Usage of Antibiotics and
Occurence of Antibiotic Resistance
in Switzerland

Swiss Antibiotic Resistance Report 2020

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StAR

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Foreword

1 Foreword

In recent months, everyone has been focused on COVID-19. Although the issue of antibiotic resistance is no longer at the forefront of public awareness, this problem must continue to be tackled vigorously. Antibiotics are essential for treating bacterial infections. When antibiotics are no longer effective due to antibiotic resistance, vital treatment is often no longer successful. Even though COVID-19 is a viral disease, patients have often been given antibiotics to treat the disease's secondary effects. The World Health Organization WHO has expressed the concern that the COVID-19 crisis has made the situation of antibiotic resistance even worse, jeopardizing the progress made.

COVID-19 has also revealed the close connection between human and animal health. Most health problems hinge on a complexity of factors and can only be effectively addressed using a One Health approach. The Swiss antibiotic resistance strategy StAR is also based on this approach. One Health is now recognized worldwide as the leading approach for tackling many health problems, especially antibiotic resistance.

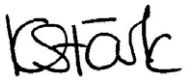
In a bid to address antibiotic resistance, Switzerland has taken action directed both at human and animal health, and at the environment. To measure the impact of the actions taken, it is essential to monitor antibiotic consumption and antibiotic resistance. The data on antibiotic consumption provide a timely indication of whether improvements have been achieved in the appropriate use of antibiotics. Ultimately, what matters is whether progress has been made in terms of resistance. It has been proven that the improper use of antibiotics has an influence on the development of resistance. However, this effect often only becomes apparent with a time delay and is not clear for every type of resistance.

This present Swiss Antibiotic Resistance Report (SARR) contains substantial improvements. Monitoring data is only really meaningful when all sectors are represented. The One Health approach for combatting resistance to antibiotics not only addresses human and veterinary medicine, but also focuses on the environment. For the first time, this SARR also includes a separate chapter on resistance in the environment.

Antibiotic consumption and resistance data from human and veterinary medicine were first presented in two separate chapters; since 2018, specific types of resistance have been examined in detail in a joint chapter across sectors. The report in 2018 specifically addressed methicillin-resistant *Staphylococcus aureus* (MRSA); this report specifically addresses resistance to carbapenems. Carbapenems are antibiotics that are only authorized for human medicine, and not for veterinary medicine. Mapping the antibiotic resistance in humans and animals is therefore particularly interesting and demonstrates how important it is to take into account antibiotic resistance in pets.

We would like to thank all those who have been involved in the preparation of the SARR report. We hope you enjoy reading it!

Stefan Kuster
Federal Office of Public Health



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1 Vorwort

In den letzten Monaten war Covid-19 das Thema, das die Bevölkerung beschäftigt hat. Obwohl das Thema Antibiotikaresistenzen dadurch im Bewusstsein etwas in den Hintergrund geraten ist, muss diese Problematik weiter mit Nachdruck angegangen werden. Antibiotika sind für die Therapie von bakteriellen Infektionen unverzichtbar. Sind Antibiotika wegen Resistenzen nicht mehr wirksam, so fehlen oft lebenswichtige Therapien. Obwohl Covid-19 eine virale Erkrankung ist, mussten Sekundärinfektionen bei Patienten oft mit Antibiotika behandelt werden. Die Weltgesundheitsorganisation WHO hat Befürchtungen geäussert, dass sich die Situation der Antibiotikaresistenzen wegen der Covid-19-Krise noch verschlechtert hat und bereits gemachte Fortschritte wieder gefährdet sind.

Covid-19 hat auch gezeigt, wie eng die Gesundheit von Mensch und Tier miteinander verbunden sind. Die meisten Gesundheitsprobleme sind von komplexen Faktoren abhängig und können oft nur mit dem sogenannten One Health-Ansatz erfolgreich bekämpft werden. Auf diesem Ansatz beruht auch die Strategie Antibiotikaresistenzen StAR. One Health ist mittlerweile als massgebender Ansatz für die Bewältigung vieler Probleme im Gesundheitsbereich, im Speziellen der Antibiotikaresistenzen, weltweit anerkannt.

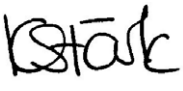
In der Schweiz wurden sowohl im Human-, Tier- als auch im Umweltbereich Massnahmen getroffen, um die Situation der Antibiotikaresistenzen zu verbessern. Um die Wirkung der Massnahmen zu beurteilen, ist es unumgänglich, den Antibiotikaverbrauch und die Antibiotikaresistenzen zu überwachen. Die Daten zum Antibiotikaverbrauch geben zeitnah Hinweise, ob Verbesserungen beim sachgemässen Antibiotikaverbrauch erzielt wurden. Letztlich zählt jedoch, ob auch Fortschritte bei den Resistenzen erreicht wurden. Es ist erwiesen, dass der unsachgemässe Antibiotikaeinsatz einen Einfluss auf die Resistenzbildung hat. Dieser Effekt ist jedoch oft nur zeitverzögert zu erkennen und nicht bei jeder Art von Resistenz eindeutig.

Im vorliegenden Swiss Antibiotic Resistance Report (SARR) gibt es inhaltliche Verbesserungen. Die Überwachungsdaten sind erst dann wirklich aussagekräftig, wenn alle Sektoren abgebildet werden. Im Rahmen des One Health-Ansatzes zur Bekämpfung der Resistenzen hat neben Human- und Veterinärmedizin auch die Umwelt eine wichtige Bedeutung. Im vorliegenden SARR wurde erstmals auch ein separates Kapitel über Resistenzen in der Umwelt integriert.

Nachdem die Antibiotikaverbrauchs- und Resistenzdaten von Human- und Veterinärmedizin anfangs nur in separaten Kapiteln aufgezeigt wurden, werden seit 2018 in einem gemeinsamen Kapitel spezifische Resistenzen sektorübergreifend näher beleuchtet. Im Jahr 2018 waren dies Methicillin-resistenten *Staphylococcus aureus* (MRSA), im vorliegenden Bericht werden Resistenzen gegen Carbapeneme spezifisch diskutiert. Carbapeneme sind Antibiotika, die nur in der Humanmedizin, nicht aber in der Veterinärmedizin zugelassen sind. Die Darstellung der Resistenzlage im Human- und Veterinärbereich ist deswegen besonders interessant und zeigt, wie wichtig es ist, auch die Resistenzsituation bei den Heimtieren zu berücksichtigen.

Wir danken allen, die sich bei der Erarbeitung des SARR-Berichts eingesetzt haben und wünschen Ihnen eine spannende Lektüre!

Stefan Kuster
Bundesamt für Gesundheit



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1 Avant-propos

Ces derniers mois, le COVID-19 était le thème dominant au cœur des préoccupations du public. Même si la résistance aux antibiotiques est quelque peu passée au second plan, nous devons continuer d'insister sur cette problématique. Les antibiotiques sont en effet incontournables pour traiter les infections bactériennes. Si des résistances les rendent inefficaces, ce sont souvent des traitements vitaux qui deviennent impossibles. De plus, bien que le COVID-19 soit une maladie virale, il déclenche fréquemment des infections secondaires devant être traitées avec des antibiotiques. L'Organisation mondiale de la santé a exprimé la crainte que la situation en matière de résistance aux antibiotiques se soit encore détériorée à cause de la crise du COVID-19 et que les progrès déjà accomplis soient compromis.

Le COVID-19 a aussi montré à quel point santé humaine et santé animale sont liées. La plupart des problèmes sanitaires dépendent de facteurs complexes et ne peuvent être souvent combattus efficacement que par l'approche One Health, sur laquelle repose la stratégie Antibiorésistance (StAR). One Health est devenue la référence mondiale pour affronter de nombreux problèmes de santé publique, en particulier celui de la résistance aux antibiotiques.

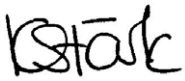
En Suisse, des mesures ont été prises dans les domaines humain et animal, mais aussi environnemental, pour améliorer la situation en matière d'antibiorésistance. Pour évaluer leur efficacité, il est indispensable de surveiller l'évolution de la consommation d'antibiotiques et celle des résistances. Les données sur la consommation offrent des indices immédiats pour évaluer si des progrès ont été accomplis concernant l'utilisation rationnelle de ces médicaments. Mais il importe aussi, en fin de compte, d'observer si la résistance a évolué dans un sens favorable. Il est établi que l'usage excessif des antibiotiques a une influence sur le développement de la résistance. Néanmoins, cet effet ne peut souvent être détecté qu'assez tardivement et n'apparaît pas de manière évidente pour tous les types de résistance.

La présente édition du Swiss Antibiotic Resistance Report (SARR) bénéficie d'améliorations en termes de contenu. Nous avons jugé que les données de surveillance ne sont vraiment pertinentes que si tous les secteurs sont représentés. Dans le cadre de l'approche One Health, l'environnement entre en ligne de compte au même titre que la médecine humaine et vétérinaire. Cette édition est d'ailleurs la première à intégrer un chapitre séparé sur les résistances dans l'environnement.

Alors qu'initialement, les données sur la consommation et la résistance étaient présentées uniquement dans des chapitres distincts, le rapport inclut depuis 2018 un chapitre commun qui examine plus en détail un type de résistance spécifique, sous un angle intersectoriel. En 2018, il y était question du *Staphylococcus aureus* résistant à la méticilline (SARM) et, cette fois-ci, des résistances aux carbapénèmes. Ces derniers sont des antibiotiques autorisés seulement en médecine humaine, et non comme traitements vétérinaires. L'examen de la situation au niveau de la résistance dans ces deux domaines s'avère ainsi particulièrement intéressant et montre l'importance de prendre également en compte le cas des animaux de compagnie.

Nous remercions toutes les personnes qui se sont impliquées dans la production du rapport et vous en souhaitons une lecture instructive.

Stefan Kuster
Office fédéral de la santé publique



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1 Premessa

Durante gli ultimi mesi, la COVID-19 è stata la preoccupazione principale della popolazione. Sebbene, per questo motivo, la questione della resistenza agli antibiotici sia stata un po' trascurata. Questo problema deve ora continuare ad essere affrontato con vigore. Gli antibiotici sono indispensabili per curare le infezioni batteriche. Se cessano di essere efficaci a causa delle resistenze, spesso vengono a mancare terapie d'importanza vitale. Nonostante la COVID-19 sia una malattia virale, spesso le infezioni secondarie dei pazienti hanno dovuto essere trattate con antibiotici. L'Organizzazione mondiale della sanità (OMS) ha paventato che la crisi COVID-19 ha ulteriormente peggiorato la situazione delle resistenze agli antibiotici, mettendo in pericolo i progressi già compiuti.

La COVID-19 ha anche mostrato quanto fosse stretto il nesso tra la salute umana e quella animale. La maggior parte dei problemi di salute dipende da fattori complessi che spesso possono essere combattuti efficacemente adottando il cosiddetto approccio One Health, su cui si basa la Strategia nazionale contro le resistenze agli antibiotici (StAR). Nel frattempo, l'approccio One Health è diventato il riferimento mondiale per affrontare numerosi problemi in ambito sanitario, in particolare quello delle resistenze agli antibiotici.

In Svizzera sono state adottate misure nei settori della medicina umana, in quello della medicina veterinaria nonché dell'agricoltura e dell'ambiente per migliorare la situazione delle resistenze agli antibiotici. Per valutarne gli effetti, è indispensabile sorvegliare l'uso degli antibiotici e le resistenze a queste sostanze. I dati relativi al consumo degli antibiotici indicano se sono stati registrati miglioramenti grazie a un loro uso corretto. Tuttavia, ciò che conta alla fine è compiere progressi sul fronte delle resistenze. È provato che un impiego improprio degli antibiotici influisce sullo sviluppo di resistenze. Ma questo effetto è spesso riconosciuto soltanto a posteriori e non per tutti i tipi di resistenza è così evidente.

Il presente Swiss Antibiotic Resistance Report (SARR) presenta alcuni miglioramenti nel contenuto. I dati che emergono dalla sorveglianza sono effettivamente significativi se tutti i settori sono rappresentati. Nel quadro dell'approccio One Health per la lotta alle resistenze, oltre alla medicina umana e veterinaria anche l'ambiente svolge un ruolo importante. Nel presente SARR è stato aggiunto anche un nuovo capitolo sulle resistenze agli antibiotici nell'ambiente.

Dopo che inizialmente i dati relativi all'uso degli antibiotici e alle resistenze a queste sostanze nella medicina umana e veterinaria venivano presentati in capitoli separati, dal 2018 le resistenze specifiche sono illustrate dettagliatamente in un capitolo comune a livello intersettoriale. Nel 2018 era stato tematizzato lo *Staphylococcus aureus* resistente alla meticillina (MRSA), mentre nel presente rapporto sono discussi specificamente la resistenza ai carbapenemi. I carbapenemi sono antibiotici omologati unicamente nell'ambito della medicina umana, ma non in veterinaria. Per questo motivo, la presentazione della situazione sulla resistenza agli antibiotici nei settori della medicina umana e della veterinaria è di particolare interesse e mostra quanto sia importante considerare anche gli animali domestici.

Teniamo a ringraziare tutti coloro che hanno partecipato all'allestimento del rapporto SARR auguriamo una buona lettura.

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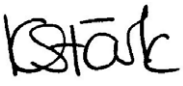
Ufficio federale della sanità pubblica



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e di veterinaria

2

Summary

2 Summary

Resistance in bacteria of human clinical isolates

Since 2010, 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 almost one third of all European countries. In contrast, MRSA rates are increasing in wound and abscess samples from outpatients, now even exceeding the rates observed in bacteremia. Penicillin resistance in *Streptococcus pneumoniae* decreased in earlier years, but has remained stable during the last 10 years. However, non-susceptibility to most other antibiotics has further decreased. In contrast to earlier reports, we have noted a significant increase in Vancomycin-resistant *Enterococcus faecium* rates during the last four years. This was mainly due to a regional/national outbreak, associated with the spread of an ST769 clone. Further close monitoring is essential and has been established in close collaboration with swissnoso.

In contrast, we have observed a steady increase in quinolone resistance and 3rd/4th generation cephalosporin resistance in *Escherichia coli* and *Klebsiella pneumoniae* during the last decade. However, rates of Quinolone-resistant *E. coli* and 3rd/4th generation cephalosporin resistant *K. pneumoniae* have remained constant during the last four years. Fortunately, carbapenem resistance is still rare in *E. coli* and *K. pneumoniae*, although numbers are increasing steadily in Switzerland, mirroring the situation in neighboring countries. Due to its importance, obligation to report was introduced in Switzerland on 1.1.2016, and all isolates are collected in the National Reference Center for Emerging Resistance NARA since 1.1.2019. In addition, a specific chapter on carbapenem-resistant Enterobacterales has been added to this report.

In *Pseudomonas aeruginosa*, non-susceptibility rates have stabilized or even slightly decreased, after resistance rates had increased between 2010 and 2015 for all antibiotics. *Acinetobacter* spp. resistance rates, including rates of carbapenem-resistance, remained stable.

Antibiotic consumption in human medicine

In Swiss acute care hospitals, consumption of antibacterial agents for systemic use (ATC group J01) increased by 13% to 51.8 DDDs (defined daily doses) per 100 bed-days between 2010 and 2019. The total consumption of antibacterial agents (ATC group J01) for systemic use was 1.6 DDDs per 1,000 inhabitants per day in 2019. The consumption rate in Swiss hospitals is slightly below the European median (1.8; range: 0.8–2.5). The most commonly used class of antibiotics was the penicillins (ATC group J01C), followed by the class of other beta-lactam antibacterials, including cephalosporins (ATC group J01D) and quinolones (ATC group J01M). Combination of penicillins with beta-lactamase inhibitors increased by 16% between 2010 and 2019. Fluoroquinolones decreased by 39% while third-generation cephalosporins increased by 46%. Following a constant increase until 2013, the consumption of carbapenems has been declining since then (-26%). According to WHO AWaRe classification, antibiotics from the Watch and Reserve groups represented 49% of total consumption in 2019.

In outpatient care, the total consumption of antibacterial agents for systemic use (ATC group J01) was 9.1 DDDs per 1,000 inhabitants per day in 2019. It remained stable in comparison to 2018 (9.1 DIDs) and 2017 (9.0 DIDs). It was relatively low in comparison to the European median (18.4; range: 8.9–32.4). 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). Fluoroquinolones and third-generation cephalosporins decreased by 24% and 29% respectively between 2016 and 2019. Sulfonamides and nitrofurantoin increased by 16% and 28% respectively during the same period. Antibiotics from the Watch and Reserve groups represented 36% of total consumption in 2019.

Resistance in zoonotic bacteria

Most importantly, in poultry, the resistance rate to ciprofloxacin in *Campylobacter jejuni (C. jejuni)* and *C. coli* has increased significantly in the last years. The resistance rate to ciprofloxacin rose to 51.4% for *C. jejuni* and 66.7% for *C. coli* in 2016. In 2018, a significant decrease was detected for the first time, with 45.7% for *C. jejuni* and 40.5% for *C. coli*. In contrast, resistance to tetracycline increased for *C. coli* (54.1%), but decreased for *C. jejuni* (30.4%). Resistance to erythromycin was still rarely found. Resistance patterns of *C. jejuni* and *C. coli* isolated from chicken meat follow the trend observed for broilers.

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. Hence, the reversal of trends in *C. jejuni* and *C. coli* resistance is good news.

In fattening pigs, the resistance rates in *Campylobacter coli (C. coli)* against ciprofloxacin has increased significantly in the last years, up to 55.9% in 2019. Concerning erythromycin, we have also noticed an increase in the resistance, although on a low level (3.9%). Likewise, we have remarked a slightly higher resistance rate for streptomycin, from 81.4% in 2017 to 84.7% in 2019.

In Switzerland, *Salmonella (S.)* spp. rarely occur in livestock. Therefore, the risk of *Salmonella* transmission to humans from food produced from 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 *Escherichia (E.) coli* isolated from livestock in Switzerland.

For commensal *E. coli* from broilers in Switzerland, the resistance rates against different antimicrobial classes show no common trend. Increasing trends for resistance rates to ampicillin and ciprofloxacin are found in commensal *E. coli* isolates from broilers, but decreasing trends are observed for sulfonamides and tetracycline. In contrast, trends for resistance levels of *E. coli* from fattening pigs and slaughter calves are generally more similar. There is no antimicrobial class for which a significant increase could be detected. Over the years, decreasing trends are obvious for sulfonamides, tetracyclines and ampicillin, and fluoroquinolone resistance levels are constantly low for both livestock species.

The prevalence of ESBL/pAmpC-producing *E. coli* has decreased significantly for broilers (52.4% in 2016 to 30.6% in 2018) and slightly for fattening pigs (2019: 13.1%); the prevalence of ESBL/pAmpC-producing *E. coli* in slaughter calves remains stable compared to 2017 (32.9% in 2019). Overall, a decreasing trend of ESBL/pAmpC-producing *E. coli* is seen in broilers and fattening pigs since 2014, while the prevalence in slaughter calves remains stable on a high level (>30%) since 2015.

No carbapenemase-producing *E. coli* were found in livestock species.

In Switzerland, the occurrence of methicillin-resistant *Staphylococcus (S.) aureus* (MRSA) in fattening pigs at slaughter has increased constantly since detection of MRSA became part of the monitoring in 2009. Starting at 2% in 2009, the MRSA prevalence reached 52.8% in 2019.

In contrast, the prevalence for MRSA in veal calves has decreased to 3.8%, which is the lowest detected level since 2013. The genotypes belong to the clonal complex (CC) 398, which is typically livestock-associated (LA-MRSA).

Resistance in indicator bacteria from meat

Compared to 2014 and 2016, the prevalence of ESBL/pAmpC-producing *E. coli* in chicken meat further strongly decreased for Swiss meat in 2018 (2014: 65.5%; 2016: 41.9%, 2018: 21.1%). In chicken meat from abroad, the detection rate of ESBL/pAmpC-producing *E. coli* also decreased in 2018, but still remains higher than in Swiss meat (2014: 88.9%; 2016: 81.5%, 2018: 63.1%).

In contrast, in pork and beef meat a very low prevalence of ESBL/pAmpC-producing *E. coli* was detected (<1%) This difference might be related to the lower prevalence of ESBL/pAmpC-producing *E. coli* in Swiss pigs and calves and the distinct slaughtering process of these animals. No carbapenemase-producing *E. coli* were found in fresh meat samples.

The detection rates for MRSA in Swiss fresh meat was zero for chicken meat in 2018 and pork and beef meat in 2019. This is in line with the low detection rate for MRSA in previous years. Since 2014, the prevalence of MRSA in chicken decreased continuously until 2018. In 2014, 16.1% of foreign chicken meat was tested positive for MRSA, in 2016 the prevalence decreased to 9.3%. In 2018, only 3.9% of the foreign produced chicken meat was contaminated with MRSA. Swiss chicken meat showed a very low prevalence of 1% in 2014; in 2016 and 2018, none of the samples tested were MRSA positive. In Swiss pork meat, a very low prevalence of 0.7% was found in 2017, identical to the prevalence found in 2015, despite the fact that the MRSA prevalence in nasal swabs from Swiss fattening pigs increased from 25.7% to 52.8% in the same time period. The data confirmed that fresh meat 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.

In 2019, an annual monitoring of antimicrobial resistance in veterinary pathogens was initiated by the Federal Food Safety and Veterinary Office (FSVO) and implemented at the Swiss national reference laboratory for antimicrobial resistance (ZOBA).

For various reasons, the presented data must be interpreted with caution. First of all, the overall low number of isolates may lead to overinterpretation of calculated resistances

rates. With more data in the future, the trends will become more evident. Moreover, it must be noted that the analyzed isolates are exclusively derived from animals which were not pretreated with antimicrobials before the sample was taken. This is of relevance when comparing our data with data from other study populations.

For mastitis pathogens, *Streptococcus uberis* turned out to be more critical in terms of antimicrobial treatment than *Staphylococcus aureus*. When comparing *Escherichia coli* isolated from different animal species and indications, remarkable differences were detected. Only isolates from bovine mastitis and poultry showed no resistance to 3rd or 4th generation cephalosporines, whereas *Escherichia coli* isolates from companion UTI expressed resistance against these critically important antimicrobials. Carbapenem-resistant *Escherichia coli* were not detected in 2019.

Sales of antimicrobials in veterinary medicine

The sales volume of antimicrobials continued to decline, in 2018 by only 1.3%, in 2019 more pronouncedly with a decline of 7.1%. Overall, 32,397 kg of antimicrobials were sold for veterinary medicine in 2018 and 30,108 kg in 2019. This amounts to a decline of 52% (33 tons) since 2010. The decrease is mainly due to a fall in sales of medicated premixes. The sales rankings of the various classes of antimicrobials changed in 2018: earlier, sulfonamides had been in first place; since 2018, penicillins are the main class sold, followed by sulfonamides and tetracyclines. These three classes are often sold as medicated premixes. The quantity of antibiotics approved for pets only comprises 2.6% of the total volume; the sales for pets decreased by 5.3% in 2018 and slightly increased by 1.6% in 2019. The sales of the highest-priority critically important antibiotic classes for human medicine decreased in 2018 and 2019; the sales of macrolides decreased by 7% in 2018 and by another 20% in 2019. The sales of fluoroquinolones declined by 11% in 2018 and by 9.9% in 2019. The sales of cephalosporins (3rd/4th generation) decreased by approximately 4.7% in 2018 and 1.3% in 2019. The sales volume of colistin has declined by approximately 86% since 2010. Expressed in correlation to the biomass under exposure, the level is 0.3 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.

2 Zusammenfassung

Resistenz bei Bakterien aus klinischen Isolaten vom Menschen

Seit 2010 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 in fast einem Drittel aller europäischen Länder feststellen. In Wund- und Abszessproben von ambulanten Patientinnen und Patienten nahmen die MRSA-Raten hingegen zu und liegen inzwischen sogar über den Raten, die bei Bakteriämien beobachtet wurden. Die Penicillin-Resistenz bei *Streptococcus pneumoniae* war zuvor rückläufig, blieb im Verlauf der letzten 10 Jahre jedoch stabil. Die Resistenz gegenüber den meisten anderen Antibiotika hat jedoch weiter abgenommen. Im Gegensatz zu früheren Berichten haben wir in den letzten vier Jahren einen signifikanten Anstieg der Raten des Vancomycin-resistenten *Enterococcus faecium* festgestellt. Dies war hauptsächlich auf einen regionalen/nationalen Ausbruch zurückzuführen, der mit der Verbreitung eines ST769-Klons im Zusammenhang stand. Eine weitere engmaschige Überwachung ist unerlässlich und wurde in enger Zusammenarbeit mit swissnoso eingerichtet.

Im Gegensatz dazu wurde im letzten Jahrzehnt bei *Escherichia coli* und *Klebsiella pneumoniae* eine stete Zunahme der Resistenzraten gegenüber Chinolonen und Cephalosporinen der dritten und vierten Generation festgestellt. Die Raten der Chinolon-Resistenz bei *E. coli* und der Resistenz gegenüber Cephalosporinen der dritten und vierten Generation bei *K. pneumoniae* sind in den letzten vier Jahren jedoch konstant geblieben. Erfreulicherweise bleibt die Resistenz gegenüber Carbapenemen bei *E. coli* und *K. pneumoniae* selten, obwohl die Zahlen in der Schweiz kontinuierlich ansteigen und somit die Situation in den Nachbarländern widerspiegeln. Aufgrund ihrer Bedeutung wurde in der Schweiz am 1. Januar 2016 eine Meldepflicht eingeführt. Seit dem 1. Januar 2019 werden zudem alle Isolate im Nationalen Referenzlaboratorium zur Früherkennung und Überwachung neuartiger Antibiotikaresistenzen NARA gesammelt. Darüber hinaus wurde dieser Bericht um ein spezielles Kapitel über Carbapenem-resistente Enterobacterales erweitert.

Bei *Pseudomonas aeruginosa* haben sich die Resistenzraten stabilisiert oder sind sogar leicht zurückgegangen, nachdem sie zwischen 2010 und 2015 für alle Antibiotika angestiegen waren. Bei *Acinetobacter* spp. blieben die Resistenzraten, einschliesslich der Raten der Carbapenemase-Resistenz, stabil.

Antibiotikaverbrauch in der Humanmedizin

In den Schweizer Akutspitälern stieg der Verbrauch von Antibiotika zur systemischen Anwendung (ATC-J01) zwischen 2010 und 2019 um 13% auf 51,8 definierte Tagesdosen (Defined Daily Doses, DDD) pro 100 Bettentage an. Der Gesamtverbrauch von Antibiotika (ATC-J01) zur systemischen Anwendung belief sich 2019 auf 1,6 DDD pro 1000 Einwohnerinnen und Einwohner pro Tag. Die Verbrauchsrate liegt in Schweizer Spitälern knapp unter dem europäischen Median (1,8; Bereich: 0,8–2,5). Die am häufigsten verwendete Antibiotikagruppe waren die Penicilline (ATC-J01C), gefolgt von der Klasse der anderen Beta-Laktam-Antibiotika, einschliesslich der Cephalosporine (ATC-J01D) und der Chinolone (ATC-J01M). Der Verbrauch der Kombination von Penicillinen mit Beta-Laktamase-Inhibitoren ist zwischen 2010 und 2019 um 16% angestiegen. Der Verbrauch von Fluorochinolonen ist um 39% zurückgegangen, während derjenige der Cephalosporine der dritten Generation um 46% angestiegen ist. Nach einem konstanten Anstieg bis 2013 war der Verbrauch von Carbapenemen rückläufig (–26%). Nach der WHO AWaRe-Klassifizierung machten Antibiotika aus den Gruppen Watch und Reserve im Jahr 2019 49% des Gesamtverbrauchs aus.

In der ambulanten Versorgung belief sich der Gesamtverbrauch von Antibiotika zur systemischen Anwendung (ATC-J01) im 2019 auf 9,1 DDD pro 1000 Einwohnerinnen und Einwohner pro Tag. Er blieb im Vergleich zu 2018 (9,1) und 2017 (9,0) stabil. Im Vergleich zum europäischen Median (18,4; Bereich: 8,9–32,4) war er relativ gering. 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 Verbrauch von Fluorochinolonen und Cephalosporinen der dritten Generation sank zwischen 2016 und 2019 um jeweils 24 und 29%. Der Verbrauch von Sulfonamiden und Nitrofurantoin stieg im gleichen Zeitraum um jeweils 16 und 28%. Antibiotika aus den Gruppen Watch und Reserve machten im Jahr 2019 36% des Gesamtverbrauchs aus.

Resistenzen bei Zoonose-Erregern

In Geflügel hat die Resistenz gegenüber Ciprofloxacin bei *Campylobacter jejuni* (*C. jejuni*) und *C. coli* in den letzten Jahren signifikant zugenommen. Die Resistenzrate gegenüber Ciprofloxacin stieg 2016 bei *C. jejuni* auf 51,4% und bei *C. coli* auf 66,7% an. 2018 wurde mit 45,7% bei *C. jejuni* und 40,5% bei *C. coli* erstmalig ein signifikanter Rückgang fest-

gestellt. Die Resistenz gegenüber Tetracyclin stieg bei *C. coli* (54,1%) dagegen an; bei *C. jejuni* sank sie (30,4%). Eine Resistenz gegenüber Erythromycin wurde weiterhin selten festgestellt. Die Resistenzmuster von *C. jejuni* und *C. coli*, die aus Hühnerfleisch isoliert wurden, folgen dem Trend, der bei Mastpoulets beobachtet wurde.

Gemäss der WHO gelten Fluorochinolone und Makrolide als kritische Antibiotika mit höchster Priorität in der Humanmedizin, weil diese Wirkstoffgruppen bei schweren Verlaufsformen der Campylobacteriose beim Menschen bevorzugt zum Einsatz kommen. Aus diesem Grund ist die Trendumkehr bei der Resistenz von *C. jejuni* und *C. coli* eine gute Nachricht.

Bei Mastschweinen ist die Resistenz bei *Campylobacter coli* (*C. coli*) gegenüber Ciprofloxacin in den letzten Jahren signifikant angestiegen; im Jahr 2019 auf bis zu 55,9%. Hinsichtlich Erythromycin wurde ebenfalls eine Zunahme der Resistenz festgestellt, wenn auch auf niedrigem Niveau (3,9%). Ebenfalls wurde eine etwas höhere Resistenzrate gegenüber Streptomycin festgestellt, die von 81,4% im Jahr 2017 auf 84,7% im Jahr 2019 angestiegen ist.

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

Resistenzen bei Indikatorkeimen in Tieren

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

Bei kommensalen *E. coli* aus Schweizer Mastpoulets weisen die Resistenzraten gegenüber unterschiedlichen antimikrobiellen Klassen keinen gemeinsamen Trend auf. Bei den Resistenzraten gegenüber Ampicillin und Ciprofloxacin finden sich steigende Trends bei kommensalen *E. coli*-Isolaten von Mastpoulets, während bei Sulfonamiden und Tetrazyklinen abnehmende Trends zu beobachten sind. Dagegen sind die Trends bei Resistenzniveaus von *E. coli* bei Mastschweinen und Mastkälbern im Allgemeinen ähnlicher. Es gibt keine Klasse, für die ein signifikanter Anstieg festgestellt werden konnte. Im Verlauf der Jahre sind bei Sulfonamiden, Tetracyclinen und Ampicillin rückläufige Tendenzen erkennbar, während die Fluorchinolon-Resistenzniveaus bei beiden Nutztierarten konstant niedrig bleiben.

Die Prävalenz von ESBL/pAmpC-produzierenden *E. coli* ist bei Mastpoulets signifikant (52,4% in 2016 auf 30,6% in 2018) und bei Mastschweinen leicht (2019: 13,1%) zurückgegangen; die Prävalenz von ESBL/pAmpC-produzierenden *E. coli* bei Mastkälbern bleibt im Vergleich zu 2017 stabil (32,9% in 2019). Insgesamt ist seit 2014 ein rückläufiger Trend der ESBL/pAmpC-produzierenden *E. coli* bei Mastpoulets und Mastschweinen zu beobachten, während die Prävalenz bei Mastkälbern seit 2015 auf einem hohen Niveau (>30%) stabil bleibt.

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 im Jahre 2009 Teil der Überwachung wurde. Von anfänglichen 2% (2009) stieg die MRSA-Prävalenz im Jahr 2019 auf 52,8%.

Bei Mastkälbern sank die MRSA-Prävalenz dagegen auf 3,8%, wobei es sich um den niedrigsten festgestellten Wert seit 2013 handelt. Diese Genotypen gehören zur klonalen Linie CC398, die zu den sogenannten nutztierassoziierten MRSA (LA-MRSA) gehört.

Resistenzen bei Indikatorkeimen aus Fleisch

Im Vergleich zu 2014 und 2016 zeigt die Prävalenz von ESBL/pAmpC-produzierenden *E. coli* in Schweizer Hühnerfleisch im 2018 weiterhin einen starken Rückgang (2014 65,5%; 2016: 41,9%, 2018: 21,1%). Bei Hühnerfleisch aus dem Ausland ging im Jahr 2018 die Nachweisrate von ESBL/pAmpC-produzierenden *E. coli* ebenfalls zurück, ist aber immer noch höher als bei Schweizer Fleisch (2014: 88,9%; 2016: 81,5%, 2018: 63,1%).

Demgegenüber wurde in Schweine- und Rindfleisch eine geringe Prävalenz ESBL/pAmpC-produzierender *E. coli* nachgewiesen (<1%). Dieser Unterschied ist möglicherweise auf die niedrige 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.

Die MRSA-Nachweisraten in Schweizer Frischfleisch lagen 2018 für Hühnerfleisch und 2019 für Schweine- und Rindfleisch bei null. Dies steht im Einklang mit tiefen MRSA-Nachweisraten in den vergangenen Jahren. Seit 2014 ist die Prävalenz von MRSA beim Huhn bis 2018 kontinuierlich zurückgegangen. 2014 wurden 16,1% des ausländischen Hühnerfleisches positiv auf MRSA getestet. 2016 sank die Prävalenz auf 9,3%. 2018 waren nur 3,9% des im Ausland erzeugten Hühnerfleisches mit MRSA kontaminiert. In Schweizer Hühnerfleisch zeigte sich 2014 eine sehr niedrige Prävalenz von 1%. 2016 und 2018 wurde in den untersuchten Proben keine MRSA nachgewiesen. Im Schweizer Schweinefleisch wurde 2017 eine sehr niedrige Prävalenz von 0,7% festgestellt, die der Prävalenz aus dem Jahr 2015 entspricht, obwohl die MRSA-Prävalenz in Nasenabstrichen von Schweizer Mastschweinen im gleichen Zeitraum von 25,7% auf 52,8% gestiegen ist. 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 ihnen, 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.

Im Jahr 2019 wurde das jährliche Antibiotikaresistenz-Monitoring für Tierpathogene durch das Bundesamt für Lebensmittelsicherheit und Veterinärwesen (BLV) initiiert und am Zentrum für Zoonosen, bakterielle Tierkrankheiten und Antibiotikaresistenz (ZOBA) implementiert.

Die vorgelegten Daten sind aus verschiedenen Gründen mit Vorsicht zu interpretieren. Zunächst kann die geringe Gesamtanzahl von Isolaten zu einer Überinterpretation der berechneten Resistenzen führen. Wenn in der Zukunft mehr Daten vorliegen, werden die Trends deutlicher werden. Darüber hinaus ist zu beachten, dass die untersuchten Isolate ausschliesslich von Tieren stammen, die vor der Probenentnahme nicht mit Antibiotika vorbehandelt wurden. Dies ist beim Vergleich unserer Daten mit Daten aus anderen Studienpopulationen von Bedeutung.

Bei Mastitis-Erregern erwies sich *Streptococcus uberis* hinsichtlich der antimikrobiellen Behandlung als kritischer als *Staphylococcus aureus*. Beim Vergleich von *Escherichia coli*, die aus verschiedenen Tierarten und aufgrund verschiedener Indikationen isoliert wurden, zeigten sich bemerkenswerte Unterschiede. Nur Isolate von Rindermastitis und Geflügel zeigten keine Resistenz gegen Cephalosporine der dritten oder vierten Generation, während *Escherichia coli*-Isolate aus Harnwegsinfektionen von Heimtieren eine Resistenz gegen diese kritisch wichtigen Antibiotika zeigten. Carbapenem-resistente *Escherichia coli* wurden 2019 nicht nachgewiesen.

Vertrieb von Antibiotika in der Veterinärmedizin

Die Gesamtmenge der verkauften Antibiotika ging weiter zurück: 2018 um lediglich 1,3% und 2019 deutlicher um 7,1%. 2018 wurden insgesamt 32 397 kg und 2019 30 108 kg Antibiotika zur Behandlung von Tieren verkauft. Dies entspricht einem Rückgang seit 2010 um 52% (33 t). Der Rückgang ist hauptsächlich auf eine Reduktion der Verkäufe von Arzneimittelvormischungen zurückzuführen. Die Reihenfolge der meistverkauften Wirkstoffklassen veränderte sich im Jahr 2018. Während zuvor Sulfonamide an erster Stelle standen, stellen seit 2018 die Penicilline die meistverkaufte Klasse dar, gefolgt von Sulfonamiden und Tetracyclinen. Diese drei Wirkstoffklassen sind häufig in Arzneimittelvormischungen enthalten. Der Anteil der Wirkstoffe, die nur für Heimtiere zugelassen sind, macht lediglich 2,6% der Gesamtmenge aus. Die Vertriebsmengen für Heimtiere gingen 2018 um 5,3% zurück und zeigten 2019 einen leichten Anstieg um 1,6%. Die Vertriebsmengen der kritischen Antibiotikaklassen mit höchster Priorität für die Humanmedizin waren 2018 und 2019 rückläufig. Die Verkäufe der Makrolide gingen 2018 um 7% und 2019 um weitere 20% zurück. Bei den Fluorchinolonen nahmen die Vertriebsmengen 2018 um 11% und 2019 um 9,9% ab. Die Verkäufe der Cephalosporine der dritten und vierten Generation gingen 2018 um rund 4,7% und 2019 um rund 1,3% zurück. Bei Colistin ging das Verkaufsvolumen seit 2010 um rund 86% zurück. Ausgedrückt in Bezug zur Populationsbiomasse wurde in der Schweiz 0,3 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.

2 Résumé

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

Depuis 2010, différentes tendances se dessinent chez les bactéries à Gram positif et à Gram négatif : les taux de résistance à la méticilline de *Staphylococcus aureus* (SARM) dans les isolats invasifs ont encore nettement reculé, en particulier en Suisse romande. Une évolution similaire a été observée dans presque un tiers des pays européens. Les taux de SARM sont quant à eux en hausse dans les échantillons prélevés sur des plaies et des abcès de patients recevant des soins ambulatoires et dépassent maintenant même les taux de bactériémie. La résistance à la pénicilline de *Streptococcus pneumoniae*, qui affichait autrefois une tendance à la baisse, est restée stable durant les dix dernières années. Cependant, la résistance envers la plupart des autres antibiotiques a continué de décroître. Contrairement aux rapports précédents, nous avons constaté une augmentation significative des taux d'*Enterococcus faecium* résistants à la vancomycine au cours des quatre dernières années. Cette situation est principalement imputable à une flambée régionale ou nationale, liée à la propagation d'un clone ST769. Une surveillance stricte est essentielle et elle a été mise en place en étroite collaboration avec Swissnoso.

En revanche, la résistance aux quinolones et aux céphalosporines de troisième et quatrième génération se développe de façon régulière chez *Escherichia coli* (*E. coli*) et *Klebsiella pneumoniae (K. pneumoniae)* depuis une décennie. Les taux d'*E. coli* résistants aux quinolones et de *K. pneumoniae* résistants aux céphalosporines de troisième et quatrième génération sont néanmoins restés constants au cours des quatre dernières années. Fort heureusement, la résistance aux carbapénèmes demeure rare chez *E. coli* et *K. pneumoniae*, bien que les chiffres ne cessent de croître à l'échelle nationale, à l'image de la situation dans les pays voisins. En raison de leur importance, il est obligatoire de déclarer ces micro-organismes en Suisse depuis le 1er janvier 2016, et tous les isolats sont recueillis au Centre national de référence pour la détection précoce des résistances émergentes aux antibiotiques (NARA) depuis le 1er janvier 2019. Par ailleurs, un chapitre spécifique sur les entérobactéries résistantes aux carbapénèmes a été ajouté à ce rapport.

Chez *Pseudomonas aeruginosa*, les taux de résistance aux antibiotiques se sont stabilisés, voire ont légèrement reculé après avoir affiché une progression entre 2010 et 2015. Les taux de résistance chez *Acinetobacter* spp. sont demeurés constants (y compris résistance aux carbapénèmes).

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 13 % pour passer à 51,8 DDD entre 2010 et 2019. La consommation totale d'antibactériens à usage systémique (classe ATC J01) était de 1,6 DDD pour 1000 habitants et par jour en 2019. Le taux de consommation dans les hôpitaux suisses se situait quant à lui un peu en dessous de la valeur médiane européenne (1,8 ; étendue : 0,8 à 2,5). La classe des antibiotiques les plus fréquemment utilisés était celle des pénicillines (classe ATC J01C), suivie des autres bétalactamines, qui comprennent des céphalosporines (classe ATC J01D) et des quinolones (classe ATC J01M). La combinaison pénicillines et inhibiteurs de bêta-lactamases a progressé de 16 % entre 2010 et 2019. Les fluoroquinolones ont régressé de 39 % tandis que les céphalosporines de troisième génération ont progressé de 46 %. À la suite d'une hausse permanente depuis 2013, la consommation de carbapénèmes n'a ensuite cessé de décliner (–26 %). Selon la classification AWaRe de l'OMS, les antibiotiques des groupes Watch et Reserve représentaient 49 % de la consommation totale en 2019.

En milieu ambulatoire, la consommation totale d'antibactériens à usage systémique (classe ATC J01) était de 9,1 DDD pour 1000 habitants et par jour en 2019 ; une proportion restée stable par rapport à 2018 (9,1) et à 2017 (9,0) et qui demeure relativement faible en comparaison avec la valeur médiane européenne (18,4 ; étendue : 8,9 à 32,4). La classe des antibiotiques les plus fréquemment utilisés était celle des pénicillines (classe ATC J01C), suivie des macrolides, des lincosamides et des streptogramines (classe ATC J01F), des tétracyclines (classe ATC J01A) et des fluoroquinolones (classe ATC J01MA). Les fluoroquinolones et les céphalosporines de troisième génération ont perdu respectivement 24 % et 29 % entre 2016 et 2019. À l'inverse, les sulfonamides et la nitrofurantoïne ont grimpé de 16 % et de 28 % durant la même période. Les antibiotiques des groupes Watch et Reserve représentaient 36 % de la consommation totale en 2019.

Résistance des bactéries zoonotiques

Concernant la volaille, en particulier, la résistance de *Campylobacter jejuni* (*C. jejuni*) et de *Campylobacter coli* (*C. coli*) à la ciprofloxacine s'est fortement accentuée ces dernières années, avec des taux respectifs de 51,4 % et de

66,7 % en 2016. En 2018, une baisse importante a été constatée pour la première fois : à un taux de 45,7 % chez *C. jejuni* et de 40,5 % chez *C. coli*. Pour ce qui est de la résistance à la tétracycline, elle a augmenté pour *C. coli* (54,1 %) mais diminué pour *C. jejuni* (30,4 %). La résistance à l'érythromycine (2,9 %) n'a encore une fois été que rarement observée. Les schémas de résistance d'isolats de *C. jejuni* et de *C. coli* à partir de la viande de poulet suivent la tendance observée pour les poulets de chair.

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. Le revirement de tendance concernant *C. jejuni* et *C. coli* est donc une bonne nouvelle.

Chez les porcs d'engraissement, le taux de résistance à la ciprofloxacine des souches de *Campylobacter coli* (*C. coli*) a nettement accéléré au cours des dernières années, passant ainsi à 55,9 % en 2019. Un accroissement de la résistance a également été enregistré au niveau de l'érythromycine, toutefois à un faible niveau (3,9 %). De même, la résistance à la streptomycine est devenue légèrement plus importante, passant de 81,4 % en 2017 à 84,7 % en 2019.

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 *E. coli* isolés à partir d'animaux de rente.

S'agissant d'*E. coli* dans la flore commensale des poulets de chair, on n'observe pas de tendance commune en matière de taux de résistance à différentes catégories d'antimicrobiens. Les taux de résistance à l'ampicilline et à la ciprofloxacine en flore commensale dans les isolats d'*E. coli* chez les poulets de chair gagnent du terrain tandis que l'on observe des tendances à la baisse pour les tétracyclines et les sulfonamides. À l'inverse, les niveaux de résistance d'*E. coli* chez les porcs d'engraissement et les veaux de boucherie sont généralement plus uniformes. Aucune catégorie d'antimicrobien n'a fait l'objet d'une hausse sensible. Sur plusieurs années, on observe une tendance baissière évidente pour les sulfonamides, les tétracyclines et l'ampicilline, et la résistance aux fluoroquinolones reste constamment faible pour les deux animaux de rente en question.

La prévalence de l'*E. coli* producteur de BLSE/AmpC a beaucoup diminué chez les poulets de chair (52,4 % en 2016 contre 30,6 % en 2018) et un peu chez les porcs d'engraissement (2019 : 13,1 %) ; la prévalence de cette bactérie chez les veaux de boucherie est quant à elle restée stable par rapport à 2017 (32,9 % en 2019). Dans l'ensemble, on constate une tendance décroissante de l'*E. coli* producteur de BLSE/AmpC dans les cheptels de poulets de chair et de porcs d'engraissement depuis 2014, tandis que sa prévalence chez les veaux de boucherie demeure constante à un niveau élevé (> 30 %) depuis 2015.

Aucun *E. coli* producteur de carbapénèmases n'a été identifié sur 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, à savoir depuis 2009. La prévalence des SARM est passée de 2 % à 52,8 % en dix ans.

Toutefois, ce taux a dégringolé à 3,8 % chez les veaux d'engraissement, à savoir au niveau le plus bas enregistré depuis 2013. Ces génotypes font partie d'un certain complexe clonal CC 398, typiquement associé aux animaux de rente.

Résistance des germes indicateurs dans la viande

Comparée à 2014 et à 2016, la prévalence de l'*E. coli* producteur de BLSE/AmpC dans la viande de poulet suisse a poursuivi sa chute libre en 2018 (2014 : 65,5 % ; 2016 : 41,9 % ; 2018 : 21,1 %). En ce qui concerne la viande de poulet importée, le taux de détection de cette bactérie a également reculé en 2018, mais il reste plus élevé que celui enregistré pour la viande suisse (2014 : 88,9 % ; 2016 : 81,5 % ; 2018 : 63,1 %).

À l'opposé, les taux détectés dans la viande de porc et de bœuf ont été très faibles (< 1 %). Cet écart pourrait 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 carbapénèmases n'a été identifié dans les échantillons de viande fraîche.

Les taux de détection de SARM dans la viande suisse fraîche étaient de zéro pour la viande de poulet en 2018 ainsi que pour la viande de bœuf en 2019 : un résultat en accord avec ceux enregistrés au cours des années précédentes. Les SARM identifiés chez les poulets n'ont cessé de décroître entre 2014 et 2018. En 2014, 16,1 % de la viande de poulet étrangère avait été testée positive, contre 9,3 % en 2016 et seulement 3,9 % en 2018. La viande de poulets élevés en Suisse a affiché une très faible prévalence de 1 % en 2014, et aucun échantillon n'a été testé positif aux SARM en 2016 et en 2018. En 2017, un taux très modéré de 0,7 %, identique à celui de 2015, a été détecté dans la viande de porc suisse, malgré le fait que la prévalence des SARM issue des prélèvements nasaux chez les porcs d'engraissement suisses a progressé de 25,7 % à 52,8 % durant la même période. Ces données confirment que la viande fraîche n'est pas considérée comme une source pertinente de transmission des SARM à l'être humain.

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 un manque d'informations en matière de surveillance de l'antibiorésistance dans la perspective « One-Health ».

En 2019, l'Office fédéral de la sécurité alimentaire et des affaires vétérinaires (OSAV) a lancé un projet de surveillance annuelle de l'antibiorésistance des agents pathogènes animaux et l'a mis en œuvre au Centre des zoonoses, des maladies animales d'origine bactérienne et de l'antibiorésistance (ZOBA).

Pour différentes raisons, les données présentées doivent être interprétées avec prudence. Premièrement, le nombre généralement faible d'isolats pourrait conduire à une interprétation exagérée des taux de résistance calculés. Les tendances deviendront plus claires lorsqu'il y aura davantage de données. De plus, il convient de souligner que les isolats analysés proviennent exclusivement d'animaux n'ayant pas été traités aux antibiotiques avant le prélèvement de l'échantillon : un point important si l'on compare ces données avec celles d'autres populations étudiées.

Au niveau des pathogènes responsables des mammites, *Streptococcus uberis* s'est révélé plus critique que *Staphylococcus* en termes de traitement antibiotique. Des différences remarquables ressortent de la comparaison d'isolats d'*E. coli* de diverses espèces animales et pour diverses indications. Seuls les isolats de mammite bovine et de volaille n'ont enregistré aucune résistance aux céphalosporines de troisième et quatrième génération, alors que les isolats d'*E. coli* allant de pair avec les infections urinaires ont affiché une résistance contre ces antimicrobiens critiques. Aucun *E. coli* résistant aux carbapénèmes n'a été décelé en 2019.

Vente d'antibiotiques utilisés en médecine vétérinaire

Le volume de vente d'antibiotiques a continué de décliner, de seulement 1,3 % en 2018 mais de 7,1 % en 2019. Dans l'ensemble, 32 397 kg d'antibiotiques ont été vendus pour la médecine vétérinaire en 2018 et 30 108 kg en 2019, ce qui équivaut à un fléchissement de 52 % (33 tonnes) depuis 2010. Ce recul est principalement dû à une baisse des ventes des prémélanges pour aliments médicamenteux. Le classement des ventes d'antimicrobiens a changé en 2018 : auparavant, les sulfonamides se classaient en tête, mais depuis 2018, les pénicillines arrivent en haut de la liste, suivis par les sulfonamides et les tétracyclines. Ces trois classes sont souvent vendues sous forme de prémélanges pour aliments médicamenteux. La part des antibiotiques autorisés uniquement pour les animaux domestiques correspond à 2,6 % de la quantité totale ; les ventes pour les animaux domestiques ont reculé de 5,3 % en 2018 et légèrement augmenté (de 1,6 %) en 2019. Les ventes d'antimicrobiens critiques de première priorité en médecine humaine ont diminué en 2018 et en 2019 ; les ventes de macrolides de 7 % en 2018 et de 20 % supplémentaires en 2019. Les ventes de fluoroquinolones ont chuté de 11 % en 2018 et de 9,9 % en 2019. Celles de céphalosporines de troisième et quatrième génération ont régressé d'environ 4,7 % en 2018 et de 1,3 % en 2019. Les ventes de colistine ont reculé d'environ 86 % depuis 2010. Exprimé en corrélation avec la biomasse analysée, en Suisse, 0,3 mg de colistine a été vendu par kg d'animal de rente produit (population correction unit, PCU). Ces quantités sont inférieures à la moyenne européenne et répondent ainsi 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.

2 Sintesi

Resistenze nei batteri presenti in isolati clinici per la medicina umana

Dal 2010, nei batteri gram-positivi e gram-negativi sono state osservate diverse tendenze. Da una parte, è stato registrato un costante calo dei tassi di *Staphylococcus aureus* resistente alla meticillina (MRSA) negli isolati invasivi, in particolare nella Svizzera occidentale. Tale tendenza è stata peraltro osservata anche in quasi un terzo della totalità dei Paesi europei. D'altra parte, i tassi di MRSA in campioni estratti da ferite e ascessi di pazienti ambulatoriali sono in aumento e attualmente superano addirittura quelli osservati nelle batteriemie. La resistenza alla penicillina nello *Streptococcus pneumoniae*, che era diminuita negli anni precedenti, negli ultimi dieci anni è invece rimasta stabile. In compenso, la non suscettibilità alla maggior parte degli altri antibiotici è diminuita ulteriormente. In controtendenza rispetto ai rapporti precedenti, negli ultimi quattro anni è stato rilevato un significativo aumento dei tassi di *Enterococcus faecium* resistente alla vancomicina. Tale aumento è imputabile principalmente a un focolaio regionale/nazionale legato alla diffusione di un clone ST769. Pertanto, è essenziale continuare a monitorare da vicino la situazione in stretta collaborazione con swissnoso.

D'altra parte, negli ultimi dieci anni è stato in generale osservato un costante aumento della resistenza ai chinoloni e alle cefalosporine di terza e quarta generazione nei batteri *Escherichia coli* e *Klebsiella pneumoniae*. Negli ultimi quattro anni invece il tasso di *E. coli* resistenti ai chinoloni e il tasso di *K. pneumoniae* resistenti alle cefalosporine di terza e quarta generazione sono rimasti costanti. Fortunatamente, nell'*E. coli* e nella *K. pneumoniae*, la resistenza ai carbapenemi è ancora rara, sebbene si stia assistendo a un costante aumento dei numeri in Svizzera, che rispecchia la situazione nei Paesi confinanti. Vista l'importanza del fenomeno, il 1° gennaio 2016 in Svizzera è stato introdotto l'obbligo di notifica di questa resistenza e dal 1° gennaio 2019 tutti gli isolati sono raccolti dal laboratorio di riferimento nazionale per il riconoscimento precoce di nuove forme di resistenza agli antibiotici (NARA). Inoltre, nel presente rapporto è stato aggiunto un capitolo specifico sugli enterobatteri resistenti ai carbapenemi.

Rispetto al periodo tra il 2010 e il 2015 in cui si è registrato un aumento della resistenza a tutti gli antibiotici, nei *Pseudomonas aeruginosa* i tassi di non suscettibilità si sono stabilizzati o sono addirittura in calo. Negli *Acinetobacter* spp. i tassi di resistenza sono rimasti stabili, ivi compresa la resistenza ai carbapenemi.

Consumo di antibiotici nella medicina umana

Tra il 2010 e 2019, negli ospedali per cure acute svizzeri il consumo di agenti antibatterici per uso sistemico (gruppo ATC J01) è aumentato del 13 per cento, corrispondente a 51,8 dosi definite giornaliere (DDD) per 100 giorni di degenza. In totale, nel 2019 il consumo di agenti antibatterici (gruppo ATC J01) per uso sistemico è stato di 1,6 DDD per 1000 abitanti. Il tasso di consumo negli ospedali svizzeri è leggermente al di sotto della mediana europea (1,8; intervallo: 0,8–2,5). La classe di antibiotici più usata è stata quella delle penicilline (gruppo ATC J01C), seguita dalla classe degli altri antibiotici beta-lattamici, comprese le cefalosporine (gruppo ATC J01D) e dai chinoloni (gruppo ATC J01M). Tra il 2010 e il 2019, la combinazione di penicilline e inibitori della beta-lattamasi è aumentata del 16 per cento. L'impiego dei fluorochinoloni è diminuito del 39 per cento, mentre il consumo delle cefalosporine di terza generazione è aumentato del 46 per cento. Dopo un aumento costante fino al 2013, per i carbapenemi si è assistito a un calo del consumo (–26%). Secondo la classificazione AWaRe dell'Organizzazione mondiale della sanità (OMS), gli antibiotici appartenenti ai gruppi «Watch» e «Reserve» hanno rappresentato il 49 per cento del consumo totale nel 2019.

Nelle cure ambulatoriali, il consumo totale di agenti antibatterici per uso sistemico (gruppo ATC J01) nel 2019 è stato pari a 9,1 DDD per 1000 abitanti, ed è rimasto quindi in linea con i valori del 2018 (9,1 DID) e del 2017 (9,0 DID). In questo caso, si tratta di un dato relativamente basso rispetto alla mediana europea (18,4; intervallo: 8,9–32,4). La classe di antibiotici più 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). Tra il 2016 e il 2019, i fluorochinoloni e le cefalosporine di terza generazione hanno registrato rispettivamente un calo del 24 per cento e del 29 per cento. Nello stesso periodo, l'impiego di sulfamidici e nitrofurantoina è invece aumentato rispettivamente del 16 per cento e del 28 per cento. Del totale consumato nel 2019, gli antibiotici appartenenti ai gruppi «Watch» e «Reserve» rappresentano il 36 per cento.

Resistenze nei batteri zoonotici

Per quanto concerne il pollame, il dato più significativo degli ultimi anni è il netto aumento registrato nella resistenza alla ciprofloxacina nel *Campylobacter jejuni* (*C. jejuni*) e nel *Campylobacter coli* (*C. coli*). Nel 2016, il tasso di resistenza alla ciprofloxacina è cresciuto del 51,4 per cento per il *C. jejuni* e

del 66,7 per cento per il *C. coli*. Nel 2018 è stata rilevata invece per la prima volta una diminuzione significativa, rispettivamente del 45,7 per cento per il *C. jejuni* e del 40,5 per cento per il *C. coli*. Per contro, la resistenza alle tetracicline è aumentata per il *C. coli* (+54,1%), ma diminuita per il *C. jejuni* (–30,4%). La resistenza all'eritromicina invece continua a essere rara. L'andamento della resistenza del *C. jejuni* e del *C. coli* isolati nella carne di pollo segue la tendenza osservata nei polli da ingrasso.

Secondo l'OMS, in medicina umana i fluorochinoloni e i macrolidi sono gli antimicrobici di importanza critica della massima priorità, in quanto tali gruppi di sostanze rappresentano la terapia d'elezione per trattare forme gravi di campilobatteriosi o salmonellosi negli esseri umani. Pertanto l'inversione di tendenza osservata nelle resistenze del *C. jejuni* e del *C. coli* è un dato confortante.

Negli ultimi anni, i tassi di resistenza alla ciprofloxacina del *Campylobacter coli* (*C. coli*) nei suini da ingrasso sono aumentati significativamente, arrivando al 55,9 per cento nel 2019. Anche per quanto riguarda l'eritromicina è stata registrata una maggiore resistenza, la quale tuttavia si attesta su un livello basso (3,9%). Similmente, si è rilevato un tasso di resistenza leggermente più elevato per la streptomicina, con un incremento dall'81,4 per cento nel 2017 all'84,7 per cento nel 2019.

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*.

Resistenze nei batteri indicatori negli animali

La resistenza antimicrobica è generalmente diffusa nell'*E. coli* isolato dagli animali da reddito in Svizzera.

Nell'*E. coli* commensale isolato da polli da carne in Svizzera non sono individuabili tendenze comuni per i tassi di resistenza a diverse classi antimicrobiche. Da una parte, nell'*E. coli* commensale isolato da polli da carne si registra una tendenza all'aumento dei tassi di resistenza all'ampicillina e alla ciprofloxacina, dall'altra tuttavia si osserva un indebolimento delle resistenze alle tetracicline e ai sulfamidici. Al contrario, nei suini da ingrasso e nei vitelli da macello si possono osservare generalmente tendenze più simili per quanto riguarda i livelli di resistenza dell'*E. coli*. Non esiste una classe antimicrobica per la quale sia stato osservato un aumento significativo. Nel corso degli anni è stata registrata una netta tendenza decrescente per i sulfamidici, le tetracicline e l'ampicillina e i livelli di resistenza ai fluorochinoloni sono costantemente bassi per entrambe le specie di animali da reddito.

La prevalenza di *E. coli* produttori di ESBL/pAmpC è diminuita significativamente nei polli da carne (dal 52,4% nel 2016 al 30,6% nel 2018) e leggermente nei suini da ingrasso (2019: 13,1%); la prevalenza dei succitati batteri rimane invece stabile nei vitelli da macello rispetto al 2017 (32,9% nel 2019). Complessivamente, dal 2014 si sta registrando un calo di *E. coli* produttori di ESBL/pAmpC nei polli da carne e nei suini da ingrasso, mentre la prevalenza nei vitelli da macello rimane stabile su un livello elevato (> 30%) dal 2015.

Nelle specie di animali da reddito non vi è traccia di *E. coli* produttori di carbapenemasi.

Da quando nel 2009 nel monitoraggio è stato incluso lo *S. aureus* resistente alla meticillina (MRSA), nei macelli svizzeri l'incidenza di questo batterio nei suini da ingrasso è aumentata costantemente. Con un tasso iniziale del 2 per cento nel 2009, la prevalenza dell'MRSA nel 2019 ha raggiunto il 52,8 per cento.

Al contrario, la prevalenza di MRSA nei vitelli è scesa al 3,8 per cento, toccando il minimo storico dal 2013. Questi genotipi fanno parte del complesso clonale CC 398, che tipicamente è associato agli animali da reddito (livestock associated meticillin resistant *Staphylococcus aureus*, LA-MRSA).

Resistenze nei batteri indicatori presenti nella carne

Rispetto al 2014 e al 2016, nel 2018 la prevalenza di *E. coli* produttori di ESBL/pAmpC nella carne di pollo svizzera è decisamente diminuita (2014: 65,5%; 2016: 41,9%, 2018: 21,1%). Anche nella carne di pollo importata dall'estero i tassi di *E. coli* produttori di ESBL/pAmpC rilevati nel 2018 sono risultati in calo, ma rimangono comunque più alti che nella carne svizzera (2014: 88,9%; 2016: 81,5%, 2018: 63,1%).

Per contro, nella carne suina e bovina è stata osservata una prevalenza di *E. coli* produttori di ESBL/pAmpC molto contenuta (< 1%): questa differenza potrebbe essere correlata a una prevalenza bassa dei batteri in questione nei suini e nei vitelli svizzeri nonché al processo di macellazione diverso di questi animali. Nei campioni di carne fresca invece non vi è traccia di *E. coli* produttori di carbapenemasi.

I tassi di rilevamento di MRSA nella carne fresca svizzera sono stati pari a zero per la carne di pollo nel 2018 e per la carne suina e bovina nel 2019, in linea con i dati bassi degli anni precedenti. Dal 2014 al 2018, la prevalenza di MRSA nella carne di pollo è diminuita costantemente: partendo dal 2014, anno in cui era risultato positivo all'MRSA il 16,1 per cento della carne di pollo prodotta all'estero, si è passati al 9,3 per cento nel 2016, per scendere ulteriormente a un esiguo 3,9 per cento nel 2018. Per quanto riguarda la carne di pollo svizzera, già nel 2014 la prevalenza di MRSA era molto bassa (1%) e nel 2016 e nel 2018 nessuno dei campioni testati è risultato positivo all'MRSA. Anche nella carne suina svizzera la prevalenza di MRSA osservata nel 2017 era appena dello 0,7 per cento, identica a quella del 2015, benché la prevalenza di MRSA nei tamponi nasali praticati sui suini da ingrasso fosse aumentata dal 25,7 per cento al 52,8 per cento nello stesso periodo. I dati tuttavia confermano che la

carne fresca non è considerata una fonte rilevante di trasmissione di questo batterio agli umani.

Resistenze nei batteri da isolati clinici per la medicina veterinaria

Il monitoraggio della resistenza antimicrobica per i patogeni rilevanti negli animali da reddito e da compagnia è essenziale per i veterinari, in quanto consente di scegliere la terapia antibiotica più appropriata, dato che spesso non è possibile svolgere un antibiogramma prima di iniziare il trattamento. Inoltre, tali dati colmano un'altra importante lacuna riguardante il monitoraggio della resistenza antimicrobica secondo l'approccio One Health.

Nel 2019, l'Ufficio federale della sicurezza alimentare e di veterinaria (USAV) ha istituito e implementato presso il laboratorio nazionale di riferimento per la resistenza antimicrobica (ZOBA) un monitoraggio annuale delle resistenze antimicrobiche nei patogeni animali.

Per diversi motivi, i dati presentati devono essere interpretati con cautela. Innanzitutto, il numero complessivamente esiguo di isolati potrebbe far erroneamente sovrastimare i tassi di resistenza calcolati. In futuro, tuttavia, le tendenze risulteranno più evidenti grazie a una maggiore quantità di dati. Inoltre, è bene sottolineare che gli isolati analizzati provengono esclusivamente da animali che prima del prelievo del campione non erano stati sottoposti a un pretrattamento con antimicrobici. Questa informazione è rilevante se si confrontano questi dati con quelli di altre popolazioni oggetto di studi.

Fra i patogeni della mastite, lo *Streptococcus uberis* è risultato più critico in termini di trattamento antimicrobico dello *Staphylococcus aureus*. Confrontando gli *E. coli* isolati da diverse specie animali e indicazioni sono emerse differenze notevoli. Solo gli isolati prelevati da bovini affetti da mastite e da pollame non presentavano resistenza alla terza e quarta generazione di cefalosporine, mentre gli isolati di *E. coli* prelevati da animali da compagnia affetti da infezioni del tratto urinario hanno espresso una resistenza a questi antimicrobici di importanza critica. Infine, nel 2019 non sono stati rilevati *E. coli* resistenti ai carbapenemi.

Vendite di antimicrobici nella medicina veterinaria

Il volume di vendite degli antimicrobici è diminuito costantemente, dell'1,3 per cento nel 2018 e di un più marcato 7,1 per cento nel 2019. Complessivamente ne sono stati venduti per usi veterinari 32 397 kg nel 2018 e 30 108 kg nel 2019. Dal 2010 si può segnalare un calo delle vendite del 52 per cento (33 tonnellate), principalmente imputabile a una diminuzione delle vendite di premiscele medicate. Le classifiche di vendita delle diverse classi di antimicrobici sono cambiate nel 2018: in precedenza al primo posto si trovavano i sulfamidici, mentre dal 2018 in poi la classe più venduta è quella delle penicilline, seguite da sulfamidici e tetracicline. Queste tre classi spesso sono vendute sotto forma di premiscele medicate. La quantità di antibiotici omologati per gli animali da compagnia ammonta solo al 2,6 per cento del volume totale e nel 2018 le vendite per questa categoria sono diminuite del 5,3 per cento, mentre sono leggermente aumentate dell'1,6 per cento nel 2019. Le vendite delle classi di antimicrobici di importanza critica della massima priorità ad uso umano sono diminuite sia nel 2018 che nel 2019. Nel 2018 le vendite di macrolidi sono scese del 7 per cento e nel 2019 di un altro 20 per cento. Anche le vendite dei fluorochinoloni hanno registrato un calo dell'11 per cento nel 2018 e di un ulteriore 9,9 per cento nel 2019. Quelle di cefalosporine (di terza e quarta generazione) sono diminuite del 4,7 per cento circa nel 2018 e dell'1,3 per cento nel 2019. Il volume di vendita della colistina è diminuito all'incirca dell'86 per cento dal 2010. Per la Svizzera, questo dato espresso in correlazione alla biomassa esposta corrisponde a un livello di colistina pari a 0,3 mg/PCU: si tratta di un valore al di sotto della media europea e in linea con la riduzione della colistina a un livello pari o inferiore a 1 mg/PCU richiesta ai Paesi europei per mantenere l'efficacia di questo antibiotico nel trattamento di infezioni gravi nell'essere umano.

3

Introduction

3 Introduction

3.1 Antibiotic resistance

Antibiotic resistance is responsible for increased morbidity and mortality and generates significant health care costs. Alternative treatments may have more serious side effects, and may 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

The Swiss Centre for Antibiotic Resistance ANRESIS was established in the framework of the National Research Program 49 on 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 National Center for Infection Control (SWISSNOSO), the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA), PharmaSuisse, the Swiss Society of Pharmacists, and others.

The first microbiology laboratories participated in ANRESIS in 2004. The surveillance system expanded continuously during the following years, with 30 microbiology laboratories participating in 2020 (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 database since 2014. The open data structure allows further developments.

The advisory board of ANRESIS 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 in- and outpatient setting, we used the antibiotic consumption data from IQVIA™, a private drug market investigation company providing an exhaustive dataset of antibiotic consumption.

Moreover, the consumption of antibiotics in the inpatient setting has been monitored since 2006 by means of a sentinel network of hospital pharmacies. Yearly, data of approximately 60 hospitals or hospital sites are collected on a voluntary basis. These acute care hospitals are distributed all over the geographic territory and represent 40% of the total number of acute somatic care hospitals (excluding psychiatric centers, rehabilitation centers, and other specialized clinics) and 75% of all bed-days in this category in Switzerland (see Chapter 14, Materials and methods).

For the outpatient setting, we also used the data from PharmaSuisse, based on prescriptions at the individual level and obtained from privately run pharmacies.

DDD values for some of the most used antibacterials (e. g. amoxicillin, amoxicillin-clavulanic acid, meropenem, ciprofloxacin, colistin) were changed in 2019 by the WHO Collaborating Centre for Drug Statistics Methodology (see Annex I). All results were updated retrospectively with the new DDDs. Thus, the results of this report cannot be compared with those of the former reports.

3.2.2 Resistance monitoring in human medicine

ANRESIS collects and analyzes anonymous antibiotic resistance data provided by the participating clinical microbiology laboratories (www.anresis.ch). These laboratories are homogeneously distributed across the geographic territory. They include university laboratories, which mainly represent isolates 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 80% of all annual hospitalization days and approximately 30% of all practitioners in Switzerland. The provided epidemiological data enable a stratification of the 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 (https://www.bag.admin.ch/bag/de/home/das-bag/publikationen/periodika/bag-bulletin.html): 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, along with veterinary data, are published in this national report every two years.

3.2.3 Resistance monitoring in veterinary clinical samples

In 2019, an annual monitoring of antimicrobial resistance in veterinary pathogens was initiated by the Federal Food Safety and Veterinary Office (FSVO) and implemented at the Swiss national reference laboratory for antimicrobial resistance (Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance, ZOBA). Targeted bacteria and animal species combination comprises relevant pathogens and diseases. Isolates come from veterinary diagnostic laboratories in Switzerland. For the comparability of results over time, it is mandatory that only isolates from animals which did not receive antimicrobial treatment prior to sampling are included. Susceptibility testing is performed at the ZOBA using the broth microdilution method. In contrast to the monitoring in healthy livestock, the tested antimicrobials are those approved for veterinary use. Moreover, isolates are classified as susceptible or resistant according to the clinical breakpoints published by the Clinical and Laboratory Standards Institute or, if not available, according to the clinical breakpoints defined in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. An excerpt of data derived from this monitoring program is presented in Chapter 11 ("Resistance in bacteria from animal clinical isolates"). Thanks to this monitoring, it was possible to bridge a relevant gap in surveillance of antimicrobial resistance. Data are transmitted to the database of the Swiss Centre for Antimicrobial Resistance (ANRESIS), the nationwide system for resistance data for both human and veterinary medicine (www.anresis.ch). In this way, all data are accessible via INFECT, which is an interface for empirical antimicrobial chemotherapy developed in 2018 for human medicine. INFECT VET was implemented in March 2020. This online tool provides fast and intuitive access to the latest antimicrobial resistance data on Swiss veterinary pathogens and assists veterinarians by offering reliable empirical treatment options (www.vet.infect.info).

3.3 About ARCH-Vet

The use of antimicrobials in livestock is a subject of public concern, as resistant bacteria can be selected and 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). Since 2014, this antimicrobial resistance monitoring follows the European-wide harmonized program. 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). Data on sales of veterinary antimicrobials and results of the resistance monitoring are published yearly in the ARCH-Vet report. Since 2013, data published in the ARCH-Vet reports are included in the biennial Swiss Antibiotic Resistance Report. For the fourth 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 are 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). These data are transmitted to the Food Safety and Veterinary Office (FSVO), where they are processed and analyzed. The data cover 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 in slaughterhouses 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 adopted measures.

Examined species

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. Cecum and nasal swab samples are taken by official veterinarians at the slaughterhouse, and meat samples of the respective animal species by official inspectors at the retail level. Resistance tests are performed for the zoonotic pathogens *Campylobacter jejuni* and *C. coli*, and for the indicator *Escherichia coli*. Since 2009, nasal swab samples from fattening pigs and calves have also been tested for methicillin-resistant *Staphylococcus aureus* (MRSA) using a selective enrich-

ment procedure published by Overesch et al. (2011). From 2011 to 2014, tests were 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* follow 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 at least 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 are the target for *C. jejuni* and *E. coli* in broilers, for *C. coli* and *E. coli* in 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 inhabitants. The samples are taken at different retailers, proportionate to their market share throughout the country. Moreover, the sampling plan differentiates between domestically and foreign produced meat samples, according to the proportion of domestic and imported meat.

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 and the Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA). We are pleased to present the Swiss data on the consumption of antimicrobials and on antimicrobial resistance, both in humans and in animals.

Though these data are presented in a single report, it is important to be aware of the fact that differences between the monitoring systems in terms of 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 unit of measurement comparable to the DDD in human medicine is not yet available.

Antibiotic resistance data
The main issues when comparing antimicrobial resistance data originating from humans and 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. For the veterinary sector, isolates from clinical submissions and bacteria originate from samples taken from healthy food-producing animals and meat thereof in the framework of an active monitoring are analyzed.

Laboratory methods
Susceptibility testing in human isolates is performed 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 (Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance, ZOBA, Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern) using the broth microdilution method.

Criteria of resistance
Human and veterinary clinical isolates are classified as "susceptible", "intermediate" or "resistant" by applying clinical breakpoints, quantitative resistance data are not available for most of the human 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, pharmacokinetics 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 livestock at slaughter and meat thereof uses epidemiological cutoff values (ECOFFs) to separate susceptible wild-type bacterial populations from isolates that have developed reduced susceptibility to a given antimicrobial agent by acquisition of antimicrobial resistance genes. So-called non-wild-type organisms are assumed to exhibit acquired or mutational resistance mechanisms and are referred to as "microbiologically resistant." ECOFF values allow no statement on the potential therapeutic success of an antimicrobial, but as they are able to indicate acquisition of 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, but the ECOFF could be lower than the clinical breakpoint.

That means that although the bacteria may be "microbiologically resistant," the antimicrobial may still be effective at the therapeutic level.

In order to improve comparability, as stipulated in the national Strategy against Antibiotic Resistance (StAR), cooperation and coordination between the different monitoring networks must be further strengthened and the systems refined.

3.5 Authors and contributions

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Color code

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

- Cephalosporins 1st and 2nd generation
- Cephalosporins 3rd and 4th generation
- Other cephalosporins and penems
- Monobactams
- Beta-lactamase sensitive penicillins
- Penicillins with extended spectrum
- Beta-lactamase resistant penicillins
- Comb. of penicillins, incl. beta-lactamase inhibitor
- Carbapenems
- Macrolides, lincosamides and streptogramins
- Aminoglycosides
- Sulfonamides and trimethoprim
- Fluoroquinolones
- Antimycobacterials
- Tetracyclines
- Chloramphenicol
- Others

4

Abbreviations

4 Abbreviations

ACB	*Acinetobacter calcoaceticus-Acinetobacter baumannii complex*
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 Enterobacteriales
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 cut off 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 Susceptibility 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 unit
ISO	International Organization for Standardization
LA-MRSA	Livestock-associated MRSA
LMA	Potassium-aluminum sulfate
LOD	Limit of detection
LOQ	Limit of quantification
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
NAWA	National Surface Water Quality Monitoring Network
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	Swiss Strategy on Antibiotic Resistance
SVGW	Swiss association of the gas and water industry
t	*spa* type
UTI	Urinary tract infection
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 Introduction

The heyday of antibacterial discovery and development was reached during the 1980s and 90s when the rate of approvals was the highest. The number of newly approved antibacterials then declined due to lack of investment and innovation in their development. The WHO warns of growing difficulties in the treatment of patients suffering from infections with multiresistant pathogens [1]. Figure 5. a shows Swissmedic approval of products with antibacterials over time [2].

Besides the decline of new antibacterials, the supply shortages appear to be another challenge for clinicians. As of June 2020, the Federal Office for National Economic Supply (FONES) reported the shortage of 11 products with antibacterials, corresponding to 42% of all shortages of products considered as essential in accordance with the Ordinance on the Essential Human Medicines Reporting Office [3]. Two of these products have even been withdrawn from the Swiss market.

It must be noted that all calculations were based on the 2019 WHO DDD values (see Chapter 14, Materials and methods and Annex I) and may therefore differ from previous reports.

5.2 Hospital care

5.2.1 Total antibiotic consumption

Taking into account the hospitals that participated in the monitoring system both in 2010 and 2019 (n = 42), the number of DDDs of systemic antibiotics (ATC group J01) increased by 2% during this period. However, this value must be adjusted to the indicators of hospital activity, which allows comparability among hospitals. The number of admissions increased (+11%), while the number of bed-days slightly decreased (–11%). This means that more patients were admitted to hospitals, but that their length of stay was shorter in 2019 than in 2010. Due to the rising number of admissions and the decreasing length of stay over the last 10 years, the total consumption of systemic antibiotics in DDDs per 100 bed-days in all hospitals participating in the monitoring increased by +13% from 46.0 (weighted mean, range: 11.8–86.4) in 2010 to 51.8 (range: 31.4–68.9) in 2019, while the total consumption in DDDs per 100 admissions decreased by 11% (Figure 5. b). In 2019, total antibiotic consumption was lower in small-size hospitals (47.6 DDDs per 100 bed-days) than in medium-size (50.7) and large-size (55.5) hospitals.

Figure 5. a: Number of products with antibacterials (originals, without generics) approved by Swissmedic over the years.

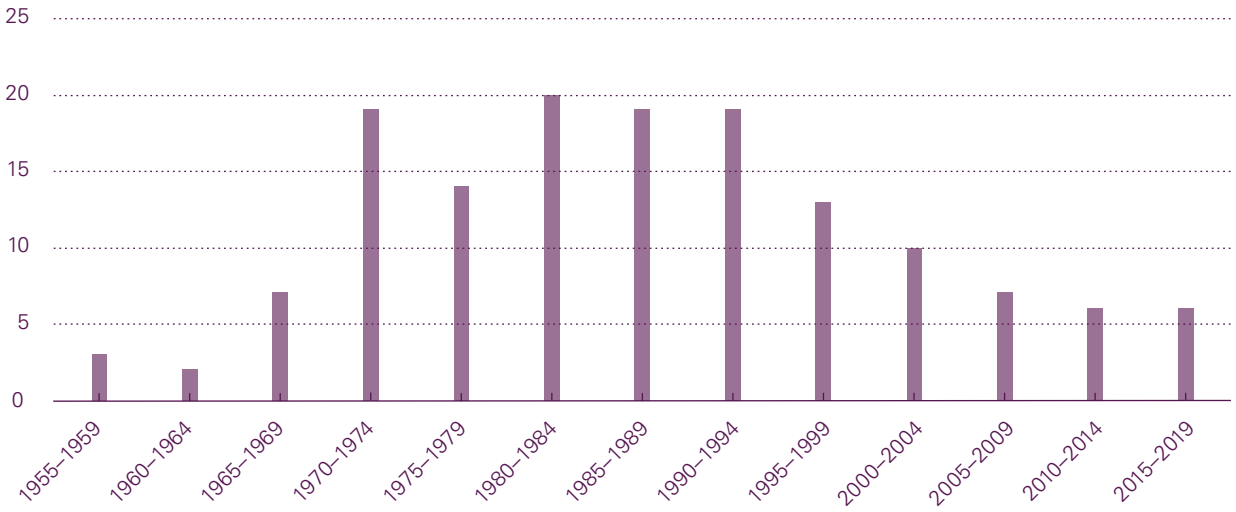


Figure 5. b: Total antibiotic consumption (ATC group J01) expressed in DDDs per 100 bed-days (bars) and in DDDs per 100 admissions (dark line) in the hospitals and intensive care units contributing to ANRESIS over the period 2010–2019. The number of hospital networks (or sites) contributing to ANRESIS is indicated in the table.

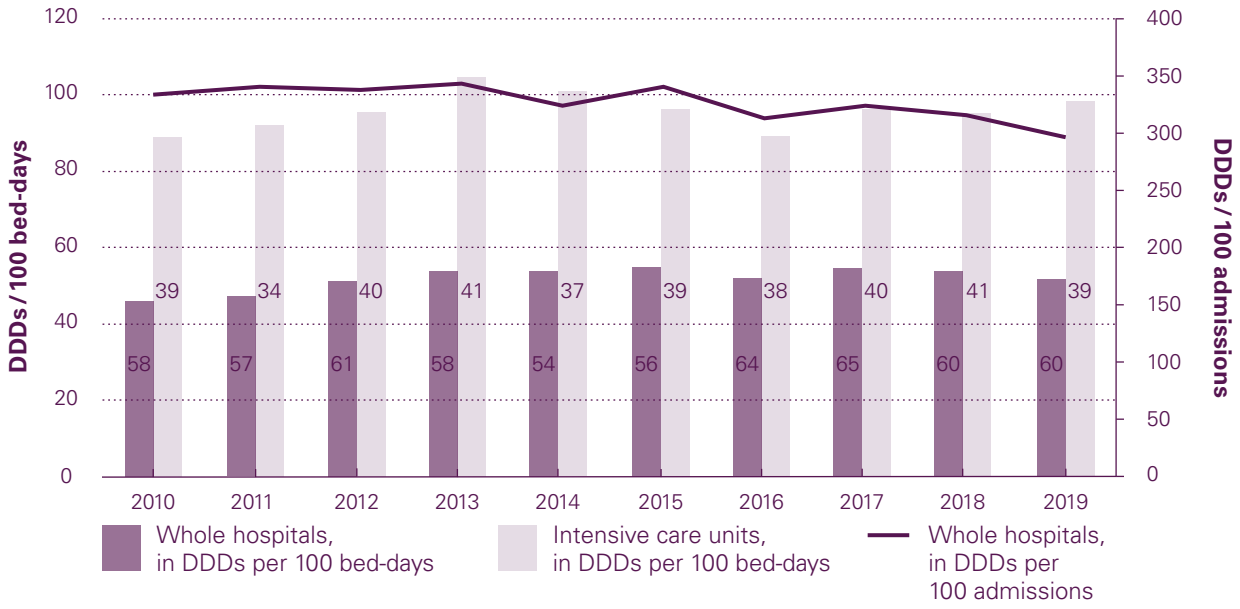


Table 5. a: Antibiotic consumption according to the AWaRe categorization of the WHO in the inpatient setting, Switzerland (2017–2019).

AWaRe groups**	Consumption*			Relative consumption		
	2017	2018	2019	2017	2018	2019
Access group	27.9	27.8	26.5	51%	52%	51%
Watch group	25.7	25.3	24.7	47%	47%	48%
Reserve group	0.8	0.7	0.7	2%	1%	1%

* Consumption expressed in DDDs per 100 bed-days

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

In 2019, total antibiotic consumption was relatively similar in the three linguistic regions: 48.9 DDDs per 100 bed-days in the French-speaking region (17 hospitals, including 2 university hospitals), 45.9 in the Italian-speaking region (5 hospitals) and 53.6 in the German-speaking region (38 hospitals, including 3 university hospitals). The consumption increased in the French-speaking part by 7%, in the German-speaking part by 14% and in the Italian-speaking regions by 14%.

The total consumption of antibacterial agents (ATC group J01) for systemic use was 1.6 DDDs per 1,000 inhabitants per day in 2019 (1.5 DID in 2018; using the IQVIATM dataset). In comparison, the median consumption was 1.8 per 1,000 inhabitants per day (range 0.8–2.5) in 2018 in the countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [4].

We have observed that according to the AWaRe classification (see Chapter 14, Materials and methods), the Access group represented 51% of antibiotics (26.5 DDDs per 100 bed-days) in 2019, the Watch group 48% (24.7) and the Reserve group 1% (0.7) (Table 5. a). The proportion of antibiotics within the Access and Watch category of total consumption has remained largely unchanged over the past 10 years.

However, the proportion of antibiotics from the Reserve group has increased over the last 10 years from 0.3 DDDs per 100 bed-days in 2010 to 0.7 (+104%) in 2019. This can be explained mainly by an increase in the use of daptomycin and by the use of antibiotics that are new on the market (e. g. ceftarolin, ceftazidime-avibactam), although their consumption is still low.

5.2.2 Antibiotic consumption in hospitals contributing to ANRESIS by antibiotic class and by specific antibiotic

In 2019, consumption of penicillins (ATC group J01C) ranked first among antibiotic classes, representing 43% of the total consumption. It was followed by the consumption of other beta-lactam antibacterials, including cephalosporins (ATC group J01D), and by quinolones (ATC group J01M) (24% and 8%, respectively) (Figure 5. c).

Table 5. b shows the consumption of antibiotic classes expressed in DDDs per 100 bed-days in sentinel hospitals over the period 2010–2019. The use of 6 of the 22 antibiotic classes decreased between 2010 and 2019 (aminoglycosides, carbapenems, fluoroquinolones, fusidic acid, metronidazole (oral), and rifamycins). The most important progression in consumption between 2010 and 2019 was observed for the nitrofuran derivates (+200%), other antibacterials (including daptomycin and fosfomycin, +196%), the fourth-generation cephalosporins (+90%), and the antipseudomonal penicillins associated with a beta-lactamase inhibitor (+54%).

Consumption of penicillins increased by 17% between 2010 and 2019 (Table 5. b). Within this class, the association of amoxicillin and clavulanic acid was the most frequently prescribed antibiotic and ranged from 13.2 DDDs per 100 bed-days in 2010 to 14.6 in 2019 (+11%) (Figure 5. d). The association of piperacillin and tazobactam increased by 54%, from 1.9 in 2010 to 2.9 DDDs per 100 bed-days in 2019.

The use of second-, third- and fourth-generation cephalosporins increased markedly between 2010 and 2019. (+33%, 46% and 90%, resp.). In 2019, cefuroxime (second generation) and ceftriaxone (third generation) were the most widely used cephalosporins (Figure 5. d).

Cephalosporins recently approved by Swissmedic (ceftobiprole, ceftolozane-tazobactam, ceftaroline, ceftazidime-avibactam) have rarely been used in hospitals contributing to ANRESIS.

Following a constant increase until 2013, the consumption of carbapenems has been declining since then: imipenem-cilastatin (–42%), meropenem (–12%) and ertapenem (–26%) (Figure 5. d).

The consumption of fluoroquinolones has steadily decreased over the last 10 years (–39%). Ciprofloxacin was the most widely used fluoroquinolone in 2019 (2.8 DDDs per 100 bed-days, 71% of fluoroquinolone consumption) (Figure 5. d). Ciprofloxacin and norfloxacin consumption decreased most during this period (–39% and –82%, respectively). Levofloxacin consumption was relatively stable between 2010 and 2019, reaching 1.0 DDD per 100 bed-days in 2019.

Figure 5. c: Distribution of the total antibiotic consumption (ATC group J01) per antibiotic class in the inpatient setting in 2019 in Switzerland.

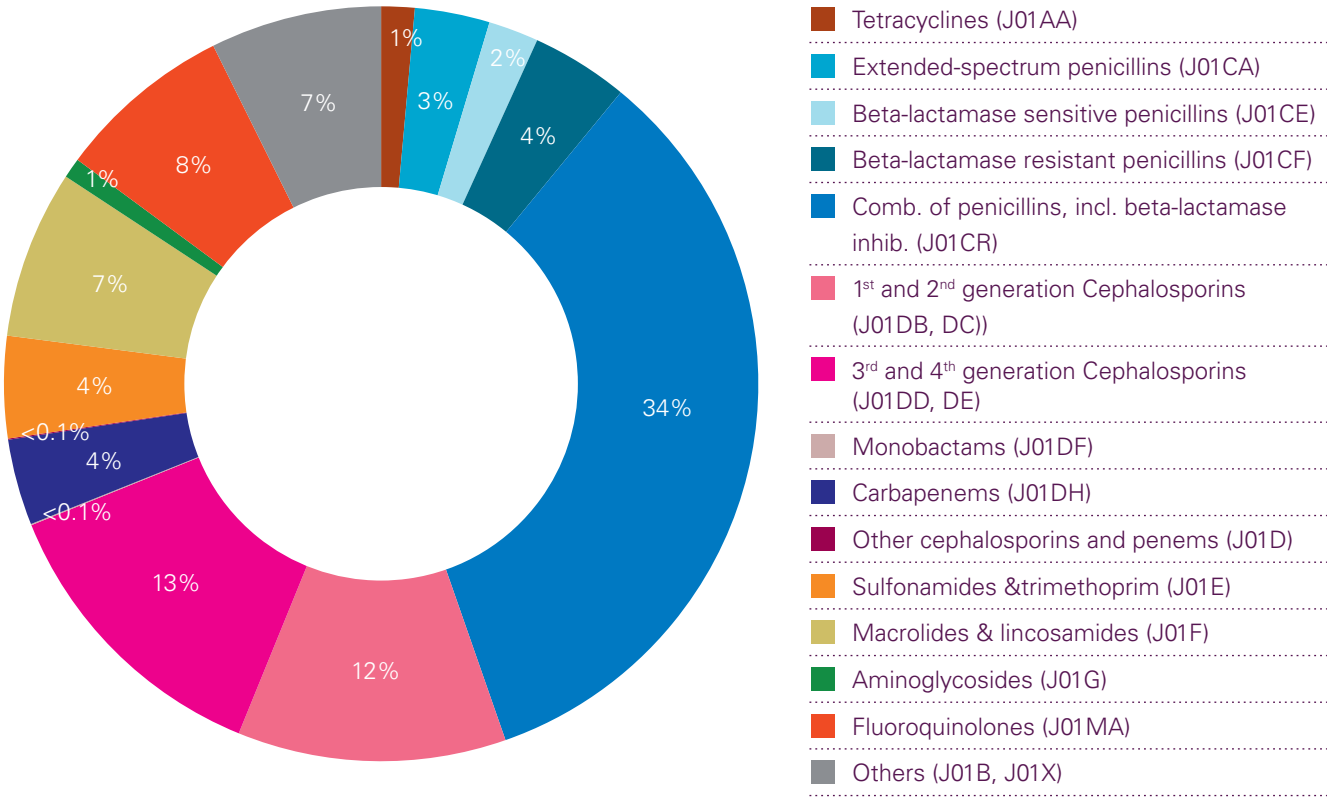


Table 5. b: Consumption of antibiotic classes expressed in DDDs per 100 bed-days in hospitals contributing to ANRESIS in Switzerland (2010–2019).

ATC group	Antibiotic class	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
J01A	Tetracyclines	0.6	0.5	0.6	0.6	0.6	0.6	0.8	0.7	0.8	0.7
J01CA	Penicillins with extended spectrum (amoxicillin)	1.2	1.2	1.3	1.6	1.5	1.6	1.4	1.5	1.8	1.7
J01CE	Beta-lactamase-sensitive penicillins	1.1	1.3	1.5	1.3	1.2	1.3	1.3	1.2	1.2	1.1
J01CF	Beta-lactamase-resistant penicillins	1.8	1.9	2.1	2.1	2.4	2.5	2.4	2.6	2.2	2.2
J01CR02	Penicillins and beta-lactamase inhibitor (amoxicillin and clavulanic acid)	13.2	13.3	14.8	15.1	14.6	13.9	14.8	15.2	15.2	14.6
J01CR03-05	Penicillins and beta-lact. inhibitor (anti-pseudomonal)	1.9	2.0	2.4	2.7	2.7	2.8	2.7	2.7	2.7	2.9
J01DB	Cephalosporins – first generation	1.0	1.0	1.0	1.0	1.2	1.2	0.8	0.9	1.1	1.1
J01DC	Cephalosporins – second generation	3.7	3.7	3.9	4.3	4.6	5.1	4.9	4.6	4.7	4.9
J01DD	Cephalosporins – third generation	3.8	4.2	4.4	4.9	5.0	5.7	5.5	5.6	5.7	5.6
J01DE	Cephalosporins – fourth generation	0.5	0.7	0.7	0.8	0.8	0.9	0.8	1.0	1.1	1.0
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	2.2	2.3	2.4	2.6	2.5	2.4	2.0	2.3	2.0	1.9
J01DI	Other cephalosporins and penems	0.0		0.0		0.0	0.0	0.0	0.0	0.0	0.0
J01E	Sulfonamides and trimethoprim	1.9	2.0	2.7	2.6	2.3	2.3	2.2	2.5	2.3	2.3
J01FA	Macrolides	2.7	2.6	2.8	3.0	3.0	3.1	2.8	2.8	2.9	2.7
J01FF	Lincosamides	0.8	0.8	0.9	1.0	1.0	1.1	0.9	1.1	1.1	1.1
J01G	Aminoglycoides	0.8	0.7	0.7	0.7	0.6	0.7	0.5	0.8	0.5	0.5
J01MA	Fluoroquinolones	6.4	6.0	5.9	6.0	5.9	5.8	4.9	4.8	4.5	3.9
J01XA	Glycopeptides	1.0	1.1	1.1	1.2	1.3	1.4	1.1	1.3	1.3	1.4
J01XB	Polymyxins	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1
J01XC	Fusidic acid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01XD	Nitroimidazole derivates	1.2	1.1	1.2	1.2	1.2	1.2	1.2	1.2	1.3	1.2
J01XE	Nitrofuran derivates (nitrofurantoin)	0.1	0.2	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.4
J01XX	Other antibacterials	0.3	0.4	0.5	0.6	0.7	0.7	0.7	0.9	0.9	0.7
J01	Antibacterial agents for systemic use	46.0	47.3	51.3	53.8	53.6	54.9	52.1	54.4	53.8	51.8
A07AA	Intestinal Antiinfectives*									0.0	0.0
J04AB	Rifamycins	1.0	0.9	0.8	0.8	0.9	0.7	0.7	0.8	0.8	0.7
P01AB	Nitroimidazole derivates (metronidazole oral)	0.9	0.9	0.9	0.8	0.8	0.8	0.8	0.8	0.9	0.7

* Collected since 2018

Macrolide consumption (ATC group J01FA) has remained relatively stable over the last 10 years, amounting to 2.7 DDDs per 100 bed-days in both 2010 and 2019. Clarithromycin was the most widely used macrolide in 2019 (2.0 DDDs per 100 bed-days, 75% of total macrolide consumption) (Figure 5. d). The consumption of azithromycin and erythromycin in 2019 amounted to 0.5 and 0.2 DDDs per 100 bed-days, respectively. Clindamycin, the only lincosamide currently in use in Swiss hospitals, increased by 37% in the period 2010–2019 (1.1 DDDs per 100 bed-days in 2019).

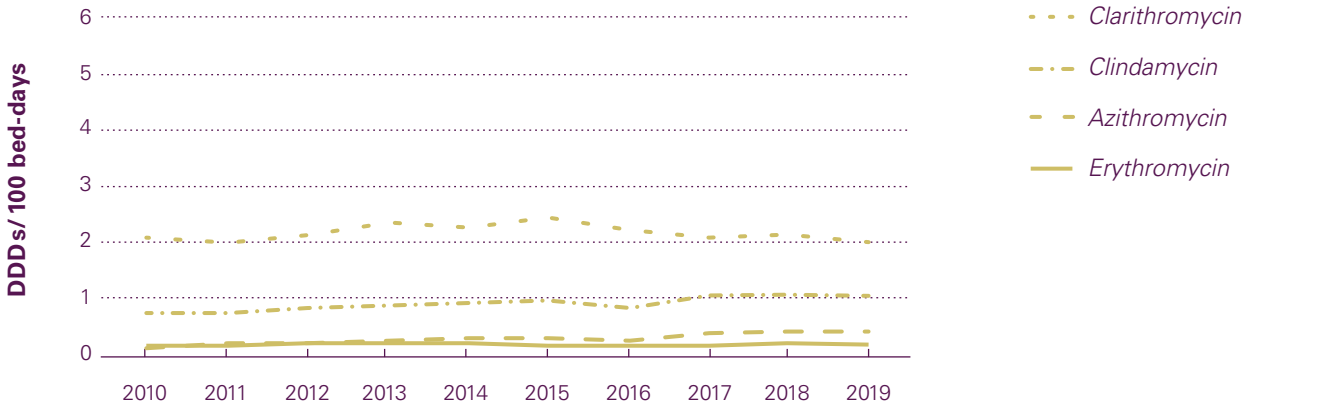
Among antibiotics active against resistant Gram-positive bacteria. we observed an increase by 51% in consumption of vancomycin between 2010 and 2019 (Figure 5. d). Consumption of daptomycin has increased by 121% since 2010 (0.4 DDDs per 100 bed-days in 2019). Linezolid and teicoplanin have rarely been used in hospitals contributing to ANRESIS.

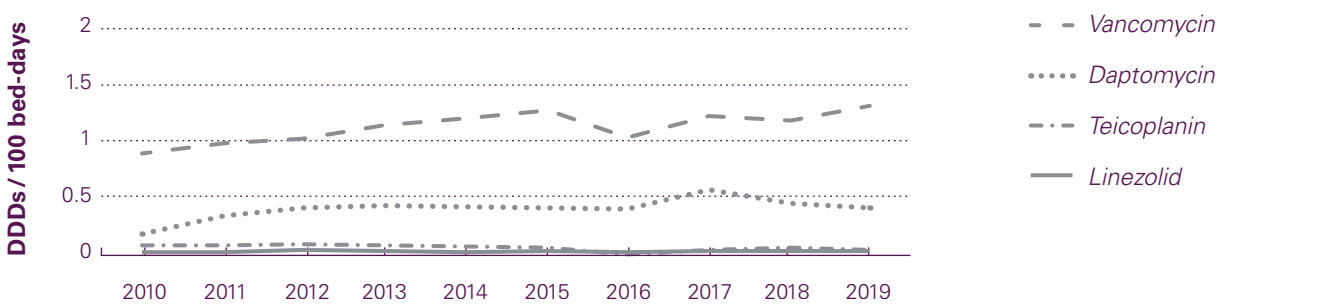
The proportion of the broadest-spectrum antibiotics has levelled off in recent years at about 11% of total antibiotic consumption. In the present report, this category includes aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin, piperacillin-tazobactam, ticarcillin and ticarcillin-tazobactam. In 2019, piperacillin-tazobactam (2.9 DDDs per 100 bed-days) and meropenem (1.0) were the most frequently used of these antibiotics.

5.2.3 Total antibiotic consumption in intensive care units of hospitals contributing to ANRESIS

Global use of systemic antibiotics (ATC group J01) in the ICU has remained relatively stable in recent years. (Figure 5. b). Since 2010, consumption in the ICU has risen by 11%, from 88.9 DDDs per 100 bed-days to 98.5 in 2019. In 2019, total

Figure 5. d: Consumption of antibiotics expressed in DDDs per 100 bed-days in hospitals contributing to ANRESIS in Switzerland (2010–2019).





antibiotic consumption was lower in the intensive care units of small-size hospitals (79.0 DDDs per 100 bed-days) than in intensive care units of medium-size (89.7) and large-size (112.2) hospitals.

5.3 Outpatient care

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

In 2019, the total consumption of antibacterial agents for systemic use (ATC group J01) was 9.1 DDDs per 1,000 inhabitants per day. It remained stable compared to 2018 (9.1 DIDs) and 2017 (9.0 DIDs) (Table 5. c). In comparison, the median consumption in 2018 was 18.4 DDDs per 1,000 inhabitants per day (range between 8.9 in the Netherlands and 32.4 in Greece) in the countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [4].

We have observed that according to the AWaRe classification (see Chapter 14, Materials and methods) the Access group represented 64% of antibiotics (5.8 DIDs), the Watch group 36% (3.3 DIDs), the Reserve group 0.3% (0.02 DIDs) in 2019 (Table 5. d). The proportion of the Watch group decreased by 16% and the Reserve group has remained stable since 2016.

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

Consumption of penicillins (including amoxicillin-clavulanic acid, ATC group J01C) ranked first among antibiotic classes, amounting to 40% of the total antibiotic consumption (ATC group J01) in 2019 (Figure 5. e). It was followed by the consumption of macrolides, lincosamides and streptogramins (14%, ATC group J01F), tetracyclines (14%, ATC group J01A), fluoroquinolones (12%, ATC group J01MA), beta-lactam antibacterials other than penicillins (including cephalosporins, 7%, ATC group J10D), sulfonamides and trimethoprim (5%, ATC group J01E), and other antibacterials (6%, ATC group J01X).

The overall consumption of penicillins remained stable in 2019 (3.6 DIDs, 40% of total antibiotic consumption) compared to 2016 (3.6 DIDs). Combinations of penicillins and beta-lactamase inhibitors were the most frequently used group of systemic antibiotics in 2019 (2.5 DIDs, 27% of total antibiotic consumption) and accounted for 68% of total penicillin consumption (Table 5. c). Among penicillins, those with an extended spectrum, namely amoxicillin, were the second most frequently used group (1.0 DID, 29% of penicillin consumption). The relative consumption of beta-lactamase-sensitive penicillins was low in Switzerland (1% of total antibiotic consumption in 2019), while in countries participating in the ESAC-Net this indicator ranged from <0.1% to 27.2% in 2018 (Table 5. e) [4]. However, the re-

Table 5. c: Consumption of antibiotic classes expressed in DDDs per 1,000 inhabitants per day in the outpatient setting in Switzerland (2017–2019).

ATC Group	Antibiotic class	2016	2017	2018	2019
J01A	Tetracyclines	1.4	1.3	1.4	1.3
J01CA	Extended-spectrum penicillins (amoxicillin)	0.9	0.9	1.0	1.0
J01CE	Beta-lactamase-sensitive penicillins	0.1	0.1	0.1	0.1
J01CF	Beta-lactamase-resistant penicillins	0.0	0.0	0.0	0.0
J01CR02	Penicillins and beta-lactamase inhibitor (amoxicillin and clavulanic acid)	2.5	2.4	2.4	2.5
J01CR03-05	Penicillins and beta-lact. inhibitor (anti-pseudomonal)	0.0	0.0	0.0	0.0
J01DB	Cephalosporins – first generation	0.0	0.0	0.0	0.0
J01DC	Cephalosporins – second generation	0.6	0.6	0.6	0.6
J01DD	Cephalosporins – third generation	0.1	0.1	0.1	0.1
J01DE	Cephalosporins – fourth generation	0.0	0.0	0.0	0.0
J01DF	Monobactams	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.0	0.0	0.0	0.0
J01DI	Other cephalosporins and penems	0.0	0.0	0.0	0.0
J01E	Sulfonamides and trimethoprim	0.4	0.4	0.5	0.5
J01FA	Macrolides	1.3	1.2	1.2	1.1
J01FF	Lincosamides	0.2	0.2	0.2	0.2
J01G	Aminoglycoides	0.0	0.0	0.0	0.0
J01MA	Fluoroquinolones	1.4	1.3	1.2	1.1
J01XA	Glycopeptides	0.0	0.0	0.0	0.0
J01XB	Polymyxins	0.0	0.0	0.0	0.0
J01XC	Fusidic acid	0.0	0.0	0.0	0.0
J01XD	Nitroimidazole derivates	0.0	0.0	0.0	0.0
J01XE	Nitrofuran derivates (nitrofurantoin)	0.4	0.4	0.4	0.5
J01XX	Other antibacterials	0.1	0.1	0.1	0.1
J01	Antibacterial agents for systemic use	9.5	9.0	9.1	9.1
J04AB	Rifamycins	0.2	0.2	0.2	0.2
P01AB	Nitroimidazole derivates (metronidazole oral)	0.2	0.2	0.2	0.2

Table 5. d: Antibiotic consumption according to the AWaRe classification of the WHO in the outpatient setting in Switzerland (2017–2019).

AWaRe groups**	Consumption*			Relative consumption (%)		
	2017	2018	2019	2017	2018	2019
Access group	5.4	5.7	5.8	60%	62%	64%
Watch group	3.6	3.5	3.3	40%	38%	36%
Reserve group	0.0	0.0	0.0	0.3%	0.3%	0.3%

* Consumption expressed in DDDs per 1,000 inhabitants per day
** See Annex I for the list of antibiotics and their corresponding AWaRe group

lative consumption of penicillins associated with beta-lactamase inhibitors was relatively high (27%) in comparison with countries participating in the ESAC-Net (range: 0.1%–44.9%) in 2018 [4]. At the substance level, amoxicillin-clavulanic acid and amoxicillin were the most frequently used antibiotics in 2019 (2.5 and 1.0 DIDs, resp.), of which both consumptions remained stable between 2018 and 2019.

The cephalosporins (ATC group J01DB-DE) slightly decreased from 0.75 DID in 2016 to 0.66 DID in 2019. Cefuroxime, cefpodoxime and cefaclor represented 81%, 13% and

Figure 5. e: Distribution of the total antibiotic consumption (ATC group J01) per antibiotic class in the outpatient setting in 2019 in Switzerland.

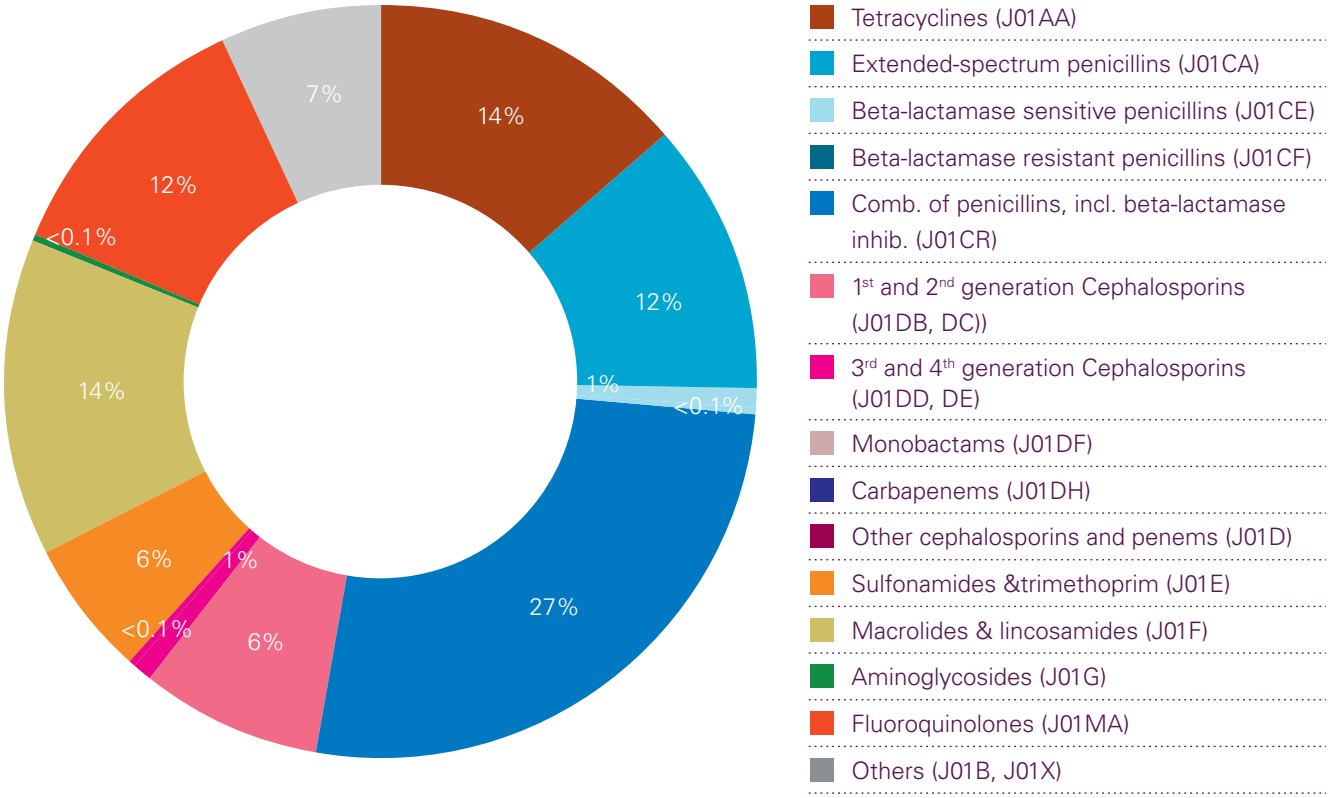


Table 5. e: ESAC quality indicators for consumption of antibacterials for systemic use (ATC group J01) in the outpatient setting in Switzerland (2017–2019).

Year	Consumption[a]					Relative consumption[b]				Broad/Narrow[c]
	J01	J01C	J01D	J01F	J01M	J01CE_%[d]	J01CR_%	J01DD+DE_%	J01MA_%	J01_B/N
2017	9.0	3.4	0.7	1.4	1.3	1.2	26.4	1.5	14.8	40.9
2018	9.1	3.5	0.7	1.3	1.2	1.2	26.5	1.2	13.2	39.7
2019	9.1	3.6	0.7	1.3	1.1	1.0	27.2	1.1	11.8	46.1
p0*	8.9	2.9	0.0	0.5	0.3	0.1	0.1	0.2	2.3	0.16
p25*	13.2	5.0	0.6	1.9	0.8	0.7	11.4	0.7	5.6	4.45
p50*	17.2	6.8	1.6	2.8	1.2	2.3	18.9	2.3	8.2	18.44
p75*	20.8	9.2	2.7	3.6	2.3	6.4	27.7	4.2	10.3	50.82
p100*	32.4	13.8	7.9	6.4	5.4	27.2	37.4	10.9	18.9	624.04

[a] Consumption for penicillins (J01C), cephalosporins (J01D), macrolides, lincosamides and streptogramins (J01F) and quinolones (J01M) expressed in DDDs 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 percentages 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 suggests better quality indicator, the colour code was applied inversely.

* Values in the community, EU/EEA countries, 2018 [4].

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]

4% resp. of cephalosporin consumption in 2019. The relative consumption of third- and fourth-generation cephalosporins (ATC Code J01DD-DE) was 1% in 2019, compared with a range of < 0.1% to 7.2% in countries participating in the ESAC-Net in 2018 (Table 5. e) [4].

Fluoroquinolone consumption was 1.1 DDDs per 1,000 inhabitants per day in 2019 in Switzerland, accounting for 12% of the total antibiotic consumption in the outpatient setting. Although we have observed a slight downward trend (–23% since 2016), consumption remained high compared to countries participating in the ESAC-Net, where the relative consumption of fluoroquinolones ranged from 2.3% to 18.6% in 2018 (Table 5. e) [4]. At the substance level, ciprofloxacin was the most frequently used fluoroquinolone (67%), followed by levofloxacin (14%), norfloxacin (10%), moxifloxacin (7%) and ofloxacin (2%) in 2019. Norfloxacin has decreased by 42% since 2016.

In the macrolide, lincosamide and streptogramin group, (ATC Code J01F), only macrolides and lincosamides have been used in Switzerland (1.1 and 0.18 DDDs per 1,000 inhabitants per day in 2019) (Table 5. c). Consumption of macrolides and lincosamides remained stable between 2018 and 2019. Clarithromycin, azithromycin and erythromycin accounted for 56%, 44% and < 0.1% resp. of the macrolides in 2019. Among the lincosamides, clindamycin consumption was 0.17 DDD per 1,000 inhabitants per day in 2019 and has remained stable since 2016.

Tetracycline consumption slightly decreased from 1.4 DDDs per 1,000 inhabitants per day in 2018 to 1.3 in 2019 (–5%), accounting for 14% of the total antibiotic consumption. Doxycycline was the most frequently used tetracycline (78%), followed by limecycline (13%), and minocycline (8%). Minocycline has decreased by 41% since 2016.

Nitrofurantoin and fosfomycin accounted for resp. 5% and 1% of the total antibiotic consumption. Nitrofurantoin has increased by 28% since 2016.

The ratio of consumption of broad-spectrum penicillins, cephalosporins and macrolides to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides was relatively high (46.1) compared to countries participating in the ESAC-Net, where this ratio ranged from 0.2 to 266.5 in 2018 (Table 5. e) [4].

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 (2016–2019).

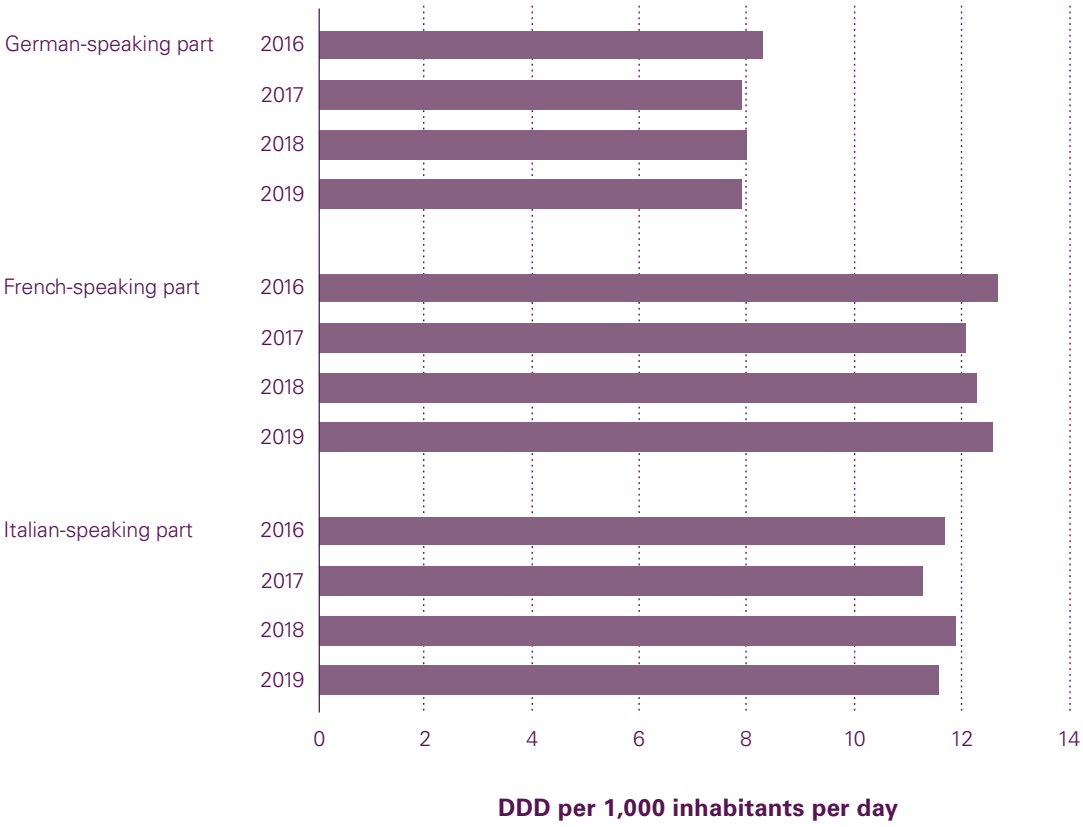
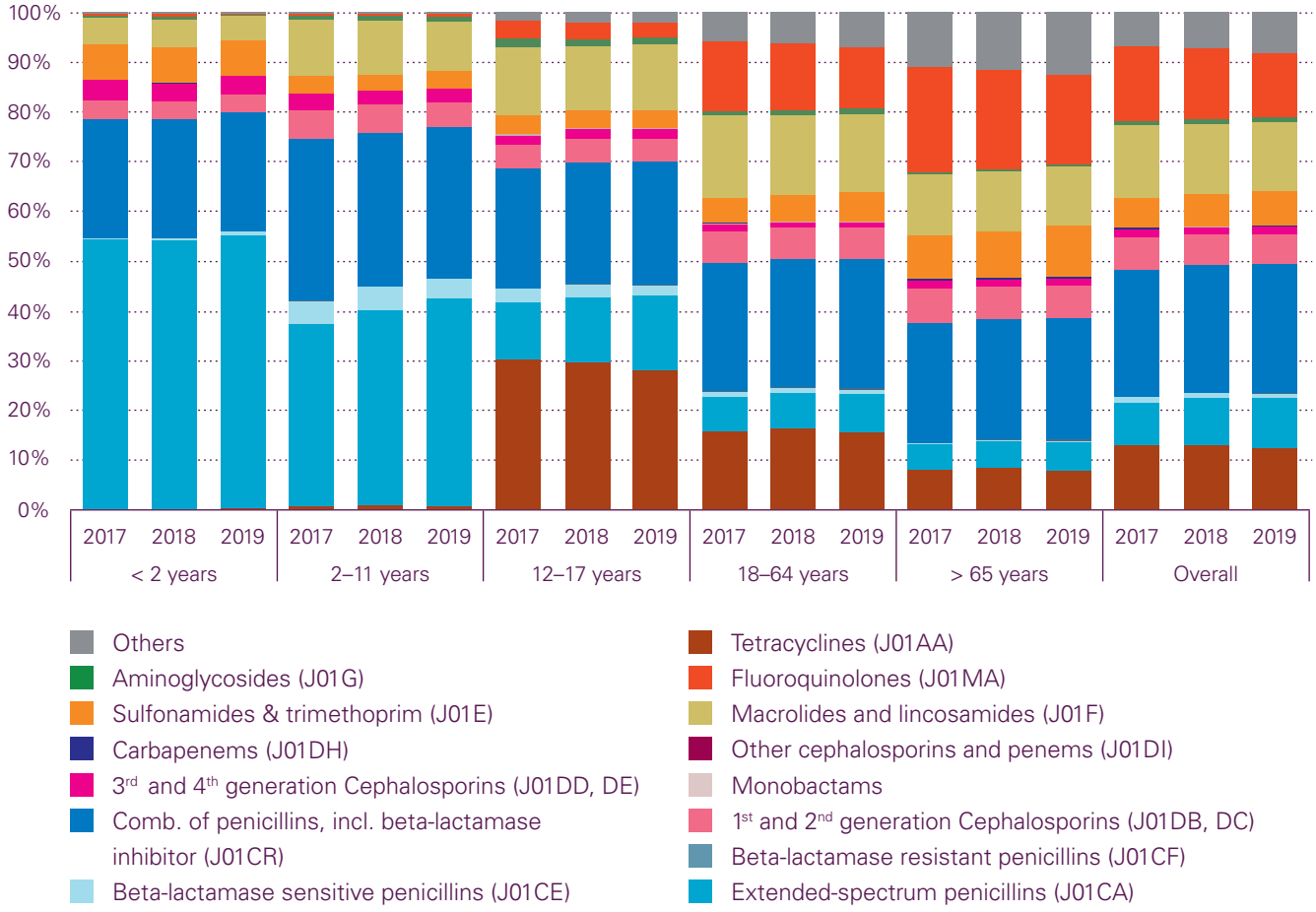


Figure 5. g: Antibiotic classes per age group and overall as a proportion of the total consumption in the outpatient setting in Switzerland (2017–2019).



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

In 2019, the German-speaking part of Switzerland presented lower antibiotic consumption (7.9 DIDs) than the Italian-speaking (11.6) and French-speaking parts (12.6) (Figure 5. f). The three regions have remained stable since 2016.

We observed a higher proportion of fluoroquinolones in the Italian-speaking part of Switzerland (15%) than in the German- (12%) and French-speaking parts (11%) in 2019.

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

Penicillins with an extended spectrum (namely amoxicillin) were the antibiotic group most commonly used among children aged less than two years (55% of the total antibiotic consumption in 2019) and between 2–11 years (42%), whereas penicillins associated with beta-lactamase inhibitors were the most frequently used antibiotics in the age groups 18–64 (26%) and > 65 (25%) (Figure 5. g). Penicillins with an extended spectrum (amoxicillin) and penicillins associated with beta-lactamase inhibitors (amoxicillin-clavulanic acid) represented 79% of the total antibiotic consumption in patients less than 2 years old (2–11 years: 72%; 12–17: 40%; 18–64: 34%; > 65: 31%). The proportion of tetracycline (limecycline and minocycline) consumption was above average in patients between 12 and 17 years of age (28% 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. 10% and 1% of the total antibiotic consumption in patients aged 65 and over in 2019.

5.4 Discussion

In Swiss acute care hospitals, total antibiotic consumption increased from 46.0 to 51.8 DDDs per 100 bed-days between 2010 and 2019. When expressed in DDDs per 100 admissions, the consumption of antibiotics reveals a decreas-

ing trend. This discrepancy can be explained by an increasing number of admissions and a decreasing number of bed-days in hospitals due to the shorter length of hospital stays. Expressed in DDDs per 1,000 inhabitants per day, the total antibiotic consumption (1.6) was lower than the median (1.8) obtained in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [4]. The most commonly used class of antibiotics was the penicillins (ATC Code J01C), followed by 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 9.1 DDDs per 1,000 inhabitants per day in 2019, which was low compared to countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [4]. The most commonly 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 compared to 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 [5, 6]. 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 [7]. Concerning the inpatient setting, a sentinel network such as ANRESIS, 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

Antimicrobial use in acute care hospitals: national point prevalence survey on healthcare-associated infections and antimicrobial use

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From 2017 to 2019, Swissnoso performed national point prevalence surveys (PPS) on healthcare-associated infections and the use of antimicrobials in Swiss acute care hospitals. The protocol was based on the document issued by the European Centre of Disease Prevention and Control in 2016 and was not changed over time.[1] Hospitals collected data on inpatients, hospitalized on any day between April and June.[2,3]

For antimicrobial use, the following data were collected: agent, route, dosage and indication as judged by the prescriber (treatment of community-, hospital- or long-term care-acquired infection, surgical or medical prophylaxis), diagnosis by anatomical site in case of treatment, documentation of the reason for antimicrobial prescription in the patient chart and change of the current antimicrobial regimen.[4] In case of changed regimen, additional information on the last change was obtained: escalation, de-escalation, change from intravenous to oral, or any other type of change. The prevalence of antimicrobial use was reported as the percentage of patients receiving one or more antimicrobials on the survey day. The Anatomical Therapeutic Chemical (ATC) classification system was used for data analysis. Drugs were defined to the 5th level of the ATC classification. Results were further stratified into broad-spectrum antimicrobials (piperacillin/tazobactam, third- and fourth-generation cephalosporins, monobactams, carbapenems, fluoroquinolones, glycopeptides, polymyxins, daptomycin and oxazolidinones) and antibiotics of the AWaRe watch and reserve groups.

Information on antimicrobial use was available from 12,931, 4001, and 5,706 patients from 96, 20, and 34 acute care hospitals in 2017, 2018, and 2019, respectively. On average, 33.0% (95% CI: 32.2–33.8%), 30.4% (95% CI: 29.0–31.9%), and 31.9% (95% CI: 30.7–33.1%) of the patients received one or more antimicrobials on the day of survey. 20.0% of patients received a broad-spectrum antimicrobial and 14.4% an antimicrobial of the AWaRe watch or reserve group in 2019. This remained stable since 2017. 34.6% of antimicrobial regimes were changed since the treatment initiation. De-escalation was the most frequent reason for the change (12.7%), followed by escalation (12.1%), switch from intravenous to oral (8.3%) and change due to adverse event (1.5%). The most important indication for antimicrobial use was the treatment of community-acquired infections, mainly lower respiratory and urinary tract infections (Figure 1). Surgical prophylaxis was the second most common indication for the use of antimicrobials.

Antimicrobial consumption was at European average, the use of broad-spectrum antibiotics in the lower third. Swiss acute care hospitals should invest in antimicrobial stewardship, particularly in reducing the use of broad-spectrum antibiotics.

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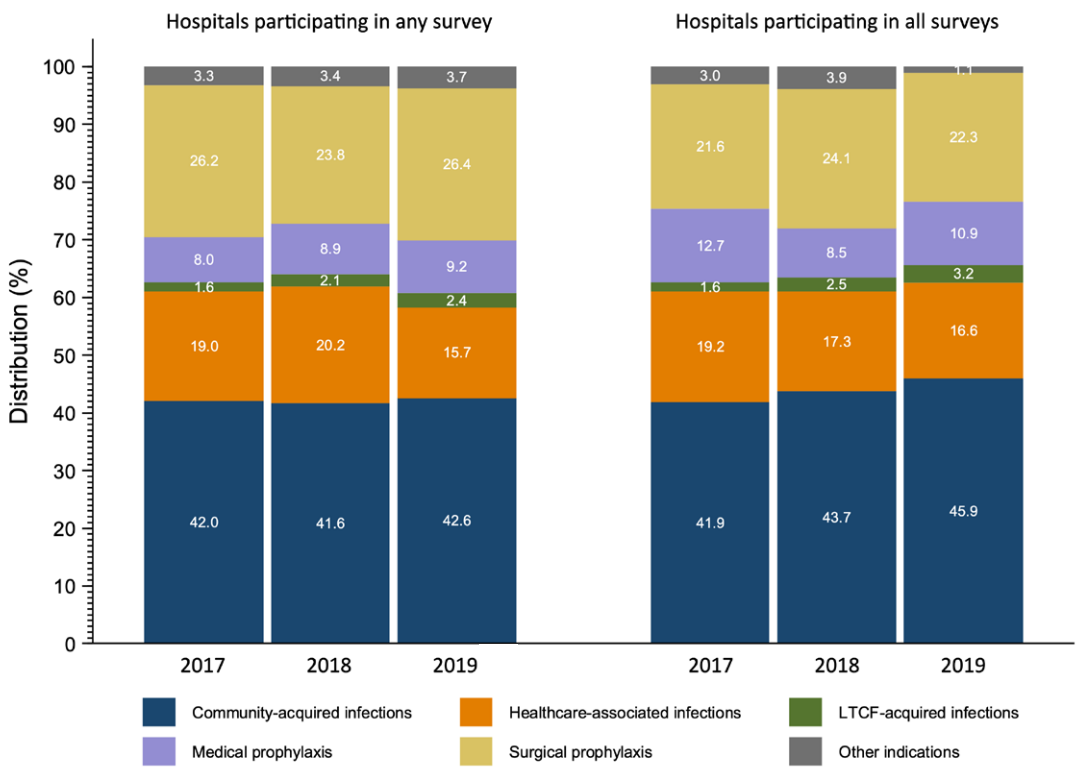
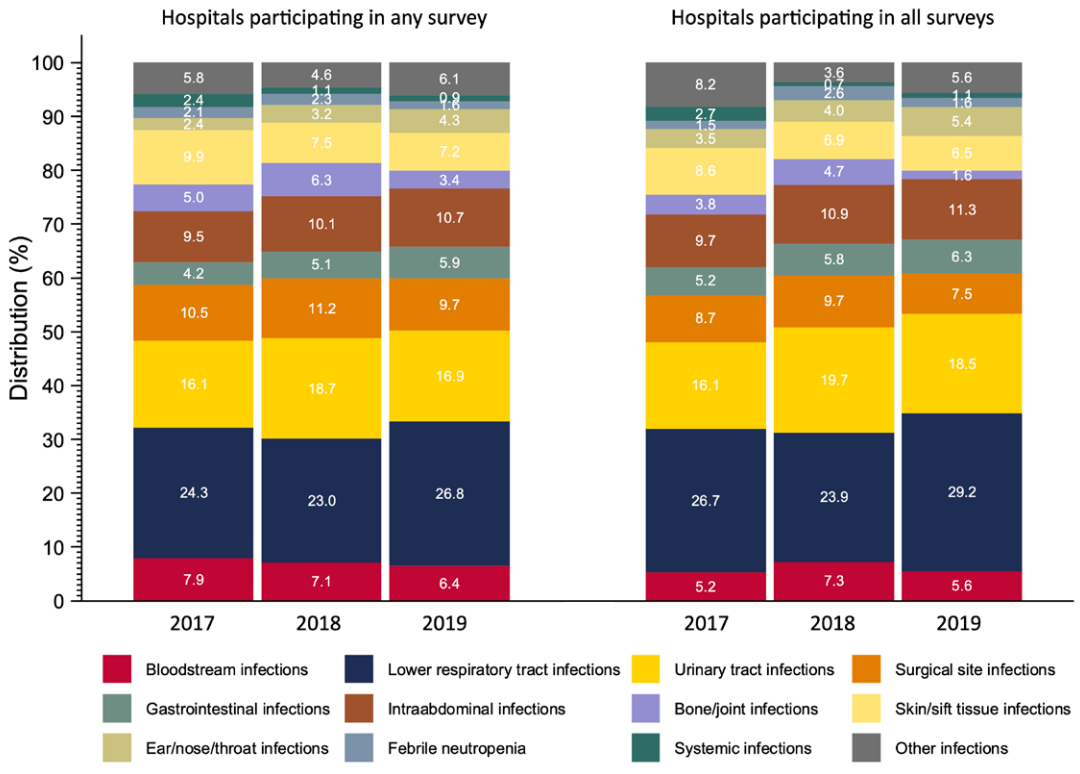
Figure 1: Summarizes the indications for antimicrobial use, stratified by year and participation in all years (a) and the diagnoses for antimicrobial use, stratified by year and participation in all years (b).



(b)



Textbox

Antibacterial prescribing in the outpatient setting: results from a sentinel network of physicians ("Sentinella" network), Switzerland

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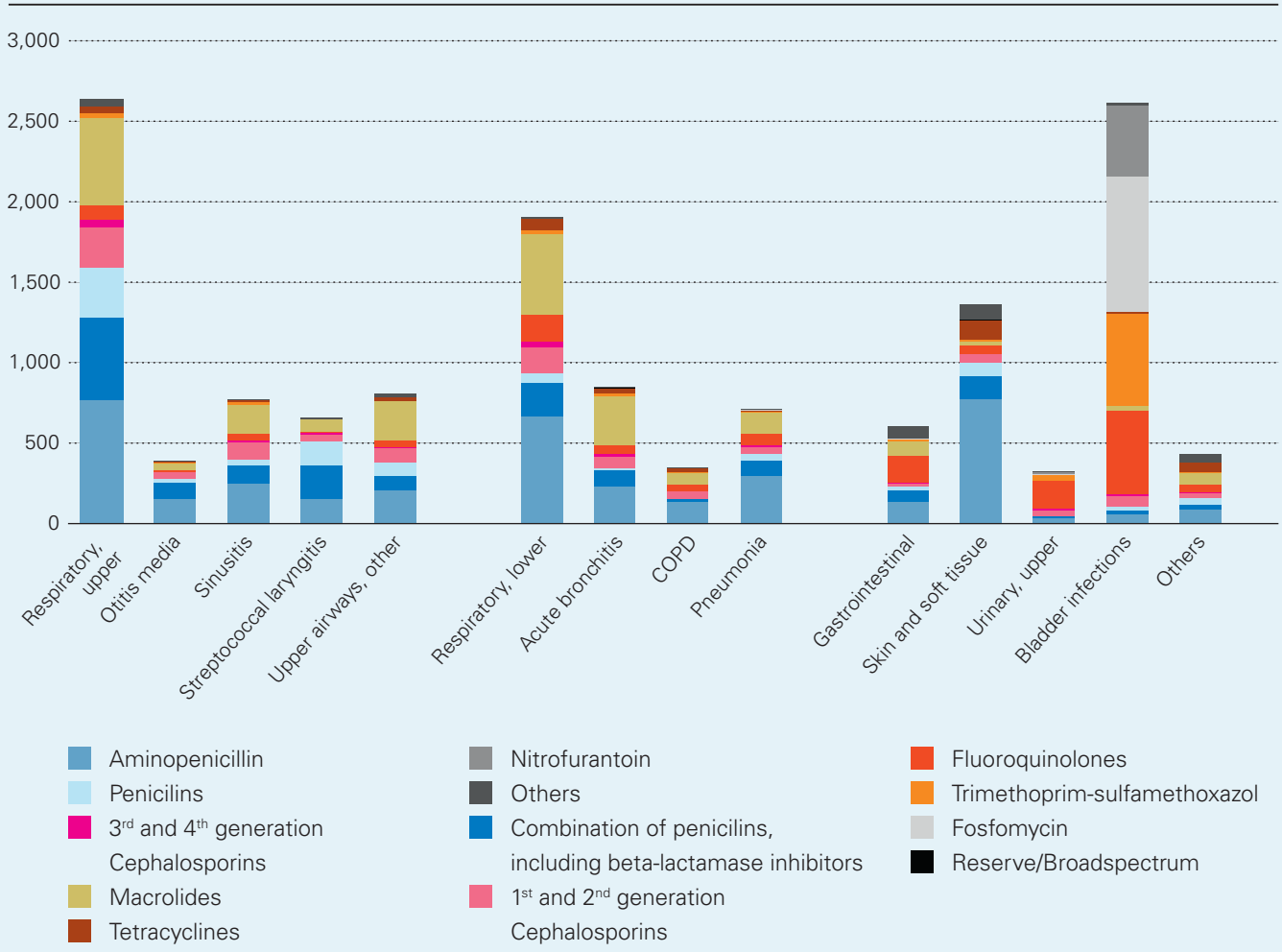
Background: Inappropriate or unnecessary use of antibacterials may foster the development of antibiotic resistance. Our goals were to assess the global antibacterial use, the number of antibacterial prescriptions and the proportion of antibacterial classes per clinical indication in the outpatient setting in Switzerland.

Methods: We analyzed all consultations with antibacterial prescriptions reported by general and internal medicine practitioners between 2017 and 2019 using the representative Swiss Sentinel Surveillance Network "Sentinella" (n = 146, 2018). The network covers all regions of Switzerland. Extrapolation on the population level was performed by attributing the estimated covered population to each Sentinella physician. Data from pediatricians were excluded.

Results: A total of 13,401 antibacterial prescriptions were issued by participating physicians in 2019, corresponding to 9,887.9 antibacterial prescriptions per 100,000 inhabitants.

Figure 1: Antibacterial prescriptions by indications and antibacterial family issued by general practitioners participating in the Sentinella network, expressed in number of prescriptions per 100,000 inhabitants for 2019.



"Respiratory, upper" includes otitis media, sinusitis, streptococcal laryngitis and upper airways.
"Respiratory, lower" includes acute bronchitis, chronic obstructive pulmonary disease (COPD) and pneumonia.

This number remains stable compared to 2017 (9,162.1) and 2018 (10,144.3). The number of antibacterial prescriptions per 1000 consultations was 27.6 in 2019 compared to 25.5 in 2017 and 28.2 in 2018. Out of all 2019 prescriptions, 26% were for bladder infections, 27% for upper respiratory tract infections and 19% for lower respiratory tract infections. Penicillins were the most commonly used antibacterial family (41%), followed by macrolides (13%) and fluoroquinolones (12%). Fosfomycin (32%), trimethoprim-sulfamethoxazole (22%), fluoroquinolones (20%) and nitrofurantoin (17%) were the most often prescribed antibacterials for bladder infections (Figure 1). For lower respiratory tract infections, amoxicillin (35%), macrolides (26%) and penicillins with beta-lactamase inhibitors (11%) were the most frequently prescribed antibacterial classes.

Conclusions: Even if antibiotic consumption in Switzerland is low in comparison with other European countries, the quality of the antibacterial prescriptions can be optimized, particularly by reducing (i) the use of antibacterials in acute bronchitis, a viral infection in more than 90% of cases, and (ii) the use of fluoroquinolones for bladder infections. Resources for antibiotic stewardship programs in the outpatient setting are also needed in countries with low antibacterial consumption.

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 continue to decline (Table 6 a). In 2018, given sales of 32,397 kg, the yearly decline was 1.3%. In 2019, the reduction was even more pronounced with 7.1% (total volume 30,183 kg). Since 2010 the total decline amounts to 52% (33,197 kg). The decrease is mainly due to a fall in sales of medicated premixes.

The sales rankings of the various classes of antibiotics changed in 2018. Since then, penicillins come in first place, followed by sulfonamides and tetracyclines. These three classes are often sold as medicated premixes.

The quantity of sold antibiotics approved only for companion animals comprises 2.6% of the total volume.

Regarding the highest-priority critically important antibiotic classes for human medicine [1], the sales of macrolides decreased around 7% in 2018 and another 20.2% in 2019. Fluoroquinolones too were sold less in both years (11% in 2018, 8.9% in 2019). The sales of cephalosporins (3rd/4th generation) decreased approximately 4.7% in 2018 and 11.3% in 2019.

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 has remained unchanged compared to previous years (Table 6. b). The biggest sales volumes are products licensed for oral application (2018: 63%, 2019: 60%), followed by parenteral (2018: 26%, 2019: 27%), intramammary (2018: 9%, 2019: 10%), intrauterine (2%) and topical formulations (1%). During the last two years, 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 amount of sales 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 of sales has decreased continuously since 2010 by 52%. Penicillins account for the bulk of agents followed by sulfonamides and

Table 6. a: Sales of antibiotic classes between 2010 and 2019.

Sales (kg)										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Sulfonamides	25,696	23,123	21,556	18,942	17,009	14,959	13,130	10,181	9,292	8,406
Penicillins	11,210	11,460	10,997	10,875	10,344	10,016	9,694	9,610	9,823	9,785
Tetracyclines	14,749	13,737	12,043	11,631	10,402	8,683	8,177	6,856	7,218	6,226
Aminoglycosides	3,222	3,324	3,207	3,124	3,125	3,104	2,997	2,471	2,523	2,465
Macrolides	3,828	3,481	3,313	3,112	2,807	2,632	1,988	1,594	1,482	1,183
Trimethoprim	1,704	1,549	1,368	1,148	1,102	904	829	591	608	582
Polymyxins	1,489	1,454	1,058	855	773	503	372	328	235	207
Cephalosporins	568	565	542	530	522	495	431	381	363	322
Fluoroquinolones	415	394	359	413	404	407	304	228	203	185
Amphenicols	258	284	232	202	188	217	273	378	499	571
Others*	165	477	318	343	274	227	182	210	152	177
Total	**63,305**	**59,849**	**54,992**	**51,176**	**46,950**	**42,147**	**38,379**	**32,826**	**32,397**	**30,108**

* Lincosamides, imidazoles, nitrofurans, pleuromutilins, polypeptides excluding polymyxins (until 2013), steroidal antibiotics, quinolones (until 2014)
Due to late corrections in the data the amount of penicillins sold 2017 was 499 kg higher than reported last year.

Table 6. b: Sales of antimicrobials according to the administration route between 2010 and 2019.

Sales (kg)	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Oral	**50,143**	**46,476**	**42,005**	**38,756**	**34,697**	**30,015**	**26,113**	**21,411**	**20,288**	**18,063**
Premix	44,125	40,606	36,181	33,021	29,079	24,336	20,621	17,223	15,750	13,050
Others*	6,017	5,871	5,824	5,735	5,618	5,679	5,492	4,188	4,538	5,013
Intramammary	**3,595**	**3,734**	**3,655**	**3,482**	**3,375**	**3,193**	**2,672**	**2,753**	**2,795**	**2,885**
Dry cow products	1,209	1,323	1,315	1,336	1,343	1,064	918	824	912	826
Lactating cow products	2,386	2,411	2,340	2,146	2,033	2,129	1,754	1,930	1,884	2,059
Parenteral	**8,356**	**8,431**	**8,200**	**7,876**	**7,724**	**7,934**	**8,580**	**7,752**	**8,373**	**8,225**
Intrauterine	**905**	**857**	**815**	**767**	**864**	**719**	**726**	**612**	**654**	**628**
Topical/external	**306**	**350**	**318**	**296**	**290**	**286**	**287**	**298**	**287**	**307**
Sprays	280	321	299	278	272	270	271	284	272	293
Others**	27	30	18	18	19	16	16	15	15	13
Total	**63,305**	**59,849**	**54,992**	**51,176**	**46,950**	**42,147**	**38,377**	**32,826**	**32,397**	**30,108**

* Tablets, capsules, powders, suspensions, granules

** Ointments, drops, gels

Table 6. c: Sales of different antibiotic classes licensed for livestock animals between 2010 and 2019.

Sales (kg)										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Sulfonamides	25,672	23,118	21,556	18,942	17,009	14,959	13,130	10,181	9,292	8,406
Penicillins	10,793	11,023	10,582	10,437	9,893	9,573	9,249	9,143	9,375	9,325
Tetracyclines	14,746	13,731	12,038	11,626	10,398	8,679	8,172	6,851	7,214	6,222
Aminoglycosides	3,215	3,317	3,199	3,115	3,114	3,095	2,988	2,462	2,513	2,456
Macrolides	3,806	3,459	3,289	3,089	2,784	2,610	1,967	1,574	1,463	1,164
Trimethoprim	1,702	1,548	1,368	1,148	1,102	904	829	591	608	582
Colistin	1,489	1,454	1,057	854	773	502	372	327	234	206
Fluoroquinolones	388	371	335	384	379	384	282	207	184	169
Cephalosporins	237	249	237	228	241	234	190	163	162	144
Amphenicols	–	–	–	183	169	199	244	341	463	529
Others*	303	616	449	310	241	197	152	181	125	130
Total	**62,350**	**58,886**	**54,111**	**50,316**	**46,103**	**41,337**	**37,575**	**32,020**	**31,634**	**29,334**

* Lincosamide, pleuromutilins, quinolones, amphenicols (until 2012)

tetracyclines. Also, in livestock the highest-priority critically important antibiotics were sold less than the years before. The sales of macrolides decreased by more than 8% in 2018 and 26% in 2019 (Table 6. c). Even the sales of long-acting, single-dose injection products follow a downward trend. The sales of fluoroquinolones and third- and fourth-generation cephalosporins started decreasing in 2016. This trend continued: fluoroquinolones decreased 12% in 2018, and 10% in 2019; third- and fourth-generation cephalosporins 8% in 2018 and 30% in 2019. In summary, since 2015, the highest-priority critically important antibiotics decreased approximately 50% in all categories. One of the explanations for this positive development is the revision of the Ordinance on Veterinary Medicinal Products, which came into effect in April 2016. Since then, critical antimicrobials such as macrolides, fluoroquinolones and 3rd/4th generation cephalosporins are not allowed to be administered to livestock.

The sales of colistin have declined by approximately 86% since 2010. Expressed in correlation to the biomass under exposure (population correction unit (PCU), see Chapter 6.2.2.), the level in 2019 is 0.3 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 lower 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 correlated to the weight of the livestock population [2]. The amount of active ingredients is divided by the estimated most likely weight at treatment, termed 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 dairy cows, sheep, sows and horses in the standing population and the number of slaughtered cattle, pigs, lambs, horses, poultry and turkeys in the corresponding year multiplied by the estimated weight in kg at the time of treatment. 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 by PCU for the years 2010 to 2019.

The figure shows faster decreasing sales of antimicrobials in the last 10 years compared to the population biomass. The reduction of milligrams active ingredients per PCU indicates that the decrease of sales of antimicrobials is not due to a smaller animal 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 Switzerland in the framework of the Swiss Antibiotic Resistance Strategy (StAR) [4] seem to have a persistent positive effect on the awareness of veterinarians and farmers using antimicrobials in Switzerland.

6.2.3 Medicated premixes

Medicated premixes accounted for 49% of the total sales in 2018 and 43% in 2019. A steady decrease in sales of medicated premixes has been observed since 2010 (–70%). 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.

Medicated premixes are available in several combinations of active ingredients: products containing a single active ingre-

Figure 6. a: Antimicrobial sales for livestock animals between 2010 and 2019 compared to the population biomass (total PCU) and the sales of active ingredients per PCU.

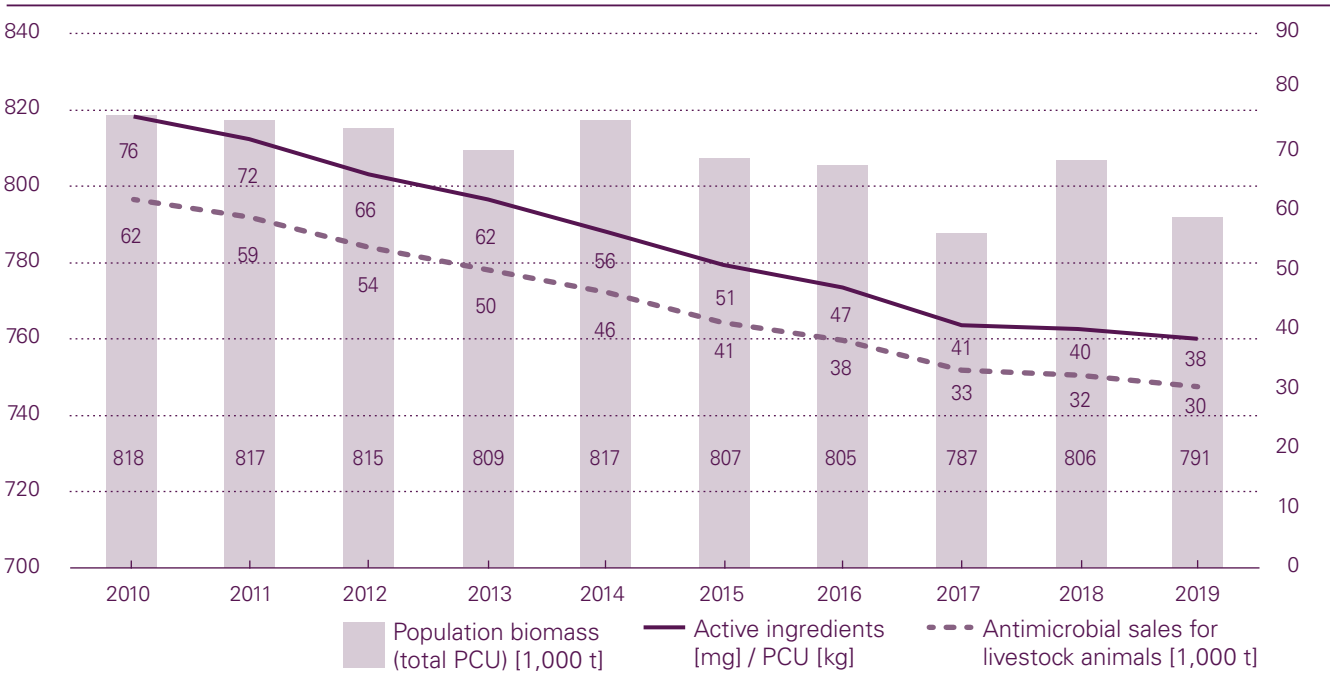


Table 6. d: Sales of antimicrobials licensed as premixes between 2010 and 2019, according to antibiotic classes.

Sales (kg)										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Sulfonamides	20,236	17,788	16,319	13,931	12,141	10,028	8,285	6,450	5,183	3,865
Tetracyclines	12,983	12,006	10,359	9,968	8,673	7,038	6,382	5,174	5,440	4,494
Penicillins	4,610	4,722	4,309	4,461	4,198	3,840	3,363	3,379	3,232	3,145
Macrolides	3,420	3,078	2,907	2,751	2,413	2,263	1,696	1,417	1,289	1,036
Colistin	1,472	1,438	1,045	844	763	500	370	326	231	203
Trimethoprim	1,249	1,124	937	740	626	453	373	322	249	167
Others*	156	450	305	326	265	215	151	156	127	140
Total	**44,125**	**40,606**	**36,181**	**33,021**	**29,079**	**24,336**	**20,621**	**17,223**	**15,750**	**13,050**

* Pleuromutilins, fluoroquinolones, lincosamide (until 2017), aminoglycosides (until 2017), quinolones (until 2014)

Figure 6. b: Sales of antimicrobials (in kg) licensed for intramammary use between 2010 and 2019 separated into dry cow products and products for use during lactation.

Table 6. e: Sales of antimicrobials licensed for intramammary use between 2010 and 2019 according to antibiotic class.

Sales (kg)										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Dry cow products										
Total	1,209	1,323	1,315	1,336	1,343	1,064	918	824	912	826
Products for use during lactation										
Penicillins	1,785	1,813	1,774	1,644	1,545	1,652	1,366	1,543	1,484	1,659
Aminoglycosides	445	436	406	376	370	361	275	292	305	312
Cephalosporine	56	60	55	52	56	59	60	59	62	60
Others*	101	102	104	74	62	57	53	36	31	27
Total	2,386	2,411	2,340	2,146	2,033	2,129	1,754	1,930	1,884	2,059
Grand Total	3,595	3,734	3,655	3,482	3,375	3,193	2,672	2,753	2,795	2,885

* Lincosamides, macrolides, polymyxins (until 2015)

dient, 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 increased slightly (1.5/3.1%) in both years. Nevertheless, since 2008, the amount has been reduced by nearly 25%. In 2018 and 2019, approximately 70% of all antimicrobials licensed for intramammary use were products for the treatment of mastitis during lactation. The sale of products for drying off increased in 2018 (10%), then decreased in 2019 (10%), whereas the sales of products for use during lactation decreased slightly in 2018 (2.4%) and increased in 2019 (8.5%) (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 not changed significantly in the last years.

6.3 Sales of antimicrobials licensed for companion animals

The quantity of antibiotics approved exclusively for use in companion animals amounts to approximately 2.6% of the total volume. Since 2012, products licensed for both live-

Table 6. f: Sales of antibiotic classes licensed for companion animals between 2010 and 2019.

Sales (kg)										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Penicillins	417	438	415	438	450	443	446	467	448	460
Cephalosporins	331	316	304	302	281	262	241	217	201	177
Fluoroquinolones	27	23	24	29	25	23	22	21	19	16
Aminoglycosides	7	7	8	9	10	9	10	9	9	8
Sulfonamides*	24	5	–	–	–	–	–	–	–	–
Others**	149	173	129	82	80	74	84	92	86	113
Total	**955**	**962**	**881**	**860**	**847**	**810**	**802**	**806**	**763**	**775**

* No licensed products since 2012

** Lincosamides, imidazoles, nitrofurans, polypeptides, steroidal antibiotics, tetracyclines, trimethoprims, amphenicols, macrolides, polymyxins

stock and companion animals are added to the category "livestock animals", in accordance with the guidelines of the ESVAC project [2]. This is especially relevant for active ingredients for parenteral application, as the major part 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 was 763 kg in 2018 and 775 kg in 2019; the sales decreased by 5.3% in 2018 and slightly increased by 1.6% in 2019. The antimicrobial sales for companion animals have decreased by approximately 19% since 2010. Penicillins were the most important active ingredient group, followed by cephalosporins and fluoroquinolones (Table 6. f). The decreasing trend of sales of cephalosporins has continued during the past two years (2018: 8%; 2019: 12%).

6.4 Discussion

There is a constant high awareness in veterinarians as well as in farmers concerning the use of antimicrobials. The decrease in the volume of antimicrobials sold for use in veterinary medicine is ongoing. This is mainly due to a fall in the sales of medicated premixes. However, the ban since April 2016 on the sale of critical antimicrobials for stock has also supported the decrease within the last years. Especially the constant 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 actual 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 the treatment duration.

Information concerning 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 collected for group therapies since January 2019, and since October 2019 for individual therapies. The recording of prescription data is crucial to improve target measures for prevention and prudent use, and to follow up on their effects. A first analysis of these data is expected for the end of 2020.

References

[1] WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). Critically important antimicrobials for human medicine. 6th revision, 2018

[2] European Medicines Agency, Sales of veterinary antimicrobial agents in 31 European countries in 2017 (EMA/294674/2019)

[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)

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 and the most frequent pathogen in humans. 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 settings.

In 2019, resistance to fosfomycin and nitrofurantoin was still very low (Table 7. a), although it is known that plasmid-encoded fosfomycin resistance determinants are circulating in Switzerland. These antibiotics can only be used for non-invasive urinary tract infections and represent an important option in ambulatory care. Trimethoprim-sulfamethoxazole still remains a first-line option in lower urinary tract infections [https://ssi.guidelines.ch/]. Non-susceptibility rates decreased from 29.9% in 2015 to 27.3 % in 2019, and are even significantly lower in urinary samples (22.1% in 2019, Figure 7. a). Since resistance testing is usually not performed for uncomplicated lower urinary tract infections, ANRESIS data still overestimate the resistance rate. In a recent study by A. Plate *et al.*, susceptibility rates to trimethoprim-sulfamethoxazole in uncomplicated lower urinary tract infections were 85.7% [1].

Fluoroquinolones should not be used as first line treatment for lower urinary tract infections, in particular to reserve its efficacy for invasive infections. Fluoroquinolone non-susceptibility has steadily increased from 10.3% in 2004 to 20.5% in 2015, but has since stabilized between 18.6 and 20.5% (18.7% in 2019). Whether this is already due to the promotion of ciprofloxacin-free antibiotic regimens for uncomplicated lower urinary tract infections has to be further analyzed. In EU/EAA states, a slight but significant increase in fluoroquinolone resistance from 24.8 to 25.3% was observed from 2015 to 2018 [2]. Because *E. coli* is also one of the most important pathogens in the outpatient setting, we

Table 7. a: Non-susceptibilitiy rates of invasive *Escherichia coli* isolates in humans for 2019.

***Escherichia coli* (invasive)**											**2019**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	1,358	54.6%	3,810	48%	366	45.9%	5,534	49.5%	48.8–50.2	–	↓
Amoxicillin-clavulanic acid	1,359	36.3%	4,157	27%	366	21.3%	5,882	28.8%	28.2–29.4	–	↑
Piperacillin-tazobactam	1,354	11.2%	3,972	7.7%	366	5.5%	5,692	8.4%	8.0–8.8	–	↑
Cephalosporin, 2nd gen.	910	18.2%	3,468	21.9%	366	15.3%	4,744	20.7%	20.1–21.3	↑	–
Cephalosporin, 3rd/4th gen.	1,359	14.8%	4,175	10.3%	366	11.2%	5,900	11.4%	11.0–11.8	↑	↑
Carbapenems[1]	1,359	0.1%	4,164	0.0%	366	0.0%	5,889	0.1%	0.1–0.1	–	↑
Aminoglycosides	1,354	11.9%	4,160	9%	366	11.2%	5,880	9.8%	9.4–10.2	–	↑
Trimethoprim-sulfamethoxazole	1,359	29.3%	3,806	26.6%	366	26.5%	5,531	27.3%	26.7–27.9	–	↓
Fluoroquinolones[2]	1,359	23.4%	4,169	17.3%	366	16.1%	5,894	18.7%	18.2–19.2	–	↑
Nitrofurantoin	416	1.2%	954	0.4%	0	0.0%	1,370	0.7%	0.5–0.9	–	↓
Fosfomycin	650	2.2%	1,165	1.2%	0	0.0%	1,815	1.5%	1.2–1.8	–	–

[1] Carbapenems: imipenem, meropenem

[2] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.

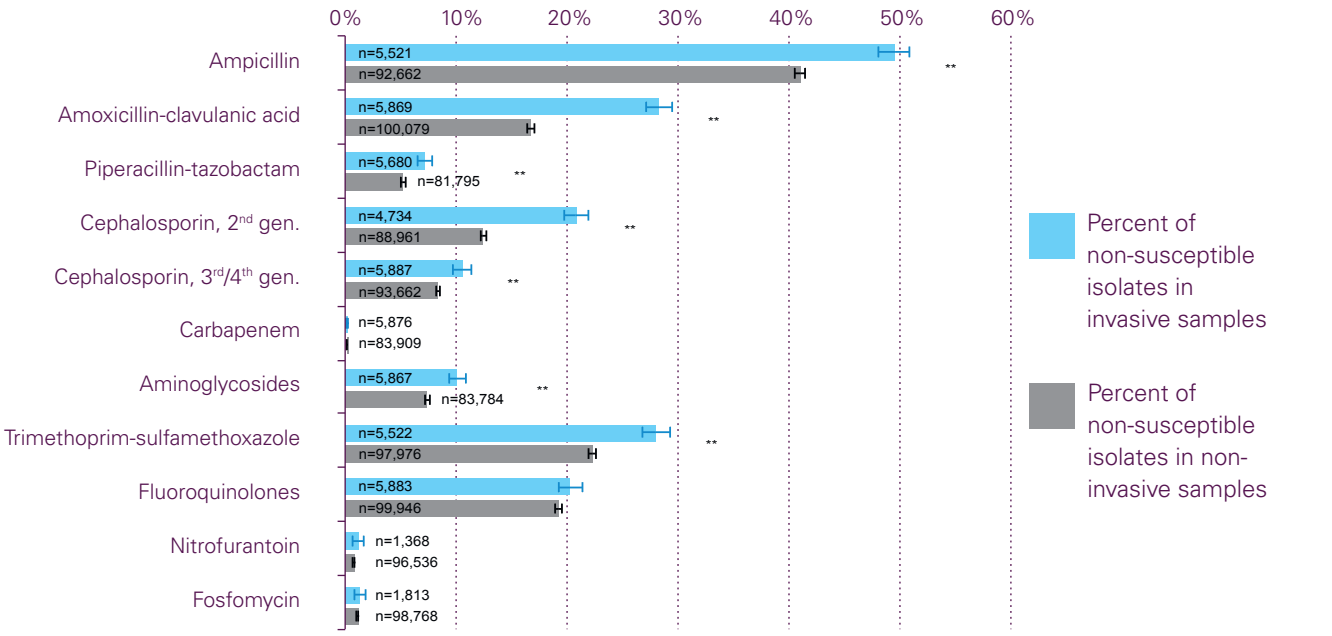
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.

Trends were modelled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the correspondent outcome (increase, decrease).

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.

As for quinolones, the steadily increasing non-susceptibility rates to 3rd/4th generation cephalosporins from 0.9% in 2004 to 11.7% in 2018 did not further increase in 2019, but stabilized at 11.4%. However, this too could be due to the connection of additional laboratories to ANRESIS, more frequently sending resistance data from first line hospitals. In EU/EAA states, a slight increase from 14.6% to 15.1% was observed between 2015 and 2018 [2]. 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.

Figure 7. a: Comparison of non-susceptibility rates in invasive versus outpatient urinary samples in *Escherichia coli* isolates in humans for 2019.



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 2010 an 2019.

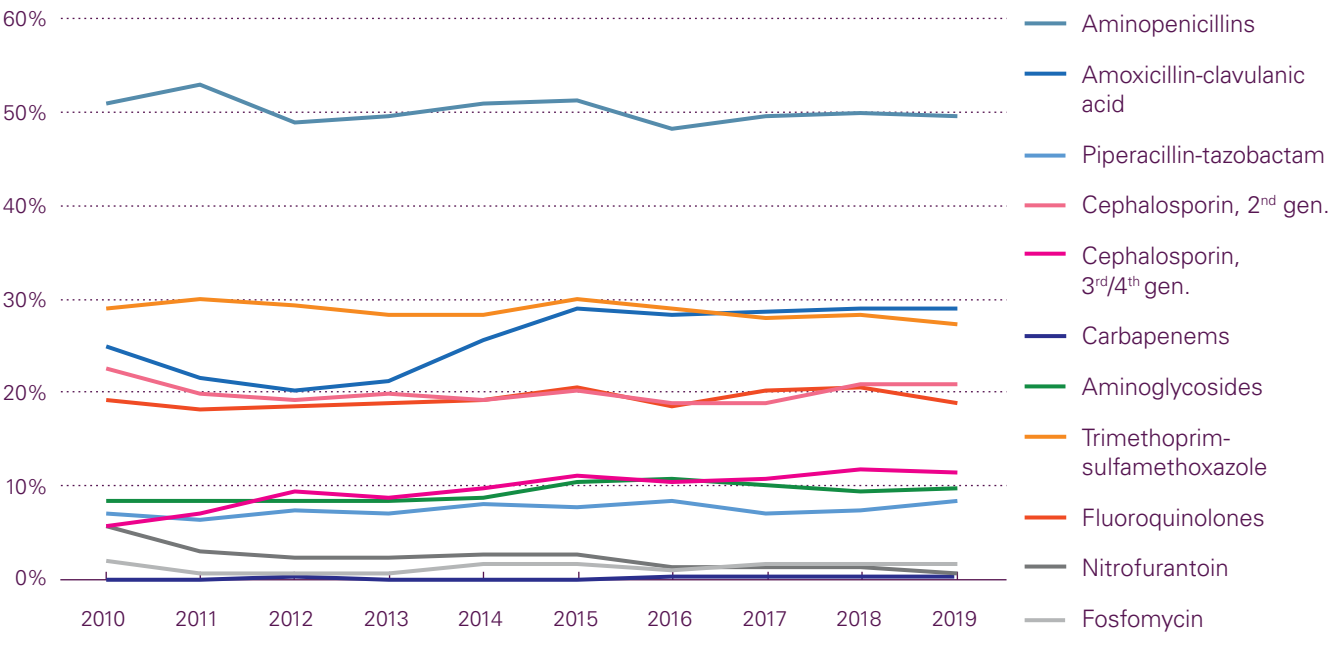


Table 7. b: Non-susceptibility combinations in invasive *E. coli* isolates in humans 2019. Only isolates tested against all five antibiotic groups (aminopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n = 5513/5901 [93.4%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**2,606**	**47.3%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**1,732**	**31.4%**
Aminopenicillins	1,560	28.3%
Aminoglycoside	17	0.3%
Fluroquinolones	155	2.8%
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**557**	**10.1%**
Third-generation cephalosporins + fluoroquinolones	1	0.0%
Aminopenicillins + fluoroquinolones	311	5.6%
Aminopenicillins + third-generation cephalosporins	130	2.4%
Aminoglycoside + fluoroquinolones	4	0.1%
Aminopenicillins + aminoglycosides	111	2.0%
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**379**	**6.9%**
Aminopenicillins + third-generation cephalosporins + fluoroquinolones	218	4.0%
Aminoglycoside + third-generation cephalosporins + fluoroquinolones	1	0.0%
Aminopenicillins + fluoroquinolones + aminoglycosides	114	2.1%
Aminopenicillins + third-generation cephalosporins + aminoclycosides	46	0.8%
Resistance to four antimicrobial groups		
Total (all four-group combinations)	**238**	**4.3%**
Aminopenicillins + carbapenems + third-generation cephalosporins + fluoroquinolones	1	0.0%
Aminopenicillins + third-generation cephalosporins +aminoglycosides + fluoroquinolones	237	4.3%
Resistance to five antimicrobial groups		
Total (all five-group combinations)	**1**	**0.0%**
Aminopenicillins + third-generation cephalosporins +aminoglycosides + fluoroquinolones + carbapenems	1	0.0%

However, no clear trend 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 2018). Nevertheless, increasing rates of carbapenemase-producing Enterobacteriaceae (CPE) around the world are alarming. In order to survey these trends more accurately, knowledge regarding the genetic mechanisms is indispensable. The Federal Office of Public Health has therefore introduced an obligation to report CPE starting 1.1.2016, and all strains are collected by the National Reference Center for Emerging Antibiotic Resistance in Fribourg (NARA, www.nara-antibiotic-resistance.ch) since 2019. A detailed analysis of Swiss data from 2013 to 2018 has been accepted for publication in Eurosurveillance [3] and is summarized in chapter 13 of this report.

Colistin, a rather toxic reserve antibiotic belonging to the polymyxin group, might in future become more important as a "last resort antibiotic" for the treatment of infections due to carbapenemase producers. Actually, colistin resistance is rare in Switzerland, but reports from China describing a mobile plasmid encoding a colistin resistance gene (mcr types), are worrisome [4]. So far, colistin resistance is not systematically tested in Switzerland, although testing algorithms and adequate testing methods have been published by the NARA.

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, af-

Figure 7. c: Multiresistance in invasive *E. coli* isolates in humans between 2010 and 2019 (for details refer to Table 7. b).

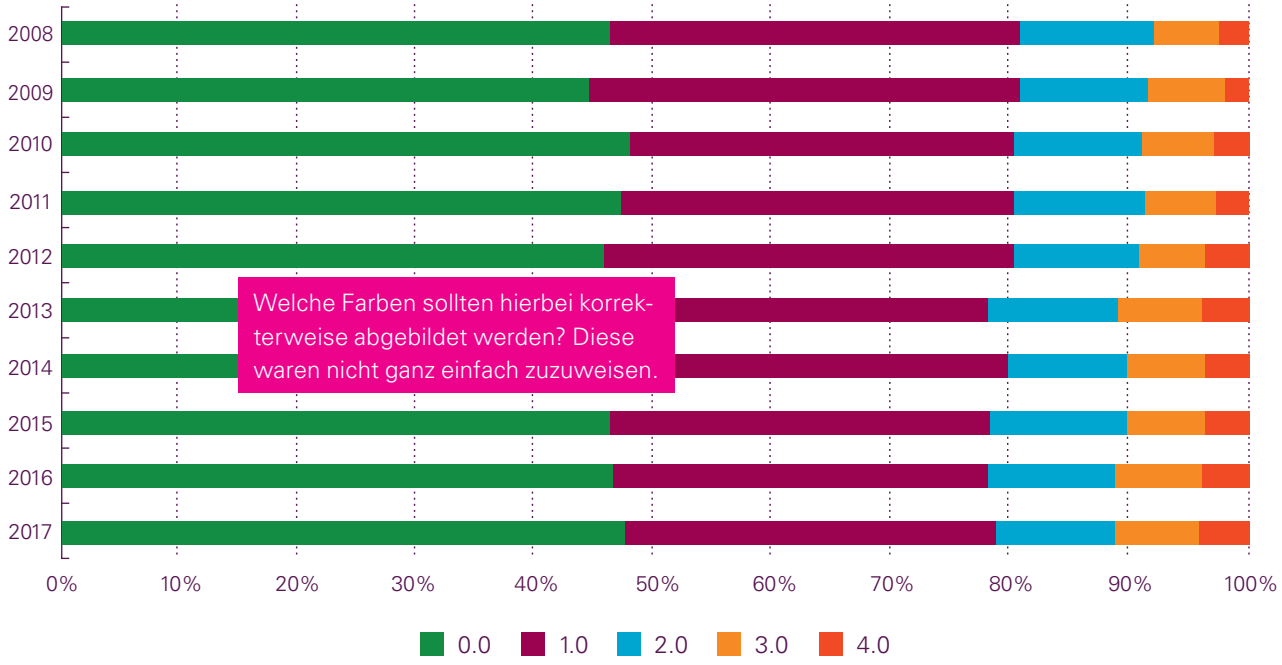


Table 7. c: Non-susceptibility rates of invasive *Klebsiella pneumoniae* isolates in humans in 2019.

Klebsiella pneumoniae											**2019**
Antimicrobials	**West**		**North–East**		**South**		**Total**			**Trend**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Amoxicillin-clavulanic acid	284	19	851	13.5	64	9.4	1,199	14.6	13.6–15.6	–	–
Piperacillin-tazobactam	284	17.3	807	9.7	64	6.2	1,155	11.3	10.4–12.2	–	↑
Cephalosporin, 2nd gen.	210	15.7	704	18	64	15.6	978	17.4	16.2–18.6	–	–
Cephalosporin, 3rd/4th gen.	284	12	854	7.1	64	10.9	1,202	8.5	7.7–9.3	–	↑
Carbapenems	285	0.7	851	0.2	64	1.6	1,200	0.4	0.2–0.6	–	–
Aminoglycosides	281	8.2	852	3.2	64	6.2	1,197	4.5	3.9–5.1	–	–
Trimethoprim-sulfamethoxazole	284	16.5	777	10.6	64	14.1	1,125	12.3	11.3–13.3	–	–
Fluoroquinolones[1]	284	14.1	854	8.7	64	9.4	1,202	10	9.1–10.9	–	↑

[1] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin
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.
Trends were modelled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the correspondent outcome (increase, decrease).

fecting 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 from human clinical isolates. As in *E. coli*, increasing resistance to 3rd/4th generation cephalosporins was a main issue between 2004 (1.3%) and 2014 (9.9%). Since then, it has remained stable or has even decreased slightly to 8.5% in 2019, which compares favorably with the EU/EEA average of 31.7% in 2018. However, stabilization of this increasing resistance trend was also observed in EU/EEA states between 2016 and 2018 [2]. The same trend with maximal non-susceptibility rates in 2014 was observed for 2nd generation cephalosporins and aminoglycosides, with a maximum in 2016 for amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole and with a maximum in 2018 for fluoroquinolones. 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 7.5% in 2018.

However, there are considerable differences between different Swiss regions (Table 7. c), with higher non-suscepti-

Figure 7. d: Non-susceptibility rates in invasive *Klebsiella pneumoniae* isolates in humans from 2010 to 2019.

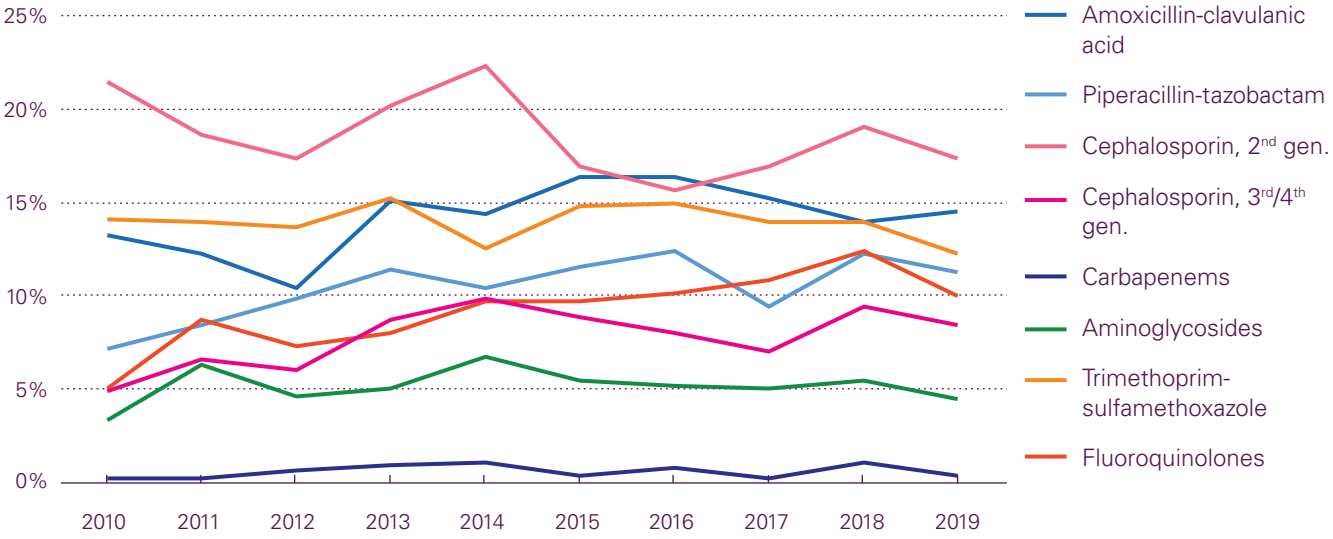
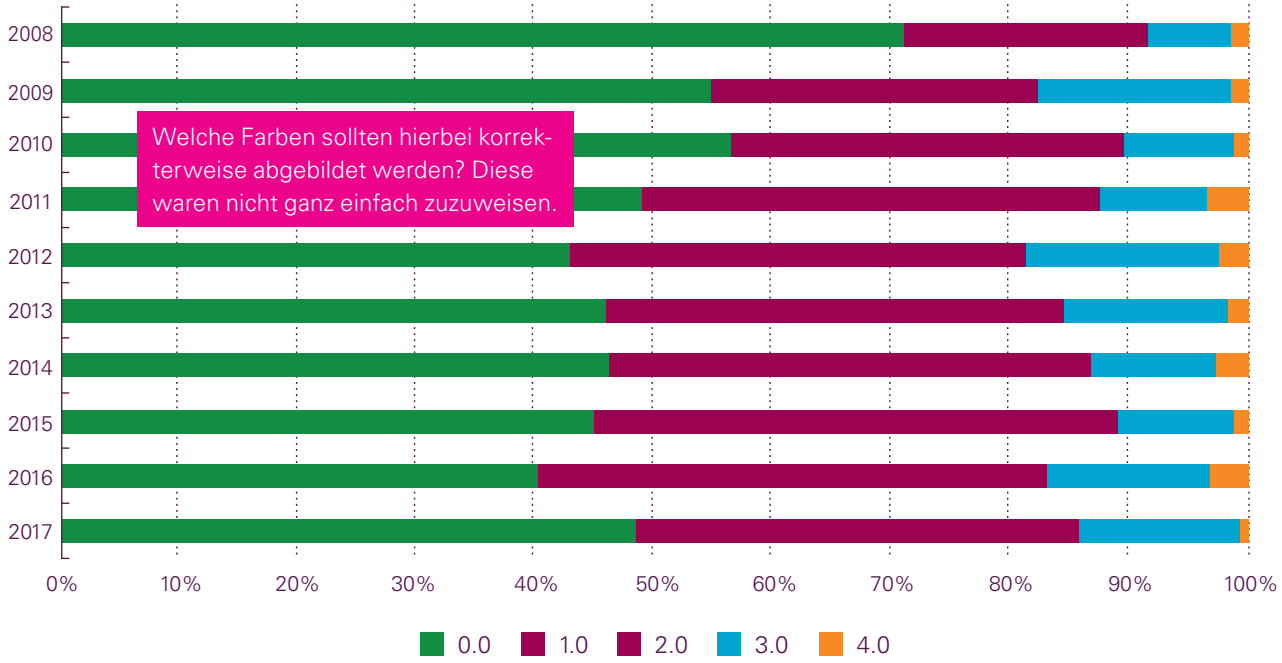


Table 7. d: Non-susceptibility combinations in invasive *K. pneumoniae* isolates in humans in 2019. Only isolates tested against all four antibiotic groups (third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n = 1194/1203 [99.3%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**1040**	**87.1%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**73**	**6.1%**
Fluroquinolones	40	3.4%
Third-generation cephalosporins	28	2.3%
Aminoglycoside	5	0.4%
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**38**	**3.2%**
Third-generation cephalosporins + fluoroquinolones	30	2.5%
Aminoglycoside + fluoroquinolones	7	0.6%
Aminoglycoside + third-generation cephalosporins	1	0.1%
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**41**	**3.4%**
Carbapenems + third-generation cephalosporins + fluoroquinolones	2	0.2%
Aminoglycoside + third-generation cephalosporins + fluoroquinolones	39	3.2%
Resistance to four antimicrobial groups		
Total (all four-group combinations)	**2**	**0.2%**
Aminoglycoside + carbapenems + third-generation cephalosporins + fluoroquinolones	2	0.2%

bility rates in Western Switzerland for most antibiotics, including 3rd/4th generation cephalosporins. Carbapenem non-susceptibility is highest in southern Switzerland (1.6%), mirroring but still much lower than the carbapenem resistance rate observed in Italy in that species (26.8% in 2018). More details concerning carbapenemase-producing Enterobacterales are summarized in chapter 13. Interestingly, several *K. pneumoniae* isolates that produce a carbapenemase and that co-produce a 16 S rRNA methylase conferring pandrug resistance to aminoglycosides and/or that are resistant to colistin have been reported throughout Switzerland. Their identification raises the spectrum of truly pandrug resistant *K. pneumoniae*. Co-resistance is frequent, details are shown in Table 7. d and Figure 7. e.

Figure 7. e: Multiresistance in invasive *K. pneumoniae* isolates in humans from 2010 to 2019 (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 fibrosis 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 among the rare orally-given antibiotics which retain activity against *P. aerugino-*

Table 7. e: Non-susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans in 2019.

Pseudomonas aeruginosa											**2019**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Piperacillin-tazobactam	132	15.9%	362	7.7%	35	14.3%	529	10.2%	8.9–11.5	–	–
Ceftazidime	110	12.7%	386	6.2%	35	8.6%	531	7.7%	6.5–8.9	–	↑
Cefepime	132	12.1%	376	6.9%	35	8.6%	543	8.3%	7.1–9.5	↑	↑
Carbapenem[1]	132	20.5%	384	10.7%	35	11.4%	551	13.1%	11.7–14.5	–	↑
Aminoglycosides	132	7.6%	385	10.1%	35	0.0%	552	8.9%	7.7–10.1	–	↑
Ciprofloxacin	131	10.7%	385	8.6%	35	11.4%	551	9.3%	8.1–10.5	–	–

[1] Carbapenems: imipenem, meropenem
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.
Trends were modelled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the correspondent outcome (increase, decrease).

Table 7. f: Non-susceptibility combinations in invasive *P. aeruginosa* isolates in humans in 2019. Only isolates tested against all five antibiotics or antibiotic groups (piperacillin-tazobactam, cefepime, carbapenems, aminoglycosides, ciprofloxacin) were considered (n = 515/554 [93.0%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**377**	**73.2%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**76**	**14.7%**
Piperacillin-tazobactam	12	2.3%
Ciprofloxacin	14	2.7%
Cefepime	1	0.2%
Carbapenems	26	5.0%
Aminoglycoside	23	4.5%
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**29**	**5.7%**
Piperacillin-tazobactam + ciprofloxacin	2	0.4%
Cefepime + piperacillin-tazobactam	7	1.3%
Carbapenems + piperacillin-tazobactam	4	0.8%
Carbapenems + ciprofloxacin	8	1.6%
Cefepime + carbapenems	2	0.4%
Aminoglycosides + piperacillin-tazobactam	1	0.2%
Aminoglycosides + cefepime	3	0.6%
Aminoglycosides + carbapenems	2	0.4%
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**16**	**3.2%**
Cefepime + piperacillin-tazobactam + ciprofloxacin	3	0.6%
Carbapenems + piperacillin-tazobactam + ciprofloxacin	1	0.2%
Cefepime + carbapenems + piperacillin-tazobactam	4	0.8%
Cefepime + carbapenems + ciprofloxacin	1	0.2%
Aminoglycosides + piperacillin-tazobactam + ciprofloxacin	1	0.2%
Aminoglycosides + cefepime + piperacillin-tazobactam	2	0.4%
Aminoglycosides + cefepime + ciprofloxacin	1	0.2%
Aminoglycosides + carbapenems + ciprofloxacin	1	0.2%
Aminoglycosides + cefepime + carbapenems	2	0.4%
Resistance to four antimicrobial groups		
Total (all four-group combinations)	**10**	**1.9%**
Cefepime + carbapenems + piperacillin-tazobactam + ciprofloxacin	7	1.3%
Aminoglycosides + carbapenems + piperacillin-tazobactam + ciprofloxacin	1	0.2%
Aminoglycosides + cefepime + carbapenems + piperacillin-tazobactam	1	0.2%
Aminoglycosides + cefepime + carbapenems + ciprofloxacin	1	0.2%
Resistance to five antimicrobial groups		
Total (all five-group combinations)	**7**	**1.3%**
Aminoglycosides + cefepime + carbapenems + piperacillin-tazobactam + ciprofloxacin	7	1.3%

sa. Following increasing resistance rates between 2010 and 2015 for all antibiotics, non-susceptibility rates stabilized or even slightly decreased thereafter.

Decreasing resistance trends between 2016 and 2018 were observed in the EU/EEA for aminoglycosides, ceftazidime, piperacillin-tazobactam and carbapenems, while resistance to fluoroquinolones remained stable during this period [2]. In Switzerland in 2019, non-susceptibility rates were around 13% for carbapenems, around 10% for piperacillin-tazobactam, around 9% for aminoglycosides and ciprofloxacin, and were lowest for ceftazidime and cefepime (8%). These rates are mostly lower than those observed in neighboring countries such as France and Italy. Swiss regional data are given in Table 7. e, data on co-resistance in Table 7. f and Figure 7. g.

Figure 7. f: Non-susceptibility rates of invasive *Pseudomonas aeruginosa* isolates in humans from 2010 to 2019.

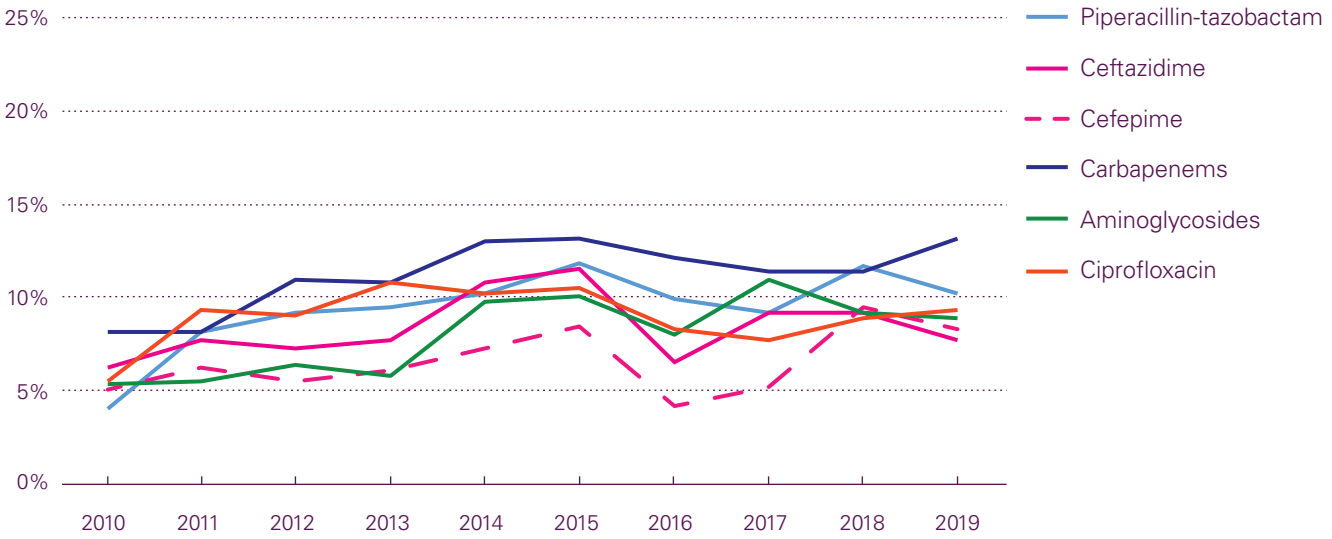
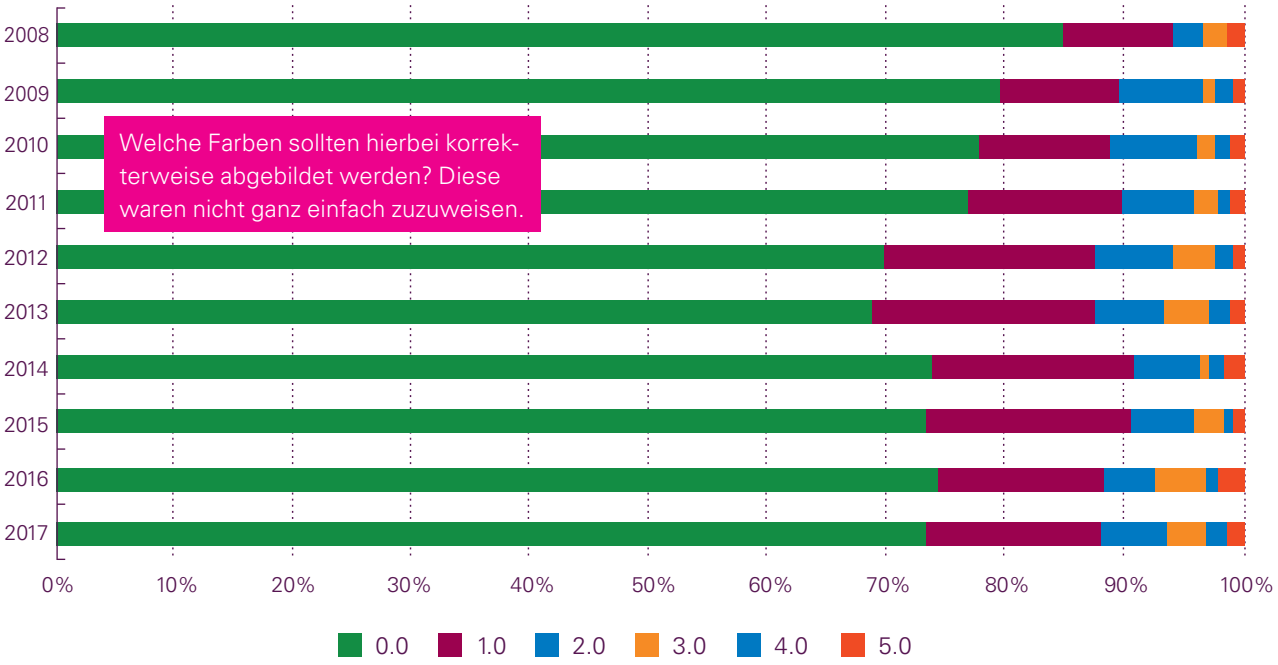


Figure 7. g: Multiresistance in invasive *Pseudomonas aeruginosa* isolates in humans between 2010 and 2019 (for details refer to Table 7. f).



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 resistance trends on the genus level, in accordance with the European resistance networks EARS-Net and CAESAR.

Acinetobacter spp. infections are an important concern regarding hospital-acquired infections in immunocompromised patients. They can cause respiratory, urinary, wound infections and septicemia. Meningitis has also been reported.

Table 7. g: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans for 2019. Due to small numbers, non-susceptibility rates for southern Switzerland are not shown.

Acinetobacter spp.											2019
	West		North–East		South		Total			Trend	
Antimicrobial	n	%	n	%	n	%	n	%	95% CI	4y	10y
Carbapenems[1]	11	–	50	6.0%	5	–	66	4.5%	1.9–7.1	–	–
Aminoglycosides	11	18.2%	49	10.2%	5	–	65	10.8%	7.0–14.6	–	–
Trimethoprim-sulfamethoxazole	7	28.6%	46	6.5%	5	–	58	8.6%	4.9–12.3	↓	↓
Ciprofloxacin	10	60.0%	48	50.0%	5	40.0%	63	50.8%	44.5–57.1	↑	↑

[1] Carbapenems: imipenem, meropenem
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.
Trends were modelled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the correspondent outcome (increase, decrease).

Figure 7. h: Non-susceptibility rates of invasive *Acinetobacter* spp. isolates in humans between 2010 and 2019.

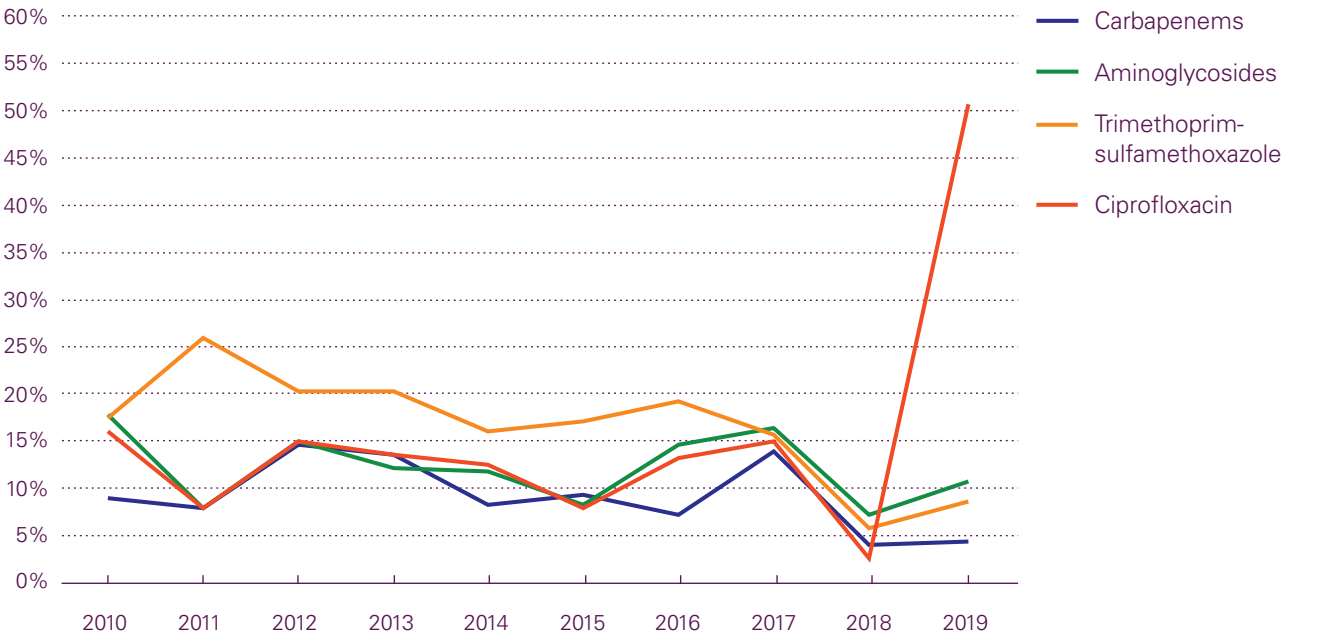


Table 7. h: Non-susceptibility combinations in invasive *Acinetobacter* spp. isolates in humans in 2019. Only isolates tested against all three antibiotic groups (aminoglycosides, ciprofloxacin and carbapenems) were considered (n = 61/67 [91.0%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**29**	**47.5%**
Single resistance (to indicated antimicrobial group)		
Total (all single resistance types)	**26**	**42.6%**
Ciprofloxacin	26	42.6%
Resistance to two antimicrobial groups		
Total (all two-group combinations)	**4**	**6.6%**
Carbapenems + ciprofloxacin	1	1.6%
Aminoglycoside + ciprofloxacin	3	4.9%
Resistance to three antimicrobial groups		
Total (all three-group combinations)	**2**	**3.3%**
Aminoglycoside + carbapenems + ciprofloxacin	2	3.3%

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.

With the new EUCAST clinical breakpoint definition, version 9.0 from 1.1.2019, a broad intermediate category was newly introduced for ciprofloxacin, to reflect that higher dosing may be needed for the treatment of these infections. This led to an artificial increase in the ciprofloxacin non-susceptibility rates as reported in our tables and figures. When considering resistance only, ciprofloxacin-resistance is stable, with 10.7% in 2010 and 6.3% in 2019. In general, non-susceptibility rates are higher in western Switzerland than in north-eastern Switzerland (Table 7. g). Although a north-south gradient in antibiotic resistance can be observed in Europe for nearly all antibiotics, differences are most prominent for A*cinetobacter* spp. In 2018, resistance rates ranged from < 5% in northern countries to > 90% in southern countries for all of the antibiotics tested. The EU/EEA population means in 2018 were 32% for carbapenems and aminoglycosides, and 36% for fluoroquinolones [2]. Taking into consideration the changing breakpoints over time, it is probable that no significant trends are observed in Switzerland from 2010 to 2019. We performed a detailed analysis for carbapenem resistance, showing stable resistance rates from 2005 to 2016 [5]. A detailed analysis of other antibiotics has not been performed so far. Details on multiresistances are given in Table 7. h and Figure 7. i.

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. Serotyping (to survey the impact of vaccinations on serotype distribution) and antibacterial resistance testing is performed for all isolates. Results of the latter are then sent to anresis.ch. However, in this report we analyzed data from the ANRESIS database, which may differ slightly from data of the National Reference Center for invasive *S. pneumoniae*. Penicillin-susceptible isolates (PSSP) were considered as ceftriaxone-susceptible, even if not tested.

In 2019, 6.7% of all isolates were penicillin non-susceptible (PNSP, Table 7. i). In comparison, PNSP rates in EU/EEA countries in 2020 ranged from 0.1% in Belgium to 40% in Romania. However, an exact comparison with other countries is difficult, as 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 (29.1%) than in Italy (9.2%) and Germany (5.3%) [2]. These differences are mirrored

Figure 7. i: Multiresistance in invasive *Acinetobacter* spp. isolates in humans between 2010 and 2019 (for details refer to Table 7. h).

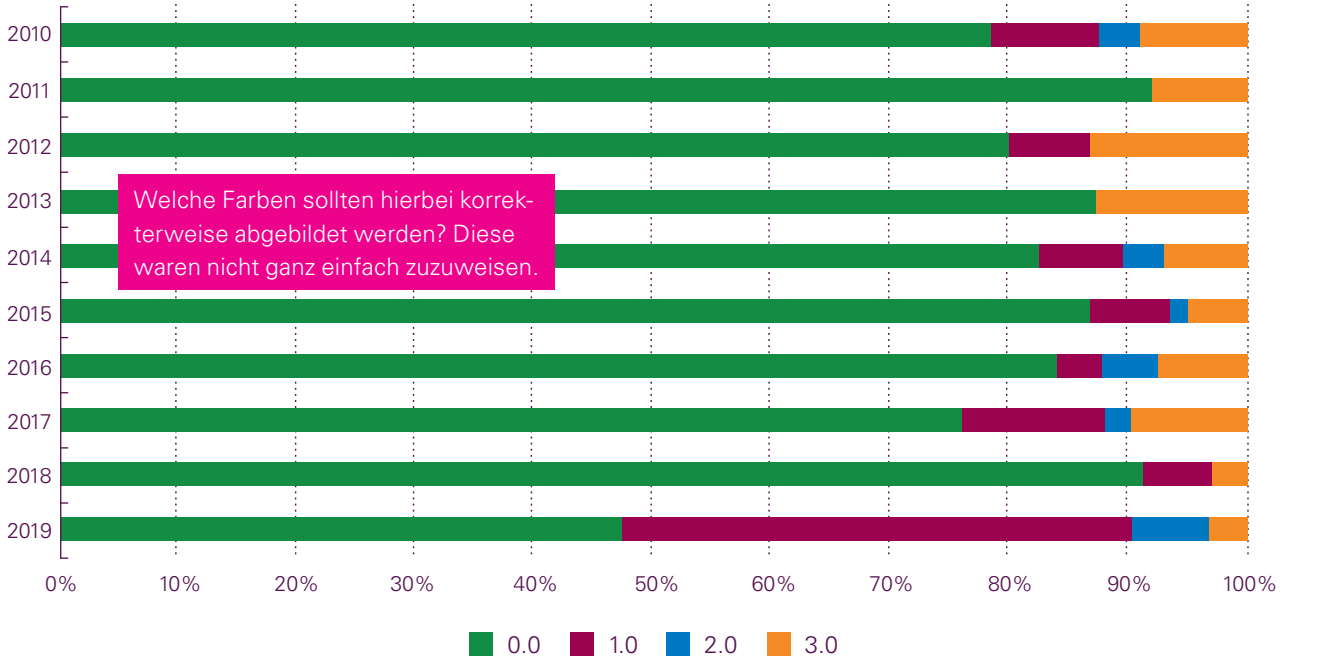


Table 7. i: Non-susceptibility rates of invasive *Streptococcus pneumoniae* isolates in humans in 2019.

Streptococcus pneumoniae											2019
	West		North–East		South		Total			Trend	
Antimicrobial	n	%	n	%	n	%	n	%	95% CI	4y	10y
Penicillin[1]	124	11.3%	544	5.1%	38	13.2%	706	6.7%	5.8–7.6	–	–
Ceftriaxone[2]	124	0.0%	544	0.9%	38	0.0%	706	0.7%	0.4–1.0	–	↓
Trimethoprim-sulfamethoxazole	69	10.1%	262	6.9%	38	7.9%	369	7.6%	6.2–9.0	–	↓
Erythromycin	126	10.3%	379	7.1%	38	13.2%	543	8.3%	7.1–9.5	–	↓
Levofloxacin	101	2.0%	357	0.8%	38	0.0%	496	1.0%	0.6–1.4	–	↓

[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
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.
Trends were modelled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the correspondent outcome (increase, decrease).

Figure 7. j: Non-susceptibility rates in invasive PSSP (penicillin-susceptible *Streptococcus pneumoniae*) and PNSP (penicillin non-susceptible *Streptococcus pneumoniae*) isolates in humans in 2019

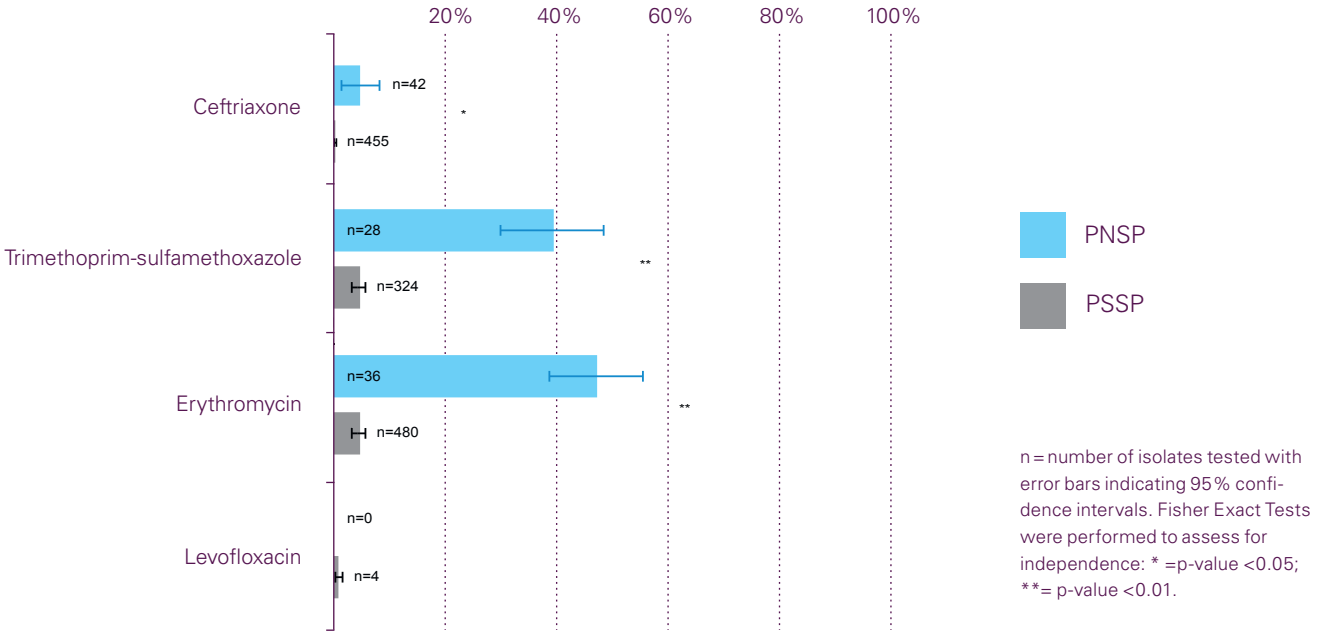
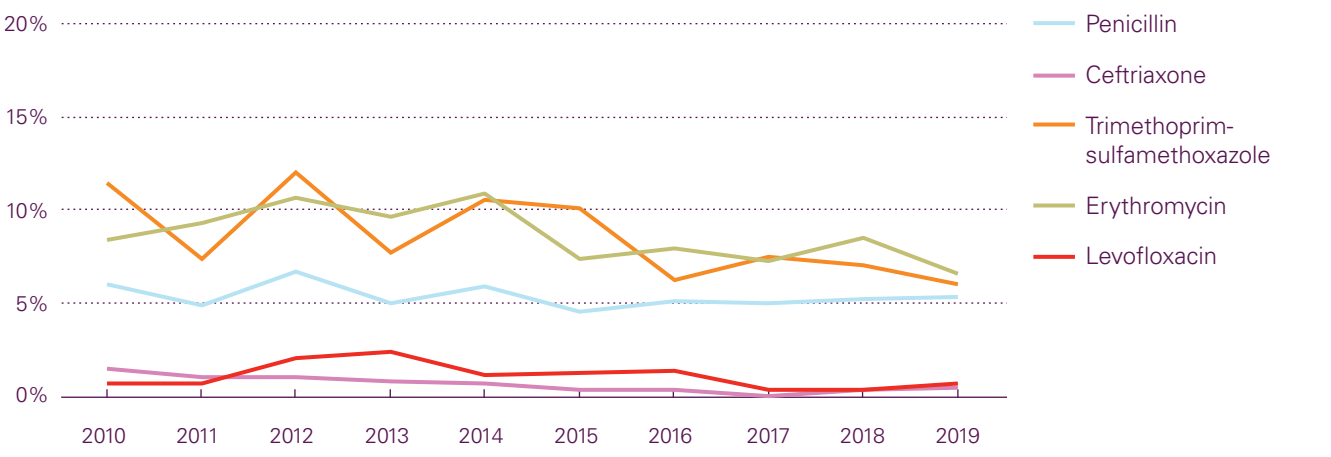


Figure 7. k: Non-susceptibility rates of invasive *Streptococcus pneumoniae*.



within Switzerland, with higher PNSP rates in the French and Italian speaking parts 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 1% in Switzerland in 2019, with a decreasing trend since 2013 (maximum 3.1%). As shown in Figure 7. j, resistance is higher in PNSP than in PSSP for ceftriaxone, trimethoprim-sulfamethoxazole and erythromycin.

Over the last ten years, significant decreases in antibiotic resistance in *S. pneumoniae* were observed for ceftriaxone, trimethoprim-sulfamethoxazole, erythromycin and levofloxacin (Table 7. i, Figure 7. k). This could at least in part be attributed to a vaccine-related decrease of the intrinsically more resistant serotypes [6].

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, they can also cause serious infections, mainly in hospital settings, such as urinary tract infections, bacteremia, endocarditis, and intra-abdominal infections in seriously ill patients and immunocompromised hosts. The vast majority of enterococcal infections are caused by *Enterococcus faecalis* and *Enterococcus faecium*.

While E. faecalis isolates still remain susceptible to many antibiotics, including aminopenicillins, E. faecium isolates are usually resistant to aminopenicillins. In addition, *E. faecium* shows higher resistance rates to aminoglycosides as 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 9.9 % in Switzerland versus 27.1% in Europe) and has significantly decreased during the last ten years. A decrease in gentamicin HLR in *E. faecalis* was also observed in one third of all European countries [2]. In contrast to the United States, vancomycin resistance was still rare in Switzerland and far below the EU/ EEA average of 17.3% in *E. faecium* in 2018 [2]. However, we have noted a significant increase in vancomycin resistant *E. faecium* during the last years, due to a regional/national outbreak associated with the spread of clone ST769 [7–8]. Surveillance of enterococci, particularly vancomycin-resistant enterococci (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 now largely 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 to detect *S. aureus* methicillin/oxacillin resistance is discouraged by EUCAST and CLSI guidelines. 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 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. MRSA are resistant to all betalactam, including combinations with betalactam inhibitors (e.g. amoxicillin-clavulanic acid). In 2019, the MRSA rate in Switzerland was 3.4%, with slightly higher rates in southern and western Switzerland (Table 7. k). This rate is far below the European average of 16.4%, but above MRSA rates in Northern countries such as Norway (0.9%), the Netherlands (1.2%), Denmark (1.7%), Sweden (1.9%) and Finland (2.0%) in 2018 [2]. 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 wound 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. [9], MRSA rates and, similarly, non-susceptibility rates to most other antibiotics as well, are nowadays higher in the ambulatory skin infection setting (7.2%) than in bacteremia (3.4%) (Figure 7. m). While MRSA rates in hospitals have been decreasing since several years, community MRSA (cMRSA) infections are increasing [9]. 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 be treated by a surgical procedure only, and do not need antibiotic therapy.

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 8.5% in 2010 to 3.4% in 2019. Decreasing trends from 2016 to 2018 were also reported in almost

Table 7. j: Non-susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans in 2019.

Enterococcus faecalis											2019
	West		North–East		South		Total			Trend	
Antimicrobial	n	%	n	%	n	%	n	%	95% CI	4y	10y
Aminopenicillins	158	0.0%	489	0.0%	48	0.0%	695	0.0%	0.0–0.0	–	–
Gentamicin HLR[1]	92	12.0%	284	9.2%	48	10.4%	424	9.9%	8.4–11.4	↓	↓
Streptomycin HLR[1]	2	0.0%	90	21.1%	0	0.0%	92	20.7%	16.5–24.9	–	↓
Tetracycline	52	59.6%	51	84.3%	0	0.0%	103	71.8%	67.4–76.2	–	–
Vancomycin	153	0.0%	543	0.6%	48	0.0%	744	0.4%	0.2–0.6	–	–
Linezolid	108	0.9%	258	0.0%	48	0.0%	414	0.2%	0.0–0.4	–	↓

Enterococcus faecium											2019
	West		North–East		South		Total			Trend	
Antimicrobial	n	%	n	%	n	%	n	%	95% CI	4y	10y
Aminopenicillins	78	74.4%	243	70.4%	20	95.0%	341	72.7%	70.3–75.1	↓	↓
Gentamicin HLR[1]	46	39.1%	186	22.6%	20	40.0%	252	27.0%	24.2 - 29.8	–	↓
Streptomycin HLR[1]	1	0.0%	65	61.5%	0	0.0%	66	60.6%	54.6 - 66.6	–	↓
Tetracycline	29	41.4%	34	61.8%	0	0.0%	63	52.4%	46.1–58.7	–	↑
Vancomycin	78	0.0%	305	1.6%	20	10.0%	403	1.7%	1.1–2.3	–	↑
Linezolid	57	0.0%	145	0.0%	20	0.0%	222	0.0%	0.0–0.0	–	–

[1] HLR=high-level resistance
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.
Trends were modelled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the correspondent outcome (increase, decrease).

Figure 7. I: Non-susceptibility rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans between 2010 and 2019 (HLAR = High-level aminoglycoside resistance).

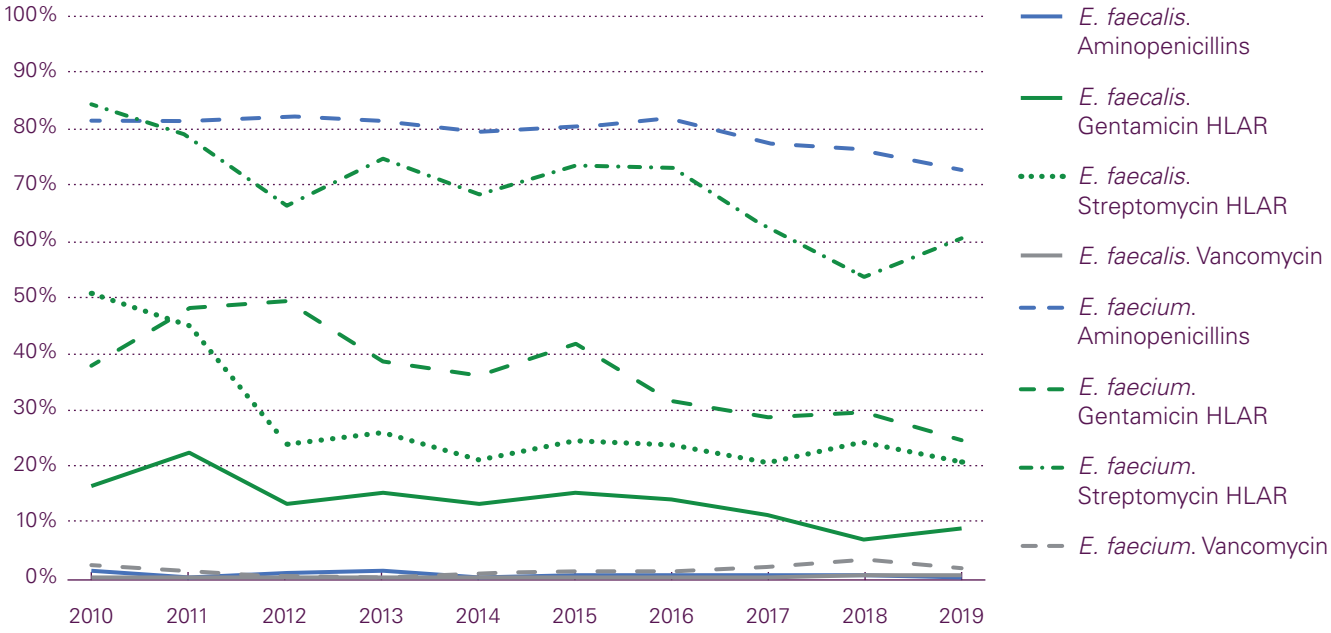
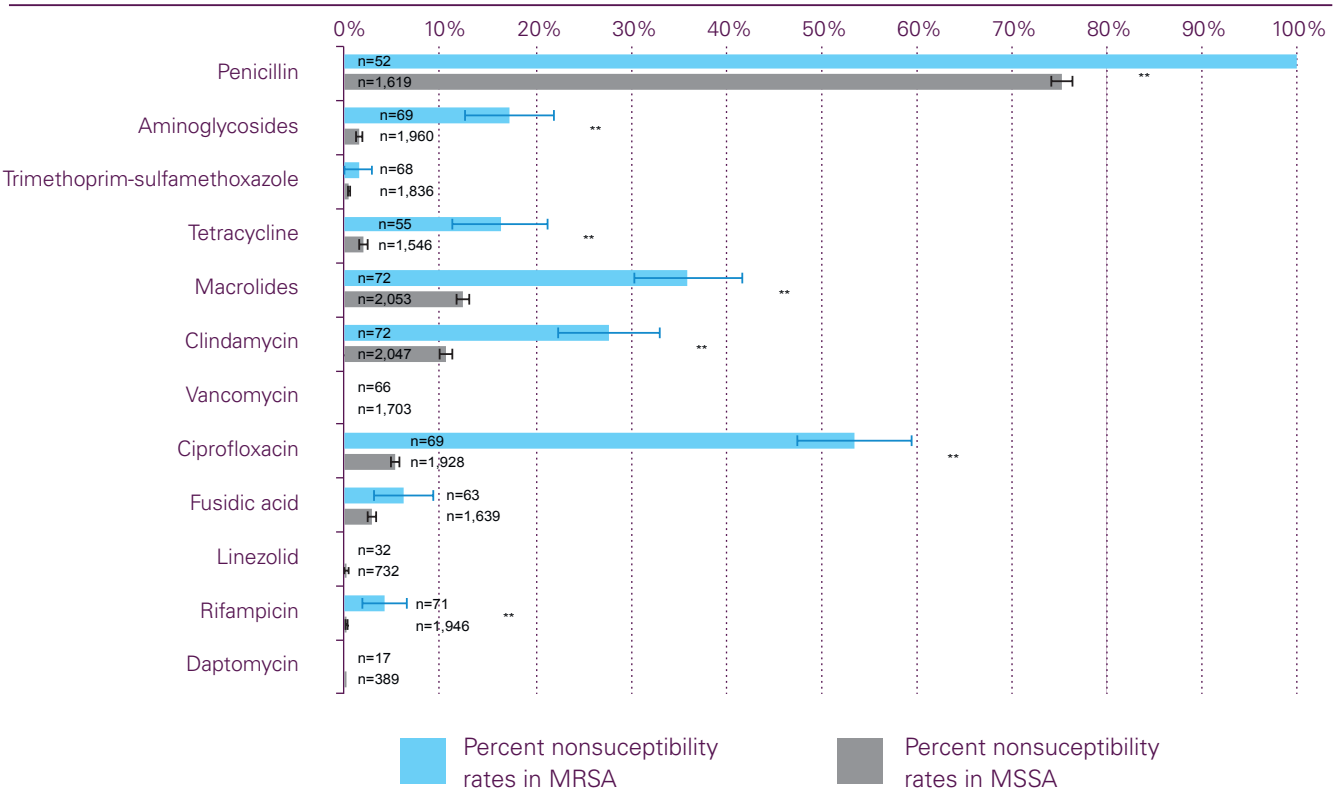


Table 7. k: Susceptibility rates of invasive *Staphylococcus aureus* isolates in humans in 2019.

Staphylococcus aureus											2019
	West		North–East		South		Total			Trend	
Antimicrobial	n	%	n	%	n	%	n	%	95% CI	4y	10y
Penicillin	307	68.1%	1,304	77.7%	116	80.2%	1,727	76.1%	75.1–77.1	–	–
MRSA	432	5.1%	1,618	2.7%	77	7.8%	2,127	3.4%	3.0–3.8	–	↓
Aminoglycosides	444	2.0%	1,523	2.1%	116	1.7%	2,083	2.1%	1.8–2.4	–	↓
Trimethoprim-sulfamethoxazole	447	0.9%	1,398	0.6%	116	0.9%	1,961	0.7%	0.5–0.9	–	–
Tetracycline	297	1.7%	1,241	2.8%	116	0.9%	1,654	2.5%	2.1–2.9	–	–
Macrolides	446	19.3%	1,618	11.6%	116	16.4%	2,180	13.4%	12.7–14.1	–	–
Clindamycin	446	18.2%	1,613	9.5%	116	11.2%	2,175	11.4%	10.7–12.1	↑	–
Vancomycin	405	0.0%	1,305	0.0%	116	0.0%	1,826	0.0%	0.0–0.0	–	–
Ciprofloxacin	371	7.3%	1,566	6.6%	116	10.3%	2,053	6.9%	6.3–7.5	↓	↓
Fusidic acid	362	5.2%	1,275	2.4%	116	1.7%	1,753	3.0%	2.6–3.4	–	–
Linezolid	261	0.4%	504	0.2%	0	0.0%	765	0.3%	0.1–0.5	–	–
Rifampicin	443	0.7%	1,513	0.2%	116	0.0%	2,072	0.3%	0.2–0.4	–	–
Daptomycin	132	0.0%	274	0.4%	4	0.0%	410	0.2%	0.0–0.4	–	–

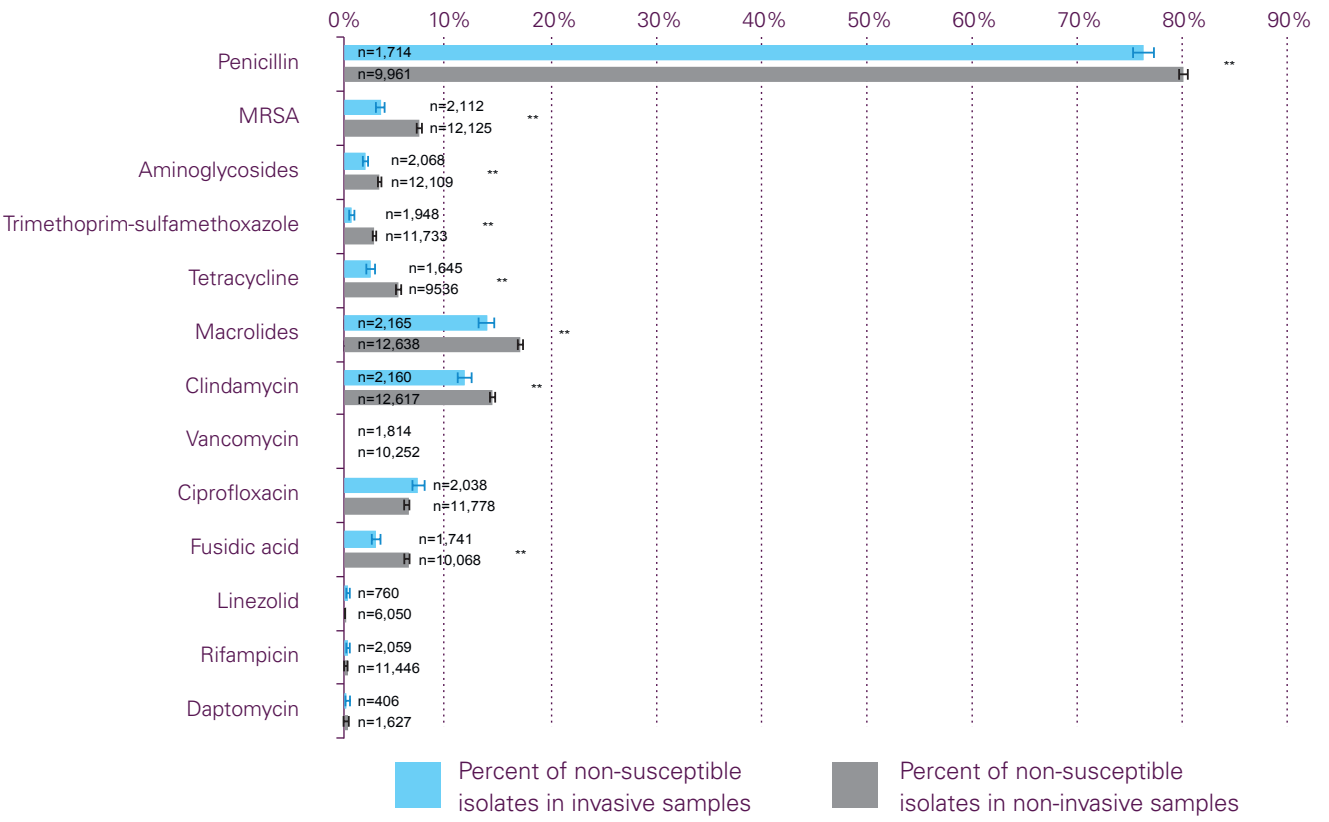
West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions.
95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression.
Trends were modelled with logistic regressions. Arrows represent a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

Figure 7. n: Non-susceptibility rates of invasive MRSA (methicillin-resistant *Staphylococcus aureus*) and MSSA (methicillin-susceptible *Staphylococcus aureus*) isolates in humans in 2019.



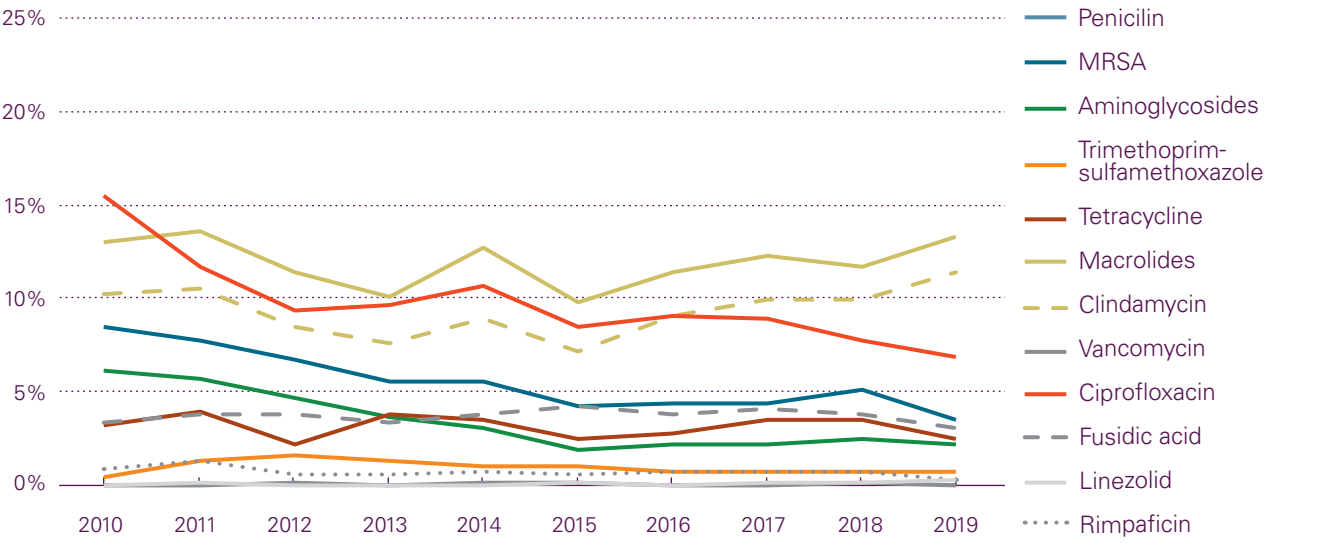
n = number of isolates tested, with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence:
* = p-value <0.05; ** = p-value <0.01.

Figure 7. m: Comparison of non-susceptibility rates of *Staphylococcus aureus* in invasive versus outpatient wound/abscess samples in humans in 2019.



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 2010 and 2019.



one third of all European countries, leading to an overall decrease in the population-weighted mean of EU/EEA states from 19.0% to 16.4% during this time period [2]. 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 and aminoglycosides in *Staphylococcus aureus* isolates (Figure 7. i). After an initial decrease of non-susceptibility rates against macrolides and clindamycin, these rates increased again over the past 4 years back to the levels observed in 2010.

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8

Resistance in zoonotic bacteria from livestock, meat thereof and humans

8 Resistance in zoonotic bacteria from livestock, meat thereof and humans

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

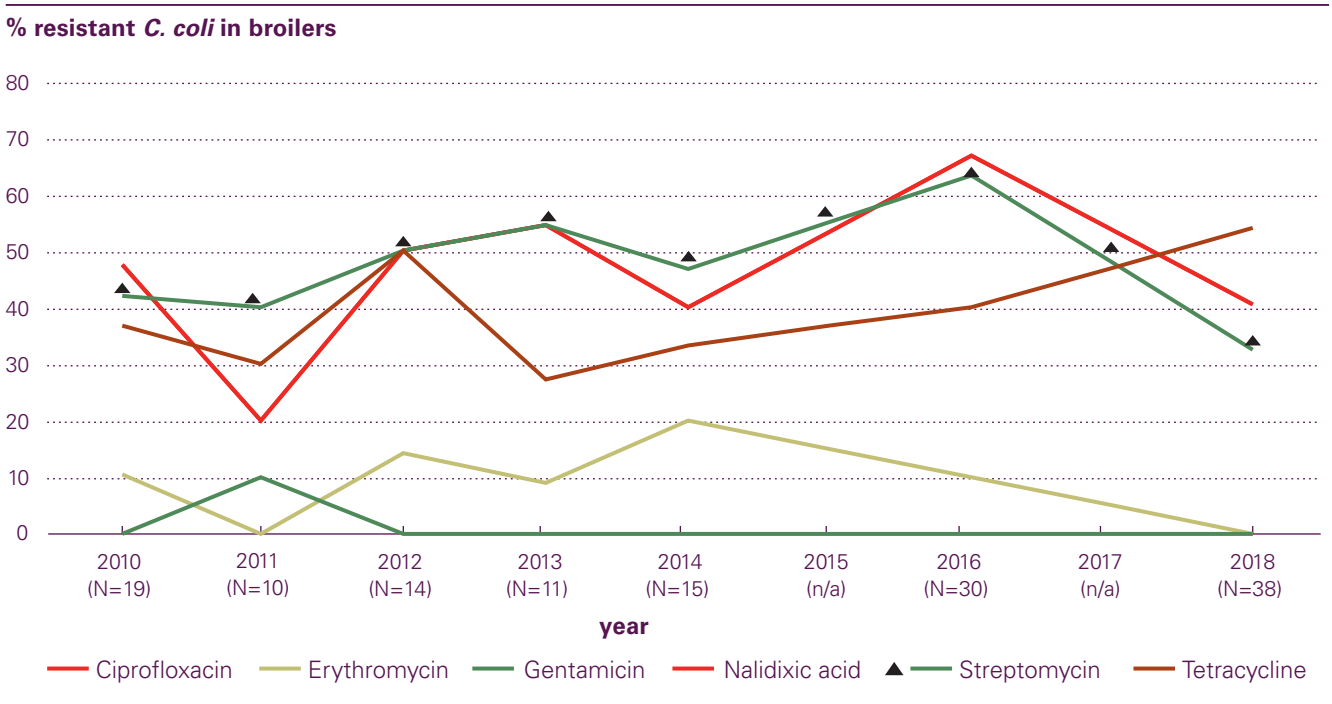
8.1 *Campylobacter* spp.

Campylobacter (C.) jejuni and *C. coli* are responsible for human campylobacteriosis, the most prevalent food-borne zoonosis in Europe, with more than 240.000 reported cases per year [1]. In Switzerland, the healthcare costs for human campylobacteriosis have been valued at approx. 29–45 million euro per year [2]. Campylobacteriosis in humans causes (bloody) diarrhea with dysentery syndrome, including cramps, fever and pain. In contrast to the situation in humans, *C. jejuni* and *C. coli* are found as commensals in the intestine of broilers and *C. coli* in the intestine of pigs [1].

Antibiotic treatment is not crucial in uncomplicated cases of human campylobacteriosis, but treatment may be necessary if the clinical course becomes life threatening. Treatment with antibiotics may include macrolides, such as erythromycin or azithromycin. Fluoroquinolones, such as ciprofloxacin, were also recommended in the past, but resistance rates of *C. jejuni* and *C. coli* against these antibiotic classes are increasing in both human and broiler *Campylobacter* isolates. Hence, fluoroquinolones are no longer propagated as a therapeutical option [1]. In Switzerland, only a few antimicrobials are licensed for treatment of poultry [3]. Some of them, such as ciprofloxacin, are classified as highest-priority critically important antimicrobial substances for humans according to the World Health Organization (WHO) [4].

Fresh raw poultry meat is highly contaminated with *Campylobacter* spp. [1, 5]. Hence, incorrect handling of raw poultry meat and the consumption of undercooked contaminated poultry meat are the main causes of human campylobacteriosis [1]. Meat from cattle and pigs and contact with pets are of lesser importance. Source attribution studies from 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) [6, 7].

Figure 8. a: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. coli* from broilers between 2010 and 2018 (N = total number of tested isolates; values for 2015 and 2017 interpolated [n/a]).



Hence, monitoring of antimicrobial resistance (AMR) of these pathogens is of great importance for human public health.

This chapter includes antimicrobial resistance rates of *C. jejuni* and *C. coli* in broilers and chicken meat from 2018 and *C. coli* in fattening pigs from 2019. Moreover, antimicrobial resistance rates from human *Campylobacter* spp. are shown.

8.1.1 *Campylobacter* spp. in broilers

In 2018, a random sample of 642 broiler flocks was examined at slaughter using pooled cecal samples (5 pooled samples per flock). *C. jejuni* was identified in 142 samples (22.1%) and *C. coli* in 38 samples (5.9%). AMR tests were performed on 138 *C. jejuni* and 37 *C. coli* strains. Antimicrobial resistance testing was performed against aminoglycosides, fluoroquinolones, macrolides and tetracyclines.

High levels of fluoroquinolone resistance were detected in *C. jejuni* (45.7%), as well as in *C. coli* (40.5%) (Figure 8. a, Figure 8. b). In both species, a decreasing trend was observed compared to 2016. Moreover, in *C. coli* a high level of tetracycline resistance was found (54.1%), whereas for *C. jejuni* the resistance rate to tetracycline was lower (30.4%). Almost one third (32.4%) of all *C. coli* isolates were resistant to streptomycin, but not to gentamicin. In contrast, only 2.9% of all *C. jejuni* were resistant to streptomycin. Very low levels of macrolide resistance (erythromycin) were found in *C. jejuni* (n=5, 3.6%) and none in *C. coli* (Figure 8. a, Figure 8. b).

Overall, 45.7% of *C. jejuni* and 18.9 % of *C. coli* displayed no resistance to any antimicrobial substances tested (Table 8. a, Table 8. b). In *C. coli*, 17 isolates (46.0%) and in *C. jejuni* 40 isolates (29.0%) were resistant to just one antibiotic class, mainly to tetracyclines in *C. coli* and fluoroquinolones in *C. jejuni*. Nine out of the 37 isolates (24.3%) of *C. coli* and 32 out of 138 (23.2%) of the *C. jejuni* isolates showed resistance to two antibiotic classes. In *C. jejuni*, almost all expressed co-resistance against fluoroquinolones and tetracyclines. In *C. coli*, various dual combinations occurred. Four isolates of *C. coli* (10.8%) and two of the *C. jejuni* (1.5%) were resistant to three antibiotic classes. Finally, one single isolate (0.7%) of *C. jejuni* was resistant to four antibiotic classes (Table 8. a, Table 8. g). Overall, *C. coli* isolates showed more antimicrobial resistance than *C. jejuni* isolates (Figure 8. c, Figure 8. d).

The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.8.1 and Table II.8.2).

Due to remarkable differences in resistance rates of human isolates throughout Switzerland, the region of the flocks was integrated in the analyses of antimicrobial resistance in livestock for the first time. Because of the very low numbers of isolates, statistically significant conclusions could not yet be drawn (Table 8. c).

Regarding *C. coli*, the central part of Switzerland showed a higher number of susceptible isolates than the south-western and eastern regions. On the other hand, resistance rates against aminoglycosides and tetracyclines were highest in the central region. For *C. jejuni*, the number of fully suscep-

Figure 8. b: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. jejuni* from broilers between 2010 and 2018 (N = total number of tested isolates; values for 2015 and 2017 interpolated [n/a]).

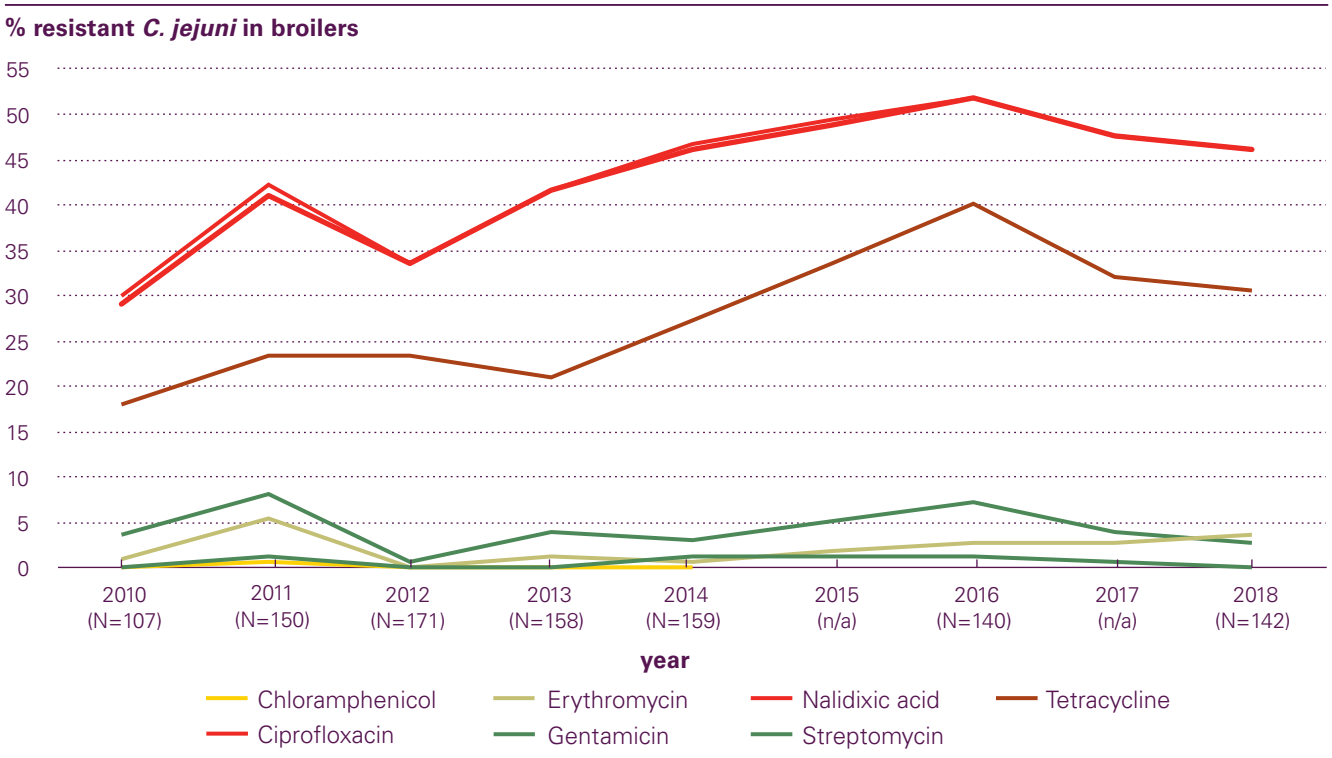


Table 8. a: Non-susceptibility combinations in commensal *C. coli* in broilers in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**37**	
Number of Resistances: 0	**7**	**18.9%**
–	7	100.0%
Number of Resistances: 1	**17**	**45.9%**
Aminoglycosides	3	17.6%
Fluoroquinolones	6	35.3%
Tetracyclines	8	47.1%
Number of Resistances: 2	**9**	**24.3%**
Aminoglycosides – Fluoroquinolones	1	11.1%
Aminoglycosides – Tetracyclines	4	44.4%
Fluoroquinolones – Tetracyclines	4	44.4%
Number of Resistances: 3	**4**	**10.8%**
Aminoglycosides – Fluoroquinolones – Tetracyclines	4	100.0%

Aminoglycosides: Streptomycin, Gentamicin, Fluoroquinolones, Nalidixic acid, Ciprofloxacin, Tetracyclines, Tetracycline, Macrolides, Erythromycin

Table 8. b: Non-susceptibility combinations in commensal *C. jejuni* in broilers in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**138**	
Number of Resistances: 0	**63**	**45.7%**
–	63	100.0%
Number of Resistances: 1	**40**	**29.0%**
Aminoglycosides	1	2.5%
Fluoroquinolones	31	77.5%
Macrolides	1	2.5%
Tetracyclines	7	17.5%
Number of Resistances: 2	**32**	**23.2%**
Fluoroquinolones – Tetracyclines	29	90.6%
Macrolides – Tetracyclines	3	9.4%
Number of Resistances: 3	**2**	**1.4%**
Aminoglycosides – Fluoroquinolones – Tetracyclines	2	100.0%
Number of Resistances: 4	**1**	**0.7%**
Aminoglycosides – Fluoroquinolones – Macrolides – Tetracyclines	1	100.0%

Aminoglycosides: Streptomycin, Gentamicin, Fluoroquinolones, Nalidixic acid, Ciprofloxacin, Tetracyclines, Tetracycline, Macrolides, Erythromycin

tible isolates was highest in the central region. Moreover, fluoroquinolone resistance rates were lower than in other regions. Possibly, with more data in the future, the significance of the existing differences in resistance rates between regions in Switzerland will be substantiated.

8.1.2 *Campylobacter* in fattening pigs

In 2019, a random sample of 350 fattening pigs was investigated at slaughter using single cecal samples per slaughter batch. *C. coli* was isolated from 229 out of 350 samples (65.4%). All isolates were subjected to susceptibility testing. The same antibiotics as for broilers were tested.

In fattening pigs, the highest level of antimicrobial resistance was identified for the aminoglycoside streptomycin (84.7%), followed by very high resistance rates to tetracyclines (63.3%) and fluoroquinolones (55.9%) (Figure 8. e). In contrast, resistance rates to macrolides were low (3.9%). For aminoglycosides, the picture was not uniform, as resistance to gentamicin – in contrast to streptomycin – did not occur.

Figure 8. c: Resistance pattern in *C. coli* from broilers in 2018.

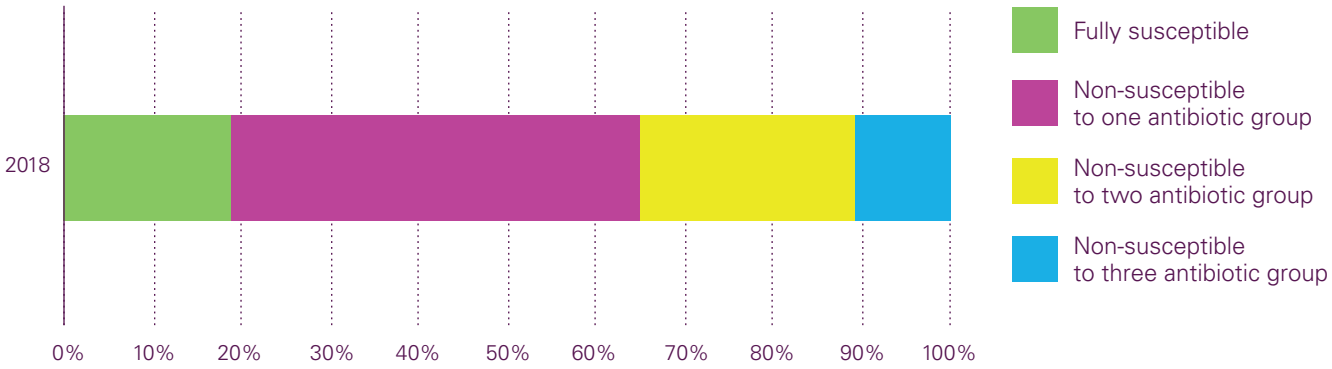


Figure 8. d: Resistance pattern in *C. jejuni* from broilers in 2018.

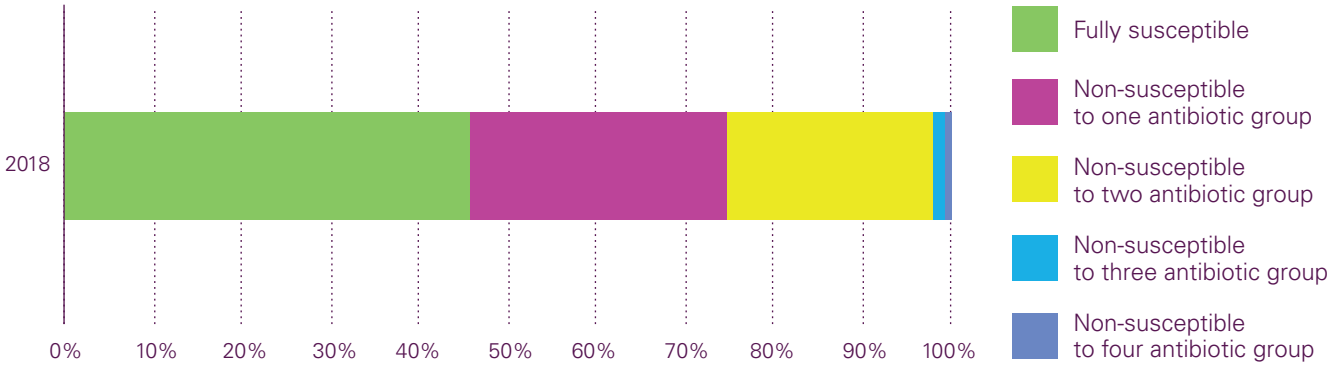


Table 8. c: Non-susceptibility rates in commensal *C. coli* and *C. jejuni* from broilers in 2018 in different regions in Switzerland.

Campylobacter coli	**(n=37)**								**2018**
Antimicrobial	**South-West**		**Center**		**East**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	0	0.00%	6	16.20%	1	2.70%	7	18.90%	9.5–34.2
Aminoglycosides	4	10.80%	7	19.80%	1	2.70%	12	32.40%	16.9–48.5
Fluoroquinolones	5	13.50%	5	13.50%	5	13.50%	15	40.50%	26.3–56.5
Tetracyclines	7	19.80%	9	24.30%	4	10.80%	20	54.10%	38.4–69.0
Macrolides	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0.0–9.4
Campylobacter jejuni	**(n=138)**								**2018**
Antimicrobial	**South-West**		**Center**		**East**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	19	13.40%	30	21.10%	14	9.90%	63	45.70%	37.6–54.0
Aminoglycosides	2	1.40%	1	0.70%	1	0.70%	4	2.90%	1.1–7.2
Fluoroquinolones	27	19.00%	23	16.20%	13	9.20%	63	45.70%	37.6–54.0
Tetracyclines	17	12.00%	15	10.60%	10	7.00%	42	30.40%	23.4–38.6
Macrolides	2	1.40%	1	0.70%	2	0.70%	5	3.60%	1.6–8.2

South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI). 95% CI: 95% confidence interval, Aminoglycosides: Streptomycin, Gentamicin; Fluoroquinolones: Nalidixic acid, Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin

There are no significance changes of resistance rates compared to 2017. A constant high level of resistance was found for tetracyclines and streptomycin over time, whereas the high level of fluoroquinolone resistance (55.9%) has increased over the last ten years. In 2019, macrolide resistance was only found in a small number of samples in conjunction with other resistances.

Out of the 229 isolates, only 9 (3.9%) were fully susceptible to all tested antibiotic classes (Table 8. d). Of the 229 isolates, 55 were resistant to one antibiotic class, which corresponds to a prevalence of 24%. Mainly resistance to streptomycin was expressed. One third (34.1%) of the isolates were resistant to two antibiotic classes, mainly co-resistance to streptomycin and tetracyclines or fluoroquinolones. Eighty-three samples were resistant to three antibiotic classes (36.2%), nearly all showed co-resistance against aminoglycosides, tetracyclines and fluoroquinolones. Finally, four isolates were resistant to four antibiotic classes, i. e. co-resistance to aminoglycosides, fluoroquinolones, macrolides and tetracyclines (Table 8. d).

The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.8.3).

Overall, *C. coli* isolates from fattening pigs showed less fully susceptible isolates than *C. coli* isolates from broilers (Figure 8. c, Figure 8. f).

As the population of pigs is very low in the south-western region, porcine *C. coli* isolates from this region were rare in comparison to the other regions. For the central and the eastern regions, no clear differences in resistance rates were observed (Table 8. e). Possibly, with more data in the future, the significance of the existing differences in resistance rates between regions in Switzerland will be substantiated.

8.1.3 *Campylobacter* spp. in chicken meat

In 2018, *C. jejuni*/coli was analyzed for the first time within the antimicrobial resistance monitoring program. Three hundred and twelve (312) samples of retail chicken meat (209 of Swiss origin and 103 of foreign origin) were investigated for the presence of *C. jejuni*/coli and antibiotic resistance of these isolates. From 312 samples, 24 *C. coli* and 116 *C. jejuni* were isolated, corresponding to a prevalence of 7.7% for *C. coli* and 37.2% for *C. jejuni*. Of the Swiss meat samples, 38.8% were positive (4.8% of *C. coli* and 34% of *C. jejuni*). In meat samples from abroad, the prevalence was slightly higher (13.6% of *C. coli* and 43.7% of *C. jejuni*) (Table 8. f).

Resistance was assessed for 112 *C. jejuni* and the 24 *C. coli* isolates. High to very high resistance was detected for fluoroquinolones, i.e. 75% of *C. coli* and 58.9% of *C. jejuni* (Table 8. g). Low and high resistance levels were found for aminoglycosides, 3.6% for *C. jejuni* and 37.5% for *C. coli*. Regarding tetracycline resistance, high and very high resis-

Table 8. d: Non-susceptibility combinations in commensal *C. coli* from fattening pigs in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**229**	
Number of Resistances: 0	**9**	**3.9%**
–	9	100.0%
Number of Resistances: 1	**55**	**24.0%**
Aminoglycosides	37	67.3%
Fluoroquinolones	14	25.5%
Tetracyclines	4	7.3%
Number of Resistances: 2	**78**	**34.1%**
Aminoglycosides – Fluoroquinolones	20	25.6%
Aminoglycosides – Macrolides	2	2.6%
Aminoglycosides – Tetracyclines	48	61.5%
Fluoroquinolones – Macrolides	2	2.6%
Fluoroquinolones – Tetracyclines	6	7.7%
Number of Resistances: 3	**83**	**36.2%**
Aminoglycosides – Fluoroquinolones – Tetracyclines	82	98.8%
Aminoglycosides – Macrolides – Tetracyclines	1	1.2%
Number of Resistances: 4	**4**	**1.7%**
Aminoglycosides – Fluoroquinolones – Macrolides – Tetracyclines	4	100.0%

Aminoglycosides: Streptomycin, Gentamicin; Fluoroquinolones: Nalidixic acid, Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin

Table 8. e: Non-susceptibility rates in commensal *C. coli* a from fattening pigs in 2019 in different regions in Switzerland.

Campylobacter coli **(n=229)**									**2019**
Antimicrobial	**South-West**		**Center**		**East**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	0	0.00%	6	2.60%	3	1.30%	9	3.90%	2.1–7.3
Aminoglycosides	9	3.90%	81	35.40%	90	39.30%	180	84.70%	79.5–88.8
Fluoroquinolones	6	2.60%	56	24.40%	54	23.60%	116	55.90%	49.4–62.2
Tetracyclines	5	2.20%	64	28.00%	61	26.60%	130	63.30%	56.9–69.3
Macrolides	0	0.00%	4	1.70%	3	1.30%	7	3.90%	2.1–7.3

South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI). 95% CI: 95% confidence interval, Aminoglycosides: Streptomycin, Gentamicin; Fluoroquinolones: Nalidixic acid, Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin

Table 8. f: Number of *C. jejuni/coli* positive samples by origin of chicken meat in 2018.

Origin	**No. of samples**	**No. of *C. coli* positive samples (%)**	**No. of *C. jejuni* positive samples (%)**
Germany	36	2	6
Hungary	26	6	14
Slovenia	31	3	22
France	9	3	3
unknown	1	0	0
Total foreign countries	**103**	**14 (13.6%)**	**45 (43.7%)**
Switzerland	**209**	**10 (4.8%)**	**71 (34.0%)**

Figure 8. e: Trends in ciprofloxacin, erythromycin, gentamicin, nalidixic acid, streptomycin and tetracycline resistance in *C. coli* from fattening pigs between 2010 and 2019 (N= total number of tested isolates; values for 2014, 2016 and 2018 are interpolated [n/a]).

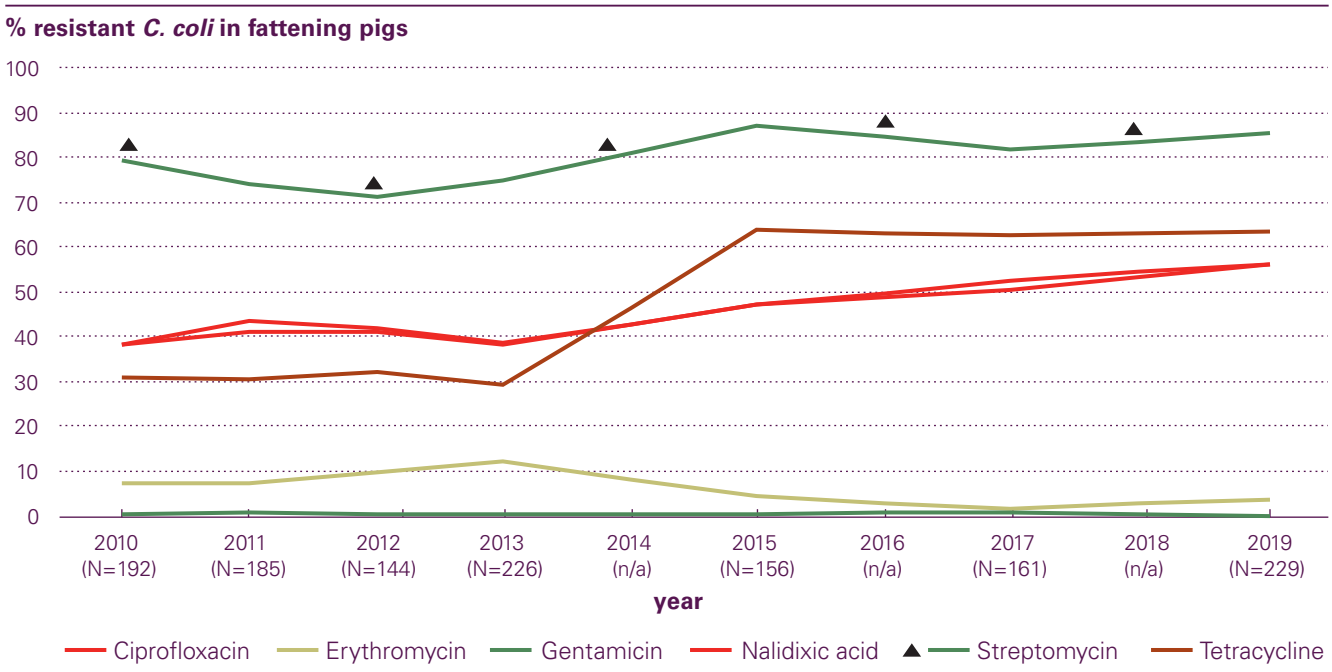


Figure 8. f: Resistance pattern in *C. coli* from fattening pigs in 2019.

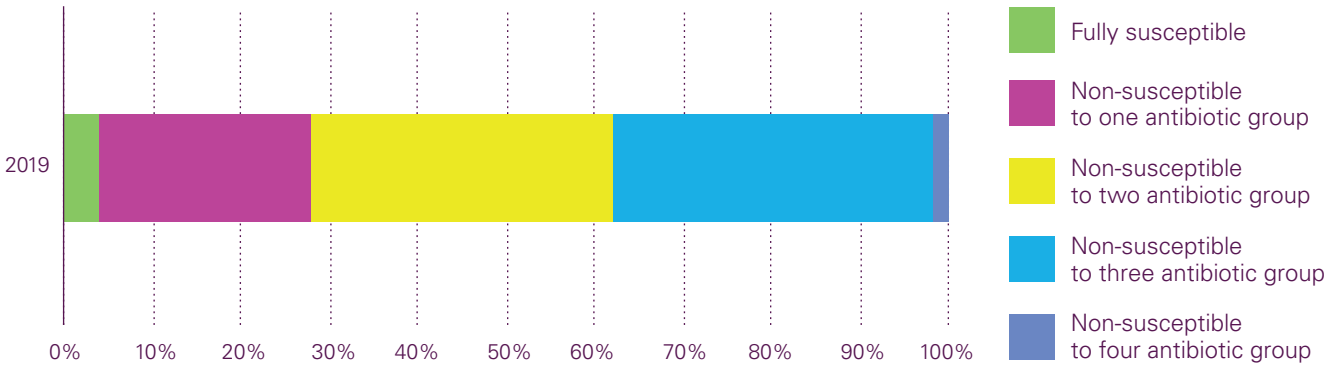


Table 8. g: Antimicrobial resistance in *C. coli* and *C. jejuni* from chicken meat in 2018.

2018	*C. coli* (n=24)			*C. jejuni* (n=112)		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ciprofloxacin	18	75.0%	55.1–88.0	66	58.9%	49.7–67.6
Erythromycin A	0	0.0%	0.0–13.8	1	0.9%	0.2–4.9
Gentamicin	0	0.0%	0.0–13.8	0	0.0%	0.0–3.3
Nalidixic acid	18	75.0%	55.1–88.0	64	57.1%	47.9–65.9
Streptomycin	9	37.5%	21.2–57.3	4	3.6%	1.4–8.8
Tetracycline	14	58.3%	38.8–75.5	39	34.8%	26.6–44.0

Table 8. h: Non-susceptibility combinations in *C. coli* from chicken meat in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**24**	
Number of Resistances: 0	**4**	**16.7%**
–	4	100.0%
Number of Resistances: 1	**5**	**20.8%**
Fluoroquinolones	4	80.0%
Tetracyclines	1	20.0%
Number of Resistances: 2	**9**	**37.5%**
Aminoglycosides – Fluoroquinolones	2	22.2%
Aminoglycosides – Tetracyclines	1	11.1%
Fluoroquinolones – Tetracyclines	6	66.7%
Number of Resistances: 3	**6**	**25.0%**
Aminoglycosides – Fluoroquinolones - Tetracyclines	6	100.0%

Aminoglycosides: Streptomycin, Gentamicin; Fluoroquinolones: Nalidixic acid, Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin

tance was observed, with 34.8% for *C. jejuni* and 58.3% for *C. coli*. Concerning macrolides, none of the isolates were resistant.

Out of 24 isolates of *C. coli* found in chicken meat, 5 (20.8%) isolates were resistant to one antibiotic. Concerning *C. jejuni*, 35 out of 112 (31.3 %) were resistant to one antibiotic (Figure 8. h, Figure 8. i). 37.5% of the 24 *C. coli* isolates and 26.8% of the 112 *C. jejuni* isolates were resistant to two antibiotics. Microbiological resistance to three antibiotic classes was found in 6 isolates (25%) of *C. coli* and 5 isolates of *C. jejuni* (4.5%).

The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.8.4 and Table II.8.5).

8.1.4 *Campylobacter* spp. in humans

A total of 7,306 laboratory-confirmed cases of human campylobacteriosis were reported in 2019 (85.1 per 100,000 inhabitants). In ANRESIS, resistance data were available for 2,768 isolates (37.9%): 2,505 were identified as *C. jejuni* (90.5%) and 263 as *C. coli* (9.5%). Resistance data for 2019 are shown in Table 8. j, trends in figure 8. g. Overall, resistance rates were higher in *C. coli*, and higher for fluoroquinolones (71.5% for *C. coli* vs. 60.8% for *C. jejuni*) than for macrolides (14.6% for *C. coli* vs. 0.8% for *C. jejuni*). Fluoroquinolone-resistance has increased significantly during the last 10 years in *C. jejuni*. Decreasing resistance trends are observed in broilers and, so far, have not been seen in human isolates. A detailed analysis of human samples is provided in the text box by Adrian Egli.

8.1.5 Discussion

Regarding the resistance pattern of *C. coli* in broilers, we have observed a significant decrease of resistance to most of the antibiotics in the last years. In 2018, the resistance rate of ciprofloxacin was 40.5% compared to 66.9% in 2016. For erythromycin, we noticed the same pattern, the antimicrobial susceptibility was 10% in 2016 and no resistant isolates were detected in 2018. A remarkable decrease was also found for streptomycin, decreasing from 66.3% to 32.4%. However, we have observed, since 2013, an increase in tetracycline resistance, i.e. 27.3% in 2013 and 54.1% in 2018.

Concerning the resistance level of *C. jejuni* in broilers, we have also noticed a decrease in the antimicrobial resistance among all tested antibiotics except erythromycin. Between 2012 and 2016, we observed an increase of resistance among many antibiotics such as ciprofloxacin (33.3% in 2012 and 51.4% in 2016), gentamicin (0% in 2012 and 2.9% in 2016), nalidixic acid (33.3% in 2012 and 51.4% in 2016), tetracycline (23.4% in 2012 and 40% in 2016) and erythromycin (0% in 2012, 3.6% in 2018). However, from 2016 onward there was a remarkable decline in the resistance against most antimicrobials. Resistance rates against ciprofloxacin and nalidixic acid decreased to 45.7%, gentamycin to 0%, streptomycin decreased from 7.1% in 2016 to 2.9% in 2018 and finally tetracycline went from 40% in 2016 to 30.4% in 2018.

Fully susceptible isolates were generally fewer in chicken meat (*C. coli* 16.7% and *C. jejuni* 37.5%) than in broilers (C. coli 18.9% and *C. jejuni* 46%). Among *C. jejuni* and *C. coli* isolates recovered from poultry meat, as with isolates from broilers, the highest levels of resistance were noted for ciprofloxacin, nalidixic acid and tetracycline.

Overall, our findings concerning antimicrobial resistance in *Campylobacter* spp. from broilers and meat thereof are in agreement with reports from other European countries, but some trends differ markedly between European countries [8]. For example, trends for resistance against fluoroquinolones are not the same for all countries: Spain, Iceland, Austria and Belgium record a decrease in the ciprofloxacin resistance rates of *C. jejuni* from broilers, whereas other Europe-

Figure 8. g: Trends in resistance to fluoroquinolones and macrolides in *C. coli* and *C. jejuni* from human clinical isolates in Switzerland between 2010 and 2019.

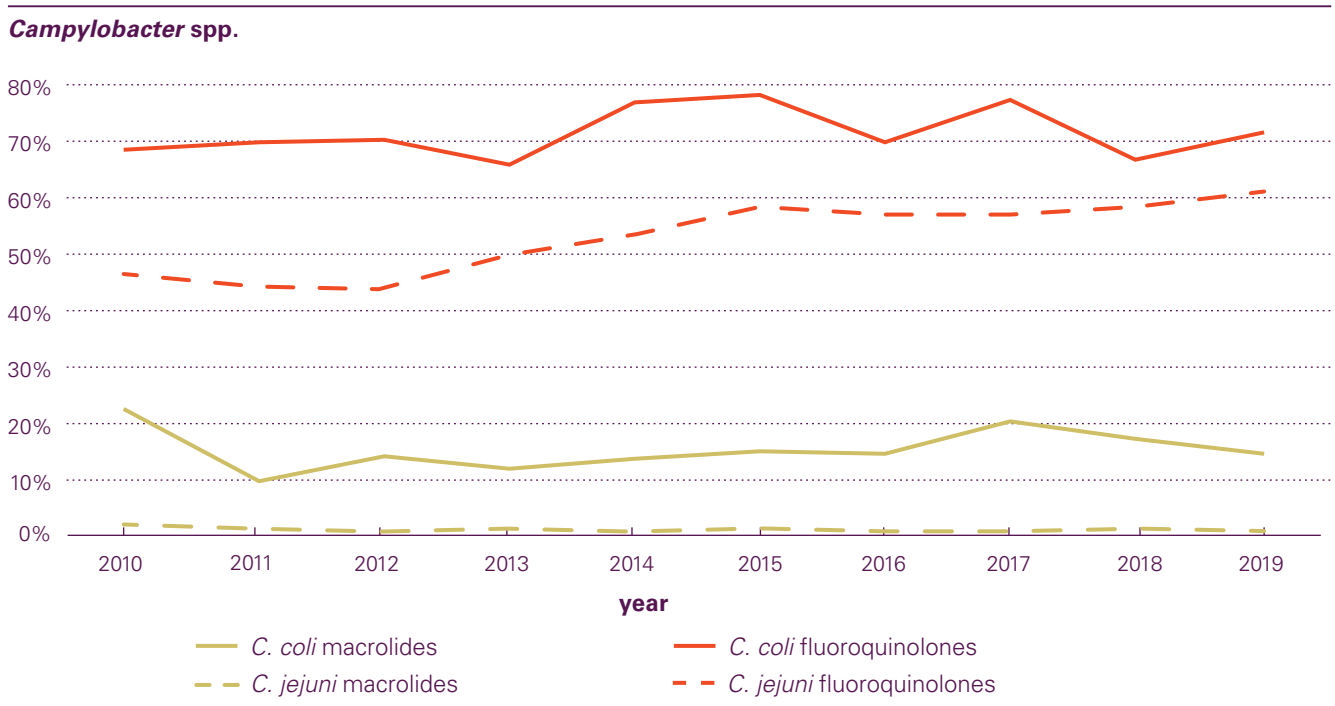


Table 8. i: Non-susceptibility combinations in *C. jejuni* from chicken meat in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**112**	
Number of Resistances: 0	**42**	**37.5%**
–	42	100.0%
Number of Resistances: 1	**35**	**31.3%**
Fluoroquinolones	31	88.6%
Tetracyclines	4	11.4%
Number of Resistances: 2	**30**	**26.8%**
Fluoroquinolones – Tetracyclines	30	100.0%
Number of Resistances: 3	**5**	**4.5%**
Aminoglycosides – Fluoroquinolones – Tetracyclines	4	80.0%
Fluoroquinolones – Macrolides – Tetracyclines	1	20.0%

Aminoglycosides: Streptomycin, Gentamicin; Fluoroquinolones: Nalidixic acid, Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin

Table 8. j: Non-susceptibility rates of *C. coli* and *C. jejuni* from human clinical isolates in 2019.

Campylobacter coli											**2019**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Macrolides[1]	98	14.3%	137	11.7%	25	32%	260	14.6%	12.4–16.8	–	–
Fluoroquinolones[2]	103	69.9%	135	73.3%	25	68%	263	71.5%	68.7–74.3	–	–
Campylobacter jejuni											**2019**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Macrolides[1]	745	0.7%	1638	0.9%	116	0.9%	2499	0.8%	0.6–1.0	–	↓
Fluoroquinolones[2]	766	62.7%	1623	59.4%	116	67.2%	2505	60.8%	59.8–61.8	↑	↑

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

an countries such as Denmark reported increasing resistance rates. Moreover, Spain, Germany and the Netherlands reported decreasing resistance rates against tetracycline in *C. jejuni* from broilers, as is the case in Switzerland. Whether the differences between countries regarding the occurrence of resistance in animal isolates are associated to differences in the use of antimicrobials needs to be clarified in the future. To date, directly comparable data on the usage of antimicrobials in European countries, such as needed to undertake meaningful association studies, are not available.

Fluoroquinolones and macrolides were recommended as antibiotics to treat severe human campylobacteriosis, which is the most common zoonosis worldwide. Resistance against fluoroquinolones having increased in the past, they were removed from the list of recommended antibiotics. Considering this background, the current observed decreasing trend of resistance in *C. coli/jejuni* from broilers is of highest relevance for human medicine, although until now, this trend was not observed in human isolates. Concerning macrolides, the resistance situation for *C. coli/jejuni* isolates from broilers as well as from chicken meat is still favorable in view of human campylobacteriosis, as resistant *C. jejuni* isolates occurred only occasionally in broilers and meat thereof. The reason for the observed decrease of quinolone resistance in Swiss *C. coli/jejuni* in the last two years remains unclear. Interestingly, the point mutation in the quinolone-resistance-determining region (QRDR), responsible for most of the observed quinolone resistances, does not lead to fitness costs for the bacterium [9]. Therefore, it is possible that measures taken years ago in the Swiss broiler production process might have now come into effect. To preserve the favorable resistance situation against macrolides and to further decrease the resistance rate against quinolones, the use of these antibiotics should be limited to the absolutely necessary level.

The assessment of the situation is different concerning *C. coli i*n pigs. Since 2015, the trend is relatively stable, even though we have observed an augmentation in the resistance

Figure 8. h: Resistance pattern in *Salmonella* spp. from cattle for 2018 and 2019.

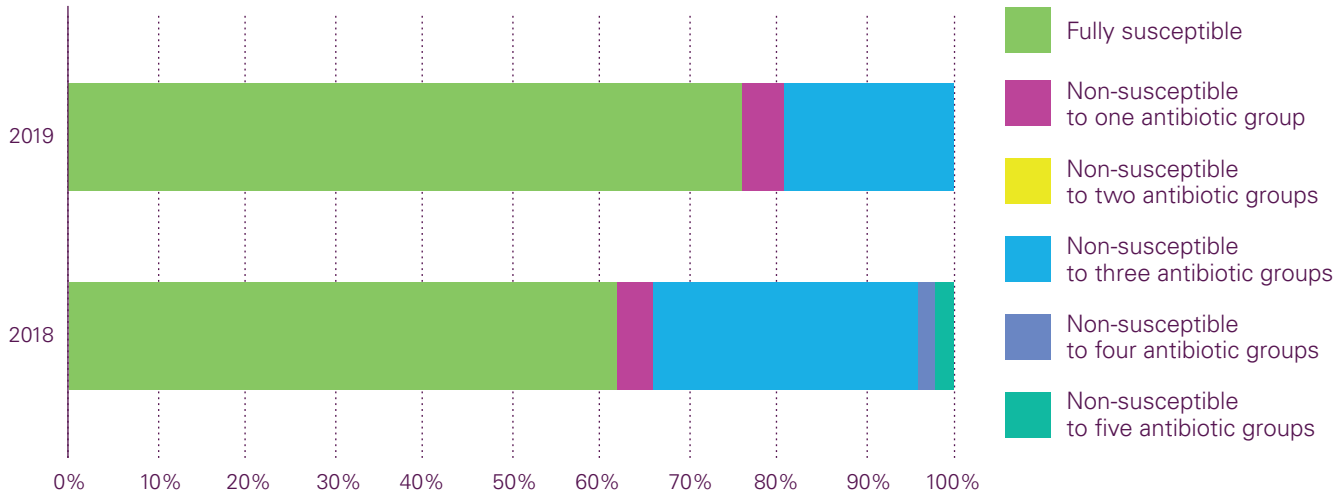
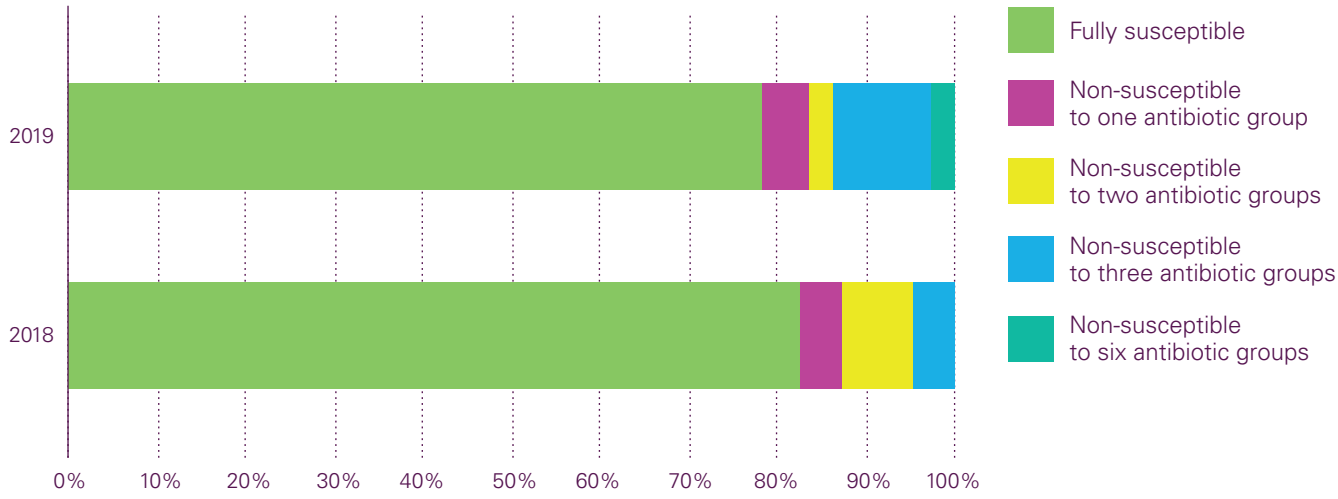


Figure 8. i: Resistance pattern in *Salmonella* spp. from poultry for 2018 and 2019.



pattern for many antibiotics since 2017. Indeed, the resistance level of ciprofloxacin, at 50.3% in 2017, increased to 55.9% in 2019. The same trend was seen with resistance against nalidixic acid. Concerning macrolides, and more specifically erythromycin, we have also noticed an increase in the resistance, which was at 1.9% in 2017 and 3.9% in 2019. We have also remarked a higher resistance rate for streptomycin, from 81.4% in 2017 to 84.7% in 2019. Furthermore, tetracycline resistance among *C. coli* was higher, with values of 62.1% in 2017 and 63.3% in 2019. Data from EFSA for *C. coli* from fattening pigs are not available. Data on the antimicrobial usage in Swiss fattening pigs, needed to assess possible associations of antimicrobial usage and development of resistance in commensals like *C. coli.*, will be available in the future. A recent Swiss study showed that a total amount of 610 kg of antimicrobials or 894,688 DCD_{CH} (Defined Course Dose for Switzerland) were used in the entire Swiss pig production in 2017. Penicillins, sulfonamides and tetracyclines were the most frequently used antimicrobial classes, fluoroquinolones accounted for less than 1% [10]. Hartmann et al. found, that fluoroquinolones are rarely used in the fattening period, but frequently used in sows (18.6%) and suckling pigs (29.0%) [11].

8.2 *Salmonella* spp.

Salmonella is the second most important zoonotic bacterial pathogen in Switzerland and the EU [1, 5]. Salmonellosis in humans has to be notified (ordinance of the FOPH on laboratory reports), whereas the notification of resistance profiles is not mandatory. In 2018, 1,467 human cases of salmonellosis were reported in Switzerland. 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 are fluoroquinolones for adults and third-generation cephalosporins for children.

Table 8. k: Non-susceptibility combinations in *Salmonella* spp. from cattle in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**50**	
Number of Resistances: 0	**31**	**62.0%**
–	31	100.0%
Number of Resistances: 1	**2**	**4.0%**
Sulfonamides	2	100.0%
Number of Resistances: 3	**15**	**30.0%**
Penicillins – Sulfonamides – Tetracyclines	15	100.0%
Number of Resistances: 4	**1**	**2.0%**
Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	100.0%
Number of Resistances: 5	**1**	**2.0%**
Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	1	100.0%

Penicillins: Ampicillin; Sulfonamides: Sulfamethoxazole, Tetracyclines: Tetracycline, Tigecycline; Diaminopyrimidine derivatives: Trimethoprim; Amphenicols: Chloramphenicol

Table 8. l: Non-susceptibility combinations in *S.* Typhimurium from cattle in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**25**	
Number of Resistances: 0	**25**	**100.0%**
–	25	100.0%

Table 8. m: Non-susceptibility combinations in *S.* Typhimurium, monophasic variant from cattle in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**13**	
Number of Resistances: 1	**1**	**7.7%**
Sulfonamides	1	100.0%
Number of Resistances: 3	**10**	**76.9%**
Penicillins – Sulfonamides – Tetracyclines	10	100.0%
Number of Resistances: 4	**1**	**7.7%**
Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	100.0%
Number of Resistances: 5	**1**	**7.7%**
Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	1	100.0%

Penicillins: Ampicillin; Sulfonamides: Sulfamethoxazole; Tetracyclines: Tetracycline, Tigecycline; Diaminopyrimidine derivatives: Trimethoprim; Amphenicols: Chloramphenicol

Table 8. o: Non-susceptibility combinations in *S.* Typhimurium from cattle in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**11**	
Number of Resistances: 0	**11**	**100.0%**
–	11	100.0%

Table 8. n: Non-susceptibility combinations in *Salmonella* spp. from cattle in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**21**	
Number of Resistances: 0	**16**	**76.2%**
–	16	100.0%
Number of Resistances: 1	**1**	**4.8%**
Polymyxins	1	100.0%
Number of Resistances: 3	**4**	**19.0%**
Amphenicols – Diaminopyrimidine derivatives – Sulfonamides	1	25.0%
Penicillins – Sulfonamides – Tetracyclines	3	75.0%

Penicillins: Ampicillin; Sulfonamides: Sulfamethoxazole; Tetracyclines: Tetracycline, Tigecycline; Diaminopyrimidine derivatives: Trimethoprim; Amphenicols: Chloramphenicol; Polymyxins: Colistin

Animals can either be carriers of *Salmonella* spp. without showing any clinical signs or they can be diseased by *Salmonella* spp. Poultry in particular often shows no signs of infection. In contrast, 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 contaminated food. A wide variety of foodstuffs of animal (e.g. eggs, fresh meat) and plant (e.g. salads, spices, seeds) origin can be contaminated with *Salmonella*. In special settings (e.g. reptiles), *Salmonella* can also be transmitted through direct contact with infected animals. Salmonellosis in livestock is notifiable (ordinance of the FSVO on epizootic diseases) and in poultry an active eradication program is in place.

Reported cases of salmonellosis in animals are very rare in Switzerland, with 98 reported cases in 2018 [5]. Moreover, the overall prevalence of *Salmonella* spp. in Swiss livestock is low (<2% in poultry, fattening pigs) compared to European countries [1, 5]. Out of 3,317 chicken meat samples (carcasses and meat), 4 (0.1%) were *Salmonella* spp. positive in 2018 in Switzerland. In addition, 8 (2.0%) out of 395 turkey meat samples (carcasses and meat) were positive for *Salmonella* spp.

In Europe, *S.* Enteritidis and *S.* Typhimurium are the most common serovars in human infections [1]. *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. Because of the very low prevalence of *Salmonella* spp. in Swiss livestock and food thereof, the risk of infection for the Swiss population through food produced in Switzerland is low.

All isolated *Salmonella* strains from animals undergo antimicrobial testing at the Swiss national reference laboratory, and resistance data from livestock isolates are transmitted to EFSA. Antibacterial susceptibility was tested in one isolate from each animal species involved per incident. Amongst others, testing included 3rd and 4th generation cephalosporines and meropenem for detection of ESBL/pAmC- and carbapenemase-producing *Salmonella* spp. In this chapter, data regarding *Salmonella* spp. including *S.* and its monophasic variant isolated from infected or diseased poultry and cattle are shown.

In anresis.ch, information on antimicrobial resistances 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. Serovar typing in human medicine is only performed for a minority of isolates. Although this information, in contrast to susceptibility testing results, is interesting for epidemiologic purposes, 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 profiles.

8.2.1 *Salmonella* in animals

In contrast to the isolates from the national monitoring program, the overall low number and different sources of *Salmonella* spp. isolates available from livestock and food thereof do not allow reliable statistical analysis, and resistance rates and trends need to be discussed with caution, as these isolates are not a random sample and differ from year to year.

For cattle, antimicrobial resistance data regarding 50 *Salmonella* spp., including 25 *S.* Typhimurium, 13 *S.* Typhimurium, monophasic variants and 5 *S.* Enteritidis (data not shown), were available in 2018. In 2019, 21 bovine *Salmonella* spp. were available, including 11 *S.* Typhimurium, 4 *S.* monophasic variant (data not shown) and 3 *S.* Enteritidis (data not shown) (Table 8. k to Table 8. o).

Overall, the vast majority of *Salmonella* spp. isolated from cattle were fully susceptible to all tested antimicrobial classes (2018: 62%, 2019: 76.2%, Figure 8. h). Especially, all *S.* Typhimurium isolates were fully susceptible (Table 8. l

and Table 8. o). In contrast, 10 out of 13 *S.* Typhimurium, monophasic variants expressed multi-drug resistance to penicillins, sulfonamides and tetracyclines. A single S. Typhimurium monophasic variant isolate additionally showed resistance to amphenicols and trimethoprim. All eight S. Enteritidis were fully susceptible, except one isolate, which was resistant against sulfonamides.

Poultry antimicrobial resistance data from 64 *Salmonella* spp., including 13 *S.* Typhimurium monophasic variants, 12 *S.* Typhimurium and 9 *S.* Enteritidis (data not shown), were available in 2018. In 2019, 36 *Salmonella* spp., including 11 *S.* Typhimurium, 5 *S.* Typhimurium monophasic variant (data not shown) and 6 *S.* Enteritidis (data not shown) were available (Table 8. p to Table 8. t).

As with bovine *Salmonella* spp., the vast majority of *Salmonella* spp. isolated from poultry were fully susceptible to all tested antimicrobial classes (2018: 83%, 2019: 78%, Figure 8. i). All *S.* Typhimurium isolates were fully susceptible (Table 8. r and Table 8. t), whereas 3 out of 13 *S.* Typhimurium monophasic variants expressed multi-drug resistance to penicillins, sulfonamides and tetracyclines. All 15 *S.* Enteritidis were fully susceptible to all tested antimicrobials.

8.2.2 *Salmonella* in humans

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.

In ANRESIS, information on antimicrobial resistance was available only for a minority of the 1550 cases observed in 2019 in Switzerland. Resistance rates are only available for aminopenicillins, ceftriaxone, trimethoprim-sulfamethoxazole and fluoroquinolones (Table 8. u). Serovar typing in human medicine is only performed for a minority of all 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 profiles (Table 8. u). From 2010 to 2019, nonsusceptibility-rates decreased for aminopenicillins, but increased for fluoroquinolones (Figure 8. j).

Table 8. p: Non-susceptibility combinations in *Salmonella* spp. from poultry in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**64**	
Number of Resistances: 0	**53**	**82.8%**
–	53	100.0%
Number of Resistances: 1	**3**	**4.7%**
Penicillins	1	33.3%
Sulfonamides	2	66.7%
Number of Resistances: 2	**5**	**7.8%**
Penicillins – Sulfonamides	5	100.0%
Number of Resistances: 3	**3**	**4.7%**
Penicillins – Sulfonamides – Tetracyclines	3	100.0%

Penicillins: Ampicillin; Sulfonamides: Sulfamethoxazole; Tetracyclines: Tetracycline, Tigecycline

Table 8. q: Non-susceptibility combinations in *S.* Typhimurium monophasic variant from poultry in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**13**	
Number of Resistances: 0	**5**	**38.5%**
–	5	100,0%
Number of Resistances: 2	**5**	**38.5%**
Penicillins – Sulfonamides	5	100.0%
Number of Resistances: 3	**3**	**23.1%**
Penicillins – Sulfonamides – Tetracyclines	3	100.0%

Penicillins: Ampicillin; Sulfonamides: Sulfamethoxazole; Tetracyclines: Tetracycline, Tigecycline

Table 8. r: Non-susceptibility combinations in *S.* Typhimurium from poultry in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**12**	
Number of Resistances: 0	**12**	**100.0%**
–	12	100.0%

Table 8. s: Non-susceptibility combinations in *Salmonella* spp. from poultry in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**36**	
Number of Resistances: 0	**29**	**80.6%**
–	29	100.0%
Number of Resistances: 1	**2**	**5.6%**
Fluoroquinolones	1	50.0%
Polymyxins	1	50.0%
Number of Resistances: 2	**1**	**2.8%**
Amphenicols – Fluoroquinolones	1	100.0%
Number of Resistances: 3	**4**	**11.1%**
Penicillins – Sulfonamides – Tetracyclines	4	100.0%

Penicillins: Ampicillin; Sulfonamides: Sulfamethoxazole; Tetracyclines: Tetracycline, Tigecycline; Diaminopyrimidine derivatives: Trimethoprim; Amphenicols: Chloramphenicol; Polymyxins: Colistin

Table 8. t: Non-susceptibility combinations in *S.* Typhimurium from poultry in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**11**	
Number of Resistances: 0	**11**	**100.0%**
–	11	100.0%

Table 8. u: Non-susceptibility rates of *Salmonella* from human clinical isolates for 2019.

***Salmonella* ser. Enteritidis**											**2019**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	41	9.8%	45	13.3%	1	100.0%	87	12.6%	9.0–16.2	–	–
Ceftriaxone	42	0.0%	42	0.0%	0	0.0%	84	0.0%	0.0–0.0	–	–
Fluoroquinolones	38	15.8%	46	21.7%	1	0.0%	85	18.8%	14.6–23.0	↑	↑
Trimethoprim-sulfame	42	2.4%	48	0.0%	1	0.0%	91	1.1%	0.0–2.2	–	–
***Salmonella* ser. Typhimurium**											**2019**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	19	36.8%	20	15.0%	1	0.0%	40	25.0%	18.2–31.8	–	↓
Ceftriaxone	18	5.6%	10	0.0%	1	0.0%	29	3.4%	0.0–6.8	–	↑
Fluoroquinolones[1]	18	27.8%	20	0.0%	1	0.0%	39	12.8%	7.5–18.1	–	↑
Trimethoprim-sulfame	19	15.8%	21	4.8%	1	0.0%	41	9.8%	5.2–14.4	–	–

[1] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

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.

8.2.3 Discussion

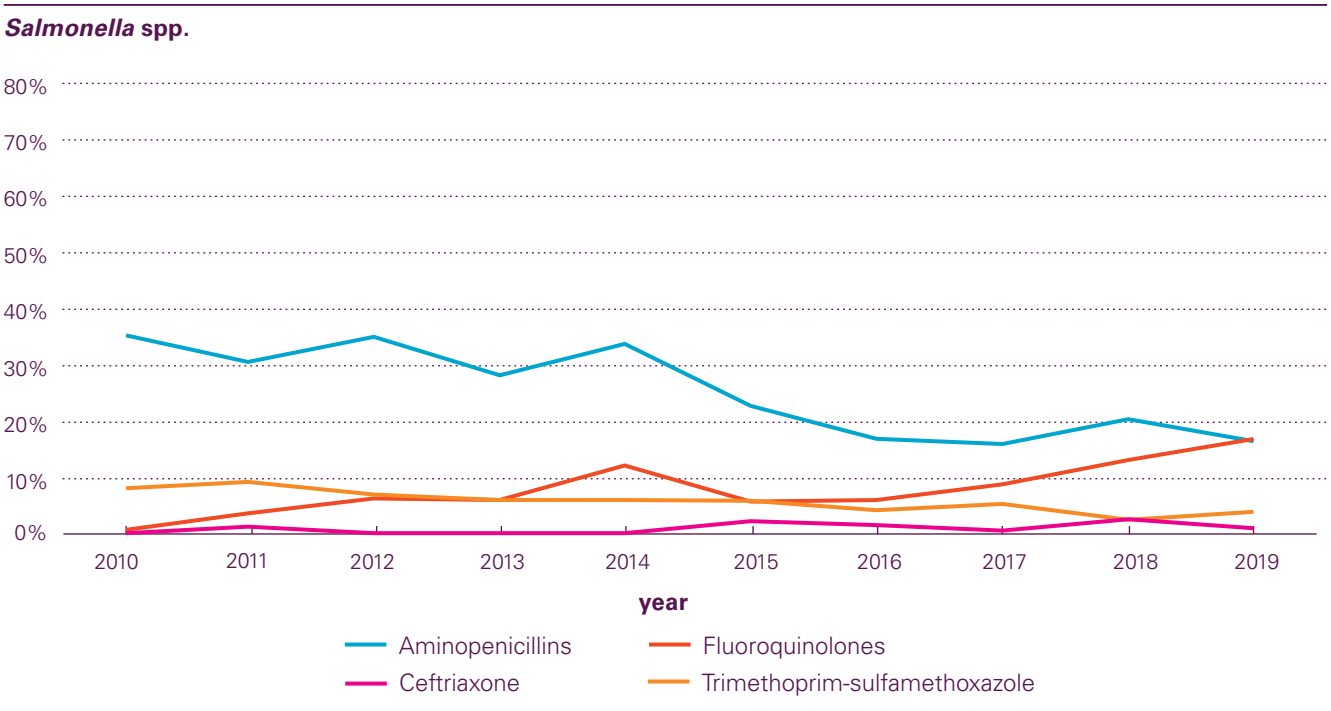
As a consequence of long-term control programs, the prevalence of *Salmonella* spp. in food-producing animals in Switzerland is very low. Accordingly, only a few, non-representative *Salmonella* spp. isolates from livestock are available, either from clinical cases or from healthy poultry from the national *Salmonella* spp. eradication programs. Hence, rates of resistance and their long-term trends should be interpreted with caution.

Between 2017 and 2019, full susceptibility rates of *Salmonella* spp. to all tested antimicrobials decreased from 80.7% in 2017 to 78% in 2019 for poultry isolates. In cattle, 62% of all bovine *Salmonella* spp. were fully susceptible in 2017 and 2018, and this rate increased to 79.2% in 2019. Importantly, neither ESBL/pAmC- nor carbapenemase-producing *Salmonella* spp. isolates were found in cattle or poultry. Quinolones and third-generation cephalosporins, such as ceftriaxone, are critically important antimicrobials for the treatment of human salmonellosis. In 2018 and 2019, resistance to ciprofloxacin or third-generation cephalosporins was found neither in poultry nor in cattle *Salmonella* spp. isolates. Only resistances to ampicillin, sulfamethoxazole, tetracycline and amphenicols have been detected in *Salmonella* spp. from the two livestock species. As these antimicrobials have been used in Swiss animal farming for many years, rates of resistance most probably reflect the actual selection pressure.

Within Europe, the proportion of completely susceptible *Salmonella* spp. isolates from broilers ranges from 6.2% in Slovenia to 90.9% in Ireland [8]. Generally, complete susceptibility levels are higher among isolates from laying hens, ranging from 46.4% in Italy to 94.8% in France. However, the prevalence of particular serovars in different countries and animal populations and their associated patterns of resistance may account for the differences in *Salmonella* spp. data regarding the levels of multiple drug resistance and complete susceptibility. Notably, this was observed in the rare data from Switzerland. *S.* Typhimurium monophasic variant is one of the serovars which exhibits more antimicrobial resistances than others, e.g. *S.* Typhimurium and *S.* Enteritidis. Moreover, multi-drug resistant *S.* Infantis has emerged in various European countries and recently in Switzerland in both humans and livestock [12–15]. Within the few *Salmonella* spp. isolates from pigs available between 2018 and 2019, a single ESBL/pAmC-producing *S.* Infantis from pigs was isolated in 2019.

Colistin is an antimicrobial substance belonging to the polymyxin class. Because of its effectiveness against carbapenemase-producing Gram-negative bacteria, it is nowadays considered a highest priority antimicrobial for the treatment of serious human infections [4]. *Salmonella* spp. of different origins (humans, animals, food) carrying plasmid-mediated colistin resistance conferred by mcr-1, mcr-2, mcr-3, mcr-4 and mcr-5 genes have been detected in various serovars of *Salmonella* spp. [16]. Microbiological resistance to colistin

Figure 8. j: Trends in resistance to aminopenicillins. ceftriaxone, fluoroquinolones and trimethoprim-sulfamethoxazole in non-typhoidal Salmonella (serovars Typhimurium and Enteritidis combined) from human clinical isolates in Switzerland between 2010 and 2019.



was not detected within the 171 *Salmonella* spp. isolates from poultry and cattle having undergone susceptibility testing in 2018 and 2019.

For various reasons, a direct comparison of resistance rates against defined antimicrobials between *Salmonella* in animals and in human clinical isolates is not possible. First of all, antimicrobials licensed and used for both species differ markedly, although antimicrobial classes are comparable. Moreover, methods used for susceptibility testing (various in human medicine / microbroth dilution in veterinary monitoring) and interpretative criteria (clinical breakpoint in human isolates / epidemiological cutoff in animal isolates) differ substantially. Nevertheless, detection of critically important multi-drug resistant *Salmonella* spp., such as ESBL/pAmpC- and carbapenemase-producing bacteria or colistin resistant bacteria, is comparable. Therefore, regarding the favorable resistance situation of *Salmonella* spp. from Swiss livestock in comparison to more resistant human *Salmonella* isolates, it is likely that a substantial part of the *Salmonella* infections in humans 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.

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Textbox

Antibiotic Resistance of 34,539 *Campylobacter* spp. isolated from human sources: National Surveillance Data of Switzerland from 2007 to 2018

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Background: In Switzerland, acute gastroenteritis is often caused by bacteria, and is of importance due to substantial healthcare costs. *Campylobacter* is a more common cause of gastroenteritis than *Salmonella*, with about 7,000 to 8,000 registered episodes caused by *Campylobacter* spp. annually. The number of non-confirmed infections is also considerable. Natural reservoirs of *Campylobacter* can be found in wild birds, cattle, chicken, dogs, and cats. Infection of humans with *C. jejuni* and *C. coli* is usually through the food chain, by way of preparation and handling of poultry meat, ready-to-eat products, non-pasteurized milk, contaminated water, or by direct contact with colonized animals. Human-to-human transmission is very rare. Clinical infections can have different presentations. Symptomatic disease, so called campylobacteriosis, usually occurs two to five days after infection, with diarrhea, abdominal pain, and fever. Bacteremia, as well as other severe complications including the Reiter-Syndrome, meningitis, or Guillain-Barré Syndrome are very rare. Infected patients usually recover within a few days without therapy. If treatment is required, a short course with erythromycin or ciprofloxacin is usually administered.

In recent years, an increase in antimicrobial resistances (AMR) in isolates of *Campylobacter* spp. has been reported. This may lead to difficulties in treating patients with more complicated clinical courses. However, little is known about temporal trends and geographical patterns of AMR in *Campylobacter* spp. strains within Switzerland.

The overall goal of our analysis was to describe antibiotic resistance in *Campylobacter* spp. from 2007 to 2018 in Switzerland. Our objectives were (i) to describe the frequency of distribution of all included *Campylobacter* spp. over time; (ii) to describe the temporal and geographical pattern of antibiotic resistance of *C. jejuni* and *C. coli*; (iii) to examine whether antibiotic resistance of *C. jejuni* and *C. coli* is associated with epidemiological parameters; and (iv) to describe the antibiotic resistance profiles of *C. jejuni* and *C. coli* in invasive episodes.

Methods: We used prospectively collected anonymized data from 2007 to 2018 from the ANRESIS antibiotic surveillance framework in Switzerland. The network covers approximately two thirds of reported laboratory data (www.anresis.ch). We conducted pre-defined, descriptive and exploratory statistical analyses. No *a priori* hypothesis was tested. For each year and geographic region, the frequency of isolates resistant to specific antibiotics was calculated. Finally, we examined the association of antimicrobial resistance with demographic and epidemiological variables and invasiveness (bacteremia and other primary sterile body sites).

Results: The full dataset contained 34,539 human isolates of 11 *Campylobacter* spp. plus isolates identified to the genus level only. Since 2010, bacterial isolates can be significantly better identified to the species level. The main analysis focused on *C. jejuni* (n = 26,661) and *C. coli* (n = 2,235), representing 99% of all isolates characterized to the species level. Other species included *C. fetus* (n = 203), *C. lari* (n = 22), and *C. upsaliensis* (n = 15). A small proportion of *C. jejuni* and *C. coli* isolates were invasive, n = 329 (1.1%). A total of 103,538 antibiotic tests were documented, representing 2,273 to 3,308 isolates collected for antibiotic resistance testing annually. Antibiotic resistance profiles for all *C. jejuni* and *C. coli* are given in **Table 1** and **Table 2**, respectively. Overall, ciprofloxacin resistance was high in *C. jejuni* (50.5%) and *C. coli* (69.6%), whereas erythromycin resistance was lower in both *C. jejuni* (1.1%) and *C. coli* (14.5%).

Over time, we observed an increasing rate of resistance to ciprofloxacin and tetracycline in both species. We also observed resistance to doxycycline in *C. jejuni* and to clarithromycin in *C. coli*. The temporal patterns of *C. jejuni* AMR are shown in more detail in **Figure 1**. Most geographic patterns of AMR were homogeneous, with exceptions: a higher rate of resistance to erythromycin was observed in *C. coli* in the South of Switzerland compared to the rest of Switzerland; in both species, a lower rate of resistance to tetracycline was observed in central-eastern and central-western Switzerland than in the rest of the country.

Our data provide no evidence for an association of AMR with demographic or epidemiological variables of the patient (age, gender, outpatients, or long-term care facilities). Invasive isolates showed similar resistance patterns in comparison to all other isolates: for example, ciprofloxacin resistance was observed in respectively 48.5% and 50.5% of "only invasive" and "all" isolates.

Conclusions: The introduction of MALDI-TOF mass spectrometry most likely significantly improved the identification process of bacteria. This method allows to easily allocate resistance patterns to specific species. We observed temporal and geographical differences in AMR patterns. As campylobacteriosis is often epidemiologically linked to the handling of raw chicken meat and travels abroad, these differences in AMR may be linked to practice changes outside of human medicine. Linkage of databases including resistance patterns of isolates from food and animals would be very helpful for further epidemiological studies.

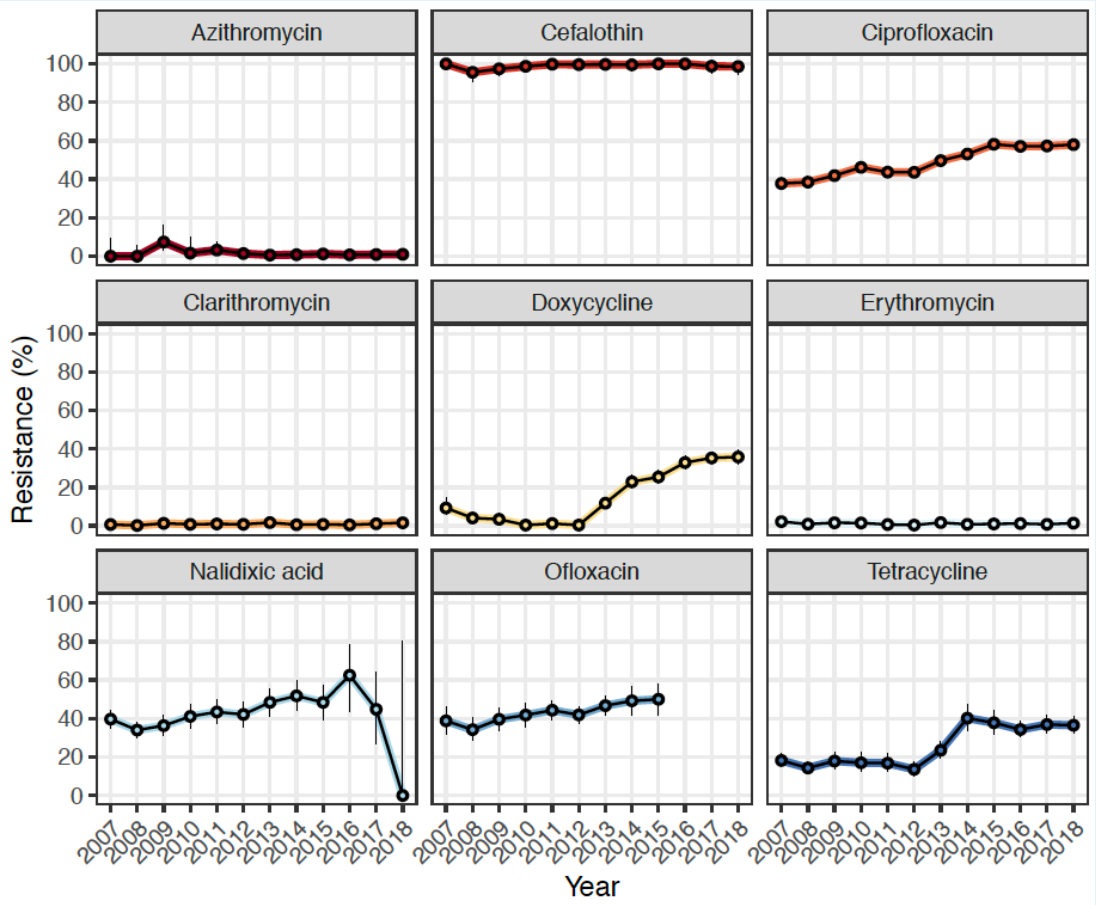
Table 1: Antibiotic resistance of all *C. jejuni* isolates (n = 26,661). Only antibiotics with more than 50 measurements are shown. *Cefazolin was only measured from 2007 to 2009.

Antibiotic	Samples (n)	Resistant (n)	Resistance (%) [95% CI]
Azithromycin	9705	94	1.0 [0.8, 1.2]
Cefalothin	2906	2881	99.1 [98.7, 99.4]
Cefazolin*	402	401	99.8 [98.4, 100]
Ciprofloxacin	25775	13012	50.5 [49.9, 51.1]
Clarithromycin	5855	55	0.9 [0.7, 1.2]
Doxycycline	6093	1205	19.8 [18.8, 20.8]
Erythromycin	18313	196	1.1 [0.9, 1.2]
Nalidixic acid	2644	1081	40.9 [39, 42.8]
Ofloxacin	2647	1130	42.7 [40.8, 44.6]
Tetracycline	4665	1187	25.4 [24.2, 26.7]

Table 2: Antibiotic resistance of all *C. coli* isolates (n = 2,235). Only antibiotics with more than 50 measurements are shown.

Antibiotic	Samples (n)	Resistant (n)	Resistance (%) [95% CI]
Azithromycin	803	119	14.8 [12.5, 17.5]
Cefalothin	103	101	98.1 [92.5, 99.7]
Ciprofloxacin	1968	1370	69.6 [67.5, 71.6]
Clarithromycin	369	67	18.2 [14.4, 22.6]
Doxycycline	409	224	54.8 [49.8, 59.6]
Erythromycin	1367	198	14.5 [12.7, 16.5]
Nalidixic acid	214	129	60.3 [53.4, 66.8]
Tetracycline	489	240	49.1 [44.6, 53.6]

Figure 1: Temporal trends for antibiotic resistance in *C. jejuni* in Switzerland.



Textbox

Rapid Increase of Extended-Spectrum Cephalosporin-Resistant *Shigella sonnei* Isolates: Spread of Common Plasmids and International Clones

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Shigella sonnei is a leading cause of diarrhea in high-income countries, with the majority of cases described in returning travelers and men who have sex with men. The emergence of antibiotic-resistant *S. sonnei* isolates is nowadays a matter of concern. The high resistance rates to first line antibiotic options (e. g., ciprofloxacin and azithromycin) have made ceftriaxone the drug of choice for empirical treatment [1]. However, a significant increase in extended-spectrum cephalosporin-resistant (ESC-R) isolates has recently been recorded, especially in Asia [2]. Usually, these isolates produce extended-spectrum ß-lactamases (ESBL) of the CTX-M-type. However, only a few studies have implemented whole-genome sequencing (WGS) to characterize the $bla_{\text{CTX-M-}}$carrying plasmids in detail and to study the clonal expansion of these pathogens.

The Swiss Centre for Antibiotic Resistance (ANRESIS) has recently noted an increase in ESC-R *S. sonnei* isolates at the national level. In particular, respectively 53, 39, 85, and 56 *S. sonnei* isolates were identified in 2016, 2017, 2018 and 2019 by participating laboratories. Of these, respectively 2 (3.8%), 5 (12.8%), 12 (14.1%) and 21 (37.5%) were reported as ESC-R. Therefore, to understand this alarming epidemiological phenomenon, we analyzed 25 representative isolates (of which 14 were ESC-R) collected between 2016 and 2019 at the Institute for Infectious Diseases (IFIK), MCL Medizinische Laboratorien, and labormedizinisches zentrum Dr. Risch. Susceptibility tests (MICs) were performed implementing the GNX2F microdilution panels (ThermoFisher), while WGS was achieved using both NovaSeq-6000 (Illumina) and MinION (Oxford Nanopore) platforms.

The ESC-R isolates produced CTX-M-3 (n = 5), CTX-M-15 (n = 6), CTX-M-27 (n = 1), CTX-M-55 (n = 1) or CTX-M-134 (n = 1) ESBLs. The $bla_{\text{CTX-M-3}}$ and $bla_{\text{CTX-M-15}}$ genes in particular were frequently carried by identical IncI1-pST57 and IncFII plasmids, respectively. Moreover, they also exhibited a high genetic identity with plasmids previously reported in other Enterobacterales (e. g., *Escherichia coli, Shigella flexneri*) isolated on different continents. We also noted that several plasmids co-carried the *erm(B)* and/or *mph(A)* genes conferring high-level resistance to azithromycin (MICs > 256 mg/L) and other macrolides. This finding is concerning, as the spread of these MDR plasmids may limit our therapeutic choices.

According to the Multilocus Sequence Typing (MLST) analysis, both ESC-R and susceptible *S. sonnei* isolates belonged to the sequence type (ST)152, giving the impression that a single clone was spreading across Switzerland. This data was surprising, since most of our strains had a clinical origin in very different countries (e. g., North Africa, rather than Central Europe) and spanned a 4-year period.

Therefore, to better comprehend this intriguing phenomenon, an accurate core-genome analysis was performed [3]. As a result, 4 main clusters were observed, each including strains differing by less than 58 Single Nucleotide Variants (SNVs), as well as both $bla_{\text{CTX-M}}$-positive and $bla_{\text{CTX-M}}$-negative isolates. Moreover, most isolates belonging to the same cluster shared an identical core-genome ST (cgST). For instance, cluster-1 included four isolates of cgST113036, of which only three harbored the IncI1-pST57 $bla_{\text{CTX-M-3}}$-positive plasmid; cluster-2 comprised three isolates, two of which were CTX-M-3 producers of cgST115537 and one non-ESBL-positive of cgST118753.

The 25 *S. sonnei* isolates also underwent a phylogenetic comparison with 131 internationally deposited strains from the Enterobase *Escherichia/Shigella* database. As a result, matching isolates (i. e. those with the same cgST and differing by less than 8 SNVs) have been reported in other countries (e. g., the UK, USA, France and the Netherlands) in the same study period (**Figure 1**). Moreover, strains highly related to ours have been reported in the USA, Egypt, Vietnam, and Italy [4].

Our results suggest that some common clusters of *S. sonnei* might spread worldwide and could be imported to Switzerland after international trips. Such clusters include, in part, isolates that do not possess bla_{ESBL}-harboring plasmids, indicating their tendency to further acquire them from other Enterobacterales. Overall, our findings underline the importance of continuously conducting epidemiological surveys implementing the WGS approach and linking the results with other countries [5].

Figure 1: SNV tree dendrogram of the Swiss *S. sonnei* (n=25) and the international strains (n=131).

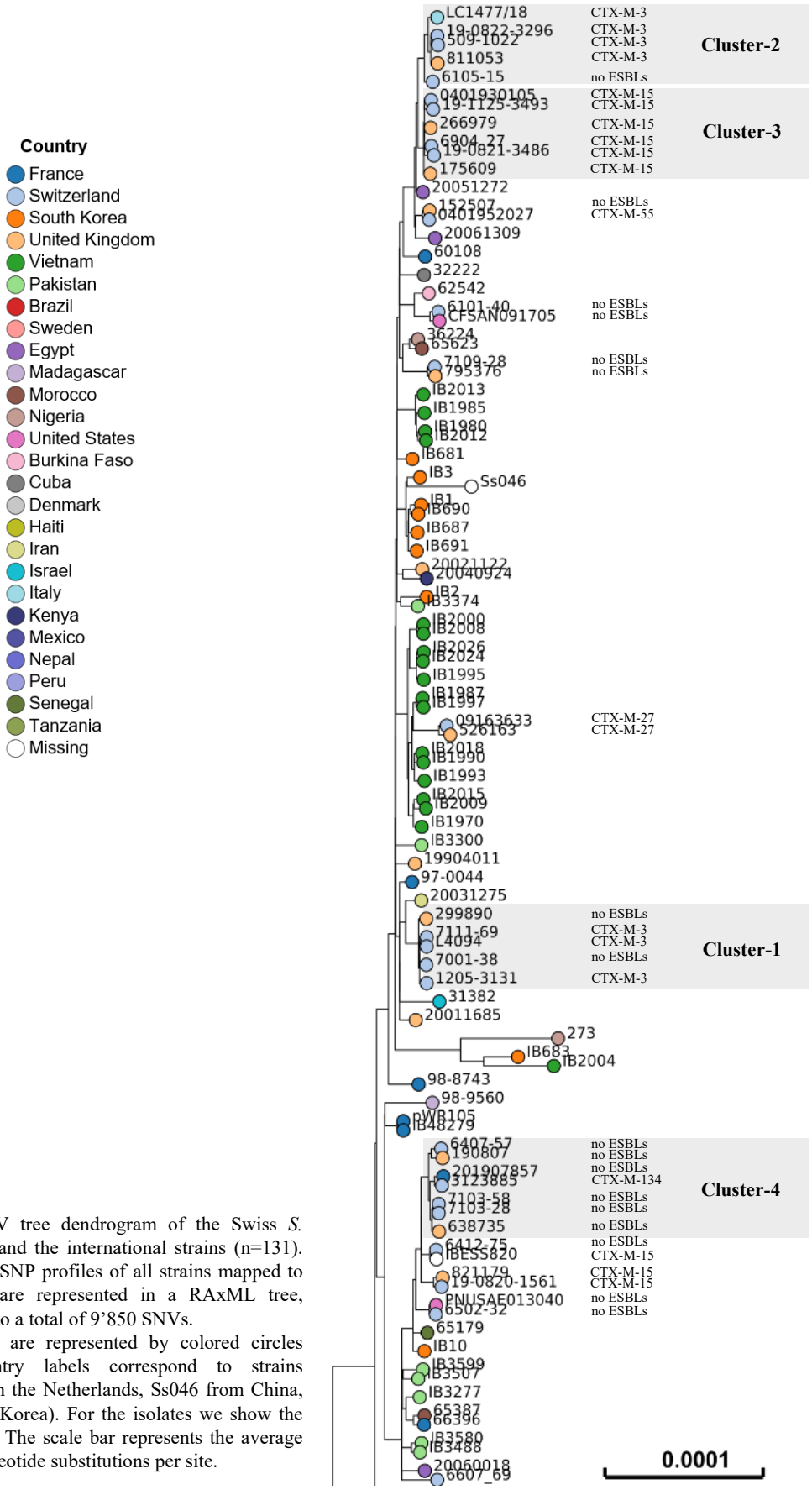

Figure 1. SNV tree dendrogram of the Swiss *S. sonnei* (n=25) and the international strains (n=131). The combined SNP profiles of all strains mapped to the reference are represented in a RAxML tree, corresponding to a total of 9'850 SNVs.
Country labels are represented by colored circles (missing country labels correspond to strains IBESS820 from the Netherlands, Ss046 from China, and 53G from Korea). For the isolates we show the ESBL (if any). The scale bar represents the average number of nucleotide substitutions per site.

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9

Resistance in indicator bacteria in livestock animals from samples at slaughter

9 Resistance in indicator bacteria in livestock animals from samples at slaughter

Antimicrobial resistance among commensal bacteria from the intestinal flora of healthy food-producing animals, e. g. *Escherichia (E.) coli*, can be used as an "indicator" for factors such as 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 [1]. Antimicrobial resistance in indicator bacteria from healthy food-producing animals is monitored in order to provide information about the types of resistance present in intestinal bacteria of food-producing animals, which can potentially be transferred to bacteria in humans. Therefore, such monitoring is relevant to both public and animal health. 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.

With the emergence of multi-drug resistant bacteria in the last decades in human and veterinary medicine, the monitoring was expanded to ESBL/pAmpC-producing and carbapenemase-producing *E. coli*.

Moreover, methicillin-resistant *Staphylococcus aureus* (MRSA), a commensal bacterium which can be found in soft tissues of healthy animals, was included in the antimicrobial resistance monitoring.

All isolates tested were isolated from samples of healthy animals at slaughter (e.g. cecum for *E. coli;* nasal swabs for MRSA).

Figure 9. a: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from broilers between 2010 and 2018 (N = total number of tested isolates, values for 2015 and 2017 interpolated [n/a].

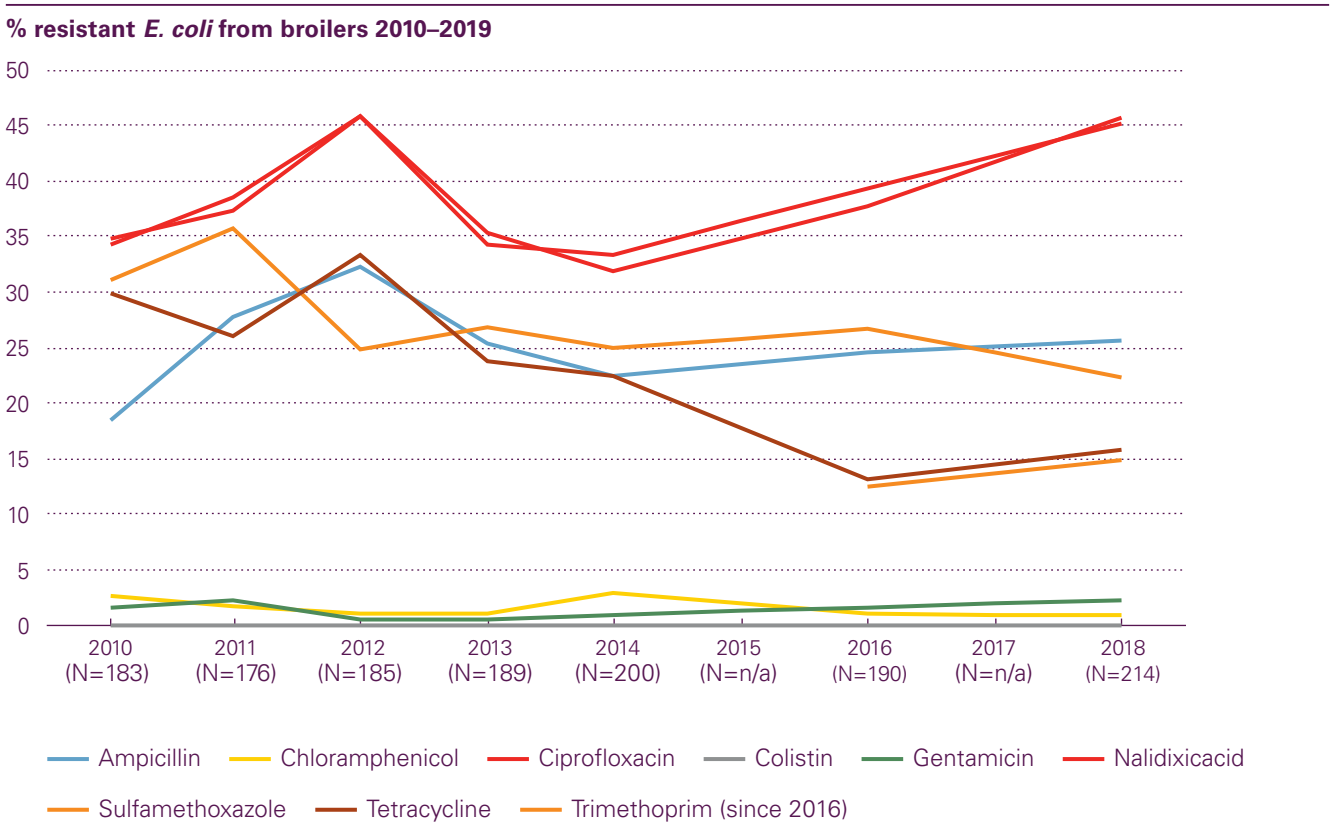
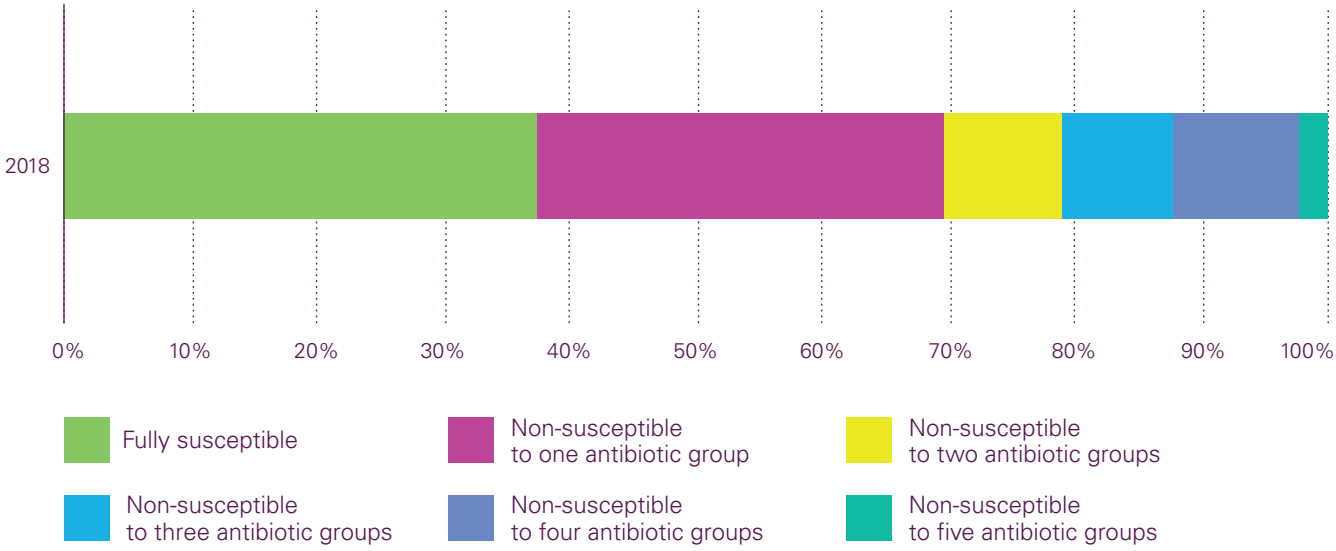


Figure 9. b: Resistance pattern in *E. coli* from broiler 2018.



9.1 *Escherichia coli*

9.1.1 *Escherichia coli* in broilers

In 2018, a random sample of 214 broiler flocks was examined at slaughter for the occurrence of antimicrobial resistance patterns in indicator *E. coli* using cecal samples (5 pooled cecal samples per flock). Indicator *E. coli* was isolated from all samples by the direct detection method. The highest levels of antimicrobial resistance were detected for fluoroquinolones (45%), ampicillin (26%), sulfonamides (22%), tetracyclines and trimethoprim (15% each) (Figure 9. a). Compared to 2016, a marked increase of antimicrobial resistance against fluoroquinolones was observed, whereas the resistance rates against ampicillin, aminoglycosides and amphenicols increased only slightly. For resistance against sulfonamides we noted a slight decrease (Figure 9. a). Neither presumptive ESBL/AmpC producers nor colistin resistance were identified.

Overall, 37.4% of all *E. coli* displayed no resistance to any antimicrobial substances tested (Figure 9. b). 69 isolates (32.2%) were resistant to just one antibiotic class, mainly to fluoroquinolones. 20 out of the 214 isolates (9.3%) showed resistance to two antibiotic classes, 9 of these expressed co-resistance against fluoroquinolones combined with penicillins. 19 isolates (8.9%) were resistant to 3 antibiotic classes, and 21 isolates (9.8%) resistant to 4 antibiotic classes (Table 9. a). Finally, 5 isolates (2.3%) showed multi-drug resistance against 5 antimicrobial classes.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimicrobial resistance in livestock. Due to the very low number of isolates, statistically significant conclusions could not yet be drawn (Table 9. b). Overall, non-susceptibility rates for antimicrobials tested are higher in the south-western and central region than in the eastern cantons of Switzerland.

9.1.2 *Escherichia coli* in fattening pigs

In 2019, a random sample of 207 fattening pigs was examined at slaughter for the occurrence of antimicrobial resistance patterns in indicator *E. coli* using cecal samples. Indicator *E. coli* were isolated from 189 samples by the direct detection method. The highest levels of antimicrobial resistance were detected for sulfonamides (30.2%), tetracyclines (21.2%), trimethoprim and ampicillin (12.7% each) (Figure 9. c).

Compared to 2017, we observed a decrease in antimicrobial resistance against sulfonamides, trimethoprim, ampicillin and chloramphenicol (Figure 9. c). Resistance against tetracyclines and fluoroquinolones has not changed since 2017. Neither presumptive ESBL/AmpC producers nor colistin, azithromycin or tigecycline resistances were identified.

Overall, 58.7% of all *E. coli* displayed no resistance to any antimicrobial substances tested (Table 9. c, Figure 9. d). 37 isolates (19.6%) were resistant to just one antibiotic class, mainly to sulfonamides and tetracyclines. 18 of the 189 isolates (9.5%) showed resistance to 2 antibiotic classes. 12 isolates (6.3%) were resistant to 3 antibiotic classes, and 9 isolates (4.8%) were resistant to 4 antibiotic classes. Finally, 1 isolate each (0.5%) showed multi-drug resistance against 5 and 6 antimicrobial classes, respectively.

Table 9. a: Non-susceptibility combinations in commensal *E. coli* in broilers in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**214**	
Number of Resistances: 0	**80**	**37.4%**
–	80	100.0%
Number of Resistances: 1	**69**	**32.2%**
Diaminopyrimidine derivatives	1	1.4%
Fluoroquinolones	52	75.4%
Penicillins	5	7.2%
Sulfonamides	5	7.2%
Tetracyclines	6	8.7%
Number of Resistances: 2	**20**	**9.3%**
Diaminopyrimidine derivatives – Fluoroquinolones	3	15.0%
Fluoroquinolones – Penicillins	9	45.0%
Fluoroquinolones – Sulfonamides	2	10.0%
Fluoroquinolones – Tetracyclines	3	15.0%
Penicillins – Tetracyclines	3	15.0%
Number of Resistances: 3	**19**	**8.9%**
Aminoglycosides – Amphenicols – Fluoroquinolones	1	5.3%
Aminoglycosides – Fluoroquinolones – Sulfonamides	3	15.8%
Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins	1	5.3%
Diaminopyrimidine derivatives – Fluoroquinolones – Sulfonamides	1	5.3%
Diaminopyrimidine derivatives – Penicillins – Sulfonamides	5	26.3%
Diaminopyrimidine derivatives – Sulfonamides – Tetracyclines	2	10.5%
Fluoroquinolones – Penicillins – Sulfonamides	2	10.5%
Fluoroquinolones – Penicillins – Tetracyclines	2	10.5%
Penicillins – Sulfonamides – Tetracyclines	2	10.5%
Number of Resistances: 4	**21**	**9.8%**
Aminoglycosides – Fluoroquinolones – Penicillins – Sulfonamides	1	4.8%
Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	8	38.1%
Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	6	28.6%
Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	6	28.6%
Number of Resistances: 5	**5**	**2.3%**
Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	1	20.0%
Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	4	80.0%
Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	6	28.6%
Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	6	28.6%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidime; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; Polymyxins: Colistin; Amphenicols: Chloramphenicol
The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.09.1).

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimicrobial resistance in livestock. Due to the very low number of isolates, statistically significant conclusions could not be drawn yet (Table 9. d). Overall, non-susceptibility rates are high in the central and eastern regions of Switzerland.

9.1.3 *Escherichia coli* in slaughter calves

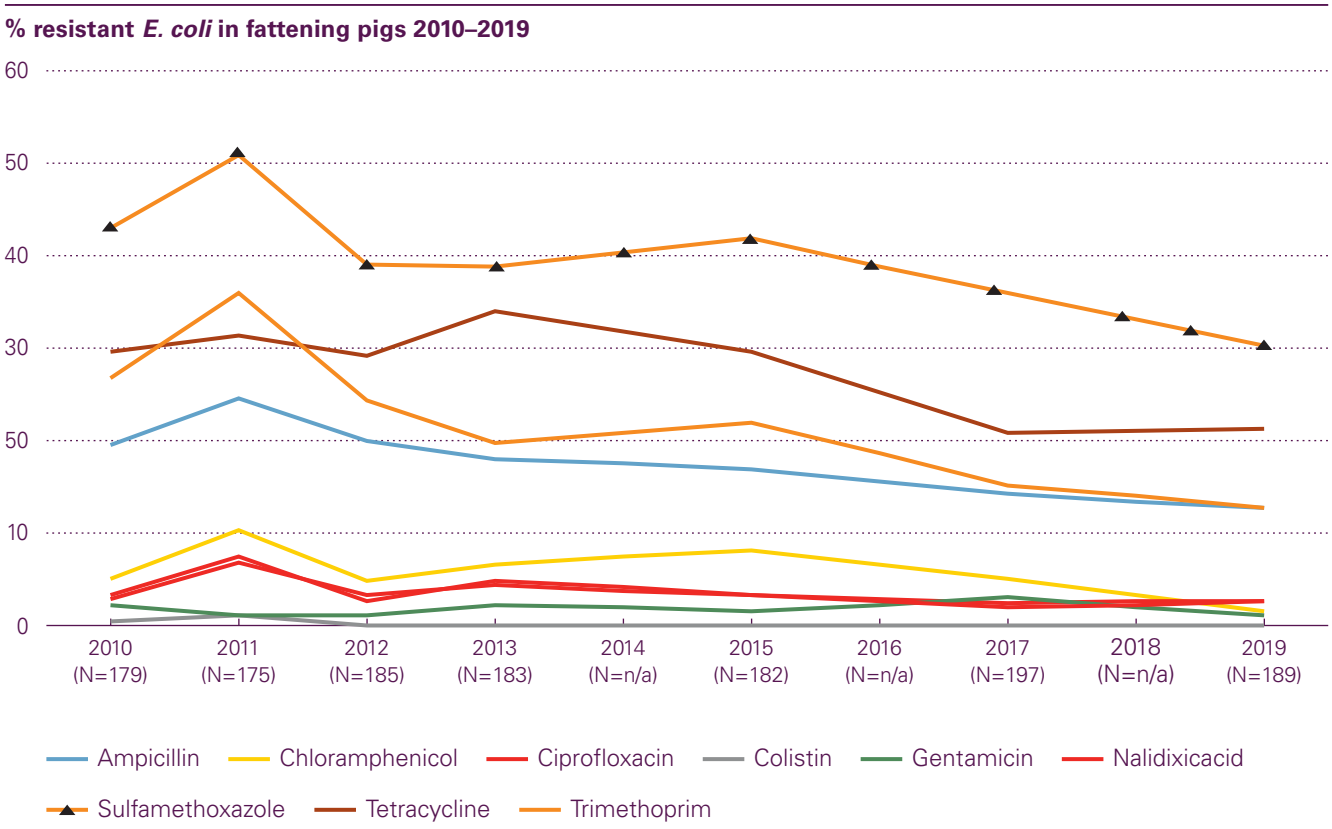
In 2019, a random sample of 212 calves was examined at slaughter for the occurrence of antimicrobial resistance patterns in indicator *E. coli* using cecal samples. Indicator *E. coli* could be isolated from 199 samples by the direct detection method. The highest levels of antimicrobial resistance were

Table 9. b: Non-susceptibility rates in commensal *E. coli* from broilers in 2018 in different regions in Switzerland.

***Escherichia coli* (N = 214)**									
Antimicrobial	**South-West**		**Center**		**East**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	31	38.8%	36	45.0%	13	16.3%	80	37.4%	31.1–44.0
Diaminopyridine derivates	12	37.5%	11	34.4%	9	28.1%	32	15.0%	10.8–20.4
Fluoroquinolones	34	34.3%	37	37.4%	28	28.3%	99	46.3%	39.7–52.9
Tetracyclines	11	32.4%	16	47.1%	7	20.6%	34	15.9%	11.6–21.4
Sulfonamides	15	31.3%	20	41.7%	13	27.1%	48	22.4%	17.4–28.5
Penicillins	19	34.6%	22	40.0%	14	25.5%	55	25.7%	20.3–31.9

South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI). 95% CI: 95% confidence interval, Fluoroquinolones: Ciprofloxacin; Tetracyclines: Tetracycline; Sulfonamides: Sulfamethoxazole; Penicillins: Ampicillin; Diaminophyridine derivates: Trimethoprim

Figure 9. c: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from fattening pigs between 2010 and 2019 (N = total number of tested isolates, values for 2014, 2016 and 2018 interpolated [n/a])



detected for tetracyclines (36.2%), sulfonamides (31.2%), ampicillin (26.1%), trimethoprim (13.1%) and chloramphenicol (7.0%) (Figure 9. e). Compared to 2017, we observed a marked decrease in antimicrobial resistance against sulfonamides, ampicillin and tetracyclines, whereas the resistance rates against fluroquinolones, aminoglycosides and amphenicols did not change markedly. Two isolates were identified as presumptive ESBL/AmpC producers. Colistin resistance was not detected.

Overall, 60.4% of all *E. coli* displayed no resistance to any antimicrobial substances tested (Table 9. e, Figure 9. f). Ten isolates (5.1%) were resistant to just 1 antibiotic class, mainly to penicillins or tetracyclines. 17 of the 199 isolates (8.6%) showed resistance to 2 antibiotic classes. 24 isolates (12.2%) were resistant to 3 antibiotic classes, 12 isolates (6.1%) resistant to 4 antibiotic classes and 11 isolates against 5 antimicrobial classes. Finally, 4 isolates showed multi-drug resistance against 5 to 9 antimicrobial classes including two presumptive ESBL/pAmpC producers.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimi-

Table 9. c: Non-susceptibility combinations in commensal *E. coli* in fattening pigs in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**189**	
Number of Resistances: 0	**111**	**58.7%**
–	111	100.0%
Number of Resistances: 1	**37**	**19.6%**
Diaminopyrimidine derivatives	1	2.7%
Fluoroquinolones	1	2.7%
Penicillins	2	5.4%
Sulfonamides	18	48.6%
Tetracyclines	15	40.5%
Number of Resistances: 2	**18**	**9.5%**
3rd generation cephalosporins – Sulfonamides	1	5.6%
Diaminopyrimidine derivatives – Sulfonamides	5	27.8%
Fluoroquinolones – Tetracyclines	1	5.6%
Penicillins – Sulfonamides	6	33.3%
Sulfonamides – Tetracyclines	5	27.8%
Number of Resistances: 3	**12**	**6.3%**
Amphenicols – Diaminopyrimidine derivatives – Sulfonamides	1	8.3%
Diaminopyrimidine derivatives – Fluoroquinolones – Tetracyclines	1	8.3%
Diaminopyrimidine derivatives – Penicillins – Sulfonamides	2	16.7%
Diaminopyrimidine derivatives – Sulfonamides – Tetracyclines	4	33.3%
Penicillins – Sulfonamides – Tetracyclines	4	33.3%
Number of Resistances: 4	**9**	**4.8%**
Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides	1	11.1%
Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	11.1%
Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	7	77.8%
Number of Resistances: 5	**1**	**0.5%**
Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Sulfonamides – Tetracyclines	1	100.0%
Number of Resistances: 6	**1**	**0.5%**
Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	100.0%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidime; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; polymyxins: colistin; Amphenicols: Chloramphenicol
The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.09.2).

Table 9. d: Non-susceptibility rates in commensal *E. coli* from fattening pigs in 2019 in different regions of Switzerland.

***Escherichia coli* (N=178)**									
Antimicrobial	**South-West**		**Center**		**East**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	3	2.9%	57	55.3%	43	41.8%	103	57.9%	50.5–64.9
Diaminopyridine derivates	3	13.6%	10	45.5%	9	40.9%	22	12.4%	8.3–18.0
Fluoroquinolones	0	0.0%	2	40.0%	3	60.0%	5	2.8%	1.2–6.4
Tetracyclines	1	2.7	18	48.7%	18	48.7%	37	20.8%	15.5–27.3
Sulfonamides	5	9.1%	24	43.6%	26	47.3%	55	30.9%	24.6–38.0
Penicillins	2	8.3%	10	41.7%	12	50.0%	24	6.7%	3.9–11.4

South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI). 95% CI: 95% confidence interval; Fluoroquinolones: Ciprofloxacin; Tetracyclines: Tetracycline; Sulfonamides: Sulfamethoxazole; Penicillins: Ampicillin; Diaminophyridine derivates: Trimethoprim

Figure 9. d: Resistance pattern in *E. coli* from fattening pigs 2019.

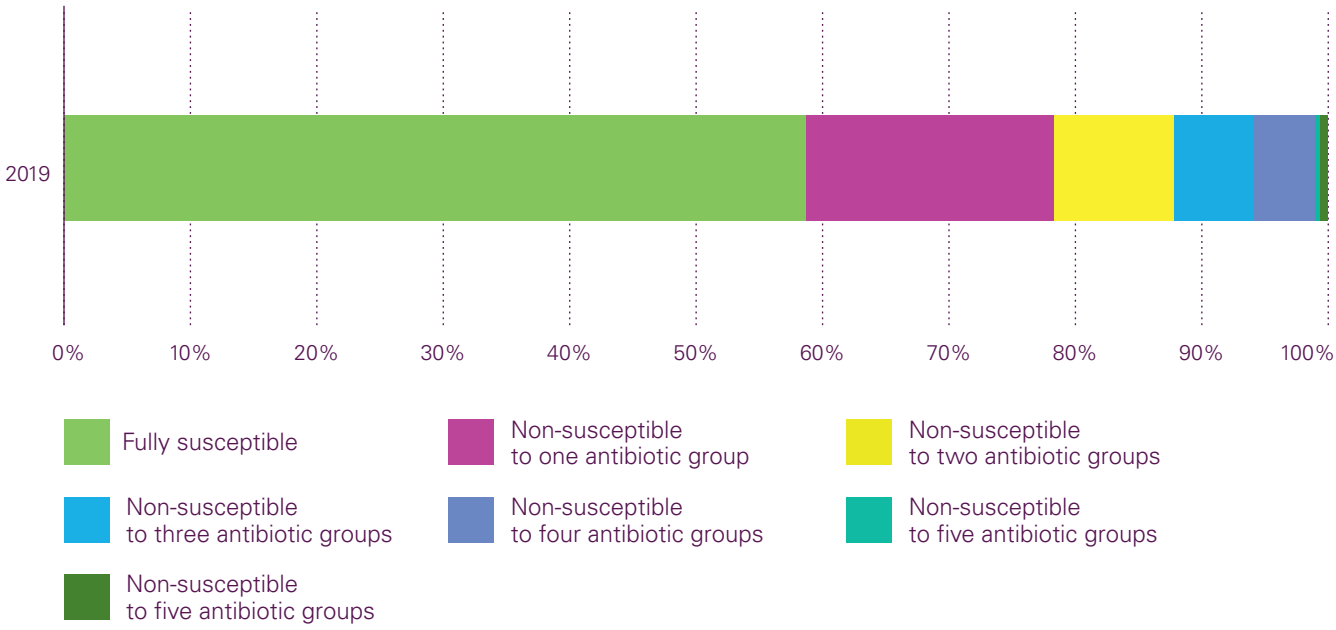
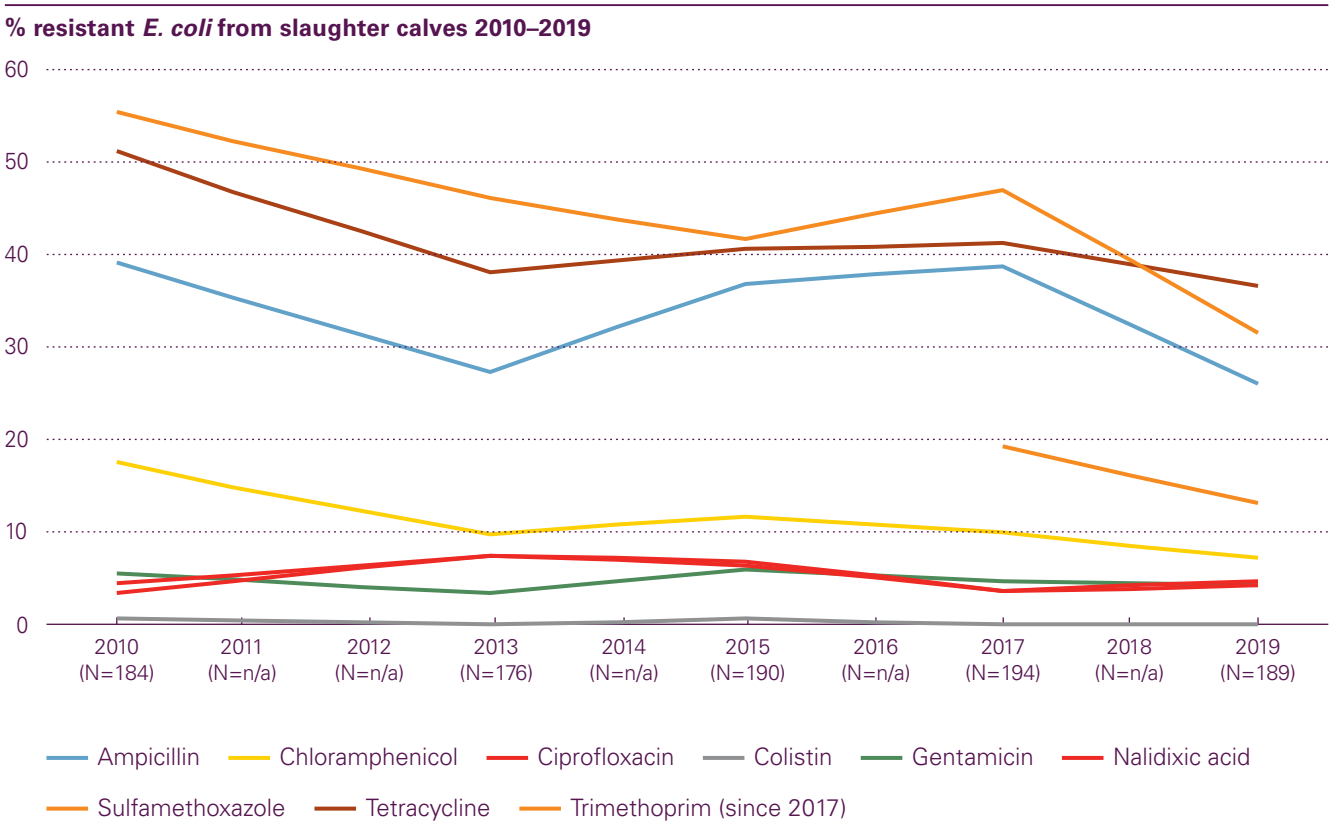


Figure 9. e: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from slaughter calves between 2010 and 2019 (N = total number of tested isolates, values for 2011, 2012, 2014, 2016 and 2018 interpolated [n/a]).



crobial resistance in livestock. Due to the very low number of isolates, statistically significant conclusions could not yet be drawn (Table 9. f). Overall, non-susceptibility rates in the central region of Switzerland are higher than in the other regions.

9.1.4 Discussion

The resistance rates against different antimicrobial classes for commensal *E. coli* from broilers in Switzerland show no common trend (Figure 9. a). Resistance rates against critical-

Table 9. e: Non-susceptibility combinations in commensal *E. coli* in slaughter calves in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**197**	
Number of Resistances: 0	**119**	**60.4%**
–	119	100.0%
Number of Resistances: 1	**10**	**5.1%**
Penicillins	3	30.0%
Tetracyclines	7	70.0%
Number of Resistances: 2	**17**	**8.6%**
Diaminopyrimidine derivatives – Penicillins	1	5.9%
Diaminopyrimidine derivatives – Sulfonamides	2	11.8%
Diaminopyrimidine derivatives – Tetracyclines	1	5.9%
Penicillins – Tetracyclines	3	17.6%
Sulfonamides – Tetracyclines	10	58.8%
Number of Resistances: 3	**24**	**12.2%**
Amphenicols – Penicillins – Tetracyclines	1	4.2%
Amphenicols – Sulfonamides – Tetracyclines	1	4.2%
Diaminopyrimidine derivatives – Sulfonamides – Tetracyclines	2	8.3%
Fluoroquinolones – Sulfonamides – Tetracyclines	2	8.3%
Penicillins – Sulfonamides – Tetracyclines	18	75.0%
Number of Resistances: 4	**12**	**6.1%**
Aminoglycosides – Penicillins – Sulfonamides – Tetracyclines	1	8.3%
Amphenicols – Penicillins – Sulfonamides – Tetracyclines	4	33.3%
Diaminopyrimidine derivatives – Fluoroquinolones – Sulfonamides – Tetracyclines	2	16.7%
Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	5	41.7%
Number of Resistances: 5	**11**	**5.6%**
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Sulfonamides – Tetracyclines	1	9.1%
Aminoglycosides – Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	9.1%
Aminoglycosides – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	2	18.2%
Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	4	36.4%
Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	3	27.3%
Number of Resistances: 6	**1**	**0.5%**
Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	100.0%
Number of Resistances: 7	**2**	**1.0%**
Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins - Sulfonamides - Tetracyclines	1	50.0%
Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	50.0%
Number of Resistances: 9	**1**	**0.5%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Penems and monobactams – Penicillins – Sulfonamides – Tetracyclines	1	100.0%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidime; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; polymyxins: colistin; Amphenicols: Chloramphenicol
The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.09.3).

Figure 9. f: Resistance pattern in *E. coli* from slaughter calves for 2019.

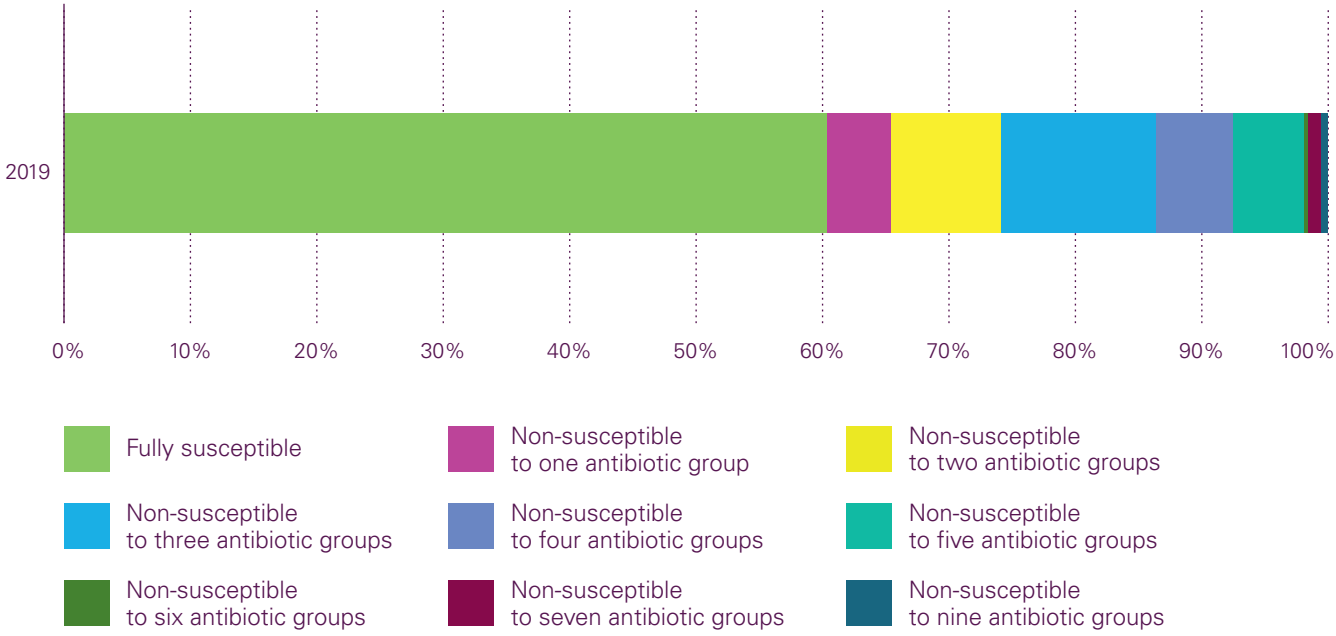


Table 9. f: Non-susceptibility rates in commensal *E. coli* from slaughter calves in 2019 in different regions in Switzerland.

***Escherichia coli* (N = 155)**									
Antimicrobial	**South-West**		**Center**		**East**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	9	9.8%	51	55.4%	32	34.8%	92	59.4%	51.5–66.8
Diaminopyridine derivates	6	33.3%	10	55.6%	2	11.1%	18	11.6%	7.5–17.6
Fluoroquinolones	1	14.3%	5	71.4%	1	14.3%	7	4.5%	2.2–9.0
Tetracyclines	11	19.3%	33	57.9%	13	22.8%	57	36.8%	29.6–44.6
Sulfonamides	9	18.4%	28	57.1%	12	24.5%	49	31.6%	24.8–39.3
Penicillins	7	18.4%	23	60.5%	8	21.1%	38	24.5%	18.4–31.8

South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI). 95% CI: 95% confidence interval; Fluoroquinolones: Ciprofloxacin; Tetracyclines: Tetracycline; Sulfonamides: Sulfamethoxazole; Penicillins: Ampicillin; Diaminophyridine derivates: Trimethoprim

ly important fluoroquinolones has increased constantly on a high level since 2014; resistance against ampicillin increased as well, but on a lower level. On the contrary, resistance rates against tetracyclines and sulfonamides have decreased since 2014. The proportion of fully susceptible isolates is 37.4%.

In contrast, trends for resistance levels of *E. coli* from fattening pigs and slaughter calves are generally more similar (Figures 9. c and 9. d). There is no antimicrobial class for which a significant increase could be detected. Over the years, decreasing trends are obvious for sulfonamides, tetracyclines and ampicillin and levels of fluoroquinolone resistances are constantly on a low level for both livestock species. The same is true for resistance against amphenicols. The proportion of fully susceptible isolates is 58.7% and 60.4% for fattening pigs and slaughter calves, respectively.

These overall resistance differences between poultry, porcine and bovine *E. coli* populations are also visible in the data from the European antimicrobial resistance monitoring until 2017, with distinct discrepancies in some countries [1]. Concerning fluoroquinolone resistance in *E. coli* from broilers, a decrease was noted in the Netherlands as well as in Ireland. Moreover, in Poland and France still increasing trends for antimicrobial resistances in *E. coli* from fattening pigs and in Austria and Belgium from slaughter calves were found. If different trends in antimicrobial resistance may reflect differences in usage of antimicrobials, further analyzes are needed in the future. In broilers, mostly fluoroquinolones and penicillins are used. Therefore, the increasing trends in antimicrobial resistance against these two classes may indicate that the usage of these antimicrobials is still at a level that increases resistance, despite efforts to minimize usage of antimicrobials in Swiss livestock. However, the resistance

prevalence in broiler flocks is also influenced by factors such as age and flock management, and different possible routes of transmission of ESBL/pAmpC-producing bacteria in the broiler production pyramid are known [6]

Sulfonamides, tetracyclines and penicillins are the most widely used antimicrobials in pigs and calves in Switzerland. The overall positive trends in decreasing antimicrobial resistance rates against these antimicrobials are not diminished by the detection of two ESBL/pAmpC-producing *E. coli* in slaughter calves. The detection of such *E. coli* isolates during the non-selective method succeeds only by chance and is not a sign of an increasing prevalence of these multi-drug resistant bacteria. This is shown by the data from the selective detection described in the following chapter. In contrast to our findings, von Ah *et al.* (2019) analyzed the occurrence of quinolone-resistant *E. coli* in environmental samples from Swiss pig farms. With selective enrichment they found high proportions of quinolone-resistant *E. coli* in manure, on pen walls and in dust samples. But the prevalence was higher in breeding farms than in samples from fattening farms [2]. Comparing resistance rates of *E. coli* from Swiss slaughter calves at the end of the fattening period with data from the beginning of the fattening period, the resistance rates for tetracyclines, sulfonamides and ampicillin are found to be more prevalent at the beginning, too, but on a higher level [3]. Moreover, Hausherr *et al.* demonstrated that approx. 50% of the resistant *E. coli* isolates showed decreased susceptibility to quaternary ammonium compounds as well [3]. The decreasing trends in antimicrobial resistance against these classes may reflect the decreasing trends in usage of these antimicrobials in Swiss livestock production. Reliable data on usage of antimicrobials in the future should provide a better knowledge of the potential drivers in the development of antimicrobial resistance in commensal *E. coli*.

9.2 ESBL/pAmpC-producing *Escherichia coli*

In the last decade, 3rd generation cephalosporin-resistant bacteria have increasingly been detected among livestock in various countries [1]. The activity of beta-lactamases enables these multidrug-resistant bacteria to inactivate beta-lactam-antimicrobials by breaking their beta-lactam ring. A broad variety of types could be detected [4]. As a rule, extended spectrum beta-lactamase-(ESBL) producing bacteria are resistant to 3rd and 4th generation cephalosporins and monobactams, but susceptible to clavulanic acid. In contrast, plasmid-mediated AmpC beta-lactamase-producing bacteria are resistant to 3rd generation cephalosporins, including beta-lactamase inhibitors such as clavulanic acid and cephamycins. On the other hand, they do not usually mediate resistance to 4th generation cephalosporins. But various mixed resistance patterns between these have been described.

Both ESBL and pAmpC are produced by intestinal bacteria. Most of them are commensals and do not induce any illness in the host. But 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. Moreover, 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, clinical cases may take a severe course in vulnerable patients such as elderly people or patients with a weak immune system, rendering antimicrobial treatment necessary. Pathogenic bacteria harboring ESBL or pAmpC resistance genes are difficult to treat, thus prolonging or worsening disease course [5]. 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. As a consequence, *E. coli* isolates from livestock animals are also used to measure the spread of bacteria that produce ESBL or pAmpC.

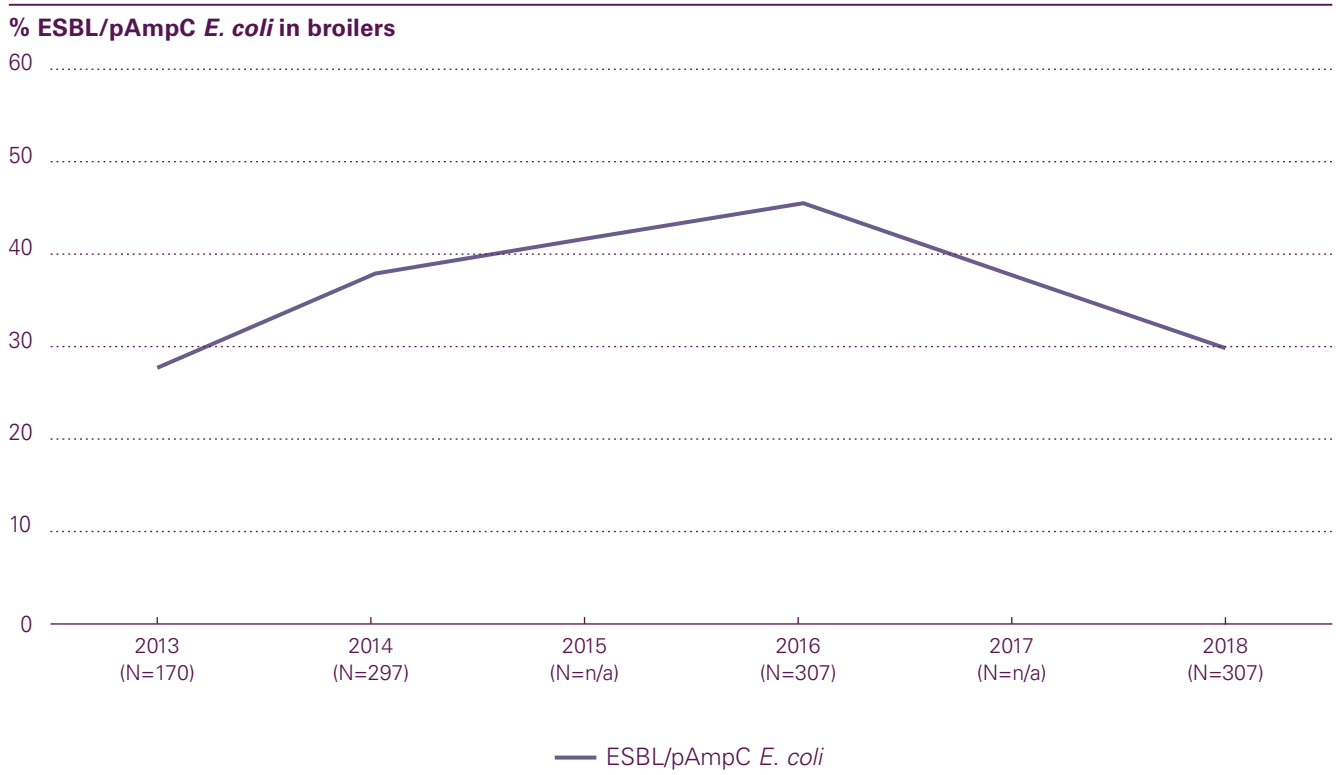
9.2.1 ESBL/pAmpC-producing *Escherichia (E.) coli* in broilers

In 2018, a random sample of 307 broiler flocks was investigated at slaughter for the occurrence of ESBL/AmpC-producing *E. coli* using cecal samples (5 pooled cecal samples per flock). By applying selective enrichment methods, 94 isolates of presumptive ESBL/AmpC-producing *E. coli* were isolated. This corresponds to a flock prevalence of 30.6% (Figure 9. g). Compared to 2016, the prevalence of ESBL/AmpC-producing *E. coli* decreased significantly in the Swiss broiler population.

Details on multi-drug resistance patterns are shown in Table 9. g. Besides resistance to 3rd and 4th generation cephalosporins, ESBL/pAmpC-producing *E. coli* showed high resistance levels to ciprofloxacin (66%), sulfonamides (53.2%) and tetracyclines (37.2%). In contrast, resistance rates to macrolides (1%) and aminoglycosides (9.6%) were low. No resistance against carbapenems was observed. 97 isolates (84%) were resistant to a 4th generation cephalosporin (e. g. cefepime), which serves as an indicator for the presence of ESBL-producers. On the other hand, 37.2% of the isolates were resistant to cefoxitin, which is an indicator for pAmpC-producers.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimicrobial resistance in livestock. Because of the very low number of isolates, statistically significant conclusions could not yet be drawn (Table 9. h).

Figure 9. g: Prevalence of ESBL/pAmpC-producing *Escherichia coli* from broilers between 2013 and 2018 (N = total number of tested isolates, values for 2015 and 2017 interpolated [n/a].



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

In 2019, a random sample of 306 fattening pigs was investigated at slaughter for the occurrence of ESBL/AmpC-producing *E. coli* using cecal samples. By applying selective enrichment methods, 40 isolates of presumptive ESBL/AmpC-producing *E. coli* were isolated. This corresponds to a herd prevalence of 13.1% (Figure 9. h). Compared to 2017 the prevalence of ESBL/AmpC-producing *E. coli* decreased in the Swiss fattening pig population.

Besides resistance to 3rd and 4th generation cephalosporins, ESBL/pAmpC-producing *E. coli* showed high resistance levels to sulfonamides and tetracyclines (57.5% each), trimethoprim (35.0%), ciprofloxacin (42.5%), amphenicols (25%) and gentamicin (22.5%). In contrast, resistance rates to macrolides (1%) was low. No resistance against carbapenems was observed. 30 isolates (75%) were resistant to a 4th generation cephalosporin (e.g. cefepime), which serves as an indicator for the presence of ESBL-producers. On the other hand, 35.0% of the isolates were resistant to cefoxitin, which is an indicator for pAmpC-producers.

Details on multi-drug resistance patterns are shown in Table 9. i. Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimicrobial resistance in livestock. Because of the very low number of isolates, statistically significant conclusions could not yet be drawn (Table 9. j).

9.2.3 ESBL/pAmpC-producing *Escherichia coli* in slaughter calves

In 2019, a random sample of 298 slaughter calves was investigated for the occurrence of ESBL/AmpC-producing *E. coli* using cecal samples. By applying selective enrichment methods, 98 isolates of presumptive ESBL/AmpC-producing *E. coli* were isolated. This corresponds to a herd prevalence of 32.9% (Figure 9. i). Compared to 2017, the prevalence of ESBL/AmpC-producing *E. coli* did not change in the Swiss slaughter calf population.

Details on multi-drug resistance patterns are shown in Table 9. k. Besides resistance to 3rd and 4th generation cephalosporins, ESBL/pAmpC-producing *E. coli* showed high resistance levels to sulfonamides (78.6%) and tetracyclines (79.6%), gentamicin (48%), trimethoprim (42.9%), ciprofloxacin (41.8%) and amphenicols (36.7%). In contrast, resistance rates to macrolides (7%) were lower. No resistance against carbapenems was observed. 69 isolates (70.4%) were resistant to a 4th generation cephalosporin (e.g. cefepime), which serves as an indicator for the presence of ESBL-producers. On the other hand, 33.7% of the isolates were resistant to cefoxitin, which is an indicator for pAmpC-producers.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimicrobial resistance in livestock. Because of the very low num-

Table 9. g: Non-susceptibility combinations in ESBL/pAmpC-producing *E. coli* in broilers in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**94**	
Number of Resistances: 2	**1**	**1.1%**
3rd generation cephalosporins – Penicillins	1	100.0%
Number of Resistances: 3	**9**	**9.6%**
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins	6	66.7%
3rd generation cephalosporins – Cephamycin – Penicillins	3	33.3%
Number of Resistances: 4	**29**	**30.9%**
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Penicillins	6	20.7%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins	12	41.4%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Sulfonamides	3	10.3%
3rd generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins	8	27.6%
Number of Resistances: 5	**14**	**14.9%**
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins	5	35.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Penicillins - Sulfonamides	1	7.1%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Penicillins – Sulfonamides	2	14.3%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Sulfonamides – Tetracyclines	3	21.4%
3rd generation cephalosporins – Aminoglycosides – Cephamycin – Penicillins – Sulfonamides	1	7.1%
3rd generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides	1	7.1%
3rd generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	1	7.1%
Number of Resistances: 6	**13**	**13.8%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Fluoroquinolones – Penicillins – Sulfonamides	2	15.4%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides	1	7.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	3	23.1%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	5	38.5%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	2	15.4%
Number of Resistances: 7	**23**	**24.5%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	3	13.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	1	4.3%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones - Penicillins – Sulfonamides – Tetracyclines	19	82.6%
Number of Resistances: 8	**4**	**4.3%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	1	25.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	25.0%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	25.0%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	25.0%

Resistance patterns	Number of isolates	% of total
Number of Resistances: 10	**1**	**1.1%**
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	100.0%

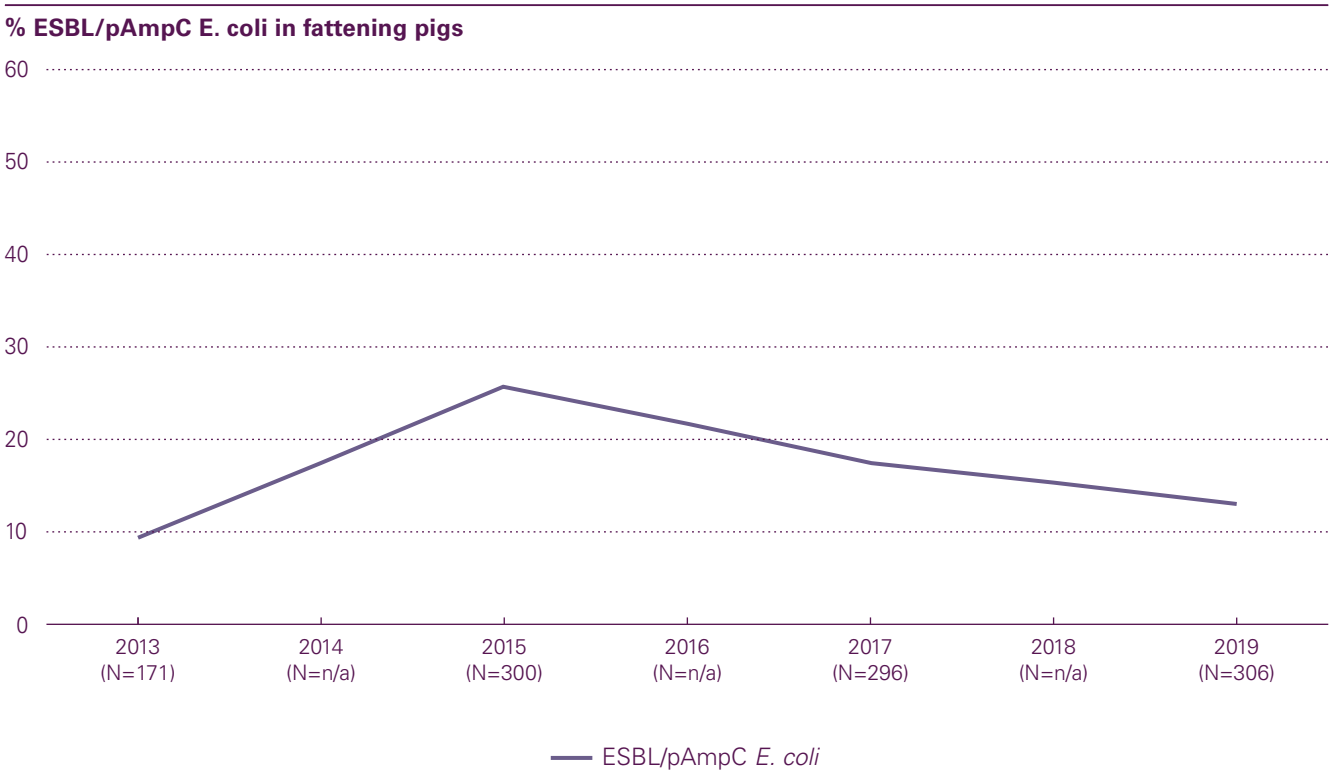
Penicillins: Ampicillin, 3rd gen; Cephalosporins: Cefotaxime, Ceftazidime; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; Polymyxins: Colistin; Amphenicols: Chloramphenicol
The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.09.4).

Table 9. h: Number of ESBL/pAmpC-producing *E. coli* in broilers in 2018 by Swiss region.

Swiss region	No. of samples*	No. of ESBL/pAmpC-producing *E. coli* positive samples (%)
South-West	117	30 (25.2%)
Central	127	42 (33.1%)
East	62	22 (35.5%)
Total	**306**	**94 (30.6%)**

* the region of one sample the region was unknown
South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI).

Figure 9. h: Prevalence of ESBL/pAmpC-producing *Escherichia coli* from fattening pigs between 2013 and 2019 (N = total number of tested isolates, values for 2014, 2016 and 2018 interpolated [n/a].



ber of isolates, statistically significant conclusions could not yet be drawn (Table 9. l).

9.2.4 Discussion

Using selective enrichment methods, ESBL/pAmpC-producing *E. coli* were found in 30.6% of all broiler flocks in 2018, 13.1% of fattening pigs and 32.9% of slaughter calves in 2019. Hence, the prevalence of ESBL/pAmpC-producing *E. coli* decreased significantly for broilers (2016: > 50%) and slightly for fattening pigs; the prevalence of ESBL/pAmpC-producing *E. coli* in slaughter calves remained stable compared to 2017. Overall, a decreasing trend of ESBL/pAmpC-producing *E. coli* is seen in broilers and fattening pigs since 2014, while the prevalence in

Table 9. i: Non-susceptibility combinations in ESBL/pAmpC-producing *E. coli* in fattening pigs in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**40**	
Number of Resistances: 3	**7**	**17.5%**
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins	5	71.4%
3rd generation cephalosporins – Cephamycin – Penicillins	2	28.6%
Number of Resistances: 3	**9**	**9.57%**
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins	6	66.7%
3rd generation cephalosporins – Cephamycin – Penicillins	3	33.3%
Number of Resistances: 4	**10**	**25.0%**
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Penicillins	1	10.0%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins	3	30.0%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Tetracyclines	2	20.0%
3rd generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins	2	20.0%
3rd generation cephalosporins – Cephamycin – Penicillins – Sulfonamides	1	10.0%
3rd generation cephalosporins – Cephamycin – Penicillins – Tetracyclines	1	10.0%
Number of Resistances: 5	**6**	**15.0%**
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Penicillins – Sulfonamides	1	16.7%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins – Tetracyclines	1	16.7%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins– Sulfonamides – Tetracyclines	2	33.3%
3rd generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Penicillins – Sulfonamides	1	16.7%
3rd generation cephalosporins – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	1	16.7%
Number of Resistances: 7	**7**	**17.5%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Fluoroquinolones – Penicillins – Sulfonamides	1	14.3%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Penems and monobactams – Penicillins – Sulfonamides – Tetracyclines	1	14.3%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	4	57.1%
3rd generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	1	14.3%
Number of Resistances: 8	**8**	**20.0%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	1	12.5%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	2	25.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	12.5%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	12.5%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	2	25.0%
3rd generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	1	12.5%

slaughter calves has remained stable on a high level (>30%) since 2015.

Using the same selective method as in the European monitoring, comparatively lower rates of ESBL/AmpC-producing *E. coli* were found in Switzerland than in other European countries. Within the EU, in 2017 the mean prevalence of ESBL/pAmpC-producing *E. coli* in calves was 44.5%, in fattening pigs 43.8% and in broilers 48.3%, but differences between countries are obvious. For example, the prevalence of *E. coli*

Resistance patterns	Number of isolates	% of total
Number of Resistances: 9	**2**	**5.0%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	50.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	50.0%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidime; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracycline; Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; Polymyxins: Colistin; Amphenicols: Chloramphenicol
The distribution of the minimum inhibitory concentrations (MICs) are shown in the online version in Annex II (Table II.09.5).

Table 9. j: Number of ESBL/pAmpC-producing *E. coli* in fattening pigs in 2019 by Swiss region.

Swiss region	No. of samples*	No. of ESBL/pAmpC-producing *E. coli* positive samples (%)
South-West	14	3 (21.4%)
Central	147	16 (10.9%)
East	127	19 (15.0%)
Total	**306**	**40 (13.1%)**

* the region of 18 samples was unknown
South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI).

Figure 9. i: Prevalence of ESBL/pAmpC-producing *Escherichia coli* from slaughter calves between 2013 and 2019 (N = total number of tested isolates, values for 2014, 2016 and 2018 interpolated [n/a].

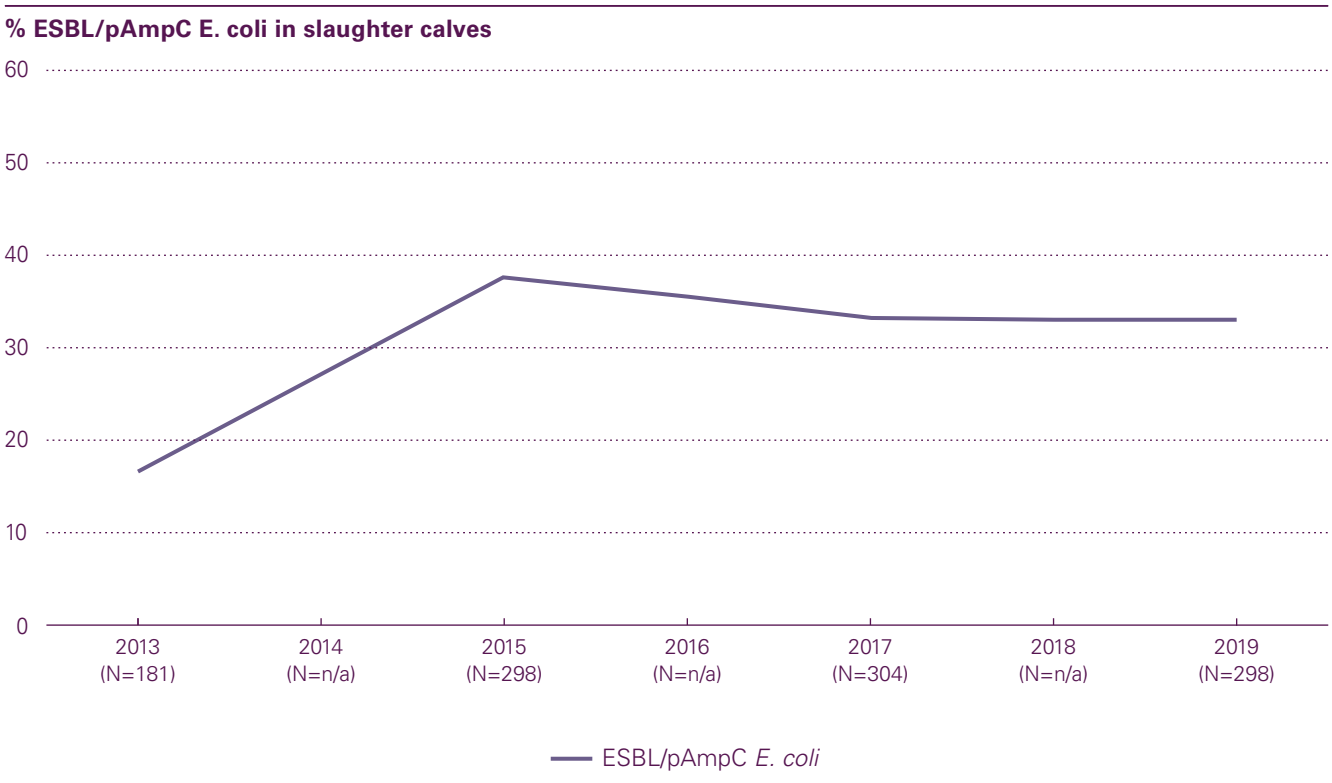


Table 9. k: Non-susceptibility combinations in ESBL/pAmpC-producing *E. coli* in slaughter calves in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**98**	
Number of Resistances: 2	**1**	**1.0%**
3rd generation cephalosporins – Penicillins	1	100.0%
Number of Resistances: 3	**6**	**6.1%**
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins	2	33.3%
3rd generation cephalosporins – Cephamycin – Penicillins	3	50.0%
3rd generation cephalosporins – Penicillins – Tetracyclines	1	16.7%
Number of Resistances: 4	**9**	**9.2%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Penicillins	4	44.4%
3rd generation cephalosporins – 4th generation cephalosporins –Fluoroquinolones – Penicillins	4	44.4%
3rd generation cephalosporins – Cephamycin – Penicillins – Tetracyclines	1	11.1%
Number of Resistances: 5	**15**	**15.3%**
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Fluoroquinolones – Penicillins	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Macrolides – Penicillins	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins – Tetracyclines	2	13.3%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Sulfonamides – Tetracyclines	4	26.7%
3rd generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Penicillins – Sulfonamides	1	6.7%
3rd generation cephalosporins – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	6	40.0%
Number of Resistances: 6	**17**	**17.3%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Fluoroquinolones – Penicillins	1	5.9%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Penicillins – Sulfonamides – Tetracyclines	4	23.5%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	5.9%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	3	17.6%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	2	11.8%
3rd generation cephalosporins – Aminoglycosides – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	5	29.4%
3rd generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	5.9%
Number of Resistances: 7	**19**	**19.4%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	5.3%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	1	5.3%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	2	10.5%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	2	10.5%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	6	31.6%
3rd generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Penicillins – Sulfonamides - Tetracyclines	6	31.6%
3rd generation cephalosporins – Aminoglycosides – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	5.3%

Resistance patterns	Number of isolates	% of total
Number of Resistances: 8	**20**	**20.4%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	1	5.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	9	45.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	5.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Penicillins – Sulfonamides – Tetracyclines	1	5.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	3	15.0%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	3	15.0%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	5.0%
3rd generation cephalosporins – Amphenicols - Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	5.0%
Number of Resistances: 9	**9**	**9.2%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	1	11.1%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	2	22.2%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	11.1%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	3	33.3%
3rd generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	2	22.2%
Number of Resistances: 10	**2**	**2.0%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	50.0%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	50.0%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidime; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; Polymyxins: Colistin; Amphenicols: Chloramphenicol
The distribution of the minimum inhibitory concentrations (MICs) are shown in the online version in Annex II (Table II.09.6).

Table 9. I: Number of ESBL/pAmpC-producing *E. coli* in slaughter calves in 2019 by Swiss region.

Swiss region	No. of samples*	No. of ESBL/pAmpC-producing *E. coli* positive samples (%)
South-West	32	11 (34.4%)
Central	130	47 (36.2%)
East	69	14 (20.3%)
Total	**298**	**98 (32.9%)**

* the region of 68 samples was unknown
South-West (cantons FR, VD, VS, NE, GE, JU), Center (cantons BE, LU,OW, NW, SO, BS, BL, AG), East (cantons ZH, UR, SZ, GL, ZG, SH, AR, AI, SG, GR, TG, TI).

ESBL and/or AmpC-producers ranges from 0.8% (Cyprus) to 87.4% (Italy) in fattening pigs; from 7.1% (Denmark) to 89.0% (Italy) in calves under 1 year of age; and from 10.3% (the UK) to 100% (Malta) in broilers [1]. Besides regional differences, in many European countries an overall slight decrease of the prevalence of ESBL/AmpC-producing *E. coli* has been observed, and some member states report a considerable improvement, such as Switzerland for broilers.

The prevalence in broiler flocks is influenced by different factors such as age, flock management including use of antimicrobials; and different possible routes of transmission of ESBL/pAmpC-producing bacteria in the broiler production pyramid are known [6]. In pigs, ESBL/pAmpC-producing *E. coli* are not only found at the end of the fattening period in healthy pigs, but also in clinical cases of diarrhea in neonatal and post-weaning piglets [7]. For veal calves it was shown that the prevalence of ESBL/pAmpC-producing *E. coli* decreased between the beginning and the end of the fattening period [8], which needs to be considered when interpreting ESBL/pAmpC-producing *E. coli* prevalence measured at the end of the fattening period as in the European monitoring system.

The main drivers for the detected trends in ESBL/pAmpC-producing *E. coli* prevalence in Switzerland remains unclear. Reliable data an antimicrobial usage in livestock may contribute to the identification of risk factors and thereby further improve the situation concerning the occurrence of ESBL/pAmpC-producing *E. coli* in the Swiss livestock population.

The large heterogeneity of resistance genes in ESBL/pAmpC-producing *E. coli* makes the comparison of different genes and resistance patterns from isolates of food-producing animals, raw meat and humans difficult. Even though exposure to animals is regarded as a risk factor, evidence for a direct transfer of ESBL/AmpC-producing bacteria from animals to humans through close contact is limited [9]. Recently, Dorado-Garcia *et al.* (2018) performed a comprehensive study on the molecular relatedness of ESBL/pAmpC-producing *E. coli* from different sources, including livestock and humans. They showed that besides distinguishable ESBL/AmpC-producing *E. coli* transmission cycles in different hosts, they could not demonstrate a close epidemiological linkage of ESBL/AmpC genes and plasmid replicon types between livestock and humans [10].

9.3 Carbapenemase-producing *Escherichia coli*

In 2018, 307 pooled cecal samples from broiler flocks were analyzed for the presence of carbapenemase-producing *E. coli* using selective enrichment methods. In 2019, the same method was applied on 306 cecal samples from fattening pigs and 298 cecal samples from slaughter calves. As in previous years, none of the samples tested positive for carbapenemase-producing *E. coli*. More details on the situation of carbapenemase-producing gram-negative bacteria in Switzerland are given in Chapter 13 in this report.

9.4 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. It is also part of the normal flora of a broad variety of animals. Infections with *S. aureus* can occur when skin or tissues are damaged [11]. Beta-lactamase-resistant modified semi-synthetic penicillin such as methicillin was introduced in 1959 for human medicine. However, one year later, the first methicillin-resistant *S. aureus* (MRSA) appeared [12]. In the following decades, MRSA emerged as a major cause of health-care associated infections, although its occurrence was restricted to hospitals and other health-care facilities ("hospital-acquired (HA) MRSA"). In the 1990s, an increasing incidence of hospital-independent human MRSA infections was observed [13]. These so-called "community-acquired (CA) MRSA" had been reported by many countries worldwide. More recently, with the emergence of MRSA in animals, MRSA gained a "One Health" dimension [14]. Numerous studies have shown that especially pigs can be heavily colonized with MRSA. These "livestock-associated (LA) MRSA" can be associated with infections not only in animals but also in humans. 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 [15–16].

9.4.1 MRSA in fattening pigs

In 2019, a random sample of 303 fattening pigs was investigated at slaughter for the occurrence of MRSA using nasal swab samples. By applying a one-step enrichment method, 160 MRSAs were isolated. This corresponds to a herd prevalence of 52.8% (Figure 9. j). Compared to 2017, the prevalence of MRSA has once more increased in the Swiss fattening pig population. All isolates are livestock-associated MRSA (Clonal Complex 398). The distribution of the minimum inhibitory concentrations (MICs) is shown in the online version in Annex II (Table II.09.7).

Details on multi-drug resistance pattern are shown in Table 9. m. Besides resistance to beta-lactam antibiotics, MRSA showed very high resistance levels to tetracyclines (95.0%), high resistance rates to trimethoprim and ciprofloxacin (31.4% each) and tiamulin, streptomycin and clindamycin (28.3% each). Moreover, resistance rates against quinupristin/dalfopristin (27.0%) and gentamycin as well as kanamycin was high (17.0% each). In contrast, only one isolate showed resistance against rifampicin (0.6%) and no re-

sistance against vancomycin, linezolid and mupirocin was detected. All MRSAs, except one, belonged to the livestock-associated clonal complex 398.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of the flocks was, for the first time, integrated in the analyses of antimicrobial resistance in livestock. Because of the very low number of isolates, statistically significant conclusions could not yet be drawn (Table 9. n).

9.4.2 MRSA in slaughter calves

In 2019, a random sample of 299 slaughter calves was investigated for the occurrence of MRSA using nasal swab samples. By applying a one-step enrichment method, 11 MRSAs were isolated. This corresponds to a herd prevalence of 3.8% (Figure 9. k). Compared to 2017, the prevalence of MRSA decreased to the lowest detected level since 2013 in the Swiss slaughter calf population.

Details on multi-drug resistance patterns are shown in Table 9. o. Besides resistance to beta-lactam antibiotics, MRSA showed very high resistance levels to tetracyclines (100.0%), high resistance rates to clindamycin and erythromycin (54.5% each), and to ciprofloxacin (45.5%). Moreover, resistance rates against quinupristin/dalfopristin and streptomycin (36.4%) and tiamulin and trimethoprim (27.3% each) was high. In contrast, no isolate showed resistance against rifampicin, vancomycin, linezolid or mupirocin. All MRSAs belonged to the livestock-associated clonal complex 398.

Because of the very low number of MRSA isolates in Swiss slaughter calves, the analysis concerning differences between different regions in Switzerland was not conducted.

9.4.3 Discussion

In Switzerland, the prevalence of MRSA in fattening pigs at slaughter has increased continuously and significantly since the first analyses in 2009. In 2016, Bangerter *et al.* [17] conducted comprehensive studies of the individual colonization dynamics of MRSA throughout Swiss pig production. It could be shown that almost all pigs from an MRSA-positive herd changed their MRSA status several times, which implies that pigs are transiently rather than permanently colonized. Therefore, the authors recommended defining farms as MRSA-positive or MRSA-negative and allowing the trade of pigs only within herds of the same status to avoid the further spread of MRSA. At that time, the MRSA prevalence in Swiss fattening pigs was approx. 20%. Nowadays, this strategy is outdated, as nearly every second fattening pig is MRSA positive. As no MRSA prevention measures will be taken in the Swiss pig production in the future, the MRSA prevalence in Swiss fattening pigs will further increase, and it is questionable whether future monitoring of MRSA in Switzerland is important.

Figure 9. k: Prevalence of ESBL/pAmpC-producing *Escherichia coli* from slaughter calves between 2014 and 2019 (N = total number of tested isolates, values for 2014, 2016 and 2018 interpolated [n/a].

Table 9. m: Non-susceptibility combinations in MRSA infattening pigs in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**159***	
Number of Resistances: 2	**3**	**1.9%**
Cephamycin – Penicillins	1	33.3%
Penicillins – Tetracyclines	2	66.7%
Number of Resistances: 3	**36**	**22.6%**
Aminoglycosides – Penicillins – Tetracyclines	3	8.3%
Cephamycin – Penicillins – Tetracyclines	33	91.7%
Number of Resistances: 4	**50**	**31.4%**
Aminoglycosides – Cephamycin – Penicillins – Tetracyclines	32	64.0%
Amphenicols – Cephamycin – Penicillins – Tetracyclines	1	2.0%
Cephamycin – Diaminopyrimidine derivatives – Penicillins – Tetracyclines	1	2.0%
Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	16	32.0%
Number of Resistances: 5	**16**	**10.1%**
Aminoglycosides – Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	2	12.5%
Amphenicols – Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	12	75.0%
Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Tetracyclines	1	6.3%
Cephamycin – Fluoroquinolones – Penicillins – Steroid antibiotics – Tetracyclines	1	6.3%
Number of Resistances: 6	**16**	**10.1%**
Aminoglycosides – Amphenicols – Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	4	25.0%
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Tetracyclines	3	18.8%
Aminoglycosides – Cephamycin – Lincosamides – Macrolides – Penicillins – Tetracyclines	1	6.3%
Amphenicols – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	6.3%
Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Penicillins – Pleuromutilins – Streptogramin	7	43.8%
Number of Resistances: 7	**4**	**2.5%**
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Pleuromutilins – Tetracyclines	1	25.0%
Aminoglycosides – Diaminopyrimidine derivatives – Lincosamides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	1	25.0%
Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	2	50.0%
Number of Resistances: 8	**16**	**10.1%**
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Lincosamides – Penicillins – Pleuromutilins – Tetracyclines	1	6.3%
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	2	12.5%
Aminoglycosides – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	1	6.3%
Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	12	75.0%
Number of Resistances: 9	**15**	**9.4%**
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Lincosamides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	6	40.0%
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	8	53.3%
Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	1	6.7%

Resistance patterns	Number of isolates	% of total
Number of Resistances: 10	**2**	**1.3%**
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Lincosamides – Penicillins – Pleuromutilins – Steroid antibiotics – Streptogramin – Tetracyclines	1	50.0%
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Steroid antibiotics – Streptogramin – Tetracyclines	1	50.0%
Number of Resistances: 11	**1**	**0.6%**
Aminoglycosides – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	1	100.0%

* one isolate could not be analyzed
Penicillins: Penicillin; Cephamycin: Cefoxitin; Sulfonamides: Sulfamethoxazole; Aminoglycosides: Gentamicin, Kanamycin, Streptomycin; Fluoroquinolones: Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin; Diaminopyrimidine derivatives: Trimethoprim; Pleuromutilins: Tiamulin; Amphenicols: Chloramphenicol; Lincosamides: Clindamycin; Streptogramin: Quino-/Dalfopristin; Steroid antibiotics: Fusidic acid

Table 9. n: Number of MRSA in fattening pigs in 2019 by Swiss region.

Swiss region	No. of samples*	No. of MRSA-positive samples (%)
West-South	8	4 (50.0%)
Mid	132	67 (50.8%)
East	136	72 (52.9%)
Total	**303**	**160 (52.8%)**

* from 17 sample the region was unknown

Figure 9. j: Prevalence of MRSA from fattening pigs between 2013 and 2019 (N = total number of tested isolates, values for 2014, 2016 and 2018 interpolated [n/a].

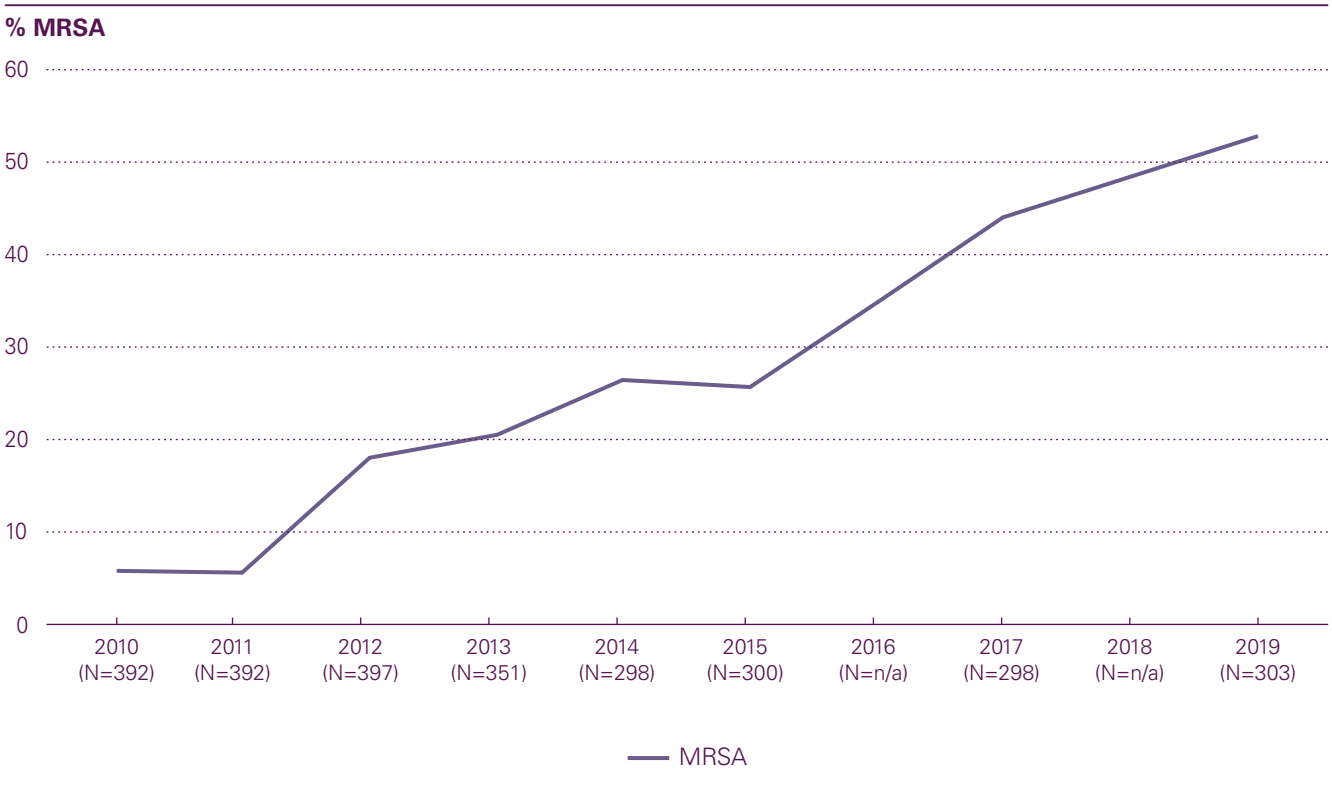


Table 9. o: Non-susceptibility combinations in MRSA slaughter calves in 2019.

Resistance patterns	Number of isolates	% of total
Grand Total	**9**	
Number of Resistances: 1	**1**	**11.1%**
Aminoglycosides	1	100.0%
Number of Resistances: 3	**1**	**11.1%**
Cephamycin – Penicillins – Tetracyclines	1	100.0%
Number of Resistances: 4	**2**	**22.2%**
Aminoglycosides – Cephamycin – Penicillins – Tetracyclines	1	50.0%
Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	1	50.0%
Number of Resistances: 5	**1**	**11.1%**
Amphenicols – Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	1	100.0%
Number of Resistances: 7	**1**	**11.1%**
Cephamycin – Fluoroquinolones – Lincosamides – Macrolides – Penicillins – Streptogramin – Tetracyclines	1	100.0%
Number of Resistances: 8	**2**	**22.2%**
Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	2	100.0%
Number of Resistances: 9	**1**	**11.1%**
Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Lincosamides – Macrolides – Penicillins – Pleuromutilins – Streptogramin – Tetracyclines	1	100.0%

* three isolates could not be analyzed
Penicillins: Penicillin; Cephamycin: Cefoxitin; Sulfonamides: Sulfamethoxazole; Aminoglycosides: Gentamicin, Kanamycin, Streptomycin; Fluoroquinolones: Ciprofloxacin; Tetracyclines: Tetracycline; Macrolides: Erythromycin; Diaminopyrimidine derivatives: Trimethoprim; Pleuromutilins: Tiamulin; Amphenicols: Chloramphenicol; Lincosamides: Clindamycin; Streptogramin: Quino-/Dalfopristin; Steroid antibiotics: Fusidic acid

Humans in close contact with livestock are at higher risk of being carriers of livestock-associated MRSA [16]. 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. Hence, it will be of interest to see whether, in future, more livestock-associated MRSAs will be diagnosed in the context of severe infections in hospitalized humans (septicemia) in Switzerland.

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Textbox

Methicillin-Resistant *Macrococcus caseolyticus* in the Nose of Pigs and Cattle in Switzerland

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Macrococcus caseolyticus belongs to the normal skin flora of dairy animals and can also be found in milk and meat. In rare cases, it has been associated with infections in dogs and cattle (1). These past years, macrococci have come under more scrutiny due to their potential to acquire and spread antibiotic resistance genes, including methicillin resistance genes *mecB* and *mecD*, to the closely related *Staphylococcus aureus* (2, 3).

However, dissemination and prevalence of methicillin-resistant M. *caseolyticus* in food-producing animals in Switzerland was unknown. We therefore took advantage of the samples intended for the national monitoring of methicillin-resistant *S. aureus* (MRSA) in pigs and cattle in Switzerland to determine the prevalence of methicillin-resistant *M. caseolyticus* in the nasal cavities of these animals at slaughterhouses in 2019. The samples were taken based on a representative sampling strategy aiming at analyzing approximately 300 samples taken at the nine largest Swiss slaughterhouses for pigs and calves.

Methicillin-resistant *M. caseolyticus* were isolated on MRSA-selective agar plates and identified using Maldi Tof mass spectrometry. The strains were characterized using different molecular tools. The prevalence of methicillin-resistant *M. caseolyticus* in calves was 11.37% (95% CI, 8.25–15.47%), which was higher than the prevalence of MRSA [3.68% (95% CI, 2.07–6.47%)] in the same samples. On the other hand, the prevalence of methicillin-resistant *M. caseolyticus* in pigs was 2.65% (95% CI, 1.35–5.14%) and lower than that of MRSA [52.81% (95% CI, 47.18–58.36%)]. The positive samples from calves originated from animals raised in 12 cantons and those from pigs in 5 cantons. The majority of the *M. caseolyticus* strains (n = 40) contained the *mecD* gene, while the *mecB* gene was only detected in two strains. In addition to resistance to beta-lactams, resistance to tetracyclines, aminoglycosides, macrolides, lincosamides and fusidic acid were also detected.

Based on 7 allele multilocus sequence typings (MLST), the strains were highly diverse, indicating that the spread of methicillin-resistant *M. caseolyticus* in Switzerland is not associated with a common source and a predominant clonal lineage. Nevertheless, the presence of methicillin-resistant *M. caseolyticus* in the nasal cavities of calves and pigs raises the question whether raw milk or whey feeding play a role in the dissemination of these strains in food-producing animals. In this regard, methicillin-resistant *M. caseolyticus* has already been detected in bulk tank milk in other countries (4), but the situation in Switzerland is not known.

Further attention should be paid to *Macrococcus*, which appears to be an important reservoir of genes conferring resistance to critically important antibiotics and which has the potential to cause infections.

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10

Resistance in indicator bacteria from meat

10 Resistance in indicator bacteria from meat

Antimicrobial resistance in indicator bacteria isolated from the intestinal tract of healthy livestock is monitored in order to provide information about the prevalence and types of resistance present in intestinal bacteria of animal origin. During the slaughter process, carcasses are contaminated with these bacteria and may reach the consumers by way of fresh meat and products thereof. Hence, monitoring of multidrug resistant bacteria in fresh meat of broilers, cattle and pigs helps to assess the risk for transmission to humans via handling and consumption of fresh meat. This transmission route is relevant for zoonotic bacteria such as *Campylobacter* as well. Data on findings for *Campylobacter* on fresh meat are presented in Chapter 8 of this report.

This chapter includes antimicrobial resistance rates of ESBL/pAmpC- and carbapenemase-producing *Escherichia (E.) coli* in chicken meat from 2018 and in pork and beef meat from 2019. Moreover, antimicrobial resistance rates of methicillin-resistant *Staphylococcus aureus* (MRSA) in chicken meat from 2018 and in pork and beef meat from 2019 are presented.

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

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

In 2018, 312 samples of retail chicken meat (209 samples of Swiss origin and 103 of foreign origin) were investigated for the presence of ESBL/pAmpC-producing *E. coli*. By applying a selective enrichment method, 109 samples were positive, corresponding to a prevalence of 34.9% (Table 10. a). Of the 209 Swiss samples, 44 were positive, which corresponds to a prevalence of 21.1%. Regarding foreign meat, 65 out of 103 were positive (63.1%). All isolates were subjected to antimicrobial susceptibility testing. Apart from the resistance to beta-lactam antibiotics, high to very high microbial resistance was detected for fluoroquinolones (67.9%), sulfonamides (46.8%) and tetracyclines (31.2%). A moderate to low proportion of isolates showed phenotypic resistance to diaminopyrimidines (23.9%), aminoglycosides (13.8%), amphenicols (2.8%), macrolides (1.8%) and polymyxins (0.9%). Microbiological resistance to tigecycline, meropenem and imipenem was not detected.

The prevalence of ESBL/pAmpC-producing *E. coli* in chicken meat has decreased since 2014 in both domestically produced chicken meat and meat from abroad (Figure 10. a). In 2016, 41.9% of all Swiss chicken meat was found to be positive for ESBL/pAmpC-producing *E. coli*, whereas 64.9% of all chicken meat produced abroad was positive. Swiss chicken meat was less contaminated with ESBL/pAmpC-producing *E. coli* than chicken meat produced abroad. Moreover, the decreasing trend is more pronounced in Swiss chicken meat (Figure 10. a.).

Overall, 28.4% of all ESBL/pAmpC-producing *E. coli* displayed resistance to 3rd/4th generation cephalosporins combined with resistance to fluoroquinolones only, and one single isolate displayed additional singular resistance to sulfonamides (Table 10. b). The vast majority of the ESBL/pAmpC-producing *E. coli* displayed resistance to 3rd and 4th generation cephalosporins combined with additional resistance to various antimicrobial classes.

Table 10. a: Number of ESBL/pAmpC producing *E. coli* positive samples of chicken meat by origin in 2018.

Origin	No. of samples	No. of ESBL/pAmpC-producing *E. coli* (%)
Germany	36	15
Hungary	26	21
Slovenia	31	26
France	9	3
Unknown	1	0
Total foreign countries	**103**	**65 (63.1%)**
Switzerland	**209**	**44 (21.1%)**

Figure 10. a: Trends in prevalence of ESBL/pAmpC-producing *E. coli* in chicken meat between 2014 and 2018 (N = total number of tested isolates; values for 2015 and 2017 interpolated [n/a]).

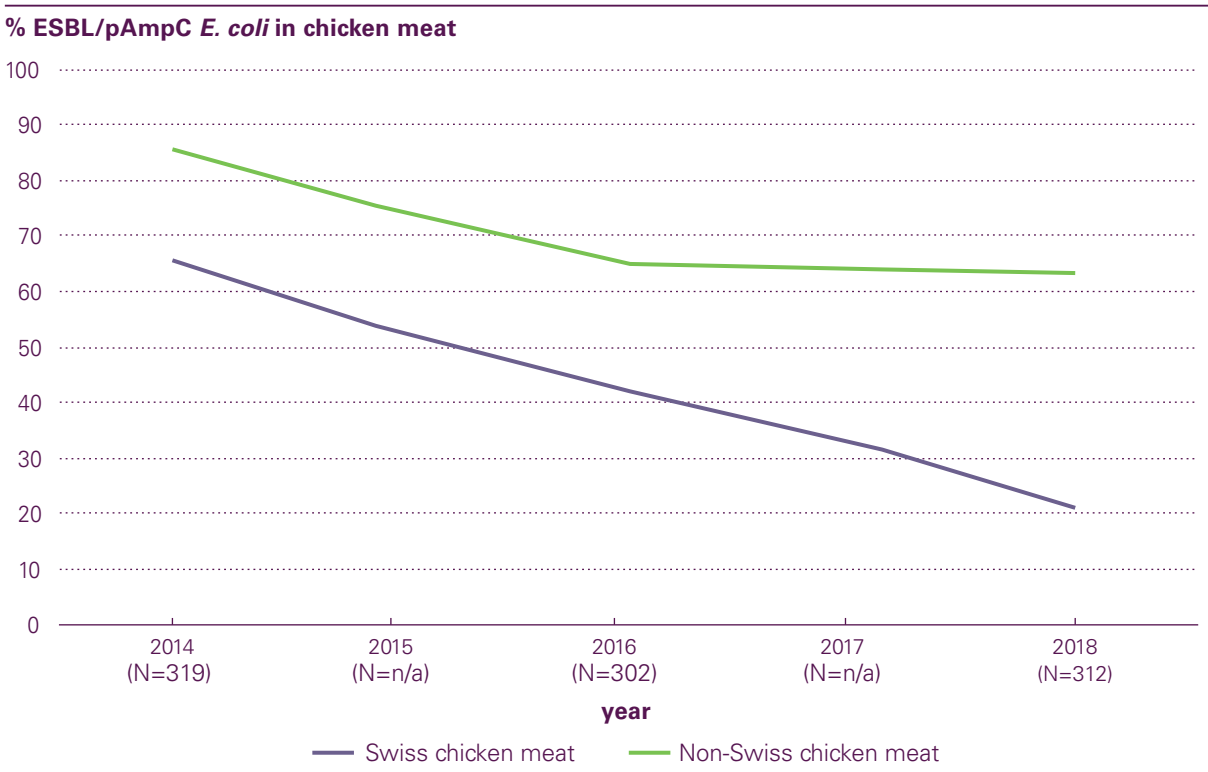

Table 10. c: Number of ESBL/pAmpC-producing *E. coli* positive samples of Swiss pork meat in 2015, 2017 and 2019.

Year of sampling	No. of samples	No. ESBL/ pAmpC-producing *E. coli* (%)
2015	301	3 (1.0%)
2017	302	1 (0.3%)
2019	311	2 (0.7%)

10.1.2. ESBL/pAmpC-producing *Escherichia coli* in pork meat

In 2019, 311 samples of Swiss pork meat at retail were investigated for the presence of ESBL/pAmpC-producing *E. coli*. By applying a selective enrichment method, two samples were positive, corresponding to a prevalence of 0.7% (Table 10. c). Hence, in contrast to chicken meat, the prevalence of ESBL/pAmpC-producing *E. coli* in Swiss pork meat remains stable on a very low level (< 1%), with sporadically positive tested samples (Table 10. c). Due to this sporadic occurrence, resistance patterns are not shown.

10.1.3. ESBL/pAmpC-producing *Escherichia coli* in beef meat

In 2019, 309 samples of beef meat (260 domestically produced and 49 from abroad) were investigated for the presence of ESBL/pAmpC-producing *E. coli*. By applying a selective enrichment method, one Swiss sample was positive, corresponding to a prevalence of 0.4% for Swiss beef meat and of 0.3% for all beef meat (Table 10. d). In 2017, two out of 299 Swiss beef samples, and in 2015 one out of 298 Swiss beef meat samples were positive for ESBL/pAmpC-producing *E. coli*. Same as in pork meat, the prevalence of ESBL/pAmpC-producing *E. coli* in beef meat remains stable on a very low level (< 1%), with sporadically positive tested samples. Due to this sporadic occurrence, resistance patterns are not shown.

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

In total, 312 chicken meat samples in 2018, and 301 pork meat and 309 beef meat samples in 2019 were collected from retailers and analyzed for the presence of carbapenemase-producing *E. coli* using selective enrichment methods. Same as in the years before, none of the meat samples tested positive for carbapenemase-producing *E. coli*.

Table 10. b: Non-susceptibility combinations of ESBL/pAmpC-producing *E. coli* in chicken meat in 2018.

Resistance patterns	Number of isolates	% of total
Grand Total	**109**	
Number of Resistances: 2	**2**	**1.8%**
3rd generation cephalosporins – Penicillins	2	100.0%
Number of Resistances: 3	**15**	**13.8%**
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins	9	60.0%
3rd generation cephalosporins – Cephamycin – Penicillins	6	40.0%
Number of Resistances: 4	**34**	**31.2%**
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Penicillins	2	5.9%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins	21	61.8%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Sulfonamides	1	2.9%
3rd generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins	10	29.4%
Number of Resistances: 5	**17**	**15.6%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Penicillins – Sulfonamides	2	11.8%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins	4	23.5%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins	1	5.9%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Penicillins – Sulfonamides	1	5.9%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins – Sulfonamides	3	17.6%
3rd generation cephalosporins – 4th generation cephalosporins – Penicillins – Sulfonamides – Tetracyclines	4	23.5%
3rd generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins	1	5.9%
3rd generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides	1	5.9%
Number of Resistances: 6	**15**	**13.8%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Fluoroquinolones – Penicillins – Sulfonamides	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Penicillins – Sulfonamides – Tetracyclines	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Tetracyclines	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	4	26.7%
3rd generation cephalosporins – 4th generation cephalosporins – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	5	33.3%
Number of Resistances: 7	**15**	**13.8%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Penicillins – Sulfonamides – Tetracyclines	4	26.7%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides	2	13.3%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidim; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; Polymyxins: Colistin; Amphenicols: Chloramphenicol

Resistance patterns	Number of isolates	% of total
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	6.7%
3rd generation cephalosporins – 4th generation cephalosporins – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	7	46.7%
Number of Resistances: 8	**6**	**5.5%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	2	33.3%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penems and monobactams – Penicillins – Sulfonamides	1	16.7%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	16.7%
3rd generation cephalosporins – Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	16.7%
3rd generation cephalosporins – Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	16.7%
Number of Resistances: 9	**5**	**4.6%**
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Amphenicols – Cephamycin – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	20.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	20.0%
3rd generation cephalosporins – 4th generation cephalosporins – Aminoglycosides – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Polymyxins – Sulfonamides – Tetracyclines	1	20.0%
3rd generation cephalosporins – 4th generation cephalosporins – Amphenicols – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Penicillins – Sulfonamides – Tetracyclines	1	20.0%
3rd generation cephalosporins – 4th generation cephalosporins – Cephamycin – Diaminopyrimidine derivatives – Fluoroquinolones – Macrolides – Penicillins – Sulfonamides – Tetracyclines	1	20.0%

Penicillins: Ampicillin; 3rd gen. Cephalosporins: Cefotaxime, Ceftazidim; 4th gen. Cephalosporins: Cefepime; Cephamycin: Cefoxitin; Sulfonamides: Sulfomethoxazole; Aminoglycosides: Gentamicin; Fluoroquinolones: Ciprofloxacin, Nalidixic acid; Tetracyclines: Tetracycline, Tigecycline; Macrolides: Azithromycin; Diaminopyrimidine derivatives: Trimethoprim; Polymyxins: Colistin; Amphenicols: Chloramphenicol

Table 10. d: Number of ESBL/pAmpC-producing *E. coli* positive samples of beef meat by origin in 2019.

Origin	No. of samples	No. ESBL/ pAmpC-producing *E. coli* (%)
Argentina	7	0
Australia	1	0
Austria	1	0
Brazil	1	0
Estonia	2	0
Ireland	12	0
Italy	1	0
Latvia	1	0
Lithuania	3	3
Paraguay	8	0
Romania	1	0
Uruguay	10	0
US	1	0
Total foreign countries	**49**	**0**
Switzerland	**260**	**1 (0.4%)**

10.2 Methicillin-resistant *Staphylococcus aureus* (MRSA)

10.2.1 MRSA in chicken meat

By applying selective enrichment methods, four MRSA isolates were obtained from 312 samples of retail chicken meat (209 samples of Swiss origin, 103 samples of foreign origin). All four MRSAs were isolated from German chicken meat samples (Table 10. e). Consequently, the prevalence in externally produced chicken meat was 3.9%, while the prevalence for Swiss chicken meat was 0.0%.

From 2014 to 2018, the prevalence of MRSA in chicken decreased continuously. In 2014, 16.1% of all foreign chicken meat was tested positive for MRSA, in 2016 the prevalence decreased to 9.3%. In 2018, only 3.9% of the foreign produced chicken meat was contaminated with MRSA. Swiss chicken meat showed a very low prevalence of 1% in 2014. In 2016 and 2018, none of the samples tested were MRSA-positive. Due to this sporadic occurrence, resistance patterns are not shown.

10.2.2 MRSA in pork meat

In 2019, 311 samples of Swiss pork meat at retail were investigated for the presence of MRSA. By applying a selective enrichment method, one sample was positive, corresponding to a prevalence of 0.3% (Table 10. f). Hence, the prevalence of MRSA in Swiss pork meat remains stable on a very low level (<1%), with sporadically positive tested samples (Table 10. f). Due to this sporadic occurrence, resistance patterns are not shown.

10.2.3 MRSA in beef meat

In 2019, 309 samples of beef meat (260 domestically produced and 49 from abroad) were investigated for the presence of MRSA. By applying a selective enrichment method, none of the beef samples was positive for MRSA in 2019. This is in agreement with results from 2015 and 2107, when none of the beef samples were positive for MRSA as well.

10.3 Discussion

10.3.1 ESBL/pAmpC-producing *Escherichia coli* in meat

Compared to 2014 and 2016, the prevalence of ESBL/pAmpC-producing *E. coli* in chicken meat in 2018 has further strongly decreased for Swiss meat (2014: 65.5%; 2016: 41.9%, 2018: 21.1%). In chicken meat from abroad, the detection rate of ESBL/pAmpC-producing *E. coli* also decreased in 2018, but still remains higher than in Swiss meat (2014: 88.9%; 2016: 81.5%, 2018: 63.1%). As the detection method was not modified during the last reporting period, this decrease is a true biological finding.

Table 10. e: Number of methicillin-resistant *Staphylococcus aureus* (MRSA) positive samples by origin of chicken meat in 2018.

Origin	No. of samples	No. of methicillin-resistant *Staphylococcus aureus* MRSA (%)
Germany	36	4
Hungary	26	0
Slovenia	31	0
France	9	0
Unknown	1	0
Total foreign countries	**103**	**4 (3.9%)**
Switzerland	**209**	**0**

Table 10. f: Number of methicillin-resistant *Staphylococcus aureus* (MRSA) positive samples of Swiss pork meat in 2015, 2017 and 2019.

Origin	No. of samples	No. of methicillin-resistant *Staphylococcus aureus* MRSA (%)
2015	301	2 (0.7%)
2017	302	2 (0.7%)
2019	311	1 (0.3%)

The prevalence of ESBL/pAmpC-producing *E. coli* in chicken meat is influenced by the prevalence in broilers. Hence, a significant decrease in the prevalence of ESBL/pAmpC-producing *E. coli* was also observed for Swiss broilers between 2016 and 2018 (Chapter 9). The prevalence of ESBL/pAmpC-producing *E. coli* in Swiss broilers, with 30.6% in 2019, was not much higher than the prevalence in Swiss chicken meat (21.1%). It is not known whether measures during slaughter and/or meat processing contributing to this positive development were taken by the Swiss poultry industry. Comparable significant decreasing trends in the same time period in other European countries may argue in favor of measures that have been taken by the poultry industries on supranational levels [1, 2].

Although the trend in the detection of ESBL/pAmpC-producing *E. coli* in Swiss chicken meat is promising compared to the prevalence of ESBL/pAmpC-producing *E. coli* in pork and beef meat, the detection rate is still remarkably high. Therefore, chicken meat poses highest risks regarding both exposure to humans and hazard characterization [3]. As a consequence, the poultry industry must further optimize its producing processes, and for consumers adequate kitchen hygiene and proper cooking of raw chicken meat are essential.

The very low prevalence of ESBL/pAmpC-producing *E. coli* in pork and beef meat (<1%) compared to the prevalence in fattening pigs (13.1%) and veal calves (32.9%) could be attributed to good hygiene measures during the slaughtering process.

ESBL/pAmpC-producing bacteria have increasingly been found in humans [1]. Here, they either occur harmlessly in the guts of healthy individuals or can 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 outpatient settings (see Chapter 7. 1) [4]. Resistance genes of ESBL/pAmpC-producing *E. coli* display a large heterogeneity [5]. Hence, 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, and results of epidemiological studies on genetic relatedness of human- versus livestock-derived isolates are not always conclusive [5, 6]. A recent study by Dorado-Garcia *et al.* (2018) analyzed the molecular relatedness of ESBL/pAmpC-producing *E. coli* in a One Health approach. The authors found distinguishable ESBL/AmpC-producing *E. coli* transmission cycles in different hosts. On the other hand, a close epidemiological linkage of ESBL/AmpC genes and plasmid replicon types between livestock farms and humans in general could not be shown [7].

10.3.2 Carbapenemase-producing *Escherichia coli* in meat

Carbapenems are the most recently developed β-lactams currently available on the market and are reserved for treatment of serious infections with multidrug-resistant bacteria in human medicine [8, 9]. Despite the fact that they are not licensed for treatment of food-producing animals, carbapenem-resistant bacteria were recently found sporadically in livestock and products thereof in Europe [10]. Since 2015, testing for carbapenem-resistant *E. coli* in chicken, pork and beef meat is included in the national monitoring program. Until 2019, no carbapenem-resistant *E. coli* could be detected in fresh meat samples. These results are generally in accordance with the results of the European voluntary monitoring system. In 2015 and 2016, a total of 6,751 (2015) and 11,935 (2016) samples where investigated for the presence of carbapenem-resistant *E. coli* [1]. Only one sample of chicken meat from Romania tested positive for the presence of a carbapenem-producing *E. coli*.

10.3.3 Methicillin-resistant *Staphylococcus aureus* (MRSA) in meat

Our current data on MRSA detection in meat confirms what was shown earlier, i.e. that in Switzerland and Europe, meat is not a relevant source of MRSA infection or colonization for humans [11, 12]. The detection rates for MRSA in Swiss fresh meat was zero for chicken meat in 2018, and pork and beef meat in 2019. In Swiss pork meat, a very low prevalence of 0.7% was found in 2017, identical to the prevalence found in 2015, despite the fact that the MRSA prevalence in nasal swabs from Swiss fattening pigs increased from 25.7% to 52.8% in the same time period. One of the pork strains was not even a livestock-associated MRSA, which may indicate that the meat was contaminated by human handling. A recent Swiss study analyzed MRSA from animals, meat and humans by whole-genome sequencing for epidemiological relatedness. The results confirmed that there is no indication that either poultry meat or pork plays a major role in human colonization with MRSA in Switzerland [13]. Moreover, Collineau *et al.* (2018) conclude from a Swiss risk association study that MRSA in meat does not pose a high risk for exposure to humans [3].

Our results are in overall agreement with the findings in Europe [1]. In the period 2017/2018, EFSA reported very low to low MRSA prevalence in pig meat (0.7% to 5.9%), low to moderate prevalence in meat from cattle (2.1% to 11.3%) and low to high prevalence in broiler meat (1.3% to 20.2%) depending on the country. In contrast to chicken meat, high to extremely high prevalence was detected in turkey meat (42.7% to 100%).

Because of the very low prevalence of MRSA in Swiss fresh meat, the continuous monitoring of MRSA in fresh meat will be discontinued from 2020 on.

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11

Resistance in animal pathogens from animal clinical isolates

11 Resistance in animal pathogens 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 this topic.

In 2019, an annual monitoring of antimicrobial resistance in veterinary pathogens was initiated by the Federal Food Safety and Veterinary Office (FSVO) and implemented at the Swiss national reference laboratory for antimicrobial resistance (ZOBA).

The sampling plan includes various pathogens/animals and indication combinations. All strains were isolated from clinical submissions of diseased animals by ten Swiss laboratories (university, cantonal, private) across Switzerland (Table 11. a). Susceptibility testing of all isolates was performed by the ZOBA with the broth microdilution method, which guarantees full comparability of data within the project period and with data from the national resistance monitoring. Samples from animals having undergone antimicrobial treatment prior to sampling were excluded from this study. In contrast to the monitoring of isolates from healthy slaughter animals, minimal inhibitory concentration data were interpreted according to clinical breakpoints. Minimal inhibitory concentrations as well as interpretative values are transmitted to the database of the Swiss center for antimicrobial resistance (ANRESIS), which is a nationwide system for resistance data for both human and veterinary medicine (www.anresis.ch). Accordingly, all data are accessible via INFECT, which is an INterface For Empirical antimicrobial ChemoTherapy, developed in 2018 for human medicine. INFECT VET has been implemented since March 2020. This online tool provides fast and intuitive access to the latest antimicrobial resistance data in Swiss veterinary pathogens, and assists veterinarians by offering reliable empirical treatment options (www.vet.infect.info). Results presented here are an excerpt of selected pathogens, which were analyzed in the framework of this project in 2019.

11.1 Mastitis pathogens

Mastitis is defined as an inflammatory process in the mammary gland that, besides trauma or chemical irritation, often results from microbial infection [1]. Mastitis is usually treated with antibiotics, which are often prescribed without prior susceptibility testing [2]. Therefore, monitoring of antimicrobial resistance in frequently detected mastitis pathogens is of great importance for veterinarians. Isolates independent of the clinical presentation (e. g. subclinical, acute, chronic) were included in the program.

Table 11. a: Sample distribution by animal, microorganism and sample origin of the monitoring of antimicrobial resistance in veterinary pathogens in 2019.

Antimicrobials	Microorganism	Sample origin					
		Abscess	Faeces	Milk	Respiratory tract	Skin	Urine
Cat	*Escherichia coli*						35
Cattle	*Escherichia coli*		3	54			
	Pasteurella multocida				2		
	Staphylococcus aureus			60			
	Streptococcus uberis			56			
Dog	*Escherichia coli*						40
	Staphylococcus pseudintermedius					22	
Goat	*Corynebacterium pseudotuberculosis*	8					
Horse	*Streptococcus equi subspecies zooepidemicus*					6	
Pig	*Escherichia coli*		7				
Poultry	*Escherichia coli*		102				

Table 11. b: Susceptibility rates of *Staphylococcus aureus* isolates from bovine mastitis in 2019.

Antimicrobial class	Antimicrobial	*Staphylococcus aureus*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)	95% CI
Tetracyclines	Tetracycline	60	58	97.0	88–100
Penicillins with extended spectrum	Ampicillin	60	60	100	93–100
Beta-lactamase sensitive penicillins	Penicillin	60	55	92.0	81–97
3rd & 4th generation Cephalosporins	Cefoperazone	60	60	100	93–100
	Ceftiofur	60	60	100	93–100
Macrolides & lincosamides & streptogramines	Clindamycin	60	60	100	93–100
	Erythromycin	60	60	100	93–100
	Pirlimycin	60	60	100	93–100
	Quinupristin-dalfopristin	60	60	100	93–100
Aminoglycosides	Gentamicin	60	60	100	93–100
Quinolones	Ciprofloxacin	60	59	98.0	90–100
Others	Vancomycin	60	60	100	93–100

CI: Confidence interval

* Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 4th ed. CLSI supplement VET08. Wayne, PA: Clinical and Laboratory Standards Institute; 2018

11.1.1 *Staphylococcus aureus*

Staphylococcus (S.) aureus is a major cause of clinical bovine mastitis in Switzerland and worldwide [1, 3]. It can be detected in approximately 57% of all dairy herds in Switzerland [3].

In 2019, a total of 60 bovine *S. aureus* mastitis isolates were investigated. Against penicillin, a low resistance rate of 8% was detected (Table 11. b). All isolates were susceptible to ampicillin. Besides these therapeutically relevant resistances, *S. aureus* isolates also showed low resistance rates to tetracyclines (3%) and ciprofloxacin (2%). No resistances against the 3rd generation cephalosporins ceftiofur and cefoperazone and no MRSAs were detected.

11.1.2 *Streptococcus uberis*

In 2019, a total of 56 bovine *Streptococcus uberis* mastitis isolates were investigated. A high resistance rate of 44% against penicillin was detected (Table 11. c). Moreover, high resistance rates against tetracyclines (29%), clindamycin (27%), erythromycin (25%) and pirlimycin (22%) were detected. Notably, isolates showed a moderate resistance rate of 13% against ceftiofur. All isolates were susceptible to vancomycin.

11.1.3 *Escherichia coli*

In 2019, a total of 54 bovine *Escherichia coli* mastitis isolates were investigated. A high resistance rate (22%) against cefalothin was detected (Table 11. d). Moderate resistance rates against ampicillin (19%) and tetracyclines (11%) were found. Moreover, some isolates expressed resistance against gentamicin (6%) and ciprofloxacin (7%). All isolates were susceptible to colistin, 3rd and 4th generation cephalosporines and carbapenems.

11.1.4 Discussion

In 2019, resistance data of bovine *S. aureus* isolates from all over Switzerland were available for the first time. When comparing these data with the resistance rates of *S. aureus* against penicillin (16.1%) and ampicillin (16.1%) detected in the framework of the pilot study in 2016/2017 [4], resistance rates seem to decrease in 2019. As the isolate population differs between these two studies, this trend should be interpreted with caution; future data with a comparable isolate population may confirm this trend. Comparable data for European mastitis pathogens were recently published [5]. On the European level, higher resistance rates for bovine *S. aureus* from mastitis cases were detected. Thereby, 25.5% of all European S. aureus were resistant to penicillin, and 7.3% to tetracycline (3% in Swiss isolates). Our data pointed out that recommended first line antimicrobials for the treatment of *S. aureus*, such as penicillin [6], showed a low resistance rate (8%).

For *S. uberis* the situation is different. Comparing current resistance rates with resistance rates from the previous study 2016/2017, the resistance rates for penicillin (44%), pirlimycin (22%) and erythromycin (25%) increased in 2019. Recently published antimicrobial resistance data on Swiss *S. uberis* isolates from 2017 showed a resistance rate of approx. 1% to penicillin, 12% to pirlimycin and 16 % to erythromycin (n=153), which is lower than the resistance rate of the monitoring 2019 [7]. European *S. uberis* isolates expressed lower resistance rates against penicillin (13%) and

Table 11. c: Susceptibility rates of *Streptococcus uberis* isolates from bovine mastitis in 2019.

Antimicrobial class	Antimicrobial	*Streptococcus uberis*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)*	95% CI
Tetracyclines	Tetracycline	56	40	71.0	58–81
Beta-lactamase sensitive penicillins	Penicillin	56	31	56.0	43–69
3rd & 4th generation Cephalosporins	Ceftiofur	56	49	87.0	76–94
Macrolides & lincosamides & streptogramine	Clindamycin	56	41	73.0	60–83
	Erythromycin	56	42	75.0	62–84
	Pirlimycin	56	44	78.0	65–87
Others	Vancomycin	56	56	100	92–100

CI: Confidence interval

* Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 4th ed. CLSI supplement VET08. Wayne, PA: Clinical and Laboratory Standards Institute; 2018

Table 11. d: Susceptibility rates of *Escherichia coli* isolates from bovine mastitis in 2019.

Antimicrobial class	Antimicrobial	*Escherichia coli*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)	95% CI
Tetracyclines	Tetracycline	54	48	89.0	77–95
Extended spectrum penicillins	Ampicillin	54	44	81.0	69–90
1st & 2nd generation Cephalosporins	Cefalothin	54	42	78.0	65–87
3rd & 4th generation Cephalosporins	Cefotaxime	54	54	100	92–100
	Ceftiofur	54	54	100	92–100
Carbapenems	Imipenem	54	54	100	92–100
Aminoglycosides	Gentamicin	54	51	94.0	84–99
Quinolones	Ciprofloxacin	54	50	93.0	82–97
Others	Colistin	54	54	100	92–100

CI: Confidence interval

* Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 4th ed. CLSI supplement VET08. Wayne, PA: Clinical and Laboratory Standards Institute; 2018

pirlimycin (16%) than the Swiss monitoring isolates, but comparable susceptibility rates to erythromycin (76%) were detected [5].

Gentamicin is recommended for first line treatment of *E. coli*-caused bovine mastitis [6]. Currently, the resistance rates for this antimicrobial are low (6%). In comparison to the pilot study in 2016/2017, an overall decrease of antimicrobial resistance, except for tetracyclines, was observed. For European *E. coli* isolates, no data for gentamicin are available. Susceptibility rates to ampicillin (76.0%) and tetracycline (76.4%) were lower compared to susceptibility rates from the current Swiss monitoring (ampicillin (81.0%) and tetracycline (89.0%).

Noteworthy is the fact that Swiss isolates were included for the first time within the study of El Garch *et al.* (2020) "Antimicrobial susceptibility of nine udder pathogens recovered from bovine clinical mastitis milk in Europe 2015–2016: VetPath results" [5]. Within European bovine *S. aureus* isolates, the resistance rate for penicillin was much higher (25.5%) and slightly higher for erythromycin (3.6%) and pirlimycin (3.2%). Resistance rates of European *S. uberis* isolates were comparably high for erythromycin (23.6%), higher for tetracyclines (37.5%), but lower for pirlimycin (15.9%). In European *E. coli* isolates, the resistance rate for ampicillin (24%) was higher than in Swiss isolates.

11.2 Pathogenic *Escherichia coli* from poultry

In 2019, a total of 102 *Escherichia coli* isolates from diseased poultry were investigated. High resistance rates against cefalothin (29%), enrofloxacin (28%) and tetracyclines (22%) were detected (Table 11. e). Moderate resistance rates against ampicillin (19%) and ciprofloxacin (12%) were found. All isolates, except one, were susceptible to colistin. No resistance against 3rd and 4th generation cephalosporines and carbapenems were detected.

Table 11. e: Susceptibility rates of *Escherichia coli* isolates from poultry in 2019.

Antimicrobial class	Antimicrobial	*Escherichia coli*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)	95% CI
Tetracyclines	Tetracycline	102	80	78.0	69–85
Extended spectrum penicillins	Ampicillin	102	83	81.0	73–88
1st & 2nd generation Cephalosporins	Cefalothin	102	72	71.0	61–79
3rd & 4th generation Cephalosporins	Cefotaxime	102	102	100	96–100
Carbapenems	Imipenem	102	102	100	96–100
Aminoglycosides	Gentamicin	102	102	100	96–100
Quinolones	Ciprofloxacin	102	90	88.0	80–93
	Enrofloxacin	102	73	72.0	62–79
Others	Colistin	102	101	99	94–100

CI: Confidence interval

* Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 4th ed. CLSI supplement VET08. Wayne, PA: Clinical and Laboratory Standards Institute; 2018

Discussion

E. coli of poultry with various clinical diagnoses were analyzed for their resistance profile. Results on molecular characterization of strains regarding possible identification of avian pathogenic *E. coli* (APEC) were not available. Compared with data from the previous study (2016/2017), resistance rates against ampicillin (2017: 17%) and tetracycline (2017: 19.3%) were comparable to rates from 2019. In contrast, resistance rates against cefalothin increased to 29% in 2019 (2017: 13.6% intermediate, 3% resistant). The same trend was also observed for enrofloxacin, with an increase to 28% in 2019 (2017: 12% intermediate, 1% resistant). In 2019, all isolates tested were susceptible to 3rd and 4th generation cephalosporins. Only one isolate showed resistance to colistin. In 2018, resistance rates of *E. coli* from clinical poultry cases to ampicillin were comparably high to isolates from healthy broilers at slaughter (25.7% for indicator *E. coli* compared to 19% for pathogenic *E. coli*). The same was observed for tetracycline (15.9% for indicator *E. coli* compared to 22% for pathogenic *E. coli*). Interestingly, the resistance rate against ciprofloxacin (45.8%) for indicator *E. coli* was much higher than the rate in pathogenic *E. coli* (12%). Comparing our data with German antimicrobial resistance of pathogenic *E. coli* in poultry in 2017, resistance rates for ampicillin (43%), tetracycline (26%) and gentamicin (2%) were higher in isolates from Germany, but lower for enrofloxacin (2%) [8].

11.3 Pathogens from companion animals

In small veterinary practices, highest priority critically important antimicrobials such as fluoroquinolones (e. g. enrofloxacin, ciprofloxacin, marbofloxacin and pradofloxacin) and extended-spectrum cephalosporins (e. g. cefovecin and, limited to some countries, cefpodoxime) are frequently used [9]. Therefore, antimicrobial resistance in companion animals has become a focus of the One-Health perspective [10].

11.3.1 *Staphylococcus pseudintermedius* from canine skin infections

Staphylococcus (S.) pseudintermedius is an opportunistic pathogen, normally found as a commensal on skin and mucosa of dogs. Like other staphylococci, *S. pseudintermedius* is recognized as the leading cause of skin, ear, and postoperative bacterial infections in dogs [11]. *S. pseudintermedius* has gained more importance in veterinary as well as in human medicine in recent years, due to the emergence of methicillin-resistant *S. pseudintermedius* (MRSP). In veterinary clinics, the prevalence for MRSP in cases of canine pyoderma can amount to 66% [12]. However, 22% of all clinically healthy dogs can also be carriers of MRSP [13]. 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, although they are rare [14–15]. Colonization and/or infection may therefore not only be a concern for veterinarians treating the infected animals, but also represent a risk for pet owners.

In 2019, a total of 22 canine *S. pseudintermedius* isolates were investigated. A high resistance rate against ampicillin (50%) was detected (Table 11. f). Moreover, high resistance rates were detected against clindamycin (32%), tetracyclines (23%) and erythromycin (27%). One isolate expressed resistance against gentamicin (5%). All isolates were susceptible to 1st to 4th generation cephalosporins and imipenem. No methicillin-resistant *S. pseudintermedius* were detected.

Table 11. f: Susceptibility rates of *Staphylococcus pseudintermedius* isolates from canine skin infections in 2019.

Antimicrobial class	Antimicrobial	*Staphylococcus pseudintermedius*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)	95% CI
Tetracyclines	Tetracycline	22	17	77.0	56–90
Extended spectrum penicillins	Ampicillin	22	11	50.0	31–69
1st & 2nd generation Cephalosporins	Cefalothin	22	22	100	82–100
3rd & 4th generation Cephalosporins	Cefovecin	22	22	100	82–100
Macrolides & lincosamides & streptogramines	Clindamycin	22	15	68.0	47–84
	Erythromycin	22	16	73.0	51–87
	Quinupristin-dalfopristin	22	22	100	82–100
Aminoglycosides	Gentamicin	22	21	95.0	76–100
Quinolones	Ciprofloxacin	22	22	100	82–100
	Enrofloxacin	22	22	100	82–100
	Marbofloxacin	22	22	100	82–100
Others	Vancomycin	22	22	100	82–100
	Linezolid	22	22	100	82–100

CI: Confidence interval; * Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 4th ed. CLSI supplement VET08. Wayne, PA: Clinical and Laboratory Standards Institute; 2018

Table 11. g: Susceptibility rates of *Escherichia coli* isolates from canine urogenital tract infections in 2019.

Antimicrobial class	Antimicrobial	*Escherichia coli*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)	95% CI
Tetracyclines	Tetracycline	40	33	82.0	68–91
Extended spectrum penicillins	Ampicillin	40	34	85.0	70–93
1st & 2nd generation Cephalosporins	Cefalothin	40	29	72.0	56–83
3rd & 4th generation Cephalosporins	Cefovecin	40	38	95.0	82–99
	Cefotaxime	40	40	100	89–100
Carbapenems	Imipenem	40	40	100	89–100
Aminoglycosides	Gentamicin	40	40	100	82–100
Quinolones	Ciprofloxacin	40	34	85.0	70–93
	Enrofloxacin	40	34	85.0	70–93
	Marbofloxacin	40	34	85.0	70–93
Others	Colistin	40	40	100	89–100

Table 11. h: Susceptibility rates of *Escherichia coli* isolates from feline urogenital tract infections in 2019.

Antimicrobial class	Antimicrobial	*Escherichia coli*			
		Number of isolates tested	Number of susceptible isolates	Susceptibility (%)	95% CI
Tetracyclines	Tetracycline	35	32	91.0	77–98
Extended spectrum penicillins	Ampicillin	35	29	82.9	67–92
1st & 2nd generation Cephalosporins	Cefalothin	35	27	77.0	61–88
3rd & 4th generation Cephalosporins	Cefovecin	35	33	94.0	80–99
	Cefotaxime	35	33	94.0	80–99
Carbapenems	Imipenem	35	35	100	88–100
Aminoglycosides	Gentamicin	35	35	100	88–100
Quinolones	Ciprofloxacin	35	34	97.0	84–100
Others	Colistin	35	35	100	88–100

11.3.2 Escherichia coli from canine and feline urogenital tract infections

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 [16]. Antimicrobial treatment is in many cases 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* [17]. Moreover, zoonotic potential of extraintestinal *E. coli* from dogs to humans has been reported [17].

***Escherichia coli* from canine urogenital tract infections**
In 2019, a total of 40 *Escherichia coli* isolates from canine urogenital tract infections were investigated. A high resistance rate against cefalothin (28%) was detected. Moderate resistance rates were found for tetracyclines (18%), ampicillin (15%) and enro-, cipro- and marbofloxacin (15% each) (Table 11. g). Two isolates showed resistance to cefovecin (5%). All isolates were susceptible to colistin. No resistance against carbapenems was detected.

***Escherichia coli* from feline urogenital tract infections**
In 2019, a total of 35 *Escherichia coli* isolates from feline urogenital tract infections were investigated. 17.1% of the isolates were resistant against ampicillin. A high resistance rate against cefalothin (23%) was detected, and two isolates showed resistance to cefovecin and cefotaxime (6%). Moreover, low resistance rates against tetracyclines (9%) and ciprofloxacin (3%) were detected. All isolates were susceptible to gentamicin and colistin. No resistances against carbapenems were detected.

11.3.3 Discussion

For *S. pseudintermedius* from canine infections, a very strong increase in resistance against ampicillin was detected, from 2% in 2016/2017 to 50% in 2019, but only a low number of isolates (n=22) was available. Resistances against 1st to 3rd generation cephalosporins as well as MRSP were not detected. The German antimicrobial resistance report 2017 showed that resistance rates for ampicillin (57%) and erythromycin (28%) are within the same range as Swiss isolates in 2019, but lower for clindamycin (28%) [8]. In contrast, European canine *S. pseudintermedius* isolates from 2008 to 2010 showed a much lower resistance rate of 9.2% for ampicillin, whereas resistance to 1st generation cephalosporins was much higher (23%) [18].

Resistance rates of *E. coli* from UTI in Swiss companion animals showed a comparable pattern. They expressed high resistance rates against ampicillin (approx. 25%) and cefalothin (approx. 25%), which was also the case in the previous study from 2016/2017 [4]. In German canine *E. coli* from UTI, comparable ampicillin resistance rates were detected; for feline isolates, data were not available [8]. Moreover, 2 out of 35 feline *E. coli* isolates were confirmed as ESBL/pAmpC-producers (5%), whereas none of the canine *E. coli* showed resistance to 3rd generation cephalosporins. In contrast, Zogg *et al.* (2018) detected a much higher prevalence of ESBL/pAmpC producers (20.8%) among *Enterobacterales* isolated from Swiss clinical cases of dogs and cats [19]. These differences are most probably due to the different populations used in the two studies. Zogg *et al.* analyzed isolates recruited from admission to a university veterinary clinic. As pretreatment was not an exclusion criterion, it can be assumed that a relevant number of companion animals were treated with antimicrobials prior to sampling. It is not known if multiple isolates from the same animal, due to repeated (control) sampling over time, were excluded. High resistance rates against ampicillin and only sporadically detected multi-drug-resistant *E. coli* were also described in a comparable European study of canine and feline UTI *E. coli* [20]. It is noteworthy that resistance against fluoroquinolones was higher in canine isolates (15%) than in feline isolates (3%), a fact that was observed previously [4]. Resistance against enrofloxacin was also recorded in canine UTI *E. coli* from Germany and Europe [8, 120]. De Jong *et al.* (2018) analyzed the molecular background of fluoroquinolone resistance in canine and feline UTI *E. coli* [21]. They concluded that mutations in the quinolone resistance determining region (QRDR) are more relevant than plasmid mediated quinolone resistance (PMQR).

11.4 Summary and outlook

The Swiss antimicrobial resistance monitoring in animal pathogens isolated from clinical cases started in 2019; hence, the data are presented here for the first time. They must be interpreted with caution for various reasons. First of all, the overall low number of isolates may lead to overinterpretation of calculated resistances rates. With more data in the future, the trends will become more evident. Moreover, it must be noted that the analyzed isolates originate exclusively from animals, which were not pretreated with antimicrobials before the sample was taken. This is of relevance when comparing our data with data from other study populations. It has been shown that isolates from animals under treatment may express significantly higher antimicrobial resistance rates than isolates from untreated animals. For monitoring purposes, comparability of results over time is of greatest importance. Therefore, trends in antimicrobial resistance rates should not be influenced by the number of non-treated versus pretreated animals in the study population. Thanks to this approach, Swiss data are directly comparable with other national monitoring programs, e. g. the German Germ-Vet. Finally, results shown in this chapter represent only a small excerpt of data that have been elaborated. Only pathogen/animal/indication combinations for which clinical breakpoints issued by the Clinical and Laboratory Standards Institute (CLSI) are currently available were chosen. This will in future be completed with data on the minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90} value) for all antimicrobials tested.

Besides the limitations explained above, it was possible to draw conclusions on antimicrobial resistance in the various animal pathogens. For mastitis pathogens, *Streptococcus uberis* turned out to be more critical in terms of antimicrobial treatment than *Staphylococcus aureus*. When comparing *Escherichia coli* isolated from different animal species and indications, remarkable differences were detected. Only isolates from bovine mastitis and poultry showed no resistance to 3rd or 4th generation cephalosporines, whereas *Escherichia coli* isolates from companion animal UTI expressed resistance against these critically important antimicrobials. Carbapenem-resistant *Escherichia coli* were not detected in 2019.

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Textbox

VetCAST: European clinical breakpoints for veterinary medicine

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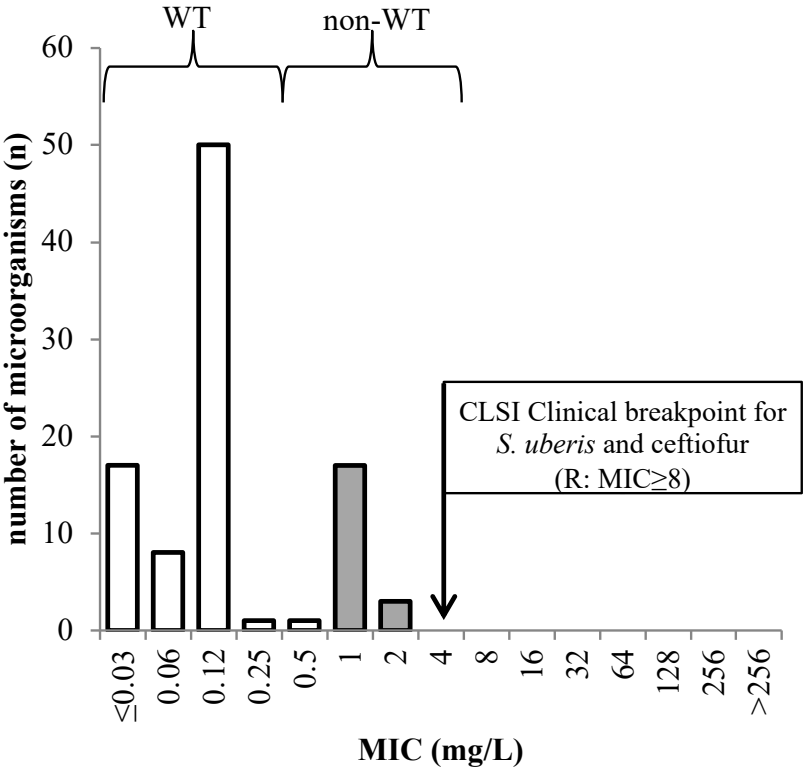
Antimicrobial susceptibility testing (AST) plays a key role in targeted antimicrobial therapy, and clinical breakpoints (CBPs) are indispensable for its interpretation. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) deals with breakpoints and technical aspects of phenotypic *in vitro* antimicrobial susceptibility testing in human medicine in Europe. It also functions as the official breakpoint committee of the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC). In 2015, the Veterinary Committee on Antimicrobial Susceptibility Testing (VetCAST) was formed as a subcommittee of EUCAST, dealing with all aspects of antimicrobial susceptibility testing of bacterial pathogens of animal origin and those with zoonotic potential.

For nearly 50 years, the American Clinical Laboratory and Standards Institute (CLSI) has been an internationally recognized committee with separate standing subcommittees for AST in human and veterinary medicine. The CLSI issues CBPs for veterinary medicine. However, the principles in setting them remain unclear and some CBPs seem to be worth reviewing. For example, the current CLSI CBP for ceftiofur against *Streptococcus uberis* with broth dilution is ≥ 8 mg/L (CLSI 2018). This CBP appears to be too high, as it does not differentiate between the tentative wild-type population and the non-wild-type population exhibiting elevated MICs due to acquired resistance mechanisms (Figure 1).

Therefore, one of the main tasks of VetCAST is the determination of specific European CBPs for animal species, drug substances and disease conditions based on the EUCAST approaches for human medicine with adaption to specific requirements and limitations in veterinary medicine. Toutain *et al.* (2017) have published the overall concept and recommendations for veterinary CBP implementation in Europe (Toutain, Bousquet-Mélou *et al.* (2017)). In August 2019, the

Figure 1: Schematic representation of a CLSI clinical breakpoint that does not differentiate between the wild-type and the non-wild-type population of *Streptococcus uberis* against ceftiofur. Horizontal numbers tentative the range of ceftiofur dilutions tested. Vertical numbers show the number of isolates expressing the corresponding MIC. MIC: minimal inhibitory concentration, R: Resistant, WT: wild-type population



first rationale document for florfenicol CBPs proposed for *Mannheimia haemolytica* (S ≤ 2 mg/L) and *Pasteurella multocida* (S ≤ 1 mg/L) of bovine origin was published on the EUCAST homepage (www.eucast.org). These CBPs differ slightly from the CBPs issued by the CLSI. Schönecker *et al.* (2020) showed that VetCAST CBPs matched the MIC distribution of isolate populations better than CLSI CBPs (Schönecker *et al.* 2020, under revision). Such differences highlight the need for further refinement of clinical breakpoints in veterinary medicine according to the VetCAST approach.

Because of the current lack of specific European CBPs for veterinary medicine, European veterinary diagnostics laboratories use a broad variety of different interpretative criteria, e.g. CLSI veterinary clinical breakpoints, EUCAST human clinical breakpoints and/or epidemiological cut-off values (ECOFFs). Hence, a second major task of VetCAST is the development of guidelines on the use of interpretive criteria for AST if VetCAST CBPs are lacking. These guidelines should assist veterinary diagnostic laboratories in the selection of appropriate interpretative criteria and support harmonisation of diagnostic AST in veterinary medicine on the European level. On behalf of VetCAST, an expert team was appointed to establish and publish such guidelines. In a first step, the team has compiled currently available interpretative criteria for specific antimicrobial/indication combinations for commonly occurring pathogens of livestock and companion animals. Recommendations for the most appropriate criteria, including the most applicable methods, will be provided, and general advice for cases which are not covered by the specific list will complete the guidelines. The complete guidance document will be published on the VetCAST homepage later in 2020.

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12

Antibiotics in the water cycle

12 Antibiotics in the water cycle

12.1 Sources to the environment

Antibiotics are applied in high quantities in human and veterinary medicine. Approximately 30,000 kg, mainly sulfonamides, penicillins, and tetracyclines, were sold in veterinary medicine in Switzerland in 2019, a decline of 52% compared to 2010 (SARR 2020, Chapter 6). Consumption data for human medicine are of the same order of magnitude, with penicillins, cephalosporins and fluoroquinolones being the main applied substance groups (SARR 2020, Chapter 5). After intake, humans and animals excrete antibiotics, partly unchanged, and these end up in wastewater or soils via application of manure.

Conventional wastewater treatment plants (WWTPs) only partly remove polar organic micropollutants such as antibiotics, and therefore release them into receiving waters. Consequently, WWTPs have been identified as a major source of antibiotics for the aquatic environment. A mass flow model underlines these findings; it accurately predicted concentrations of antibiotics in Swiss rivers based on consumption data, the excretion rate, the elimination rate in WWTPs and the dilution factor in receiving waters (Ort 2009).

Since 2016, selected WWTPs in Switzerland are being upgraded with an additional treatment step for the elimination of micropollutants from municipal wastewater. The technical processes (e. g. ozonation or powdered activated carbon) eliminate a large spectrum of micropollutants to varying extents. Especially antibiotics are very well eliminated (> 90%). The upgrade must be completed by 2040 at the latest. At this point, approximately 70% of all Swiss municipal wastewaters will be treated against micropollutants, leading to a strong reduction of the load of antibiotics being released from WWTPs into the aquatic environment.

The aim of the upgrading program is to protect flora and fauna as well as the quality of drinking water resources. This is important since rivers infiltrate into groundwater, the main source of drinking water in Switzerland. Micropollutants such as antibiotics can be removed during riverbank filtration by sorption to particles or by biological degradation. However, certain polar and persistent antibiotics are not removed during riverbank filtration and ultimately reach groundwater. Since 2006, the application of sewage sludge to fields is no longer allowed in Switzerland. But manure application to soils may lead to a contamination of groundwater with antibiotics used in veterinary medicine by direct leaching from soils into groundwater.

12.2 Data collection from monitoring programs and independent measurement campaigns

Data on antibiotics originate from different sources. For wastewater, effluent concentrations of antibiotics come from cantonal or research measurement campaigns or the legal WWTP performance surveillance which is required after the upgrade. The 24h to 48h effluent samples were collected between 2015 and 2019 at 102 municipal WWTPs, of which ten are equipped with an additional treatment step for the elimination of micropollutants.

River water is regularly analyzed by the National Surface Water Quality Monitoring Network (NAWA). In this network, the Federal Office for the Environment (FOEN) and the cantonal authorities document and evaluate the water quality of rivers. In 2018, the monitoring of micropollutants started at 18 NAWA sites. These sites are mainly situated on the Swiss Plateau and cover different land use types and sources of micropollutants. Six antibiotics are among the surveyed micropollutants: azithromycin, clarithromycin and erythromycin (used in human medicine), sulfamethazine (used in veterinary medicine) as well as sulfamethoxazole and trimethoprim (used in both human and veterinary medicine). Sampling is carried out as continuous two-week composite samples throughout the year. More recently, the analysis of micropollutants is now conducted at additional sites.

Groundwater has been monitored for antibiotics by the NAQUA National Groundwater Monitoring since 2013. NAQUA is operated by the FOEN in close collaboration with the cantonal authorities (FOEN 2019, FOEN 2020a). It comprises approximately 550 groundwater quality monitoring sites representing different typical hydrogeological settings and anthropogenic pressures. 135 of these NAQUA monitoring sites are located close to rivers, and are more or less impacted by infiltrating river water. The most important groundwater contaminants are monitored on a long-term basis at the national scale, including the sulfonamide antibiotic sulfamethoxazole. At each monitoring site, one to four grab samples are analyzed every year. In addition, pilot studies focus on a larger spectrum of substances at selected monitoring sites during short periods. In 2017 and 2018, 13 antibiotics were investigated as part of the pilot study "Screening micropollutants" at 32 monitoring sites.

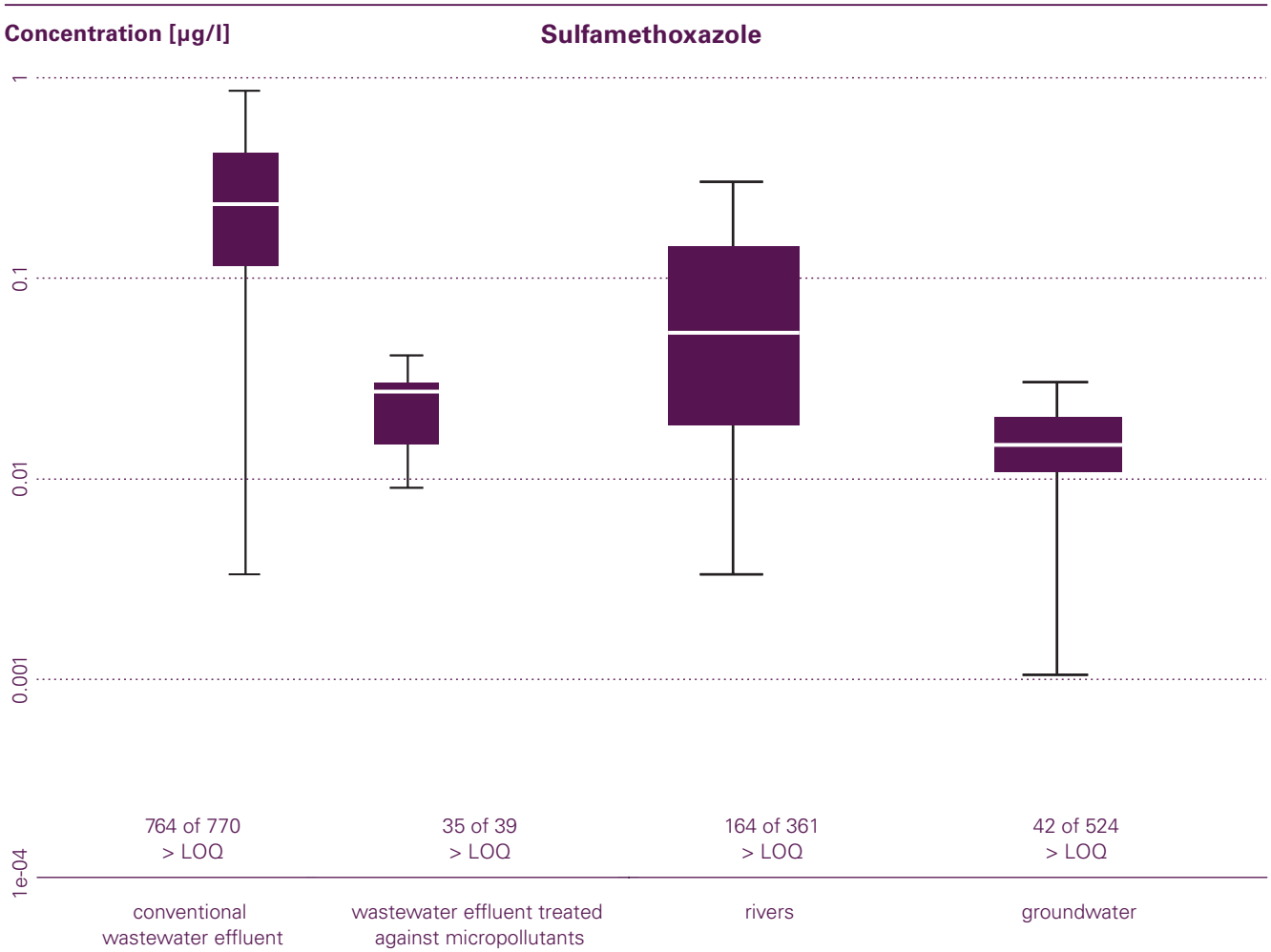
12.3 Antibiotics in treated municipal wastewater, surface water and groundwater

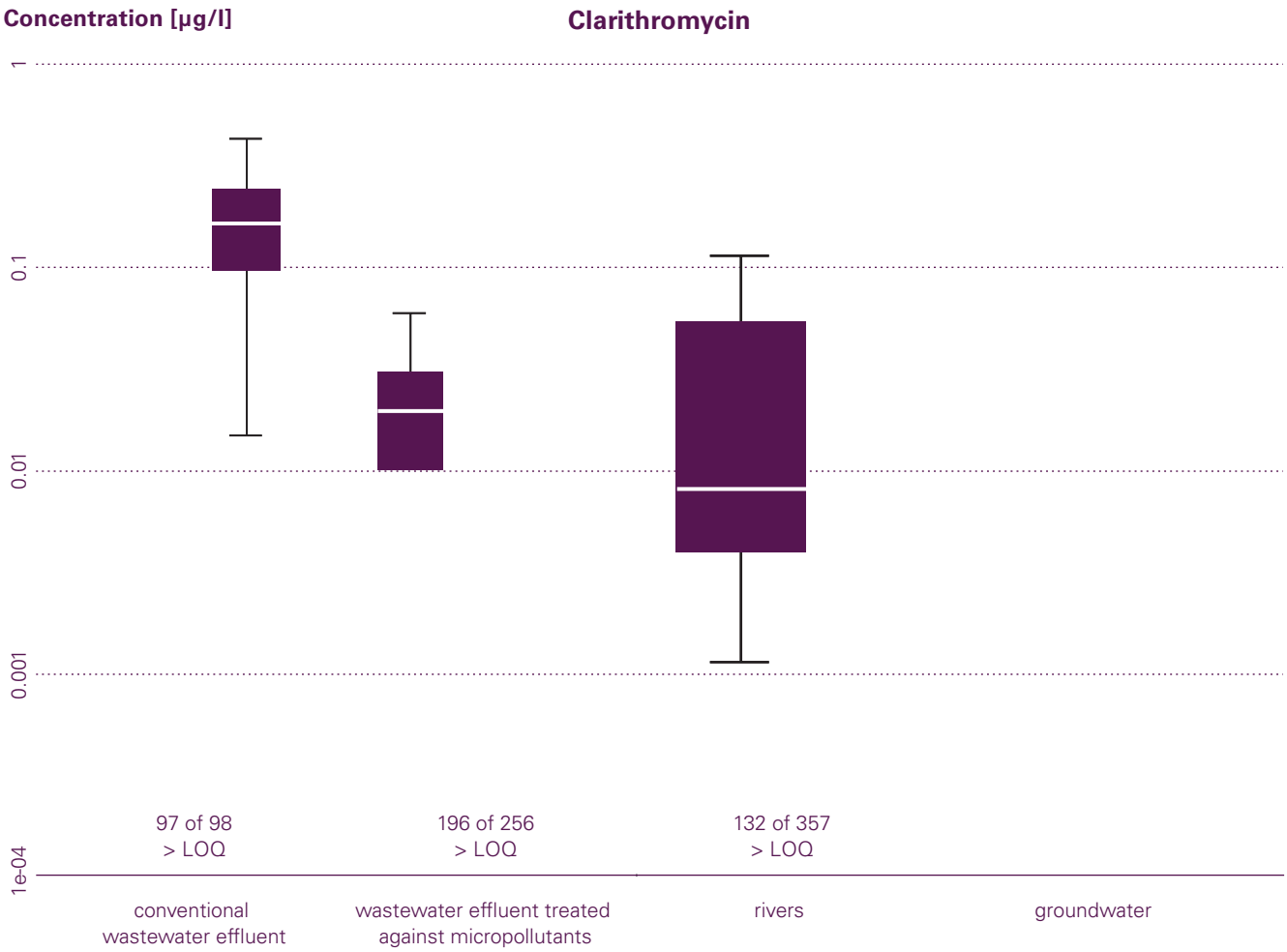
Figure 1 shows concentrations of the antibiotics sulfamethoxazole and clarithromycin as boxplots in conventional wastewater effluent, wastewater effluent treated against micropollutants, river water and groundwater. For conventional WWTPs without an additional treatment step against micropollutants, the effluent concentrations of sulfamethoxazole and clarithromycin ranged from 0.02 to 0.85 µg/l and 0.02 to 0.57 µg/l, respectively, with 8 and 1% of the measured values below the limit of quantification (LOQ) (Figure 1). The medians were 0.23 and 0.16 µg/l, respectively. Azithromycin, sulfamethazine, sulfapyridin, trimethoprim, ciprofloxacin, clindamycin, levofloxacin, norfloxacin, ethambutol, and metronidazole were found in concentrations 1 to 10 times lower than sulfamethoxazole or clarithromycin (data not shown). This clearly shows that different antibiotics are present in significant amounts in conventional wastewater effluent.

In wastewater treated against micropollutants, effluent concentrations of sulfamethoxazole and clarithromycin were one order of magnitude lower (medians of 0.03 and 0.02 µg/l, respectively), and 10 and 23% of the measured values were below the LOQ. This clearly shows the strong elimination effect for the two antibiotics by an additional treatment step (mainly ozonation or powdered activated carbon treatment).

In river water, sulfamethoxazole and clarithromycin were found in concentrations from 0.003 to 0.718 µg/l and 0.001 to 0.178 µg/l, respectively, with 55 and 63% of the measured values below the LOQ (Figure 1). The medians of 0.055 and 0.008 µg/l are approximately one order of mag-

Figure 1: Sulfamethoxazole and clarithromycin in conventional wastewater effluent, wastewater effluent treated against micropollutants, river water and groundwater (only sulfamethoxazole). The number of data points per antibiotic and water type above the limit of quantification (LOQ) is indicated below the respective boxplot; these data points were included in the boxplot. The LOQ is a substance- and water type-specific parameter but was typically 0.01 µg/l in wastewater, 0.001-0.07 µg/l in river water and 0.0005 to 0.02 µg/l in groundwater. Values below the LOQ are not included in the boxplot. Outliers are not shown.





nitude below the medians of conventionally treated wastewater due to dilution with uncontaminated river water. Overall, sulfamethoxazole was found in 45% of all samples, followed by clarithromycin (37%), trimethoprim (18%), sulfamethazine (6%), azithromycin (4%) and erythromycin (below 1%). The affected rivers, with a significant fraction of treated wastewater in their discharge, were mainly medium-sized to large (e. g. Rhine, Aare, Furtbach or Glatt) (Figure 2). But also the Beggingerbach, a medium-sized river without wastewater but with a high intensity of agriculture in its catchment, was affected by the veterinary antibiotic sulfamethazine. These results confirm wastewater as the main source of antibiotics in river water with additional inputs from veterinary medicine.

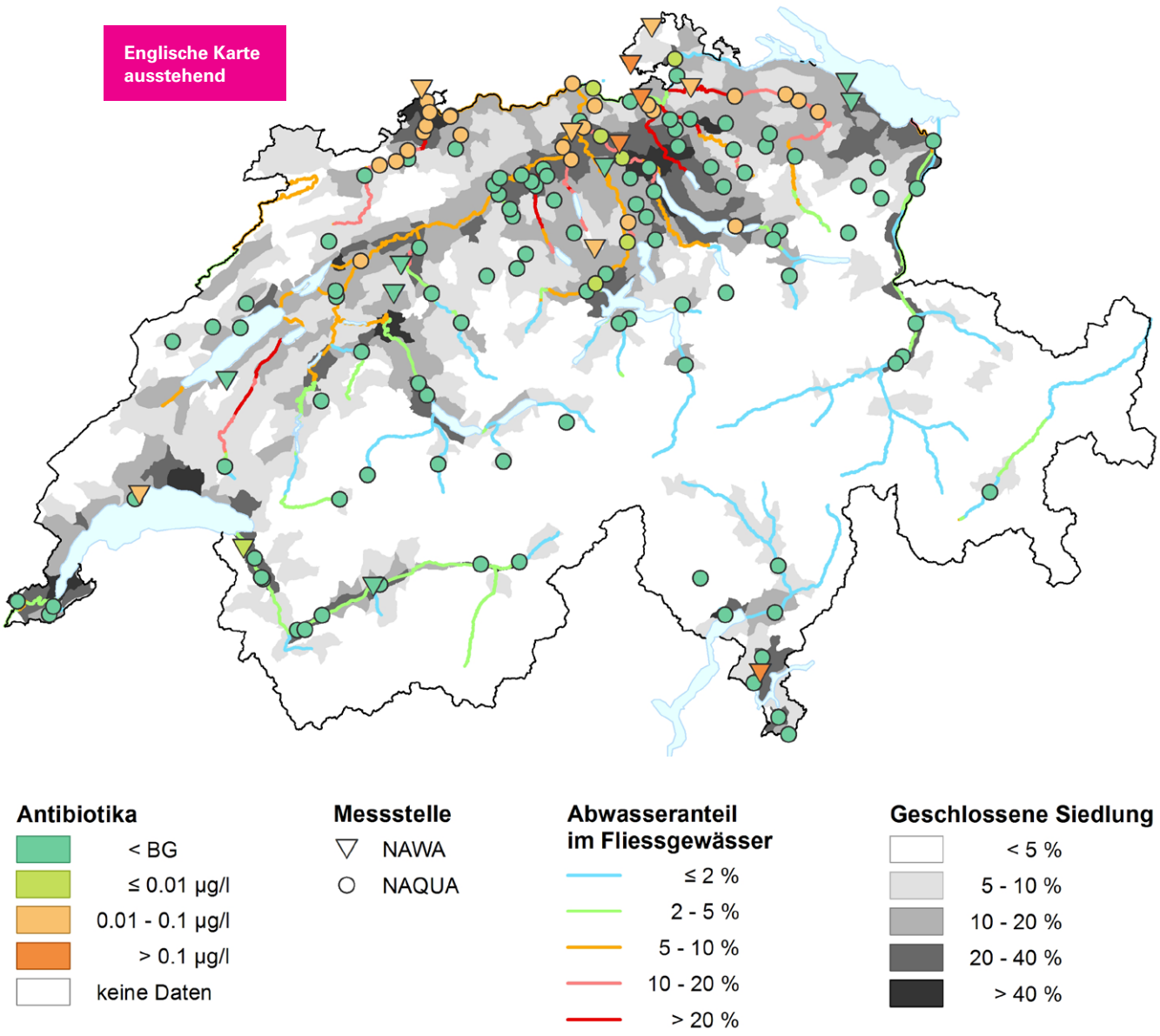
Mobile and persistent antibiotics enter groundwater mainly via infiltration of river water into the subsoil. Sulfamethoxazole is the antibiotic appearing by far most frequently in groundwater (FOEN 2020b). In 2017, it was detected at 25% of the 135 groundwater monitoring sites near rivers. Its median concentration was 0.015 µg/l (Figure 1), which is significantly lower than in river water. Most affected are groundwater monitoring sites adjacent to rivers containing more than 5% of domestic wastewater discharge, such as Birs, Glatt or Thur.

Sulfamethazine and sulfapyridine, two other sulfonamide antibiotics, were also detected in groundwater, but in very low concentrations (maximum 0.002 µg/l). Sulfamethazine is exclusively used in veterinary medicine. It is spread to fields via liquid manure and probably leaches directly from the soil into the groundwater. 13 other antibiotics used in human and/or veterinary medicine – namely sulfadiazine, sulfathiazole, amoxicillin, oxacillin, erythromycin, vancomycin, clindamycin, linezolid, metronidazole and trimethoprim – were analyzed at selected monitoring sites in a pilot study in 2017/2018. None of these antibiotics were detected in groundwater. This illustrates that the number and concentration of detected antibiotics is much lower in groundwater than in river water due to degradation and sorption during riverbank filtration or soil passage. However, certain mobile and persistent antibiotics applied in human and veterinary medicine may reach groundwater.

12.4 Conclusions

Antibiotics are present in treated wastewater effluent, river water and groundwater. Their concentrations decrease from wastewater to river water due to dilution, and further de-

Figure 2: Antibiotics in groundwater and river water in relation to percentage of wastewater in selected rivers. Monitoring sites are part of the NAQUA National Groundwater Monitoring and the NAWA National Surface Water Monitoring Network. Rivers with a discharge Q347 >2000 l/s are plotted.



crease in groundwater due to degradation and sorption during riverbank filtration or soil passage. Sulfamethoxazole is the antibiotic most widespread in groundwater, while most others are not found in groundwater.

Whether these concentrations directly promote the development of antibiotic resistance in the environment is currently unknown. However, emissions of antibiotics to the environment should be minimized as much as possible based on the precautionary principle. Consequently, Switzerland is upgrading selected WWTPs to eliminate micropollutants such as antibiotics from wastewater. The upgrade program started in 2016; the presented values for river water and groundwater are from 2017 and 2018. In 2018, four WWTPs treating approximately 5% of Switzerland's wastewater were already equipped with an additional treatment step against micropollutants. The elimination effect of >90% for antibiotics in wastewater is clearly visible in the WWTP effluent concentrations in Figure 1. However, the effect is not yet visible in river water (or groundwater for which recharge times are much longer). It is expected that the effect of the WWTP upgrade program will be visible in the coming years in river water, mainly for antibiotics used in human medicine. Until 2040, approximately 70% of all Swiss wastewaters will be treated against micropollutants. This should lead to a significant reduction of the load of antibiotics being released from WWTPs into the environment.

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13

One Health spotlight on carbapenemase-producing Enterobacterales (CPE)

13 One Health spotlight on carbapenemase-producing Enterobacterales (CPE)

13.1 Introduction

Carbapenems are highly effective broad-spectrum antibiotics, used for severe infections with some multidrug-resistant microorganisms, in particular extended-spectrum betalactamase-producing Enterobacterales [1]. Their use is restricted mainly to humans. In farm animals, the use of carbapenems is not allowed; in small animals (dogs and cats), it is restricted to very specific cases when certain criteria are fulfilled [2].

Surveillance of carbapenem-resistant Enterobacterales is complex and cannot be based on resistance testing only, as it can be mediated via different mechanisms such as permeability defects, efflux pumps or by the production of carbapenemase enzymes. Therefore, to understand the spread of these microorganisms, genetic analyses are needed. Carbapenemase-producing Enterobacterales (CPE) are of special concern due to their multi-resistance and their ability to rapidly spread vertically and horizontally, enabled by resistance genes on transmissible genetic elements such as plasmids.

In contrast to several regions in Asia, America and Europe where CPE are endemic, only sporadic cases have been reported in Switzerland in the past. However, aggravations of the epidemiological situations in neighbouring European countries and increased reporting of individual CPE cases in Switzerland are worrisome and have led to an increased surveillance activity in this regard.

13.2 Human Medicine

In humans, the increased use of carbapenems has led to an increasing number of CPE cases worldwide. As a consequence, other reserve antibiotics with a greater propensity for adverse effects, such as colistin, have to be administrated more frequently, leading to increased mortality, morbidity and healthcare costs. As stated previously, in Enterobacterales the non-susceptibility to carbapenems is often mediated by the production of carbapenemase enzymes. CPE are classified according to their amino acid sequences, i. e. as KPC, VIM, IMP, NDM or OXA genotypes. Within Europe, different genotypes are heterogeneously distributed: KPC and VIM have extensively been reported in southern Europe, interregional NDM spread has been observed in eastern and northern Europe, and OXA-48 is widespread in some western European countries (e. g. France) [3].

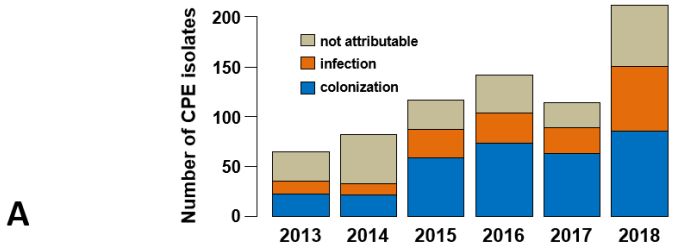
In Switzerland, several individual CPE cases and local outbreaks have been reported since 2009, and CPE were defined as notifiable pathogens by the Swiss Federal Office of Public Health in 2016. However, no systematically collected epidemiological Swiss data has been published so far. Recently, Michael Gasser and Alban Ramette systematically analysed CPE data collected by the Swiss Antibiogram Committee (SAC, 2013–2015) and the Federal Office of Public Health (FOPH, 2016–2018) in order i) to describe CPE distributions and trends of different genera and genotypes on a national, regional and hospital level and ii) to identify epidemiological factors associated with changes in case incidence [4].

In this study, it was found that yearly detected CPE isolates have more than tripled, from 65 in 2013 to 212 in 2018 (Figure 13). This increase was observed in isolates from both infections and screenings of patients admitted to hospitals for other reasons, and was most pronounced in 2018.

The most frequently isolated CPE species were *Klebsiella* spp. (56%) and *Escherichia coli* (27%) (see Table 13). During the study period (2013–2018), relative proportions of *E. coli* increased from 20% to 34%, whereas Klebsiella spp. decreased from 59% to 44%. The most frequent genotypes were OXA-48-type (43%), KPC (25%), and NDM (21%). In different regions of Switzerland there were considerable differences in the frequency of CPE isolates per 100,000 inhabitants (Figure 13) and the distribution of CPE genotypes showed characteristic regional patterns: in contrast to the French-speaking parts (West, Geneva) where OXA-48-types were the predominant genotypes (around 60%), KPC was the most frequently detected genotype in Ticino (South) (63%). This distribution mirrors the situation in Western Europe, where high rates of OXA-48-types are observed in France, whereas KPC is the predominant genotype in Italy. According to the trends in neighbouring European countries, we might also witness further spread of the OXA-48-type and NDM-producing *E. coli*, and a stabilization or decrease of KPC producers.

In addition to time (years) and region, the gender was identified as a significant risk factor in a multivariable analysis, as isolates were predominately (62%) from male patients. In order to detect regional clusters, a simulated cluster analysis by WHONET-SatScan was performed. In five out of eight

Figure 13: A. Total number of CPE isolates related to colonization and infection from 2013–2018 (data from SAC and FOPH). B. Number of CPE isolates per 100,000 inhabitants of different ANRESIS regions 2018 (data from FOPH). Visit www.anresis.ch for an interactive view of this graph, including absolute numbers of CPE isolates 2013–2019.



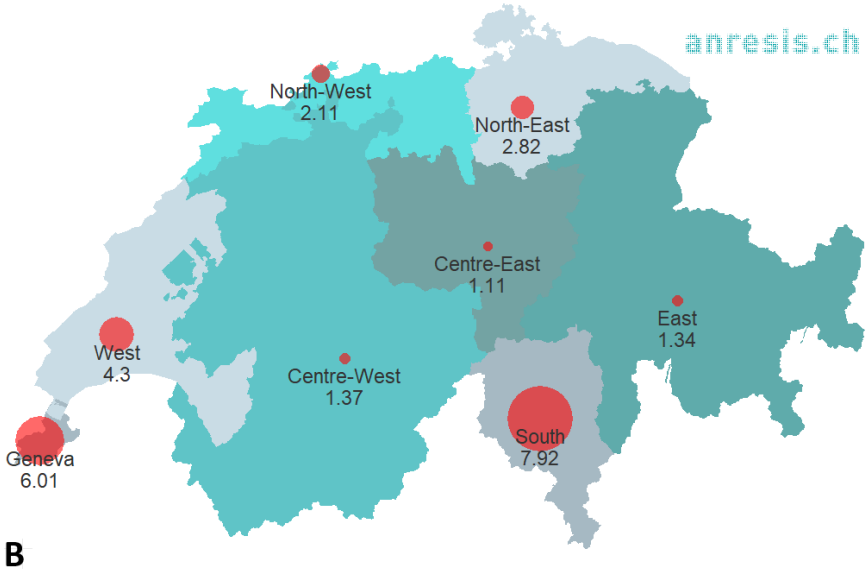


Table 13: Total number of CPE isolates per genus and genotype from 2013 to 2018. Adapted from Gasser, Ramette *et al.* (4).

		Klebsiella spp.	*Escherichia coli*	*Entero-bacter* spp.	*Citrobacter* spp.	*Proteus* spp.	*Providencia* spp.	Others	Total
IMP	**n**	1	0	0	0	0	0	0	1
	%	100; <1	0; 0	0; 0	0; 0	0; 0	0; 0	0; 0	0
KPC	**n**	153	9	5	1	0	1	2	171
	%	90; 40	5; 5	3; 9	<1; 3	0; 0	<1; 14	1; 17	25
NDM	**n**	66	41	21	9	3	5	1	146
	%	45; 17	28; 22	14; 40	6; 28	2; 33	3; 71	<1; 8	21
OXA-181	**n**	7	17	0	1	0	0	1	26
	%	27; 2	65; 9	0; 0	4; 3	0; 0	0; 0	4; 8	4
OXA-48-type	**n**	144	113	15	13	0	1	6	292
	%	50; 38	39; 61	5; 28	5; 41	0; 0	<1; 14	2; 50	43
OXA-other	**n**	1	1	0	0	0	0	0	2
	%	50; <1	50; <1	0; 0	0; 0	0; 0	0; 0	0; 0	0
VIM	**n**	11	5	12	8	6	0	2	44
	%	25; 3	11; 3	27; 23	18; 25	14; 67	0; 0	5; 17	7
Total	**n**	383	186	53	32	9	7	12	682
	%	56	27	8	5	1	1	2	100

Marginal percentages respectively per row and column are shown. The category "others" includes *Pluralibacter* spp., *Raoultella* spp., *Salmonella* spp., *Serratia* spp. and unknowns. The category "OXA-other" includes the OXA-232 and OXA-244 genotypes.

Table 14: Monitoring program on carbapenem-resisant *E. coli* in livestock and meat thereof 2015–2019.

Year	Sample type	Number of samples (n)	Number of carbapenemase-producing *E. coli* (n)
2015	fattening pigs – cecum	300	0
	veal calves – cecum	298	0
	chicken mea	319	0
	pork meat	301	0
	beef meat	298	0
2016	broiler – pooled caecum	307	0
	chicken meat	302	0
2017	fattening pigs – cecum	296	0
	veal calves – cecum	304	0
	pork meat	302	0
	beef meat	299	0
2018	broiler – pooled caecum	307	0
	chicken meat	312	0
2019	fattening pigs – cecum	306	0
	veal calves – cecum	298	0
	pork meat	311	0
	beef meat	309	0

regions of Switzerland, significant clusters were identified, resulting in a total of seven clusters. Three of them were confirmed as local outbreaks by genetic analyses.

These analyses have shown the importance of a timely and detailed national surveillance for CPE. An important step was taken towards this goal in 2016, when the Federal Office of Public Health declared CPE reporting as mandatory. In addition, since 2019 all isolates suspected to contain CPE need to be sent to the Swiss national reference laboratory NARA (www.nara-antibiotic-resistance.ch) for in depth genotyping and physical storage. Epidemiological data (e.g. travel history, invasiveness of disease or antibiotic pretreatments) are collected by the Federal Office of Public Health. In 2020, the Swiss Centre for Antibiotic Resistance ANRESIS, in close collaboration with NARA, established an up-to-date representation of Swiss CPE data, which is now accessible to the public (see www.anresis.ch).

13.3 Veterinary Medicine (livestock and meat)

Since 2015, detection of carbapenemase-producing *E. coli* is included in the national antimicrobial resistance monitoring program for livestock and meat thereof (Table 14). The method is harmonized at the European level and is based on an enrichment step in non-selective buffered peptone water followed by plating out on two different selective agar plates for detection of carbapenemase-producing *Enterobacterales*, including OXA-48 phenotypes. From 2015 to 2018, only colonies suspected to contain *E. coli* were further analysed; since 2018, the presence of *Klebsiella* spp. has been included in the analysis of CPE. Moreover, all *Salmonella* strains isolated within the framework of the Swiss national surveillance program on *Salmonella* in chicken or from clinical cases of various animal species are analysed for their antimicrobial resistance pattern by micro broth dilution. Meropenem is included as a screening substance for CPE.

No carbapenemase-producing *E. coli* or *Salmonella* spp. were detected, whether in samples from the primary production level or in fresh meat. These results are in accordance with results reported by the European food safety authority (EFSA). In the period from 2017 to 2018, 18 European member states as well as Norway and Switzerland analysed more than 30,000 samples from livestock and meat for the presence of carbapenemase-producing *E. coli* on a voluntary basis, with negative results [5]. Only in one case in 2017, one isolate with a carbapenemase phenotype from a cecal sample collected at slaughter from a pig in Germany was detected within the ESBL/pAmpC monitoring program. The isolate was confirmed to produce VIM-1. In the previous period (2015–2016), approximately 17,000 samples were tested within Europe. In 2016, three *E. coli* from broilers and chicken meat, respectively, were isolated in Romania and have been confirmed as $bla_{\text{OXA-162}}$ carriers [5].

13.4 Veterinary Medicine (Small animals)

Unlike in human medicine, the use of carbapenems in veterinary medicine is controversially discussed. Carbapenems are not allowed for use in farm animals, and only exceptionally used in companion animals. While β-lactam antibiotics are the most commonly used antimicrobials in cats and dogs, critically important antimicrobials such as fluoroquinolones and higher generation cephalosporins are also routinely used. Until very recently, reports of carbapenem resistance have been very rare in veterinary medicine.

In 2018, a large prospective, longitudinal, observational study was funded by the Federal Food Safety and Veterinary Office to assess risk factors for prevalence, and acquisition and carriage of multidrug resistant organisms (MDRO) in dogs and cats presented to five veterinary clinics/hospitals in Switzerland. Nasal/oropharyngeal and rectal swabs were collected from 183 dogs and 88 cats presented to 5 veterinary hospitals/clinics. In addition, nasal swabs and stool samples were collected from 50 owners and 108 employees of three Swiss veterinary clinics and one private practice.

The admission prevalence of MDRO carriage in pets was 15.5% (95%CI 11.4–20.4%); at admission, MDR- (ESBL or *pAmpC*) *E. coli* predominated, accounting for 34.1% of all MDRO isolates. One *E. coli* isolate from a dog additionally displayed resistance to carbapenem, due to the presence of a plasmid-mediated carbapenemase gene ($bla_{OXA-181}$) [6,7].

Overall discharge prevalence of MDRO carriage in pets was 32.6% (95%CI 26–39.8%), but varied significantly among care facilities (range 17.2–42.7%). Predominant hospital-acquired isolates among the three largest clinics were: ESBL-*E. coli* (16.1%) and ESBL-producing *Klebsiella pneumoniae* (ESBL-*Kp*) (12.9%). At discharge, 71.4% (25/35) of all MDR *E. coli* displayed resistance to ertapenem. Carbapenem resistance was due to the presence of plasmidic $bla_{oxa-181}$ (22 isolates, clinic 1), bla_{oxa-48} (1 isolate, clinic 1) or bla_{NDM-5} (2 isolates, clinic 2). *K. pneumoniae* were isolated from 38.5% (25/82) of all animals, the large majority were of the CTX-M-1/-3/-15 ESBL and DHA-1 pAmpC subtypes, and only one isolate from clinic 1 displayed a carbapenemase-encoding gene (bla_{OXA-48}) [6,7].

Resistant bacteria were isolated from 9 out of 50 owners (5/9 ESBL-*E. coli*; 4/8 MRCoNS; 1/8 MRSA). Interspecies transfer of MDRO between owners and dogs was not documented. However, two employees of veterinary clinics (1.9%) were shown to be colonized at the gut level with CPE. One employee (clinic 1) carried ST410-OXA-181-*Ec* (strain *Ec*-042; GenBank: CP042934–CP042936) and one (clinic 2) carried ST167-NDM-5-*Ec* (strain *Ec*-050; GenBank: CP043227–CP043230). Five carbapenemase-producing *E. coli* (two ST410-OXA-181-*Ec* and three OXA-48 producers of ST155, ST641 and ST4038) were also present in the hospital environment of clinic 1 [8].

In conclusion, this study has revealed that despite the fact that carbapenems are not routinely used in companion animal medicine, international epidemic CPE clones (e.g. ST410-OXA-181-*Ec* and ST167-NDM-5-*Ec*) disseminate in companion animal veterinary clinics and may also colonize veterinary staff. While transmission of CPE to owners has not been documented, enteral carriage in pets contributes to the spread of CPE in the environment. Therefore, veterinary institutions must urgently implement optimal infection control practices (e.g. efficient cleaning and disinfection procedures).

13.5 Discussion

Carbapenems are mainly used in human medicine as reserve antibiotics. After a slight increase in prescription up to 2013, carbapenem use in Switzerland has stabilized over the last six years. On the other hand, CPE prevalence in human medicine more than tripled from 2013 to 2018. Although most cases were sporadic, some small local outbreaks were detected. Single reports and genotype distribution suggest that most CPE cases are imported. Although epidemiological parameters such as the travel history should be reported to the FOPH with each isolate, this is unfortunately not done frequently, making more detailed analyses of this important feature impossible.

In veterinary medicine, carbapenems are not used in farm animals and only rarely in small animals (cats and dogs). Until 2019, carbapenem resistance was not reported in animals. However, epidemic CPE clones have recently been detected in companion animal veterinary clinics and veterinary staff. It is not known whether the veterinary staff introduced the CPE in the clinic or the colonization happened in the animal clinic.

Nevertheless, these observations show that antibiotic resistance can be present in multiple settings and may be transmitted from one compartment to the other, and that this can only be tackled using a collaborative One Health approach.

In human medicine, CPE reporting is mandatory; this should also be considered in the veterinary field. Moreover, CPE isolates from human, animal and environmental samples should be analysed together, to immediately detect inter-compartment spreading of this important resistance.

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Textbox

Antibiotic-resistant bacteria in dogs and cats: guidelines for risk reduction

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Small animal clinics and practices too are facing patients carrying antibiotic-resistant bacteria. For risk reduction, guidelines needed to be developed.

A working group of human and veterinary medicine experts developed a guide for dog or cat owners with pets carrying antibiotic-resistant bacteria, namely *methicillin-resistant staphylococci*, and extended spectrum beta-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceae. A review for veterinary practitioners provides background information on the most important antibiotic-resistant bacteria in dogs and cats and on their occurrence, and discusses risk factors in dogs, cats and humans. Measures to reduce the risk of transmission to humans are outlined.

To reduce the development and dissemination of resistant bacteria in small animal clinics and practices, the Vetsuisse Faculty Zurich developed infection prevention and control guidelines by. These contain detailed information on the role of hand hygiene, personal hygiene, cleaning and disinfection, quarantine measures and antimicrobial stewardship in companion animal medicine.

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14

Materials and methods

14 Materials and methods

14.1 Data on antibacterial consumption in human medicine

14.1.1 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]. Since 2018, we have also collected data regarding intestinal anti-infectives (ATC group A07AA, including vancomycin oral und fidaxomicin) for the inpatient setting. Antibiotic consumption (in grams or millions of International Units) were converted into defined daily doses (DDD) using the 2019 release of the DDD by the World Health Organization Collaborating Centre for Drug Statistics Methodology (see Annex I). DDD values for some of the most frequently used antibacterials (e. g. amoxicillin, amoxicillin-clavulanic acid, meropenem, ciprofloxacin, colistin) were submitted to upward adjustment in 2019 by the WHO Collaborating Centre for Drug Statistics Methodology [2]. All results were updated retrospectively for the years 2010-2019 with the new DDDs. Thus, the results of this report cannot be compared with those of the former reports.

14.1.2 Data sources in the inpatient setting

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

(i) 2019 data were collected on behalf of the Swiss Federal Office of Public Health through the IQVIA™ database which provides pharmaceutical sales data. This exhaustive dataset included the antibiotics sold to hospitals (IQVIA™ channel: SPI). 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.

(ii) A network of voluntary acute care hospitals participating in the surveillance system ANRESIS 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) [3]. Data were collected from the entire hospitals, and separately from the adult intensive care units (ICU) when possible. In this report, we have described the antibiotic consumption for the period 2010 to 2019. Fifty-nine hospital sites participated in 2010 and 60 in 2019, of which 33 were small-size (<200 beds), 20 medium-size (200–500 beds) and 7 large-size hospitals (>500 beds, which includes five Swiss university hospitals). In 2018, the hospital network represented 40% of the total number of acute somatic care hospitals and 75% of all bed-days in this category in Switzerland. In 2010, 40 hospital sites also provided data on adult ICUs. This number corresponds to 39 (13 small-size, 19 medium-size and 7 large-size hospitals) in 2019, representing 52% 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 has excluded 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 per 100 bed-days.

The measurement units for reporting antibiotic consumption in the inpatient setting are DDDs per 1,000 inhabitants per day (DID), DDDs per 100 bed-days and DDDs per 100 admissions [1]. The quantity of J01 group antibiotics was the denominator when measuring relative consumption.

14.1.3 Data sources in the outpatient setting

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

(iii) Data for the years 2016 to 2019 were collected on behalf of the Swiss Federal Office of Public Health through the IQVIA™ database which provides pharmaceutical sales data. This exhaustive dataset included the antibiotics sold from pharmaceutical industries to pharmacies and dispensing physicians. (IQVIA™ channels: APO/

SD). 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 at the national level and by linguistic region (German-speaking, French-speaking and Italian-speaking parts of Switzerland).

(iv) PharmaSuisse, the Swiss Society of Pharmacists, provided data for the years 2017 to 2019 through the updating of the database that is entrusted to the professional cooperative of the Swiss pharmacists (OFAC, Geneva). 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 53% of all pharmacies in 2019 in Switzerland (57% in 2017, 53% in 2018). All antibiotics are 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; > 65 years of age).

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

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

14.1.4 Categorization of antibiotics in the 2019 Access, Watch and Reserve groups

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) [4, 5]:

- 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. They must be targets of stewardship programs and monitoring.
- 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. They must be targets of stewardship programs and monitoring.
- 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.

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14.2 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 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 the "mixed group", as 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).

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14.3 Bacterial isolates from humans (clinical probes)

Currently, 30 microbiology laboratories are linked to ANRESIS (www.anresis.ch). These laboratories send their results from routine testing of all clinical bacteriology cultures to the ANRESIS database on a regular basis (weekly or monthly). 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 in this report 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 outpatient departments) were included and labelled accordingly. Screening results and antibiotic resistance test results analyzed by a 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 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. Unfortunately, most microbiological laboratories send only qualitative, interpreted resistance data (SIR), although we prefer quantitative antibiotic resistance testing results. Resistance data are not validated by ANRESIS, but only by the laboratory sending the data. All laboratories participating in ANRESIS are approved by Swissmedic and are enrolled in at least one external quality control program.

Despite the change of the definitions of the susceptibility testing categories S, I and R introduced by EUCAST in 2019, we have decided to report non-susceptibility as in earlier reports. 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. Multi-resistance was analyzed in accordance with the EARS-Net methodology, to allow comparability with European data. The Wilson score method was used for the 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 the 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 3.6.1

14.4 Bacterial isolates from animals and meat thereof

14.4.1 Sampling of healthy animals at the slaughter-house

Stratified random samples were taken in the years 2018 and 2019 (Table 14. a and Table 14. 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, as well as the seven largest pig and 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 60% of all slaughtered animals belonging to the species in question were part of the sample. In 2018, samples were taken from 642 broiler flocks. Random cecum samples were taken from five broilers per flock. In 2019, 350 cecum samples and 303 nasal swab samples were collected from fattening pigs and 298 cecum samples and 299 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 2010 to 2019. In earlier years, sampling procedures and la-

boratory analyses (excluding ESBL/pAmpC-producing *E. coli*, which changed in 2015) were performed in a similar manner.

14.4.2 Sampling of meat at retailers

In accordance with European directives meat samples (min. 50 g) were taken from fresh, 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 the retailers. Moreover, the proportion of imported and domestically produced meat within each meat category is included in the sampling plan.

In 2018, 312 chicken meat samples (209 samples of Swiss origin and 103 of foreign origin), in 2019 311 pork (all Swiss origin) and 309 beef samples (260 samples of Swiss origin, 49 samples of foreign origin) were collected (Table 14. a, Table 14.b).

14.4.3 Sampling for clinical isolates from animals

For *Salmonella*, no special monitoring at slaughter is feasible due to the very low prevalence of *Salmonella* spp. in Swiss livestock. Therefore, *Salmonella* isolates sent to ZOBA in 2018 and 2019 in connection with its function as a reference laboratory for *Salmonella* spp. at the primary production le-

Table 14. a: Antimicrobial resistance monitoring in livestock, 2018.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cecum – broilers	642	*Campylobacter jejuni/coli*	180
Cecum – broilers	224	*E. coli*	214
Cecum – broilers	307	ESBL/pAmpC-prod. *E. coli*	94
Cecum – broilers	307	Carbapenemase-prod. *E. coli*	0
Meat – broilers	312	*Campylobacter jejuni/coli*	140
Meat – broilers	312	ESBL/pAmpC-prod. *E. coli*	109
Meat – broilers	312	Carbapenemase-prod. *E. coli*	0
Meat – broilers	312	MRSA	4
Clinical material / diverse species	–	*Salmonella* spp.	182
Clinical material / diverse species	–	*S.* Typhimurium	51
Clinical material / diverse species	–	*S.* Typhimurium, monophasic variant	41
Clinical material / diverse species	–	*S.* Enteritidis	31

Table 14. b: Antimicrobial resistance monitoring in livestock, 2019.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cecum – fattening pigs	350	*Campylobacter jejuni/coli*	229
Cecum – fattening pigs	207	*E. coli*	189
Cecum – fattening pigs	306	ESBL/pAmpC-prod. *E. coli*	40
Cecum – fattening pigs	306	Carbapenemase-prod. *E. coli*	0
Nasal swab – fattening pigs	303	MRSA	160
Cecum – calves	212	*E. coli*	199
Cecum – calves	298	ESBL/pAmpC-prod. *E. coli*	98
Cecum – calves	298	Carbapenemase-prod. *E.coli*	0
Nasal swab – calves	299	MRSA	11
Meat – fattening pigs	310	ESBL/pAmpC-prod. *E. coli*	2
Meat – fattening pigs	310	Carbapenemase-prod. *E.coli*	0
Meat – fattening pigs	310	MRSA	1
Meat – beef	309	ESBL/pAmpC-prod. *E. coli*	1
Meat – beef	309	Carbapenemase-prod. *E.coli*	0
Meat – beef	309	MRSA	2
Clinical material / diverse species	–	*Salmonella* spp.	107
Clinical material / diverse species	–	*S. Typhimurium*	41
Clinical material / diverse species	–	*S.* Typhimurium, monophasic variant	11
Clinical material / diverse species	–	*S. Enteritidis*	14

vel, as well as isolates from ZOBA's own diagnostic activities were included in the monitoring (Table 14. a and Table 14. 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). Results from selected *Salmonella* spp. from livestock, isolated in 2018 and 2019, are presented in this report. Methods in previous years were applied in a similar manner.

In 2019, an annual monitoring of antimicrobial resistance in veterinary pathogens was initiated by the Federal Food Safety and Veterinary Office (FSVO) and implemented at the Swiss national reference laboratory for antimicrobial resistance ZOBA. The sampling plan includes various pathogens/animals and indication combinations (Table 14. c). All strains were isolated from clinical submissions of diseased animals by ten Swiss laboratories (university, cantonal, private) across Switzerland. Samples from animals with antimicrobial treatment prior to sampling were excluded from this study. The planned number of isolates was achieved for pathogenic *Escherichia coli* from poultry.

Results of selected bacteria (staphylococci, streptococci and *E. coli*) are presented in Chapter 11 ("Resistance in bacteria from animal clinical isolates").

14.5 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 has increased over the years. The Swiss Society of Microbiology encourages the use of EUCAST breakpoints and provides recommendations on its 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 and no systematic collection of multi-resistant isolates.

The antibiotic resistance data presented in this report were extracted from the database using the analysis tool KNIME. 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

Table 14. c: Antimicrobial resistance monitoring in veterinary pathogens, 2019.

Animal species	Indication	Bacterial species	Number of isolates planned (n)
Cattle	Mastitis	*Staphylococcus aureus*	100
Cattle	Mastitis	*Streptococcus uberis*	100
Cattle	Mastitis	*Escherichia coli*	100
Cattle	Respiratory tract infection	*Pasteurella multocida*	30
Cattle	Enteritis	Pathogene *Escherichia coli*	30
Pigs	Enteritis	Pathogene *Escherichia coli*	100
Poultry	All	*Escherichia coli*	100
Dogs	Urogenitaltract infection	*Escherichia coli*	100
Dogs	Skin infection	*Staphylococcus pseudintermedius*	100
Cats	Urogenitaltract infection	*Escherichia coli*	100
Cats	Skin infection	*Streptococcus equi* subsp. *zooepidemicus*	30
Small ruminants	Enterotoxaemia	*Clostridium perfringens* (Typen B, C, D, E)	30
Small ruminants	Abscess	*Corynebacterium pseudotuberculosis*	30

when tested and interpreted as resistant in accordance with the breakpoint used by the local laboratory. In most cases, quantitative resistance data are not provided and are not used in this report. 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 seen in ciprofloxacin susceptibility in *Acinetobacter* spp. and is always an important issue in *S. pneumoniae*, for which, in addition to changing breakpoints over time, different breakpoints are used for different kinds of infections.

14.6 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.

14.6.1 Samples of healthy animals in slaughterhouses and meat thereof

Cecal samples from fattening pigs, calves and broilers were tested for *Campylobacter* spp. and *E. coli* using direct detection methods. For *Campylobacter* spp., modified charcoal cefoperazone deoxycholate agar (mCCDA) was used, and for *E. coli* MacConkey 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.

The MRSA detection method was modified in 2019, following recommendations of the European reference laboratory for antimicrobial resistance (EURL, The National Food Institute, Lyngby, Denmark). Before 2019, nasal swab or meat samples were transferred consecutively into two different enrichment broths, followed by cultivation on chromogenic MRSA-selective agar [1]. Since 2019, only the saline enrichment broth is used [2]. 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 [3].

Since 2015, 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). 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 and 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 carbapenemase production was carried out phenotypically by MIC determination on EUVSEC2 plates or the Carba blue test [4], respectively.

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, Scientific, UK) according to CLSI guidelines [5]. The MIC was defined as the lowest antimicrobial concentration at which no visible bacterial growth occurred.

The European Union recommends 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 between wild types and non-wild types. These are set and published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Interpretation of MICs followed the ECOFFs laid down in the European decision 2013/652/EU, excluding MRSA, for which ECOFFs according to EUCAST were used (Table 14. d).

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 %

All data were transmitted to the database of the Federal Food Safety and Veterinary Office (FSVO) and further sent

Table 14. d: 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 / 512[h]	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, [h] 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.

to the European Food Safety Agency (EFSA). All results are included in the annual European Union summary reports on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food, published by the European Food Safety Authority and the European Centre for Disease Prevention and Control.

14.6.2 Samples of clinical animal isolates

Swiss laboratories sent targeted isolates, derived from animals that were not treated with antimicrobials prior to sampling according to the information of the veterinarian, to ZOBA. At ZOBA, re-identification of the bacterial species 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 Scientific, UK) according to CLSI guidelines [5]. 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 [6]. 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 targeted organ.

Minimal inhibitory concentrations as well as interpretative values are transmitted to the database of the Swiss center for antimicrobial resistance (ANRESIS), which is a nationwide system for resistance data for both human and veterinary medicine (www.anresis.ch).

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[6] CLSI. Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals. 4th ed. CLSI supplement VET08. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

Annex I

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), antibiotics against amoebiasis and other protozoal diseases (ATC group P01AB) and intestinal anti-infectives (ATC group A07AA) with administration route, defined daily dose (DDD) and classification by groups, i.e. Access, Watch or Reserve (see Chapter 14, Materials and methods) according to the WHO.

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Access [A], Watch [W], Reserve [R] or Others [O]
J01A	Doxycycline	oral	0.1	A
	Doxycycline	parenteral	0.1	A
	Lymecycline	oral	0.6	W
	Minocycline	parenteral	0.2	R
	Minocycline	oral	0.2	W
	Tetracycline	oral	1	W
	Tetracycline	parenteral	1	W
	Tigecyclin	parenteral	0.1	R
J01B	Chloramphenicol	parenteral	3	A
J01C	Amoxicillin	oral	1.5	A
	Amoxicillin	parenteral	3	A
	Amoxicillin-clavulanic acid	oral	1.5	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	W
	Piperacillin-tazobactam	parenteral	14	W
	Temocillin	parenteral	4	W
	Ticarcillin	parenteral	15	W
	Ticarcillin-clavulanic acid	parenteral	15	W

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Access [A], Watch [W], Reserve [R] or Others [O]
J01D	Aztreonam	parenteral	4	R
	Aztreonam	inhaled	0.225	R
	Cefaclor	oral	1	W
	Cefamandole	parenteral	6	W
	Cefazolin	parenteral	3	A
	Cefepime	parenteral	4	W
	Cefixime	oral	0.4	W
	Cefotaxime	parenteral	4	W
	Cefoxitin	parenteral	6	W
	Cefpodoxime	oral	0.4	W
	Cefprozil	oral	1	W
	Ceftaroline	parenteral	1.2	R
	Ceftazidime	parenteral	4	W
	Ceftazidime-avibactam	parenteral	6	R
	Ceftibuten	oral	0.4	W
	Ceftobiprole	parenteral	1.5	R
	Ceftolozane-tazobactam	parenteral	3	R
	Ceftriaxone	parenteral	2	W
	Cefuroxime	oral	0.5	W
	Cefuroxime	parenteral	3	W
	Ertapenem	parenteral	1	W
	Imipenem	parenteral	2	W
	Meropenem	parenteral	3	W
J01E	Sulfadiazine	oral	0.6	O
	Sulfadiazine	parenteral	0.6	O
	Trimethoprim	oral	0.4	A
	Trimethoprim-sulfamethoxazole	oral (tablets)	4 UD (= 4 tabl)	A
	Trimethoprim-sulfamethoxazole	oral (suspension)	8 UD (= 40ml)	A
	Trimethoprim-sulfamethoxazole	parenteral	20 UD (= 20ml)	A
J01F	Azithromycin	oral	0.3	W
	Azithromycin	parenteral	0.5	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
	Pristinamycin	oral	2	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	1	W
	Netilmicin	oral	0.35	W
	Netilmicin	parenteral	0.35	W
	Streptomycin	parenteral	1	W
	Tobramycin	inhaled	0.3	W
	Tobramycin	parenteral	0.24	W

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Access [A], Watch [W], Reserve [R] or Others [O]
J01M	Ciprofloxacin	oral	1	W
	Ciprofloxacin	parenteral	0.8	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	9	R
	Daptomycin	parenteral	0.28	R
	Fosfomycin	oral	3	W
	Fosfomycin	parenteral	8	R
	Fusidic acid	oral	1.5	W
	Fusidic acid	parenteral	1.5	W
	Linezolid	oral	1.2	R
	Linezolid	parenteral	1.2	R
	Metronidazole	parenteral	2	A
	Nitrofurantoin	oral	0.2	A
	Ornidazole	parenteral	1	O
	Polymyxin B	parenteral	0.15	R
	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	W
	Rifampicin	parenteral	0.6	W
	Rifamycin	parenteral	0.6	W
	Rifabutin	oral	0.15	W
P01AB	Metronidazole	rectal	2	A
	Metronidazole	oral	2	A
	Ornidazole	oral	1.5	O
A07AA	Vancomycin	oral	2	W
	Rifaximin	oral	0.6	W
	Fidaxomicin	oral	0.4	O

Annex II

Distribution of minimal inhibitory concentrations (MICs) in bacterial isolates from livestock and meat thereof

Annex II

Distribution of minimal inhibitory concentrations (MICs) in bacterial isolates from livestock and meat thereof

Tables II.08.1–II.08.5 show distribution of MICs in *Campylobacter jejuni/coli* from livestock and meat thereof, tables II.09.1–II.09.7 MIC data from indicator bacteria derived from livestock and table II.10.1 those from meat. Vertical red lines indicate epidemiological cutoff values for resistance according to EUCAST used as interpretative criterion for microbiological resistance. The white areas indicate the dilution range tested for each antimicrobial agent. Values above this range indicate MIC values > the highest concentration in the range. Values at the lowest concentration tested indicate MIC-values ≤ the lowest concentration in the range.

Table II.08.1: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Campylobacter coli* from broilers (n=37), 2018.

	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					15	7					3	10	2							
Erythromycin (Erythromycin A)								22	10	4	1									
Gentamicin						23	14													
Nalidixic acid										13	9			4	11					
Streptomycin						1		14	9	1		2	10							
Tetracycline							13	4			1	1	1	3	14					

Table II.08.2: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Campylobacter jejuni* from broilers (n=138), 2018.

	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					56	19			1		11	40	11							
Erythromycin (Erythromycin A)								104	25	4	2					3				
Gentamicin					78	51	8	1												
Nalidixic acid									4	48	21	2		9	54					
Streptomycin						7	36	84	5	2			4							
Tetracycline							95	1		1		3	4	10	24					

Table II.08.3: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Campylobacter coli* from fattening pigs (n = 229), 2019.

	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					74	23	4			2	40	60	26							
Erythromycin (Erythromycin A)								153	42	20	5	1		1		7				
Gentamicin					8	45	142	34												
Nalidixic acid										38	49	14		16	112					
Streptomycin							1	4	21	9	1	21	172							
Tetracycline							61	19	4	2	6	16	59	36	26					

Table II.08.4: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Campylobacter coli* from chicken meat (n = 24), 2018.

	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					4	2					3	12	3							
Erythromycin (Erythromycin A)								15	6	2	1									
Gentamicin					1	10	13													
Nalidixic acid										2	3	1	1	5	12					
Streptomycin							1	9	5				9							
Tetracycline							8	2			1	1	1	3	8					

Table II.08.5: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Campylobacter jejuni* from chicken meat (n = 112), 2018.

	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					37	7	2				9	46	11							
Erythromycin (Erythromycin A)								83	22	6						1				
Gentamicin					59	47	6													
Nalidixic acid								2	5	32	9			9	55					
Streptomycin						11	34	53	9	1		1	3							
Tetracycline							69	4	1				3	9	26					

Table II.09.1: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Escherichia coli* from broilers (n=214), 2018.

	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	69	80	7	1		1	53					
Azithromycin									14	90	100	10								
Cefotaxim						214														
Ceftazidim							214													
Chloramphenicol											200	12		1		1				
Ciprofloxacin		99	15	2	13	65	11	6			2	1								
Colistin								213	1											
Gentamicin							128	74	7		1	4								
Meropenem			214																	
Nalidixic acid										114	3		3	34	39	21				
Sulfamethoxazole											90	54	20	2	1	2		3	42	
Tetracycline									162	17	1			20	14					
Tigecycline						181	33													
Trimethoprim						131	45	6						32						

Table II.09.2: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Escherichia coli* from fattening pigs (n=189), 2019.

	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	55	97	6				24					
Azithromycin									30	134	25									
Cefotaxim						189														
Ceftazidim							189													
Chloramphenicol											186		1	1	1					
Ciprofloxacin		175	9		1	4														
Colistin								189												
Gentamicin							137	49	1				1	1						
Meropenem			189																	
Nalidixic acid										184					4	1				
Sulfamethoxazole											100	22	8	2				1	56	
Tetracycline									142	6	1			23	17					
Tigecycline						177	9	3												
Trimethoprim						138	22	5						24						

Table II.09.3: Distribution (n) of Minimal Inhibitory Concentration (MIC) (mg/L) in *Escherichia coli* from slaughter calves (n=199), 2019.

	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								8	49	84	6				52					
Azithromycin									23	140	31	4	1							
Cefotaxim						197					2									
Ceftazidim							197	1	1											
Chloramphenicol											182	3	1	1	3	9				
Ciprofloxacin		173	17		2	6						1								
Colistin								198	1											
Gentamicin							140	48	3		1	4	1	2						
Meropenem			199																	
Nalidixic acid										190	1			2	4	2				
Sulfamethoxazole											11	16	9						62	
Tetracycline									119	7	1		2	25	45					
Tigecycline						185	14													
Trimethoprim						139	32	2						26						

Table II.09.4: Distribution (n) of MICs (mg/L) in ESBL/pAmpC-producing *Escherichia coli* from broilers (n=94), 2018.

1st panel

	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	92					
Azithromycin									16	58	18	1	1							
Cefotaxim							1	8	7	20	58									
Ceftazidim							12	10	14	12	11	35								
Chloramphenicol											90	1				3				
Ciprofloxacin		28	4		9	23	7	2			13	8								
Colistin								94												
Gentamicin							48	36	1			3	2	4						
Meropenem			94																	
Nalidixic acid										34	5		4	3	14	34				
Sulfamethoxazole											26	12	3	3				3	47	
Tetracycline													1	13	21					
Tigecycline						66	25	3												
Trimethoprim						49	11							34						

2nd panel

	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				7	8	23	8	17	8	14	4	4		1						
Cefotaxim							2	8	4	17	80	13	10	6	4					
Cefotaxime + Clavulanic acid				52	7	1	7	1	2	7	16	1								
Cefoxitin								1	13	19	26	11	4	20						
Ceftazidim							6	14	16	8	11	21	16	2						
Ceftazidime + Clavulanic acid					34	24	2	4	6	5	18	1								
Ertapenem		69	21	4																
Imipenem					49	45														
Meropenem			94																	
Temocillin									7	31	49	7								

Table II.09.5: Distribution (n) of MICs (mg/L) in ESBL/pAmpC-producing *Escherichia coli* from fattening pigs (n = 40), 2019.

1st panel	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															40					
Azithromycin									2	23	14				1					
Cefotaxim								2	9	5	24									
Ceftazidim							2	9	6	8	8	7								
Chloramphenicol											30				6	4				
Ciprofloxacin		22	1			4	5		2		2	4								
Colistin								39	1											
Gentamicin							22	9		1	1	1	1	5						
Meropenem			40																	
Nalidixic acid										23	6	2			2	7				
Sulfamethoxazole											14	3							23	
Tetracycline									16	1				6	17					
Tigecycline						38	2													
Trimethoprim						20	6							14						

2nd panel	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	6	3	3	3	6	9	4	2								
Cefotaxime								5	5	6		8	3	10	3					
Cefotaxime / clavulanic acid				24	3			8	3	1		1								
Cefoxitin									4	20	2	8	2	4						
Ceftazidime							2	6	9	8	5	7		3						
Ceftazidime / clavulanic acid					18	7	2		6	3	3			1						
Ertapenem		28	9	3																
Imipenem					20	19	1													
Meropenem			39		1															
Temocillin									3	14	21	2								

Table II.09.6: Distribution (n) of MICs (mg/L) in ESBL/pAmpC-producing *Escherichia coli* from slaughter calves (n=98), 2019.

1st panel

	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															98					
Azithromycin									6	53	28	4	3	4						
Cefotaxim							2	6	20	10	60									
Ceftazidim							1	20	18	15	28	16								
Chloramphenicol											62		3		11	22				
Ciprofloxacin		52	5		2	12	13				3	11								
Colistin								97	1											
Gentamicin							34	16	1		6	5	11	25						
Meropenem			98																	
Nalidixic acid										62	13	2		2	1	18				
Sulfamethoxazole											12	2	5	2				1	76	
Tetracycline									19	1		1	1	16	60					
Tigecycline						86	12													
Trimethoprim						39	16	1						42						

2nd panel

	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	19	3	5	4	9	28	17	3								
Cefotaxime							2	9	12	16	2	8	18	19	12					
Cefotaxime / clavulanic acid				56	7	2	4	12	14	2		1								
Cefoxitin									7	41	17	9	9	14	1					
Ceftazidime							1	18	15	17	26	17	4							
Ceftazidime / clavulanic acid					28	35	3	2	8	9	12	1								
Ertapenem		72	22	4																
Imipenem					58	40														
Meropenem			98																	
Temocillin										31	60	7								

Table II.09.6: Distribution (n) of MICs (mg/L) in Methicllin-resistant *Staphylococcus aureus* (MRSA) from fattening pigs (n=159), 2019.

	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											95	62	2							
Chloramphenicol										6	133		1	18	1					
Ciprofloxacin						83	26		1	2	22	25								
Clindamycin					113	1				7	38									
Erythromycin						36	98					25								
Fusidic acid							156	2		1										
Gentamicin								132		1	5	9	12							
Kanamycin										130	2			9	18					
Linezolid								6	144	9										
Mupirocin							159													
Penicillin										159										
Quinupristin / Dalfopristin							111	5	30	10	3									
Rifampicin		158					1													
Streptomycin										58	56		1	44						
Sulfamethoxazole														156	2			1		
Tetracycline							8						151							
Tiamulin							104	10			45									
Trimethoprim									109	1				49						
Vancomycin								159												

Table II.10.1: Distribution (n) of MICs (mg/L) in ESBL/pAmpC-producing *Escherichia coli* from chicken meat, 2018.

1st panel

	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	106					
Azithromycin									16	67	23	1	2							
Cefotaxim								7	9	32	61									
Ceftazidim							3	15	13	14	21	43								
Chloramphenicol											103	3		1	1	1				
Ciprofloxacin		24	8	3	9	21	3	6	4	6	13	12								
Colistin								108		1										
Gentamicin							51	41	2		2	3	3	7						
Meropenem			109																	
Nalidixic acid										37	5	1	4	12	13	37				
Sulfamethoxazole											34	16	8						51	
Tetracycline									70	5			2	8	24					
Tigecycline						83	24	2												
Trimethoprim						62	15	5	1					26						

2nd panel

	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	16	32	18	11	3	12	8	2	1							
Cefotaxim							2	3	12	30	30	10	13	8	1					
Cefotaxime + Clavulanic acid				59	6		1		5	18	17	3								
Cefoxitin								1	8	36	19	6	15	19	5					
Ceftazidim							3	13	13	14	17	27	19	3						
Ceftazidime + Clavulanic acid					40	24	1		4	14	21	5								
Ertapenem		74	23	11	1															
Imipenem					65	43	1													
Meropenem			109																	
Temocillin									4	41	60	4								

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