levofloxacin, cotrimoxazole, and oxacillin. Additional e-tests for penicillin G and ceftriaxone are performed for all oxacillin non-susceptible strains.

11.6 Susceptibility testing, cut-off, processing antibiotic resistance data from animal isolates

The pig, calf and broiler samples were tested for *Campylobacter* spp., *Salmonella* spp., *E. coli* and *Enterococcus* spp. at the national reference laboratory for antibiotic resistance (ZOBA, University of Bern) using internationally standardised microbiological methods. *Campylobacter* spp., *E. coli* and enterococci from faecal swabs were isolated by direct detection on selective culture media. Therefore, modified charcoal cefoperazone deoxychelate agar (mCCDA), Mac Conkey agar and Slanetz-Bartley agar, respectively, were used. Identification of suspicious colonies was carried out by the direct transfer method using matrix-assisted laser desorption/ionisation time-of-flight mass spectroscopy (MALDI TOF MS) (Biotyper 3.0, Bruker Daltonics, Bremen, Germany) following manufactures recommendations.
MRSA detection was performed by transferring the nasal swab samples consecutively in two different enrichment broth, following cultivating on chromogenic MRSA-selective agar (method according to the European reference laboratory of the EU, RL for Antimicrobial Resistance, The National Food Institute, Lyngby, Denmark). Confirmation as *S. aureus* was carried out by MALDI TOF M*S.* The methicillin resistance gene mecA and determination of the clonal complex (CC) CC398 was carried out by means of multiplex real-time PCR as previously published [1]. Spa type was determined as previously described and analysed using the Ridom StaphType software (Ridom StaphType, Ridom GmbH, Würzburg, Germany) [2].
Detection of ESBL/AmpC-forming intestinal bacteria was carried out by incubating the pooled cloacal swab samples and faecal swab samples in a selective enrichment medium MacConkey broth, supplemented with 4 mg/l ceftazidime (Oxoid, Ltd, Basingstoke, England) and then cultivating them on a selective agar (chromID ESBL, bioMérieux Inc. Mary l'Etoile, France; modified method described by Endimiani [3]). The suspicious colonies were identified by MALDI TOF MS as *E. coli.* Confirmation of the isolated *E. coli* by beta-lactamase type was carried out phenotypically by MIC determination on an ESB1F plate (Trek Diagnostics Systems, East Grinstead, England).

Clinical submissions from dogs, cats and horses were cultured according to standard bacterial culture methods. All staphyloccoci isolates which were derived from ear/eye/nose swabs, urine and skin/wound specimens were included in the analysis. Identification to the species level was done by MALDI TOF MS or using the VITEK Compact system wih Vitek GD ID card (bioMérieux Inc. Mary l'Etoile, France).

The minimal inhibitory concentration (MIC) of the antibiotics was determined by both microdilution in cation-adjusted Müller-Hinton with (for *Campylobacter*) or without lysed horse blood using Sensititre susceptibility plates (Trek Diagnostics S.ystems, East Grinstead, England) according to CLSI guidelines. The MIC was defined as the lowest antibiotic concentration at which no visible bacterial growth occurred (Table 11. b).
Clinical staphyloccoci isolates were tested for susceptibility using the Vitek Compact 2 system with Vitek AST GP69 cards (bioMérieux, Inc. Mary l'Etoile, France). The isolates were subcultured onto tryptic soy 5% sheep blood agar plates (BBL Trypticase soy agar [TSA] II; BD Diagnostic Systems) in ambient air at 37°C before testing. Isolates were classified as susceptible or resistant according to clinical breakpoints issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines Version 3.0 (www.eucast.org) or, if not available, the Clinical and Laboratory Standards Institute document M31-A3 (CLSI). Methicillin-resistance was screened by cefoxitin and confirmed by slide latex agglutination test for the detection of Penicillin Binding Protein (PBP) 2a (Oxoid, Pratteln, Switzerland).

Resistance prevalence rates were described using the following terminology:

Minimal:	<0.1%		
Very low:	0.1%	to	1%
Low:	>1%	to	10%
Moderate:	>10%	to	20%
High:	>20%	to	50%
Very high:	>50%	to	70%
Extremely high:	>70%		

It is recommended that antibiotic resistance is monitored by assessment of MIC values based on epidemiological cut-off (ECOFF) values. Bacterial strains are regarded as microbiologically resistant if their MIC value is above the highest MIC value observed in the wild-type population of the bacteria (WT). The epidemiological cut-off distinguishes wild-types from non-wild-types and is set and published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). It is sometimes different from the clinical breakpoint, which relates primarily to the extent to which the pathogen may respond to treatment and so takes account of aspects of pharmacodynamics and pharmacokinetics as well as specific features of the host and the target organ.
Wherever possible, the EUCAST ECOFF-values were used to interpret the MIC results.

Table 11. b: Epidemiological cut-off values used to interpret MIC results.

		Campylobacter spp.	*E. coli* / *Salmonella* spp.	*Enterococcus* spp.	MRSA
Substance class	**Antimicrobials**	**ECOFF (µg / ml) WT <**	**ECOFF (µg / ml) WT <**	**ECOFF (µg / ml) WT <**	**ECOFF (µg / ml) WT <**
Penicillins	Ampicillin		8	4	
	Amoxicillin/Clavulanic acid			4	
	Penicillin				0.125
	Piperacillin/Tazobactam		8		
Cephalosporins	Cefotaxime		0.25c/0.5d		
	Cefotaxime/Clavulanic acid		**		
	Ceftazidime		0.5c/2d		
	Ceftazidime/Clavulanic acid		**		
	Cefazolin		8l		
	Cefepime		4ck		
	Cefoxitin		8c		4
	Cefpodoxime		2 c		
	Ceftriaxon		1l		
	Cephalotin		8l		
Carbapenems	Imipenem		0.5c		
	Meropenem		8ck		
Amphenicols	Chloramphenicol	16	16	32	16g
	Florfenicol		16	8	
Tetracyclines	Tetracycline	1a/2b	8	4	1
(Fluoro)quinolone	Ciprofloxacin	0.5	0.064	4	1g
	Nalidixic acid	16	16		
Sulfonamids	Sulfamethoxazole		64c/256dk		128g
Lincosamides	Clindamycin				0.25
Aminoglycosides	Gentamicin	2	2	512 k	2
	Kanamycin		8c/8k d		8g
	Neomycin			16 k	
	Streptomycin	4b	16	512 e/128 f	16g
Polymyxins	Colistin		2		
Macrolides	Erythromycin	4 a/8 b		4	1
Polipeptides	Bacitracin			32	
Glycopeptides	Vancomycin			4	2
Ionophors	Salinomycin			8k	
Nitrofuran	Nitrofurantoin			32 e/256 f	
Diaminopyrimidins	Trimethoprim		2		2
Oxazolidons	Linezolid			4	4g
Streptogramins	Quinupristin/Dalfopristin			1 f	1g
Ansamycins	Rifampin				0.032
Pleuromutilins	Tiamulin				2g
Monocarbolic acid	Mupirocin				1
Fusidans	Fusidic acid				0.5

a *C. jejuni,* b *C. coli*, c *E. coli*, d *Salmonella* spp., e *E. faecalis*, f *E. faecium;* g ECOFF for *Staph. aureus,* k EUCAST-clinical breakpoint (ECOFF not defined or outside test-range); CLSI-clinical breakpoint (EUCAST clinical breakpoint not defined or outside test-range);
** Interpretation according CLSI-standards (M100-S22, vol. 32 no. 3, Clinical and Laboratory Standard Institute, Wayne, PA.).

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Annex I

Defined daily dose (DDD) of antibiotics for patient treatment

Annex I: Defined daily dose (DDD) of antibiotics for patient treatment

Table I.1: List of defined daily dose (DDD) according to WHO for each antibiotic and administration route from antibacterials for systemic use (ATC group J01), antibiotics for treatment of tuberculosis (ATC group J04AB) and antibiotics against amoebiasis and other protozoal diseases(ATC group P01AB). Data from J04AB and P01AB are included in the total antibiotic consumption.

ATC Group	Antibiotic Name	Administration route	DDD [g]
J01A	Doxycycline	oral	0.1
	Doxycycline	parenteral	0.1
	Lymecycline	oral	0.6
	Minocycline	oral	0.2
	Tetracycline	oral	1
	Tetracycline	parenteral	1
	Tigecyclin	parenteral	0.1
J01C	Amoxicillin	oral	1
	Amoxicillin	parenteral	1
	Amoxicillin-clavulanic acid	oral	1
	Amoxicillin-clavulanic acid	parenteral	3
	Flucloxacillin	oral	2
	Flucloxacillin	parenteral	2
	Phenoxymethylpenicillin	oral	2
	Benzathine phenoxymethylpenicillin	oral	2
	Benzathine benzylpenicillin	parenteral	3.6
	Piperacillin	parenteral	14
	Piperacillin-tazobactam	parenteral	14
	Ticarcillin	parenteral	15
	Ticarcillin-clavulanic acid	parenteral	15
J01D	Aztreonam	parenteral	4
	Cefaclor	oral	1
	Cefamandole	parenteral	6
	Cefazolin	parenteral	3
	Cefepime	parenteral	2
	Cefixime	oral	0.4
	Cefotaxime	parenteral	4
	Cefoxitin	parenteral	6
	Cefpodoxime	oral	0.4
	Cefprozil	oral	1
	Cefprozil	parenteral	1
	Ceftaroline	parenteral	1.2
	Ceftazidime	parenteral	4
	Ceftibuten	oral	0.4
	Cefuroxime	oral	0.5
	Cefuroxime	parenteral	3
	Ertapenem	parenteral	1
	Imipenem	parenteral	2
	Meropenem	parenteral	2

ATC Group	Antibiotic Name	Administration route	DDD [g]
J01E	Sulfadiazine	oral	0.6
	Sulfadiazine	parenteral	0.6
	Trimethoprim	oral	0.4
	Trimethoprim-sulfamethoxazole	oral	1.92
	Trimethoprim-sulfamethoxazole	parenteral	1.92
J01F	Azithromycin	oral	0.3
	Clarithromycin	oral	0.5
	Clarithromycin	parenteral	1
	Clindamycin	oral	1.2
	Clindamycin	parenteral	1.8
	Erythromycin	oral	2
	Erythromycin	parenteral	1
	Roxithromycin	oral	0.3
	Spiramycin	oral	3
J01G	Amikacin	parenteral	1
	Gentamicin	oral	0.24
	Gentamicin	other	0.24
	Gentamicin	parenteral	0.24
	Neomycin	oral	5
	Netilmicin	oral	0.35
	Netilmicin	parenteral	0.35
	Streptomycin	parenteral	1
	Tobramycin	inhaled	0.3
	Tobramycin	parenteral	0.24
J01M	Ciprofloxacin	oral	1
	Ciprofloxacin	parenteral	0.5
	Levofloxacin	oral	0.5
	Levofloxacin	parenteral	0.5
	Moxifloxacin	oral	0.4
	Moxifloxacin	parenteral	0.4
	Norfloxacin	oral	0.8
	Ofloxacin	oral	0.4
	Ofloxacin	parenteral	0.4
J01X	Colistin	oral	3
	Colistin	inhaled	3
	Colistin	parenteral	3
	Daptomycin	parenteral	0.28
	Fosfomycin	oral	3
	Fosfomycin	parenteral	8
	Fusidic acid	oral	1.5
	Fusidic acid	parenteral	1.5

ATC Group	Antibiotic Name	Administration route	DDD [g]
J01X	Linezolid	oral	1.2
	Linezolid	parenteral	1.2
	Metronidazole	parenteral	1.5
	Nitrofurantoin	oral	0.2
	Ornidazole	parenteral	1
	Teicoplanin	parenteral	0.4
	Vancomycin	oral	2
	Vancomycin	parenteral	2
J04AB	Rifampicin	oral	0.6
	Rifampicin	parenteral	0.6
	Rifamycin	parenteral	0.6
	Rifabutin	oral	0.15
P01AB	Metronidazole	rectal	2
	Metronidazole	oral	2
	Ornidazole	oral	1.5

Annex II

Distribution of minimal inhibitory concentrations (MICs) in bacterial isolates from animals

Annex II: Distribution of minimal inhibitory concentrations (MICs) in bacterial isolates from animals

In all reported tables of Annex II (distribution of MICs in bacterial isolates from animals) vertical red lines denote cut-off values for resistance. The white areas indicate the dilution range tested for each antimicrobial agent. Values above this range indicate MIC values > the highest concentration in the range. Values at the lowest concentration tested indicate MIC-values ≤ the lowest concentration in the range. Vertical bars indicate the epidemiological cut-off values, used as breakpoints.

Table II.1: Distribution (n) of MICs (mg/L) in *Salmonella* Enteritidis from poultry, pigs and cattle.

Minimal Inhibitory Concentration (MIC) / poultry, pigs, cattle / *Salmonella* Enteritidis / Number of Isolates (N=6)																			
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048
Ampicillin								2	4										
Cefotaxime				3	3														
Ceftazidime						6													
Chloramphenicol											6								
Ciprofloxacin		4		2															
Colistin									6										
Florfenicol										6									
Gentamicin						3	3												
Kanamycin										6									
Nalidixic acid										6									
Streptomycin									2	3		1							
Sulfamethoxazole													2	4					
Tetracycline								3	3										
Trimethoprim							6												

Table II.2: Distribution (n) of MICs (mg/L) in *Salmonella* Typhimurium from poultry, pigs and cattle.

Minimal Inhibitory Concentration (MIC) / poultry, pigs, cattle / *Salmonella* Typhimurium / Number of Isolates (N=48)																			
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048
Ampicillin								31	14					3					
Cefotaxime				34	14														
Ceftazidime						46	2												
Chloramphenicol										7	38				3				
Ciprofloxacin		19		29															
Colistin									48										
Florfenicol									1	41	3		2	1					
Gentamicin						14	34												
Kanamycin										48									
Nalidixic acid										48									
Streptomycin										5	33	6	1	1	2				
Sulfamethoxazole											1	5	23	16					3
Tetracycline								1	43	1				1	2				
Trimethoprim							47	1											

Table II.3: Distribution (n) of MICs (mg/L) in monophasic *Salmonella* Typhimurium from pigs and cattle.

Minimal Inhibitory Concentration (MIC) / pigs, cattle / monophasic *Salmonella* Typhimurium / Number of Isolates (N=17)																			
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048
Ampicillin														17					
Cefotaxime				15	2														
Ceftazidime						17													
Chloramphenicol										1	16								
Ciprofloxacin		4	13																
Colistin									16	1									
Florfenicol										16	1								
Gentamicin						3	13	1											
Kanamycin										17									
Nalidixic acid										17									
Streptomycin																17			
Sulfamethoxazole																			17
Tetracycline															17				
Trimethoprim							16	1											

Table II.4: Distribution (n) of MICs (mg/L) in *Campylobacter jejuni* from broilers.

Minimal Inhibitory Concentration (MIC) / broilers / *Campylobacter jejuni* / Number of Isolates (N=157)														
	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Chloramphenicol								81	69	5	2			
Ciprofloxacin			48	39	2	3			2	63				
Erythromycin						89	48	17	1		1		1	
Gentamicin				123	32	1		1						
Nalidixic acid								28	58	5	1	3		62
Streptomycin							149	2		2	1	3		
Tetracycline					96	26	2	3			2	28		

Table II.5: Distribution (n) of MICs (mg/L) in *Campylobacter coli* from broilers.

Minimal Inhibitory Concentration (MIC) / broilers / *Campylobacter coli* / Number of Isolates (N=11)														
	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Chloramphenicol								1	7	2		1		
Ciprofloxacin			1	3	1					6				
Erythromycin						2	2	3	3		1			
Gentamicin				2	5	4								
Nalidixic acid									5				1	5
Streptomycin							5				2	4		
Tetracycline					3	4		1		1		2		

Table II.6: Distribution (n) of MICs (mg/L) in *Campylobacter coli* from pigs.

Minimal Inhibitory Concentration (MIC) / pigs / *Campylobacter coli* / Number of Isolates (N=226)														
	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Chloramphenicol								46	138	40	2			
Ciprofloxacin			82	52	4	2	1		18	67				
Erythromycin						63	59	62	12	2		1	27	
Gentamicin				73	110	39	2	1			1			
Nalidixic acid								14	97	26	2		12	75
Streptomycin							46	11	1	11	69	88		
Tetracycline					82	53	17	8	8		16	42		

Table II.7: Distribution (n) of MICs (mg/L) in *Enterococcus faecalis* from broilers.

Minimal Inhibitory Concentration (MIC) / broilers / *Enterococcus faecalis* / Number of Isolates (N=155)																	
	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	4096
Amoxicillin/Clavulanic acid 2:1						155											
Ampicillin						154	1										
Bacitracin								2	53	71	9			20			
Chloramphenicol							58	96			1						
Ciprofloxacin				45	107	2				1							
Erythromycin				34	78	13	4	3	1	22							
Florfenicol						92	63										
Gentamicin												154			1		
Linezolid					29	126											
Neomycin									1	35	106	8	5				
Nitrofurantoin										154	1						
Salinomycin					143	7	5										
Streptomycin												150					5
Tetracycline					95	1		1	1	3	54						
Vancomycin					61	86	8										

Table II.8: Distribution (n) of MICs (mg/L) in *Enterococcus faecium* from broilers.

Minimal Inhibitory Concentration (MIC) / broilers / *Enterococcus faecium* / Number of Isolates (N=58)																	
	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	4096
Amoxicillin/Clavulanic acid 2:1						53	5										
Ampicillin						46	9	3									
Bacitracin								3	8	7	10	3	2	25			
Chloramphenicol						4	8	44	1	1							
Ciprofloxacin				3	17	20	17	1									
Erythromycin				22	10	10		2	2	12							
Florfenicol						19	39										
Gentamicin												58					
Linezolid					3	50	5										
Neomycin								13	40	4			1				
Nitrofurantoin										31	23	4					
Quinupristin/Dalfopristin*				1	21	7	29										
Salinomycin					5	1	7	45									
Streptomycin												56					2
Tetracycline					40			1	3	1	13						
Vancomycin					51	6	1										

Table II.9: Distribution (n) of MICs (mg/L) in *Enterococcus faecalis* from veal calves.

Minimal Inhibitory Concentration (MIC) / veal calves / *Enterococcus faecalis* / Number of Isolates (N=108)																	
	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	4096
Amoxicillin/Clavulanic acid 2:1)						107	1										
Ampicillin						107	1										
Bacitracin								7	44	37	5			15			
Chloramphenicol							32	42	2	2	30						
Ciprofloxacin				33	68	7											
Erythromycin				19	28	11	4	1	4	41							
Florfenicol						62	46										
Gentamicin												92	1			4	11
Linezolid				1	36	71											
Neomycin								1	6	24	21	10	46				
Nitrofurantoin										101	6	1					
Salinomycin					106	2											
Streptomycin												54	2		8	18	26
Tetracycline					24				1	3	80						
Vancomycin					47	37	23	1									

Table II.10: Distribution (n) of MICs (mg/L) in *Enterococcus faecium* from veal calves.

Minimal Inhibitory Concentration (MIC) / veal calves / *Enterococcus faecium* / Number of Isolates (N=68)																	
	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	4096
Amoxicillin/Clavulanic acid 2:1)						66	2										
Ampicillin						66	2										
Bacitracin								6	1	18	38	5					
Chloramphenicol						1	7	60									
Ciprofloxacin				6	54	3	3	2									
Erythromycin				2	2	12	44	2		6							
Florfenicol						19	49										
Gentamicin												68					
Linezolid				1		65	2										
Neomycin								8	42	16	2						
Nitrofurantoin										6	37	24		1			
Quinupristin/Dalfopristin*				4	4	6	54										
Salinomycin					11	57											
Streptomycin												66					2
Tetracycline					61			1		1	5						
Vancomycin					67	1											

Table II.11: Distribution (n) of MICs (mg/L) in *Escherichia coli* from broilers.

Minimal Inhibitory Concentration (MIC) / broilers / *Escherichia coli* / Number of Isolates (N=189)																		
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024
Ampicillin							1	9	54	69	8			48				
Cefotaxime				173	14	1					1							
Ceftazidime						186	2				1							
Chloramphenicol									2	46	133	6	1		1			
Ciprofloxacin	16	95	7	4	8	40	9	4		1	1	4						
Colistin									189									
Florfenicol									6	85	95	3						
Gentamicin						10	105	70	3					1				
Kanamycin										177	7					5		
Nalidixic acid										117	1	6	1	9	55			
Streptomycin										64	83	13	10	7	8	4		
Sulfamethoxazole											45	43	43	7				
Tetracycline								19	109	16			5	13	27			
Trimethoprim							136	26		1				26				

Table II.12: Distribution (n) of MICs (mg/L) in *Escherichia coli* from pigs.

Minimal Inhibitory Concentration (MIC) / pigs / *Escherichia coli* / Number of Isolates (N=183)																		
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024
Ampicillin								6	56	83	5		1	32				
Cefotaxime				171	10						2							
Ceftazidime						176	5		1	1								
Chloramphenicol									7	40	117	7	4	2	6			
Ciprofloxacin	31	116	25	2	1	5					2	1						
Colistin									183									
Florfenicol									9	69	100	5						
Gentamicin						29	92	54	4	1			2	1				
Kanamycin										168	8			1		6		
Nalidixic acid										172	3			1	7			
Streptomycin									1	47	43	6	13	17	23	33		
Sulfamethoxazole											50	35	23	4	1	2		
Tetracycline								18	90	11	2	1	4	15	42			
Trimethoprim							136	8	3			2		34				

Table II.13: Distribution (n) of MICs (mg/L) in *Escherichia coli* from veal calves.

Minimal Inhibitory Concentration (MIC) / veal calves / *Escherichia coli* / Number of Isolates (N=176)																		
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024
Ampicillin								4	43	72	9			48				
Cefotaxime				150	26													
Ceftazidime						171	5											
Chloramphenicol									2	41	110	6	4	1	12			
Ciprofloxacin	25	116	21	1	2	8		1			1	1						
Colistin									176									
Florfenicol									4	83	79	5	1	1	3			
Gentamicin						13	116	39	2	1		2	1	2				
Kanamycin										147	4	2				23		
Nalidixic acid										162	1			3	10			
Streptomycin									2	36	61	5	9	20	6	37		
Sulfamethoxazole											39	29	21	6	1			
Tetracycline								16	87	5	1		4	15	48			
Trimethoprim							124	13						39				

Table II.14: Distribution (n) of MICs (mg/L) in ESBL/pAmpC suspected *Escherichia coli* from broilers.

Minimal Inhibitory Concentration (MIC) / broilers / ESBL / pAmpC – suspected *Escherichia coli* / Number of Isolates (N=47)																			
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048
Ampicillin														47					
Cefotaxime									2	2	4	8	10	15	6				
Ceftazidime						1	2	16	9	3	4	11	1						
Cefazolin												1	46						
Cefepime								7	6	18	14		2						
Cefoxitin										34	6			3	4				
Cefpodoxime											1	1	5	40					
Ceftriaxone								1	3	1	5	4	10	15	8				
Cefalotin													47						
Chloramphenicol									2	14	30			1					
Ciprofloxacin		27	1		5	7	2	1				4							
Colistin									47										
Florfenicol									2	30	15								
Gentamicin						4	24	15	1				3						
Imipenem							47												
Kanamycin										43	1		3						
Meropenem									47										
Nalidixic acid										29				6	12				
Piperacillin/Tazobactam										43	4								
Streptomycin										8	11	12	4	5	6	1			
Sulfamethoxazole											3		5	3					36
Tetracycline								2	20	2			1	5	17				
Trimethoprim							13	1						33					

Table II.15: Distribution (n) of MICs (mg/L) in ESBL/pAmpC suspected *Escherichia coli* from pigs.

Minimal Inhibitory Concentration (MIC) / pigs / ESBL / pAmpC – suspected *Escherichia coli* / Number of Isolates (N=16)																			
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048
Ampicillin														16					
Cefotaxime									1				5	3	7				
Ceftazidime								1	1	3	4	4	1		2				
Cefazolin													16						
Cefepime								1	1	5	6	2	1						
Cefoxitin										10	4				2				
Cefpodoxime												1		15					
Ceftriaxone									1					3	4	8			
Cefalotin													16						
Chloramphenicol										4	8		2		2				
Ciprofloxacin	1		5				1		2			1		6					
Colistin									16										
Florfenicol										5	10				1				
Gentamicin						11					1			4					
Imipenem							16												
Kanamycin										8			2	3	1	2			
Meropenem									16										
Nalidixic acid										7		1			8				
Piperacillin/Tazobactam										9	5		1	1					
Streptomycin										3	1		1	4	1	3			
Sulfamethoxazole											1		1	2	1				11
Tetracycline									4					1	11				
Trimethoprim							9	1						6					

Table II.16: Distribution (n) of MICs (mg/L) in ESBL/pAmpC suspected *Escherichia coli* from veal calves.

Minimal Inhibitory Concentration (MIC) / veal calves / ESBL / pAmpC – suspected *Escherichia coli* / Number of Isolates (N=30)	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048
Ampicillin														30					
Cefotaxime									2		4		2	12	10				
Ceftazidime								3	3	1	7	14	2						
Cefazolin													30						
Cefepime								3	4	7	12	2	2						
Cefoxitin										19	8	1		1	1				
Cefpodoxime												2		28					
Ceftriaxone									2			3	1	5	10	9			
Cefalotin													30						
Chloramphenicol										5	12	1	1	2	9				
Ciprofloxacin	1	6		1	1	3					1	17							
Colistin									30										
Florfenicol									1	9	15	2			3				
Gentamicin						1	7	1			1	3	13	4					
Imipenem							30												
Kanamycin										8		2	9	2	1	8			
Meropenem									30										
Nalidixic acid										8	2				20				
Piperacillin/Tazobactam										19	9	1	1						
Streptomycin										3	4	3	2	4	9	5			
Sulfamethoxazole											1	4							25
Tetracycline														4	26				
Trimethoprim							7	3						20		0			

Table II.17: Distribution (n) of MICs (mg/L) in MRSA from pigs.

Minimal Inhibitory Concentration (MIC) / Pigs / MRSA / Number of Isolates (N=73)	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024
Cefoxitin											10	60	3					
Chloramphenicol										3	65	5						
Ciprofloxacin						22	46	1	1		3							
Clindamycin					10				1	1	61							
Erythromycin						5	8					60						
Fusidic acid							71		1	1								
Gentamicin								67		1		1	4					
Kanamycin										65	2			6				
Linezolid								1	69	3								
Mupirocin							70	1								2		
Penicillin										73								
Quinupristin/Dalfopristin							8	2	6	47	10							
Rifampin		72						1										
Streptomycin										3	22	2		46				
Sulfamethoxazole														71				2
Tetracycline													73					
Tiamulin							7	3			63							
Trimethoprim									4					69				
Vancomycin								73										

Table II.18: Distribution (n) of MICs (mg/L) in MRSA from veal calves.

Minimal Inhibitory Concentration (MIC) / veal calves / MRSA / Number of Isolates (N=10)																		
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024
Cefoxitin												9	1					
Chloramphenicol											6	4						
Ciprofloxacin						6	2			1		1						
Clindamycin					2						8							
Erythromycin						1	1					8						
Fusidic acid							10											
Gentamicin								8				1	1					
Kanamycin										8					2			
Linezolid								2	8									
Mupirocin							9	1										
Penicillin										10								
Quinupristin/Dalfopristin							3	3		3	1							
Rifampin		10																
Streptomycin										1	6			3				
Sulfamethoxazole														9	1			
Tetracycline							1						9					
Tiamulin							6	1			3							
Trimethoprim									6		1			3				
Vancomycin								10										

Annex III

Tables of multi-resistance patterns in bacterial isolates from animals

Annex III: Tables of multi-resistance patterns in bacterial isolates from animals

Table III.1: Multi-resistance patterns of *Salmonella* spp. from poultry.

Number of Resistances	Number of Isolates	Serovar	Ampicillin	Cefotaxime	Ceftazidime	Ciprofloxacin	Colistin	Nalidixic acid	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
5 ABM	1	*S.* Indiana										

ABM: antimicrobial substances

Table III.2: Multi-resistance patterns of *Salmonella* spp. from pigs.

Number of Resistances	Number of Isolates	Serovar	Ampicillin	Chloramphenicol	Cefotaxime	Ceftazidime	Ciprofloxacin	Colistin	Florfenicol	Gentamicin	Kanamycin	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
6 ABM	1	*S.* Typhimurium													
4 ABM	2	*S.* Kedougou													
4 ABM	3	*S.* Typhimurium (monophasic variant)													

ABM: antimicrobial substances

Table III.3: Multi-resistance patterns of *Salmonella* spp. from cattle.

Number of Resistances	Number of Isolates	Serovar	Ampicillin	Chloramphenicol	Cefotaxime	Ceftazidime	Colistin	Florfenicol	Gentamicin	Kanamycin	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
6 ABM	2	*S.* Typhimurium												
5 ABM	1	*S.* Typhimurium (monophasic variant)												
4 ABM	13	*S.* Typhimurium (monophasic variant)												

ABM: antimicrobial substances

Table III.4: Multi-resistance patterns of *Campylobacter jejuni* from broilers.

Number of Resistances	Number of Isolates	Chloramphenicol	Ciprofloxacin	Erythromycin	Gentamicin	Nalidixic acid	Streptomycin	Tetracycline
4 ABM	2							
3 ABM	23							
2 ABM	40							

ABM: antimicrobial substances

Table III.5: Multi-resistance patterns of *Campylobacter coli* from broilers.

Number of Resistances	Number of Isolates	Chloramphenicol	Ciprofloxacin	Erythromycin	Gentamicin	Nalidixic acid	Streptomycin	Tetracycline
6 ABM	1							
3 ABM	1							
	2							
2 ABM	1							
	2							

ABM: antimicrobial substances

Table III.6: Multi-resistance patterns of *Campylobacter coli* from pigs.

Number of Resistances	Number of Isolates	Chloramphenicol	Ciprofloxacin	Erythromycin	Gentamicin	Nalidixic acid	Streptomycin	Tetracycline
5 ABM	8							
	1							
4 ABM	22							
	5							
3 ABM	29							
	4							
	3							
	3							
2 ABM	22							
	15							
	7							
	1							

ABM: antimicrobial substances

Table III.7: Multi-resistance patterns of *Enterococcus faecalis* from broilers.

Number of Resistances	Number of Isolates	Bacitracin	Chloramphenicol	Ciprofloxacin	Erythromycin	Florfenicol	Gentamicin	Neomycin	Nitrofurantoin	Streptomycin	Tetracycline
6 ABM	1										
	1										
4 ABM	4										
	4										
	1										
3 ABM	14										
	12										
	1										
2 ABM	22										
	7										
	3										

ABM: antimicrobial substances

Table III.8: Multi-resistance patterns *Enterococcus faecium* from broilers.

Number of Resistances	Number of Isolates	Ampicillin	Bacitracin	Ciprofloxacin	Erythromycin	Florfenicol	Neomycin	Nitrofurantoin	Quinupristin / Dalfopristin*	Salinomycin	Streptomycin	Tetracycline
6 ABM	1											
	1											
5 ABM	2											
	1											
	1											
	1											
4 ABM	5											
	1											
	1											
	1											
3 ABM	8											
	3											
	2											
	2											
	1											
	1											
	1											
	1											
	1											
2 ABM	8											
	3											
	2											
	1											

ABM: antimicrobial substances

Table III.9: Multi-resistance patterns of *Enterococcus faecalis* from veal calves.

Number of Resistances	Number of Isolates	Amoxicillin / Clavulanic acid 2:1	Bacitracin	Chloramphenicol	Erythromycin	Florfenicol	Gentamicin	Neomycin	Nitrofurantoin	Streptomycin	Tetracycline	Vancomycin
7 ABM	3											
	1											
6 ABM	7											
	5											
	1											
5 ABM	9											
	2											
	2											
4 ABM	8											
	3											
	3											
	2											
	2											
	1											
	1											
	1											
	1											
3 ABM	5											
	3											
	1											
2 ABM	23											
	1											
	1											
	1											

ABM: antimicrobial substances

Table III.10: Multi-resistance patterns of *Enterococcus faecium* from veal calves.

Number of Resistances	Number of Isolates	Ampicillin	Bacitracin	Ciprofloxacin	Erythromycin	Florfenicol	Gentamicin	Neomycin	Nitrofurantoin	Quinupristin / Dalfopristin*	Salinomycin	Streptomycin	Tetracycline
6 ABM	2												
	2												
5 ABM	1												
	1												
4 ABM	9												
	1												
	1												
3 ABM	26												
	3												
	1												
2 ABM	9												
	1												
	1												
	1												
	1												
	1												

ABM: antimicrobial substances

Table III.11: Multi-resistance patterns of *Escherichia coli* from broilers.

Number of Resistances	Number of Isolates	Ampicillin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Florfenicol	Gentamicin	Kanamycin	Nalidixic acid	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
7 ABM	1	■				■			■	■			■	■	
	1	■				■					■	■	■	■	■
6 ABM	3	■				■					■		■	■	■
	1					■				■	■	■	■	■	
	1	■				■						■	■	■	■
5 ABM	3	■										■	■	■	■
	1	■	■	■		■					■				
	1				■							■	■	■	■
	1	■				■							■	■	■
	1	■				■					■	■	■		
	1	■				■					■	■		■	
	1					■				■	■		■	■	
4 ABM	6	■				■					■			■	
	4	■											■	■	■
	3	■				■					■		■		
	1	■				■					■			■	
	1	■				■					■	■			
	1					■					■	■		■	
	1					■					■	■	■		
3 ABM	4					■					■			■	
	4	■				■					■				
	3					■					■		■		
	3											■	■		■
	2											■	■	■	
	2												■	■	■
	2									■		■	■		
	2	■										■		■	
	2	■											■		■
	1					■					■	■			
	1					■					■			■	
2 ABM	32					■					■				
	5	■												■	
	5	■											■		
	1												■	■	
	1											■		■	
	1												■		■
	1												■		■

ABM: antimicrobial substances

Table III.12: Multi-resistance patterns of *Escherichia coli* from pigs.

Number of Resistances	Number of Isolates	Ampicillin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Kanamycin	Nalidixic acid	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
8 ABM	1	■			■	■				■		■	■	■
7 ABM	1	■			■			■			■	■	■	■
	1	■				■				■	■	■	■	■
	1	■	■	■							■	■	■	■
6 ABM	2	■			■						■	■	■	■
	1	■			■				■		■	■	■	
	1	■						■	■		■	■	■	
	1	■				■				■	■	■	■	
	1	■	■	■							■	■	■	
5 ABM	4	■									■	■	■	■
	1	■							■		■	■	■	
	1					■				■	■	■	■	
	1	■				■				■	■	■		
	1	■			■							■	■	■
	1	■							■			■	■	■
	1				■						■	■	■	■
	1					■					■	■	■	■
	1								■		■	■	■	■
4 ABM	8										■	■	■	■
	4	■									■	■	■	
	2				■						■	■		■
	1				■						■	■	■	
	1				■				■		■			■
	1	■							■		■		■	
	1							■			■	■	■	
	1	■									■	■		■
3 ABM	14										■	■	■	
	4										■	■		■
	2	■									■	■		
	2	■										■		■
	1											■	■	■
	1					■				■			■	
	1	■						■				■		
	1				■						■	■		
	1	■											■	■
	1										■		■	■
2 ABM	5										■	■		
	2					■				■				
	1	■											■	
	1										■		■	

ABM: antimicrobial substances

Table III.13: Multi-resistance patterns of *Escherichia coli* from veal calves.

Number of Resistances	Number of Isolates	Ampicillin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Florfenicol	Gentamicin	Kanamycin	Nalidixic acid	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
8 ABM	1														
	1														
7 ABM	2														
	1														
	1														
	1														
6 ABM	3														
	3														
	2														
	2														
	1														
	1														
5 ABM	9														
	4														
	3														
	1														
	1														
	1														
	1														
	1														
4 ABM	10														
	4														
	3														
	1														
	1														
3 ABM	8														
	4														
	2														
	1														
	1														
2 ABM	4														
	2														
	2														
	2														
	1														
	1														

ABM: antimicrobial substances

Table III.14: Multi-resistance patterns of ESBL/AmpC suspected *Escherichia coli* from broilers.

Number of Resistances	Number of Isolates	Ampicillin	Cefotaxime	Cefotaxime/Clavulanic acid	Ceftazidime	Ceftazidime/Clauvulanic acid	Cefazolin	Cefepime	Cefoxitin	Cefpodoxime	Ceftriaxone	Cefalotin	Chloramphenicol	Ciprofloxacin	Colistin	Florfenicol	Gentamicin	Imipenem	Kanamycin	Meropenem	Nalidixic acid	Piperacillin/Tazobactam	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
16 ABM	3																									
13 ABM	1																									
	1																									
12 ABM	1																									
	1																									
11 ABM	4																									
	2																									
	1																									
	1																									
10 ABM	7																									
	5																									
	3																									
	1																									
	1																									
	1																									
9 ABM	2																									
	1																									
	1																									
	1																									
	1																									
8 ABM	3																									
	1																									
	1																									
	1																									
7 ABM	1																									
6 ABM	1																									

ABM: antimicrobial substances

Table III.15: Multi-resistance patterns of ESBL/AmpC suspected *Escherichia coli* from pigs.

Number of Resistances	Number of Isolates	Ampicillin	Cefotaxime	Cefotaxime / Clavulanic acid	Ceftazidime	Ceftazidime / Clauvulanic acid	Cefazolin	Cefepime	Cefoxitin	Cefpodoxime	Ceftriaxone	Cefalotin	Chloramphenicol	Ciprofloxacin	Colistin	Florfenicol	Gentamicin	Imipenem	Kanamycin	Meropenem	Nalidixic acid	Piperacillin / Tazobactam	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
18 ABM	1																									
	1																									
17 ABM	1																									
13 ABM	1																									
	1																									
12 ABM	1																									
	1																									
	1																									
	1																									
	1																									
11 ABM	1																									
	1																									
10 ABM	1																									
	1																									
	1																									
	1																									

ABM: antimicrobial substances

Table III.16: Multi-resistance patterns of ESBL/AmpC suspected *Escherichia coli* from veal calves.

Number of Resistances	Number of Isolates	Ampicillin	Cefotaxime	Cefotaxime/Clavulanic acid	Ceftazidime	Ceftazidime/Clauvulanic acid	Cefazolin	Cefepime	Cefoxitin	Cefpodoxime	Ceftriaxone	Cefalotin	Chloramphenicol	Ciprofloxacin	Colistin	Florfenicol	Gentamicin	Imipenem	Kanamycin	Meropenem	Nalidixic acid	Piperacillin/Tazobactam	Streptomycin	Sulfamethoxazole	Tetracycline	Trimethoprim
18 ABM	1																									
17 ABM	2																									
	1																									
16 ABM	5																									
	1																									
15 ABM	2																									
	1																									
14 ABM	1																									
	1																									
13 ABM	3																									
	2																									
	1																									
	1																									
	1																									
	1																									
12 ABM	1																									
	1																									
11 ABM	1																									
	1																									
	1																									
10 ABM	1																									

ABM: antimicrobial substances

Table III.17: Multi-resistance patterns of MRSA from pigs.

Number of Resistances	Number of Isolates	spa-type	Cefoxitin	Ciprofloxacin	Clindamycin	Erythromycin	Fusidic acid	Gentamicin	Kanamycin	Mupirocin	Penicillin	Quinupristin / dalfopristin*	Rifampin	Tetracycline	Tiamulin	Streptomycin	Sulfamethoxazole
15 ABM	1	t 034															
13 ABM	1	t 011															
11 ABM	2	2 x t-034															
9 ABM	37	36 x t-034															
		1 x t-011															
	1	t 034															
8 ABM	21	21 x t-034															
7 ABM	1	t-011															
6 ABM	1	t-011															
5 ABM	1	t-034															
	1	t-034															
	1	t-011															
	1	t-011															
4 ABM	1	t-011															
3 ABM	3	3 x t-011															

ABM: antimicrobial substances

Table III.18: Multi-resistance patterns of MRSA from veal calves.

Number of Resistances	Number of Isolates	spa-type	Cefoxitin	Ciprofloxacin	Clindamycin	Erythromycin	Fusidic acid	Gentamicin	Kanamycin	Mupirocin	Penicillin	Quinupristin / dalfopristin*	Rifampin	Tetracycline	Tiamulin	Streptomycin	Sulfamethoxazole
11 ABM	2	2 x t 034															
9 ABM	1	t 034															
7 ABM	1	t 1255															
5 ABM	4	4 x t 011															
4 ABM	1	t 032															
3 ABM	1	t 011															

ABM: antimicrobial substances

Annex IV

anresis.ch participants and steering committee

Annex IV: anresis.ch participants and steering committee

Table IV.1: Hospital pharmacies participating in anresis.ch.

Hospital pharmacies
Aarau, Kantonsspital Aarau, Spitalapotheke
Baar, Zuger Kantonsspital, Spitalapotheke
Baden, Kantonsspital Baden, Spitalapotheke
Basel, St.Claraspital, Spitalapotheke
Basel, Universitätsspital Basel, Spital-Pharmazie
Bellinzona, Ospedale regionale di Bellinzona e Valli, Servicio di farmacia ospedaliera EOFARM
Bern, Hirslanden Klinik Beau-Site, Apotheke
Bern, Inselspital, Institut für Spitalpharmazie
Bern, Spitalnetz, Spitalpharmazie
Biel, Spitalzentrum, Apotheke
Bruderholz, Kantonsspital Baselland, Spitalapotheke
Chur, Kantonsspital Graubünden, Institut für Spitalpharmazie
Fribourg, HFR Hôpital cantonal, Pharmacie
Genève, Hôpitaux Universitaires de Genève (HUG), Pharmacie
La Chaux-de-Fonds, Hôpital neuchâtelois, Service de Pharmacie
Langenthal, SRO Oberaargau, Spitalapotheke
Lausanne, Centre Hospitalier Universitaire Vaudois (CHUV)
Liestal, Kantonsspital Baselland, Spitalapotheke
Luzern, Hirslanden Klinik St. Anna, Spitalapotheke
Luzern, Luzerner Kantonsspital, Zentrum für Spitalpharmazie
Morges, Pharmacie Interhospitalière de la Côte (PIC)
Moutier, Hôpitaux Jura/Jura bernois, Pharmacie interjurassienne
Rebstein, Spitalregion RWS, Spital Grabs, Spitalapotheke
Schaffhausen, Spitäler Schaffhausen, Spitalapotheke
Schlieren, Spital Limmattal, Spitalapotheke
Sion, Hôpital du Valais, Institut Central (ICHV), Service de pharmacie
Solothurn, Solothurner Spitäler, Spitalapotheke
St. Gallen, Kantonsspital St. Gallen, Spitalapotheke
Thun, Spital STS, Spitalapotheke
Unterseen, Spitäler fmi, Spitalapotheke
Vevey, Pharmacie des Hôpitaux de l'Est Lémanique (PHEL)
Winterthur, Kantonsspital Winterthur, Spitalapotheke
Yverdon, Pharmacie des Hôpitaux du Nord Vaudois et de la Broye (PHNVB)
Zürich, Stadtspital Triemli, Spitalapotheke
Zürich, Universitätsspital Zürich, Spitalhygiene

Table IV.2: Laboratories participating in anresis.ch.

Laboratories	data included
Aarau, Zentrum für Labormedizin, Kantonsspital Aarau	since 2006
Baden, Kantonsspital Baden, Zentrallabor, Bereich Mikrobiologie	since 2004
Basel, Labor Universitäts Kinderklinik beider Basel UKBB	2004–2010[1]
Basel, Universitätsspital Basel, Klinische Mikrobiologie	since 2008
Bellinzona, Dipartimento di medicina di laboratorio EOLAB, Servizio di microbiologia	since 2004
Bern, Institut für Infektionskrankheiten	since 2004
Chur, Kantonsspital Graubünden, Zentrallabor	since 2004
Frauenfeld/Münsterlingen, Kantonsspitäler, Spital Thurgau AG, Institut für Labormedizin	since 2007
Fribourg, Laboratoire HFR – Hôpital cantonal, microbiologie	since 2004
Genève, Hôpitaux Universitaires de Genève (HUG), Laboratoire de Bactériologie	since 2004
La Chaux-de-Fonds, ADMED Microbiologie	since 2008
Labor Dr. Güntert AG, Luzern	2005–2012
Labormedizinisches Zentrum Dr. Risch, Bern	since 2007
Lausanne, Université de Lausanne, Institut de Microbiologie	since 2006
Luzern, Kantonsspital Luzern, Zentrum für Labormedizin	since 2004
Polytest Labor Zug AG	2004-2006
Schaffhausen, Spitäler Schaffhausen, Zentrallabor	since 2004
Sitten, Institut Central des Hôpitaux Valaisans (ICHV), Zentralinstitut	since 2004
St. Gallen, Zentrum für Labormedizin	since 2009
Unilabs S.A., Genf	since 2007
Viollier AG, Basel	since 2004
Zürich, Universität Zürich, Institut für Medizinische Mikrobiologie	since 2005
Zürich, Universitäts-Kinderspital Zürich, Infektionslabor	since 2004

[1] Since 2011 data included in Basel, Universitätsspital Basel, Klinische Mikrobiologie

Table IV.3: anresis.ch steering committee members 2014.

Raymond Auckenthaler	Synlab SUISSE
Marisa Dolina	Dipartimento di medicina di laboratorio EOLAB, Servizio di microbiologia, Bellinzona
Olivier Dubuis	Viollier AG, Basel
Reno Frei	Klinische Mikrobiologie, Universitätsspital Basel
Daniel Koch	Bundesamt für Gesundheitswesen BAG
Andreas Kronenberg	Institut für Infektionskrankheiten, Universität Bern
Stephane Luyet	Schweizerische Konferenz der kantonalen GesundheitsdirektorInnen GDK
Patrice Nordmann	Microbiologie médicale et moléculaire, Dpt Médecine, Université de Fribourg
Vincent Perreten	Institut für Veterinär-Bakteriologie, Universität Bern
Jean-Claude Piffaretti	Interlifescience, Massagno
Guy Prod'hom	CHUV, Institut de microbiologie, Lausanne
Jacques Schrenzel	HUG, Laboratoire de Bactériologie, Genève
Martin Täuber	Institut für Infektionskrankheiten, Universität Bern
Andreas Widmer	Abteilung für Spitalhygiene, Universität Basel
Giorgio Zanetti	CHUV, Service de médecine préventive hospitalière, Lausanne
Reinhard Zbinden	Institut für medizinische Mikrobiologie, Universität Zürich

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