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

Swiss Antibiotic Resistance Report 2018

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Table of contents

1 Foreword 6
Vorwort 7
Avant-propos 8
Prefazione 9

2 Summary 12
Zusammenfassung 15
Synthèse 18
Sintesi 22

3 Introduction 26
3.1 Antibiotic resistance 26
3.2 About anresis.ch 26
3.3 About ARCH-Vet 27
3.4 Guidance for readers 28
3.5 Authors and contributions 29

4 Abbreviations 32

5 Antibacterial consumption in human medicine 36
5.1 Hospital care 36
5.2 Outpatient care 40
5.3 Discussion 44
Textbox: Antibiotic Prescriptions in Outpatient Medical Care 46

6 Sales of antimicrobials in veterinary medicine 48
6.1 Sales of antimicrobials for use in animals 48
6.2 Sales of antimicrobials for use in livestock animals 49
6.3 Sales of antimicrobials licensed for companion animals 51
6.4 Discussion 52
Textbox: Antibiotic Substances in the Water Cycle 53

7 Resistance in bacteria from human clinical isolates 56
7.1 *Escherichia coli* 56
Textbox: Temporal and Regional Prevalence of Carbapenemase-Producing Enterobacteriaceae from 2013 to 2017 in Switzerland 59
Textbox: The National Reference Center for Emerging Antibiotic Resistance (NARA) 60
7.2 *Klebsiella pneumoniae* 60
7.3 *Pseudomonas aeruginosa* 63
7.4 *Acinetobacter* spp. 63
Textbox: Carbapenem-Resistant Acinetobacter baumannii from 2005 to 2016 in Switzerland. 66
7.5 *Streptococcus pneumoniae* 68
7.6 Enterococci 71
7.7 *Staphylococcus aureus* 71
Textbox: Treatment of the Tree Disease Fire Blight with Antibiotics 75
Textbox: Antibacterial Resistance in the Aquatic Environment 76

8 Resistance in zoonotic bacteria in animals from primary production samples 80
8.1 *Campylobacter* spp. 80
8.2 *Salmonella* spp. 84
Textbox: Persistence of Quinolone and Tetracycline Resistance in Thermophilic *Campylobacter* from Poultry 85
Textbox: Modern Microbiological Surveillance for Antibiotic Drug Resistance 93

9 Resistance in indicator bacteria from livestock animals 98
9.1 *Enterococci* 98
9.2 *Escherichia coli* 103
9.3 ESBL/pAmpC-producing *Escherichia coli* 105
9.4 Methicillin-resistant *Staphylococcus aureus* (MRSA) 110
Textbox: *Mcr-1*-Based Colistin Resistance: Filling Knowledge Gaps in View of the Spread of Plasmid-Mediated Colistin Resistance in Switzerland 115

10 Resistance in bacteria isolated from meat 118
10.1 ESBL/pAmpC- and carbapenemase-producing *Escherichia coli* 118
10.2 MRSA in meat 120
10.3 Discussion 121

11 Resistance in bacteria from animal clinical isolates 126
11.1 *Staphylococcus* spp. 126
11.2 *Streptococcus equi* subspecies *zooepidemicus* 127
11.3 *Escherichia coli* in dogs 128
11.4 Discussion 129

12 Analysis 134
12.1 Association Between Antibiotic Consumption and Resistance in Animals and in Humans, a One-Health Approach 134
12.2 Molecular features of Swiss methicillin-resistant *Staphylococcus aureus* (MRSA) 138

13 Materials and methods 146
13.1 Data on antibacterial consumption in human medicine 146
13.2 Data on antimicrobial sales in veterinary medicine 147
13.3 Bacterial isolates from humans (clinical probes) 147
13.4 Bacterial isolates from animals and meat thereof 149
13.5 Susceptibility testing, breakpoints, processing antibiotic resistance data from human isolates 149
13.6 Susceptibility testing, cut-offs, breakpoints, processing antimicrobial resistance data from animal isolates 151

Annex 155
Annex I: Antibiotics with defined daily dose (DDD) and AWaRe classification according to the WHO Essential Medicines List 156
Annex II: Distribution of minimal inhibitory concentrations (MICs) and resistance patterns in bacterial isolates from animals and meat 159

Index 191
Figures, tables and textboxes

1

Foreword

1 Foreword

One Health is now recognized globally as a pivotal approach to overcoming a large number of healthcare-related problems, especially antibiotic resistance. Just like veterinary medicine, agriculture and environmental protection agencies, the field of human medicine faces challenges in its efforts to maintain the health of everyone. The World Health Organization's Global Action Plan, and – for example – the efforts being made by the G20 nations or the European Union, all put the One-Health approach center stage as a way of dealing with and combating the issue of antibiotic resistance.

This approach obviously has great significance in the context of the "Monitoring" field of activity in StAR, which can only deliver truly meaningful information if all areas contribute and cross-area analysis takes place.

Monitoring involves the collection of data on antibiotic resistance on the one hand and data on antibiotic consumption in human and veterinary medicine on the other. These data provide a good overview of the situation in the various areas. Although inappropriate use of antibiotics is known to have an effect on the development of resistance, there is often a time lag in recognizing the connection among other things, and it is not apparent in every type of resistance. Obtaining a better understanding of how resistance comes about (what causes resistance in which bacteria and in which areas) and the paths by which it is transmitted requires analysis in greater depth by an interdisciplinary team that brings together expertise from the various areas and disciplines.

The Swiss Antibiotic Resistance Report 2018 integrates for the first time a One-Health analysis (see Chapter 12). This firstly involved an evaluation of antibiotic consumption data in human and veterinary medicine compared with antibiotic resistances in humans and animals. Secondly, typing data for methicillin-resistant *Staphylococcus aureus (MRSA)* from humans and animals were compared to investigate the question of whether the same "types" occur in humans as in animals.

Future editions of the Swiss Antibiotic Resistance Report will each take an in-depth look at a different resistant bacterium.

We would like to thank everyone who contributed to this report for their work and hope you will find it instructive reading.

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Veterinary Office

1 Vorwort

One Health ist mittlerweile als massgebender Ansatz für die Bewältigung vieler Probleme im Gesundheitsbereich, im Speziellen der Antibiotikaresistenzen, weltweit anerkannt. Gefordert ist der Humanbereich genauso wie der Tier-, der Landwirtschafts- und der Umweltbereich, um die Gesundheit aller zu erhalten. Der Global Action Plan der Weltgesundheitsorganisation WHO und beispielsweise die Anstrengungen der G20-Staaten oder der Europäischen Union stellen alle den One-Health-Ansatz ins Zentrum, um das Problem der Antibiotikaresistenzen und deren Bekämpfung anzugehen.

Dieser Ansatz hat selbstverständlich auch im StAR-Handlungsfeld «Überwachung» eine grosse Bedeutung. Die Überwachungsdaten sind erst dann wirklich aussagekräftig, wenn alle Bereiche beitragen und eine übergreifende Analyse erfolgt.

Bei der Überwachung werden zum einen Daten zu Antibiotikaresistenzen, zum anderen Daten zum Antibiotikaverbrauch in der Human- und Veterinärmedizin gesammelt. Diese Daten ermöglichen einen guten Überblick über die Situation in den verschiedenen Bereichen.

Es ist bekannt, dass der unsachgemässe Antibiotikaeinsatz einen Einfluss auf die Resistenzbildung hat. Jedoch ist dieser Zusammenhang unter anderem oft nur zeitverzögert zu erkennen und nicht bei jeder Art von Resistenz eindeutig. Für ein besseres Verständnis der Resistenzentstehung (wodurch entstehen in welchen Gebieten Resistenzen bei welchen Bakterien) und der verantwortlichen Übertragungswege braucht es weitergehende Analysen durch ein interdisziplinäres Team, welches die Expertise aus den verschiedenen Bereichen und Disziplinen zusammenbringt.

Im vorliegenden Swiss Antibiotic Resistance Report 2018 wird zum ersten Mal eine One-Health-Analyse integriert (siehe Kapitel 12). Dabei wurde einerseits eine vergleichende Auswertung der Antibiotikaverbrauchsdaten in der Human- und Veterinärmedizin mit den Antibiotikaresistenzdaten bei Mensch und Tier durchgeführt. Andererseits wurden Typisierungsdaten von Methicillin-resistenten *Staphylococcus aureus (MRSA)* von Menschen und Tieren verglichen, um die Frage zu klären, ob die gleichen «Typen» sowohl beim Menschen als auch beim Tier vorkommen.

In den nächsten Ausgaben des Swiss Antibiotic Resistance Report soll jeweils ein anderer resistenter Keim vertieft betrachtet werden.

Wir danken allen Beteiligten des Reports für ihre Arbeit und wünschen Ihnen eine erkenntnisreiche Lektüre!

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1 Avant-propos

L'approche One Health est devenue la référence mondiale pour affronter de nombreux problèmes de santé publique, en particulier celui de la résistance aux antibiotiques. Il s'agit de mobiliser la médecine humaine, la médecine vétérinaire, l'agriculture et la protection de l'environnement dans le but de préserver la santé de tous. Cette approche est au cœur du Plan d'action mondial de l'Organisation mondiale de la santé OMS et, par exemple, des efforts déployés par les États du G20 et l'Union européenne pour s'atteler à la problématique de la lutte contre la résistance aux antibiotiques.

L'approche One Health occupe tout naturellement une place importante dans le champ d'action « Surveillance » de la stratégie Antibiorésistance. En effet, pour que les données récoltées dans ce cadre soient vraiment pertinentes, il faut que tous les domaines participent et qu'une analyse globale soit réalisée.

La surveillance consiste à collecter des données relatives, d'une part, à la résistance aux antibiotiques et, d'autre part, à l'usage de ces produits en médecine humaine et vétérinaire. Ces données offrent un bon aperçu de la situation dans les différents domaines.

Nous savons que l'usage excessif d'antibiotiques a une influence sur le développement d'une résistance. Néanmoins, cette relation de causalité ne peut souvent être connue qu'à posteriori et n'est pas évidente avec tous les types de résistance. Afin de mieux comprendre l'apparition des résistances (ce qui les provoque, où elles apparaissent et chez quelles bactéries) ainsi que les modes de transmission responsables, de plus amples analyses sont nécessaires. Ces dernières doivent être menées par une équipe interdisciplinaire, afin que les expertises issues des différents domaines et disciplines soient mises en commun.

Le *Swiss Antibiotic Resistance Report 2018* est le premier rapport à intégrer une analyse One Health (voir chapitre 12). Il présente, d'une part, une évaluation comparant les données sur l'usage des antibiotiques en médecine humaine et vétérinaire avec les données relatives à la résistance aux antibiotiques chez l'homme et l'animal. D'autre part, les données de typage pour le *Staphylococcus aureus* résistant à la méticilline (SARM) ont été confrontées dans le but de déterminer si les mêmes « types » sont présents chez l'homme et chez l'animal.

Les prochaines éditions du *Swiss Antibiotic Resistance Report* se pencheront chacune sur un germe résistant différent.

Nous remercions tous les participants au rapport pour leur travail et vous souhaitons une lecture instructive.

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1 Prefazione

L'approccio One Health è diventato la referenza mondiale per affrontare numerosi problemi in ambito sanitario, in particolare quello delle resistenze agli antibiotici. Allo scopo di preservare la salute di tutti vengono promossi gli ambiti concernenti l'essere umano, gli animali, l'agricoltura e l'ambiente. Il Piano d'azione globale dell'Organizzazione mondiale della sanità OMS e, per esempio, gli sforzi profusi dagli Stati del G20 o dell'Unione europea puntano tutti sull'approccio One Health per gestire e contrastare il problema delle resistenze agli antibiotici.

Questo approccio riveste naturalmente grande importanza anche nell'area d'intervento «Sorveglianza» della Strategia contro le resistenze agli antibiotici (StAR). Tuttavia, affinché i dati raccolti in questo quadro siano davvero significativi è necessario che tutti i settori partecipino e che sia effettuata un'analisi globale.

Nell'ambito della sorveglianza vengono raccolti dati relativi, da un lato, alle resistenze agli antibiotici e, dall'altro, al consumo di questi medicamenti nella medicina umana e veterinaria. Questi dati offrono un buon quadro della situazione in diversi settori.

È noto che l'uso scorretto degli antibiotici influisce sullo sviluppo di resistenze. Tuttavia, questo rapporto di causalità viene spesso riconosciuto soltanto a posteriori e non è evidente per tutti i tipi di resistenza. Per comprendere meglio lo sviluppo di resistenze (per quali cause, in quali ambiti e in quali batteri) e le vie di trasmissione responsabili sono necessarie analisi più approfondite da parte di un team interdisciplinare, che possa sfruttare congiuntamente competenze specialistiche di diversi ambiti e discipline.

Lo *Swiss Antibiotic Resistance Report 2018* integra per la prima volta un'analisi One Health (cfr. capitolo 12). Presenta, da un lato, un'analisi comparativa tra i dati sul consumo di antibiotici in medicina umana e veterinaria e quelli sulle resistenze a questi medicamenti nell'essere umano e negli animali e, dall'altro, effettua un confronto dei dati sulla tipizzazione dello *Staphylococcus aureus* resistente alla meticillina (MRSA) in campo umano e veterinario per determinare se gli stessi «tipi» del batterio siano presenti sia nell'essere umano che negli animali.

Le prossime edizioni dello *Swiss Antibiotic Resistance Report* si concentreranno ciascuna su un agente patogeno resistente differente.

Ringraziamo tutti coloro che hanno collaborato al report e auguriamo una lettura istruttiva!

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2

Summary

2 Summary

Resistance in bacteria of human clinical isolates

Since 2008, different trends have been observed in Gram-positive and Gram-negative bacteria. Methicillin-resistant *Staphylococcus aureus* (MRSA) rates have continued to decrease significantly in invasive isolates, mainly in the western part of Switzerland. This trend was also observed in several other European countries, including the neighboring countries Germany, France and Austria. In contrast, MRSA rates are increasing in wound and abscess samples from outpatients. Penicillin resistance in *Streptococcus pneumoniae* has also decreased over time. This effect is mainly due to a reduction in the prevalence of more resistant serotypes, due to the introduction of pneumococcal vaccines. Vancomycin resistance in enterococci is still very low, but increasing rates observed during the last months are worrisome.

In contrast, we have observed a steady increase in quinolone resistance and 3rd/4th 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. During the last two years, this trend seems to have stabilized in Switzerland, as well as in some other European countries. Fortunately, carbapenem resistance still is rare in *E. coli* and *K. pneumoniae*. While carbapenem resistance in *E. coli* is rare in most European countries as well, increasing carbapenem resistance is observed in Europe in *K. pneumoniae*; in 2016 resistance rates above 25% have even been described in Italy, Greece and Romania. To allow a closer monitoring of the distribution of carbapenemase-producing Enterobacteriaceae, an obligation to report these microorganisms was introduced in Switzerland on 1.1.2016.

In *Pseudomonas aeruginosa*, the increasing resistance rates for piperacillin-tazobactam and ceftazidime peaked in 2015 and have slightly decreased since then, while resistance rates for aminoglycosides are steadily increasing. No significant trends were observed in *Acinetobacter* spp. and in contrast to Europe, carbapenemase rates were stable.

Antibiotic consumption in human medicine

In Swiss acute care hospitals, consumption of antibacterial agents for systemic use (ATC group J01) increased by 16% to 62.2 DDDs (defined daily doses) per 100 bed-days between 2007 and 2017, whereas it was relatively stable when expressed in DDDs 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 group J01C), followed by the other beta-lactam antibacterials, including cephalosporins (ATC group J01D) and quinolones (ATC group J01M).

In outpatient care, the total consumption of antibacterial agents for systemic use (ATC group J01) was 10.7 DDDs per 1,000 inhabitants per day in 2017. The most commonly used class of antibiotics was the penicillins (ATC group J01C), followed by the macrolides, lincosamides and streptogramins (ATC group J01F), tetracyclines (ATC group J01A) and fluoroquinolones (ATC group J01MA). The relative consumption of fluoroquinolones and penicillins associated with beta-lactamase inhibitors was relatively high in comparison with countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).

Resistance in zoonotic bacteria

In poultry, the resistance rate to ciprofloxacin and tetracycline in *Campylobacter jejuni (C. jejuni)* has increased significantly in the last years. From 15% in 2006, the resistance rate to ciprofloxacin rose to 51.4% in 2016, and to 40% for tetracycline. In contrast, resistance to erythromycin (2.9%) was rarely found. According to the WHO, fluoroquinolones and macrolides are highest-priority critically important antimicrobials in human medicine, because these substance groups represent the treatment of choice for serious forms of campylobacteriosis or salmonellosis in humans.

In fattening pigs, the resistance rate to streptomycin in *Campylobacter coli (C. coli)* decreased from 2006 to 2012. Subsequently, the resistance rate has increased significantly in the last years, up to 81.4% in 2017. The resistance rates for tetracycline (62.1%) and ciprofloxacin (50.3%) did not change significantly between 2015 and 2017.

Salmonella spp. occur only rarely in livestock in Switzerland. Therefore, the risk of *Salmonella* transmission to humans from food produced with Swiss animals is considered low. Moreover, their resistance rates are constantly low, especially in *S.* Enteritidis and *S.* Typhimurium.

Resistance in indicator bacteria in animals

Antimicrobial resistance is generally widespread in enterococci and *E. coli* isolated from livestock in Switzerland.

The enterococcal species *E. faecalis* and *E. faecium* isolated from broilers showed opposite trends in resistance rates. Whereas for *E. faecalis* resistance to ampicillin and tetracycline has increased since 2012, the resistance rates of *E. faecium* isolates decreased within the same period. A comparable effect was seen with enterococci isolates from veal calves. Vancomycin-resistant enterococci (VRE) have only occasionally been detected in the last years. No VRE have been detected in broilers in 2016, nor in fattening pigs and veal calves in 2017.

High resistance rates to ampicillin (14.2%–38.7%), sulfamethoxazole (46.9%–26.8%) and tetracycline (13.2%–41.2%) are found in commensal *E. coli* isolates from broilers, fattening pigs and veal calves. Additionally, high resistance to ciprofloxacin was found in isolates from broilers (37.9%). Resistance to these substances increased in isolates from broilers between 2006 and 2012, then clearly decreased until 2014, whereas no decrease could be detected in 2016, except for tetracycline. In isolates from calves, a decreasing trend for resistance was also observed from 2006 to 2013. However, resistances to tetracycline, sulfamethoxazole and ampicillin increased again until 2014, with a steady state in 2015 and 2017. In fattening pigs, the resistance rates in *E. coli* isolates showed a steady state or a slightly decreasing trend from 2013 to 2017 for the abovementioned antimicrobials.

ESBL/pAmpC-producing *E. coli* were detected in 52.4% of broiler flocks, in 17.6% of fattening pigs and in 33.2% of veal calves. The increase of the ESBL/pAmpC prevalence in broilers is ongoing, although on a lower level than in previous years (2014: 41.8%). In contrast, the ESBL prevalence of fattening pigs (2015: 25.7%) has decreased and remained on a high level for calves (2015: 37.6%).
No carbapenemase-producing *E. coli* were found in species of livestock.

In Switzerland, the occurrence of methicillin-resistant *S. aureus* (MRSA) in fattening pigs at slaughter has increased constantly since detection of MRSA became part of the monitoring. Starting at 2% in 2009 and increasing to 20.8% in 2013, the MRSA prevalence reached 44.0% in 2017. Moreover, the same trend but on a lower level is seen for MRSA carriage of veal calves. The actual prevalence in 2017 was 8.1%. The results reported for MRSA confirm that *spa* type t034 and *spa* type t011 are becoming widespread in Switzerland's population of slaughtered pigs. These genotypes belong to the clonal complex CC 398, which is typically livestock-associated (LA-MRSA). LA-MRSA can be transmitted between animals and humans. An analysis on MRSA carriage in Swiss inpatients detected two cases of LA-MRSA carriage (n=163) in Swiss patients.

Resistance in indicator bacteria from meat

In 49.3% of chicken meat samples, ESBL/pAmpC-producing *E. coli* have been detected. The prevalence differs markedly between Swiss meat (41.9%) and meat produced abroad (64.9%). For both, the overall prevalence has decreased in the reporting time (2014: Swiss meat 65.5%; meat from abroad: 85.6%). Although a decreasing trend has been detected, the prevalence of these multidrug-resistant *E. coli* are still very high, which corresponds to the finding of a high prevalence of ESBL/pAmpC-producing *E. coli* in broilers.

In contrast, only one ESBL/pAmpC-producing *E. coli* was detected in pork (n=302) and two ESBL/pAmpC-producing *E. coli* have been found in beef samples (n=299). This difference might be related to the lower prevalence of ESBL/pAmpC-producing *E. coli* in Swiss pigs and calves and the distinct slaughtering processes of these animals. No carbapenemase-producing *E. coli* were found in fresh meat samples.

MRSA was only detected in considerable amounts in chicken meat produced abroad (2016: 9.3%). In 2016, no MRSA was detected in Swiss chicken meat samples (n=205). Moreover, no MRSA was found in Swiss beef (n=299) and only two MRSA cases were detected in Swiss pork (n=301). The latter is of special interest, as the strong increase of MRSA in fattening pigs (prevalence 44.0%) seemed not to increase the prevalence of MRSA in fresh meat thereof. The data confirmed that food is not regarded as a relevant source of MRSA transmission to humans.

Resistance in bacteria from animal clinical isolates

Monitoring of antimicrobial resistance for relevant pathogens from diseased livestock and companion animals is important for veterinarians, as it allows them to make appropriate therapeutic antibiotic choices, which oftentimes cannot be based on an antibiogram prior to the first treatment. Moreover, these data fill another important gap regarding monitoring of antimicrobial resistance from the One-Health perspective.

Therefore, in 2015, the Federal Food Safety and Veterinary Office (FSVO) launched a pilot project for the monitoring of veterinary pathogens in Switzerland, together with the Swiss national reference laboratory for antibacterial resistance, the Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA).

All strains were isolated from clinical submissions of diseased animals analyzed by the ZOBA. Samples from animals with antimicrobial treatment prior to sampling were excluded from this study. In contrast to the monitoring of isolates from healthy slaughter animals, minimal inhibitory concentration (MIC) data were interpreted according to clinical breakpoints. Exemplarily, for small-animal medicine, resistance data of *S. pseudintermedius*, isolated from wound infections of dogs, and *E. coli*, isolated from canine urogenital tract infections, are reported. *Staphylococcus aureus* from bovine mastitis samples and *Streptococcus equi* subspecies *zooepidemicus,* derived from purulent infections from horses, completed the data set.

The presence of high levels of resistance to important antimicrobials underlines the need for systematic monitoring of

antimicrobial resistance. Infections in animals caused by multidrug-resistant pathogens must be expected for veterinary pathogens. However, the use of critically important antimicrobials cannot be supported by the data presented, as first-line antibiotics with sufficient efficacy are available for the different clinical settings. In the future, this monitoring will be even more representative, as isolates from other Swiss laboratories will be included from 2019 onwards.

Sales of antimicrobials in veterinary medicine

The sales volume of antimicrobials continued to decline in 2016 and 2017. Overall, 38 377 kg of antimicrobials were sold for veterinary medicine in 2016 and 32 328 kg in 2017. This amounts to a decline of 53% (37 tons) since 2008. The decrease is mainly due to a fall in sales of medicated premixes. The sales rankings of the various classes of antimicrobials remained unchanged: sulfonamides are in first place, followed by penicillins and tetracyclines. These three classes are often sold as medicated premixes. The quantity of antibiotics approved only for pets comprises 2,5% of the total volume. The sales of the highest-priority critically important antibiotic classes for human medicine decreased in 2016 and 2017; the sales of macrolides have decreased by 25% in 2016 and another 20% in 2017. The sales of fluoroquinolones declined by 21% in 2016 and by 25% in 2017. The sales of cephalosporins (3rd/4th generation) decreased by about 23% in 2016 as well as in 2017. The sales volume of colistin has declined approximately 79% since 2008. Expressed in correlation to the biomass under exposure, the level is 0.4 mg colistin/PCU for Switzerland. This is below the European average and in line with the requested reduction of colistin to a level of 1 mg/PCU or below for European countries in order to maintain its efficacy in the treatment of severe infections in humans.

Analysis

For the first time in Switzerland, an analysis to compare human and veterinary data on antibiotic use, and an attempt to evaluate associations between use and resistance, was conducted in this report. The objective was to analyze the Swiss antibiotic consumption and resistance data in a similar fashion as the JIACRA report. However, due to a lack of data and time, only a preliminary analysis was conducted. With improved data, more significant analyses will be possible in the upcoming years, focussing on potential associations between use of antibiotics and resistance.

In order to understand the epidemiology of methicillin-resistant *S. aureus* (MRSA) and the risk for the transmission from animals to humans, a study into the molecular characteristics of this pathogen was undertaken. Molecular features of Swiss MRSA strains, isolated from livestock and meat thereof with MRSA isolates from healthy veterinarians and farmers as well as human isolates from Swiss hospitals were compared. With this analysis, useful information on the distribution of hospital-acquired (HA) MRSA, community-acquired (CA) MRSA and livestock-associated (LA) MRSA in human and veterinary settings can be provided, helping to obtain insights into transmission risks in Switzerland. Swiss fattening pigs have shown a strong increase in the prevalence of MRSA carriage over the last ten years. The prevalence of MRSA in Swiss pork, beef and chicken meat is very low. The detected MRSA belonged to the LA-MRSA type. A study with Swiss veterinarians and farmers revealed that the majority of MRSA from veterinarians and farmers belonged to the LA-MRSA type. This is in line with findings on MRSA isolated from livestock, which also belong to the LA-MRSA type. The vast majority of MRSA isolated from inpatients are HA- and CA-MRSA; however, in two patients a LA-MRSA was detected. Continuous monitoring is needed, including molecular typing of both human and animal MRSA isolates.

2 Zusammenfassung

Resistenz bei Bakterien aus klinischen Isolaten vom Menschen

Seit 2008 wurden bei grampositiven und gramnegativen Bakterien unterschiedliche Trends beobachtet. Die Zahlen Methicillin-resistenter *Staphylococcus aureus* (MRSA) verzeichneten in invasiven Isolaten weiterhin einen deutlichen Rückgang, vor allem in der Westschweiz. Dieser Trend liess sich auch in einigen anderen europäischen Ländern feststellen, einschliesslich der Nachbarländer Deutschland, Frankreich und Österreich. In Wund- und Abszessproben von ambulanten Patientinnen und Patienten nahmen die MRSA-Raten hingegen zu.

Die Penicillin-Resistenz bei *Streptococcus pneumoniae* ging im Laufe der Zeit zurück. Der Grund dafür ist wahrscheinlich die Einführung von Pneumokokken-Impfstoffen, die zu einer Abnahme der resistenteren Serotypen führte. Die Vancomycin-Resistenz bei Enterokokken ist nach wie vor sehr tief, aber der in den vergangenen Monaten beobachtete Anstieg der Resistenzraten ist besorgniserregend.

Im Gegensatz dazu wurde bei *Escherichia coli* und *Klebsiella pneumoniae* eine stete Zunahme der Resistenzraten gegenüber Chinolonen und Cephalosporinen der dritten und vierten Generation festgestellt. Dies ist in den meisten europäischen Ländern zu beobachten und passt zur weiten Verbreitung von Extended-Spectrum-Beta-Laktamase-(ESBL-)produzierenden Isolaten. In den vergangenen zwei Jahren scheint sich dieser Trend in der Schweiz sowie in gewissen anderen europäischen Ländern stabilisiert zu haben. Erfreulicherweise bleibt die Resistenz gegenüber Carbapenemen bei *E. coli* und *K. pneumoniae* selten. Während dies bei *E. coli* auch in den meisten europäischen Ländern so ist, wird in Europa eine zunehmende Carbapenem-Resistenz bei *K. pneumoniae* verzeichnet: 2016 wurden in Italien, Griechenland und Rumänien Resistenzraten von über 25 % festgestellt. Um eine enge Überwachung der Verteilung von Carbapenemase-produzierenden Enterobacteriaceae sicherzustellen, gilt in der Schweiz seit dem 1. Januar 2016 eine Meldepflicht für diese Mikroorganismen.

Bei *Pseudomonas aeruginosa* erreichte die Resistenz gegenüber Piperacillin-Tazobactam und Ceftazidim 2015 einen Höhepunkt und ist seither leicht rückläufig, während die Resistenz gegenüber Aminoglykosiden eine stetige Zunahme verzeichnete. Keine bedeutenden Veränderungen wurden bei *Acinetobacter* spp. beobachtet und im Gegensatz zu Europa blieben die Carbapenemase-Raten bei diesem Erreger stabil.

Antibiotikaverbrauch in der Humanmedizin

In den Schweizer Akutspitälern stieg der Verbrauch von Antibiotika zur systemischen Anwendung (ATC-J01) zwischen 2007 und 2017 um 16 % auf 62,2 definierte Tagesdosen (Defined Daily Doses, DDD) pro 100 Bettentage an, während der Verbrauch berechnet in DDD pro 100 Einweisungen relativ konstant blieb. Diese Diskrepanz lässt sich mit der steigenden Anzahl Einweisungen und der aufgrund der kürzeren Spitalaufenthalte sinkenden Anzahl Bettentage erklären. Die am häufigsten verwendete Antibiotikagruppe waren die Penicilline (ATC-J01C), gefolgt von den anderen Beta-Laktam-Antibiotika, einschliesslich der Cephalosporine (ATC-J01D) und der Chinolone (ATC-Gruppe J01M).

In der ambulanten Versorgung belief sich 2017 der Gesamtverbrauch an Antibiotika zur systemischen Anwendung (ATC-J01) auf 10,7 DDD pro 1000 Einwohnerinnen und Einwohner und pro Tag. Die am häufigsten verwendete Antibiotikagruppe waren die Penicilline (ATC-J01C), gefolgt von den Makroliden, Lincosamiden und Streptograminen (ATC-J01F), den Tetracyclinen (ATC-J01A) und den Fluorochinolonen (ATC-J01MA). Der relative Verbrauch von Fluorochinolonen und Penicillinen in Kombination mit Beta-Laktamase-Inhibitoren war relativ hoch im Vergleich mit Ländern, die sich am European Surveillance of Antimicrobial Consumption Network (ESAC-Net) beteiligen.

Resistenzen bei Zoonose-Erregern

Bei *Campylobacter jejuni (C. jejuni)* in Geflügel hat die Resistenz gegenüber Ciprofloxacin und Tetracyclin in den letzten Jahren signifikant zugenommen. Von 15 % im Jahr 2006 stieg sie bei Ciprofloxacin auf 51,4 % und bei Tetracyclin auf 40 % im Jahr 2016 an. Eine Resistenz gegenüber Erythromycin wurde hingegen selten festgestellt (2,9 %). Gemäss der WHO gelten Fluorochinolone und Makrolide als kritische Antibiotika mit höchster Priorität in der Humanmedizin, weil diese Wirkstoffgruppen bei schweren Verlaufsformen der Campylobacteriose oder der Salmonellose beim Menschen bevorzugt zum Einsatz kommen.

Bei Mastschweinen ist die Resistenz bei *Campylobacter coli (C. coli)* gegenüber Streptomycin zwischen 2006 und 2012 gesunken. Danach stieg die Resistenzrate signifikant an und erreichte im Jahr 2017 81,4 %. Die Resistenz gegenüber Tetracyclin (62,1 %) und Ciprofloxacin (50,3 %) zeigte zwischen 2015 und 2017 keine grosse Veränderung.

Salmonella spp. sind bei Schweizer Nutztieren nur selten zu verzeichnen. Aus diesem Grund kann das Risiko einer Übertragung auf den Menschen von *Salmonella* über Fleisch von Schweizer Nutztieren als gering betrachtet werden. Zudem werden bei *Salmonella*, insbesondere bei *S.* Enteritidis und *S.* Typhimurium, konstant tiefe Resistenzraten verzeichnet.

Resistenzen bei Indikatorkeimen in Tieren

Bei Enterokokken und *E. coli*-Isolaten von Nutztieren in der Schweiz sind antimikrobielle Resistenzen im Allgemeinen weit verbreitet.

Die Enterokokkenspezies *E. faecalis* und *E. faecium* in Isolaten von Mastpoulets zeigten bei den Resistenzraten gegenläufige Trends. Während bei *E. faecalis* die Resistenz gegenüber Ampicillin und Tetracyclin seit 2012 zugenommen hat, waren die Resistenzraten bei den *E. faecium*-Isolaten im gleichen Zeitraum rückläufig. Eine vergleichbare Entwicklung war bei den Enterokokkenisolaten von Mastkälbern zu beobachten. Vancomycin-resistente Enterokokken (VRE) wurden in den vergangenen Jahren nur vereinzelt nachgewiesen. 2016 wurden bei Mastpoulets und 2017 bei Mastschweinen und Mastkälbern keine VRE entdeckt.

In kommensalen *Escherichia coli*-Isolaten von Mastpoulets, Mastschweinen und Mastkälbern wurden häufig hohe Resistenzen gegenüber Ampicillin (14,2 %–38,7 %), Sulfamethoxazol (46,9 %–26,8 %) und Tetracyclin (13,2 %–41,2 %) festgestellt. Zudem wurde in *E. coli*-Isolaten von Mastpoulets eine hohe Resistenz gegenüber Ciprofloxacin (37,9 %) nachgewiesen. Die Resistenz gegenüber diesen Wirkstoffen stieg bei Isolaten von Mastpoulets zwischen 2006 und 2012 an, war dann bis 2014 klar rückläufig, während sich im Jahr 2016 lediglich bei Tetracyclin eine Abnahme feststellen liess. In Isolaten von Mastkälbern wurde zwischen 2006 und 2013 ein sinkender Trend beobachtet. Die Resistenz gegenüber Tetracyclin, Sulfamethoxazol und Ampicillin nahm hingegen bis 2014 erneut zu und verblieb 2015 und 2017 auf diesem Niveau. Bei *E. coli*-Isolaten von Mastschweinen wies die Resistenzsituation bei den erwähnten mikrobiellen Wirkstoffen zwischen 2013 und 2017 keine Veränderung oder einen leicht sinkenden Trend auf.

In 52,4 % der Mastpouletbestände, in 17,6 % der Mastschweinbestände und in 33,2 % der Mastkälberbestände wurden ESBL/pAmpC-produzierende *E. coli* gefunden. Bei den Mastpoulets ist immer noch eine steigende ESBL/pAmpC-Prävalenz festzustellen, wenn auch in schwächerer Form als in den vergangenen Jahren (2014: 41,8 %). Bei den Mastschweinen hingegen war die ESBL/pAmpC-Prävalenz rückläufig (2015: 25,7 %), während sie bei den Mastkälbern auf hohem Niveau blieb (2015: 37,6 %).

Bei Nutztieren wurden keine Carbapenemase-produzierenden *E. coli* gefunden.

In der Schweiz stieg das Vorkommen von Methicillin-resistenten *S. aureus* (MRSA) bei Mastschweinen bei der Schlachtung signifikant an, seit der Nachweis von MRSA Teil der Überwachung wurde. Von anfänglichen 2 % im Jahr 2009 stieg die MRSA-Prävalenz auf 20,8 % im Jahr 2013 und erreichte 2017 schliesslich 44,0 %. Der gleiche Trend, wenn auch auf tieferem Niveau, wurde bei den Mastkälbern beobachtet. Im Jahr 2017 betrug die Prävalenz 8,1 %. Die Resultate bezüglich MRSA bestätigen, dass sich in der Schweizer Schlachtschweinepopulation vor allem der *spa* Typ t034 und der *spa* Typ t011 stark ausbreiten. Diese Genotypen gehören zur klonalen Linie CC398, die zu den sogenannten nutztierassoziierten MRSA (LA-MRSA) gehört. LA-MRSA können vom Tier auf den Menschen übertragen werden. In einer Analyse auf MRSA-Besiedelung bei stationären Schweizer Patientinnen und Patienten wurden zwei Fälle von LA-MRSA-Besiedelung (n=163) nachgewiesen.

Resistenzen bei Indikatorkeimen aus Fleisch

In 49,3 % der Hühnerfleischproben wurden ESBL/pAmpC-produzierende *E. coli* entdeckt. Die Prävalenz unterscheidet sich stark, je nachdem ob es sich um Schweizer Fleisch (41,9 %) oder um ausländisches Fleisch (64,9 %) handelt. Bei beiden ist die Gesamtprävalenz im Berichtszeitraum zurückgegangen (2014: Schweizer Fleisch 65,5 %; ausländisches Fleisch: 85,6 %). Trotz des rückläufigen Trends ist die Prävalenz dieser multiresistenten *E. coli* nach wie vor sehr hoch, was mit der festgestellten hohen Prävalenz von ESBL/pAmpC-produzierenden *E. coli* in Mastpoulets übereinstimmt.

Demgegenüber wurden nur in einer Schweinefleischprobe (n=302) und in zwei Rindfleischproben (n=299) ESBL/pAmpC-produzierende *E. coli* nachgewiesen. Dieser Unterschied ist möglicherweise auf die tiefere Prävalenz von ESBL/pAmpC-produzierenden *E. coli* bei Schweizer Schweinen und Kälbern sowie auf die unterschiedlichen Schlachtmethoden zurückzuführen. In Frischfleischproben wurden keine Carbapenemase-produzierenden *E. coli* gefunden.

MRSA wurden in grösseren Mengen nur in ausländischem Hühnerfleisch gefunden (2016: 9,3 %). Im Jahr 2016 wurden in Proben von Schweizer Hühnerfleisch (n=205) keine MRSA nachgewiesen. In Schweizer Rindfleisch (n=299) wurden ebenfalls keine und in Schweizer Schweinefleisch (n=301) nur in zwei Proben MRSA entdeckt. Das zweite Ergebnis ist von besonderem Interesse, da der starke Anstieg von MRSA in Mastschweinen (Prävalenz 44,0 %) anscheinend nicht zu einer Zunahme der MRSA-Prävalenz in Schweinefrischfleisch geführt hat. Diese Daten bestätigten, dass Lebensmittel keine relevante Quelle für eine MRSA-Übertragung auf den Menschen sind.

Resistenz bei Bakterien aus klinischen Isolaten von Tieren

Die Überwachung der Antibiotikaresistenz von relevanten Krankheitserregern bei erkrankten Nutz- und Heimtieren ist für Tierärztinnen und Tierärzte wichtig. Dies ermöglicht ih-

nen, eine angemessene therapeutische Wahl der Antibiotika zu treffen, bei der oftmals nicht auf ein vor der ersten Behandlung erstelltes Antibiogramm abgestützt werden kann. Zudem wird mit diesen Daten eine weitere grosse Lücke in der Überwachung der Antibiotikaresistenz nach dem One-Health-Ansatz geschlossen.

Zu diesem Zweck lancierte das Bundesamt für Lebensmittelsicherheit und Veterinärwesen (BLV) zusammen mit dem nationalen Referenzlaboratorium für Antibiotikaresistenz, dem Zentrum für Zoonosen, bakterielle Tierkrankheiten und Antibiotikaresistenz (ZOBA), im Jahr 2015 ein Pilotprojekt für die Überwachung von Antibiotikaresistenzen bei tierpathogenen Erregern in der Schweiz.

Alle Stämme wurden aus klinischem Material von erkrankten Tieren isoliert und vom ZOBA analysiert. Proben von Tieren, die vor der Probenahme eine Antibiotikabehandlung erhalten hatten, wurden aus der Studie ausgeschlossen. Im Gegensatz zur Überwachung von Isolaten von gesunden Schlachttieren, wurden die Daten zur minimalen Hemmstoffkonzentration (MHK) anhand der klinischen Grenzwerte ausgewertet. In der Kleintiermedizin beispielsweise wurden Resistenzdaten für *S. pseudintermedius* aus Wundinfektionen bei Hunden und für *E. coli* aus Infektionen des Urogenitaltraktes bei Katzen erhoben. *Staphylococcus aureus* aus bovinen Mastitisproben und *Streptococcus equi* subspecies *zooepidemicus* aus eitrigen Infektionen bei Pferden vervollständigten den Datensatz.

Die hohe Resistenz gegenüber wichtigen Antibiotika unterstreicht die Notwendigkeit einer systematischen Überwachung der Antibiotikaresistenz. Bei Tieren ist mit Infektionen durch multiresistente Erreger zu rechnen. Die Verwendung von kritischen Antibiotika kann jedoch mit den vorliegenden Daten nicht gestützt werden, da für die verschiedenen klinischen Settings genügend wirksame First-line-Antibiotika verfügbar sind. In Zukunft wird diese Überwachung noch repräsentativer sein, da ab 2019 Isolate von anderen Schweizer Laboratorien eingeschlossen werden.

Vertrieb von Antibiotika in der Veterinärmedizin

Die Gesamtmenge der verkauften Antibiotika ging in den Jahren 2016 und 2017 weiter zurück. 2016 wurden insgesamt 38377 kg und im Jahr 2017 32328 kg Antibiotika zur Behandlung von Tieren verkauft. Dies entspricht einem Rückgang seit 2008 um 53 % (37 t). Der Rückgang ist hauptsächlich auf eine Reduktion der Verkäufe von Arzneimittelvormischungen zurückzuführen. Unverändert blieb die Reihenfolge der meistverkauften Wirkstoffklassen: An erster Stelle stehen die Sulfonamide, gefolgt von Penicillinen und Tetracyclinen. Diese drei Wirkstoffklassen sind häufig in Arzneimittelvormischungen enthalten. Der Anteil der Wirkstoffe, die nur für Heimtiere zugelassen sind, macht 2,5 % der Gesamtmenge aus.

Die Vertriebsmengen der kritischen Antibiotikaklassen mit höchster Priorität für die Humanmedizin waren 2016 und 2017 rückläufig. Die Verkäufe der Makrolide gingen 2016 um 25 % und 2017 um weitere 20 % zurück. Bei den Fluorchinolonen nahmen die Vertriebsmengen 2016 um 21 % und 2017 um 25 % ab. Die Verkäufe der Cephalosporine der dritten und vierten Generation gingen 2016 und 2017 um rund 23 % zurück. Bei Colistin ging das Verkaufsvolumen seit 2008 um rund 79 % zurück. Ausgedrückt in Bezug zur Populationsbiomasse wurde in der Schweiz 0,4 mg Colistin/PCU (Population Correction Unit) verkauft. Dies liegt unter dem europäischen Durchschnitt und entspricht der Forderung nach einer Reduktion von Colistin auf 1 mg/PCU oder weniger in den europäischen Ländern, um die Wirksamkeit bei der Behandlung von schweren Infektionen beim Menschen zu erhalten.

Analyse

Zum ersten Mal in der Schweiz wurde in diesem Bericht eine Analyse durchgeführt, um human- und veterinärmedizinische Daten zum Antibiotikaeinsatz zu vergleichen. Zudem wurde versucht, die Zusammenhänge zwischen Einsatz und Resistenz zu evaluieren. Das Ziel bestand darin, die Schweizer Daten zu Antibiotikaverbrauch und -resistenz in ähnlicher Weise wie im JIACRA-Bericht zu analysieren. Mangels Daten und Zeit erfolgte jedoch nur eine Voranalyse. Mit verbesserten Daten werden in den kommenden Jahren signifikantere Analysen mit Fokus auf den möglichen Zusammenhängen zwischen Antibiotikaeinsatz und -resistenz möglich sein.

Um die Epidemiologie Methicillin-resistenter *S. aureus* (MRSA) und das Risiko der Übertragung vom Tier auf den Menschen zu erfassen, wurde eine Studie über die molekularen Merkmale dieses Erregers durchgeführt. Aus Nutztieren und deren Fleisch isolierte Schweizer MRSA-Stämme wurden bezüglich molekularer Eigenschaften mit MRSA-Isolaten gesunder Tierärzte und Landwirte sowie mit menschlichen Isolaten aus Schweizer Spitälern verglichen. Diese Analyse kann nützliche Informationen zur Verbreitung von im Spital erworbenen MRSA (HA-MRSA), ambulant erworbenen MRSA (CA-MRSA) und nutztierassoziierten MRSA (LA-MRSA) in human- und veterinärmedizinischen Settings liefern und dazu beitragen, Erkenntnisse zu den Übertragungsrisiken in der Schweiz zu gewinnen. Schweizer Mastschweine zeigten eine starke Zunahme bei der Prävalenz der MRSA-Besiedelung über die letzten zehn Jahre. Die MRSA-Prävalenz bei Schweizer Schweine-, Rind- und Hühnerfleisch ist sehr tief. Die nachgewiesenen MRSA gehören zum Typ LA-MRSA. Eine Studie mit Schweizer Tierärzten und Landwirten ergab, dass die Mehrheit der MRSA bei Tierärzten und Landwirten ebenfalls vom Typ LA-MRSA ist. Das stimmt mit den Ergebnissen bei den aus Nutztieren isolierten MRSA überein, die auch zum Typ LA-MRSA gehören. Die grosse Mehrheit der aus stationären Patientinnen und Patienten isolierten MRSA sind HA- und CA-MRSA. Bei zwei Patienten wurden jedoch LA-MRSA nachgewiesen. Es ist ein kontinuierliches Monitoring erforderlich, das die molekulare Typisierung menschlicher wie auch tierischer MRSA-Isolate beinhaltet.

2 Synthèse

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

Depuis 2008, 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) dans les isolats invasifs ont nettement reculé, en particulier en Suisse romande. Cette tendance a également pu être observée dans différents pays européens, comme les pays limitrophes que sont l'Allemagne, la France et l'Autriche. En revanche, les taux de SARM sont en augmentation dans les échantillons prélevés sur des plaies et des abcès de patients recevant des soins ambulatoires. 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 restent très faibles, toutefois leur progression au cours de ces derniers mois est préoccupante.

En revanche, la résistance aux quinolones et aux céphalosporines de troisième et quatrième génération croît de façon régulière chez *Escherichia coli (E. coli)* et *Klebsiella pneumoniae (K. pneumoniae).* Cette évolution a pu être observée dans la plupart des pays européens et coïncide avec la large distribution des isolats producteurs de bêta-lactamases à spectre élargi (BLSE) ; cette tendance semble s'être stabilisée au cours des deux dernières années en Suisse comme dans d'autres pays européens. Heureusement, la résistance aux carbapénèmes est encore rare chez *E. coli* et *K. pneumoniae.* Dans la majorité des pays européens, on observe toutefois une résistance aux carbapénèmes croissante chez *K. pneumoniae,* alors que la résistance chez *E. coli* reste rare ; en 2016, des taux de résistance dépassant les 25 % ont été décrits en Italie, en Grèce et en Roumanie. Afin d'assurer une surveillance accrue de la distribution d'entérobactéries productrices de carbapénèmases (EPC), une obligation de déclaration de ces micro-organismes est entrée en vigueur au 1er janvier 2016 en Suisse.

Chez *Pseudomonas aeruginosa,* les fortes progressions dans les taux de résistance pour la pipéracilline-tazobactam et la ceftazidime ont connu un pic en 2015 et ont légèrement reculé depuis, alors que les taux de résistance pour les aminoglycosides sont en constante progression. Aucune tendance particulière n'a été observée chez *Acinetobacter* spp. et les taux de résistance pour les carbapénèmases sont stables contrairement à ceux des autres pays européens.

Consommation d'antibiotiques en médecine humaine

Dans les hôpitaux suisses de soins aigus, la consommation de médicaments antibactériens à usage systémique (classe ATC J01) pour 100 journées d'hospitalisation a crû de 16 % à 62,2 DDD (Defined Daily Doses) entre 2007 et 2017. 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 des antibiotiques les plus fréquemment utilisés était celle des pénicillines (classe ATC J01C), suivie des autres bétalactamines qui comprennent notamment les céphalosporines (classe ATC J01D), et des quinolones (classe ATC J01M).

En milieu ambulatoire, la consommation totale d'antibactériens à usage systémique (classe ATC J01) était de 10.7 DDD pour 1 000 habitants et par jour en 2017. La classe des antibiotiques les plus fréquemment utilisés était celle des pénicillines (classe ATC J01C), suivie des macrolides, lincosamides et streptogramines (classe ATC J01F), tétracyclines (classe ATC J01A) et fluoroquinolones (classe ATC J01MA). La consommation relative de fluoquinolones et de pénicillines incluant des inhibiteurs de bêta-lactamases était relativement élevée par rapport à celle des pays membres du Réseau européen de surveillance de la consommation d'antimicrobiens (ESAC-Net).

Résistance des bactéries zoonotiques

Concernant la volaille, la résistance de *Campylobacter jejuni (C. jejuni)* à la ciprofloxacine et à la tétracycline a augmenté de manière significative ces dernières années. De 15 % en 2006, le taux de résistance à la ciprofloxacine est passé à 51,4 % en 2016, la résistance à la tétracycline atteignant 40 %. En revanche, la résistance à l'érythromycine (2,9 %) n'a été que rarement constatée. Selon l'OMS, les fluoroquinolones et les macrolides appartiennent à la catégorie des antimicrobiens critiques de première priorité dans la médecine humaine, 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 d'engraissement, le taux de résistance à la streptomycine des souches de *Campylobacter coli (C. coli)* a baissé entre 2006 et 2012. Ce taux a connu une forte croissance ces dernières années, atteignant 81,4 % en 2017. Les

résistances à la tétracycline (62,1 %) et à la ciprofloxacine (50,3 %) sont restées quant à elles relativement stables entre 2015 et 2017.

En Suisse, les *Salmonella* spp. sont rares chez les animaux de rente. Aussi le risque de transmission de salmonelles à l'homme à partir d'aliments produits avec de la viande suisse est-il considéré comme faible. De plus, leurs taux de résistance restent bas, en particulier chez *S.* Enteritidis et *S.* Typhimurium.

Résistance des germes indicateurs chez les animaux

En Suisse, la résistance antimicrobienne est généralement répandue chez les entérocoques et *E. coli* isolés à partir d'animaux de rente.

Les entérocoques *E. faecalis* et *E. faecium* isolés à partir de poulets de chair ont montré une tendance inverse : tandis que la résistance d'*E. faecalis* à l'ampicilline et à la tétracycline augmente depuis 2012, les taux de résistance dans les isolats d'*E. faecalis* ont diminué dans la même période. Un phénomène analogue a été observé avec des isolats d'entérocoques prélevés chez les veaux d'engraissement. Ces dernières années, des entérocoques résistants à la vancomycine (ERV) n'ont été détectés qu'occasionnellement. Aucun ERV n'a été décelé chez les poulets de chair en 2016, ni chez les porcs et les veaux d'engraissement en 2017.

On observe des taux élevés de résistance à l'ampicilline (14,2 % à 38,7 %), au sulfaméthoxazole (46,9 % à 26,8 %) et à la tétracycline (13,2 % à 41,2 %) en flore commensale dans des isolats d'*E. coli* chez les poulets de chair, les porcs et les veaux d'engraissement. De plus, une résistance élevée à la ciprofloxacine a été découverte dans des isolats prélevés chez des poulets de chair (37,9 %). Les résistances à ces substances ont augmenté dans les isolats provenant de poulets de chair entre 2006 et 2012, avant de diminuer sensiblement jusqu'en 2014 ; ce recul n'a pas été observé en 2016 si ce n'est pour la tétracycline. Dans les isolats prélevés chez les veaux d'engraissement, une tendance à une diminution des résistances a été observée entre 2006 et 2013. Toutefois, les résistances à la tétracycline, au sulfaméthoxazole et à l'ampicilline ont à nouveau augmenté jusqu'en 2014 pour se stabiliser en 2015 et 2017. De 2013 à 2017, les taux de résistance aux antibiotiques mentionnés ci-dessus dans les isolats d'*E. coli* provenant de porcs d'engraissement étaient plutôt stables ou en léger recul.

Des *E. coli* producteurs de BLSE/AmpC ont été identifiés dans 52,4 % des cheptels de poulets de chair examinés, 17,6 % de ceux de porcs d'engraissement et 33,2 % de ceux de veaux d'engraissement. La prévalence de BLSE/AmpC chez les poulets de chair ne cesse de croître, même si cette croissance est moins forte qu'au cours des années précédentes (41,8 % en 2014). En revanche, la prévalence de BLSE chez les porcs d'engraissement (25,7 % en 2015) a diminué ; elle est restée élevée chez les veaux (37,6 % en 2015).

Aucun *E. coli* producteur de carbapénémases n'a été identifié chez les animaux de rente.

En Suisse, la prévalence des *Staphylococcus aureus* résistants à la méticilline (SARM) chez les porcs d'engraissement au moment de l'abattage progresse constamment depuis que sa détection fait partie intégrante des mesures de surveillance. La prévalence des SARM est passée de 2 % en 2009 à 20,8 % en 2013 pour atteindre 44 % en 2017. La même tendance a été observée dans une moindre mesure chez les veaux d'engraissement. En 2017, la prévalence effective était de 8,1 %. Les résultats pour les SARM confirment en particulier que les types spa t034 et spa t011 sont en passe de s'étendre largement dans les cheptels de porcs d'abattage. Ces génotypes font partie d'un certain complexe clonal CC 398, typiquement associés aux animaux de rente. Les SARM associés aux animaux de rente (livestock-associated, LA-MRSA) peuvent se transmettre de l'animal à l'homme. Une étude relative aux porteurs de SARM parmi les patients hospitalisés en Suisse a révélé deux cas (n=163).

Résistance des germes indicateurs dans la viande

Des *E. coli* producteurs de BLSE/AmpC ont été découverts dans 49,3 % des échantillons de viande de poulet. La prévalence est sensiblement différente selon qu'il s'agit de viande suisse (41,9 %) ou de viande d'importation (64,9 %). On observe toutefois une diminution globale de la prévalence dans ces deux types de viande dans la période sous revue (65,5 % pour la viande suisse et 85,6 % pour la viande importée en 2014). Bien qu'une tendance à la baisse ait été observée, la prévalence de ces *E. coli* multirésistants reste très élevée et liée à une forte prévalence d'*E. coli* producteurs de BLSE/AmpC chez les poulets de chair.

En revanche, l'*E. coli* producteur de BLSE/AmpC a été identifié dans un seul échantillon de porc (n=302) et deux de bœuf (n=299). Cet écart peut s'expliquer par la prévalence plus basse de cette bactérie chez les porcs et les veaux suisses et la différence dans les méthodes d'abattage. Aucun *E. coli* producteur de carbapénémases n'a été identifié dans les échantillons de viande fraîche.

Des SARM ont été trouvés en grande quantité uniquement dans la viande de poulets d'origine étrangère (9,3 % en 2016). En 2016, aucun SARM n'a été identifié dans les échantillons de viande de poulets élevés en Suisse (n=205), ni dans la viande de bœufs suisses (n=299) et seulement deux cas ont été observés dans la viande de porcs suisses (n=301). Ce dernier résultat est particulièrement intéressant car il montre que malgré la forte augmentation de SARM identifiés chez les porcs d'engraissement (prévalence de 44,0 %), leur prévalence dans la viande fraîche semble ne pas avoir progressé. Ces données confirment que l'alimentation n'est pas considérée comme une source pertinente de transmission des SARM à l'homme.

Résistance des bactéries dans les isolats cliniques chez l'animal

La surveillance de l'antibiorésistance des agents pathogènes d'importance clinique sur le cheptel malade et les animaux de compagnie est particulièrement utile aux vétérinaires dans leur choix de l'antibiothérapie la plus appropriée, ceux-ci ne pouvant généralement pas s'appuyer sur un antibiogramme préalable au premier traitement. Ces données comblent en outre une autre lacune importante dans la surveillance de l'antibiorésistance selon l'approche One Health.

Aussi, en 2015, l'Office fédéral de la sécurité alimentaire et des affaires vétérinaires (OSAV) a-t-il lancé un projet pilote de surveillance des agents pathogènes animaux en Suisse, conjointement avec le Centre des zoonoses, des maladies animales d'origine bactérienne et de l'antibiorésistance (ZOBA), laboratoire de référence en matière de résistance aux antimicrobiens en Suisse.

Toutes les souches proviennent d'isolats cliniques prélevés chez des animaux malades examinés par le ZOBA. Les échantillons provenant d'animaux auxquels un traitement antimicrobien avait été administré avant le prélèvement ont été exclus de l'étude. À la différence de la surveillance d'isolats d'animaux abattus en bonne santé, les données relatives à la concentration minimale inhibitrice (CMI) ont été interprétées en fonction de valeurs cliniques limites. Par exemple, en médecine des petits animaux, des données sont recueillies sur la résistance des *S. pseudintermedius* isolés à partir de plaies infectées chez des chiens, et des E. coli isolés à partir d'infections des voies urogénitales canines. L'ensemble des données a été complété par celles concernant des *Staphylococcus aureus* trouvés sur des échantillons de mammite bovine et des *zooepidemicus,* sous-espèces des *Streptococcus equi,* provenant d'infections purulentes chez des chevaux.

Le haut niveau de résistance à des antimicrobiens importants souligne la nécessité d'assurer une surveillance systématique. Il faut s'attendre de plus en plus à ce que des agents pathogènes multirésistants provoquent des infections chez des animaux. Toutefois, les données présentées ne justifient pas l'usage d'agents antimicrobiens d'importance critique, des antibiotiques de première intention suffisamment efficaces pour traiter les différents cas cliniques étant disponibles. Cette surveillance sera encore plus représentative à l'avenir puisqu'à partir de 2019, elle portera également sur les isolats d'autres laboratoires suisses.

Vente d'antibiotiques utilisés en médecine vétérinaire

Les ventes d'antibiotiques à usage vétérinaire ont continué à diminuer en 2016 et 2017. Globalement, 38 377 kg de médicaments de ce type ont été vendus en 2016 et 32 328 kg en 2017, soit une baisse atteignant 53 % (37 tonnes) depuis 2008. Ce recul est principalement dû à une baisse des ventes des prémélanges pour aliments médicamenteux.

Le classement des ventes d'antimicrobiens reste inchangé : les sulfonamides sont en tête, suivis des pénicillines et des tétracyclines. Ces trois classes sont souvent vendues sous forme de prémélanges pour aliments médicamenteux. La part des antibiotiques autorisés uniquement pour les animaux s'élève à 2,5 % de la quantité totale.

Les ventes d'antimicrobiens critiques de première priorité en médecine humaine ont diminué en 2016 et 2017 ; les ventes de macrolides ont baissé de 25 % en 2016 et de 20 % supplémentaires en 2017. Les ventes de fluoroquinolones ont chuté de 21 % en 2016 et de 25 % en 2017. Celles de céphalosporines de troisième et quatrième génération ont diminué d'environ 23 % en 2016 et dans la même proportion en 2017. Les ventes de colistine ont baissé d'environ 79 % depuis 2008. Exprimées en corrélation avec la biomasse analysée, les ventes de colistine atteignent 0,4 mg/PCU (population correction unit) en Suisse. Ces quantités sont inférieures à la moyenne européenne et répondent à l'exigence de l'Union européenne (UE) de réduire la colistine à 1 mg/PCU maximum pour maintenir l'efficacité du traitement d'infections graves chez l'être humain.

Analyses

L'étude présentée dans ce rapport est la première du genre en Suisse. Elle vise à comparer les données humaines et animales de l'utilisation des antibiotiques, et tente d'évaluer les liens entre l'administration de ces médicaments et l'antiobiorésistance. L'objectif est d'examiner les informations relatives à la consommation et aux résistances en Suisse comme le fait le rapport JIACRA dans l'Union européenne. Toutefois, par manque de temps et de données, seule une analyse préliminaire a été menée. Dans les années à venir, lorsque des informations plus solides seront disponibles, il sera possible d'effectuer des recherches plus significatives, et de se concentrer sur les potentielles relations entre l'utilisation des antibiotiques et les résistances observées.

Une étude des caractéristiques moléculaires du Staphylococcus aureus résistant à la méticilline (SARM) a été entreprise dans le but de comprendre l'épidémiologie de cette bactérie et le risque qu'elle se transmette des animaux aux êtres humains. Cette analyse a permis de comparer les caractéristiques moléculaires de souches prélevées sur du bétail et de la viande avec celles de souches provenant d'isolats humains, constitués à partir de vétérinaires et de fermiers en bonne santé ainsi que de patients d'hôpitaux suisses. L'étude fournit des informations utiles à propos de la dissémination des SARM nosocomiales (HA-SARM), d'origine communautaire (CA-SARM) et associées au bétail (LA SARM) dans les contextes humain et vétérinaire. Elle nous aide ainsi à mieux évaluer les risques de transmission en Suisse. Dans notre pays, la prévalence du portage de SARM a connu une forte augmentation chez les porcs à l'en-

grais au cours des dix dernières années. La prévalence dans la viande suisse de porc, de bœuf et de poulet est très basse. Les souches détectées appartiennent au type LA-SARM. Une étude réalisée avec des vétérinaires et des fermiers avait révélé que la majorité des SARM provenant de ces personnes était de type LA ; ce constat corrobore les résultats obtenus à propos de souches prélevées sur du bétail, qui sont du même type. La grande majorité des SARM provenant de patients hospitalisés sont de type HA ou CA ; cependant, une souche de type LA a été détectée chez deux d'entre eux. Il est donc nécessaire d'assurer une surveillance continue et d'effectuer un typage moléculaire d'isolats de SARM à la fois chez les humains et chez les animaux.

2 Sintesi

Resistenza nei batteri presenti in isolati clinici umani

Diverse sono le tendenze osservate a livello di batteri gram-positivi e gram-negativi a partire dal 2008. I tassi di *Staphylococcus aureus* resistente alla meticillina (MRSA) hanno continuato a diminuire notevolmente negli isolati invasivi, perlopiù nella parte occidentale della Svizzera. La stessa tendenza è stata osservata in numerosi altri Paesi europei, incluse la Germania, la Francia e l'Austria. Per contro, i tassi di MRSA sono in aumento nei campioni prelevati da ferite e ascessi di pazienti ambulatoriali. È diminuita nel corso del tempo anche la resistenza alla penicillina in *Streptococcus pneumoniae*, perlopiù a seguito di una riduzione nella prevalenza di sierotipi più resistenti, dovuta all'introduzione di vaccini antipneumococchi. La resistenza degli enterococchi alla vancomicina è ancora molto bassa, ma sono stati osservati tassi di incremento preoccupanti negli ultimi mesi.

È stato invece riscontrato un costante aumento della resistenza al chinolone e alle cefalosporine di terza e quarta generazione in *Escherichia coli* e *Klebsiella pneumoniae*. Lo stesso incremento è stato osservato nella maggior parte dei Paesi europei ed è in linea con l'ampia distribuzione di isolati produttori di beta-lattamasi a spettro esteso (ESBL). Negli ultimi due anni questa tendenza sembra essersi stabilizzata in Svizzera e in altri Paesi europei. In *E. coli* e *K. pneumoniae* è fortunatamente ancora rara la resistenza ai carbapenemi. Mentre però la resistenza in *E. coli* è rara anche nella maggior parte dei Paesi europei, una crescente resistenza ai carbapenemi si osserva in Europa per *K. pneumoniae*; nel 2016 tassi di resistenza superiori al 25 per cento sono stati riportati in Italia, Grecia e Romania. Per consentire un monitoraggio più preciso della distribuzione delle enterobatteriacee produttrici di carbapenemasi, il 1° gennaio 2016 è stato introdotto in Svizzera l'obbligo di notifica di questi microrganismi.

In *Pseudomonas aeruginosa* l'aumento dei tassi di resistenza alla piperacillina-tazobactam e alla ceftazidima ha raggiunto un picco nel 2015 e da allora è leggermente diminuito, mentre i tassi di resistenza agli amminoglucosidi sono in costante aumento. Nessun cambiamento rilevante si segnala invece in *Acinetobacter* spp. A differenza che in Europa, i tassi di carbapenemasi sono rimasti stabili.

Consumo di antibiotici nella medicina umana

Tra il 2007 e il 2017, il consumo di antibiotici ad uso sistemico (gruppo ATC J01) negli ospedali svizzeri per cure acute è aumentato del 16 per cento a 62,2 dosi definite giornaliere (DDD, Defined Daily Doses) per 100 giorni di degenza, mentre è rimasto relativamente stabile se espresso in DDD per 100 ricoveri. Tale discrepanza può essere spiegata da un tendenziale aumento del numero di ricoveri e una riduzione del numero di giorni di degenza, dovuta a una minore durata del soggiorno in ospedale. La classe di antibiotici più comunemente usata è stata quella delle penicilline (gruppo ATC J01C), seguita dagli altri antibatterici beta-lattamici, compresi le cefalosporine (gruppo ATC J01D) e i chinoloni (gruppo ATC J01M).

Nell'ambito delle cure ambulatoriali, nel 2017 il consumo totale di antibiotici ad uso sistemico (gruppo ATC J01) è stato di 10,7 DDD al giorno ogni 1000 abitanti. La classe di antibiotici più comunemente usata è stata quella delle penicilline (gruppo ATC J01C), seguita da macrolidi, lincosamidi e streptogramine (gruppo ATC J01F), tetracicline (gruppo ATC J01A) e fluorochinoloni (gruppo ATC J01MA). Il consumo relativo di fluorochinoloni e penicilline associati ad inibitori della beta-lattamasi è risultato comparativamente alto rispetto a quello dei Paesi che partecipano alla Rete europea di sorveglianza del consumo di antimicrobici (ESAC-Net).

Resistenza nei batteri zoonotici

Nel pollame, il tasso di resistenza alla ciprofloxacina e alla tetraciclina di *Campylobacter jejuni (C. jejuni*) è aumentato significativamente negli ultimi anni, passando dal 15 per cento nel 2006 al 51,4 per cento nel 2016 per la ciprofloxacina e al 40 per cento per la tetraciclina. È invece stata rilevata raramente una resistenza all'eritromicina (2,9 %). L'Organizzazione mondiale della sanità (OMS) considera i fluorochinoloni e i macrolidi degli antibiotici critici di massima priorità nella medicina umana, poiché questi gruppi di principi attivi costituiscono la terapia elettiva di gravi forme di campilobatteriosi o salmonellosi nell'uomo.

Nei suini da ingrasso, il tasso di resistenza alla streptomicina di *Campylobacter coli (C. coli)* è diminuito tra il 2006 e il 2012, per poi aumentare significativamente negli ultimi anni fino a toccare l'81,4 per cento nel 2017. I tassi di resistenza alla tetraciclina (62,1 %) e alla ciprofloxacina (50,3 %) non sono cambiati significativamente tra il 2015 e il 2017.

La *Salmonella* spp. è presente solo raramente negli animali da reddito in Svizzera. Il rischio di una sua trasmissione all'uomo tramite alimenti prodotti a partire da animali svizzeri è dunque considerato basso. Inoltre presenta tassi di resistenza costantemente bassi, specie nel caso di *S. enteritidis* e *S. typhimurium*.

Resistenza nei batteri indicatori negli animali

In generale l'antibiotico-resistenza è ampiamente diffusa negli enterococchi e nell'*E. coli* isolati da animali da reddito allevati in Svizzera.

I tassi di resistenza delle specie di enterococchi *E. faecalis* ed *E. faecium* isolate dai polli da carne presentano tendenze opposte. Mentre per *E. faecalis* la resistenza alla tetraciclina e all'ampicillina è aumentata dal 2012, nello stesso periodo i tassi di resistenza degli isolati di *E. faecium* sono diminuiti. Un effetto comparabile è stato osservato negli enterococchi isolati dai vitelli da carne, nei quali gli enterococchi resistenti alla vancomicina (VRE) sono stati rilevati soltanto sporadicamente negli ultimi anni. Nel 2016 non sono stati rilevati VRE nei polli da carne, né nei suini da ingrasso e nei vitelli da carne nel 2017.

Sono stati riscontrati tassi elevati di resistenza all'ampicillina (14,2 %-38,7 %), al sulfametoxazolo (46,9 %-26,8 %) e alla tetraciclina (13,2 %-41,2 %) negli isolati di *E. coli* commensale provenienti da polli da carne, suini da ingrasso e vitelli da carne. Inoltre, è stata riscontrata un'elevata resistenza alla ciprofloxacina negli isolati provenienti da polli da carne (37,9 %). In questi ultimi, la resistenza a questi principi attivi è aumentata dal 2006 al 2012, poi è nettamente diminuita fino al 2014, mentre per il 2016 non è stato riscontrato alcun decremento, fatta eccezione per le tetracicline. Dal 2006 al 2013 è stata osservata una tendenza alla diminuzione della resistenza negli isolati provenienti da vitelli, ma le resistenze alla tetraciclina, al sulfametoxazolo e all'ampicillina sono nuovamente aumentate fino al 2014, stabilizzandosi dal 2015 al 2017. Nei suini da ingrasso, i tassi di resistenza ai succitati antibiotici negli isolati di *E. coli* sono stabili o in leggera diminuzione dal 2013 al 2017.

Dei ceppi di *E. coli* produttori di ESBL/pAmpC sono stati rilevati nel 52,4 per cento dei gruppi di polli da carne, nel 17,6 per cento dei suini da ingrasso e nel 33,2 per cento dei vitelli da carne. Nei polli da carne, l'aumento della prevalenza di ESBL/pAmpC prosegue, anche se a un livello inferiore a quello degli anni precedenti (2014: 41,8 %). La prevalenza di ESBL è invece diminuita nei suini da ingrasso (2015: 25,7 %) ed è rimasta elevata per i vitelli (2015: 37,6 %).

In nessuna specie di animali da reddito sono stati trovati *E. coli* produttori di carbapenemasi.

In Svizzera, la presenza di *S. aureus* resistente alla meticillina (MRSA) nei suini da ingrasso alla macellazione è significativamente aumentata da quando l'MRSA è entrato a far parte del monitoraggio. Dal 2 per cento del 2009, la prevalenza è passata al 20,8 per cento nel 2013 e ha toccato il 44,0 per cento nel 2017. La stessa tendenza, seppur a un livello inferiore, si riscontra per la presenza di MRSA nei vitelli da carne. L'effettiva prevalenza nel 2017 è stata dell'8,1 per cento. I risultati riportati per l'MRSA confermano che lo spa tipo t034 e lo *spa* tipo t011 si stanno diffondendo nella popolazione svizzera di suini macellati. Entrambi questi genotipi appartengono al complesso clonale CC 398, tipicamente associato agli animali da reddito (LA-MRSA). Il batterio LA-MRSA può essere trasmesso dagli animali all'uomo. Un'analisi della presenza dell'MRSA nei pazienti ricoverati in Svizzera ha rivelato due casi di pazienti svizzeri portatori di LA-MRSA (n=163).

Resistenza nei batteri indicatori presenti nella carne

Nel 49,3 per cento dei campioni di carne di pollo sono stati riscontrati *E. coli* produttori di ESBL/pAmpC. La prevalenza varia notevolmente tra la carne svizzera (41,9 %) e quella prodotta all'estero (64,9 %). Per entrambe, la prevalenza complessiva è diminuita nel periodo oggetto del rapporto (2014: carne svizzera 65,5 %; carne dall'estero: 85,6 %). Nonostante sia stata rilevata una tendenza alla diminuzione, la prevalenza di *E. coli* multiresistenti è tuttora molto alta e corrisponde all'elevata prevalenza di *E. coli* produttori di ESBL/pAmpC nei polli da carne.

Per contro, si è registrata una sola occorrenza di *E. coli* produttori di ESBL/pAmpC nella carne di maiale (n=302); altre due sono state riscontrate in campioni di carne bovina (n=299). La differenza potrebbe essere correlata alla minore prevalenza di questi batteri nei maiali e nei vitelli svizzeri e ai processi di macellazione distinti di questi animali. Non sono stati trovati *E. coli* produttori di carbapenemasi nei campioni di carne fresca.

L'MRSA è stato rilevato in quantità notevoli soltanto nella carne di pollo prodotta all'estero (2016: 9,3 %). Nel 2016 non è stata riscontrata alcuna contaminazione da MRSA nei campioni di carne di pollo svizzera (n=205), né nella carne di manzo svizzera (n=299) e sono stati segnalati soltanto due casi di MRSA nella carne di maiale di produzione nazionale (n=301). Quest'ultimo dato è particolarmente interessante poiché il forte incremento dell'MRSA nei suini da ingrasso (prevalenza 44,0 %) non sembra averne aumentato la prevalenza nella carne suina fresca. I dati confermano che il cibo non è da considerarsi una fonte rilevante di trasmissione dell'MRSA all'uomo.

Resistenza nei batteri da isolati clinici di animali

Il monitoraggio della resistenza agli antimicrobici nei germi patogeni rilevanti provenienti da animali da reddito o da compagnia ammalati è importante per i veterinari perché consente loro di scegliere gli antibiotici più appropriati per la terapia, dato che spesso non è possibile effettuare un antibiogramma prima di iniziarla. Inoltre, questi dati colmano un'altra importante lacuna nel monitoraggio della resistenza agli antimicrobici dal punto di vista One Health.

Pertanto, nel 2015 l'Ufficio federale della sicurezza alimentare e di veterinaria (USAV) ha lanciato un progetto pilota per il monitoraggio degli agenti patogeni veterinari in Svizzera, in collaborazione con il laboratorio di riferimento nazionale per

il riconoscimento precoce di nuove forme di resistenza agli antibiotici e con il Centro per le zoonosi, le malattie animali di origine batterica e la resistenza agli antibiotici (ZOBA).

Tutti i ceppi sono stati isolati da campioni clinici di animali malati analizzati dallo ZOBA. Sono stati esclusi dallo studio i campioni provenienti da animali già in terapia antibiotica prima del prelievo del campione. A differenza di quanto avviene nel monitoraggio degli isolati di animali da macello sani, i dati della concentrazione minima inibitoria (MIC) sono stati interpretati in base a breakpoint clinici. Sono riportati, a titolo di esempio per la medicina dei piccoli animali, i dati sulla resistenza di *S. pseudintermedius* isolato dalle infezioni di ferite del cane e di *E. coli* isolato dalle infezioni del tratto urogenitale del cane. Completano la raccolta di dati lo *Staphylococcus aureus* da campioni di mastite bovina e lo *Streptococcus equi* sub species *zooepidemicus* derivato dalle infezioni purulente del cavallo.

La presenza di livelli di resistenza elevati ad antibiotici importanti sottolinea la necessità di un monitoraggio sistematico. Negli animali ci si deve attendere delle infezioni causate da agenti patogeni veterinari multiresistenti. Questi dati non devono tuttavia incoraggiare il ricorso agli antimicrobici di importanza critica, dato che esistono antibiotici di prima scelta sufficientemente efficaci per i diversi quadri clinici. L'inclusione di isolati da altri laboratori svizzeri a partire dal 2019 renderà questo monitoraggio ancora più rappresentativo.

Vendite di antibiotici nella medicina veterinaria

Nel 2016 e nel 2017, il volume di vendita degli antimicrobici ha continuato a diminuire. Complessivamente, nel settore della medicina veterinaria sono stati venduti 38377 kg di antimicrobici nel 2016 e 32328 kg nel 2017, con un calo del 53 per cento (37 tonnellate) dal 2008, dovuto prevalentemente a una diminuzione delle vendite di premiscele medicate. La classifica di vendita delle diverse classi di antibiotici è rimasta invariata: i sulfamidici sono al primo posto, seguiti da penicilline e tetracicline. Queste tre classi sono spesso vendute come premiscele medicate. La quantità di antibiotici omologati unicamente per gli animali da compagnia costituisce il 2,5 per cento del volume totale. Nel 2016 e nel 2017, le vendite di classi di antibiotici critici di massima priorità per la medicina umana sono diminuite; quelle dei macrolidi hanno subìto una contrazione del 25 per cento nel 2016 e di un altro 20 per cento nel 2017. Le vendite di fluorichinoloni sono scese del 21 per cento nel 2016 e del 25 per cento nel 2017, quelle di cefalosporine di terza e quarta generazione del 23 per cento circa nel 2016 e nel 2017. Il volume di vendita della colistina è diminuito approssimativamente del 79 per cento dal 2008. Espresso in correlazione alla biomassa esposta, il livello per la Svizzera è di 0,4 mg/PCU di colistina, inferiore alla media europea e in linea con la richiesta di riduzione della colistina a un livello pari o inferiore a 1 mg/PCU per i Paesi europei, in modo da preservarne l'efficacia nel trattamento di gravi infezioni nell'uomo.

Analisi

Questo rapporto è il primo in Svizzera a effettuare un'analisi che confronta i dati sull'uso di antibiotici nei settori umano e veterinario e a cercare di valutare le correlazioni tra uso e resistenza. Lo scopo era quello di analizzare i dati sul consumo di antibiotici e sulle antibiotico-resistenze in Svizzera, sulla falsariga del rapporto JIACRA. Tuttavia, data la mancanza di dati e di tempo, è stata condotta solo un'analisi preliminare. Migliorando i dati sarà possibile negli anni a venire condurre analisi più significative, focalizzandosi sulle potenziali correlazioni tra uso di antibiotici e antibiotico-resistenze.

Al fine di comprendere l'epidemiologia dello *S. aureus* resistente alla meticillina (MRSA) e il rischio di trasmissione dagli animali all'essere umano, è stato condotto uno studio delle caratteristiche molecolari di questo agente patogeno. Nella fattispecie, sono stati confrontati i ceppi di MRSA isolati da animali da reddito e carne svizzeri con isolati di MRSA provenienti da veterinari e allevatori sani e isolati umani prelevati da ospedali svizzeri. L'analisi ha permesso di ottenere informazioni utili sulla distribuzione dei tipi «MRSA acquisito in ospedale (HA-MRSA)», «MRSA acquisito in comunità (CA-MRSA)» e «MRSA associato ad animali da reddito (LA-MRSA)» in contesti umani e veterinari, e dunque di capire meglio i rischi di trasmissione in Svizzera. Nei suini svizzeri da ingrasso si è registrato un forte aumento della prevalenza di MRSA negli ultimi dieci anni. La prevalenza di MRSA nella carne di maiale, manzo e pollo svizzeri era molto bassa e il ceppo di MRSA rilevato era del tipo LA-MRSA. Uno studio realizzato insieme a veterinari e allevatori ha rilevato che il ceppo di MRSA più diffuso tra questi attori era del tipo LA-MRSA. Questo dato è in linea con i risultati delle analisi di MRSA isolato da animali da reddito, anch'esso del tipo LA-MRSA. Nei pazienti ricoverati, invece, si riscontrano per la maggior parte i tipi HA-MRSA e CA-MRSA; in due pazienti, tuttavia, è stata rilevata la presenza del tipo LA-MRSA. È necessario un monitoraggio continuo, che comprenda la tipizzazione molecolare di isolati di MRSA sia umani che 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, and require longer treatments and hospital 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 these 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

The Swiss Centre for Antibiotic Resistance anresis.ch was established in the framework of the National Research Program 49 Antibiotic Resistance. After termination of the NRP49, 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 of Bern. Since 2016, the project is financed by the Swiss Federal Office of Public Health and the Institute for Infectious Diseases in Bern; it 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, with 25 microbiology laboratories participating in 2018 (www.anresis.ch). Moreover, additional databases were included, such as the bacteremia database (2006), the antibiotic consumption database (2006 for inpatients, 2015 for outpatients) and the *Clostridium difficile* database (2017). Data on antibiotic resistance in clinical veterinary isolates are also collected in the anresis.ch database since 2014. The open data structure allows further developments.

The steering committee of anresis.ch is composed of specialists from microbiology, infectious diseases, hospital epidemiology, veterinary medicine, and public health.

3.2.1 Monitoring of antibiotic consumption in human medicine

For the inpatient setting, the consumption of antibiotics has been monitored since 2006 by means of a sentinel network of hospital pharmacies. Yearly, data of approximately 70 hospitals are collected on a voluntary basis. These acute care hospitals are distributed all over the geographic territory and represent 41 % of the total number of acute somatic care hospitals (excluding psychiatric centers, rehabilitation centers, other specialized clinics) and 64 % of all beds in this category in Switzerland (see Chapter 13, Materials and methods). The participating hospitals receive a benchmarking report, allowing them to compare their results with those of other hospitals of similar size.

For the outpatient setting, the consumption of antibiotics has been monitored through two sources of data: (i) IQVIA™, a private drug market investigation company provides an exhausted dataset of antibiotic consumption and (ii) the data from PharmaSuisse are based on prescriptions at the individual level and are obtained from privately run pharmacies. The coverage is approximately 65 % of all pharmacies in Switzerland.

3.2.2 Monitoring of resistance in human medicine

anresis.ch collects and analyzes anonymous antibiotic resistance data provided by the participating clinical microbiology laboratories (www.anresis.ch). 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 analyses including isolates from non-sterile sites. Collected data represent at least 70 % of annual hospitalization days and approximately 30 % of all practitioners in Switzerland. The epidemiological data provided allow for stratification of resistance results according to the hospital-versus-outpatient situation, age groups, and anatomical location of the infection.

Antibiotic resistance data are continuously available on www.anresis.ch and www.infect.info. The proportion of the following multiresistant bacteria in invasive isolates is reported and updated monthly in the weekly Bulletin of the Federal Office of Public Health (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 every two years along with veterinary data in this national report.

3.3 About ARCH-Vet

The use of antimicrobials in livestock is a subject of public concern, as resistant bacteria can be selected and can enter the food chain and eventually infect people. Hence, a system to enable the continuous monitoring of resistance in livestock 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, this system compiles data on sales of antimicrobial agents for veterinary medicine in accordance with article 36 of the Federal Ordinance on Veterinary Medicines (FOVM; SR 812.212.27). From 2009 to 2016, data on sales of veterinary antimicrobials and results of the resistance monitoring were published yearly in the ARCH-Vet report. Since 2017, data on sales of veterinary antimicrobials are published yearly in the ARCH-Vet report and bi-annual together with the results of the resistance monitoring in the Swiss Antibiotic Resistance Report. For the third time, the ARCH-Vet data are published together with the anresis.ch data in the present report.

3.3.1 Sales of antimicrobials in veterinary medicine

Sales data is used to estimate the consumption of antimicrobial agents in veterinary medicine. Marketing authorization holders (MAH) report the sales of antimicrobial veterinary medicinal products annually to Swissmedic (Swiss Agency for Therapeutic Products). This data are transmitted to the Food Safety and Veterinary Office (FSVO), where it is processed and analyzed. The data covers 100% of the authorized antimicrobial veterinary medicinal products. The sales data are also transmitted to the European Medicines Agency (EMA) and published within the framework of the European Surveillance of Veterinary Antimicrobial Consumption Project (sales of veterinary antimicrobial agents in 29 EU/EEA countries in 2014; EMA/61769/2016).

3.3.2 Monitoring of resistance in zoonotic and indicator bacteria from healthy animals at slaughterhouse and meat thereof

The main goals of the standardized monitoring of antimicrobial resistance in zoonotic and indicator (commensal) bacteria isolated from healthy livestock and meat thereof 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 antimicrobial resistance and allows the evaluation of the impact of measures taken.

Species examined

Cattle, pigs and broilers are monitored because of their importance in meat production. Samples of cattle and pigs are taken alternately every other year with broilers. Caecum and nasal swab samples are taken by official veterinarians at the slaughterhouse and meat samples of the respective animal species by official inspectors at retail level. Resistance tests are performed for the zoonotic pathogens *Campylobacter* (*C.*) *jejuni* and *C. coli* and for the indicator bacteria *Escherichia coli, Enterococcus (E.) faecalis* and *E. faecium.* Since 2009, nasal swab samples from fattening pigs and calves have been also tested for methicillin-resistant *Staphylococcus aureus* (MRSA) using a selective enrichment procedure published by Overesch et al. (2011). From 2011 to 2014, 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 published by Vogt et al. (2014). Since 2015 analyses for the detection of ESBL/pAmpC- and carbapenemase-producing *E. coli* follows the European-wide harmonized methods according to the protocols published by the European reference laboratory for antimicrobial resistance (EU RL AMR, Lyngby, Denmark). *Salmonella* isolates available from clinical submissions from various animal species and from the national control program for *Salmonella* in poultry are also included for resistance testing. Meat samples are tested for MRSA, ESBL/pAmpC- and carbapenemase-producing *E. coli* only.

Sampling

Stratified random samples of slaughtered animals are taken in slaughterhouses. At least 60% of the slaughtered animals of the concerned species must potentially form part of the sample. Every slaughterhouse taking part in the program collects 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 ad minimum 170 isolates in order to reach this accuracy. The sample size must be adjusted to reflect prevalence in previous years for the concerned 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 (e.g. *Salmonella* spp.), it is not always possible to obtain 170 isolates. 170 isolates is the target for *C. jejuni, E. coli* and *E. faecium* in broilers, *C. coli* and *E. coli* for fattening pigs and for *E. coli* in cattle.

Meat samples are collected in all Swiss cantons. The number of samples per canton is proportionate to the number of its inhabitants. The samples are taken at different retailers proportionate to their market share throughout the country. For beef and pork meat, only domestic meat is collected, as

the main part of consumed beef and pork meat is produced in Switzerland. For broiler meat, two thirds of the samples were domestic meat and one third imported meat.

3.3.3 Monitoring of resistance in animal bacteria from clinical samples

In 2015 the FSVO together with the national reference laboratory for antimicrobial resistance (ZOBA) launched a pilot project on antimicrobial resistance monitoring in veterinary pathogens from livestock and companion animals. Targeted bacteria and animal species combination comprises relevant pathogens and clinical cases. Isolates should ideally derive from all veterinary diagnostic laboratories in Switzerland. For the comparability of results over time it is mandatory that only isolates from animals which didn't get antimicrobial treatment prior to sampling are included. Susceptibility testing was performed at the ZOBA with the broth microdilution method. In contrast to the monitoring in healthy livestock, antimicrobials tested are those approved for veterinary use. Moreover, isolates were classified as susceptible or resistant according to clinical breakpoints published by the Clinical and Laboratory Standards Institute, or, if not available by clinical breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. An excerpt of data derived from this pilot project is presented in Chapter 11 ("Resistance in bacteria from animal clinical isolates"). With this monitoring a relevant gap in surveillance of antimicrobial resistance could be bridged. Starting in 2019, this monitoring will be conducted on an annual basis. Results will be presented in reports.

Since 2014 the ZOBA provides antibiotic resistance data of veterinary pathogens from dogs, cats and horses via interface to the anresis database. In the future, data from this monitoring should be included as well.

3.4 Guidance for readers

The present 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 Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (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 in 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 1,000 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 and meat, bacteria originate from samples taken of healthy food-producing animals and meat thereof 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 and meat isolates are tested at the Swiss national reference laboratory for antimicrobial resistance (the Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance, ZOBA, Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern) using a standardized broth 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 and meat thereof uses epidemiological cutoff 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 have to be further 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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Color code

This is the color code that is used in various figures in this report.

- Ionophore
- Nitrofuran
- Oxazolidone
- Fluoroquinolone
- Glycopeptide
- Aminoglycoside
- Epoxide-AB
- Polypeptide
- Sulfonamide
- Steroidal antibiotics
- Amphenicole
- Ansamycin
- Tetracycline
- Lincosamide
- Streptogramin
- Macrolide
- Penicillin
- Carbapenem
- Cephalosporin

4

Abbreviations

4 Abbreviations

ACB	*Acinetobacter calcoaceticus-Acinetobacter baumannii*
AFSSA	French Food Safety Agency
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	Antimicrobial resistance
ANRESIS	Swiss Centre for Antibiotic Resistance
ARB	Antibiotic resistant bacteria
ARG	Antibiotic resistance gene
AST	Antimicrobial susceptibility testing
ATC	Anatomical Therapeutic Chemical
AWARE	Access, Watch and Reserve antibiotic categories as defined by the WHO Expert Committee on Selection and Use of Essential Medicines
CAESAR	Central Asian and Eastern European Surveillance on Antimicrobial Resistance
CC	Clonal complex
CI	Confidence interval
CLSI	Clinical Laboratory Standards Institute
CPE	Carbapenemase-producing Enterobacteriaceae
CSF	Cerebrospinal fluid
CTX	Cefotaxime
DCDvet	Defined course doses for animals
DD	Disc diffusion
DDD	Defined daily dose
DDDvet	Defined daily dose for animals
DID	Defined daily dose per 1,000 inhabitants and per day
EARSS	European Antimicrobial Resistance Surveillance System
ECCMID	European Congress of Clinical Microbiology and Infectious Diseases
ECDC	European Centre for Disease Prevention and Control
ECOFF	Epidemiological cutoff value
EEA	European Economic Area
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Market Research Association
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	Extended-spectrum beta-lactamase
ESCR	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	Federal Food Safety and Veterinary Office
GP	General practitioner
GSASA	Swiss Association of Public Health Administration and Hospital Pharmacists
HLR	High-level resistance
ICU	Intensive care units
ISO	International Organization for Standardization
LA-MRSA	Livestock-associated MRSA
LMA	Potassium-aluminum sulfate
LOD	Limit of detection
LPS	Lipopolysaccharide
MALDI TOF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy
mCCDA	Modified charcoal cefoperazone deoxycholate agar
mcr	plasmid-mediated colistin resistance
MDR	Multidrug resistant
MIC	Minimal inhibitory concentration
MIC_{90}	Minimal inhibitory concentration required to inhibit the growth of 90% of the isolates tested
MLST	Multilocus sequence typing
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSP	Methicillin-resistant *Staphylococcus pseudintermedius*
MSM	Men who have sex with men
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NAQUA	National Groundwater Monitoring

NARA	National Reference Centre for the Early Detection and Monitoring of Antibiotic Resistance
NRP	National research project
OFAC	Professional cooperative of the Swiss pharmacists
OIE	World Organization for Animal Health
PAC	Powdered activated carbon
pAmpC	Plasmid-mediated AmpC-beta-lactamase
PBP	Penicillin-binding protein
PCU	Population correction unit
PCR	Polymerase chain reaction
PNSP	Penicillin-non-susceptible *Streptococcus pneumoniae*
PSSP	Penicillin-susceptible *Streptococcus pneumoniae*
PVL	Panton-Valentine Leukocidin
SFSO	Swiss Federal Statistical Office
SIB	Swiss Institute of Bioinformatics
SIR	Susceptible – Intermediate – Resistant
SNF	Swiss National Science Foundation
SNP	Single-nucleotide polymorphism
spp.	Species
SSI	Swiss Society of Infectious Diseases
SSM	Swiss Society for Microbiology
SSP	Swiss Society of Pharmacists, PharmaSuisse
StAR	Nationale Strategie Antibiotika-resistenzen (National strategy of antibiotic resistance)
SVGW	Swiss association of the gas and water industry
t	*spa* type
VetCAST	EUCAST Veterinary Subcommittee on Antimicrobial Susceptibility Testing
VMD	Veterinary Medicines Directorate
VRE	Vancomycin-resistant enterococci
WGS	Whole genome sequencing
WHO	World Health Organization
WWTP	Wastewater treatment plant
ZOBA	Center for Zoonoses, Animal Bacterial 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 contributing to anresis.ch

Taking into account the hospital sites that have participated each year since 2007 in the surveillance system anresis.ch (n=32), the number of DDDs of systemic antibiotics (ATC group J01) has increased by 14% since then. However, this needs to be adjusted to indicators of hospital activity.

The number of admissions increased (+17%), while the number of bed-days was relatively stable (–6%). This means that more patients are admitted to hospitals, but that their length of stay is shorter in 2017 than in 2007. The total consumption of systemic antibiotics in DDDs per 100 bed-days increased by 16%, from 53.6 (weighted mean, range: 20.5–77.8) in 2007 to 62.2 (range: 40.7–85.2) in 2017 (Figure 5. a). The antibiotic consumption in DDDs per 100 admissions remained stable from 2007 to 2017 (–9%). In 2017, total antibiotic consumption was lower in small-size hospitals (56.0 DDDs per 100 bed-days) than in medium-size (63.4) and large-size (69.4) hospitals. This increasing trend was observed in the three hospital size categories.

In 2017, total antibiotic consumption was relatively similar in the three linguistic regions: 59.2 DDDs per 100 bed-days in the French-speaking (18 hospitals), 56.7 in the Italian-speaking (5 hospitals) and 63.8 in the German-speaking region (44 hospitals). The consumption in the German-speaking region increased by 22% between 2007 and 2017, while it remained stable in the French-speaking (+6%) and the Italian-speaking regions (+3%).

The total consumption of antibacterial agents for systemic use was 1.3 DDDs per 1,000 inhabitants per day in 2016. In comparison, the median consumption was 2.1 per 1,000 inhabitants per day (range 1.0–2.9) in 2016 in the countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1].

We have observed that according to the AWaRe classification (see Chapter 13, Materials and methods), the Core-Access group represented 56% of antibiotics (36.3 DDDs per 100 bed-days), the Watch group 31% (20.2), the Reserve group 5% (3.0) and the "Others" group 8% (5.0) in 2017 (Table 5. a). The antibiotic consumption from the Reserve group has been increasing since 2015.

Figure 5. a: Total antibiotic consumption (ATC group J01) expressed in DDDs per 100 bed-days (bars) and in DDDs per 100 admissions (dark line) in the hospitals and intensive care units contributing to anresis.ch over the period 2007–2017. The number of hospital networks (or sites) contributing to anresis.ch is indicated in the corresponding bars.

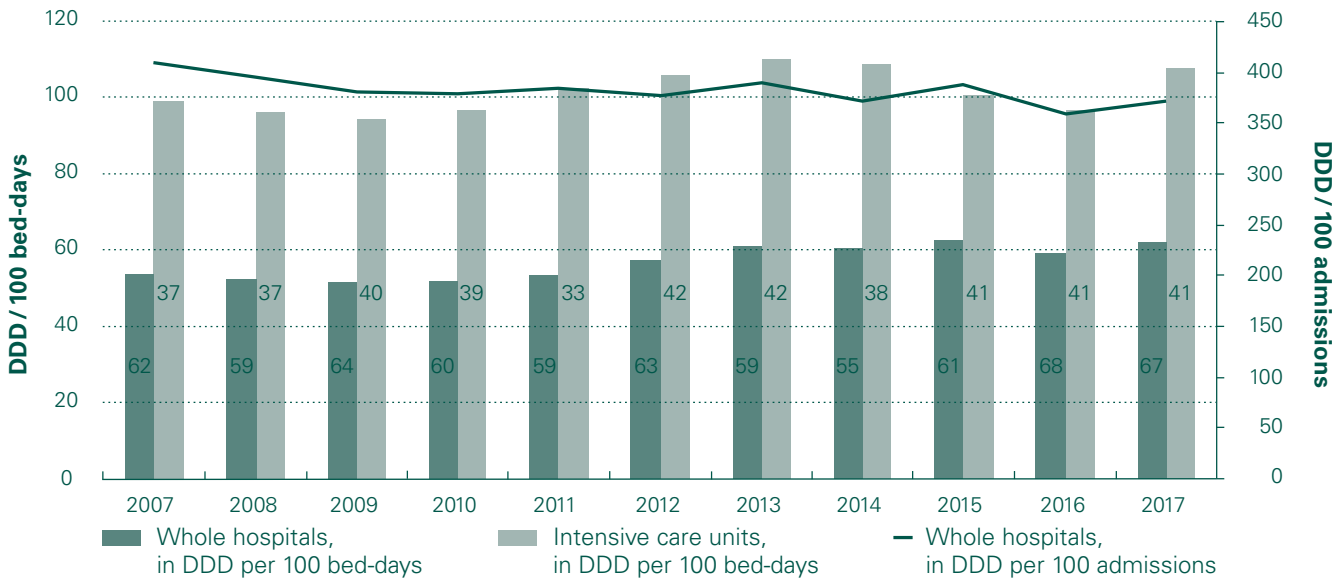


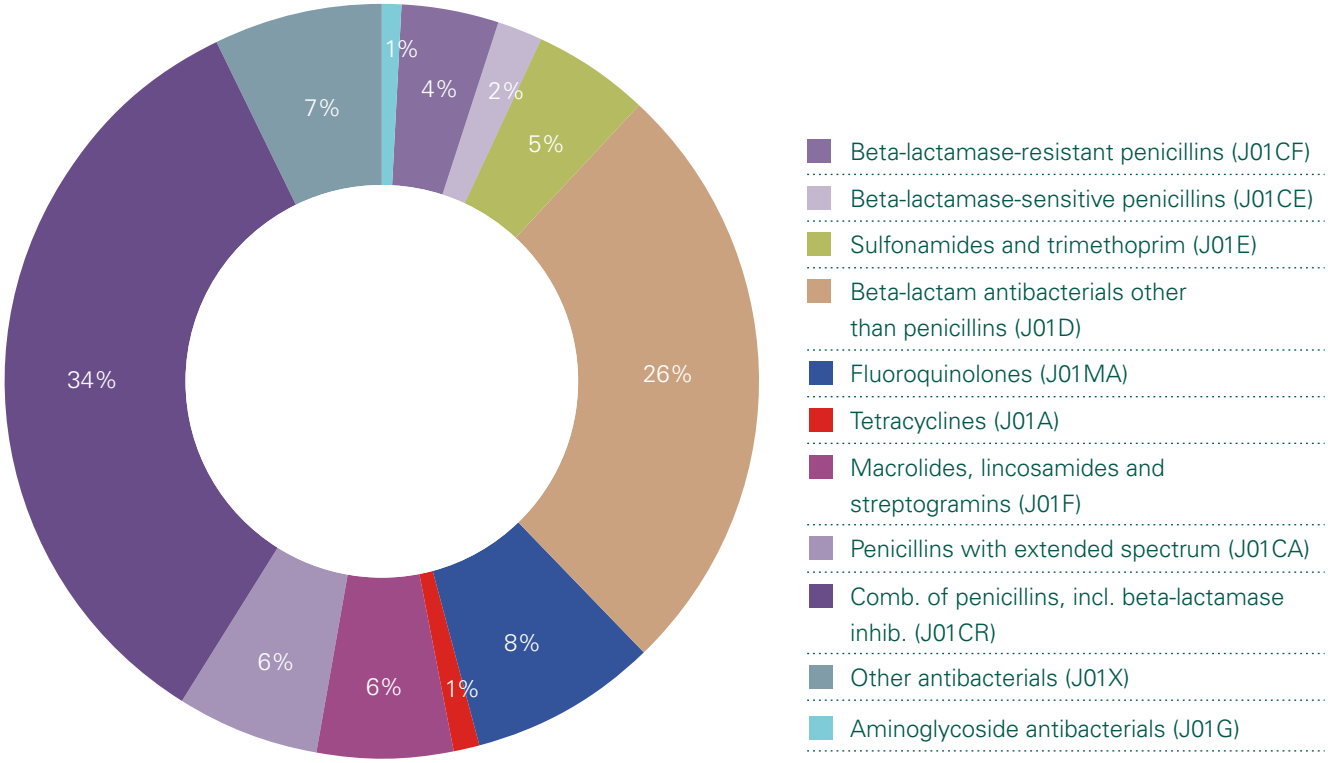
Table 5. a: Antibiotic consumption according to the AWaRe categorization of the WHO in the inpatient setting, Switzerland (2015–2017).

AWaRe groups**	Consumption*			Relative consumption		
	2015	2016	2017	2015	2016	2017
Core-Access group	33.0	32.8	36.3	53%	55%	56%
Watch group	21.6	19.2	20.2	35%	32%	31%
Reserve group	2.4	2.2	3.0	4%	4%	5%
Others	5.4	4.9	5.0	9%	8%	8%

* Consumption expressed in DDD per 100 bed-days

** See Annexe I for the list of antibiotics and their corresponding AWaRe group

Figure 5. b: Distribution of the total antibiotic consumption (ATC group J01) per antibiotic class in the inpatient setting in 2017 in Switzerland.



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

In 2017, consumption of penicillins (ATC group J01C) ranked first among antibiotic classes, representing 46% of the total consumption. It was followed by the consumption of other beta-lactam antibacterials, including cephalosporins (ATC group J01D), and then by quinolones (ATC group J01M) (26% and 8%, respectively) (Figure 5. b).

Table 5. b shows the consumption of antibiotic classes expressed in DDDs per 100 bed-days in sentinel hospitals over the period 2007–2017. The use of eight of the 22 antibiotic classes decreased between 2007 and 2017 (first-generation cephalosporins, fluoroquinolones, glycopeptides, macrolides, nitroimidazole derivates, polymixins, rifamycins and tetracyclines). The most important progression (more than 100%) in consumption between 2007 and 2017 was observed for the fourth-generation cephalosporins, the nitrofuran derivates, the antipseudomonal penicillins associated with a beta-lactamase inhibitor, and the other antibacterials (including daptomycin, fosfomycin).

Consumption of penicillins increased 23% between 2007 and 2017 (Table 5. b). Within this class, the association of amoxicillin and clavulanic acid was the most frequently prescribed antibiotic and ranged from 16.8 in 2007 to 18.4 DDDs per 100 bed-days in 2017 (+10%) (Figure 5. c). The association of piperacillin and tazobactam increased by 120% from 1.3 in 2007 to 2.8 DDDs per 100 bed-days in 2017.

Table 5. b: Consumption of antibiotic classes expressed in DDDs per 100 bed-days in hospitals contributing to anresis.ch in Switzerland (2007–2017).

ATC group	Antibiotic class	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
J01G	Aminoglycosides	0.8	0.7	0.7	0.8	0.7	0.7	0.7	0.6	0.6	0.5	0.8
J01CF	Beta-lactamase-resistant penicillins	1.7	1.6	1.7	1.8	1.9	2.1	2.0	2.4	2.4	2.4	2.5
J01CE	Beta-lactamase-sensitive penicillins	0.9	0.9	1.1	1.1	1.3	1.5	1.3	1.2	1.3	1.3	1.2
J01DH	Carbapenems	2.2	2.2	2.4	2.4	2.6	2.8	3.1	3.0	2.8	2.4	2.7
J01DB	Cephalosporins – first generation	1.2	1.3	1.2	1.1	1.1	1.0	1.0	1.1	1.5	1.1	1.2
J01DC	Cephalosporins – second generation	3.9	3.8	3.6	3.6	3.6	3.8	4.3	4.6	4.8	4.5	4.4
J01DD	Cephalosporins – third generation	3.7	3.7	3.7	3.8	4.0	4.2	4.9	4.9	5.7	5.4	5.7
J01DE	Cephalosporins – fourth generation	0.7	1.1	0.9	1.1	1.3	1.5	1.6	1.5	1.7	1.7	2.1
J01MA	Fluoroquinolones	7.9	7.3	6.7	6.5	6.1	6.0	6.2	6.1	5.9	5.0	5.0
J01XA	Glycopeptides	0.8	0.9	0.8	1.0	1.1	1.1	1.2	1.3	1.3	1.0	0.5
J01FF	Lincosamides	0.9	0.9	0.9	0.8	0.8	0.9	1.0	1.0	1.0	0.9	1.1
J01FA	Macrolides	3.1	2.9	2.7	2.6	2.5	2.7	3.0	2.9	3.1	2.8	2.8
J01XE	Nitrofuran derivates (nitrofurantoin)	0.1	0.1	0.1	0.1	0.2	0.3	0.3	0.4	0.4	0.4	0.4
P01AB	Nitroimidazole derivates (metronidazole oral)	0.9	0.9	0.8	0.8	0.8	0.9	0.8	0.8	0.8	0.7	0.7
J01XX	Other antibacterials	0.1	0.1	0.2	0.3	0.4	0.6	0.7	0.8	0.9	0.9	1.2
J01CR02	Penicillins and beta-lactamase inhibitor (amoxicillin and clavulanic acid)	16.8	16.0	16.7	16.3	16.5	18.1	18.5	17.9	17.4	18.4	18.4
J01CR03-05	Penicillins and beta-lact. inhibitor (anti-pseudomonal)	1.3	1.5	1.6	1.8	1.9	2.3	2.7	2.7	2.8	2.6	2.8
J01CA	Penicillins with extended spectrum (amoxicillin)	2.5	2.7	2.5	2.5	2.7	2.8	3.4	3.4	3.7	3.2	3.6
J01XB	Polymyxins (colistin)	0.1	0.2	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.0
J04AB	Rifamycins	1.0	1.0	0.9	1.0	0.9	0.8	0.8	0.9	0.7	0.7	0.8
J01E	Sulfonamides and trimethoprim	2.1	2.1	1.9	1.9	2.0	2.4	2.4	2.5	2.4	2.2	2.7
J01A	Tetracyclines	0.7	0.7	0.5	0.6	0.5	0.5	0.6	0.6	0.6	0.8	0.7
J01	Antibacterial agents for systemic use (total)	53.6	52.7	51.6	52.0	53.3	57.4	61.0	60.7	62.4	59.2	62.2

The use of second- and third-generation cephalosporins increased markedly between 2007 and 2017. In 2017, cefuroxime (second generation) and ceftriaxone (third generation) were the most widely used cephalosporins (Figure 5. c).

Cephalosporins recently approved by Swissmedic (ceftobiprole, ceftolozane-tazobactam and ceftaroline) have rarely been used in hospitals contributing to anresis.ch.

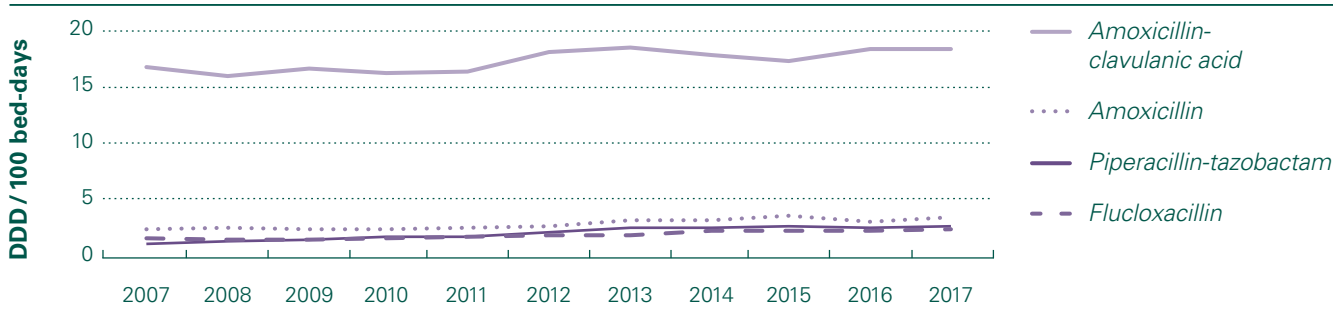
Following a constant increase until 2013, the consumption of carbapenems has remained stable since then. This is due to a 55% decrease in the consumption of imipenem and cilastatin between 2007 and 2017, whereas consumption of meropenem and ertapenem increased (+43% and +64%, respectively) over the same period (Figure 5. c).

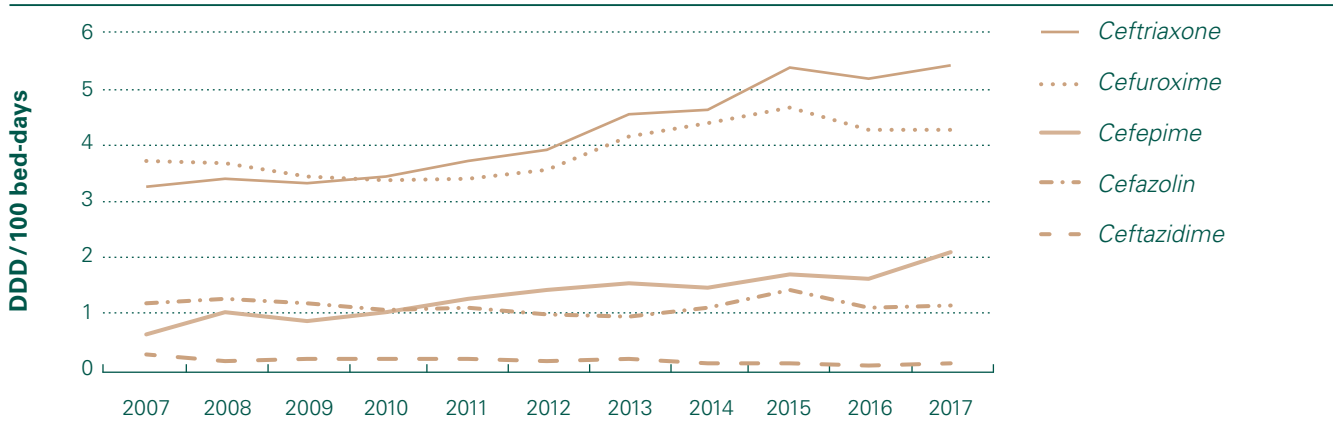
Fluoroquinolone consumption decreased during the years 2007–2017. Ciprofloxacin was the most widely used fluoroquinolone (3.7 DDDs per 100 bed-days, 75% of fluoroquinolone consumption) in 2017 (Figure 5. c). Ciprofloxacin, norfloxacin and ofloxacin use decreased between 2007 and 2017 (–32%, –84% and –98%, resp.). The consumption of levofloxacin was relatively stable during the years 2007 to 2017, accounting for 0.9 DDDs per 100 bed-days in 2017.

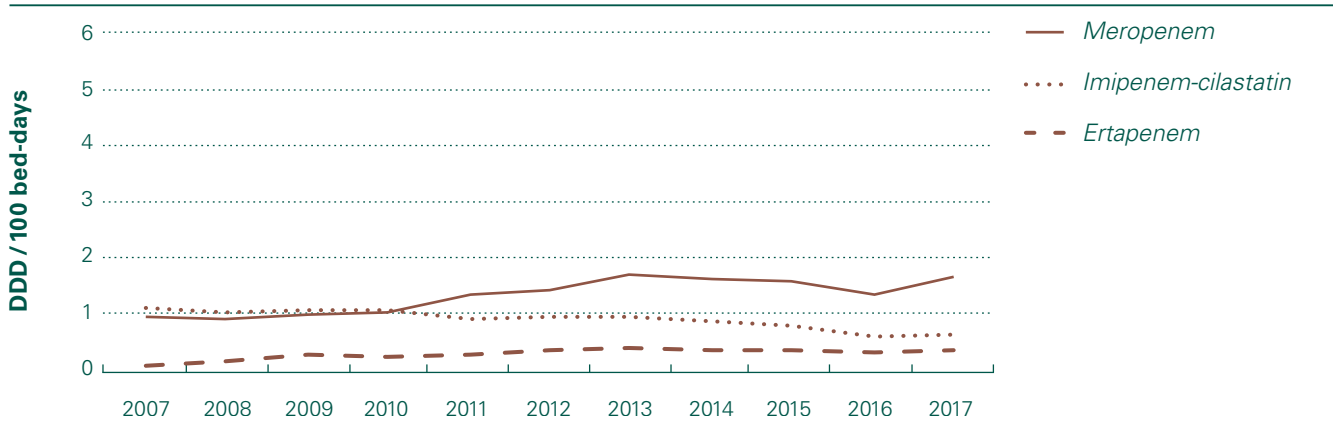
Macrolide consumption (ATC group J01FA) has remained relatively stable, going from 3.1 DDDs per 100 bed-days in 2007 to 2.8 in 2017 (–8%). Clarithromycin was the most widely used macrolide (2.1 DDDs per 100 bed-days, 76% of macrolide consumption) (Figure 5. c). It was followed by azithromycin (0.4 DDDs per 100 bed-days, 16%) and erythromycin (0.2 DDDs per 100 bed-days, 8%). The consumption of clindamycin (ATC group J01FF01) has increased by 18% over the period 2007–2017 (1.1 DDDs per 100 bed-days in 2017).

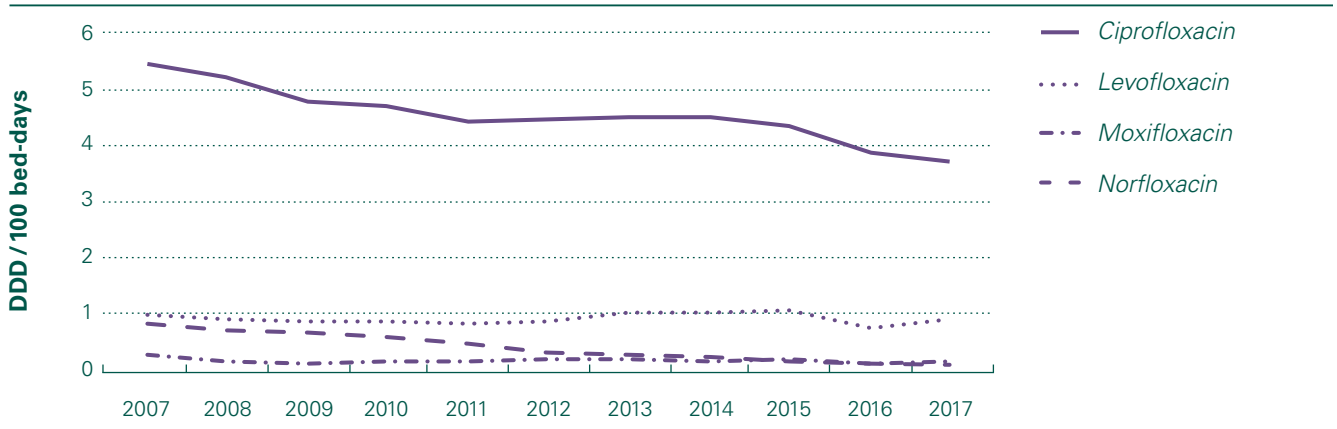
Among antibiotics active against resistant Gram-positive bacteria, we have observed an increase by 52% in consumption of vancomycin between 2007 and 2017 (Figure 5. c). Consumption of daptomycin has constantly increased (0.6 DDDs per 100 bed-days in 2017). Linezolid and tedizolid have rarely been used in hospitals contributing to anresis.ch. The proportion of the broadest-spectrum antibiotics has constantly increased, going from 8% of total antibiotic consumption in 2007 to 12% in 2017. This category includes aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin, piperacillin-tazobactam, ticarcillin and ticarcillin-tazobactam in the present report. In 2017, piperacillin-tazobactam was the most frequently used of these antibiotics

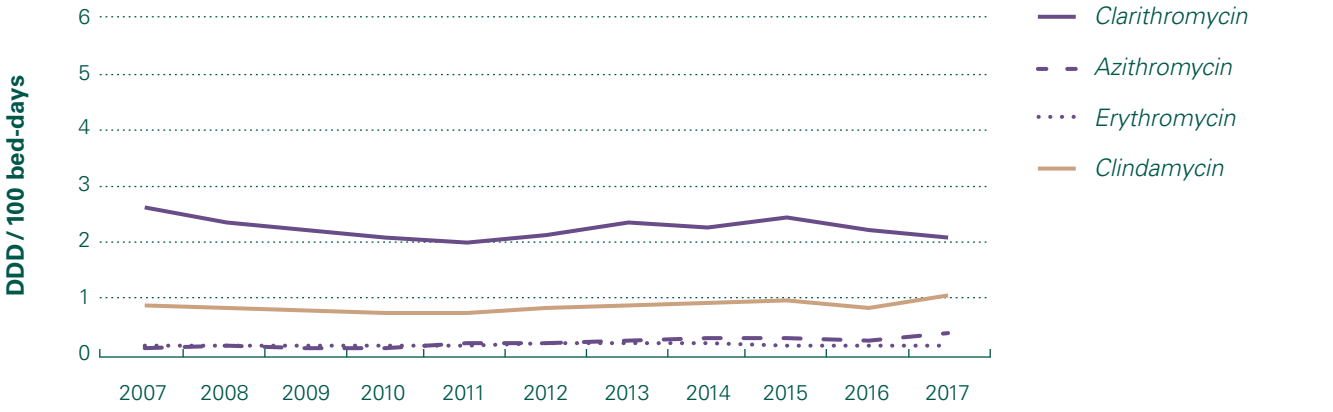
Figure 5. c: Consumption of antibiotics expressed in DDDs per 100 bed-days in hospitals contributing to anresis.ch in Switzerland (2007–2017).

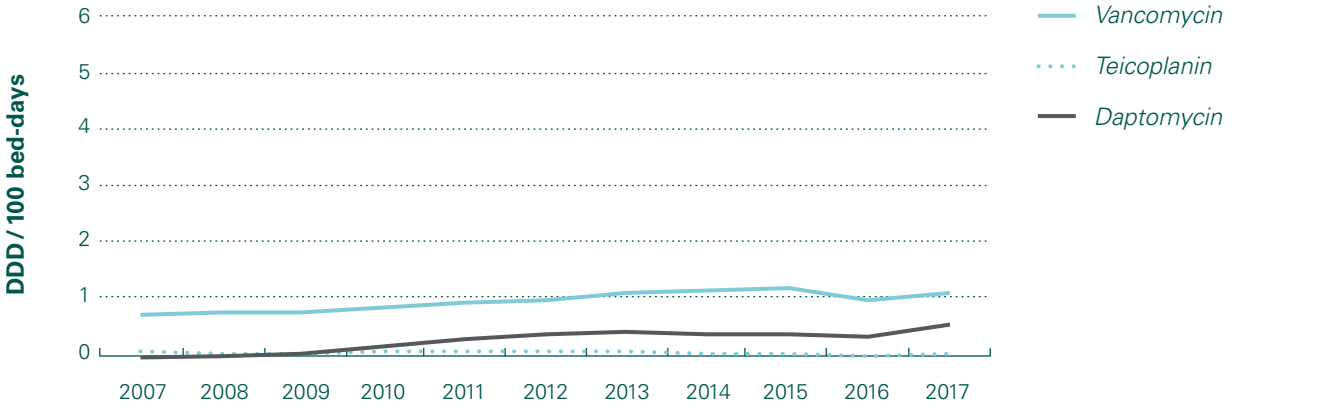












in the sentinel hospitals (37% of the broadest-spectrum antibiotic use), followed by cefepime (29%), meropenem (23%), imipenem-cilastatin (9%) and ceftazidime (2%).

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

Global use of systemic antibiotics (ATC group J01) remained relatively stable, ranging from 99.3 DDDs per 100 bed-days in 2007 to 108.0 in 2017 (+8%) (Figure 5. a). In 2017, total antibiotic consumption was lower in the intensive care units of small-size hospitals (88.2 DDDs per 100 bed-days) than in intensive care units of medium-size (96.5) and large-size (120.3) hospitals.

5.2 Outpatient care

5.2.1 Total antibiotic consumption in the outpatient setting using IQVIA™ dataset

In 2017, the total consumption of antibacterial agents for systemic use (ATC group J01) was 10.7 DDDs per 1,000 inhabitants per day (DID). It has slightly declined in comparison with 2016 (11.1 DIDs) and 2015 (11.3 DIDs) (Table 5. c). In comparison, the median consumption was 21.9 DDDs per 1,000 inhabitants per day (range between 10.4 in the Netherlands and 36.3 in Greece) in 2016 in the countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1].

The number of packages per 1,000 inhabitants per day was 1.3 in 2017. It has remained stable in comparison with 2016 and 2015 (1.3 for both years). In comparison, the median consumption was 3.1 packages per 1,000 inhabitants per day (range between 1.0 in Sweden and 4.7 in France) in 2016 in the countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1].

We have observed that according to the AWaRe classification (see Chapter 13, Materials and methods) the Core-Access group represented 65% of antibiotics (6.8 DIDs), the Watch group 25% (2.6 DIDs), the Reserve group 0.2% (< 0.05 DIDs) and the "Others" group 10% (1.1 DIDs) in 2017 (Table 5. d). These proportions have remained stable since 2015.

5.2.2 Antibiotic consumption in the outpatient setting by antibiotic class and by specific antibiotic using IQVIA™ dataset

Consumption of penicillins (including amoxicillin-clavulanic acid, ATC group J01C) ranked first among antibiotic classes, amounting to 48% of the total antibiotic consumption in

Table 5. c: Consumption of antibiotic classes expressed in DDDs per 1,000 inhabitants per day in the outpatient setting in Switzerland (2015–2017).

ATC Group	Antibiotic class	2015	2016	2017
J01G	Aminoglycosides	0.02	0.02	0.02
J01CF	Beta-lactamase-resistant penicillins	0.01	0.01	0.01
J01CE	Beta-lactamase-sensitive penicillins	0.11	0.12	0.10
J01DH	Carbapenems	0.00	0.00	0.00
J01DB	Cephalosporins – first generation	0.00	0.00	0.00
J01DC	Cephalosporins – second generation	0.62	0.61	0.57
J01DD	Cephalosporins – third generation	0.16	0.14	0.11
J01DE	Cephalosporins – fourth generation	0.00	0.00	0.00
J01MA	Fluoroquinolones	1.53	1.40	1.28
J01XA	Glycopeptides	0.00	0.00	0.00
J01FF	Lincosamides	0.17	0.17	0.17
J01FA	Macrolides	1.35	1.27	1.20
J01XE	Nitrofuran derivates (nitrofurantoin)	0.37	0.36	0.36
P01AB	Nitroimidazole derivates (metronidazole oral)	0.76	0.76	0.77
J01XX	Other antibacterials (fosfomycin)	0.10	0.10	0.11
J01CR	Penicillins and beta-lactamase inhibitors (amoxicillin and clavulanic acid)	3.80	3.74	3.59
J01CA	Penicillins with extended spectrum (amoxicillin)	1.29	1.38	1.40
J01XB	Polymyxins (colistin)	0.01	0.01	0.01
J04AB	Rifamycins	0.13	0.13	0.13
J01E	Sulfonamides and trimethoprim	0.43	0.43	0.45
J01A	Tetracyclines	1.30	1.37	1.29
J01	Antibacterial agents for systemic use (total)	11.30	11.15	10.70

Table 5. d: Antibiotic consumption according to the AWaRe categorization of the WHO in the outpatient setting in Switzerland (2015–2017).

AWaRe groups**	Consumption*			Relative consumption		
	2015	2016	2017	2015	2016	2017
Core-Access group	6.8	6.9	6.8	61%	63%	65%
Watch group	3.1	2.8	2.6	28%	26%	25%
Reserve group	< 0.05	< 0.05	< 0.05	0.2%	0.2%	0.2%
Others	1.2	1.2	1.1	11%	11%	10%

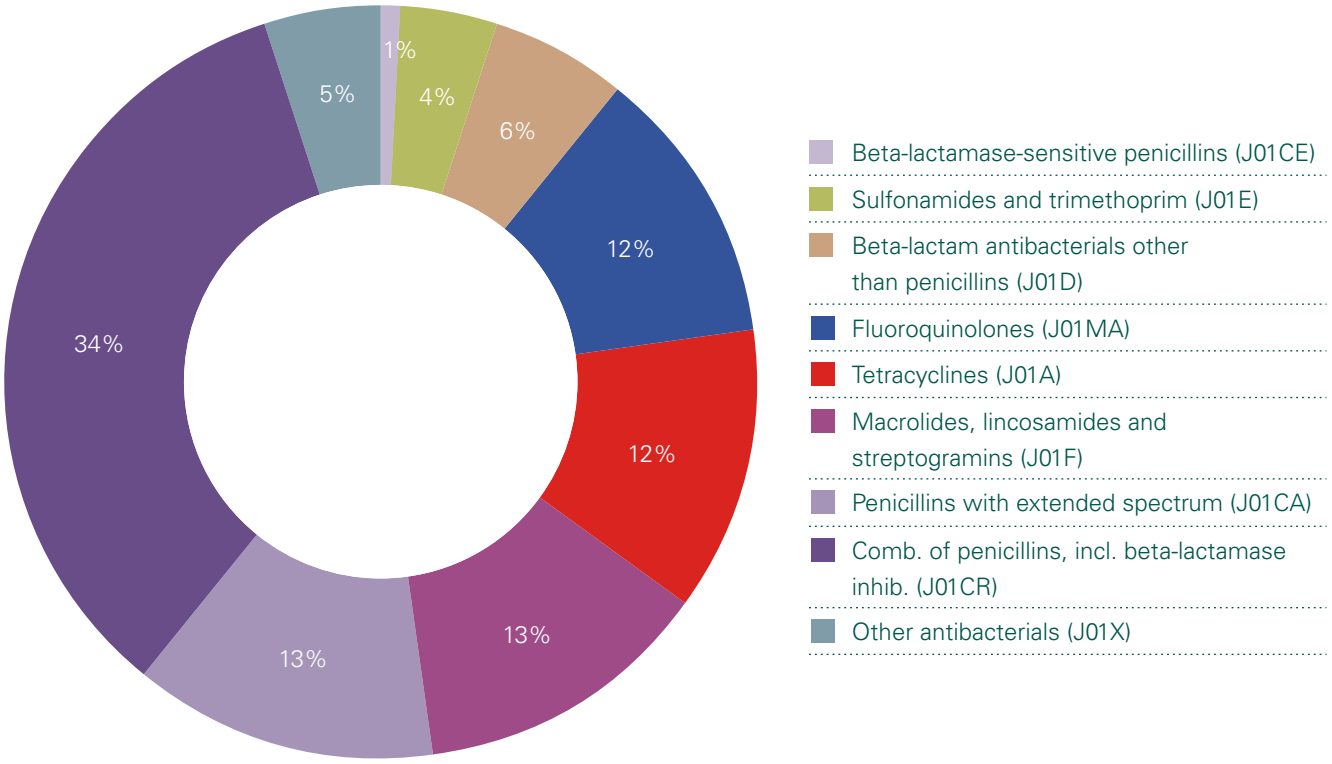
* Consumption expressed in DDD per 1,000 inhabitants and per day

** See Annex I for the list of antibiotics and their corresponding AWaRe group

2017 (Figure 5. d). It was followed by the consumption of macrolides, lincosamides and streptogramins (13%, ATC group J01F), tetracyclines (12%, ATC group J01A), fluoroquinolones (12%, ATC group J01MA), beta-lactam antibacterials other than penicillins (including cephalosporins, 6%, ATC group J10D), sulfonamides and trimethoprim (4%, ATC group J01E) and other antibacterials (5%, ATC group J01X).

The overall consumption of penicillins remained stable in 2017 (5.1 DIDs, 48% of total antibiotic consumption) compared to 2015 (5.2 DIDs). Combinations of penicillins and beta-lactamase inhibitors were the most frequently used group of systemic antibiotics in 2017 (3.6 DIDs, 34% of total antibiotic consumption) and of penicillins (70% of penicillins consumption) (Table 5. c). Among penicillins, those with an extended spectrum, namely amoxicillin, were the second most frequently used group (1.4 DIDs, 27% of penicillin consumption). The relative consumption of beta-lactamase-sensitive penicillins was low in Switzerland (1% of total antibiotic consumption in 2017), as this indicator ranged from < 0.1% to 26.7% in 2016 in countries participating in the ESAC-Net (Figure 5. e) [1]. However, the relative consumption of penicillins associated with beta-lactamase inhibitors was relatively high (34%) in comparison with countries participating in the ESAC-Net (range: 0.1%–44.2%) in 2016 [1]. At the substance level, amoxicillin-clavulanic acid and amoxicillin were the

Figure 5. d: Distribution of the total antibiotic consumption (ATC group J01) per antibiotic class in the outpatient setting in 2017 in Switzerland.



most frequently used antibiotics in 2017 (3.6 and 1.4 DIDs, resp.), of which both consumptions remained stable between 2016 and 2017.

The cephalosporins (ATC group J01DB-DE) remained stable in 2017 (0.69 DIDs) compared to 2015 (0.78 DIDs). Cefuroxime, cefpodoxime and cefaclor represented 79%, 14% and 4% resp. of cephalosporin consumption in 2017. The relative consumption of third- and fourth-generation cephalosporins (ATC Code J01DD-DE) was 1% in 2017, compared with a range of < 0.1% to 7.2% in countries participating in the ESAC-Net in 2016 (Figure 5. e) [1].

Fluoroquinolone consumption was 1.3 DDDs per 1,000 inhabitants per day in 2017 in Switzerland, accounting for 12% of the total antibiotic consumption in the outpatient setting. Although we have observed a slight downward trend (–8% between 2016 and 2017), their consumption has remained high in comparison with countries participating in the ESAC-Net, where the relative consumption of fluoroquinolones ranged from 2.3% to 21.4% in 2016 (Figure 5. e) [1]. At the substance level, ciprofloxacin was the most frequently used fluoroquinolone (66%), followed by levofloxacin (13%), norfloxacin (12%), moxifloxacin (8%) and ofloxacin (1%) in 2017.

In the macrolide, lincosamide and streptogramin group, (ATC Code J01F), only macrolides and lincosamides have been used in Switzerland (1.2 and 0.17 DDDs per 1,000 inhabitants per day in 2017) (Table 5. c). Macrolide consumption decreased slightly (–5%) between 2016 and 2017, while lincosamide consumption remained stable. Clarithromycin, azithromycin and erythromycin accounted for 59%, 41% and 1% resp. of the macrolides in 2017. Among the lincosamides, clindamycin consumption was 0.17 DDDs per 1,000 inhabitants per day in 2017 and has remained stable since 2015.

Tetracycline consumption decreased slightly, from 1.4 DDDs per 1,000 inhabitants per day in 2016 to 1.3 in 2017 (–6%), accounting for 12% of the total antibiotic consumption. Doxycycline was the most frequently used tetracycline (76%), followed by minocycline (13%), and limecycline (12%).

Nitrofurantoin and fosfomycin accounted for resp. 3% and 1% of the total antibiotic consumption.

The ratio of the consumption of broad-spectrum penicillins, cephalosporins and macrolides to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides was relatively high (52.0) in comparison with countries participating in the ESAC-Net, where this ratio ranged from 0.2 to 234.2 in 2016 (Figure 5. e) [1].

5.2.3 Antibiotic consumption in the outpatient setting by linguistic region using IQVIA™ dataset

In 2017, the German-speaking part of Switzerland had lower antibiotic consumption (9.2 DIDs) than the Italian-speaking (13.4) and French-speaking parts (14.5) (Figure 5. f). The three regions have shown a decreasing trend since 2015, especially marked in the Italian-speaking part of Switzerland

Figure 5. e: ESAC quality indicators for consumption of antibacterials for systemic use (ATC group J01) in the outpatient setting in Switzerland (2015–2017).

Year	Consumption[a]					Relative consumption[b]				Broad/Narrow[c]
	J01	J01C	J01D	J01F	J01M	J01CE_%[d]	J01CR_%	J01DD+DE_%	J01MA_%	J01_B/N
2015	11.3	5.2	0.8	1.5	1.5	0.9	33.6	1.4	13.6	51.5
2016	11.1	5.3	0.8	1.4	1.4	1.0	33.6	1.2	12.6	47.0
2017	10.7	5.1	0.7	1.4	1.3	0.9	33.6	1.1	12.0	52.0
p0*	10.4	4.3	< 0.1	0.5	0.4	< 0.1	0.1	< 0.1	2.3	0.2
p25*	15.2	6.5	0.6	1.8	0.9	0.6	14.5	0.1	5	6.1
p50*	19.8	9.6	1.7	2.8	1.4	2.3	23.8	0.5	7.8	13.4
p75*	24.2	13.0	2.8	3.6	2.4	5.2	32.4	2.2	9.6	45.9
p100*	36.3	19.8	7.5	6.1	7.1	26.7	44.2	7.2	21.4	234.2

[a] Consumption for penicillins (J01C), cephalosporins (J01D), macrolides, lincosamides and streptogramins (J01F) and quinolones (J01M) expressed in DDD per 1,000 inhabitants per day.

[b] Relative consumption of beta-lactamase-sensitive penicillins (J01CE), combinations of penicillins, including beta-lactamase inhibitor (J01CR), third- and fourth-generation cephalosporins (J01(DD+DE)) and fluoroquinolones (J01MA) expressed as percentage of the total antibiotic consumption (J01).

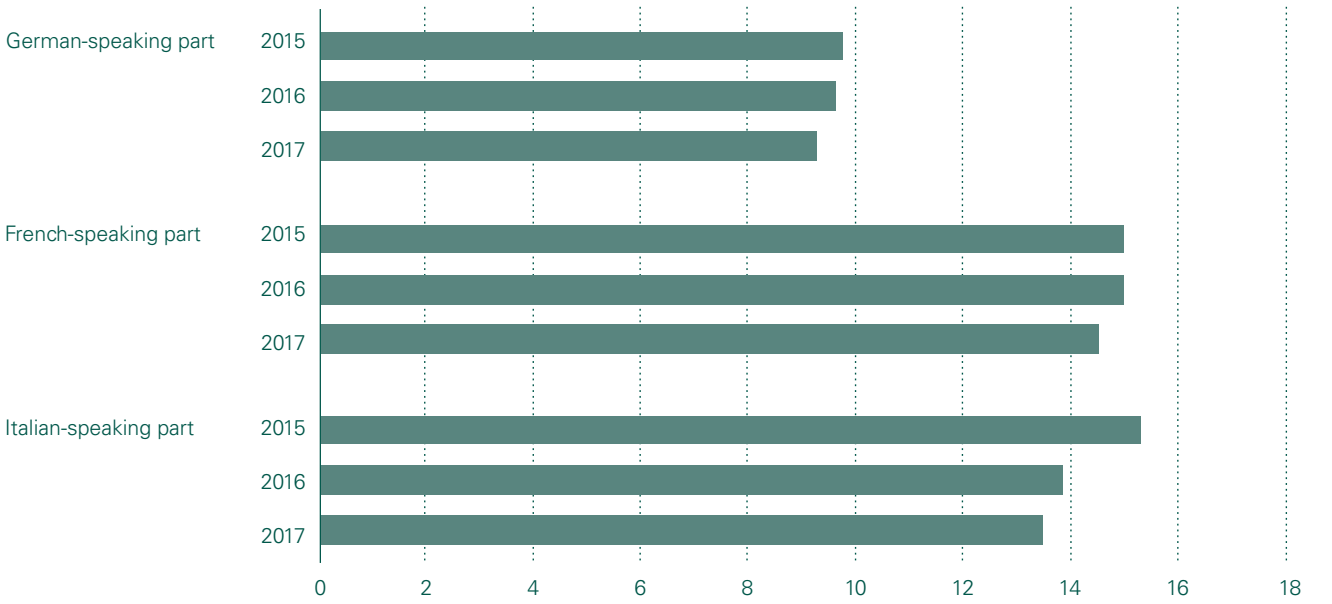
[c] Ratio of the consumption of broad-spectrum penicillins, cephalosporins and macrolides (J01(CR+DC+DD+(F-FA01))) to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides (J01(CE+DB+FA01))

[d] As higher quartile suggest better quality indicator, the color code was applied inversely.

* Values in the community, EU/EEA countries, 2016 [1].

Values within the first quartile [p0; p25]
Values within the first quartile [p25; p50]
Values within the first quartile [p50; p75]
Values within the first quartile [p75; p100]

Figure 5. f: Total antibiotic consumption (ATC group J01) expressed in DDDs per 1,000 inhabitants per day by linguistic region in the outpatient setting in Switzerland (2015–2017).



(–12 %). We observed a higher proportion of fluoroquinolones in the Italian-speaking part of Switzerland (15 %) than in the German- (13 %) and French-speaking parts (10 %) in 2017.

5.2.4 Antibiotic consumption in the outpatient setting by antibiotic class using PharmaSuisse dataset

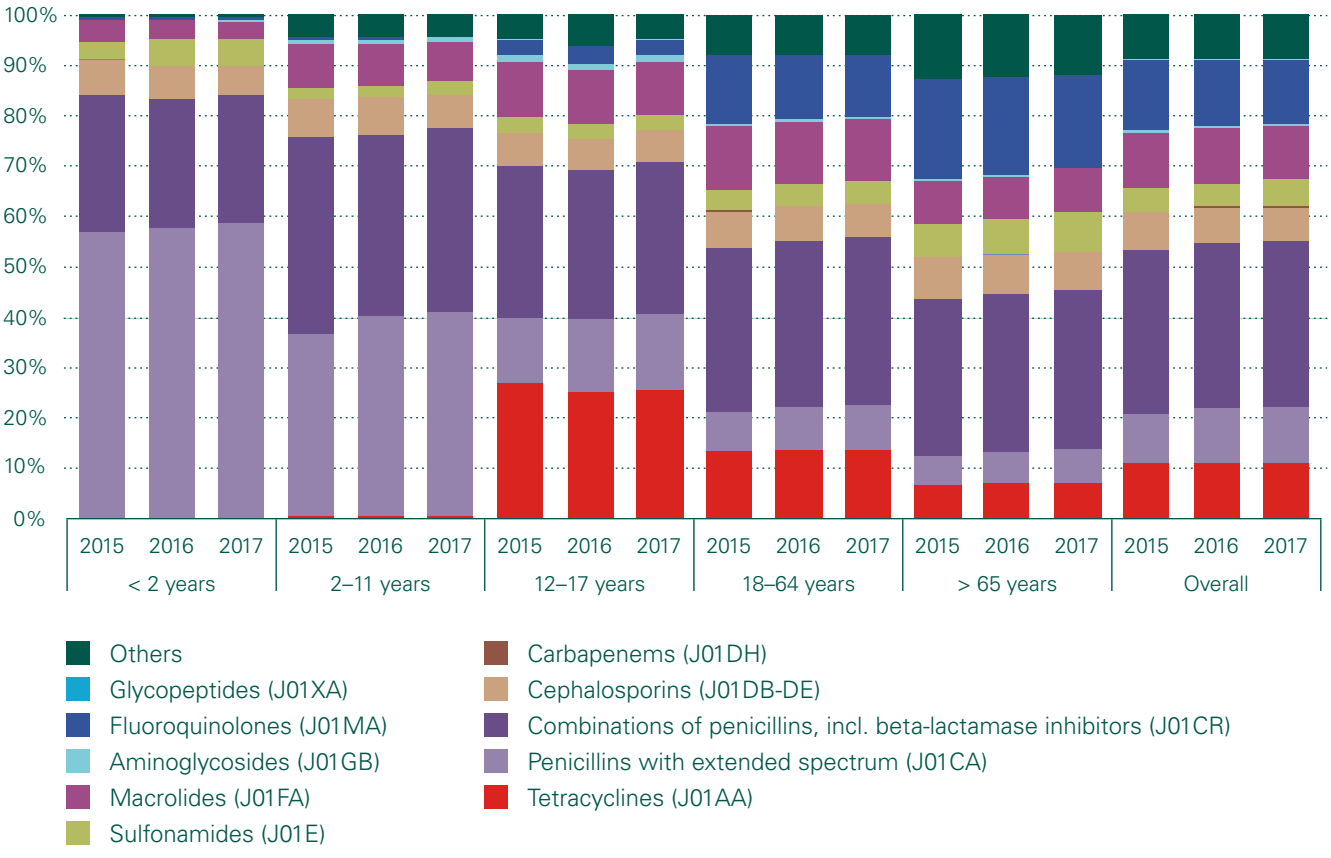
Penicillins with an extended spectrum (namely amoxicillin) were especially used in children aged less than two years (69 % of penicillin consumption in 2017), whereas penicillins associated with beta-lactamase inhibitors were the most frequently used penicillins in the other age groups (2–11 years: 45 %; 12–17: 64 %; 18–64: 77 %; > 65: 82 %) (Figure 5. g). Penicillins with an extended spectrum (amoxicillin) and penicillins associated with beta-lactamase inhibitors (amoxicillin-clavulanic acid) represented 85 % of the total antibiotic consumption in patients less than 2 years old (2–11 years: 77 %; 12–17: 46 %; 18–64: 42 %; > 65: 39 %). Tetracyclines (limecycline and minocycline) were especially used in patients between 12 and 17 years of age (26 % of their total antibiotic consumption). Seniors aged 65 and over were relatively high consumers of fluoroquinolones (18 % of their total antibiotic consumption). Nitrofurantoin and fosfomycin represented resp. 8 % and 1 % of the total antibiotic consumption in patients aged 65 and over in 2017.

5.3 Discussion

In Swiss acute care hospitals, total antibiotic consumption increased from 53.6 to 62.2 DDDs per 100 bed-days between 2007 and 2017, whereas it was relatively stable when expressed in DDDs 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 stays. Expressed in DDDs per 1,000 inhabitants per day, the total antibiotic consumption (1.3) was lower than the median (2.1) obtained in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [3]. 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 antibiotics for systemic use was 10.7 DDDs per 1,000 inhabitants per day in 2017, which was lower than observed in countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [3]. It is to note that the dataset used to measure the total antibiotic consumption differs between the Swiss Antibiotic Resistance Report 2016 (data from pharmacies only) and this report (data from pharmacies and self-dispensing physicians), which explains the difference in use between those reports. The most com-

Figure 5. g: Antibiotic classes per age group and overall as a proportion of the total consumption in the outpatient setting in Switzerland (2015–2017).



monly used class of antibiotics was the penicillins (ATC Code J01C), followed by the macrolides, lincosamides and streptogramins (ATC Code J01F), the tetracyclines (ATC Code J01A) and the quinolones (ATC Code J01M). The relative consumption of fluoroquinolones and penicillins, including beta-lactamase inhibitors, remained relatively high in comparison with countries participating in the ESAC-Net. The German-speaking part of Switzerland had lower antibiotic consumption than the Italian-speaking and French-speaking parts.

Our methodology has several limitations [4, 5]. 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 [6]. Concerning the inpatient setting, a sentinel network like 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 express the antibiotic consumption mostly in DDDs 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.

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Textbox

Antibiotic Prescriptions in Outpatient Medical Care

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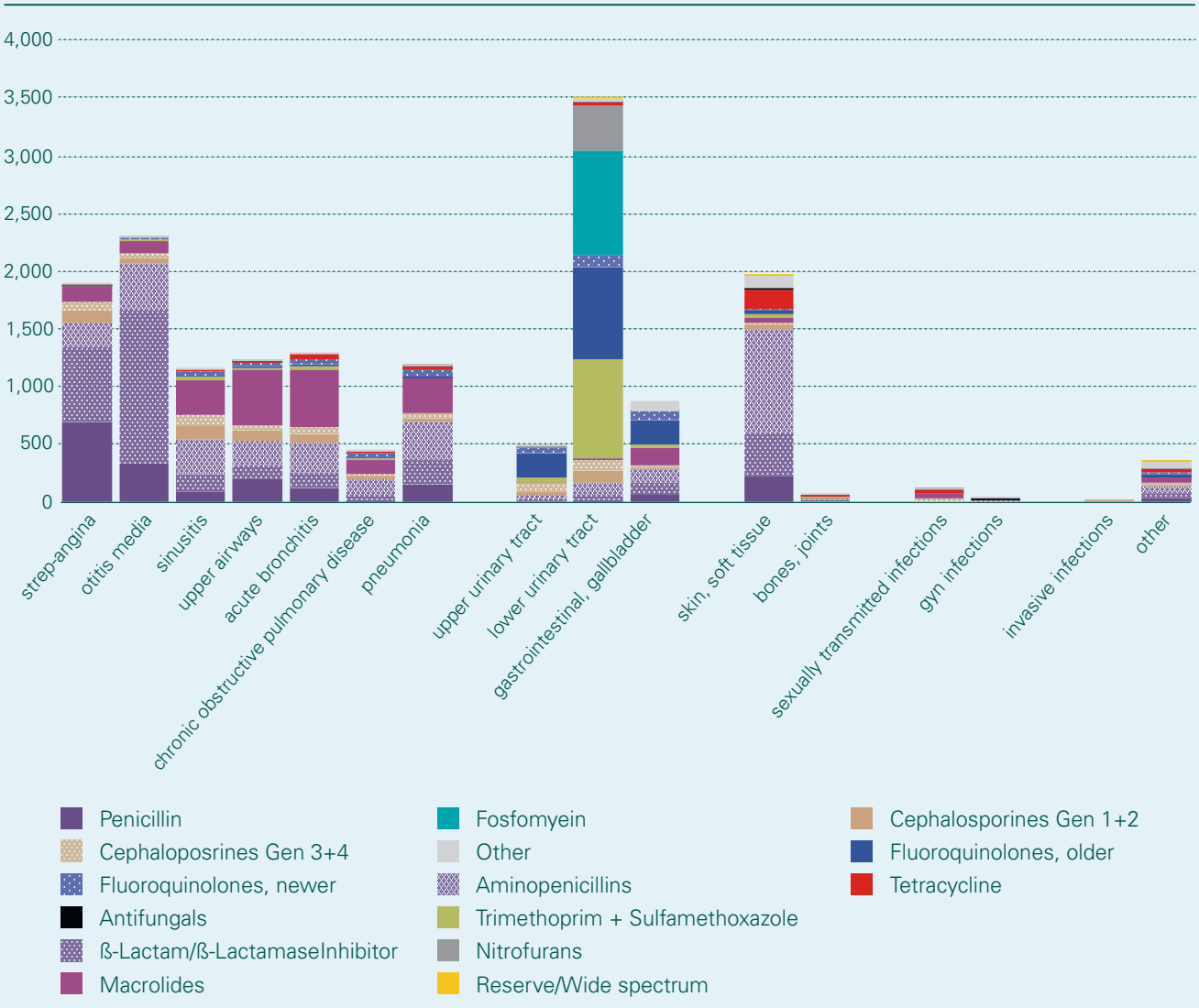
There are only limited data available on practical antibiotic prescriptions in Switzerland, especially regarding the attitude of the treating practitioner. Between 2006 and 2013, a study took place in the Sentinella Network (www.sentinella.ch), a co-project of dedicated general practitioners, the Federal Office of Public Health and the university institutes for family medicine, antibiotic prescriptions were surveyed. This study was resumed in 2017 to compare the present practice to the trend observed at that time.

The principal observation during the first study was that the amount of prescribed antibiotics per consultation and population remains stable whereas the relative proportion of prescriptions for the group of penicillin antibiotic as well as the "other" antibiotic increased over time.

Encouragingly, the number of prescriptions per 1,000 consultations (29) as well as per 100,000 inhabitants (10,400) were significantly lower in 2017 compared to the period of the old study (34–40 per 1,000 consultations respectively 14,000–16,000 per 100,000 inhabitants). As expected, the antibiotic groups of penicillines, macrolides, trimethoprim-sulfamethoxazone, the old Fluoroquinolones and fosfomycin were dominating. If the decreasing trend will continue or not will be revealed in the following years.

Figure 1: Antibiotic prescriptions 2017 by indication and antibiotic group, expressed in number of prescriptions per 100,000 inhabitants.



6

Sales of antimicrobials in veterinary medicine

6 Sales of antimicrobials in veterinary medicine

6.1 Sales of antimicrobials for use in animals

The sales of antimicrobials are in a constant decline (Table 6. a.). In 2016, a total of 38,377 kg of antimicrobials (–9%) were sold, as compared to 32,327 kg in 2017 (–15.8%). This amounts to a decline of 53% (37,503 kg) since 2008. The decrease is mainly due to a fall in sales of medicated premixes.

The sales rankings of the various classes of antibiotics remained unchanged: sulfonamides come in first place, followed by penicillins and tetracyclines. These three classes are often sold as medicated premixes.

The quantity of antibiotics approved only for companion an-

Table 6. a: Sales of antibiotic classes between 2008 and 2017.

Sales (kg)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Sulfonamides	29,129	27,261	25,696	23,123	21,556	18,942	17,009	14,959	13,130	10,181
Penicillins	11,275	10,698	11,272	11,516	11,055	10,930	10,389	10,057	9,694	9,111
Tetracyclines	16,719	15,559	14,749	13,737	12,043	11,631	10,402	8,683	8,177	6,856
Aminoglycosides	3,721	3,573	3,222	3,324	3,207	3,124	3,125	3,104	2,997	2,471
Macrolides	4,287	4,026	3,828	3,551	3,369	3,166	2,858	2,680	1,988	1,594
Trimethoprim	1,858	1,752	1,704	1,549	1,368	1,148	1,102	904	829	591
Polymyxins	1,577	1,544	1,489	1,454	1,058	855	773	503	372	328
Cephalosporins	501	520	568	565	542	530	522	495	431	381
Fluoroquinolones	433	427	415	394	359	413	404	407	304	228
Amphenicoles	253	271	258	284	232	202	188	217	273	378
Others*	139	135	165	477	318	343	274	227	182	210
Total	**69,830**	**65,705**	**63,305**	**59,849**	**54,992**	**51,176**	**46,950**	**42,147**	**38,379**	**32,327**

* Imidazoles, nitrofurans, pleuromutilins, lincosamides, polypeptides excluding polymyxins (until 2013), steroidal antibiotics, quinolones (until 2014)

Table 6. b: Sales of antimicrobials according to the administration route in 2008–2017.

Sales (kg)	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Oral	**55,132**	**51,993**	**50,143**	**46,476**	**42,005**	**38,756**	**34,697**	**30,015**	**26,113**	**21,033**
Premix	48,794	45,714	44,125	40,606	36,181	33,021	29,079	24,336	20,621	16,845
Others*	6,338	6,279	6,017	5,871	5,824	5,735	5,618	5,679	5,492	4,188
Intramammary	**4,505**	**4,015**	**3,595**	**3,734**	**3,655**	**3,482**	**3,375**	**3,193**	**2,672**	**2,753**
Dry cow products	1,439	1,291	1,209	1,323	1,315	1,336	1,343	1,064	918	824
Lactating cow products	3,066	2,724	2,386	2,411	2,340	2,146	2,033	2,129	1,754	1,930
Parenteral	**8,986**	**8,537**	**8,356**	**8,431**	**8,200**	**7,876**	**7,724**	**7,934**	**8,580**	**7,631**
Intrauterine	**870**	**870**	**905**	**857**	**815**	**767**	**864**	**719**	**726**	**612**
Topical/external	**337**	**291**	**306**	**350**	**318**	**296**	**290**	**286**	**287**	**298**
Sprays	241	253	280	321	299	278	272	270	271	284
Others**	96	38	27	30	18	18	19	16	16	15
Total	**69,830**	**65,705**	**63,305**	**59,849**	**54,992**	**51,176**	**46,950**	**42,147**	**38,377**	**32,327**

* Tablets, capsules, powders, suspensions, granules
** Ointments, drops, gels

imals comprises 2.5 % of the total volume.
An error was identified for the conversion factor of all products containing benzathine penicillin and procaine penicillin. This led to an overestimation of sold penicillins of around 20 % (about 2,000 kg) in the previous reports. The data has been corrected and is published correctly since 2015.

Regarding the highest-priority critically important antibiotic classes for human medicine [1], the sales of macrolides have decreased by 25 % in 2016 and another 20 % in 2017. Also, fluoroquinolones were sold less frequently. The sales declined by 21 % in 2016 and by 25 % in 2017. The sales of cephalosporins (3th/4th generation) decreased by about 23 % in 2016 as well as in 2017.

Active ingredient groups are listed individually only if at least three different products from three different marketing authorization holders are licensed. All others are summarized in the category "Others."

The distribution of antimicrobials according to the administration route remained unchanged compared to previous years (Table 6. b). The biggest sales volumes are for products licensed for oral application (2016: 68 %, 2017: 65 %), followed by parenteral (2016: 22 %, 2017: 23 %), intramammary (2016: 7 %, 2017: 9 %), intrauterine (2 %) and topical formulations (1 %). Products authorized for oral application were mainly sold in the form of premixes.

6.2 Sales of antimicrobials for use in livestock animals

6.2.1 General

The sales amount of antimicrobials for livestock animals includes products approved for livestock animals and products approved for livestock and companion animals (mixed registrations). This is in accordance with the procedure used by the ESVAC project [2]. The amount has decreased continuously since 2008 (–54 %). Sulfonamides account for the bulk of agents, followed by penicillins and tetracyclines. Also, in livestock, the highest-priority critically important antibiotics were sold less often than before 2016. The sales of macrolides have decreased by more than 20 % in both years (2016 and 2017) (Table 6. c). Even the sales of long-acting, single-dose injection products show a downward trend. The turnover of amphenicols, reported since 2013, has increased in the last two years (2016: +22 %; 2017: +39 %). The sales of fluoroquinolones and third- and fourth- generation cephalosporins started decreasing in 2016, approximately 20 % each year. A possible explanation for this positive development is the revision of the Ordinance on Veterinary Medicinal Products, which came into effect in April 2016. Since then, administration of critical antimicrobials such as macrolides, fluoroquinolones and 3rd /4th generation cephalosporins to livestock is prohibited to be given for stock.

The sales of colistin have declined by approximately 79 % since 2008. Expressed in correlation to the biomass under exposure (population correction unit, PCU; see Chapter 6.2.2), the level is 0.4 mg colistin / PCU for Switzerland. This is below the European average and in line with the requested reduction of colistin to a level of 1 mg/PCU or below for European countries in order to maintain its efficacy in the treatment of severe infections in humans.

6.2.2 Antimicrobial sales in relation to the livestock population weight (Population Correction Unit Method)

The amount of sales of antimicrobials depends on the size of the animal population. To compare sales in individual countries and across countries, the ESVAC project (European Surveillance of Veterinary Antimicrobial Consumption, EMA) developed a method to express antimicrobial sales corre-

Table 6. c: Sales of different antibiotic classes licensed for livestock animals between 2008 and 2017.

Sales (kg)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Sulfonamides	29,088	27,231	25,672	23,118	21,556	18,942	17,009	14,959	13,130	10,181
Penicillins	10,827	10,226	10,793	11,023	10,582	10,437	9,893	9,573	9,249	8,644
Tetracyclines	16,704	15,546	14,746	13,731	12,038	11,626	10,398	8,679	8,172	6,851
Aminoglycosides	3,688	3,549	3,215	3,317	3,199	3,115	3,114	3,095	2,988	2,462
Macrolides	4,265	4,003	3,806	3,459	3,289	3,089	2,784	2,610	1,967	1,574
Trimethoprim	1,854	1,749	1,702	1,548	1,368	1,148	1,102	904	829	591
Colistin	1,577	1,543	1,489	1,454	1,057	854	773	502	372	327
Fluoroquinolones	408	403	388	371	335	384	379	384	282	207
Cephalosporins	169	203	237	249	237	228	241	234	190	163
Amphenicoles	–	–	–	–	–	183	169	199	244	341
Others*	263	271	303	616	449	310	241	197	152	181
Total	**68,843**	**64,723**	**62,350**	**58,886**	**54,111**	**50,316**	**46,103**	**41,337**	**37,575**	**31,521**

* Pleuromutilins, lincosamide, quinolones, amphenicoles (until 2012)

lated to the weight of an animal livestock population [2]. The amount of active ingredients is divided by the estimated most likely weight at treatment (population correction unit, PCU). Companion animals are not taken into account, as the number is unknown in many countries. PCU is a technical unit of measurement and consists of the number of live (dairy cows, sheep, sows, horses) and slaughtered animals (cattle, pigs, lambs, horses, poultry, turkeys) in the corresponding year multiplied by the estimated weight at the time of treatment (expressed in kg). Imports and exports of live animals are also taken into account. Figure 6. a shows the normalization of antimicrobial sales for livestock animals in Switzerland using the PCU method for the years 2008 to 2017.

The figure shows decreasing sales of antimicrobials in the last ten years, despite a relatively steady population biomass. The reduction of milligram active ingredients per PCU indicates that the decrease of sales of antimicrobials is not primarily due to a smaller livestock population. It can be assumed that the reduction in sales is most probably due to a reduction in the number of treatments performed. The efforts made in the framework of the national strategy on antibiotic resistance (StAR) [4] in Switzerland seem to have a positive effect on the awareness of veterinarians and farmers using antimicrobials in Switzerland.

6.2.3 Medicated premixes

Medicated premixes accounted for 53 % of the total sales in 2016 and 52 % in 2017. A steady decrease in sales of medicated premixes has been observed since 2008 (–66 %). Sulfonamides, tetracyclines and penicillins are the three main classes of active ingredients contained in premixes (Table 6 d). This reduction is the main reason for the decrease in the sales of antimicrobials.

Figure 6. a: Antimicrobial sales for livestock animals in the years 2008–2017 compared to the population biomass (total PCU) and the sales of active ingredients per PCU.

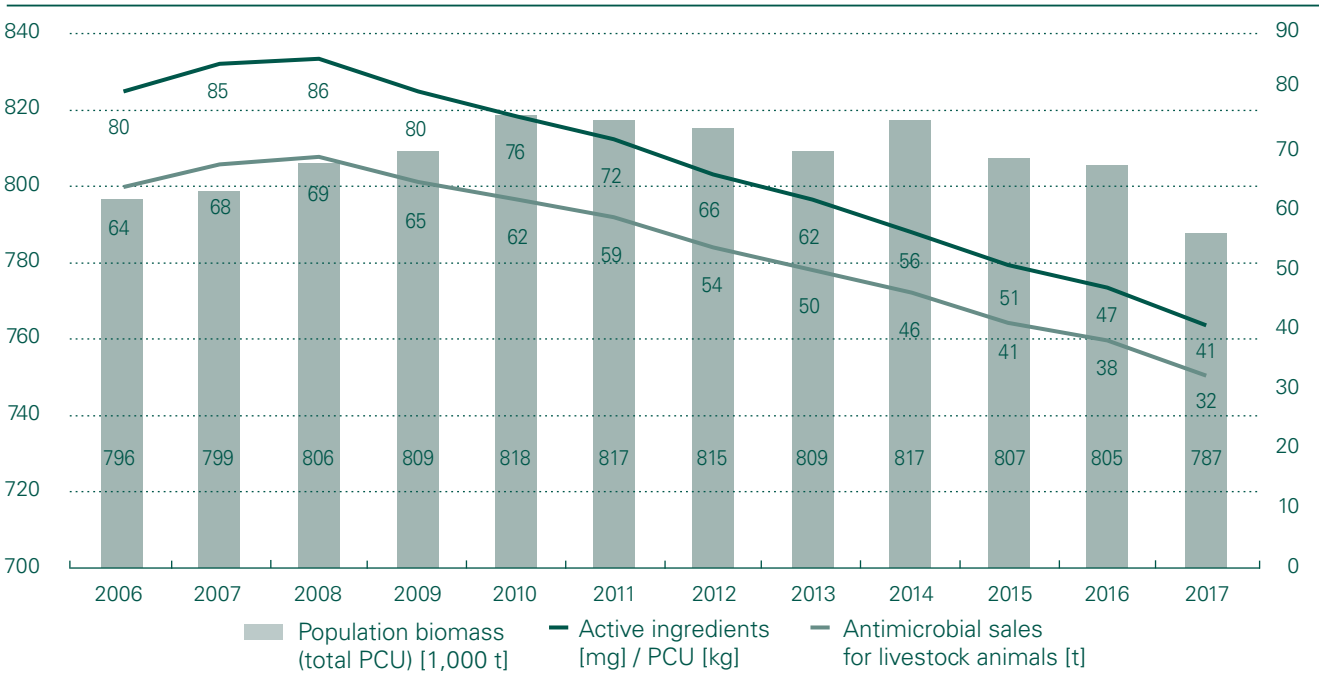


Table 6. d: Sales of antimicrobials licensed as premixes from 2008 to 2017, according to antibiotic class.

Sales (kg)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Sulfonamides	23,075	21,412	20,236	17,788	16,319	13,931	12,141	10,028	8,285	6,450
Tetracyclines	15,008	13,880	12,983	12,006	10,359	9,968	8,673	7,038	6,382	5,174
Penicillins	3,874	3,836	4,610	4,722	4,309	4,461	4,198	3,840	3,363	3,001
Macrolides	3,782	3,624	3,420	3,078	2,907	2,751	2,413	2,263	1,696	1,417
Colistin	1,544	1,525	1,472	1,438	1,045	844	763	500	370	326
Trimethoprim	1,399	1,320	1,249	1,124	937	740	626	453	373	322
Others*	111	118	156	450	305	326	265	215	151	156
Total	**48,794**	**45,714**	**44,125**	**40,606**	**36,181**	**33,021**	**29,079**	**24,336**	**20,621**	**16,845**

* Pleuromutilins, fluoroquinolones, lincosamide, aminoglycosides, quinolones (until 2014)

Medicated premixes are available in several combinations of active ingredients: products containing a single active ingredient, two active ingredients (usually a sulfonamide combined with trimethoprim) or three active ingredients (a tetracycline combined with a sulfonamide and a macrolide).

6.2.4 Antimicrobials authorized for intramammary use

The sales of products for intramammary use showed a decrease in 2016 (–18%), whereas in 2017 the sales increased slightly (3%). Nevertheless, since 2008, sales have been reduced by nearly 40%. Two thirds of all antimicrobials licensed for intramammary use are products for the treatment of mastitis during lactation, and one third are products for drying off. In the past two years, the sales of the latter products have in average decreased by 12%, whereas in 2017 the sales of products for use during lactation increased slightly (Figure 6. b). The distribution by antibiotic classes shows that penicillins are predominant, accounting for 80% of all active ingredients administered into the udder (Table 6. e). Sales of products containing cephalosporins for the treatment of mastitis during lactation have been increasing slightly since 2014.

6.3 Sales of antimicrobials licensed for companion animals

The quantity of antibiotics approved exclusively for use in companion animals amounts to approximately 2,5% of the total volume. Since 2012, products licensed for both livestock and companion animals are added to the category

Figure 6. b: Sales of antimicrobials (in kg) licensed for intramammary use in 2008–2015 separated into dry cow products and products for use during lactation.

Table 6. e: Sales of antimicrobials licensed for intramammary use in 2008–2017 according to antibiotic class.

Sales (kg)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Dry cow products										
Total	**1,439**	**1,291**	**1,209**	**1,323**	**1,315**	**1,336**	**1,343**	**1,064**	**918**	**824**
Products for use during lactation										
Penicillins	2,326	2,052	1,785	1,813	1,774	1,644	1,545	1,652	1,366	1,543
Aminoglycosides	558	492	445	436	406	376	370	361	275	292
Cephalosporine	35	51	56	60	55	52	56	59	60	59
Others**	147	129	101	102	104	74	62	57	53	36
Total	**3,066**	**2,724**	**2,386**	**2,411**	**2,340**	**2,146**	**2,033**	**2,129**	**1,754**	**1,930**
Total	**4,505**	**4,015**	**3,595**	**3,734**	**3,655**	**3,482**	**3,376**	**3,193**	**2,672**	**2,754**

** Lincosamides, macrolides, polymyxins

Table 6. f: Sales of antibiotic classes licensed for companion animals in 2008–2017.

Sales (kg)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Penicillins	385	412	417	438	415	438	450	443	446	467
Cephalosporins	332	317	331	316	304	302	281	262	241	217
Fluoroquinolones	25	24	27	23	24	29	25	23	22	21
Aminoglycosides	33	24	7	7	8	9	10	9	10	9
Sulfonamides*	41	30	24	5	-	-	-	-	-	-
Others**	171	174	148	173	129	82	81	74	85	92
Total	**988**	**982**	**955**	**962**	**881**	**860**	**847**	**810**	**804**	**806**

* No licensed products since 2012

** Imidazoles, nitrofurans, polypeptides, steroidal antibiotics, tetracyclines, trimethoprimes, amphenicoles, macrolides, lincosamides

"livestock animals," in accordance with the guidelines of the ESVAC project [2]. This is especially relevant for active ingredients for parenteral application, as most of these products are licensed for both livestock and companion animals. The consequence is a slight underestimation of the use in companion animals.

The amount sold for companion animals in 2017 was 806 kg, slightly more than in 2016 (+0.4 %). Nonetheless, the antimicrobial sales for companion animals has decreased about 18 % (–182 kg) since 2008. Penicillins were the most important active ingredient group, followed by cephalosporins and fluoroquinolones (Table 6. f). The slightly decreasing trend of sales of cephalosporins has continued during the past two years (2016: –8 %; 2017: –10 %).

6.4 Discussion

There is a constant increase of awareness in veterinarians as well as in farmers. The decrease in the volume of antimicrobials sold for use in veterinary medicine is ongoing since 2008. This is mainly due to a fall in the sales of medicated premixes. However, the prohibition of selling critical antimicrobials for stock since April 2016 has also supported the decrease within the last years. Especially the significant decline in sales of highest-priority critically important antibiotic classes is encouraging. The reduction of milligram active ingredients per PCU indicates that the reason for the decrease is most likely a reduced number of treatments. However, the data should be interpreted cautiously as they are based on sales figures only. Relevant information about target species (livestock animals, companion animals, mixed), route of administration (parenteral, oral, topical/external, intrauterine, intramammary) and galenics are solely based on the marketing authorization (summary of product characteristics). Therefore, the report does not contain any data regarding effective use at the species level. Different dosages for different antibiotic classes and target species are not taken into account and can differ widely. Various potencies of antimicrobials can only be corrected using standardized daily doses (in keeping with the defined daily doses [DDD] used in human medicine). Therefore, ESVAC has recently published technical units of measurements to report antimicrobial consumption data in animals [5]. Defined daily doses for animals (DDDvet) and defined course doses for animals (DCDvet) take into account differences between species and substances as well as treatment duration.

Information about treatment intensities, i.e. the number of animals treated in relation to a given population, can only be provided by data at the veterinary or farm level. These data are currently not available in Switzerland. To establish a correlation with the development of resistance to antimicrobials, the reduction of total volumes of antimicrobials sold is less relevant than the number of treatments per animal or the number of animals treated per unit of time. A system to collect veterinary prescription data will be available in 2019. The recording of prescription data is crucial to better target measures for prevention and prudent use, and to follow up on their effects.

References

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[3] European Medicines Agency 2016. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health (EMA/231573/2016)

[4] Swiss Confederation 2015. Strategy on Antibiotic Resistance Switzerland

[5] European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2016 Defined daily doses for animals (DDDvet) and defined course doses for animals (DCDvet) (EMA/224954/2016)

Textbox

Antibiotic Substances in the Water Cycle

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[1] WWEA: Office of Waste, Water, Energy and Air, Zurich
[2] Eawag, Swiss Federal Institute of Aquatic Science and Technology, Dübendorf
[3] FOEN, Federal Office for the Environment, Bern

Antibiotics are used in high quantities in veterinary and human medicine. In 2016, approximately 38,000 kg of veterinary antibiotics, mainly sulfonamides, penicillins, and tetracyclines, were distributed in Switzerland with a decreasing trend as compared to the previous years (SARR 2018). Consumption data of human antibiotics are harder to obtain but are in the same order of magnitude, while penicillins, fluoroquinolones and sulfonamides are used in highest quantities (Singer et al., 2016). After intake by animals and humans, antibiotics are partly excreted unchanged, thereafter finding their way into the aquatic environment. Municipal wastewater treatment plants (WWTPs) were found to be the major discharge point for antibiotics, mainly resulting from domestic consumption and excretion by humans. In conventional wastewater treatment, antibiotics, like other polar micropollutants, are only partly removed and are discharged into the receiving waters. It was shown that concentrations of antibiotics in Swiss rivers can be precisely predicted with a mass flow model which takes into account the consumption of antibiotics, their excretion rate, their elimination in wastewater treatment and the water flow in rivers (Kuroda et al., 2015). Through river bank filtration, antibiotics can also reach groundwater.

Figure 1 shows concentrations of three antibiotics analyzed in the canton of Zurich in samples of wastewater treatment plant effluents, in river water and in groundwater. Sulfamethoxazole, ciprofloxacin and clarithromycin were detected in the highest concentrations (up to 600 ng/L in the WWTP effluents), while concentrations in river water were one order of magnitude lower due to dilution. In groundwater, only sulfamethoxazole was found above the limit of detection (LOD 10 ng/L).

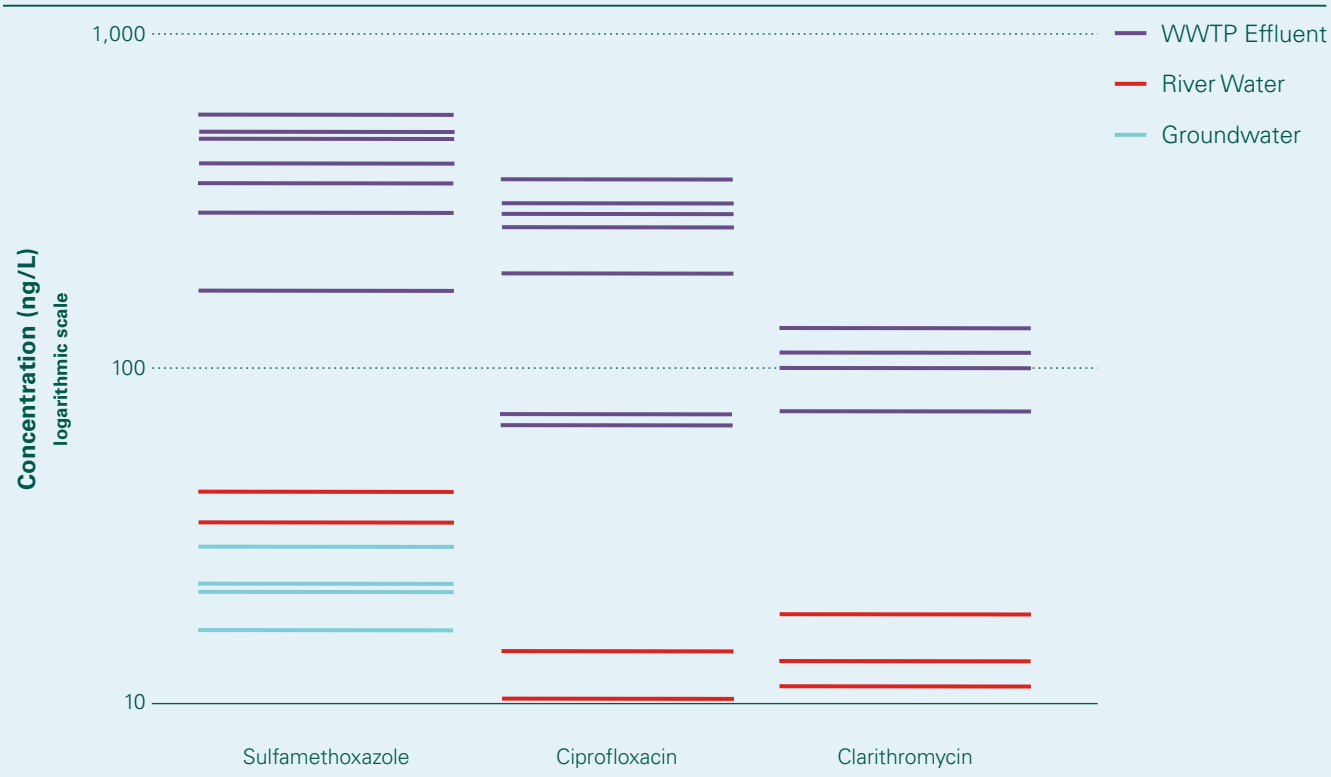
A nationwide record of antibiotics in Swiss groundwater is provided by the NAQUA National Groundwater Monitoring (FOEN 2018). Since 2013, the antibiotic sulfamethoxazole is analyzed at all the approximately 550 NAQUA monitoring sites, which are operated by the Federal Office for the Environment FOEN in close collaboration with the cantonal authorities. The specific focus on this antibiotic is due to the results of two pilot studies, which were realized in 2004/2005, and 2007/2008 respectively, on more than 80 pharmaceuticals as well as 200 micropollutants ("screening"). According to its persistence during bank filtration, sulfamethoxazole proved to be the antibiotic most frequently detected in groundwater. In 2014, sulfamethoxazole appeared at 7 % of all NAQUA monitoring sites. Concentrations were low and did not exceed 100 ng/L.

Further indicators of wastewater, such as the artificial sweetener acesulfame or the dishwashing additive benzotriazole, were detected more frequently and at higher concentrations in groundwater. Overall, wastewater indicators appeared at more than one third of all NAQUA monitoring sites, indicating that wastewater is an important source of synthetic chemicals in groundwater.

Most of the affected NAQUA monitoring sites are located close to streams and rivers containing a significant amount of treated wastewater. Wastewater in these rivers often exceeds 5 % of water discharge. Although an important part of the wastewater-derived substances is degraded or sorbed to clay and silt particles during riverbank filtration, another part may be transferred with the infiltration water into the groundwater of adjacent gravel bed aquifers. Especially substances with low degradation and low sorption potential, such as the antibiotic sulfamethoxazole, are relevant and affect groundwater quality at larger scales.

Whether high concentrations of antibiotics in the water cycle directly promote the development of antibiotic resistances (see also Textbox "Antibacterial Resistance in the Aquatic Environment") in the environment is currently unknown. It has been shown that antibiotic-resistant bacteria preferentially develop where large amounts of antibiotics are used. Potential hotspots are hospitals and sites where veterinary pharmaceuticals are applied. The NFP72 project *Swiss River*

Figure 1: Concentration of the antibiotics sulfamethoxazole, ciprofloxacin, and clarithromycin in the effluent of a wastewater treatment plant (WWTP), in river water and in groundwater in a catchment of the canton of Zurich (detection limit 10 ng/L).



Resistome therefore investigates how antibiotic resistance spreads in water and how stable it is in this medium.
Based on the precautionary principle, inputs of antibiotics into the environment and the water cycle should be minimized as far as possible. In Switzerland, selected wastewater treatment plants will be upgraded by 2040 in order to eliminate a broad spectrum of micropollutants, including antibiotics. With this upgrade, the discharge of micropollutants into surface waters will be reduced by two thirds. Groundwater, which is the most important drinking water source in Switzerland, will benefit from these improvements as well.

References

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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 (after respiratory tract infections) the second most frequent infectious disease in ambulatory care, increasing resistance trends directly affect the hospital as well as the ambulatory setting.

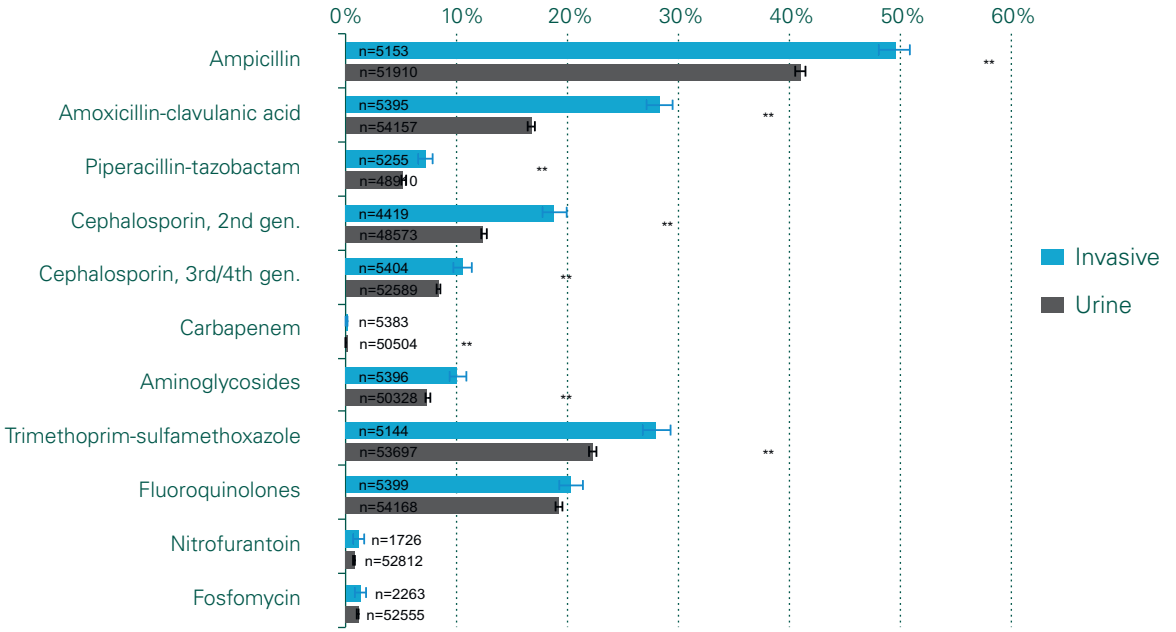
In 2017, resistance to fosfomycin and nitrofurantoin was still very low (Table 7. a). These antibiotics can only be used for non-invasive urinary tract infections. Therefore, they represent an important option in ambulatory care. In contrast to earlier years, and probably due to classification of these antibiotics as first choice options to treat uncomplicated lower urinary tract infections, these antibiotics now are tested in nearly all urinary samples on a routine basis. While fluoroquinolone non-susceptibility has steadily increased from 10.3% in 2004 to 20.5% in 2015, non-susceptibility rates have stabilized during the last two years (20.3% in 2017). Whether this is already due to the promotion of ciprofloxacin-free antibiotic regimens for uncomplicated lower urinary tract infections has to be analyzed in additional studies. In EU/EAA states, a significant decrease in fluoroquinolone resistance from 22.8 to 21.0% was observed from 2013 to 2016 [1]. Although non-susceptibility to trimethoprim-sulfamethoxazole is still higher, a decrease was observed from 29.9% in 2015 to 28% in 2017, and significant lower rates are observed in urinary samples (22% in 2017, Figure 7. a). Therefore, trimethoprim-sulfamethoxazol still remains a first-line option in non-invasive ambulatory urinary tract infections [2]. Because *E. coli* is also one of the most important pathogens in the outpatient setting, we have compared non-susceptibility rates of outpatient urinary samples with invasive samples (Figure 7. a), demonstrating a lower non-susceptibility rate in the outpatient setting for most of the antibiotics tested. Probably these data still overestimate the true non-susceptibility rate in the uncomplicated lower urinary tract infections due to sampling bias [3].

Table 7. a: Non-susceptibility rates of invasive *Escherichia coli* isolates in humans for 2017.

***Escherichia coli* (invasive)**											**2017**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	1382	53.6%	3414	48.0%	357	47.3%	5153	49.5%	48.1–50.9	↓	–
Amoxicillin-clavulanic acid	1380	35.8%	3658	26.5%	357	17.4%	5395	28.3%	27.1–29.5	↑	↑
Piperacillin-tazobactam	1376	8.1%	3522	7.0%	357	4.5%	5255	7.1%	6.4–7.8	–	↑
Cephalosporin, 2nd gen.	845	18.1%	3218	20.0%	356	10.1%	4419	18.8%	17.7–20	–	↓
Cephalosporin, 3rd/4th gen.	1382	12.7%	3665	9.8%	357	9.2%	5404	10.5%	9.7–11.4	–	↑
Carbapenem[1]	1370	0.1%	3656	0.1%	357	0.0%	5383	0.1%	0–0.2	–	–
Aminoglycosides	1379	12.0%	3660	9.5%	357	8.1%	5396	10.1%	9.3–10.9	↑	↑
Trimethoprim-sulfamethoxazole	1381	30.1%	3406	27.5%	357	25.2%	5144	28.0%	26.8–29.3	–	–
Fluoroquinolones[2]	1377	22.0%	3665	19.6%	357	20.2%	5399	20.3%	19.2–21.4	–	↑
Nitrofurantoin	487	1.4%	1239	1.0%	0	–	1726	1.1%	0.7–1.7	↓	↓
Fosfomycin	739	1.1%	1523	1.4%	1	0.0%	2263	1.3%	0.9–1.8	–	–

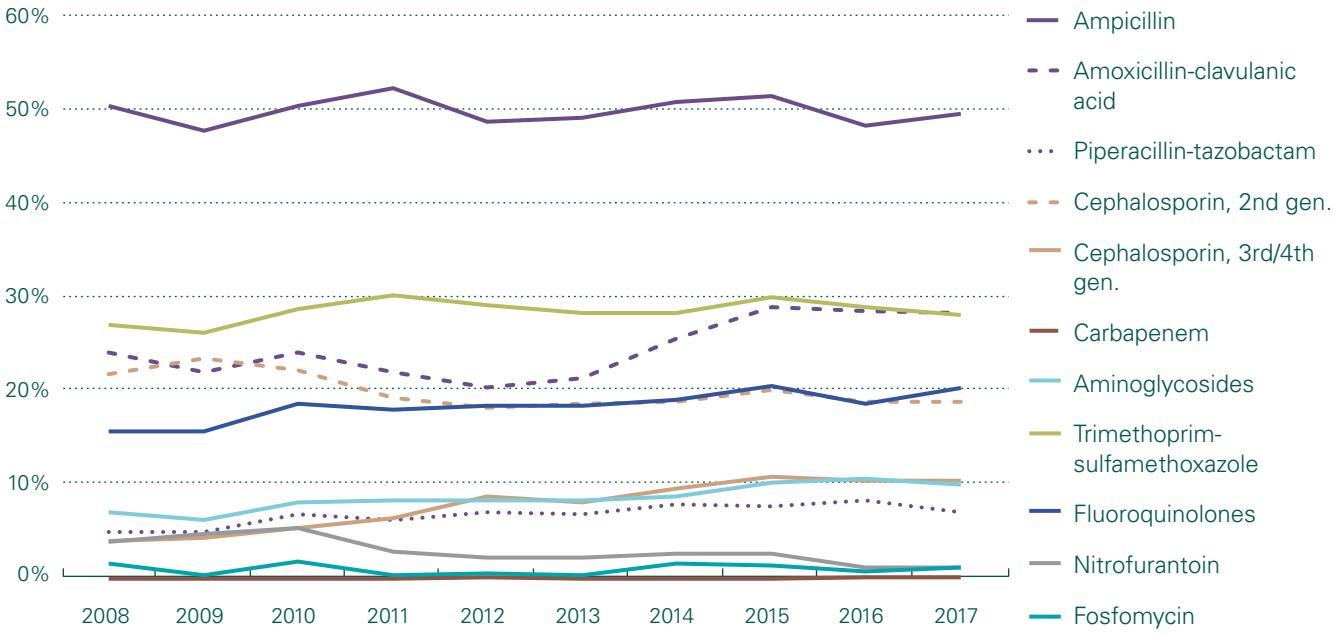
West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.
[1] Carbapenems: imipenem, meropenem
[2] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

Figure 7. a: Comparison of non-susceptibility rates in invasive versus outpatient urinary samples in *Escherichia coli* isolates in humans for 2017.



n=number of isolates tested with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence: * =p-value <0.05; **= p-value <0.01.

Figure 7. b: Non-susceptibility rates in invasive *Escherichia coli* isolates in humans between 2008 and 2017.



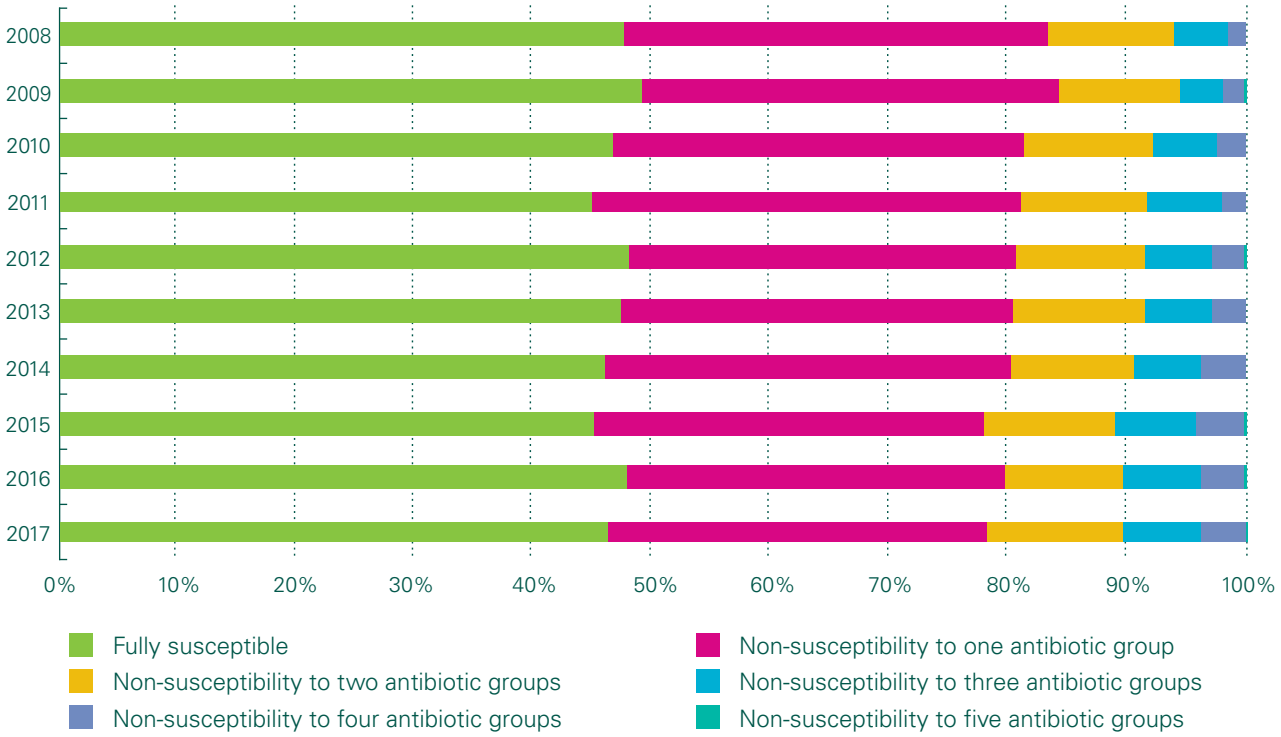
As for quinolones, the steadily increasing non-susceptibility rates to 3rd/4th generation cephalosporins from 0.9% in 2004 to 11.0% in 2015 has stabilized at 10.5% in 2017. In EU/EAA states, a slight decrease from 13.1% to 12.4% was observed between 2013 and 2016. Whether these trends will persist has to be observed in future. For Switzerland, a more detailed analysis of the recent trends since 2013 is planned for different settings. Non-susceptibility rates for aminoglycosides and piperacillin-tazobactam have also stabilized since 2015, which, at least in part, could be attributable to cross-resistance. Multiresistance is frequent. However, only a slight increase for *E. coli* isolates resistant to two to five antibiotic groups was observed during the last ten years (Table 7. b, Figure 7. c).

Carbapenem-resistance in *E. coli* is still very rare (0.1%) and comparable to the EU/EAA states (<0.1% on average in 2016). Nevertheless, increasing rates of carbapenem-producing Enterobacteriaceae (CPE) around the world are alarming. In order to survey these trends more accurately, knowledge regarding the genetic mechanisms is indispensable, therefore, the Federal Office of Public Health has in-

Table 7. b: Non-susceptibility combinations in invasive *E. coli* isolates in humans 2017. Only isolates tested against all five antibiotic groups (aminopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n=5119/5405 [94.7 %]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**2373**	**46.4%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**1631**	**31.9%**
Aminopenicillins	1436	28.1%
Fluoroquinolones	166	3.2%
Aminoglycosides	29	0.6%
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**585**	**11.4%**
Aminopenicillins + fluoroquinolones	356	7.0%
Aminopenicillins + third-generation cephalosporins	117	2.3%
Aminopenicillins + aminoglycosides	98	1.9%
Other antimicrobial group combinations	14	0.3%
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**335**	**6.5%**
Aminopenicillins + third-generation cephalosporins + fluoroquinolones	174	3.4%
Aminopenicillins + fluoroquinolones + aminoglycosides	126	2.5%
Aminopenicillins + third-generation cephalosporins + aminoclycosides	34	0.7%
Aminopenicillins + third-generation cephalosporins + carbapenems	1	0.0%
Resistance to four antimicrobial groups		
Total (all four-group combinations)	**194**	**3.8%**
Aminopenicillins + third-generation cephalosporins +aminoglycosides + fluoroquinolones	194	3.8%
Resistance to five antimicrobial groups		
Aminopenicillins + third-generation cephalosporins + fluoroquinolones + aminoglycosides + carbapenems	1	0.0%

Figure 7. c: Multiresistance in invasive *E. coli* isolates in humans between 2008 and 2017 (for details refer to Table 7. b).



troduced an obligation to report CPE starting 1.1.2016. In combination with data from earlier years, collected by the Swiss Society for Microbiology since 2013, we were able to perform a first more detailed analysis for this report (see Textbox: "Temporal and Regional Prevalence of Carbapenemase-Producing Enterobacteriaceae from 2013 to 2017 in Switzerland"). As the determination of the genotype is becoming more and more complex, it was decided that in future all CPE isolates will be sent to the NARA for more detailed analyses (see Textbox: "The National Reference Center for Emerging Antibiotic Resistance (NARA)."

Colistin, a rather toxic reserve antibiotic belonging to the polymyxin group, might in future become more important as a "last resort antibiotic" for carbapenemase-producing Gram-negatives. So far, colistin resistance is very rare in Switzerland (see Textbox: *"Mcr-1* Based Colistin Resistance: Filling Knowledge Gaps in View of the Spread of Plasmid-Mediated Colistin Resistance in Switzerland", Chapter 9), but reports from China, describing a mobile plasmid encoding a colistin resistance gene (mcr-1), are worrisome [4]. Currently, algorithms for testing and reporting colistin resistance in Switzerland are under development.

Textbox

Temporal and Regional Prevalence of Carbapenemase-Producing Enterobacteriaceae from 2013 to 2017 in Switzerland

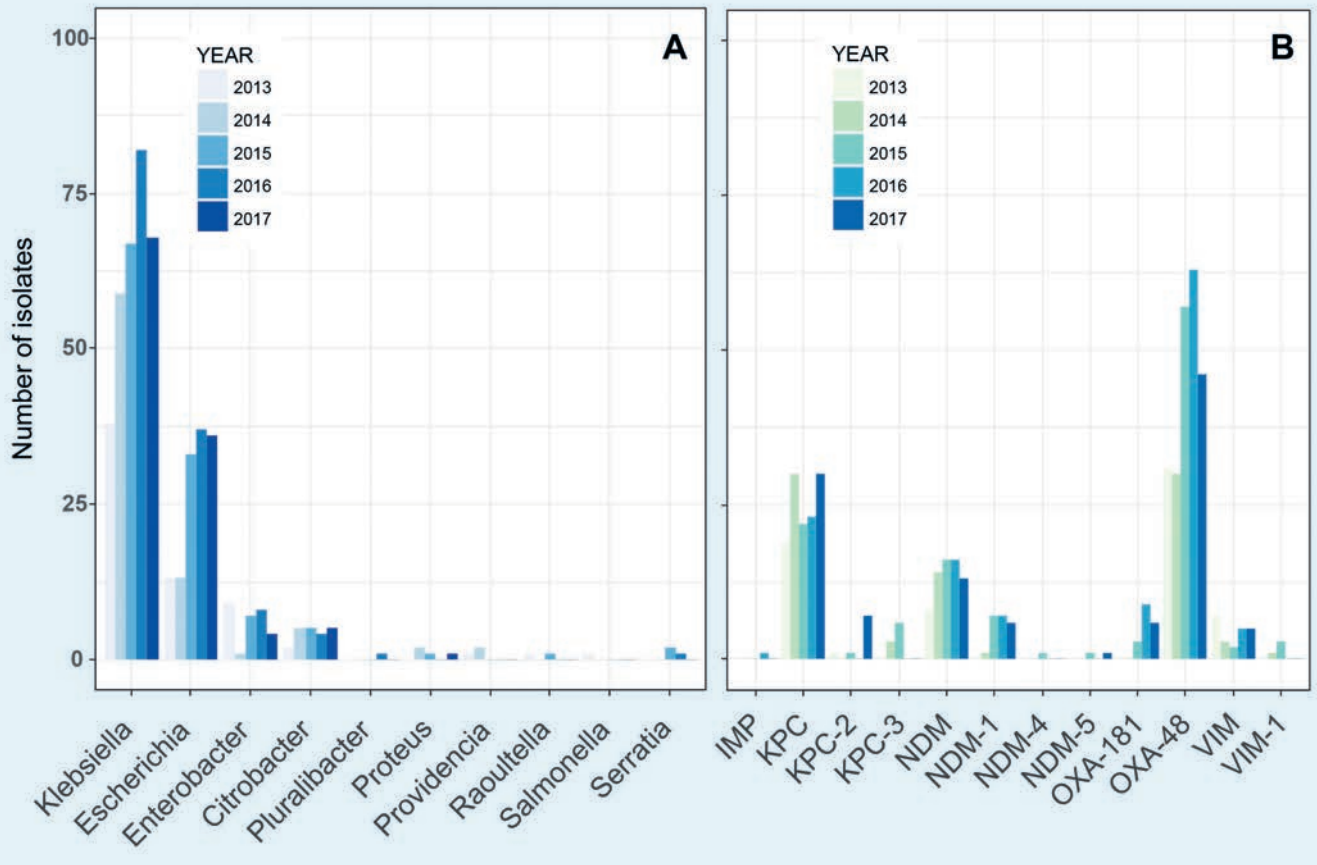
Alban Ramette[1]

[1] Institute for Infectious Diseases, University of Bern, Bern

Increasing rates of carbapenemase-producing Enterobacteriaceae (CPE) have been observed in Europe and all over the world. CPE represent a great concern because of their broad resistance to multiple antibiotics, which considerably reduces therapeutic options.

From 2016 onwards, CPE have been defined as a notifiable disease by the Swiss Federal Office of Public Health. Before 2016, the Swiss Society for Microbiology defined a network of eight Swiss expert laboratories capable of identifying and characterizing CPE according to EUCAST guidelines. All Swiss microbiology laboratories were asked to send all suspected human CPE cases to one of the expert laboratories for characterization of the isolates. Data from 2013 to 2015 (before mandatory reporting) and from 2016 to 2017 were then collected by the Swiss Centre for Antibiotic Resistance anresis.ch and analyzed for temporal and regional trends.

Figure 1: Number of carbapenemase-producing isolates per A) Enterobacteriaceae genus and B) genotypes.



From 2013 to 2015, the total number of CPE isolates ranged from 65 to 116 per year, and in 2016 and 2017, total CPE numbers were 142 and 114, respectively, indicating a stabilization of the number of CPE cases in the last three years. The most frequently isolated species were consistently *K. pneumoniae*, followed by *E. coli* (Fig. 1A). The most frequently observed carbapenemase genotypes were OXA-48 and OXA-48-like, KPC, and NDM (Fig. 1B). At the regional level, highest CPE numbers were identified in the Geneva and north-eastern regions from 2013 to 2016, where potential regional outbreaks could be identified. Further statistical analyses of risk factors confirmed a slight increase over time of the total number of CPE isolates, higher prevalence in the Geneva region, and more isolates originating from male patients. All types of specimens (blood, respiratory tract, stool, urine, wounds) were associated with high CPE numbers. Sensitivity analyses that included the joint 18 laboratories from 2013 to 2015 and 2016 did not change the observed trends.

Molecular data indicate a high diversity of different carbapenemases, with OXA-48-like, KPC- and NDM-type carbapenemases being the most prevalent in Switzerland. Overall OXA-48-like and NDM producers are increasing only slightly over time, which is in contrast to the situation in neighboring European countries where the increase has been more substantial. Temporal and regional trends were identified, and due to the current mandatory reporting scheme, a continuous surveillance of the situation in Switzerland has been achieved.

See related abstract:

Ramette A, Zbinden R, Schrenzel J, Nordmann P, Perisa D, Kronenberg A (2018) Prevalence of carbapenemase-producing Enterobacteriaceae in Switzerland from 2013 to 2017. 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Madrid, Spain, 21–24 April 2018. www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=62978

Textbox

The National Reference Center for Emerging Antibiotic Resistance (NARA)

Patrice Nordmann[1]

[1] University of Fribourg

At the beginning of 2017, the National Reference Center for Emerging Antibiotic Resistance (NARA) was created by the FOPH at the University of Fribourg, Medical and Molecular Microbiology Department, headed by Prof P. Nordmann (MD, PhD, Spec Microbiology). The aims of this center are multiple: (i) early identification of emerging antibiotic resistance traits in Gram-negative and Gram-positive bacteria by using microbiology, biochemistry and genetics, (ii) comparison of emerging resistant strains as a source of potential outbreaks, (iii) evaluation of novel antibiotics and novel diagnostic techniques, and (iv) development of novel rapid diagnostic tests for emerging antibiotic resistances. NARA contributes to the diagnostics of emerging antibiotic resistances in all types of health facilities located in Switzerland (private and public settings). Most of the results are given within 72 hours. Among the recent achievements of the NARA, one may note the first international identification of the plasmid-mediated MCR-1 polymyxin resistance associated with carbapenemase in *Escherichia coli*, the identification of the first outbreak of multidrug resistance associating carbapenemase and pan-drug resistance to aminoglycosides in *Klebsiella pneumoniae,* and the development of the first test for a rapid identification (2–3 hours) of polymyxin resistance in Enterobacteriaceae.

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. Most common sites of infection are the urinary tract and the lung (pneumonia). In contrast to *E. coli*, they are intrinsically resistant to aminopenicillins.

In this report, we only present 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 between 2004 (1.3 %) and 2014 (9.9 %), but since then, we have observed a slight decrease to 7.7 % in 2017. This compares favorably with the EU/EEA average of 25.7 % in 2016. As in Switzerland, a significant decrease was observed in EU/EEA states from 2013 to 2016, although trends were very different in individual countries [1]. There are considerable differences between different Swiss regions (Table 7. c), with higher non-susceptibility rates in western Switzerland for most antibiotics, including 3rd/4th generation cephalosporins. In contrast, carbapenem non-suscepti-

bility is highest in southern Switzerland, mirroring the carbapenem resistance in Europe, with rates of 0.4% in France and very high carbapenem resistance rates in Italy (33.9% in 2016). While the same trend with maximal non-susceptibility rates in 2014 was observed for 2nd generation cephalosporins and aminoglycosides, this was not the case for amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazol and quinolones, for which non-susceptibility rates are still increasing slightly. No significant trends were observed for carbapenem resistance, which is still below 1% in Switzerland, and therefore much lower than the mean EU/EEA rate of 6.1% in 2016. First data of a more detailed analysis on carbapenemase producers in Enterobacteriaceae is shown in the Textbox "Temporal and Regional Prevalence of Carbapenemase-Producing Enterobacteriaceae from 2013 to 2017 in Switzerland". Co-resistance is frequent, details are shown in Table 7. d and Figure 7. e.

Table 7. c: Non-susceptibility rates of invasive *Klebsiella pneumoniae* isolates in humans in 2017.

Klebsiella pneumoniae											**2017**
Antimicrobials	**West**		**North–East**		**South**		**Total**			**Trend**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Amoxicillin-clavulanic acid[1]	224	21.9%	686	13.8%	52	13.5%	962	15.7%	13.5–18.1	–	↑
Piperacillin-tazobactam	224	12.9%	661	9.7%	52	9.6%	937	10.5%	8.7–12.6	–	↑
Cephalosporin, 2nd gen.	160	18.1%	601	18.0%	52	11.5%	813	17.6%	15.1–20.4	↓	↑
Cephalosporin, 3rd/4th gen.	224	12.1%	687	6.3%	52	7.7%	963	7.7%	6.2–9.5	–	↑
Carbapenems	224	0.4%	685	0.1%	52	1.9%	961	0.3%	0.1–0.9	–	–
Aminoglycosides	224	8.9%	687	4.4%	52	3.8%	963	5.4%	4.1–7	–	↑
Trimethoprim-sulfamethoxazole	224	16.5%	636	13.8%	52	15.4%	912	14.6%	12.4–17	–	↑
Fluoroquinolones[1]	223	16.1%	688	9.6%	52	17.3%	963	11.5%	9.7–13.1	–	↑

[1] At least one out of ciprofloxacin, norfloxacin, ofloxacin
Trends were modelled with logistic regressions. Arrows represent a significant effect ($p<0.05$) of the year on the correspondent outcome (↑ increase, ↓ decrease).
West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.

Figure 7. d: Non-susceptibility rates in invasive *Klebsiella pneumoniae* isolates in humans 2008–2017.

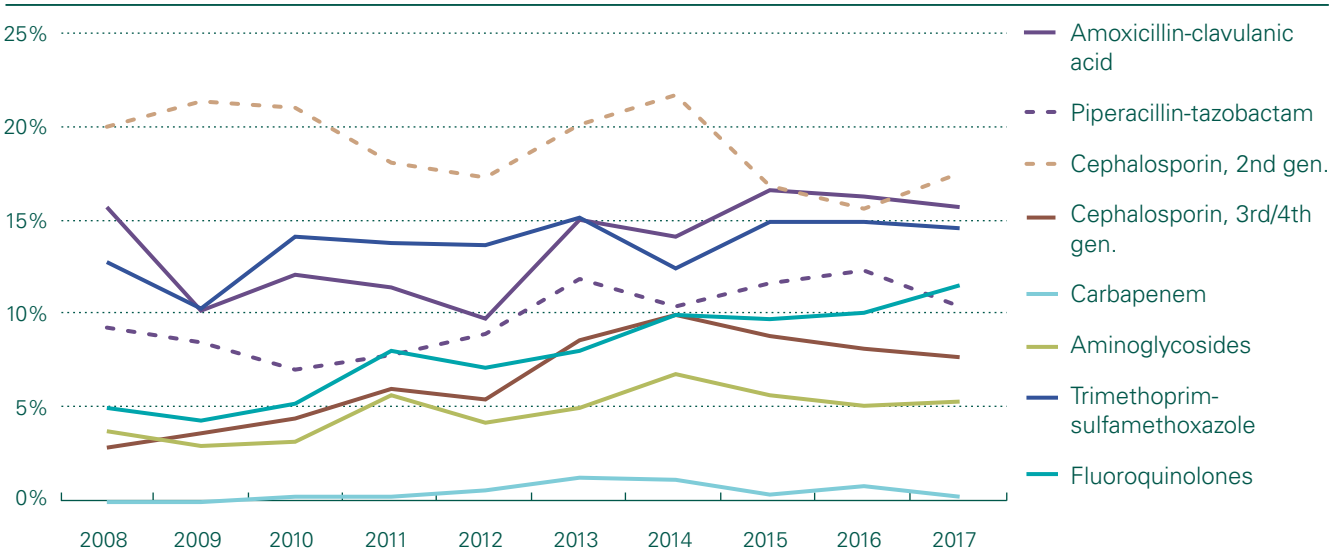
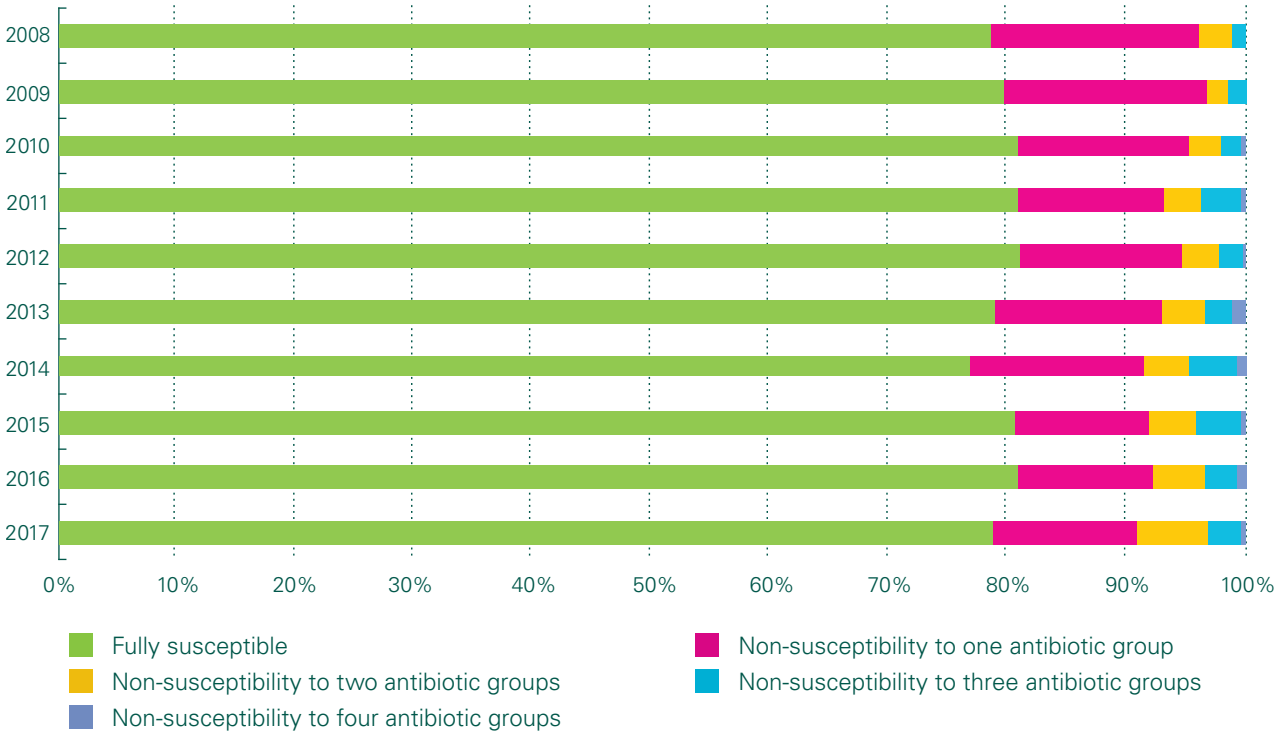


Table 7. d: Non-susceptibility combinations in invasive *K. pneumoniae* isolates in humans in 2017. Only isolates tested against all four antibiotic groups (third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n=959/964 [99.5 %]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**756**	**78.8%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**116**	**12.1%**
Third-generation cephalosporins	78	8.1 %
Fluoroquinolones	31	3.2 %
Aminoglycosides	7	0.7 %
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**56**	**5.8%**
Third generation cephalosporin + fluoroquinolones	42	4.4 %
Third-generation cephalosporins + aminoglycosides	7	0.7 %
Aminoglycosides + fluoroquinolones	7	0.7 %
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**28**	**2.9%**
Third-generation cephalosporins + aminoglycosides + fluoroquinolones	28	2.9 %
Resistance to four antimicrobial groups		
Third-generation cephalosporins + aminoglycosides + fluoroquinolones + carbapenems	3	0.3 %

Figure 7. e: Multiresistance in invasive *K. pneumoniae* isolates in humans from 2008–2017 (for details refer to Table 7. d).



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 bloodstream 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 caused by *P. aeruginosa* in immunocompetent hosts are external otitis (swimmer's ear) and sinusitis.

P. aeruginosa is intrinsically resistant to amoxicillin, amoxicillin-clavulanic acid, first and second generation cephalosporins, cefixime, cefpodoxime, ceftriaxone, ertapenem, as well as tetracyclines, including tigecycline and trimethoprim-sulfamethoxazole. Quinolones are the only orally available antibiotic with activity against *P. aeruginosa*. While we reported an increase in resistance for all antibiotics except ciprofloxacin from 2013 to 2015 in the last report, we now observe a significant decrease of cefepime resistance, taking into account data from 2014 to 2017. Non-significant, slight decreases in non-susceptibility rates have been observed since 2015 for all other antibiotics except aminoglycoside. Even if considering tobramycin resistance alone (which has the lowest epidemiological cut-off for *P. aeruginosa* of all aminoglycosides), we observe a comparable increase in non-susceptibility rates. Decreasing resistance trends between 2013 and 2016 were observed in the EU/EEA for fluoroquinolones, aminoglycosides and carbapenems, while, in contrast to Switzerland, resistance to ceftazidime has increased. In 2017, non-susceptibility rates were around 11 % for carbapenems and aminoglycosides, around 9 % for piperacillin-tazobactam and ceftazidime and were lowest for ciprofloxacin (7.7 %) and cefepime (5 %). Regional data are given in Table 7. e, data on co-resistance in Table 7. f and Figure 7. g.

7.4 *Acinetobacter* spp.

Acinetobacter spp. are Gram-negative, strictly aerobic coccobacilli. These opportunistic pathogens, which can be found in soil and water, are intrinsically resistant to many antibiotic agents. *Acinetobacter* spp. can roughly be divided into two groups: The *Acinetobacter calcoaceticus – Acinetobacter baumannii* (ACB) complex and the non-ACB group, including a large number of environmental species with low pathogenicity. Because the correct identification to the species level is difficult, we herein analyze, in accordance with the European resistance networks EARS-Net and CAESAR, resistance trends on the genus level.

Table 7. e: Susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans 2017.

Pseudomonas aeruginosa											**2017**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Piperacillin-tazobactam	120	11.7%	373	7.8%	31	9.7%	524	8.8%	6.6–11.5	–	↑
Ceftazidime	96	11.5%	383	8.4%	31	6.5%	510	8.8%	6.7–11.6	–	↑
Cefepime	119	3.4%	366	6.0%	31	0.0%	516	5.0%	3.5–7.3	↓	–
Carbapenem	120	15.0%	382	10.5%	31	6.5%	533	11.3%	8.8–14.2	–	–
Aminoglycosides	120	7.5%	384	13.0%	31	0.0%	535	11.0%	8.6–14	-	↑
Ciprofloxacin	119	5.9%	384	8.6%	31	3.2%	534	7.7%	5.7–10.3	–	–

West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.

Figure 7. f: Non-susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans from 2008 to 2017.

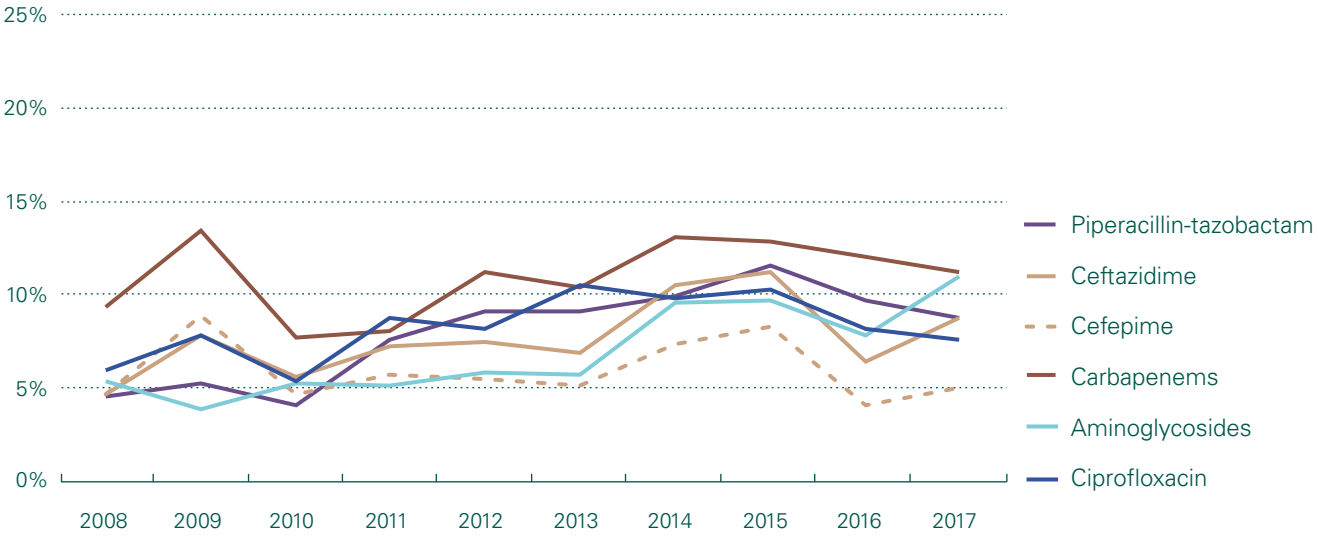


Table 7. f: Non-susceptibility combinations in invasive *P. aeruginosa* isolates in humans in 2017. Only isolates tested against all five antibiotics or antibiotic groups (piperacillin-tazobactam, cefepime, carbapenems, aminoglycosides, ciprofloxacin) were considered (n=501/536 [93.5 %]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**368**	**73.5%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**85**	**17.0%**
Aminoglycosides	33	6.6%
Carbapenem	25	5.0%
Piperacillin-tazobactam	13	2.6%
Ciprofloxacin	12	2.4%
Cefepime	2	0.4%
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**27**	**5.4%**
Piperacillin-tazobactam + cefepime	6	1.2%
Carbapenem + ciprofloxacin	5	1.0%
Carbapenem + aminoglycosides	5	1.0%
Aminoglycosides + ciprofloxacin	4	0.8%
Other antimicrobial group combinations	7	1.4%
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**13**	**2.6%**
Piperacillin-tazobactam + cefepime + carbapenem	3	0.6%
Piperacillin-tazobactam + carbapenem + aminoglycosides	3	0.6%
Piperacillin-tazobactam + carbapenem + ciprofloxacin	2	0.4%
Carbapenem + aminoglycosides + ciprofloxacin	2	0.4%
Other antimicrobial group combinations	3	0.6%
Resistance to four antimicrobial groups		
Total (all four-group combinations)	**4**	**0.8%**
Piperacillin-tazobactam + cefepime + carbapenem + aminoglycosides	1	0.2%
Piperacillin-tazobactam + cefepime + carbapenem + ciprofloxacin	1	0.2%
Piperacillin-tazobactam + carbapenem + aminoglycosides + ciprofloxacin	1	0.2%
Cefepime + carbapenem + aminoglycosides + ciprofloxacin	1	0.2%
Resistance to five antimicrobial groups		
Piperacillin-tazobactam + cefepime + carbapenem + aminoglycosides + ciprofloxacin	4	0.8%

Figure 7. g: Multiresistance in invasive *Pseudomonas aeruginosa* isolates in humans between 2008 and 2017 (for details refer to Table 7. f).

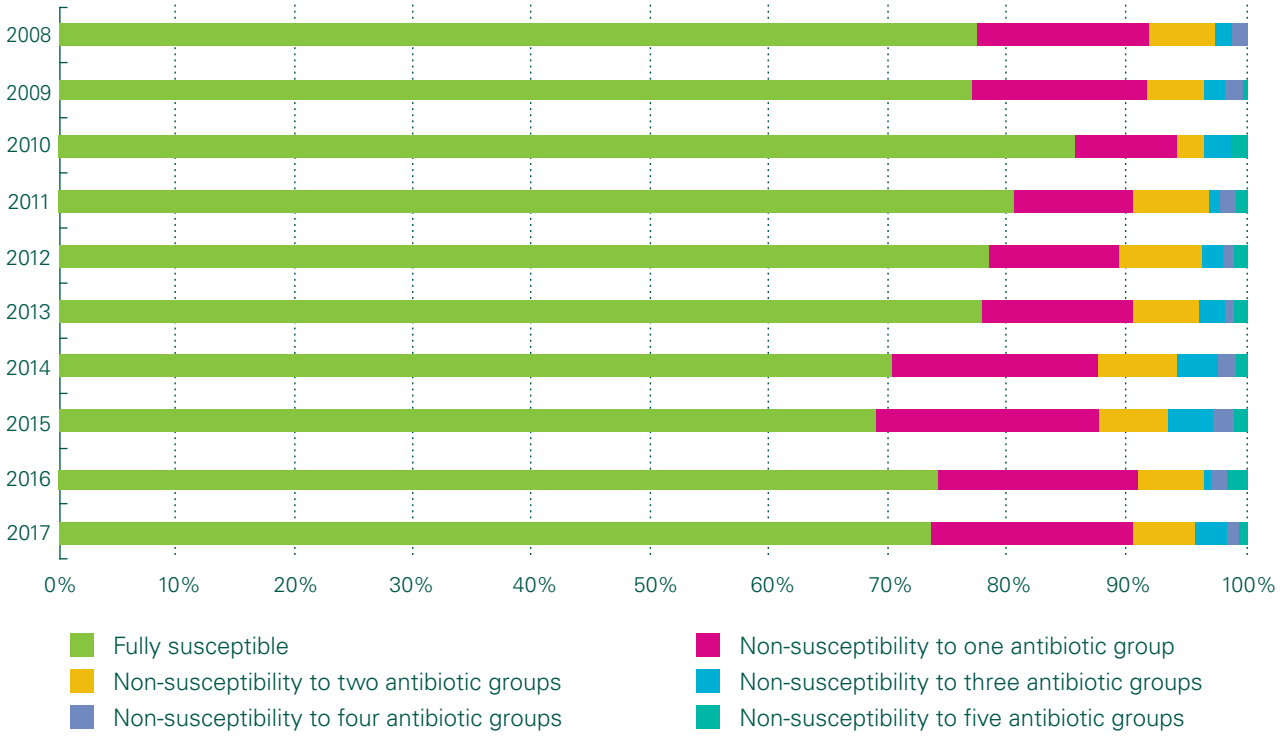


Table 7. g: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans for 2017. Due to small numbers, non-susceptibility rates for southern Switzerland are not shown.

Acinetobacter spp.											**2017**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Carbapenem[1]	27	25.9%	61	9.8%	5	0.0%	93	14.0%	8.4–22.5	–	–
Aminoglycosides	27	25.9%	58	13.8%	5	0.0%	90	16.7%	10.4–25.7	–	–
Trimethoprim-sul-famethoxazole	25	24.0%	53	13.2%	5	0.0%	83	15.7%	9.4–25	–	–
Ciprofloxacin	27	14.8%	61	16.4%	5	0.0%	93	15.1%	9.2–23.7	–	–

West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.
[1] Carbapenems: imipenem, meropenem

Acinetobacter spp. 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 *Acinetobacter* spp. are severe underlying diseases, prolonged hospital stays, especially in ICUs during antibiotic administration, mechanical ventilation and surgical procedures.

Around one quarter of *Acinetobacter* spp. isolates are not susceptible to at least one of the three most important antibiotics, i.e. carbapenems (14%), aminoglycosides (17%) and ciprofloxacin (15%, Table 7. g, 7. h). Except for ciprofloxacin, non-susceptibility rates are higher in western Switzerland than in north-eastern Switzerland. Although a north-south gradient in antibiotic resistance can be observed in Europe for nearly all antibiotics, differences are most prominent in *Acinetobacter* spp. In 2016, resistance rates ranged from <5% in northern countries to >80% in southern/eastern countries for all of the antibiotics tested. The EU/EEA population means in 2016 were 35% for carbapenems and aminoglycosides, and 39% for fluoroquinolones [1]. In Switzerland, no significant trend can be observed since 2008 (Table 7. g and Figure 7. h). Notably we could not find an increase in carbapenem-resistance as described for Europe (see Textbox: "Carbapenem-Resistant *Acinetobacter baumannii* from 2005 to 2016 in Switzerland"). Details on multiresistances are given in Table 7. h and Figure 7. i.

Textbox

Carbapenem-Resistant *Acinetobacter baumannii* from 2005 to 2016 in Switzerland

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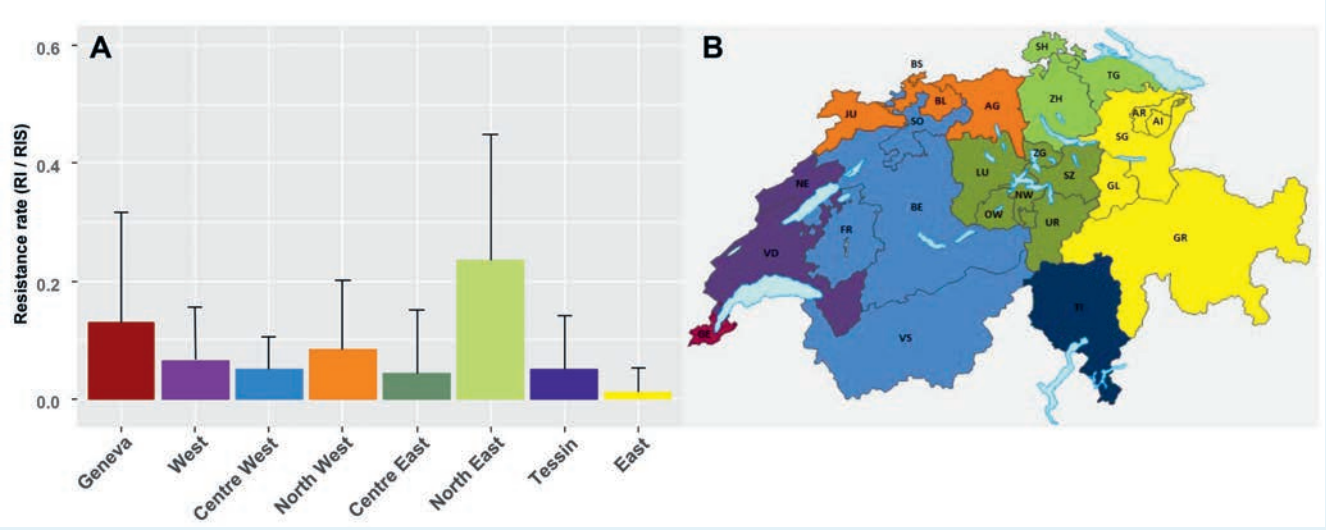
Over the last years, the endemic establishment of *A. baumannii* resistant to carbapenems, a last-line group of -lactam antibiotics used to treat patients infected with multidrug-resistant Gram-negative bacteria, has worsened in Europe and worldwide. In the *Acinetobacter* genus, several species present a risk for opportunistic infections and belong to the so-called *Acinetobacter calcoaceticus-Acinetobacter baumannii* (ACB) complex. In contrast, "non-ACB" *Acinetobacter* species generally present lower pathogenicity and are often found in the environment. We have analyzed the temporal and regional fluctuations of the number of carbapenem-susceptible and -resistant *Acinetobacter* spp. in Switzerland. We have restricted our analyses to invasive isolates from blood cultures or cerebrospinal fluid to ensure that they are comparable with international reports. We have used the qualitative data (SIR) and accompanying epidemiological information, such as sample location, provider of the sample, patient sex and age group, as provided by the participating laboratories.

From 2005 to 2016, a total of 800 invasive *Acinetobacter* isolates were identified in the anresis.ch database, consisting of 707 carbapenem-susceptible and 93 carbapenem-resistant isolates, respectively. After removal of duplicates, 58 resistant or intermediate isolates were identified out of 632 cases (resistance rate 9.2 %) over the study period. Four out of 58 carbapenem-resistant isolates were isolated from cerebrospinal fluid, the rest from blood cultures. Co-resistance to other antibiotics, such as aminoglycosides (47/55, 86 %), trimethoprim-sulfamethoxazole (42/54, 78 %) and fluoroquinolones (47/55, 86 %), was high, whereas no colistin resistance was reported for 23 isolates tested. There was a significant increase in the total number of *Acinetobacter* isolations over time, with about 30 isolates per year on average, increasing at a yearly rate of about three new isolates. When only ACB complex species were considered, there were 18 isolates per year on average, increasing at an average rate of one new isolate per year. The largest number of resistant isolates belonged to the ACB complex (55/299, 18.4 %), while resistance rates were much lower in non-ACB species (1/184, 0.5 %).

Yet, from 2005 to 2016, the overall yearly number of carbapenem-resistant ACB and non-ACB isolates did not increase, with an average of about five *Acinetobacter* isolates per year (mostly ACB isolates). The north-eastern region, with a total of 24 resistant *Acinetobacter* (22 of which were ACB) isolations from 2005 to 2016, was significantly above all other regions in terms of number of resistant strains. This was mainly attributable to an outbreak in a single hospital (data not shown). These geographic differences were confirmed when examining yearly average resistance rates per region (Fig. 1A, 1B): there was no significant temporal trend

Figure 1: *Acinetobacter* resistance rates (number of resistant isolates compared to total number of isolates) per region from 2005 to 2016 in Switzerland. Standard deviation bars represent annual fluctuations per region. B) Map of the Swiss regions defined in this study.



in resistance rates for all *Acinetobacter* or ACB isolates. Only the north-eastern region presented higher rates on average than other regions.

In summary, this first nationwide surveillance study indicates that resistance rates of invasive carbapenem-resistant *Acinetobacter* in Switzerland are stable at a low level on a yearly basis, but that they display large temporal and regional disparities. Our results also indicate the existence of a diverse pool of *A. baumannii* and related species in Swiss hospital settings. We have confirmed the implication of carbapenem-resistant ACB complex isolates in the vast majority of clinical infections and nosocomial outbreaks that involved *Acinetobacter* isolates. Our analyses, which conjointly cover both multiple years and multiple regions, highlight the usefulness of surveillance approaches that integrate different temporal and spatial resolution levels. Further surveillance efforts are needed to detect and control *Acinetobacter* outbreaks, and to limit the endemic establishment of resistant isolates in new health facilities and across regions.

See related publication:

Ramette A, Kronenberg A, and the Swiss Centre for Antibiotic Resistance (ANRESIS) 2018 Prevalence of carbapenem-resistant *Acinetobacter baumannii* from 2005 to 2016 in Switzerland. BMC Infect Dis. 2018 Apr 3;18(1):159. doi: 10.1186/s12879-018-3061-5. www.ncbi.nlm.nih.gov/pubmed/29614963

Figure 7. h: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans between 2008 and 2017.

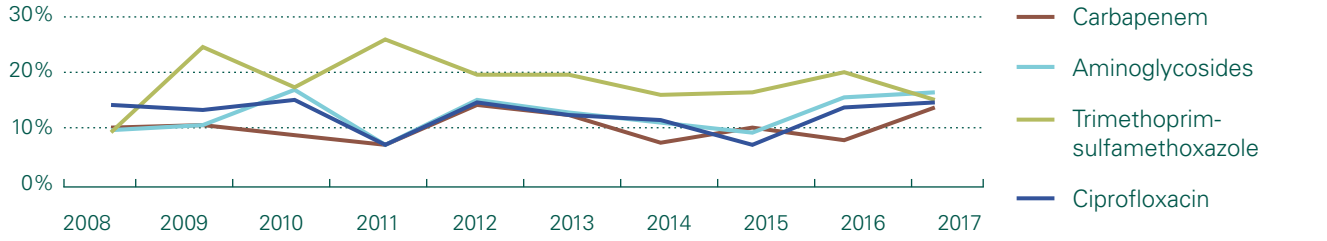


Table 7. h: Non-susceptibility combinations in invasive *Acinetobacter* spp. isolates in humans in 2017. Only isolates tested against all three antibiotic groups (aminoglycosides, ciprofloxacin and carbapenems) were considered (n=90/93 [96.8 %]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**68**	**75.6%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**11**	**12.2%**
Ciprofloxacin	4	4.4 %
Aminoglycosides	4	4.4 %
Carbapenems	3	3.3 %
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**2**	**2.2%**
Ciproxin + aminoglycosides	1	1.1 %
Aminoglycosides + carbapenems	1	1.1 %
Resistance to all three antimicrobial groups		
Total (all three-group combinations)	**9**	**10.0%**
Third-generation cephalosporins + aminoglycosides + fluoroquinolones		

Figure 7. i: Multiresistance in invasive *Acinetobacter* spp. isolates in humans between 2008 and 2017 (for details refer to Table 7. h).

Table 7. i: Non-susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans in 2017.

Streptococcus pneumoniae											2017
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Penicillin[1]	168	13.1%	754	5.0%	57	7.0%	979	6.5%	5.2–8.3	–	↓
Ceftriaxone[2]	168	3.6%	754	0.1%	57	0.0%	979	0.7%	0.3–1.5	–	↓
Trimethoprim-sulfamethoxazole	168	15.5%	754	8.5%	57	8.8%	979	9.7%	8–11.7	↓	–
Erythromycin	168	13.1%	754	6.9%	57	12.3%	979	8.3%	6.7–10.2	–	↓
Levofloxacin	168	0.0%	754	0.0%	57	0.0%	979	0.0%	0–0.4	–	–

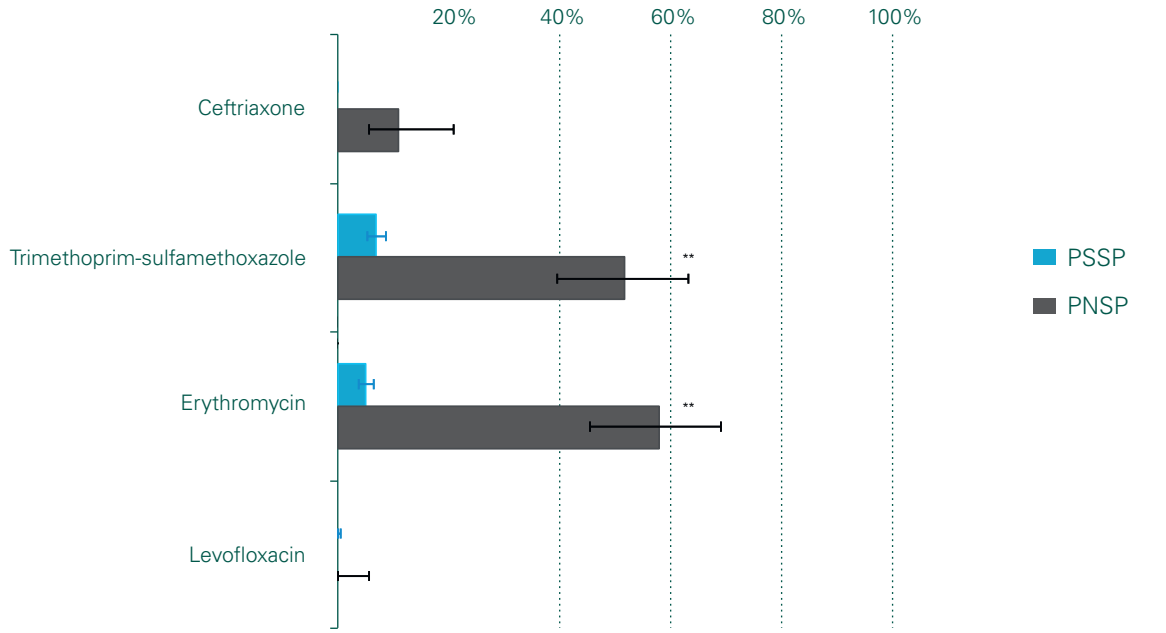
West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.
[1]Penicillin non-susceptible defined as MIC ≥ 0.064 mg/l, penicillin-resistant defined as MIC ≥2 mg/l
[2]Penicillin-susceptible isolates were not tested but set automatically to ceftriaxone-susceptible

7.5 *Streptococcus pneumoniae*

Streptococcus pneumoniae is a common cause of upper respiratory tract infections such as sinusitis and otitis media, but is also a common pathogen found in invasive pneumonia, bloodstream infections and meningitis. Since 2002, all invasive isolates of *S. pneumoniae* are sent by the clinical microbiology laboratories to the National Reference Center for invasive *S. pneumoniae*, located at the Institute for Infectious Diseases of the 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 have analyzed the anresis.ch data of *S. pneumoniae* from this reference center, as these data are complete and AMR testing is standardized. E-tests were 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.

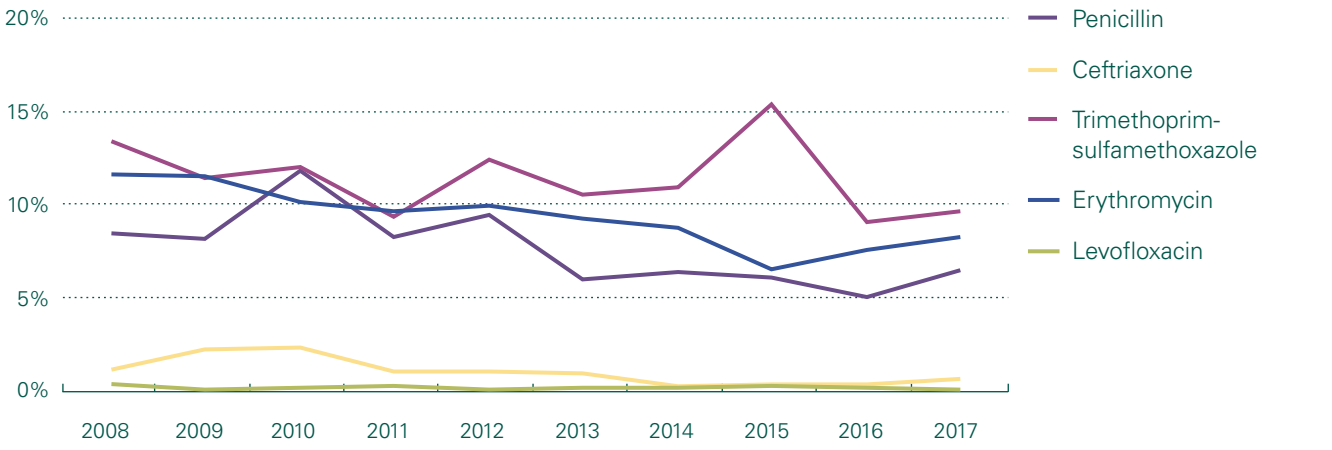
In 2017, the PNSP rate in Switzerland was 6.5% (Table 7. i). In comparison, PNSP rates in EU/EEA countries in 2016 ranged from 0.4% in Belgium to 41% in Romania. However,

Figure 7. j: Non-susceptibility rates in invasive PSSP (penicillin-susceptible isolates) and PNSP (penicillin non-susceptible isolates) in humans in 2017.



n=number of isolates tested with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence: * =p-value <0.05; **= p-value <0.01.

Figure 7. k: Non-susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans between 2008 and 2017.



an exact comparison with other countries is difficult, because different breakpoints are used. Therefore, no average non-susceptibility rate is given for Europe. Despite these restrictions, non-susceptibility rates essentially seem to be higher in France (25.3%) than in Italy (6.5%) and Germany (4,0%) [1]. These differences are mirrored within Switzerland, with higher PNSP rates in the French-speaking part as well (Table 7. i). Ceftriaxone non-susceptibility is below 1%. With 8.3%, the macrolide non-susceptibility rate is slightly higher than the penicillin non-susceptibility rate, with higher resistance rates in western and southern Switzerland. Resistance against levofloxacin was nonexistent in Switzerland in 2017. As shown in Figure 7. j, resistance is higher in PNSP than in PSSP for trimethoprim-sulfamethoxazole and erythromycin, but not for levofloxacin, where we did not observe any non-susceptibility.

Over the last ten years, significant decreases in antibiotic resistance in *S. pneumoniae* were observed for penicillin, ceftriaxone and erythromycin (Table 7. i, Figure 7. k). A recent study published by the National Reference Center for invasive *S. pneumoniae* showed that such trends can be provoked by the vaccine-related decrease of the intrinsically more resistant serotypes [5]. A similar (although in the long-term not significant) trend was observed for trimethoprim-sulfamethoxazole. The reason for the single peak in this trend, which was restricted to 2015, remains unclear.

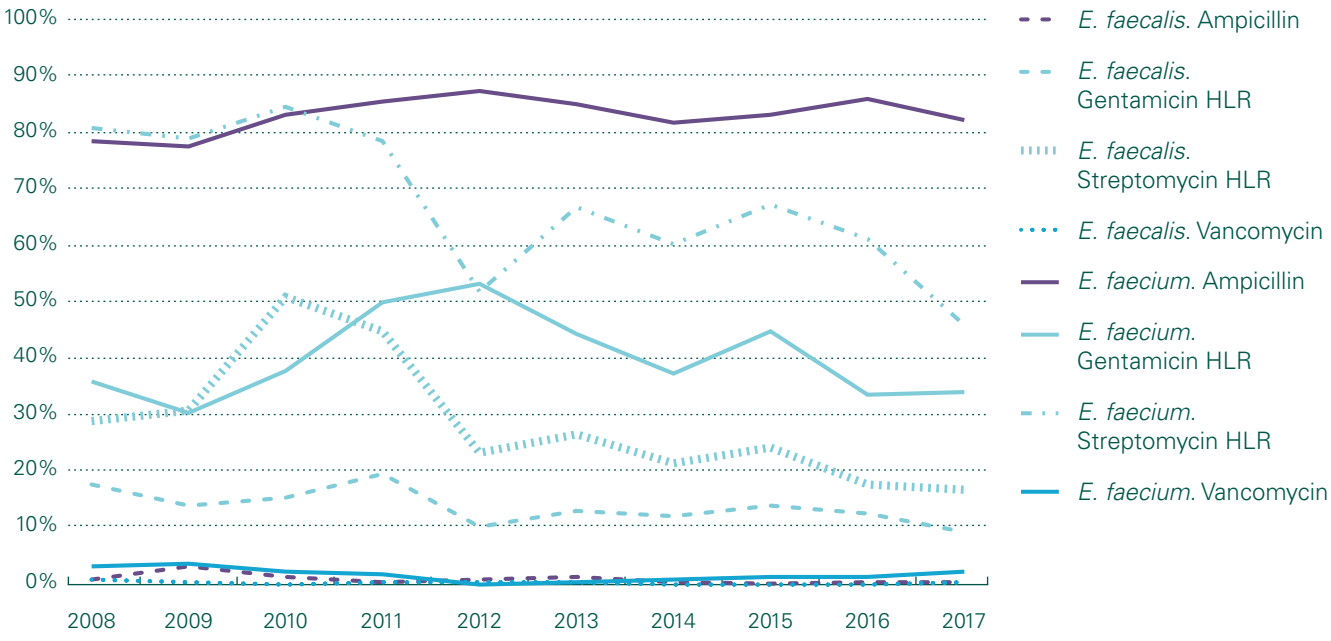
Table 7. j: Non-susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans in 2017.

Enterococcus faecalis											2017
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Ampicillin	125	0.0%	345	0.0%	45	2.2%	515	0.2%	0–1.1	–	↓
Gentamicin HLR[1]	53	11.3%	239	8.4%	45	11.1%	337	9.2%	6.6–12.8	–	↓
Streptomycin HLR[1]	3	66.7%	146	15.8%	0	–	149	16.8%	11.6–23.6	–	↓
Tetracycline	48	10.4%	68	73.5%	0	–	116	47.4%	38.6–56.4	–	↑
Vancomycin	188	1.1%	388	0.0%	46	0.0%	622	0.3%	0.1–1.2	–	–
Linezolid	136	0.0%	279	0.4%	45	2.2%	460	0.4%	0.1–1.6	–	↓

Enterococcus faecium											2017
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Ampicillin	89	84.3%	267	82.4%	31	77.4%	387	82.4%	78.3–85.9	–	–
Gentamicin HLR[1]	26	19.2%	193	37.3%	29	24.1%	248	33.9%	28.3–40	–	–
Streptomycin HLR[1]	2	100.0%	109	45.0%	0	–	111	45.9%	37–55.2	↓	↓
Tetracycline	22	0.0%	26	34.6%	0	–	48	18.8%	10.2–31.9	–	↑
Vancomycin	119	0.8%	266	2.3%	31	6.5%	416	2.2%	1.1–4.1	–	–
Linezolid	92	0.0%	169	0.0%	31	0.0%	292	0.0%	0–1.3	–	–

West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.
[1]HLR=high-level resistance

Figure 7. I: Non-susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans between 2008 and 2017.



7.6 Enterococci

Enterococci belong to the normal gastrointestinal flora of humans and animals. As such, they are often considered as commensals with low pathogenicity. However, mainly in the hospital setting, they can also cause serious infections, such as urinary tract infections, bacteremia, endocarditis, and intraabdominal infections, in particular in seriously ill patients and immunocompromised hosts. 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 99.8 % are even susceptible to aminopenicillins, *E.* faecium isolates, on the other hand, are usually resistant to aminopenicillin. In addition, *E. faecium* shows clearly higher resistance rates to high-level aminoglycosides compared to *E. faecalis* (Table 7. j). Aminoglycoside non-susceptibility is still fairly low compared to the EU/EEA weighed average (e.g. a gentamicin high-level resistance (HLR) in *E. faecalis* of 9.2 % in Switzerland versus 30.5 % in Europe) and has significantly decreased during the last ten years. A decrease in gentamicin HLR in *E. faecalis* was also observed in almost one quarter of all European countries [1]. In contrast to the United States, vancomycin resistance is still rare in Switzerland and far below the EU/ EEA average of 11.8 % in *E. faecium* in 2016 [1]. As seen in Table 7. j and Figure 7. l, vancomycin resistance did not increase between 2008 and 2017, but we have noted a slight increase in 2018 (data not shown), at least in part attributable to a recent outbreak of a vancomycin-resistant *E. faecium* clone ST796 in Switzerland [7]. Surveillance of enterococci, particular VRE, is crucial, since very few antibiotics remain active, and these are commonly associated with much higher toxicity than penicillin.

7.7 *Staphylococcus aureus*

Staphylococcus aureus belong 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, they have successfully spread into the community over the last years.

There are different methods to detect MRSA, and the methods used for screening have 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* gene detection. Due to poor correlation with the presence of *mecA* (the gold standard for defining methicillin-resistance), 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 drug 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 of the following: methicillin, oxacillin, flucloxacillin or cefoxitin. Confirmation tests, such as PBP2a agglutination or direct detection of the *mecA* gene, are typically not forwarded to anresis.ch. MRSA are resistant to all beta-lactams, including combinations with beta-lactam inhibitors (e.g. amoxicillin-clavulanic acid). In 2017, the MRSA rate in Switzerland was 4.4 %, with slightly higher rates in southern Switzerland (Table 7. k). This rate is far below the European average of 13.7 %, but above MRSA rates in northern countries such as the Netherlands (1.2 %), Norway (1.2 %), Denmark (2.0 %), Finland (2.2 %) and Sweden (2.3 %) in 2016 [1]. Co-resistance in MRSA is frequent and is depicted in Figure 7. n.

Staphylococcus aureus also remains an important pathogen in the ambulatory setting, where it is the major causative agent of wounds infections and abscesses. A comparison of the resistance rates of invasive samples with outpatient samples from wound and abscesses is shown in Figure 7. m. As already shown by Olearo et al. [6], MRSA rates, and similarly, non-susceptibility rates to most other antibiotics as well, are nowadays higher in the ambulatory skin infection setting (10.2 %) than in bacteremia (4.4 %) (Figure 7. m). While MRSA rates in hospitals have been decreasing since several years, community MRSA (cMRSA) infections are increasing [6]. In addition, they often harbor the Panton-Valentine Leukocidin (PVL) toxin, leading to the formation of abscesses. Importantly, wound infections and even skin abscesses usually can only be treated by a surgical procedure.

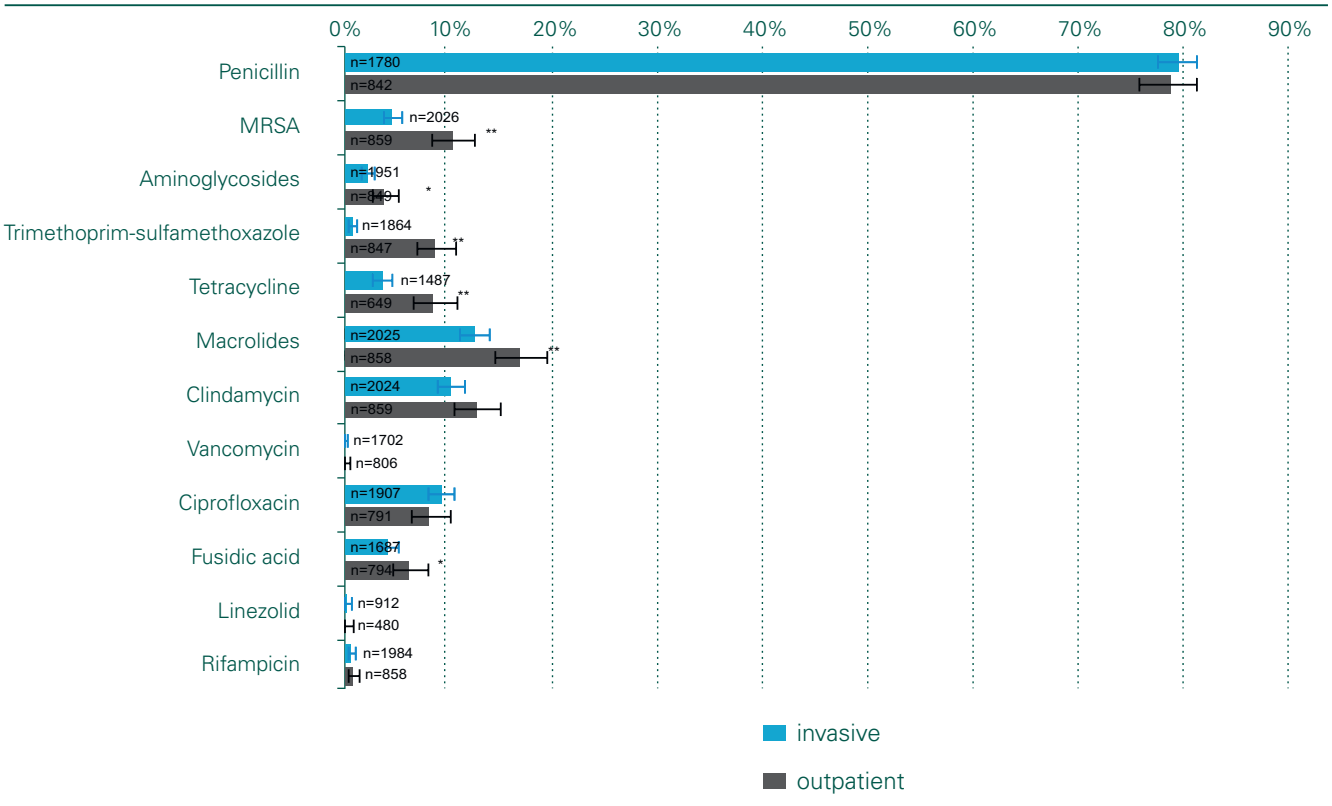
Development of resistances during the last ten years is shown in Figure 7. o. Over the past ten years, we have observed a significant decrease in invasive MRSA rates in Switzerland, from 10.1 % in 2008 to 4.4 % in 2017. Decreasing trends from 2013 to 2016 were also reported in more than one third of all European countries, leading to an overall decrease in the population-weighted mean of EU/EEA states from 18.1 % to 13.7 % during this time period. The decrease in invasive MRSA rates was more pronounced in the Western part of Switzerland (data not shown). The decrease in the MRSA rate runs parallel to significant decreases in the non-susceptibility rates against ciprofloxacin, macrolides and, to a lesser extent, clindamycin and aminoglycosides in *Staphylococcus aureus* isolates (Figure 7. i).

Table 7. k: Susceptibility rates of invasive *Staphylococcus aureus* isolates in humans in 2017.

Staphylococcus aureus											2017
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Penicillin	438	81.3%	1217	78.3%	125	85.6%	1780	79.6%	77.6–81.4	–	↑
MRSA	470	5.1%	1432	3.8%	124	8.1%	2026	4.4%	3.6–5.4	–	↓
Aminoglycosides	470	3.6%	1356	1.6%	125	1.6%	1951	2.1%	1.6–2.8	–	↓
Trimethoprim–sulfamethoxazole	470	0.2%	1269	0.7%	125	1.6%	1864	0.6%	0.4–1.1	–	–
Tetracycline	324	4.3%	1038	3.3%	125	2.4%	1487	3.4%	2.6–4.5	–	–
Macrolides	470	16.6%	1430	11.2%	125	9.6%	2025	12.3%	11–13.9	–	↓
Clindamycin	470	13.4%	1429	9.1%	125	8.0%	2024	10.0%	8.8–11.4	–	↓
Vancomycin	430	0%	1147	0%	125	0%	1702	0%	0–0.2	–	–
Ciprofloxacin	402	7.5%	1380	9.2%	125	13.6%	1907	9.1%	7.9–10.5	–	↓
Fusidic acid	400	6.8%	1162	3.0%	125	5.6%	1687	4.1%	3.2–5.1	–	–
Linezolid	285	0.4%	626	0%	1	–	912	0.1%	0–0.6	–	–
Rifampicin	470	0.6%	1389	0.6%	125	0%	1984	0.6%	0.3–1	–	–

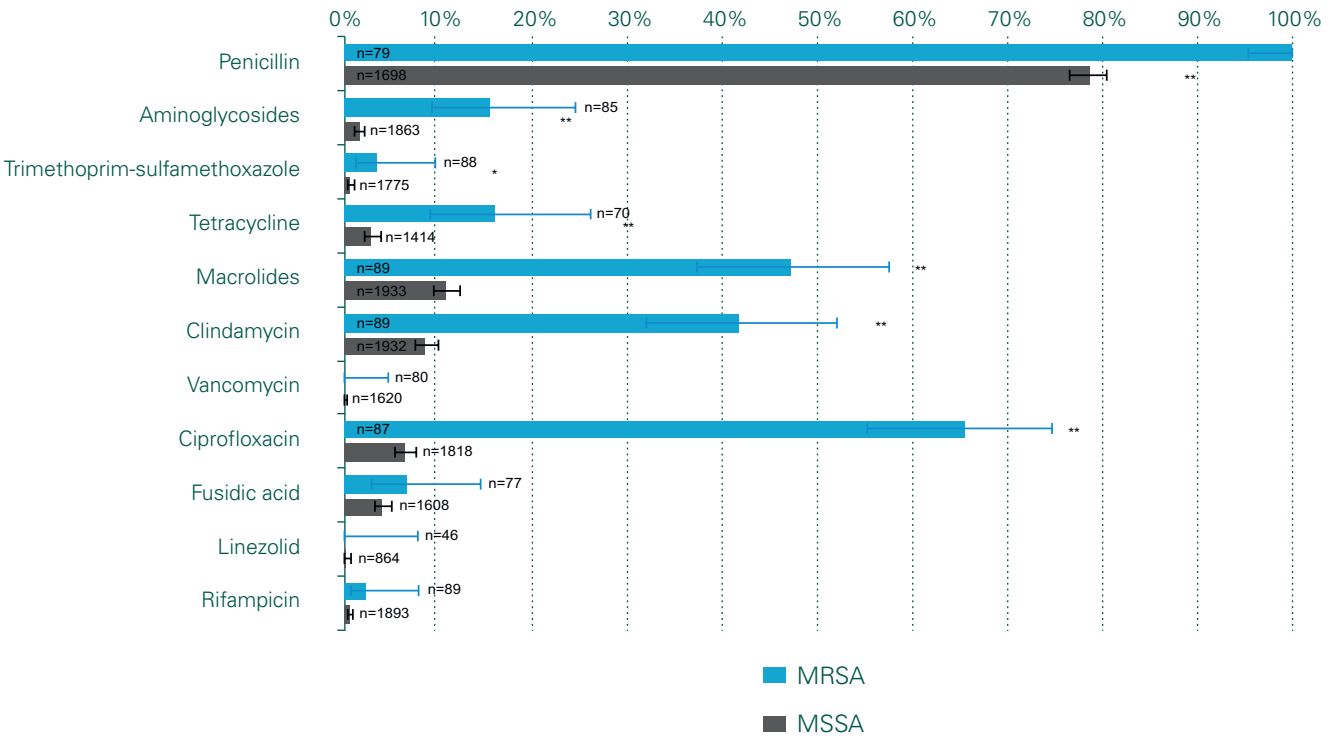
West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.

Figure 7. m: Comparison of non-susceptibility rates in invasive versus outpatient wound/abscess samples in *Staphylococcus aureus* in humans in 2017.



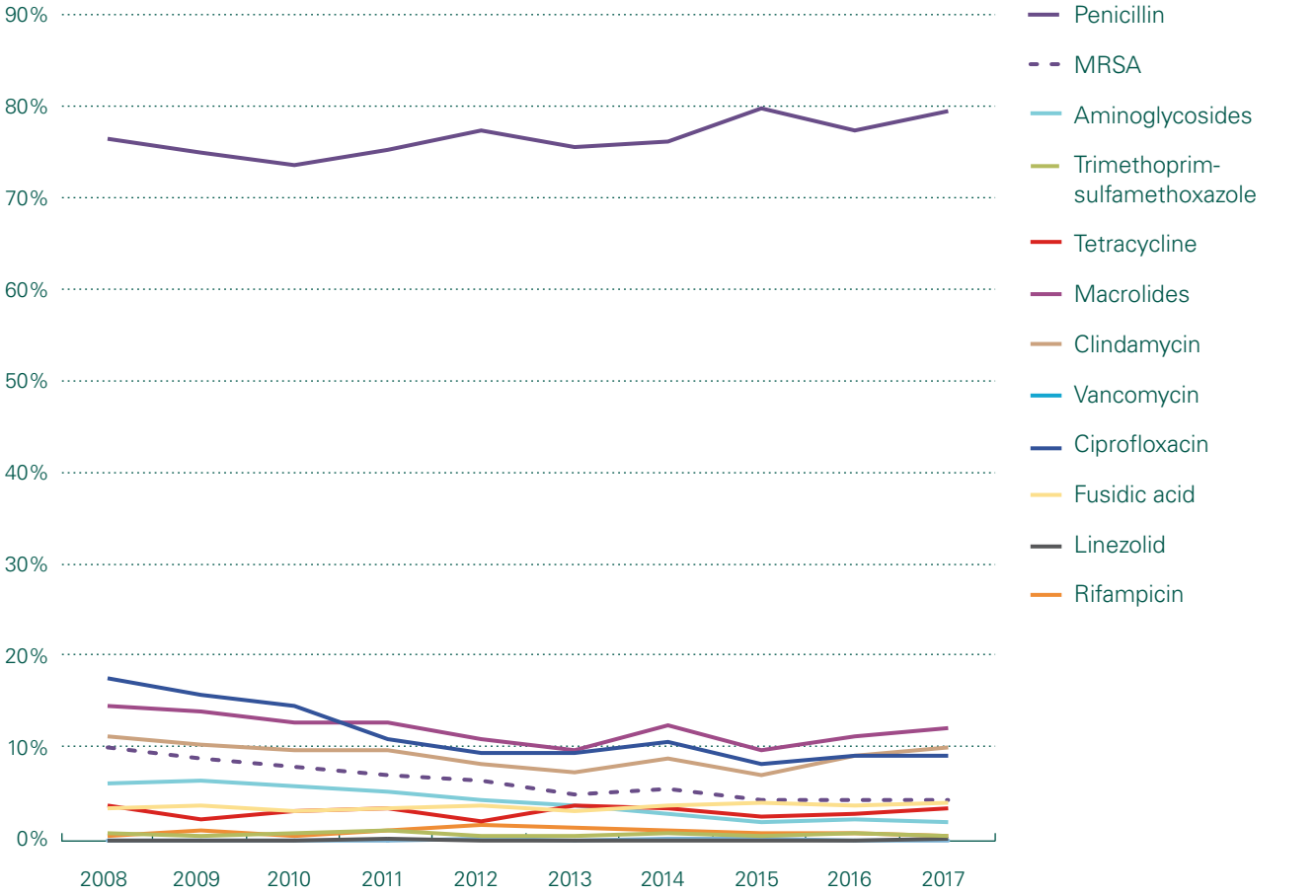
n=number of isolates tested, with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence: * = p-value <0.05; **= p-value <0.01.

Figure 7. n: Non-susceptibility rates of invasive MRSA (methicillin-resistant *Staphylococcus aureus*) and MSSA (methicillin-susceptible *Staphylococcus aureus*) isolates in humans 2017.



n=number of isolates tested, with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence: * = p-value <0.05; **= p-value <0.01.

Figure 7. o: Non-susceptibility rates of invasive *Staphylococcus aureus* isolates in humans between 2008 and 2017.



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[7] www.eurosurveillance.org/co

Textbox

Treatment of the Tree Disease Fire Blight with Antibiotics

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The bacterium *Erwinia amylovora* damages apple, pear as well as other trees and plants of the Rosaceae family. Trees are mainly infected by way of their flowers, and therefore pollinating insects are usually responsible for the spread of *E. amylovora,* respectively fire blight. In 1991, for the first time, fire-blight-infected plants of a pear orchard were detected and destroyed in Switzerland. Years with heavy infections led to the destruction of 50 ha and 100 ha of fruit-producing orchards in 2000 and 2007, respectively. For 2008, a plant protection product containing the antibiotic streptomycin as the active ingredient was authorized for three applications during the flowering season of apple and pear trees. Trials in other countries have shown that, compared to other products, streptomycin has the best protection efficacy. Although the decision was welcomed by fruit producers, it was criticized by beekeepers and consumers. In addition to the authorization of streptomycin, the international research project "Gemeinsam gegen Feuerbrand" was launched in 2008 and was financed by Switzerland, Germany, Austria and Liechtenstein. The aim was to identify alternative plant protection measures to replace streptomycin applications. In the framework of this project, for example, several apple varieties presenting robustness against fire blight were found using specific tests. Streptomycin having originally been applied during the flowering season of the trees, antibiotic residues were detected in honey of hives near treated orchards. For this reason, conditions were tightened over time. Starting in 2010, only two streptomycin applications in the evening, when bees do not fly, were authorized. Nevertheless, in the years 2010 to 2012 several tons of honey containing streptomycin residues were destroyed. This has resulted in the authorization of only one streptomycin application per season since 2014, as well as the authorization of three applications of the alternative product potassium aluminum sulfate (LMA) which has an overall average protection efficacy of approximately 73 per cent. Since the year 2016, authorization of streptomycin has no longer been granted. The decision was based on the fact that alternatives such as robust apple varieties as well as five plant protection products including LMA were available. The decision was published shortly after the Swiss government accepted the national strategy on antibiotic resistance.

Treatment possibilities against fire blight for apple and pear orchards

3 × streptomycin	2008–2009	
2 × streptomycin	2010–2013	
1 × streptomycin	2014–2015	3 × LMA
0 × streptomycin	from 2016	3 × LMA + 4 other products

Beside the research performed within "Gemeinsam gegen Feuerbrand" for alternative plant protection measures to replace streptomycin use, specific research projects to assess environmental effects were launched and financed by different federal offices as well as the Swiss Expert Committee for Biosafety. The effect of streptomycin applications on antibiotic resistances in bacterial communities of orchards was tested. After streptomycin applications in the spring, a temporary increase in antibiotic resistance genes was found. A return to the original level was observed in autumn or the next spring[1]. Applications of plant protection products in orchards are not possible without drift. Therefore, sheep in two groups were analyzed. In the group grazing on a meadow next to an orchard treated with streptomycin (simulation), more antibiotic multiresistant bacteria were found than in the control group grazing on an untreated meadow[2].

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Textbox

Antibacterial Resistance in the Aquatic Environment

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Antibiotic resistance research and policy is naturally focused on resistance in human pathogens. The Swiss National Strategy on Antibiotic Resistance (StAR) includes veterinary medicine, agriculture as well as the environment within its One-Health approach. This is a consequence of the now prevailing view that emergence, evolution and dissemination of resistance can only be properly understood and effectively combated by taking into account that resistances emerge and spread from various sources. While a dissemination of resistant pathogens is the most immediate concern, the release, spread, accumulation and further evolution of mobile antibiotic resistance genes (ARGs) in the environment is undesirable and may in the long term contribute to the antibiotic resistance problem.

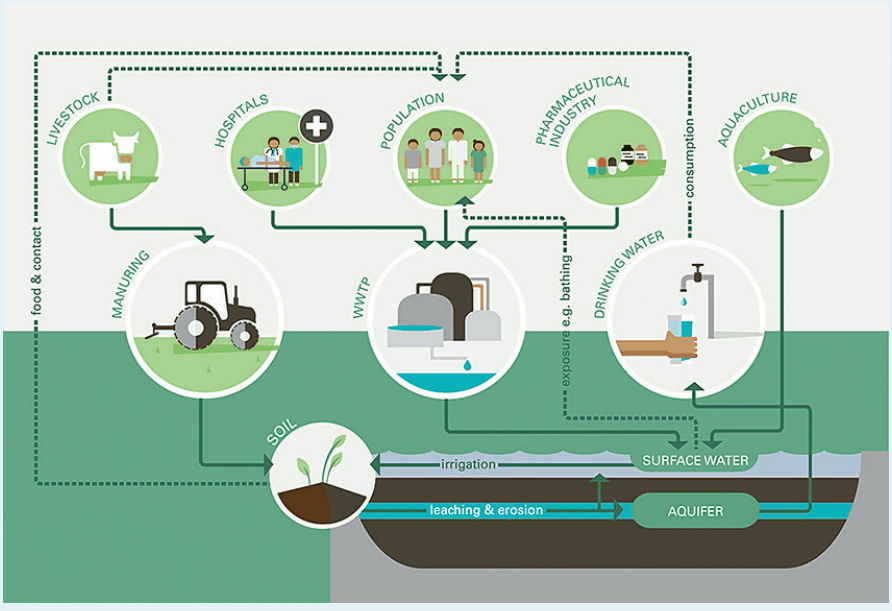
The use of antibiotics in human and veterinary medicine leads to a selection of antibiotic-resistant bacteria (ARB), not only in pathogens but also in commensal microbes. Consequently, ARB and ARG are discharged with household and hospital wastewater. They are also applied to fields and pastures with feces or manure and can finally reach lakes, rivers or groundwater. Aquaculture (fish breeding) and wastewaters from antibiotic production may provide other sources of antibiotics, ARBs and ARGs (Figure 1).

Currently there are no monitoring programs for antibiotic resistance in the environment in Switzerland. An overview of the state of knowledge for Switzerland can be found in a recent review by Czekalski et al., 2016.

Conventional biological wastewater treatment plants typically reduce the total number of ARBs or ARGs by more than 95% (Czekalski *et al.*, 2016). Nevertheless, the number of ARBs and ARGs released with treated wastewater is higher than the background in Swiss surface waters. Wastewater treatment plants enrich for ARB, resulting in a relatively high proportion of ARB in the treated wastewater.

Based on the revised Swiss Water Protection legislation, selected Swiss wastewater treatment plants will be upgraded

Figure 1: Sources of antibiotics and antibiotic-resistant bacteria and potential distribution in aquatic environments.



by 2040, with treatment steps for the elimination of micropollutants, including antibiotics. Ozonation and powdered activated carbon (PAC) are currently the standard treatment options. Determining whether these techniques also reduce ARBs and ARGs was the goal of several initial studies. Results showed that (i) PAC only removes ARBs and ARGs in combination with ultrafiltration (which is costly) and that (ii) ozonation in combination with a post-treatment against oxidation by-products only has limited effects on the resistance load (Czekalski et al., 2016). Whether the latter treatment technique can be optimized is currently under investigation.

For the time being, wastewater discharge increases the abundance of certain ARGs and ARBs in the receiving waters. To what extent agricultural sources also contribute is not well studied. But whatever the sources, resistant bacteria, including problematic ESBL-producing Enterobacteriaceae are present in surface water bodies throughout the Swiss plateau (Zurfluh et al., 2013).

Infiltration of surface water provides a potential trajectory of insufficiently treated wastewater into groundwater, the main drinking water resource, making it a direct human health issue. Fecal bacteria, potentially including ARBs, may thereby migrate into the aquifer if not attenuated during riverbank filtration. Results from a pilot study of the NAQUA National Groundwater Monitoring have shown that most of the sampled pumping stations located close to rivers in unconsolidated porous aquifers were free of fecal bacteria, even though some of them displayed fecal traces in terms of the genetic detection of human enteric viruses (Pronk et al., 2014). Vulnerable consolidated aquifers were more frequently affected by fecal bacteria which often also co-occurred with human virus genes. Furthermore, groundwater from all aquifer types contained a high number of indigenous bacteria (> 1000 cells per ml), indicating the potential for ARG transfer.

Beside sewage as a source of fecal contamination and ARBs, groundwater may also be impacted by agricultural land use. Specific investigations at selected NAQUA monitoring sites applying microbial-source-tracking techniques revealed the occurrence of both human-derived markers and markers from livestock (ruminants) (Diston et al., 2015). Findings suggest pharmaceutical residues (e.g. sulfamethoxazole as an indicator parameter) and other wastewater tracers in groundwater, occasionally accompanied by human-specific microbial markers. Although antibiotic resistance was not covered in this study, it reveals various fecal contamination sources and thereby illustrates the potential transfer of antibiotic resistances into groundwater.

Drinking water of course typically undergoes disinfection treatment and has to fulfill strict microbiological quality requirements. The Swiss association of the gas and water industry (SVGW) and Eawag recently conducted a survey of eight Swiss drinking water suppliers, covering a range of raw water sources and treatment options (Bürgmann & Imminger, 2017). The occurrence of (commensal) ARBs and ARGs in the raw water was very variable, with the lowest numbers in groundwater including bank filtrate, and higher concentrations in surface water sources. Treatment always strongly reduces ARBs, although some regrowth can occur during network distribution. Overall, these results indicate that drinking water is not a major exposure pathway to environmental ARBs and ARGs.

Switzerland has excellent sanitation and drinking water treatment. Whereas contaminated water may spread resistant pathogens in some parts of the world, this is of no relevance in Switzerland. ARBs and ARGs are not wanted in the water cycle and the aim is to further reduce their input into the natural waters. A risk assessment for antibiotic resistance in the environment needs to be established and more knowledge in this field is required. However, measures at the source, namely in human and veterinary medicine as well as in agriculture, are a priority, as reflected in the Swiss National Strategy Antibiotic Resistance (StAR).

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8

Resistance in zoonotic bacteria in animals from primary production samples

8 Resistance in zoonotic bacteria in animals from primary production samples

Zoonoses are diseases that are transmissible from animals to humans. Infection can be acquired by contaminated food or through direct contact with animals. 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 *Campylobacter* spp.

Campylobacter is by far the most commonly reported cause of human food-borne zoonoses in Switzerland as well as in the EU [1, 2]. The main cause of infection is *C. jejuni*, followed by *C. coli*. While *Campylobacter* causes acute gastroenteritis in humans, broilers and pigs are usually asymptomatic carriers. Beside these reservoir hosts, *Campylobacter* can be detected in cattle, sheep and fowl, domestic pets and wild animals [3].

Fresh raw poultry meat is highly contaminated with *Campylobacter*. Hence, incorrect handling of raw poultry meat and the consumption of undercooked contaminated poultry meat and poultry liver are the two main causes for human campylobacteriosis. Meat from cattle and pigs and contact with pets are of lesser importance. A molecular typing of isolates from humans and animals collected between 2001 and 2012 in Switzerland identified chicken as the main source for human campylobacteriosis (71 % of all human cases were attributed to chicken, 19 % to cattle, 9 % to dogs and 1 % to pigs) [4].

Campylobacteriosis is usually self-limiting in humans and does not require antibacterial treatment. However, treatment with antibiotics is necessary for severe cases, whereby resistance to antimicrobials in *Campylobacter* is a source of concern. Resistance can lead to therapy failure and longer treatment duration. Fluoroquinolones, such as ciprofloxacin, and macrolides, such as clarithromycin or azithromycin, represent standard therapies for severe cases of campylobacteriosis and therefore are considered as critically important antimicrobials of highest priority [5].

This chapter includes antimicrobial resistances of *Campylobacter jejuni* and *Campylobacter coli* in livestock and humans. Broilers were investigated in 2016 and fattening pigs in 2017.

8.1.1 *Campylobacter* spp. in broilers

At present, only a few antimicrobial products are licensed for use in poultry in Switzerland. More than half of them contain antimicrobial substances that belong to the highest-priority critically important antimicrobials according to the WHO [5].

Table 8. a: *Campylobacter jejuni* and *Campylobacter coli* from broilers in 2016.

2016	*Campylobacter jejuni (N=140)*			*Campylobacter coli (N=30)*		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ciprofloxacin	72	51.4	43.2–59.6	20	66.7	48.8–80.8
Erythromycin	4	2.9	1.1–7.1	3	10.0	3.5–25.6
Gentamicin	2	1.4	0.4–5.1	0	0.0	0.0–11.4
Nalidixic acid	72	51.4	43.2–59.6	20	66.7	48.8–80.8
Streptomycin	10	7.1	3.9–12.6	19	63.3	45.5–78.1
Tetracycline	56	40.0	32.3–48.3	12	40.0	24.6–57.7
Number of resistances	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
None	54	38.6	30.9–46.8	6	20.0	9.5–37.3
1 antimicrobial	14	10.0	6.1–16.1	3	10.0	3.5–25.6
2 antimicrobials	28	20.0	14.2–27.4	4	13.3	5.3–29.7
3 antimicrobials	34	24.3	17.9–32.0	8	26.7	14.2–44.4
4 antimicrobials	8	5.7	2.9–10.9	6	20.0	9.5–37.3
>4 antimicrobials	2	1.4	0.4–5.1	3	10.0	3.5–25.6

Number of resistant strains (n) and prevalence of resistance (%) with 95 % confidence interval (95 % CI)

They should be used with caution in view of antimicrobial resistance in human and veterinary medicine. In the absence of authorized products with sulfonamides or tetracyclines, fluoroquinolones (e.g. enrofloxacin) or penicillins (e.g. amoxicillin) are often used as first-line treatments in Swiss broiler production.

In 2016, a random sample of 496 broiler flocks was investigated at slaughter in the framework of the antimicrobial resistance monitoring program using cecum samples (5 pooled samples per flock). *Campylobacter jejuni* was detected in 141 samples (28.4 %) and *Campylobacter coli* in 30 samples (6.0 %). Susceptibility testing was performed for 140 *C. jejuni* isolates and 30 *C. coli* isolates (Table 8. a). Complete susceptibility to all tested antimicrobials was found in 38.6 % of the *C. jejuni* isolates and in 20.0 % of the *C. coli* isolates.

High to very high levels of resistance to (fluoro-)quinolones (ciprofloxacin and nalidixic acid) and tetracycline were found in *C. jejuni* as well as in *C. coli* (between 40.0 % and 66.7 %) (Table 8. a). Very high microbiological resistance to streptomycin was found in *C. coli* (63.3 %). Close to a third of all *C. jejuni* isolates (31.4 %) were resistant to at least three of the tested antimicrobials. Two *C. jejuni* isolates (1.4 %) were resistant to all six tested antimicrobials: ciprofloxacin, erythromycin, gentamicin, nalidixic acid, streptomycin and tetracycline.

In 2016, only 30 *C. coli* isolates were available from broilers. This small number of isolates does not allow the detection of statistically significant trends over the years.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.6 and Table I.7), as well as multiple resistance patterns (Table I.37 and Table I.38).

8.1.2 *Campylobacter coli* in fattening pigs

In 2017, a random sample of 296 fattening pigs was investigated at slaughter in the framework of the antimicrobial resistance monitoring program using cecum samples. *Campylobacter coli* was isolated in 161 out of 296 samples (54.4 %). All isolates were subjected to susceptibility testing (Table 8. b).

In *C. coli* from fattening pigs, the highest level of microbiological resistance was found for streptomycin (81.4 %). Very high levels of microbiological resistance were found for tetracycline (62.1 %), nalidixic acid (52.2 %) and ciprofloxacin (50.3 %). Lower levels of resistance were detected for erythromycin (1.9 %) and gentamicin (1.2 %). Only 5.6 % of the *C. coli* isolates were fully sensitive to all tested antimicrobials, while 32.3 % showed resistance to four or more antimicrobials (Table 8. b).

The distribution of the minimum inhibitory concentrations (MICs) and multiple resistance patterns for *C. coli* are shown in Annex II (Table I.8 and Table I.39).

8.1.3 *Campylobacter* spp. in humans

A total of 7,219 laboratory-confirmed cases of human campylobacteriosis were reported in 2017 (85.4 per 100,000 inhabitants). *C. jejuni* caused 72 % of the cases with known species (6,003 cases), while in 20 % of all cases no distinction was made between *C. jejuni* and *C. coli*. In anresis.ch, resistance data were available for 2,614 isolates (36.2 %): 2,384 were identified as *C. jejuni* (91.2 %) and 230 as *C. coli* (8.8 %). Resistance data for 2017 are shown in Table 8. c.

Table 8. b: *Campylobacter coli* from fattening pigs in 2017.

2017	*Campylobacter coli (N=161)*		
Antimicrobials	**n**	**%**	**95% CI**
Ciprofloxacin	81	50.3	42.7–57.9
Erythromycin	3	1.9	0.6–5.3
Gentamicin	2	1.2	0.3–4.4
Nalidixic acid	84	52.2	44.5–59.7
Streptomycin	131	81.4	74.6–86.6
Tetracycline	100	62.1	54.4–69.2
Number of resistances	**n**	**%**	**95% CI**
None	9	5.6	3.0–10.3
1 antimicrobial	31	19.3	13.9–26.0
2 antimicrobials	47	29.2	22.7–36.6
3 antimicrobials	22	13.7	9.2–19.8
4 antimicrobials	50	31.1	24.4–38.6
>4 antimicrobials	2	1.2	0.3–4.4

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

Table 8. c: Non-susceptibility rates of *Campylobacter coli* and *Campylobacter jejuni* from human clinical isolates in 2017.

Campylobacter coli											**2017**
Antimicrobial	**West**		**North–East**		**South**		**Total**			**Trend**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Macrolides[1]	79	10.1%	131	20.6%	17	52.9%	227	19.4%	14.8 – 25	–	↑
Quinolones[2]	82	81.7%	131	75.6%	17	70.6%	230	77.4%	71.6–82.3	–	↑
Campylobacter jejuni											**2017**
Antimicrobial	**West**		**North–East**		**South**		**Total**			**Trend**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Macrolides[1]	733	1.1%	1558	0.6%	90	1.1%	2381	0.8%	0.5 – 1.2	–	↓
Quinolones[2]	731	57.6%	1563	56.4%	90	56.7%	2384	56.8%	54.8–58.8	↑	↑

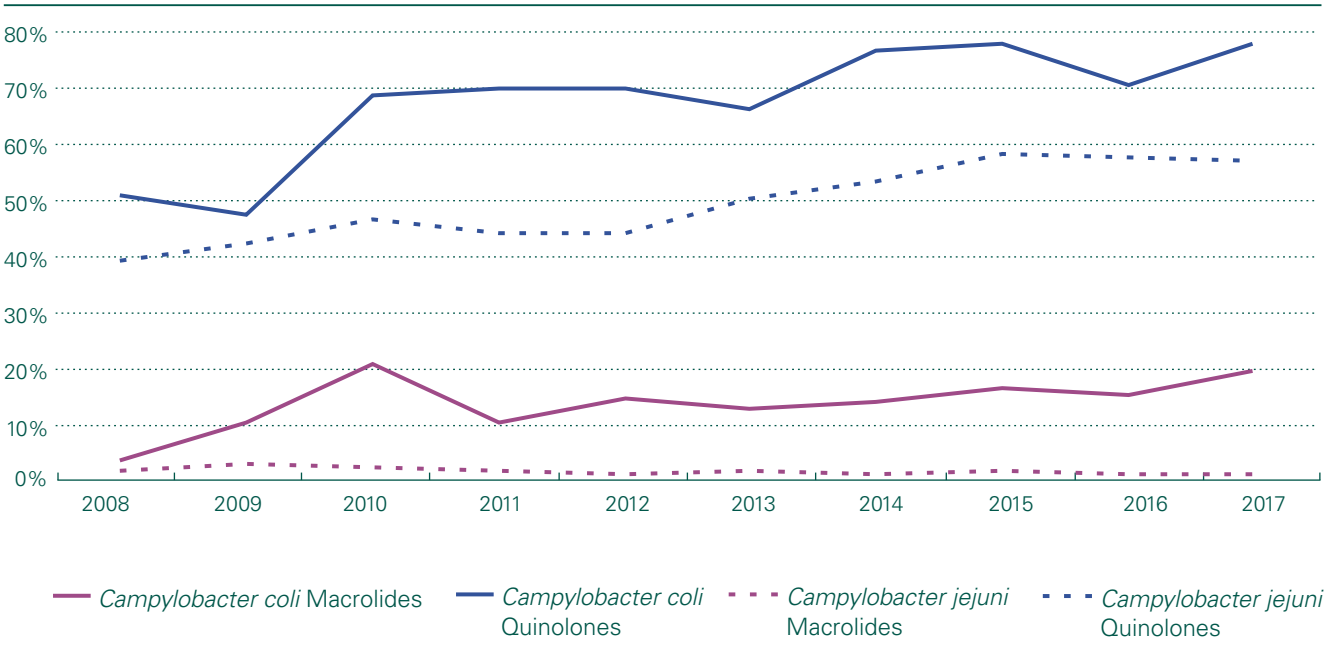
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.
[1] Macrolides: erythromycin, clarithromycin, azithromycin
[2] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

8.1.4 Discussion

The increase of resistance to ciprofloxacin in *C. jejuni* from broilers is of special concern, as fluoroquinolones and macrolides are the drugs of choice for the treatment of severe human campylobacteriosis. Their efficacy for the treatment of *Campylobacter* infections in humans should be preserved. Studies estimate that *Campylobacter* from broilers accounts for 50–80% of all human campylobacteriosis cases. Hence, resistant *Campylobacter* isolates from broilers can be passed on to humans [3], [4], [6].

In *C. jejuni* from broilers, microbiological resistance to ciprofloxacin has displayed a statistically significant increasing trend over the last ten years (Figure 8. b). The same trend is observed in human clinical isolates as well (Figure 8. a). While in broilers an increase from 18.3% resistant isolates in 2008 to 51.4% in 2016 was observed, quinolone resistance rates in clinical isolates from humans rose from 38.6% to 56.8% during the same time interval. Moreover, the resistance rate to tetracycline increased again in 2016 to 40%.

Figure 8. a: Trends in resistance to fluoroquinolones and macrolides in *Campylobacter coli* and *Campylobacter jejuni* from human clinical isolates in Switzerland between 2008 and 2017.



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 in fattening pigs and cattle. Resistance to other tested antimicrobials (erythromycin, gentamicin and streptomycin) remained stable or low (Figure 8. b).

Data on microbiological resistance in *C. jejuni* from broilers from 27 European countries in 2016 showed average levels of resistance of 66.9% to ciprofloxacin, 50.7% to tetracycline, 6.1% to streptomycin and 1.3% to erythromycin [7]. As in previous years, resistance levels varied greatly among countries and were generally much lower in Nordic countries than in other European countries [7]. Levels of resistance for *C. jejuni* in Switzerland were below the European averages, except for streptomycin, which were slightly higher. Besides Switzerland, Austria, the Czech Republic, Denmark, Finland, France, Germany, Hungary, the Netherlands and Spain also observed a statistically significant increasing trend of resistance to ciprofloxacin in *C. jejuni* from broilers over the last years [7].

In *C. coli* from fattening pigs, levels of microbiological resistance to streptomycin decreased significantly before 2012, but thereafter an increasing trend was observed until 2015. In 2017, the rate of resistance to streptomycin was lower than in 2015 (81.4% vs. 86.5%). The rate of resistance to tetracycline doubled between 2013 (29.2%) and 2015 (63.5%), and remained on the same level in 2017 (62.1%). Microbiological resistance levels to ciprofloxacin have increased steadily since 2008, apart from a slight fall in 2013, and the resistance level reached 50.3% in 2017. The prevalence of resistance to erythromycin has consistently been around 10% since monitoring began in 2006, and has reached an all-time low of 1.9% in 2017 (Figure 8. c). Information in anresis.ch on antimicrobial resistance was available for more than one third of the reported human *Campylobacter* cases. Resistance levels were reported for fluoroquinolones and macrolides. Resistance levels of fluoroquinolones were very high (above 50%), and the trend has been rising over the last ten years.

Similar average levels of resistance to ciprofloxacin for *C. jejuni* (average 54.6%) and *C. coli* (average 63.8%) isolated from humans were found in 17 EU countries in 2016. Resistance levels varied considerably between different countries, ranging from 33.3% to 94.0% for *C. jejuni* and from 31.3% to 100.0% for *C. coli* [7]. As a result, the European Food Safety Authority and the European Centre for Disease Prevention and Control no longer consider fluoroquinolones appropriate for the routine empirical treatment of human campylobacteriosis due to the high level of resistance [7]. In Switzerland, resistance levels to macrolides (erythromycin) are generally low, whereas in EU countries, resistance levels range from 0.0% to 6.6% for *C. jejuni* (average 2.1%) and from 0.0% to 63.2% for *C. coli* (average 11.0%) [7].

The available data do not allow a direct comparison of resistance in *Campylobacter* isolates from humans and animals. The sampling strategy and methodology used for testing isolates are not the same for animals and humans. In contrast, interpretation based on clinical breakpoints (human isolates) or epidemiological cutoffs (animal isolates) are equal, except for tetracyclines. Therefore, 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 *Campylobac-*

Figure 8. b: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. jejuni* from broilers between 2008 and 2016 (N = total number of tested isolates; values for 2015 interpolated [n/a]).

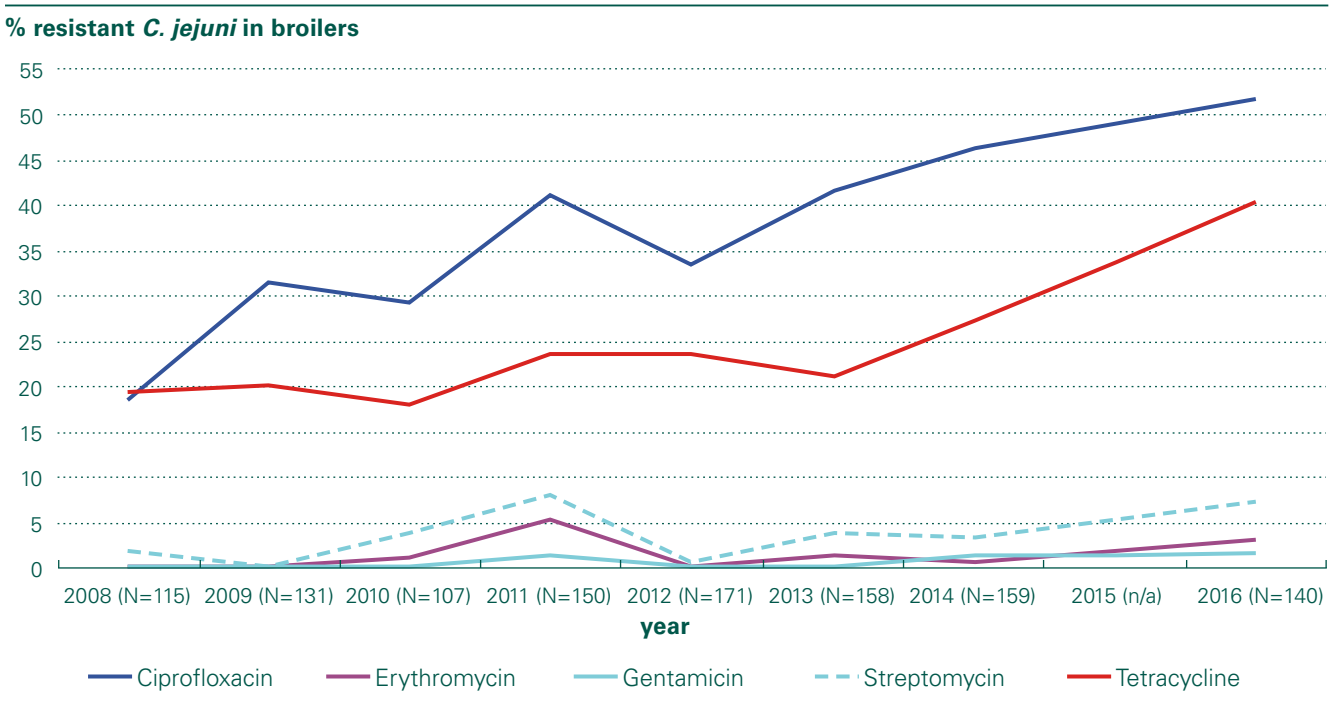
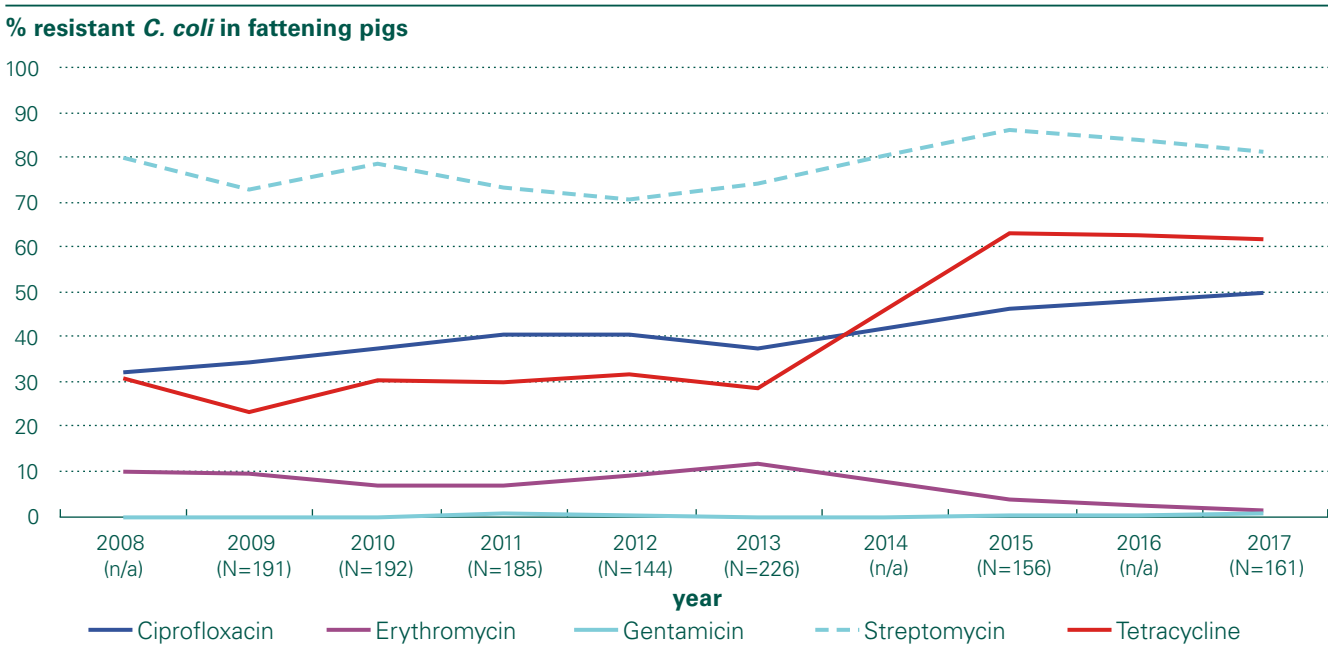


Figure 8. c: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. coli* from fattening pigs between 2008 and 2017 (N = total number of tested isolates; values for 2008, 2014 and 2016 interpolated [n/a]).



ter among animals, especially *C. jejuni* and *C. coli* from broilers. *Campylobacter* infections may be acquired from domestically produced and imported meat or during foreign travel. A study in Switzerland has shown that resistance levels for ciprofloxacin differ substantially in isolates from domestically produced and imported broiler meat [9]. On the other hand, another Swiss study has shown that campylobacteriosis derived from abroad does not occur very frequently among Swiss patients [10]. Knowledge on the molecular mechanisms responsible for the significant increase of the resistance level to ciprofloxacin and tetracycline in *Campylobacter* is urgently needed. Facts concerning the persistence of quinolone and tetracycline resistance in thermophilic *Campylobacter* from poultry is summarized in Textbox "Persistence of quinolone and tetracycline resistance in thermophilic *Campylobacter* from poultry."

8.2 *Salmonella* spp.

Salmonella is the second most important zoonotic bacterial pathogen in Switzerland and the EU [1], [2]. Salmonellosis in humans has to be notified (ordinance of the FOPH on laboratory reports), whereas the notification of resistance profiles of these findings is not mandatory.

Human salmonellosis usually does not require antimicrobial treatment. However, 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 close to one third of the reported human *Salmonella* cases. Resistance rates are only available for aminopenicillins, ceftriaxone, trimethoprim-sulfamethoxazole and quinolones (Table 8. d). Serovar typing in human medicine is only performed 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 antimicrobial resistance profile.

Animals can be carriers of *Salmonella* without showing any clinical signs. Poultry in particular often show no signs of infection. In cattle, *Salmonella* infection can cause fever, diarrhea and abortion. Fever and diarrhea are less common in pigs. 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*. In special settings (e. g. reptiles) *Salmonella* can also be transmitted through direct contact with infected 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 pork, beef 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 per incident. Isolates obtained from poultry flock samples collected within the national control program for *Salmonella* are also included in the data.

Textbox

Persistence of Quinolone and Tetracycline Resistance in Thermophilic *Campylobacter* from Poultry

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Since 2008, Switzerland has observed a steady decrease in sales of tetracycline and, since 2016, also of fluoroquinolones for use in food-producing animals, although species-specific data are not available so far. Unfortunately, this positive development did not directly translate to a reduction of the respective resistance rates in thermophilic *Campylobacter*. Possible reasons for this outcome are discussed hereafter.

Resistance to fluoroquinolones in *Campylobacter* (*C.*) *jejuni* and *C. coli* is normally mediated through the point mutation C257T in the quinolone-resistance-determining region (QRDR) of the *gyrA* gene (encoding DNA gyrase) [1]. This single point mutation is sufficient to confer resistance, and no further modifications are necessary. Previous studies of Swiss isolates were able to detect this mutation in all phenotypically resistant human strains [2] as well as in chicken meat isolates from retail and from slaughter [3]. The point mutation in the QRDR was additionally found to entail no fitness cost. As a matter of fact, it might even enhance the ability to colonize the chicken host [4]. Furthermore, *Campylobacter* were found to rapidly develop quinolone resistance even under treatment [5]. Thus, it is not surprising that over the last years we have seen a steady increase in quinolone-resistant isolates from both humans and livestock. Likewise, the EFSA reports a statistically significant increasing trend for fluoroquinolone-resistant *Campylobacter* in poultry in several other European countries [6]. Nevertheless, there are large differences between countries, with the Nordic European countries showing far lower rates of resistance compared to other European countries, including Switzerland [6]. Veterinary use of fluoroquinolones is strictly regulated in Denmark, where the poultry industry even completely ceased their usage in 2009. This measure was able to halt the increasing trend of ciprofloxacin resistance in *Campylobacter*, making Denmark one of the countries with the lowest rates. However, a lasting decrease was not observed [7]. Similar results were obtained in the US, where quinolone resistance levels in slaughter chickens remained constant after the FDA withdrew the approval for enrofloxacin use in poultry in 2005 [7]. This highlights the difficulty of fighting quinolone resistance in thermophilic *Campylobacter* once it is established, even using very strict measures, and does not bode well for the future.

The situation appears slightly more hopeful for tetracycline. Tetracycline resistance in thermophilic *Campylobacter* is normally mediated by the *tet*(O) gene encoding a ribosomal protection protein [8]. The gene can be located on the chromosome or on transferable plasmids [8, 9]. Location on transferable plasmids allows for a rapid spread of resistance following tetracycline use. *Tet*(O)-carrying plasmids can also harbor additional resistance genes, e.g. to kanamycin [9], which can lead to coselection of resistances. However, so far there are no reports (known to the authors) of the *tet*(O) gene increasing fitness of *Campylobacter* in absence of the antibiotic. Thus, in the long run, efforts to reduce tetracycline resistance might be more rewarding than for quinolones. Nevertheless, an increasing trend in tetracycline resistance over the last years was also observed in other European countries [6].

Genetic analyses to determine whether the molecular mechanisms responsible for the observed parallel increase of quinolone and tetracycline resistance in thermophilic *Campylobacter* in poultry are linked or not will be a task for the future.

In conclusion, long-term and international commitment will be necessary to reduce resistance, especially quinolone resistance, in *Campylobacter.* Additionally, it should not be forgotten that decreasing *Campylobacter* prevalence in food would also be highly beneficial, reducing the incidence of human cases and thus also decreasing quinolone use in humans.

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Table 8. d: Non-susceptibility rates of *Salmonella* from human clinical isolates in 2017.

Salmonella ser. enteritidis											2017
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillin	99	4.0%	74	12.2%	5	0.0%	178	7.3%	4.3–12.1	–	–
Ceftriaxone	99	0.0%	44	0.0%	1	0.0%	144	0.0%	0–2.6	–	–
Trimethoprim–sulfamethoxazole	98	3.1%	70	7.1%	5	0.0%	173	4.6%	2.4–8.9	–	–
Quinolones	82	8.5%	66	9.1%	5	0.0%	153	8.5%	5–14	–	↑

Salmonella ser. typhimurium											2017
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillin	16	81.3%	26	38.5%	3	66.7%	45	55.6%	41.2–69.1	–	–
Ceftriaxone	16	6.3%	21	0.0%	0	–	37	2.7%	0.5–13.8	–	↑
Trimethoprim–sulfamethoxazole	16	18.8%	23	8.7%	3	0.0%	42	11.9%	5.2–25	–	–
Quinolones	16	18.8%	26	15.4%	3	0.0%	45	15.6%	7.7–28.8	–	↑

West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.

8.2.1 *Salmonella* in animals

This chapter includes antimicrobial resistances of *S.* Enteritidis, *S.* Typhimurium and its monophasic variant in livestock, derived from diseased and/or infected animals. Poultry and cattle samples were available in 2016 and 2017. Isolates from pigs were detected in 2017 only.

In 2016, a total of 80 *Salmonella* isolates (29 from poultry, 51 from cattle) originating from different holdings and/or different sampling dates were available for susceptibility testing and are presented in Table 8. e and Table 8. f.
S. Typhimurium was identified in 41 (6 from poultry, 35 from cattle), *S.* Enteritidis in 29 (22 from poultry, 7 from cattle) and monophasic *S.* Typhimurium in 10 (1 from poultry, 9 from cattle) of the 80 isolates.

One of the *S.* Enteritidis isolates was resistant to colistin, while the other 28 isolates were fully susceptible to all tested antimicrobials. *S.* Enteritidis isolates are included in the *Salmonella* spp. columns in Table 8. e and Table 8. f. Approximately 80% of the *S.* Typhimurium isolates from poultry (5 isolates) and cattle (28 isolates) were susceptible to all tested antimicrobials.

Table 8. e: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from poultry in 2016.

2016	*Salmonella* spp. *(N=29)*			*Salmonella* Typhimurium *(N=6)*			Monophasic *Salmonella* Typhimurium (N=1)		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	1	3.4	0.6–17.2	0	0.0	0.0–39.0	1	100.0	20.7–100.0
Azithromycin	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Cefotaxime	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Ceftazidime	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Chloramphenicol	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Ciprofloxacin	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Colistin	2	6.9	1.9–22.0	1	16.7	3.0–56.4	0	0.0	0.0–79.3
Gentamicin	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Meropenem	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Nalidixic acid	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Sulfamethoxazole	1	3.4	0.6–17.2	0	0.0	0.0–39.0	1	100.0	20.7–100.0
Tetracycline	1	3.4	0.6–17.2	0	0.0	0.0–39.0	1	100.0	20.7–100.0
Tigecycline	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Trimethoprim	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
Number of resistances									
None	26	89.7	73.6–96.4	5	83.3	43.6–97.0	0	0.0	0.0–79.3
1 antimicrobial	2	6.9	1.9–22.0	1	16.7	3.0–56.4	0	0.0	0.0–79.3
2 antimicrobials	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
3 antimicrobials	1	3.4	0.6–17.2	0	0.0	0.0–39.0	1	100.0	20.7–100.0
4 antimicrobials	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3
>4 antimicrobials	0	0.0	0.0–11.7	0	0.0	0.0–39.0	0	0.0	0.0–79.3

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

One *S.* Typhimurium isolate from poultry was microbiologically resistant to colistin (Table 8. e). Multiple resistance to ampicillin, sulfamethoxazole and tetracycline was found in four of the 35 *S.* Typhimurium isolates from cattle. One isolate was additionally resistant to chloramphenicol (Table 8. f). Two *S.* Typhimurium isolates from cattle were resistant to sulfamethoxazole only, and one isolate was resistant to ampicillin and sulfamethoxazole.
The single monophasic *S.* Typhimurium isolate from poultry showed microbiological resistance to three antimicrobials (ampicillin, sulfamethoxazole, tetracycline) (Table 8. e). All nine monophasic *S.* Typhimurium isolates from cattle were resistant to ampicillin and sulfamethoxazole (Table 8. f). Eight of the nine isolates were additionally resistant to tetracycline.

The distribution of the minimum inhibitory concentrations (MICs) and multiresistance patterns for *Salmonella* spp. isolates for 2016 is shown in Annex II (Table I.1 to Table I.2 and Table I.32 to Table I.33).

In 2017, 31 *Salmonella* spp. isolates from poultry, 66 from cattle and 10 from pigs underwent susceptibility testing (Table 8. g, Table 8. h and Table 8. i). *S.* Typhimurium was identified in 51 (12 from poultry, 39 from cattle), *S.* Enteritidis in 26 (15 from poultry, 9 from cattle, 2 from pigs) and monophasic *S.* Typhimurium in 30 (4 from poultry, 18 from cattle, 8 from pigs) of the 107 isolates.

All 26 *S.* Enteritidis isolates from poultry, cattle and pigs were fully susceptible to all tested antimicrobials. *S.* Enteritidis isolates are included in the *Salmonella* spp. column in Table 8. g, Table 8. h, and Table 8. i.

The majority of *S.* Typhimurium isolates from poultry (83.3 %) and from cattle (82.1 %) were susceptible to all tested antimicrobials (Table 8. g and Table 8. h). Among the other *S.* Typhimurium isolates from poultry, one was microbiologically resistant to colistin and one to ampicillin and sulfamethoxazole. Also, two *S.* Typhimurium isolates from cattle showed resistance to ampicillin, chloramphenicol, sulfamethoxazole and tetracycline. Resistance to ampicillin, sulfamethoxazole and tetracycline was observed in one *S.* Typhimurium isolate. Single resistance to tetracycline was detected in 4 *S.* Typhimurium isolates from cattle.

Three of the four monophasic *S.* Typhimurium isolates from poultry showed microbiological resistance to three antimicrobials (ampicillin, sulfamethoxazole, tetracycline) and one was resistant to sulfamethoxazole only (Table 8. g). Sixteen monophasic *S.* Typhimurium isolates from cattle were resistant to ampicillin, sulfamethoxazole and tetracycline. Re-

Table 8. f: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from cattle in 2016.

2016	*Salmonella* spp. *(N=51)*			*Salmonella* Typhimurium *(N=35)*			Monophasic *Salmonella* Typhimurium (N=9)		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	14	27.5	17.1–40.9	5	14.3	6.3–29.4	9	100.0	70.1–100.0
Azithromycin	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Cefotaxime	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Ceftazidime	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Chloramphenicol	1	2.0	0.3–10.3	1	2.9	0.5–14.5	0	0.0	0.0–29.9
Ciprofloxacin	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Colistin	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Gentamicin	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Meropenem	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Nalidixic acid	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Sulfamethoxazole	16	31.4	20.3–45.0	7	20.0	10.0–35.9	9	100.0	70.1–100.0
Tetracycline	12	23.5	14.0–36.8	4	11.4	4.5–26.0	8	88.9	56.5–98.0
Tigecycline	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Trimethoprim	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9
Number of resistances									
None	35	68.6	55.0–79.7	28	80.0	64.1–90.0	0	0.0	0.0–29.9
1 antimicrobial	2	3.9	1.1–13.2	2	5.7	1.6–18.6	0	0.0	0.0–29.9
2 antimicrobials	2	3.9	1.1–13.2	1	2.9	0.5–14.5	1	11.1	2.0–43.5
3 antimicrobials	11	21.6	12.5–34.6	3	8.6	3.0–22.4	8	88.9	56.5–98.0
4 antimicrobials	1	2.0	0.3–10.3	1	2.9	0.5–14.5	0	0.0	0.0–29.9
>4 antimicrobials	0	0.0	0.0–7.0	0	0.0	0.0–9.9	0	0.0	0.0–29.9

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

sistance to ampicillin and sulfamethoxazole was detected in one isolate (Table 8. h). The two monophasic *S.* Typhimurium isolates from pigs showed microbiological resistance to ampicillin, sulfamethoxazole and tetracycline (Table 8. i).

The distribution of the minimum inhibitory concentrations (MICs) and multiresistance patterns for *Salmonella* spp. isolates in 2017 is shown in Annex II (Table I.3 to Table I.5 and Table I.34 to Table I.36).

8.2.2 Non-typhoidal *Salmonella* in human clinical isolates

For salmonellosis, 1,848 laboratory-confirmed cases in humans were reported in 2017. This represents a notification rate of 22 cases per 100,000 inhabitants. The most frequently reported serovars were *S.* Enteritidis (38%), *S.* Typhimurium (13%) and the monophasic variant 4,12,:i:- (11%). Resistance data from anresis.ch were available for about one third of all laboratory-confirmed cases.

Resistance in non-typhoidal human *Salmonella* isolates was high for aminopenicillin (20.6%), intermediate for quinolones (10.9%) and low for ceftriaxone and trimethoprim-sulfamethoxazole (1.1% and 3.7% respectively). In 2017, the most frequently isolated serovars were *S.* Enteritidis (n=178) and *S.* Typhimurium (n=45), but 389 isolates were not specified to the serovar level. Non-susceptibility rates were higher in *S.* Typhimurium than in *S.* Enteritidis for aminopenicillins (55.6% vs. 7.3%), trimethoprim-sulfamethoxazole (11.9% vs. 4.6%) and fluoroquinolones (15.6% vs. 8.5%). Ceftriaxone resistance was rare in both serovars (Table 8. d). Annual non-susceptibility rates have been stable for ceftriaxone since 2008 and have decreased significantly for aminopenicillins and trimethoprim-sulfamethoxazole during the last ten years (Tab. 8.d, Fig. 8. d). For quinolones, the annual non-susceptibility rates increased significantly from 2008 to 2017, but have remained stable during the last four years.

8.2.3 Discussion

The prevalence of *Salmonella* spp. in food-producing animals in Switzerland is very low as a consequence of long-term control programs. Because of this, only a few *Salmonella* isolates from animals, either from clinical material or from *Salmonella* eradication programs, were available over the last years (Figure 8. e). Hence, rates of resistance and their long-term trends should be interpreted with caution.

Between 2016 and 2017, susceptibility of *Salmonella* spp. to all tested antimicrobials decreased from 89.7% to 80.7% for isolates from poultry and from 68.6% to 62.1% for isolates from cattle. Overall, the situation regarding antibiotic resis-

Table 8. g: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from poultry in 2017.

2017	*Salmonella* spp. *(N=31)*			*Salmonella* Typhimurium *(N=12)*			Monophasic *Salmonella* Typhimurium (N=4)		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	4	12.9	5.1–28.9	1	8.3	1.5–35.4	3	75.0	30.1–95.4
Azithromycin	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Cefotaxime	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Ceftazidime	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Chloramphenicol	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Ciprofloxacin	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Colistin	1	3.2	0.6–16.2	1	8.3	1.5–35.4	0	0.0	0.0–49.0
Gentamicin	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Meropenem	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Nalidixic acid	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Sulfamethoxazole	5	16.1	7.1–32.6	1	8.3	1.5–35.4	4	100.0	51.0–100.0
Tetracycline	3	9.7	3.3–24.9	0	0.0	0.0–24.3	3	75.0	30.1–95.4
Tigecycline	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Trimethoprim	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
Number of resistances									
None	25	80.7	63.7–90.8	10	83.3	55.2–95.3	0	0.0	0.0–49.0
1 antimicrobial	2	6.5	1.8–20.7	1	8.3	1.5–35.4	1	25.0	4.6–69.9
2 antimicrobials	1	3.2	0.6–16.2	1	8.3	1.5–35.4	0	0.0	0.0–49.0
3 antimicrobials	3	9.7	3.3–24.9	0	0.0	0.0–24.3	3	75.0	30.1–95.4
4 antimicrobials	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0
>4 antimicrobials	0	0.0	0.0–11.0	0	0.0	0.0–24.3	0	0.0	0.0–49.0

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

tance in poultry and cattle can be considered good and is similar to neighboring countries such as Austria, France, Germany and Italy [7].

Quinolones and third-generation cephalosporins such as ceftriaxone are critically important antimicrobials for the treatment of human salmonellosis. Resistance to ciprofloxacin or third-generation cephalosporins was neither found in *Salmonella* spp. isolates from poultry nor from cattle nor from pigs in 2016 and 2017. Resistances to ampicillin, sulfamethoxazole and tetracycline have been high in the last years and have increased from 2016 to 2017 after a decline from 2014 to 2015 (Figure 8. e). These antimicrobials have been used in animal farming for many years, and rates of resistance reflect the actual selection pressure.

Microbiological resistance to colistin was detected in three isolates out of 60 *Salmonella* spp. isolates from poultry having undergone susceptibility testing in 2016 and 2017. All *Salmonella* spp. isolates from cattle and pigs tested in 2016 and 2017 were susceptible to colistin. In the EU, the rate of microbiological resistance to colistin among *Salmonella* spp. from broiler flocks was 2.5% in 2016 [7]. It is being investigated whether the resistance to colistin of these three *Salmonella* spp. isolates in Switzerland is associated with the recently described plasmid-mediated colistin resistance (*mcr*-1) [11] or with other resistance mechanisms. So far, in Switzerland, the *mcr*-1 gene has only been detected in a clinical *E. coli* isolate from a patient with renal deficiency [12] and one *E. coli* isolate from a Swiss slaughter pig in 2015. Furthermore, the *mcr*-1 gene was present in ESBL-producing *E. coli* strains isolated from chicken meat imported from Germany and Italy [13] and in one ESBL-producing *E. coli* strain from river water in Switzerland and in two ESBL-producing *E. coli* strains isolated from imported vegetables from Vietnam and Thailand [14].

The frequency of resistance to aminopenicillins in human non-typhoidal *Salmonella* spp. isolates in Switzerland (20.6%) was lower than the mean level of resistance to ampicillin in 23 different EU member states in 2016 (29.5%) [7]. Since 2011, resistance levels to quinolones in Switzerland increased to 12.7% in 2014 and decreased to 10.9% in 2017. This is equal to the mean value for ciprofloxacin resistance in EU member states in 2016 (11.0%), but variation between member states is considerable (0.0– 36.0% resistant isolates).

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 / epidemiological cutoff in animal isolates) may differ substantially. As the only information available is qualitative data from human isolates, a re-

interpretation of the results using the same cutoff values is not possible. Regarding the favorable *Salmonella* situation in Swiss livestock, it is likely that a substantial part of *Salmonella* infections is acquired through imported food or foreign travel. Data on antimicrobial resistance in *Salmonella* from imported food and information regarding the origin of the infection (domestic/abroad) would be necessary to complete the picture.

Table 8. h: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from cattle in 2017.

2017	*Salmonella* spp. *(N=66)*			*Salmonella* Typhimurium *(N=39)*			Monophasic *Salmonella* Typhimurium (N=18)		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	20	30.3	20.6–42.2	3	7.7	2.7–20.3	17	94.4	74.2–99.0
Azithromycin	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Cefotaxime	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Ceftazidime	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Chloramphenicol	2	3.0	0.8–10.4	2	5.1	1.4–16.9	0	0.0	0.0–17.6
Ciprofloxacin	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Colistin	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Gentamicin	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Meropenem	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Nalidixic acid	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Sulfamethoxazole	21	31.8	21.8–43.8	3	7.7	2.7–20.3	18	100.0	82.4–100.0
Tetracycline	23	34.8	24.5–46.9	7	17.9	9.0–32.7	16	88.9	67.2–96.9
Tigecycline	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Trimethoprim	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6
Number of resistances									
None	41	62.1	50.1–72.9	32	82.1	67.3–91.0	0	0.0	0.0–17.6
1 antimicrobial	5	7.6	3.3–16.5	4	10.3	4.1–23.6	1	5.6	1.0–25.8
2 antimicrobials	1	1.5	0.3–8.1	0	0.0	0.0–9.0	1	5.6	1.0–25.8
3 antimicrobials	17	25.8	16.7–37.4	1	2.6	0.5–13.2	16	88.9	67.2–96.9
4 antimicrobials	2	3.0	0.8–10.4	2	5.1	1.4–16.9	0	0.0	0.0–17.6
>4 antimicrobials	0	0.0	0.0–5.5	0	0.0	0.0–9.0	0	0.0	0.0–17.6

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

Figure 8. d: Trends in aminopenicillin, ceftriaxone, trimethoprim-sulfamethoxazole and fluoroquinolone resistance in non-typhoidal *Salmonella* from human clinical isolates between 2008 and 2017.

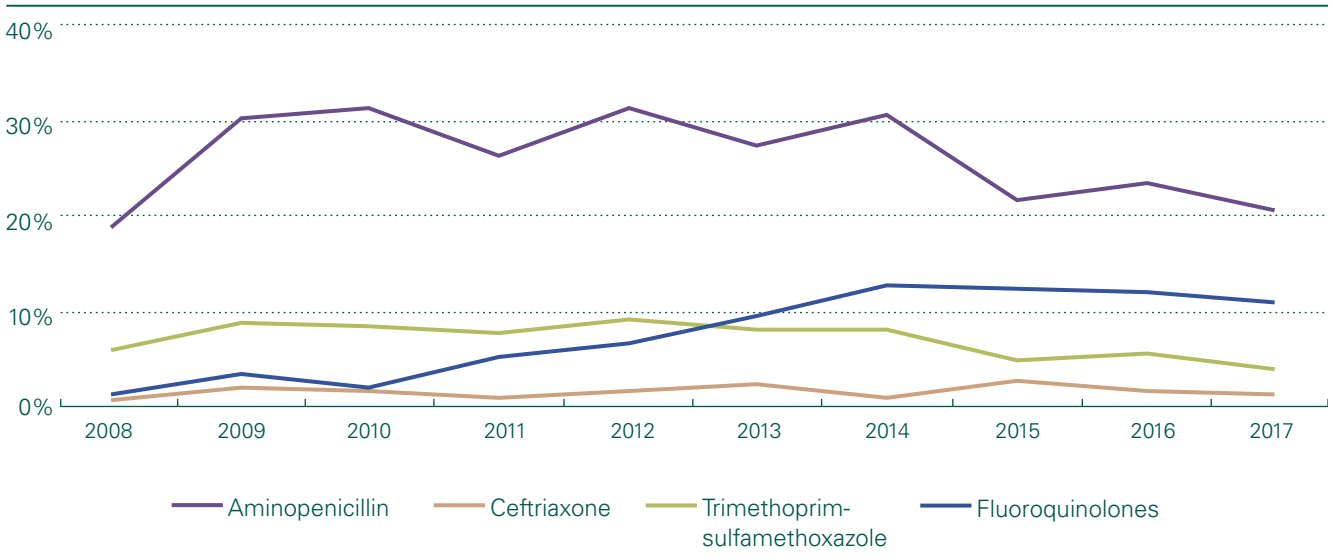
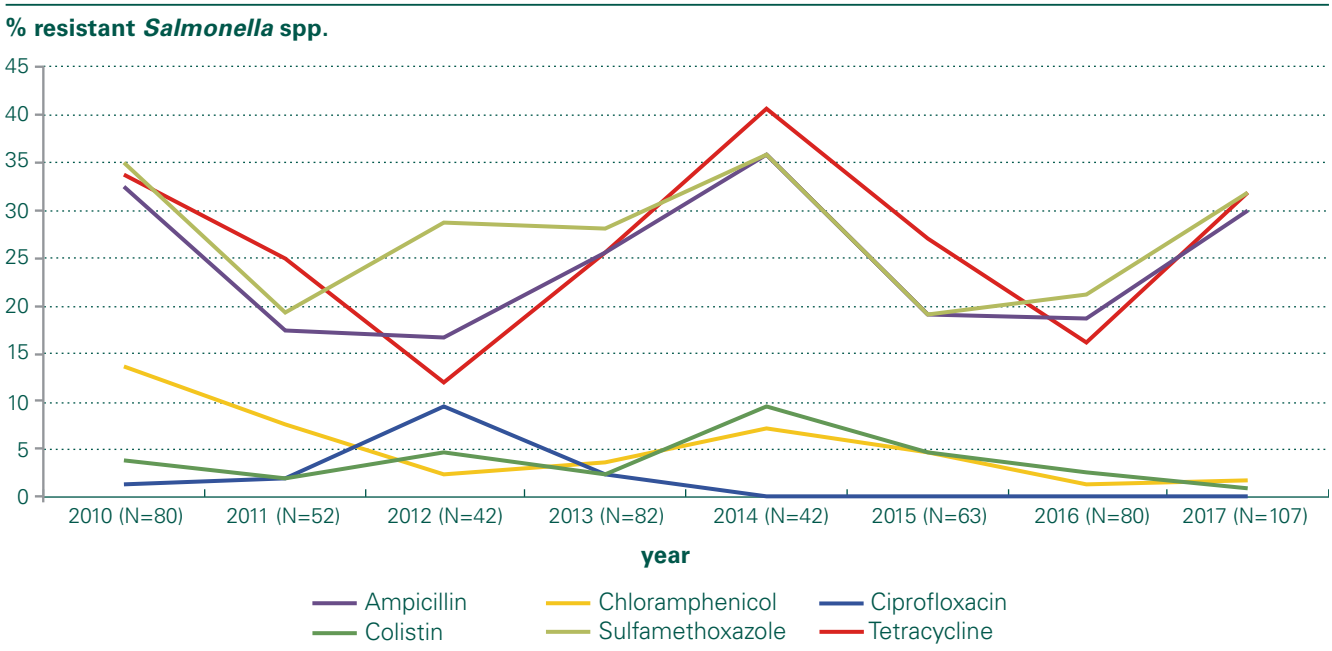


Table 8. i: Occurrence of resistance in *Salmonella* spp. and monophasic *Salmonella* Typhimurium from fattening pigs in 2017.

2017	*Salmonella* spp. *(N=10)*			*Monophasic Salmonella* Typhimurium *(N=8)*		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	8	80.0	49.0–94.3	8	100.0	67.6–100.0
Azithromycin	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Cefotaxime	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Ceftazidime	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Chloramphenicol	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Ciprofloxacin	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Colistin	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Gentamicin	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Meropenem	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Nalidixic acid	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Sulfamethoxazole	8	80.0	49.0–94.3	8	100.0	67.6–100.0
Tetracycline	8	80.0	49.0–94.3	8	100.0	67.6–100.0
Tigecycline	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Trimethoprim	0	0.0	0.0–27.8	0	0.0	0.0–32.4
Number of resistances	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
None	2	20.0	5.7–51.0	0	0.0	0.0–32.4
1 antimicrobial	0	0.0	0.0–27.8	0	0.0	0.0–32.4
2 antimicrobials	0	0.0	0.0–27.8	0	0.0	0.0–32.4
3 antimicrobials	8	80.0	49.0–94.3	8	100.0	67.6–100.0
4 antimicrobials	0	0.0	0.0–27.8	0	0.0	0.0–32.4
>4 antimicrobials	0	0.0	0.0–27.8	0	0.0	0.0–32.4

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

Figure 8. e: Trends in ampicillin, chloramphenicol, ciprofloxacin, colistin, sulfamethoxazole and tetracycline resistance in *Salmonella* spp. from poultry, pigs and cattle between 2010 and 2017 (N = total number of tested isolates).



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Textbox

Modern Microbiological Surveillance for Antibiotic Drug Resistance

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Abstract
Controlling multidrug-resistant (MDR) bacterial pathogens urgently requires new technical solutions. Molecular typing technologies such as whole genome sequencing (WGS) allow high-resolution tracking of spatiotemporal patterns of pathogen transmission. But molecular surveillance can only realize its full potential when combined with rapid turnaround and interoperable and curated clinical and epidemiological metadata. To reach this goal, different centers need to share sequence and metadata in a timely fashion. To facilitate such data sharing, a common database with streamlined analysis workflows is necessary.

The challenge of antibiotic resistance and the technological revolution ahead
The European Centre for Disease Prevention and Control (www.ecdc.europe.eu) and the national surveillance system for antibiotic resistance and consumption (www.anresis.ch) have documented the rapid increase of multidrug-resistant (MDR) pathogens. The O'Neill report predicts that by 2050 the global expansion of MDR pathogens may exceed ten million fatal cases per year, thereby exceeding todays cancer-related deaths. Similarly, the emergence of MDR bacteria in veterinary medicine leads to a high economic burden and constitutes a serious public health concern. The human and animal compartments are tightly linked via various environmental sources such as sewage waters, farming, and the food chain. The transmission dynamics within and between compartments is poorly understood, but high-resolution typing via WGS can elucidate such transmissions. However, to derive actionable inferences and effective counter measures from such methods, the following three key requirements need to be met (Egli A et al. Swiss Medical Weekly 2018 in press):

(i) A comprehensive high-resolution, portable, cost-effective and close to real-time molecular typing method to separate related from non-related pathogens;
(ii) Seamless integration of "classical" clinical and epidemiological metadata such as date of isolation, geographical location, and the source of isolation with WGS data;
(iii) Timely sharing and merging interoperable metadata in the context of public health threats.

These goals require interdisciplinary teams consisting of microbiologists, bioinformaticians, infectious disease specialists and epidemiological experts. Stakeholders such as hospitals and governmental institutions need to maintain a surveillance platform where relevant information is gathered and analyzed in order to rapidly identify potential sources, to inform decision makers, and thus enable the interruption of the transmission chain.

High-throughput whole genome sequencing (WGS) and genome data analysis of bacterial pathogens is a clear technological revolution in clinical microbiology, as bacterial typing at the highest resolution is now possible, while also allowing for the identification of resistance and virulence genes. Transmission rates and routes within compartments can be analyzed in the context of spatiotemporal information [1]. It is expected that improving standardized workflows, e.g. through ISO accreditation and analytical bioinformatic pipelines, will substantially reduce costs over the next years, thus permitting comprehensive WGS. The international GenomeTrakr network (accessdata.fda.gov) has already sequenced tens of thousands of bacterial genomes each year, mostly to combat food-borne diseases.

The workflow for WGS includes a wet and a dry lab component. In the wet lab, samples are processed and sequenced. Afterwards, in the dry lab, WGS data is analyzed in order to detect differences in the bacterial sequences and to visualize their relationships [2]. The main goal is the reconstruction of a phylogeny that approximates a transmission tree. Due to differences in the analytical flow across Swiss labs, the Swiss Institute of Bioinformatics (SIB) has initiated a nationwide quality assessment ring trial focusing on bacterial phylogeny. Similarly, the ECDC has recently published an expert opinion on WGS as a tool for public health surveillance of MDR pathogens. The ECDC has concluded that the estab-

lishment of standards and systems enabling EU-wide use of WGS as the method of choice for typing microbial pathogens will replace other methods, and that this will improve the accuracy and effectiveness of disease surveillance, outbreak investigation and evaluation of prevention policies [3].

A Swiss molecular surveillance platform for MDR pathogens

Gathering interoperable pathogen, host and environmental metadata is required to provide a better understanding of transmission dynamics and thereby guide containment of such MDR pathogens. Specific tools such as *Microreact* (microreact.org) or *Nextstrain* (nextstrain.org; Figure 1A) visualize transmission within a spatiotemporal context. However, to date, there is no specific platform in Switzerland and Europe that allows integration of WGS data from various diagnostic or reference laboratories with a special focus on surveillance of antibiotic resistance in combination with pathogen, host and environmental metadata.

A key feature of such a surveillance platform has to be the interoperability of data. This can be achieved with a common syntax and nomenclature starting at the time of data entry, species descriptions, and minimal datasets of documented microbiological, host and environmental information. Healthcare-focused vocabularies and ontologies such as Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT) (www.e-health-suisse.ch) or LOINC (loinc.org) may offer detailed descriptions of the sample context [4]. Synergy effects from standardized workflows and integration of the data base with the sequence bioinformatics at the individual centers should make immediate data sharing the default. Only through timely sharing can outbreak clusters be detected early and acted upon. Any delay in sharing quickly dissipates the public health benefit.

Our goal is therefore to establish a Swiss Pathogen Surveillance Platform (www.spsp.ch; Figure 1B) with initial funding from the NRP72 program. We will build upon the *Nextstrain* tool and start with methicillin-resistant *Staphylococcus aureus* as a proof-of-concept pathogen. We will gradually expand to different pathogens such as ESBL- and carbapenemase-producing Enterobacteriaceae as well as other pathogenic bacteria, and incorporate specific aspects such as food safety.

We anticipate that such a platform will generate an immense benefit for public health and research institutions in Switzerland. The platform will make it possible to (i) identify risks of MDR bacterial pathogen transmission for hospitals and public health in Switzerland, (ii) describe and explore these risks by predicting dynamics of spread, and (iii) produce outcome control measurements of interventions, e.g. by monitoring the reduction of transmission of particular clones. In contrast to other existing resources, our project envisions real-time surveillance functionality, including the automated modelling of transmission events, epidemiological warning functions, and linkage with high-resolution geographical data.

Ethical considerations regarding epidemiological surveillance

From an individual's point of view, the collection and analysis of patient data and molecular typing of pathogens raises ethical and patient privacy issues. Switzerland participates in the Nagoya protocol and the declaration of Taipei of the World Medical Association (www.bafu.admin.ch and www.wma.net). In addition, the collection and usage of data for research is clearly regulated via the Human Research Act (www.swissethics.ch). From a societal point of view, the transmission and spread of pathogens must be controlled at early stages. An epidemiological surveillance database is most efficient if data is shared. However, the requirements of individual data protection and public health focusing on the potential impact of MDR and virulent pathogens have to be carefully analyzed and discussed, in order to balance individual protection with the potential of earlier public health action.

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Figure 1: Pathogen surveillance using molecular typing data. (A) The Nextstrain tool (www.nextstrain.org) offers phylogenetic trees of multiple pathogens, e.g. Ebola virus outbreak in West Africa. Colors represent different geographic regions. The x-axis reflects a time scale during the outbreak.

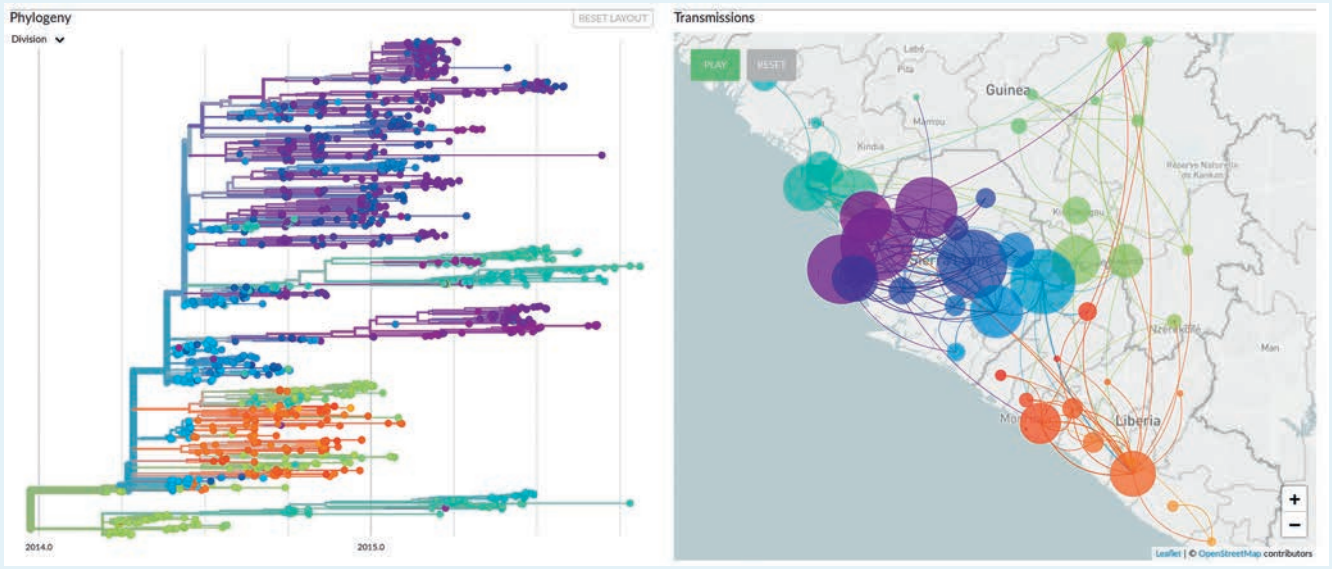
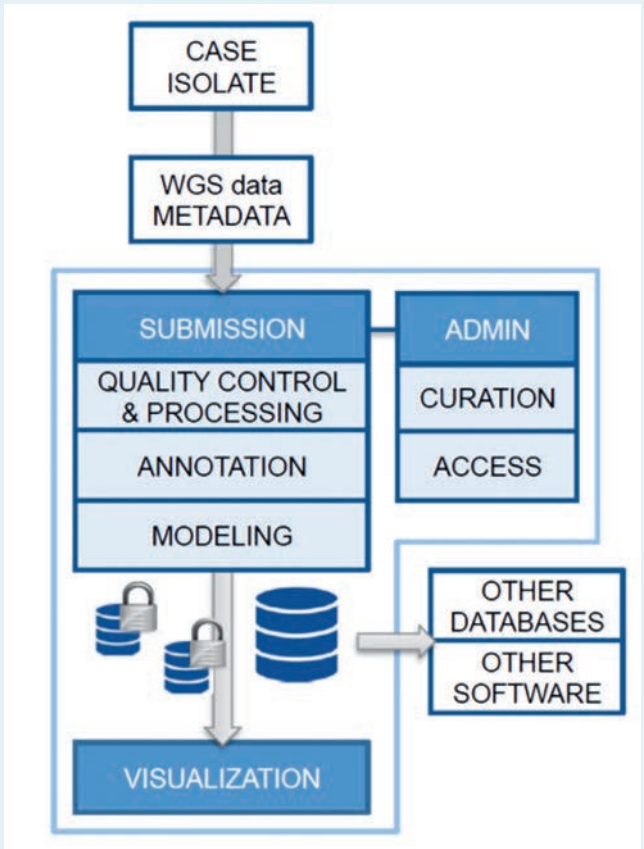


Figure 2: Envisioned workflow for the surveillance platform. After isolating a strain, collecting epidemiological data and sequencing it, the user uploads raw data and metadata into a central or local/private database using the submission portal. After submission, these data are quality controlled and then (semi-)automatically processed to perform tasks such as genome assembly, and MLST, SNP and resistance calling. The resulting data are used for phylogenetics and predictive modelling, e.g. transmission dynamics. All these data are stored in a structured database with controlled access, and visualized in a user-friendly interface. For open data, the structured database may also be used/queried by other applications or pushed to external databases and knowledge bases. In addition to the submission portal, an administration portal to manage users and rights, as well as a curating portal to edit controlled vocabularies and define curated reference strains and variants (e.g. for resistance) will be developed.



9

Resistance in indicator bacteria from livestock animals

9 Resistance in indicator bacteria from livestock animals

The prevalence of antimicrobial resistance among certain bacteria of the intestinal flora can be used as an indicator of the selective pressure from use of antimicrobial agents in various populations. These bacteria constitute a reservoir of potentially transferable resistance genes that can be spread horizontally to other bacteria, including zoonotic bacteria. Antimicrobial 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. Antimicrobial use leads to a selection pressure for resistant bacteria in the intestinal flora of affected animals. 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 the context of monitoring antimicrobial resistance, enterococci are indicator bacteria for the occurrence of resistances in Gram-positive intestinal bacteria from livestock. Resistance can be transferred from animals to humans either by direct transmission of resistant bacterial strains or by horizontal gene transfer of resistance genes among bacteria [1]. Enterococci are generally found as commensals in the gastrointestinal tract of animals and humans. In a hospital setting, however, they can cause diseases such as urinary tract infections, sepsis or endocarditis in patients with a weakened immune system. Of particular concern in this regard are vancomycin-resistant enterococci (VRE), which can spread rapidly and are difficult to treat. The responsible resistance gene is located on a transposon and can therefore

Table 9. a: Occurrence of resistance in *Enterococcus faecalis* and *Enterococcus faecium* from broilers in 2016.

2016	*Enterococcus faecalis (N=31)*			*Enterococcus faecium (N=247)*		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	0	0.0	0.0–11.0	10	4.0	2.2–7.3
Chlorampenicol	1	3.2	0.6–16.2	0	0.0	0.0–1.5
Ciprofloxacin	1	3.2	0.6–16.2	7	2.8	1.4–5.7
Daptomycin	0	0.0	0.0–11.0	16	6.5	4.0–10.3
Erythromycin	11	35.5	21.1–53.1	53	21.5	16.8–27.0
Gentamicin	0	0.0	0.0–11.0	0	0.0	0.0–1.5
Linezolid	0	0.0	0.0–11.0	0	0.0	0.0–1.5
Quinupristin/Dalfopristin*	–	–	–	141	57.1	50.9–63.1
Teicoplanin	0	0.0	0.0–11.0	0	0.0	0.0–1.5
Tetracycline	20	64.5	46.9–78.9	56	22.7	17.9–28.3
Tigecycline	0	0.0	0.0–11.0	3	1.2	0.4–3.5
Vancomycin	1	3.2	0.6–16.2	0	0.0	0.0–1.5
Number of resistances						
None	0	0.0	0.0–11.0	66	26.7	21.6–32.6
1 antimicrobial	9	29.0	16.1–46.6	93	37.7	31.8–43.8
2 antimicrobials	11	35.5	21.1–53.1	73	29.6	24.2–35.5
3 antimicrobials	10	32.3	18.6–49.9	13	5.3	3.1–8.8
4 antimicrobials	1	3.2	0.6–16.2	2	0.8	0.2–2.9
>4 antimicrobials	0	0.0	0.0–11.0	0	0.0	0.0–1.5

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)
* Natural resistance of *E. faecalis*

easily be spread horizontally to other bacteria, prompting particular fears that vancomycin resistance might be passed from enterococci to methicillin-resistant *Staphylococcus aureus* (MRSA).

This chapter includes antimicrobial resistances of *Enterococcus faecalis* and *Enterococcus faecium* in livestock. Broilers were investigated in 2016 and calves in 2017.

9.1.1 *Enterococcus* spp. in broilers

In 2016, a random sample of 349 broiler flocks was investigated at slaughter for the occurrence of enterococci in the framework of the antimicrobial resistance monitoring program using cecal samples (5 pooled cecal samples per flock). *E. faecalis* was identified in 31 samples (8.9 %) and *E. faecium* in 247 samples (70.8 %). Susceptibility testing was performed for all available enterococci isolates (Table 9. a).

Full susceptibility to all tested antimicrobials was observed for 26.7 % of *E. faecium* isolates, but for none of the *E. faecalis* isolates. Multiple resistance to four of the tested antimicrobials was observed for one *E. faecalis* (3.2 %) and two *E. faecium* (0.8 %) isolates.

For *E. faecalis*, very high to high levels of microbiological resistance to tetracycline (64.5 %) and erythromycin (35.5 %) was found. One *E. faecalis* isolate was resistant to vancomycin (3.2 %). *E. faecium* isolates showed a very high level of resistance to quinupristin/dalfopristin (57.1 %) and high resistance to erythromycin (21.5 %) and tetracycline (22.7 %). Low levels of resistance in *E. faecium* were observed for ampicillin (4.0 %), ciprofloxacin (2.8 %), daptomycin (6.5 %) and tigecycline (1.2 %).

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.9 to Table I.10) and multiresistance patterns for *E. faecium* is shown in Annex II (Table I.40).

9.1.2 *Enterococcus* spp. in calves

In 2017, a random sample of 296 slaughter calves was investigated at slaughter for the occurrence of enterococci in the framework of the antimicrobial resistance monitoring program using cecal samples. 46 *Enterococcus faecalis* strains (15.5 %) and 129 *Enterococcus faecium* strains (43.6 %) were isolated and subjected to susceptibility testing (Table 9. b).

67.4 % of the *E. faecalis* and 4.7 % of the *E. faecium* isolates showed microbiological resistance to tetracycline. A high level of resistance to erythromycin was found for both *E. faecalis* and *E. faecium* (37.0 % and 20.2 % respectively).

E. faecalis isolates additionally showed a high level of resis-

Table 9. b: Occurrence of resistance in *Enterococcus faecalis* and *Enterococcus faecium* from slaughter calves in 2017.

2017	*Enterococcus faecalis (N=46)*			*Enterococcus faecium (N=129)*		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ampicillin	0	0.0	0.0–7.7	1	0.8	0.1–4.3
Chlorampenicol	8	17.4	9.1–30.7	0	0.0	0.0–2.9
Ciprofloxacin	1	2.2	0.4–11.3	1	0.8	0.1–4.3
Daptomycin	0	0.0	0.0–7.7	2	1.6	0.4–5.5
Erythromycin	17	37.0	24.5–51.4	26	20.2	14.1–27.9
Gentamicin	11	23.9	13.9–37.9	0	0.0	0.0–2.9
Linezolid	0	0.0	0.0–7.7	0	0.0	0.0–2.9
Quinupristin/Dalfopristin*	-	-	-	124	96.1	91.2–98.3
Teicoplanin	0	0.0	0.0–7.7	0	0.0	0.0–2.9
Tetracycline	31	67.4	53.0–79.1	6	4.7	2.1–9.8
Tigecycline	1	2.2	0.4–11.3	4	3.1	1.2–7.7
Vancomycin	0	0.0	0.0–7.7	0	0.0	0.0–2.9
Number of resistances						
None	0	0.0	0.0–7.7	3	2.3	0.8–6.6
1 antimicrobial	15	32.6	20.9–47.0	95	73.6	65.4–80.5
2 antimicrobials	13	28.3	17.3–42.5	25	19.4	13.5–27.0
3 antimicrobials	2	4.3	1.2–14.5	5	3.9	1.7–8.8
4 antimicrobials	12	26.1	15.6–40.3	1	0.8	0.1–4.3
>4 antimicrobials	4	8.7	3.4–20.3	0	0.0	0.0–2.9

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)
* Intrinsic resistance of *E. faecalis*

tance to gentamicin (23.9%) and a moderate level of resistance to chloramphenicol (17.4%). 96.1% of the *E. faecium* isolates were microbiologically resistant to quinupristin/dalfopristin. A low level of resistance to tigecycline was observed for *E. faecalis* and *E. faecium* (2.2% and 3.1%, respectively). Resistance to linezolid, teicoplanin or vancomycin was not observed for either isolates.

Only 2.3% of the *E. faecium* and none of the *E. faecalis* isolates were fully susceptible to all tested antimicrobials. Multiple resistance to at least 4 of the tested antimicrobials was observed for 16 *E. faecalis* (34.8%) and 1 *E. faecium* (0.8%) isolates.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.11 to Table I.12) and multiresistance patterns for *E. faecium* are shown in Annex II (Table I.41).

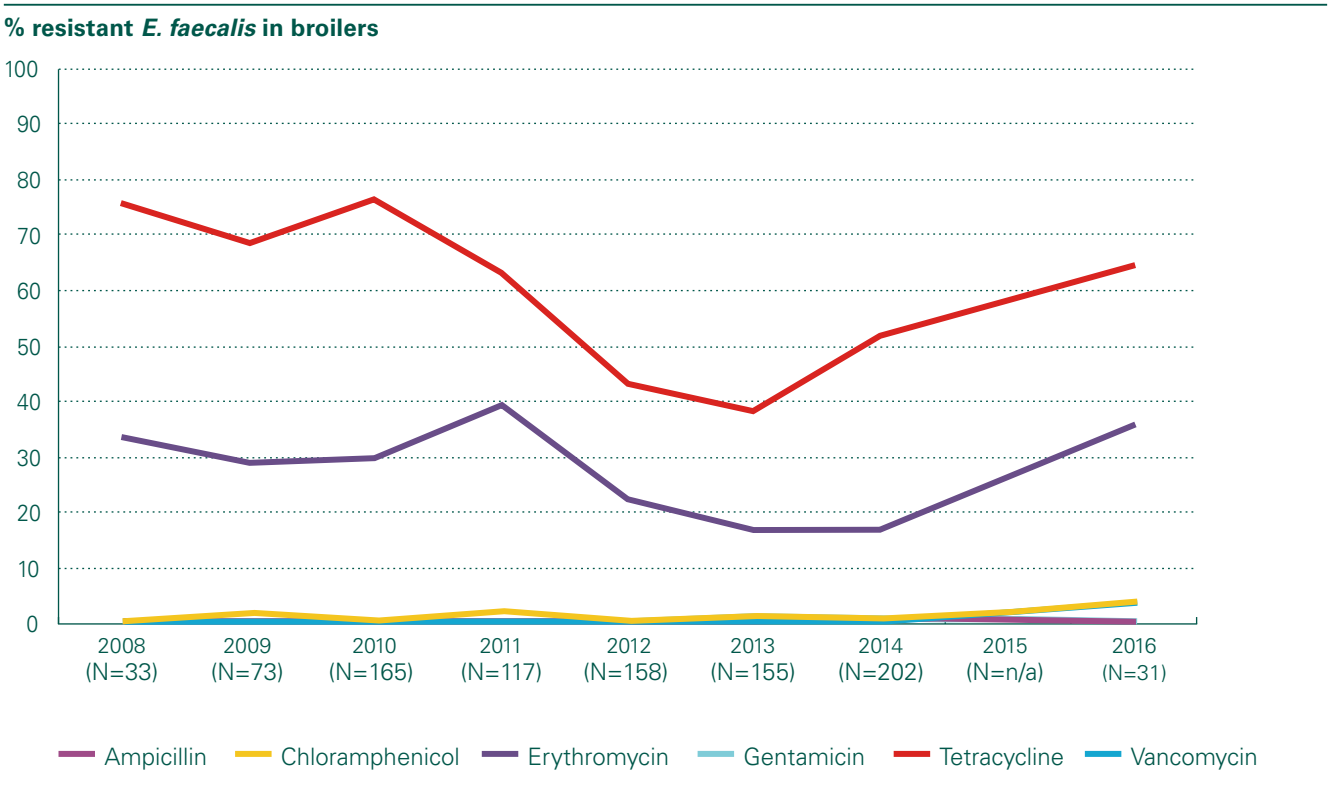
9.1.3 Discussion

Resistance to antimicrobials is generally widespread in enterococci isolated from livestock in Switzerland. Resistances to erythromycin and tetracycline are often found in isolates from broilers and slaughter calves. Long-term trends of both resistances vary among enterococci and types of animals (Figures 9 a–d). In the past years, a significant decreasing trend of microbiological resistance to tetracycline and erythromycin has been observed for *E. faecalis* isolates from broilers. However, resistance to tetracycline increased again since 2014 and reached 64.5% in 2016 (Figure 9. a). Resistance to erythromycin increased in *E. faecalis* from broilers, but decreased in *E. faecium* from broilers. In *E. faecalis* from calves, the resistance to erythromycin is stable and decreased for *E. faecium* by 11% from 2015 to 2017 (Figure 9. c and Figure 9. d). However, trends should be interpreted with caution, due to low numbers of isolates for *E. faecalis.*

Ampicillin is a first-line treatment for infections caused by enterococci in human medicine, and is also used in combination with gentamicin for severe infections. In 2016, ampicillin resistance was not observable among *E. faecalis* isolates from broilers and remained at a low level for *E. faecium* (4.0%). The resistance rate for ampicillin among *E. faecalis* and *E. faecium* from calves was respectively zero and very low (0.8%). Gentamicin resistance in *E. faecalis* from calves is high (23.9%) while it is zero to very low in *E. faecalis* and *E. faecium* from broilers and in *E. faecium* from slaughter calves.

In the current reporting period, resistance to vancomycin was found in only one *E. faecalis* isolate from broilers. No enterococci isolates were resistant to linezolid. Vancomycin, a glycopeptide antibiotic, is used in combination with gentamicin instead of ampicillin if resistance to ampicillin is present. Linezolid is the drug of choice for the treatment of severe infections with vancomycin-resistant enterococci (VRE).

Figure 9. a: Trends in ampicillin, chloramphenicol, erythromycin, gentamicin, tetracycline and vancomycin resistance in *Enterococcus faecalis* from broilers between 2008 and 2016 (N = total number of tested isolates; values for 2015 interpolated [n/a]).



The emergence of vancomycin resistance in bacteria from livestock in the past was linked to the use of avoparcin as a growth promoter. As a result, avoparcin was prohibited as a growth promoter in Europe in 1997. After the ban, a decreased incidence of VRE in the livestock population and a smaller proportion of people with VRE gut colonization could be verified [2]. Rates of resistance are low to very low in all European countries in which the level of vancomycin resistance in enterococci was investigated [3]. Resistance monitoring in livestock in Switzerland has not detected vancomycin resistance in enterococci for many years. However, resistance was occasionally detected, i.e. in one *E. faecalis* isolate from calves in 2013, two *E. faecium* isolates from fattening pigs in 2015 and one *E. faecalis* isolates from broilers in 2016.

Very high levels of microbiological resistance to quinupristin/dalfopristin in *E. faecium* from broilers and slaughter calves remain widespread. *E. faecalis* is not susceptible to quinupristin/dalfopristin due to its intrinsic resistance. The drug combination was originally recommended as an alternative for the treatment of VRE infections in humans. Nowadays, new antimicrobials such as linezolid or tigecycline are available for the treatment of human VRE infections.

In veterinary medicine, quinopristin/dalfopristin has never been used. Other streptogramins (e.g. virginiamycin) had been used for prophylactic treatment (although not in Switzerland). This type of indication has been prohibited in veterinary medicine throughout Europe since the late 1990s.

One explanation for the high resistance levels in isolates from livestock could be cross-resistance of streptogramins, macrolides and lincosamides. Both macrolides and lincosamides are often used as medicated premixes in Swiss livestock.

Monitoring of antimicrobial resistance in humans in Switzerland shows that the proportion of clinical infections with vancomycin-resistant enterococci in the past years is at a low level (1.2 % in 2017) [4]. VRE remains a widely feared hospital pathogen. However, transmission to humans via animals or food of animal origin plays a negligible role due to its very low prevalence in animals.

Since 2014, enterococci isolates have been tested for resistance to newer antimicrobials such as daptomycin, teicoplanin and tigecycline, given their importance for human health. In 2016 and 2017, all enterococci isolates from broilers and from calves have been tested. Microbiological resistance to daptomycin was found in 16 *E. faecium* isolates from broilers (6.5 %) and two *E. faecium* isolates from slaughter calves (1.6 %). None of the enterococci isolates from broilers or slaughter calves showed resistance to teicoplanin.

Resistance to tigecycline was found in three *E. faecium* isolates from broilers (1.2 %), one *E. faecalis* isolate from calves and four *E. faecium* isolates from calves (3.1 %). Tigecycline is not used in veterinary medicine, but plays an important role in the treatment of human VRE infections. A co-selection of resistance to tigecycline and tetracycline cannot be excluded as they are chemically related to each other.

Figure 9. b: Trends in ampicillin, erythromycin, quinupristin/dalfopristin, tetracycline and vancomycin resistance in *Enterococcus faecium* from broilers between 2008 and 2016 (N = total number of tested isolates; values for 2015 interpolated [n/a]).

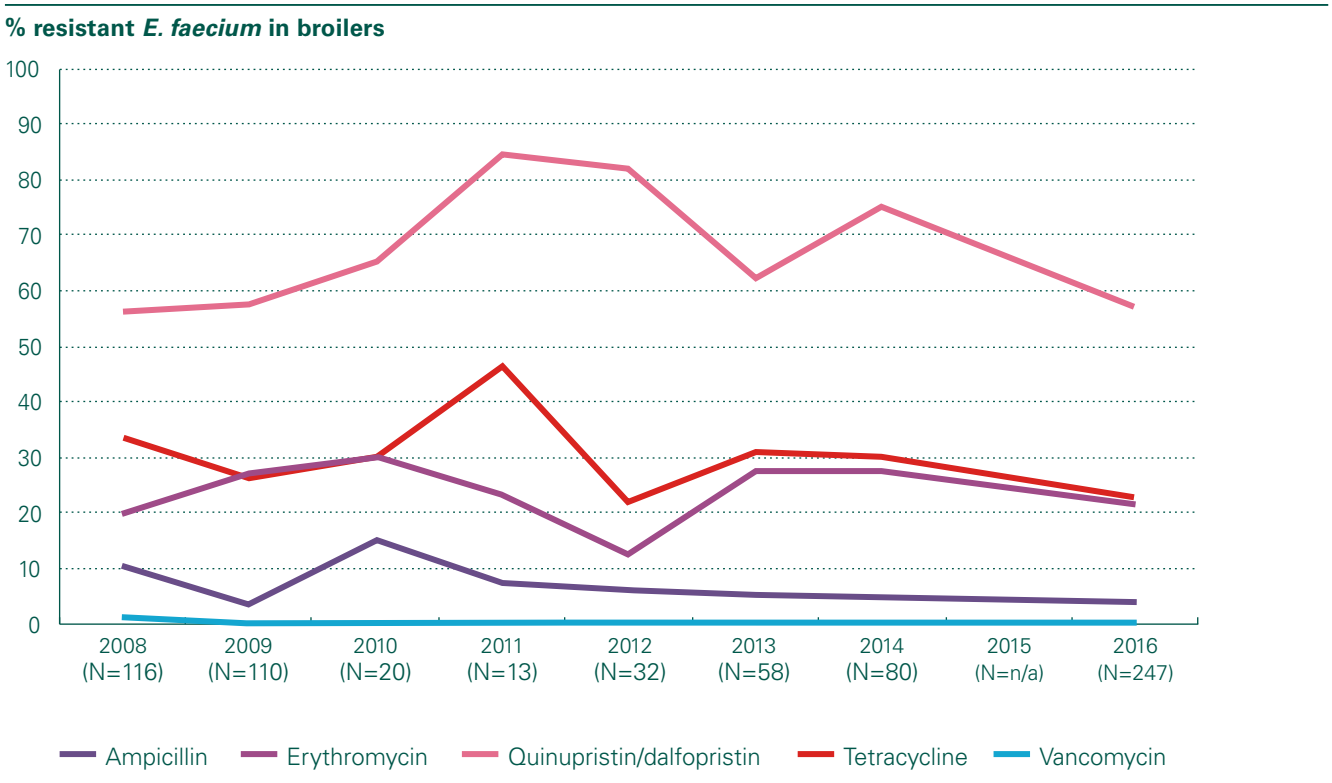


Figure 9. c: Trends in ampicillin, chloramphenicol, erythromycin, gentamicin, tetracycline and vancomycin resistance in *Enterococcus faecalis* from slaughter calves between 2008 and 2016 (N = total number of tested isolates; values for 2008, 2009, 2011, 2012, 2014 and 2016 interpolated [n/a]).

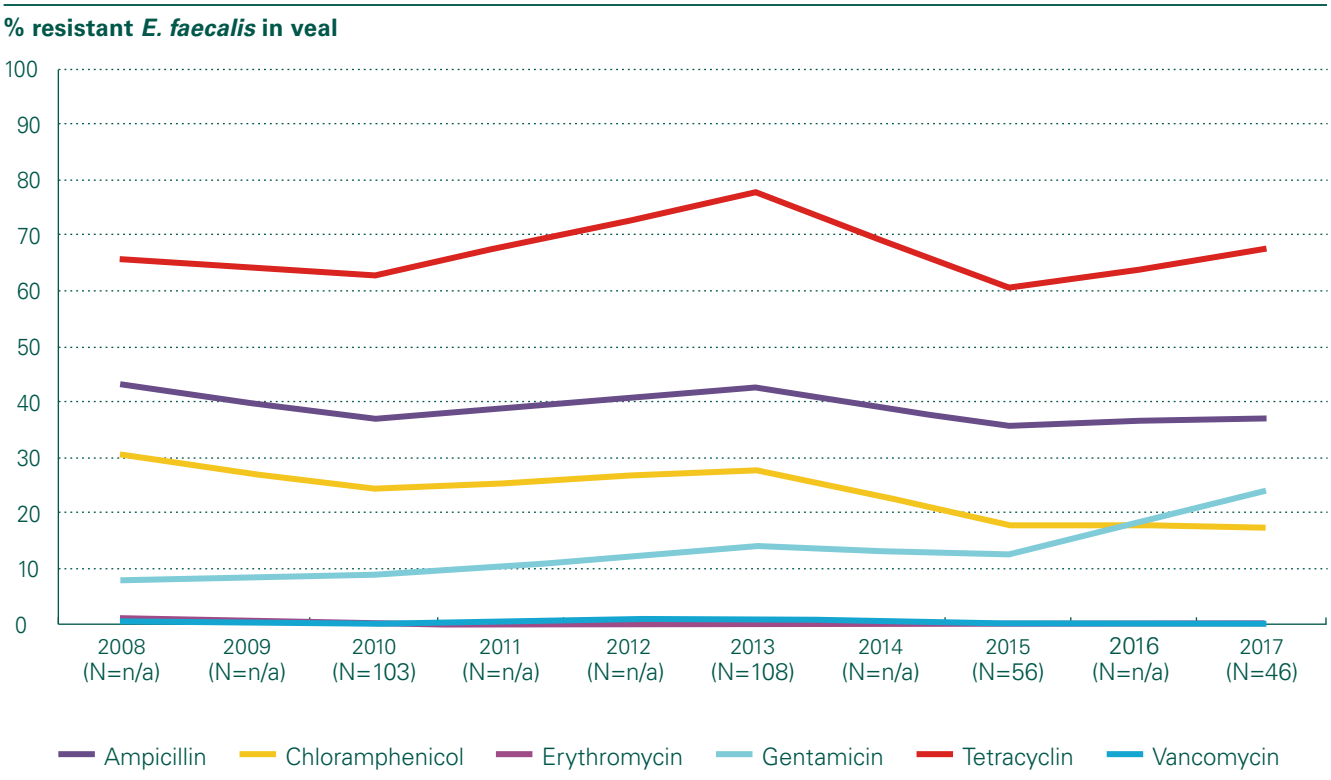


Figure 9. d: Trends in ampicillin, erythromycin, quinupristin/dalfopristin, tetracycline and vancomycin resistance in *Enterococcus faecium* from slaughter calves between 2008 and 2016 (N = total number of tested isolates; values for 2008, 2009, 2011, 2012, 2014 and 2016 interpolated [n/a]).

9.2 *Escherichia coli*

9.2.1 *Escherichia coli* from broilers

In 2016, a random sample of 196 broiler flocks was investigated at slaughter for the occurrence of *E. coli* in the framework of the antimicrobial-resistance-monitoring program using cecal samples (5 pooled cecal samples per flock). 190 *Escherichia coli* strains were isolated and subjected to susceptibility testing (Table 9. d).

Of the 190 tested *E. coli* isolates, 38.9% were susceptible to all tested antimicrobials, whereas 8.9% of the tested isolates were microbiologically resistant to more than four antimicrobials. None of the isolates were resistant to cefotaxime, ceftazidime or meropenem and hence, no presumptive ESBL/AmpC producers were detected. Microbiological resistance was most frequently detected for ampicillin, ciprofloxacin, nalidixic acid, sulfamethoxazole, tetracycline and trimethoprim, with resistance levels between 12.6% and 39.5%. These are slightly higher levels than in 2014. An exception is the resistance rate to tetracycline, which decreased compared to 2014 (Figure 9. e).

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I. 13) and multiresistance patterns are shown in Annex II (Table I. 42).

9.2.2 *Escherichia coli* from fattening pigs

In 2017, a random sample of 216 fattening pigs was investigated at slaughter for the occurrence of *E. coli* in the framework of the antimicrobial-resistance-monitoring program using cecal samples. *E. coli* was isolated from 197 samples which were subjected to susceptibility testing (Table 9. e).

Susceptibility to all tested antimicrobials was found in 55.8% of the isolates. High levels of resistance to sulfamethoxazole (36.0%) and tetracycline (20.8%) were found, as well as a moderate level of resistance to trimethoprim (15.2%) and ampicillin (14.2%). Resistance levels in 2017 were generally lower than those in previous years, especially for sulfamethoxazole and tetracycline (Figure 9. e). None of the isolates were resistant to cefotaxime, ceftazidime or meropenem and hence, no presumptive ESBL/AmpC producers were detected.

Table 9. d: Occurrence of resistance in *Escherichia coli* from broilers in 2016.

2016			***Escherichia coli (N=190)***
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	47	24.7	19.1–31.3
Azithromycin	0	0.0	0.0–2.0
Cefotaxime	0	0.0	0.0–2.0
Ceftazidime	0	0.0	0.0–2.0
Chlorampenicol	2	1.1	0.3–3.8
Ciprofloxacin	72	37.9	31.3–45.0
Colistin	0	0.0	0.0–2.0
Gentamicin	3	1.6	0.5–4.5
Meropenem	0	0.0	0.0–2.0
Nalidixic acid	75	39.5	32.8–46.6
Sulfamethoxazole	51	26.8	21.0–33.6
Tetracycline	25	13.2	9.1–18.7
Tigecycline	0	0.0	0.0–2.0
Trimethoprim	24	12.6	8.6–18.1
Sulfamethoxazole	50	25.0	19.5–31.4
Temocillin	0	0.0	0.0–1.9
Tetracycline	45	22.5	17.3–28.8
Tigecycline	0	0.0	0.0–1.9
Trimethoprim	24	12.0	8.2–17.2
Number of resistances			
None	74	38.9	32.3–46.0
1 antimicrobial	26	13.7	9.5–19.3
2 antimicrobials	45	23.7	18.2–30.2
3 antimicrobials	20	10.5	6.9–15.7
4 antimicrobials	8	4.2	2.1–8.1
>4 antimicrobials	17	8.9	5.7–13.9

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

Table 9. e: Occurrence of resistance in *Escherichia coli* from fattening pigs in 2017.

2017			*Escherichia coli (N=197)*
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	28	14.2	10.0–19.8
Azithromycin	1	0.5	0.1–2.8
Cefotaxime	0	0.0	0.0–1.9
Ceftazidime	0	0.0	0.0–1.9
Chlorampenicol	10	5.1	2.8–9.1
Ciprofloxacin	5	2.5	1.1–5.8
Colistin	0	0.0	0.0–1.9
Gentamicin	6	3.0	1.4–6.5
Meropenem	0	0.0	0.0–1.9
Nalidixic acid	4	2.0	0.8–5.1
Sulfamethoxazole	71	36.0	29.7–43.0
Tetracycline	41	20.8	15.7–27.0
Tigecycline	0	0.0	0.0–1.9
Trimethoprim	30	15.2	10.9–20.9
Sulfamethoxazole	76	41.8	34.8–49.0
Temocillin	0	0.0	0.0–2.1
Tetracycline	54	29.7	23.5–36.7
Tigecycline	0	0.0	0.0–2.1
Trimethoprim	40	22.0	16.6–28.5
Number of resistances			
None	110	55.8	48.9–62.6
1 antimicrobial	37	18.8	13.9–24.8
2 antimicrobials	17	8.6	5.5–13.4
3 antimicrobials	16	8.1	5.1–12.8
4 antimicrobials	11	5.6	3.1–9.7
>4 antimicrobials	6	3.0	1.4–6.5

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.14) and multiresistance patterns are shown in Annex II (Table I.46).

9.2.3 *Escherichia coli* from slaughter calves

In 2017, a random sample of 204 calves was investigated at slaughter for the occurrence of *E. coli* in the framework of the antimicrobial-resistance-monitoring program using cecal samples. *E. coli* was isolated from 194 samples which were subjected to susceptibility testing (Table 9. f).

Of the isolates, 47.9% were susceptible to all antimicrobials tested. High levels of resistance to ampicillin (38.7%), sulfamethoxazole (46.9%) and tetracycline (41.2%) were found, and a moderate resistance level to trimethoprim (19.1%). None of the isolates were resistant to cefotaxime, ceftazidime or meropenem and hence, no presumptive ESBL/AmpC producers were detected.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.15) and multiresistance patterns are shown in Annex II (Table I.44).

9.2.4 Discussion

In the context of monitoring antimicrobial resistance, *E. coli* are indicator bacteria for the occurrence of resistances in Gram-negative intestinal bacteria from livestock. They constitute a reservoir of resistance genes that can be transferred horizontally to other bacteria including zoonotic pathogens.

From 2008 to 2012, the prevalence of *E. coli* from broilers in Switzerland exhibiting resistance to ciprofloxacin increased significantly (Figure 9. e). In the following years, the resistance rate decreased markedly from 46% in 2012 to 32% in 2014, but increased again to 37.9% in 2016. The rates of resistance to ampicillin and sulfamethoxazole have remained rather stable since the last assessment in 2014, while the resistance rate of tetracycline has shown a remarkable decrease of 41%.

Resistance levels of *E. coli* from fattening pigs and slaughter calves showed opposite trends from 2015 to 2017. In pigs, resistance rates generally decreased, especially for sulfamethoxazole from 41.8% in 2015 to 36.0% in 2017 and for tetracycline from 29.7% in 2015 to 20.8% in 2017 (Fig-

Table 9. f: Occurrence of resistance in *Escherichia coli* from slaughter calves in 2017.

2017			*Escherichia coli (N=194)*
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	75	38.7	32.1–45.7
Azithromycin	0	0.0	0.0–1.9
Cefotaxime	0	0.0	0.0–1.9
Ceftazidime	0	0.0	0.0–1.9
Chlorampenicol	19	9.8	6.4–14.8
Ciprofloxacin	7	3.6	1.8–7.3
Colistin	0	0.0	0.0–1.9
Gentamicin	9	4.6	2.5–8.6
Meropenem	0	0.0	0.0–1.9
Nalidixic acid	7	3.6	1.8–7.3
Sulfamethoxazole	91	46.9	40.0–53.9
Tetracycline	80	41.2	34.5–48.3
Tigecycline	0	0.0	0.0–1.9
Trimethoprim	37	19.1	14.2–25.2
Sulfamethoxazole	79	41.6	34.8–48.7
Temocillin	0	0.0	0.0–2.0
Tetracycline	77	40.5	33.8–47.6
Tigecycline	0	0.0	0.0–2.0
Trimethoprim	30	15.8	11.3–21.6
Number of resistances			
None	93	47.9	41.0–54.9
1 antimicrobial	10	5.2	2.8–9.2
2 antimicrobials	21	10.8	7.2–16.0
3 antimicrobials	32	16.5	11.9–22.4
4 antimicrobials	24	12.4	8.5–17.7
>4 antimicrobials	14	7.2	4.3–11.7

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

ure 9. f). Resistance rates of *E. coli* from slaughter calves increased slightly from 2015 to 2017, except for ciprofloxacin which decreased from 6.8% in 2015 to 3.6% in 2017 (Figure 9. g).

Microbiological resistance is widespread in *E. coli* from livestock in Switzerland. Moderate to high resistance rates to ampicillin, sulfamethoxazole and tetracycline have been found in isolates from all animals. In broilers additionally, the resistance rate to ciprofloxacin is high. Sulfonamides, tetracyclines and penicillins are the most widely used antimicrobials in pigs and calves in Switzerland. In broilers, mostly fluoroquinolones and penicillins are used. This suggests that the resistance situation found in non-pathogenic *E. coli* from the gastrointestinal tract in livestock actually reflects the selective pressure bacteria are exposed to as a result of the use of antimicrobials during livestock production.

Although the application of chloramphenicol in livestock was prohibited in 2001, resistance was detected in broilers (1.1%), fattening pigs (5.1%) and slaughter calves (9.8%). This could potentially be due to co-selection with other antimicrobials. Additionally, cross-resistance between chloramphenicol and florfenicol has been described [5]. Florfenicol is often used in pigs and cattle to treat respiratory tract infections. However, resistance rates for chloramphenicol have shown a decreasing trend or have remained at a low level over the last years.

9.3 ESBL/pAmpC-producing *Escherichia coli*

In recent years, broad-spectrum beta-lactamase-producing intestinal bacteria have increasingly been detected among livestock in various countries. Beta-lactamases are bacterial enzymes that enable bacteria to inactivate beta-lactam antimicrobials by breaking their beta-lactam ring. ESBL-producing intestinal bacteria are resistant to most beta-lactams, especially aminopenicillins (e.g. ampicillin), cephalosporins (including third and fourth generation cephalosporins) and monobactams. Plasmid-mediated AmpC beta-lactamases mediate resistance to penicillins, second- and third-generation cephalosporins (including beta-lactamase inhibitors such as clavulanic acid) and cephamycins. However, they do not usually mediate resistance to fourth generation cephalosporins.

Figure 9. e: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from broilers between 2008 and 2016 (N = total number of tested isolates, values for 2015 interpolated [n/a]).

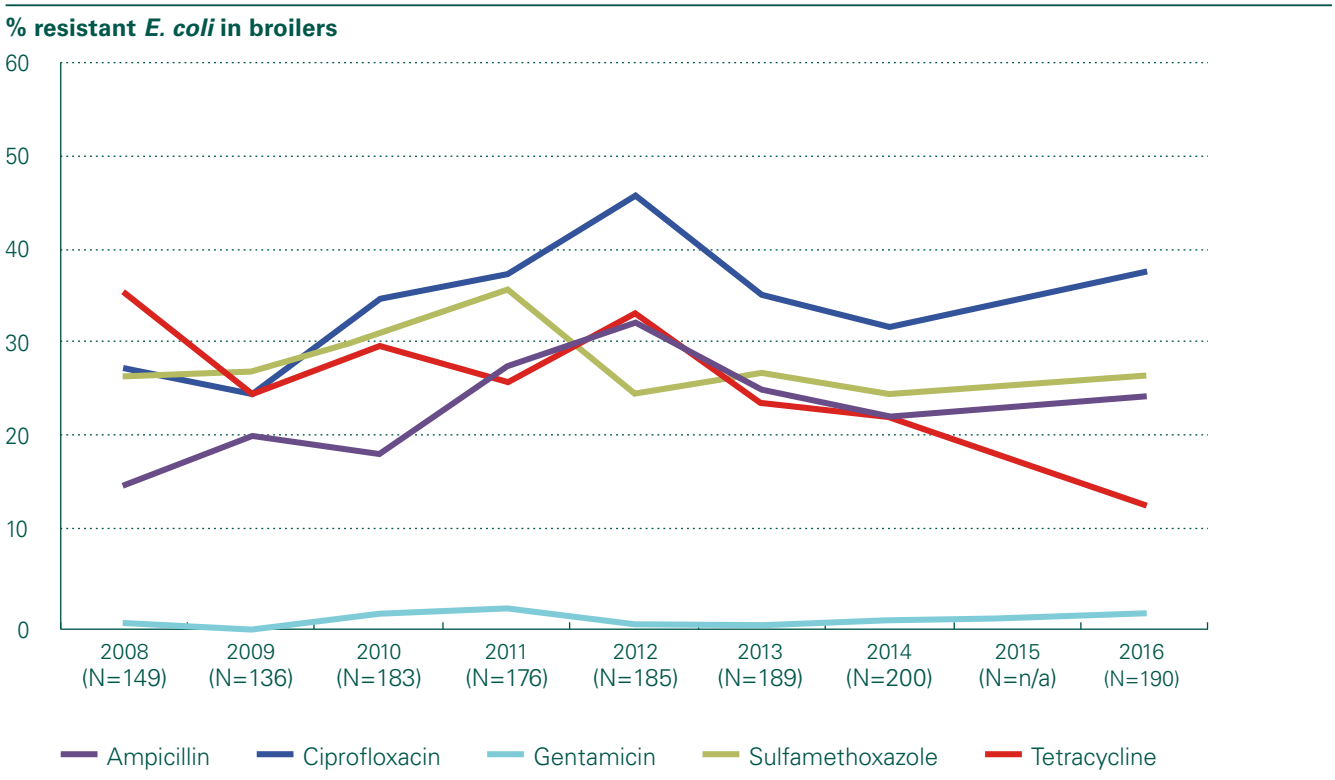
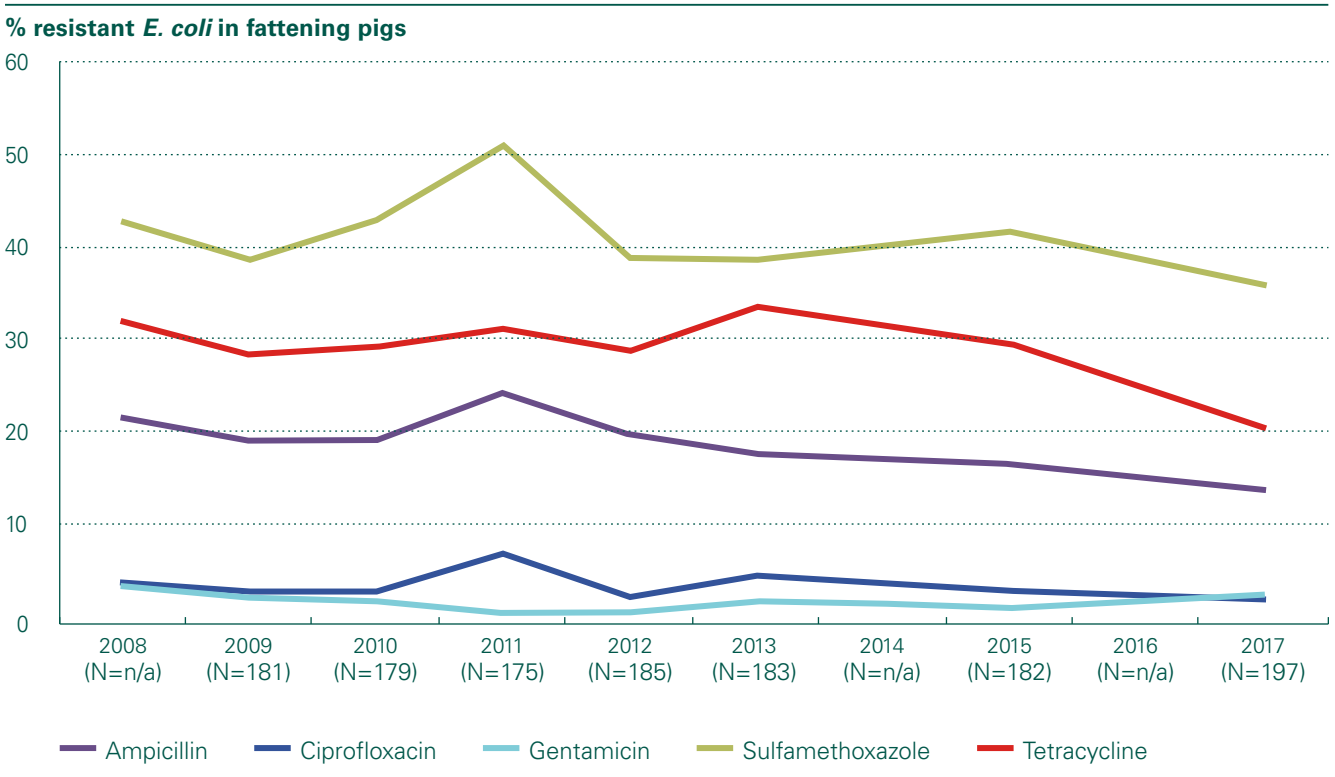


Figure 9. f: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from fattening pigs between 2008 and 2017 (N = total number of tested isolates, values for 2008, 2014 and 2016 interpolated [n/a]).



Both, ESBL and pAmpC are produced by intestinal bacteria. Most of them are commensals and do not induce any illness in the host. These bacteria constitute a reservoir for resistance genes that can be transmitted to pathogens by means of mobile genetic elements such as plasmids, integrons and transposons. However, resistance genes may also occur in zoonotic pathogens (e.g. *Salmonella* or enterohemorrhagic *E. coli*). Although diseases caused by such pathogens usually do not require antimicrobial treatment, the disease may take a severe course in vulnerable patients such as young children, elderly people or patients with a weak immune system, rendering antimicrobial treatment necessary. Pathogenic bacteria harboring an ESBL or pAmpC resistance gene are difficult to treat, thus prolonging or worsening disease course. The occurrence of such bacteria in the context of severe infections of hospitalized humans in Switzerland has increased from 0.9% in 2004 to 10.3% in 2017 [4].

As a consequence, *E. coli* isolates from animals are also used to gauge the spread of bacteria that produce ESBL or pAmpC.

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

In 2016, a random sample of 307 broiler flocks was investigated at slaughter for the occurrence of ESBL/pAmpC-producing *E. coli* using cecal samples (5 pooled cecal samples per flock). By applying selective enrichment methods, 161 isolates of presumptive ESBL/pAmpC-producing *E. coli* were isolated. This corresponds to a flock prevalence of 52.4%. 160 isolates were then subjected to susceptibility testing (Table 9. g).

Apart from resistance to beta-lactam antimicrobials, recorded resistance levels to sulfonamides (52.5%), ciprofloxacin (48.8%), nalidixic acid (45.6%), tetracycline (33.1%) and trimethoprim (25.0%) were detected. 83.1% of the isolates were resistant to cefepime. Cefepime is a fourth-generation cephalosporin which is more stable to some bacterial beta-lactamases. Thus, observed resistance to cefepime serves as an indicator for the presence of ESBL producers. 53.1% of the isolates were microbiologically resistant to cefoxitin, which is indicative of the presence of AmpC-beta-lactamases. 3.8% of the isolates showed phenotypically reduced susceptibility to ertapenem, whereas microbiological resistances to imipenem, meropenem, azithromycin, colistin, temocillin and tigecycline were not detected.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.16 and Table I.17) and multiresistance patterns are shown in Annex II (Table I. 43).

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

In 2017, 52 ESBL/pAmpC-producing *E. coli* strains were isolated with selective enrichment methods from a random

Figure 9. g: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from slaughter calves between 2008 and 2017 (N = total number of tested isolates, values for 2008, 2009, 2011, 2012, 2014 and 2016 interpolated [n/a]).

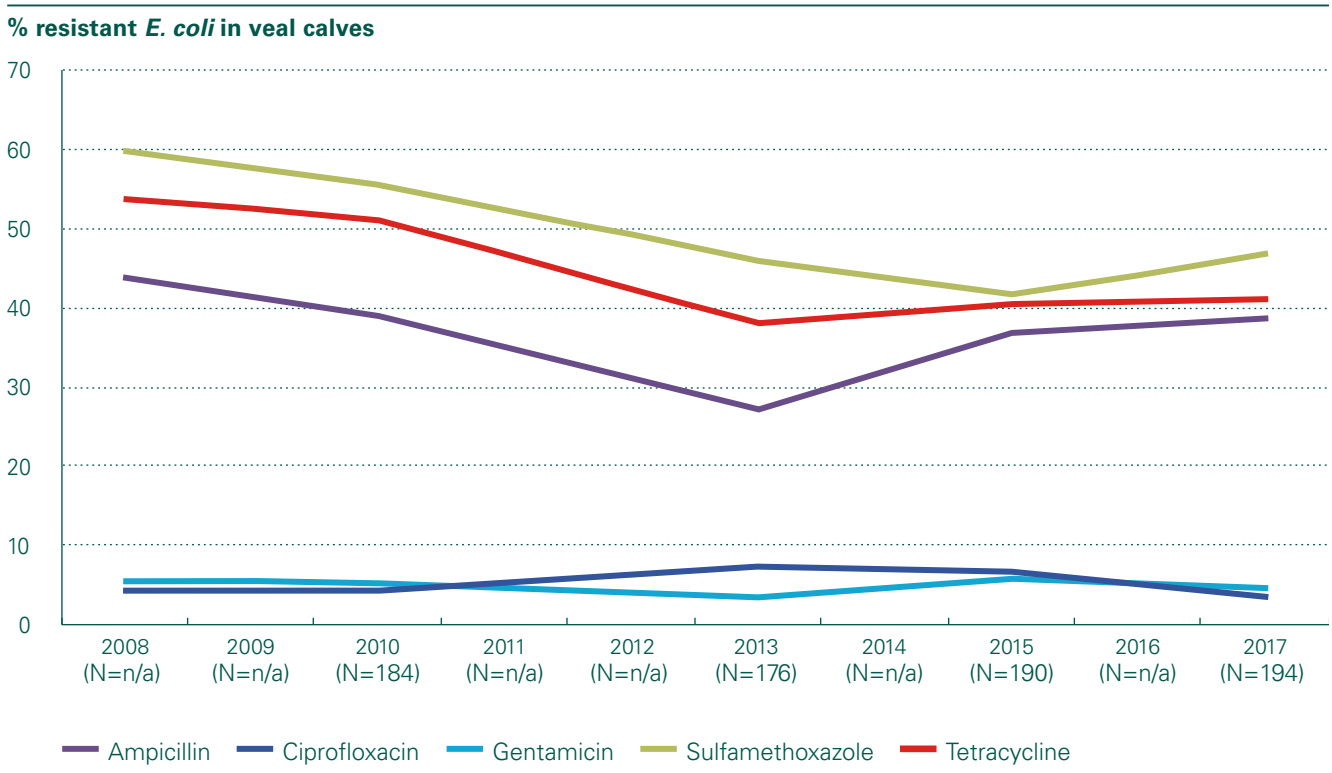


Table 9. g: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from broilers in 2016.

2016	ESBL/pAmpC-producing *Escherichia coli* (N=160)		
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	157	98.1	94.6–99.4
Azithromycin	0	0.0	0.0–2.3
Cefepime	133	83.1	76.6–88.1
Cefotaxime*	151	94.4	89.7–97.0
Cefoxitin	85	53.1	45.4–60.7
Ceftazidime*	140	87.5	81.5–91.8
Chloramphenicol	13	8.1	4.8–13.4
Ciprofloxacin	78	48.8	41.1–56.4
Colistin	0	0.0	0.0–2.3
Ertapenem	6	3.8	1.7–7.9
Gentamicin	9	5.6	3.0–10.3
Imipenem	0	0.0	0.0–2.3
Meropenem*	0	0.0	0.0–2.3
Nalidixic acid	73	45.6	38.1–53.4
Sulfamethoxazole	84	52.5	44.8–60.1
Temocillin	0	0.0	0.0–2.3
Tetracycline	53	33.1	26.3–40.7
Tigecycline	0	0.0	0.0–2.3
Trimethoprim	40	25.0	18.9–32.2
Number of resistances	**n**	**%**	**95% CI**
None	2	1.3	0.30–4.4
1 antimicrobial	2	1.3	0.30–4.4
2 antimicrobials	2	1.3	0.30–4.4
3 antimicrobials	46	28.7	22.30–36.2
4 antimicrobials	25	15.6	10.80–22.0
>4 antimicrobials	83	51.9	44.20–59.5

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)
* Result of EUVSEC2 plate

sample of 296 cecal samples from fattening pigs. This corresponds to a prevalence of 17.6%. All isolates were subjected to susceptibility testing (Table 9. h).

Apart from the resistance to beta-lactam antimicrobials, high to very high microbiological resistance levels to tetracycline (61.5%), sulfonamides (55.8%), ciprofloxacin (36.5%), nalidixic acid (32.7%), trimethoprim (25.0%) and gentamicin (21.2%) were found. The portion of isolates resistant to cefepime was 71.2%, and 34.6% of the isolates were microbiologically resistant to cefoxitin. A moderate proportion of isolates showed phenotypic resistance to chloramphenicol (9.6%), whereas the levels of resistance to azithromycin (7.7%) were low. Microbiological resistances to colistin, ertapenem, meropenem, imipenem, temocillin and tigecycline were not detected.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.18 and Table I.19) and multiresistance patterns are shown in Annex II (Table I.47).

9.3.3 ESBL/pAmpC-producing *Escherichia coli* from slaughter calves

In 2017, 101 ESBL/pAmpC-producing *E. coli* strains were isolated with selective enrichment methods from a random sample of 304 cecal samples from slaughter calves. This corresponds to a prevalence of 33.2%. All isolates were subjected to susceptibility testing (Table 9. i).

Apart from the resistance to beta-lactam antimicrobials, high to extremely high microbiological resistance levels to tetracycline (86.1%), sulfonamides (82.2%), trimethoprim (51.5%), ciprofloxacin (48.5%), gentamicin (35.6%), nalidixic acid (30.7%) and chloramphenicol (25.7%) were found. The portion of isolates resistant to cefepime was 61.4%, and 46.5% of the isolates were microbiologically resistant to cefoxitin. Levels of resistance for azithromycin (6.9%) were low. Microbiological resistances to colistin, ertapenem, imipenem, meropenem, temocillin and tigecycline were not detected.

Table 9. h: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from fattening pigs in 2017.

2017	ESBL/pAmpC-producing *Escherichia coli* (N=54)		
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	52	100.0	93.1–100.0
Azithromycin	4	7.7	3.0–18.2
Cefepime	37	71.2	57.7–81.7
Cefotaxime*	51	98.1	89.9–99.7
Cefoxitin	18	34.6	23.2–48.2
Ceftazidime*	51	98.1	89.9–99.7
Chloramphenicol	5	9.6	4.2–20.6
Ciprofloxacin	19	36.5	24.8–50.1
Colistin	0	0.0	0.0–6.9
Ertapenem	0	0.0	0.0–6.9
Gentamicin	11	21.2	12.2–34.0
Imipenem	0	0.0	0.0–6.9
Meropenem*	0	0.0	0.0–6.9
Nalidixic acid	17	32.7	21.5–46.2
Sulfamethoxazole	29	55.8	42.3–68.4
Temocillin	0	0.0	0.0–6.9
Tetracycline	32	61.5	48.0–73.5
Tigecycline	0	0.0	0.0–6.9
Trimethoprim	13	25.0	15.2–38.2
Number of resistances			
None	0	0.0	0.0–6.9
1 antimicrobial	0	0.0	0.0–6.9
2 antimicrobials	0	0.0	0.0–6.9
3 antimicrobials	12	23.1	13.7–36.1
4 antimicrobials	8	15.4	8.0–27.5
>4 antimicrobials	32	61.5	48.0–73.5

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)
* Result of EUVSEC2 plate

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I.20 and Table I.21), and multiresistance patterns are shown in Annex II (Table I.45).

9.3.4 Discussion

Using selective enrichment methods, ESBL/pAmpC-producing *E. coli* were found in 52.4% of broiler flocks, 17.6% of fattening pigs and 33.2% of slaughter calves. The prevalence of ESBL/pAmpC-producing *E. coli* has clearly increased for broilers (2014: 41.8%), and decreased for fattening pigs (2015: 25.7%) and slaughter calves (2015: 37.6%). Using the selective method, comparatively lower rates of ESBL/AmpC-producing *E. coli* were found in Switzerland than in other European countries.

Besides microbiological resistance to beta-lactam antimicrobials, the isolates showed high to extremely high rates of resistance to (fluoro-)quinolones, sulfonamides, trimethoprim and tetracycline in all three animal species. Isolates from slaughter calves and fattening pigs presented high rates of gentamicin resistance; isolates from all three animal species showed resistance to chloramphenicol, whereby only isolates from calves exhibit high resistance rates. Low levels of resistance to azithromycin were detected in isolates from fattening pigs and slaughter calves. None of the isolates from all three animal species were resistant to colistin, imipenem, meropenem, temocillin or tigecycline. Low levels of decreased susceptibility to ertapenem were found in broilers only.

An increasing spread of ESBL/pAmpC-producing *E. coli* among food-producing animals has been observed in Europe over the past years, especially among broilers. The prevalence in broiler flocks is influenced by different factors. The prevalence of resistance among individual birds increases towards the end of the fattening period. Other influencing factors include flock management, hygiene or use of antimicrobials, especially beta-lactams [6]. ESBL/pAmpC-producing *E. coli* are transmitted via eggshell contamination along the production chain from grandparents and par-

Table 9. i: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from slaughter calves in 2017.

2017	ESBL/pAmpC-producing *Escherichia coli* (N=102)		
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	101	100.0	96.3–100.0
Azithromycin	7	6.9	3.4–13.6
Cefepime	62	61.4	51.6–70.3
Cefotaxime*	100	99.0	94.6–99.8
Cefoxitin	47	46.5	37.1–56.2
Ceftazidime*	93	92.1	85.1 – 95.9
Chloramphenicol	26	25.7	18.2 – 35.0
Ciprofloxacin	49	48.5	39.0 – 58.1
Colistin	0	0.0	0.0 – 3.7
Ertapenem	0	0.0	0.0 – 3.7
Gentamicin	36	35.6	27.0 – 45.4
Imipenem	0	0.0	0.0 – 3.7
Meropenem*	0	0.0	0.0 – 3.7
Nalidixic acid	31	30.7	22.5 – 40.3
Sulfamethoxazole	83	82.2	73.6 – 88.4
Temocillin	0	0.0	0.0 – 3.7
Tetracycline	87	86.1	78.1 – 91.6
Tigecycline	0	0.0	0.0 – 3.7
Trimethoprim	52	51.5	41.9 – 61.0
Number of resistances			
None	0	0.0	0.0–3.7
1 antimicrobial	0	0.0	0.0–3.7
2 antimicrobials	3	3.0	1.0–8.4
3 antimicrobials	7	6.9	3.4–13.6
4 antimicrobials	5	5.0	2.1–11.1
>4 antimicrobials	86	85.1	76.9–90.8

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)
* Result of EUVSEC2 plate

ents to broilers [7], [8]. Once present in a broiler farm, they spread horizontally from one flock to another. Specific bacteria can also be found in the environment of farms where they are able to survive for extended periods of time, and hence are a potential source for further transmission [9]. Another study showed that a horizontal transfer of bacteria from animals to their owners is possible [10].

Until recently, ESBL/pAmpC-producing bacteria were mainly a problem in hospital settings. Lately, they have increasingly been found in the general population as well. Here, they either occur harmlessly in the guts of healthy individuals or cause diseases such as urinary tract infections. The incidence of these types of resistance has increased in Switzerland in recent years, both in hospitals and in outpatients [11].

A study carried out in Switzerland with healthy staff of meat-processing plants found ESBL-producing intestinal bacteria in 5.8% of those tested [12]. Another study, which tested 291 fecal swab samples from patients of GP practices, found ESBL-producing bacteria in 5.2% of the samples [13]. Resistance genes of ESBL/pAmpC-producing *E. coli* display a large heterogeneity. The comparison of different genes and resistance patterns from isolates of food-producing animals, raw meat and humans shows that the majority of isolates differ considerably [14], [15], [16]. Food-producing animals and especially chicken meat are seen as a relevant reservoir for ESBL/pAmpC-producing *E. coli*. Nevertheless, the vast majority of ESBL/pAmpC-producing *E. coli* colonizing humans cannot be exclusively attributed to food-producing animals or food thereof.

9.4 Methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus are skin and mucous membrane colonizing bacteria of humans and animals [17]. Usually, they do not induce any disease. However, in some cases, *S. aureus*

Table 9. j: Occurrence of resistance in MRSA from fattening pigs in 2017.

2017	Methicillin-resistant *Staphylococcus aureus* (N=131)		
Antimicrobials	**n**	**%**	**95% CI**
Cefoxitin	131	100.0	97.2–100.0
Chloramphenicol	2	1.5	0.4–5.4
Ciprofloxacin	15	11.5	7.1–18.0
Clindamycin	67	51.1	42.7–59.5
Erythromycin	59	45.0	36.8–53.6
Fusidic acid	4	3.1	1.2–7.6
Gentamicin	15	11.5	7.1–18.0
Kanamycin	16	12.2	7.7–18.9
Linezolid	0	0.0	0.0–2.8
Mupirocin	3	2.3	0.8–6.5
Penicillin	131	100.0	97.2–100.0
Quinupristin/Dalfopristin	66	50.4	41.9–58.8
Rifampicin	3	2.3	0.8–6.5
Streptomycin	67	51.1	42.7–59.5
Sulfamethoxazole	8	6.1	3.1–11.6
Tetracycline	131	100.0	97.2–100.0
Tiamulin	66	50.4	41.9–58.8
Trimethoprim	68	51.9	43.4–60.3
Vancomycin	0	0.0	0.0–2.8
Number of resistances			
None	0	0.0	0.0–2.8
1 antimicrobial	0	0.0	0.0–2.8
2 antimicrobials	0	0.0	0.0–2.8
3 antimicrobials	24	18.3	12.6–25.8
4 antimicrobials	25	19.1	13.3–26.7
>4 antimicrobials	82	62.6	54.1–70.4

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

bacteria can infect wounds and airways. Normally, these infections can be treated without any complications using antimicrobials. In contrast, methicillin-resistant *S. aureus* (MRSA) infections are difficult to treat. These bacteria are resistant to all beta-lactams (penicillins and cephalosporins) and some of them are resistant to additional classes of antimicrobials as well, leading to minimal antimicrobial treatment options and severe disease.

This chapter includes antimicrobial resistance of MRSA strains in fattening pigs and slaughter calves investigated in 2017.

9.4.1 MRSA in livestock animals

9.4.1.1 Fattening pigs

In 2017, nasal swabs from fattening pigs at slaughter were used to isolate strains of MRSA, applying selective enrichment methods. Obtained isolates were subjected to *spa* typing and susceptibility testing.

In 2017, 131 isolates were obtained from 298 nasal swabs, corresponding to a prevalence of 44.0%. Sixty-three isolates belonged to *spa* type t034, 61 to *spa* type t011, 3 to *spa* type t1451, 2 to *spa* type t899 and 1 isolate each belonged to *spa* type t2330 and t2876, respectively.

All isolates were microbiologically resistant to beta-lactam antibiotics (cefoxitin and penicillin) and tetracycline (Table 9. j). High to extremely high resistance rates were found for trimethoprim (51.9%), streptomycin (51.1%), macrolides/lincosamides (clindamycin 51.1%, erythromycin 45.0%), tiamulin (50.4%), and quinupristin/dalfopristin (50.4%). Low to moderate resistance rates were found for kanamycin (12.2%), ciprofloxacin (11.5%), gentamicin (11.5%), sulfamethoxazole (6.1%), fusidic acid (3.1%), rifampicin (2.3%), mupirocin (2.3%) and chloramphenicol. (1.5%). All isolates were susceptible to vancomycin and linezolid, two important antimicrobials for treatment of human patients.

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I. 22) and multiresistance patterns are shown in Annex II (Table I. 49.)

9.4.1.2 Slaughter calves

In 2017, 297 nasal swabs were collected from slaughter calves. By applying selective enrichment methods, 24 MRSA isolates were obtained from this random sample. Thus, the prevalence was 8.1 %. 14 isolates belonged to *spa* type t011, 7 to *spa* type t034, 1 to *spa* type t127 and 2 to *spa* type t17339.

Susceptibility testing of MRSA isolates from slaughter calves revealed that all isolates were microbiologically resistant to beta-lactames (cefoxitin and penicillin) and tetracycline. Very high to extremely high levels of microbiological resistance were found for macrolides/lincosamides (erythromycin/clindamycin, both 70.8%) and streptomycin (62.5%). The resistance levels for ciprofloxacin, gentamicin, kanamycin, quinupristin/dalfopristin, tiamulin and trimethoprim were high (20–50%). Resistance to chloramphenicol, fusidic acid, linezolid, mupirocin, rifampicin, sulfamethoxazole and vancomycin was not detected (Table 9. k).

The distribution of the minimum inhibitory concentrations (MICs) is shown in Annex II (Table I. 23) and multiresistance patterns are shown in Annex II (Table I. 48).

9.4.3 Discussion

In Switzerland, the occurrence of MRSA in fattening pigs at slaughter increased continuously and significantly from 2009 to 2017. In 2009, the prevalence was assessed at 2.0% [18], in 2011 at 5.6% [19], in 2013 at 20.8%, in 2014 at 26.5% and in 2015 at 25.7%. Since the last assessment in 2015, the prevalence of MRSA among fattening pigs increased by 71.2% to 44.0% in 2017.

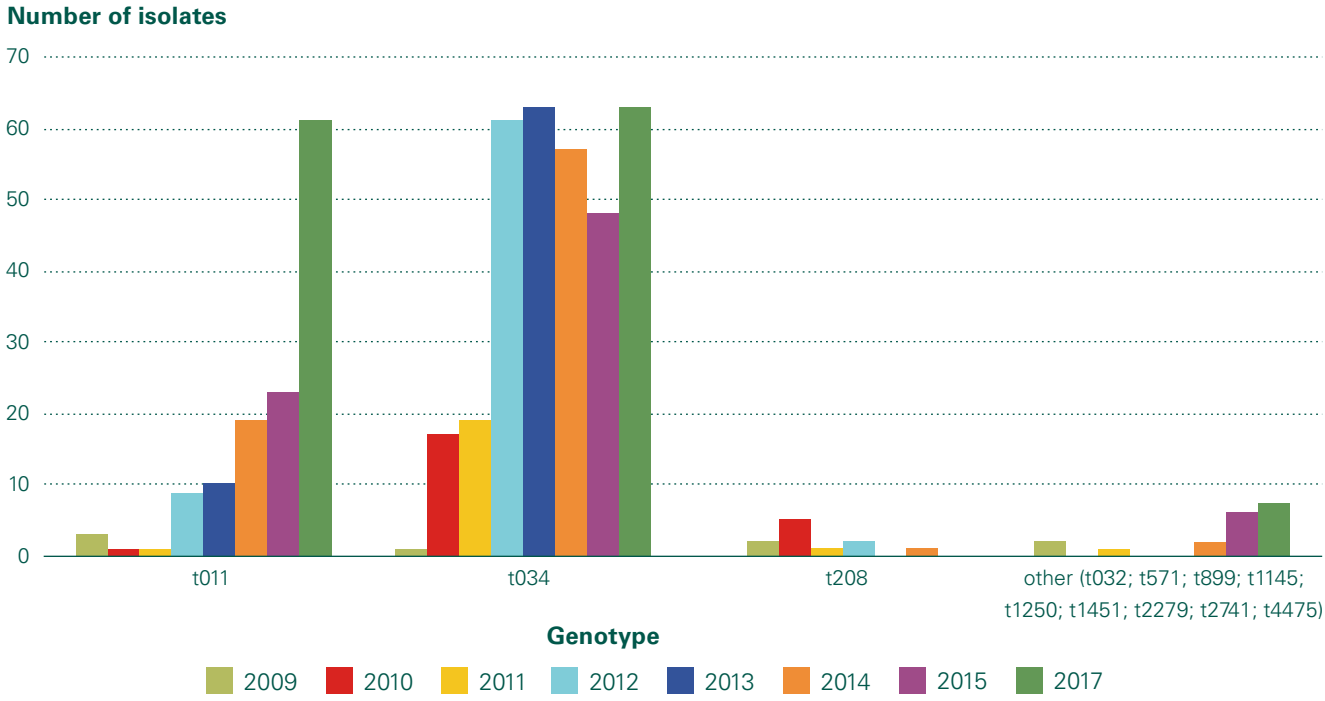
The detected *spa* types showed that until 2015 the most prevalent *spa* type in Switzerland's population of slaughtered pigs was t034 MRSA and to a lesser extent also *spa* type t011 (Figure 9. l). Interestingly, in 2017, *spa* type t011 became nearly as prevalent as *spa* type t034, and the extreme increase of MRSA prevalence is predominantly caused by this specific genotype. Both the t011 and the t034 genotypes are part of the clonal complex CC 398, which belongs to the

Table 9. k: Occurrence of resistance in MRSA from slaughter calves in 2017.

2017	Methicillin-resistant *Staphylococcus aureus* (N=24)		
Antimicrobials	**n**	**%**	**95% CI**
Cefoxitin	24	100.0	86.2–100.0
Chloramphenicol	0	0.0	0.0–13.8
Ciprofloxacin	10	41.7	24.5–61.2
Clindamycin	17	70.8	50.8–85.1
Erythromycin	17	70.8	50.8–85.1
Fusidic acid	0	0.0	0.0–13.8
Gentamicin	5	20.8	9.2–40.5
Kanamycin	6	25.0	12.0–44.9
Linezolid	0	0.0	0.0–13.8
Mupirocin	0	0.0	0.0–13.8
Penicillin	24	100.0	86.2–100.0
Quinupristin/Dalfopristin	9	37.5	21.2–57.3
Rifampicin	0	0.0	0.0–13.8
Streptomycin	15	62.5	42.7–78.8
Sulfamethoxazole	0	0.0	0.0–13.8
Tetracycline	24	100.0	86.2–100.0
Tiamulin	9	37.5	21.2–57.3
Trimethoprim	12	50.0	31.4–68.6
Vancomycin	0	0.0	0.0–13.8
Number of resistances			
None	0	0.0	0.0–13.8
1 antimicrobial	0	0.0	0.0–13.8
2 antimicrobials	0	0.0	0.0–13.8
3 antimicrobials	0	0.0	0.0–13.8
4 antimicrobials	2	8.3	2.3–25.8
>4 antimicrobials	22	91.7	74.2–97.7

Number of resistant strains (n) and prevalence of resistance (%) with 95% confidence interval (95% CI)

Figure 9. h: Number of MRSA genotypes from fattening pigs between 2009 and 2017.



livestock-associated MRSA (LA-MRSA). MRSA CC398 is mostly found in fattening pigs, cattle and poultry, but can be transmitted between animals and humans. Not only in Switzerland but also in other European countries, most of the MRSA *spa* types detected in livestock were associated with LA-MRSA CC398 [20].

In 2017, all MRSA isolates obtained from fattening pigs at slaughter showed microbiological resistance to beta-lactams (cefoxitin and penicillin) and tetracycline. Very high resistance rates were detected for clindamycin (51.1 %), erythromycin (45.0 %), quinupristin/dalfopristin (50.4 %), streptomycin (51.1 %), tiamulin (50.4 %) and trimethoprim (51.9 %). All MRSA were susceptible to linezolid and vancomycin. Nearly all MRSA *spa* type t034 (98.4 %) showed resistance to more than four antimicrobials, whereas only 24.6 % of MRSA *spa* type t011 exhibited broad-spectrum resistance to more than four antimicrobials. However, the latter include therapeutically relevant antimicrobials such as gentamicin and kanamycin. In 2017, 34 isolates were resistant to nine antimicrobials. These findings underline the multiresistant nature of MRSA.

Colonization of fattening pigs with MRSA may occur during transportation to the slaughterhouse or at slaughter itself (cross-contamination). Due to this fact, the validity of data recorded at the stage of slaughter may be limited with regard to showing the change of MRSA occurrence in fattening pigs [21].

Overall data for 2017 illustrate the fact that the occurrence of MRSA in fattening pigs needs to be further investigated. Bangerter et al. [21] have conducted comprehensive studies of the individual colonization dynamics of MRSA throughout Swiss pig production. Humans in close contact with livestock are at higher risk of being carriers of livestock-associated MRSA [22]. Although colonization of healthy humans with MRSA usually does not induce disease, MRSA introduced in hospitals may cause infections that are almost impossible to treat. At least, the occurrence of MRSA in the context of severe infections in hospitalized humans (septicemia) has decreased significantly in the past years, with a prevalence of 12.8 % in 2004, as opposed to 4.1 % in 2017 [4].

The prevalence of MRSA in slaughter calves has increased from 2.1 % in 2010 to 8.1 % in 2017. These data indicate an increasing trend as well. Therefore, the occurrence of MRSA in slaughter calves needs to be further observed.

A comparative analysis of current molecular findings from Swiss human, animal and meat MRSA isolates is described in Chapter 12.

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Textbox

Mcr-1-Based Colistin Resistance: Filling Knowledge Gaps in View of the Spread of Plasmid-Mediated Colistin Resistance in Switzerland

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In the past, the use of colistin has been mostly limited to veterinary medicine due to its rather severe side effects. But given the increase in multiresistant Gram-negative bacteria, the WHO recently relabeled colistin as a "critically important antibiotic." The so far identified mechanisms of resistance were chromosomally encoded, and included modifications of the outer membrane components, mainly through the covalent addition of either phosphoethanolamine or 4-deoxy-aminoarabinose to the lipopolysaccharide (LPS), leading to a more positively charged LPS, thus reducing the affinity of positively charged polymyxin molecules.

The first description of a plasmid-borne mobilized colistin resistance gene *mcr-1* in 2016 caused great concern, as the ease of potential spread on a conjugative plasmid-encoding resistance to polymyxins might drastically change the resistance situation with regard to colistin. In line with this, *mcr-1* mediated colistin resistance in Enterobacteriaceae (mainly *E. coli*, but rarely also from a few other enterobacterial isolates, i.e. *K. pneumoniae*, *Citrobacter freundii*, and *Salmonella* spp. *enterica*) has since been reported from a wide range of geographical locations.

This project, based on a One-Health approach and funded by the Swiss Federal Office of Public Health, aimed to provide first baseline data to estimate the occurrence and spread of *mcr-1*-harboring Enterobacteriaceae in Switzerland. Studies on the animal level (livestock; isolates from infections of dogs and cats), on the food level (raw poultry and turkey meat on the retail level), on the healthy human level (employees of food-processing companies) and on isolates from clinical cases (urinary tract infections, bacteremia, diarrhea) were performed. Moreover, based on molecular characterization data of the isolates, an improved understanding of the epidemiology and spreading potential of *mcr-1*-harboring Enterobacteriaceae should be provided.

The prevalence in human isolates in Switzerland remains very low (Liassine et al., 2016; Zurfluh et al., 2017a). Very recently, the first *mcr-1*-harboring *Salmonella enterica* subsp. *Enterica* serovar 4,5,12:i:- strain isolated from blood of a patient in Switzerland was found (Carrol et al. submitted).

However, a reservoir of the *mcr-1* resistance gene in the livestock sector opens the possibility of a transfer of *mcr*-harboring strains through the food chain to the human population.

Multilocus sequence typing (MLST) revealed many distinct sequence types which showed abundant diversity among *mcr-1*-positive *E. coli* isolates from different origins. Sequencing data provide evidence that the *mcr-1* gene can

Table 1: Overview and key characteristics of sequenced *mcr-1*-harboring plasmids from strains of different origins isolated in Switzerland

Plasmid	Origin	size (bp)	Inc type	*mcr-1* gene cassette	Additional resistance genes
pPC11	*E. coli* (chicken meat, Germany)	59.826	**IncI2**	IS*Apl*1-*mcr1*-orf	none
pS38	*E. coli* (chicken meat, Italy)	247.885	**IncHI2**	Tn6330	*estX-3, aadA2, aadA1a, aadA1b, cmlA1, sul3, dfrA1b, mefB, tetA, bla*$_{CTX-M-1}$
pPF11	*E. coli* (chicken meat, Germany)	33.308	**IncX4**	*mcr1*-orf	none
pPF52	*E. coli* (turkey meat, Germany)	33.298	**IncX4**	*mcr1*-orf	none
pH226B	*E. coli* (vegetables, Thailand)	209.401	**IncHI1**	*mcr1*-orf	none
pCDF8	*E. coli* (UTI, human)	*33.660*	**IncX4**	*mcr1-orf*	none
pColR598_1	*E. coli* (human, diarrhea)	*60.920*	**IncI2**	*mcr1-orf*	none
pColR598_2	*E. coli* (human, diarrhea)	*33.252*	**IncX4**	*mcr1-orf*	none
pColR664	*E. coli (human, diarrhea)*	*60.885*	**IncI2**	*mcr1-orf*	none

rarely be chromosomally integrated. Transferable IncI2-(size 60–61 kbp) and IncX4-(size 33–35 kbp)type plasmids (Zurfluh et al., 2017b) harboring *mcr-1* are mainly associated with colistin-resistant strains (human and food) isolated in Switzerland (Table 1). All IncI2 and IncX4 plasmids harbored no resistance determinants other than the *mcr-1* gene. Moreover, it should be mentioned that most of the sequenced *mcr-1*-harboring plasmids lack the IS*Apl1* element, which is a key element mediating translocation of *mcr-1* into various plasmid backbones.

Increased surveillance of the dissemination of the *mcr-1* gene throughout the international food market (e.g. imported poultry and turkey meat, vegetables) and the situation in clinical strains, mainly in carbapenemase-producing Enterobacteriaceae, is a keystone when addressing the emergence of MCR-producing bacteria.

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10

Resistance in bacteria isolated from meat

10 Resistance in bacteria isolated from meat

Bacteria of the intestinal flora of livestock constitute a reservoir of potentially transferable resistance genes that can be spread horizontally to other bacteria, including zoonotic bacteria. Hence, antimicrobial 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. During the slaughter process, carcasses are contaminated with these intestinal bacteria and reach the consumers by way of fresh meat and products thereof. Monitoring of multidrug resistant bacteria in fresh meat of broilers, cattle and pigs help to assess the risk for transmission of multidrug resistant bacteria to humans via handling and consumption of fresh meat.

10.1 ESBL/pAmpC- and carbapenemase-producing *Escherichia coli*

10.1.1 ESBL/pAmpC-producing *Escherichia coli* in chicken meat

In 2016, 302 samples of retail chicken meat were collected (205 domestic samples, i.e. chicken meat produced in Switzerland, and 97 imported samples, i.e. chicken meat produced abroad). By applying selective enrichment methods, 149 (49.3 %) presumptive ESBL/pAmpC-producing *E. coli* strains were detected.

Out of 205 domestic samples (chicken meat of Swiss origin), 86 were tested positive (41.9 %). In contrast, 63 out of 97 foreign samples were tested positive, corresponding to a prevalence of 64.9 % (Table 10. a).

All of these isolates were then subjected to susceptibility testing (Table 10. b). Apart from the resistance to beta-lactam antimicrobials, high to very high microbiological resistance levels to tetracycline (45.0 %), sulfonamides (61.1 %), ciprofloxacin (63.1 %), nalidixic acid (57.0 %) and trimethoprim (28.9 %) were found. The portion of isolates resistant to cefepime was 75.8 %, and 53.7 % of the isolates were microbiologically resistant to cefoxitin. A moderate proportion of isolates showed phenotypic resistance to gentamicin (14.1 %), chloramphenicol (10.7 %), whereas the level of resistance to azithromycin (0.7 %) was very low. Microbiological resistances to colistin, ertapenem, meropenem, imipenem, temocillin and tigecycline were not detected.

The distribution of the minimum inhibitory concentrations (MICs) and the multiresistant pattern are shown in Annex II (Table I. 24–I. 25 and Table I. 50).

10.1.2 ESBL/pAmpC-producing *Escherichia coli* from pork meat

In 2017, 302 Swiss pork meat samples were collected from retailers and one ESBL/pAmpC-producing *E. coli* was isolated using selective enrichment methods. This corresponds to a prevalence of approximately 0.3 %. This single isolate was subjected to antimicrobial susceptibility testing. It showed microbiological resistance to beta-lactam antimicrobials (ampicillin, cefepime, ceftazidime, cefotaxim), but not to cefoxitin. Microbiological resistance to sulfamethoxazole, chloramphenicol, nalidixic acid, tetracycline and trimethoprim was also found (Table 10. c).

The distribution of the minimum inhibitory concentrations (MIs) and the multiresistant pattern are shown in Annex II (Table I. 26–I. 27 and Table I. 52).

10.1.3 ESBL/pAmpC-producing *Escherichia coli* from beef

In 2017, 299 Swiss beef meat samples were collected from retailers and analyzed for ESBL/pAmpC-producing *E. coli* using selective enrichment methods. Only two samples (0.7 %) tested positive for suspected ESBL/pAmpC-producing *E. coli*. Besides resistance to beta-lactam antimicrobials, these strains showed additional resistance to ciprofloxacin only (Table 10 d).

The distribution of the minimum inhibitory concentrations (MIs) and the multiresistant pattern are shown in Annex II (Table I. 28–I. 29 and Table I. 51).

10.1.4 Carbapenemase-producing *Escherichia coli* from chicken, beef and pork meat

In total, 302 chicken meat, 302 pork meat and 299 beef meat samples were collected from retailers and analyzed for carbapenemase-producing *E. coli* using selective enrichment methods. None of the meat samples tested positive for carbapenemase-producing *E. coli*.

Table 10. a: Number of samples and number of ESBL/pAmpC-producing *Escherichia coli*-positive samples by origin of chicken meat for 2016.

Origin	No. of samples	No. of positive samples (%)
Germany	28	15 (53.6)
Hungary	27	22 (81.5)
Austria	17	12 (70.6)
Slovenia	14	9 (64.3)
Italy	6	3 (50.0)
France	4	1 (25.0)
Argentina	1	1 (100.0)
Total foreign countries	**97**	**63 (64.9)**
Switzerland	**205**	**86 (41.9)**

Table 10. b: Occurrence of resistance of ESBL/pAmpC-producing *Escherichia coli* from chicken meat in 2016.

***Escherichia coli* (N =149)**			**2016**
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	149	100	97.5–100.0
Azithromycin	1	0.7	0.1–3.7
Cefepime	113	75.8	68.4 – 82.0
Cefotaxime*	146	98	94.2–99.3
Cefoxitin	80	53.7	45.7–61.5
Ceftazidime*	139	93.3	88.1–96.3
Chloramphenicol	16	10.7	6.7–16.7
Ciprofloxacin	94	63.1	55.1–70.4
Colistin	0	0	0.0–2.5
Ertapenem	0	0	0.0–2.5
Gentamicin	21	14.1	9.4–20.6
Imipenem	0	0	0.0–2.5
Meropenem*	0	0	0.0–2.5
Nalidixic acid	85	57	49.0–64.7
Sulfamethoxazole	91	61.1	53.1–68.5
Temocillin	0	0	0.0–2.5
Tetracycline	67	45	37.2–53.0
Tigecycline	0	0	0.0–2.5
Trimethoprim	43	28.9	22.2–36.6
Number of resistances	**n**	**%**	**95% CI**
None	0	0	0.0–2.5
1 antimicrobial	0	0	0.0 – 2.5
2 antimicrobials	2	1.3	0.4 – 4.8
3 antimicrobials	25	16.8	11.6 – 23.6
4 antimicrobials	16	10.7	6.7 – 16.7
> 4 antimicrobials	106	71.1	63.4 – 77.8

N = total number of tested isolates, n = number of resistant isolates, % = percentage of resistant isolates, 95% CI: 95% Confidence Interval
* Result of EUVSEC2 plate

Table 10. c: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from pork meat in 2017.

Escherichia coli (N = 1)			2017
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	1	100	20.7–100.0
Azithromycin	1	100	20.7–100.0
Cefepime	1	100	20.7–100.0
Cefotaxime*	1	100	20.7–100.0
Cefoxitin	0	0	0.0–79.3
Ceftazidime*	1	100	20.7–100.0
Chloramphenicol	1	100	20.7–100.0
Ciprofloxacin	0	0	0.0–79.3
Colistin	0	0	0.0–79.3
Ertapenem	0	0	0.0–79.3
Gentamicin	0	0	0.0–79.3
Imipenem	0	0	0.0–79.3
Meropenem*	0	0	0.0–79.3
Nalidixic acid	1	100	20.7–100.0
Sulfamethoxazole	1	100	20.7–100.0
Temocillin	0	0	0.0–79.3
Tetracycline	1	100	20.7–100.0
Tigecycline	0	0	0.0–79.3
Trimethoprim	1	100	20.7–100.0
Number of resistances	**n**	**%**	**95% CI**
None	0	0	0.0–79.3
1 antimicrobial	0	0	0.0–79.3
2 antimicrobials	0	0	0.0–79.3
3 antimicrobials	0	0	0.0–79.3
4 antimicrobials	0	0	0.0–79.3
> 4 antimicrobials	1	100	20.7–100.0

N = total number of tested isolates, n = number of resistant isolates, % = percentage of resistant isolates, 95% CI: 95% Confidence Interval
* Result of EUVSEC2 plate

10.2 MRSA in meat

10.2.1 MRSA in chicken meat

Chicken meat was investigated in 2016. By applying selective enrichment methods, nine MRSA isolates were obtained from 302 samples of retail chicken meat (205 samples of Swiss origin, 97 samples of foreign origin). The isolates were subjected to *spa* typing and susceptibility testing. Three isolates belonged to the *spa* type t034 and three isolates to the *spa* type t1430. The *spa* type t2123 was found twice and t153 was detected once.

All MRSA-positive samples were chicken meat, produced abroad (eight samples from Germany, one sample from Hungary). Consequently, the prevalence in externally produced chicken meat was 9.3%, while the prevalence for Swiss chicken meat was 0.0% (Table 10 g).

Susceptibility testing confirmed MRSA, as all isolates were microbiologically resistant to beta-lactam antibiotics (cefoxitin and penicillin). Extremely high to high resistance rates were found for macrolides/lincosamides (erythromycin 77.8%, clindamycin 88.9%), tetracycline (55.6%), tiamulin (55.6%), trimethoprim (55.6%), quinupristin/dalfopristin (55.6%) and ciprofloxacin (33.3%) (Table 10. e). No microbiological resistance was detected for sulfamethoxazole, chloramphenicol, fusidic acid, gentamicin, kanamycin and streptomycin. Moreover, for antimicrobials relevant in human medicine, such as linezolid, mupirocin, rifampicin, and vancomycin, no resistant isolates were found.

The distribution of the minimum inhibitory concentrations (MIs) and the multiresistant pattern are shown in Annex II (Table I. 30 and Table I. 53).

10.2.2 MRSA in pork meat

Swiss pork meat was investigated in 2017. Two out of 301 examined samples tested positive for MRSA, corresponding to a prevalence of 0.7%. One isolate belonged to the *spa*

Table 10. d: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from beef in 2017.

Escherichia coli (N = 2)			2017
Antimicrobials	**n**	**%**	**95% CI**
Ampicillin	2	100	34.2–100.0
Azithromycin	0	0	0.0–65.8
Cefepime	1	50	9.5 – 90.5
Cefotaxime*	2	100	34.2–100.0
Cefoxitin	1	50	9.5 – 90.5
Ceftazidime*	2	100	34.2–100.0
Chloramphenicol	0	0	0.0–65.8
Ciprofloxacin	1	50	9.5 – 90.5
Colistin	0	0	0.0–65.8
Ertapenem	0	0	0.0–65.8
Gentamicin	0	0	0.0–65.8
Imipenem	0	0	0.0–65.8
Meropenem*	0	0	0.0–65.8
Nalidixic acid	0	0	0.0–65.8
Sulfamethoxazole	0	0	0.0–65.8
Temocillin	0	0	0.0–65.8
Tetracycline	0	0	0.0–65.8
Tigecycline	0	0	0.0–65.8
Trimethoprim	0	0	0.0–65.8
Number of resistances	**n**	**%**	**95% CI**
None	0	0	0.0–65.8
1 antimicrobial	0	0	0.0–65.8
2 antimicrobials	0	0	0.0–65.8
3 antimicrobials	1	50	9.5–90.5
4 antimicrobials	1	50	9.5–90.5
> 4 antimicrobials	0	0	0.0–65.8

N = total number of tested isolates, n = number of resistant isolates, % = percentage of resistant isolates, 95% CI: 95% Confidence Interval
* Result of EUVSEC2 plate

type t011 (livestock-MRSA) and the other to the *spa* type t002. The two MRSA isolates were subjected to susceptibility testing. Both MRSA were microbiologically resistant to macrolides/lincosamides, tetracycline, tiamulin, trimethoprim and quinupristin/dalfopristin. No microbiological resistance was detected for sulfamethoxazole, chloramphenicol, ciprofloxacin, fusidic acid, gentamicin, kanamycin and streptomycin. Moreover, for antimicrobials relevant in human medicine, such as linezolid, mupirocin, rifampicin, and vancomycin, no resistant isolates were found (Table 10 f).

The distribution of the minimum inhibitory concentrations (MIC) and the multi-resistant pattern are shown in Annex II (Table I. 31 and Table I. 54).

10.2.3 MRSA in beef

Swiss beef samples were investigated in 2017. All 299 samples were tested negative for MRSA.

10.3 Discussion

10.3.1 ESBL/pAmpC- and carbapenemase-producing *E. coli* in fresh meat

Using selective enrichment methods, ESBL/pAmpC-producing *E. coli* were found in 41.9% of chicken meat samples, whereas detection rates of ESBL/pAmpC-producing *E. coli* were very low for pork (0.3%) and beef (0.7%).

Compared to 2014, the prevalence of ESBL/pAmpC-producing *E. coli* in chicken meat has clearly decreased for Switzerland (2014: 65.5%; 2016: 41.9%), but also for Germany (2014: 82.2%; 2016: 53.6%) and Slovenia (2014: 94.7%; 2016: 64.3%). In contrast, the detection rate for fresh chicken meat from Hungary still remains very high (2014: 88.9%; 2016: 81.5%). As the detection method was not modified during the last reporting period, the decrease seems to be a real biological finding. It is not known whether measures were taken from the Swiss poultry industry during slaughter and/or meat processing. Comparable decreasing trends in

Table 10. e: Occurrence of MRSA from chicken meat in 2016.

Staphylococcus aureus (N = 9)			2016
Antimicrobials	**n**	**%**	**95% CI**
Cefoxitin	9	100	70.1–100.0
Chloramphenicol	0	0	0.0–29.9
Ciprofloxacin	3	33.3	12.1–64.6
Clindamycin	8	88.9	56.5–98.0
Erythromycin (Erythromycin A)	7	77.8	45.3–93.7
Fusidic acid	0	0	0.0–29.9
Gentamicin	0	0	0.0–29.9
Kanamycin	0	0	0.0–29.9
Linezolid	0	0	0.0–29.9
Mupirocin	0	0	0.00–29.9
Penicillin	9	100	70.1–100.0
Quinupristin/Dalfopristin	5	55.6	26.7–81.1
Rifampicin	0	0	0.0–29.9
Streptomycin	0	0	0.0–29.9
Sulfamethoxazole	0	0	0.0–29.9
Tetracycline	5	55.6	26.7–81.1
Tiamulin	5	55.6	26.7–81.1
Trimethoprim	5	55.6	26.7–81.1
Vancomycin	0	0	0.0–29.9
Number of resistances	**n**	**%**	**95% CI**
None	0	0	0.0–29.9
1 antimicrobial	0	0	0.0–29.9
2 antimicrobials	1	11.1	2.0–43.5
3 antimicrobials	0	0	0.0–29.9
4 antimicrobials	0	0	0.0–29.9
> 4 antimicrobials	8	88.9	56.5–98.0

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

other European countries may suggest that measures have been taken by the poultry industries on supranational levels.

The prevalence in chicken meat is influenced by the prevalence of broilers (Chapter 9). The prevalence among individual birds increases towards the end of the fattening period, and herd management, hygiene and/or use of antimicrobials, especially beta-lactams, influences the ESBL/pAmpC load [1]. Once present on a broiler farm, the bacteria spread horizontally from one herd to another. Specific bacteria can also be found in the environment of farms where they are able to survive for extended periods of time, and hence are a potential source for further transmission [2]. Another study showed that a horizontal transfer of bacteria from animals to their owners is possible [3].

Other studies from Switzerland confirm the high prevalence of ESBL/pAmpC-producing *E. coli* observed for chicken meat [4]. The prevalence of these types of resistance in chicken meat (73.3%) is much higher than the prevalence in broiler flocks (41.8%). This indicates that resistant bacteria are spreading by cross-contamination between animals, processing materials and staff during the slaughter process and/or the subsequent meat processing [5]. ESBL/pAmpC-producing *E. coli* in chicken meat represent a potential source of transmission for humans, e.g. by kitchen utensils or hands [6]. As a consequence, adequate kitchen hygiene and proper cooking of raw chicken meat are essential.

The low prevalence of ESBL/pAmpC-producing *E. coli* in pork and beef (<1%) compared to the prevalence in fattening pigs (25.7%) and veal calves (37.6%) could be attributed to good hygiene measures during slaughtering process.

ESBL/pAmpC-producing bacteria have increasingly been found in the general population as well [7]. Here, they either occur harmlessly in the guts of healthy individuals or cause diseases such as urinary tract infections. The incidence of these types of resistance has increased in Switzerland in recent years, both in hospitals and in outpatients (see Chapter 7. 1) [8]. A study carried out in Switzerland in healthy staff of meat-processing plants found ESBL-producing intestinal bacteria in 5.8% of those tested [3]. Another study, which tested 291 fecal swab samples from patients of GP practices, found ESBL-producing bacteria in 5.2% of the samples [9].

Table 10. f: Occurrence of MRSA from pork meat in 2017.

Staphylococcus aureus (N = 2)			2017
Antimicrobials	**n**	**%**	**95% CI**
Cefoxitin	2	100	34.20–100.00
Chloramphenicol	0	0	0.00–65.80
Ciprofloxacin	0	0	0.00–65.80
Clindamycin	0	0	0.00–65.80
Erythromycin (Erythromycin A)	0	0	0.00–65.80
Fusidic acid	0	0	0.00–65.80
Gentamicin	2	100	34.20–100.00
Kanamycin	2	100	34.20–100.00
Linezolid	0	0	0.00–65.80
Mupirocin	0	0	0.00–65.80
Penicillin	2	100	34.20–100.00
Quinupristin/Dalfopristin	0	0	0.00–65.80
Rifampicin	0	0	0.00–65.80
Streptomycin	0	0	0.00–65.80
Sulfamethoxazole	0	0	0.00–65.80
Tetracycline	1	50	9.50–90.50
Tiamulin	0	0	0.00–65.80
Trimethoprim	0	0	0.00–65.80
Vancomycin	0	0	0.00–65.80
Number of resistances	**n**	**%**	**95% CI**
None	0	0	0.00–65.80
1 antimicrobial	0	0	0.00–65.80
2 antimicrobials	0	0	0.00–65.80
3 antimicrobials	0	0	0.00–65.80
4 antimicrobials	1	50	9.50–90.50
> 4 antimicrobials	1	50	9.50–90.50

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

Resistance genes of ESBL/pAmpC-producing *E. coli* display a large heterogeneity. The comparison of different genes and resistance patterns from isolates of food-producing animals, raw meat and humans shows that the majority of isolates differ considerably [10]. Currently, the vast majority of ESBL/pAmpC-producing *E. coli* colonizing humans cannot be exclusively attributed to food-producing animals or food, despite the fact that food-producing animals and especially chicken meat are seen as an important reservoir for ESBL/pAmpC-producing *E. coli* [10].

10.3.2 MRSA in fresh meat

In contrast to ESBL/pAmpC-producing *E. coli* in chicken meat, food as a whole is not regarded as a relevant source of MRSA infection or colonization for humans [11]. Hence, detection rates for MRSA in Swiss fresh meat was low to zero (chicken meat from abroad 9.3%, pork 0.7% and beef 0.0%). Investigations revealed that the occurrence of MRSA in chicken meat produced abroad (9.3%) is significantly higher than in chicken meat produced in Switzerland (0.0%). Looking at the details, it becomes obvious that eight out of nine MRSA isolates were obtained from chicken meat produced in Germany (28.6%), while chicken meat from Hungary showed a low prevalence (3.7%). Chicken meat from France, Italy, Austria and Slovenia was found to be negative for MRSA, as was the case for the Swiss chicken meat samples (Table 10. g).

The MRSA investigation in chicken meat revealed results similar to those obtained in 2014. Interestingly, the detected prevalence of foreign chicken meat decreased from 16.0% in 2014 to 9.3% in 2016. As in the previous reporting period, MRSA were mostly found in chicken meat from Germany. The MRSA investigation in Swiss pork in 2017 revealed a very low prevalence of 0.7%, identical to the prevalence found in 2015. This is of special concern, as the MRSA prevalence in nasal swabs from Swiss pigs increased from 25.7% to 40.0% in the same time period. These findings confirm the very low risk of MRSA transmission from animal to humans via meat [12]. However, one of the MRSA isolates obtained from Swiss pig meat was identified as *spa* type t011, which is increasingly found in Swiss pigs. This might indicate that the contamination of the meat with MRSA had occurred during slaughter of MRSA-positive pigs, and mon-

Table 10. g: Number of samples and number of MRSA-positive samples by origin of chicken meat in 2016.

Origin	No. of samples	No. of positive samples (%)
Germany	28	8 (28.6)
Hungary	27	1 (3.7)
Austria	17	0 (0.0)
Slovenia	14	0 (0.0)
Italy	6	0 (0.0)
France	4	0 (0.0)
Argentina	1	0 (0.0)
Total foreign countries	**97**	**9 (9.3)**
Switzerland	**205**	**0 (0.0)**

itoring of MRSA in Swiss pig meat is needed, although the prevalence in the reporting period was very low. The second MRSA infection in Swiss pig meat was identified as *spa* type t002, which is often found in humans. This may indicate a contamination during processing or packaging. Again, no MRSA was found in Swiss beef in the reporting period.

Resistance patterns of MRSA isolates are associated with the *spa* types. Resistance to tetracycline for example typically occurs in livestock-associated MRSA (LA-MRSA) [13]. Indeed, the three isolates of *spa* type t034 from chicken meat were LA-MRSA and showed resistance to tetracycline, whereas the MRSA of *spa* type t153 showed no resistance to tetracycline. A contamination of the meat during processing or packaging was therefore very likely.

A comparative analysis of current molecular findings from Swiss human, animal and meat MRSA isolates is described in Chapter 12.

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11

Resistance in bacteria from animal clinical isolates

11 Resistance in bacteria from animal clinical isolates

Monitoring of antimicrobial resistance for relevant pathogens from diseased livestock and companion animals is important for veterinarians, as it enables them to make appropriate therapeutic antibiotic choices, which they often cannot base on an antibiogram prior to the first treatment. Moreover, these data fill another important gap regarding monitoring of antimicrobial resistance from the One-Health perspective. International organizations have recently focused on these topics [1]. The establishment of a European Veterinarian Committee on Antimicrobial Susceptibility Testing (VetCAST) in 2015 also proves the importance of these measures.

In 2015, the Federal Food Safety and Veterinary Office (FSVO) launched a pilot project for the monitoring of veterinary pathogens in Switzerland, together with the Swiss national reference laboratory for antibacterial resistance, the Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA) at the Institute of Veterinary Bacteriology, Vetsuisse Faculty of Bern. Results presented here are an excerpt of selected pathogens which were analyzed in the framework of this pilot project [2]. All strains were isolated from clinical submissions of diseased animals analyzed by the ZOBA. Samples from animals with antimicrobial treatment prior to sampling were excluded for this study. In contrast to the monitoring of isolates from healthy slaughter animals, MIC data were interpreted according to clinical breakpoints, as recommended by the CLSI. In cases where no clinical breakpoints were available, MIC_{90} were calculated.

11.1 *Staphylococcus* spp.

Staphylococci are Gram-positive, non-motile and non-sporulating cocci. About 40 different *Staphylococcus* species are found in animals and humans, of which some are specifically associated to their hosts. They belong to the normal microbiota in animals and humans, but are occasionally responsible for opportunistic infections. They can cause a broad spectrum of diseases with varying degrees of severity.

11.1.1 *Staphylococcus pseudintermedius* in dogs

Staphylococcus pseudintermedius is an opportunistic pathogen, normally found as a commensal on skin and mucosa of dogs. Like other *staphylococci*, *S. pseudintermedius* can act as an opportunistic pathogen, recognized as the leading cause of skin, ear, and postoperative bacterial infections in dogs [3]. *S. pseudintermedius* has gained more importance in veterinary as well as in human medicine in recent years, because of the emergence of methicillin-resistant *S. pseudintermedius* (MRSP). In veterinary clinics, the prevalence for MRSP amounts to 66%. However, 22% of clinically healthy dogs can also be carriers of MRSP [4]. Humans with close contact to dogs have a higher risk of transmission from MRSP to humans, and infections of humans with MRSP are described in the literature [5], [6]. Colonization and/or infection is therefore not only a concern for veterinarians who treat the infected animals, but also a risk for pet owners.

Table 11. a: Susceptibility rates of *Staphylococcus pseudintermedius* isolates in dogs.

Antimicrobials	n	S (n)	S (%)	I (n)	I (%)	R (n)	R (%)
Amoxicillin + clavulanic acid	44	43	97.7	0	0.0	1	2.3
Ampicillin	44	42	95.5	0	0.0	2	4.5
Cefalotin	44	44	100.0	0	0.0	0	0.0
Clindamycin	44	37	84.1	0	0.0	7	15.9
Enrofloxacin	44	43	97.7	1	2.3	0	0.0
Marbofloxacin	44	44	100.0	0	0.0	0	0.0
Erythromycin	44	37	84.1	0	0.0	7	15.9
Gentamicin	44	41	93.2	3	6.8	0	0.0
Oxacilin + 2%NaCl	44	43	97.7	0	0.0	1	2.3
Penicillin G	44	33	75.0	0	0.0	11	25.0
Tetracycline	44	32	72.7	0	0.0	12	27.3
Trimethoprim-sulfamethoxazole	44	43	97.7	0	0.0	1	2.3

A total of 44 isolates of *S. pseudintermedius* in dogs were investigated in 2016/2017. The origin of these bacteria strains was either canine skin or mucosal infections. None of the dogs were treated with antimicrobials before sampling.

High resistance rates of these strains to tetracycline (27.3 %) and penicillin (25.0 %) were detected. Moderate resistance rates were detected against clindamycin (15.9 %) and erythromycin (15.9 %) (Table 11. a). The joint appearance of these resistances together with the high MIC_{90} values (Table 11. b) for the other tested macrolides indicate a macrolide-lincosamid-streptogramin resistance (MLS).

Low resistance rates were found for ampicillin (4.5 %), amoxicillin-clavulanic acid (2.3 %) and sulfamethoxazole-trimethoprim (2.3 %). One isolate showed resistance to oxacillin, but methicillin-resistance was not confirmed. This isolate showed resistance against eight out of 13 antimicrobials. No resistance to the tested fluoroquinolones could be detected. MIC_{90} values were low for ticarcillin, cephalosporins and macrolides. Moreover, MIC_{90} values for antimicrobials critically important in human medicine do not hint at potentially acquired resistances (Table 11. b).

11.1.2 *Staphylococcus aureus* from bovine mastitis

S. aureus is a major cause of clinical bovine mastitis worldwide [7], and can be detected in approximately 57 % of all herds in Switzerland. For single animals, the prevalence amounted to 14.4 % in 2013 [8]. Mastitis is usually treated with antibiotics, which are often prescribed without prior susceptibility testing. Given the recent establishment of molecular-based diagnostics of mastitis pathogens, the use of antibiotics without prior evaluation of an antibiogram is also expected to increase in the coming years [9].

In 2016/2017, a total of 56 bovine *Staphylococcus aureus* mastitis isolates were investigated. Against penicillin and ampicillin, a moderate resistance rate of 16.1 % was detected (Table 11. c). Besides these therapeutically relevant resistances, *S. aureus* isolates showed only low resistance rates to tetracycline (3.6 %) and ciprofloxacin (1.8 %). No resistances to the cephalosporins ceftiofur and cefalotin and no MRSA were detected.

MIC_{90} values for other cephalosporins, macrolides, clindamycin and fluoroquinolone were low (Table 11. d). Moreover, MIC_{90} values for critically important antimicrobials in human medicine do not hint at acquired resistance so far.

11.2 *Streptococcus equi* subspecies *zooepidemicus*

Streptococcus spp. are Gram-positive, non-motile cocci, mainly oxidase- and catalase-negative. In contrast to *S. equi* subspecies *equi*, which is exclusively detected in horses, *S. equi* subspecies *zooepidemicus* is associated with a wide variety of diseases in horses and other species, including humans [10]. *S. equi* subsp. *zooepidemicus* is usually found in young horses, which are infected via nose or mouth. Afterwards, colonization of mucosal surfaces and the tonsils takes place, and persistence of bacteria in the naropharynx can lead to spreading into the environment and thereby to

Table 11. b: MIC_{90} rates of *Staphylococcus pseudintermedius* isolates in dogs in 2016/2017.

Antimicrobials	Test range [mg/L]	MIC_{90} [mg/L]
Cefoperazon	0.06–32	0.5
Cefotaxime	0.015–32	0.5
Cefovecin	0.25–8	0.25
Cefoxitin	2–16	2
Cefquinom	0.015–32	0.5
Ceftiofur	0.03–64	0.25
Ciprofloxacin	0.008 - 16	0.25
Linezolid	0.03–64	1
Pirlimycin	0.03–64	8
Quinupristin-Dalfopristin	0.015–32	0.5
Ticarcillin	8–64	8
Ticarcillin + clavulanic acid	8–64	8
Tilmicosin	0.06–128	256*
Tulathromycin	0.06–32	64*
Tylosin	0.06 - 128	256*
Vancomycin	0.015–32	1

MIC_{90} (Minimal Inhibitory Concentration 90): The minimal concentration in mg/L of an antimicrobial required to inhibit the growth of 90 % of the bacteria tested.

Table 11. c: Susceptibility rates of *Staphylococcus aureus* isolates in bovine mastitis in 2016/2017.

Antimicrobials	n	S (n)	S (%)	I (n)	I (%)	R (n)	R (%)
Amoxicillin + clavulanic acid	56	56	100.0	0	0.0	0	0.0
Ampicillin	56	47	83.9	0	0.0	9	16.1
Ceftiofur	56	56	100.0	0	0.0	0	0.0
Cefalotin	56	56	100.0	0	0.0	0	0.0
Cirpofloxacin	56	55	98.2	0	0.0	1	1.8
Erythromycin	56	56	100.0	0	0.0	0	0.0
Gentamicin	56	56	100.0	0	0.0	0	0.0
Penicillin G	56	47	83.9	0	0.0	9	16.1
Pirlimycin	56	56	100.0	0	0.0	0	0.0
Tetrazycline	56	54	96.4	0	0.0	2	3.6
Trimethoprim-sulfamethoxazole	56	56	100.0	0	0.0	0	0.0

Table 11. d: MIC_{90} rates of *Staphylococcus aureus* isolates in bovine mastitis in 2016/2017.

Antimicrobials	Test range [mg/L]	MIC_{90} [mg/L]
Cefoperazon	0.06–32	2
Cefotaxime	0.015–32	2
Cefquinom	0.015–32	0.5
Clindamycin	0.03–64	0.25
Enrofloxacin	0.008–16	0.25
Linezolid	0.03–64	4
Marbofloxacin	0.008–16	0.5
Quinupristin-Dalfopristin	0.015–32	0.5
Tilmicosin	0.06–128	1
Tulathromycin	0.06–64	8
Tylosin	0.06–128	2

MIC_{90} (Minimal Inhibitory Concentration 90): The minimal concentration in mg/L of an antimicrobial required to inhibit the growth of 90 % of the bacteria tested.

infection of other species. Its zoonotic potential is documented in a recent publication of a human infection due to *S. equi* subspecies *zooepidemicus* [11]. In most cases, antimicrobial therapy is part of the therapy.

Twenty-two isolates of *Streptococcus equi* subsp. *zooepidemicus* were detected in clinical cases of wound infection or septicemia in horses in 2016/2017. An earlier treatment with antimicrobials could only be excluded in 17 cases, whereas for five strains the therapeutic background remained unknown.

High resistance and intermediate rates of 27.2 % and 31.8 % were found against clindamycin (Table 11. e). Moreover, high resistance and intermediate rates (27.2 %, 22.7 %) were detected for tetracycline. In contrast, 90.0 % of the isolates showed susceptibility to penicillin. Furthermore, all isolates were sensitive to ampicillin and erythromycin. When looking at MIC_{90} values of antimicrobials without clinical breakpoints, no elevated values were measured for these antimicrobials, including those which are critically important for human medicine (Table 11. f).

11.3 *Escherichia coli* in dogs

E. coli is an important cause of opportunistic infections in veterinary medicine. As in human medicine, especially infection of the urogenital tract with *E. coli* occurs frequently [12]. Antimicrobial treatment is the therapy of choice. In human medicine, the antimicrobial resistance of extraintestinal pathogenic *E. coli* associated with urogenital tract infections has increased dramatically in the last decade and is linked to predominant clones of *E. coli* [12]. Moreover, zoonotic potential of extraintestinal *E. coli* from dogs to humans has been reported [13]. Hence, knowledge regarding antimicrobial resistances of extraintestinal *E. coli* isolated from urogenital tract infections of diseased dogs is important for both human and veterinary medicine.

Between 2016 and 2017, 29 *E. coli* strains were isolated from urinary tract infections in dogs. The animals were not treated with antimicrobials before sampling.

High resistance rates (20.7 %) were detected for ampicillin and cefalotin. Moreover, the resistance rates for cefazolin

Table 11. e: Susceptibility rates of *Streptococcus equi* subspecies *zooepidemicus* isolates in horses.

Antimicrobials	n	S (n)	S (%)	I (n)	I (%)	R (n)	R (%)
Ampicillin	22	22	100.0	0	0.0	0	0.0
Clindamycin	22	9	40.9	7	31.8	6	27.2
Erythromycin	22	22	100.0	0	0.0	0	0.0
Penicillin G	22	20	90.9	0	0.0	1	4.5
Tetracycline	22	11	50.0	5	22.7	6	27.2

Table 11. f: MIC_{90} rates of *Streptococcus equi* subspecies *zooepidemicus* isolates in horses in 2016/2017.

Antimicrobials	Test range [mg/L]	MIC_{90} [mg/L]
Amoxicillin + calvulanic acid	0.03–64	0.06
Cefalotin	0.06–128	0.12
Cefoperazon	0.06–32	0.25
Cefotaxime	0.015–2	0.06
Cefquinom	0.015–32	0.06
Ceftiofur	0.03–64	0.25
Ciprofloxacin	0.008–16	2
Enrofloxacin	0.008–16	2
Gentamicin	0.12–256	8
Linezolid	0.03–64	2
Marbofloxacin	0.008–16	2
Oxacillin+	0.015–8	0.12
Pirlimycin	0.03–64	2
Quinupristin-Dalfopristin	0.015–32	0.5
Sulfamethoxazol-Trimethoprim	0.015–32	0.5
Tilmicosin	0.06–128	0.5
Tulathromycin	0.06–32	2
Tylosin	0.06–128	0.25

MIC_{90} (Minimal Inhibitory Concentration 90): The minimal concentration in mg/L of an antimicrobial required to inhibit the growth of 90 % of the bacteria tested.

(17.2 %) and amoxicillin + clavulanic acid (10.3 %) were moderate (Table 11. g). Low resistance rates were found for enrofloxacin, marbofloxacin and tetracycline (6.9 %), and only one isolate was resistant to gentamicin and trimethoprim-sulfamethoxazole (3.4 %). No ESBL/pAmpC-or carbapenemase-producing *E. coli* was detected.

The cephalosporins without available clinical breakpoints for dogs, including cefovecin and ceftiofur but excepting cefquinom, a 4th generation cephalosporin, showed relatively high MIC_{90} values (Table 11. h). The MIC_{90} values for colistin as well as doxycycline and florfenicol were low. In contrast, MIC_{90} values for nalidixic acid and ticarcillin were high.

11.4 Discussion

Data from the first Swiss monitoring pilot project on antimicrobial resistance for veterinary pathogens are presented in this report, [2]. Although only isolates from diagnostic submissions of the ZOBA were included, isolate selection, methodology and interpretation were performed according to internationally ongoing programs. Therefore, these data are comparable with data from international studies, such as ComPath [14], [15] and VetPath [16] studies or GermVet [17]. In contrast, comparability to data presented in previous Swiss reports is limited, as the choice of isolates and the method used in these reports were different from the current study.

The high resistance rate of Swiss *S. pseudintermedius* to penicillin described in this report was comparable to resistance rates detected in other European countries [15]. In contrast, German canine *S. pseudintermedius* isolates showed much higher resistance rates for clindamycin, erythromycin, tetracycline and penicillin than Swiss isolates [17]. On the other hand, MIC_{90} values for cephalosporins in Germany and Switzerland were similarly low. The low resistance rates of Swiss *S. pseudintermedius* isolates to ampicillin and amoxicillin-clavulanic acid, which are also observed in Europe, are therapeutically very important and should be preserved for the future by prudent use of antimicrobials. In contrast to Swiss *S. pseudintermedius* isolates, European

Table 11. g: Susceptibility rates of *E. coli* isolates in dogs.

Antimicrobials	n	S (n)	S (%)	I (n)	I (%)	R (n)	R (%)
Amoxiciline + clavulanic acid	29	23	79.3	3	10.3	3	10.3
Ampicilin	29	22	75.9	1	3.4	6	20.7
Cefalotin	29	16	55.2	7	24.1	6	20.7
Ciprofloxacin	29	27	93.1	0	0,0	2	6.9
Enrofloxacin	29	27	93.1	0	0,0	2	6.9
Gentamicin	29	28	96.6	0	0,0	1	3.4
Marbofloxacin	29	27	93.1	0	0,0	2	6.9
Tetracycline	29	26	89.7	1	3.4	2	6.9
Trimethoprim-sulfamethoxazole	29	28	96.6	0	0,0	1	3.4
Imipenem	29	29	100.0	0	0,0	0	0,0
Cefazolin	29	n.d.	n.d.	n.d.	n.d	5	17.2

Table 11. h: MIC_{90} of *E. coli* isolates in dogs in 2016/17.

Antimiocrobials	Test range [mg/L]	MIC_{90} [mg/L]
Cefoperazon	0.06 – 32	32
Cefotaxime	0.015 – 32	16
Cefovecin	0.25 – 8	16*
Cefoxitin	2 – 16	32*
Cefquinom	0.015 – 32	0.5
Ceftiofur	0.03 – 64	16
Colistin	0.03 – 64	0.5
Doxycylin	0.06 – 128	8
Florfenicol	0.12 – 256	16
Nalidixic acid	0.06 – 128	256*
Neomycin	0.12 – 64	1
Streptomycin	0.25 – 512	16
Ticarcillin	8 – 64	128*
Ticarcillin + clavulanic acid	8 – 64	32

MIC_{90} (Minimal Inhibitory Concentration 90): The minimal concentration in mg/L of an antimicrobial required to inhibit the growth of 90 % of the bacteria tested.

studies reported detectable resistances to fluoroquinolones, albeit on a low level. Whereas in 2014/2015 methicillin-resistant *S. pseudintermedius* (MRSP) isolates were detected, data of this pilot project could not confirm the presence of any MRSP within the selected isolates. Amongst others, this difference might be at least partially explained by the more specific choice of isolates. In the last report, antimicrobially treated as well as untreated animals were included, whereas in this report only untreated dogs were included in the sampling. Moreover, the isolates from the previous report were mainly derived from dogs hospitalized in small animal clinics, whereas the current data also include dogs from small animal practitioners.

In our study, resistances to penicillin and ampicillin (16.1 %) were found to be the most prevalent resistances in *S. aureus* isolates from bovine mastitis. Penicillin resistance of Swiss *S. aureus* isolates from mastitis samples has been described previously. Overesch et al. (2013) reported penicillin resistance in 16 % of Swiss *S. aureus* strains (n= 287) [18]. These strains were tested without selection of origin (e.g. cattle with or without antimicrobial treatment prior to sampling). The fact that, five years later exactly the same resistance rate is found for untreated isolates alone, argues for an increasing trend of resistance in the last years. The study from VetPath showed that the 25 % resistance rate found in European countries is comparable to that in Switzerland [16]. Fortunately, in contrast to previous studies in Switzerland, no MRSA was detected within the strains tested. This pointed to a recently low prevalence of these multidrug-resistant pathogens in cases of bovine mastitis. Most of the *S. aureus* strains were found to be susceptible to aminoglycosides, macrolides and fluoroquinolones, which are antibiotics frequently used for mastitis treatment in Switzerland. The use of critically important antimicrobials could not be supported by our data, as first-line antibiotics with sufficient efficacy are available and potentially resistant isolates could be identified by susceptibility testing.

For *S. equi* subspecies *zooepidemicus*, very few data on antimicrobial resistance are available to date, as this pathogen is not part of most of the monitoring systems in Europe. In Sweden, *S. equi* subspecies *zooepidemicus* isolates showed a lower resistance rate to clindamycin (6%) [19]. In accordance with Swiss data, Swedish *S. equi* subspecies *zooepidemicus* isolates are highly susceptible to penicillin and erythromycin. Tetracyclines are not recommended due to high resistance rates, but also due to the fact that inherent susceptibility is above concentrations that can be obtained during therapy.

For Swiss extraintestinal *E. coli* isolates, high to moderate resistance rates were detected for ampicillin, amoxicillin/clavulanic acid and cephalosporins. The detected resistance rates are slightly higher than comparable data from European countries [14]. Moreover, MIC_{90} values for other cephalosporins, except the 4th generation cephalosporin cefquinom, pointed to acquired resistance to this therapeutically relevant group of antimicrobials. In contrast, resistance rates for sulfamethoxazole-trimethoprim, tetracycline and gentamicin are favorably low. Compared to the last Swiss antibiotic resistance report published in 2016, which states that in 2014 9 out of 82 strains (10.3%) and in 2015 15 out of 192 strains (7.8%) were confirmed as ESBL, the prevalence for ESBL isolated from urinary tract infection in dogs in this strain collection was zero. Besides the low number of isolates, the different conditions applied for strain collection, as discussed in the context of detection of MRSP, are the most important reason for this phenomenon. Zogg et al. (2018) published data on high prevalences of ESBL-producing bacteria isolated from urogenital tract infection in Swiss dogs and cats. Unfortunately, these studies focused on uropathogenic *E. coli,* which differ markedly from opportunistic extraintestinal *E. coli* in their virulence and resistance pattern [20]. Moreover, in a second study, not only *E. coli,* but all ESBL-producing Enterobacteriaceae were described, leading to a much higher detected ESBL prevalence than for *E. coli* alone [21].

Selected data from the first Swiss monitoring pilot project on antimicrobial resistance for veterinary pathogens exemplified the value of conducting a Swiss monitoring of resistances for veterinary pathogens. In the future, this monitoring will be even more representative, as isolates from other Swiss laboratories will be included from 2019 on. Furthermore, additional bacterial species, including other relevant Gram-positive and Gram-negative pathogens will be reported. Moreover, animal species under observation need to encompass livestock as well, e.g. pigs and calves, as these animals receive relevant amounts of antimicrobials for therapeutic and/or metaphylactic reasons. Secondly, in order to detect real changes in resistance rates over time, a consistent monitoring with defined methodology is needed and will be introduced in 2019 for Switzerland.

Our results demonstrate 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.

The presence of high levels of resistance to important antimicrobials underlines the need for a systematic monitoring of antimicrobial resistance. Infections in animals caused by multidrug-resistant pathogens must increasingly be expected for veterinary pathogens. As in human medicine, clinical settings in particular are faced with the presence of methicillin-resistant staphylococci and extended-spectrum-beta-lactamase-producing Enterobacteriaceae, linked to a high risk of nosocomial infections. Possible therapy options for severe infections with multiresistant bacteria have to strictly follow the guidelines for prudent use, and critically important antimicrobials for human medicine should not be applied to animals. The presence of multidrug-resistant bacteria 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.

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12

Analysis

12 Analysis

12.1 Association between antibiotic consumption and resistance in animals and in humans, a One-Health approach

12.1.1 Introduction

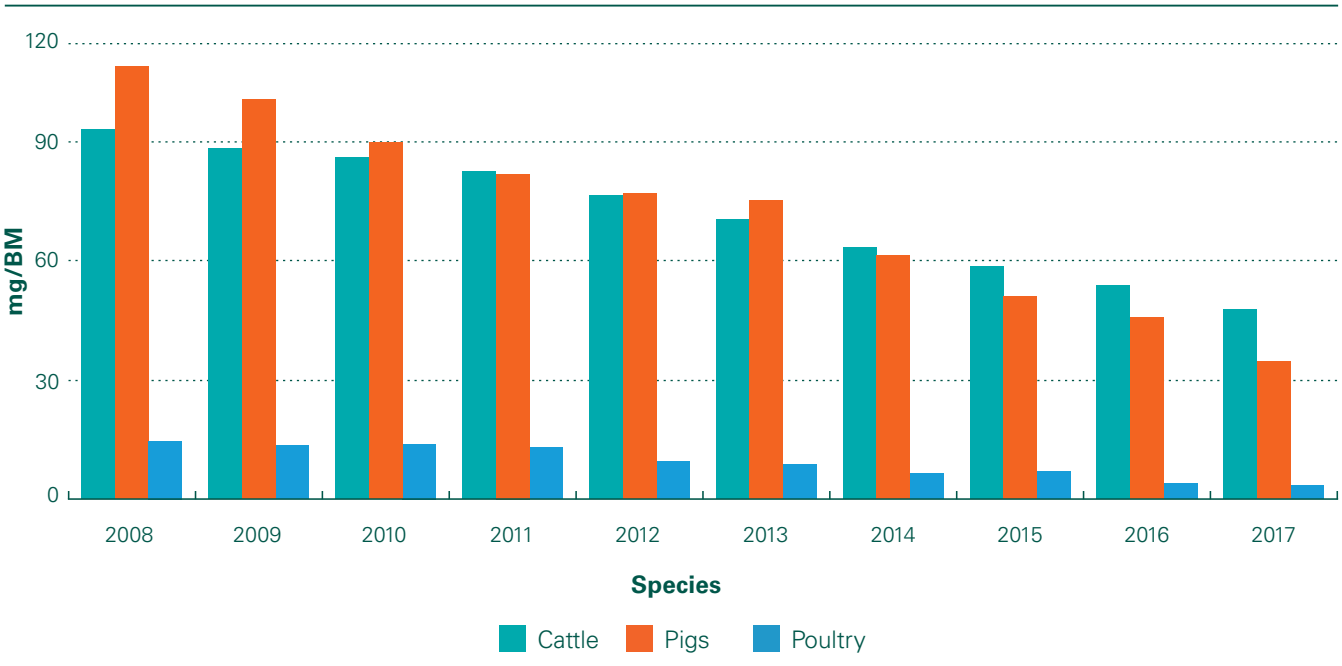
Resistant bacteria are present in multiple settings (e.g. humans, livestock, meat, pets, water, environment), and may be transmitted from one compartment to the other. Therefore, antibiotic resistance represents a difficult challenge. It is a threat that needs to be tackled using a collaborative approach, enrolling stakeholders from different fields to interchange knowledge and find solutions. Antibiotic resistance is a health concern that can only be addressed through a One-Health approach.

Hence, the European Food Safety Authority (EFSA), the European Centre for Disease Prevention and Control (ECDC) and the European Medicine Agency (EMA) launched the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) [1]. In these reports, associations between the use of antibiotics and the prevalence of resistant bacteria were explored for humans and livestock, using data from several European countries. In addition, a possible link between the use of antibiotics in the veterinary setting and the occurrence of resistance in humans was evaluated.

In Switzerland, a One-Health approach to reduce antibiotic resistance (StAR) has also been fostered [2]. In this context, we attempt to jointly analyze human and veterinary data for the first time in this report.

The objective was to analyze the Swiss antibiotic consumption and resistance data in a similar fashion as the JIACRA report. This will allow us to assess the relationship between the antibiotic consumption and resistance for humans and

Figure 12. a: Longitudinal Study Extrapolation of veterinary antibiotic sales (2008–2017).



livestock at national level. However, due to a lack of data and time, only a preliminary analysis could be conducted.

12.1.2 Results

In order to analyze associations between antibiotic usage and resistance in animals, we first had to estimate the usage per animal species from the national sales data. The human use data were transformed into mg of active ingredient per kg of body mass (mg/BM) to allow a better comparison to the veterinary consumption metrics.

Veterinary antibiotic consumption data
As described in this report, veterinary antibiotic sales decreased substantially from 2008 to 2017. Figure 12. a provides an estimate of the distribution among the main livestock species – cattle, pigs and poultry. According to the results from the Longitudinal Study Extrapolation model (see Chapter 13 Materials and methods), we estimate that the largest decrease in antibiotic use occurred in pigs and cattle. During the considered time period, antibiotic consumption in cattle decreased from 96.6 to 49.0 mg/BM, whereas the reduction in the pig sector was from 109.4 to 34.7 mg/BM.

Veterinary antibiotic use and resistance
Results on the association between antibiotic usage and antibiotic resistance were inconsistent. While for some combinations of antibiotic and bacteria the prevalence of resistance decreased with decreasing usage (e.g. tetracycline usage and resistance in *Campylobacter coli* in pigs), this effect was not detectable for the majority of combinations. For some resistances, even an increase in prevalence of resistance was observed with decreasing usage (e.g. tetracycline usage and resistance in *E. coli* in pigs, figure 12.b).

Human antibiotic consumption data
The estimated inpatient antibiotic consumption increased slightly from 2008 to 2017, although a consistent trend was not observed. This value varied from a minimum of 18.0 mg/

Figure 12. b: Association between the use of tetracyclines in pigs and the resistance levels in (A) *E. coli* (p = 0.07) and (B) *Campylobacter coli* (p < 0.05, but the data has a poor model fit).

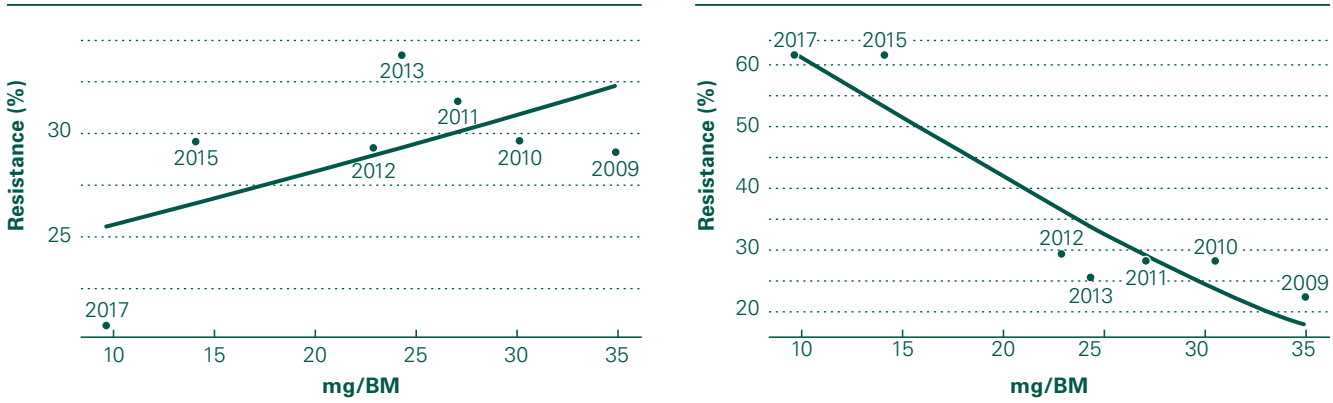
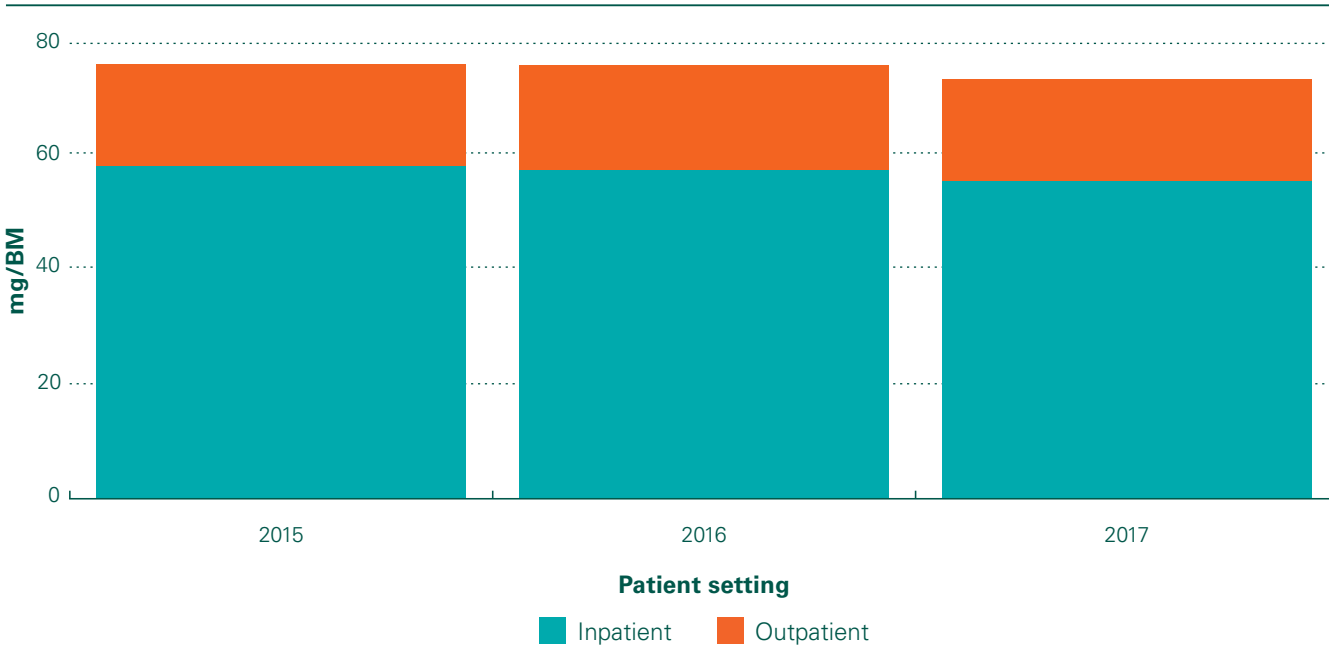


Figure 12. c: Human antibiotic consumption in mg per kg of biomass (mg/BM) in Switzerland (2015–2017).



BM in 2016 to a maximum of 16.3 mg/BM in 2011. With respect to outpatient antibiotic use, the values ranged from 57.8 mg/BM in 2015 to 55.2 mg/BM in 2017. Figure 12. c illustrates the antibiotic consumption in both patient settings from 2015 to 2017.

Human antibiotic consumption and resistance

The models assessing the relationship between inpatient antibiotic consumption and resistance also yielded inconsistent results. The inpatients' use of 3rd and 4th generation cephalosporins was associated with an increased prevalence of resistance to this group (namely cefotaxime and ceftriaxone) in *E. coli* in inpatient blood isolates. On the other hand, the inpatient consumption of quinolones (mainly fluoroquinolones) was negatively associated with the resistance prevalence to ciprofloxacin in blood *E. coli* isolates from inpatients (Figure 12. d).

Comparison between antibiotic consumption in veterinary and human medicine

Figure 12. e provides a comparison of the total antibiotic consumption in livestock and humans, using mg/BM as the consumption metric. Livestock species presented a reduced antibiotic consumption per biomass when compared to the use of these substances in human medicine.

Antibiotic consumption in livestock and resistance in human isolates

No statistically significant results were obtained when assessing the relationship between cephalosporin consumption in livestock and the prevalence of resistance in *E. coli* blood isolates from outpatients. This analysis was conducted for resistance to cefotaxime and ceftriaxone in human outpatients.

Figure 12. d: Association between (A) the inpatient use of 3rd and 4th generation cephalosporins and the occurrence of cefotaxime resistance in inpatients ($p < 0.05$); (B) the use of quinolones in inpatients and the occurrence of ciprofloxacin resistance ($p < 0.05$), in blood *E. coli* isolates in hospitalized patients.

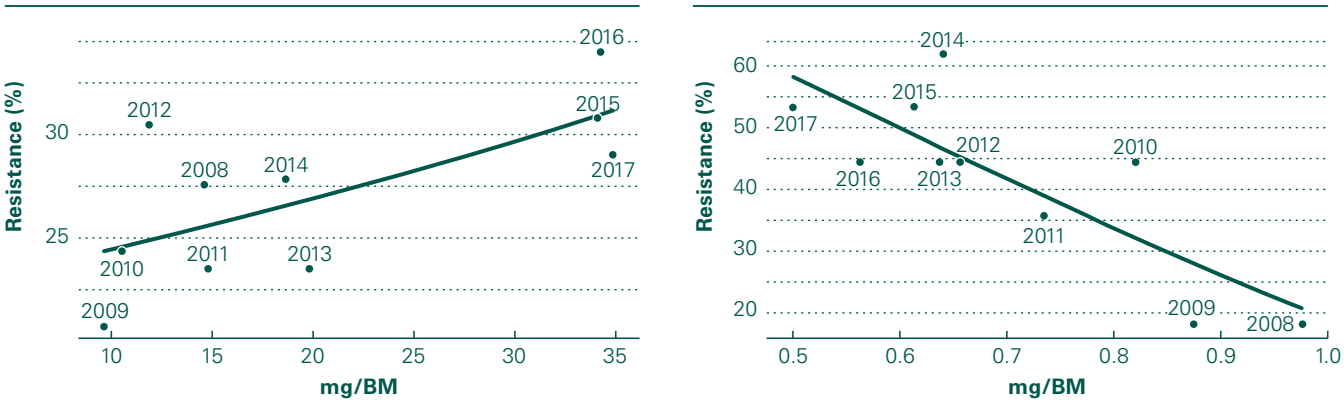
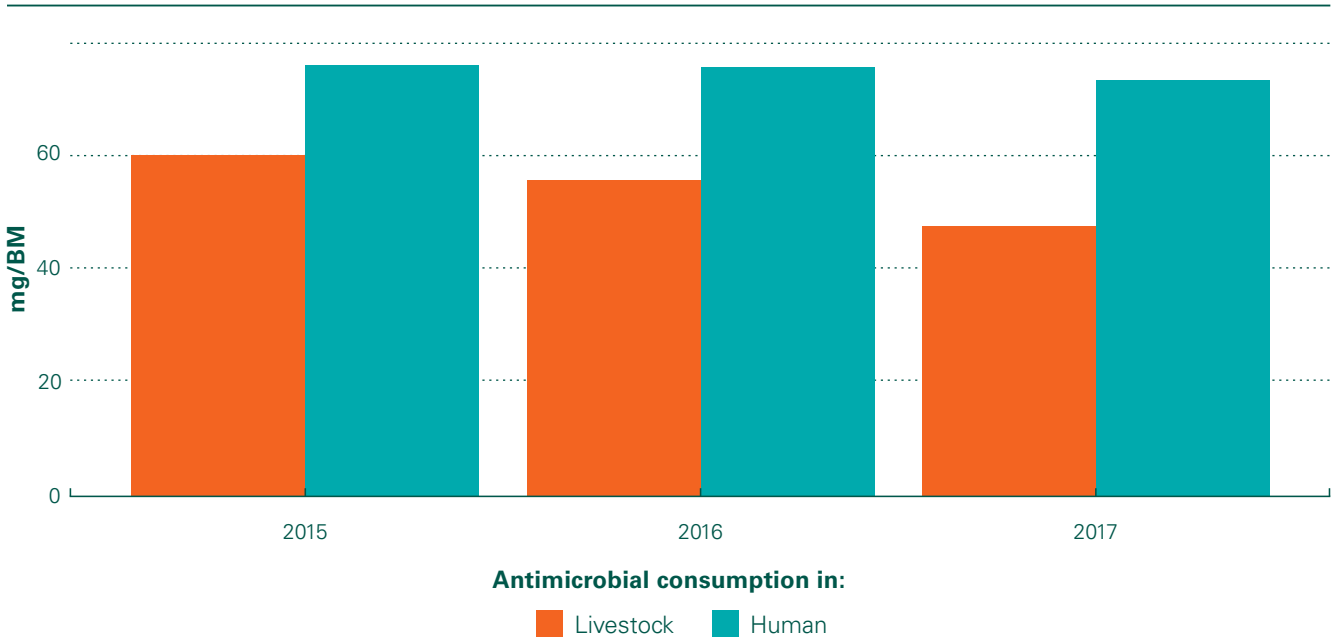


Figure 12. e: Antibiotic consumption in livestock and humans in mg of active ingredient per kg of biomass (mg/BM) for the time period between 2015 and 2017.



12.1.3 Discussion

For the first time in Switzerland, this analysis compared human and veterinary data on antibiotic use, and attempted to evaluate associations between use and resistance.

Veterinary antibiotic sales decreased substantially from 2008 onwards. The reduction of antibiotic consumption in pigs and cattle was estimated to contribute the most to the abovementioned decrease. Such a trend is linked to several factors, of which the most important are likely to be: a) the bovine viral diarrhea eradication program; b) the commercialization of porcine circovirus-2 vaccines; c) multiple campaigns to raise awareness on the topic of prudent use of antibiotics; d) several measures to foster prudent use. With respect to the use of antibiotics in the human sector, an overall decrease was observed from 2015 to 2017. As reported for 18 of the 28 countries participating in JIACRA, the antibiotic consumption corrected for the population biomass in Switzerland was lower in food-producing animals than in humans. However, caution should be used when comparing the antibiotic consumption in the veterinary and human settings. Due to data limitations in the veterinary sector, a weight-based indicator was used. It is known that treatment incidence metrics provide a better estimate of the antibiotic selection pressure applied in the population. The selected metric for this analysis might have influenced the results obtained. With the initiation of the "Informationssystem Antibiotika in der Veterinärmedizin" (IS-ABV) database, the data required for the use of treatment incidence metrics will also be available for livestock species. This is an improvement which should be applied in future analysis. In addition, mg/biomass in humans was calculated using an average body weight of 62.5 kg. As antibiotic therapies vary considerably in mg, defined daily doses (DDD) are usually used when analyzing human consumption data. The corresponding numbers are analyzed in chapter 5 of this report.

It is generally accepted that the use of antibiotics is linked to the selection of resistant bacteria. Nonetheless, our analysis showed inconsistent results, with a limited number of models yielding a positive and statistically significant association and a good model fit. This is in contrast to the JIACRA report, in which more associations could be established. However, it should be emphasized that the JIACRA analysis included more data points. In addition, data points represented individual countries in a given year (in our analysis, data points represented individual years in the same country).

Several factors might have influenced the obtained results. Firstly, the analyses were conducted with a very limited number of data points, making it difficult to test potential associations between the use and resistance of antibiotics. In addition, temporality was not taken into account, assuming that the levels of antibiotic resistance were independent for each year. It should also be noted that this analysis is subjected to what has been described as the ecological fallacy. This is related to the fact that the measurements of antibiotic use and resistance were not acquired from the same individuals.

As also mentioned in the JIACRA report, differences between the systems of collection, testing and reporting of data on use of antibiotics and antibiotic resistance from humans and food-producing animals hamper direct comparisons. As an example, all isolates from food-producing animals are from healthy animals, whereas all human isolates are from ill patients. Co-resistance might also play a role, given that it might prevent a decrease of resistance prevalence when reducing the use of a given antibiotic class. This was not taken into account in the analyses performed. It should also be stressed that multiple factors can influence the occurrence of resistance in bacteria and not solely antibiotic use (e.g. infection dynamics of bacteria). Finally, in a complex ecosystem, reducing one single influential factor (e.g. the use of antibiotics in animals) will not have an immediate and direct effect on the measured outcome. In the present case in particular, resistance will persist in other ecological niches, even if one of those niches has experienced a decrease in antibiotic use.

As previously described, the analysis performed has limitations that need to be acknowledged. However, it establishes a first step to improve the usefulness of monitoring data on antibiotic use and resistance. Certain data limitations will be improved in the future. Given that antibiotic consumption data for outpatients were only available for a short period of time (2015–2017), associations with outpatient resistance were not tested. This remains an objective to be reached in the next years. The associations between the use of antibiotics in livestock and the occurrence of resistance in the outpatient setting will also be expanded to more substances in the upcoming years. With respect to the methodological limitations, ecological analyses are not tailored to establish causation, but they are useful in generating and exploring hypotheses. Data quality allowing, other methodologies may be used in the future.

In conclusion, a preliminary analysis of the association between antibiotic consumption and resistance was conducted using data collected at the national level. Further improvements will be made to the analysis in the upcoming years. With improved data (e.g. in veterinary medicine more exact data on the use of antibiotics; in human medicine more data on the use of antibiotics in outpatients), more significant analyses to analyze possible associations between use of antibiotics and resistance will be feasible. The investigation conducted also allowed us to highlight some of the difficulties in producing a combined human-livestock analysis.

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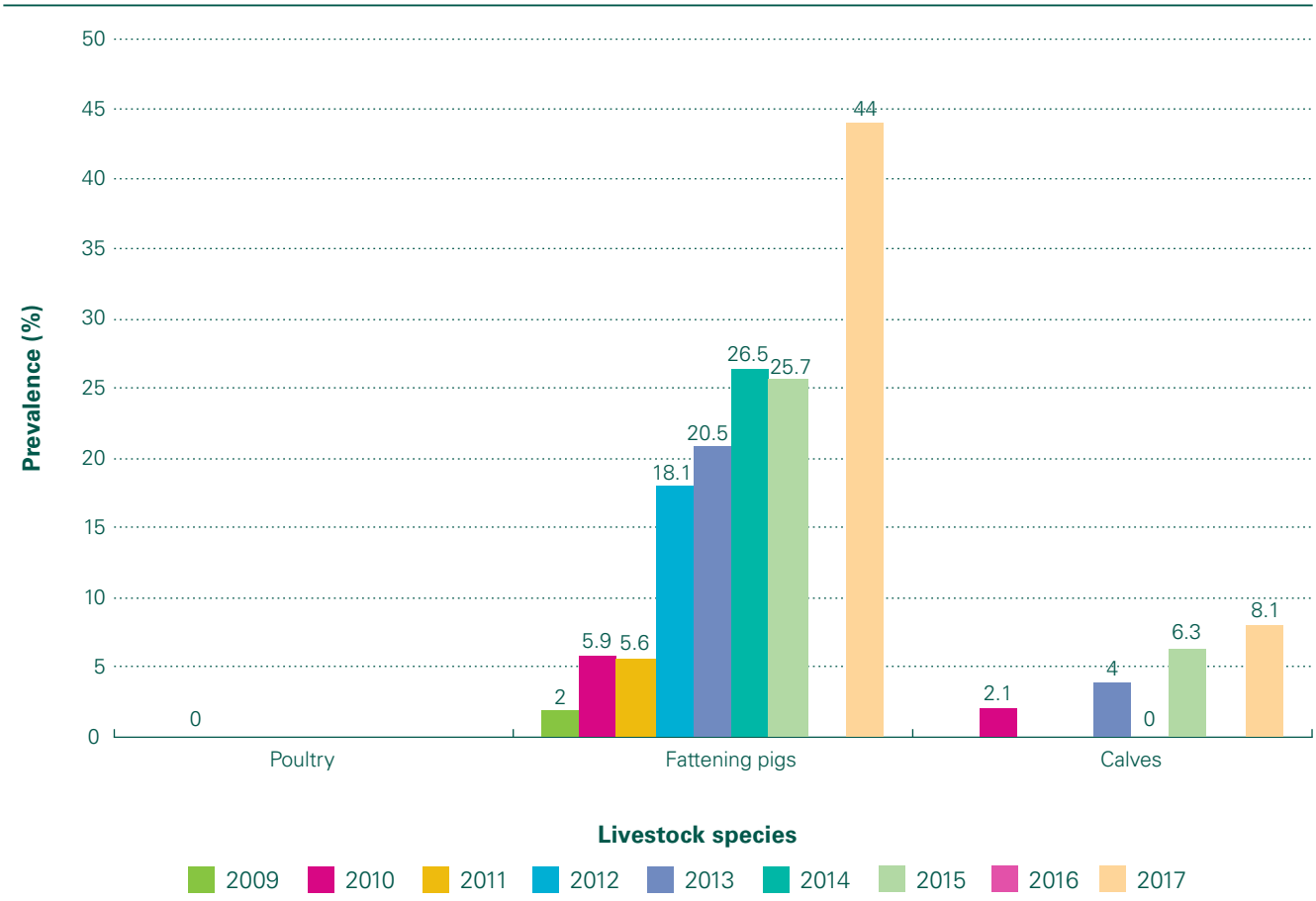
12.2 Molecular features of Swiss methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus (*S.*) *aureus* is a commensal bacterium, which is found on skin and soft tissues in approximately one third of healthy humans and is also part of the normal flora of a broad variety of animals [1] [2]. Infections with *S. aureus* can occur when skin or tissues are damaged. Penicillins were the first line of treatment for *S. aureus* infections, but resistance developed quickly after these substances were marketed. The introduction of beta-lactamase-resistant modified semi-synthetic penicillin such as methicillin in 1959 seemed to solve the problem. However, one year later, the first methicillin-resistant *S. aureus* (MRSA) appeared [3]. Resistance to methicillin is not mediated by a beta-lactamase. Instead, it occurs due to the acquisition of a mobile genetic element called staphylococcal cassette chromosome mec (SCCmec). SCC carry a *mecA* gene, which encodes an altered penicillin-binding protein (PBP2a) with decreased affinity to beta-lactam antibiotics [2].

In the following decades, MRSA emerged as a major cause of health-care-associated infections in humans. Its occurrence was restricted to hospitals and other health care facilities ("hospital-acquired (HA) MRSA"). In the 1990s, an increasing incidence of human MRSA infections that appeared independently from hospitals was observed [4]. These so-called "community-acquired (CA) MRSA" had been reported by many countries worldwide. With the emergence of MRSA in animals more recently, MRSA has gained a One-Health dimension [5]. Numerous studies have shown that especially pigs can be heavily colonized with MRSA [6] [7] [8] [9]. These "livestock-associated (LA) MRSA" can be associated with infections not only in animals but also in humans [9] [10]. Humans with regular and close contact to pigs, such as farmers, slaughterhouse workers and veterinarians, have a higher risk of being colonized with LA-MRSA, and thus of developing infections [6] [11] [12] [13] [14]. Although production and clinical use of methicillin has stopped, the term "MRSA" has persisted and nowadays describes *S. aureus* which are completely resistant to beta-lactam antibiotics. The treatment of MRSA in human settings is even more complicated due to the acquisition of a variety of additional multiple resistances, including vancomycin, linezolid and daptomycin [2].

Figure 12.2 a: MRSA prevalence in Swiss livestock between 2009 and 2017.



The identification of a phenotypically resistant, *mec*A-negative MRSA from bovine mastitis has led to the discovery of a *mecA* divergent gene variant called *mec*C (formerly *mecA*LGA251) [15]. This variant shares only 69% homology to the *mec*A gene. Significant differences in susceptibility testing have been revealed: in contrast to PBP2amecA, PBP2amecC has a higher affinity to oxacillin than to cefoxitin [16]. Until now the prevalence of MRSA with this new variant is very low [17]. A third *mec*A gene variant was recently found in *Macrococcus caseolyticus*, which is named *mec*B, since this variant was discovered before the *mec*C variant [18]. In 2018, the first mecB carrying *S. aureus,* isolated from a patient in Germany, was published [19].

In order to understand the epidemiology of MRSA and the risk for the transmission from animals to humans, an in-depth look into the molecular characteristics of this pathogen is mandatory. By means of multilocus sequence typing (MLST), based on sequence data of internal fragments of seven housekeeping genes, a highly discriminatory and reproducible tool was established. Moreover, with the introduction of the eBURST analysis, an internationally standardized grouping of related sequence types (STs) and clonal complexes (CC) was implemented [20] [21] [22]. Although MLST is the gold standard for epidemiological purposes, the method is rather laborious and expensive. Therefore, typing of the polymorphic X region of the protein *A* gene (*spa* gene) was established and proved to be highly concordant with the grouping of sequence types [23] [24].

This chapter compares molecular features of Swiss MRSA strains, isolated from livestock and meat thereof with MRSA isolates from healthy veterinarians and farmers as well as human isolates from Swiss hospitals. With this analysis, useful information on the distribution of HA-, CA- and LA-MRSA in human and veterinary settings can be provided, helping to obtain insights into transmission risks in Switzerland.

12.2.1 MRSA carriage in Swiss livestock

Poultry

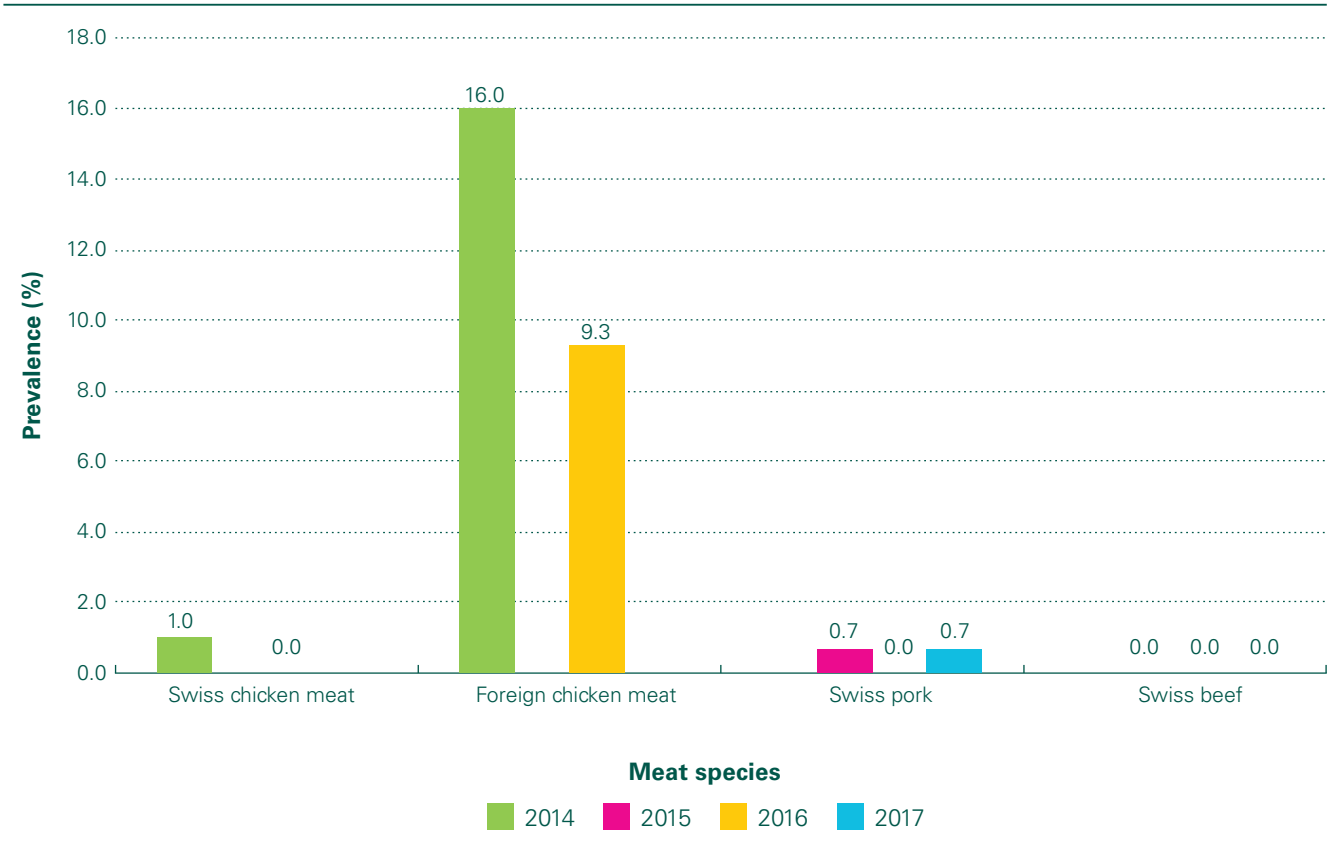
In 2010, 398 cloacal swabs from broilers at slaughter were analyzed for MRSA. No MRSA was detected (Figure 12.2.a). Therefore, MRSA in broilers was not included in the regular antimicrobial resistance monitoring in Switzerland, as the risk for humans is assumed to be very low.

Calves

In 2017, 297 nasal swabs were collected from slaughter calves. Twenty-four MRSA isolates were obtained from this random sample (8.1%, Figure 12.2.a). A steady increase of MRSA in samples from Swiss calves could be observed, starting with a prevalence of 2.1% in 2009 and increasing to 4.0% in 2013 and 6.3% in 2015.

Of the 24 MRSA isolates in 2017, 23 isolates belonged to the LA-MRSA type (14 × *spa* type t011, 7 × *spa* type t034, 2 × *spa* type t17339) (Figure 12.2.c). The two *spa* types t17339

Figure 12.2 b: MRSA prevalence in fresh meat between 2014 and 2017.



were so far found exclusively in Swiss livestock. One MRSA belonged to *spa* type t127 (ST1), a CA-MRSA.

Fattening pigs

In Switzerland, the occurrence of MRSA in fattening pigs at slaughter increased continuously and significantly from 2009 to 2017. In 2009, the prevalence was assessed at 2.0% [24], in 2011 at 5.6% [25], in 2013 at 20.8%, in 2014 at 26.5% and in 2015 at 25.7%. The prevalence of MRSA among fattening pigs increased to 44.0% in 2017 (Figure 12.2.a).

All 131 isolates belonged to the LA-MRSA type (63 × *spa* type t034, 61 × *spa* type t011, 3 × *spa* type t1451, 2 × *spa* type t899, 1 × *spa* type t2330, 1 × *spa* type t2876).

12.2.2 MRSA in fresh meat

MRSA in chicken meat

In 2014, fresh chicken meat samples were analyzed for MRSA for the first time. Out of 319 samples (194 from domestic production and 125 from foreign production), 22 MRSA were isolated. Twenty MRSA were derived from chicken meat samples produced abroad (16%), whereas only two strains were isolated from Swiss chicken meat (1.0%). In 2016, analyses of 302 samples revealed a decrease of the MRSA prevalence in chicken meat produced abroad (9 isolates, 9.3%). No MRSA was detected in Swiss chicken meat (Figure 12.2.b).

Eight isolates were typed as LA-MRSA (3 × *spa* type t034, 3× *spa* type t1430, 2 × *spa* type t2123). One isolate belonged to *spa* type t153, which is not categorized (Figure 12.2.c).

MRSA in beef

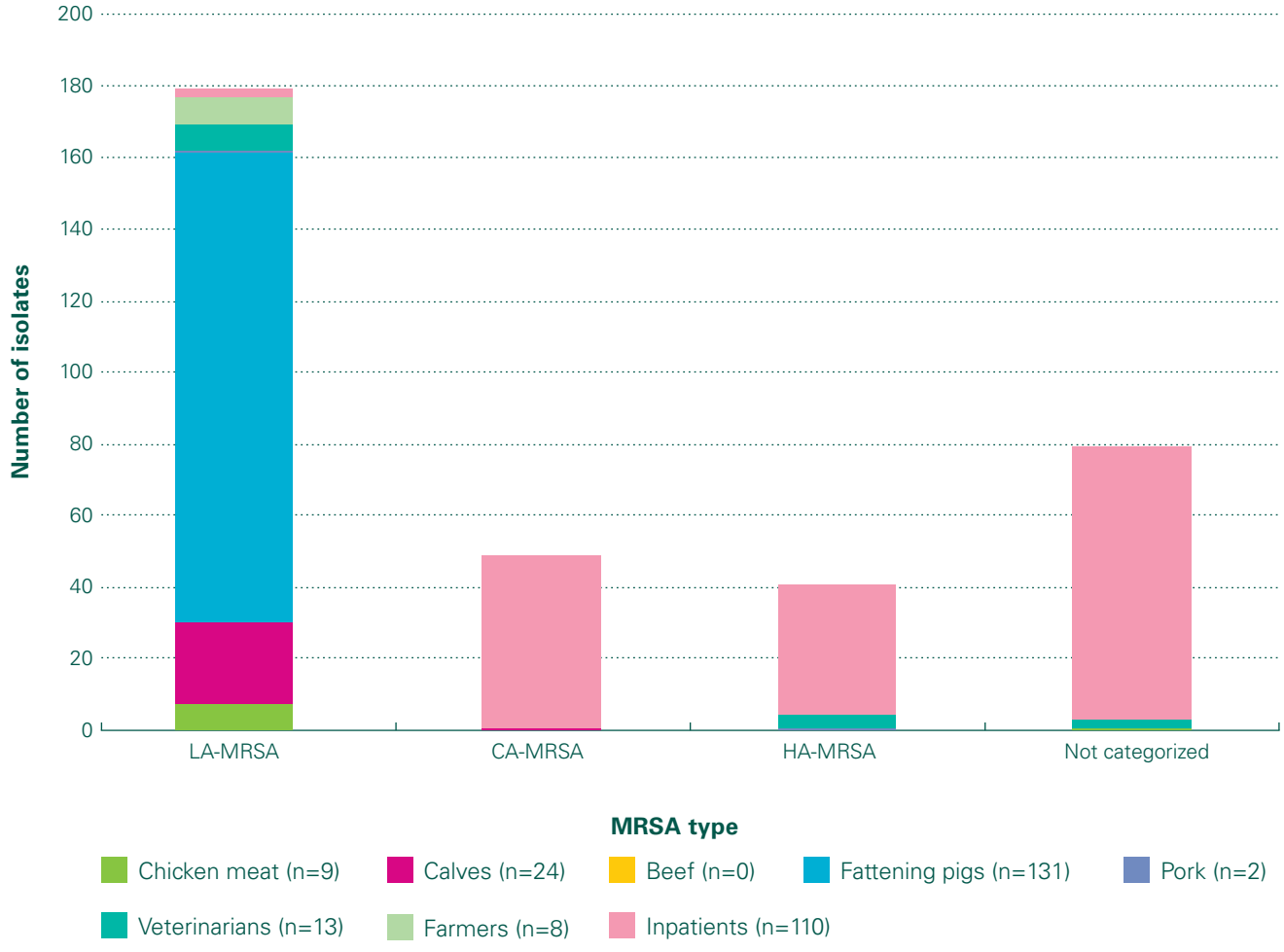
Fresh beef was not investigated in 2014. In 2015 and 2017, all 298 and 299 samples, respectively, were tested negative for MRSA (Figure 12.2.b).

MRSA in pork

In 2014, pork was not investigated. In 2015, two out of 302 Swiss fresh pork meat samples were tested positive for MRSA (0.7%). Moreover, two out of 301 examined samples were tested positive for MRSA in 2017, corresponding to the same prevalence of 0.7% as in 2015 (Figure 12.2.b).

One MRSA belonged to the LA-MRSA type (*spa* type t034), whereas the other MRSA isolate was categorized as HA-MRSA (spa type t002) (Figure 12.2.c).

Figure 12.2 c: MRSA types from humans, animals and meat in 2016/2017.



12.2.3 MRSA carriage in Swiss humans

MRSA in healthy veterinarians and farmers

In 2017, two studies on MRSA carriage in Swiss veterinarians and farmers were conducted on a voluntary basis at the ZOBA. At the annual conference of the Swiss Society of Veterinarians (GST), veterinarians were asked to take nasal swabs from themselves. Additionally, all volunteers provided information on their working area. A total of 212 veterinarians participated. Nearly half of the veterinarians worked exclusively with small animals (n=102), whereas 62 veterinarians worked in a large animal practice. Twenty veterinarians worked in combined practices with small and large animals without horses, another two had combined practices with horses, and 13 were equine specialists (Table 12.2.1).

The overall detection rate for MRSA in nasal swabs from Swiss veterinarians was 6.1 % (95 % CI 3.6–10.2).

A total of 13 MRSA were isolated, of which 7 belonged to the LA-MRSA type (*spa* type t011), whereas four were typed as HA-MRSA (2 × *spa* type t003, 1 x *spa* type t118, 1 × *spa* type t038), two MRSA (*spa* types t7424 and t133) could not be categorized (Figure 12.2.c). LA-MRSA of *spa* type t011 were detected in equine specialists (3), large animal veterinarians (2) and in veterinarians working in combined practices with or without horses.

In contrast, in small animal specialists, only HA-MRSA (2 × *spa* type t003, 1 × *spa* type t038) and one non-categorized MRSA (*spa* type t7424) were detected.

Interestingly, in one large animal veterinarian, an HA-MRSA type was detected (*spa* type t118) which could not be derived from animals. A second non-categorized MRSA was detected (*spa* type t7424) in a large animal veterinarian. No CA-MRSA was detected.

In 2017, a comparable study with Swiss farmers was conducted at the Suisse Tier exhibition. In total, 156 farmers took nasal swabs from themselves, in some cases more than one person per farm was sampled. Eight MRSA carriers could be identified (5.1 % [95 % CI 2.6–9.7]). All MRSA belonged to the LA-MRSA type (Figure 12.2.c). Three farmers had fattening cattle exclusively, another farmer exclusively fattening pigs. Of the remaining four farmers, one farmer held dairy and fattening cattle, two farmers poultry and fattening cattle and one farmer fattening cattle and pigs.

MRSA in hospital patients

MRSA in the inpatient setting is of major concern as a cause of health-care-associated infections and bacteremia. The proportion of MRSA carriage among all *S. aureus* isolates from patients decreased from 14 % in 2004 to 8 % in 2014 [26]. Strong differences were found between the French- and Italian-speaking regions and the German-speaking region, with lower proportions in the latter. As no regular typing of all MRSA isolates in human medicine is conducted, available *spa* types of 163 MRSA strains, isolated in 2017 from patients of the University hospital Basel (n=110) and the cantonal hospital Luzern (n=53) were grouped for the occurrence of HA-, CA- and LA-MRSA (Figure 12.2.c). Thirty-six HA-MRSA (*spa* type t002, t032, t118, t038, t003, t067) were detected (22.1 % [95 %CI 16.4–29.1]). Community-acquired MRSA were found in 48 patients (*spa* type t008, t012, t019, t021, t044, t127, t685, t304) (29.5 % [95 %CI 22.9–36.9]). Two LA-MRSA, *spa* type t011, were found within this group of human MRSA (1.2 % (95 % CI 0.3–4.4)). The remaining 77 isolates belonged to diverse, non-categorized MRSA (*spa* types t153, t133, t7424, t056, t065, t084, t085, t088, t091, t11475, t1198, t121, t1339, 1473, t14949, t1510, t159, t2334, t1816, t1597, t2231, t318, t359, t3169, t4256, t334, t4103, t321, t69556, t665, t447, t688, t583, t852, t570, t843, t4897, t790, t437, t657, t303, t3841, t5100, t6172, t662).

Table 12.2.1: Detection of MRSA in nasal swabs from Swiss veterinarians in 2017.

Working area	Samples (n)	MRSA positive (n)	Detection rate (%)	95%CI
Small animal	102	4	3.9	1.5–9.6
Small animal and horses	6	0	0	0.0–39.0
Large animal	62	4	6.5	2.5–15.4
Large animal and horses	2	1	50	9.4–90.5
Large and small animals	20	1	5	0.8–23.6
Horses	13	3	23	8.1–50.2
Others:				
Laboratory	1	0	0	0.0–79.3
Administration	2	0	0	0.0–65.7
Industry	1	0	0	0.0–79.3
Not known	3	0	0	0.0–56.1
Total	212	13	6.1	3.6–10.2

12.2.4 Discussion

Swiss fattening pigs have shown a strong increase in the prevalence of MRSA carriage over the last ten years, reaching 44.0% in 2017. Factors influencing this increase were analyzed by Bangerter et al. (2016) [27]. Moreover, in Swiss calves at slaughter, a similar trend was observed, albeit at a lower level (Figure 12.2. a). The zoonotic potential of such strains via meat or direct animal contact is of public health concern.

So far, the risk for public health due to ingestion of MRSA-positive meat and products is assumed to be low [27]. This was underlined by our data, as the prevalence of MRSA in Swiss pork, beef and chicken meat is very low (Figure 12.2. c). MRSA were only detected in chicken meat from abroad, but with a decreasing trend from 2014 to 2016. The detected MRSA belonged to the LA-MRSA type.

In contrast, the risk of humans being colonized by MRSA via close contact to animals carrying MRSA is evident. Persons at risk, such as farmers, veterinarians and slaughterhouse workers, are more likely to be colonized with MRSA than the community at large [29]. Persistence of MRSA carriage depends on duration and intensity of animal contact and was shown to last in the absence of exposure, e.g. during holidays [30] [31]. The study with Swiss veterinarians and farmers in 2017 revealed that 6.1% of the sampled veterinarians and 5.1% of the tested Swiss farmers carried MRSA in their nasal mucosa. These detection rates are clearly higher than data from comparable studies in the past; Huber et al. (2011) detected MRSA in 3% of nasal swabs from persons at risk [32]. Moreover, another study from 2012 revealed 3.8% MRSA in Swiss veterinarians [33]. The majority of MRSA from veterinarians and farmers belonged to the LA-MRSA type (Figure 12.2.c). This is in line with the findings on MRSA isolated from livestock, which also belong to the LA-MRSA type and consist mainly of *spa* types t034 and t011. In these cases, transmission from animal to humans is likely. Interestingly, veterinarians specialized in small animals turned out to be carriers of HA-MRSA, which cannot be derived from animals but from human to human contact. Moreover, especially in dogs, *S. aureus* does not belong to the normal flora. Therefore, the risk of transmission of MRSA from dogs to humans is very low. In contrast, equine specialists have a higher risk for transmission of MRSA from horses to veterinarians. This was previously published by Sieber et al. (2011) and our data confirmed that LA-MRSA is more frequently found in veterinarians working with horses [34].

The increasing MRSA colonization of Swiss livestock may lead to an increasing MRSA colonization of Swiss persons at risk and, in consequence, to a higher proportion of patients entering Swiss medical care facilities. Our data has shown that presently the vast majority of MRSA isolated from inpatients in two hospitals in the German-speaking region are HA- and CA-MRSA. This was also recently published by Seidl et al. (2015) for inpatient MRSA from the University Hospital Zurich [35]. However, the detection of a LA-MRSA in two patients indicates that the above-mentioned transmission can occur in Switzerland.

Thanks to more rigorous hygiene management in Swiss hospitals, the overall proportion of MRSA among *S. aureus* isolates has decreased over the last decade. However, the steady increase of MRSA in Swiss livestock should be monitored carefully, as it may represent a potential risk for transmission of MRSA into health care facilities.

Therefore, continuous monitoring, including molecular typing of both human and animal MRSA isolates, is needed.

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13

Materials and methods

13 Materials and methods

13.1 Data on antibacterial consumption in human medicine

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

Data were collected regarding antibacterials for systemic consumption (group J01 of the ATC classification), antibiotics for treatment of tuberculosis (ATC group J04AB) and agents against amoebiasis and other protozoal diseases (ATC group P01AB) [1]. Antibiotic consumption (in grams or millions of International Units) were converted into defined daily doses (DDD) using the 2016 release of the DDD by the World Health Organization Collaborating Centre for Drug Statistics Methodology (see Annex I).

13.1.2 Data sources in the inpatient setting

For the inpatient setting, a network of voluntary acute care hospitals participating in the surveillance system anresis.ch was set up in 2004. We excluded data from ambulatory, rehabilitation, as well as long-term care geriatric and long-term care psychiatric units of these hospitals and specialized clinics. To measure the representativeness, we used the number of hospitals, number of beds (activity type A), number of bed-days (without days of discharge) from general acute care hospitals (typology K111-K123 from FOPH) [2]. Data were collected from the entire hospitals, and separately from the adult intensive care units (ICUs) when possible. In this report, we described the antibiotic consumption for the period 2007 to 2017. Sixty-two hospital sites participated in 2007 and 67 in 2017, of which 39 were small-size (<200 beds), 19 medium-size (200–500 beds) and 9 large-size hospitals (>500 beds, which includes the five Swiss university hospitals). In 2016, the hospital network represented 41 % of the total number of acute somatic care hospitals and 64 % of all beds in this category in Switzerland. In 2007, thirty-seven hospital sites also provided data on adult ICUs. This number increased to 41 (17 small-size, 16 medium-size and 8 large-size hospitals) in 2017, representing 64 % 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 DDDs per 100 occupied bed-days and as DDDs 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 DDDs, towards a slightly higher number of DDDs/100 bed-days.

13.1.3 Data sources in the outpatient setting

In the outpatient setting, data were based on two sources of data:

(i) Data for the years 2015 to 2017 were collected on behalf of the Swiss Federal Office of Public Health through IQVIA™ database which provides pharmaceutical sales data. This exhaustive dataset included the antibiotics sold to pharmacies and dispensing physicians. As IQVIA™ follows the EphMRA classification, we accordingly collected antibiotic use data from the J01, D10B (minocycline, doxycycline oral, lymecycline), G01A1 (metronidazole oral, ornidazole oral), G04A1 (fosfomycin) and G04A9 (nitrofurantoin) classes. It allowed us to measure antibiotic consumption by linguistic region (German-speaking, French-speaking and Italian-speaking parts of Switzerland).

(ii) PharmaSuisse, the Swiss Society of Pharmacists, provided data for the years 2013 to 2017 through the updating of the database that is entrusted to the professional cooperative of the Swiss pharmacists (OFAC, Genève). Prescription orders were collected at the individual level from the public pharmacies and invoices produced for health insurance companies on behalf of pharmacies. The coverage was approximately 65 % of all pharmacies in Switzerland. All antibiotics were dispensed with a prescription. The data included the quantities of antibiotics sold to a number of individuals per age group (<2; 2–11; 12–17; 18– 64; >64 years of age).

The major difference between both datasets is that prescriptions from self-dispensing physicians were included in the IQVIA™ database and not included in the PharmaSuisse database.

The measurement units for reporting antibiotic consumption in the outpatient setting are DDDs per 1,000 inhabitants per day (DID) and number of packages per 1,000 inhabitants per day [1]. The quantity of J01 group antibiotics was the denominator when measuring relative consumption.

13.1.4 Categorization of antibiotics in 2017 Core-Access, Watch and Reserve groups

In 2017, the WHO Expert Committee on Selection and Use of Essential Medicines recommended the categorization of antibiotics into the following categories: Access, Watch and Reserve (AWaRe) [3]:

- The Access group contains first- and second-choice antibiotics for empirical treatment of common infections.
- The Watch group contains antibiotic classes within the Access group with higher potential for selecting and promoting the spread of resistance. Antibiotics of this group should be limited to a small number of syndromes and patient groups.
- The Core-Access group are those antibiotics in the Access group that are not part of the Watch group.
- The Reserve group contains antibiotic classes that are of crucial importance for the treatment of multidrug-resistant organisms. They should be used as last-resort treatment, when all other alternatives have failed.
- Antibiotics that are not listed in one of the above groups fall into the category "Others."

See Annex I for the list of antibiotics and their corresponding AWaRe group.

References

[1] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2017. Oslo, 2018. Available at www.whocc.no/atc_ddd_index/

[2] Federal Office of Public Health, Chiffres-clés des hôpitaux suisses, 2016. Available at www.bag.admin.ch/cchs

[3] WHO Expert Committee on Selection and Use of Essential Medicines. EML 2017, Part III Guidance for interpreting the AWaRe categorization of antibiotics for drug utilization studies. Geneva, 2018.

13.2 Data on antimicrobial sales in veterinary medicine

The list of veterinary products which were granted marketing authorization during the years under review in this report (2016 and 2017) was extracted semi-automatically from the internal Swissmedic database on the basis of their ATCvet codes [1] and completed with the products which were withdrawn from the market in the period under review. Marketing authorization holders were then asked to report sales figures for their products. Products authorized for export only were excluded. They cannot be used in Switzerland and do not contribute to the development of resistance in Switzerland.

The obtained data was transmitted from Swissmedic to the Federal Food Safety and Veterinary Office (FSVO) where it was entered and assessed in a Microsoft Access database specifically developed for this purpose. The entry of each product consists of a unique identification number, the brand name, the ATCvet code, information on the authorized method of application and the target animal group. Pharmaceutical premixes are indicated separately. The entry additionally includes the number of sold "basic units" (e.g. vials [incl. volume], tablets, injectors, tubes or pouches/bags [incl. weight]).

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. The volume of active substance contained in each product and each basic unit is recorded. In the case of antimicrobials declared in International Units, conversion factors according to the template of the European Surveillance of Veterinary Antimicrobial Consumption Project (ESVAC) of the European Medicines Agency [2] 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. Target animal groups are recorded on the basis of marketing authorizations. The only distinction that can be drawn is between "farm animals," "pets" and "mixed group" because specific records on the actual target animals of administered products are not available. Specific animal species or age groups were only recorded if these were clearly mentioned in the marketing authorization (e.g. intramammary injectors for cows or products to treat piglets).

References

[1] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATCvet classification 2015. Oslo, 2014, http://www.whocc.no/atcvet

[2] European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2015. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013. EMA/387934/2015

13.3 Bacterial isolates from humans (clinical probes)

Currently, 25 microbiology laboratories are linked to anresis.ch (www.anresis.ch). These laboratories send their 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. Nevertheless, all main analyses were performed on invasive isolates only, to allow comparison with international data. Additionally, for *E. coli* and *S. aureus,* data from outpatients (ambulatory physicians or hospital outpa-

tient departments) were included and labelled as such. Screening results and antibiotic resistance test results done as reference laboratory are labelled specifically and are not included in this report. In case of multiple isolates, only the first isolate from a given patient and calendar year was taken into account. anresis.ch provides epidemiological information such as sample location, provider of the sample, patient sex and age. In contrast, clinical data such as diagnosis, therapy or outcome are not available. Although we prefer quantitative antibiotic-resistance-testing results, the majority of microbiological laboratories unfortunately send only 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 by Swissmedic and are enrolled in at least one external quality control program.

Non-susceptibility is defined as an isolate being either resistant or intermediately susceptible to a given antibiotic. Non-susceptibility to an antibiotic group is defined as a microorganism with non-susceptibility against at least one antibiotic of the given group. Multiresistance was analyzed in accordance with the EARS-Net methodology, to allow comparability with European data. The Wilson score method [1] was used for calculation of the 95% confidence interval of proportions of non-susceptibility. Independence between two factors (e.g. co-resistance in MRSA/MSSA or PNSP/PSSP, comparison of resistance rates in invasive and outpatient samples) was analyzed by means of the Fisher Exact Test. Logistic regression was used for analysis of trends. A $p < 0.05$ of a z-test for the predictor variable "year" was considered as significant and is represented by an arrow. Statistical analyses were performed using R version 3.4.3.

Table 13. a: Antimicrobial resistance-monitoring-program in 2016.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cecum – broilers	496	*Campylobacter spp.*	170
Cecum – broilers	196	*E. coli*	190
Cecum – broilers	349	Enterococci	278
Cecum – broilers	307	ESBL-prod. *E. coli*	160
Cecum – broilers	307	Carbapenemase-prod. *E. coli*	0
Meat – broilers	302	ESBL-prod. *E. coli*	149
Meat – broilers	302	Carbapenemase-prod. *E. coli*	0
Meat – broilers	302	MRSA	9
Clinical material / all species	–	*S. enteritidis*	39
Clinical material / all species	–	*S.* Typhimurium	54
Clinical material / all species	–	Monophasic *S.* typhimurium	13

Table 13. b: Antimicrobial resistance-monitoring-program in 2017.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cecum – fattening pigs	296	*Campylobacter spp.*	170
Cecum – fattening pigs	216	*E. coli*	197
Cecum – fattening pigs	296	ESBL-prod. *E. coli*	52
Cecum – fattening pigs	296	Carbapenemase-prod. *E. coli*	0
Nasal swab – fattening pigs	298	MRSA	131
Cecum – calves	204	*E. coli*	194
Cecum – calves	296	Enterococci	175
Cecum – calves	304	ESBL-prod. *E. coli*	101
Cecum – calves	304	Carbapenemase-prod. *E.coli*	0
Nasal swab – calves	297	MRSA	24
Meat – fattening pigs	302	ESBL-prod. *E. coli*	1
Meat – fattening pigs	301	MRSA	2
Meat – fattening pigs	302	Carbapenemase-prod. E.coli	0
Meat – beef	299	ESBL-prod. *E. coli*	2
Meat – beef	299	MRSA	0
Meat – beef	299	Carbapenemase-prod. *E.coli*	0
Clinical material / all species	–	*S.* Typhimurium	58
Clinical material / all species	–	Monophasic *S.* Typhimurium	31
Clinical material / all species	–	*S. enteritidis*	28

Reference

[1] Newcombe RG (1998). Two-sided confidence intervals for the single proportion: Comparison of seven methods. Statistics in Medicine, 17, 857–872

13.4 Bacterial isolates from animals and meat thereof

13.4.1 Sampling of healthy animals at the slaughterhouse

Stratified random samples were taken in the years 2016 and 2017 (Table 13. a and Table 13. b). Sampling was spread evenly throughout each year, on the basis of a sampling plan established for meat inspections. Samples were collected at the five largest poultry slaughterhouses, the seven largest pig slaughterhouses and the seven largest cattle slaughterhouses. Every slaughterhouse taking part in the program collected a number of samples proportional to the number of animals of the species slaughtered per year. This procedure ensured that at least 75% of slaughtered animals belonging to the species in question were part of the sample. In 2016, samples were taken from 496 broiler flocks. Random cecum samples were taken from five broilers per flock. In 2017, 304 cecum samples and 302 nasal swab samples were collected from fattening pigs and 304 cecum samples and 297 nasal swab samples from calves. Samples were sent to the National Reference Laboratory for antimicrobial resistance (ZOBA) for further analyses.

For calves and fattening pigs, the intention was to take samples from one animal selected at random per farm and to avoid taking several samples a year from any particular farm.

The results discussed in this report illustrate the data from 2008 to 2017. In the previous years, sampling procedures and laboratory analyses, excluding ESBL/pAmpC- and carbapenemase-producing *E. coli*, were performed in a similar way.

13.4.2 Sampling of meat at retailers

In 2016 and 2017, meat samples (min. 50 g) were taken from fresh, skinless, chilled, packed and untreated meat sold at the retail level. Samples were collected in all Swiss cantons throughout each year. The applied sampling scheme considered each canton's population density and market shares of retailers.

In 2017, 302 pork and 299 beef samples of domestic production were collected (Table 13. b). Approximately half of the chicken meat consumed in Switzerland is imported. Hence, imported and domestic chicken meat accounted for approximately one third and two thirds respectively of the 302 chicken meat samples in 2016 (Table 13. a).

13.4.3 Sampling for clinical isolates from animals

For *Salmonella*, no special monitoring at slaughter was feasible due to the very low prevalence of *Salmonella* spp. in Swiss livestock. Therefore, *Salmonella* isolates sent to ZOBA in 2016 and 2017 in connection with its function as a reference laboratory for *Salmonella* spp. at the primary production level as well as isolates from its own diagnostic activities were included in the monitoring (Table 13. a and Table 13. b). Most of these isolates were from clinical material of various animal species. They also included a small number of isolates derived from samples isolated as part of the national *Salmonella*-monitoring program 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 illustrate the data from 2008 to 2017. Sampling procedures in previous years were performed in a similar way.

Staphylococci, streptococci and *E. coli* strains described in Chapter 11 ("Resistance in bacteria from animal clinical isolates") were isolated from diagnostic submissions of bovine, canine and equine origin, sent to the diagnostic unit of the ZOBA by veterinarian practitioners and clinics in 2015/2016. These data are part of the pilot project for a monitoring program on antimicrobial resistance of clinical isolates from diseased animals launched by the Food Safety and Veterinary Office (FSVO) in 2015. Targeted bacterial and animal species combinations as well as antimicrobials tested are therefore different from the European harmonized monitoring program in livestock. Isolates are derived from animals without antimicrobial treatment before the sample was taken.

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

There are no mandatory Swiss guidelines for antibiotic resistance testing. Most laboratories initially followed CLSI guidelines and changed to EUCAST guidelines between 2011 and 2013. General use of automated systems increased over the 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 guidelines other 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,

Table 13. c: Epidemiological cutoff values used for the interpretation of MIC data derived from isolates in samples from healthy animals at slaughterhouse and meat thereof (including *Salmonella* spp. from clinical samples)

ECOFF (µg / ml) WT ≤					
Substance class	**Antimicrobials**	***Campylobacter* spp.**	***E. coli/ Salmonella* spp.**	***Enterococcus* spp.**	**MRSA**
Penicillins	Ampicillin		8	4	
	Oxacillin				2
	Penicillin				0.125
	Temocillin		32		
Cephalosporins	Cefotaxime		0.25[c] / 0.5[d]		
	Cefotaxime / Clavulanic acid		**		
	Ceftazidime		0.5[c] / 2[d]		
	Ceftazidime / Clavulanic acid		**		
	Cefepime		0.125[c]		
	Cefoxitin		8		4
Carbapenems	Ertapenem		0.06		
	Imipenem		0.5[c] / 1[d]		
	Meropenem		0.125		
Amphenicol	Chloramphenicol	16	16	32	16[g]
Tetracyclines	Tetracycline	1[a] / 2[b]	8	4	1
Glycylcyclines	Tigecycline		1	0.25	
(Fluoro-)quinolone	Ciprofloxacin	0.5	0.064	4	1[g]
	Nalidixic acid	16	16		
Sulfonamids	Sulfamethoxazole		64[c] / 256[d, h]		128[g]
Lincosamides	Clindamycin				0.25
Aminoglycosides	Gentamicin	2	2	32 / 512h	2
	Kanamycin				8[g]
	Streptomycin	4			16[g]
Polymyxins	Colistin		2		
Macrolides	Erythromycin	4[a] / 8[b]		4	1
	Azithromycin		16		
Cyclic lipopeptides	Daptomycin			4	
Glycopeptides	Vancomycin			4	2
	Teicoplanin			2	
Diaminopyrimidins	Trimethoprim		2		2
Oxazolidons	Linezolid			4	4[g]
Streptogramins	Quinupristin / Dalfopristin			1[f]	1[g]
Ansamycins	Rifampin				0.032
Pleuromutilins	Tiamulin				2[g]
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 *S. aureus*, EUCAST clinical breakpoint (ECOFF not defined or outside test range); CLSI-clinical breakpoint (EUCAST clinical breakpoint not defined or outside test-range);
** Interpretation according to EUCAST guideline for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance, v. 1.0, 2013.

which is provided to all participating laboratories. For data selection, we used a methodology identical to the antibiotic surveillance systems of the ECDC (EARSS) and of the WHO Europe (CASEAR), restricting the analyzed isolates to invasive isolates from blood cultures or cerebrospinal fluid. Isolates from foreign countries were excluded. Doubles were defined as identical microorganisms 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 by 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 intermediately 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 is especially true for *S. pneumoniae,* for which, in addition to changing breakpoints over time, different breakpoints are used for different kinds 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, in addition to serotyping, repeats antibiotic-resistance testing in a standardized manner. This means that all isolates are tested for erythromycin, levofloxacin, co-trimoxazole, and oxacillin. Additional e-tests for penicillin G and ceftriaxone are performed for all oxacillin-non-susceptible strains.

13.6 Susceptibility testing, cut-offs, breakpoints, processing antimicrobial resistance data from animal isolates

All analyses of animal samples were conducted at the national reference laboratory for antimicrobial resistance (ZOBA, Vetsuisse Faculty, University of Bern) using internationally standardized microbiological methods.

13.6.1 Samples of healthy animals at slaughterhouse and meat thereof

Cecal samples from fattening pigs, calves and broilers were tested for *Campylobacter* spp., *E. coli,* and *Enterococcus* spp. using direct detection methods. For *Campylobacter* spp., modified charcoal cefoperazone deoxycholate agar (mCCDA) was used, for *E. coli* MacConkey agar and for enterococci Slanetz-Bartley agar. After appropriate incubation, suspicious colonies were transferred onto non-selective sheep blood agar plates. Identification of suspicious colonies was carried out by the direct transfer method, using matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI TOF MS) (Biotyper 3.0, Bruker Daltonics, Bremen, Germany) following the manufacturer's recommendations.

MRSA detection was performed according to published methods. In brief, nasal swab or meat samples were transferred consecutively into two different enrichment broths, followed by cultivation on chromogenic MRSA-selective agar [1]. Confirmation for *S. aureus* was carried out by MALDI TOF MS (Biotyper 3.0, Bruker Daltonics, Bremen, Germany). Methicillin-resistance-gene-*mec*A detection and determination of the clonal complex (CC) CC398 were carried out by a multiplex real-time PCR, as previously published [2]. *Spa* type was determined as previously described and analyzed using the Ridom StaphType software (Ridom StaphType, Ridom GmbH, Würzburg, Germany) [3].

Detection of ESBL/pAmpC- and carbapenemase-producing *E. coli* was carried out on cecal and meat samples according to the protocol of the European reference laboratory for antimicrobial resistance (EURL, The National Food Institute, Lyngby, Denmark). In brief, samples were pre-enriched in a non-selective broth. After incubation, one loop full of broth was plated onto MacConkey agar with 1 µg/ml Cefotaxime (CTX) (Tritium, The Netherlands) for the detection of ESBL/pAmpC producing *E. coli*. For carbapenemase-producing *E. coli*, two different selective agar plates were used (CARBA agar plates, OXA-48 agar plates, BioMérieux Inc., Marcy l'Étoile, France). After appropriate incubation, suspicious colonies were transferred onto non-selective sheep blood agar plates. Suspected *E. coli* colonies were identified by MALDI TOF MS (Biotyper 3.0, Bruker Daltonics, Bremen,

Germany). Confirmation of ESBL/pAmpC or carbapenemaseproduction was carried out phenotypically by MIC determination on an EUVSEC2 plate.

Isolates were cryoconserved in specific media at –80°C until susceptibility testing was performed. The minimal inhibitory concentration (MIC) of the antimicrobials was determined by broth microdilution in cation-adjusted Müller-Hinton with (for *Campylobacter*) or without lysed horse blood, using Sensititre susceptibility plates (Trek Diagnostics Systems, Thermo Fisher, UK) according to CLSI guidelines [4]. The MIC was defined as the lowest antimicrobial concentration at which no visible bacterial growth occurred.

It is recommended that antimicrobial resistance be monitored by the assessment of MIC values based on epidemiological cutoff (ECOFF) values. Bacterial strains are considered microbiologically resistant if their MIC value is above the highest MIC value observed in the wild-type population of the bacteria (WT). The ECOFF distinguishes wild types from non-wild types. These are set and published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Interpretation of MIC followed the ECOFFs laid down in the European decision 2013/652/EU, excluding MRSA, for which ECOFFs according to EUCAST were used (Table 13. c).

Resulting microbiological 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 %

13.6.2 Samples of clinical animal isolates

Clinical submissions from diseased dogs, cattle and horses were cultured according to standard bacterial culture methods. All isolates derived from ear/eye/nose swabs, skin/wound specimens, mastitis milk and urine from animals, and not treated with antimicrobials prior to sampling were included in the analysis. Identification to the bacterial species level was performed by MALDI TOF MS (Biotyper 3.0, Bruker Daltonics, Bremen, Germany).

Isolates were cryoconserved in specific media at –80°C until susceptibility testing was performed. The minimal inhibitory concentration (MIC) of the antimicrobials was determined by broth microdilution in cation-adjusted Müller-Hinton with (for streptococci) or without lysed horse blood, using Sensititre susceptibility plates (Trek Diagnostics Systems, Thermo Fisher, UK) according to CLSI guidelines [4]. The MIC was defined as the lowest antimicrobial concentration at which no visible bacterial growth occurred.

Isolates were classified as susceptible or resistant according to clinical breakpoints published by the Clinical and Laboratory Standards Institute [5] or, if not available, by clinical breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (www.eucast.org). The clinical breakpoint relates primarily to the extent to which the pathogen may respond to treatment, by taking into account aspects of pharmacodynamics and pharmacokinetics as well as specific features of the host and the target organ. If no clinical breakpoints were available at all, MIC_{90} values were calculated. MIC_{90} value is defined as the minimal inhibitory concentration at which 90 % of the isolates tested are inhibited. Trend analyses of MIC_{90} values can serve as an indicator for possible resistance development within a given bacteria population.

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13.7 Methodological approach for the One-Health analysis

Data on antibacterial use and resistance

Statistics on veterinary antibacterial consumption were based on sales data. Estimates per species (pigs, cattle and poultry) were calculated using the Longitudinal Study Extrapolation (LSE) method described by Carmo *et al.* (2017) [1]. Estimates were produced at the antibacterial class level using mg of active ingredient per kg of biomass (mg/BM) as the consumption metric. Resistance data for livestock resulted from the yearly monitoring system put in place by the Federal Food Safety and Veterinary Office. The time period considered was 2008 to 2017.

With respect to the data used from the human sector, inpatient antibacterial usage was calculated based on a representative sample of acute care hospitals participating in the anresis-network (www.anresis.ch) [2]. The time period considered was 2008 to 2017. Antibacterial consumption was extrapolated to the national level according to the proportion of bed-days from the hospitals participating in the anresis network. With the objective of having a similar indicator of antibacterial consumption to the one used in the veterinary calculations (i.e. mg/BM), data on the number of Swiss inhabitants was gathered [3]. To calculate the total Swiss human biomass, it was assumed that the average weight of a Swiss inhabitant was 62.5 kg, as described in the JIACRA report [4]. Data for outpatient antibacterial consumption were analyzed for the time period 2015 to 2017.

Selection of antimicrobial/organism combinations

For animals, the analysis of association between antibacterial use and resistance was conducted for the following bacteria: *Escherichia coli* (*E. coli)*, *Campylobacter coli* (only for pigs) and *Campylobacter jejuni* (only for poultry). The analysis was completed for cephalosporins, fluoroquinolones and macrolides (only for *Campylobacter coli*). Moreover, tetracyclines and sulfonamides were also considered for pigs and cattle, given their importance in terms of overall sales.

The analysis of association between antibacterial use and resistance in humans (use of 3rd and 4th generation cephalosporins and resistance to cefotaxime and ceftriaxone; and use of quinolones and resistance to ciprofloxacin) was conducted for *E. coli* blood isolates from hospitalized patients. Bacterial isolates from the central nervous system were not used due to their limited number.

In addition to the abovementioned tested associations, the relationship between the use of cephalosporins in livestock (pigs, cattle and poultry) and cefotaxime and ceftriaxone resistance in *E. coli* blood isolates from outpatients was analyzed, too.

Statistical analysis

Associations between antibacterial consumption and resistance were established using binomial regressions with a logistic link. Weights were attributed to the number of isolates tested to account for differences between the years. Analyses were not conducted if less than 6 years of data existed with at least 40 isolates tested per year. The procedure was conducted using the software R, including the packages "dplyr," "tidyr" and "ggplot2" [6].

References

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Annex

Annex I

Antibiotics with defined daily dose (DDD) and AWaRe classification according to the WHO Essential Medicines List

Table I.1: 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) with administration route, defined daily dose (DDD) and classification by groups, i.e. Core-Access, Watch or Reserve (see Chapter 13 Materials and methods) according to the WHO.

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Core-Access [A], Watch [W], Reserve [R] or Others [O]
J01A	Doxycycline	oral	0.1	A
	Doxycycline	parenteral	0.1	A
	Lymecycline	oral	0.6	O
	Minocycline	oral	0.2	O
	Tetracycline	oral	1	O
	Tetracycline	parenteral	1	O
	Tigecyclin	parenteral	0.1	R
J01B	Chloramphenicol	parenteral	3	A
J01C	Amoxicillin	oral	1	A
	Amoxicillin	parenteral	1	A
	Amoxicillin-clavulanic acid	oral	1	A
	Amoxicillin-clavulanic acid	parenteral	3	A
	Benzylpenicillin	parenteral	3.6	A
	Flucloxacillin	oral	2	A
	Flucloxacillin	parenteral	2	A
	Phenoxymethylpenicillin	oral	2	A
	Benzathine phenoxymethylpenicillin	oral	2	A
	Benzathine benzylpenicillin	parenteral	3.6	A
	Piperacillin	parenteral	14	O
	Piperacillin-tazobactam	parenteral	14	W
	Temocillin	parenteral	2	O
	Ticarcillin	parenteral	15	O
	Ticarcillin-clavulanic acid	parenteral	15	W

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Core-Access [A], Watch [W], Reserve [R] or Others [O]
J01D	Aztreonam	parenteral	4	R
	Cefaclor	oral	1	O
	Cefamandole	parenteral	6	O
	Cefazolin	parenteral	3	A
	Cefepime	parenteral	2	R
	Cefixime	oral	0.4	W
	Cefotaxime	parenteral	4	W
	Cefoxitin	parenteral	6	O
	Cefpodoxime	oral	0.4	W
	Cefprozil	oral	1	O
	Ceftaroline	parenteral	1.2	R
	Ceftazidime	parenteral	4	W
	Ceftibuten	oral	0.4	W
	Ceftobiprole	parenteral	1.5	R
	Ceftolozane-tazobactam	parenteral	3	R
	Ceftriaxone	parenteral	2	W
	Cefuroxime	oral	0.5	O
	Cefuroxime	parenteral	3	O
	Ertapenem	parenteral	1	W
	Imipenem	parenteral	2	W
	Meropenem	parenteral	2	W
J01E	Sulfadiazine	oral	0.6	O
	Sulfadiazine	parenteral	0.6	O
	Trimethoprim	oral	0.4	A
	Trimethoprim-sulfamethoxazole	oral	1.92	A
	Trimethoprim-sulfamethoxazole	parenteral	1.92	A
J01F	Azithromycin	oral	0.3	W
	Clarithromycin	oral	0.5	W
	Clarithromycin	parenteral	1	W
	Clindamycin	oral	1.2	A
	Clindamycin	parenteral	1.8	A
	Erythromycin	oral	2	W
	Erythromycin	parenteral	1	W
	Roxithromycin	oral	0.3	W
	Spiramycin	oral	3	W
J01G	Amikacin	parenteral	1	A
	Gentamicin	oral	0.24	A
	Gentamicin	other	0.24	A
	Gentamicin	parenteral	0.24	A
	Neomycin	oral	5	O
	Netilmicin	oral	0.35	O
	Netilmicin	parenteral	0.35	O
	Streptomycin	parenteral	1	O
	Tobramycin	inhaled	0.3	O
	Tobramycin	parenteral	0.24	O

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Core-Access [A], Watch [W], Reserve [R] or Others [O]
J01M	Ciprofloxacin	oral	1	W
	Ciprofloxacin	parenteral	0.5	W
	Levofloxacin	oral	0.5	W
	Levofloxacin	parenteral	0.5	W
	Moxifloxacin	oral	0.4	W
	Moxifloxacin	parenteral	0.4	W
	Norfloxacin	oral	0.8	W
	Ofloxacin	oral	0.4	W
	Ofloxacin	parenteral	0.4	W
J01X	Colistin	oral	3	R
	Colistin	inhaled	3	R
	Colistin	parenteral	3	R
	Daptomycin	parenteral	0.28	R
	Fosfomycin	oral	3	O
	Fosfomycin	parenteral	8	R
	Fusidic acid	oral	1.5	O
	Fusidic acid	parenteral	1.5	O
	Linezolid	oral	1.2	R
	Linezolid	parenteral	1.2	R
	Metronidazole	parenteral	1.5	A
	Nitrofurantoin	oral	0.2	A
	Ornidazole	parenteral	1	O
	Polymyxin B	parenteral	0.15	W
	Tedizolid	oral	0.2	R
	Tedizolid	parenteral	0.2	R
	Teicoplanin	parenteral	0.4	W
	Vancomycin	oral	2	W
	Vancomycin	parenteral	2	W
J04AB	Rifampicin	oral	0.6	–
	Rifampicin	parenteral	0.6	–
	Rifamycin	parenteral	0.6	–
	Rifabutin	oral	0.15	–
P01AB	Metronidazole	rectal	2	A
	Metronidazole	oral	2	A
	Ornidazole	oral	1.5	O

Annex II

Distribution of minimal inhibitory concentrations (MICs) and resistance patterns in bacterial isolates from animals and meat

Tables I.1 – I.23 show distribution of MICs in bacterial isolates from animals, tables I.24 – I.31 MIC data from isolates derived from meat. Vertical red lines indicate epidemiological cutoff values for resistance according to EUCAST. 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 cutoff values, used as interpretative criterion for microbiological resistance.

Tables I.32 – I.48 show multiresistance patterns in bacterial isolates from animals, tables I.49 – I.54 data from isolates derived from meat. The term "multiresistance pattern" is different from "multidrug resistance" (MDR). Multiresistance patterns describe only the number of detected resistances to all antimicrobials tested, even though some antimicrobial classes may be represented by more than one antimicrobial.

Table I.1: Distribution (n) of MICs (mg/L) in *Salmonella* spp. from poultry, 2016.

Minimal Inhibitory Concentration (MIC) / poultry / *Salmonella* spp. / Number of Isolates (N=29)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								6	22						1					
Azithromycin										21	8									
Cefotaxime						28	1													
Ceftazidime							29													
Chloramphenicol											29									
Ciprofloxacin		3	25	1																
Colistin								20	7	1	1									
Gentamicin							29													
Meropenem			27	2																
Nalidixic acid										29										
Sulfamethoxazole											1	1	7	14	4	1		1		
Tetracycline									28						1					
Tigecycline						22	7													
Trimethoprim						21	8													

Table I. 2: Distribution (n) of MICs (mg/L) in *Salmonella* spp. from cattle in 2016.

Minimal Inhibitory Concentration (MIC) / cattle / *Salmonella* spp. / number of isolates (N=51)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								21	16						14					
Azithromycin										44	7									
Cefotaxime						51														
Ceftazidime							51													
Chloramphenicol											50				1					
Ciprofloxacin		15		34	2															
Colistin								44	7											
Gentamicin							49	2												
Meropenem			46	5																
Nalidixic acid										47	4									
Sulfamethoxazole													11	17	7				16	
Tetracycline									39					1	11					
Tigecycline						42	9													
Trimethoprim						42	9													

Table I. 3: Distribution (n) of MICs (mg/L) in *Salmonella* spp. from cattle, 2017.

Minimal Inhibitory Concentration (MIC) / cattle / *Salmonella* spp. / number of isolates (N=66)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								30	16						20					
Azithromycin										53	13									
Cefotaxime						64	2													
Ceftazidime							66													
Chloramphenicol											64				2					
Ciprofloxacin		13		52	1															
Colistin								58	8											
Gentamicin							65	1												
Meropenem			63	3																
Nalidixic acid										63	3									
Sulfamethoxazole											1	15	22	5	1	1	1		20	
Tetracycline									43			2	2	1	18					
Tigecycline						53	13													
Trimethoprim						64	2													

Table I. 4: Distribution (n) of MICs (mg/L) in *Salmonella spp.* from poultry in 2017.

Minimal Inhibitory Concentration (MIC) / poultry / *Salmonella* spp. / number of isolates (N=31)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								11	16						4					
Azithromycin										24	7									
Cefotaxime						31														
Ceftazidime							31													
Chloramphenicol											31									
Ciprofloxacin		5	26																	
Colistin								27	3	1										
Gentamicin							30	1												
Meropenem			26	5																
Nalidixic acid										30	1									
Sulfamethoxazole											2	11	6	6	1			1	4	
Tetracycline									28						3					
Tigecycline						20	11													
Trimethoprim						26	5													

Table I. 5: Distribution (n) of MICs (mg/L) in *Salmonella* spp. from pigs, 2017.

Minimal Inhibitory Concentration (MIC) / cattle / *Salmonella* spp. / number of isolates (N=66)																				
	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	4096
Ampicillin									2						8					
Azithromycin										8	2									
Cefotaxime						10														
Ceftazidime							10													
Chloramphenicol											10									
Ciprofloxacin		1	9																	
Colistin								10												
Gentamicin							10	0												
Meropenem			10																	
Nalidixic acid										10										
Sulfamethoxazole												1	1							
Tetracycline									2						8					
Tigecycline						3	6	1												
Trimethoprim						10														

Table I. 6: Distribution (n) of MICs (mg/L) in *Campylobacter jejuni* from broilers, 2016.

Minimal Inhibitory Concentration (MIC) / broilers / *Campylobacter jejuni* / number of isolates (N=140)																				
	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	4096
Ciprofloxacin					56	11	1			2	46	16	8							
Erythromycin								122	8	6		1			1	2				
Gentamicin					58	54	25	1					2							
Nalidixic acid									24	35	8	1		11	61					
Streptomycin						5	48	69	8		6	1	3							
Tetracycline							77	7	1		1	3	5	8	38					

Table I. 7: Distribution (n) of MICs (mg/L) in *Campylobacter coli* from broilers, 2016.

Minimal Inhibitory Concentration (MIC) / broilers / *Campylobacter 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	1,024	2,048	4,096
Ciprofloxacin					7	3			1		7	9	3							
Erythromycin								13	10	3	1					3				
Gentamicin					3	9	14	4												
Nalidixic acid										4	5	1		6	14					
Streptomycin								4	4	3	1	5	13							
Tetracycline							13	2	3	1	1		1	5	4					

Table I. 8: Distribution (n) of MICs (mg/L) in *Campylobacter coli* from fattening pigs, 2017.

Minimal Inhibitory Concentration (MIC) / fattening pigs / *Campylobacter coli* / number of isolates (N=161)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ciprofloxacin					66	11	3			8	29	40	4							
Erythromycin								109	34	11	4					3				
Gentamicin					21	68	66	4			2									
Nalidixic acid									5	45	23	4	3	15	66					
Streptomycin								13	14	3	5	31	95							
Tetracycline							54	4	3	1	4	23	41	17	14					

Table I. 9: Distribution (n) of MICs (mg/L) in *Enterococcus faecalis* from broilers, 2016.

Minimal Inhibitory Concentration (MIC) / broilers / *Enterococcus faecalis* / number of isolates (N=31)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin							2	23	6											
Chloramphenicol										3	26	1		1						
Ciprofloxacin						1	3	20	6				1							
Daptomycin							1	11	15	4										
Erythromycin								12	4	4		2	1			8				
Gentamicin											10	21								
Linezolid								3	26	2										
Teicoplanin							31													
Tetracycline								10	1				1	7	12					
Tigecycline				9	17	5														
Vancomycin								18	10	2						1				

Table I. 10: Distribution (n) of MICs (mg/L) in *Enterococcus faecium* from broilers, 2016.

Minimal Inhibitory Concentration (MIC) / broilers / *Enterococcus faecium* / number of isolates (N=247)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin							90	57	56	34	8	1			1					
Chloramphenicol										66	178	3								
Ciprofloxacin						1	4	50	87	98	7									
Daptomycin						6	4	18	90	113	16									
Erythromycin								117	58	19	7	4	2	1	1	38				
Quinupristin/ Dalfopristin							45	61	42	95	3	1								
Gentamicin											155	87	5							
Linezolid							1	11	188	47										
Teicoplanin							246	1												
Tetracycline								185	3	3	6	2	1	26	21					
Tigecycline			34	125	70	15	3													
Vancomycin								221	24	2										

Table I. 11: Distribution (n) of MICs (mg/L) in *Enterococcus faecalis* from calves, 2017.

Minimal Inhibitory Concentration (MIC) / veal calves / *Enterococcus faecalis* / number of isolates (N=46)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin							5	39	2											
Chloramphenicol										27	10		1	8						
Ciprofloxacin						1	26	17	1				1							
Daptomycin							11	31	3	1										
Erythromycin								27		2						17				
Gentamicin											27	7	1			1	1	2	7	
Linezolid								21	25											
Teicoplanin							46													
Tetracycline								15				1		22	8					
Tigecycline			2	9	26	8		1												
Vancomycin								31	15											

Table I. 12: Distribution (n) of MICs (mg/L) in *Enterococcus faecium* from calves, 2017.

Minimal Inhibitory Concentration (MIC) / veal calves / *Enterococcus faecium* / number of isolates (N=129)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin							13	60	55	0	1									
Chloramphenicol										84	43	1	1							
Ciprofloxacin							66	56	3	3	1									
Daptomycin						1		18	8	100	1	1								
Erythromycin								3	9	91	23	1				2				
Gentamicin											100	29								
Linezolid								2	119	8										
Quinupristin/ Dalfopristin							3	2	12	112										
Teicoplanin							127	2												
Tetracycline								122	1				1	2	3					
Tigecycline			18	50	44	13	3	1												
Vancomycin								127	2											

Table I. 13: Distribution (n) of MICs (mg/L) in *Escherichia coli* from broilers, 2016.

Minimal Inhibitory Concentration (MIC) / broilers / *Escherichia coli* / number of isolates (N=190)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								9	78	49	7				47					
Azithromycin									7	79	95	9								
Cefotaxime						190														
Ceftazidime							190													
Chloramphenicol											178	10			1	1				
Ciprofloxacin		101	12	5	23	42	4	1			1	1								
Colistin								190												
Gentamicin							139	44	4			3								
Meropenem			188	2																
Nalidixic acid										112	3		5	29	30	11				
Sulfamethoxazole											26	25	56	32	6	2	1	5	37	
Tetracycline									151	14			2	10	13					
Tigecycline						183	7													
Trimethoprim						82	67	12	5					24						

Table I. 14: Distribution (n) of MICs (mg/L) in *Escherichia coli* from fattening pigs, 2017.

Minimal Inhibitory Concentration (MIC) / fattening pigs / *Escherichia coli* / number of isolates (N=197)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								7	67	91	4			1	27					
Azithromycin									14	113	68	1	1							
Cefotaxime						197														
Ceftazidime							197													
Chloramphenicol											181	6	3	5		2				
Ciprofloxacin		177	14	1		4					1									
Colistin								196	1											
Gentamicin							168	23			3		2	1						
Meropenem			194	3																
Nalidixic acid										191	2				3	1				
Sulfamethoxazole											41	37	33	15	1	1	1	1	67	
Tetracycline									134	21	1	2	1	16	22					
Tigecycline						178	16	3												
Trimethoprim						83	69	14	1					30						

Table I. 15: Distribution (n) of MICs (mg/L) in Escherichia coli from calves, 2017.

Minimal Inhibitory Concentration (MIC) / veal calves / *Escherichia coli* / number of isolates (N=194)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin								3	38	72	6				75					
Azithromycin									13	101	68	12								
Cefotaxime						194														
Ceftazidime							194													
Chloramphenicol											171	4	3	4	2	10				
Ciprofloxacin		168	17	2	3	2					1	1								
Colistin								192	2											
Gentamicin							165	19	1				1	8						
Meropenem			194																	
Nalidixic acid										183	3	1		2	3	2				
Sulfamethoxazole											24	40	33	6	3			1	87	
Tetracycline									98	15	1			25	55					
Tigecycline						169	23	2												
Trimethoprim						72	64	17	4				1	36						

Table I. 16: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from broilers, 2016, 1st panel.

Minimal Inhibitory Concentration (MIC) / broilers / *Escherichia coli* / number of isolates (N=160)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin									2		1		2	2	153					
Azithromycin									12	108	38	2								
Cefotaxime						10	2	7	7	13	121									
Ceftazidime							23	35	17	10	52	23								
Chloramphenicol											144	3	2		1	10				
Ciprofloxacin		67	12	3	13	34	9	4	1	1	7	9								
Colistin								160												
Gentamicin							115	34	2	1		3	4	1						
Meropenem			155	5																
Nalidixic acid										78	7	2	11	8	22	32				
Sulfamethoxazole											3	18	24	31	8	1	0	4	71	
Tetracycline									104	2	1		1	28	24					
Tigecycline						145	14	1												
Trimethoprim						46	65	9						40						

Table I. 17: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from broilers, 2016, 2nd panel.

Minimal Inhibitory Concentration (MIC) / broiler / *Escherichia coli* / number of isolates (N=160)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefepime				10	17	68	7	2	14	22	18	2								
Cefotaxime						9	3	8	5	13	69	25	22	6						
Cefotaxime / clavulanic acid				64	17	2	1	1	6	38	31									
Cefoxitin								1	13	44	17	6	16	52	11					
Ceftazidime						12	8	24	28	17	64	7								
Ceftazidime / clavulanic acid					62	20	1	2	8	42	25									
Ertapenem		88	57	9	6															
Imipenem					97	62	1													
Meropenem			153	7																
Temocillin									12	77	68	3								

Table I. 18: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from fattening pigs, 2017, 1st panel.

Minimal Inhibitory Concentration (MIC) / fattening pigs / *Escherichia coli* / number of isolates (N=52)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin										1	1			2	50					
Azithromycin									2	21	26	1	1	3						
Cefotaxime						3	1	4	11		35									
Ceftazidime							4	14	8	17	8	3								
Chloramphenicol											48				2	4				
Ciprofloxacin		32	2	1		3			4	3	2	7								
Colistin								54												
Gentamicin							37	6					4	7						
Meropenem			51	3																
Nalidixic acid										35	2	0			5	12				
Sulfamethoxazole											7	8	6	3					30	
Tetracycline									19	2			1	12	20					
Tigecycline						43	8	3												
Trimethoprim						20	17	4						13						

Table I. 19: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from fattening pigs, 2017, 2nd panel.

Minimal Inhibitory Concentration (MIC) / fattening pigs / *Escherichia coli* / number of isolates (N=52)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefepime				4	11	3			7	15	9	3								
Cefotaxime						1	2	5	9		4	10	10	9	2					
Cefotaxime / clavulanic acid				31	5	1	2	11	1	1										
Cefoxitin									2	14	18	6	5	7						
Ceftazidime							1	18	4	16	10	3								
Ceftazidime / clavulanic acid					21	12	3	3	8	4	1									
Ertapenem		40	9	3																
Imipenem					28	20	4													
Meropenem			48	4																
Temocillin										29	17	5	1							

Table I. 20: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from calves, 2017, 1st panel.

Minimal Inhibitory Concentration (MIC) / veal calves / *Escherichia coli* / number of isolates (N=101)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin													3	4	94					
Azithromycin									4	42	42	6		7						
Cefotaxime						1	6	19	12	10	53									
Ceftazidime							8	16	18	22	23	14								
Chloramphenicol											72	3	2	1	8	15				
Ciprofloxacin		45	7		2	17	9	1	2		4	14								
Colistin								100	1											
Gentamicin							60	5			5	6	7	18						
Meropenem			99	2																
Nalidixic acid										56	9	5		5	4	22				
Sulfamethoxazole											5	1	7	5	2				81	
Tetracycline									14				1	29	57					
Tigecycline						76	21	4												
Trimethoprim						17	25	5	2					52						

Table I. 21: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from calves, 2017, 2nd panel.

Minimal Inhibitory Concentration (MIC) / veal calves / *Escherichia coli* / number of isolates (N=101)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefepime				19	20	3	5	4	10	19	12	8	1							
Cefotaxime						1	5	22	9	12	6	11	11	16	8					
Cefotaxime / clavulanic acid				46	9	7	15	15	7	1	1									
Cefoxitin									4	33	17	16	15	10	6					
Ceftazidime						2	6	16	18	25	22	11	1							
Ceftazidime / clavulanic acid					38	18	8	11	15	5	5	1								
Ertapenem		73	21	7																
Imipenem					78	22	1													
Meropenem			100	1																
Temocillin									6	55	36	4								

Table I. 22: Distribution (n) of MICs (mg/L) in Methicillin-resistant *Staphylococcus aureus* (MRSA) from fattening pigs, 2017.

Minimal Inhibitory Concentration (MIC) / fattening pigs / MRSA / number of osolates (N=131)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefoxitin											53	69	9							
Chloramphenicol										22	104	3	1	1						
Ciprofloxacin						71	44	1	1	1	9	4								
Clindamycin					64		1	1		8	57									
Erythromycin						24	48				1	58								
Fusidic acid							127	1		3										
Gentamicin								114	2		3	4	8							
Kanamycin										112	3	1	2	1	12					
Linezolid								30	96	5										
Mupirocin							128									3				
Penicillin									2	129										
Quinupristin / Dalfopristin							62	3	43	17	6									
Rifampicin		128					2	1												
Streptomycin										23	36	5	1	66						
Sulfamethoxazole														121	2	1	1	6		
Tetracycline													131							
Tiamulin							60	4	1		66									
Trimethoprim									63					68						
Vancomycin								129	2											

Table I. 23: Distribution (n) of MICs (mg/L) in Methicillin-resistant Staphylococcus aureus (MRSA) from calves, 2017.

Minimal Inhibitory Concentration (MIC) / veal calves / MRSA / number of isolates (N=24)																				
	0.01	0.02	0.03	0.06	0.13	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefoxitin											9	15								
Chloramphenicol										1	20	3								
Ciprofloxacin						11	3		4		2	4								
Clindamycin					7						17									
Erythromycin						1	6					17								
Fusidic acid							24													
Gentamicin								19				2	3							
Kanamycin										18				1	5					
Linezolid								4	20											
Mupirocin							24									1				
Penicillin										24										
Quinupristin / Dalfopristin							7	8	1	3	5									
Rifampicin		24																		
Streptomycin										4	5		1	14						
Sulfamethoxazole														24						
Tetracycline													24							
Tiamulin							13	2			9									
Trimethoprim									12					12						
Vancomycin								24												

Table I. 24: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from chicken meat, 2016, 1st panel.

Minimal Inhibitory Concentration (MIC) / chicken meat / *Escherichia coli* / number of isolates (N=149)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin													2	5	142					
Azithromycin									19	101	26	2			1					
Cefotaxime						3	3	11	12	22	98									
Ceftazidime							10	25	16	12	56	30								
Chloramphenicol											132	1	8	3	2	3				
Ciprofloxacin		47	7	1	10	37	9	5	3	2	18	10								
Colistin								149												
Gentamicin							96	30	2	2		8	8	3						
Meropenem			149																	
Nalidixic acid										55	6	3	5	11	29	40				
Sulfamethoxazole											7	14	24	13	6			4	81	
Tetracycline									78	4		2	3	31	31					
Tigecycline						139	10													
Trimethoprim						67	30	9						43						

Table I. 25: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from chicken meat, 2016, 2nd panel.

Minimal Inhibitory Concentration (MIC) / chicken meat / *Escherichia coli* / number of isolates (N=149)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefepime				6	30	54	13	6	6	22	11	1								
Cefotaxime						3	5	10	11	19	55	27	15	4						
Cefotaxime / clavulanic acid				61	11				12	38	25	1	1							
Cefoxitin									11	38	20	7	16	45	12					
Ceftazidime						6	4	18	20	25	49	21	5	1						
Ceftazidime / clavulanic acid					57	15		2	10	37	24	3	1							
Ertapenem		86	49	14																
Imipenem					79	68	2													
Meropenem			145	4																
Temocillin								1	14	80	50	4								

Table I. 26: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from pork meat, 2017, 1st panel.

Minimal Inhibitory Concentration (MIC) / pork meat / *Escherichia coli* / number of isolates (N=1)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin															1					
Azithromycin														1						
Cefotaxime											1									
Ceftazidime										1										
Chloramphenicol																1				
Ciprofloxacin											1									
Colistin								1												
Gentamicin							1													
Meropenem			1																	
Nalidixic acid																1				
Sulfamethoxazole																			1	
Tetracycline															1					
Tigecycline						1														
Trimethoprim														1						

Table I. 27: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from pork meat, 2017, 2nd panel.

Minimal Inhibitory Concentration (MIC) / pork meat / *Escherichia coli* / number of isolates (N=1)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefepime											1									
Cefotaxime													1							
Cefotaxime / clavulanic acid					1															
Cefoxitin											1									
Ceftazidime								1												
Ceftazidime / clavulanic acid							1													
Ertapenem		1																		
Imipenem						1														
Meropenem			1																	
Temocillin												1								

Table I. 28: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from beef, 2017, 1st panel

Minimal Inhibitory Concentration (MIC) / beef meat / *Escherichia coli* / number of isolates (N=2)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Ampicillin															2					
Azithromycin											1	1								
Cefotaxime								1			1									
Ceftazidime										1	1									
Chloramphenicol											2									
Ciprofloxacin			1			1														
Colistin								2												
Gentamicin							1	1												
Meropenem			2																	
Nalidixic acid										2										
Sulfamethoxazole													1	1						
Tetracycline									1	1										
Tigecycline						2														
Trimethoprim							0	2												

Table I. 29: Distribution (n) of MICs (mg/L) in suspected ESBL/pAmpC-producing *Escherichia coli* from beef, 2017, 2nd panel.

Minimal Inhibitory Concentration (MIC) / beef meat / *Escherichia coli* / number of isolates (N=2)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefepime					1					1										
Cefotaxime									1			1								
Cefotaxime / clavulanic acid				1				1												
Cefoxitin											1		1							
Ceftazidime										1	1									
Ceftazidime / clavulanic acid						1			1											
Ertapenem		1		1																
Imipenem					2															
Meropenem			2																	
Temocillin											1	1								

Table I. 30: Distribution (n) of MICs (mg/L) in MRSA from chicken meat, 2016.

Minimal Inhibitory Concentration (MIC) / chicken meat / MRSA / number of isolates (N=9)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefoxitin												1	7	1						
Chloramphenicol											1	6	2							
Ciprofloxacin							4	2					3							
Clindamycin						1						8								
Erythromycin							1	1					7							
Fusidic acid								9												
Gentamicin									9											
Kanamycin											9									
Linezolid									2	7										
Mupirocin								9												
Oxacilin											9									
Penicillin								2	2	3	2									
Rifampicin		9																		
Streptomycin											6	3								
Sulfamethoxazole																				
Tetracycline								4						5						
Tiamulin								4				5								
Trimethoprim										4										
Vancomycin									9											

Table I. 31: Distribution (n) of MICs (mg/L) in MRSA from pork meat, 2017.

Minimal Inhibitory Concentration (MIC) / pork meat / MRSA / number of isolates (N=2)																				
	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096
Cefoxitin											1	1								
Chloramphenicol										1	1									
Ciprofloxacin						1	1													
Clindamycin					2															
Erythromycin							2													
Fusidic acid							2													
Gentamicin										1		1								
Kanamycin													1	1						
Linezolid									2											
Mupirocin							2													
Penicillin										2										
Quinupristin / Dalfopristin							2													
Rifampicin		2																		
Streptomycin										2										
Sulfamethoxazole														1	1					
Tetracycline							1						1							
Tiamulin							2													
Trimethoprim									2											
Vancomycin								2												

Table I. 32: Multiresistance patterns of *Salmonella* spp. from poultry, 2016.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
1 ABM	2														
0 ABM	26														

ABM: antimicrobial

Table I. 33: Multiresistance patterns of *Salmonella* spp. from cattle, 2016.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
4 ABM	1														
3 ABM	11														
2 ABM	2														
1 ABM	2														
0 ABM	35														

ABM: antimicrobial

Table I. 34: Multiresistance patterns of *Salmonella* spp. from poultry, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
3 ABM	3														
2 ABM	1														
1 ABM	1														
0 ABM	23														

ABM: antimicrobial

Table I. 35: Multiresistance patterns of *Salmonella* spp. from cattle, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
4 ABM	2														
3 ABM	17														
2 ABM	1														
1 ABM	4														
	1														
0 ABM	41														

Table I. 36: Multiresistance patterns of *Salmonella* spp. from pig, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
3 ABM	8														
0 ABM	2														

Table I. 37: Multiresistance patterns of *Campylobacter jejuni* from broilers, 2016.

Number of resistences	Number of isolates	Ciprofloxacin	Erythromycin (Erythromycin A)	Gentamicin	Nalidixic acid	Streptomycin	Tetracycline
6 ABM	2						
4 ABM	7						
	1						
3 ABM	34						
2 ABM	28						
1 ABM	12						
	1						
	1						
0 ABM	54						

Table I. 38: Multiresistance patterns of *Campylobacter colii* from broilers, 2016.

Number of resistences	Number of isolates	Ciprofloxacin	Erythromycin (Erythromycin A)	Gentamicin	Nalidixic acid	Streptomycin	Tetracycline
5 ABM	3						
4 ABM	6						
3 ABM	7						
	1						
2 ABM	3						
	1						
1 ABM	2						
	1						
0 ABM	6						

Table I. 39: Multiresistance patterns of *Campylobacter colii* from fattening pigs, 2017.

Number of resistences	Number of isolates	Ciprofloxacin	Erythromycin (Erythromycin A)	Gentamicin	Nalidixic acid	Streptomycin	Tetracycline
5 ABM	1						
	1						
4 ABM	48						
	1						
	1						
3 ABM	18						
	3						
	1						
2 ABM	39						
	8						
1 ABM	21						
	7						
	2						
	1						
0 ABM	9						

Table I. 40: Multiresistance patterns of *Enterococcus faecium* from broilers, 2016.

Number of resistences	Number of isolates	Ampicillin	Chloramphenicol	Ciprofloxacin	Daptomycin	Erythromycin (Erythromycin A)	Gentamicin	Linezolid	Quinupristin/Dalfopristin	Teicoplanin	Tetracycline	Tigecycline	Vancomycin
4 ABM	1			R	R				R			R	
	1	R				R			R		R		
3 ABM	4					R			R		R		
	2	R							R		R		
	2	R				R			R				
	1								R		R	R	
	1				R				R		R		
	1				R	R			R				
	1			R		R					R		
	1			R		R			R				
2 ABM	32					R			R				
	29								R		R		
	4	R							R				
	3				R				R				
	1					R					R		
	1				R							R	
	1			R							R		
	1			R					R				
	1	R									R		
1 ABM	58								R				
	14										R		
	10					R							
	9				R								
	2			R									
0 ABM	66												

Table I. 41: Multiresistance patterns of *Enterococcus faecium* from calves, 2017.

Number of resistences	Number of isolates	Ampicillin	Chloramphenicol	Ciprofloxacin	Daptomycin	Erythromycin (Erythromycin A)	Gentamicin	Linezolid	Quinupristin/Dalfopristin	Teicoplanin	Tetracycline	Tigecycline	Vancomycin
4 ABM	1												
3 ABM	3												
	1												
	1												
2 ABM	21												
	3												
	1												
1 ABM	93												
	1												
	1												
0 ABM	3												

Table I. 42: Multiresistance patterns of *Escherichia coli* from broilers, 2016.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
7 ABM	1														
6 ABM	4														
5 ABM	8														
	2														
	1														
	1														
4 ABM	3														
	2														
	1														
	1														
	1														
3 ABM	5														
	5														
	4														
	3														
	2														
	1														
2 ABM	36														
	3														
	2														
	2														
	1														
	1														
1 ABM	9														
	9														
	4														
	4														
0 ABM	74														

Table I. 43: Multiresistance patterns of suspected ESBL/AmpC-producing *Escherichia coli* from broilers, 2016.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefepime	Cefotaxime	Cefoxitin	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Ertapenem	Gentamicin	Imipenem	Meropenem	Nalidixic acid	Sulfamethoxazole	Temocillin	Tetracycline	Tigecycline	Trimethoprim
11 ABM	6																			
	1																			
10 ABM	3																			
	1																			
	1																			
9 ABM	14																			
	2																			
	2																			
	1																			
	1																			
	1																			
8 ABM	10																			
	4																			
	3																			
	1																			
7 ABM	2																			
	2																			
	1																			
	1																			
	1																			
	1																			
	1																			
	1																			
	1																			
	1																			
6 ABM	11																			
	8																			
	4																			
	3																			
	2																			
	1																			
	1																			
5 ABM	29																			
	7																			
	5																			
	1																			
	1																			
	1																			

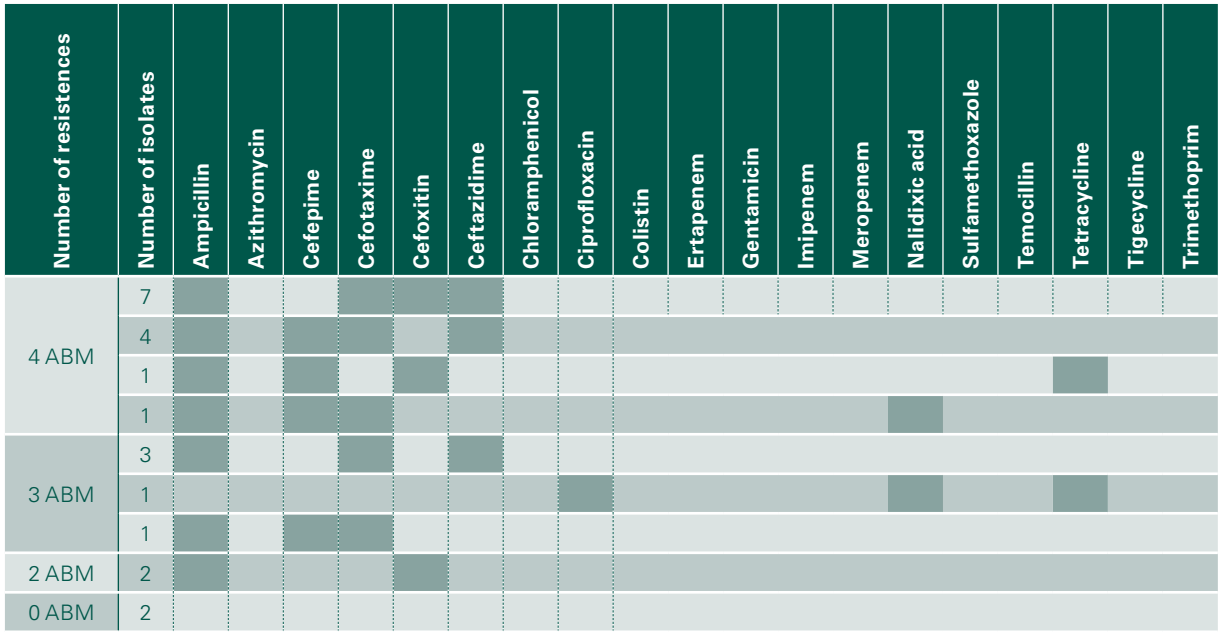

Number of resistences
Number of isolates
Ampicillin
Azithromycin
Cefepime
Cefotaxime
Cefoxitin
Ceftazidime
Chloramphenicol
Ciprofloxacin
Colistin
Ertapenem
Gentamicin
Imipenem
Meropenem
Nalidixic acid
Sulfamethoxazole
Temocillin
Tetracycline
Tigecycline
Trimethoprim
4 ABM
7
4
1
1
3 ABM
3
1
1
2 ABM
2
0 ABM
2

Table I. 44: Multiresistance patterns of *Escherichia coli* from calves, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
7 ABM	2	R				R	R				R	R	R		R
	1	R					R		R		R	R	R		R
6 ABM	2	R					R				R	R	R		R
	2	R				R			R			R	R		R
	1	R				R	R				R	R	R		
5 ABM	4	R				R						R	R		R
	2	R							R			R	R		R
4 ABM	14	R										R	R		R
	7	R				R						R	R		
	1						R				R	R	R		
	1					R						R	R		R
	1	R							R			R	R		
3 ABM	22	R										R	R		
	4	R										R			R
	3											R	R		R
	1					R						R	R		
	1	R							R			R			
	1	R				R							R		
2 ABM	13											R	R		
	4	R										R			
	2	R							R						
	1											R			R
	1	R											R		
1 ABM	4											R			
	4	R													
	1														R
	1												R		
0 ABM	93														

Table I. 45: Multiresistance patterns of suspected ESBL/AmpC-producing *Escherichia coli* from calves, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefepime	Cefotaxime	Cefoxitin	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Ertapenem	Gentamicin	Imipenem	Meropenem	Nalidixic acid	Sulfamethoxazole	Temocillin	Tetracycline	Tigecycline	Trimethoprim
12 ABM	1	R	S	R	R	R	R	R	R	S	S	R	S	S	R	R	S	R	S	R
11 ABM	5	R	S	R	R	S	R	R	R	S	S	R	S	S	R	R	S	R	S	R
	3	R	S	R	R	S	R	S	R	S	S	R	S	S	R	R	S	R	S	R
	1	R	I	I	R	S	R	R	R	S	S	R	S	S	R	R	S	R	S	R
	1	R	R	R	R	S	R	S	R	S	S	S	S	S	R	R	S	R	S	R
10 ABM	3	R	S	R	R	S	R	S	R	S	S	R	S	S	R	R	S	R	S	R
	2	R	R	R	R	S	R	S	R	S	S	S	S	S	R	R	S	R	S	R
	2	R	R	R	R	S	R	R	R	S	S	R	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	S	R	R	S	S	R	S	S	R	R	S	R	S	R
	1	R	S	R	R	S	R	R	R	S	S	R	S	S	S	R	S	R	S	R
	1	R	R	S	R	R	R	R	S	S	S	R	S	S	S	R	S	R	S	R
	1	R	R	R	R	R	R	S	S	S	S	R	S	S	S	R	S	R	S	R
9 ABM	3	R	S	S	R	R	R	R	S	S	S	R	S	S	S	R	S	R	S	R
	3	R	S	R	R	S	R	S	R	S	S	S	S	S	R	R	S	R	S	R
	2	R	S	S	R	R	R	R	R	S	S	S	S	S	R	R	S	R	S	S
	1	R	S	S	R	R	R	S	R	S	S	S	S	S	R	R	S	R	S	R
	1	R	S	R	R	S	R	S	R	S	S	R	S	S	R	R	S	R	S	S
	1	R	S	R	R	S	R	R	S	S	S	R	S	S	S	R	S	R	S	R
	1	R	S	R	R	R	R	S	R	S	S	S	S	S	S	R	S	R	S	R
	1	R	S	R	R	R	R	R	S	S	S	R	S	S	S	R	S	R	S	S
8 ABM	8	R	S	R	R	S	R	S	R	S	S	S	S	S	S	R	S	R	S	R
	4	R	S	S	R	R	R	S	R	S	S	S	S	S	R	R	S	R	S	S
	3	R	S	R	R	S	S	R	S	S	S	R	S	S	S	R	S	R	S	R
	1	R	S	S	R	R	S	R	S	S	S	R	S	S	S	R	S	R	S	R
	1	R	S	S	R	R	R	R	S	S	S	R	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	S	S	R	S	S	S	S	S	R	R	S	R	S	R
	1	R	S	R	R	S	R	S	S	S	S	S	S	S	S	R	S	R	S	R
	1	R	S	R	R	S	R	S	R	S	S	S	S	S	R	R	S	R	S	S
	1	R	S	R	R	R	R	S	S	S	S	S	S	S	S	R	S	R	S	R
	1	R	S	R	R	R	R	S	R	S	S	R	S	S	S	R	S	R	S	S
7 ABM	6	R	S	S	R	R	R	S	S	S	S	S	S	S	S	R	S	R	S	R
	1	R	S	S	R	R	R	S	S	S	S	R	S	S	S	R	S	R	S	S
	1	R	S	S	R	R	R	R	S	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	S	S	S	S	S	S	S	S	R	S	R	S	R
	1	R	S	R	R	S	R	S	S	S	S	R	S	S	S	R	S	R	S	R
	1	R	S	R	R	S	R	S	S	S	S	R	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	S	R	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	S	R	S	S	S	S	S	R	S	S	R	S	S
	1	R	S	R	R	S	R	R	S	S	S	S	S	S	S	R	S	R	S	S
6 ABM	9	R	S	S	R	R	R	S	S	S	S	S	S	S	S	R	S	R	S	S
	5	R	S	R	R	S	R	S	R	S	S	S	S	S	S	S	S	R	S	S

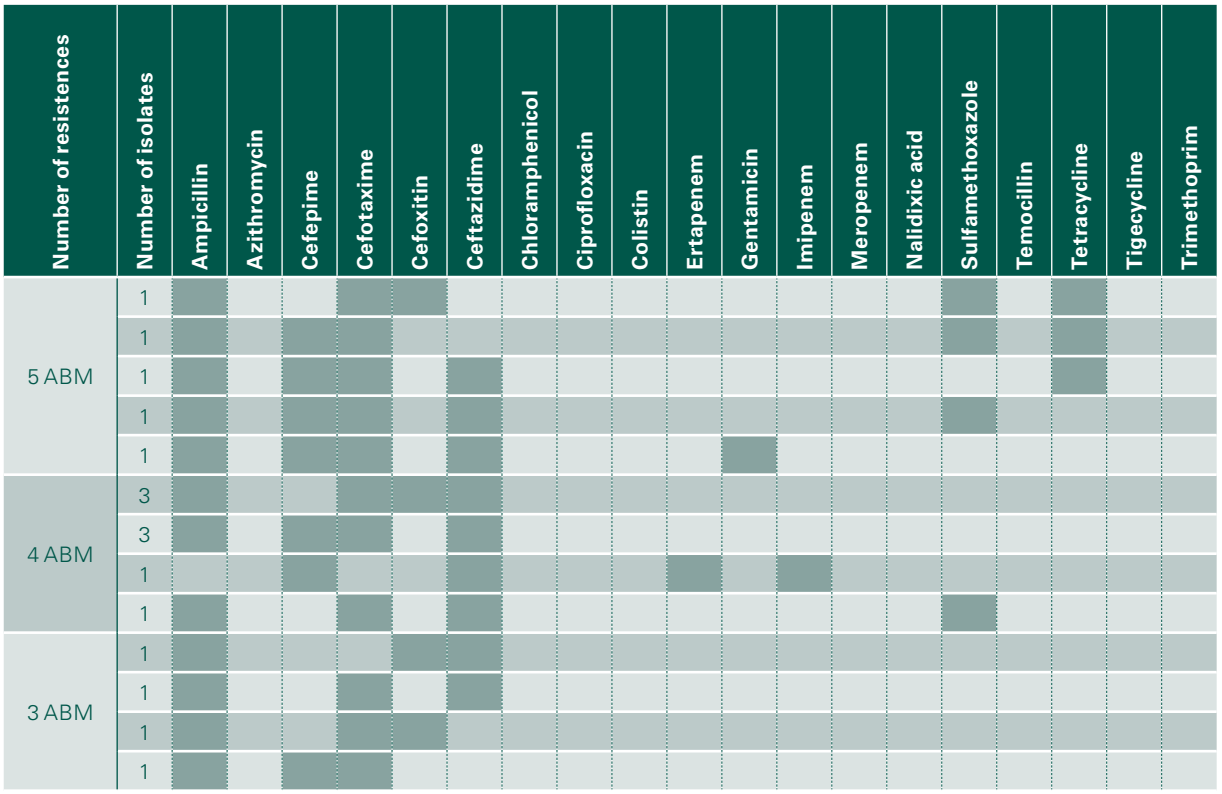

Number of resistences
Number of isolates
Ampicillin
Azithromycin
Cefepime
Cefotaxime
Cefoxitin
Ceftazidime
Chloramphenicol
Ciprofloxacin
Colistin
Ertapenem
Gentamicin
Imipenem
Meropenem
Nalidixic acid
Sulfamethoxazole
Temocillin
Tetracycline
Tigecycline
Trimethoprim
5 ABM
1
1
1
1
1
4 ABM
3
3
1
1
3 ABM
1
1
1
1

Table I. 46: Multiresistance patterns of *Escherichia coli* from fattening pigs, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefotaxime	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Gentamicin	Meropenem	Nalidixic acid	Sulfamethoxazole	Tetracycline	Tigecycline	Trimethoprim
8 ABM	1														
6 ABM	1														
5 ABM	3														
	1														
4 ABM	4														
	2														
	2														
	1														
	1														
	1														
3 ABM	5														
	3														
	3														
	3														
	1														
	1														
2 ABM	6														
	5														
	4														
	1														
	1														
1 ABM	23														
	13														
	1														
0 ABM	110														

Table I. 47: Multiresistance patterns of suspected ESBL/AmpC-producing *Escherichia coli* from fattening pigs, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefepime	Cefotaxime	Cefoxitin	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Ertapenem	Gentamicin	Imipenem	Meropenem	Nalidixic acid	Sulfamethoxazole	Temocillin	Tetracycline	Tigecycline	Trimethoprim
12 ABM	1	R	S	S	S	S	I	S	R	S	S	R	S	S	R	S	S	R	S	R
11 ABM	2	R	R	R	R	S	R	S	R	S	S	R	S	S	R	R	S	R	S	R
	1	R	S	R	R	S	R	R	R	S	S	R	S	S	R	R	S	R	S	R
	1	R	R	R	R	R	R	S	R	S	S	S	S	S	R	R	S	R	S	R
10 ABM	1	R	S	R	R	S	R	S	R	S	S	R	S	S	R	R	S	R	S	R
9 ABM	1	R	S	S	R	S	R	S	R	S	S	S	S	S	R	R	S	R	S	R
	1	R	S	R	R	S	R	S	R	S	S	S	S	S	R	R	S	R	S	R
	1	R	S	R	R	S	R	R	S	S	S	R	S	S	S	R	S	R	S	R
	1	R	S	R	R	S	R	R	R	S	S	S	S	S	R	R	S	R	S	S
8 ABM	1	R	S	S	R	R	R	S	R	S	S	S	S	S	R	R	S	S	S	R
	1	R	S	R	R	S	R	S	R	S	S	R	S	S	R	S	S	R	S	S
	1	R	S	R	R	S	R	R	R	S	S	R	S	S	R	S	S	S	S	S
7 ABM	4	R	S	S	R	R	R	S	R	S	S	S	S	S	R	S	S	R	S	S
	3	R	S	R	R	S	R	S	S	S	S	S	S	S	S	R	S	R	S	R
	1	R	S	R	S	R	R	R	S	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	S	S	S	S	R	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	R	S	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	R	R	R	R	S	R	S	S	S	S	S	R	S	S	S	S	S
6 ABM	7	R	S	R	R	S	R	S	S	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	S	R	R	R	S	S	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	S	R	S	S	S	S	S	S	S	S	R	S	S
5 ABM	2	R	S	R	R	S	R	S	S	S	S	R	S	S	S	S	S	S	S	S
	2	R	S	R	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S	S
	1	S	S	R	S	R	R	S	S	S	R	S	R	S	S	S	S	S	S	S
	1	S	S	R	R	R	R	S	S	S	S	S	S	S	S	R	S	S	S	S
	1	R	S	S	R	R	R	S	S	S	S	S	S	S	S	R	S	S	S	S
	1	R	S	R	R	S	S	S	S	S	S	S	S	S	S	R	S	R	S	S
	1	R	S	R	R	S	R	S	S	S	S	S	S	S	S	S	S	R	S	S
	1	R	S	R	R	S	R	S	S	S	S	S	S	S	S	R	S	S	S	S
	1	R	S	R	R	S	R	S	R	S	S	S	S	S	S	S	S	S	S	S
4 ABM	3	R	S	S	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S	S
	3	R	S	R	R	S	R	S	S	S	S	S	S	S	S	S	S	S	S	S
	1	R	S	S	S	R	R	S	S	S	S	S	S	S	S	R	S	S	S	S
	1	R	S	S	R	S	R	S	S	S	S	S	S	S	S	S	S	R	S	S
3 ABM	2	R	S	S	R	S	R	S	S	S	S	S	S	S	S	S	S	S	S	S

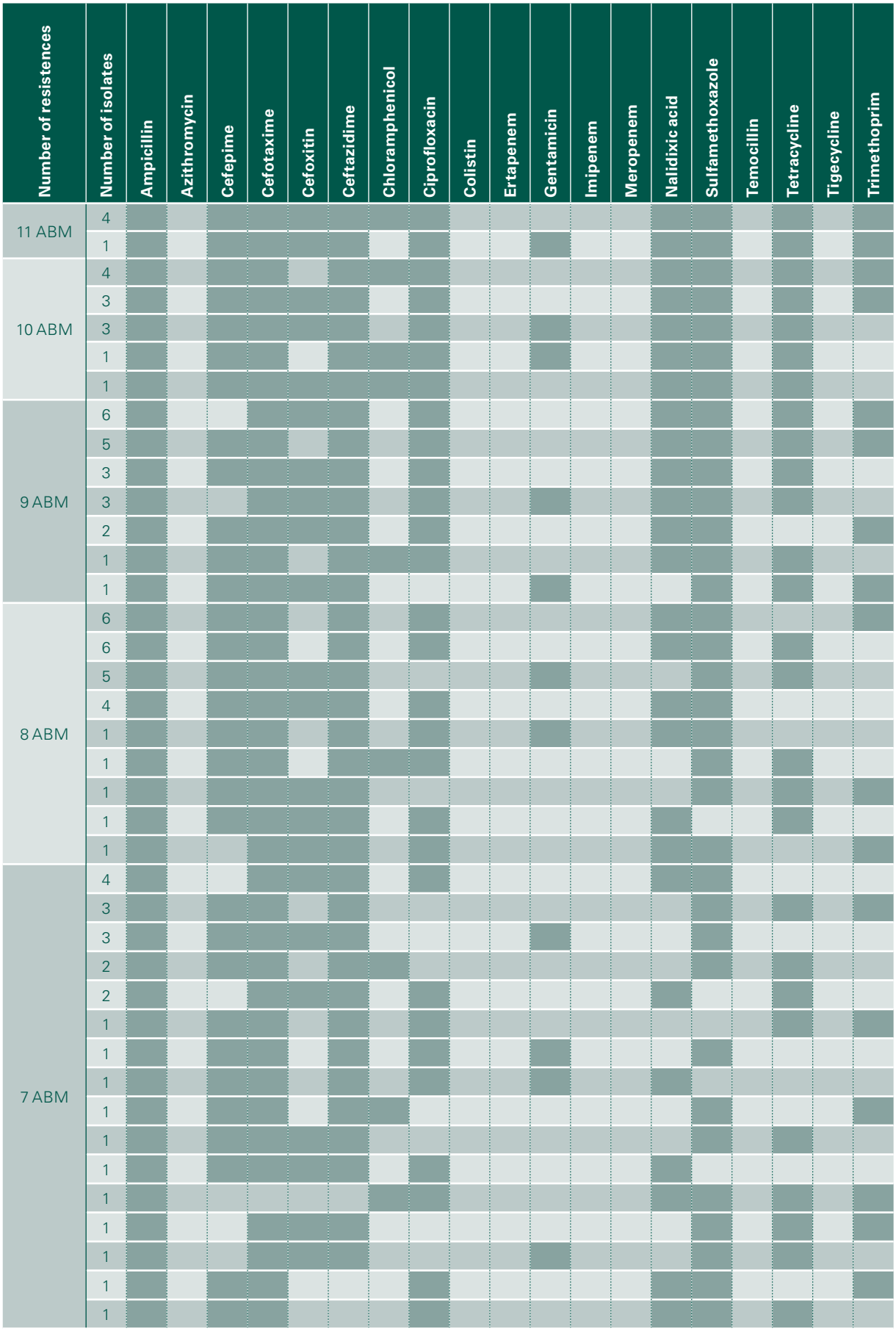
Table I. 48: Multiresistance patterns of Methicillin-resistant *Staphylococcus aureus* from calves, 2017.

Number of resistences	Number of isolates	Cefoxitin	Chloramphenicol	Ciprofloxacin	Clindamycin	Erythromycin (Erythromycin A)	Gentamicin	Kanamycin	Linezolid	Mupirocin	Penicillin	Quinupristin/Dalfopristin	Rifampicin	Streptomycin	Sulfamethoxazole	Tetracycline	Tiamulin	Trimethoprim	Vancomycin
10 ABM	2	■			■		■	■			■	■				■	■	■	
	2	■		■	■	■					■	■		■		■	■	■	
9 ABM	5	■			■	■					■	■		■		■	■	■	
8 ABM	1	■		■	■		■	■			■					■		■	
7 ABM	2	■		■			■	■			■					■		■	
	1	■		■	■	■					■			■		■			
6 ABM	4	■			■	■					■			■		■			
	1	■				■		■			■			■		■			
5 ABM	2	■			■	■					■					■			
	2	■		■							■			■		■			
4 ABM	2	■		■							■					■			

Table I. 49: Multiresistance patterns of Methicillin-resistant *Staphylococcus aureus* (MRSA) from fattening pigs, 2017.

Number of Resistences	Number of isolates	Cefoxitin	Chloramphenicol	Ciprofloxacin	Clindamycin	Erythromycin (Erythromycin A)	Gentamicin	Kanamycin	Linezolid	Mupirocin	Penicillin	Quinupristin/Dalfopristin	Rifampicin	Streptomycin	Sulfamethoxazole	Tetracycline	Tiamulin	Trimethoprim	Vancomycin
14 ABM	1	■			■		■	■			■	■	■	■	■	■	■	■	
13 ABM	2	■			■	■	■	■		■	■	■	■	■	■	■	■		
10 ABM	2	■	■		■	■					■	■		■		■	■	■	
9 ABM	34	■			■	■					■	■		■		■	■	■	
	3	■		■	■						■	■		■		■	■	■	
	2	■			■						■	■		■	■	■	■	■	
8 ABM	18	■			■	■					■	■				■	■	■	
	2	■			■						■	■			■	■	■	■	
	1	■		■			■	■			■			■		■		■	
7 ABM	2	■			■						■	■				■	■	■	
	1	■			■	■	■	■			■					■			
	1	■		■				■			■			■	■	■			
	1	■		■			■	■			■					■		■	
6 ABM	1	■					■	■			■			■		■			
	1	■				■					■			■		■		■	
5 ABM	7	■					■	■			■					■			
	1	■		■							■					■		■	
	1	■		■							■			■		■			
4 ABM	18	■									■			■		■			
	7	■		■							■					■			
	1						■	■			■					■			
3 ABM	24	■									■					■			

Table I. 50: Multiresistance patterns of suspected ESBL/AmpC-producing *Escherichia coli* from chicken meat, 2016.



Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefepime	Cefotaxime	Cefoxitin	Ceftazidime	Chloramphenicol	Ciprofloxacin	Colistin	Ertapenem	Gentamicin	Imipenem	Meropenem	Nalidixic acid	Sulfamethoxazole	Temocillin	Tetracycline	Tigecycline	Trimethoprim
6 ABM	7																			
	7																			
	5																			
	1																			
	1																			
	1																			
5 ABM	12																			
	4																			
	2																			
	2																			
	1																			
4 ABM	5																			
	3																			
	1																			
	1																			
3 ABM	4																			
	2																			
	1																			

Table I. 51: Multiresistance patterns of suspected ESBL/AmpC-producing *Escherichia coli* from beef, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefepime	Cefotaxim	Cefoxitin	Ceftazidim	Chloramphenicol	Ciprofloxacin	Colistin	Ertapenem	Gentamicin	Imipenem	Meropenem	Nalidixic acid	Sulfamethoxazole	Temocillin	Tetracycline	Tigecycline	Trimethoprim
5 ABM																				
4 ABM																				

Table I. 52: Multiresistance patterns of suspected ESBL/AmpC-producing *Escherichia coli* from pork meat, 2017.

Number of resistences	Number of isolates	Ampicillin	Azithromycin	Cefepime	Cefotaxim	Cefoxitin	Ceftazidim	Chloramphenicol	Ciprofloxacin	Colistin	Ertapenem	Gentamicin	Imipenem	Meropenem	Nalidixic acid	Sulfamethoxazole	Temocillin	Tetracycline	Tigecycline	Trimethoprim
11 ABM																				

Table I. 53: Multiresistance patterns of methicillin-resistant *Staphylococcus aureus* (MRSA) from chicken meat, 2016.

Number of resistences	Number of isolates	Cefoxitin	Chloramphenicol	Ciprofloxacin	Clindamycin	Erythromycin (Erythromycin A)	Gentamicin	Kanamycin	Linezolid	Mupirocin	Penicillin	Quinupristin/Dalfopristin	Rifampicin	Streptomycin	Sulfamethoxazole	Tetracycline	Tiamulin	Trimethoprim	Vancomycin
8 ABM	4																		
7 ABM	1																		
5 ABM	3																		
2 ABM	1																		

Table I. 54: Multiresistance patterns of methicillin-resistant *Staphylococcus aureus* (MRSA) from pork meat, 2017.

Number of resistences	Number of isolates	Cefoxitin	Chloramphenicol	Ciprofloxacin	Clindamycin	Erythromycin (Erythromycin A)	Gentamicin	Kanamycin	Linezolid	Mupirocin	Penicillin	Quinupristin/Dalfopristin	Rifampicin	Streptomycin	Sulfamethoxazole	Tetracycline	Tiamulin	Trimethoprim	Vancomycin
5 ABM	1																		
4 ABM	1																		

Index

Figures, tables and textboxes

Figures

pp.

36 Figure 5. a: Total antibiotic consumption (ATC group J01) expressed in DDDs per 100 bed-days (bars) and in DDDs per 100 admissions (dark line) in the hospitals and intensive care units contributing to anresis.ch over the period 2007–2017. The number of hospital networks (or sites) contributing to anresis.ch is indicated in the corresponding bars.

37 Figure 5. b: Distribution of the total antibiotic consumption (ATC group J01) per antibiotic class in the inpatient setting in 2017 in Switzerland.

39 Figure 5. c: Consumption of antibiotics expressed in DDDs per 100 bed-days in hospitals contributing to anresis.ch in Switzerland (2007–2017).

42 Figure 5. d: Distribution of the total antibiotic consumption (ATC group J01) per antibiotic class in the outpatient setting in 2017 in Switzerland.

43 Figure 5. e: ESAC quality indicators for consumption of antibacterials for systemic use (ATC group J01) in the outpatient setting in Switzerland (2015–2017).

43 Figure 5. f: Total antibiotic consumption (ATC group J01) expressed in DDDs per 1,000 inhabitants per day by linguistic region in the outpatient setting in Switzerland (2015–2017).

44 Figure 5. g: Antibiotic classes per age group and overall as a proportion of the total consumption in the outpatient setting in Switzerland (2015–2017).

46 Figure 1: Antibiotic prescriptions 2017 by indication and antibiotic group, expressed in number of prescriptions per 100,000 inhabitants.

50 Figure 6. a: Antimicrobial sales for livestock animals in the years 2008–2017 compared to the population biomass (total PCU) and the sales of active ingredients per PCU.

51 Figure 6. b: Sales of antimicrobials (in kg) licensed for intramammary use in 2008–2015 separated into dry cow products and products for use during lactation.

54 Figure 1: Concentration of the antibiotics sulfamethoxazole, ciprofloxacin, and clarithromycin in the effluent of a wastewater treatment plant (WWTP), in river water and in groundwater in a catchment of the canton of Zurich (detection limit 10 ng/L).

57 Figure 7. a: Comparison of non-susceptibility rates in invasive versus outpatient urinary samples in *Escherichia coli* isolates in humans for 2017.

57 Figure 7. b: Non-susceptibility rates in invasive *Escherichia coli* isolates in humans between 2008 and 2017.

58 Figure 7. c: Multiresistance in invasive *E. coli* isolates in humans between 2008 and 2017 (for details refer to table 7. b).

59 Figure 1: Number of carbapenemase-producing isolates per A) Enterobacteriaceae genus and B) genotypes.

61 Figure 7. d: Non-susceptibility rates in invasive *Klebsiella pneumoniae* isolates in humans 2008–2017.

62 Figure 7. e: Multiresistance in invasive *K. pneumoniae* isolates in humans from 2008–2017 (for details refer to Table 7. d).

64 Figure 7. f: Non-susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans from 2008 to 2017.

65 Figure 7. g : Multiresistance in invasive *Pseudomonas aeruginosa* isolates in humans between 2008 and 2017 (for details refer to Table 7. f).

66 Figure 1: *Acinetobacter* resistance rates (number of resistant isolates compared to total number of isolates) per region from 2005 to 2016 in Switzerland. Standard deviation bars represent annual fluctuations per region. B) Map of the Swiss regions defined in this study.

67 Figure 7. h: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans between 2008 and 2017.

68 Figure 7. i: Multiresistance in invasive *Acinetobacter* spp. isolates in humans between 2008 and 2017 (for details refer to Table 7. h).

69 Figure 7. j: Non-susceptibility rates in invasive PSSP (penicillin-susceptible isolates) and PNSP (penicillin non-susceptible isolates) in humans in 2017.

69 Figure 7. k: Non-susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans between 2008 and 2017.

70 Figure 7. l: Non-susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans between 2008 and 2017.

72 Figure 7. m: Comparison of non-susceptibility rates in invasive versus outpatient wound/abscess samples in *Staphylococcus aureus* in humans in 2017.

73 Figure 7. n: Non-susceptibility rates of invasive MRSA (methicillin-resistant *Staphylococcus aureus*) and MSSA (methicillin-susceptible *Staphylococcus aureus*) isolates in humans 2017.

73 Figure 7. o: Non-susceptibility rates of invasive *Staphylococcus aureus* isolates in humans between 2008 and 2017.

76 Figure 1: Sources of antibiotics and antibiotic-resistant bacteria and potential distribution in aquatic environments.

82 Figure 8. a: Trends in resistance to fluoroquinolones and macrolides in *Campylobacter* coli and *Campylobacter jejuni* from human clinical isolates in Switzerland between 2008 and 2017.

83 Figure 8. b: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. jejuni* from broilers between 2008 and 2016 (N = total number of tested isolates; values for 2015 interpolated [n/a]).

84 Figure 8. c: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. coli* from fattening pigs between 2008 and 2017 (N = total number of tested isolates; values for 2008, 2014 and 2016 interpolated [n/a]).

90 Figure 8. d: Trends in aminopenicillin, ceftriaxone, trimethoprim-sulfamethoxazole and fluoroquinolone resistance in non-typhoidal *Salmonella* from human clinical isolates between 2008 and 2017.

91 Figure 8. e: Trends in ampicillin, chloramphenicol, ciprofloxacin, colistin, sulfamethoxazole and tetracycline resistance in *Salmonella* spp. from poultry, pigs and cattle between 2010 and 2017 (N = total number of tested isolates).

95 Figure 1: Pathogen surveillance using molecular typing data. (A) The Nextstrain tool (www.nextstrain.org) offers phylogenetic trees of multiple pathogens. e.g. Ebola virus outbreak in West Africa. Colors represent different geographic regions. The x-axis reflects a time scale during the outbreak.

95 Figure 2: Envisioned workflow for the surveillance platform. After isolating a strain, collecting epidemiological data and sequencing it, the user uploads raw data and metadata into a central or local/private database using the submission portal. After submission, these data are quality controlled and then (semi-)automatically processed to perform tasks such as genome assembly, and MLST, SNP and resistance calling. The resulting data are used for phylogenetics and predictive modelling, e.g. transmission dynamics. All these data are stored in a structured database with controlled access, and visualized in a user-friendly interface. For open data, the structured database may also be used/queried by other applications or pushed to external databases and knowledge bases. In addition to the submission portal, an administration portal to manage users and rights, as well as a curating portal to edit

controlled vocabularies and define curated reference strains and variants (e.g. for resistance) will be developed.
100 Figure 9. a: Trends in ampicillin, chloramphenicol, erythromycin, gentamicin, tetracycline and vancomycin resistance in *Enterococcus faecalis* from broilers between 2008 and 2016 (N = total number of tested isolates; values for 2015 interpolated [n/a]).
101 Figure 9. b: Trends in ampicillin, erythromycin, quinupristin/dalfopristin, tetracycline and vancomycin resistance in *Enterococcus faecium* from broilers between 2008 and 2016 (N = total number of tested isolates; values for 2015 interpolated [n/a])
102 Figure 9. c: Trends in ampicillin, chloramphenicol, erythromycin, gentamicin, tetracycline and vancomycin resistance in *Enterococcus faecalis* from slaughter calves between 2008 and 2016 (N = total number of tested isolates; values for 2008, 2009, 2011, 2012, 2014 and 2016 interpolated [n/a]).
102 Figure 9. d: Trends in ampicillin, erythromycin, quinupristin/dalfopristin, tetracycline and vancomycin resistance in *Enterococcus faecium* from slaughter calves between 2008 and 2016 (N = total number of tested isolates; values for 2008, 2009, 2011, 2012, 2014 and 2016 interpolated [n/a]).
106 Figure 9. e: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from broilers between 2008 and 2016 (N = total number of tested isolates, values for 2015 interpolated [n/a]).
106 Figure 9. f: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from fattening pigs between 2008 and 2017 (N = total number of tested isolates, values for 2008, 2014 and 2016 interpolated [n/a]).
107 Figure 9. g: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from slaughter calves between 2008 and 2017 (N = total number of tested isolates, values for 2008, 2009, 2011, 2012, 2014 and 2016 interpolated [n/a]).
113 Figure 9. h: Number of MRSA genotypes from fattening pigs between 2009 and 2017.
134 Figure 12. a: Longitudinal Study Extrapolation of veterinary antibiotic sales (2008–2017).
135 Figure 12. b: Association between the use of tetracyclines in pigs and the resistance levels in (A) *E. coli* ($p = 0.07$) and (B) *Campylobacter coli* ($p < 0.05$, but the data has a poor model fit).
135 Figure 12. c: Human antibiotic consumption in mg per kg of biomass (mg/BM) in Switzerland (2015–2017).
136 Figure 12. d: Association between (A) the inpatient use of 3rd and 4th generation cephalosporins and the occurrence of cefotaxime resistance in inpatients ($p < 0.05$); (B) the use of quinolones in inpatients and the occurrence of ciprofloxacin resistance ($p < 0.05$), in blood *E. coli* isolates in hospitalized patients.
136 Figure 12. e: Antibiotic consumption in livestock and humans in mg of active ingredient per kg of biomass (mg/BM) for the time period between 2015 and 2017.
138 Figure 12.2 a: MRSA prevalence in Swiss livestock between 2009 and 2017.
139 Figure 12.2 b: MRSA prevalence in fresh meat between 2014 and 2017.
140 Figure 12.2 c: MRSA types from humans, animals and meat in 2016/2017.

Tables

pp.
37 Table 5. a: Antibiotic consumption according to the AWaRe categorization of the WHO in the inpatient setting, Switzerland (2015–2017).
38 Table 5. b: Consumption of antibiotic classes expressed in DDDs per 100 bed-days in hospitals contributing to anresis.ch in Switzerland (2007–2017).
41 Table 5. c: Consumption of antibiotic classes expressed in DDDs per 1,000 inhabitants per day in the outpatient setting in Switzerland (2015–2017).
41 Table 5. d: Antibiotic consumption according to the AWaRe categorization of the WHO in the outpatient setting in Switzerland (2015–2017).
48 Table 6. a: Sales of antibiotic classes between 2008 and 2017.
48 Table 6. b: Sales of antimicrobials according to the administration route in 2008–2017.
49 Table 6. c: Sales of different antibiotic classes licensed for livestock animals between 2008 and 2017.
50 Table 6. d: Sales of antimicrobials licensed as premixes from 2008 to 2017, according to antibiotic class.
51 Table 6. e: Sales of antimicrobials licensed for intramammary use in 2008–2017 according to antibiotic class.
52 Table 6. f: Sales of antibiotic classes licensed for companion animals in 2008–2017.
56 Table 7. a: Non-susceptibility rates of invasive *Escherichia coli* isolates in humans for 2017.
58 Table 7. b: Non-susceptibility combinations in invasive *E. coli* isolates in humans 2017. Only isolates tested against all five antibiotic groups (aminopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n=5119/5405 [94.7%]).
61 Table 7. c: Non-susceptibility rates of invasive *Klebsiella pneumoniae* isolates in humans in 2017.
62 Table 7. d: Non-susceptibility combinations in invasive *K. pneumoniae* isolates in humans in 2017. Only isolates tested against all four antibiotic groups (third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n=959/964 [99.5%]).
63 Table 7. e: Susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans 2017.
64 Table 7. f: Non-susceptibility combinations in invasive *P. aeruginosa* isolates in humans in 2017. Only isolates tested against all five antibiotics or antibiotic groups (piperacillin-tazobactam, cefepime, carbapenems, aminoglycosides, ciprofloxacin) were considered (n=501/536 [93.5%]).
65 Table 7. g: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans for 2017. Due to small numbers, non-susceptibility rates for southern Switzerland are not shown.
67 Table 7. h: Non-susceptibility combinations in invasive *Acinetobacter* spp. isolates in humans in 2017. Only isolates tested against all three antibiotic groups (aminoglycosides, ciprofloxacin and carbapenems) were considered (n=90/93 [96.8%]).
68 Table 7. i: Non-susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans in 2017.
70 Table 7. j: Non-susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans in 2017.
72 Table 7. k: Susceptibility rates of invasive *Staphylococcus aureus* isolates in humans in 2017.

80 Table 8. a: *Campylobacter jejuni* and *Campylobacter coli* from broilers in 2016.
81 Table 8. b: *Campylobacter coli* from fattening pigs in 2017.
82 Table 8. c: Non-susceptibility rates of *Campylobacter coli* and *Campylobacter jejuni* from human clinical isolates in 2017.
86 Table 8. d: Non-susceptibility rates of *Salmonella* from human clinical isolates in 2017.
87 Table 8. e: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from poultry in 2016.
88 Table 8. f: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from cattle in 2016.
89 Table 8. g: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from poultry in 2017.
90 Table 8. h: Occurrence of resistance in *Salmonella* spp., *Salmonella* Typhimurium and its monophasic variant from cattle in 2017.
91 Table 8. i: Occurrence of resistance in *Salmonella* spp. and monophasic *Salmonella* Typhimurium from fattening pigs in 2017.
98 Table 9. a: Occurrence of resistance in *Enterococcus faecalis* and *Enterococcus faecium* from broilers in 2016.
99 Table 9. b: Occurrence of resistance in *Enterococcus faecalis* and *Enterococcus faecium* from slaughter calves in 2017.
103 Table 9. d: Occurrence of resistance in *Escherichia coli* from broilers in 2016.
104 Table 9. e: Occurrence of resistance in *Escherichia coli* from fattening pigs in 2017.
105 Table 9. f: Occurrence of resistance in *Escherichia coli* from slaughter calves in 2017.
108 Table 9. g: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from broilers in 2016.
109 Table 9. h: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from fattening pigs in 2017.
110 Table 9. i: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from slaughter calves in 2017.
111 Table 9. j: Occurrence of resistance in MRSA from fattening pigs in 2017.
112 Table 9. k: Occurrence of resistance in MRSA from slaughter calves in 2017.
115 Table 1: Overview and key characteristics of sequenced *mcr-1*-harboring plasmids from strains of different origins isolated in Switzerland
119 Table 10. a: Number of samples and number of ESBL/pAmpC-producing *Escherichia coli* positive samples by origin of chicken meat for 2016
119 Table 10. b: Occurrence of resistance of ESBL/pAmpC-producing *Escherichia coli* from chicken meat in 2016.
120 Table 10. c: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from pork meat in 2017.
121 Table 10. d: Occurrence of resistance in ESBL/pAmpC-producing *Escherichia coli* from beef in 2017.
122 Table 10. e: Occurrence of MRSA from chicken meat in 2016.
123 Table 10. f: Occurrence of MRSA from pork meat in 2017.
124 Table 10. g: Number of samples and number of MRSA-positive samples by origin of chicken meat in 2016.
126 Table 11. a: Susceptibility rates of *Staphylococcus pseudintermedius* isolates in dogs.
127 Table 11. b: MIC_{90} rates of *Staphylococcus pseudintermedius* isolates in dogs in 2016/2017.
128 Table 11. c: Susceptibility rates of *Staphylococcus aureus* isolates in bovine mastitis in 2016/2017.
128 Table 11. d: MIC_{90} rates of *Staphylococcus aureus* isolates in bovine mastitis in 2016/2017.
129 Table 11. e: Susceptibility rates of *Streptococcus equi* subspecies *zooepidemicus* isolates in horses.
129 Table 11. f: MIC_{90} rates of *Streptococcus equi* subspecies *zooepidemicus* isolates in horses in 2016/2017.
130 Table 11. g: Susceptibility rates of *E. coli* isolates in dogs.
130 Table 11. h: MIC_{90} of *E. coli* isolates in dogs in 2016/17.
141 Table 12.2.1: Detection of MRSA in nasal swabs from Swiss veterinarians in 2017.
148 Table 13. a: Antimicrobial-resistance-monitoring program in 2016.
148 Table 13. b: Antimicrobial-resistance-monitoring program in 2017.
150 Table 13. c: Epidemiological cutoff values used for the interpretation of MIC data derived from isolates in samples from healthy animals at slaughterhouse and meat thereof (including *Salmonella* spp. from clinical samples)

Textboxes

pp.

46 Textbox: Antibiotic Prescriptions in Outpatient Medical Care
53 Textbox: Antibiotic Substances in the Water Cycle
59 Textbox: Temporal and Regional Prevalence of Carbapenemase-Producing Enterobacteriaceae from 2013 to 2017 in Switzerland
60 Textbox: The National Reference Center for Emerging Antibiotic Resistance (NARA)
66 Textbox: Carbapenem-Resistant *Acinetobacter baumannii* from 2005 to 2016 in Switzerland
75 Textbox: Treatment of the Tree Disease Fire Blight with Antibiotics
76 Textbox: Antibacterial Resistance in the Aquatic Environment
85 Textbox: Persistence of Quinolone and Tetracycline Resistance in Thermophilic Campylobacter from Poultry
93 Textbox: Modern Microbiological Surveillance for Antibiotic Drug Resistance
115 Textbox: *Mcr-1*-Based Colistin Resistance: Filling Knowledge Gaps in View of the Spread of Plasmid-Mediated Colistin Resistance in Switzerland