Usage of Antibiotics and
Occurrence of Antibiotic Resistance
in Switzerland

Swiss Antibiotic Resistance Report 2022

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Federal Office of Public Health FOPH
Communicable Diseases

Federal Food Safety and Veterinary Office FSVO
Animal Health

Strategy on Antibiotic Resistance
StAR

Publishing details
© Federal Office of Public Health FOPH
Published by the Federal Office of Public Health FOPH
Publication date: November 2022
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Project coordination: Adrian Heuss, advocacy ag
Design and layout: diff. Kommunikation AG, Bern
Source: SFBL, Distribution of Publications, CH-3003 Bern
www.bundespublikationen.admin.ch
Order number: 316.402.22eng

www.star.admin.ch

Please cite this publication as:
Federal Office of Public Health and Federal Food Safety and Veterinary Office.
Swiss Antibiotic Resistance Report 2022. Usage of Antibiotics and Occurrence of Antibiotic Resistance
in Switzerland. November 2022.

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Foreword

1 Foreword

Over the last two years, the COVID-19 pandemic has overshadowed other health issues, including infections with bacteria that are resistant to antibiotics. These infections are not as visible as sudden outbreaks of infectious diseases, yet they are an increasing problem worldwide, and is often referred to as a "silent pandemic."

The steadily increasing resistance to antibiotics in humans and animals, which makes it difficult or even impossible to treat diseases with antibiotics, was the reason why the Strategy on Antibiotic Resistance (StAR) was drawn up in 2015.

Since then, much has happened in all the affected sectors – human medicine, veterinary medicine, agriculture and the environment. For example, guidance has been developed for proper use of antibiotics, and handbooks and recommendations have been developed to reduce the introduction and spread of (resistant) germs in hospital settings, (veterinary) practices and in livestock breeding. Also, thanks to the National Research Programme "Antimicrobial Resistance" (NRP 72), various new optimization approaches have been identified. The NRP followed a holistic, cross-disciplinary One Health approach. The most important research findings from NRP 72 are summarized in chapter 13 "One Health spotlight."

COVID-19 did not lead to an increase in antibiotic consumption as was feared. Through more stringent hygiene (increased handwashing, disinfection and mask-wearing) and by reducing contact, there were even some positive effects, including with regard to antibiotic resistance.

The pandemic also highlighted the importance of research and international cooperation. As with COVID-19, the health of humans and animals is closely related when it comes to antibiotic resistance – both are dependent on complex factors and can be tackled more efficiently through the One Health approach. One Health is now recognized worldwide as a key approach for tackling many problems in the area of health, not only antibiotic resistance.

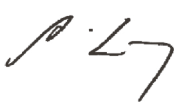
The pandemic also shone a light on the importance of timely and comprehensive monitoring and surveillance. This is a central element of StAR and has been optimized across all areas. For example, resistance monitoring has been continually stepped up and antibiotic consumption monitoring has been extended: every time an antibiotic treatment is administered in veterinary medicine, this is now recorded in the Information System on Antibiotics in Veterinary Medicine (IS ABV), and the latest Swiss Antibiotic Resistance Report (SARR) contains an analysis of these data for the first time.

In human medicine, the Sentinella network, which monitors prescriptions, is now integrated in the SARR. In the area of the environment, too, resistance is being monitored.

All of these measures within the framework of StAR are having an impact: antibiotic use has fallen slightly in human medicine and there have been significant reductions in veterinary medicine. While the resistance situation is not yet optimal in all areas in Switzerland, the levels of some types of resistance are stagnating, and others are gradually falling. Progress has been made and many instruments have been developed and made available. However, in implementation in particular, further efforts are necessary.

In the Global Health Security Index, Switzerland was awarded top marks for its efforts in the area of antimicrobial resistance. However, antibiotic resistance remains a real risk. A new study estimates that 1.3 million people die worldwide every year because of antibiotic resistance. That is more than the number of victims of malaria or HIV – and the figures are rising. Further efforts are therefore necessary to achieve the objective of StAR: to ensure that antibiotics remain effective for humans and animals in the long term.

We would like to thank all those who were involved in the 2022 Swiss Antibiotic Resistance Report. Wishing you an interesting read.



Anne Lévy
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1 Vorwort

In den letzten beiden Jahren liess die Covid-19-Pandemie andere Gesundheitsthemen in den Hintergrund rücken, so auch Infektionen mit antibiotikaresistenten Bakterien. Antibiotikaresistenzen sind nicht so sichtbar wie plötzlich auftretende Infektionskrankheiten; weltweit sind sie jedoch ein fortschreitendes Problem, es wird oft von einer «stillen Pandemie» gesprochen.

Die kontinuierlich zunehmenden Antibiotikaresistenzen bei Mensch und Tier, die eine Behandlung von Erkrankungen mit Antibiotika erschweren oder gar verunmöglichen, waren der Grund, im Jahr 2015 die Strategie Antibiotikaresistenzen (StAR) ins Leben zu rufen.

Seitdem ist in allen beteiligten Bereichen – Humanmedizin, Veterinärmedizin, Landwirtschaft, Umwelt – viel passiert: So wurden beispielsweise Leitlinien für den sachgemässen Einsatz von Antibiotika entwickelt, es wurden Handbücher und Empfehlungen erstellt, um die Einschleppung und Verschleppung von (resistenten) Keimen in Spitälern, (Tierarzt-)Praxen und Tierhaltungen zu reduzieren. Auch dank des Nationalen Forschungsprogramms «Antimikrobielle Resistenz» (NFP 72) konnten diverse neue Optimierungsansätze gefunden werden. Das NFP verfolgte dabei einen ganzheitlichen, disziplinübergreifenden One-Health-Ansatz. Die wichtigsten Forschungsresultate des NFP 72 sind im Kapitel 13 «One Health spotlight» zusammengefasst.

Covid-19 hatte nicht wie befürchtet eine Erhöhung des Antibiotikaverbrauchs zur Folge. Durch intensivierte Hygiene (vermehrtes Händewaschen, Desinfektion, Mundschutz) und Kontaktreduktion waren sogar positive Effekte zu verzeichnen, auch hinsichtlich der Antibiotikaresistenzen.

Auch wurde durch die Pandemie aufgezeigt, wie wichtig die Forschung und die internationale Kooperation sind. Wie bei Covid-19 ist auch bei den Antibiotikaresistenzen die Gesundheit von Mensch und Tier eng miteinander verbunden; beide sind von komplexen Faktoren abhängig und können mit dem sogenannten One-Health-Ansatz effizienter bekämpft werden. One Health ist mittlerweile weltweit als wichtiger Ansatz für die Bewältigung vieler Probleme im Gesundheitsbereich anerkannt, nicht nur bei den Antibiotikaresistenzen.

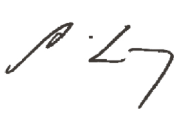
Die Pandemie hat uns zudem vor Augen geführt, wie wichtig eine zeitnahe und umfangreiche Überwachung ist. Sie ist zentraler Baustein von StAR und wurde in allen Bereichen optimiert: So wurde die Resistenzüberwachung kontinuierlich intensiviert und die Antibiotika-Verbrauchsüberwachung ausgedehnt; mit dem Informationssystem Antibiotikaverbrauch (IS ABV) wird im Veterinärbereich neu jede Antibiotikaverwendung registriert; im vorliegenden Swiss Antibiotic Resistance Report (SARR) ist erstmals eine Auswertung dieser Daten enthalten.

Im Humanbereich ist das Sentinella-Netzwerk, das eine Überwachung der Verschreibungen durchführt, nun in den SARR integriert. Auch im Umweltbereich werden die Resistenzen überwacht.

All diese Massnahmen im Rahmen von StAR zeigen Wirkung: Im Humanbereich ist der Antibiotikaverbrauch leicht gesunken, im Veterinärbereich hat es signifikante Rückgänge gegeben. Die Resistenzsituation ist in der Schweiz in allen Bereichen zwar noch nicht optimal, aber bei einigen Resistenzen stagnieren die Werte, andere gehen allmählich sogar zurück. Wichtige Weichen wurden gestellt, viele Instrumente entwickelt und verfügbar gemacht. Insbesondere bei der Umsetzung sind jedoch weitere Bemühungen notwendig.

Im Global Health Security Index werden der Schweiz für ihre Bemühungen im Bereich Antibiotikaresistenz Bestnoten bescheinigt. Jedoch sind die Antibiotikaresistenzen weiterhin ein reales Risiko. Eine neue Studie schätzt, dass weltweit 1,3 Millionen Menschen jährlich an resistenten Bakterien sterben. Das sind mehr Opfer als durch Malaria oder HIV – und die Zahlen steigen weiter. Es sind daher weitere Anstrengungen notwendig, um das Ziel der StAR zu erreichen: den langfristigen Erhalt der Wirksamkeit von Antibiotika für Mensch und Tier.

Wir danken allen, die sich bei der Erarbeitung des SARR-2022-Berichts engagiert haben, und wünschen Ihnen eine spannende Lektüre!



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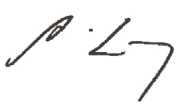
1 Avant-propos

Au cours des deux dernières années, la pandémie de COVID-19 a fait passer d'autres thématiques sanitaires au second plan, notamment les infections dues à des bactéries résistantes aux antibiotiques. Moins visible que les maladies infectieuses qui apparaissent brusquement, l'antibiorésistance n'en constitue pas moins un problème croissant dans le monde entier. On parle d'ailleurs souvent de « pandémie silencieuse ».

L'augmentation continue de la résistance aux antibiotiques chez les êtres humains et les animaux, qui rend le traitement des maladies par antibiotiques plus difficile, voire impossible, a motivé le lancement de la stratégie Antibiorésistance (StAR) en 2015.
Depuis, bien des choses ont évolué dans tous les domaines concernés : médecine humaine, médecine vétérinaire, agriculture, environnement. Des guidelines pour l'utilisation appropriée des antibiotiques ont vu le jour, des manuels et des recommandations ont été établis pour réduire l'introduction et la propagation de germes (résistants) dans les hôpitaux, les cabinets (vétérinaires) et les élevages. Mentionnons encore le Programme national de recherche sur la résistance aux antimicrobiens (PNR 72), qui a permis de mettre au point diverses approches d'optimisation novatrices. Dans ce contexte, le PNR a suivi une approche One Health globale et pluridisciplinaire. Les principaux résultats de recherche du PNR 72 sont résumés dans le chapitre 13 « One Health spotlight ».

Le COVID-19 n'a pas conduit à une augmentation de la consommation d'antibiotiques comme on pouvait le craindre. L'hygiène accrue (lavage régulier des mains, désinfection, port du masque) et la réduction des contacts ont même eu des effets positifs, notamment en ce qui concerne l'antibiorésistance.

La pandémie a également mis en évidence l'importance de la recherche et de la coopération internationale. Comme pour le COVID-19, la santé humaine et la santé animale sont étroitement liées pour ce qui concerne la résistance aux antibiotiques ; toutes deux dépendent de facteurs complexes, que l'approche dite « One Health » permet d'aborder plus efficacement. One Health est aujourd'hui reconnue dans le monde entier comme une approche cruciale pour répondre à de nombreux problèmes sanitaires, pas uniquement en matière d'antibiorésistance.



Anne Lévy
Office fédéral de la santé publique

En outre, la pandémie nous a rappelé l'importance d'une surveillance en temps réel et exhaustive. Cette dernière constitue l'élément central de la StAR et a été optimisée dans tous les domaines : ainsi, la surveillance de l'antibiorésistance a été continuellement renforcée et celle de la consommation d'antibiotiques étendue ; grâce au système d'information sur les antibiotiques en médecine vétérinaire (SI ABV), chaque utilisation d'antibiotiques dans le domaine vétérinaire est désormais enregistrée ; le présent Rapport sur la résistance aux antibiotiques en Suisse (Swiss Antibiotic Resistance Report – SARR) contient pour la première fois une évaluation de ces données.
Dans le domaine humain, le réseau Sentinella qui effectue une surveillance des prescriptions, est à présent intégré dans le SARR. Dans le domaine de l'environnement, les résistances font également l'objet d'une surveillance.

Toutes ces mesures prises dans le cadre de la StAR portent leurs fruits : la consommation d'antibiotiques a légèrement baissé en médecine humaine, tandis que des baisses significatives ont été constatées dans le domaine vétérinaire. Certes, la situation en matière d'antibiorésistance n'est pas encore optimale en Suisse dans tous les domaines. Mais dans certains d'entre eux, les valeurs stagnent, alors que dans d'autres on constate une diminution progressive. D'importants jalons ont été posés, de nombreux instruments ont été développés et rendus disponibles. Toutefois, il reste encore du chemin à faire, notamment en ce qui concerne la mise en œuvre.

Le Global Health Security Index attribue à la Suisse les meilleures notes pour ses efforts en matière de résistance aux antibiotiques. Cependant, ce problème continue à présenter un risque réel. Une nouvelle étude estime que 1,3 million de personnes meurent chaque année dans le monde en raison de bactéries résistantes. Ce sont plus de victimes que celles causées par le paludisme ou le VIH – et les chiffres continuent d'augmenter. Des efforts supplémentaires sont donc nécessaires pour atteindre l'objectif de la StAR : préserver durablement l'efficacité des antibiotiques pour l'homme et l'animal.

Nous remercions toutes les personnes qui ont participé à l'élaboration du rapport SARR 2022 et vous souhaitons une bonne lecture !

Hans Wyss
Office fédéral de la sécurité alimentaire
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1 Premessa

Negli ultimi due anni la pandemia di COVID-19 ha messo in secondo piano altre tematiche relative alla salute, come per esempio le infezioni da batteri resistenti agli antibiotici. Le resistenze agli antibiotici non sono così percepibili come le malattie infettive improvvise, ma rappresentano un problema progressivo in tutto il mondo, tanto che spesso si parla di «pandemia tacita».

Il continuo aumento di resistenze agli antibiotici negli umani e negli animali, resistenze che rendono difficile o addirittura impossibile una terapia antibiotica, è stato il motivo per cui nel 2015 si è deciso di istituire la Strategia contro le resistenze agli antibiotici (StAR).

Da allora sono successe molte cose in tutti i settori coinvolti: medicina umana, medicina veterinaria, agricoltura e ambiente. Per esempio, sono state messe a punto le linee guida per un uso appropriato degli antibiotici, creati manuali ed emanate raccomandazioni allo scopo di ridurre l'introduzione e la diffusione di germi (resistenti) negli ospedali, negli ambulatori (veterinari) e negli allevamenti. Anche grazie al programma nazionale di ricerca PNR 72 «Resistenza antimicrobica» è stato possibile trovare diversi nuovi approcci di ottimizzazione. Il PNR ha adottato un approccio One Health olistico e interdisciplinare. I principali risultati del PNR 72 sono riassunti nel capitolo 13 «One Health spotlight».

La pandemia di COVID-19 non ha causato, come temuto, un aumento del consumo di antibiotici. Grazie a una maggiore igiene (frequente lavaggio delle mani, disinfezione, mascherine) e alla riduzione dei contatti, sono stati registrati persino effetti positivi anche per quanto riguarda le resistenze agli antibiotici.

La pandemia ha rivelato anche l'importanza della ricerca e della cooperazione internazionali. Come per la COVID-19, anche per le resistenze agli antibiotici la salute umana e quella animale sono strettamente legate tra loro. Entrambe dipendono da fattori complessi e possono essere affrontate in modo più efficace con il cosiddetto approccio One Health, che nel frattempo è riconosciuto in tutto il mondo come importante approccio per la gestione di numerosi problemi nel settore sanitario, non solo per le resistenze agli antibiotici.

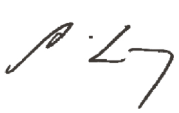
La pandemia ci ha inoltre mostrato l'importanza di una sorveglianza tempestiva e completa, la quale è una componente centrale di StAR ed è stata ottimizzata in tutti i settori. Per esempio, è stata costantemente intensificata la sorveglianza delle resistenze ed estesa quella del consumo di antibiotici; con il sistema d'informazione sugli antibiotici nella medicina veterinaria (SI AMV) ora viene registrata ogni prescrizione di antibiotici in questo campo; l'attuale Swiss Antibiotic Resistance Report (SARR) presenta per la prima volta un'analisi di questi dati.

Nel settore della medicina umana, la rete Sentinella, che monitora le prescrizioni, è ora integrata nel SARR. Le resistenze vengono monitorate anche nel settore dell'ambiente.

Tutte queste misure adottate nell'ambito della strategia StAR producono i loro effetti: nel settore della medicina umana il consumo di antibiotici è leggermente diminuito, mentre in quello veterinario si è registrato un calo significativo. La situazione relativa alle resistenze agli antibiotici in Svizzera non è ancora ottimale in tutti i settori, ma per alcune resistenze i valori sono stabili e per altre stanno persino lentamente riducendosi. Sono state gettate importanti basi, sviluppati e resi disponibili molti strumenti. Tuttavia, sono necessari ulteriori sforzi, soprattutto per quanto riguarda l'attuazione.

Il Global Health Security Index assegna alla Svizzera il massimo dei voti per il suo impegno nel campo delle resistenze agli antibiotici. Ma queste ultime rimangono un rischio reale. Un nuovo studio stima che in tutto il mondo 1,3 milioni di persone muoiano ogni anno a causa di batteri antibiotico-resistenti: sono più vittime di quelle causate dalla malaria o dall'HIV, e le cifre continuano a crescere. È pertanto necessario compiere ulteriori sforzi per raggiungere l'obiettivo della strategia StAR: assicurare a lungo termine l'efficacia degli antibiotici per gli umani e gli animali.

Ringraziamo tutti coloro che hanno partecipato con impegno alla redazione del rapporto SARR 2022 e vi auguriamo buona lettura!



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2

Summary

2 Summary

Antibiotic consumption in human medicine

In 2021, total consumption of antibacterials (in hospital and outpatient care combined, ATC code J01) was 8.6 DDD (defined daily doses) per 1,000 inhabitants per day. Antibacterial consumption slightly decreased between 2012 and 2019 (–7%). However, a decrease by 19% was observed between 2019 and 2021, probably due to the COVID-19 pandemic. Antibacterial consumption in outpatient care accounted for 85% of total consumption in 2021. Antibacterial consumption (ATC code J01) was higher in the French- and the Italian-speaking regions compared to the German-speaking region.

In Switzerland, the antibiotics of the Watch group, which are particularly critical for the development of resistance, have been reduced by almost 40% in the last ten years (2012: 5.4 DDD per 1,000 inhabitants per day; 2019: 4.0; 2021: 3.1). Their share of all antibiotic prescriptions was 36% in 2021, falling below the WHO target of 40% for the first time.

In Swiss acute-care hospitals, consumption of antibacterial agents for systemic use (ATC code J01) remained relatively stable (+2%), from 50.5 DDD per 100 bed-days to 51.5 between 2012 and 2021. The total consumption of antibacterials for systemic use (ATC code J01) was 1.3 DDD per 1,000 inhabitants per day in 2021. The consumption rate in Swiss hospitals is slightly below the European median (1.6; range: 0.8–2.2). The most commonly used class of antibiotics was the penicillins (ATC code J01C), followed by the class of other beta-lactam antibacterials, including cephalosporins (ATC code J01D) as well as macrolides and lincosamides (ATC code J01F). Fluoroquinolones decreased by 43%, while third-generation cephalosporins increased by 42% between 2012 and 2021. In Switzerland, the overall consumption of carbapenems remained relatively stable (–2%) over the last ten years. However, there are quite strong regional differences. In the German- and French-speaking regions, there was a decline of –4% and –13%, respectively, between 2012 and 2021, while in the Italian-speaking region the consumption of carbapenems increased by 122% in the same period.

In outpatient care, the total consumption of antibacterial agents for systemic use (ATC code J01) was 7.3 DDD per 1,000 inhabitants per day in 2021. It slightly decreased by 8% between 2012 and 2019 (from 9.8 to 9.0), and then decreased by 19% between 2019 and 2021, probably due to the COVID-19 pandemic. Antibacterial consumption was relatively low in comparison to the European median (15.0; range: 7.1–26.4). The most commonly used class of antibiotics was the penicillins (ATC code J01C), followed by tetracyclines (ATC code J01A), macrolides, lincosamides and streptogramins (ATC code J01F) and fluoroquinolones (ATC code J01MA). Fluoroquinolones decreased by 54% between 2012 and 2021.

Antibiotic consumption in veterinary medicine

Since October 2019, all prescriptions of antibiotics must be recorded by veterinarians in the information system for antibiotics in veterinary medicine (IS ABV). The analyses in this section are based on the data recorded in the IS ABV for the year 2020 only.

Among livestock, 78.8% of all antibiotics were prescribed for cattle, including, among others, dairy cows and fattening calves. The second highest use of antibiotics was in pigs (13.5%), followed by small ruminants (1.1%) and poultry (0.8%). In accordance with 2020 sales data, the main prescribed antibiotic class for all livestock species was penicillin. Particularly in the poultry sector, penicillin constitutes the main antibiotic class. Sulfonamides and tetracyclines were the next two often-used classes. Among companion animals, the highest amount of antibiotics was prescribed for horses (62.2%). However, horses are heavy animals that require a large amount of antibiotic for each prescription. The second highest amount of antibiotics is used in dogs (32.0%), followed by cats (5.7%). The main antibiotic classes prescribed for companion animals were sulfonamides (42.3%) and penicillins (28.3%).

Among all animals, by far the most commonly used active substances were so-called first-line antibiotics. This shows that they are indeed used first, which is in line with good prescribing practice in Switzerland. The total amount of active ingredient per antibiotic class was previously the only key figure available. Now, for the first time, it can be shown how much active ingredient was prescribed for each livestock category. However, the informative value of this indicator is limited. The number of animal treatments is an important indicator, as it provides a good overview of how many treatments with antibiotics have taken place in a livestock category. In future analyses, this indicator will be central, especially if it is set in relation to population size.

The sales volume of antimicrobials continued to decline, in 2020 by 4.1%, in 2021 less pronouncedly by 1.6%. Overall, 28,871 kg of antimicrobials were sold for veterinary medicine in 2020 and 28,402 kg in 2021. This amounts to a decline of 49% (27 tons) since 2012. The decrease is mainly due to a fall in sales of medicated premixes. In 2020 and 2021 too, peni-

cillins were the main class sold, followed by sulfonamides and tetracyclines. These three classes are often sold as medicated premixes. The quantity of antibiotics approved for companion animals only comprises approximately 3% of the total volume; the sales for companion animals increased by 2.4% in 2020 and 9.3% in 2021. 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 2020 and by another 9% in 2021. Fluoroquinolones were sold less often in 2020, but in 2021 came back to the same level as 2019. The sales of third- and fourth-generation cephalosporins decreased by approximately 18% in 2020, but remained stable in 2021. The sales volume of colistin has declined by approximately 92% since 2012. Expressed in correlation to the biomass under exposure, the level for Switzerland was 0.1 mg colistin/PCU in 2021. 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.

Resistance in bacteria of human clinical isolates

Since 2012, 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 observed in EU/EEA states as well. 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 throughout the last ten years. However, resistance to most other antibiotics has further decreased. As already described in earlier reports, we have noted a significant increase in vancomycin-resistant *Enterococcus faecium* rates during the last ten years. This was mainly due to a regional/national outbreak, associated with the spread of an ST796 clone. Further close monitoring is essential. Actualized cantonal data are published monthly on the ANRESIS website.

The steady increase in quinolone- and third/fourth generation cephalosporin resistance in *Escherichia coli* and *Klebsiella pneumoniae* described in earlier reports leveled off during the last four years, and even slightly reversed for quinolones in *E. coli*. 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. Actualized data are published regularly on the ANRESIS website.

In *Pseudomonas aeruginosa*, resistance rates increased for cefepime and aminoglycosides, while we observed a decrease in trimethoprim-sulfamethoxazole resistance in *Acinetobacter* spp.

Resistance in zoonotic bacteria

Most importantly, in poultry, the resistance rate to ciprofloxacin in *Campylobacter jejuni (C. jejuni)* and *Campylobacter coli (C. coli)* has increased significantly in the past years. The resistance rate to ciprofloxacin rose to 47.5% for *C. jejuni* and 51.5% for *C. coli* in 2020. Resistance to tetracycline remained stable for *C. coli* (51.5%), and decreased for *C. jejuni* (29.6%). Resistance to erythromycin was still rarely found.

According to the WHO, fluoroquinolones and macrolides are highest-priority critically important antimicrobials in human medicine, as these substance groups represent the treatment of choice for serious forms of campylobacteriosis or salmonellosis in humans.

In fattening pigs, the resistance rates in *Campylobacter coli* against ciprofloxacin have increased significantly in the last years, up to 53.9% in 2021 (stable compared to 2019, 55.9%). Concerning erythromycin, we have also noticed a decrease in the resistance, and no isolate was resistant against erythromycin in 2021.

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.

Resistance rates of commensal *E. coli* from broilers in Switzerland in 2020 showed an overall decreasing trend for all antimicrobials tested. Nevertheless, resistance rates against critically important fluoroquinolones are still on a high level (>40%). Trends in resistance levels of *E. coli* from fattening pigs increased between 2019 and 2021 for most of the antimicrobials tested, and especially for tetracyclines. No significant decrease of resistance against any antimicrobial class tested could be detected. For slaughter calves, there is no obvious general trend for resistance rates against the antimicrobials tested. Decreasing resistance rates against tetracyclines, sulfonamides and trimethoprim were detected.

The prevalence of ESBL/AmpC-producing *E. coli* has continued to decrease for broilers (52.4% in 2016 to 10.0% in 2020), and slightly for fattening pigs (5.9% in 2021) and slaughter calves (23.8% in 2021). Overall, a decreasing trend of ESBL/AmpC-producing *E. coli* is observed in all species since 2015/2016.

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 53.6% in 2021.

In contrast, the prevalence for MRSA in veal calves remains at a low prevalence of 6.1%. The genotypes belong to the clonal complex (CC) 398, which is typically livestock-associated (LA-MRSA).

Resistance in indicator bacteria from meat

Compared to the previous years, the prevalence of ESBL/AmpC-producing *E. coli* in chicken meat further decreased for Swiss meat in 2020 (2014: 65.5%, 2018: 21.1%, 2020: 10.2%). In chicken meat from abroad, the detection rate of ESBL/AmpC-producing *E. coli* remained stable in 2020 compared to 2018, and still remains higher than in Swiss meat (2014: 88.9%, 2018: 63.1%, 2020: 61.8%).

In contrast, in pork and beef meat, no ESBL/AmpC-producing *E. coli* were detected in 2021. This difference might be related to the lower prevalence of ESBL/AmpC-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 (all species).

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 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 2021, more than 700 isolates were sent by Swiss university, cantonal and private veterinary diagnostic laboratories to the ZOBA and tested for antimicrobial resistance using the broth microdilution method. All isolates were derived from clinically ill animals. In 2019, only isolates from animals that had not received antimicrobial treatment were examined. However, as it turned out to be very difficult for the laboratories to obtain information on the antimicrobial pre-treatment status, isolates are accepted regardless of their pre-treatment status since 2020. In 2020, however, the number of isolates sent in was sometimes very low, but this situation improved significantly in 2021.

For mastitis pathogens, *Streptococcus uberi*s turned out to be more critical in terms of antimicrobial treatment than *Staphylococcus aureus*. However, the antibiotics recommended, especially penicillin, can still be recommended for the treatment of *Str. uberis* mastitis and there is no need to use critical antibiotics in the standard case. 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 third or fourth generation cephalosporines, whereas *Escherichia coli* isolates from urogenital tract infection of companion animals expressed resistance against these critically important antimicrobials. Carbapenem-resistant *Escherichia coli* were not detected.

2 Zusammenfassung

Antibiotikaverbrauch in der Humanmedizin

2021 belief sich der Gesamtverbrauch von Antibiotika (in der stationären und ambulanten Versorgung zusammen, ATC-J01) auf 8,6 DDD (Defined Daily Doses, definierte Tagesdosen) pro 1000 Einwohnerinnen und Einwohner und Tag. Zwischen 2012 und 2019 ging der Verbrauch leicht um 7% zurück. Zwischen 2019 und 2021 war gar ein Rückgang von 19% auszumachen, was auf die Covid-19-Pandemie zurückzuführen sein dürfte. 2021 entfielen 85% des Gesamtverbrauchs von Antibiotika auf die ambulante Versorgung. Weiter war der Antibiotikaverbrauch (ATC-J01) in den französisch- und italienischsprachigen Regionen höher als in der Deutschschweiz.

In der Schweiz ist der Gebrauch der Antibiotika aus der Gruppe «Watch», die besonders kritisch sind für die Entwicklung von Resistenzen, in den letzten 10 Jahren um fast 40% zurückgegangen (2012: 5,4 DDD pro 1000 Einwohner und Tag; 2019: 4; 2021: 3,1). Ihr Anteil an der Verschreibung aller Antibiotika lag 2021 bei 36% und damit erstmals unter dem WHO-Ziel von 40%.

In den Schweizer Akutspitälern blieb der Verbrauch von Antibiotika zur systemischen Anwendung (ATC-J01) mit 50,5 bis 51,5 DDD pro 100 Bettentage zwischen 2012 und 2021 relativ stabil (+2%). Der Gesamtverbrauch von Antibiotika zur systemischen Anwendung (ATC-J01) belief sich 2021 auf 1,3 DDD pro 1000 Einwohnerinnen und Einwohner pro Tag. Die Verbrauchsrate liegt in Schweizer Spitälern knapp unter dem europäischen Median (1,6; Bereich: 0,8–2,2). Die am häufigsten verwendete Antibiotikagruppe waren die Penicilline (ATC-J01C), gefolgt von der Klasse der anderen Beta-Laktam-Antibiotika, einschliesslich Cephalosporinen (ATC-J01D) sowie Makroliden und Lincosamiden (ATC-J01F). Der Verbrauch von Fluorochinolonen ging um 43% zurück, während derjenige der Cephalosporine der dritten Generation zwischen 2012 und 2021 um 42% anstieg. Der Gesamtverbrauch von Carbapenemen blieb in der Schweiz mit –2% über die vergangenen zehn Jahre relativ stabil. Allerdings sind erhebliche regionale Unterschiede festzustellen. In der deutsch- und französischsprachigen Schweiz war zwischen 2012 und 2021 ein Rückgang von 4% bzw. 13% zu beobachten, während in der italienischsprachigen Schweiz der Verbrauch von Carbapenemen im gleichen Zeitraum um 122% anstieg.

In der ambulanten Versorgung belief sich der Gesamtverbrauch von Antibiotika zur systemischen Anwendung (ATC-J01) im Jahr 2021 auf 7,3 DDD pro 1000 Einwohnerinnen und Einwohner pro Tag. Zwischen 2012 und 2019 kam es zu einem leichten Rückgang um 8% (von 9,8 auf 9,0) und zwischen 2019 und 2021 zu einem weiteren Rückgang um 19%, der wahrscheinlich der Covid-19-Pandemie zugeschrieben werden kann. Im Vergleich zum europäischen Median war der Antibiotikaverbrauch relativ gering (15,0; Bereich: 7,1–26,4). Die am häufigsten verwendete Antibiotikagruppe waren die Penicilline (ATC-J01C), gefolgt von den Tetrazyklinen (ATC-J01A), den Makroliden, Lincosamiden und Streptograminen (ATC-J01F) sowie den Fluorochinolonen (ATC-J01MA). Der Verbrauch von Fluorochinolonen ging zwischen 2012 und 2021 um 54% zurück.

Antibiotikaverbrauch in der Veterinärmedizin

Seit Oktober 2019 sind Tierärztinnen und Tierärzte verpflichtet, alle Antibiotikaverschreibungen im Informationssystem Antibiotika in der Veterinärmedizin (IS ABV) zu erfassen. Die Auswertungen in diesem Abschnitt beruhen auf den für das Jahr 2020 erfassten Daten.

Bei den Nutztieren wurden 78,8% aller Antibiotika für Tiere der Rindergattung, einschliesslich u. a. Milchkühen und Mastkälbern, verschrieben. Am zweithöchsten war der Antibiotikaeinsatz bei Schweinen (13,5%), gefolgt von kleinen Wiederkäuern (1,1%) und Geflügel (0,8%). Gemäss den Daten zum Antibiotikavertrieb aus dem Jahr 2020 war Penicillin bei Nutztieren insgesamt die am häufigsten verschriebene Antibiotikaklasse. Vor allem im Geflügelsektor ist dies die wichtigste Klasse. Darauf folgten Sulfonamide und Tetrazykline.

Bei den Heimtieren wurde Pferden am häufigsten Antibiotika verschrieben (62,2%). Allerdings handelt es sich bei Pferden auch um Tiere mit hohem Körpergewicht, was hohe Verschreibungsmengen erfordert. Die zweithöchste Menge an Antibiotika wird Hunden (32,0%), gefolgt von Katzen (5,7%), verschrieben. Sulfonamide und Penicilline sind mit 42,3% bzw. 28,3% die bedeutendste verschriebene Antibiotikaklasse bei Heimtieren.

Mit Blick auf sämtliche Tiere waren die sogenannten «First-Line-Antibiotika» die mit Abstand am häufigsten verwendeten Wirkstoffe. Dies zeugt davon, dass die Tierärzteschaft die Empfehlungen der guten Verschreibungspraxis in der Schweiz umsetzt. Die gesamte Wirkstoffmenge pro Antibiotikaklasse war bisher die einzig verfügbare Kennzahl. Nun kann erstmals aufgezeigt werden, wie viel Wirkstoff bei welcher Nutztierkategorie verschrieben wurde. Die Aussagekraft der Kennzahl «Wirkstoffmenge» ist jedoch begrenzt. Die Anzahl Tierbehandlungen ist eine wichtige Kennzahl, da sie einen guten Überblick bietet, wie viele Behandlungen

mit Antibiotika in einer Nutztierkategorie erfolgt sind. Die Anzahl Tierbehandlungen wird daher in zukünftigen Auswertungen eine zentrale Kennzahl sein – insbesondere, wenn sie ins Verhältnis zur Populationsgrösse gesetzt wird.

Die Gesamtmenge der verkauften Antibiotika ging weiter zurück: 2020 um 4,1% und 2021 weniger deutlich um 1,6%. 2020 wurden insgesamt 28 871 kg und 2021 28 402 kg Antibiotika zur Behandlung von Tieren verkauft. Dies entspricht einem Rückgang um 49% (27 t) seit 2012. Der Rückgang ist hauptsächlich auf eine Reduktion der Verkäufe von Arzneimittelvormischungen zurückzuführen. Sowohl 2020 als auch 2021 stellten die Penicilline die meistverkaufte Wirkstoffklasse dar, gefolgt von Sulfonamiden und Tetrazyklinen. Diese drei Wirkstoffklassen sind häufig in Arzneimittelvormischungen enthalten. Der Anteil der Antibiotika, die nur für Heimtiere zugelassen sind, macht rund 3% der Gesamtmenge aus. Die Vertriebsmengen für Heimtiere zeigten 2020 und 2021 einen Anstieg um 2,4% bzw. 9,3%. Die Vertriebsmengen der kritischen Antibiotikaklassen mit höchster Priorität für die Humanmedizin waren 2018 und 2019 rückläufig. Die Verkäufe der Makrolide gingen 2020 um 7% und 2021 um weitere 9% zurück. Bei den Fluorochinolonen nahm die Vertriebsmenge 2020 ab, stieg allerdings 2021 wieder auf das Niveau von 2019 an. Die Verkäufe der Cephalosporine der dritten und vierten Generation gingen 2020 um rund 18% zurück, blieben jedoch 2021 stabil. Bei Colistin ging das Verkaufsvolumen seit 2012 um zirka 92% zurück. Ausgedrückt in Bezug zur Populationsbiomasse wurde in der Schweiz 0,1 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.

Resistenz bei Bakterien aus klinischen Isolaten vom Menschen

Seit 2012 wurden bei grampositiven und gramnegativen Bakterien unterschiedliche Trends beobachtet. Die Zahlen Methicillin-resistenter *Staphylococcus aureus* (MRSA) verzeichneten in invasiven Isolaten weiterhin einen deutlichen Rückgang, vor allem in der Westschweiz. Dieser Trend liess sich auch in EU- und EWR-Staaten feststellen. In Wund- und Abszessproben von ambulanten Patientinnen und Patienten nehmen die MRSA-Raten hingegen zu und liegen inzwischen sogar über den Raten, die bei Bakteriämien beobachtet wurden. Die Penicillin-Resistenz bei *Streptococcus pneumoniae* war in den vergangenen Jahren rückläufig, blieb im Verlauf der letzten zehn Jahre aber stabil. Die Resistenz gegenüber den meisten anderen Antibiotika hat jedoch weiter abgenommen. Wie bereits in früheren Berichten erwähnt, haben wir in den letzten zehn Jahren einen signifikanten Anstieg der Raten des Vancomycin-resistenten *Enterococcus faecium* beobachtet. 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. Auf der Website von ANRESIS werden regelmässig aktualisierte Zahlen der Kantone veröffentlicht.

Die in früheren Berichten beschriebene stetige Zunahme der Resistenz gegen Chinolone und Cephalosporine der dritten und vierten Generation bei *Escherichia coli* und *Klebsiella pneumoniae* ist in den letzten vier Jahren abgeflacht, und bei den *E. coli* war sogar wieder eine leicht höhere Empfindlichkeit auf Chinolone feststellbar. 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 neuer Antibiotikaresistenzen und Resistenzmechanismen (NARA) gesammelt. Auf der Website von ANRESIS werden regelmässig aktualisierte Zahlen veröffentlicht.

Bei *Pseudomonas aeruginosa* haben sich die Resistenzraten gegenüber Cefepim und Aminoglykosiden erhöht, während wir bei *Acinetobacter* spp. einen Rückgang der Resistenz gegenüber Trimethoprim/Sulfamethoxazol beobachtetet haben.

Resistenzen bei Zoonose-Erregern

In Geflügel hat die Resistenz gegenüber Ciprofloxacin bei *Campylobacter jejuni* und *Campylobacter coli* in den letzten Jahren signifikant zugenommen. Die Resistenzrate gegenüber Ciprofloxacin stieg 2020 bei *C. jejuni* auf 47,5% und bei *C. coli* auf 51,5% an. Die Resistenz gegenüber Tetrazyklin blieb bei *C. coli* stabil (51,5%) und sank bei *C. jejuni* (29,6%). Eine Resistenz gegenüber Erythromycin wurde weiterhin selten festgestellt.

Gemäss der WHO gelten Fluorochinolone und Makrolide als kritische Antibiotika mit höchster Priorität in der Humanmedizin, weil diese Wirkstoffgruppen bei schweren Verlaufsformen der Campylobacteriose oder Salmonellose beim Menschen bevorzugt zum Einsatz kommen.

Bei Mastschweinen ist die Resistenz bei *C. coli* gegenüber Ciprofloxacin in den letzten Jahren signifikant angestiegen; im Jahr 2021 auf bis zu 53,9% (stabil gegenüber 55,9% im Jahr 2019). Hinsichtlich Erythromycin wurde eine Abnahme der Resistenz festgestellt, und 2021 zeigte kein Isolat eine Resistenz gegen Erythromycin.

Salmonella spp. sind bei Schweizer Nutztieren nur selten zu verzeichnen. Aus diesem Grund kann das Risiko einer Übertragung von *S.* spp. auf den Menschen über Fleisch von Schweizer Nutztieren als gering betrachtet werden. Zudem werden bei *S.* 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 sind die Resistenzraten 2020 gegenüber sämtlichen getesteten antimikrobiellen Stoffen insgesamt rückläufig. Dennoch sind die Resistenzraten gegenüber den als kritisch eingestuften Fluorchinolonen immer noch hoch (>40%). Die Resistenzraten bei *E. coli* aus Mastschweinen zeigten gegenüber den meisten getesteten antimikrobiellen Stoffen – und insbesondere gegenüber Tetrazyklinen – nach oben. Es gibt keine antimikrobielle Klasse, für die ein signifikanter Rückgang von Resistenzen festgestellt werden konnte. Bei Mastkälbern lässt sich in Bezug auf die getesteten antimikrobiellen Stoffe kein klarer allgemeiner Trend erkennen. Bei Tetrazyklinen, Sulfonamiden und Trimethoprim waren rückläufige Resistenzraten zu beobachten.

Die Prävalenz von ESBL/AmpC-produzierenden *E. coli* ging bei Mastpoulets weiter zurück (von 52,4% 2016 auf 10,0% 2020), und bei Mastschweinen und Mastkälbern war ein leicht rückläufiger Trend zu verzeichnen (2021: 5,9% bzw. 23,8%). Insgesamt ist seit 2015/2016 bei allen Spezies ein rückläufiger Trend in Bezug auf ESBL/AmpC-produzierende *E. coli* feststellbar.

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

In der Schweiz nahm das Vorkommen von MRSA bei Mastschweinen zum Zeitpunkt der Schlachtung konstant zu, seit der Nachweis von MRSA im Jahr 2009 Teil der Überwachung wurde. So stieg die MRSA-Prävalenz von anfänglichen 2% (2009) auf 53,6% im Jahr 2021.

Bei Mastkälbern verharrt die MRSA-Prävalenz dagegen auf niedrigen 6,1%. Diese Genotypen gehören zur klonalen Linie CC398, die zu den sogenannten nutztierassoziierten MRSA (LA-MRSA) gehört.

Resistenzen bei Indikatorkeimen aus Fleisch

Im Vergleich zu den Vorjahren zeigte die Prävalenz von ESBL/AmpC-produzierenden *E. coli* in Schweizer Hühnerfleisch 2020 einen weiteren Rückgang (2014: 65,5%, 2018: 21,1%, 2020: 10,2%). Zudem blieb die Nachweisrate von ESBL/AmpC-produzierenden *E. coli* bei Hühnerfleisch aus dem Ausland im Jahr 2020 verglichen mit 2018 stabil, ist aber immer noch höher als bei Schweizer Fleisch (2014: 88,9%; 2018: 63,1%, 2020: 61,8%).

Demgegenüber wurden 2021 in Schweine- und Rindfleisch keine ESBL/AmpC-produzierenden *E. coli* nachgewiesen. Dieser Unterschied ist möglicherweise auf die niedrigere Prävalenz von ESBL/AmpC-produzierenden *E. coli* bei Schweizer Schweinen und Kälbern sowie auf die unterschiedlichen Schlachtmethoden zurückzuführen. In Frischfleischproben wurden keine Carbapenemase-produzierenden *E. coli* gefunden (alle Spezies).

Resistenz bei Bakterien aus klinischen Isolaten von Tieren

Die Überwachung der antimikrobiellen Resistenz 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 2021 wurden mehr als 700 Isolate von universitären, kantonalen und privaten Veterinärdiagnostiklaboratorien in der Schweiz an das Zentrum für Zoonosen, bakterielle Tierkrankheiten und Antibiotikaresistenz (ZOBA) eingesandt und dort mittels Mikrodilutionsverfahren auf ihre antimikrobielle Resistenz untersucht. Alle Isolate stammten von klinisch kranken Tieren. 2019 wurden lediglich Isolate von Tieren untersucht, die keine antimikrobielle Behandlung erhalten hatten. Da es aber für die Labore sehr schwierig ist, Informationen über den antimikrobiellen Vorbehandlungsstatus zu erhalten, werden seit 2020 Isolate unabhängig von ihrem Vorbehandlungsstatus akzeptiert. 2020 fiel die Anzahl eingesandter Isolate allerdings teilweise sehr niedrig aus. Diese Situation hat sich jedoch 2021 deutlich gebessert.

Bei Mastitis-Erregern erwies sich *Streptococcus uberis* hinsichtlich der antimikrobiellen Behandlung als kritischer als *Staphylococcus aureus*. Die empfohlenen Antibiotika, insbesondere Penicillin, können jedoch zur Behandlung von *S.-uberis*-Mastitiden weiterhin empfohlen werden, und es besteht im Normalfall keine Notwendigkeit, kritische Antibiotika einzusetzen. Beim Vergleich von *E. 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 *E. coli*-Isolate aus Harnwegsinfektionen von Heimtieren eine Resistenz gegen diese kritisch wichtigen Antibiotika zeigten. Carbapenem-resistente *E. coli* wurden nicht nachgewiesen.

2 Résumé

Consommation d'antibiotiques en médecine humaine

En 2021, la consommation totale d'antibiotiques (soins hospitaliers et ambulatoires ensemble, classe ATC J01) s'élevait à 8,6 DDD (doses définies journalières) par 1000 habitants par jour. La consommation d'antibiotiques a légèrement reculé entre 2012 et 2019 (–7 %). Une diminution de 19 % a été constatée entre 2019 et 2021, probablement en raison de la pandémie de COVID-19. La consommation d'antibiotiques chez les patients ambulatoires représentait 85 % de la consommation totale en 2021. Elle (classe ATC J01) était plus élevée dans les régions francophone et italophone que dans la région germanophone de la Suisse.

En Suisse, les antibiotiques du groupe « watch », qui sont particulièrement critiques pour le développement des résistances, ont diminué de presque 40 % dans les 10 dernières années (2012 : 5,4 DDD par 1000 habitants par jour ; 2019 : 4,0 ; 2021 : 3,1). Leur proportion par rapport à toutes les prescriptions antibiotiques était de 36 % en 2021, inférieure pour la première fois à la valeur cible de l'OMS fixée à 40 %.

Dans les hôpitaux suisses de soins aigus, la consommation d'agents antibactériens à usage systémique (classe ATC J01) est restée relativement stable (+2 %), passant de 50,5 DDD par 100 journées d'hospitalisation en 2012 à 51,5 en 2021. La consommation totale d'antibactériens à usage systémique (classe ATC J01) se montait à 1,3 DDD par 1000 habitants par jour en 2021. Le taux de consommation dans les hôpitaux suisses était légèrement inférieur à la médiane européenne (1,6 ; étendue : 0,8-2,2). La classe d'antibiotiques la plus communément utilisée était celle des pénicillines (classe ATC J01C), suivie par la classe des autres antibactériens bêta-lactamines, y compris les céphalosporines (classe ATC J01D), et par les macrolides et les lincosamides (classe ATC J01F). Les fluoroquinolones ont reculé de 43 %, tandis que les céphalosporines de troisième génération ont progressé de 42 % entre 2012 et 2021. En Suisse, la consommation totale de carbapénèmes est restée relativement stable (–2 %) ces dix dernières années. Toutefois, on constate des différences régionales assez marquées. Entre 2012 et 2021, les régions germanophone et francophone ont affiché un recul de –4 % et –13 %, respectivement, tandis que la consommation de carbapénèmes a augmenté de 122 % dans la région italophone pendant la même période.

Chez les patients ambulatoires, la consommation totale d'agents antibactériens à usage systémique (classe ATC J01) était de 7,3 DDD par 1000 habitants par jour en 2021. Elle a légèrement reculé (de 8 %), passant de 9,8 en 2012 à 9,0 en 2019, puis a diminué de 19 % entre 2019 et 2021, probablement en raison de la pandémie de COVID-19. La consommation d'antibactériens était relativement basse par rapport à la médiane européenne (15,0 ; étendue : 7,1-26,4). La classe d'antibiotiques la plus communément utilisée était celle des pénicillines (classe ATC J01C), suivie par celle des tétracyclines (classe ATC J01A), des macrolides, des lincosamides et des streptogramines (classe ATC J01F), et des fluoroquinolones (classe ATC J01MA). Les fluoroquinolones ont reculé de 54 % entre 2012 et 2021.

Consommation d'antibiotiques en médecine vétérinaire

Depuis octobre 2019, toutes les prescriptions d'antibiotiques doivent être consignées par les vétérinaires dans le système d'information sur les antibiotiques en médecine vétérinaire (SI ABV). Les analyses mentionnées dans cette section se fondent sur les données enregistrées dans le SI ABV pour l'année 2020 uniquement.

Chez les animaux de rente, 78,8 % de tous les antibiotiques ont été prescrits pour le bétail, notamment pour les vaches laitières et les veaux d'engraissement. Le deuxième usage le plus important d'antibiotiques se rapportait aux porcs (13,5 %), suivis par les petits ruminants (1,1 %) et les volailles (0,8 %). Selon les données de ventes de 2020, les pénicillines formaient la classe d'antibiotiques la plus prescrite pour toutes les espèces d'animaux de rente. Dans le secteur de la volaille, en particulier, les pénicillines constituaient la principale classe d'antibiotiques. Les sulfamidés et les tétracyclines étaient les classes le plus souvent utilisées après les pénicillines. Chez les animaux de compagnie, la quantité d'antibiotiques la plus importante était prescrite aux chevaux (62,2 %). Cela étant, ce sont des animaux lourds qui ont besoin d'une grande quantité d'antibiotiques à chaque prescription. En deuxième position venaient les chiens (32,0 %), suivis par les chats (5,7 %). Les sulfamidés (42,3 %) et les pénicillines (28,3 %) constituaient les principales classes d'antibiotiques prescrites aux animaux de compagnie.

Tous animaux confondus, les antibiotiques dits de première intention étaient de loin les substances actives les plus utilisées. Cela montre que ces substances sont bien utilisées en premier, ce qui est conforme aux bonnes pratiques de prescription en Suisse. Auparavant, la quantité totale de principe actif par classe d'antibiotique constituait le seul chiffre clé disponible. À présent, et pour la première fois, on peut déterminer la quantité de principe actif prescrite pour chaque

catégorie d'animaux de rente. Cet indicateur présente toutefois un caractère informatif limité. Le nombre de traitements animaux est un indicateur important, dans la mesure où il donne un bon aperçu du nombre de traitements aux antibiotiques entrepris pour une catégorie donnée d'animaux de rente. Cet indicateur sera essentiel dans les analyses menées à l'avenir, surtout s'il est mis en relation avec la taille de la population.

Le volume des ventes d'antibiotiques a continué à reculer, de 4,1 % en 2020, et plus légèrement, de 1,6 %, en 2021. Au total, 28 871 kg d'antibiotiques ont été vendus pour la médecine vétérinaire en 2020, contre 28 402 kg en 2021, soit un recul de 49 % (27 tonnes) depuis 2012. Cette diminution est surtout due à une chute des ventes de prémélanges médicamenteux. En 2020 et en 2021, également, les pénicillines étaient la classe la plus vendue, suivie par les sulfamidés et les tétracyclines. Ces trois classes sont souvent distribuées sous forme de prémélanges médicamenteux. La quantité d'antibiotiques autorisés uniquement pour les animaux domestiques ne correspondait qu'à environ 3 % du volume total ; les ventes pour ces animaux ont augmenté de 2,4 % en 2020 et de 9,3 % en 2021. Les ventes des classes d'antibiotiques critiques de première priorité en médecine humaine ont diminué en 2018 et en 2019 ; les ventes de macrolides ont reculé de 7 % en 2020 et d'encore 9 % en 2021. Si les fluoroquinolones se sont moins vendues en 2020, en 2021, elles sont revenues au même niveau qu'en 2019. Les ventes de céphalosporines de troisième et de quatrième génération ont diminué d'environ 18 % en 2020, mais sont restées stables en 2021. Le volume des ventes de colistine a baissé d'environ 92 % depuis 2012. Exprimé en corrélation avec la biomasse analysée, le niveau en Suisse était de 0,1 mg de colistine/PCU (kg de population d'animaux de rente) en 2021. Inférieur à la moyenne européenne, ce niveau est en conformité avec la demande d'amener la colistine à un niveau de 1 mg/PCU ou moins dans les pays européens afin de maintenir son efficacité pour le traitement des infections graves chez l'être humain.

Résistance des bactéries dans les isolats cliniques humains

Depuis 2012, plusieurs tendances se dessinent chez les bactéries à Gram positif et à Gram négatif. Les taux de *Staphylococcus aureus* résistant à la méticilline (SARM) ont continué à diminuer de manière significative dans les isolats invasifs, principalement en Suisse romande. Cette tendance a également été constatée dans des États de l'UE/EEE. En revanche, les taux de SARM augmentent dans les échantillons issus de plaies et d'abcès de patients ambulatoires et dépassent même, à présent, les taux observés dans les bactériémies. La résistance à la pénicilline chez *Streptococcus pneumoniae*, qui avait diminué par le passé, reste stable depuis dix ans. Toutefois, la résistance à la plupart des autres antibiotiques continue à baisser. Comme exposé dans des rapports antérieurs, nous constatons une augmentation significative des taux d'*Enterococcus faecium* résistant à la vancomycine ces dix dernières années. Cela est surtout lié à une flambée régionale/nationale, associée à la diffusion d'un clone, ST796. Il est essentiel de continuer à surveiller de près la situation. Les données cantonales actualisées sont publiées chaque mois sur le site Internet d'ANRESIS.

L'augmentation constante de la résistance aux quinolones et aux céphalosporines de troisième et quatrième génération chez *Escherichia coli* et *Klebsiella pneumoniae* décrite dans des rapports antérieurs s'est stabilisée ces quatre dernières années, et s'est même légèrement inversée pour les quinolones chez *E. coli*. Heureusement, la résistance aux carbapénèmes demeure rare chez *E. coli* et *K. pneumoniae*, bien que les chiffres soient en constante augmentation en Suisse, ce qui reflète la situation dans les pays limitrophes. Au vu de l'importance de cette résistance, depuis le 1er janvier 2016, il est obligatoire de la déclarer, et tous les isolats sont recueillis par le Centre national de référence pour les résistances émergentes (NARA) depuis le 1er janvier 2019. Les données actualisées sont publiées régulièrement sur le site Internet d'ANRESIS.

Chez *Pseudomonas aeruginosa,* les taux de résistance ont augmenté pour le céfépime et les aminoglycosides, alors que nous avons observé une diminution de la résistance au triméthoprime-sulfaméthoxazole chez *Acinetobacter* spp.

Résistance des bactéries zoonotiques

Concernant en particulier les volailles, le taux de résistance à la ciprofloxacine chez *Campylobacter jejuni (C. jejuni)* et *Campylobacter coli (C. coli)* a augmenté de manière significative ces dernières années. Le taux de résistance à la ciprofloxacine est passé à 47,5 % pour *C. jejuni* et à 51,5 % pour *C. coli* en 2020. La résistance à la tétracycline est restée stable chez *C. coli* (51,5 %), et a diminué chez *C. jejuni* (29,6 %). La résistance à l'érythromycine est demeurée rare.

Selon l'OMS, les fluoroquinolones et les macrolides sont les antimicrobiens critiques de première priorité en médecine humaine, dans la mesure où ces groupes de substances constituent le traitement de choix pour les formes graves de campylobactériose ou de salmonellose chez l'homme.

Chez les porcs d'engraissement, les taux de résistance à la ciprofloxacine chez *Campylobacter coli* ont augmenté de façon significative ces dernières années, atteignant 53,9 % en 2021 (un taux stable par rapport à 2019, 55,9 %). Concernant l'érythromycine, nous avons constaté un recul de la résistance, et aucun isolat ne s'est révélé résistant à l'érythromycine en 2021.

En Suisse, *Salmonella (S.)* spp. est rarement présente chez les animaux de rente. En conséquence, on considère que le risque que *Salmonella* soit transmise à l'homme par des denrées alimentaires issues d'animaux suisses est faible. De plus, les taux de résistance restent bas, en particulier chez *S.* Enteritidis et *S.* Typhimurium.

Résistance des bactéries indicatrices chez les animaux

De manière générale, la résistance aux antimicrobiens est répandue chez les *Escherichia (E.) coli* isolées parmi les animaux de rente en Suisse.

Les taux de résistance de l'*E. coli* commensale isolée chez les poulets de chair en Suisse en 2020 ont montré une tendance globale à la baisse pour tous les antimicrobiens testés. Malgré tout, les taux de résistance à des fluoroquinolones d'importance critique demeurent élevés (>40 %). Les niveaux de résistance de l'*E. coli* isolée chez les porcs d'engraissement affichaient une tendance à la hausse entre 2019 et 2021 pour la plupart des antimicrobiens testés, en particulier pour les tétracyclines. Aucune baisse significative de la résistance à une classe d'antimicrobiens, quelle qu'elle soit, n'a pu être détectée. Chez les veaux de boucherie, on ne voit pas se dessiner clairement de tendance générale pour les taux de résistance aux antimicrobiens testés. Un recul des taux de résistance aux tétracyclines, aux sulfamidés et au triméthoprime a été observé.

La prévalence d'*E. coli* productrices de BLSE/d'AmpC a continué à diminuer chez les poulets de chair (52,4 % en 2016 contre 10,0 % en 2020), et a également légèrement reculé chez les porcs d'engraissement (5,9 % en 2021) et les veaux de boucherie (23,8 % en 2021). Globalement, une tendance à la diminution d'*E. coli* productrices de BLSE/d'AmpC est observée chez l'ensemble des espèces depuis 2015-2016.

Les différentes espèces d'animaux de rente ne présentaient pas d'*E. coli* productrices de carbapénèmases.

En Suisse, la présence de *Staphylococcus aureus* résistant à la méticilline (SARM) chez les porcs d'engraissement à l'abattage progresse constamment depuis que sa détection a été intégrée au monitorage, en 2009. La prévalence de SARM, qui était de 2 % en 2009, a atteint 53,6 % en 2021.

En revanche, la prévalence de SARM chez les veaux de boucherie demeure basse, à 6,1%. Les génotypes appartiennent au complexe clonal (CC) 398, qui est en général associé aux animaux de rente (SARM-LA).

Résistance des bactéries indicatrices dans la viande

La prévalence d'*E. coli* productrices de BLSE/d'AmpC dans la viande de poulet suisse a continué à baisser en 2020 par rapport aux années antérieures (2014 : 65,5 %, 2018 : 21,1 %, 2020 : 10,2 %). Concernant la viande de poulet provenant de l'étranger, le taux de détection de ces bactéries est également resté stable en 2020 par rapport à 2018, et demeurait plus élevé que celui de la viande suisse (2014 : 88,9 %, 2018 : 63,1 %, 2020 : 61,8 %).

En revanche, il n'a pas été détecté d'*E. coli* productrices de BLSE/d'AmpC dans la viande de porc et de bœuf en 2021. Cette différence pourrait être liée à la prévalence plus basse de ces bactéries chez les porcs et les veaux suisses et au processus d'abattage distinct de ces animaux. Les échantillons de viande fraîche (toutes espèces confondues) ne présentaient pas d'*E. coli* productrices de carbapénèmases.

Résistance des bactéries dans les isolats cliniques animaux

Pour les vétérinaires, il est important de surveiller la résistance aux antimicrobiens de certains pathogènes présents chez les animaux de rente et de compagnie malades. Cela leur permet en effet de faire des choix d'antibiotiques thérapeutiques appropriés, ne pouvant généralement pas s'appuyer sur un antibiogramme préalable au premier traitement. Par ailleurs, ces données comblent une autre lacune importante en matière de surveillance de l'antibiorésistance dans la perspective de l'approche « One Health ».

En 2021, plus de 700 isolats ont été envoyés au ZOBA par des laboratoires de diagnostic vétérinaires universitaires, cantonaux ou privés en Suisse pour analyse, à l'aide de la technique de microdilution en milieu liquide, de la résistance aux antimicrobiens. Tous les isolats provenaient d'animaux cliniquement malades. En 2019, seuls les isolats issus d'animaux qui n'avaient pas reçu de traitement antimicrobien avaient été examinés. Toutefois, il s'est avéré que les laboratoires avaient beaucoup de mal à obtenir des informations sur les éventuels traitements antimicrobiens antérieurs. Aussi, depuis 2020, les isolats sont acceptés sans restriction relative à des traitements antérieurs. Le nombre d'isolats envoyés en 2020 était parfois très bas, mais cette situation s'est améliorée de manière significative en 2021.

Pour les pathogènes à l'origine de mastites, *Streptococcus uberis* s'est révélé plus problématique en termes de traitement antimicrobien que *Staphylococcus aureus*. Cependant, les antibiotiques recommandés, en particulier la pénicilline, peuvent tout de même être conseillés pour traiter les mastites à *Str. uberis* et il n'est pas nécessaire de recourir à des antibiotiques critiques dans les cas habituels. Des différences frappantes ont été constatées lorsqu'on a comparé des *Escherichia coli* isolées à partir de différentes indications et espèces animales. Seuls les isolats de mastite bovine et de volaille ne montraient pas de résistance aux céphalosporines de troisième ou de quatrième génération, tandis que les isolats d'*Escherichia coli* issus d'infections urinaires d'animaux de compagnie se montraient parfois résistants à des antimicrobiens d'importance critique. Il n'a pas été détecté d'*Escherichia coli* résistant aux carbapénèmes.

2 Sintesi

Consumo di antibiotici nella medicina umana

Nel 2021, il consumo totale di antibatterici (in ospedale e nel settore ambulatoriale, gruppo ATC J01) è stato di 8,6 dosi definite giornaliere (DDD, Defined Daily Doses) ogni 1000 abitanti al giorno (DID). Il consumo di antibatterici è leggermente diminuito tra il 2012 e il 2019 (–7%). Tuttavia, tra il 2019 e il 2021 è stata rilevata una diminuzione del 19 per cento, probabilmente a causa della pandemia di coronavirus. Nel 2021 il consumo di antibatterici nel settore delle cure ambulatoriali rappresentava l'85 per cento del consumo totale. Il consumo di antibatterici (gruppo ATC J01) è stato più elevato nelle regioni di lingua francese e italiana rispetto alla regione germanofona.

In Svizzera, gli antibiotici del gruppo «watch», particolarmente critici per lo sviluppo della resistenza, sono stati ridotti di quasi il 40% negli ultimi 10 anni (2012: 5,4 DDD per 1000 abitanti al giorno; 2019: 4,0 ; 2021: 3,1). La loro quota su tutte le prescrizioni di antibiotici è stata del 36% nel 2021, scendendo per la prima volta al di sotto dell'obiettivo dell'OMS del 40%.

Negli ospedali svizzeri per cure acute il consumo di antibatterici ad uso sistemico (gruppo ATC J01) è rimasto relativamente stabile (+2%), passando da 50,5 DDD per 100 giorni di degenza a 51,5 tra il 2012 e il 2021. Nel 2021 il consumo totale di antibiotici ad uso sistemico (gruppo ATC J01) è stato di 1,3 DID. Il tasso di consumo negli ospedali svizzeri è leggermente inferiore alla mediana europea (1,6; intervallo: 0,8-2,2). La classe di antibiotici più comunemente usata è stata quella delle penicilline (gruppo ATC J01C), seguita dalla classe degli altri antibatterici beta-lattamici, compresi le cefalosporine (gruppo ATC J01D), i macrolidi e i lincosamidi (gruppo ATC J01F). Tra il 2012 e il 2021 i fluorochinoloni sono diminuiti del 43 per cento, mentre le cefalosporine di terza generazione sono aumentate del 42 per cento. In Svizzera il consumo complessivo di carbapenemi è rimasto relativamente stabile negli ultimi dieci anni (–2%). Esistono, tuttavia, forti differenze regionali: nelle regioni germanofone e francofone, si è registrata una diminuzione rispettivamente del 4 e del 13 per cento tra il 2012 e il 2021, mentre in quella italofona il consumo di carbapenemi è aumentato del 122 per cento nello stesso periodo.

In ambito ambulatoriale, nel 2021 il consumo totale di agenti antibatterici ad uso sistemico (gruppo ATC J01) è stato di 7,3 DDD ogni 1000 abitanti al giorno. È leggermente diminuito dell'8 per cento tra il 2012 e il 2019 (da 9,8 a 9,0), per poi diminuire ulteriormente del 19 per cento tra il 2019 e il 2021, probabilmente a causa della pandemia di coronavirus. Il consumo di antibatterici è stato relativamente basso rispetto alla mediana europea (15,0; intervallo: 7,1-26,4). La classe di antibiotici più usata è stata quella delle penicilline (gruppo ATC J01C), seguita da tetracicline (gruppo ATC J01A), macrolidi, lincosamidi e streptogramine (gruppo ATC J01F) e fluorochinoloni (gruppo ATC J01MA). Tra il 2012 e il 2021 i fluorochinoloni sono diminuiti del 54 per cento.

Consumo di antibiotici nella medicina veterinaria

Da ottobre 2019, tutte le prescrizioni di antibiotici devono essere registrate dai veterinari nel sistema d'informazione sugli antibiotici nella medicina veterinaria (SI AMV). Le analisi in questa sezione si basano sui dati registrati nel SI AMV unicamente nel 2020.

Per gli animali da reddito, il 78,8 per cento di tutti gli antibiotici è stato prescritto per i bovini, tra cui le vacche da latte e i vitelli da ingrasso. Il secondo uso più elevato di antibiotici è stato quello nei suini (13,5 %), seguito dai piccoli ruminanti (1,1 %) e dal pollame (0,8 %). In base ai dati di vendita del 2020, la principale classe di antibiotici prescritta per tutte le specie di animali da reddito è stata la penicillina. In particolare per il pollame, la penicillina rappresenta la principale classe di antibiotici. I sulfamidici e le tetracicline sono state le altre due classi più utilizzate. Per gli animali da compagnia, il maggior numero di antibiotici è stato prescritto ai cavalli (62,2 %). Tuttavia, i cavalli sono animali pesanti che richiedono un'elevata quantità di antibiotico per ogni prescrizione. Il secondo posto per quantità di antibiotici è occupato dai cani (32,0 %), seguiti dai gatti (5,7 %). Le principali classi di antibiotici prescritti per gli animali da compagnia sono state i sulfamidici (42,3 %) e le penicilline (28,3 %).

Tra tutti gli animali, i principi attivi di gran lunga più utilizzati sono stati i cosiddetti antibiotici di prima linea. Questo dimostra che vengono effettivamente utilizzati per primi, in conformità con le buone pratiche di prescrizione vigenti in Svizzera. La quantità totale di principio attivo per classe di antibiotici era in precedenza l'unico dato chiave disponibile. Ora, per la prima volta, è possibile stabilire la quantità di principio attivo prescritta per ogni categoria di animali da reddito. Il valore informativo di questo indicatore è tuttavia limitato. Il numero di trattamenti sugli animali è un indicatore importante, in quanto fornisce una buona panoramica del numero di trattamenti con antibiotici effettuati in una categoria di animali da reddito. Nelle analisi future questo indicatore sarà fondamentale, specialmente se messo in relazione con la dimensione della popolazione.

Il volume di vendita degli antimicrobici ha continuato a diminuire: nel 2020 del 4,1 per cento e nel 2021 dell'1,6 per cento, ossia in misura meno marcata. In generale, nel 2020 sono stati venduti 28 871 kg di antimicrobici per la medicina veterinaria e nel 2021 28 402 kg. Ciò corrisponde a un calo del 49 per cento (27 tonnellate) dal 2012 a oggi, dovuto prevalentemente a una diminuzione delle vendite di premiscele medicate. Sia nel 2020 sia nel 2021, le penicilline sono state la classe di antibiotici più venduta, seguita dai sulfamidici e dalle tetracicline. Queste tre classi sono spesso vendute come premiscele medicate. La quantità di antibiotici omologati unicamente per gli animali da compagnia costituisce il 3 per cento del volume totale. Nel 2020 e nel 2021, le vendite di questi antibiotici sono aumentate rispettivamente del 2,4 e del 9,3 per cento. Le vendite di classi di antibiotici critici di massima priorità per la medicina umana sono calate nel 2018 e nel 2019; quelle dei macrolidi sono diminuite del 7 per cento nel 2020 e di un ulteriore 9 per cento nel 2021. I fluorochinoloni sono stati venduti meno spesso nel 2020, ma nel 2021 hanno raggiunto lo stesso livello del 2019. Le vendite delle cefalosporine di terza e quarta generazione sono decresciute all'incirca del 18 per cento nel 2020, ma sono rimaste stabili nel 2021. Il volume di vendita della colistina è diminuito approssimativamente del 92 per cento dal 2012. Espresso in correlazione alla biomassa esposta, nel 2021 il livello per la Svizzera è stato di 0,1 mg/PCU di colistina, inferiore alla media europea e in linea con la richiesta di riduzione della colistina a un livello pari o inferiore a 1 mg/PCU per i Paesi europei, in modo da preservarne l'efficacia nel trattamento di gravi infezioni nell'uomo.

Resistenza nei batteri presenti in isolati clinici umani

Dal 2012, sono state osservate diverse tendenze a livello di batteri gram-positivi e gram-negativi. I tassi di *Staphylococcus aureus* meticillino-resistente (MRSA) hanno continuato a diminuire notevolmente negli isolati invasivi, perlopiù nella Svizzera occidentale. La stessa tendenza è stata osservata anche in Paesi dell'UE/del SEE. Per contro, i tassi di MRSA sono in aumento nei campioni prelevati da ferite e ascessi di pazienti ambulatoriali, e ora superano persino quelli osservati nelle batteriemie. La resistenza alla penicillina nello *Streptococcus pneumoniae* è diminuita in precedenza, ma è rimasta stabile negli ultimi dieci anni. Tuttavia, la resistenza alla maggior parte degli altri antibiotici è continuamente in calo. Come già descritto nei rapporti precedenti, nel corso degli ultimi dieci anni abbiamo riscontrato un aumento significativo nel tasso di *Enterococcus faecium* resistente alla vancomicina. Questo fenomeno è imputabile principalmente a un focolaio regionale/nazionale associato alla diffusione di un clone ST796. Pertanto, è essenziale continuare a monitorare da vicino la situazione. Dati cantonali aggiornati sono pubblicati mensilmente sul sito web ANRESIS.

Il costante aumento della resistenza ai chinoloni e alle cefalosporine di terza/quarta generazione nei batteri *Escherichia coli* e *Klebsiella pneumoniae*, descritto nei rapporti precedenti, si è stabilizzato negli ultimi quattro anni e la tendenza si è persino leggermente invertita per i chinoloni nell'*E. coli*. Fortunatamente, nell'*E. coli* e nella *K. pneumonia* la resistenza ai carbapenemi resta rara, anche se le cifre sono costantemente in aumento in Svizzera, rispecchiando la situazione dei Paesi limitrofi. Data l'importanza del fenomeno, l'obbligo di notifica è stato introdotto in Svizzera il 1° gennaio 2016 e tutti gli isolati sono raccolti nel laboratorio di riferimento nazionale per il riconoscimento precoce di nuove forme di resistenza agli antibiotici (NARA) dal 1° gennaio 2019. Dati aggiornati sono pubblicati periodicamente nel sito web ANRESIS.

Per gli *Pseudomonas aeruginosa*, i tassi di resistenza al cefepime e agli aminoglicosidi sono aumentati, mentre abbiamo osservato una diminuzione della resistenza al trimetoprim e al sulfametossazolo negli *Acinetobacter* spp.

Resistenza nei batteri zoonotici

Negli ultimi anni il tasso di resistenza alla ciprofloxacina nel *Campylobacter jejuni (C. jejuni)* e nel *Campylobacter coli (C. coli)* è aumentato significativamente, soprattutto nel pollame. Nel 2020 il tasso di resistenza alla ciprofloxacina è cresciuto del 47,5 per cento per il *C. jejuni* e del 51,5 per cento per il *C. coli*. La resistenza alle tetracicline è rimasta stabile per il *C. coli* (51,5%), mentre è diminuita per il *C. jejuni* (29,6%). Ancora raramente vengono rilevate resistenze all'eritromicina.

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 nell'uomo.

Nei suini da ingrasso, i tassi di resistenza alla ciprofloxacina del *Campylobacter coli* sono aumentati significativamente negli ultimi anni, arrivando al 53,9 per cento nel 2021 (rimanendo stabile rispetto al 2019, 55,9 %). Per quanto concerne l'eritromicina, abbiamo anche riscontrato una diminuzione nella resistenza e nel 2021 nessun isolato era resistente all'eritromicina.

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

Resistenza nei batteri indicatori negli animali

La resistenza antimicrobica è generalmente diffusa negli *Escherichia (E.) coli* isolati da animali da reddito allevati in Svizzera.

I tassi di resistenza dell'*E. coli* commensale proveniente da polli da carne in Svizzera nel 2020 hanno mostrato in generale un calo di tendenza per tutti gli antibiotici testati. Ciononostante i tassi di resistenza ai fluorochinoloni di importanza

critica sono ancora elevati (>40 %). Tra il 2019 e il 2021 l'andamento dei livelli di resistenza dell'*E. coli* dei suini da ingrasso è aumentato per la maggior parte degli antibiotici testati, in particolare per le tetracicline. Non è stato possibile riscontrare una diminuzione significativa della resistenza in nessuna classe di antibiotici testata. Per i vitelli da macello, non esiste una tendenza generale evidente per quanto riguarda i tassi di resistenza agli antibiotici testati. È stato osservato un calo dei tassi di resistenza alle tetracicline, ai sulfamidici e al trimetoprim.

La prevalenza di *E. coli* produttori di ESBL/pAmpC ha continuato a diminuire per i polli da carne (dal 52,4 % nel 2016 al 10,0 % nel 2020), ed è leggermente decresciuta per i suini da ingrasso (5,9 % nel 2021) e per i vitelli da macello (23,8 % nel 2021). Nel complesso, dal 2015/2016 si osserva una tendenza alla diminuzione di *E. coli* produttori di ESBL/pAmpC in tutte le specie.

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

In Svizzera la presenza di *Staphylococcus aureus* meticillino-resistenti (MRSA) nei suini da ingrasso alla macellazione è aumentata costantemente da quando l'MRSA è entrato a far parte del monitoraggio nel 2009. Dal 2 per cento nel 2009, la prevalenza di MRSA ha raggiunto il 53,6 per cento nel 2021.

Al contrario, la prevalenza di MRSA nei vitelli da carne rimane bassa (6,1 %). Questi genotipi appartengono al complesso clonale CC 398, tipicamente associato agli animali da reddito (LA-MRSA).

Resistenza nei batteri indicatori presenti nella carne

Rispetto agli anni precedenti, nel 2020 la prevalenza di *E. coli* produttori di ESBL/pAmpC nella carne di pollo svizzera ha continuato a diminuire (2014: 65,5 %, 2018: 21,1 %, 2020: 10,2 %). Nella carne di pollo importata dall'estero, i tassi di *E. coli* produttori di ESBL/pAmpC rilevati sono anche rimasti stabili nel 2020 rispetto al 2018, e continuano a essere più elevati rispetto a quelli riscontrati nella carne svizzera (2014: 88,9 %, 2018: 63,1 %, 2020: 61,8 %).

Per contro, nella carne bovina e suina, nel 2021 non sono stati riscontrati *E. coli* produttori di ESBL/pAmpC. La differenza potrebbe essere correlata alla minore prevalenza di questi batteri nei maiali e nei vitelli svizzeri e ai processi di macellazione distinti di questi animali. Non sono stati trovati *E. coli* produttori di carbapenemasi nei campioni di carne fresca (di tutte le specie).

Resistenza nei batteri da isolati clinici di animali

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

Nel 2021 oltre 700 isolati sono stati inviati dai laboratori diagnostici veterinari universitari, cantonali e privati svizzeri al Centro per le zoonosi, le malattie animali di origine batterica e la resistenza agli antibiotici (ZOBA) e testati in merito alla resistenza agli antimicrobici utilizzando il metodo della microdiluizione in brodo di coltura. Tutti gli isolati provenivano da animali clinicamente malati. Nel 2019 sono stati analizzati solo isolati provenienti da animali che non erano stati sottoposti a terapia antimicrobica. Tuttavia, poiché è risultato molto difficile per i laboratori ottenere informazioni sullo stato di precedente terapia antimicrobica, dal 2020 gli isolati vengono accettati a prescindere se sono stati o meno sottoposti a una precedente terapia di questo tipo. Nel 2020, tuttavia, il numero di isolati inviati è stato talvolta molto basso, ma la situazione è migliorata notevolmente nel 2021.

Per quanto concerne i germi patogeni della mastite, è risultato che lo *Streptococcus uberis* è più critico in termini di terapia antimicrobica rispetto allo *Staphylococcus aureus*. Tuttavia, gli antibiotici raccomandati, in particolare la penicillina, possono ancora essere raccomandati per la terapia della mastite da *Str. uberis* e nel normale dei casi non è necessario utilizzare antibiotici di importanza critica. Sono state rilevate notevoli differenze nel confronto degli *Escherichia coli* isolati da diverse specie animali e indicazioni. Solo gli isolati provenienti da bovini affetti da mastite e pollame non presentavano resistenza alle cefalosporine di terza o quarta generazione, mentre gli isolati di *Escherichia coli* provenienti da infezioni del tratto urinario (UTI, Urinary tract infection) in animali da compagnia hanno mostrato resistenza a questi antimicrobici di importanza critica. Non sono stati riscontrati *Escherichia coli* resistenti ai carbapenemi.

3

Introduction

3 Introduction

3.1 Antibiotic resistance

Antibiotic resistance in human and animal medicine is responsible for increased morbidity and mortality, and generates significant healthcare costs. Alternative treatments necessary due to resistant pathogens 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 serious concerns. The extent of antibiotic resistance correlates positively with antibiotic use. Thus, surveillance of antibiotic use and resistance in human and veterinary medicine is considered to be one 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.

For veterinary medicine, two aspects have to be considered. On the one hand, antimicrobial resistance in zoonotic and commensal bacteria from food-producing animals, which might spread via food-borne routes to humans. On the other hand, antimicrobial resistance in pathogenic bacteria isolated from diseased food-producing and companion animals, which pose similar challenges for veterinarians as they do for clinicians. Antimicrobial agents used in animals and in human medicine in Europe are frequently the same or belong to the same classes, although the route of administration and the administered quantities of antimicrobials differ substantially. Therefore, surveillance of antibiotic use and resistance in veterinary medicine is a crucial part of action plans combatting antimicrobial resistance.

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 and others.

The first microbiology laboratories participated in ANRESIS in 2004. The surveillance system expanded continuously during the following years, with 35 microbiology laboratories participating in 2022 (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). Collection of data on antibiotic resistance in pathogenic veterinary isolates within the ANRESIS database was initiated by the Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA) and ANRESIS in 2014. In 2019, an annual national monitoring program on antimicrobial resistance in pathogens from diseased animals was launched and data are included in the ANRESIS database. The open data structure in the ANRESIS database allows for further developments.

The advisory board of ANRESIS is composed of specialists from the fields of microbiology, infectious diseases, hospital epidemiology, veterinary medicine, and public health (www.anresis.ch).

3.2.1 Monitoring of antibiotic consumption in human medicine

The development of resistance is a natural phenomenon for bacteria, but is enhanced by the selective pressure exerted by antibacterial use [1, 2]. Epidemiological studies and mathematical models support a close correlation between the variation in antibiotic consumption and bacterial resistance. Monitoring of antibacterial consumption is thus an important element of a national action plan to limit the spread of bacterial resistance [1, 3].

For hospital and outpatient care, we used the antibiotic consumption data from IQVIA™, a private drug market investigation company providing an exhaustive dataset of antibacterial consumption (corresponding to sales data (sell-in) from pharmaceutical industries to public pharmacies, self-dispensing physicians and/or hospitals).

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 70 hospitals or hospital sites, distributed across all linguistic regions, are collected on a voluntary basis. These acute care hospitals are spread across the entire geographic territory, and represent 45% of the total number of acute somatic care hospitals (excluding psychiatric centers, reha-

bilitation centers, and other specialized clinics) and 75% of all bed-days in this category in Switzerland.

For the outpatient setting, we used the sales dataset from IQVIA™, but also data based on antibiotic prescriptions at the individual level: (i) data from pharmaSuisse, corresponding to invoices produced for health insurance companies on behalf of pharmacies, and (ii) data from the representative Swiss Sentinel Surveillance Network (Sentinella) network, reported by general and internal medicine practitioners and pediatricians.

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 85% of all annual hospitalization days and approximately 50% of all practitioners in Switzerland. The provided epidemiological data enable a stratification of the resistance results according to the hospital versus outpatient compartment, 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 Swiss 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. In addition, since the outbreak in 2018/2019, cantonal data on vancomycin-resistance in *Enterococci* (VRE) are updated monthly on www.anresis.ch. Since 2020 data on Carbapenemase-producing Enterobacterales (CPE) are provided and updated regularly by ANRESIS in collaboration with the NARA. More detailed data from ANRESIS, along with veterinary data, are published in the present national report every two years.

3.2.3 Resistance monitoring in veterinary pathogens

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). Samples are selected according to defined combinations of pathogens, animal species and diseases. Isolates come from veterinary diagnostic laboratories in Switzerland. Susceptibility testing is performed at the ZOBA using the broth microdilution method. In contrast to the European harmonized monitoring in healthy livestock, the tested antimicrobials are mainly those approved for veterinary use. Isolates are usually classified as susceptible or resistant according to the veterinary-specific clinical breakpoints published by the Clinical and Laboratory Standards Institute (CLSI). An excerpt of data derived from this monitoring program is presented in Chapter 11 (Resistance in animal pathogens 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). They are accessible via the veterinary version of 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 may reach humans via the food chain. Hence, a system to enable the continuous monitoring of resistance in bacteria isolated from 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.

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) annually report the sales of antimicrobial veterinary medicinal products 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 Ve-

terinary Antimicrobial Consumption Project (sales of veterinary antimicrobial agents in 31 European countries in 2019 and 2020; European Medicines Agency, 2021).

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

The main goals of the European harmonized monitoring on 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 all over Europe. 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 slaughterhouses. Meat samples of the respective animal species are taken by official inspectors at the retail level. Antimicrobial resistance is analyzed for the zoonotic pathogens *Campylobacter (C.) jejuni* and *C. coli*, and for the indicator *Escherichia (E.) coli*. Since 2009, nasal swab samples from fattening pigs and calves have also been included for the detection of methicillin-resistant *Staphylococcus aureus* (MRSA). In 2014, detection of third-generation cephalosporin-resistant *E. coli* (ESBL/AmpC-prod. *E. coli*) in broilers, pigs and cattle was established. Since 2015, analyses for the detection of ESBL/AmpC-producing *E. coli* and carbapenemase-producing *E. coli* and *Klebsiella* spp. 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 antimicrobial resistance testing. Meat samples from poultry, pigs and cattle are tested for MRSA (until 2020), ESBL/AmpC-producing *E. coli* and carbapenemase-producing *E. coli* and *Klebsiella* spp.

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 the needed number of 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, proportionately 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 About IS ABV

The Information System on Antibiotics in Veterinary Medicine (IS ABV) is a system recording antibiotic prescriptions for animals. Veterinarians must register all antibiotic prescriptions and sales for all animal species since October 2019. The database makes it possible to evaluate the intensity of treatment of livestock and companion animals. It also takes into account the different types of production, e. g., piglet rearing or dairy farming. In addition, the system will enable regional, national and international comparisons of antibiotic consumption and treatment intensity.

3.5 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. Antimicrobial consumption data from animals are the data recorded in IS ABV for the year 2020. The indicator used is the total quantity of antibiotics (weight in kg) in absolute values without denominators.

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 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," "susceptible, increased exposure" or "resistant" by applying clinical breakpoints, as 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 can be lower than the clinical breakpoint.

This 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.

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Acknowledgements

The authors are grateful to all who have provided data for this report. Many thanks to all participants not mentioned by name.

ANRESIS would like to thank all participating microbiology laboratories, hospital pharmacies and pharmaSuisse for their important contribution in providing resistance and antibiotic consumption data.

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Color code

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

- Cephalosporins first and second generation
- Cephalosporins third and fourth generation
- Other cephalosporins and penems
- Monobactams
- Beta-lactamase-sensitive penicillins
- Penicillins with extended spectrum
- Beta-lactamase-resistant penicillins
- Combination 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
AMC	Antimicrobial consumption
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 Enterobacterales
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
IS ABV	Information System for Antibiotic in Veterinary Medicine
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
PAC	Powdered activated carbon
AmpC	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 – Susceptible, increased exposure – Resistant
SNF	Swiss National Science Foundation
SNP	Single-nucleotide polymorphism
spp.	Species
SSI	Swiss Society of Infectious Diseases
SSM	Swiss Society for Microbiology
StAR	Swiss Strategy on Antibiotic Resistance
SVGW	Swiss association of the gas and water industry
t	*spa* type
URTI	Upper respiratory tract infection
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
WOAH	World Organization for Animal Health
WWTP	Wastewater treatment plant
ZOBA	Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance

5

Antibacterial consumption in human medicine

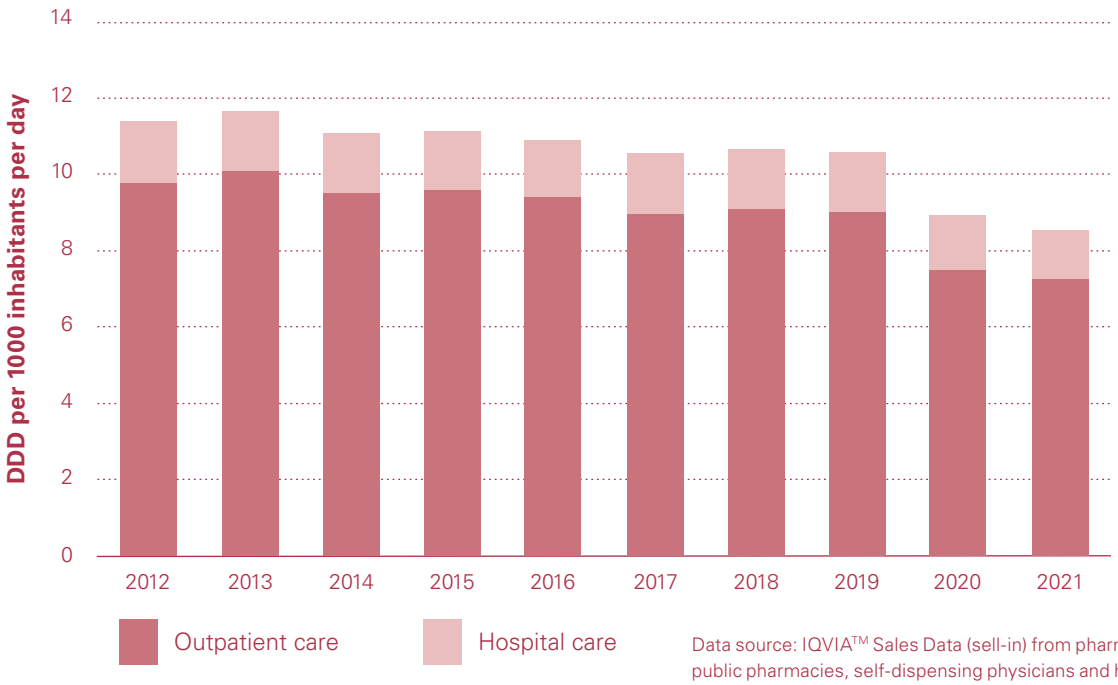
5 Antibacterial consumption in human medicine

5.1 Overall consumption (hospital and outpatient care combined)

In 2021, total consumption of antibacterials (in hospital and outpatient care combined, ATC code J01) was 8.6 DDD per 1,000 inhabitants per day (DID) using IQVIA™ Sales Data (sell-in) from pharmaceutical industries to public pharmacies, self-dispensing physicians and hospitals (Figure 5. a). Antibacterial consumption slightly decreased between 2012 and 2019 (–7%). However, a decrease by 19% was observed between 2019 and 2021, probably due to the COVID-19 pandemic. In 2020, the mean total (hospital and community sector combined) consumption of antibacterials for systemic use (ATC group J01) in the EU/EEA was 16.4 DID (country range: 8.5–28.9) [1]. Antibacterial consumption in the outpatient setting accounted for 86% of total consumption in 2012 and for 85% in 2021. Antibacterial consumption (ATC code J01) was higher in the French- and the Italian-speaking regions than in the German-speaking region (Figure 5. b).

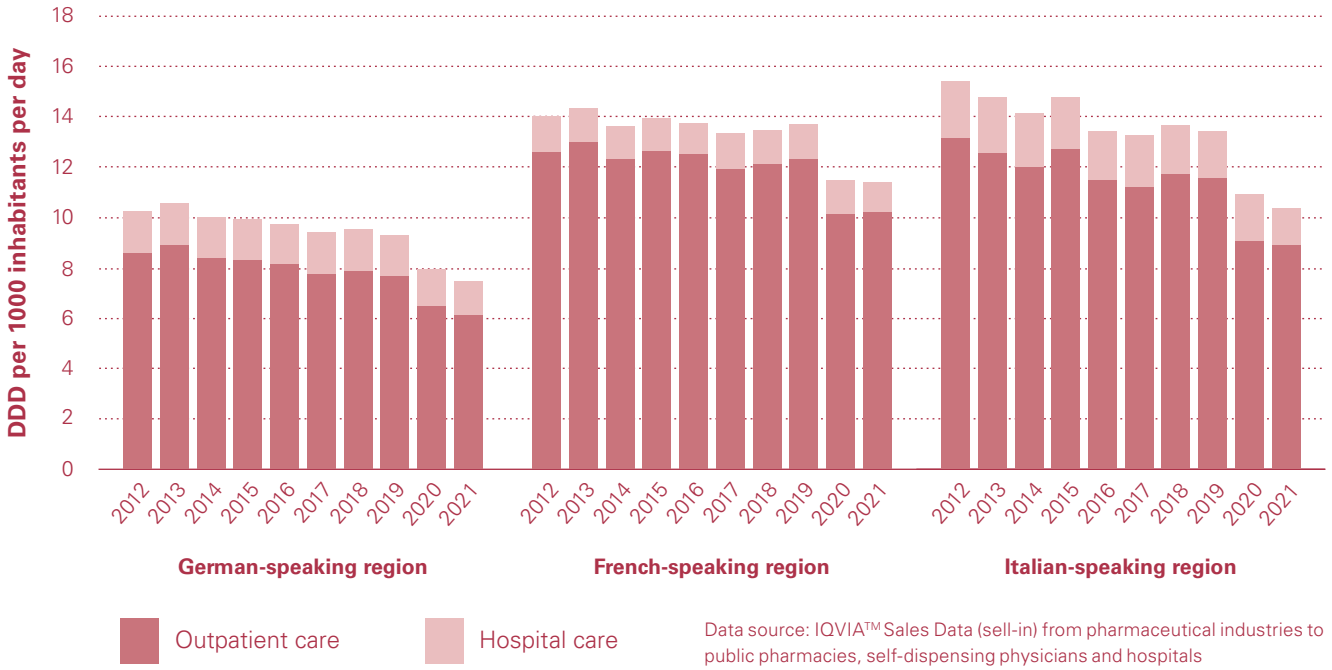
The WHO's *13th General Programme of Work 2019–2023* includes a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics [2]. For this analysis, ATC codes from the A07AA, J01, J04AB and P01AB groups were included. In Switzerland, the relative proportion of Access group antibiotic consumption accounted for 53% of total consumption (6.1 DID) in 2012 and for 61% and 64% (resp. 6.6 DID and 5.6 DID) in 2019 and 2021. In the Watch group, which includes antibiotics particularly critical for the development of resistance, a decrease has been achieved in the last ten years (2012: 5.4 DID; 2019: 4.0 DID; 2021: 3.1 DID) (Figure 5. c). Their proportion of all antibiotic prescriptions was 36% in 2021, falling below the WHO target of 40% for the first time in 2019. The relative proportion of the Reserve group remained low (0.3–0.4% of total consumption) between 2012 and 2021.

Figure 5. a: Total (hospital and outpatient care combined) antibiotic consumption expressed in DDD per 1,000 inhabitants per day, Switzerland, 2012–2021 (ATC code J01).



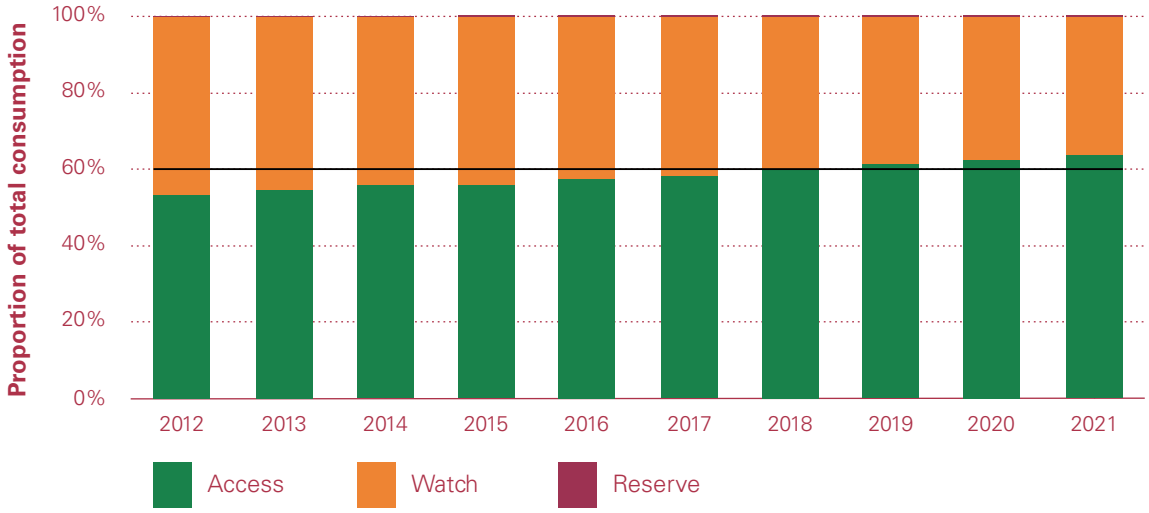
Data source: IQVIA™ Sales Data (sell-in) from pharmaceutical industries to public pharmacies, self-dispensing physicians and hospitals

Figure 5. b: Total (hospital and outpatient care combined) antibiotic consumption expressed in DDD per 1,000 inhabitants per day by linguistic region, Switzerland, 2012–2021 (ATC code J01).



Data source: IQVIA™ Sales Data (sell-in) from pharmaceutical industries to public pharmacies, self-dispensing physicians and hospitals

Figure 5. c: Total (hospital and outpatient care combined) antibiotic consumption according to the AWaRe categorization of the WHO, Switzerland, 2012–2021 (ATC codes A07AA, J01, J04AB, P01AB). The WHO recommends a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics (black line).



Data source: IQVIA™ Sales Data (sell-in) from pharmaceutical industries to public pharmacies, self-dispensing physicians and hospitals

5.2 Hospital care

5.2.1 Total antibiotic consumption

Considering the hospitals that participated in the ANRESIS monitoring both in 2012 and 2021 (n = 49), the number of DDD of systemic antibiotics (ATC code J01) decreased by 5% 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 by

Table 5. a: Consumption of antibiotic classes expressed in DDD per 100 bed-days in hospitals contributing to ANRESIS, Switzerland (2012–2021).

ATC group	Antibiotic class	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
J01A	Tetracyclines	0.5	0.6	0.6	0.6	0.8	0.7	0.7	0.8	0.8	0.8
J01CA	Penicillins with extended spectrum (amoxicillin)	1.2	1.6	1.5	1.7	1.5	1.6	1.7	1.5	1.3	1.5
J01CE	Beta-lactamase-sensitive penicillins	1.5	1.4	1.3	1.3	1.3	1.2	1.2	1.1	0.9	0.9
J01CF	Beta-lactamase-resistant penicillins	2.1	2.1	2.4	2.5	2.4	2.5	2.3	2.2	1.9	2.1
J01CR02	Penicillins and beta-lactamase inhibitor (amoxicillin and clavulanic acid)	14.7	15.3	14.7	14.2	15.0	15.0	14.9	14.5	13.9	14.1
J01CR03-05	Penicillins and beta-lact. inhibitor (antipseudomonal)	2.3	2.7	2.7	2.8	2.6	2.7	2.8	3.0	3.2	3.1
J01DB	Cephalosporins – first generation	1.0	1.0	1.1	1.5	1.2	1.4	1.2	1.3	1.3	1.4
J01DC	Cephalosporins – second generation	3.8	4.4	4.6	4.9	4.5	4.5	4.8	4.8	5.3	4.9
J01DD	Cephalosporins – third generation	4.2	5.0	5.0	5.7	5.4	5.7	5.7	5.6	6.2	6.0
J01DE	Cephalosporins – fourth generation	0.7	0.8	0.8	0.9	0.8	1.0	1.2	1.0	1.1	1.1
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	2.3	2.6	2.4	2.3	1.9	2.2	2.1	2.0	2.3	2.3
J01DI	Other cephalosporins and penems	0.0	NA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01E	Sulfonamides and trimethoprim	2.8	2.6	2.4	2.3	2.1	2.5	2.4	2.3	2.3	2.4
J01FA	Macrolides	2.7	3.0	3.0	3.1	2.8	2.8	2.8	2.6	2.6	2.2
J01FF	Lincosamides	0.9	1.0	1.0	1.0	0.9	1.1	1.1	1.0	0.9	0.9
J01G	Aminoglycoides	0.7	0.7	0.6	0.6	0.5	0.6	0.5	0.5	0.5	0.5
J01MA	Fluoroquinolones	5.8	6.1	6.0	5.7	4.8	4.8	4.4	3.9	3.4	3.1
J01XA	Glycopeptides	1.1	1.2	1.3	1.3	1.0	1.3	1.3	1.3	1.5	1.4
J01XB	Polymyxins	0.1	0.2	0.2	0.2	0.1	0.1	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	1.1	1.2	1.1	1.2	1.2	1.2	1.2	1.2	1.3	1.4
J01XE	Nitrofuran derivates (nitrofurantoin)	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.4	0.5	0.6
J01XX	Other antibacterials	0.5	0.6	0.6	0.7	0.6	0.9	0.9	0.8	0.8	0.8
J01	**Antibacterial agents for systemic use**	**50.5**	**54.4**	**53.7**	**55.0**	**51.9**	**54.1**	**53.6**	**52.1**	**52.3**	**51.5**
A07AA	Intestinal Antiinfectives*							0.4	0.5	0.6	0.5
J04AB	Rifamycins	0.8	0.8	0.9	0.7	0.7	0.9	0.8	0.8	0.7	0.7
P01AB	Nitroimidazole derivates (metronidazole oral)	0.9	0.9	0.8	0.8	0.7	0.8	0.9	0.7	0.7	0.7

* Collected since 2018

16%, while the number of bed-days decreased by 8%. This means that more patients were admitted to hospitals, but that their length of stay was shorter in 2021 than in 2012.

The total consumption of systemic antibiotics in DDD per 100 bed-days in all hospitals participating in the monitoring (for the number of participating hospitals, see Table 14. a) remained relatively stable (+2%) from 50.5 (weighted mean, range: 36.0–86.4) in 2012 to 51.5 (range: 28.4–85.3) in 2021, while the total consumption in DDD per 100 admissions decreased by 18% (ATC code J01). This discrepancy can be explained by an increasing number of admissions and a decreasing number of bed-days in hospitals due to shorter hospital stays. In 2021, total antibiotic consumption was lower in small-size hospitals (49.0 DDD per 100 bed-days) than in medium-size (50.3) and large-size (55.2) hospitals (Figure 5. d).

In 2021, total antibiotic consumption was relatively similar in the three linguistic regions: 53.1 DDD per 100 bed-days in the French-speaking region (20 hospitals, including 2 university hospitals), 46.9 in the Italian-speaking region (5 hospitals) and 51.2 in the German-speaking region (46 hospitals, including 2 university hospitals). The consumption increased by 8% in the French-speaking part, by 14% in the Italian-speaking region, and remained relatively stable in the German-speaking part (–2%) between 2012 and 2021.

When antibiotics are classified according to the AWaRe classification, it can be seen in the hospital sector that (see Chapter 14, Materials and methods) 51% of antibiotics (27.0 DDD per 100 bed-days) in 2021 were allocated to the Access group, 48% (25.3) to the Watch group and 1% (0.7) to the Reserve group. The proportion of antibiotics within the Access, Watch and Reserve categories of total consumption

has remained largely unchanged over the past ten years. The exception is 2020, where the consumption in DDD per 100 bed-days of Watch antibiotics was higher than that of Access antibiotics (data not shown).

Using the IQVIA™ dataset and weighting consumption data to the Swiss population, it can be observed that total consumption of antibacterial agents (ATC code J01) for systemic use has decreased by 20% over the last ten years to 1.3 DID in 2021 (1.6 DID in 2012) (Figure 5. a). In comparison, the population-weighted mean consumption was 1.6 DID (range 0.8–2.2) in 2020 in the countries participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [1].

Table 5. b: Comparison of indicators for the consumption of antibiotics for systemic use in the hospital setting with countries participating in the ESAC-Net.

	Consumption[a]										Relative consumption[b]							
	J01		J01C		J01DD+DE		J01DH		J01MA		J01C		J01DD+DE		J01DH		J01MA	
Year	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020
Switzerland	1.6	1.5	0.7	0.5	0.10	0.16	0.04	0.05	0.3	0.1	41.2%	37.3%	6.3%	10.9%	2.4%	3.1%	15.6%	7.7%
p0*	0.9	0.8	0.1	0.1	0.02	0.02	0.01	0.01	0.1	0.0	8.0%	6.5%	1.3%	1.2%	0.7%	1.7%	5.8%	2.8%
p25*	1.4	1.3	0.4	0.3	0.09	0.10	0.02	0.04	0.2	0.1	27.7%	22.4%	6.3%	6.8%	1.5%	2.6%	10.9%	8.2%
p50*	1.7	1.5	0.5	0.5	0.13	0.14	0.04	0.05	0.2	0.2	30.1%	30.8%	6.8%	11.2%	2.4%	3.1%	12.8%	9.6%
p75*	1.9	1.7	0.6	0.6	0.16	0.19	0.05	0.08	0.3	0.2	39.4%	39.9%	10.0%	13.3%	2.9%	4.7%	14.9%	10.9%
p100*	2.7	2.2	0.9	1.0	0.39	0.45	0.11	0.14	0.4	0.3	49.6%	55.8%	19.9%	31.3%	8.0%	7.8%	20.1%	14.2%

[a] Consumption for all antibiotics (J01), penicillins (J01C), third- and fourth-generation cephalosporins (J01(DD+DE)), carbapenems (J01DH) and fluoroquinolones (J01MA) expressed in DDD per 1,000 inhabitants per day.

[b] Relative consumption of penicillins (J01C), third- and fourth-generation cephalosporins (J01(DD+DE)), carbapenems (J01DH) and fluoroquinolones (J01MA) expressed as percentage of the total antibiotic consumption (J01).

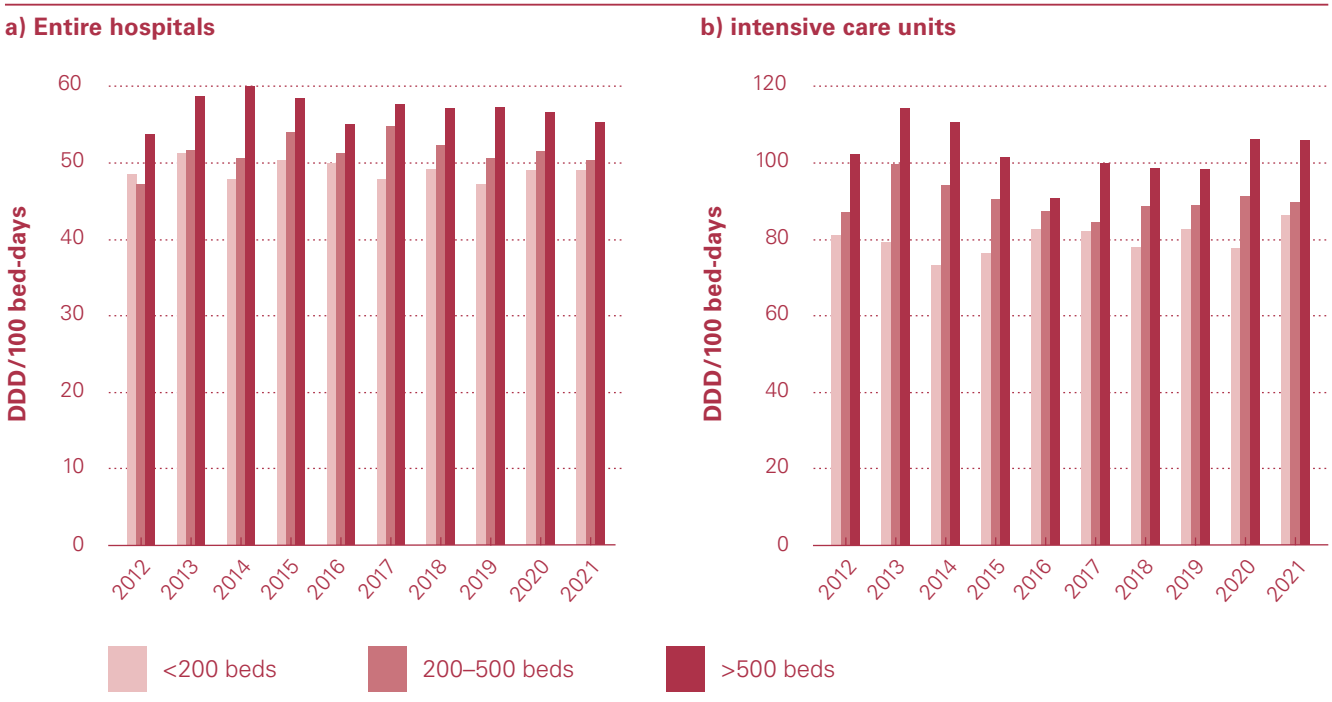
* Values in the hospital sector, EU/EEA countries, 2012 and 2020 [3, 4].

Data source for Switzerland: IQVIA™ Sales Data (sell-in) from pharmaceutical industries to the inpatient care.

- Values within the first quartile [p0; p25]
- Values within the second quartile]p25; p50]
- Values within the third quartile]p50; p75]
- Values within the fourth quartile]p75; p100]

The indicator values were grouped into four quartiles according to the quartile distribution of the countries participating in the ESAC-Net. Indicator values within the first quartile suggest better quality than indicator values within the second quartile, which suggest better quality than indicator values within the third quartile which suggest better quality than indicator values within the fourth quartile.

Figure 5. d: Antibiotic consumption expressed in DDD per 100 bed-days in hospitals contributing to ANRESIS by hospital size in the entire hospital (a) and intensive care unit only (b), 2012–2021 (ATC code J01).



5.2.2 Consumption by antibiotic class

Using the ANRESIS dataset, it can be seen that in 2021 the consumption of penicillins (ATC code J01C) ranked first among the antibiotic classes, accounting for 42% of total consumption. This was followed by the consumption of other beta-lactam antibiotics, including cephalosporins (ATC code J01D) as well as macrolides and lincosamides (ATC code J01F). Figure 5. e shows the distribution of antibacterial classes and subclasses in 2021.

Table 5. a shows the consumption of antibiotic classes expressed in DDD per 100 bed-days in sentinel hospitals from 2012 to 2021. The use of 11 of the 22 antibiotic classes decreased between 2012 and 2021 (aminoglycosides, beta-lactamase-sensitive penicillins, carbapenems, fluoroquinolones, fusidic acid, lincosamides, macrolides, nitroimidazole derivates, penicillins and beta-lactamase inhibitor, rifamycins, sulfonamides and trimethoprim). The most substantial changes between 2012 and 2021 were observed for the nitrofuran derivatives (+123%), tetracyclines (+51%), third- and fourth-generation cephalosporins (+42 and +47%, respectively) and fluoroquinolones (–47%).

Consumption of all penicillins has remained largely stable in recent years (Figure 5. f and Table 5. a), but different trends can be observed for the penicillin subcategories. For instance, the consumption of beta-lactamase sensitive penicillins has decreased by 36% in the last ten years, while the consumption of antipseudomonal penicillins has increased by 35% (Table 5. a). Compared to the rest of Switzerland, the consumption of penicillins in DDD per 100 bed-days is lower in the Italian-speaking part of Switzerland (Figure 5. f).

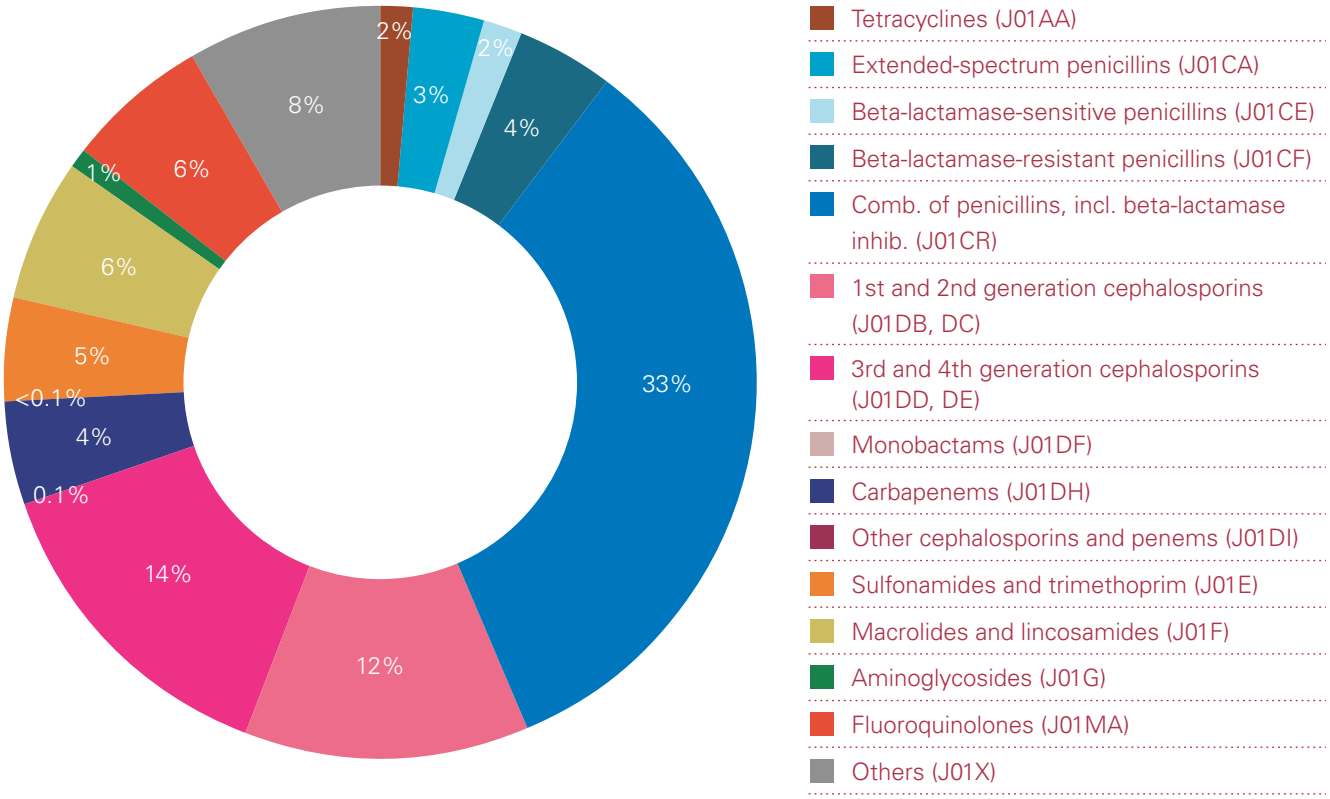
The use of cephalosporins has increased markedly between 2012 and 2021 (Figure 5. f and Table 5. a). This concerns cephalosporins of all four generations (+36% for the first-, +29% for the second-, +42% for the third- and +47% for the fourth-generation cephalosporins). A comparison of the different language regions shows a comparable trend towards increased consumption of cephalosporins (Figure 5. f).

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

The overall consumption of carbapenems remained relatively stable (–2%) in Switzerland in the last ten years (Figure 5. f and Table 5. a). However, the regional differences are rather large. In the German- and French-speaking regions, there was a decline of –4% and –13%, respectively, between 2012 and 2021, while in the Italian-speaking region the consumption of carbapenems increased by 122% during the same period (Figure 5. f).

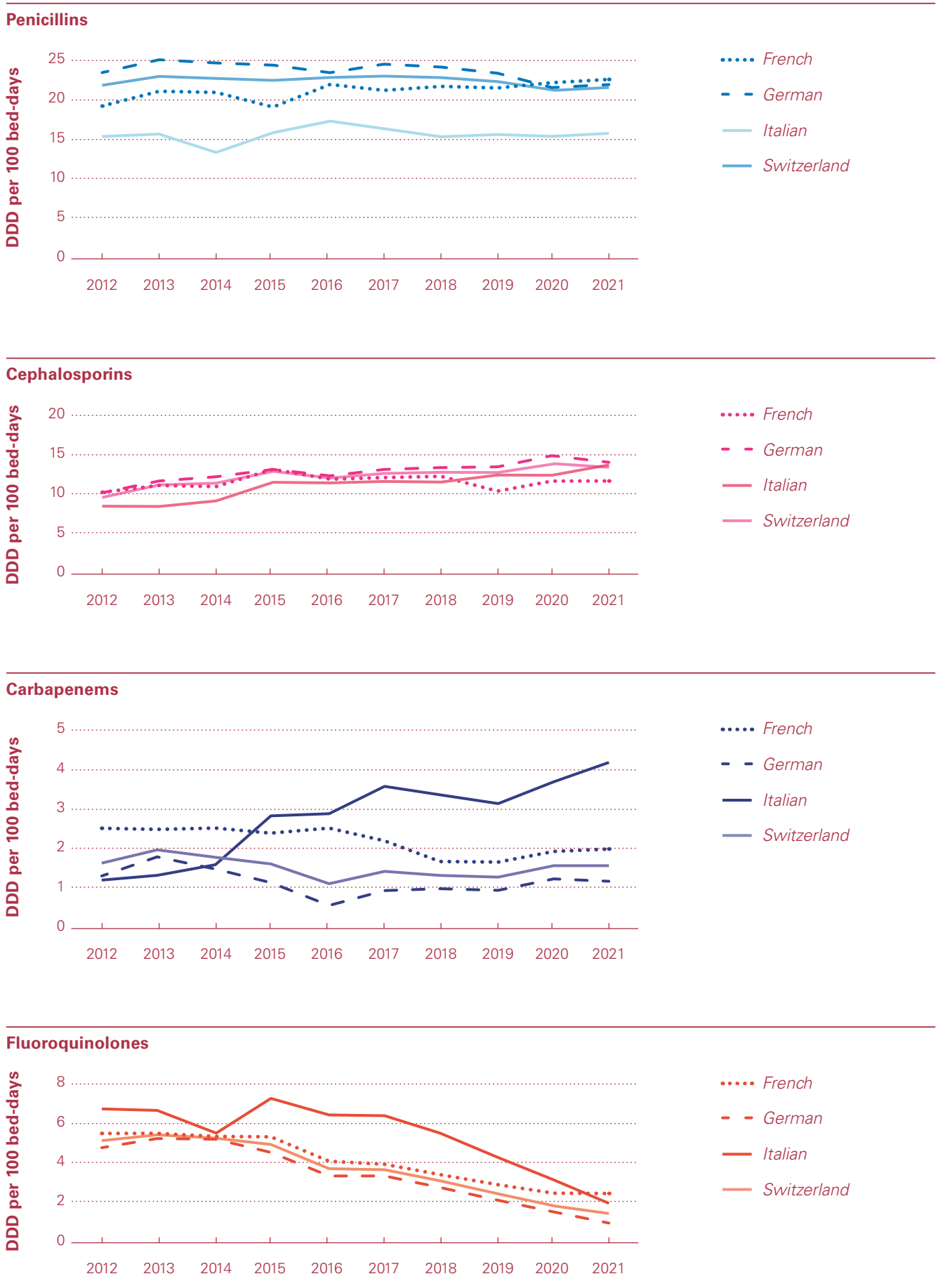
The consumption of fluoroquinolones has steadily decreased over the last ten years (–43%) (Figure 5. f and Table 5. a).

Figure 5. e: Distribution of the antibiotic consumption per antibiotic class in hospitals contributing to ANRESIS, 2021 (ATC group J01).

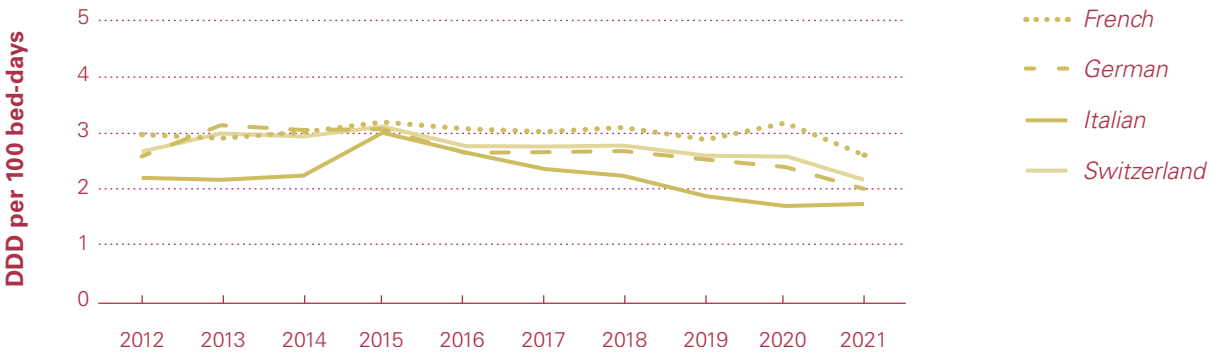


Data source: Consumption data from sentinel hospitals contributing to ANRESIS

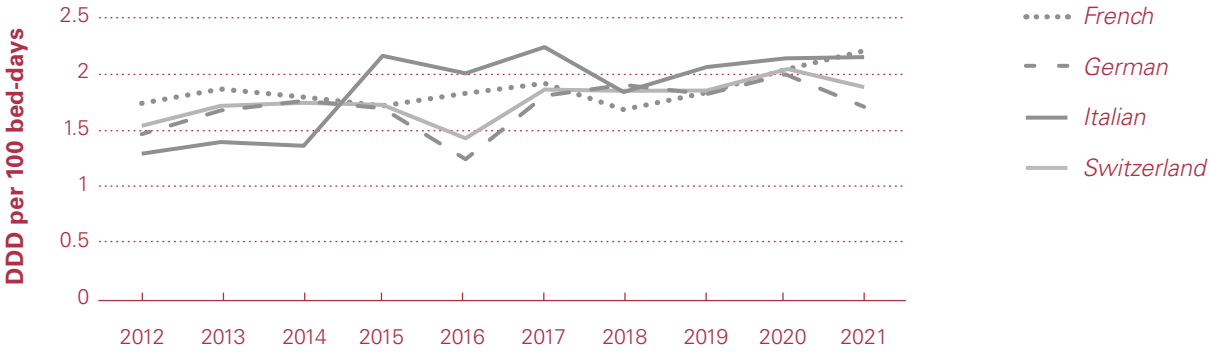
Figure 5. f: Consumption of antibiotics expressed in DDD per 100 bed-days in hospitals contributing to ANRESIS by linguistic region, 2012–2021.



Macrolides



Antibiotics active against resistant Gram-positive bacteria



Particularly noteworthy is the decline in the consumption in the Italian-speaking part of Switzerland in recent years. In 2021, the consumption of fluoroquinolones was comparable in all linguistic regions (Figure 5. f).

Macrolide consumption (ATC group J01FA) in Switzerland has decreased over the last ten years (–18%). There are regional differences with higher consumption in the French-speaking part of Switzerland and lower consumption in the Italian-speaking region (Figure 5. f).

For antibiotics active against resistant Gram-positive bacteria (vancomycin, daptomycin, teicoplanin, linezolid), a 20% increase was observed between 2012 and 2021. Consumption was comparable in all regions (Figure 5. f).

The IQVIA™ data set (sell-in) from pharmaceutical industries to hospitals) can be used to compare the consumption of the antibiotic groups with the consumption of the countries participating in the ESAC-Net (Table 5. b). The effective consumption of penicillins (ATC code J01C) and third- and fourth-generation cephalosporins is found to be above the mean of the ESAC-net countries, the consumption falls in the third quartile, while the consumption of carbapenems and fluoroquinolones are in the second and first quartile, respective. A similar conclusion can be drawn for the relative consumption: in comparison to other European countries, large amounts of penicillins are used, while the relative consumption of fluoroquinolone is low.

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

Total consumption of systemic antibiotics (ATC code J01) in the ICU has remained relatively stable in recent years (Figure 5. d). Since 2012, consumption in the ICU has been relatively stable (+2%), from 94.5 DDD per 100 bed-days to 97.0 in 2021. In 2021, total antibiotic consumption was lower in the intensive care units of small-size hospitals (86.1 DDD per 100 bed-days) than in intensive care units of medium-size (89.6) and large-size (106.0) hospitals.

5.3 Outpatient care

5.3.1 Total antibiotic consumption using the IQVIA™ data set

In 2021, the total consumption of antibacterials for systemic use (ATC code J01) was 7.3 DID. It slightly decreased, by 8%, between 2012 and 2019 (from 9.8 DID to 9.0) and then decreased by 19% between 2019 and 2021, probably due to the COVID-19 pandemic (Figure 5. a). In comparison, the EU/EEA mean consumption of antibacterials for systemic use (ATC code J01), as recorded by the countries participating in the ESAC-Net, was 15.0 DID (range between 7.1 in Austria and 26.4 in Greece) [1].

Table 5. c: Consumption of antibiotic classes expressed in DDD per 1,000 inhabitants per day in the outpatient setting, Switzerland (2012–2021).

ATC group	Antibiotic class	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
J01A	Tetracyclines	1.3	1.4	1.4	1.3	1.4	1.3	1.4	1.3	1.3	1.3
J01CA	Penicillins with extended spectrum (amoxicillin)	0.8	0.8	0.8	0.9	0.9	0.9	1.0	1.0	0.8	0.8
J01CE	Beta-lactamase-sensitive penicillins	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0
J01CF	Beta-lactamase-resistant penicillins	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01CR02	Penicillins and beta-lactamase inhibitor (amoxicillin and clavulanic acid)	2.4	2.6	2.4	2.5	2.5	2.4	2.4	2.5	1.9	1.9
J01CR03-05	Penicillins and beta-lact. inhibitor (antipseudomonal)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DB	Cephalosporins – first generation	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DC	Cephalosporins – second generation	0.7	0.7	0.6	0.6	0.6	0.6	0.6	0.6	0.4	0.4
J01DD	Cephalosporins – third generation	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1
J01DE	Cephalosporins – fourth generation	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01DI	Other cephalosporins and penems	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01E	Sulfonamides and trimethoprim	0.5	0.5	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5
J01FA	Macrolides	1.5	1.5	1.3	1.4	1.3	1.2	1.2	1.1	0.8	0.7
J01FF	Lincosamides	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
J01G	Aminoglycoides	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01MA	Fluoroquinolones	1.8	1.7	1.6	1.5	1.4	1.3	1.2	1.1	0.9	0.8
J01XA	Glycopeptides	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01XB	Polymyxins	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
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	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01XE	Nitrofuran derivates (nitrofurantoin)	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5
J01XX	Other antibacterials	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
J01	**Antibacterial agents for systemic use**	**9.8**	**10.1**	**9.5**	**9.6**	**9.4**	**9.0**	**9.1**	**9.0**	**7.5**	**7.3**
A07AA	Intestinal antibiotics*							0.0	0.0	0.0	0.0
J04AB	Rifamycins	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.2	0.1	0.1
P01AB	Nitroimidazole derivates (metronidazole oral)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

* Collected since 2018

In 2021, the German-speaking region of Switzerland had a lower antibiotic consumption (6.1 DID) than the Italian-speaking (8.9) and the French-speaking regions (10.2) (Figure 5. b). Between 2012 and 2021, the consumption in the three linguistic regions decreased by 29%, 32% and 19%, respectively.

According to the AWaRe classification (see Chapter 14, Materials and Methods), the Access group represented 66% of antibiotics (4.9 DID), the Watch group 34% (2.5 DID) and the Reserve group 0.2% (0.02 DID) in the outpatient setting in 2021 (ATC codes A07AA, J01, J04AB, P01AB). The proportion of the Access group increased by 25% and the Watch group decreased by 29% between 2012 and 2021.

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

Consumption of penicillins (ATC code J01C) ranked first among antibiotic classes, amounting for 38% of the total antibiotic consumption in 2021. It was followed by the consumption of tetracyclines (17%, ATC code J01A), macrolides, lincosamides and streptogramins (12%, ATC code J01F), fluoroquinolones (11%, ATC code J01MA), other antibacterials (8%, ATC code J01X), sulfonamides and trimethoprim (7%, ATC code J01E) and beta-lactam antibacterials other than penicillins (including cephalosporins, 6%, ATC code J01D). Figure 5. g shows the distribution of antibiotic classes and subclasses in 2021.

Table 5. d: Comparison of indicators for the consumption of antibiotics for systemic use in the outpatient setting with countries participating in the ESAC-Net.

	Consumption[a]										Relative consumption[b]							
	J01		J01C		J01D		J01F		J01M		J01CE[c]		J01CR		J01DD+DE		J01MA	
Year	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020
Switzerland	9.8	7.5	3.4	2.8	0.9	0.5	1.6	1.0	1.8	0.9	1.2%	1.3%	24.9%	25.5%	1.8%	0.9%	18.3%	11.6%
p0*	10.1	7.1	3.1	2.4	0.0	0.03	0.63	0.4	0.4	0.2	0.0%	0.1%	0.0%	0.3%	0.0%	0.1%	2.4%	1.9%
p25*	13.5	10.0	5.1	3.5	0.7	0.6	1.9	1.4	0.9	0.5	0.4%	0.9%	9.7%	9.8%	0.1%	0.6%	6.3%	5.5%
p50*	16.5	13.7	6.4	4.9	1.6	1.4	3.1	2.1	1.3	0.8	3.0%	1.9%	16.2%	17.9%	0.4%	2.3%	8.4%	8.2%
p75*	19.5	16.8	8.5	7.2	2.4	2.0	3.6	2.7	2.2	1.3	7.0%	7.4%	24.8%	28.1%	2.7%	3.6%	11.2%	9.5%
p100*	28.2	26.4	11.7	10.5	6.6	5.8	7.8	5.7	3.5	3.4	29.2%	22.4%	33.2%	37.4%	8.4%	9.0%	15.7%	16.1%

[a] Consumption for all antibiotics (J01), penicillins (J01C), cephalosporins (J01D), macrolides, lincosamides and streptogramins (J01F) and quinolones (J01M) expressed in DDD per 1,000 inhabitants per day.

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

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

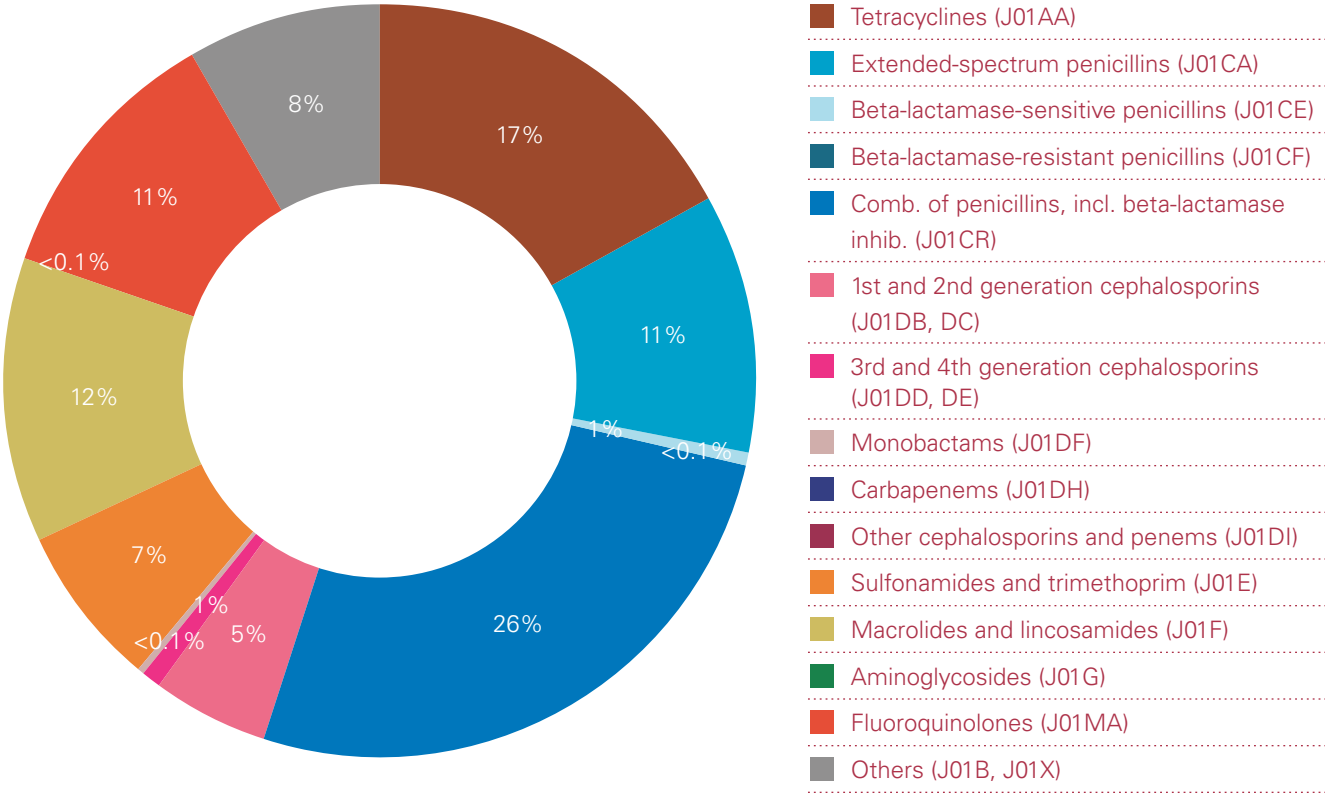
* Values in the community, EU/EEA countries, 2012 and 2020 [3, 4].

Data source for Switzerland: IQVIA™ Sales Data (sell-in) from pharmaceutical industries to public pharmacies and self-dispensing physicians.

- Values within the first quartile [p0; p25]
- Values within the second quartile]p25; p50]
- Values within the third quartile]p50; p75]
- Values within the fourth quartile]p75; p100]

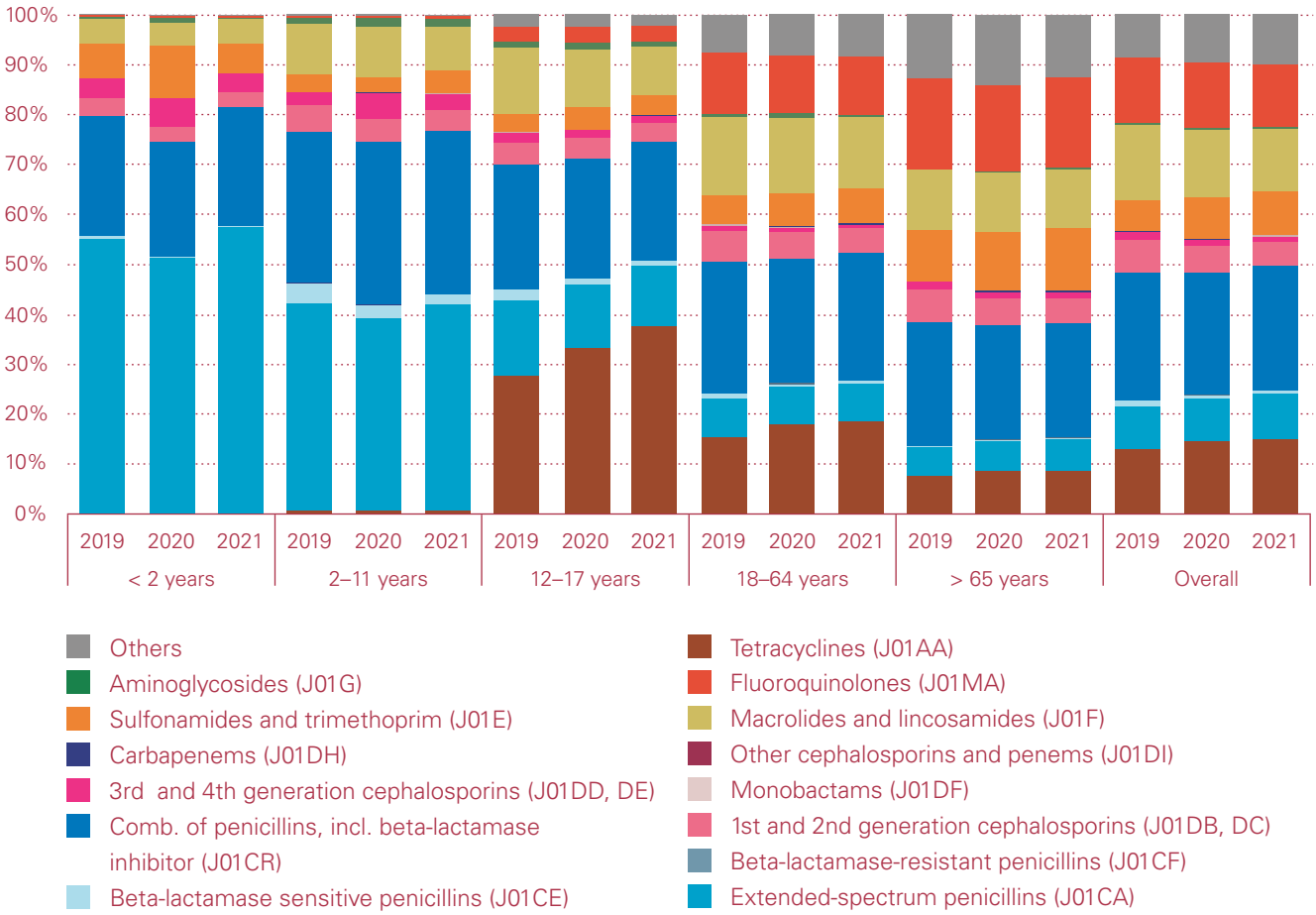
The indicator values were grouped into four quartiles according to the quartile distribution of the countries participating in the ESAC-Net. Indicator values within the first quartile suggest better quality than indicator values within the second quartile, which suggest better quality than indicator values within the third quartile which suggest better quality than indicator values within the fourth quartile.

Figure 5. g: Distribution of the antibiotic consumption per antibiotic class in the outpatient setting in 2021, Switzerland (ATC group J01).



Data source: IQVIA™ Sales Data (sell-in) from pharmaceutical industries to public pharmacies and self-dispensing physicians.

Figure 5. h: Antibiotic classes per age group and overall as a proportion of the total consumption, 2019–2021 (ATC code J01).



Data source: prescription orders collected from the public pharmacies (provided by pharmaSuisse).

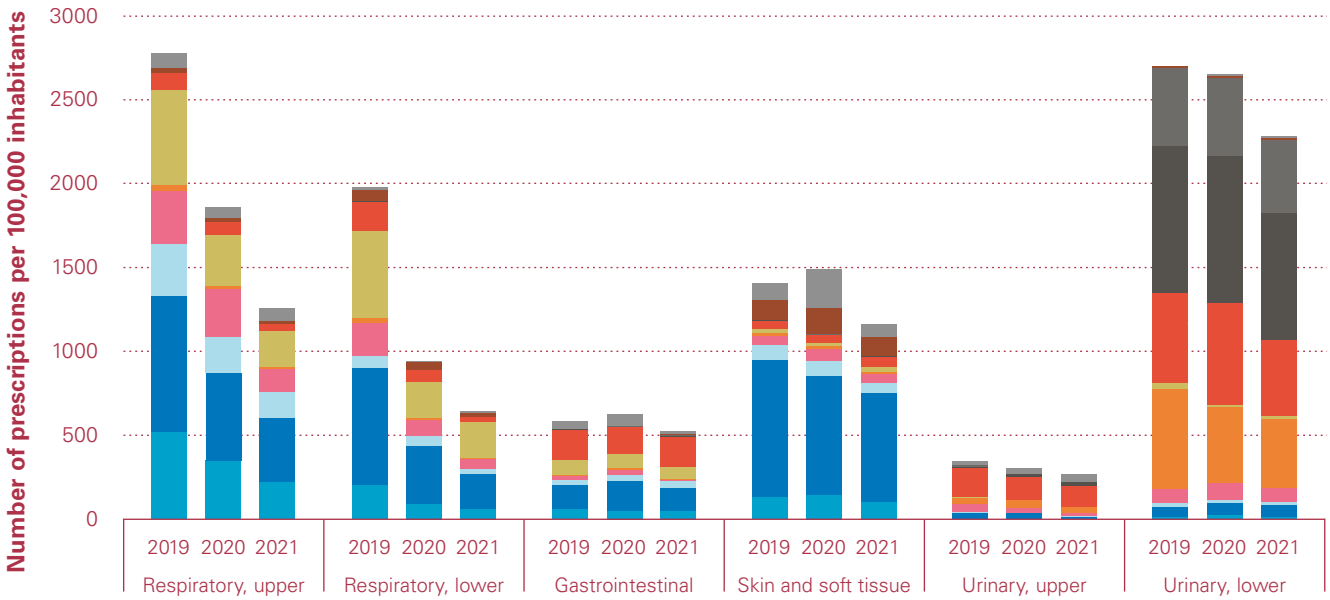
The overall consumption of penicillins decreased by 17% between 2012 (3.4 DID) and 2021 (2.8 DID). Combinations of penicillins and beta-lactamase inhibitors (J01CR) were the most frequently used group of systemic antibiotics in 2021 (1.9 DID, 26% of total J01 antibiotic consumption) (Table 5. c). They accounted for 69% of total penicillin consumption. Among penicillins, those with an extended spectrum (J01CA), namely amoxicillin, were the second most frequently used group (0.8 DID, 29% of penicillin consumption and 11% of the J01 antibiotic consumption). The relative consumption of beta-lactamase-sensitive penicillins (J01CE) was low in Switzerland (1.3% of J01 antibiotic consumption in 2020), while in countries participating in the ESAC-Net this indicator ranged from 0.1% to 22.4% in 2020, as higher percentage suggesting better quality indicator (Table 5. d) [4]. The relative consumption of penicillins associated with beta-lactamase inhibitors was relatively high (26%) in comparison with countries participating in the ESAC-Net (range: 0.3%–37.4%) in 2020 [4]. At the substance level, amoxicillin-clavulanic acid was the most frequently used antibiotic in 2021 (1.9 DID). However, consumption decreased by 21% between 2012 and 2021.

The cephalosporins (ATC codes J01DB-DE and J01DI) decreased by 50% between 2012 (0.9 DID) and 2021 (0.4 DID). Cefuroxime, cefpodoxime and ceftriaxone represented 82%, 12% and 3% resp. of cephalosporin consumption in 2021. The relative consumption of third- and fourth-generation cephalosporins (ATC codes J01DD-DE) was 0.9% in 2020, compared with a range of 0.1% to 9.0% in countries participating in the ESAC-Net in 2020 (Table 5. d) [4].

Fluoroquinolone consumption was 0.8 DID in 2021 in Switzerland, accounting for 11% of the total antibiotic consumption in the outpatient setting. Although we have observed a downward trend since 2012 (–54%), consumption remained high compared to countries participating in the ESAC-Net, where the relative consumption of fluoroquinolones ranged from 1.9% to 16.1% in 2020 (Table 5. d) [4]. At the substance level, ciprofloxacin was the most frequently used fluoroquinolone (73%), followed by levofloxacin (13%), norfloxacin (8%), moxifloxacin (4%) and ofloxacin (1%) in 2021. Norfloxacin consumption has decreased by 81% since 2012.

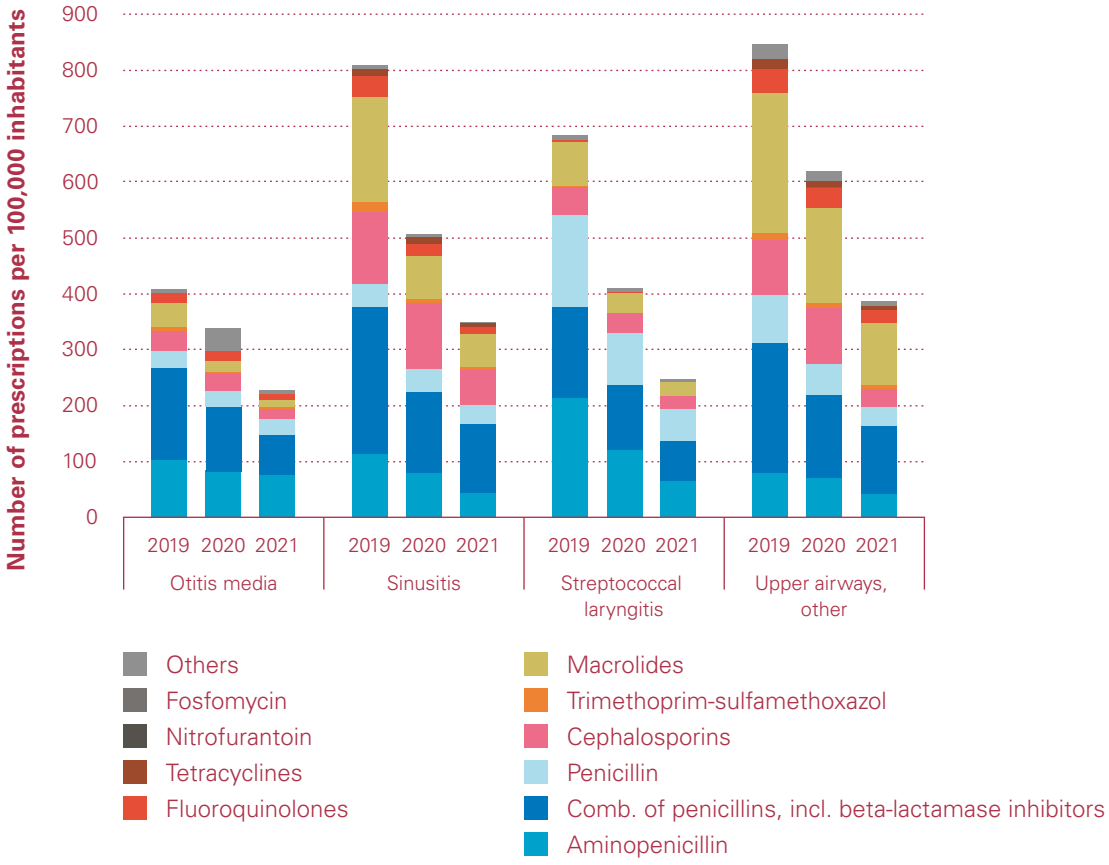
Figure 5. i: Antibiotic classes per indication as a number of prescriptions per 100,000 inhabitants issued by general practitioners, 2019–2021.

(a) by type of infections



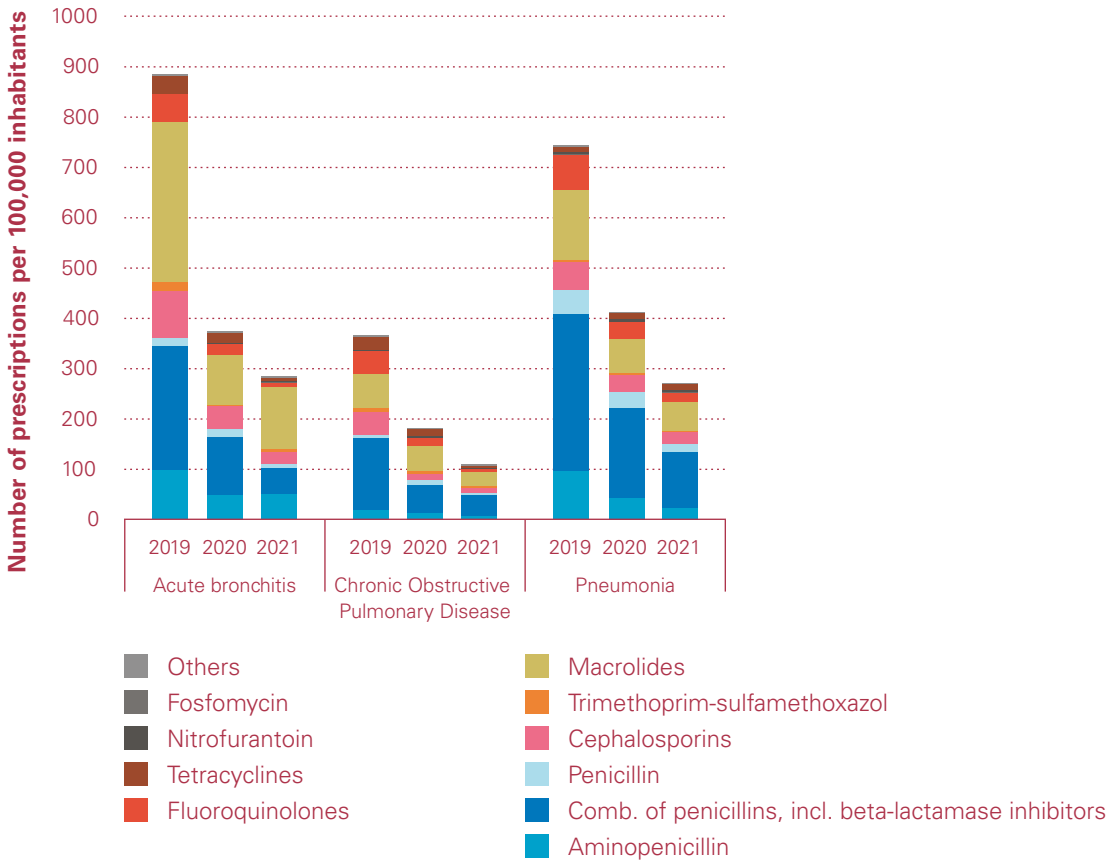
Data source: prescription orders collected from the Sentinella network.

(b) by type of upper respiratory tract infections



Data source: prescription orders collected from the Sentinella network.

(c) by type of lower respiratory tract infections



Data source: prescription orders collected from the Sentinella network.

In the macrolide, lincosamides and streptogramin group (ATC code J01F), only macrolides and lincosamides have been used in Switzerland (resp. 0.7 and 0.2 DID in 2021). Consumption of macrolides decreased by 50%, whereas that of lincosamides remained stable (–2%) between 2012 and 2021. Clarithromycin, azithromycin and erythromycin accounted for 65%, 34% and 1% resp. of the macrolides in 2021. Among the lincosamides, clindamycin consumption was 0.2 DID in 2021 and has remained stable (–2%) since 2012.

Tetracycline consumption remained stable between 2012 and 2021 (1.3 DID, –6%), accounting for 17% of the total antibiotic consumption. Doxycycline was the most frequently used tetracycline (79%), followed by limecycline (15%), and minocycline (6%). Minocycline consumption has decreased by 73% since 2012.

Nitrofurantoin and fosfomycin accounted for resp. 7% (0.5 DID) and 2% (0.1 DID) of the total antibiotic consumption in 2021. They have increased by 56% and 101% resp. since 2012.

The ratio of consumption of broad-spectrum penicillins, cephalosporins and macrolides to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides is one of the quality indicators for consumption in the outpatient setting proposed by the ESAC-Net. This ratio was high (72.8) compared to countries participating in the ESAC-Net, where this ratio ranged from 0.2 to 606.9 in 2020 [4].

5.3.3 Antibiotic use by age group using the pharmaSuisse data set

In 2021, penicillins with an extended spectrum (namely, amoxicillin, ATC code J01CA) were the antibiotic group most commonly used among children aged less than two years (58% of the total antibacterial consumption, J01) and between 2–11 years old (41%), whereas penicillins associated with beta-lactamase inhibitors (ATC code J01CR) were the most frequently used antibiotics in the age groups 18–64 (26%) and >65 (23%) (Figure 5. h). Penicillins with an extended spectrum and penicillins associated with beta-lactamase inhibitors represented 82% of the total antibiotic consumption in patients less than two years old (2–11 years: 74%; 12–17: 36%; 18–64: 33%; >65: 29%). Tetracycline was the most used antibacterial group in patients between 12 and 17 years of age (38% of their total antibiotic consumption). In this age category, lymecycline and minocycline, used as acne medication, accounted for resp. 51% and

8% of tetracycline consumption in 2021. Doxycycline accounted for 41% of tetracycline consumption. Seniors aged 65 and over were relatively high consumers of fluoroquinolones (17% of their total antibiotic consumption). In this age category, ciprofloxacin accounted for 71% of fluoroquinolone consumption, levofloxacin for 15%, norfloxacin for 9%, moxifloxacin for 4% and ofloxacin for 1%.

5.3.4 Antibiotic use by indication using the Sentinella dataset

A total of 12,031 antibacterial prescriptions were issued by 161 physicians participating in the Sentinella network in 2021, corresponding to 6,571.9 antibacterial prescriptions per 100,000 inhabitants. This was lower than in 2019 (10,951.3) and 2020 (8,386.2).

The number of antibiotic prescriptions issued by general practitioners was 6,513.2 per 100,000 inhabitants in 2021 (10,310.8 in 2019 and 8,459.9 in 2020) or 19.5 per 1,000 consultations in 2021 (27.8 in 2019 and 25.4 in 2020), amounting to a decrease of 30% between 2019 and 2021 (Figure 5. i). Antibacterials were prescribed most frequently for urinary tract infections (40%), followed by upper respiratory tract infections (19%) and skin and soft tissue infections (18%). Fosfomycin (33% of all antibacterials used for lower UTI), fluoroquinolones (19%), nitrofurantoin (19%) and trimethoprim-sulfamethoxazole (18%) were the most frequently prescribed antibacterials for lower urinary tract infections. For lower respiratory tract infections, amoxicillin-clavulanic acid (33%), macrolides (32%) and amoxicillin (11%) were the most prescribed antibacterial classes. Among respiratory tract infections, antibacterials were prescribed most frequently for sinusitis (19%), followed by acute bronchitis (15%), pneumonia (14%), streptococcal pharyngitis (13%) and otitis media (12%).

The number of antibiotic prescriptions issued by pediatricians was 6,827.4 per 1,000 consultations in 2021 (13,861.3 in 2019 and 8,052.8 in 2020) or 21.5 per 1,000 consultations in 2021 (38.2 in 2019 and 26.0 in 2020), corresponding to a decrease of 44% between 2019 and 2021. Antibacterial prescriptions were prescribed most frequently for upper respiratory tract infections (72%), followed by skin and soft tissue infections (10%), lower respiratory tract infections (9%) and urinary tract infections (7%). Amoxicillin (68% of all antibacterials used for URTI) and amoxicillin-clavulanic acid (19%) were the most frequently prescribed antibacterials for upper respiratory tract infections.

5.4 Discussion

In Swiss acute care hospitals, total antibiotic consumption increased from 50.5 to 51.5 DDD per 100 bed-days between 2012 and 2021. Expressed in DDD per 1,000 inhabitants per day, the total antibiotic consumption (1.3 in 2021) was lower than the median (1.6) obtained in the ESAC-Net in 2020 [1]. 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 7.3 DID in 2021, which was low compared to countries participating in the ESAC-Net (15.0 DID, range 7.1–26.4 DID) [2]. The most commonly used class of antibiotics was the penicillins (ATC code J01C), followed by the tetracyclines (ATC code J01A), the macrolides, lincosamides and streptogramins (ATC code J01F), 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.

Supply shortages of antibacterials appear to be a challenge for clinicians. As of July 2022, the Federal Office for National Economic Supply (FONES) reported the shortage of 35 products with antibacterials, corresponding to 30% of all shortages of products considered as essential in accordance with the Ordinance on the Essential Human Medicines Reporting Office [5]. Two of these products have even been withdrawn from the Swiss market.

Our methodology has several limitations [1, 6]. The DDD methodology allows comparisons between hospitals or countries, but 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 mostly express the antibiotic consumption in DDD per 100 bed-days, rather than per admission for the inpatient setting. The definition of bed-days has been set by the Federal Statistical Office, while the number of admissions is not an official indicator and can be subject to different interpretations among hospitals.

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Textbox

Antibiotic Prescription Patterns in Swiss Primary Care (2012 to 2019) using electronic medical records

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Background
One key driver for increasing antibiotic resistance (ABR) rates is the overuse and misuse of antibiotics [1]. Most antibiotics are prescribed in the primary care setting [2]. In order to monitor antibiotic prescriptions, most countries have established surveillance systems. However, in Switzerland, there is very little data available on antibiotic prescriptions specifically for the primary care setting. Thus, we have conducted a retrospective cross-sectional analysis to describe the patterns of antibiotic prescriptions and time trends of antibiotic prescribing in the Swiss primary care setting. This report is based on a previously published study [3].

Methods
In this analysis, we used data from the FIRE (Family medicine Research using Electronic medical records) database [4]. All available data from January 2012 to December 2019 were included in the analysis. Data obtained during the pandemic were not analyzed. We used only data provided by practices which export medication data labeled with starting and stopping dates, and we considered only new prescriptions. Antibiotic prescriptions were identified using World Health Organization (WHO) Anatomical Therapeutic Chemical Classification System (ATC) codes and Swiss pharma codes. Antibiotics were grouped by both the substance class and the WHO Access, Watch, and Reserve (AWaRe) classification. Subgroup analysis was performed for all patients for whom the general practitioner (GP) coded a diagnosis using an ICPC-2 code (International Classification of Primary Care).

Results: A total of 35,577 patients with 67,568 antibiotic prescriptions were included in the study. Broad-spectrum penicillins (BSP) (37.3%), fluoroquinolones (16.8%), and macrolides/lincosamides (12.0%) were the most frequently prescribed antibiotics. The most commonly prescribed antibiotics in these groups were amoxicillin plus beta-lactamase inhibitor (n = 20,808 prescriptions, 30.8% of all prescriptions), ciprofloxacin (n = 7,216; 10.7%) and clarithromycin (n = 4,038; 6%). According to the WHO AWaRe classification, 58.0% of all prescribed antibiotics belonged to the Access group. 41.9% of the prescribed antibiotics belonged to the Watch group. Less than 0.1% of prescriptions involved antibiotics from the Reserve group.

Analyzing time trends of antibiotic prescription, we found a 32% decline in antibiotic prescription rates, from approximately 27 prescriptions per 1,000 consultations in 2012 to 18 prescriptions per 1,000 consultations in 2019, with a yearly linear trend of –1.36 points, $p < 0.001$ (Figure 1). Regarding the most commonly prescribed antibiotic classes, we found a significant increase in BSP prescriptions by 9% (from 35.5% to 38.7%; yearly linear increase: 0.55 points; $p = 0.01$) (Figure 2). In contrast, for fluoroquinolones we found a significant reduction by 37% (from 21.4% to 13.5%; yearly linear decrease: –1.05 points, $p < 0.001$). Worth mentioning is the group of "other antibacterials" (WHO ATC class J01XB-J01XX: > 98% are nitrofurantoin and fosfomycin prescriptions), which increased significantly, i. e., more than doubled, from 5.9% to 15.8% (linear yearly increase: 1.19 points; $p < 0.001$).

In a subgroup of 9,643 patients (27.1%), ICPC-2 diagnosis codes were available. Respiratory tract infections (47.4% of all prescriptions), urological infections (31.7%), and skin infections (7.6%) were the most commonly coded indications for antibiotic prescriptions.

Discussion
In this report, antibiotic prescriptions were analyzed in the eight years preceding the pandemic. Basic prescription patterns were similar to those reported by the national and other European surveillance programs [5, 6]. The constant decline in overall antibiotic prescriptions, and especially fluoroquinolone prescriptions, is encouraging. On the other hand, our data highlight the need for continuous interventions to optimize antibiotic usage in the primary care setting. Although we are unable to evaluate the appropriateness of every single prescription, it is very likely that the excessive use of amoxicillin plus beta-lactamase inhibitor, as the most commonly used antibiotic drug, might be inappropriate to a certain degree.

Limitations

First, the data for this study come almost exclusively from the German-speaking part of Switzerland. Second, the results of the study allow only trend comparisons with the national surveillance, as the structure of the database does not allow calculation of Defined Daily Doses. Finally, the number of collaborating GPs has increased considerably in the last decade. Thus, the sample size of our study changed over the observation period.

Conclusion

Our study complements the national surveillance with specific data from the primary care setting and suggests more extensive analyses in the future. This motivates specific interventions to further optimize antibiotic use in Swiss primary care.

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Figure 1: Antibiotic prescriptions in Swiss primary care. Points represent the yearly observed numbers, and the line a smoothed curve. The 95% confidence interval band is shown in red. Number of included GPs range from *n* = 42 (2012) to *n* = 132 (2019).

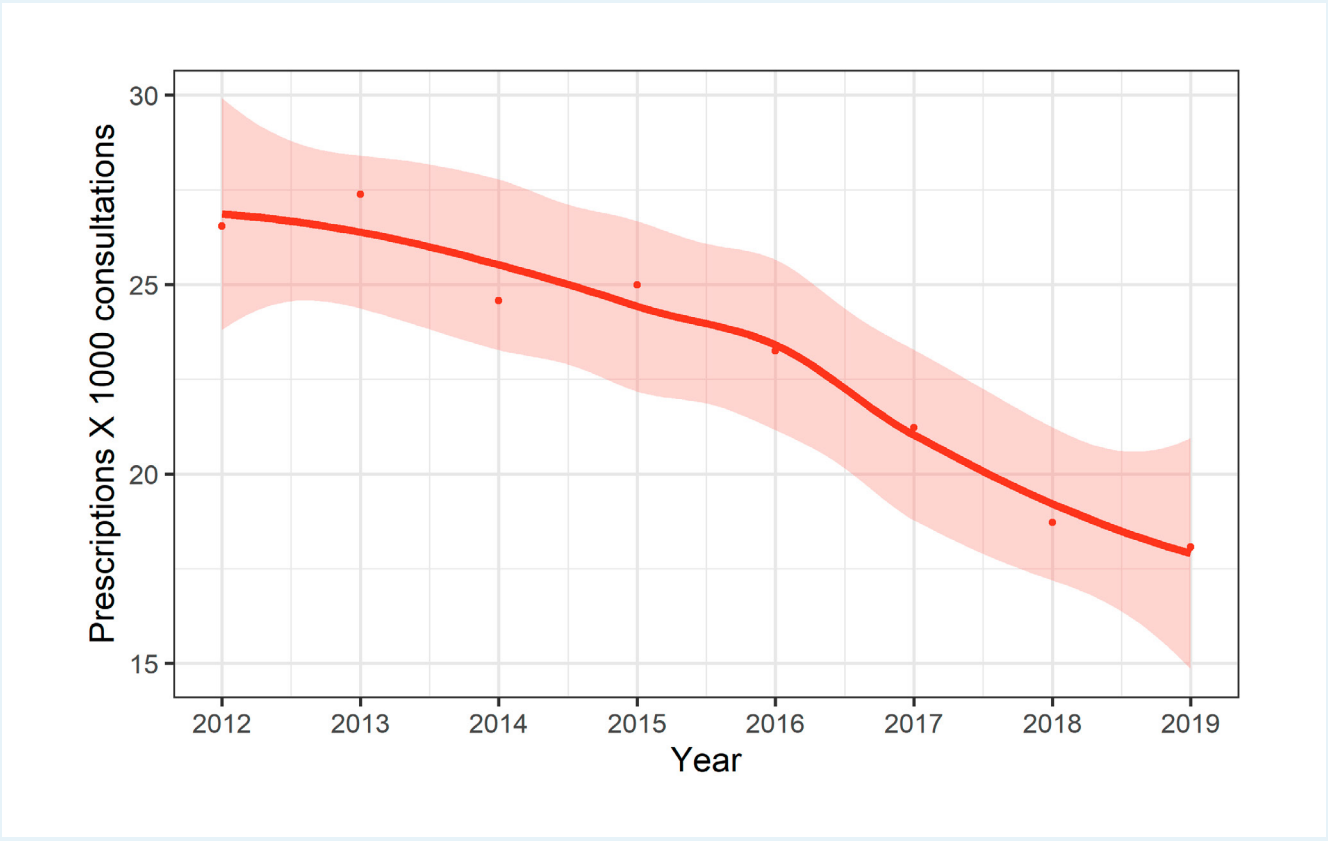
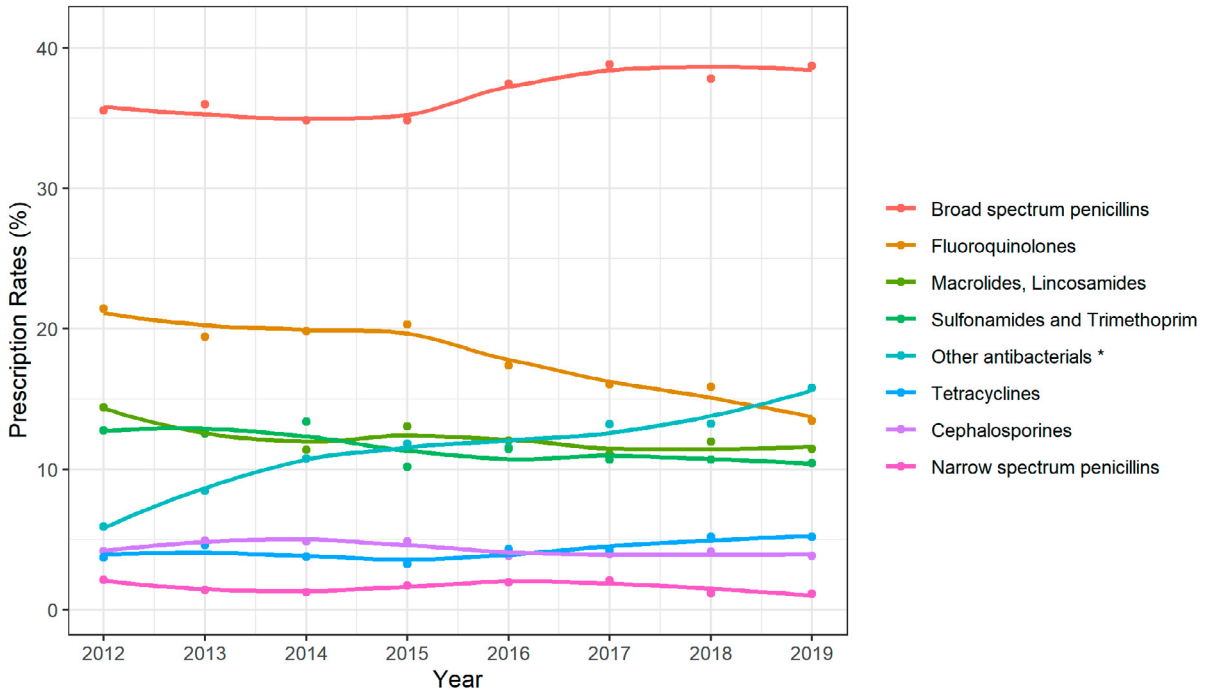


Figure 2: Antibiotic prescription patterns by drug class. Points represent the yearly observed numbers, and lines are smoothed curves. *: This group contains prescriptions from the ATC group J01XB-J01XX.



Textbox

Appropriateness of antibiotic use in Swiss hospitals and impact of routine audit and feedback: a multicenter, randomized trial

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The emergence and spread of bacteria resistant to antibacterials are an increasing public health concern, especially in Gram-negative rods such as Enterobacteriaceae producing extended-spectrum-beta-lactamases (ESBL) and carbapenemases. As bacterial resistance is correlated to antibiotic consumption, there is a need not only to support professionals and patients in reducing unnecessary use of antibiotics, but also to optimize the appropriateness of prescriptions. Multiple antibiotic stewardship interventions have been shown to improve antibacterial prescribing practices in the hospital setting, especially interventions with direct and personal feedback [1]. Nevertheless, such potentially time- and resource-consuming interventions are so far limited in Switzerland, although unnecessary or inappropriate antimicrobial therapy has been reported in acute care hospitals [2–4]. To ensure the challenging sustainability of such practices, to optimize their impact and to adapt specific resources, antibiotic stewardship interventions need to take into account the contextual determinant of prescribing decision-making.

Our project, conducted in the framework of the SNF NRP72 module 3 (http://www.nrp72.ch/en/projects/module-3-optimised-use-of-antibiotics) aimed to evaluate the impact of weekly clinical audits conducted by a tandem of an infectious disease (ID) specialist and a senior physician in charge of the patients, along with multifaceted feedback strategies aimed at reducing the use of protected anti-Gram negative antibiotics (fluoroquinolones, third- and fourth-generation cephalosporins, piperacillin-tazobactam and carbapenems) in the hospital setting. In addition to direct feedback by the auditing team, the multifaceted feedback strategy included a monthly newsletter, weekly interactive case discussions, oral presentations summarizing results of audits three and six months after the beginning of the intervention period, and a website targeting prescribers: https://www.objectif-preservation-antibiotiques.ch/. The project was conducted in internal medicine, general surgery and intensive care units (ICU) of eight acute care hospitals in four cantons of Western Switzerland. Units were allocated to either the intervention or the control group. Linear regression models of interrupted time series were performed to assess the impact of the intervention on the monthly use of protected antibiotics.

A total of 9,715 inpatients included in the intervention group were screened. 1,683 of these patients (17%) received a protected anti-Gram-negative antibiotic (Table 1). The auditing team recommended a modification of the antibiotic therapy for 24% of the patients. The recommendations were mostly stops, followed by de-escalation and a switch to the oral route (Table 2). The rate of appropriateness varied from 68% in surgical units to 92% in ICUs, and from 62% for fluoroquinolones to 85% for carbapenems. We were able to show a statistically significant decrease in the use of fluoroquinolones, fourth-generation cephalosporins and piperacillin-tazobactam in five, three and two intervention units, respectively. The use of third-generation cephalosporins and carbapenems remained unchanged in all intervention units.

These results represent the first qualitative evaluation of protected anti-Gram-negative antibiotic prescriptions in hospitals of varying sizes in French-speaking Switzerland. The observed impact on antibacterial consumption must be tempered by a good level of prescription practices (global appropriateness of prescriptions of 75%) and by a variable adhesion rate (mean 56%) to the proposals made by the auditing tandem.

Indeed, some limitations of audits with direct feedback have been raised, including individual habits of senior physicians that were no longer consistent with actual guidelines, and the rapid turnover of young residents. Moreover, some surgical wards include many specialties with different teams or external specialists limiting the scope of preventive messages. Finally, specific constraints related to surgeons' schedules made it difficult to find an appropriate time to interact with senior, decision-taking physicians. In order to establish a fruitful partnership with prescribers, regular and flexible presence in clinical wards is needed.

Continuous efforts should be made in hospitals to reduce the duration of antibiotic prescriptions, and to promote de-escalation and an earlier switch to the oral route. There is a need to raise prescribing physicians' awareness of the importance of a daily reassessment of antibacterial prescriptions.

A multifaceted strategy including audits with feedbacks, teaching rounds, provision of guidelines, educative material and continuous education should be implemented. This implies a close collaboration between an infectious disease specialist dedicated to antimicrobial stewardship interventions and the physicians in charge of patients. Actors of change must be identified in each ward, and the interaction adapted to the internal organization and the size of clinical units (one concept does not fit all).

This study provided an in-depth review of protected anti-Gram-negative antibiotic prescribing practices in Swiss hospitals and their appropriateness. In addition, we tested the feasibility, acceptability and impact of an intervention that could be incorporated into the practice of various units in small, medium and large hospitals. The results will be used to target future actions. Additionally, the development of a study website (https://www.objectif-preservation-antibiotiques.ch/) that will be maintained beyond the interventions, represents a precious education and communication tool.

Our project has been welcomed by all stakeholders, particularly by the medical directors and the medical teams. It has offered opportunities to raise awareness of the threat of antibiotic resistance and to promote best daily practices among prescribers. This project has created a positive impetus to develop antibiotic stewardship interventions in Swiss hospitals, and has highlighted the request from young physicians to be supported in their daily prescribing practices.

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Table 1: Distribution of protected anti-Gram-negative antimicrobial prescriptions among different types of units

	Total n (%)	Type of unit		
		Medical n (%)	Surgical n (%)	ICU* n (%)
Patients with prescriptions(s) of protected antimicrobial(s)	1,683	693	755	235
3rd-/4th-generation cephalosporins (n, %)	652 (39%)	331 (38%)	248 (33%)	73 (31%)
Piperacillin-tazobactam (n, %)	448 (27%)	147 (21%)	233 (31%)	68 (29%)
Carbapenems (n, %)	250 (15%)	90 (13%)	89 (12%)	71 (30%)
Fluoroquinolones (n, %)	333 (20%)	124 (18%)	184 (24%)	25 (11%)
IV fluoroquinolones (n, %)	29 (2%)	11 (2%)	12 (2%)	6 (3%)
Oral fluoroquinolones (n, %)	304 (18%)	113 (16%)	172 (23%)	19 (8%)

Table 2: Proportion of patients with optimization(s) recommended by the auditing tandem as well as adhesion rates to recommendations, listed by type of unit or targeted antimicrobial

	Total n (%)	Type of unit			Type of protected antimicrobial			
		Medical n (%)	Surgical n (%)	ICU* n (%)	C3G/ C4G** n (%)	Pip/taz** n(%)	Carba-penems n (%)	FQ ** n (%)
Patients with prescription(s) of protected antimicrobial(s)	1,683	693	755	235	652	448	250	333
Patients with optimization(s) proposed by the auditing tandem	652 (39%)	331 (38%)	248 (33%)	73 (31%)	140 (22%)	101 (23%)	37 (15%)	127 (38%)
Patients with proposition(s) followed within 24 hours by the physician in charge	448 (27%)	147 (21%)	233 (31%)	68 (29%)	91 (65%)	61 (60%)	26 (70%)	49 (39%)

* ICU: Intensive Care Unit
** C3G/C4G: third-/fourth-generation cephalosporins; Pip/taz: Piperacillin/Tazobactam; FQ: Fluoroquinolones

Textbox

Antibacterial consumption in Switzerland compared internationally

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Background

The Swiss Centre for Antibiotic Resistance monitors antibacterial consumption in the out- and inpatient settings as part of the Strategy on Antibiotic Resistance (StAR). We aimed to compare antibacterial consumption in Switzerland and internationally.

Method

IQVIA™ sell-in data from pharmaceutical industries to public pharmacies, self-dispensing physicians and hospitals were used to measure consumption, whereby the number of packages were converted into defined daily doses (DDD) and expressed in DDD per 1,000 inhabitants per day (DID). For comparison purposes, only the antibacterial agents for systemic use (ATC code J01) were included in the main analyses. Data on additional antibacterials were included in the calculation of the WHO Access, Watch and Reserve (AWaRe) classification (ATC codes A07AA, J01, J04AB, P01AB) [1,4].

Results

In Switzerland, the antibacterial consumption in the outpatient setting in 2020 was 7.5 DID (ATC code J01), with higher consumption in the French- (10.1) and Italian-speaking (9.1) regions than in the German-speaking region (6.5) (Figure 1. a). In the inpatient setting, the antibacterial consumption was 1.5 DID, with a higher consumption in the Italian-speaking region (1.8) than in the German- (1.5) and French-speaking regions (1.4) (Figure 1. b). In 2020, in the countries contributing to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), the population-weighted mean consumption was 15.0 DID (range 7.1–26.4) in the outpatient setting, and 1.6 (range 0.8–2.2) in the inpatient setting [2].

The proportion of penicillins combined with beta-lactamase inhibitors in Switzerland (27% of total J01 consumption, ATC code J01CR) was higher than the EU/EEA countries' median (16%, range: 1–30%) in 2020 [2]. The proportion of fluoroquinolone consumption in Switzerland (11% of total J01 consumption) was higher than in EU/EEA countries (median: 9%, range: 2–16%) in 2020 [2], with higher values in the Italian-speaking region (15%) than in the French- and the German-speaking regions (11%).

The WHO's *13th General Programme of Work for 2019–2023* has set a country-level target stipulating that antibiotics in the Access group should account for at least 60% of total antibiotic consumption [3]. In Switzerland, the Access group accounted for 60% in 2018 and 64% in 2021. Access antibiotics accounted for more than 60% of total consumption in 17 (59%) of 29 ESAC-Net countries, and in 3 (20%) of 15 WHO Europe AMC Network countries that provided 2018 data [4]. The population-weighted mean consumption of Access agents was 57.9% for ESAC-Net and 47.4% for the WHO Europe AMC Network [4]. Figure 1. c shows the proportions of AWaRe groups in Switzerland and in EU/EEA countries participating in the ESAC-Net [4].

Discussion

Even though antibacterial consumption is relatively low in Switzerland, fluoroquinolones and penicillins combined with beta-lactamase inhibitors showed high relative proportions in comparison with EU/EEA countries. Extended spectrum penicillins (including amoxicillin) could be promoted in Switzerland, especially in patients with respiratory tract infections, as recommended by the guidelines of the Swiss Society of Infectious Diseases [5]. Regarding the AWaRe categorization, the country-level target of at least 60% of total consumption being Access group antibiotics has been achieved in Switzerland, but the proportion of the Access group could be further improved. These findings suggest some targets for future stewardship activities in the out- and inpatient settings.

References

[1] WHO Antibiotic Classification. Available from: https://aware.essentialmeds.org/list (accessed 27 July 2022)
[2] European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA (ESAC-Net) – Annual Epidemiological Report 2020. Stockholm: ECDC; 2021.
[3] Thirteenth General Programme of Work (GPW13): methods for impact measurement. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
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[5] Swiss Society of Infectious Diseases, SGInf-Guidelines, available from: https://ssi.guidelines.ch/ (accessed 27 July 2022).

Figure 1. a: Total antibacterial consumption in Switzerland and in linguistic regions compared to EU/EEA countries in the outpatient setting, expressed in DDD per 1,000 inhabitants per day, 2020 (adapted from [2]).

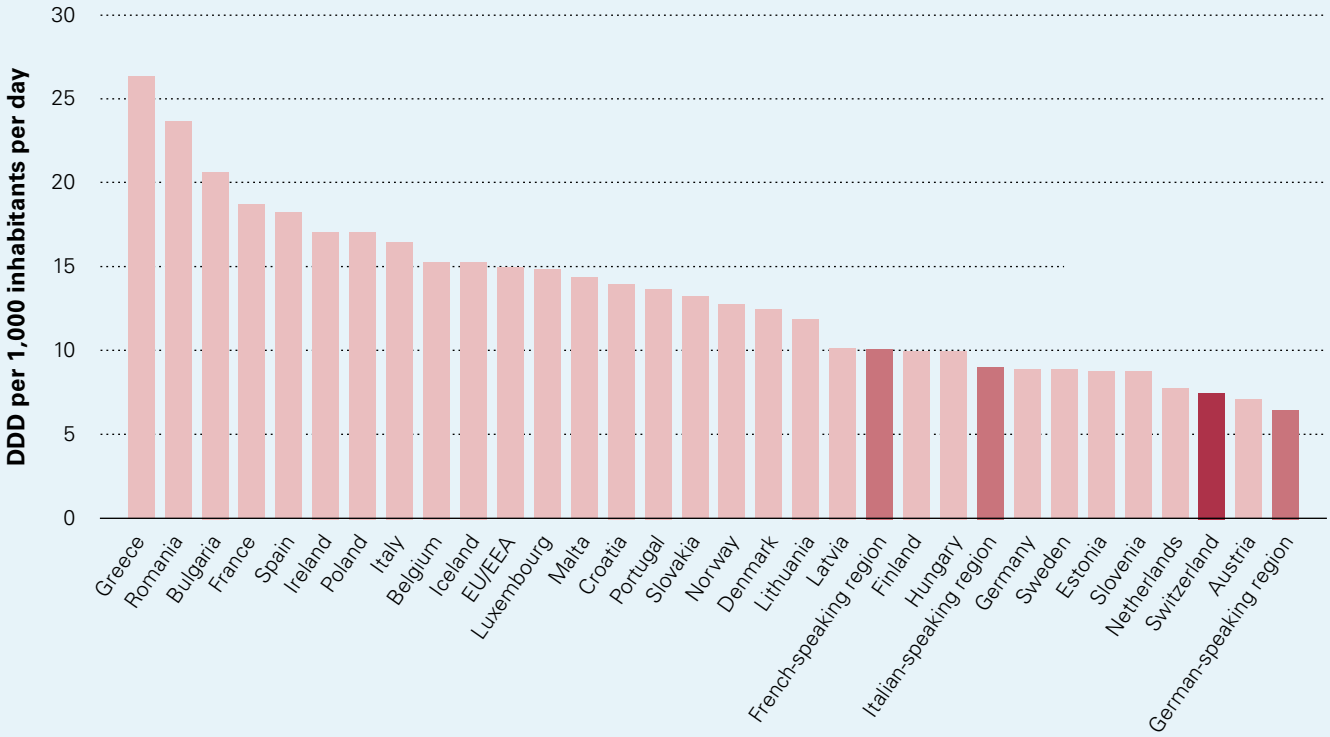


Figure 1. b: Total antibacterial consumption in Switzerland and in linguistic regions compared to EU/EEA countries in the inpatient setting, expressed in DDD per 1,000 inhabitants per day, 2020 (adapted from [2]).

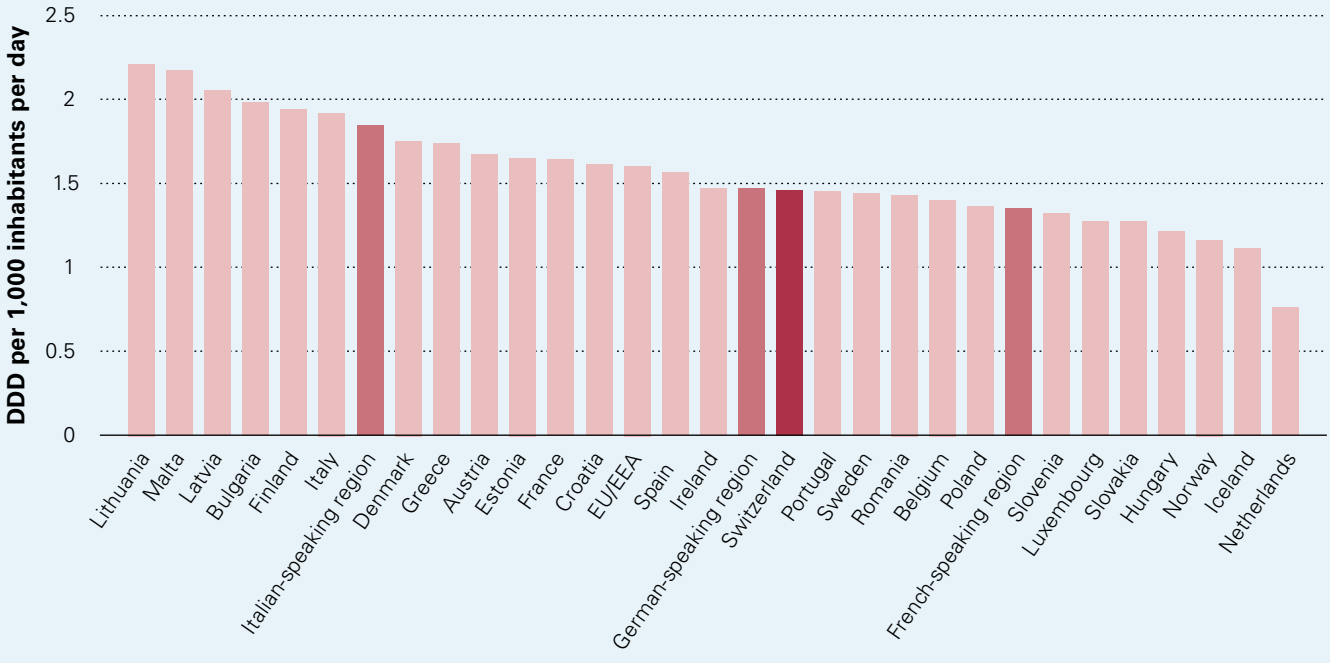
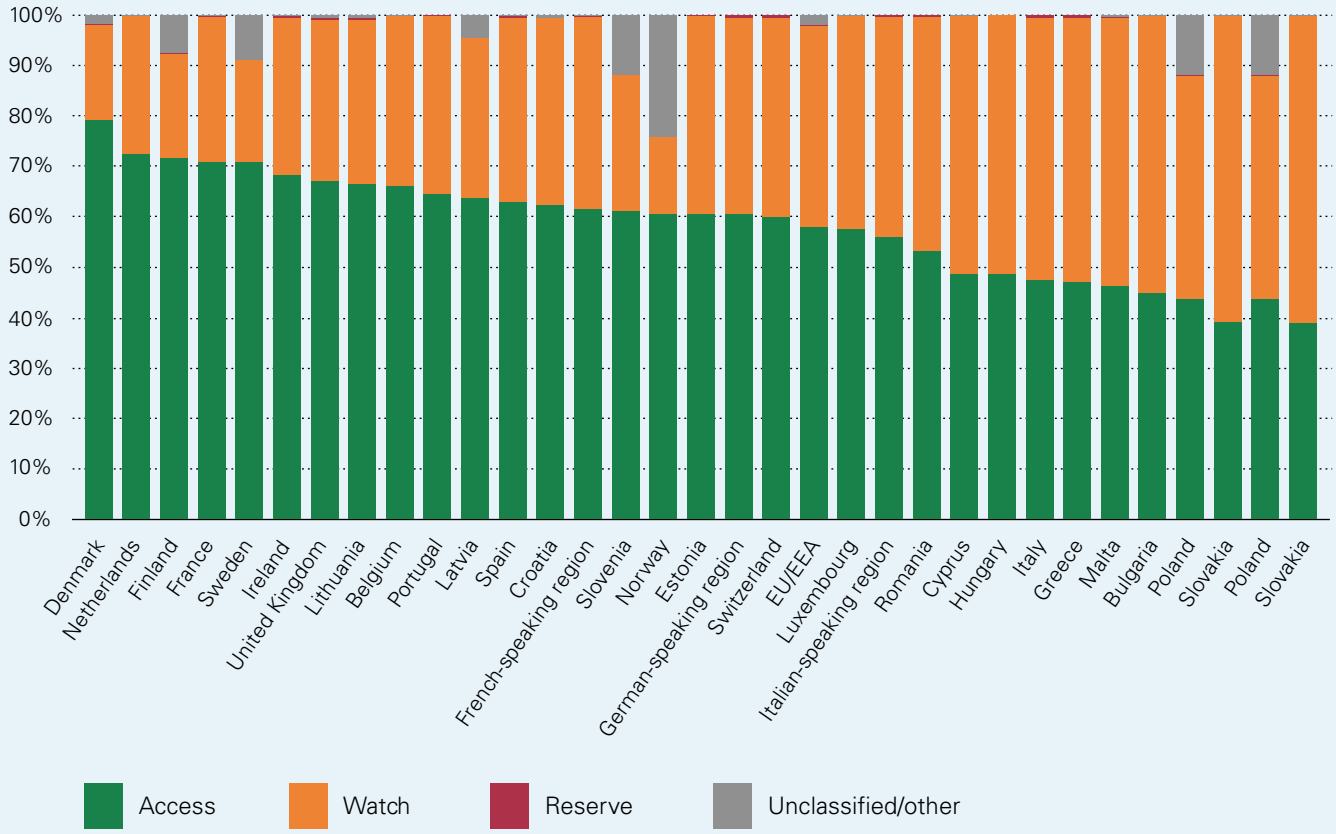


Figure 1. c: Proportion of total antibiotic consumption according to the WHO AWaRe classification in Switzerland and in linguistic regions compared to EU/EEA countries, 2018 (adapted from [4]).



6

Antimicrobial consumption in veterinary medicine

6 Antimicrobial consumption in veterinary medicine

A) 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 2020, given sales of 28,871 kg, the yearly decline was 4.1%. The reduction was less pronounced in 2021, with 1.6% (total volume 28,402 kg). Since 2012, the total decline amounts to 48% (26,590 kg). The decrease is mainly due to decreased sales of medicated premixes.

Since 2018, the ranking by sales volumes of the different antibiotic classes has not changed[1]: penicillins are the most sold antibiotics, followed by sulfonamides and tetracyclines. These three classes are often sold as medicated premixes in large packages.

The quantity of sold antibiotics approved for companion animals only comprises 3.1% of the total volume in 2021. Regarding the highest-priority critically important antibiotic classes for human medicine [1], the sales of macrolides decreased around 9% in 2020 and 2021, compared to the previous year. Fluoroquinolones were sold less in 2020, but came back to the same level as 2019 in 2021. The sales of third- and fourth-generation cephalosporins decreased by approximately 18% in 2020, but remained stable in 2021.

Grouped according to the administration route, the order of antimicrobial volumes has remained unchanged compared to previous years (Table 6. b). The biggest volumes are products licensed for oral application (2020 and 2021: 57%), followed by parenteral (2020: 29%, 2021: 31%), intramammary (2020 and 2021: 10%), intrauterine (2%) and topical formulations (1%). Like in previous years, products authorized for oral use were mainly sold as medicated premixes.

[1] Active substance classes 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."

6.2 Sales of antimicrobials for use in livestock

6.2.1 General

The amount of antimicrobial sales for livestock includes products approved for livestock species and products approved for livestock and companion animal species (mixed registrations). This is in accordance with the reporting procedure used by the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption, EMA) project [2]. Since

Table 6. a: Sales of antibiotic classes between 2012 and 2021.

Sales (kg)										
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Sulfonamides	21,556	18,942	17,009	14,959	13,130	10,181	9,292	8,406	6,697	7,148
Penicillins	10,997	10,875	10,344	10,016	9,694	9,610	9,823	9,785	9,755	9,908
Tetracyclines	12,043	11,631	10,402	8,683	8,177	6,856	7,218	6,226	6,823	5,793
Aminoglycosides	3,207	3,124	3,125	3,104	2,997	2,471	2,523	2,465	2,515	2,498
Macrolides	3,313	3,112	2,807	2,632	1,988	1,594	1,482	1,183	1,072	973
Trimethoprim	1,368	1,148	1,102	904	829	591	608	582	561	676
Polymyxins	1,058	855	773	503	372	328	235	207	148	82
Cephalosporins	542	530	522	495	431	381	363	322	314	306
Fluoroquinolones	359	413	404	407	304	228	203	185	178	186
Amphenicoles	232	202	188	217	273	378	499	571	612	686
Others*	318	343	274	227	182	210	152	177	196	146
Total	**54,992**	**51,176**	**46,950**	**42,147**	**38,377**	**32,826**	**32,397**	**30,108**	**28,871**	**28,403**

* Lincosamides, imidazoles, nitrofurans, pleuromutilins, polypeptides excluding polymyxins (until 2013), steroidal antibiotics, quinolones (until 2014)

Table 6. b: Sales of antimicrobials according to the administration route between 2012 and 2021.

Sales (kg)	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Oral	**42,005**	**38,756**	**34,697**	**30,015**	**26,113**	**21,411**	**20,288**	**18,063**	**16,590**	**16,048**
Premix	36,181	33,021	29,079	24,336	20,621	17,223	15,750	13,050	12,916	11,566
Others*	5,824	5,735	5,618	5,679	5,492	4,188	4,538	5,013	3,674	4,482
Intramammary	**3,655**	**3,482**	**3,375**	**3,193**	**2,672**	**2,753**	**2,795**	**2,885**	**2,848**	**2,784**
Dry cow products	1,315	1,336	1,343	1,064	918	824	912	826	850	797
Lactating cow products	2,340	2,146	2,033	2,129	1,754	1,930	1,884	2,059	1,997	1,988
Parenteral	**8,200**	**7,876**	**7,724**	**7,934**	**8,580**	**7,752**	**8,373**	**8,225**	**8,497**	**8,675**
Intrauterine	**815**	**767**	**864**	**719**	**726**	**612**	**654**	**628**	**643**	**595**
Topical/external	**318**	**296**	**290**	**286**	**287**	**298**	**287**	**307**	**293**	**300**
Sprays	299	278	272	270	271	284	272	293	269	294
Others**	18	18	19	16	16	15	15	13	23	6
Total	**54,992**	**51,176**	**46,950**	**42,147**	**38,377**	**32,826**	**32,397**	**30,108**	**28,871**	**28,403**

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

Table 6. c: Sales of different antibiotic classes licensed for livestock animals between 2012 and 2021.

Sales (kg)										
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Sulfonamides	21,556	18,942	17,009	14,959	13,130	10,181	9,292	8,406	6,697	7,148
Penicillins	10,582	10,437	9,893	9,573	9,249	9,143	9,375	9,325	9,318	9,431
Tetracyclines	12,038	11,626	10,398	8,679	8,172	6,851	7,214	6,222	6,818	5,787
Aminoglycosides	3,199	3,115	3,114	3,095	2,988	2,462	2,513	2,456	2,495	2,496
Macrolides	3,289	3,089	2,784	2,610	1,967	1,574	1,463	1,164	1,056	973
Trimethoprim	1,368	1,148	1,102	904	829	591	608	582	561	676
Colistin	1,057	854	773	502	372	327	234	206	148	82
Fluoroquinolones	335	384	379	384	282	207	184	169	163	169
Cephalosporins	237	228	241	234	190	163	162	144	130	139
Amphenicoles	–	183	169	199	244	341	463	529	574	608
Others*	449	310	241	197	152	181	125	130	118	27
Total	**54,111**	**50,316**	**46,103**	**41,337**	**37,575**	**32,020**	**31,634**	**29,334**	**28,078**	**27,535**

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

2012, the amount of such sales has decreased continuously and in total by 51%. Penicillins account for the bulk of agents followed by sulfonamides and tetracyclines. Highest-priority critically important antibiotics were also sold less than in previous years. The sales of macrolides decreased by more than 9% in 2020 and 8% in 2021 (Table 6. c). Even the sales of long-acting, single-dose injection products followed a downward trend. The sales of fluoroquinolones and third- and fourth-generation cephalosporins started decreasing in 2016. Fluoroquinolones decreased by almost 4% in 2020, but increased by almost 4% in 2021; third- and fourth-generation cephalosporins decreased by 21% in 2020, but increased by 2% in 2021. Overall, since 2012, highest-priority critically important antibiotics have decreased by approximately 67%. 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, macrolides, fluoroquinolones and third- and fourth-generation cephalosporins, summarized in the Ordinance and designated as "critical antimicrobials," are not allowed to be dispensed in stock to livestock.

The sales of colistin have declined by approximately 92% since 2012. Expressed in correlation to the biomass under exposure (population correction unit, PCU), see Chapter 6.2.2 below), the level in 2021 is 0.1 mg colistin/PCU for Switzerland. This is below the European average and far below the requested reduction of colistin to a level of 1 mg/PCU or lower for European countries. For some years now, the goal has been to reduce the use of colistin in veterinary medicine to a very low level, as colistin has become the last resort treatment for life-threatening infections caused by carbapenem-resistant Enterobacteriaceae in human medicine.

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 has developed a method to express antimicrobial sales correlated to the biomass of the livestock population based on available data sources for European countries [2]. To do so, the amount of active substances is divided by the sum of the estimated most likely weight at treatment of livestock animals in a given year. This denominator is termed population correction unit (PCU). Companion animals and certain livestock species are not taken into account, because in most countries the number and other data are unknown. The PCU is a technical unit of measurement aiming to normalize antibiotic treatments and livestock populations specifically for the comparison between countries. It 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 normalized antimicrobial sales for livestock animals in Switzerland by PCU for the years 2012 to 2021. In the last ten years, sales of antimicrobials compared to the population biomass have decreased faster. The reduction of milligrams active substances per PCU indicates that the decrease of sales of antimicrobials is not due to a decrease of the livestock population. Thus, it is most likely that the reduction in sales is due to a reduction in the use of antibiotics, especially a reduction of the proportion of animals treated. 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, promoting prudent use of antimicrobials in Switzerland.

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.

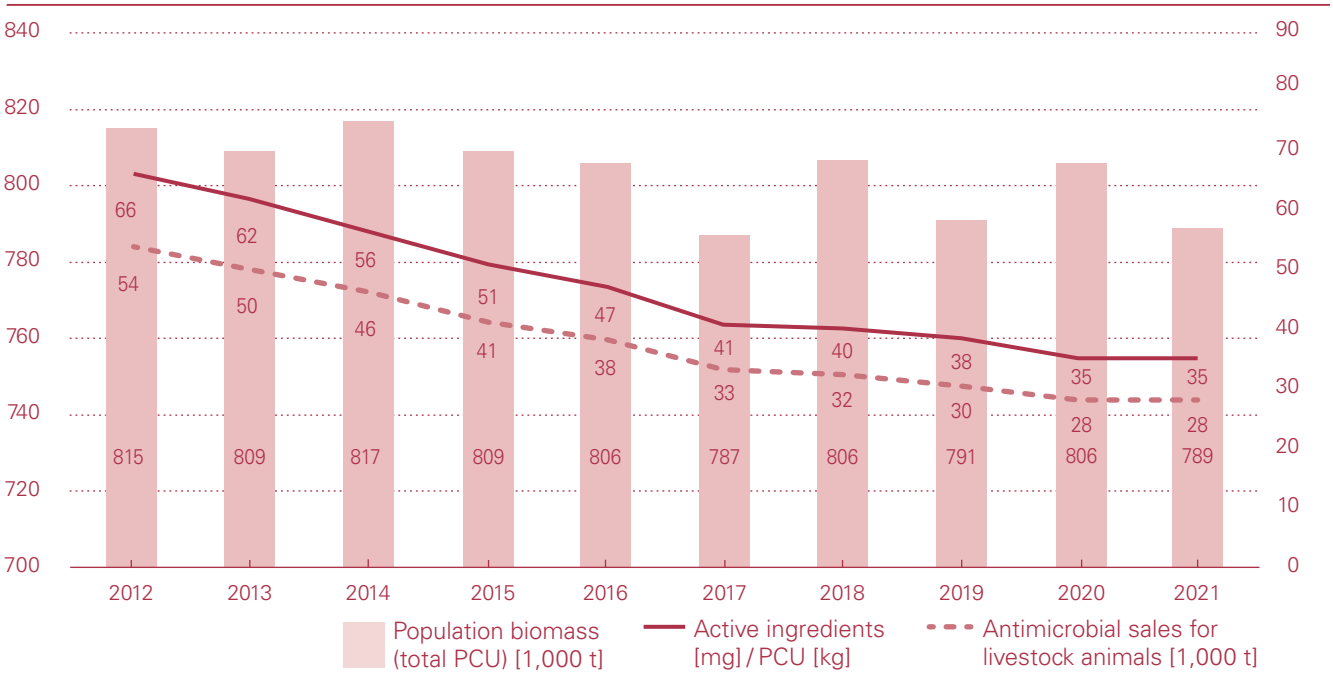


Table 6. d: Sales of antimicrobials licensed as premixes between 2012 and 2021, according to antibiotic classes.

Sales (kg)										
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Sulfonamides	16,319	13,931	12,141	10,028	8,285	6,450	5,183	3,865	3,387	3,207
Tetracyclines	10,359	9,968	8,673	7,038	6,382	5,174	5,440	4,494	4,990	4,076
Penicillins	4,309	4,461	4,198	3,840	3,363	3,379	3,232	3,145	3,166	3,146
Macrolides	2,907	2,751	2,413	2,263	1,696	1,417	1,289	1,036	923	870
Colistin	1,045	844	763	500	370	326	231	203	146	80
Trimethoprim	937	740	626	453	373	322	249	167	137	149
Others*	305	326	265	215	151	156	127	140	167	38
Total	**36,181**	**33,021**	**29,079**	**24,336**	**20,621**	**17,223**	**15,750**	**13,050**	**12,916**	**11,566**

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

6.2.3 Medicated premixes

Medicated premixes accounted for 46% of the total sales in 2020 and 42% in 2021. A steady and above-average decrease in sales of medicated premixes has been observed since 2010 (–68%). Tetracyclines, sulfonamides, and penicillins are the three main classes of active substances contained in premixes (Table 6. d). These products account for the largest share of the decline in antimicrobial sales. Medicated premixes are available in several combinations of one, two or three active substances and are used mainly for calf fattening, pigs and broilers.

6.2.4 Antimicrobials authorized for intramammary use

In the last years, the sales of products for intramammary use have remained stable with small fluctuations. The amount has been reduced by nearly 38% since 2008. In 2020 and 2021, between 70 and 71.5% of all antimicrobials licensed for intramammary use were products for the treatment of mastitis during lactation. The sales of products for drying off increased in 2020 (3%), then decreased in 2021 (6%), whereas the sales of products for use during lactation decreased slightly in 2020 (3%) and 2021 (0.5%) (Figure 6. b).

The ranking by antibiotic classes shows that penicillins are predominant, accounting for 80% of all active substances administered into the udder (Table 6. e). Sales of products containing cephalosporins (all generations) for the treatment of mastitis during lactation have increased in the last years (29% since 2012), mainly due to an increase of use of first- and second-generation cephalosporins.

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.

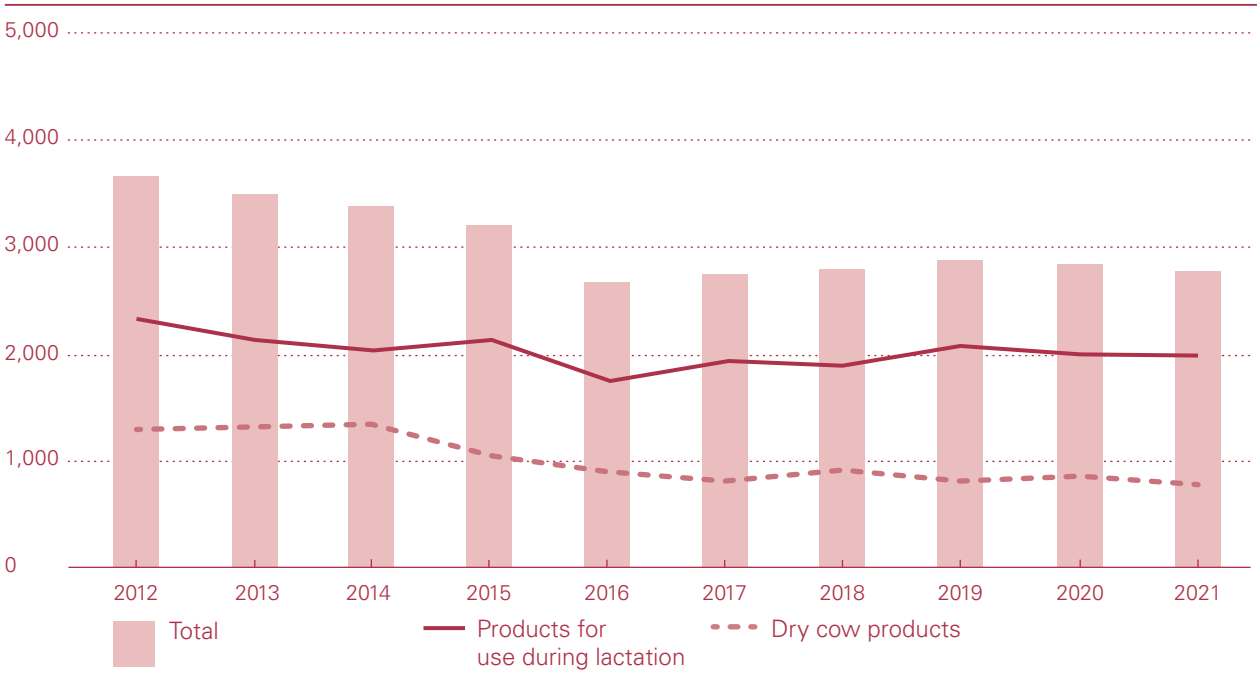


Table 6. e: Sales of antimicrobials licensed for intramammary use between 2012 and 2021 according to antibiotic class.

Sales (kg)										
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Dry cow products										
Total	1,315	1,336	1,343	1,064	918	824	912	826	850	797
Products for use during lactation										
Penicillins	1,774	1,644	1,545	1,652	1,366	1,543	1,484	1,659	1,598	1,604
Aminoglycosides	406	376	370	361	275	292	305	312	308	304
Cephalosporine	55	52	56	59	60	59	62	60	65	71
Others*	104	74	62	57	53	36	31	27	26	9
Total	2,340	2,146	2,033	2,129	1,754	1,930	1,884	2,059	1,997	1,988
Total	3,655	3,482	3,375	3,193	2,672	2,753	2,795	2,885	2,847	2,785

* Lincosamides, macrolides, polymyxins (until 2015)

Table 6. f: Sales of antibiotic classes licensed for companion animals between 2012 and 2021.

Sales (kg)										
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Penicillins	415	438	450	443	446	467	448	460	437	477
Cephalosporins	304	302	281	262	241	217	201	177	184	167
Imidazole	24	29	25	23	22	21	19	31	62	102
Fluoroquinolones	8	9	10	9	10	9	9	16	15	17
Aminoglycosides	–	–	–	–	–	–	–	8	20	2
Others**	129	82	80	74	84	92	86	82	75	102
Total	**881**	**860**	**847**	**810**	**802**	**806**	**763**	**774**	**793**	**867**

** Lincosamides, imidazoles, nitrofurans, polypeptides, steroidal antibiotics, tetracyclines, trimethoprimes, amphenicoles, macrolides, polymyxins

6.3 Sales of antimicrobials licensed for companion animals

The quantity of antibiotics approved exclusively for use in companion animals amounts to approximately 3% of the total volume. Since 2012, products licensed for both livestock and companion animals are subsumed to the category "livestock," in accordance with the guidelines of the ESVAC project [3]. The products licensed for both categories, amount to approximately 28% of the total volume. This is especially relevant for products for parenteral application, as the major part of these products are licensed for both livestock and companion animals. The consequence is an underestimation of the use in companion animals.

The amount of active substance sold for companion animals was 793 kg in 2020 and 867 kg in 2021; the sales are increasing since 2019, by 2.4% in 2020 and 9.3% in 2021. Since 2012, antimicrobial sales for companion animals have decreased by approximately 1.5%. Penicillins were the most important active substance group, followed by cephalosporins (all generations), imidazole and fluoroquinolones (Table 6. f). The decreasing trend of sales of cephalosporins has continued during the past year (2021: –9.2%), after a slight increase in 2020 (+3.8%). The increase of imidazole use in companion animals is mainly due to new licensed products containing metronidazole.

6.4 Discussion

There is a consistent high awareness in veterinarians as well as in farmers concerning the prudent use of antimicrobials. The decrease in the volume of antimicrobials sold for use in veterinary medicine continues. This is mainly due to a fall in the sales of medicated premixes. In addition, the constant decline in sales of highest-priority critically important antibiotic classes is encouraging. The reduction of milligram active substance per PCU indicates that the reason for the decrease is most likely a reduced number and extent of treatments. However, the data should be interpreted cautiously as they comprise only sales figures and the weight as an indicator. Relevant information about livestock or companion animals, target species, route of administration (parenteral, oral, topical/external, intrauterine, intramammary) and galenics are solely based on the marketing authorization (summary of product characteristics). Therefore, in contrast to the section below, this section of the report, based on sales data, does not contain any information regarding actual use at the species level; e.g., different dosages for different antibiotic classes and target species are not taken into account and can differ widely. Also, other indicators such as the defined daily dose (DDDvet) might add important perspectives by using a dose-based indicator standardized for species, route of administration and molecular weight instead of the total weight of antimicrobials. ESVAC has recently published technical units of measurements to report antimicrobial consumption data in the main livestock species [5]. This indicator is broadly in line with the defined daily doses "DDDs" used in human medicine. However, many other technical units of measurements to report antimicrobial consumption data in animals are available. Of these, both dose-based and treatment-based units of measurement are suitable for certain tasks.

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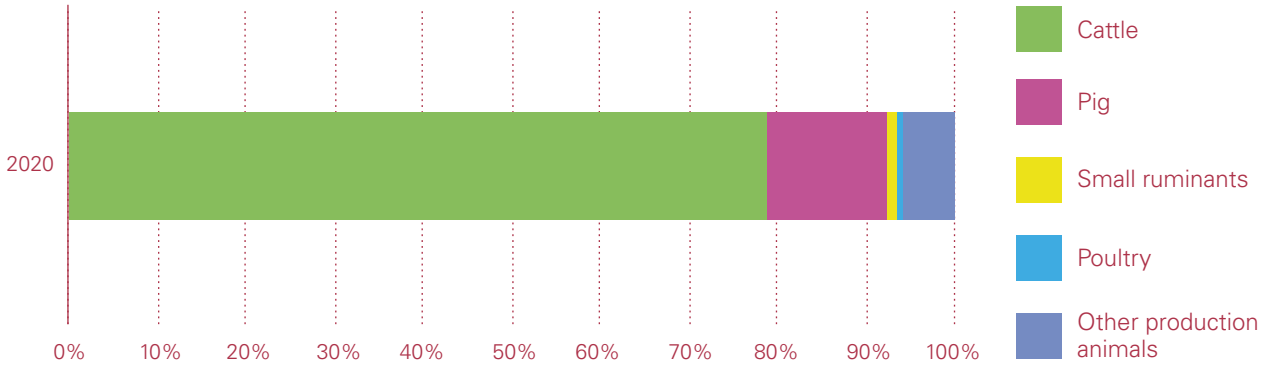
Table 6. g: Number of prescribed products per livestock species in Switzerland (2020). Products with critical antibiotics are displayed in brackets.

Number of products (critical antibiotics in brackets)					
	Cattle	Pigs	Poultry	Small ruminants	Livestock (all species)
Swiss veterinary products	166 (52)	120 (34)	37 (14)	112 (34)	183 (59)
Products for human medicine	10	0	1	5	16
Imported products	48 (9)	5 (1)	2 (1)	5 (1)	53 (9)

Table 6. h: Number of prescribed products for companion animals in Switzerland (2020). Products with critical antibiotics are displayed in brackets.

	Number of preparations (critical antibiotics in brackets)
Swiss veterinary products	187 (64)
Products for human medicine	123 (22)
Imported products	24 (3)
Formula magistralis	10

Figure 6. c: Distribution of the total antibiotic consumption per livestock species in Switzerland (2020).



B) Prescriptions of antimicrobials in veterinary medicine

6.5 Introduction

Since October 2019, all prescriptions of antibiotics must be recorded by veterinarians in the information system for antibiotics in veterinary medicine (IS ABV). The analyses in this section are based on the data recorded in IS ABV for the year 2020[2], which is the first full year after the introduction of IS ABV in which the data were recorded in full. In the first reports [1, 2], the antibiotic quantities, the number of prescriptions and the number of animal treatments were evaluated for livestock and companion animals. The indicators used are in absolute values without denominators. Thus, the results are well suited to provide initial indications of the use and quantities of antibiotics in individual livestock categories and companion animal species. As these absolute values have not yet been set in relation to the number of animals, these evaluations are only initial indications and are not suitable as a basis for comparative statements on treatment intensity between species or animal categories.

[2] In this report, the highest-priority critically important antibiotic classes for human medicine (i.e., critical antibiotics) are identified with a "*." Antibiotic classes are identified separately if there are at least three products containing this active substance. This practice was adopted for confidentiality reasons.

Figure 6. d: Distribution of the total antibiotic consumption per antibiotic class and livestock species in Switzerland (2020).

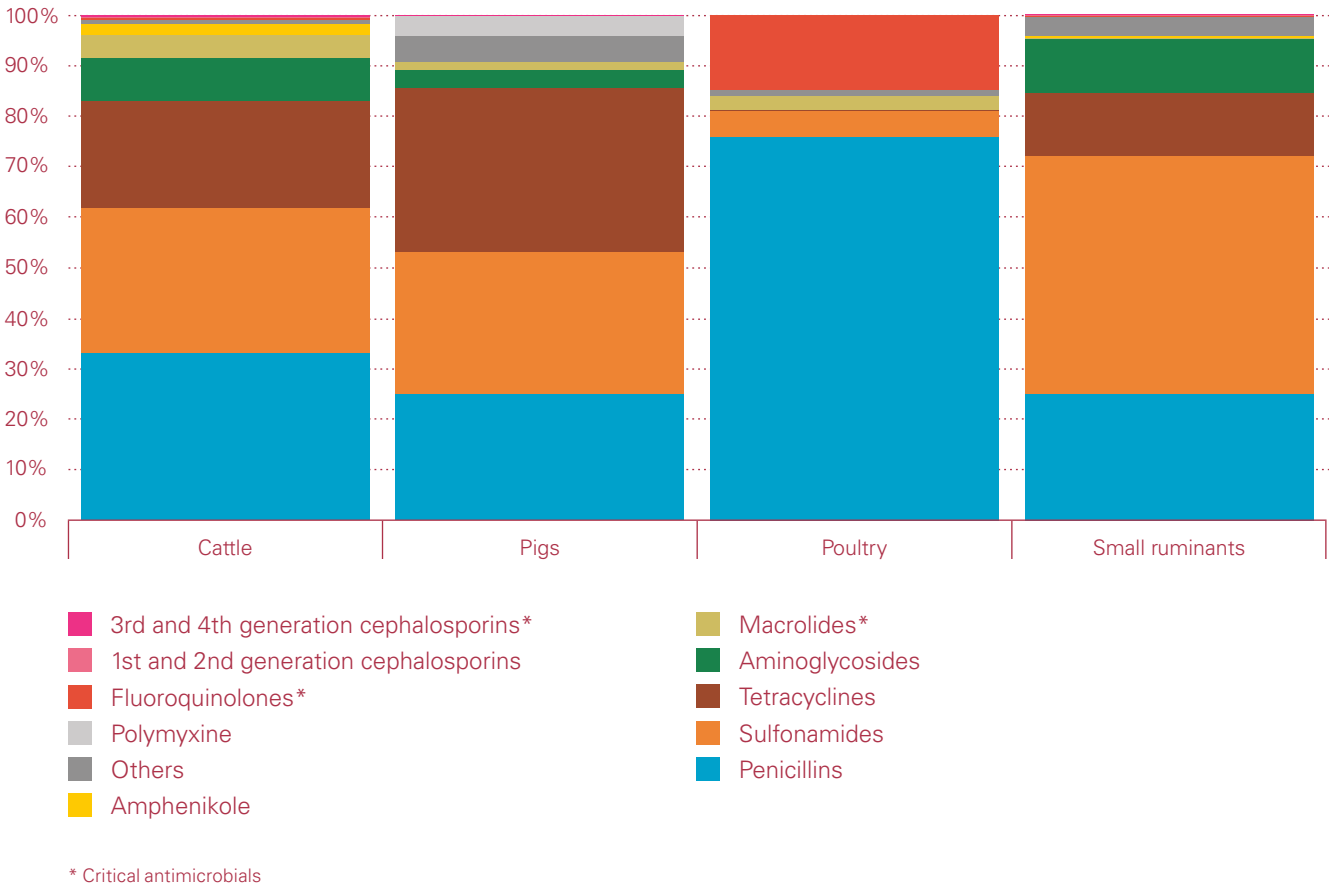
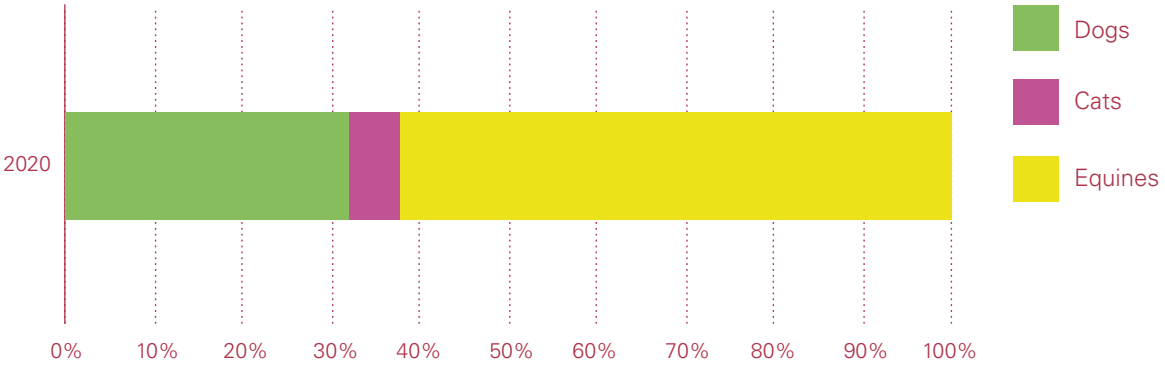


Figure 6. e: Distribution of the total antibiotic consumption per companion animal species in Switzerland (2020).



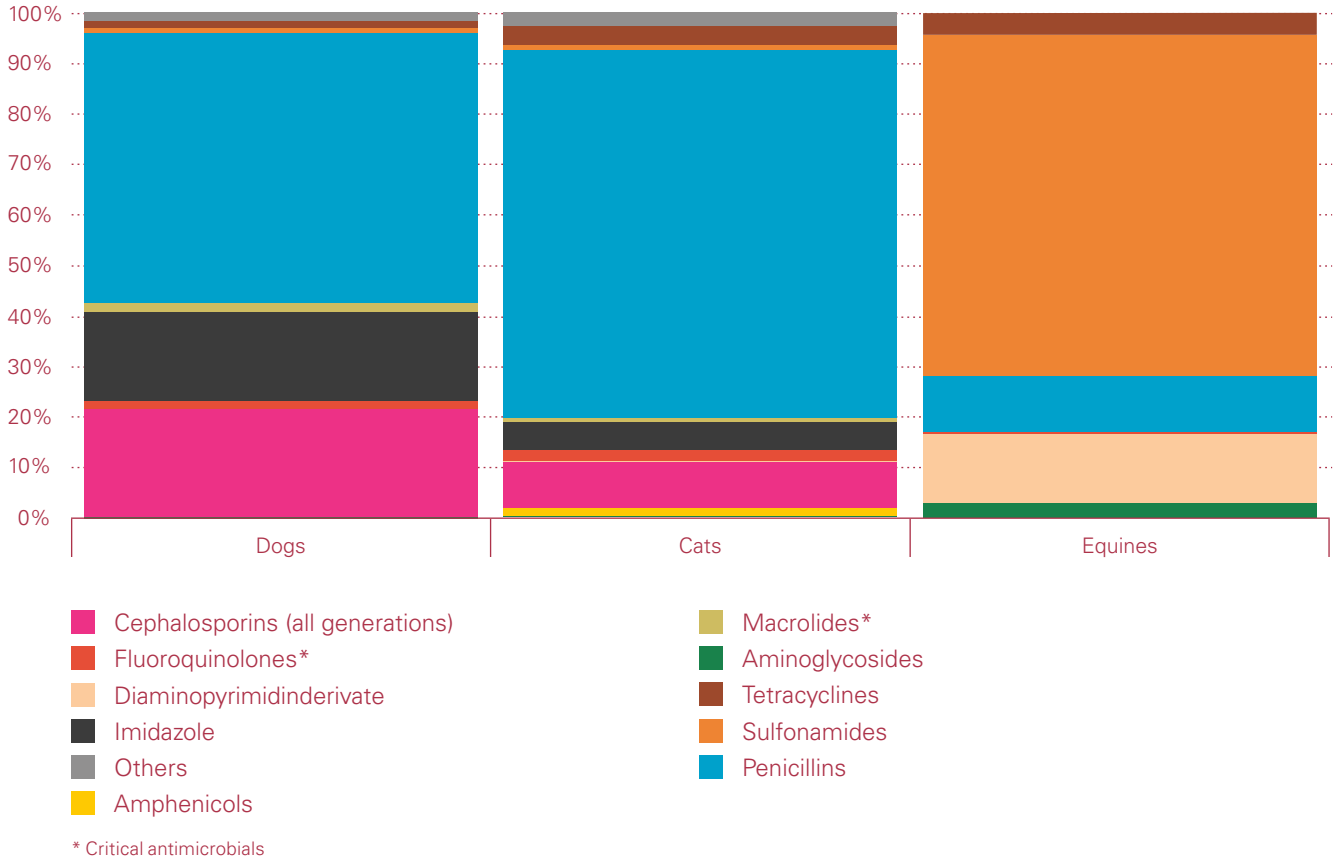
6.6 Antimicrobial usage in livestock

6.6.1 Overview

This part of the report presents the analyses of 2020 IS ABV data for livestock. Veterinarians are obliged to register all prescriptions for livestock in IS ABV. In this report, we present the results with a special focus on cattle, pigs, poultry and small ruminants (i.e., ovines and goats).

The distribution of the amount of antibiotics prescribed (Figure 6. c) illustrates the large part administered to cattle. Indeed, 78.8% of all antibiotics were prescribed to cattle, including, among others, dairy cows and fattening calves. The second highest use of antibiotics was in pigs (13.5%), followed by small ruminants (1.1%) and poultry (0.8%). 5.8% of all antibiotics used in Switzerland were prescribed to other production animal species. It must be noted, however, that the active ingredient quantity is only an indicator for the amount of active ingredients and not for the number or intensity of treatments.

Figure 6. f: Distribution of the total antibiotic consumption per antibiotic class and companion animal species in Switzerland (2020).



In accordance with the sales data for 2020, the main prescribed antibiotic class for all livestock species was penicillin. Particularly in the poultry sector, penicillin constitutes the main antibiotic class (Figure 6. d). Sulfonamides and tetracyclines were the next two often-used classes. The distribution of antibiotic use in all livestock species is presented in Figure 6. d. Critical antibiotics represent only a small proportion (4.6%) of the antibiotics prescribed in 2020 in all species. The most represented critical antimicrobial class was macrolides.

Broken down by species, the order of the highest consumption of antibiotic classes is as follows:

- Cattle were mostly prescribed penicillins (33.2%), sulfonamides (28.7%) and tetracyclines (21.1%). The other antibiotic classes represent less than 20% of all consumption for cattle.
- Pigs were mostly prescribed tetracyclines (32.5%), sulfonamides (28.0%) and penicillins (25.1%). Other antibiotics represented less than 15% of antibiotic consumption for pigs.
- Poultry were mostly prescribed penicillins (75.8%). Other antibiotic classes were prescribed significantly less often.
- Small ruminants were mainly prescribed sulfonamides (47.4) and penicillins (24.8%). Tetracyclines (12.3%) and aminoglycosides (10.7%) were also frequently prescribed. Other antibiotic classes represented less than 5%.

Products used for livestock species were mostly veterinary products licensed for use in Switzerland, some imported products and a few products from human medicine. In total, 166 different Swiss veterinary products were prescribed for cattle in 2020, 120 for pigs, 112 for small ruminants, and 37 for poultry (Tab 6. g). Under exceptional circumstances, products could also be imported with a special authorization from Swissmedic. These included forty-eight products for cattle, five for pigs and small ruminants and only two for poultry. Human products can also be used for production animals under specific circumstances that are strictly regulated (use under the cascade rule), but this practice remains infrequent according to the number of human products prescribed in 2020: ten for cattle, five for small ruminants, one for poultry and none for pigs.

6.7 Antimicrobial usage in companion animals

6.7.1 Overview

This part of the report presents the analyses of 2020 IS ABV data, focusing on dogs, cats and equines (food production and companion).

Figure 6. e illustrates the distribution of the amount of antibiotics prescribed; the largest part was prescribed for horses (62.2%). However, horses are heavy animals that require a large amount of antibiotic for each prescription. The second highest amount of antibiotics is used in dogs (32.0%), followed by cats (5.7%).

The main antibiotic classes prescribed for companion animals are sulfonamides (42.3%) and penicillins (28.3%) (Figure 6. f). Equines differ from the other two species in the repartition of the total amount of antibiotics. For equines, the main consumption concerned sulfonamides, diaminopyrimidine derivatives, and penicillins. In contrast, for cats and dogs, penicillins, cephalosporins and imidazoles take the largest share of the antibiotic consumption in 2020. With 1.8%, critical antibiotics represent only a small amount of antibiotics prescribed in all species. The most represented critical antimicrobial was fluoroquinolones.

In total, 187 different Swiss veterinary products and 64 different products with critical antibiotics were prescribed to companion animals in 2020 (Tab 6. h). 24 products were imported. Also, 123 human products were used for companion animals under specific circumstances that are strictly regulated (use under the cascade rule). Formula magistralis preparations are prepared by pharmacies according to individual prescriptions. For companion animals, they often contained metronidazole.

6.8 Discussion

This report presents only some of the results of the first analyses of IS ABV. Many new challenges were faced for this first data analysis, especially data quality and consistency. As the report presents only the antibiotic consumption data of the year 2020, no trends or tendency could be analyzed. In the next years, trends will become visible, thus presenting a more detailed, precise and accurate understanding of the consumption dynamics of antibiotics in Switzerland. IS ABV is a comprehensive database of all Swiss antibiotic consumption for animal health. The efforts made and the administrative burden taken on by veterinarians and farmers to provide quality data were essential for the completion of the data. Data quality is already improving thanks to the commitment of all actors and the implemented feedback for outlier identification.

Among all animals, by far the largest amount of active substances administered were so-called first-line antibiotics. This shows that they are indeed used first, in line with good prescribing practice in Switzerland.

The total amount of active ingredient per antibiotic class was previously the only key figure available. Now, for the first time, it can be shown how much active ingredient was prescribed for which livestock category. However, the informative value of this indicator is limited, as heavy animals require larger amounts of active ingredient than light animals. In addition, there are considerable differences in the weight of the active substances; much smaller quantities are needed for a treatment with modern antibiotics than with older antibiotics.

The number of animal treatments is an important indicator, as it provides a good overview of how many treatments with antibiotics have taken place in a livestock category. In future analyses, this indicator will be of central importance, especially if it is set in relation to population size.

References

[1] Federal Food Safety and Veterinary Office (FSVO) Erste Übersicht der Verschreibungen von Antibiotika bei Nutztieren in der Schweiz 2020, 2022.

[2] Federal Food Safety and Veterinary Office (FSVO) Bericht über Verbrauch von Antibiotika bei Heimtieren, 2022.

Textbox

Antimicrobial usage in Swiss fattening pig farms: Is there still potential for improvement?

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Antimicrobial resistance (AMR) represents a major global health problem [1]. Farm level monitoring systems have been emerging in several countries [2]. Such monitoring systems provide detailed antimicrobial usage (AMU) data that can be used to detect inappropriate usage and to identify underlying risk factors for high usage and emergence of AMR. In Switzerland, the SuisSano/Safety+ monitoring system was launched in 2015 by SUISAG, a large breeding, marketing and animal health organization. The system is run in cooperation with the veterinary authorities, pig trading companies and retailers. This AMU monitoring system is coupled with the health programs of the Swiss Pig Health Services of SUISAG and Qualiporc. One of the main objectives of the program is to foster prudent use of antimicrobials and to increase transparency. The number of farms participating in this program is steadily increasing, with more than 80% of all Swiss pig farms already taking part at the end of 2020 (SUISAG, personal communication). A recent study conducted in 291 participating farms showed a significant reduction in the usage of antimicrobials in fattening pigs on high-usage farms between 2016 and 2017 [3].

The aim of the study was to analyze AMU in fattening pig farms that took part in the SuisSano/Safety+ health program in Switzerland in the year 2020, and to discuss the potential for further improvement. Usage was examined according to the antimicrobial's class and indication for use, with emphasis on highest priority critically important antimicrobials (HPCIAs).

Data on AMU from 1,411 farms, reported in an electronic treatment journal, was used. AMU was quantified through treatment incidence (TI), based on Swiss Defined Daily Doses (DDDch). Indication of use for each antimicrobial class was analyzed with particular focus on HPCIAs.

The total TI of all antimicrobials used in the farms corresponds to 8.9 DDDch per 1,000 pig-days at risk, of which HPCIAs represented 2.6%. A total of 140 farms (9.9%) partakes in HPCIAs usage, with tylosin (73.8% of total HPCIA TI) and colistin (22.7% of total HPCIA TI) being the most frequently used antimicrobials. The most common indication for treatment with HPCIAs was gastrointestinal disorders (62.1% of total HPCIA TI).

This study shows that the efforts made in recent years to foster prudent use of antimicrobials, and especially HPCIAs in Swiss pig production, have been successful. Indeed, 90.1% (1,271 out of 1,411) of the farms did not use any HPCIAs over the year 2020. Of the recorded treatments, HPCIAs represented only 2.6% of the total TIs used in fattening pigs. Since many farms do not use any HPCIAs, knowledge can be gained from these farms to identify practices which can further reduce or even stop HPCIA usage. Moreover, information concerning indications for HPCIA usage provide input concerning where treatment options other than HPCIAs should be explored by both farmers and veterinarians.

References

[1] Aarestrup FM, Oliver Duran C, Burch DG. Antimicrobial resistance in swine production. Anim Health Res Rev. 2008;9(2):135–48.

[2] Sanders P, Vanderhaeghen W, Fertner M et al. Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes. Front Vet Sci 2020; 7: 540.

[3] Echtermann T, Müntener C, Sidler X et al. Impact of the SuisSano Health Program on antimicrobial usage on 291 pig farms in Switzerland. Vet Rec Open 2020; 7: e000389. doi:10.1136/ vetreco-2019-000389.

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 2021, resistance was still very low for fosfomycin and nitrofurantoin, the first-line antibiotics recommended for the therapy of cystitis (Table 7. a). However, resistance to fosfomycin increased slightly but significantly from 0.2% in 2012 to 1.5% in 2021 (Figure 7. b). Trimethoprim-sulfamethoxazole still remains a first-line option in lower urinary tract infections [https://ssi.guidelines.ch/]. Its resistance rate decreased significantly from 29% in 2012 to 25.4 % in 2021. Because *E. coli* is one of the most important pathogens in the outpatient setting as well, resistance rates of outpatient urinary samples are compared with invasive samples (Figure 7. a). These data not only demonstrate significantly lower resistance rates in urinary samples for trimethoprim-sulfamethoxazole (19.5% in 2021), but for most of the antibiotics tested. Since resistance testing is usually not performed for uncomplicated lower urinary tract infections, ANRESIS data still overestimate the resistance rates. 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 preserve their efficacy for invasive infections. Fluoroquinolone resistance has steadily increased from 10.3% in 2004 to 19.4% in 2015 but has since then slightly decreased to 16.6% in 2021. Although this observation could at least partly be explained by the integration of resistance data from newer, smaller laboratories within ANRESIS (which tend to have

Table 7. a: Resistance rates of invasive *Escherichia coli* isolates in humans in 2021.

***Escherichia coli* (invasive)**											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	1,098	52.1	4,075	45.3	487	43.7	5,660	46.4	45.7–47.1	↓	↓
Amoxicillin-clavulanic acid	1,091	33.5	4,423	24.8	487	21.4	6,001	26.1	25.5–26.7	↑	↑
Piperacillin-tazobactam	1,247	9.1	4,261	6.6	487	3.3	5,995	6.9	6.6–7.2	↑	↑
Cephalosporin 2nd gen.	560	16.2	3,320	11.9	419	10.5	4,299	12.4	11.9–12.9	↓	↑
Cephalosporin 3rd/4th gen.	1,305	13.4	4,458	9.6	487	8.2	6,250	10.3	9.9–10.7	–	↑
Carbapenems[1]	1,217	0	4,330	0.1	487	0	6,034	0	0.0–0.0	–	–
Aminoglycosides	1,129	13.1	4,314	8.3	487	7.2	5,930	9.1	8.7–9.5	–	↑
Trimethoprim-sulfamethoxazole	1,303	28.5	4,095	25.1	487	19.9	5,885	25.4	24.8–26.0	↓	↓
Fluoroquinolones[2]	1,302	21	4,448	15.6	486	13.8	6,236	16.6	16.1–17.1	↓	↓
Nitrofurantoin	474	0.8	911	0.4	1	0	1,386	0.6	0.4–0.8	↓	↓
Fosfomycin	479	2.5	1,539	1.2	1	0	2,019	1.5	1.2–1.8	–	↑

[1] Carbapenems: imipenem, meropenem

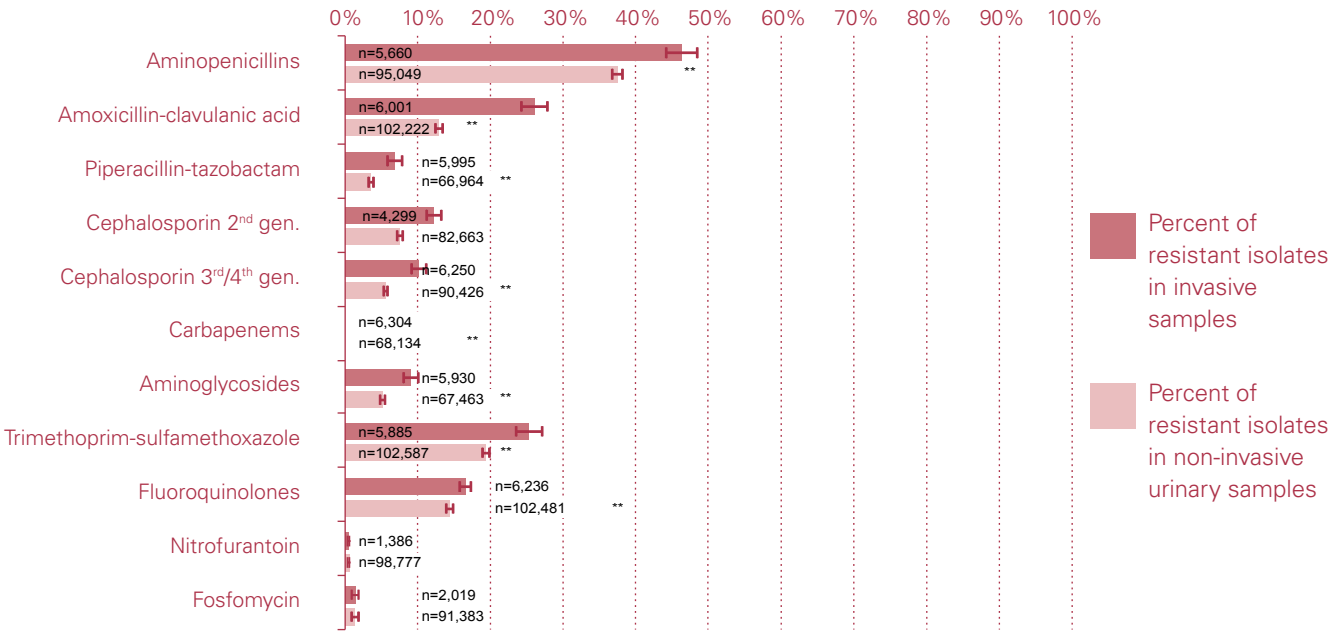
[2] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

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 modeled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the corresponding outcome (increase, decrease).

lower resistance rates), this trend seems to be real, as in EU/EEA states a similar slight, but significant decrease from 26.4% in 2016 to 23.8% in 2020 has been observed [2].

As for quinolones, resistance rates to third-/fourth-generation cephalosporins have steadily increased from 0.9% in 2004 to 11% in 2018, and have stabilized since then (10.3% in 2021). A slight but significant decrease from 15.7% to 14.9% was observed between 2016 and 2020 in EU/EEA states [2]. However, large differences between countries located in Europe and nearby geographical areas were observed, i. e., only 10 out of 40 countries (including Switzerland) reported resistance rates for third-/fourth-generation cephalosporins below 10% in 2020, whereas rates above 50% were observed in 5 eastern countries (Belarus, North Macedonia, Russian Federation, Turkey, Ukraine) [2].

Figure 7. a: Comparison of resistance rates in invasive versus outpatient urinary samples in *Escherichia coli* isolates in humans for 2021.



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: Resistance rates in invasive *Escherichia coli* isolates in humans between 2012 and 2021.

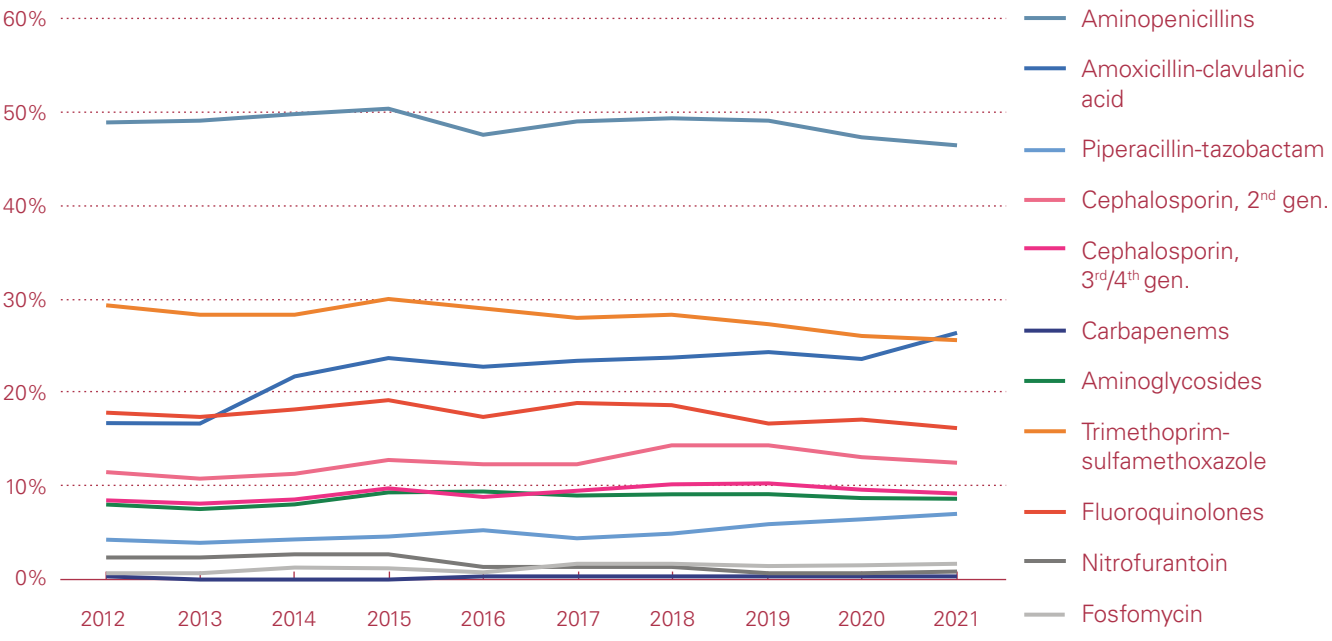


Table 7. b: Resistance combinations in invasive *E. coli* isolates in humans 2021. Only isolates tested against all five antibiotic groups (aminopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n = 5098/6226 [81.9%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**2,550**	**49.6%**
Resistance to one antimicrobial group	**1,592**	**31.0%**
Fluroquinolones	144	2.8%
Third-generation cephalosporins	4	0.1%
Aminopenicillins	1,423	27.7%
Aminoglycoside	21	0.4%
Resistance to two antimicrobial groups	**528**	**10.3%**
Aminopenicillins + fluoroquinolones	235	4.6%
Aminopenicillins + third-generation cephalosporins	141	2.7%
Aminoglycoside + fluoroquinolones	15	0.3%
Aminopenicillins + aminoglycosides	137	2.7%
Resistance to three antimicrobial groups	**304**	**5.9%**
Aminopenicillins + third-generation cephalosporins + fluoroquinolones	215	4.2%
Aminopenicillins + third-generation cephalosporins + carbapenems	1	0.0%
Aminoglycoside + fluoroquinolon + third-generation cephalosporins	1	0.0%
Aminopenicillins + fluoroquinolones + aminoglycosides	87	1.7%
Aminopenicillins + third-generation cephalosporins + aminoglycosides	41	0.8%
Resistance to four antimicrobial groups	**123**	**2.4%**
Aminopenicillins + third-generation cephalosporins + aminoglycosides + fluoroquinolones	123	2.4%
Resistance to all five antimicrobial groups	**1**	**0.0%**
Aminopenicillins + third-generation cephalosporins + aminoglycosides + fluoroquinolones + carbapenems	1	0.0%

Significant increases in resistances to aminoglycosides from 7.9% to 9.1%, to amoxicillin-clavulanic acid from 16.6% to 26.1% and to piperacillin-tazobactam from 4.1% (and even 1% in 2004) to 6.9% were observed during the last ten years in Switzerland. For all antibiotics tested (except carbapenems), resistance rates were highest in the western part of Switzerland, and lowest in Ticino (Table 7 a.). Multiresistance was frequent. 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 (less than 0.1%) and comparable to the EU/EEA population weighted means (0.2% in 2020) [2]. While there was no significant trend in Switzerland, a slight but significant increase from 0.1% to 0.2% between 2016 and 2020 was observed in EU/EEA states, and increasing rates of carbapenemase-producing Enterobacterales (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 therefore introduced an obligation to report CPE in January 2016, and since 2019 all strains are collected by the National Reference Centre for Emerging Antibiotic Resistance in Fribourg (NARA, www.nara-antibiotic-resistance.ch). A detailed analysis of Swiss CPE data from 2013 to 2018 has been published in Eurosurveillance [3], and updated data are displayed regularly on the ANRESIS homepage.

In future, colistin, a rather toxic reserve antibiotic belonging to the polymyxin group, might become more important as a "last resort antibiotic" for the treatment of infections due to carbapenemase producers. Currently, colistin resistance is rare in Switzerland, but reports from China, describing a mobile plasmid encoding a colistin resistance gene (mcr types), are worrisome [4]. Some small surveys performed in Switzerland showed very rare spread of mcr producers among human isolates [5/6]. 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, affecting patients with an impaired immune system. The most common sites of infection are the urinary tract and the lung

Figure 7. c: Multiresistance in invasive *E. coli* isolates in humans between 2012 and 2021 (for details refer to Table 7. b).

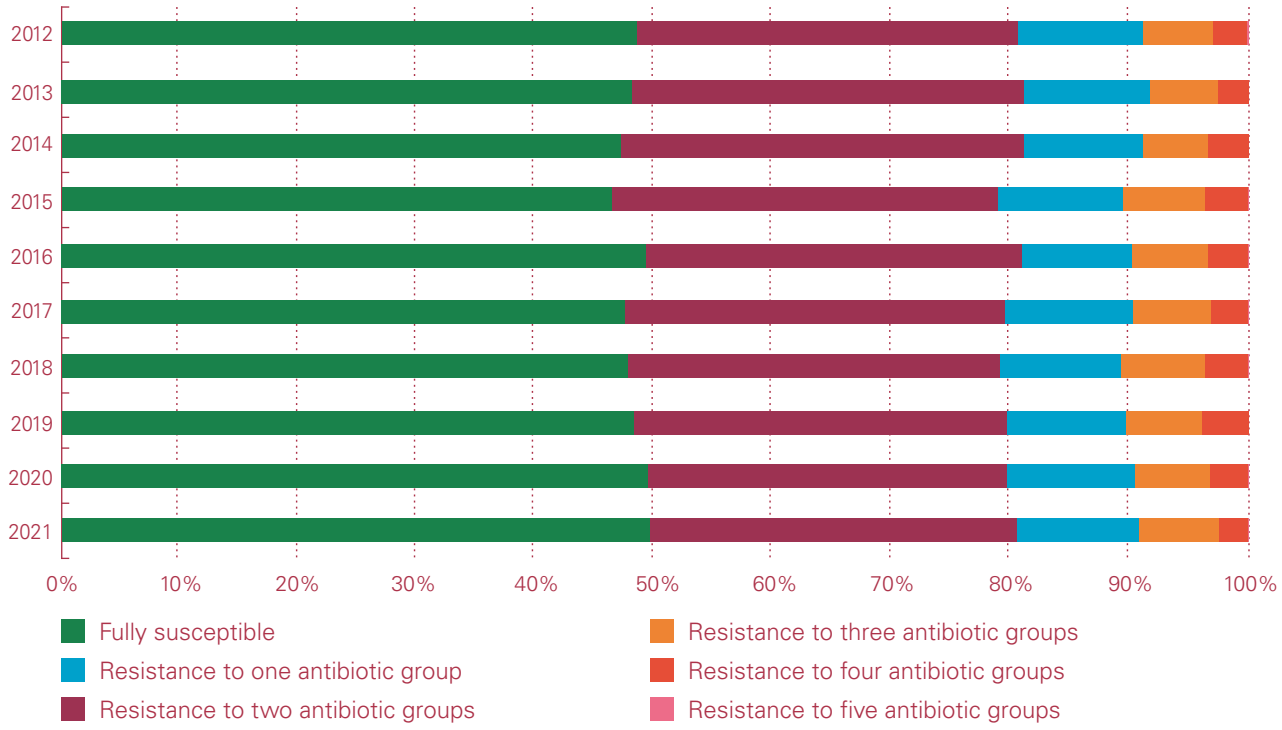


Table 7. c: Resistance rates of invasive *Klebsiella pneumoniae* isolates in humans in 2021.

Klebsiella pneumoniae											**2021**
Antimicrobial	**West**		**North–East**		**South**		**Total**			**Trend**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Amoxicillin-clavulanic acid	292	17.5	1,003	10.3	76	13.2	1,371	12	11.1–12.9	–	–
Piperacillin-tazobactam	347	14.4	964	8.5	76	6.6	1,387	9.9	9.1–10.7	↑	↑
Cephalosporin 2nd gen.	154	11	741	9.4	69	11.6	964	9.9	8.9–10.9	↓	–
Cephalosporin 3rd/4th gen.	362	8.8	1,013	7.2	76	7.9	1,451	7.6	6.9–8.3	–	–
Carbapenems[1]	334	0.9	988	0.6	76	2.6	1,398	0.8	0.6–1.0	–	–
Aminoglycosides	313	7	982	4.9	76	2.6	1,371	5.3	4.7–5.9	–	–
Trimethoprim-sulfamethoxazole	362	12.4	943	12.9	76	14.5	1,381	12.9	12.0–13.8	–	↓
Fluoroquinolones[2]	361	11.6	1,013	9	75	4	1,449	9.4	8.6–10.2	–	↑

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

(pneumonia). In contrast to *E. coli*, they are intrinsically resistant to aminopenicillins.

In this report, we present the data on *K. pneumoniae*, which is the most frequent species of the genus *Klebsiella* isolated from human clinical isolates. As species identification is more and more frequently performed by MALDI-TOF since 2017, a growing number of laboratories report *K. variicola* separately from *K. pneumoniae*. In a study from ANRESIS it was shown that *K. variicola* tend to be less resistant than *K. pneumoniae* [7]. However, with regard to homogenization and comparability with international data, other *K. pneumoniae* complex species such as *K. quasipneumoniae* and *K. variicola* are included in the present report. As in *E. coli*, increasing resistance to third-/fourth-generation cephalosporins was a main issue between 2004 (1%) and 2014 (9.2%). However, during the last ten years, the resistance rate has remained stable or has even decreased slightly (but

Figure 7. d: Resistance rates in invasive *Klebsiella pneumoniae* isolates in humans from 2012 to 2021.

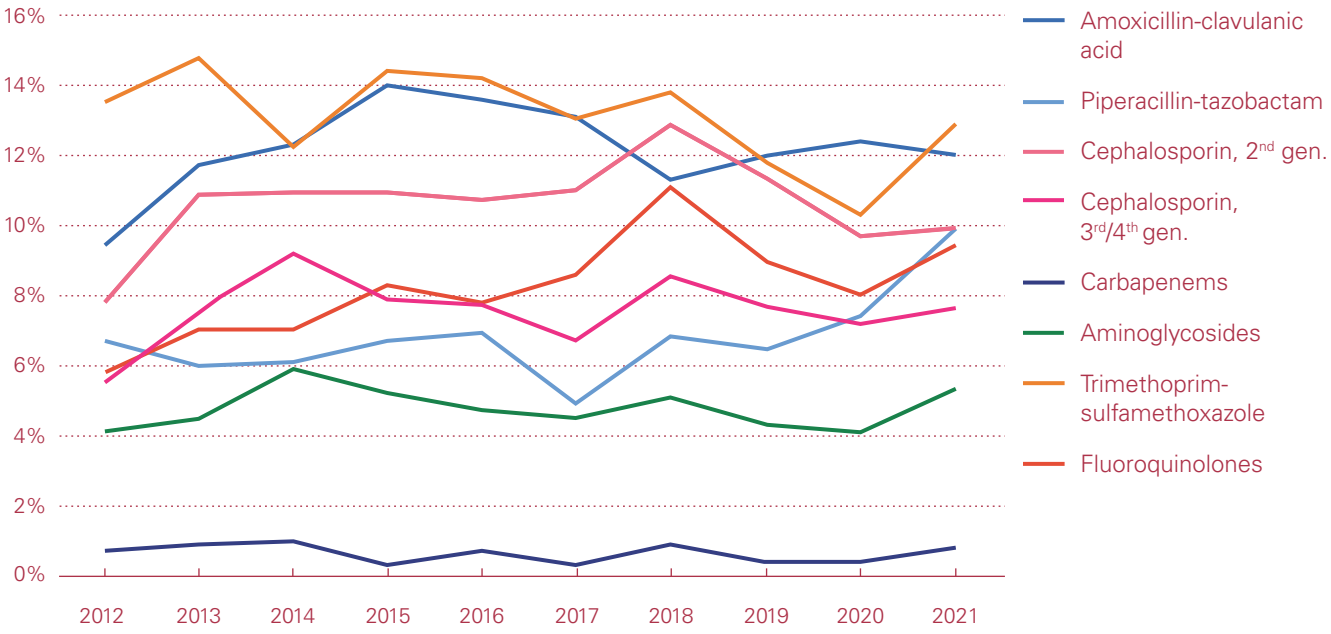


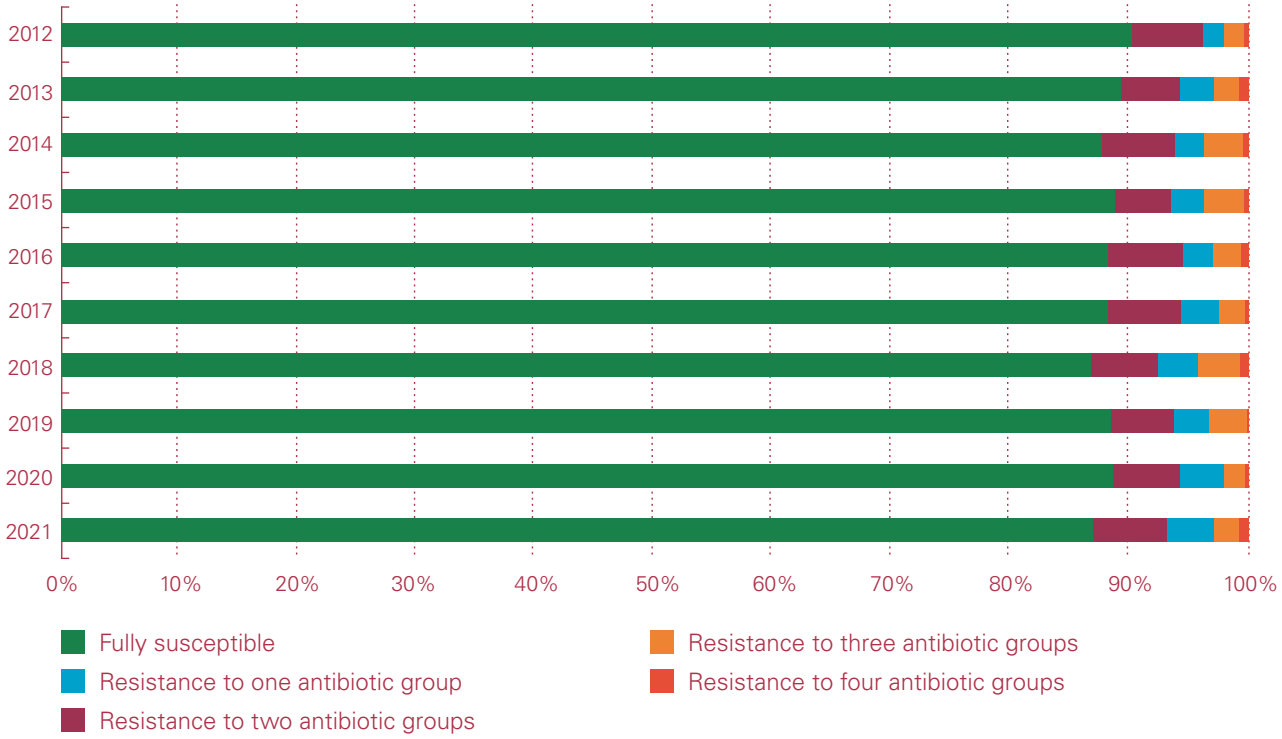
Table 7. d: Resistance combinations in invasive *K. pneumoniae* isolates in humans in 2021. Only isolates tested against all four antibiotic groups (third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n = 1320/1444 [91.4%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**1,149**	**87.0%**
Resistance to one antimicrobial group	**82**	**6.2%**
Fluroquinolones	51	3.9%
Third-generation cephalosporins	24	1.8%
Aminoglycoside	7	0.5%
Resistance to two antimicrobial groups	**53**	**4.0%**
Third-generation cephalosporins + fluoroquinolones	29	2.2%
Carbapenems + third-generation cephalosporins	1	0.1%
Aminoglycoside + fluoroquinolones	11	0.8%
Aminoglycoside + third-generation cephalosporins	12	0.9%
Resistance to three antimicrobial groups	**26**	**2.0%**
Carbapenems + third-generation cephalosporins + fluoroquinolones	26	2.0%
Resistance to all four antimicrobial groups	**10**	**0.8%**
Aminoglycoside + carbapenems + third-generation cephalosporins + fluoroquinolones	10	0.8%

not significantly) to 7.6% in 2021 (Table 7. c, Figure 7. d), which compares favorably with the EU/EEA average of 33.9% in 2020. A stabilization of resistance rates was also observed in EU/EEA states between 2016 and 2020 [2]. Very similar trends were observed for amoxicillin-clavulanic acid, aminoglycosides and trimethoprim-sulfamethoxazole, with maximal resistance rates in 2014/2015. In contrast, for piperacillin-tazobactam and quinolones, significantly increasing resistance rates were observed during the last ten years, i. e., from 6.6% to 9.9% and 5.8% to 9.4%, respectively. 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, which further increased significantly from 8.4% in 2016 to 10% in 2020.

As for *E. coli*, considerable differences were observed between different Swiss regions (Table 7. c), with higher resistance rates to third-/fourth-generation cephalosporins in western and southern Switzerland and a relatively high resistance rate of 2.6% to carbapenems in southern Switzerland,

Figure 7. e: Multiresistance in invasive *K. pneumoniae* isolates in humans from 2012–2021 (for details refer to Table 7. d).



7.3 Pseudomonas aeruginosa

mirroring higher carbapenem resistance rates in Italy (29.5% in 2020) than in France and Germany (0.5% each in 2020). Several *K. pneumoniae* isolates that produce a carbapenemase and coproduce a 16S rRNA methylase conferring pandrug resistance to all aminoglycosides and/or that are resistant to colistin have been reported throughout Switzerland. Their identification raises the spectrum of truly pandrug resistant *K. pneumoniae* [8]. Pansusceptibility decreased from 90.2% in 2012 to 87% in 2021. Details on coresistances are depicted in Table 7. d and Figure 7. e.

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.

Table 7. e: Resistance rates of invasive *Pseudomonas aeruginosa* isolates in humans in 2021.

Pseudomonas aeruginosa											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Piperacillin-tazobactam	142	12.7	464	10.3	33	12.1	639	11	9.8–12.2	–	–
Ceftazidime	140	12.1	466	8.2	33	12.1	639	9.2	8.1–10.3	–	–
Cefepime	143	10.5	474	7.8	33	9.1	650	8.5	7.4–9.6	–	↑
Carbapenems[1]	140	15.7	474	8.6	33	12.1	647	10.4	9.2–11.6	–	–
Aminoglycosides	142	7	486	17.3	33	0	661	14.2	12.8–15.6	↑	↑
Ciprofloxacin	144	10.4	482	6.8	33	0	659	7.3	6.3–8.3	–	–

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

Figure 7. f: Resistance rates of invasive *Pseudomonas aeruginosa* isolates in humans from 2012 to 2021.

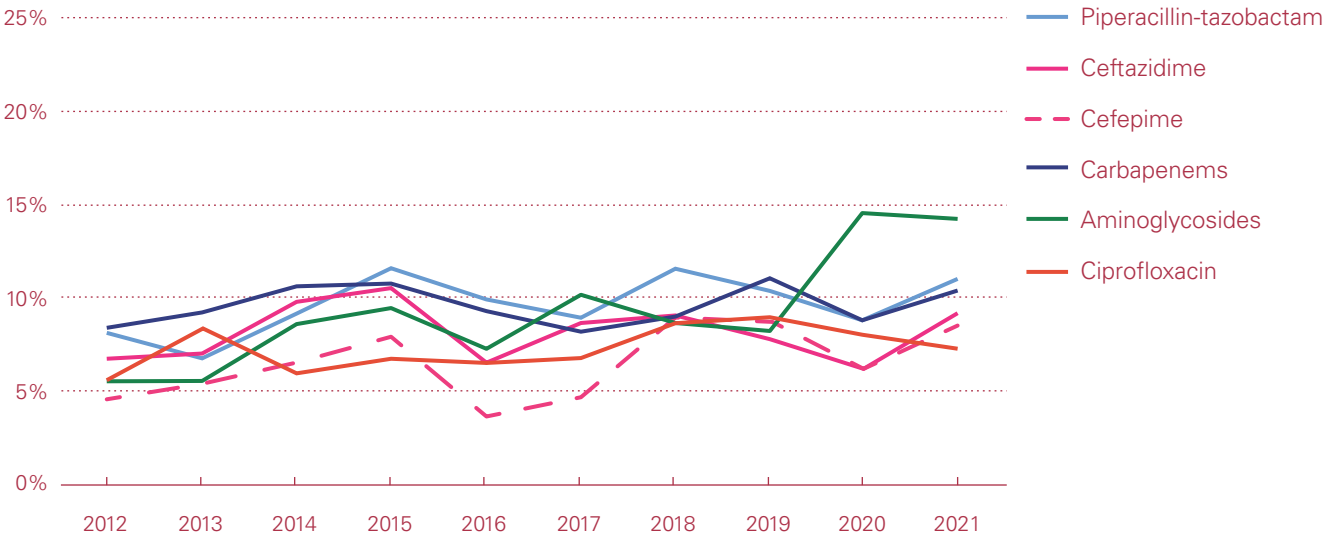
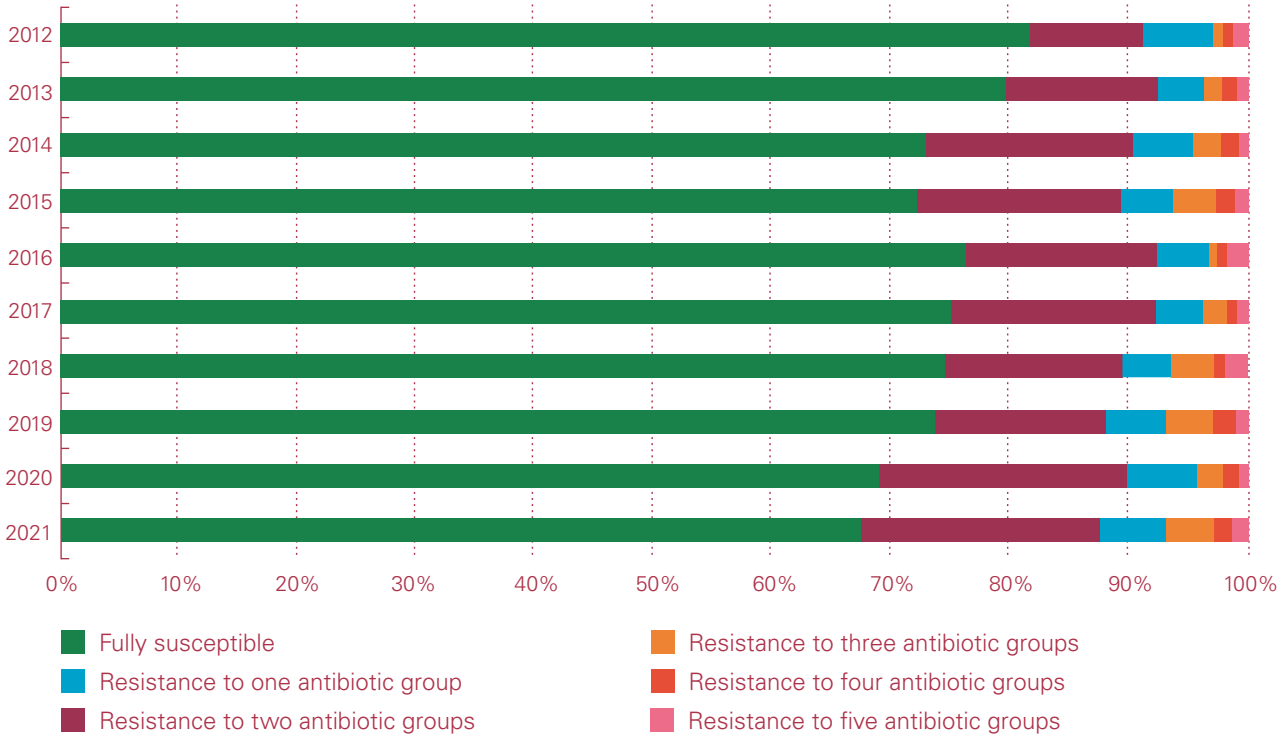


Table 7. f: Resistance combinations in invasive *P. aeruginosa* isolates in humans in 2021. Only isolates tested against all five antibiotics or antibiotic groups (piperacillin-tazobactam, cefepime, carbapenems, aminoglycosides, ciprofloxacin) were considered (n = 595/670 [88.8%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**410**	**68.9%**
Resistance to one antimicrobial group	**113**	**19.0%**
Piperacillin-tazobactam	11	1.8%
Ciprofloxacin	13	2.2%
Cefepime	1	0.2%
Carbapenems	26	4.4%
Aminoglycoside	62	10.4%
Resistance to two antimicrobial groups	**32**	**5.4%**
Piperacillin-tazobactam + ciprofloxacin	1	0.2%
Cefepime + piperacillin-tazobactam	16	2.7%
Cefepime + ciprofloxacin	1	0.2%
Carbapenems + piperacillin-tazobactam	3	0.5%
Carbapenems + ciprofloxacin	6	1.0%
Aminoglycosides + ciprofloxacin	4	0.7%
Aminoglycosides + carbapenems	1	0.2%
Resistance to three antimicrobial groups	**23**	**3.9%**
Cefepime + piperacillin-tazobactam + ciprofloxacin	4	0.7%
Cefepime + carbapenems + piperacillin-tazobactam	9	1.5%
Aminoglycosides + piperacillin-tazobactam + ciprofloxacin	1	0.2%
Aminoglycosides + cefepime + piperacillin-tazobactam	3	0.5%
Aminoglycosides + cefepime + ciprofloxacin	3	0.5%
Aminoglycosides + carbapenems + piperacillin-tazobactam	1	0.2%
Aminoglycosides + carbapenems + ciprofloxacin	2	0.3%
Resistance to four antimicrobial groups	**9**	**1.5%**
Cefepime + carbapenems + piperacillin-tazobactam + ciprofloxacin	3	0.5%
Aminoglycosides + cefepime + carbapenems + piperacillin-tazobactam	6	1.0%
Resistance to all five antimicrobial groups	**8**	**1.3%**
Aminoglycosides + cefepime + carbapenems + piperacillin-tazobactam + ciprofloxacin	8	1.3%

Figure 7. g: Multiresistance in invasive *Pseudomonas aeruginosa* isolates in humans between 2012 and 2021 (for details refer to Table 7. f).



P. aeruginosa is intrinsically resistant to amoxicillin, amoxicillin-clavulanic acid, first- and second-generation cephalosporins, cefixime, cefpodoxime, ceftriaxone, ertapenem, trimethoprim-sulfamethoxazole as well as tetracyclines, including tigecycline. Quinolones are among the rare orally given antibiotics which retain activity against *P. aeruginosa*. In Switzerland, in 2021, resistance rates were highest for aminoglycosides (14.2%), followed by piperacillin-tazobactam and carbapenems (between 10 and 11%), ceftazidime and cefepime (around 9%) and ciprofloxacin (7.3%). Swiss regional data are shown in Table 7. e, data on coresistance in Table 7. f and Figure 7. g.

Resistance rates to all antibiotics have trended upwards over the past ten years. In particular, significant increases for cefepime (from 4.6% to 8.5%) and aminoglycosides (from 5.6% to 14.2%) have led to a decrease in pansusceptible isolates from 82.2 to 68.4% (Figure 7. g). Decreasing resistance trends between 2016 and 2020 were observed in the EU/EEA for aminoglycosides, fluoroquinolones and carbapenems, while resistance to ceftazidime and piperacillin-tazobactam remained stable during this period [2].

Table 7. g: Resistance rates of invasive *Acinetobacter* spp. isolates in humans in 2021.

Acinetobacter spp.											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Carbapenems[1]	27	7.4	70	11.4	6	16.7	103	10.7	7.7–13.7	↑	–
Aminoglycosides	27	14.8	69	13	6	16.7	102	13.7	10.3–17.1	–	–
Trimethoprim-sulfamethoxazole	27	7.4	63	11.1	5	0	95	9.5	6.5–12.5	–	↓
Ciprofloxacin	26	7.7	64	15.6	6	16.7	96	13.5	10.0–17.0	↑	–

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

Figure 7. h: Resistance rates of invasive *Acinetobacter* spp. isolates in humans between 2012 and 2021.

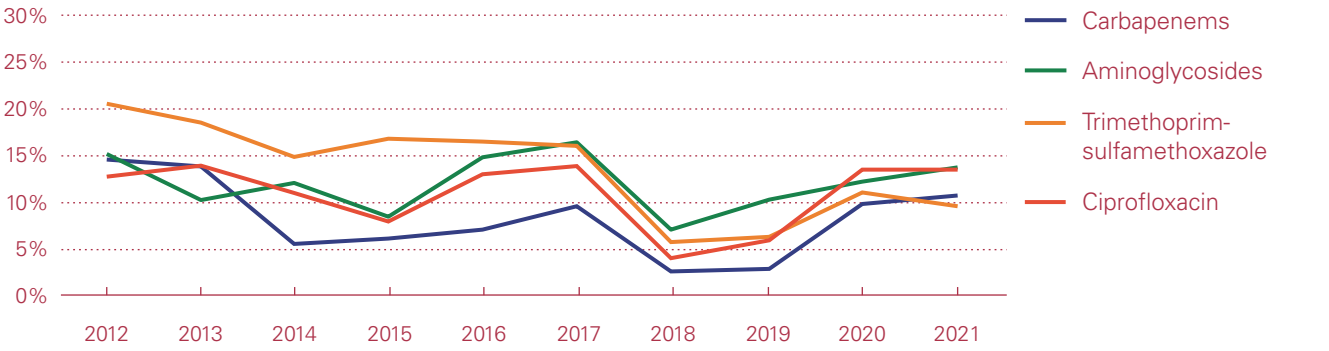
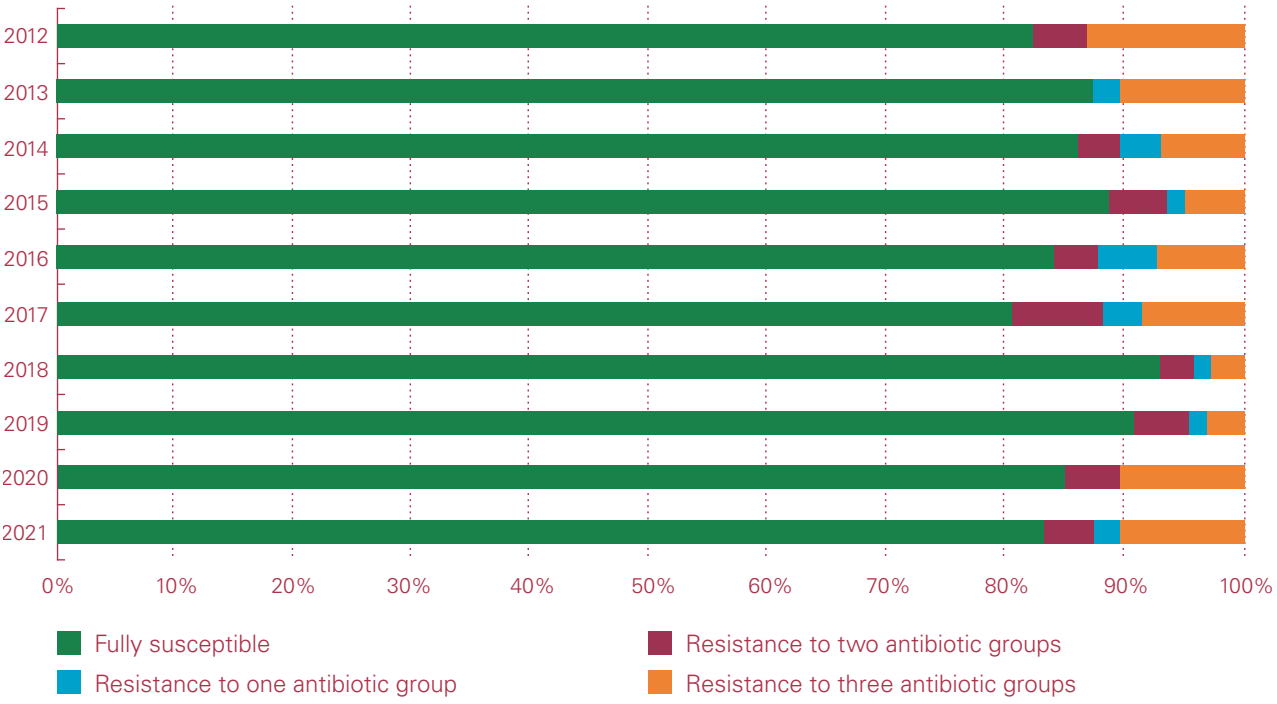


Table 7. h: Resistance combinations in invasive *Acinetobacter* spp. isolates in humans in 2021. Only isolates tested against all three antibiotic groups (aminoglycosides, ciprofloxacin and carbapenems) were considered (n = 95/103 [92.2 %]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**79**	**83.2%**
Resistance to one antimicrobial group	**4**	**4.2%**
Ciprofloxacin	2	2.1%
Aminoglycoside	2	2.1%
Resistance to two antimicrobial groups	**2**	**2.1%**
Aminoglycoside + ciprofloxacin	1	1.1%
Aminoglycoside + carbapenems	1	1.1%
Resistance to all three antimicrobial groups	**10**	**10.5%**
Aminoglycoside + carbapenems + ciprofloxacin	10	10.5%

Figure 7. i: Multiresistance in invasive *Acinetobacter* spp. isolates in humans between 2012 and 2021 (for details refer to Table 7.h).



7.4 *Acinetobacter* spp.

Acinetobacter spp. are Gram-negative, strictly aerobic coccobacilli. These opportunistic pathogens have an increased capacity to survive for longer periods in the hospital environment, can be found in soil and water too, and 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 a correct identification on the species level is difficult, hereinafter only resistance trends on the genus level, in accordance with the European resistance networks EARS-Net and CAESAR, are analyzed.

Acinetobacter spp. infections are an important concern regarding hospital-acquired infections in immunocompromised patients. They can cause respiratory, urinary and wound infections, and septicemia. Meningitis has been reported as well. Risk factors for multidrug-resistant *Acinetobacter* spp. are severe underlying diseases and prolonged hospital stays, especially in ICUs during antibiotic administration and/or mechanical ventilation.

In general, resistance rates between 9.5% and 13.7% were observed for all antibiotics analyzed (Table 7. g) in 2021, pan-susceptibility was noted in 83.2% of the isolates (Table 7. h). Interestingly resistance rates were lower in 2018 and 2019, but increased again in 2020 and 2021 to the levels of earlier years (Figure 7. h). Over the last ten years, resistance rates were relatively stable, with the exception of a significant decrease in trimethoprim-sulfamethoxazole resistance from 20.5% in 2012 to 9.5% in 2021 (Table 7. g). With the exception of aminoglycosides, resistance rates were lower in the western part of Switzerland than in the northeastern part. Resistance rates in Switzerland were much lower than the EU/EEA population weighted means in 2020 (carbapenems 38%, fluoroquinolones 41.8%, aminoglycosides 37.1%) [2]. A detailed analysis on carbapenem resistances performed by ANRESIS showed stable resistance rates from 2005 to 2016 [9].

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 Centre for invasive *S. pneumoniae*, located at the Institute for Infectious Diseases of the University of Bern. Serotyping (i. e., to survey the impact of vaccinations on the serotype distribution) and antibacterial resistance testing are performed for all isolates. Results of the latter are then sent to ANRESIS. However, only data delivered by the primary laboratories are analyzed in this report. They may differ slightly from the data of the National Reference Centre for invasive *S. pneumoniae*. Penicillin-susceptible isolates (PSSP) were considered ceftriaxone-susceptible, even if not tested.

Table 7. i: Resistance rates of invasive *Streptococcus pneumoniae* isolates in humans in 2021.

Streptococcus pneumoniae											2021
	West		North–East		South		Total			Trend	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Penicillin	70	7.1	383	3.7	22	4.5	475	4.2	3.3–5.1	–	–
Ceftriaxone	70	0	383	0	22	0	475	0	0.0–0.0	–	–
Trimethoprim-sulfamethoxazole	56	3.6	186	4.3	22	0	264	3.8	2.6–5.0	–	↓
Erythromycin	74	10.8	262	5	22	4.5	358	6.1	4.8–7.4	↓	↓
Levofloxacin	72	2.8	226	0	22	0	320	0.6	0.2–1.0	–	↓

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 modeled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the corresponding outcome (increase, decrease).

Figure 7. j: Resistance rates in invasive PSSP (penicillin-susceptible isolates) and PNSP (penicillin non-susceptible isolates) in humans in 2021.

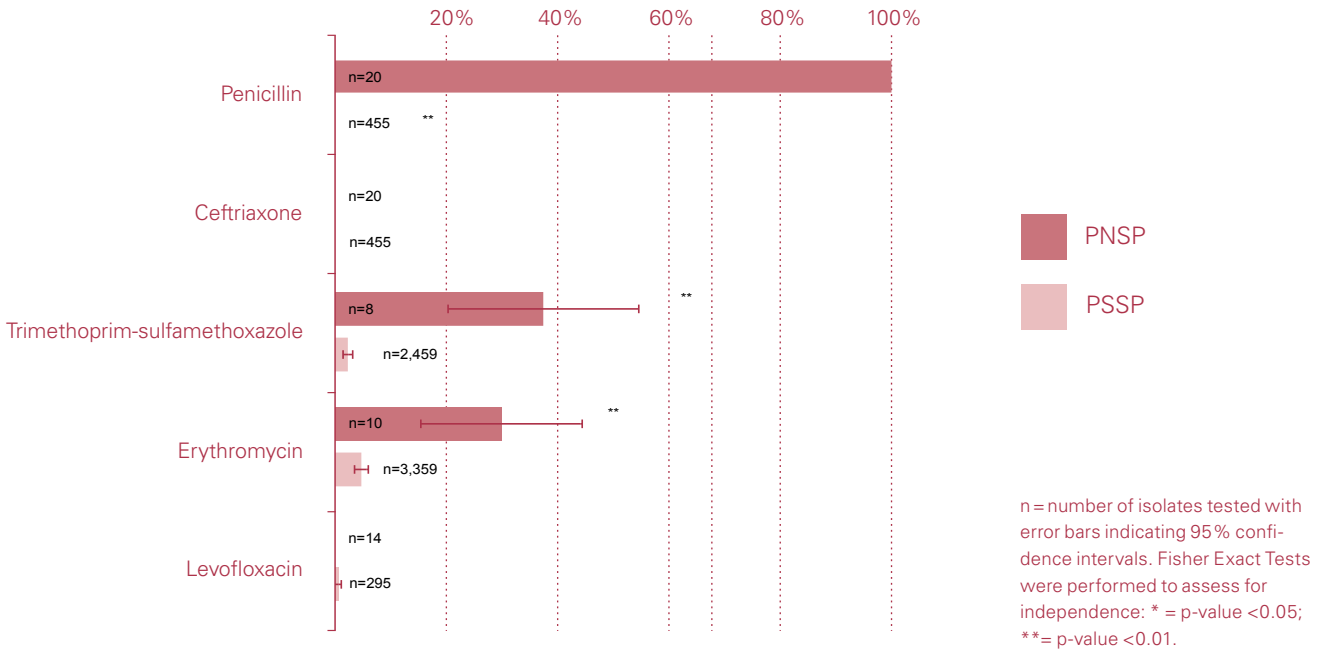
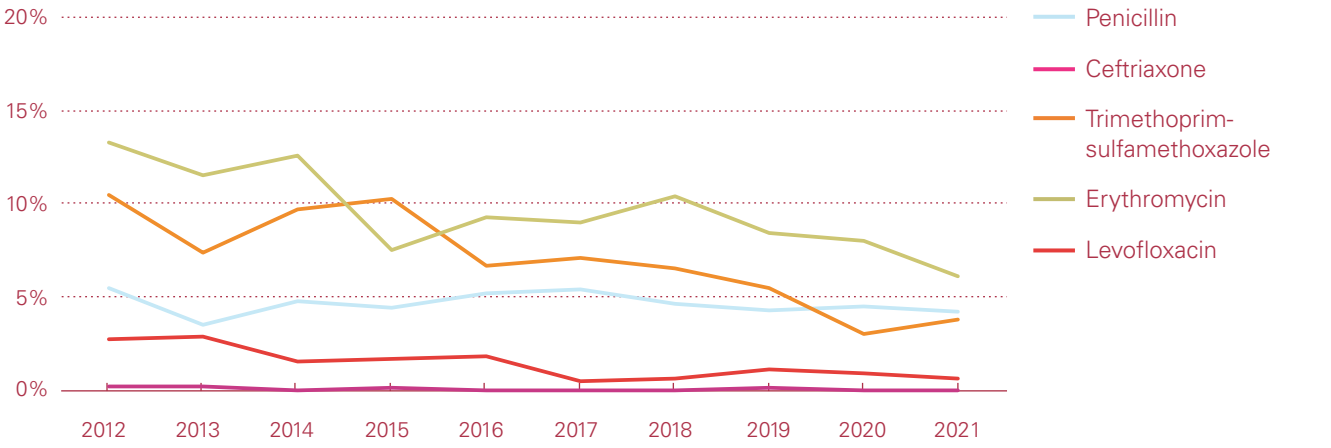


Figure 7. k: Resistance rates of invasive *Streptococcus pneumoniae* isolates in humans between 2012 and 2021.



In 2021, 4.2% of all isolates were penicillin-resistant (PNSP), (Table 7. i). The average resistance rate for EU/EEA countries in 2020 was 15.6%. PNSP rates in individual EU/EEA countries ranged between 3.9% and 56.3% in 2020 [2]. However, an exact comparison with other countries is difficult, as different breakpoints were used.

Nevertheless, resistance rates essentially seem to be higher in France (32.3%) than in Italy (13.4%) and Germany (6.1%) [2]. These differences were mirrored within Switzerland, with slightly higher PNSP rates in the French-speaking part as well (Table 7. i). Ceftriaxone resistance was below 1%. At 6.1%, the erythromycin resistance rate was slightly higher than the penicillin resistance rate, again with higher resistance rates in the western part of Switzerland. Resistance against levofloxacin was 0.6% in Switzerland in 2021. As shown in Figure 7. j, resistance rates were significantly higher in PNSPs than in PSSPs for trimethoprim-sulfamethoxazole and erythromycin.

Over the last ten years, significant decreases in antibiotic resistance in *S. pneumoniae* were observed for trimethoprim-sulfamethoxazole, erythromycin and levofloxacin (Table 7. i, Figure 7. k). This may at least in part be attributed to a vaccine-related decrease of the intrinsically more resistant serotypes [10].

7.6 Enterococci

Enterococci belong to the normal gastrointestinal flora of humans and animals. As such, they are often considered 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 critical ill patients and immunocompromised hosts. The vast majority of enterococcal infections are caused by *Enterococcus faecalis* and *E. faecium*.

While *E. faecalis* isolates remain susceptible to most antibiotics, including aminopenicillins, *E. faecium* isolates, mainly detected in the nosocomial setting, are usually resistant to aminopenicillins. In addition, *E. faecium* shows higher resistance rates to aminoglycosides than *E. faecalis* (Table 7. j). Aminoglycoside resistance is still fairly low compared to the EU/EEA population weighed average (e.g., a gentamicin high-level resistance, HLR, in *E. faecalis* of 10.8% in Switzerland versus 29% in the EU/EEA in 2020) and has slightly, but significantly, decreased during the last ten years. A decrease in gentamicin HLR in *E. faecalis* from 31.8% in 2016 to 29% in 2020 was observed on average in EU/EEA countries as well [2].

In contrast to the United States, vancomycin resistance in *E. faecium* was still rare in Switzerland (2.9% in 2020) and far below the EU/ EEA average of 16.8% in 2020 [2]. However, large geographical differences exist within EU/EEA states. Importantly, a significant increase in vancomycin resistant *E. faecium* was noted in Switzerland during the last ten years, due to a regional/national outbreak associated with the spread of the clone ST769 [11, 12]. Typical nosocomial strains currently observed include ST80 and ST117. Surveillance of vancomycin-resistant enterococci (VRE) is crucial since very few antibiotics remain active, and these are commonly associated with much higher toxicity than penicillin. Current cantonal data on VRE are updated monthly on the ANRESIS homepage.

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. As observed in many European countries [13], *S. aureus* bacteremias are also increasing in Switzerland. In a recent study by ANRESIS, an increase from 1,240 cases in 2011 to 2,260 cases in 2021 (+83%), mainly due to methicillin-susceptible *S. aureus* (MSSA), was reported [14]. However, methicillin-resistant *S. aureus* (MRSA) remains one of the most important causes of antimicrobial-resistant infections worldwide. While initially these infections were typically hospital-acquired, they have now largely spread into the community.

There are different methods to detect MRSA, and the screening methods 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

Table 7. j: Resistance rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans in 2021.

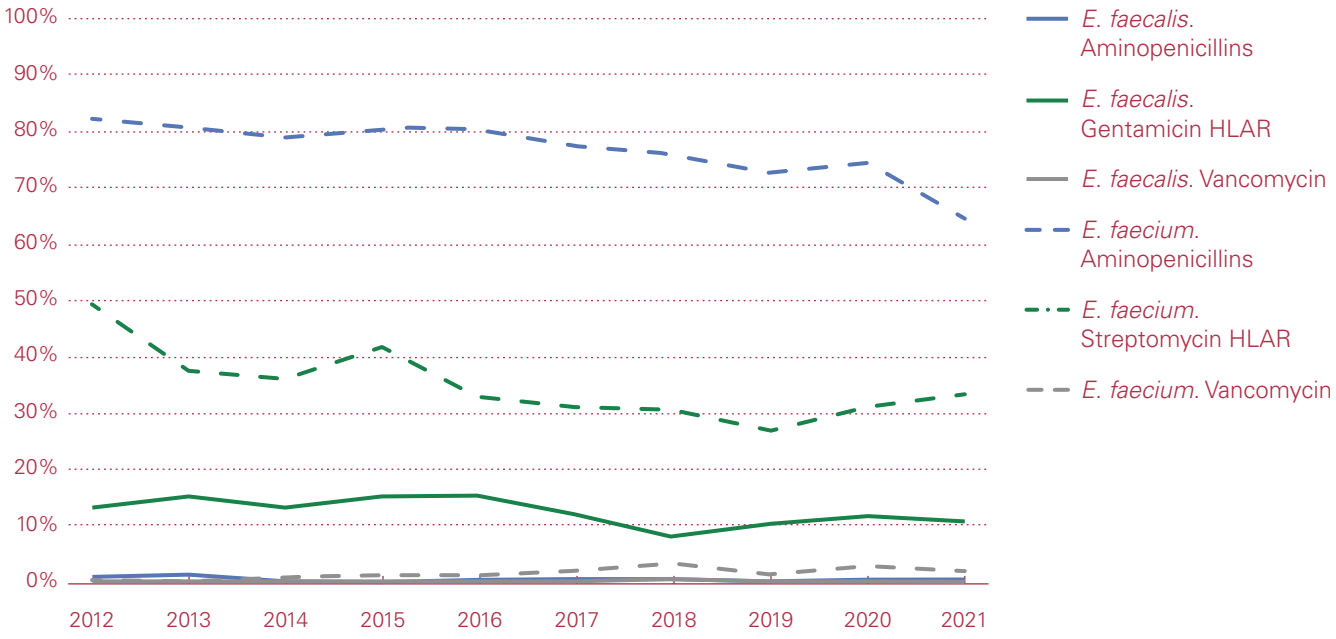
Enterococcus faecalis											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	169	1.8	622	0	235	0	1,026	0.3	0.1–0.5	–	–
Gentamicin HLAR[1]	75	18.7	332	8.4	28	17.9	435	10.8	9.3–12.3	–	↓
Tetracycline	16	31.2	103	74.8	46	100	165	77.6	74.4–80.8	↑	–
Vancomycin	208	0	687	0	235	0	1,130	0	0.0–0.0	↓	–
Linezolid	157	1.9	322	0.3	108	0	587	0.7	0.4–1.0	–	–

Enterococcus faecium											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	112	71.4	294	70.1	89	38.2	495	64.6	62.5–66.7	↓	↓
Gentamicin HLAR[1]	51	47.1	219	32.4	25	12	295	33.2	30.5–35.9	–	↓
Tetracycline	5	40	52	44.2	18	100	75	57.3	51.6–63.0	↑	↑
Vancomycin	135	2.2	369	2.2	89	1.1	593	2	1.4–2.6	–	↑
Linezolid	99	1	153	0	58	1.7	310	0.6	0.2–1.0	–	–

[1] HLAR = high level aminoglycoside 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 modeled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the corresponding outcome (increase, decrease).

Figure 7. I: Resistance rates of invasive *Enterococcus faecalis* and *Enterococcus faecium* isolates in humans between 2012 and 2021.



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 resistance to at least one of the following antibiotics: methicillin, oxacillin, flucloxacillin or cefoxitin. The results of confirmatory tests, such as the PBP2a agglutination test or the direct detection of the *mecA* gene, are typically not forwarded to ANRESIS. MRSA are resistant to all beta-lactam antibiotics, including combinations with beta-lactam inhibitors (e. g., amoxicillin-clavulanic acid). In 2021, the MRSA rate in Switzerland was 4.7%, with higher rates in southern Switzerland (18.8%), followed by western Switzerland (5.4%, Table 7. k). On average, Switzerland belongs to the 9 out of 40 (23%) European countries with MRSA rates below 5% [2]. Coresistance in MRSA is frequent and significantly higher than in MSSA for almost all antibiotics (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 wounds and abscesses is shown in Figure 7. m. As already shown by Olearo et *al.* [15], MRSA rates, and similarly resistance rates to most other antibiotics, are nowadays significantly higher in the ambulatory skin infection setting (11.6%) than in bacteremia (4.7%, Figure 7. m). While MRSA rates in hospitals have been decreasing for several years, community MRSA (cMRSA) infections are increasing [15]. In addition, they often harbor the Panton-Valentine-Leukocidin (PVL) toxin, leading to the formation of abscesses. Importantly, wound infections and even skin abscesses can usually be treated by a surgical procedure alone, and do not need antibiotic therapy.

The development of resistances during the last ten years is shown in Figure 7. o. Over the past ten years (2012–2021), a significant decrease in invasive MRSA rates, from 6.7% to 4.7%, was observed in Switzerland. A decrease in the MRSA percentage between 2016 and 2020, from 19.3% to 16.7%, was described in the population-weighted mean of EU/EEA states as well [2]. The decrease in the MRSA rate runs parallel to significant decreases in the resistance rates against aminoglycosides and ciprofloxacin in *S. aureus* isolates (Figure 7. i). In contrast, resistance rates in invasive *S. aureus* significantly increased for macrolides and clindamycin during the last ten years, from 11.2% to 13.5% and 8.3% to 11.5%, respectively.

References

[1] Plate A, Kronenberg A, Risch M, et al. Active surveillance of antibiotic resistance patterns in urinary tract infections in primary care in Switzerland. Infection. 2019;47(6):1027–1035. doi:10.1007/s15010-019-01361-y.

[2] WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022–2020 data. Copenhagen: WHO Regional Office for Europe; 2022.

[3] Ramette A, Gasser M, Nordmann P, Zbinden R, Schrenzel J, Perisa D, Kronenberg A. Temporal and regional incidence of carbapenemase-producing Enterobacterales, Switzerland, 2013 to 2018. Euro Surveill. 2021;26(15): pii=1900760.

Table 7. k: Resistance rates of invasive *Staphylococcus aureus* isolates in humans in 2021.

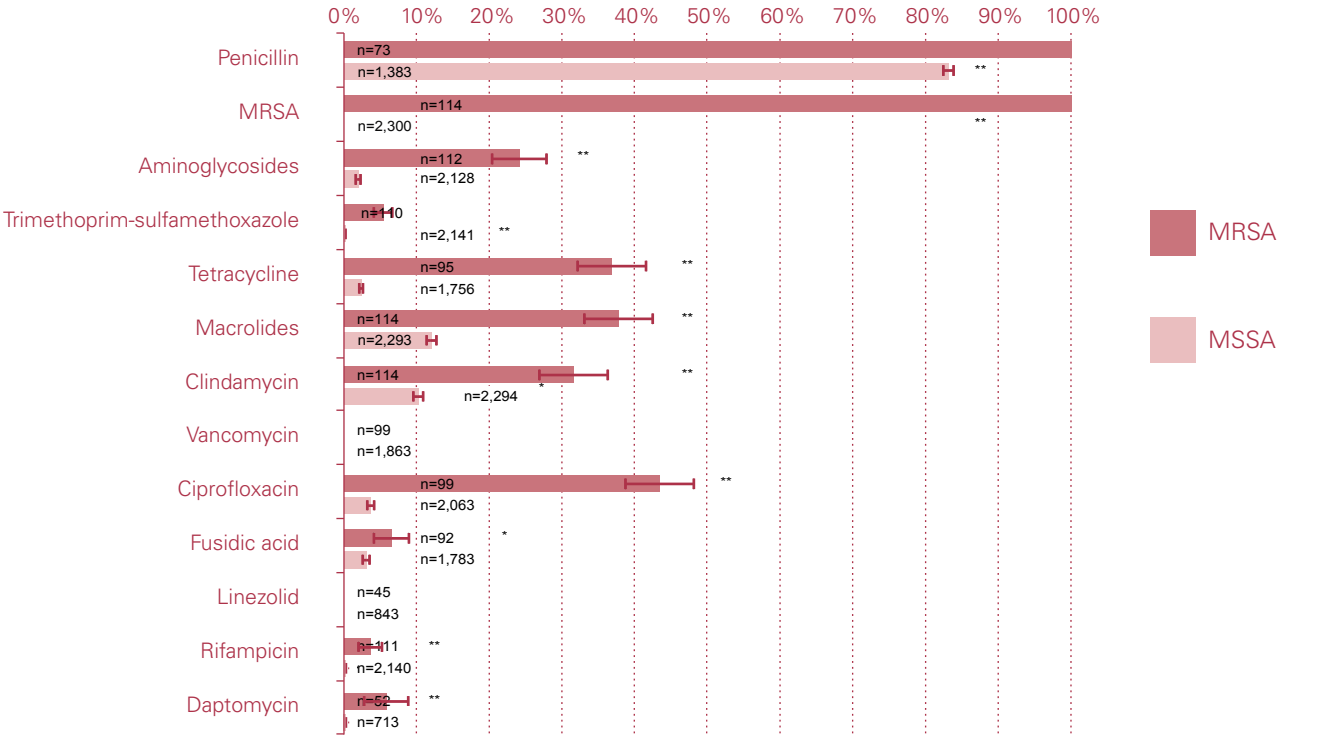
Staphylococcus aureus										2021	
	West		North–East		South		Total			Trend	
Antimicrobial	n	%	n	%	n	%	n	%	95% CI	4y	10y
Penicillin	210	93.8	1,230	82.8	146	69.2	1586	83	82.1–83.9	↑	↑
MRSA	446	5.4	1,904	4.1	64	18.8	2,414	4.7	4.3–5.1	–	↓
Aminoglycosides	467	5.8	1,746	2.6	156	1.3	2,369	3.1	2.7–3.5	–	↓
Trimethoprim-sulfamethoxazole	481	0.6	1,746	0.7	156	0.6	2,383	0.7	0.5–0.9	–	–
Tetracycline	361	4.7	1,463	4.5	156	2.6	1,980	4.4	3.9–4.9	–	–
Macrolides	479	21.3	1,904	11.4	156	15.4	2,539	13.5	12.8–14.2	–	↑
Clindamycin	480	17.9	1,904	9.7	156	12.8	2,540	11.5	10.9–12.1	↑	↑
Vancomycin	409	0.2	1,530	0	152	0	2,091	0	0.0–0.0	–	–
Ciprofloxacin	463	8.9	1,674	4.1	156	12.8	2,293	5.6	5.1–6.1	–	↓
Fusidic acid	458	3.3	1,399	3.4	146	7.5	2,003	3.6	3.2–4.0	–	–
Linezolid	279	0	607	0	3	0	889	0	0.0–0.0	–	–
Rifampicin	476	0.8	1,759	0.3	146	0.7	2,381	0.5	0.4–0.6	–	–
Daptomycin	168	0.6	557	0.5	133	2.3	858	0.8	0.5–1.1	–	–

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

Figure 7. m: Comparison of resistance rates in invasive versus outpatient wound/abscess samples in *Staphylococcus aureus* in humans in 2021.

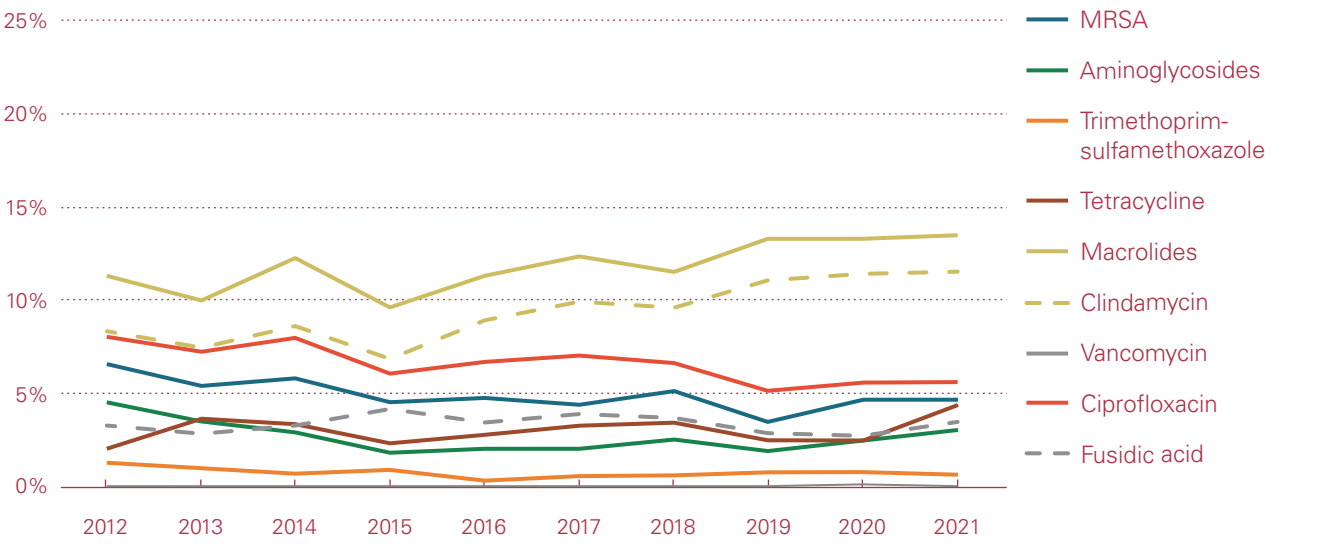
n = number of isolates tested, with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence:
** = p-value <0.01.

Figure 7. n: Resistance rates of invasive MRSA (methicillin-resistant *Staphylococcus aureus*) and MSSA (methicillin-susceptible *Staphylococcus aureus*) isolates in humans 2021.



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

Figure 7. o: Resistance rates of invasive *Staphylococcus aureus* isolates in humans between 2012 and 2021.



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Textbox

Antimicrobial resistance in *Neisseria gonorrhoeae* in Switzerland

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Antimicrobial resistance to *Neisseria gonorrhoeae* continues to be a problem for both clinical management and control of gonorrhea. Gonorrhea is the second most common sexually transmitted bacterial infection in Switzerland, with 3,463 laboratory confirmed cases reported in 2020, a more than five-fold increase since 2004 [1]. Of these cases, 83% were in men and 17% in women. Men who have sex with men (MSM) accounted for 65% of male gonorrhea cases in 2020 [1].

N. gonorrhoeae evolves rapidly and, through a wide range of mechanisms, has developed resistance to all classes of antimicrobials widely used to treat it [2]. The World Health Organization recommends changing the first-line antimicrobial used when the level of resistance exceeds 5%; above this level, blind treatment is not recommended because of the risk of treatment failure [3]. Ceftriaxone is the only antimicrobial that has fulfilled this requirement during the whole study period, and there are no other licensed drugs to replace it.

Antimicrobial susceptibility testing (AST) of cultured isolates is essential for monitoring and early warning. Molecular diagnostic tests have, however, largely replaced bacterial culture-based methods to detect *N. gonorrhoeae* in Switzerland and many other countries. Molecular diagnostic tests are highly sensitive and specific for detection of the organism, but these tests do not detect the markers of antimicrobial resistance, so resistant strains will not be identified unless they cause clinical treatment failure [3]. AST is conducted in a minority of gonorrhea cases. The Swiss Centre for Antibiotic Resistance (anresis.ch) network collects data about *N. gonorrhoeae* from laboratories across Switzerland. A report on *N. gonorrhoeae* AMR was published in the anresis.ch report in 2015. The number of laboratories contributing to anresis.ch is increasing to include those that serve outpatient clinics that treat large numbers of people with gonorrhea.

From 2004 to 2020, a total of 26,208 laboratory-confirmed gonorrhea cases were reported to the national surveillance system. During this period, results of AST for 2,611 patients were reported to anresis.ch. The proportion of reported cases for which any sample had AST increased from 7.9% in the period 2004–2007 to 10.9% from 2016 to 2020. This report covers reports about the antibiotics ciprofloxacin, azithromycin, cefixime and ceftriaxone. Results of AST are reported as delivered by laboratories (susceptible, intermediate or resistant). Most laboratories changed from CLSI to EUCAST breakpoints between 2011 and 2013. Minimal inhibitory concentration (MIC) values were available for about a third of all reported samples.

The proportion of samples resistant to ciprofloxacin is stable (50% above the clinical breakpoint 0.064 mg/L in 2020). Owing to persistently high levels of resistance, ciprofloxacin has not been recommended as a treatment for gonorrhea for many years. Overall, the proportion of isolates with resistance to cefixime, an oral extended-spectrum cephalosporin, is low (0.8%). Cefixime has been discontinued as a recommended treatment for gonorrhea, because levels of resistance started to exceed 5% from 2011 on. But small numbers of isolates continue to be reported as resistant (>0.125 mg/L) each year (Figure 1). Cefixime is no longer available in Switzerland. The current recommendation for treatment of gonorrhea is intramuscular ceftriaxone 1 g. The number of isolates with resistance to ceftriaxone remains extremely low (0.2% in 2020, Figure 1). Where MIC values are available, there has been a slight drift within the range of susceptible values since 2015. For azithromycin, the proportion with resistance has increased (15% in 2020). This level is based on a EUCAST epidemiological cut-off value of 1 g/L with uncertain clinical significance. Where MIC values are available, a drift towards higher values over time is seen.

The pattern of gonococcal antimicrobial resistance in Switzerland follows that seen in other European countries. Resistance to ceftriaxone remains rare in Switzerland. But, anresis.ch covers only one in ten diagnosed gonorrhea infections and of these, only one third has the MIC values reported. To monitor the drift towards samples with higher levels of resistance, MIC values should be reported for all samples. Surveillance for AMR in *N. gonorrhoeae* in Switzerland could be improved if more samples were sent for culture. Physicians should be encouraged to take swabs as well as urine samples before giving empirical treatment for suspected gonorrhea. Whole genome sequencing would also help by allowing genetic markers of AMR and strains involved in outbreaks to be monitored. These measures would contribute to improved control of AMR gonorrhea in Switzerland.

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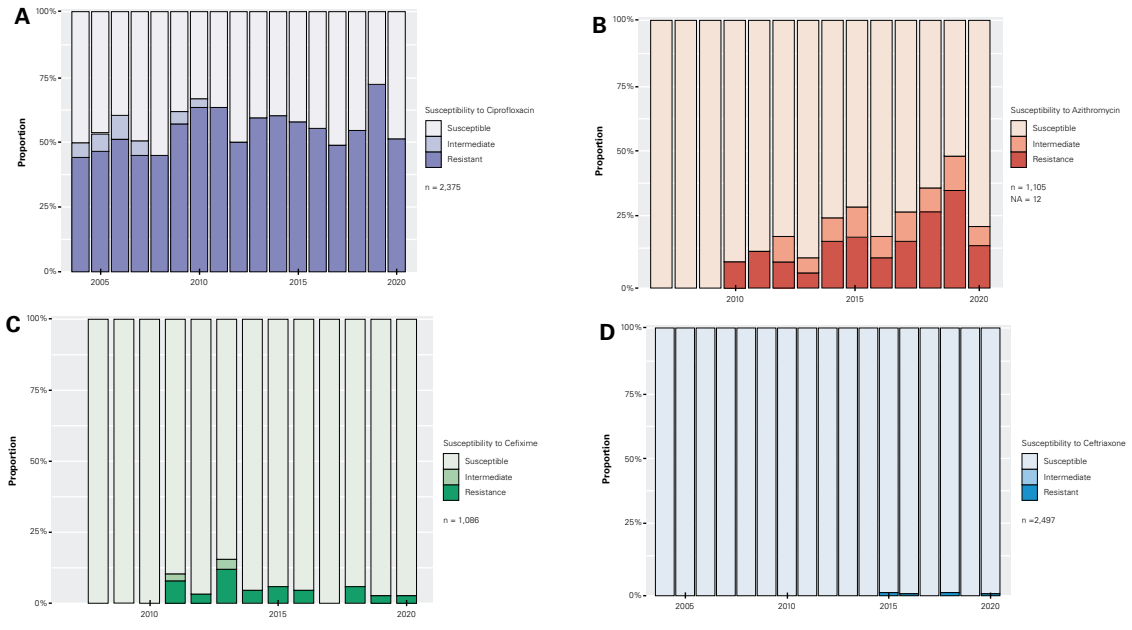
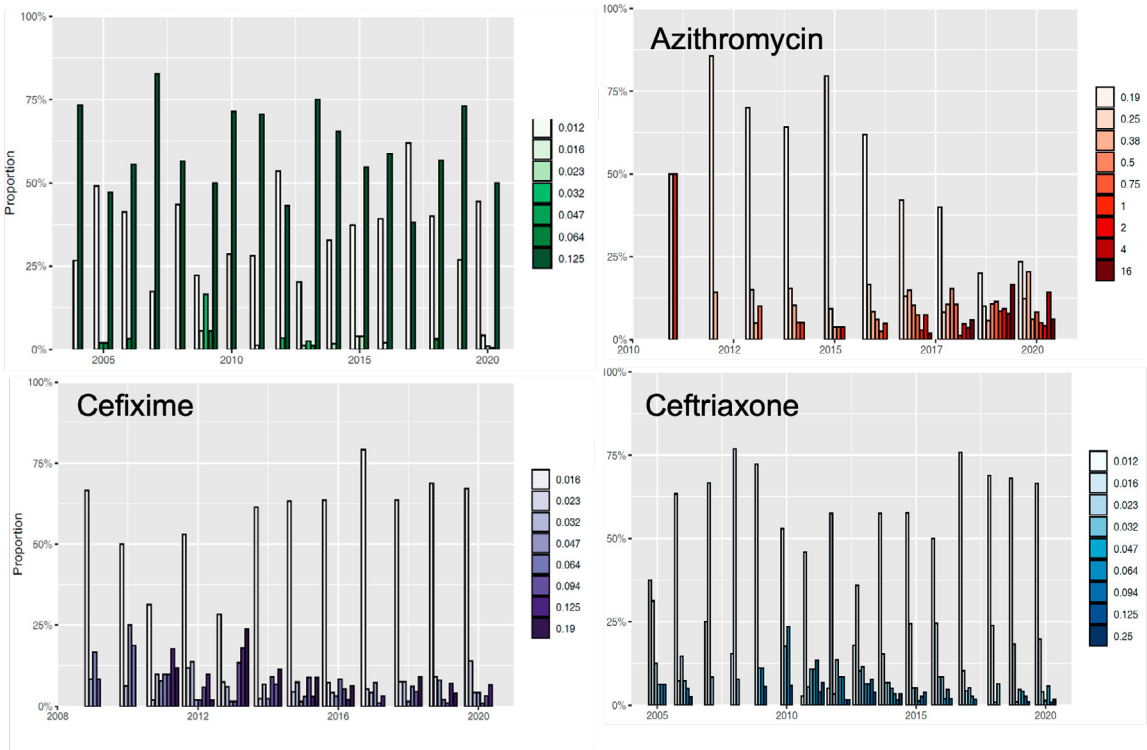
Figure 1: *Neisseria gonorrhoeae* isolates in Switzerland, 2004–2020, with results of antimicrobial susceptibility testing. Panel A, ciprofloxacin; B, azithromycin; C, cefixime; D, ceftriaxone.





Textbox

The burden of antibiotic resistant bacteria in Switzerland has significantly increased between 2010 and 2019

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Estimates of the impact of infectious diseases are needed for an accurate risk assessment as well as planning and prioritization of public health resources. In 1993, the World Bank recognized the importance of composite measures for disease burden on a global scale and introduced the disability-adjusted life years (DALYs) [1]. For each condition or disease, DALYs calculate healthy life years lost because of premature mortality and years lost living with disabilities. In 2015, Cassini *et al.* [2] estimated that infections with 16 different antibiotic resistant bacteria of public health concern resulted in approximately 170 DALYs per 100,000 population in the EU and EEA, and our group estimated 88 DALYs per 100,000 population in Switzerland [3]. A current follow-up study aims to estimate the burden caused by the same infections in Switzerland in 2019 and a temporal trend since 2010. In addition, it investigates whether different numbers of DALYs are observed in different parts of Switzerland (i. e., German-speaking part versus Latin part. French and Italian speaking parts were pooled to reduce the model's complexity) and whether the hospital type (i. e., university versus non-university hospitals) plays a role. The study is based on bloodstream infections (BSIs) with 16 antibiotic resistance-bacterium combinations, which were extracted from the ANRESIS database. Coverage correction factors were calculated yearly for different hospital types (university versus non-university) and linguistic regions, in order to obtain a total number of BSIs for the entire country. The number of BSIs were multiplied by conversion factors derived from the European Centre for Disease Prevention and Control point prevalence survey of health-care-associated infections in European acute care hospitals in 2016 and 2017 to estimate the number of non-BSIs. Associated deaths and DALYs were estimated using the ECDC BCoDE toolkit [4].

It was estimated that the number of infections increased significantly, from 3,110 (uncertainty interval UI 95% 2,516–3,844) in 2010 to 6,342 (UI 95% 5,316–7,538) in 2019, corresponding to 3,995 (UI 95% 3,327–4,805) DALYs and 6,805 (UI 95% 5,820–7,949) DALYs respectively **(Figure 1A)**. Deaths increased from 136 (UI 95% 114–161) in 2010 to 286 (UI 95% 243–335) in 2019. These numbers indicate an aggravation of the epidemiological situation in Switzerland, which was, however, curbed during the last years of the study. In a Europe-wide comparison, Switzerland is still on a low to intermediate level.

Most DALYs were associated with third-generation cephalosporin-resistant Escherichia coli **("3GCREC" in Figure 1A)**. These infections were predominately observed in males and in the elderly population. Fortunately, the burden from infections with carbapenem- or colistin-resistant pathogens, which are known for their high mortality, remained on a moderate level.

Significant differences were observed between linguistic regions and hospital types. DALYs per 100,000 population were higher in the Latin part of Switzerland than in the German-speaking part throughout the whole study period **(Figure 1B)**.

A proportionally higher number of DALYs was estimated for university hospitals (i. e., 165 (UI 95% 140–194) DALYs per 100,000 hospitalization days, than for non-university hospitals (62 (UI 95% 53–72) DALYs per 100,000 hospitalization days); a finding which is not very surprising, as larger hospitals generally accommodate more severe cases.

These differences depending on the linguistic region and the hospital type showed that stratifications also affect the overall national burden estimation (indeed, in a control experiment without stratifications a significantly higher burden was estimated). Thus, the adaption of the method from Cassini et al. using a stratified approach may also inspire other countries to develop/adapt their surveillance systems, which in turn allows a better international comparability.

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Figure 1A: Medians and 95% uncertainty intervals (black bars) of DALYs caused by infections with antibiotic-resistant bacteria in Switzerland from 2010 to 2019.

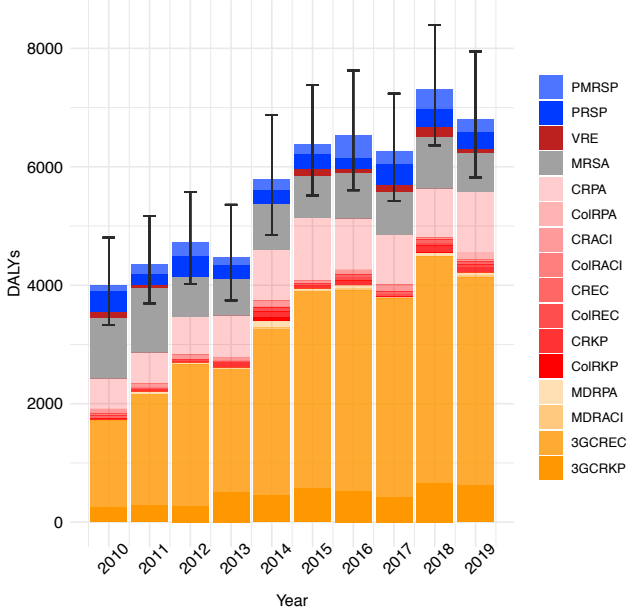
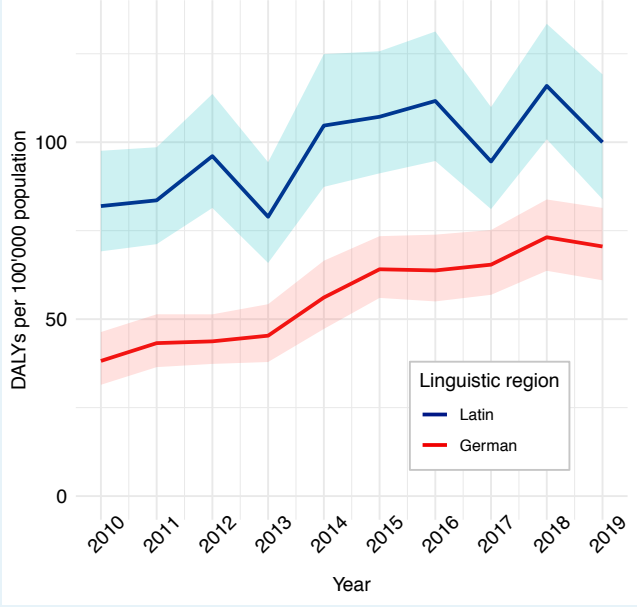


Figure 1B: DALYs per 100,000 population by linguistic region. 95% uncertainty intervals are depicted by colored ribbons.



ColRACI = colistin-resistant *Acinetobacter* spp.
CRACI = carbapenem-resistant *Acinetobacter* spp.
MDRACI = multidrug-resistant *Acinetobacter* spp. VRE = vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. ColREC = colistin-resistant *Escherichia coli*. CREC = carbapenem-resistant *E. coli*.
3GCREC = third-generation cephalosporin-resistant *E coli*. ColRKP = colistin-resistant *Klebsiella pneumoniae*.
CRKP = carbapenem-resistant *K. pneumoniae*.
3GCRKP = third-generation cephalosporin-resistant *K. pneumoniae*. ColRPA = colistin-resistant *Pseudomonas aeruginosa*. CRPA = carbapenem-resistant *P. aeruginosa*.
MDRPA = multidrug-resistant *P. aeruginosa*.
MRSA = methicillin-resistant *Staphylococcus aureus*.
PRSP = penicillin-resistant *Streptococcus pneumoniae*.
PMRSP = penicillin-resistant and macrolide-resistant *S. pneumoniae*.

Textbox

The Swiss National Reference Center for Emerging Antibiotic Resistance (NARA)

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The National Reference Laboratory for Emerging Antibiotic Resistance (NARA) was created in early 2017 at the University of Fribourg and the CHUV in Lausanne, under the direction of Professor Patrice Nordmann. This reference center receives financial support from the Federal Office of Public Health (FOPH). It groups two sites: one at the University of Fribourg (Prof. P. Nordmann) for the analysis of emerging resistance in Gram-negatives and one at the CHUV in Lausanne (Dr. D. Blanc) for emerging resistance in Gram-positives. Its tasks are multiple, i. e., (i) early identification of bacterial strains expressing novel antibiotic resistance traits; (ii) comparison of these strains with emerging resistance in order to identify their potential dissemination; (iii) development of techniques for the rapid diagnosis of emerging resistance; (iv) evaluation of the efficacy of new molecules; (v) offering advice on antibiotic therapy to treat these infections due to multidrug resistant bacteria. The offer developed by NARA is for all healthcare facilities and private or public laboratories located in Switzerland. NARA strives to report any result within 72 hours after receipt of the biological material, aware of the clinical impact of its activity. The most modern techniques of microbiology, biochemistry and genetics are used and developed for this purpose. NARA is in close contact to ANRESIS, exchanging medical results to optimize the control of antibiotic resistance in Switzerland. Although mainly aiming to analyze human isolates, NARA is also developing research projects in a One Health context.

Among the most problematic emerging antibiotic resistance issues, the spread of carbapenemase producers is of concern since they are associated with multidrug resistance to many classes of non-related antibiotics. This is the reason why, since 2018, it is mandatory to send carbapenemase producers to NARA for confirmatory analysis. Carbapenemases belong to the class A, B and D groups of ß-lactamases. Class B enzymes (metallo-enzymes) include NDM, VIM and IMP enzymes that are identified in *Enterobacterales, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. They are rapidly spreading worldwide, including in Switzerland [1]. A series of NDM variants have been identified with 26 currently known NDM derivatives. These variants efficiently hydrolyze all ß-lactams with the exception of the monobactam aztreonam. NDM-5 has been primarily identified in multidrug-resistant *E. coli* in the United Kingdom [2]. A combination of aztreonam-avibactam (AZT-AVI) is under development. It aims to be efficient against NDM producers, since AVI inhibits the activity of extended-spectrum ß-lactamases that are often expressed among NDM producers. However, a series of *E. coli* producing NDM-5 that are resistant to AZT-AVI have been identified **(Fig. 1)**. This peculiar resistance pattern is associated with a structural modification of the penicillin-binding protein 3 that is a main target of aztreonam and the expression of specific plasmid-mediated cephalosporinases, such as CMY-42 [3], [4]. AZT binds specifically to these cephalosporinases [4]. *E. coli* NDM-5 strains are regularly identified in Switzerland (92 strains at the NARA from 2017 to 2021). They belong to several ST types [5], mostly to the ST167 type in human and food contaminants [6]. This successful epidemic clone is known to be associated with both multiresistance and virulence traits and is therefore of high public health concern. Plasmids carry-

Fig. 1: *E. coli* producing NDM-5
Multidrug resistance to all available ß-lactams
Resistance to carbapenems of variable levels, depending on the molecule
Resistance to the combination of ceftazidime/tazobactam
Resistance to aztreonam, aztreonam/avibactam (not shown) and cefiderocol (not shown)

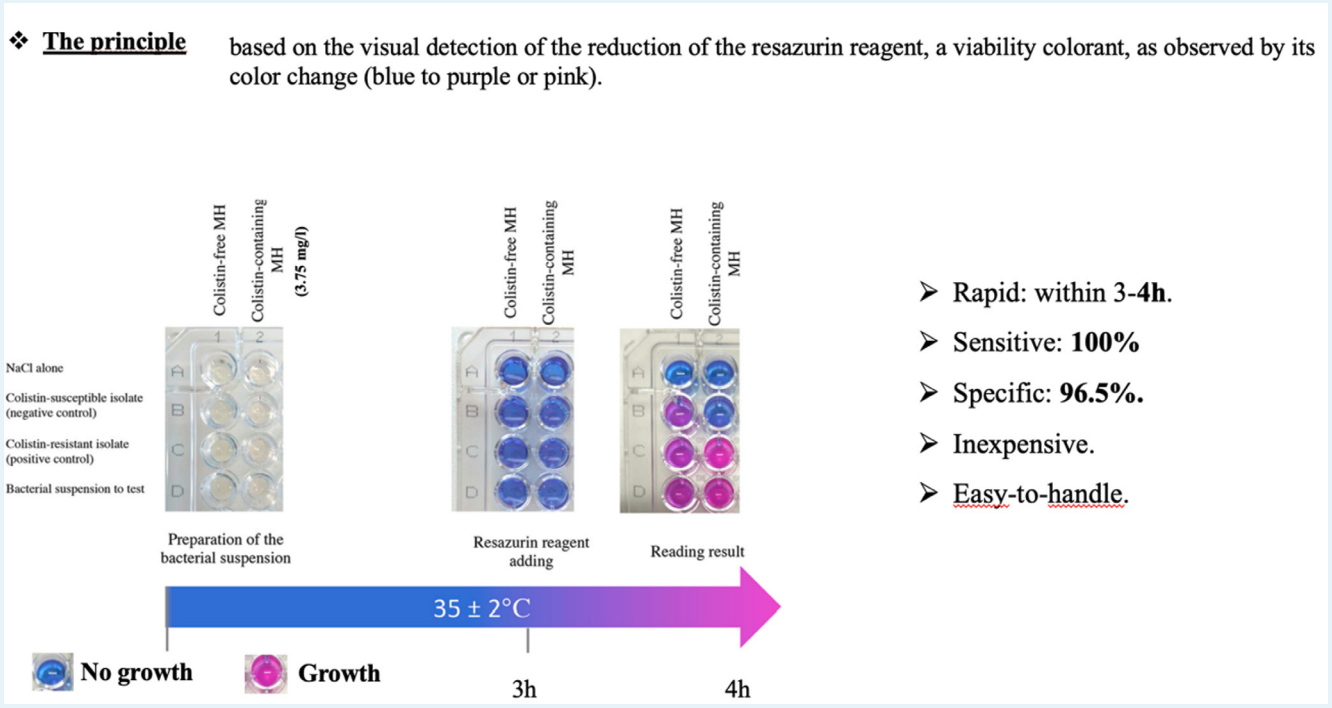
AM, Ampicillin (10 µg); TIC, Ticarcillin (75 µg); PRL, Piperacillin (30 µg); TPZ, Piperacillin/Tazobactam (30/6 µg); CZA, Ceftazidime/Avibactam (14 µg); CAZ, Ceftazidime (10 µg); TIM, Ticarcillin/clavulanic acid (75/10 µg); IPM, Imipenem (10 µg); CTX, Cefotaxime (5 µg); AMC, Amoxicillin/clavulanic acid (20/10 µg); FEP, Cefepime (30 µg); ETP, Ertapenem (10 µg); FOX, Cefoxitin (30 µg); ATM, Aztreonam (30 µg); TEM, Temocillin (30 µg); MEM, Meropenem (10 µg)

ing the NDM-5 gene have different backbones and are transferable [5]. We showed that the AZT-AVI resistant strains identified in Switzerland are spreading internationally, including in France and Germany, and that their origin is very likely in Pakistan [6]. This represents one of the best examples of globalization as a source of spread of multidrug resistant bacteria.

As for development of rapid tests, NARA has created many during the last years. It has for example developed and contributed to the industrialization of the test for rapid detection of resistance to polymyxin (colistin) resistance in *A. baumannii*, with results provided in less than four hours (turnaround time for results of the current tests is 24 to 48 hours) [7], [8] **(Fig. 2)**. It now offers the possibility to test susceptibility to polymyxins rapidly before implementing a polymyxin-based therapy.

Novel antibiotics have also been evaluated against multidrug-resistant Gram-negative bacteria at the NARA. Among them, there are combinations of known ß-lactams with recently developed ß-inhibitors such as ceftolozane-tazobactam, ceftazidime-avibactam (CZA), meropenem-vaborbactam (MEB) and imipenem-relebactam (IMR) [9]. Ceftolozane-tazobactam does not possess significant activity against carbapenemase producers where the other combinations do. None of those inhibitors have significant activity against carbapenemases of the metallo-enzyme types, i. e., mostly the NDM, IMP, and VIM types. Avibactam and relebactam belong to the same group of inhibitors, i. e., the diazabicyclooctane group, whereas vaborbactam is a boronic acid derivative. Avibactam is active against carbapenemases of the Ambler class A (KPC) and Ambler class D (OXA-48-like), while vaborbactam and relebactam are active against carbapenemases of class A only. Taking into account the inhibitory properties of the molecules and the intrinsic activity of the ß-lactams that is combined with the inhibitors, MEB was more effective (84% versus 63%) than CZA from a collection of 150 strains of carbapenemase producers representative of the strains received at the NARA (P. Nordmann, submitted). Actually, while vaborbactam is not active against OXA-48-like enzymes, many OXA-48-like producers and NDM remain susceptible to meropenem. This information may be useful, since none of the currently clinically available inhibitors are active against metallo-ß-lactamases.

Fig. 2: Rapid detection of polymyxin resistance in *Acinetobacter baumannii* (Rapid ResaPolymyxin *Acinetobacter*)



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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.

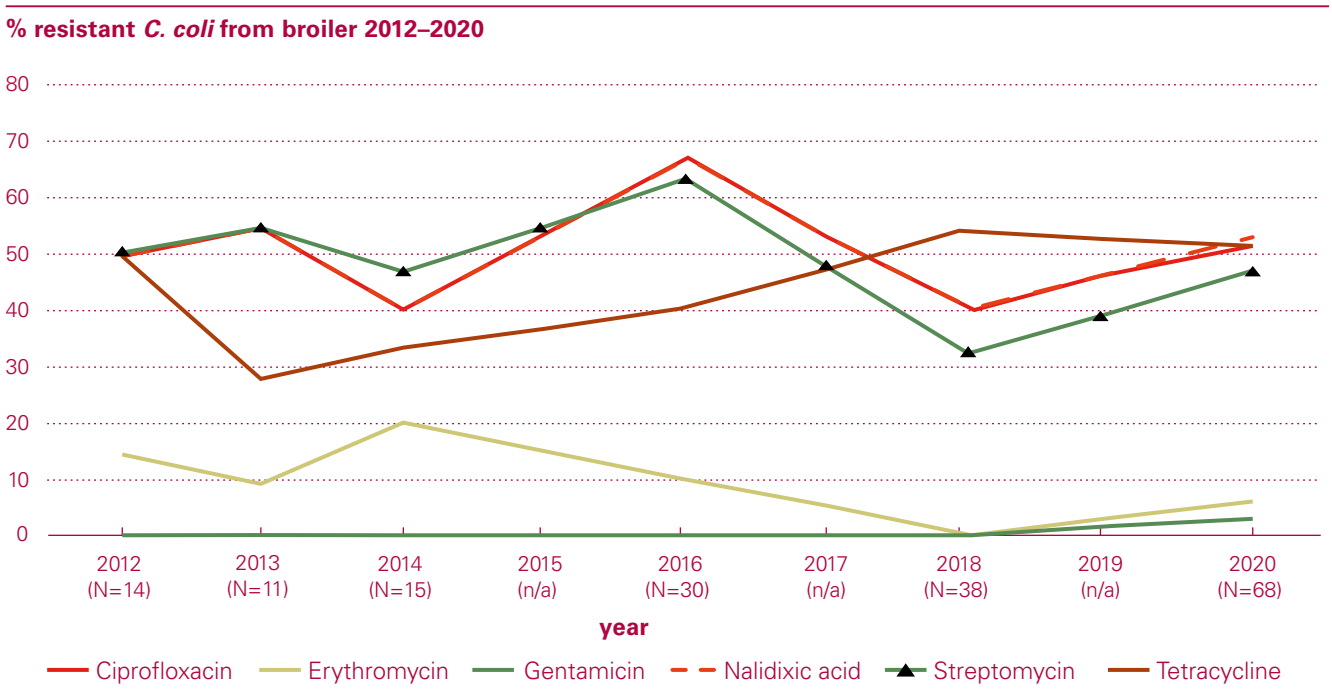
8.1 *Campylobacter* spp.

Campylobacter (C.) jejuni and *C. coli* are responsible for human campylobacteriosis, the most prevalent food-borne zoonosis in Europe. In 2020, despite the COVID-19 crisis and the lack of data from United Kingdom, more than 120,000 cases were reported [1]. In Switzerland, the healthcare costs for human campylobacteriosis have been valued at approx. 29 to 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 very high in both human and broiler *Campylobacter* isolates. Hence, fluoroquinolones are no longer fostered as a therapeutical option [1].

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 companion animals are of lesser importance. Source attribution studies from Switzerland identified chicken as the main source for human campylobacteriosis (71% of all human

Figure 8. a: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. coli* from broilers between 2012 and 2020 (N = total number of tested isolates; values for 2015, 2017 and 2019 interpolated [n/a]).



cases were attributed to chicken, 19% to cattle, 9% to dogs and 1% to pigs) [6, 7]. 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 2020, of *C. coli* in fattening pigs, and of *C. jejuni* from slaughter calves from 2021. Moreover, antimicrobial resistance rates from human *Campylobacter* spp. are shown.

8.1.1 *Campylobacter* spp. in broilers

In 2020, a random sample of 808 broiler flocks was examined at slaughter, using pooled cecal samples (5 pooled samples per flock). *C. jejuni* was identified in 179 samples (22.2%) and *C. coli* in 68 samples (8.4%). AMR tests were performed on all isolates, against aminoglycosides, fluoroquinolones, macrolides and tetracyclines.

High levels of fluoroquinolone resistance were detected in *C. jejuni* (47.5%), as well as in *C. coli* (51.5%). Moreover, in *C. coli* a high level of tetracycline resistance was found (51.5%), whereas for *C. jejuni* the resistance rate to tetracycline was lower (29.6%). Almost one half (47.1%) of all *C. coli* isolates were resistant to streptomycin, but only two were resistant to gentamicin (2.9%). In contrast, only 3.9% of all *C. jejuni* were resistant to streptomycin. Very low levels of macrolide resistance (erythromycin) were found in *C. coli* (5.9%) and none in *C. jejuni* (Figure 8. a, Figure 8. b).

Overall, 44.1% of *C. jejuni* and only 17.6% of *C. coli* displayed no resistance to any antimicrobial substances tested (Figure 8. c, Figure 8. d). In *C. coli*, 20 isolates (29.4%) and in *C. jejuni* 58 isolates (32.4%) were resistant to just one antibiotic class, mainly to tetracyclines in *C. coli* and fluoroquinolones in *C. jejuni* (Table 8. a, Table 8. b). 36.8% of *C. coli* and 21.8% of the *C. jejuni* isolates showed resistance to two antibiotic classes. In *C. jejuni*, almost all expressed coresistance against fluoroquinolones and tetracyclines. In *C. coli*, various dual combinations occurred. Overall, *C. coli* isolates showed a marked increase in antimicrobial resistance to fluoroquinolones and gentamicin from 2018 to 2020, whereas resistance rates in *C. jejuni* isolates remained stable (Figure 8. c, Figure 8. d).

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. No common trend was observed. Because of the very low numbers of isolates, statistically significant conclusions could not be drawn (Table 8. c).

8.1.2 *Campylobacter* in fattening pigs

In 2021, a random sample of 289 fattening pigs was investigated at slaughter, using single cecal samples per slaughter batch. *C. coli* was isolated from 191 samples (66.1%). All isolates were subjected to susceptibility testing. Since 2021, streptomycin and nalidixic acid are no longer measured. Instead, ertapenem and chloramphenicol have been added.

Figure 8. b: Trends in ciprofloxacin, erythromycin, gentamicin, streptomycin and tetracycline resistance in *C. jejuni* from broilers between 2012 and 2020 (N = total number of tested isolates; values for 2015, 2017 and 2019 interpolated [n/a]).

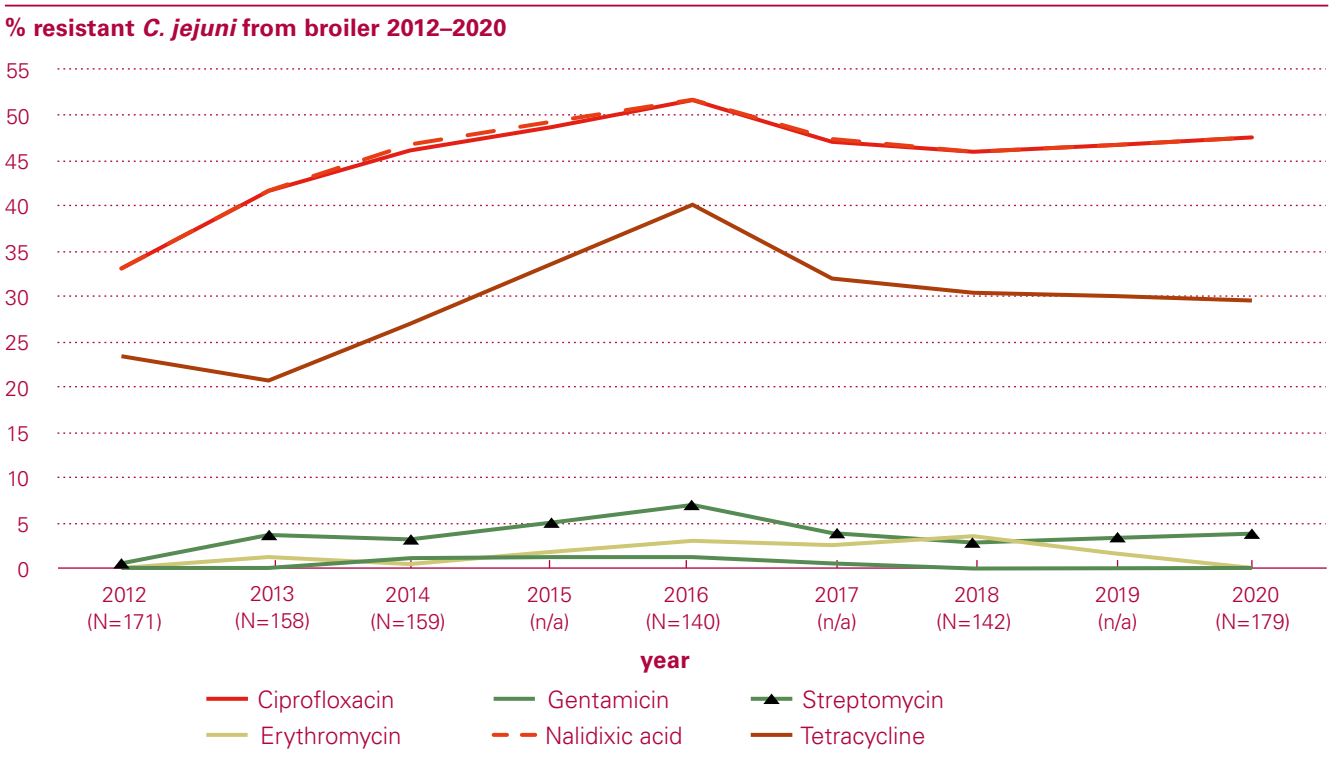


Table 8. a: Resistance combinations in commensal *C. coli* in broilers in 2020.

Resistance patterns	Number of isolates	% of total
Grand total	**68**	
Number of resistances: 0	**12**	**17.6%**
–	12	100.0%
Number of resistances: 1	**20**	**29.4%**
Aminoglycosides	7	35.0%
Fluoroquinolones	5	25.0%
Tetracyclines	8	40.0%
Number of resistances: 2	**25**	**36.8%**
Aminoglycosides – fluoroquinolones	9	36.0%
Aminoglycosides – tetracyclines	5	20.0%
Fluoroquinolones – tetracyclines	11	44.0%
Number of resistances: 3	**7**	**10.3%**
Aminoglycosides – fluoroquinolones – tetracyclines	7	100.0%
Number of resistances: 4	**4**	**5.9%**
Aminoglycosides – fluoroquinolones – macrolides – tetracyclines	4	100.0%

Aminoglycosides: streptomycin, gentamicin; fluoroquinolones: nalidixic acid, ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin

Table 8. b: Resistance combinations in commensal *C. jejuni* from broilers in 2020.

Resistance patterns	Number of isolates	% of total
Grand total	**179**	
Number of resistances: 0	**79**	**44.1%**
–	79	100.0%
Number of resistances: 1	**58**	**32.4%**
Aminoglycosides	3	3.4%
Fluoroquinolones	43	74.1%
Tetracyclines	13	22.4%
Number of resistances: 2	**39**	**21.8%**
Aminoglycosides – fluoroquinolones	2	5.1%
Fluoroquinolones – tetracyclines	37	94.9%
Number of resistances: 3	**3**	**1.7%**
Aminoglycosides – fluoroquinolones – tetracyclines	3	100.0%

Aminoglycosides: streptomycin, gentamicin; fluoroquinolones: nalidixic acid, ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin

In fattening pigs, the highest level of antimicrobial resistance was identified for tetracyclines (66.5%) and fluoroquinolones (53.9%) (Figure 8. e). In contrast, no resistance to macrolides, gentamicin, ertapenem or chloramphenicol was detected. There are no significant changes in resistance rates compared to 2019. A constant very high level of resistance was found against tetracyclines and fluoroquinolone.

Out of the 191 isolates, 16.2% were fully susceptible to all tested antibiotic classes (Table 8. d, Figure 8. f). Ninety isolates were resistant to one antibiotic class (tetracyclines or fluoroquinolones), which corresponds to a prevalence of 47.1%. One third (36.6%) of the isolates were resistant to two antibiotic classes (tetracyclines and fluoroquinolones).

As the pig density is very low in the southwestern region, porcine *C. coli* isolates from this region were rare in comparison to the other regions. For the central and eastern regions, no marked differences in resistance rates were observed (Table 8. e).

Figure 8. c: Resistance pattern in *C. coli* from broiler 2020.

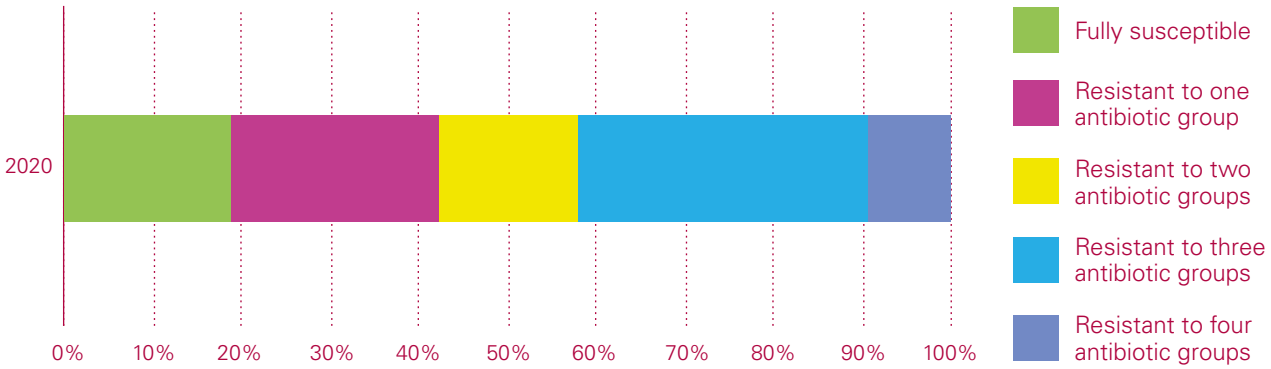


Figure 8. d: Resistance pattern in *C. jejuni* from broiler 2020.

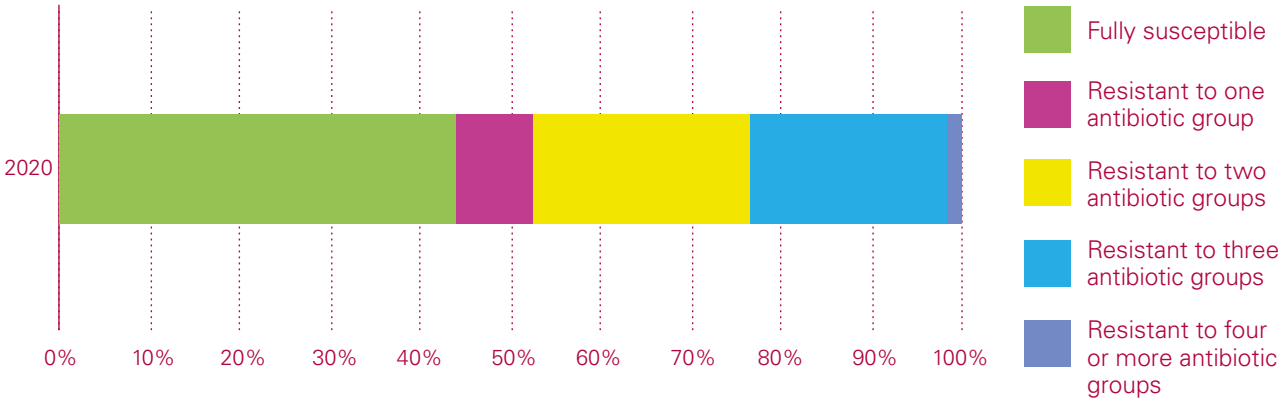


Table 8. c: Resistance rates in commensal *C. coli* and *C. jejuni* from broilers in 2020 in different regions in Switzerland.

Campylobacter coli (n=68)									**2020**
Antimicrobial	**South–West (n=22)**		**Center (n=42)**		**East (n=4)**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	4	18.2%	8	19.0%	0	0.0%	12	17.6%	10.4–28.4
Aminoglycosides	10	45.5%	19	45.2%	3	75.0%	32	47.1%	35.7–58.8
Fluoroquinolones	13	59.1%	20	47.6%	3	75.0%	36	52.9%	41.2–64.3
Tetracyclines	12	54.5%	22	52.4%	1	25.0%	35	51.5%	39.8–62.9
Macrolides	3	13.6%	1	2.4%	0	0.0%	4	5.9%	2.3–14.2
Campylobacter jejuni									**2020**
Antimicrobial	**South–West (n=63)**		**Center (n=76)**		**East (n=29)**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	34	53.9%	34	44.7%	11	37.9%	89	44.1%	37.1–51.5
Aminoglycosides	2	3.2%	4	5.3%	1	3.4%	7	3.9%	1.9–7.9
Fluoroquinolones	23	36.5%	46	60.5%	16	55.2%	85	47.5%	40.3–54.8
Tetracyclines	21	33.3%	24	31.6%	8	27.9%	53	29.6%	23.4–36.7
Macrolides	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0–2.1

95% CI: 95% confidence interval; aminoglycosides: streptomycin, gentamicin; fluoroquinolones: nalidixic acid, ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin

Table 8. d: Resistance combinations in commensal *C. coli* from fattening pigs in 2021.

Resistance patterns	Number of isolates	% of total
Grand total	**191**	
Number of resistances: 0	**31**	**16.2%**
–	31	100.0%
Number of resistances: 1	**90**	**47.1%**
Fluoroquinolones	33	36.7%
Tetracyclines	57	63.3%
Number of resistances: 2	**70**	**36.6%**
Fluoroquinolones – tetracyclines	70	1
Number of resistances: 3	**0**	**0.0%**
Number of resistances: 4	**0**	**0.0%**

Aminoglycosides: streptomycin, gentamicin; fluoroquinolones: nalidixic acid, ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin

Table 8. e: Resistance rates in commensal *C. coli* from fattening pigs in 2021 in different regions in Switzerland.

Campylobacter coli	**(n=191)**								**2019**
Antimicrobial	**South–West (n=19)**		**Center (n=94)**		**East (n=78)**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**
Susceptible	4	21.1%	12	12.8%	15	19.2%	31	16.2%	11.7–22.1
Fluoroquinolones	11	57.9%	48	51.1%	44	56.4%	103	53.9%	46.8–60.8
Tetracyclines	14	73.7%	64	68.1%	49	62.8%	127	665.0%	59.5–72.8

95% CI: 95% confidence interval; aminoglycosides: gentamicin; fluoroquinolones: ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin; amphenicols: chloramphenicol; carbapenems: ertapenem

Table 8. f: Resistance rates in commensal *C. jejuni* from slaughter calves in 2021 (n=143).

Antibiotic	n	p	95% CI
Chloramphenicol	0	0.0	0.0–2.6
Ciprofloxacin	83	58.0	49.8–65.8
Ertapenem	2	1.4	0.4–5.0
Erythromycin (Erythromycin A)	0	0.0	0.0–2.6
Gentamicin	0	0.0	0.0–2.6
Tetracycline	66	46.2	38.2–54.3
Resistances			
None	40	28.0	21.3 – 35.8
1 Antibiotic	56	39.2	31.5 – 47.3
2 Antibiotics	46	32.2	25.1 – 40.2
3 Antibiotics	1	0.7	0.1 – 3.9
4 Antibiotics	0	0.0	0.0 – 2.6
>4 Antibiotics	0	0.0	0.0 – 2.6

8.1.3 *Campylobacter* in slaughter calves

In 2021, a random sample of 294 slaughter calves was investigated at slaughter, using single cecal samples per slaughter batch for the first time. *C. jejuni* was isolated from 143 samples (48.6%). All isolates were subjected to susceptibility testing. The same antibiotics as for fattening pigs were tested.

In slaughter calves, the highest level of antimicrobial resistance was identified for fluoroquinolones (58.0%) and tetracyclines (46.2%) (Table 8. f). In contrast, no resistance to macrolides, chloramphenicol and gentamicin was detected. Two isolates showed resistance to ertapenem (1.4%).

Out of the 143 isolates, 28.0% were fully susceptible to all tested antibiotic classes (Table 8. f). 56 isolates were resis-

Figure 8. e: Trends in ciprofloxacin, erythromycin, gentamicin, nalidixic acid, streptomycin and tetracycline resistance in *C. coli* from fattening pigs between 2012 and 2021 (N = total number of tested isolates; values for 2014, 2016, 2018 and 2020 are interpolated [n/a]).

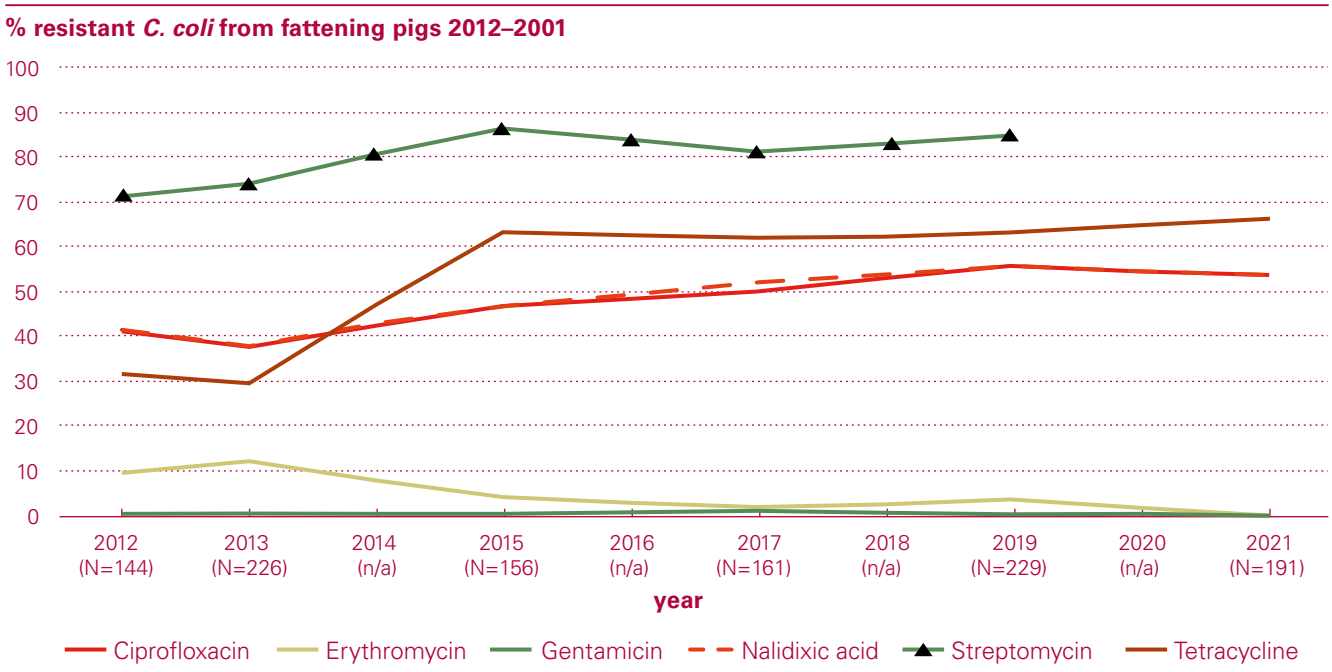


Figure 8. f: Resistance pattern in *C. coli* from fattening pigs 2021.

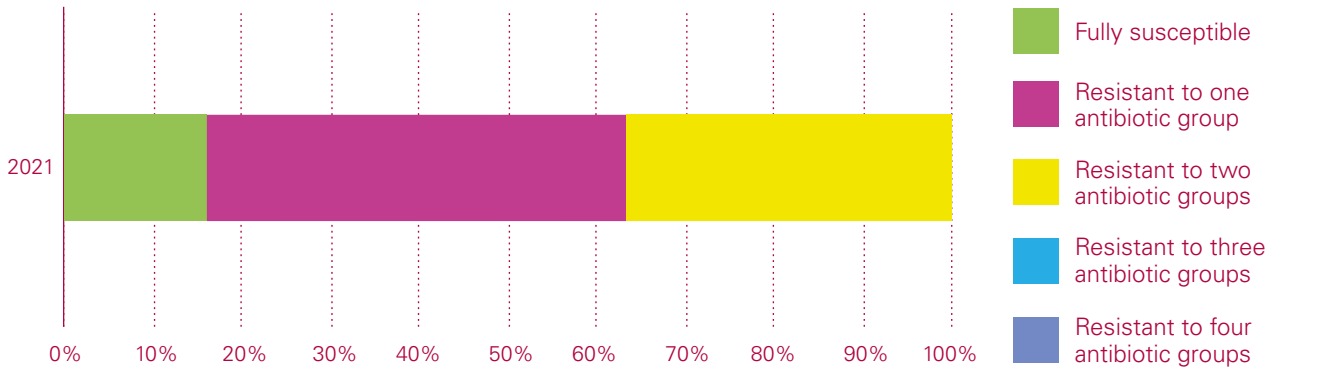


Table 8. g: Number of *C. jejuni/coli* positive samples by origin of chicken meat in 2020.

Origin	No. of samples	No. of *C. coli/C. jejuni* positive samples (%)
Germany	22	12
Hungary	48	30
Slovenia	26	25
France	14	1
Total foreign countries	**110**	**68 (61.2%)**
Switzerland	**186**	**60 (32.2%)**

tant to one antibiotic class (tetracyclines and fluoroquinolones), which corresponds to a prevalence of 39.2%. One third (32.2%) of the isolates were resistant to two antibiotic classes (tetracyclines and fluoroquinolones).

C. jejuni isolate from slaughter calves seems to exhibit comparable resistance profiles to that of *C. coli* from fattening pigs.

8.1.3 *Campylobacter* spp. in poultry meat

In 2020, 296 samples of retail poultry meat (186 of Swiss origin and 110 of foreign origin) were investigated for the presence of *C. jejuni/coli* and antibiotic resistance of these isolates. From 296 samples, 16 *C. coli* and 112 *C. jejuni* were isolated, corresponding to a prevalence of 5.4% for *C. coli* and 37.8% for *C. jejuni*. Of the Swiss meat samples, 32.2% were positive for *C. jejuni/coli*. In meat samples from abroad, the prevalence of *C. jejuni/coli* was significantly higher (61.2%) (Table 8. g).

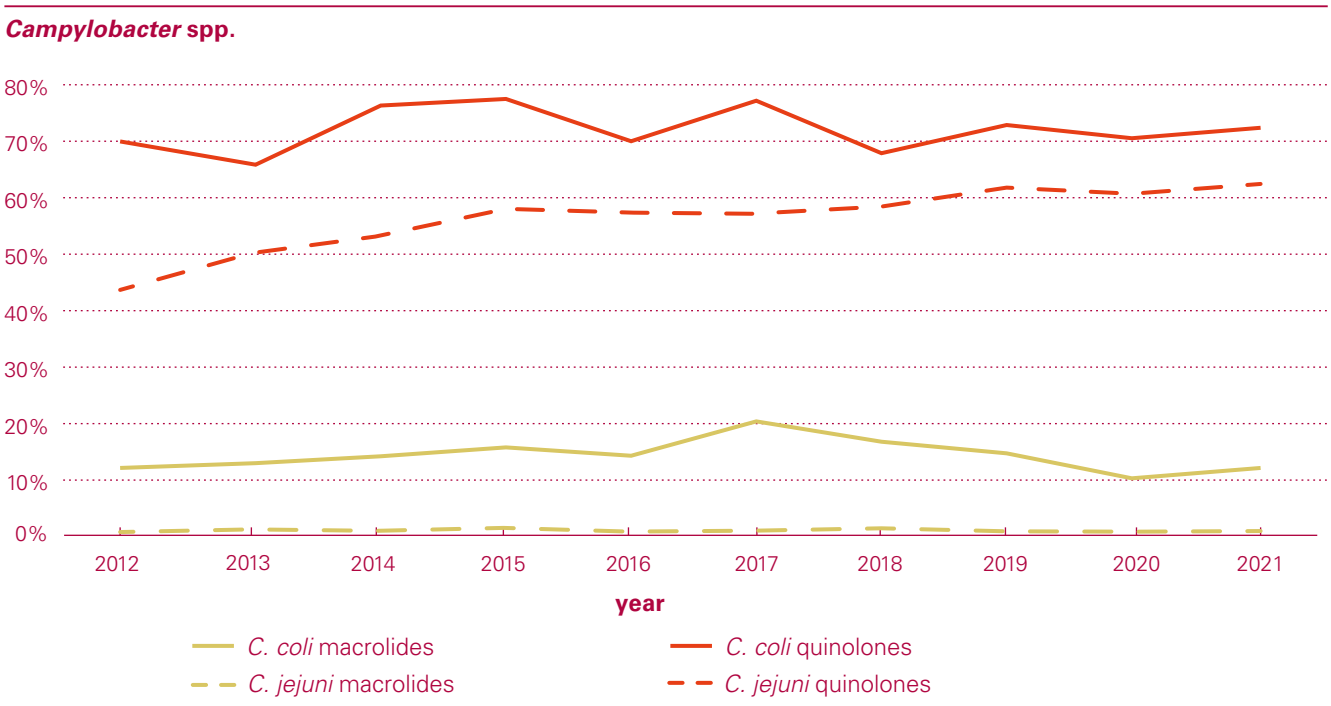
Very high resistance was detected for fluoroquinolones, i.e., 81.3% of *C. coli* and 70.5% of *C. jejuni* (Table 8. h). Moreover, high to moderate resistance levels were found to streptomycin for *C. coli* (31.3%) and *C. jejuni* (16.1%). Regarding tetracycline resistance, high and very high resistance was observed, with 51.8% for *C. jejuni* and 50% for *C. coli*. No resistance against macrolides and gentamicin was detected.

Out of 16 isolates of *C. coli* found in poultry meat, no isolates showed full susceptibility (Table 8. i.) Concerning *C. jejuni,* 27.7% were fully susceptible to the antimicrobials tested (Table 8. j). 41.2% of the *C. coli* isolates and 35.1% of the *C. jejuni* isolates were resistant to two antibiotics. Microbiological resistance to three antibiotic classes was found in 11.8% of *C. coli* and 15.3% of *C. jejuni* isolates.

Table 8. h: Antimicrobial resistance in *C. coli* and *C. jejuni* from chicken meat in 2020.

2020	*C. coli* (n=16)			*C. jejuni* (n=112)		
Antimicrobials	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Ciprofloxacin	13	81.3	57.0–93.4	79	70.5	61.5–78.2
Erythromycin A	0	0	0.0–19.4	0	0	0.0–3.3
Gentamicin	0	0	0.0–19.4	0	0	0.0–3.3
Nalidixic acid	13	81.3	57.0–93.4	79	70.5	61.5–78.2
Streptomycin	5	31.3	14.2–55.6	18	16.1	10.4–24.0
Tetracycline	8	50	28.0–72.0	58	51.8	42.6–60.8

Figure 8. g: Trends in resistance to fluoroquinolones and macrolides in *C. coli* and *C. jejuni* from human clinical isolates in Switzerland between 2012 and 2021.



8.1.4 *Campylobacter* spp. in humans

A total of 6,739 laboratory-confirmed cases of human campylobacteriosis were reported in 2021 (77.4 per 100,000 inhabitants). In ANRESIS, resistance data were available for 3,430 isolates (50.9%): 3,191 were identified as *C. jejuni* (93%) and 239 as *C. coli* (7%). Resistance data for 2021 are shown in Table 8. k, trends in Figure 8. g. Overall, resistance rates were higher in *C. coli*, and higher for fluoroquinolones (72.4% for *C. coli* vs. 62.3% for *C. jejuni*) than for macrolides (11.8% for *C. coli* vs. 0.7% for *C. jejuni*). Fluoroquinolone resistance has increased significantly during the last ten years in *C. jejuni*, while having decreased in both species for macrolides during the last four years.

8.1.5 Discussion

Regarding the resistance pattern of *C. coli* in broilers, we had observed marked changes in the resistance rates to most of the antibiotics in the last years. For 2020, an increase for fluoroquinolones and streptomycin is obvious. For erythromycin, we noticed no significant changes. Small changes are most likely due to the small numbers of isolates monitored, by which single results have a great impact on the resistance rates. In general, *C. coli* from broilers expressed very high levels of resistance to fluroquinolones and tetracyclines.

Table 8. i: Resistance combinations in *C. coli* from chicken meat in 2020.

Resistance patterns	Number of isolates	% of total
Grand total	**16**	
Number of resistances: 0	**0**	**0.0%**
–	0	100.0%
Number of resistances: 1	**7**	**43.8%**
Aminoglycosides	1	14.2%
Fluorquinolones	5	71.4%
Number of resistances: 2	**7**	**41.2%**
Aminoglycosides – fluoroquinolones	1	14.3%
Aminoglycosides – tetracyclines	1	14.3%
Fluoroquinolones – tetracyclines	5	71.4%
Number of resistances: 3	**2**	**11.8%**
Aminoglycosides – fluoroquinolones – tetracyclines	2	100.0%
Number of resistances: 4	**0**	**0.0%**

Aminoglycosides: streptomycin, fentamicin; fluoroquinolones: nalidixic acid, ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin

Table 8. j: Resistance combinations in *C. jejuni* from chicken meat in 2020.

Resistance patterns	Number of isolates	% of total
Grand total	**112**	
Number of resistances: 0	**31**	**27.7%**
–	31	100.0%
Number of resistances: 1	**24**	**21.6%**
Aminoglycosides	1	4.2%
Fluoroquinolones	22	91.7%
Tetracyclines	1	4.2%
Number of resistances: 2	**39**	**35.1%**
Fluoroquinolones – tetracyclines	39	100.0%
Number of resistances: 3	**17**	**15.3%**
Aminoglycosides – fluoroquinolones – tetracyclines	17	100.0%
Number of resistances: 4	**0**	**0.0%**

Aminoglycosides: streptomycin, gentamicin; fluoroquinolones: nalidixic acid, ciprofloxacin; tetracyclines: tetracycline; macrolides: erythromycin

Concerning the resistance level of *C. jejuni* in broilers, with many more isolates, the resistance levels are much more stable. After a slight decrease in the antimicrobial resistance among all tested antibiotics except erythromycin from 2016 to 2018, the resistance rates in 2021 did not change compared to 2018. Very high resistance rates to fluoroquinolones are of utmost importance, besides high resistance rates to tetracyclines.

Among *C. jejuni* and *C. coli* isolates recovered from poultry meat, the highest levels of resistance were noted for fluoroquinolones and tetracyclines, with even higher rates than in *C. jejuni* and *C. coli* isolates from broilers.

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 recorded a decrease in the ciprofloxacin resistance rates of *C. jejuni* from broilers, whereas other European countries such as Denmark and the United Kingdom reported increasing resistance rates. Moreover, Italy and Spain reported decreasing resistance rates against tetracycline in *C. jejuni* from broilers, whereas Germany, Spain and Austria reported increasing resistance rates. Whether the differences between countries regarding the occurrence of resistance in animal isolates are associated with differences in the use of antimicrobials could not be ruled out with the data available to date. 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, as it is still expressed in the bacterium although the selective pressure is no longer present [9].

Fluoroquinolones and macrolides were recommended as antibiotics to treat severe human campylobacteriosis, the most common zoonosis worldwide. Fluoroquinolones were removed from the list of recommended antibiotics, resistance against them having increased in the past. Considering this background, the current observed steady state of very high resistance levels in *C. coli/jejuni* from broilers and meat thereof is of highest relevance for human medicine. 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].

Concerning macrolides, the resistance situation for *C. coli/jejuni* isolates from broilers as well as from poultry meat is still favorable in terms of human campylobacteriosis, as resistant *C. jejuni* isolates occurred only occasionally in broilers and meat thereof. 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* in pigs. Since 2015, the resistance rates are relatively stable, with very high resistance rates against tetracyclines and fluoroquinolones. Concerning erythromycin, we noticed a decrease in the resistance from 12.4% in 2012 to 0% in 2021. Data from the European Food Safety Authority (EFSA) for *C. coli* from fattening pigs showed a comparable resistance pattern, with a higher resistance level against erythromycin than in Swiss isolates. Data on antimicrobial usage in Swiss fattening pigs, needed to assess possible associations between antimicrobial usage and development of resistance in commensals such as *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 DCDCH (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].

Ertapenem was newly included in the program for C. *jejuni/coli* in 2021, as there are indications of carbapenem-resistant *Campylobacter* spp. in human medicine. The isolates showing resistance to ertapenem in *Campylobacter* spp. of slaughter calves is the first finding of carbapenem-resistance in farm animals in Switzerland. Carbapenems are recognized as critically important antimicrobials (CIA) and have not been authorized for use in farm animals in Switzerland. The reasons for carbapenemase-producing bacteria occurring among farm animals are not known. A comparison with prevalence data from other European countries and previous years will be the task of the future.

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 reported (ordinance of the FOPH on laboratory reports), whereas the notification of resistance profiles is not mandatory. In 2021, 1,487 human cases of salmonellosis were reported in Switzerland.

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 must be reported (ordinance of the FSVO on epizootic diseases), and in poultry an active eradication program is in place.

Table 8. k: Resistance rates of *C. coli* and *C. jejuni* from human clinical isolates in 2021.

Campylobacter coli											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Macrolides	113	11.5%	136	10.3%	31	19.4%	280	11.8%	9.9–3.7	↓	–
Quinolones	113	73.5%	139	71.9%	31	71%	283	72.4%	69.7 - 75.1	–	–
Campylobacter jejuni											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Macrolides	1,149	0.5%	1,876	0.9%	166	0%	3,191	0.7%	0.6–0.8	↓	–
Quinolones	1,151	62.8%	1,872	62%	166	63.3%	3,189	62.3%	61.4–63.2	↑	↑

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.

Reported cases of salmonellosis in animals are very rare in Switzerland, with 127 reported cases in 2021 [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 2,668 poultry meat samples (carcasses and meat), 26 (1%) were *Salmonella* spp. positive in 2021 in Switzerland.

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.

Salmonella spp. isolated from livestock 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 third- and fourth-generation cephalosporines and meropenem for detection of ESBL/AmpC- and carbapenemase-producing *Salmonella* spp. In this chapter, data regarding *Salmonella* spp. including *S.* Typhimurium and its monophasic variant isolated from infected or diseased poultry and cattle are shown.

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 35 *Salmonella* spp., including 19 *S.* Typhimurium, 7 *S.* Typhimurium (monophasic variant) and 7 *S.* Enteritidis, were available in 2020. In 2021, 46 bovine *Salmonella* spp. were available, including 20 *S.* Typhimurium, 11 *S.* Typhimurium (monophasic variant) and 11 *S.* Enteritidis (Table 8. l to Table 8. o).

Overall, the vast majority of *Salmonella* spp. isolated from cattle were fully susceptible to all tested antimicrobial classes (2020: 80%, 2021: 71.7%, Figure 8. h). Especially, all but one *S.* Typhimurium isolates were fully susceptible (Table 8. m). In contrast, eight *S.* Typhimurium (monophasic variant) isolates from 2021 expressed multidrug resistance to penicillins, sulfonamides and tetracyclines. Another three *S.* Typhimurium (monophasic variant) isolates showed additional resistance to fluoroquinolones and polymyxins. All *S.* Enteritidis were fully susceptible.

For poultry, antimicrobial resistance data for 81 *Salmonella* spp., including 20 *S.* Typhimurium, 14 *S.* Typhimurium (monophasic variant) and 13 *S.* Enteritidis were available in 2020. In 2021, 78 *Salmonella* spp., including 10 *S.* Typhimurium, 5 *S.* Typhimurium (monophasic variant) and 21 *S.* Enteritidis 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 (2020: 69.1%, 2021: 84.6%, Figure 8. i). Only 4 out of 30 *S.* Typhimurium isolates were not fully susceptible (Table 8. q), 2 *S.* Typhimurium expressed resistance to polymyxins, and another 2 were resistant to penicillins, sulfonamides and tetracyclines. In contrast, all 19 *S.* Typhimurium (monophasic variant) expressed multidrug resistance to various antimicrobials, such as penicillins, sulfonamides, tetracyclines and aminoglycosides. 29 *S.* Enteritidis were fully susceptible to all tested antimicrobials, 5 isolates showed resistance to polymyxins.

Table 8. l: Resistance combinations in *Salmonella* spp. from cattle in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**35**	
Number of resistances: 0	**28**	**80.0%**
–	28	100.0%
Number of resistances: 3	**7**	**20.0%**
Penicillins – sulfonamides – tetracyclines	7	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**46**	
Number of resistances: 0	**33**	**71.7%**
–	33	100.0%
Number of resistances: 1	**2**	**4.4%**
Polymyxins	2	100.0%
Number of resistances: 3	**8**	**17.4%**
Penicillins – sulfonamides – tetracyclines	8	100.0%
Number of resistances: 4	**3**	**6.5%**
Fluoroquinolones – penicillins – sulfonamides – tetracyclines	2	66.7%
Penicillins – polymyxins – sulfonamides – tetracyclines	1	33.3%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol

Table 8. m: Resistance combinations in *S. Typhimurium* from cattle in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**19**	
Number of resistances: 0	**19**	**100.0%**
–	19	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**20**	
Number of resistances: 0	**19**	**95.0%**
–	19	100.0%
Number of resistances: 1	**1**	**5.0%**
Polymyxins	1	100.0%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol

Table 8. n: Resistance combinations in *S. Typhimurium* (monophasic variant) from cattle in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**7**	
Number of resistances: 3	**7**	**100.0%**
Penicillins – sulfonamides – tetracyclines	7	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**11**	
Number of resistances: 3	**8**	**72.7%**
Penicillins – sulfonamides – tetracyclines	8	100.0%
Number of resistances: 4	**3**	**27.3%**
Fluoroquinolones – penicillins – sulfonamides – tetracyclines	2	66.7%
Penicillins – polymyxins – sulfonamides – tetracyclines	1	33.3%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol

Figure 8. h: Resistance pattern in *Salmonella* spp. from cattle 2020 and 2021.

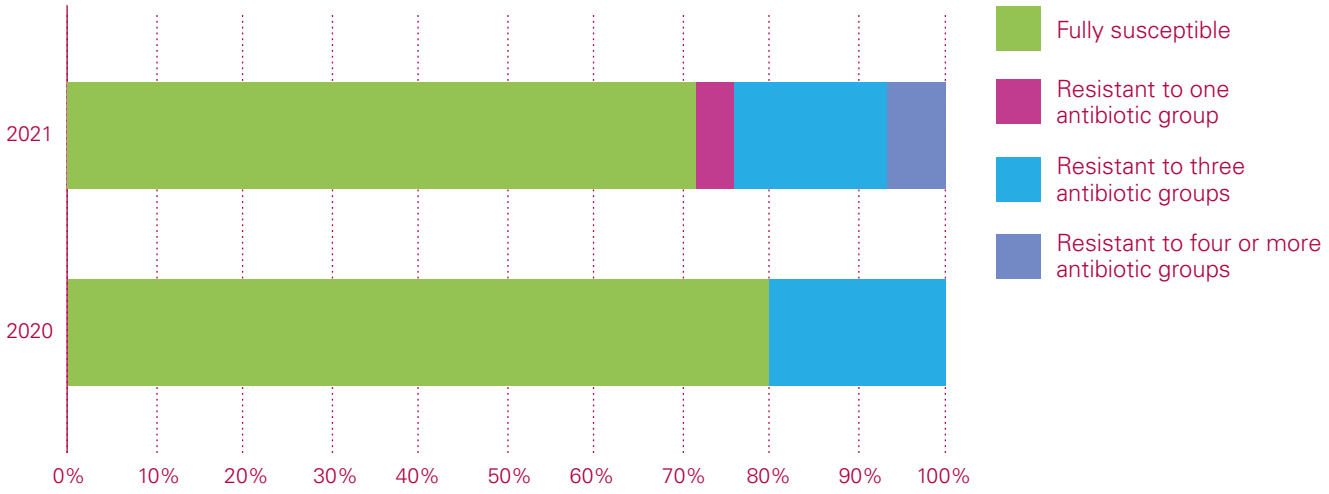


Figure 8. i: Resistance pattern in *Salmonella* spp. from hen 2020 and 2021.

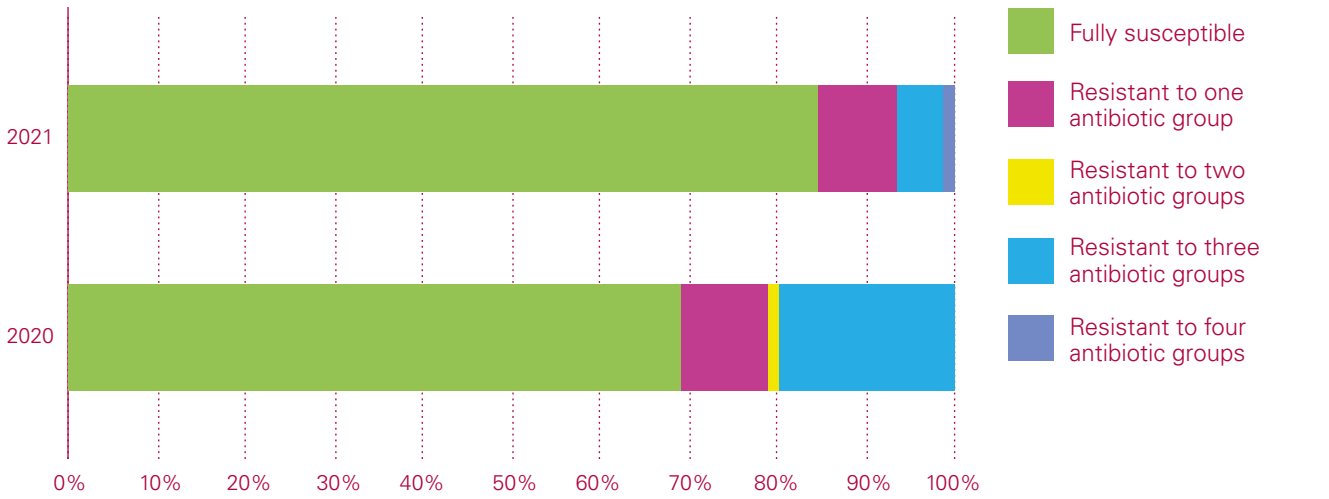


Table 8. o: Resistance combinations in *S. Enteritidis* from cattle in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**7**	
Number of resistances: 0	**7**	**100.0%**
–	7	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**11**	
Number of resistances: 0	**11**	**100.0%**
–	11	100.0%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol

Table 8. p: Resistance combinations in *Salmonella* spp. from hen in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**81**	
Number of resistances: 0	**56**	**69.1%**
–	56	100.0%
Number of resistances: 1	**8**	**9.9%**
Polymyxins	4	50.0%
Tetracyclines	4	50.0%
Number of resistances: 2	**1**	**1.2%**
Amphenicols – fluoroquinolones	1	100.0%
Number of resistances: 3	**16**	**19.8%**
Aminoglycosides – fluoroquinolones – polymyxins	1	6.3%
Penicillins – sulfonamides – tetracyclines	15	93.8%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**78**	
Number of resistances: 0	**66**	**84.6%**
–	66	100.0%
Number of resistances: 1	**7**	**9%**
Fluoroquinolones	1	14.3%
Polymyxins	6	85.7%
Number of resistances: 3	**4**	**5.1%**
Penicillins – sulfonamides – tetracyclines	4	100.0%
Number of resistances: 4	**1**	**1.3%**
Aminoglycosides – penicillins – sulfonamides – tetracyclines	1	100.0%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol

Table 8. q: Resistance combinations in *S. Typhimurium* from hen in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**20**	
Number of resistances: 0	**17**	**85.0%**
–	17	100.0%
Number of resistances: 1	**1**	**5.0%**
Polymyxins	1	100.0%
Number of resistances: 3	**2**	**10.0%**
Penicillins – sulfonamides – tetracyclines	2	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**10**	
Number of resistances: 0	**9**	**90.0%**
–	9	100.0%
Number of resistances: 1	**1**	**10.0%**
Polymyxins	1	100.0%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol; polymyxins: colistin

Table 8. r: Resistance combinations in *S. Typhimurium* (monophasic variant) from hen in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**14**	
Number of resistances: 1	**1**	**7.1%**
Tetracyclines	1	100.0%
Number of resistances: 3	**13**	**92.9%**
Penicillins – sulfonamides – tetracyclines	13	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**5**	
Number of resistances: 3	**4**	**80.0%**
Penicillins – sulfonamides – tetracyclines	4	100.0%
Number of resistances: 4	**1**	**20.0%**
Aminoglycosides – penicillins – sulfonamides – tetracyclines	1	100.0%

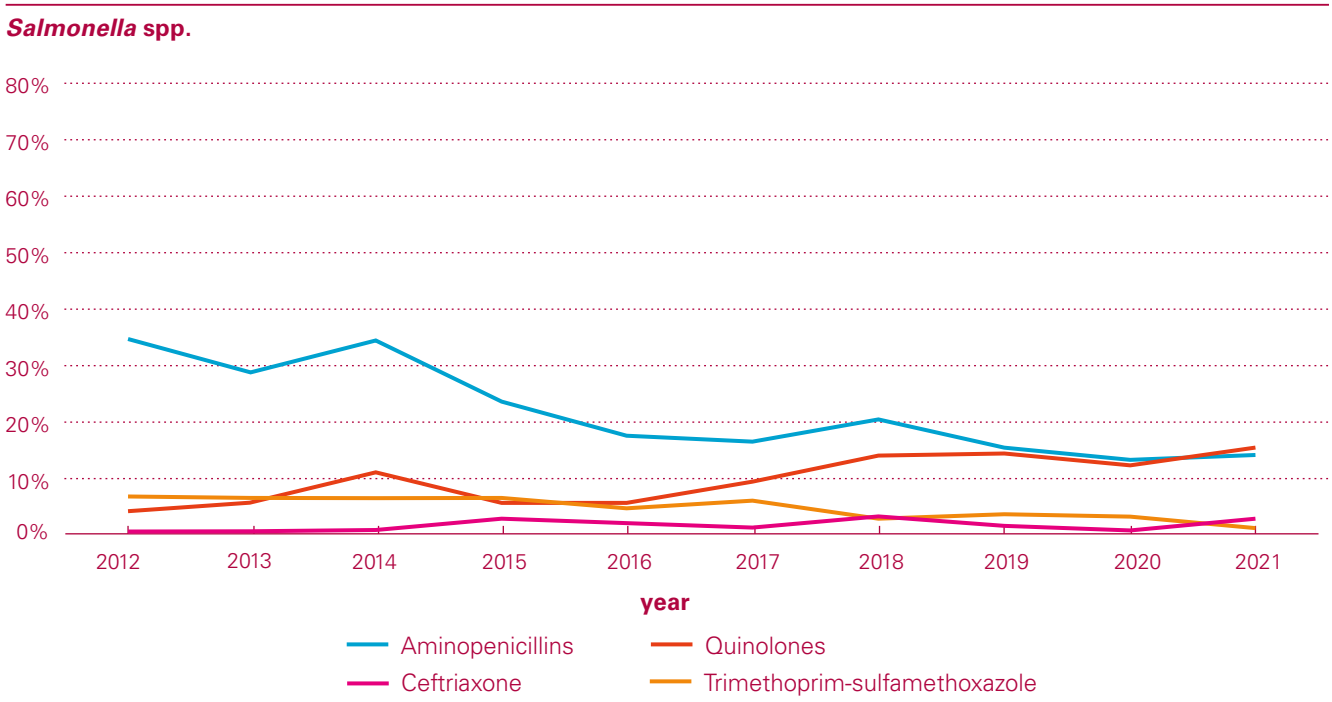
Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol; polymyxins: colistin

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 life-saving. 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 1,496 cases observed in 2021 in Switzerland. Resistance rates are only available for aminopenicillins, ceftriaxone, trimethoprim-sulfamethoxazole and fluoroquinolones (Table 8. t). 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. t). From 2012 to 2021, resistance-rates decreased for aminopenicillins, but increased for fluoroquinolones (Figure 8. j).

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 2012 and 2021.



8.2.3 Discussion

Thanks to 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.

Overall, *Salmonella* spp. from cattle and hens showed constantly very high rates of full susceptibility to the antimicrobials tested. Especially, *S.* Typhimurium and *S.* Enteritidis isolates are highly susceptible, whereas the vast majority of *S.* Typhimurium (monophasic variant) isolates regularly express multidrug resistance to important antimicrobial classes such as penicillins, sulfonamides and tetracyclines.

Fluoroquinolones and third-generation cephalosporins, such as ceftriaxone, are critically important antimicrobials for the treatment of human salmonellosis. Importantly, neither ESBL/AmpC- nor carbapenemase-producing *Salmonella* spp. isolates were found in cattle or poultry. Resistance to fluoroquinolones was found for the first time in three *Salmonella* spp. from poultry.

Data on antimicrobial resistance in *Salmonella* spp. from Switzerland are not directly comparable with data from the European monitoring, as the latter do not include isolates from clinical cases. Nevertheless, the proportion of completely susceptible *Salmonella* spp. isolates from broilers and calves at slaughter ranges from 37.3% to 48.4% and is thereby much lower than the proportion in Swiss clinical isolates from hens and cattle [8]. 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 exhibit more antimicrobial resistances than others, e.g., *S.* Typhimurium and *S.* Enteritidis. Moreover, multidrug resistant *S.* Infantis has emerged in various European countries and recently in Switzerland in both humans and livestock [12–15]. A single ESBL/AmpC-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. could develop chromosomal-linked colistin resistance, which targets diverse regulatory systems involved in lipopolysaccharide (LPS) building. Moreover, *Salmonella* spp. of different origins (humans, animals, food) carrying plasmid-mediated colistin resistance conferred by *mcr* genes have been detected in various serovars of *Salmonella* spp. [16]. Group D *Salmonella enterica* serovars differ in their susceptibility to

Table 8. s: Resistance combinations in *S. Enteritidis* from hen in 2020 and 2021.

Resistance patterns 2020	Number of isolates	% of total
Grand total	**13**	
Number of resistances: 0	**10**	**76.9%**
–	10	100.0%
Number of resistances: 1	**3**	**23.1%**
Polymyxins	3	100.0%
Resistance patterns 2021	**Number of isolates**	**% of total**
Grand total	**21**	
Number of resistances: 0	**19**	**90.5%**
–	19	100.0%
Number of resistances: 1	**2**	**9.5%**
Polymyxins	2	100.0%

Penicillins: ampicillin; sulfonamides: sulfamethoxazole, tetracyclines. Tetracycline, tigecycline, diaminopyrimidine derivatives: trimethoprim; amphenicols: chloramphenicol; polymyxins: colistin

Table 8. t: Resistance rates of *Salmonella* from human clinical isolates 2021

Salmonella ser. Typhimurium											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	11	27.3%	27	40.7%	0	0%	38	36.8%	29.0–44.6	–	↓
Ceftriaxone	7	14.3%	16	0%	0	0%	23	4.3%	0.1–8.5	–	–
Quinolones	12	8.3%	32	9.4%	0	0%	44	9.1%	4.8–13.4	–	–
Trimethoprim-sulfamethoxazole	12	0%	32	3.1%	0	%0	44	2.3%	0.0–4.6	–	–
Salmonella ser. Enteritidis											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	67	6%	57	7%	1	0%	125	6.4%	4.2–8.6	–	–
Ceftriaxone	29	0%	37	2.7%	0	0%	66	1.5%	0.0–3.0	–	–
Quinolones	68	17.6%	63	15.9%	1	0%	132	16.7%	13.5–19.9	–	↑
Trimethoprim-sulfamethoxazole	73	0%	67	0%	1	0%	141	0%	0.0–0.0	–	–

colistin and are frequently intrinsically resistant (MIC > 2 µg/ml) [17]. Microbiological resistance to colistin was detected in 14 out of 240 *Salmonella* spp. isolates (5.8%) from cattle and hens. It is important to note that six of these belong to group D *Salmonella* spp.

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 groups differ markedly, although antimicrobial classes are comparable. Moreover, methods used for susceptibility testing (various in human medicine/broth microdilution in veterinary monitoring) and interpretative criteria (clinical breakpoint in human isolates/epidemiological cutoff values in animal isolates) differ substantially. Nevertheless, detection of critically important multidrug resistant *Salmonella* spp., such as ESBL/pAmpC- and carbapenemase-producing bacteria or colistin-resistant bacteria, is comparable. Therefore, given 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

Antimicrobial resistance of *Campylobacter jejuni* from canine and bovine cases of campylobacteriosis

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Human campylobacteriosis is the most common cause of bacterial gastroenteritis worldwide. *Campylobacter* (*C.*) *jejuni* is the most frequently isolated species in humans with diarrhea [1]. In most cases, the infection is foodborne, from handling or eating undercooked poultry meat, and outbreaks have been linked to raw milk or contaminated water. Source attribution studies identified *C. jejuni* from poultry as the main source of human campylobacteriosis [2].

Therefore, antimicrobial resistance in *C. jejuni* is one key element of the European antimicrobial resistance monitoring. High microbiological resistance rates of *Campylobacter* spp. from humans to critically important antimicrobials such as fluoroquinolones are detected in Europe and Switzerland [1, 3]. *C. jejuni* from Swiss humans showed a high resistance rate to tetracycline (26%) as well [3]. Results from the Swiss antimicrobial resistance monitoring program 2020 using cecum samples from broilers showed that 48% of the isolated *C. jejuni* were microbiologically resistant to fluoroquinolones and 30% to tetracycline. The microbiological resistance rate to erythromycin was very low (0.6%). Comparable microbiological resistance rates were also found in *C. jejuni* isolated from fresh poultry meat [3].

On the other hand, much less is known about the resistance rates of *Campylobacter* spp. strains isolated from clinical cases of companion animals and cattle. Although not identified as main sources of human campylobacteriosis, *Campylobacter* spp. from these animal species could contribute to human cases, and transmission to humans is possible [2, 3]. Therefore, we determined the antimicrobial resistance rates of *C. jejuni* isolated from diseased dogs and cattle between 2015 and 2018. We used the method harmonized across Europe to compare these data to the known resistance rates of regularly monitored healthy livestock animals at slaughterhouses.

In this study, the microbiological resistance rate to ciprofloxacin in canine *C. jejuni* isolates was slightly lower (39%; n=15/39), while the microbiological resistance rate in bovine *C. jejuni* was slightly higher (61%; n=11/18) than that found in *C. jejuni* isolated from broilers (48%; n=179) [4]. Moreover, for tetracycline, the microbiological resistance rates of *C. jejuni* from dogs (23%) and cattle (33%) were comparable to that of *C. jejuni* from broilers (30%). No microbiological resistance for erythromycin was detected in diseased animals, which is comparable to the very low rate in broilers (0.6%).

Although the overall number of *C. jejuni* isolates from clinical cases of canine and bovine campylobacteriosis is limited, it is interesting that antimicrobial resistance patterns of *C. jejuni* do not differ substantially between isolates from diseased and slaughtered animals. One might expect that resistance rates are higher in diseased and maybe therefore treated animals than healthy slaughter animals. Moreover, the antimicrobial treatment regimens and antimicrobials chosen for various livestock species differ markedly, e.g., for broilers in particular only oral treatment is applied, as opposed to cattle, where treatment routes other than oral are common. Moreover, high antimicrobial resistance to ciprofloxacin and tetracycline is also common in human *C. jejuni* isolates. High antimicrobial resistance rates to ciprofloxacin turned out to be a common feature of *C. jejuni* isolated from diseased humans, dogs, as well as cattle and healthy broilers at slaughter and meat therefore. Fluoroquinolone resistance in *Campylobacter* spp. often arises from point mutations in the QRDR of the *gyrA* gen [5]. In contrast to the presence of additional resistance genes, these point mutations are not associated with a loss of fitness, leading to a rapid development of resistance which may be stable although the selective pressure disappears. Moreover, micro-

Table 1: Microbiological resistance rates of *C. jejuni* isolated from canine, feline and bovine clinical cases

Antimicrobial	Host		
	Dog (%) [95% CI]	Cat (%) [95%CI]	Cattle (%) [95% CI]
Ciprofloxacin (CIP)	15/39 (38.5%) [24.9–54.1]	3/9	11/18 (61.1%) [38.6–79.7]
Tetracycline (TET)	9/39 (23.1%) [12.7–38.3]	1/9	6/18 (33.3%) [16.3–56.3]
Erythromycin (ERY)	0/39 (0%) [0.0–9.0]	0/9	0/18 (0%) [0.0–17.6]
Gentamicin (GEN)	0/39 (0%) [0.0–9.0]	0/9	0/18 (0%) [0.0–17.6]

biological resistance to tetracycline is often detected in *C. jejuni* isolated from animals and humans. Tetracycline resistance in *Campylobacter* spp. is mediated by various *tet* genes, of which *tet(O)* is the most frequent one [6]. The *tet* genes can be located either on the chromosome or on plasmids. As tetracycline belongs to the group of first-line antimicrobials, it is often used in veterinary medicine, and antimicrobial treatment is the driver of positive selection for tetracycline-resistant bacteria.

The finding of high resistance rates of *Campylobacter* spp. to important antimicrobials for both human and veterinary medicine emphasizes the need for regular AMR monitoring, not only in healthy slaughter animals but also in clinical cases of livestock and companion animals.

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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 these populations. These bacteria constitute a reservoir of potentially transferable resistance genes that can 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 multidrug-resistant bacteria in the last decades in human and veterinary medicine, the monitoring was expanded to ESBL/AmpC-producing and carbapenemase-producing *E. coli* and, since 2020, to *Klebsiella* spp.

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

All isolates tested were derived 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 2012 and 2020 (N = total number of tested isolates, values for 2015, 2017, 2019 interpolated [n/a]).

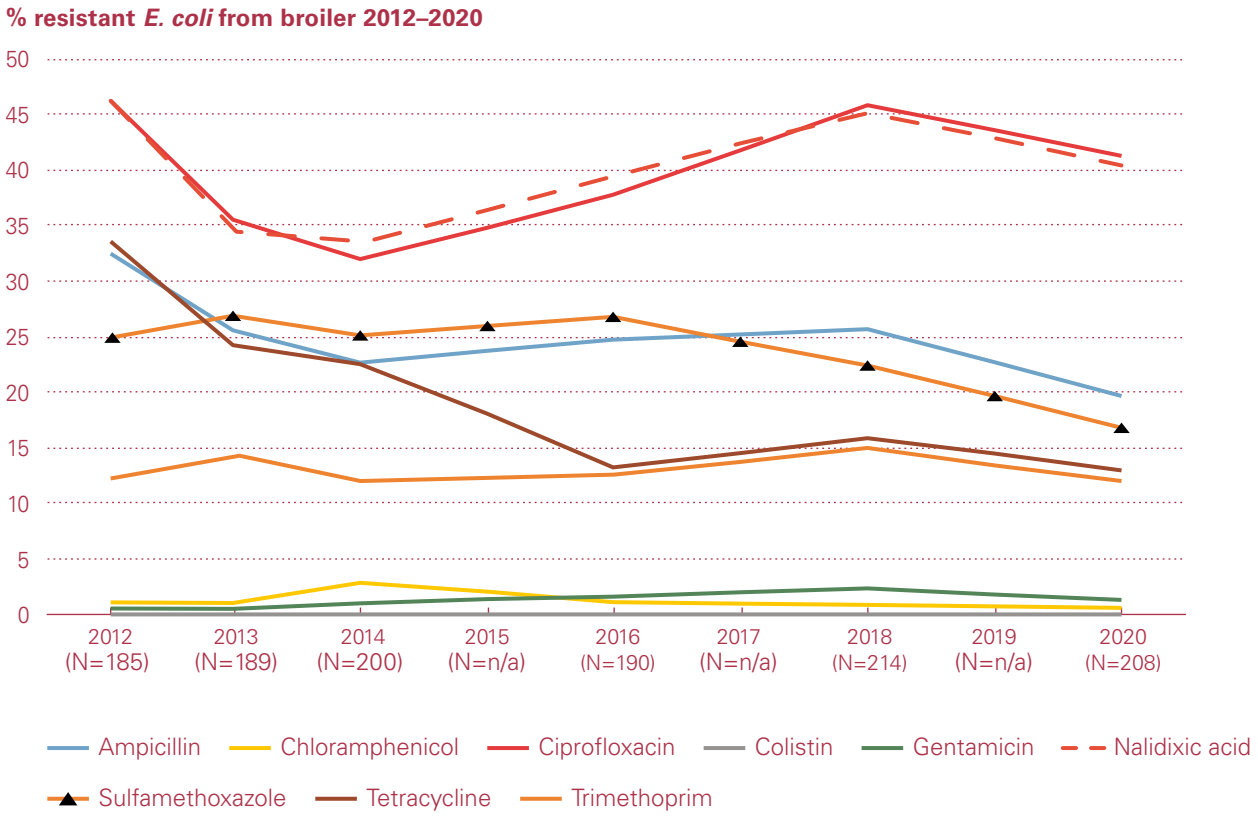
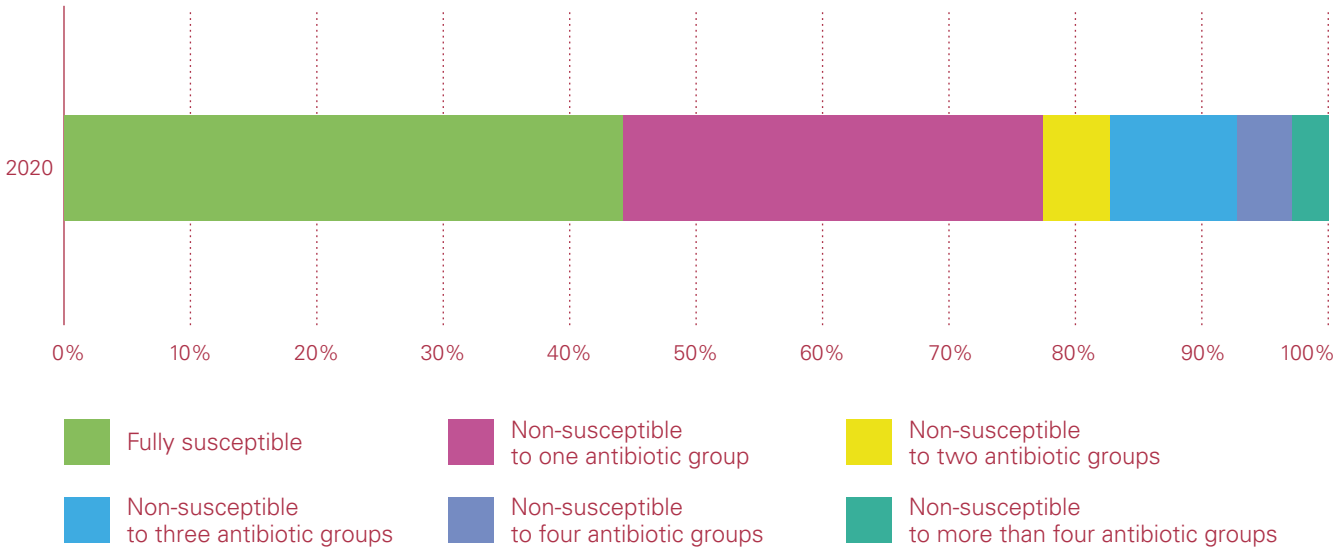


Figure 9. b: Resistance pattern in *E. coli* from broiler 2020.



9.1 *Escherichia coli*

9.1.1 *Escherichia coli* in broilers

In 2020, a random sample of 217 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* (n = 208) were isolated by the direct detection method. The highest levels of antimicrobial resistance were detected for fluoroquinolones (41.3%), ampicillin (19.7%), sulfonamides (16.8%), tetracyclines (13.0%) and trimethoprim (12.0%) (Figure 9. a). Compared to 2018, an overall decrease of antimicrobial resistance against all antimicrobial classes tested was observed. Neither presumptive ESBL/AmpC producers nor colistin resistance were identified.

Overall, 44.2% of all *E. coli* showed no resistance to any antimicrobial substance tested (Figure 9. b). 69 isolates (33.2%) were resistant to just one antibiotic class, mainly to fluoroquinolones. 11 out of the 208 isolates (5.3%) showed resistance to two antibiotic classes. 21 isolates (10.1%) were resistant to three, and nine isolates (4.3%) to four antibiotic classes (Table 9. a). Finally, six isolates (2.9%) showed multidrug resistance against five antimicrobial classes.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of origin of the flocks tested was integrated in the analyses of antimicrobial resistance in livestock. Due to the very low number of isolates, statistically significant conclusions could not be drawn (Table 9. b). In contrast to 2018, no differences in microbiological resistance rates for antimicrobials could be detected between the southwestern region, the central region and the eastern cantons of Switzerland.

9.1.2 *Escherichia coli* in fattening pigs

In 2021, a random sample of 188 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 170 samples by the direct detection method. The highest levels of antimicrobial resistance were detected for tetracyclines (30.0%), sulfonamides (29.4%), ampicillin (16.5%) and trimethoprim (14.7%) (Figure 9. c).

Compared to 2019, an increase in antimicrobial resistance against tetracyclines, and slightly increased antimicrobial resistance rates against trimethoprim, ampicillin and chloramphenicol were observed (Figure 9. c). Neither presumptive ESBL/AmpC producers nor colistin resistance were identified.

Overall, 51.8% of all *E. coli* displayed no resistance to any antimicrobial substance tested (Table 9. c, Figure 9. d). 39 isolates (22.9%) were resistant to just one antibiotic class, mainly to sulfonamides or tetracyclines. 18 isolates (10.6%) showed resistance to two antibiotic classes. Ten isolates (5.9%) were resistant to three antibiotic classes, 11 isolates (6.5%) were resistant to four antibiotic classes, and three isolates showed resistance to five antibiotic classes (1.8%). Finally, one isolate (0.5%) showed multidrug resistance against six antimicrobial classes.

Because of remarkable differences in resistance rates of human isolates across Switzerland, the region of origin of the slaughter batches was integrated in the analyses of antimicrobial resistance in livestock. Due to the very low number of isolates, statistically significant conclusions could not be

Table 9. a: Non-susceptibility combinations in commensal *E. coli* in broilers in 2020.

Resistance patterns	Number of isolates	% of total
Grand total	**208**	
Number of resistances: 0	**92**	**44.2%**
–	92	100.0%
Number of resistances: 1	**69**	**33.2%**
Fluoroquinolones	57	82.6%
Penicillins	8	11.6%
Tetracyclines	4	5.8%
Number of resistances: 2	**11**	**5.3%**
Diaminopyrimidine derivatives – fluoroquinolones	1	9.1%
Diaminopyrimidine derivatives – sulfonamides	1	9.1%
Fluoroquinolones – penicillins	2	18.2%
Fluoroquinolones – tetracyclines	4	36.4%
Penicillins – tetracyclines	3	27.3%
Number of resistances: 3	**21**	**10.1%**
Aminoglycosides – fluoroquinolones – sulfonamides	3	14.3%
Amphenicols – sulfonamides – tetracyclines	1	4.8%
Diaminopyrimidine derivatives – fluoroquinolones – penicillins	1	4.8%
Diaminopyrimidine derivatives – fluoroquinolones – sulfonamides	2	9.5%
Diaminopyrimidine derivatives – penicillins – sulfonamides	9	42.9%
Fluoroquinolones – macrolides – sulfonamides	1	4.8%
Fluoroquinolones – penicillins – sulfonamides	2	9.5%
Fluoroquinolones – sulfonamides – tetracyclines	2	9.5%
Number of resistances: 4	**9**	**4.3%**
Diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides	2	22.2%
Diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	3	33.3%
Fluoroquinolones – penicillins – sulfonamides – tetracyclines	4	44.4%
Number of resistances: 5	**6**	**2.9%**
Diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	6	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

drawn (Table 9. d). Overall, complete susceptibility rates are higher in the central and eastern regions of Switzerland than in the southwestern cantons, but from the latter, the number of isolates was low.

9.1.3 *Escherichia coli* in slaughter calves

In 2021, a random sample of 191 calves was examined at slaughter for the occurrence of antimicrobial resistance patterns in indicator *E. coli* using cecal samples. Indicator *E. coli* were isolated from 180 samples by the direct detection method. The highest levels of antimicrobial resistance were detected for tetracyclines (28.3%), sulfonamides (27.2%), ampicillin (26.1%), trimethoprim (12.2%) and chloramphenicol (7.2%) (Figure 9. e). Compared to 2019, we observed a marked decrease in antimicrobial resistance against sulfonamides, tetracyclines and fluoroquinolones, whereas the resistance rates against ampicillin and amphenicols did not change markedly. Resistance rates against aminoglycosides increased. Two isolates were identified as presumptive ESBL/AmpC producers. Colistin resistance was not detected.

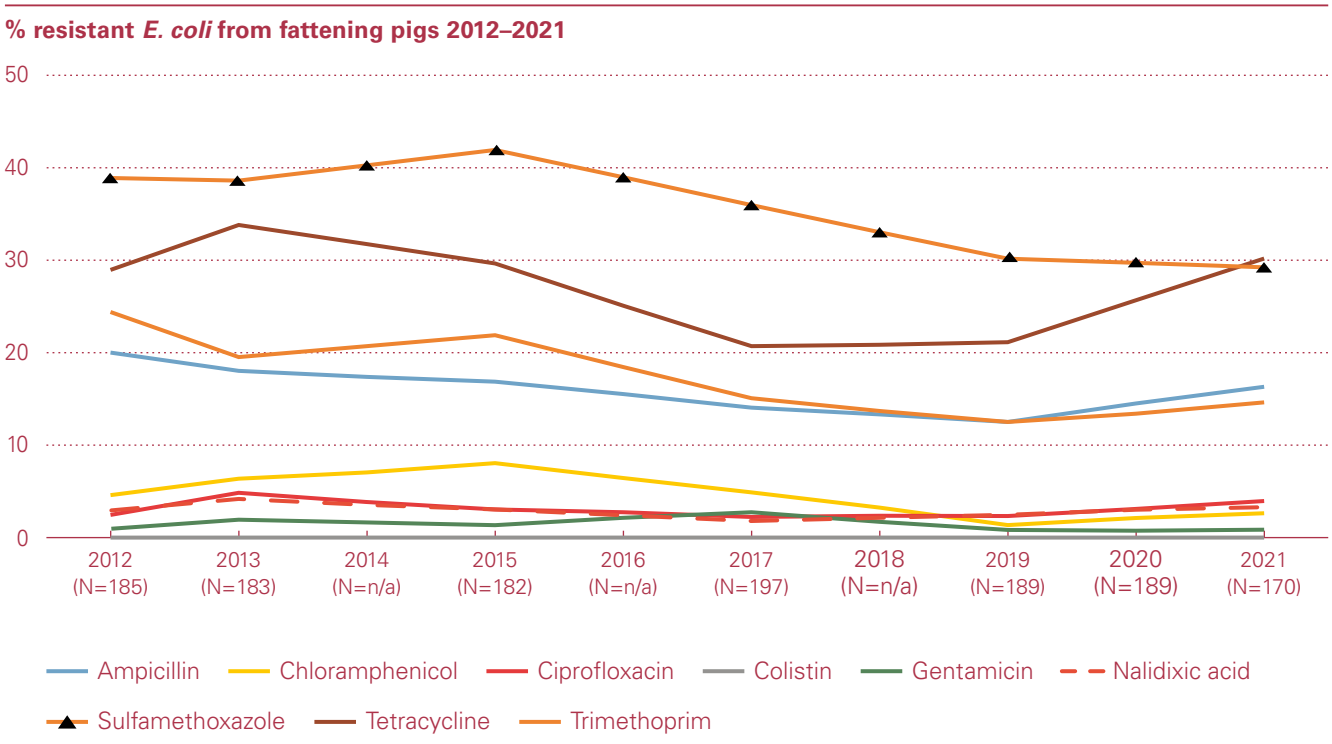
Overall, 62.8% of all *E. coli* exhibited no resistance to any antimicrobial substance tested (Table 9. e, Figure 9. f). 15 isolates (8.3%) were resistant to just one antibiotic class, mainly to penicillins or tetracyclines. 14 isolates (7.8%) showed resistance to two antibiotic classes. Another 14 isolates (7.8%) were resistant to three antibiotic classes, ten isolates (5.6%) were resistant to four, and seven isolates (3.9%) to five antimicrobial classes. Finally, six isolates (3.3%) showed multidrug resistance against six antimicrobial classes and one isolate was resistant against seven antibiotic classes.

Table 9. b: Non-susceptibility rates in commensal *E. coli* from broilers in 2018 and 2020 in different regions in Switzerland.

Escherichia coli n=208									
Antimicrobial	South-West (n=66)		Center (n=106)		East (n=36)		total		
	n	%	n	%	n	%	n	%	95% CI
Susceptible	29	43.9%	50	47.2%	13	36.1%	92	44.2%	37.6–51.0
Diaminophyridine derivates	7	10.6%	14	13.2%	4	11.1%	25	12.0%	8.3–17.1
Fluoroquinolones	31	46.9%	38	35.8%	18	50.0%	87	41.3%	34.9–48.1
Tetracyclines	9	13.6%	14	13.2%	4	11.1%	27	13.0%	9.1–18.2
Sulfonamides	13	19.7%	19	17.9%	3	8.3%	35	16.8%	12.4–22.5
Penicillins	14	21.2%	19	17.9%	8	22.2%	41	19.7%	14.9–25.6

95% CI: 95% confidence interval, fluoroquinolones: ciprofloxacin; tetracyclines: tetracycline; sulfonamides: sulfamethoxazole; penicillins: ampicillin; diaminophyridine derivates: trimethoprim
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. c: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from fattening pigs between 2012 and 2021 (N = total number of tested isolates, values for 2014, 2016, 2018, 2020 interpolated [n/a]).



9.1.4 Discussion

Resistance rates of commensal *E. coli* from broilers in Switzerland in 2020 showed an overall decreasing trend for all antimicrobials tested (Figure 9. a). Nevertheless, resistance rates against critically important fluoroquinolones are still on a high level (>40%). The proportion of fully susceptible isolates increased from 37.4% in 2018 to 44.2% in 2020.

In contrast, trends in resistance levels of *E. coli* from fattening pigs increased slightly between 2019 and 2021 for most of the antimicrobials tested (Figure 9. c). No significant decrease of resistance was detected for any antimicrobial class tested. Over the years, decreasing trends are obvious for sulfonamides, trimethoprim and ampicillin, and levels of fluoroquinolone resistances are constantly low (<5%). The same is true for resistance against amphenicols. The proportion of fully susceptible isolates decreased slightly from 58.7% in 2019 to 51.8% in 2021.

For slaughter calves, there is no obvious general trend for the resistance rates against the tested antimicrobials (Figure 9. e). Decreasing rates of resistance against tetracyclines, sulfonamides and trimethoprim were detected. Only one isolate exhibited resistance against fluoroquinolones. After a marked decrease in rates of resistance against ampicillin from 2017 to 2019, no further decrease in the resistance rate was observed in 2021.

Table 9. c: Non-susceptibility combinations in commensal *E. coli* in fattening pigs in 2021.

Resistance patterns	Number of isolates	% of total
Grand total	**170**	
Number of resistances: 0	**88**	**51.8%**
–	88	100.0%
Number of resistances: 1	**39**	**22.9%**
Aminoglycosides	1	2.6%
Penicillins	2	5.1%
Sulfonamides	12	30.8%
Tetracyclines	24	61.5%
Number of resistances: 2	**18**	**10.6%**
Diaminopyrimidine derivatives – sulfonamides	3	16.7%
Fluoroquinolones – tetracyclines	1	5.6%
Penicillins – sulfonamides	7	38.9%
Penicillins – tetracyclines	4	22.2%
Sulfonamides – tetracyclines	3	16.7%
Number of resistances: 3	**10**	**5.9%**
Amphenicols – sulfonamides – tetracyclines	1	10.0%
Diaminopyrimidine derivatives – fluoroquinolones – sulfonamides	1	10.0%
Diaminopyrimidine derivatives – penicillins – sulfonamides	4	40.0%
Diaminopyrimidine derivatives – sulfonamides – tetracyclines	2	20.0%
Fluoroquinolones – sulfonamides – tetracyclines	1	10.0%
Penicillins – sulfonamides – tetracyclines	1	10.0%
Number of resistances: 4	**11**	**6.5%**
Aminoglycosides – diaminopyrimidine derivatives – fluoroquinolones – sulfonamides – tetracyclines	3	27.3%
Diaminopyrimidine derivatives – fluoroquinolones – sulfonamides – tetracyclines	1	9.1%
Diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	7	63.6%
Number of resistances: 5	**3**	**1.8%**
Aminoglycosides – diaminopyrimidine derivatives – fluoroquinolones – sulfonamides – tetracyclines	1	33.3%
Diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	2	66.7%
Number of resistances: 6	**1**	**0.6%**
Amphenicols – 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

These overall differences in resistance between poultry, porcine and bovine *E. coli* populations are consistent with the data from the European antimicrobial resistance monitoring until 2020, but with distinct discrepancies in some countries [1].

Fluoroquinolone resistance rates of *E. coli* from broilers showed a decrease in 18 European countries, those for ampicillin and tetracyclines decreased in 15 countries [1]. As broiler production is highly concentrated internationally, with just a few suppliers of chicken for all of Europe, these global trends argue for changes in usage of antimicrobials in the companies at the top of the broiler production pyramid [2].

European trends in antimicrobial resistance rates of *E. coli* from fattening pigs are more diverse, but most of the European countries (15) reported a decrease in resistance rates against tetracyclines as well. No changes in resistance rates against ampicillin and ciprofloxacin were observed in most of the European countries. For calves, data are sparse, but most of the reporting countries observed a steady state of resistance rates in the last years.

Figure 9. d: Resistance pattern in *E. coli* from fattening pigs 2021.

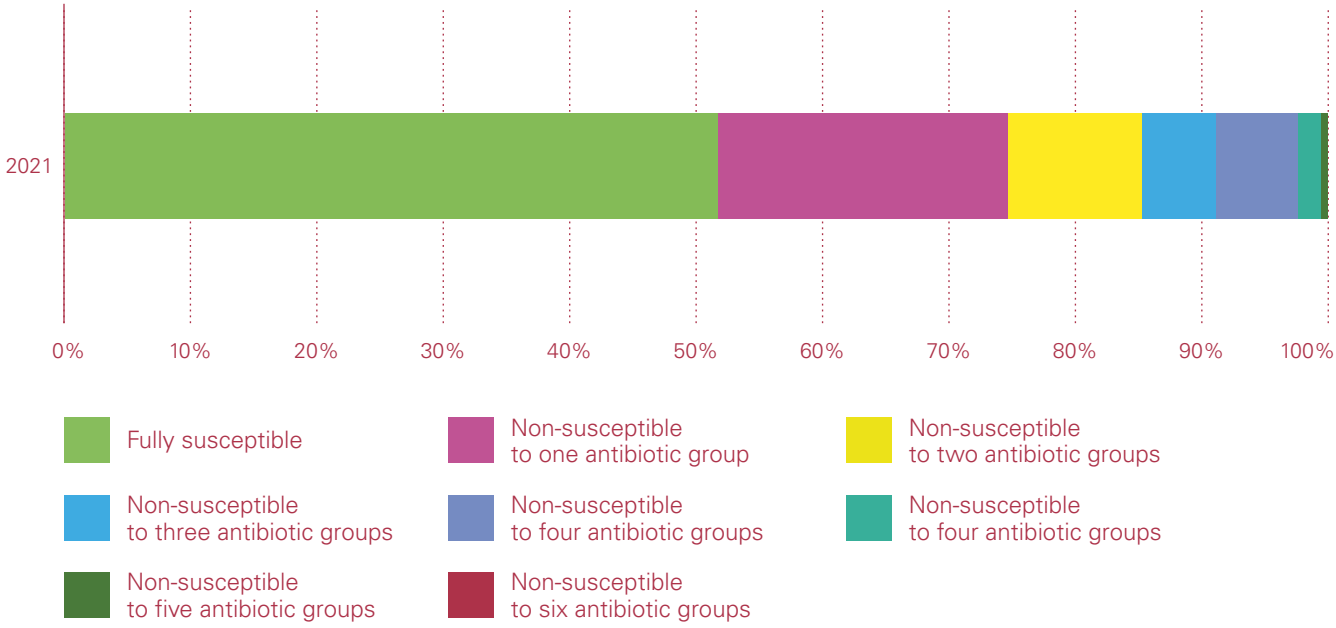


Figure 9. e: Trends in ampicillin, ciprofloxacin, gentamicin, sulfamethoxazole and tetracycline resistance in *Escherichia coli* from slaughter calves between 2010 and 2019 (N = total number of tested isolates, values for 2014, 2016, 2018, 2020 interpolated [n/a]).

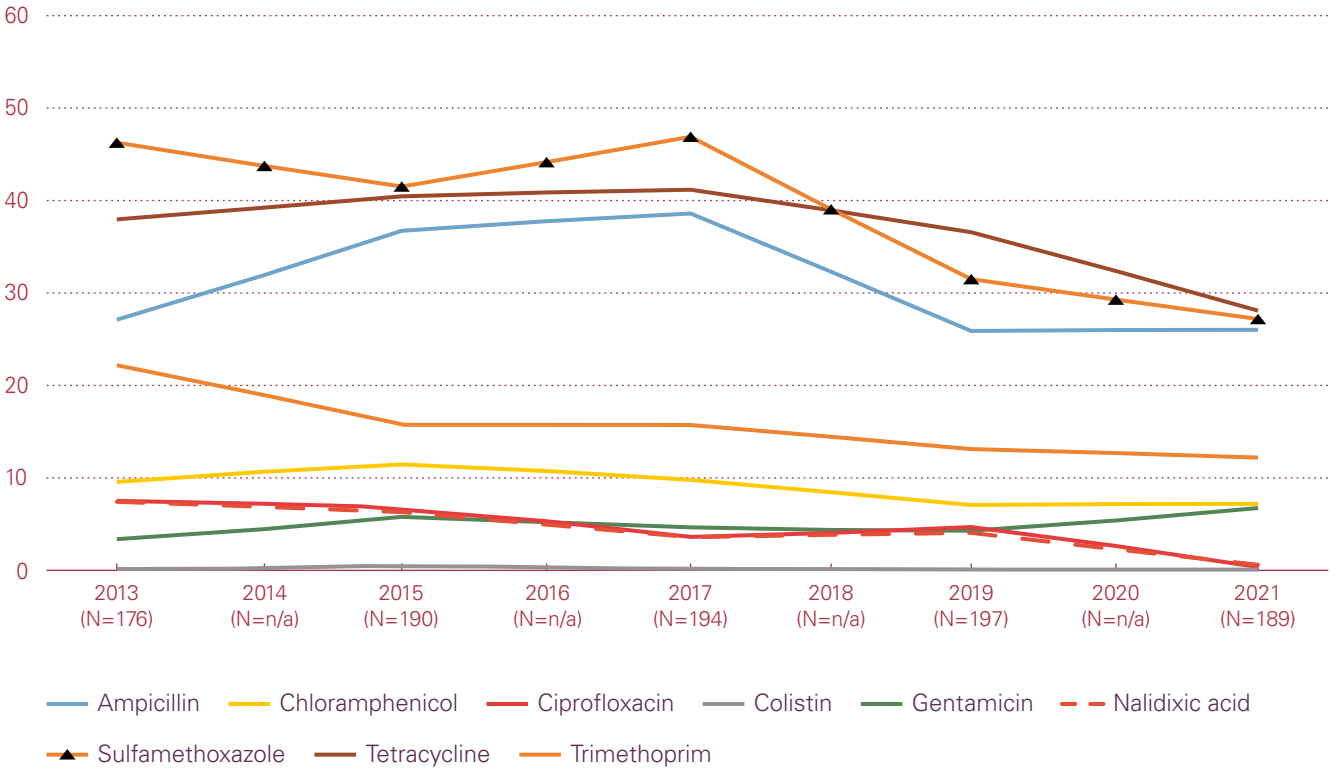


Table 9. e: Non-susceptibility combinations in commensal *E. coli* in slaughter calves in 2021.

Resistance patterns	Number of isolates	Number of isolates
Grand total	**180**	
Number of resistances: 0	**113**	**62.8%**
–	113	100.0%
Number of resistances: 1	**15**	**8.3%**
Penicillins	5	33.3%
Sulfonamides	1	6.7%
Tetracyclines	9	60.0%
Number of resistances: 2	**14**	**7.8%**
Amphenicols – penicillins	1	7.1%
Penicillins – sulfonamides	3	21.4%
Penicillins – tetracyclines	3	21.4%
Sulfonamides – tetracyclines	7	50.0%
Number of resistances: 3	**14**	**7.8%**
Aminoglycosides – sulfonamides – tetracyclines	1	7.1%
Amphenicols – sulfonamides – tetracyclines	1	7.1%
Diaminopyrimidine derivatives – pencillins – sulfonamides	2	14.3%
Diaminopyrimidine derivatives – sulfonamides – tetracyclines	1	7.1%
Penicillins – sulfonamides – tetracyclines	9	64.3%
Number of resistances: 4	**10**	**5.6%**
Amphenicols – penicillins – sulfonamides – tetracyclines	1	10.0%
Diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	8	80.0%
Fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	10.0%
Number of resistances: 5	**7**	**3.9%**
3rd-generation cephalosporins – amphenicols – penicillins – sulfonamides – tetracyclines	1	14.3%
Aminoglycosides – amphenicols – penicillins – sulfonamides – tetracyclines	1	14.3%
Aminoglycosides – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	3	42.9%
Amphenicols – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	2	28.6%
Number of resistances: 6	**6**	**3.3%**
3rd-generation cephalosporins – aminoglycosides – amphenicols – penicillins – sulfonamides – tetracyclines	1	16.7%
Aminoglycosides – amphenicols – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	4	66.7%
Aminoglycosides – diaminopyrimidine derivatives – macrolides – penicillins – sulfonamides – tetracyclines	1	16.7%
Number of resistances: 7	**1**	**0.6%**
Aminoglycosides – amphenicols – diaminopyrimidine derivatives – 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

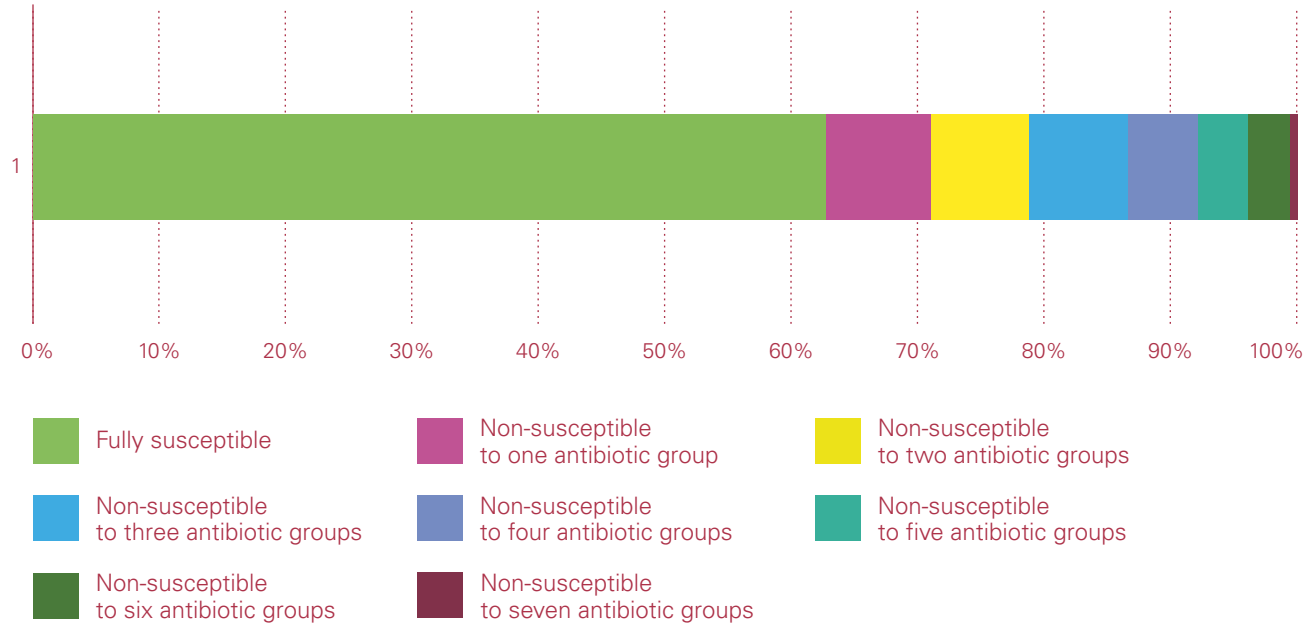
Sulfonamides, tetracyclines and penicillins are the most widely used antimicrobials in pigs and calves in Switzerland (cf. Chap. 6). The overall positive trends in decreasing rates of antimicrobial resistance against these antimicrobials are not diminished by the detection of two ESBL/AmpC-producing *E. coli* in slaughter calves. The detection of such *E. coli* isolates using the non-selective method succeeds only by chance and is not a sign of an increasing prevalence of these multidrug-resistant bacteria. This is shown by the data from the selective detection described in the following chapter.

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

Escherichia coli	n=170								
Antimicrobial	South-West (n=18)		Center (n=84)		East (n=68)		total		
	n	%	n	%	n	%	n	%	95% CI
Susceptible	5	27.8%	45	53.6%	38	55.9%	88	51.8%	44.3–59.2%
Diaminophyridine derivates	6	33.3%	14	16.7%	5	7.4%	25	14.7%	10.2–20.8%
Fluoroquinolones	3	16.7%	4	4.8%	0	0.0%	7	4.1%	2.0–8.3%
Tetracyclines	7	38.9%	24	28.6%	20	29.4%	51	30.0%	23.6–37.3%
Sulfonamides	8	44.4%	25	29.8%	17	25.0%	50	29.4%	23.1–36.7%
Penicillins	4	22.2%	16	19.0%	8	11.8%	28	16.5%	11.6–22.8%

95% CI: 95% confidence interval, fluoroquinolones: ciprofloxacin; tetracyclines: tetracycline; sulfonamides: sulfamethoxazole; penicillins: ampicillin, diaminophyridine derivates: trimethoprim
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. f: Resistance pattern in *E. coli* from slaughter calves 2021.



9.2 ESBL/AmpC-producing *Escherichia coli*

In the past, third-generation cephalosporin-resistant *Escherichia coli* have been increasingly detected among livestock in various countries, including Switzerland [1]. 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 was detected [3]. As a rule, extended spectrum beta-lactamase (ESBL) producing bacteria are resistant to third- and fourth-generation cephalosporins and monobactams, but susceptible to clavulanic acid. In contrast, plasmid-mediated AmpC beta-lactamase-producing bacteria are resistant to third-generation cephalosporins, including beta-lactamase inhibitors such as clavulanic acid and cephamycins. On the other hand, they do not usually mediate resistance to fourth-generation cephalosporins. But various mixed resistance patterns have been described.

Both ESBL and AmpC 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,

Table 9. f: Non-susceptibility combinations in ESBL/AmpC-producing *E. coli* in broilers in 2020.

Resistance patterns	Number of isolates	% of total
Grand total	**61**	
Number of resistances: 3	**11**	**18.0%**
3rd-generation cephalosporins – 4th-generation cephalosporins – penicillins	4	36.4%
3rd-generation cephalosporins – cephamycin – penicillins	4	36.4%
3rd-generation cephalosporins – fluoroquinolones – penicillins	3	27.3%
Number of resistances: 4	**26**	**42.6%**
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – penicillins	8	30.8%
3rd-generation cephalosporins – 4th-generation cephalosporins – fluoroquinolones – penicillins	12	46.2%
3rd-generation cephalosporins – 4th-generation cephalosporins – penicillins – sulfonamides	1	3.8%
3rd-generation cephalosporins – cephamycin – fluoroquinolones – penicillins	3	11.5%
3rd-generation cephalosporins – cephamycin – penicillins – tetracyclines	1	3.8%
3rd-generation cephalosporins – fluoroquinolones – penicillins – sulfonamides	1	3.8%
Number of resistances: 5	**7**	**11.5%**
3rd-generation cephalosporins – 4th-generation cephalosporins – aminoglycosides – fluoroquinolones – penicillins	1	14.3%
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – fluoroquinolones – penicillins	3	42.9%
3rd-generation cephalosporins – 4th-generation cephalosporins – penicillins – sulfonamides – tetracyclines	2	28.6%
3rd-generation cephalosporins – cephamycin – fluoroquinolones – penicillins – tetracyclines	1	14.3%
Number of resistances: 6	**12**	**19.7%**
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – fluoroquinolones – penicillins – tetracyclines	9	75.0%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides	2	16.7%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	1	8.3%
Number of resistances: 7	**2**	**3.3%**
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	1	50.0%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	50.0%
Number of resistances: 8	**3**	**4.9%**
3rd-generation cephalosporins – 4th-generation cephalosporins – aminoglycosides – amphenicols – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	1	33.3%
3rd-generation cephalosporins – 4th-generation cephalosporins – amphenicols – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	33.0%
3rd-generation cephalosporins – 4th-generation cephalosporins – amphenicols – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	33.3%

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

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 AmpC resistance genes are difficult to treat, thus prolonging or worsening disease course [4]. The occurrence of such bacteria in the context of severe infections of hospitalized humans in Switzerland increased from 0.9% in 2004 to 10.3% in 2017. As a consequence, the prevalence of ESBL/AmpC-producing *Escherichia coli* is monitored in livestock animals.

9.2.1 ESBL/AmpC-producing *Escherichia E. coli* in broilers

In 2020, a random sample of 612 broiler flocks was investigated at slaughter for the occurrence of ESBL/AmpC-producing *E. coli* using cecal samples (five pooled cecal samples per flock). By applying the European harmonized method, 61 presumptive ESBL/AmpC-producing *E. coli* were isolated. This corresponds to a flock prevalence of 10.0% (Figure 9. g). Compared to 2018, the prevalence of ESBL/AmpC-producing *E. coli* once more decreased significantly in the Swiss broiler population.

Details on multidrug resistance patterns are shown in Table 9. f. Besides resistance to third- and fourth-generation cephalosporins, ESBL/AmpC-producing *E. coli* showed high resistance levels to ciprofloxacin (62.3%) and tetracyclines (31.1%) and a moderate resistance level to sulfonamides (19.7%). In contrast, resistance rates to aminoglycosides (4.9%) and amphenicols (3.3%) were low. No resistance against colistin, azithromycin and carbapenems was observed. 48 isolates (78.7%) were resistant to a fourth-generation cephalosporin (e.g., cefepime), which serves as an indicator for the presence of ESBL producers. On the other hand, 49.2% of the isolates were resistant to cefoxitin, which is an indicator for AmpC producers.

Due to the overall low prevalence of ESBL/AmpC-producing *E. coli*, no comparison of their prevalence in different regions of Switzerland was carried out.

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

In 2021, a random sample of 289 fattening pigs was investigated at slaughter for the occurrence of ESBL/AmpC-producing *E. coli* using cecal samples. By applying the European harmonized method, 17 isolates of presumptive ESBL/AmpC-producing *E. coli* were isolated. This corresponds to a herd prevalence of 5.9% (Figure 9. h). Compared to 2019, the prevalence of ESBL/AmpC-producing *E. coli* decreased significantly in the Swiss fattening pig population.

Details on multidrug resistance patterns are shown in Table 9. g. Besides resistance to third- and fourth-generation cephalosporins, ESBL/AmpC-producing *E. coli* showed very high resistance levels to sulfonamides (70.6%), tetracyclines (52.9%) and trimethoprim (58.8%), high resistance levels to ciprofloxacin (23.5%), but low resistance levels to

Figure 9. g: Prevalence of ESBL/AmpC-producing *Escherichia coli* from broilers between 2013 and 2020 (N = total number of tested isolates, values for 2015, 2017 and 2019 interpolated [n/a]).

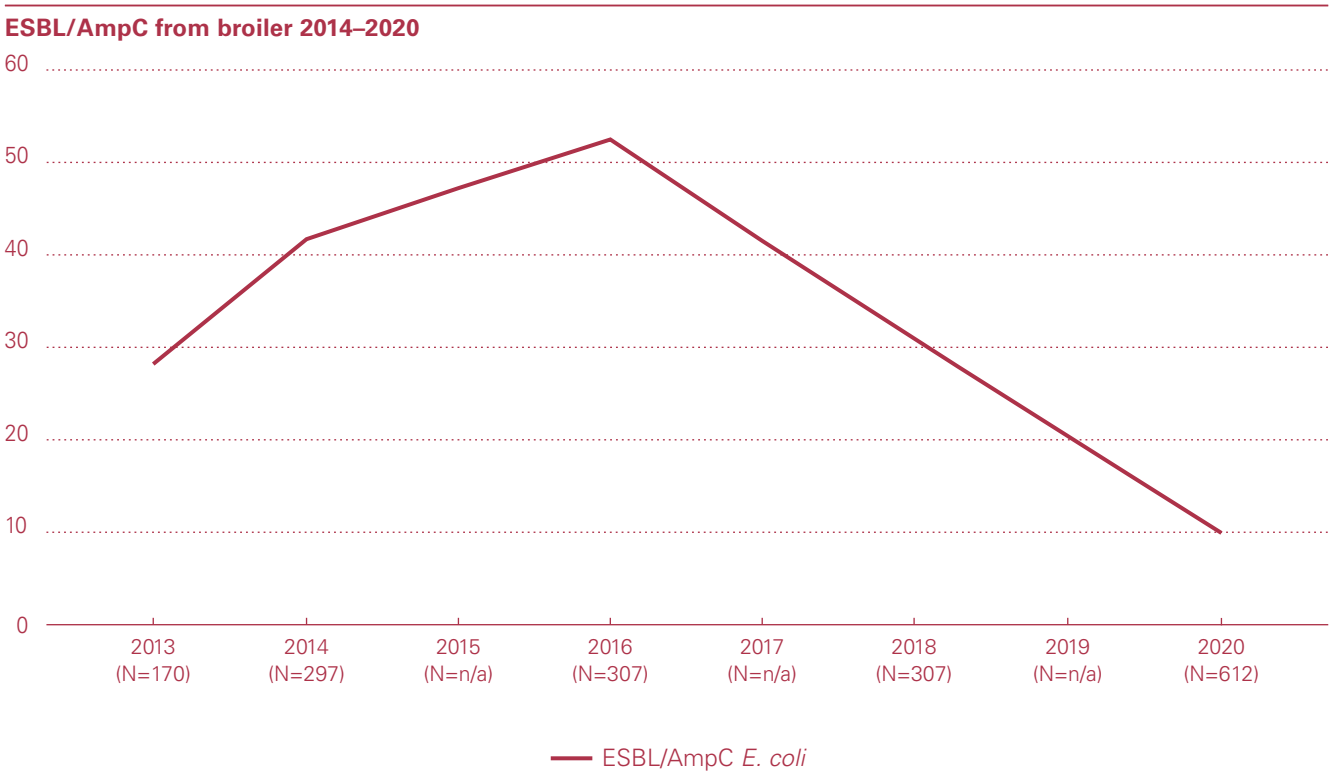


Figure 9. h: Prevalence of ESBL/AmpC *Escherichia coli* from fattening pigs between 2013 and 2021 (N = total number of tested isolates, values for 2014, 2016, 2018 and 2020 interpolated [n/a]).

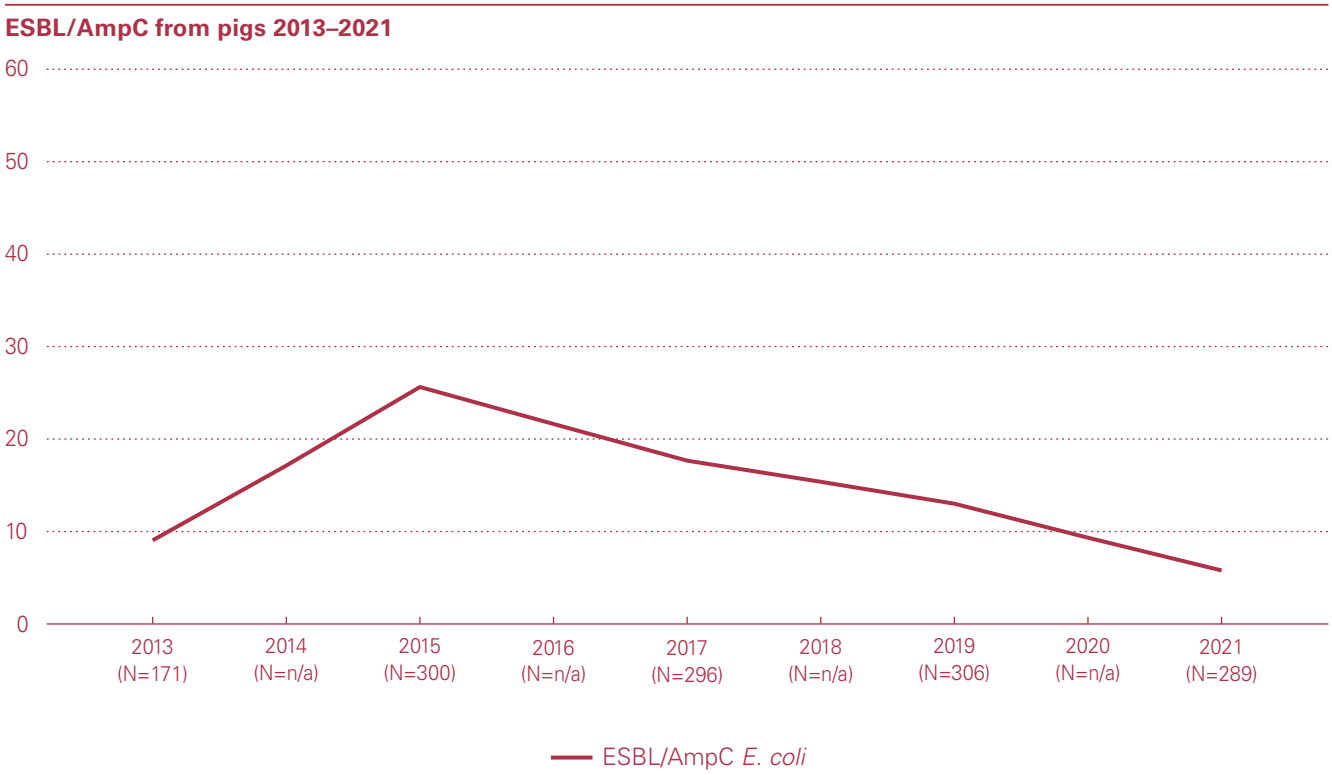


Table 9. g: Non-susceptibility combinations in ESBL/AmpC-producing *E. coli* in fattening pigs in 2021.

Resistance patterns	Number of isolates	% of total
Grand total	**17**	
Number of resistances: 2	**2**	**11.8%**
3rd-generation cephalosporins – penicillins	2	100.0%
Number of resistances: 3	**3**	**17.7%**
3rd-generation cephalosporins – fluoroquinolones – penicillins	2	66.7%
3rd-generation cephalosporins – penicillins – sulfonamides	1	33.3%
Number of resistances: 4	**5**	**29.4%**
3rd-generation cephalosporins – diaminopyrimidine derivatives – penicillins – sulfonamides	3	60.0%
3rd-generation cephalosporins – diaminopyrimidine derivatives – penicillins – tetracyclines	1	20.0%
3rd-generation cephalosporins – penicillins – sulfonamides – tetracyclines	1	20.0%
Number of resistances: 5	**4**	**23.5%**
3rd-generation cephalosporins – aminoglycosides – penicillins – sulfonamides – tetracyclines	1	25.0%
3rd-generation cephalosporins – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	3	75.0%
Number of resistances: 6	**2**	**11.8%**
3rd-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	2	100.0%
Number of resistances: 7	**1**	**5.9%**
3rd-generation cephalosporins – aminoglycosides– amphenicols – diaminopyrimidine derivatives – 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

amphenicols (5.9%) and gentamicin (11.8%). No resistance against colistin, azithromycin and carbapenems was observed. 13 isolates (76.5%) were resistant to a fourth-generation cephalosporin (e.g., cefepime), which serves as an indicator for the presence of ESBL producers. On the other hand, five isolates (29.4%) were resistant to cefoxitin, which is an indicator for AmpC producers.

Due to the overall low prevalence of ESBL/AmpC-producing *E. coli*, no comparison of their prevalence in different regions of Switzerland was carried out.

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

In 2021, a random sample of 294 slaughter calves was investigated for the occurrence of ESBL/AmpC-producing *E. coli* using cecal samples. By applying the European harmonized method, 70 isolates of presumptive ESBL/AmpC-producing *E. coli* were isolated. This corresponds to a herd prevalence of 23.8% (Figure 9. i). Compared to 2019 (32.9%), the prevalence of ESBL/AmpC-producing *E. coli* decreased to 23.8% in 2021 in the Swiss slaughter calf population.

Details on multidrug resistance patterns are shown in Table 9. h. Besides resistance to third- and fourth-generation cephalosporins, ESBL/AmpC-producing *E. coli* showed very high resistance levels to sulfonamides (78.6%), tetracyclines (81.4%) and amphenicols (57.1%), and high resistance levels to gentamicin (32.9%), trimethoprim (47.1%) and ciprofloxacin (50.0%). In contrast, the resistance rate to macrolides (7.1%) was low. No resistance against colistin and carbapenems was observed. 50 isolates (71.4%) were resistant to a fourth-generation cephalosporin (e.g., cefepime), which serves as an indicator for the presence of ESBL producers. On the other hand, 24 isolates (34.3%) were resistant to cefoxitin, which is an indicator for AmpC producers.

Due to the overall moderate prevalence of ESBL/AmpC-producing *E. coli*, no comparison of their prevalence in different regions of Switzerland was carried out.

9.2.4 Discussion

Using the European harmonized method, the prevalence of ESBL/AmpC-producing *E. coli* decreased significantly for broilers (2020: 10.0%) and fattening pigs (2021: 5.9%), and slightly for slaughter calves (23.8%).

Using the same selective method as in the European monitoring, comparable decreasing trends of ESBL/AmpC-producing *E. coli*, especially for broilers, were found in other European countries. In the EU in 2020, the mean prevalences of ESBL/AmpC-producing *E. coli* are higher for broilers (38%), fattening pigs (42.7%) and slaughter calves (36.4%), but differences between countries are obvious. In general, northern European countries showed lower prevalence of ESBL/AmpC-producing *E. coli* than southern European countries [1].

Figure 9. i: Prevalence of ESBL/AmpC *Escherichia coli* from slaughter calves between 2013 and 2021 (N = total number of tested isolates, values for 2014, 2016, 2018 and 2020 interpolated [n/a]).

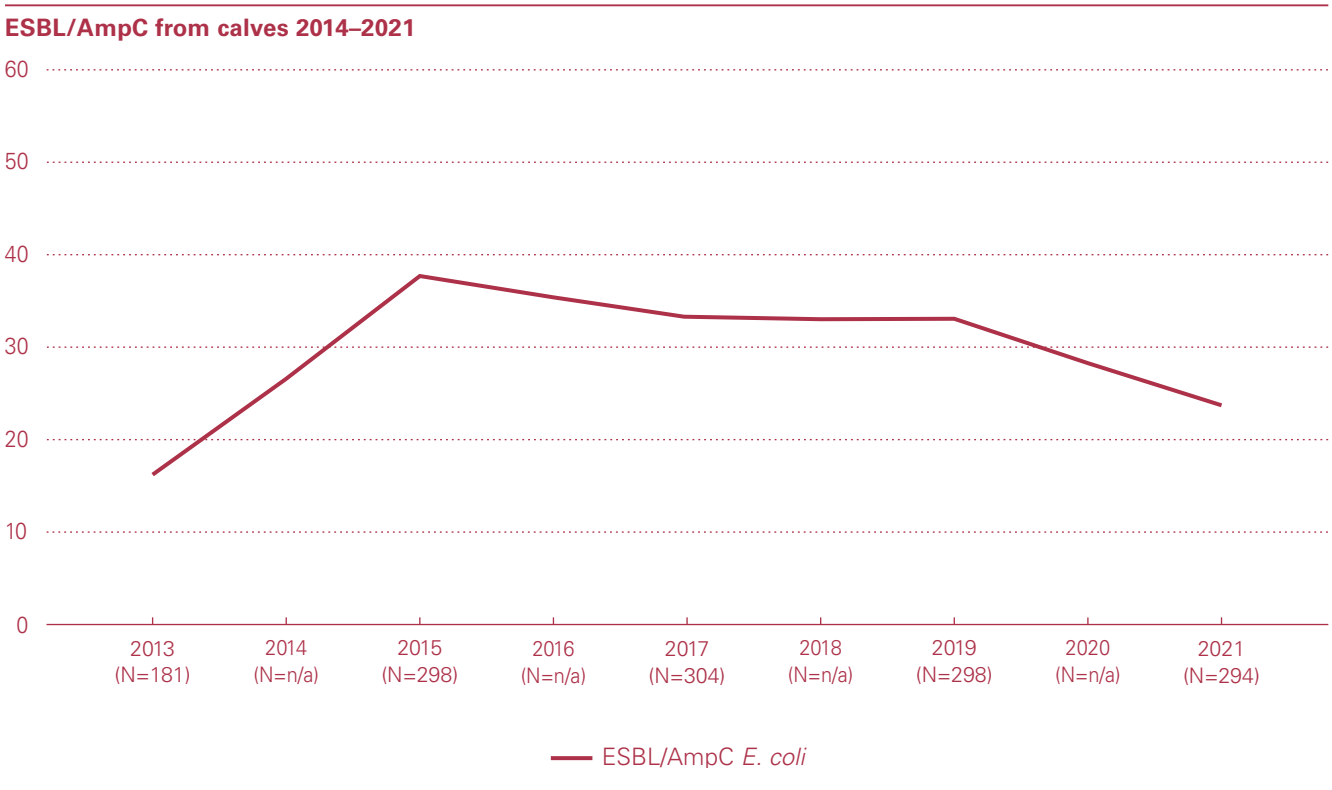


Table 9. h: Non-susceptibility combinations in ESBL/AmpC-producing *E. coli* in slaughter calves in 2021.

Resistance patterns	Number of isolates	% of total
Grand total	**70**	
Number of resistances: 2	**7**	**10.0%**
3rd-generation cephalosporins – penicillins	7	100.0%
Number of resistances: 3	**3**	**4.3%**
3rd-generation cephalosporins – aminoglycosides – penicillins	1	33.3%
3rd-generation cephalosporins – fluoroquinolones – penicillins	1	33.3%
3rd-generation cephalosporins – penicillins – tetracyclines	1	33.3%
Number of resistances: 4	**9**	**12.9%**
3rd-generation cephalosporins – diaminopyrimidine derivatives – penicillins – sulfonamides	2	22.2%
3rd-generation cephalosporins – diaminopyrimidine derivatives – penicillins – tetracyclines	1	11.1%
3rd-generation cephalosporins – fluoroquinolones – macrolides – penicillins	1	11.1%
3rd-generation cephalosporins – fluoroquinolones – penicillins – tetracyclines	3	33.3%
3rd-generation cephalosporins – penicillins – sulfonamides – tetracyclines	2	22.2%
Number of resistances: 5	**11**	**15.7%**
3rd-generation cephalosporins – aminoglycosides – penicillins – sulfonamides – tetracyclines	2	18.2%
3rd-generation cephalosporins – amphenicols – fluoroquinolones – penicillins – sulfonamides	1	9.1%
3rd-generation cephalosporins – amphenicols – penicillins – sulfonamides – tetracyclines	5	45.5%
3rd-generation cephalosporins – fluoroquinolones – penicillins – sulfonamides – tetracyclines	3	27.3%
Number of resistances: 6	**14**	**20.0%**
3rd-generation cephalosporins – aminoglycosides – amphenicols – penicillins – sulfonamides – tetracyclines	5	35.7%
3rd-generation cephalosporins – aminoglycosides – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	1	7.1%
3rd-generation cephalosporins – amphenicols – fluoroquinolones – penicillins – sulfonamides – tetracyclines	4	28.6%
3rd-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	3	21.4%
3rd-generation cephalosporins – fluoroquinolones – macrolides – penicillins – sulfonamides – tetracyclines	1	7.1%
Number of resistances: 7	**18**	**25.7%**
3rd-generation cephalosporins – aminoglycosides – amphenicols – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	8	44.4%
3rd-generation cephalosporins – amphenicols – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	9	50.0%
3rd-generation cephalosporins – daminopyrimidine derivatives – fluoroquinolones – macrolides – penicillins – sulfonamides – tetracyclines	1	5.6%
Number of resistances: 8	**8**	**11.4%**
3rd-generation cephalosporins – aminoglycosides – amphenicols – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	6	75.0%
3rd-generation cephalosporins – amphenicols – diaminopyrimidine derivatives – fluoroquinolones – macrolides – penicillins – sulfonamides – tetracyclines	2	25.0%

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 prevalence in broiler flocks is influenced by different factors such as age and flock management, including use of antimicrobials; and different possible routes of transmission of ESBL/AmpC-producing bacteria in the broiler production pyramid are known [2]. In pigs, ESBL/AmpC-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 [5]. For veal calves, it was shown that the prevalence of ESBL/AmpC-producing *E. coli* decreased between the beginning and the end of the fattening period [6]. This fact needs to be considered when interpreting the ESBL/AmpC-producing *E. coli* prevalence measured at the end of the fattening period, as performed in the European monitoring system.

The overall decreasing trends in the prevalence of ESBL/AmpC-producing *E. coli* in Swiss livestock may, among other factors, be related to the generally reduced use of antibiotics. The potential risk for direct or indirect transfer of ESBL/AmpC-producing bacteria or genes from animals to humans seems to be very low nowadays.

9.3 Carbapenemase-producing *Escherichia coli*

In 2020, 612 pooled cecal samples from broiler flocks were analyzed for the presence of carbapenemase-producing *E. coli* using the European harmonized method (Table 9. i). In 2021, the same method was applied to 288 cecal samples from fattening pigs at slaughter and 294 cecal samples from slaughter calves. As in the previous years, none of the samples tested positive for carbapenemase-producing *E. coli* or *Klebsiella* spp., which were included in the monitoring program as of 2020.

9.4 Methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus (S.) aureus is a commensal bacterium 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 [7]. 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 [8].

In the following decades, MRSA emerged as a major cause of healthcare-associated infections, although its occurrence was restricted to hospitals and other healthcare facilities ("hospital-acquired (HA) MRSA"). In the 1990s, an increasing incidence of hospital-independent human MRSA infections was observed [9]. These so-called "community-acquired (CA) MRSA" had been reported by many countries worldwide. With the emergence of MRSA in animals, MRSA gained a One Health dimension [10]. Numerous studies have shown that especially pigs can be heavily colonized with MRSA. These "livestock-associated (LA) MRSAs" can be associated with infections not only in animals but also in humans, especially in those with regular and close contact to pigs, such as farmers, slaughterhouse workers and veterinarians [11–12].

9.4.1 MRSA in fattening pigs

In 2021, a random sample of 289 fattening pigs was investigated at slaughter for the occurrence of MRSA using nasal swab samples. By applying a one-step enrichment method, 155 MRSAs were isolated. This corresponds to a herd prevalence of 53.6% (Figure 9. j). Compared to 2019, the prevalence of MRSA has not changed in the Swiss fattening pig population.

Details on multidrug resistance patterns are shown in Table 9 j. Besides resistance to beta-lactam antibiotics, MRSA showed very high resistance levels to tetracyclines (98.1%), and high resistance rates to trimethoprim (47.7%), clindamycin and tiamulin (43.2% each), quinupristin/dalfopristin (42.6%), ciprofloxacin (31.6%), erythromycin (29.7%) and streptomycin (25.2%). No resistance against rifampicin, vancomycin, linezolid or mupirocin was detected. All MRSAs belonged to the livestock-associated clonal complex 398.

Table 9. i: Number of carbapenem-resisant *E. coli* and *Klebsiella spp.* (since 2020) in cecal samples from livestock 2015–2021.

Year	Sample type	Number of samples (n)	Number of Carbapenemase-producing *E. coli* and *Klebsiella spp.* (since 2020) (n)
2015	Fattening pigs – cecum	300	0
2015	Slaughter calves – cecum	298	0
2016	Broiler – pooled cecum	307	0
2017	Fattening pigs – cecum	296	0
2017	Slaughter calves – cecum	304	0
2018	Broiler – pooled cecum	307	0
2019	Fattening pigs – cecum	306	0
2019	Slaughter calves – cecum	298	0
2020	Broiler – pooled cecum	612	0
2021	Fattening pigs – cecum	288	0
2021	Slaughter calves – cecum	294	0

Table 9. j: Non-susceptibility combinations in MRSA in fattening pigs in 2021.

Resistance patterns	Number of isolates	% of total
Grand total	**155**	
Number of resistances: 3	**13**	**8.4%**
Cephamycin – penicillins – tetracyclines	13	100.0%
Number of resistances: 4	**46**	**29.7%**
Aminoglycosides – cephamycin – penicillins – tetracyclines	27	58.7%
Cephamycin – diaminopyrimidine derivatives – penicillins – tetracyclines	1	2.2%
Cephamycin – fluoroquinolones – penicillins – tetracyclines	18	39.1%
Number of resistances: 5	**24**	**15.5%**
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – penicillins – tetracyclines	1	4.2%
Aminoglycosides – cephamycin – fluoroquinolones – penicillins – tetracyclines	4	16.7%
Amphenicols – cephamycin – fluoroquinolones – penicillins – tetracyclines	16	66.7%
Cephamycin – diaminopyrimidine derivatives – macrolides – penicillins – tetracyclines	3	12.5%
Number of resistances: 6	**8**	**5.2%**
Aminoglycosides – amphenicols – cephamycin – fluoroquinolones – penicillins – tetracyclines	1	12.5%
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – penicillins – tetracyclines	2	25.0%
Cephamycin – diaminopyrimidine derivatives – lincosamides – penicillins – pleuromutilins – streptogramin	3	37.5%
Cephamycin – diaminopyrimidine derivatives – macrolides – penicillins – Pleuromutilins – tetracyclines	1	12.5%
Cephamycin – diaminopyrimidine derivatives – macrolides – penicillins – streptogramin – tetracyclines	1	12.5%
Number of resistances: 7	**18**	**11.6%**
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – lincosamides – penicillins – pleuromutilins – tetracyclines	1	5.6%
Amphenicols – cephamycin – fluoroquinolones – lincosamides – macrolides – penicillins – tetracyclines	1	5.6%
Cephamycin – diaminopyrimidine derivatives – lincosamides – penicillins – pleuromutilins – streptogramin – tetracyclines	16	88.9%
Number of resistances: 8	**29**	**18.7%**
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – lincosamides – penicillins – pleuromutilins – streptogramin – tetracyclines	2	6.9%
Cephamycin – diaminopyrimidine derivatives – lincosamides – macrolides – penicillins – pleuromutilins – streptogramin – tetracyclines	27	93.1%
Number of resistances: 9	**15**	**9.7%**
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – lincosamides – penicillins – pleuromutilins – streptogramin – tetracyclines	4	26.7%
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – lincosamides – macrolides – penicillins – pleuromutilins – streptogramin – tetracyclines	10	66.7%
Cephamycin – diaminopyrimidine derivatives – fluoroquinolones – lincosamides – macrolides – penicillins – pleuromutilins – streptogramin – tetracyclines	1	6.7%
Number of resistances: 10	**2**	**1.3%**
Aminoglycosides – amphenicols – cephamycin – fluoroquinolones – lincosamides – macrolides – penicillins – pleuromutilins – streptogramin – tetracyclines	1	50.0%
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – lincosamides – macrolides – penicillins – pleuromutilins – streptogramin – tetracyclines	1	50.0%

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

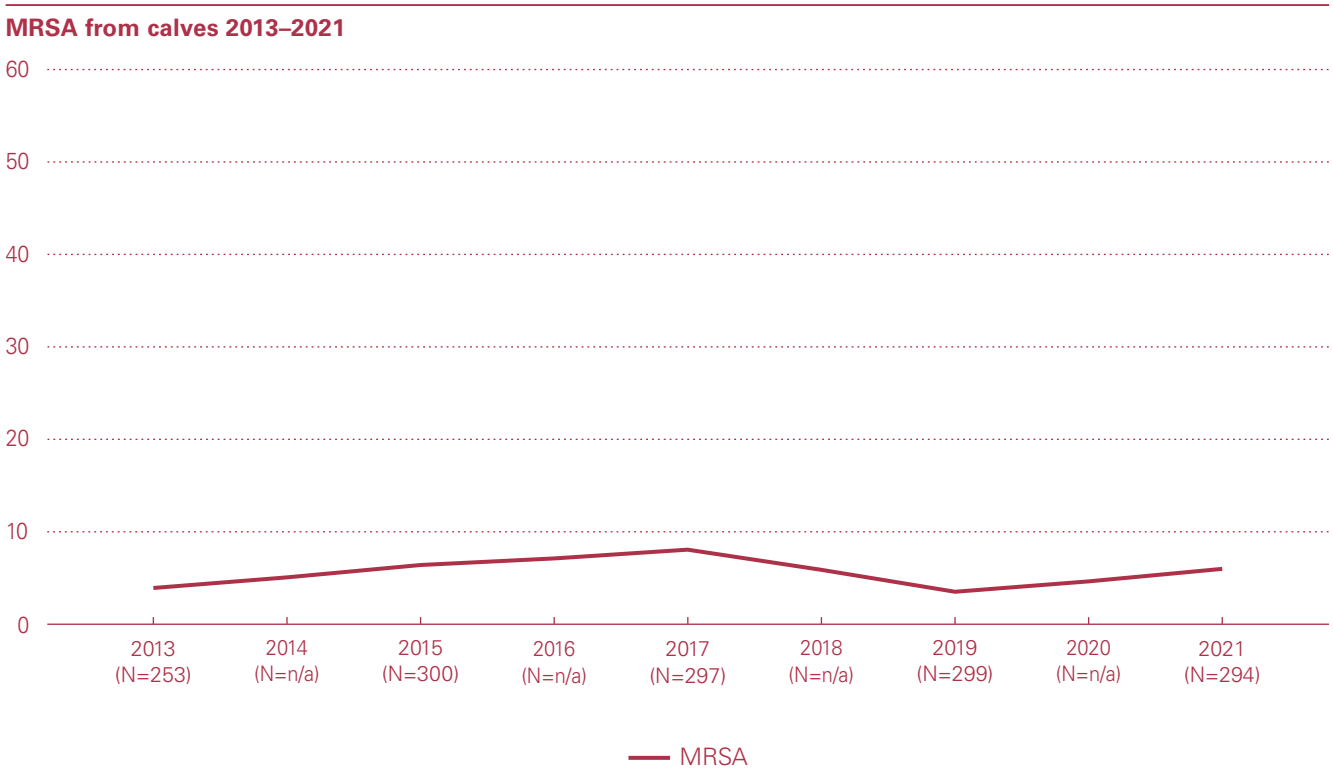
Table 9. k: Non-susceptibility combinations in MRSA in slaughter calves in 2021.

Resistance patterns	Number of isolates	% of total
Grand total	**18**	
Number of resistances: 3	**1**	**5.6%**
Cephamycin – penicillins – tetracyclines	1	100.0%
Number of resistances: 4	**2**	**11.1%**
Aminoglycosides – cephamycin – penicillins – tetracyclines	2	100.0%
Number of resistances: 5	**4**	**22.2%**
Aminoglycosides – cephamycin – fluoroquinolones – penicillins – tetracyclines	1	25.0%
Amphenicols – cephamycin – fluoroquinolones – penicillins – tetracyclines	3	75.0%
Number of resistances: 6	**4**	**22.2%**
Aminoglycosides – cephamycin – lincosamides – macrolides – penicillins – tetracyclines	4	100.0%
Number of resistances: 7	**3**	**16.7%**
Aminoglycosides – cephamycin – fluoroquinolones – lincosamides – macrolides – penicillins – tetracyclines	1	33.3%
Cephamycin – fluoroquinolones – lincosamides – macrolides – penicillins – streptogramin – tetracyclines	2	66.7%
Number of resistances: 8	**2**	**11.1%**
Aminoglycosides – cephamycin – fluoroquinolones – lincosamides – macrolides – penicillins – streptogramin – tetracyclines	1	50.0%
Amphenicols – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – lincosamides – macrolides – penicillins – tetracyclines	1	50.0%
Number of resistances: 9	**1**	**5.6%**
Aminoglycosides – cephamycin – diaminopyrimidine derivatives – lincosamides – macrolides – penicillins – pleuromutilins – streptogramin – tetracyclines	1	100.0%
Number of resistances: 10	**1**	**5.6%**
Aminoglycosides – amphenicols – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – lincosamides – penicillins – pleuromutilins – streptogramin – tetracyclines	1	100.0%

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

Figure 9. j: Prevalence of MRSA from fattening pigs between 2012 and 2021
(N = total number of tested isolates, values for 2014, 2016, 2018 and 2020 interpolated [n/a]).

Figure 9. k: Prevalence of MRSA from slaughter calves between 2013 and 2021
(N = total number of tested isolates, values for 2014, 2016, 2018 and 2020 interpolated [n/a]).



9.4.2 MRSA in slaughter calves

In 2021, a random sample of 294 slaughter calves was investigated for the occurrence of MRSA using nasal swab samples. By applying a one-step enrichment method, 18 MRSAs were isolated. This corresponds to a herd prevalence of 6.1% (Figure 9. k). Compared to 2019, the prevalence of MRSA increased slightly, but remains at a low level.
Details on multidrug resistance patterns are shown in Table 9. k. Besides resistance to beta-lactam antibiotics, MRSA showed very high resistance levels to tetracyclines (100.0%), to clindamycin (61.1%), to ciprofloxacin and erythromycin (55.6% each) and to streptomycin (50.0%). Moreover, resistance rates against quinupristin/dalfopristin (27.8%), tiamulin (11.1%) and trimethoprim (16.7%) were high to moderate. No isolate showed resistance against rifampicin, vancomycin, linezolid or mupirocin. All MRSAs except one isolate belonged to the livestock-associated clonal complex 398.

Because of the very low number of MRSA isolates in Swiss slaughter calves, the comparison of their prevalence 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. [13] conducted comprehensive studies of the individual colonization dynamics of MRSA throughout the Swiss pig production. It was shown that almost all pigs from an MRSA-positive herd changed their MRSA status several times, which implies that pigs are colonized transiently rather than permanently.

The voluntary monitoring of MRSA in the European Union also revealed that most MRSA isolates were associated with livestock-associated (LA-)MRSA.

Humans in close contact with livestock are at higher risk of being carriers of livestock-associated MRSA [12]. Although colonization of healthy humans with MRSA usually does not induce disease, MRSA introduced into hospitals may cause infections that are almost impossible to treat. Nowadays, the overall detection rate of MRSA diagnosed in the context of severe infections in hospitalized humans (septicemia) in Switzerland is decreasing, arguing for a minor risk of transmission of MRSA from persons at risk into hospitals.

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Textbox

Decreasing trends in the prevalence of third-generation cephalosporin-resistant *Escherichia coli* in broilers in Europe

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Since the beginning of the 21st century, in human medicine, extended-spectrum b-lactamase (ESBL) and plasmid-mediated AmpC b-lactamase (pAmpC) producers have emerged in Gram-negative bacteria, particularly in Enterobacterales such as *Escherichia coli* [1]. Treating infections with these multidrug resistant bacteria is challenging for clinicians and, in the past, has led to the use of last resort antimicrobials such as carbapenems [2]. Travelling to regions such as India, Asia or Africa was shown to be a risk factor for the colonization of tourists with 3GC-R-Ec [3–4]. From the One Health perspective, there have been food safety concerns about whether food-producing animals can act as reservoirs for third-generation cephalosporin-resistant *Escherichia coli* (3GC-R-Ec), which may then reach consumers via contaminated meat. Therefore, analyses on the prevalence of 3GC-R-Ec in cecal samples from broilers, pigs and calves as well as in fresh meat were introduced into the European harmonized antimicrobial resistance monitoring program in 2014 [5].

In the past, 3GC-R-Ec has been detected in all livestock species and meat thereof, albeit with marked differences between countries. Broilers have turned out to be the livestock species with the highest prevalence of 3GC-R-Ec in Europe and Switzerland, and very high contamination rates in broiler meat have been detected [5].

Since 2016, a decreasing trend in the prevalence of 3GC-R-Ec, especially in broilers and meat thereof, can be observed **(Fig. 1 and Fig. 2)**. The prevalence of 3GC-R-Ec at the European level in broilers and meat from broilers has gradually decreased from around 60% in both sample types in 2016, to 38.0% (broilers) and 30.6% (meat from broilers) in 2020. These decreasing trends are statistically significant in most European countries, including Switzerland [5].

In general, the use of antimicrobials is low in broiler production. In the past, this has raised the question for the reason for the high detection rates of 3GC-R-Ec, especially in this globally organized livestock sector. Therefore, it has been discussed whether the high detection rates are due to transfer from a higher level in the broiler production pyramid, as had previously been proposed for other types of antibiotic resistant *E. coli* [6]. More recently, it has been shown that 3GC-R-Ec are introduced into parent hatcheries via imported colonized day-old breeding stock and subsequently spread vertically and longitudinally in the broiler production [7–8].

Fig. 1: Prevalence of third-generation cephalosporin-resistant *E. coli* in broilers, reported from Norway, Switzerland and the United Kingdom, 2016–2020 (source EFSA Journal [5]).

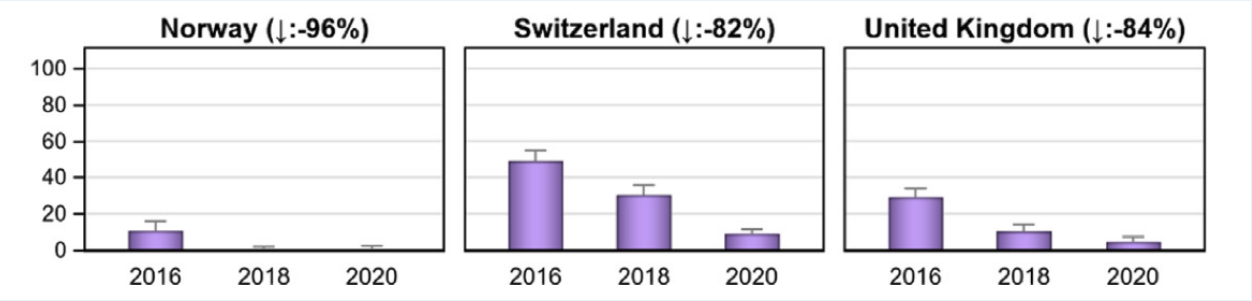
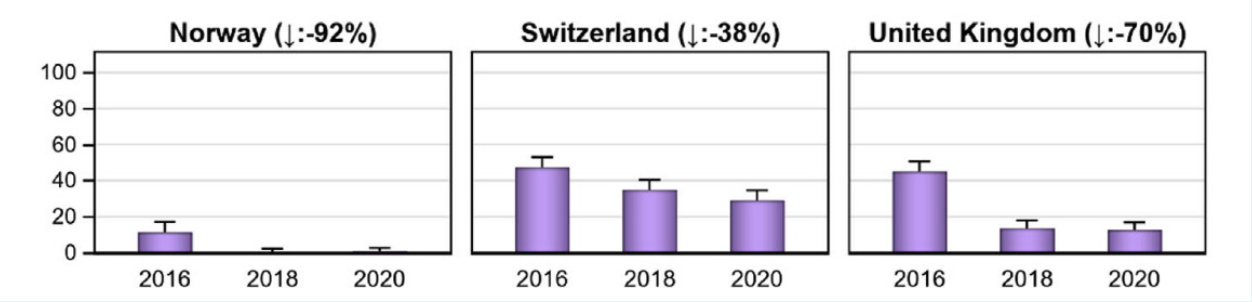


Fig. 2: Prevalence of third-generation cephalosporin-resistant *E. coli* in broiler meat, reported from Norway, Switzerland and the United Kingdom, 2016–2020 (source EFSA Journal [5]).



Nowadays, the strong decrease of 3GC-R-Ec in local broiler production all over Europe is most likely attributable to the production and selling of 3GC-R-Ec-free day-old breeding stock. Although knowledge on the exact measures taken by the international breeding companies is missing, one can hypothesize that a prophylactic use of modern cephalosporins in breeding companies has been stopped in the last years [7].

In summary, it has been shown that continuous harmonized surveillance of antimicrobial resistance in livestock in Europe provides data that, on the one hand, underlines the need for change in critical production types and, on the other hand, offers direct feedback on the effectiveness of the measures taken.

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Textbox

Occurrence of *Escherichia coli* non-susceptible to quinolones in fecal samples from fluoroquinolone-treated, contact and control pigs of different ages from 24 Swiss pig farms

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Despite their indispensability in human medicine, fluoroquinolones (FQ) are used for the treatment of bacterial infections in farm animals. This increases the risk of transferring FQ-resistant bacteria into the environment and, via the food chain, to humans [1, 2, 3]. The objective of this observational study was to perform a qualitative and quantitative follow-up of the presence of quinolone-non-susceptible *Escherichia coli* (QNSE) in fecal samples of pigs at four time points (2 weeks old, 4 weeks old, 2 weeks post weaning and during the fattening period). Moreover, differences between groups of FQ-treated pigs, pigs with contact to treated pigs, and control pigs were investigated. Additionally, quinolone and FQ resistance of *Escherichia coli* isolates from the fecal samples were investigated by determining minimum inhibitory concentrations (MICs).

40.9% of the 621 fecal samples contained QNSE. The proportion of samples with detectable QNSE from treated and contact pigs did not differ significantly, and was highest in piglets of 2 and 4 weeks of age. However, the proportions of samples with QNSE were significantly lowest in control pigs (7/90; 7.8%; CI = 3.5–14.7%) among all groups. Also, the number of colony-forming units was lowest in both weaners and fattening pigs of the control group, as compared to treated and contact groups. Following CLSI human breakpoints, in total, 50.4% of the 254 isolates in fecal samples were intermediate or resistant to ciprofloxacin.

Quinolone-non-susceptible *E. coli* were shown to be widespread in the study farms. QNSE were present in feces of pigs, independently of age or FQ background, but significantly less were found in pigs from farms without FQ usage. It is evident that through horizontal transfer there are no boundaries to QNSE and FQ-resistant bacteria when it comes to contact animals and the environment. Due to the long half-life of FQ, it is likely that only a prolonged absence of fluoroquinolone treatments in pig farming will lead to a reduced frequency of QNSE in the farm environment. Further research on the spread of QNSE and its promoting factors is necessary. Solutions need to be found to minimize the emergence and transfer of quinolone- and FQ-resistant bacteria from treated pigs to contact pigs and to farms without FQ usage. Adopting special management of antimicrobial-treated pigs in farms, restricted transport and purchase are also points of concern.

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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 may be contaminated with these bacteria, which may then 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 also relevant for zoonotic bacteria such as *Campylobacter*. Data on findings for *Campylobacter* on fresh meat are presented in Chapter 8 of this report.

This chapter includes antimicrobial resistance rates of ESBL/AmpC-producing *E. coli* and carbapenemase-producing *E. coli* and *Klebsiella* spp. in poultry meat from 2020 and in pork and beef meat from 2021.

10.1 ESBL/AmpC-producing *Escherichia coli*

10.1.1 ESBL/AmpC-producing *Escherichia coli* in poultry meat

In 2020, 296 samples of retail poultry meat (186 samples of Swiss origin and 110 of foreign origin) were investigated for the presence of ESBL/AmpC-producing *E. coli*. By applying a selective enrichment method, 87 samples were tested positive, corresponding to a prevalence of 29.4% (Table 10. a). Out of 186 Swiss samples, 19 were positive, which corresponds to a prevalence of 10.2%. Regarding foreign meat, 68 out of 110 samples were positive (61.8%). All isolates were subjected to antimicrobial susceptibility testing. Apart from the resistance to beta-lactam antibiotics, very high to high microbial resistance was detected for fluoroquinolones (74.7%), sulfonamides (40.2%) and tetracyclines (33.3%). A moderate to low proportion of isolates showed phenotypic resistance to diaminopyrimidines (21.8%), aminoglycosides (6.9%) and amphenicols (8.0%). Microbiological resistance to azithromycin, colistin, tigecycline, meropenem and imipenem was not detected.

The prevalence of ESBL/AmpC-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 Swiss chicken meat was found to be positive for ESBL/AmpC-producing *E. coli*, whereas 64.9% of chicken meat produced abroad was positive. This difference in prevalence of ESBL/AmpC-producing *E. coli* is even more pronounced in Swiss chicken meat analyzed in 2020, with a low prevalence of 10.2%. In contrast, the prevalence of ESBL/AmpC-producing *E. coli* in chicken meat from abroad is >60% since 2016 (Figure 10. a).

Overall, only 19.5% of all ESBL/AmpC-producing *E. coli* displayed resistance to third- and fourth-generation cephalosporins and cephamycin, without resistance to antimicrobials from other classes than beta-lactam antimicrobials (Table 10. b). The vast majority of the ESBL/AmpC-producing *E. coli* displayed resistance to third- and fourth-generation cephalosporins, combined with additional resistance to fluoroquinolones.

10.1.2 ESBL/AmpC-producing *Escherichia coli* in pork meat

In 2021, 309 samples of Swiss pork meat at retail were investigated for the presence of ESBL/AmpC-producing *E. coli*. Using an enrichment method, no sample was found

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

Origin	No. of samples	No. ESBL/AmpC-producing *E. coli* (%)
Germany	22	12
Hungary	48	30
Slovenia	26	25
France	14	1
Total foreign countries	**110**	**68 (61.8%)**
Switzerland	**186**	**19 (10.2%)**

Figure 10. a: Trends in prevalence of ESBL/AmpC-producing *E. coli* in chicken meat between 2014 and 2020 (N= total number of tested isolates; values for 2015, 2017 and 2020 interpolated [n/a]).

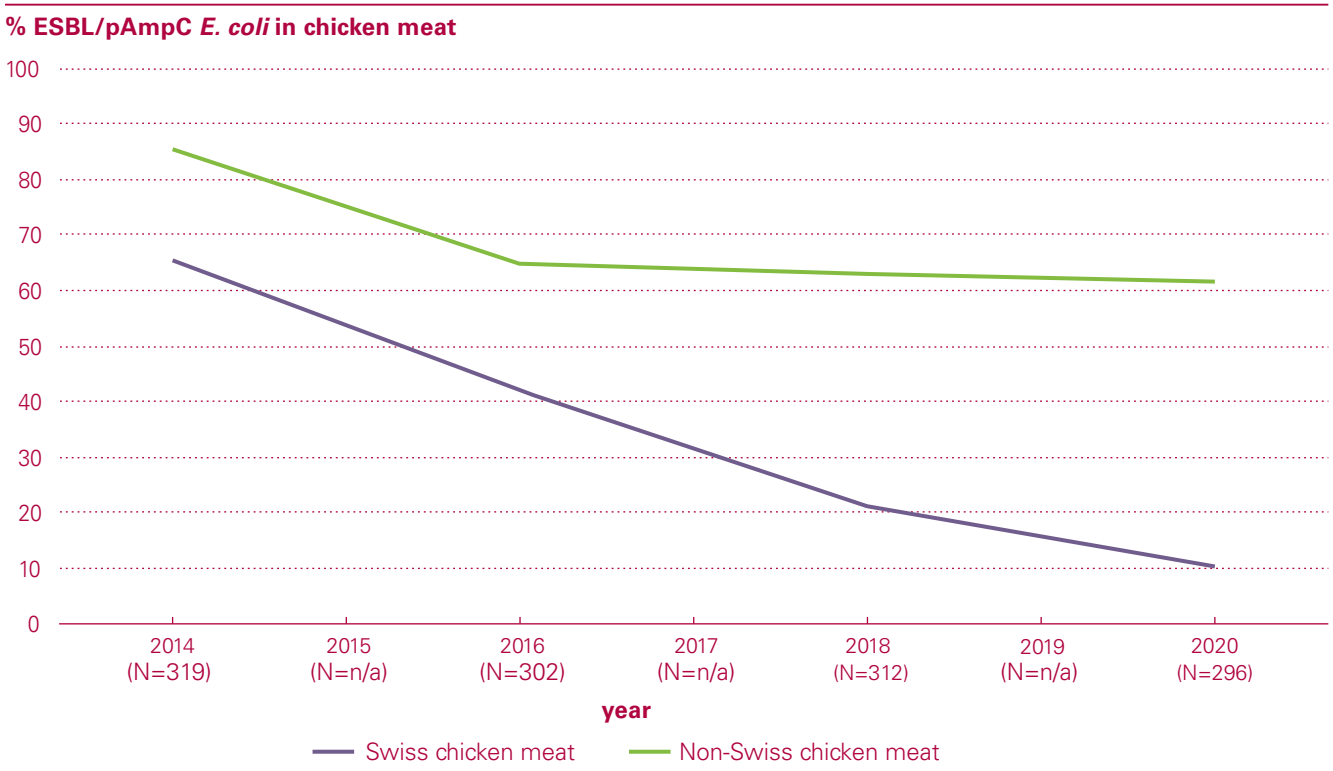

Table 10. c: Number of ESBL/AmpC-producing *E. coli* positive samples of Swiss pork meat in 2015, 2017 and 2019, 2021.

Year of sampling	No. of samples	No. ESBL/ AmpC-producing *E. coli* (%)
2015	301	3 (1.0%)
2017	302	1 (0.3%)
2019	311	2 (0.7%)
2021	309	0 (0.0%)

to be positive (Table 10. c). Hence, the prevalence of ESBL/AmpC-producing *E. coli* in Swiss pork meat remains stable on a very low level (<1%), with sporadic positive samples (Table 10. c).

10.1.3 ESBL/AmpC-producing *Escherichia coli* in beef meat

In 2021, 307 samples of beef meat (266 domestically produced and 41 from abroad) were investigated for the presence of ESBL/AmpC-producing *E. coli.* Using an enrichment method, no sample was found to be positive (Table 10. d). Same as in pork meat, the prevalence of ESBL/AmpC-producing *E. coli* in beef meat remains stable on a very low level (< 1%), with sporadic positive samples.

10.2 Carbapenemase-producing *Escherichia coli and Klebsiella* spp. in meat

In 2020, 312 chicken meat samples, and in 2021, 309 pork meat and 307 beef meat samples were collected from retailers and analyzed for the presence of carbapenemase-producing *E. coli* using an enrichment method. As in prior years, none of the meat samples tested positive for carbapenemase-producing *E. coli* (Tab. 10. e.). Since 2020, analyses are extended to the presence of carbapenemase-producing *Klebsiella* spp. and none of the meat samples tested positive.

Table 10. b: Non-susceptibility combinations of ESBL/AmpC-producing *E. coli* in chicken meat 2020.

Resistance patterns	Resistance patterns	% of total
Grand total	**87**	
Number of resistances: 3	**12**	**13.8%**
3rd-generation cephalosporins – 4th-generation cephalosporins – penicillins	7	58.3%
3rd-generation cephalosporins – cephamycin – penicillins	5	41.7%
Number of resistances: 4	**27**	**31.0%**
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – penicillins	5	18.5%
3rd-generation cephalosporins – 4th-generation cephalosporins – fluoroquinolones – penicillins	20	74.1%
3rd-generation cephalosporins – cephamycin – fluoroquinolones – penicillins	2	7.4%
Number of resistances: 5	**18**	**20.7%**
3rd-generation cephalosporins – 4th-generation cephalosporins – amphenicols – fluoroquinolones – penicillins	1	5.6%
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – fluoroquinolones – penicillins	4	22.2%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins	4	22.2%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – penicillins – sulfonamides	1	5.6%
3rd-generation cephalosporins – 4th-generation cephalosporins – fluoroquinolones – penicillins – sulfonamides	3	16.7%
3rd-generation cephalosporins – 4th-generation cephalosporins – fluoroquinolones – penicillins – tetracyclines	3	16.7%
3rd-generation cephalosporins – 4th-generation cephalosporins – penicillins – sulfonamides – tetracyclines	1	5.6%
3rd-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – penicillins	1	5.6%
Number of resistances: 6	**16**	**18.4%**
3rd-generation cephalosporins – 4th-generation cephalosporins – aminoglycosides – fluoroquinolones – penicillins – sulfonamides	1	6.3%
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – penicillins – sulfonamides	2	12.5%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides	1	6.3%
3rd-generation cephalosporins – 4th-generation cephalosporins – fluoroquinolones – penicillins – sulfonamides – tetracyclines	10	62.5%
3rd-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides	1	6.3%
3rd-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – penicillins – sulfonamides – tetracyclines	1	6.3%
Number of resistances: 7	**8**	**9.2%**
3rd-generation cephalosporins – 4th-generation cephalosporins – amphenicols – fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	12.5%
3rd-generation cephalosporins – 4th-generation cephalosporins – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	6	75.0%
3rd-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	12.5%
Number of resistances: 8	**1**	**1.2%**
3rd-generation cephalosporins – 4th-generation cephalosporins – cephamycin – diaminopyrimidine derivatives – fluoroquinolones – penicillins – sulfonamides – tetracyclines	1	100.0%
Number of resistances: 9	**5**	**5.8%**
3rd-generation cephalosporins – 4th-generation cephalosporins – aminoglycosides – amphenicols – cephamycin – fluoroquinolones – penicillins – sulfonamides – tetracyclines	5	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

Table 10. d: Number of ESBL/AmpC-producing *E. coli* positive samples of beef meat by origin in 2021.

Origin	No. of samples	No. ESBL/ AmpC-producing *E. coli* (%)
Argentina	9	0
Austria	1	0
Brasil	1	0
France	2	0
Germany	1	0
Hungary	1	0
Ireland	8	0
Latvia	2	0
Paraguay	2	0
Uruguay	13	0
US	1	0
Total foreign countries	**41**	**0**
Switzerland	**266**	**0 (0.0%)**

Table 10. e: Number of carbapenem-resistant *E. coli* and *Klebsiella* spp. (since 2020) in meat 2015-2021.

Year	No. of samples	Number of samples (n)	Number of Carbapenemase-producing *E. coli* and *Klebsiella* spp. (since 2020) (n)
2015	chicken meat	319	0
2015	pork meat	301	0
2015	beef meat	298	0
2016	chicken meat	302	0
2017	pork meat	302	0
2017	beef meat	299	0
2018	chicken meat	312	0
2019	pork meat	311	0
2019	beef meat	309	0
2020	chicken meat	312	0
2021	pork meat	309	0
2021	beef meat	307	0

10.3 Discussion

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

Compared to previous years, the prevalence of ESBL/AmpC-producing *E. coli* in poultry meat in 2020 has continued to decrease in Swiss meat (2014: 65.5%; 2016: 41.9%, 2018: 21.1%, 2020: 10.2%). In foreign chicken meat, the decreasing trend in the prevalence of ESBL/AmpC-producing *E. coli* is less pronounced, and is to date much higher than in Swiss meat (2014: 85.6%; 2016: 64.9%, 2018: 63.1%, 2020: 61.8%).

The prevalence of ESBL/AmpC-producing *E. coli* in poultry meat is directly linked to the prevalence in broilers. A significant decrease in the prevalence of ESBL/AmpC-producing *E. coli* was also observed for Swiss broilers between 2016 and 2020, with a prevalence of 10% in 2020 (Chapter 9). In addition to the above-mentioned reasons for the reduced ESBL prevalence in broilers, it is possible that measures during slaughter and/or meat processing known to contribute to this positive development were implemented by the Swiss poultry industry. Comparable significantly decreasing trends in the same time period in other European countries argue for measures that have been taken by the poultry industries on supranational levels [1, 2, 3].

Because of the promising trend in the detection rate of ESBL/AmpC-producing *E. coli* in Swiss chicken meat, it has been possible to re-evaluate the former risk ranking of ESBL/AmpC-producing *E. coli* regarding exposure of humans and hazard characterization via poultry meat [4]. However, due to the still unsolved contamination problem with *Campylobacter* spp. (Chapter 8), the poultry industry must further optimize its processes, and for consumers, adequate kitchen hygiene and proper cooking of raw chicken meat remain essential.

The very low prevalence of ESBL/AmpC-producing *E. coli* in pork and beef meat (<1%) compared to the moderate prevalence in fattening pigs (5.9%) and veal calves (23.8%) can be attributed to good hygiene measures during the slaughtering process.

ESBL/AmpC-producing bacteria have increasingly been found in humans [5]. 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) [5]. Resistance genes of ESBL/AmpC-producing *E. coli* display a large heterogeneity [6]. 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 [6, 7]. A recent study by Dorado-Garcia et al. (2018) analyzed the molecular relatedness of ESBL/AmpC-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 [8].

10.3.2 Carbapenemase-producing *Escherichia coli* in meat

Carbapenems are the most recently developed beta-lactams available on the market and are reserved for treatment of serious infections with multidrug-resistant bacteria in human medicine [9, 10]. Worldwide, infections with carbapenemase-producing bacteria are currently the most critical complication in human medicine. Despite the fact that carbapenems are not licensed for treatment of food-producing animals, carbapenem-resistant bacteria were recently found sporadically in livestock and products thereof in Europe [11]. Since 2015, testing for carbapenem-resistant *E. coli* in chicken, pork and beef meat is included in the national monitoring program. Up to 2021, no carbapenem-resistant *E. coli* and *Klebsiella* spp. could be detected in fresh meat samples. These results are generally in accordance with the results of the European voluntary monitoring system. In 2019 and 2020, a total of 27,470 meat samples were investigated for the presence of carbapenem-resistant *E. coli* [1], and only one sample of pig meat from Germany tested positive. Hence, the risk for transmission of carbapenemase-producing *E. coli* or *Klebsiella* spp. to humans via meat is negligible.

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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 focused on these topics, and there are efforts to establish a European harmonized monitoring system in this context as well [1, 2]. 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 for 2019 to 2021 includes various pathogens/animals and indication combinations (Table 14. d). However, the targeted number of isolates could not be achieved in all cases. In 2020, conditions were revised: isolates from animals with and without previous antimicrobial treatment are now accepted. However, in 2020, due to the COVID-19 pandemic, the number of samples was very low. Due to these revised conditions, the number of samples in 2021 was much higher than in the previous years. The number of isolates examined between 2019 and 2021 can be seen in Table 11. a.

All strains were isolated from clinical submissions of diseased animals by Swiss laboratories (university, cantonal, private) across the country. Susceptibility testing of all isolates was performed by the ZOBA with the broth microdilution method, which guarantees full comparability of data over the years and reinterpretation of data of past years if interpretative criteria change. Moreover, when interpretative criteria are lacking, minimal inhibitory concentrations (MICs) could be analyzed. In contrast to the European monitoring of isolates from livestock, MIC data were in general interpreted according to the current clinical breakpoints issued by the Clinical and Laboratory Standards Institute (CLSI). Categories "intermediate" and "resistant" were added up to "non-susceptibility" proportions. MIC are transmitted to the database of the Swiss Center for Antimicrobial Resistance (ANRESIS) (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 from 2019 to 2021.

11.1 Mastitis pathogens

Mastitis is defined as an inflammatory process in the mammary gland that often results from microbial infection besides trauma or chemical irritation [3]. Mastitis is frequently treated with antibiotics, which are often prescribed without prior susceptibility testing [4]. 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.

11.1.1 *Staphylococcus aureus*

Staphylococcus (S.) aureus is a major cause of clinical bovine mastitis in Switzerland and worldwide [3, 5]. It can be detected in approximately 57% of all dairy herds in Switzerland [5].

In 2021, 113 bovine *S. aureus* mastitis isolates were investigated. A low non-susceptibility rate of 7% was detected against penicillinase-sensitive penicillins. Furthermore, low non-susceptibility rates to tetracyclines (4%), macrolides (2%) and lincosamides (2%) were detected (Table 11. b). Only one of the 113 isolates examined proved to be methicillin-resistant *S. aureus* (MRSA), resulting in resistance rates to third-generation cephalosporins of 1%.

11.1.2 *Streptococcus uberis*

Streptococcus (Str.). uberis is classified as an environmental pathogen and is one of the most important mastitis pathogens in Switzerland.

In 2021, 130 bovine *Str. uberis* mastitis isolates were investigated. High rates of non-susceptibility to tetracyclines (28%), moderate rates of non-susceptibility to lincosamides (clindamycin 15%; pirlimycin 11%) and penicillin (14%), and low rates of non-susceptibility to macrolides (10%) were detected (Table 11. c). Two isolates were resistant to ceftiofur (third-generation cephalosporin) (2%).

11.1.3 *Escherichia coli*

Escherichia (E.) coli causes inflammation of the mammary gland in dairy cows. It most likely appears around parturition and during early lactation, with striking local and sometimes severe systemic clinical symptoms.

In 2021, 79 bovine *E. coli* mastitis isolates were investigated. The isolates showed high rates of non-susceptibility to aminopenicillins (24%) and tetracyclines (24%), and a moderate rate of non-susceptibility to sulfamethoxazole/trimethoprim (15%) (Table 11. d). Low non-susceptibility rates were found against amoxicillin/clavulanic acid (3%) and gentamicin (3%). All isolates were susceptible to third-generation cephalosporins and carbapenems.

11.1.4 Discussion

Comparable data for European mastitis pathogens were recently published [6]. In general, higher non-susceptibility rates for bovine *S. aureus* from mastitis cases were detected on the European level. Thereby, 25.5% of all European *S. aureus* were resistant to penicillin, and 7.3% to tetracycline (4% in Swiss isolates in 2021). Our data pointed out that recommended first-line antimicrobials for the treatment of *S. aureus*, such as penicillin, showed a low non-susceptibility rate (7%). Based on these results, the antibiotics recommended [7], in particular penicillinase-sensitive penicillins, can still be recommended for the treatment of *S. aureus* mastitis, and there is usually no need to use critical antibiotics.

For *Str. uberis*, the situation is different. European *Str. uberis* isolates expressed non-susceptibility rates against penicillin (13%) and pirlimycin (16%) comparable to that of Swiss monitoring isolates, but comparably higher non-susceptibility rates to erythromycin (24%) were detected [6]. Based on the results of 2021, the antibiotics recommended, especially penicillin, can still be recommended for the treatment of *Str. uberis* mastitis and there is no need to use critical antibiotics in the standard case.

For European *E. coli* isolates, non-susceptibility rate to ampicillin (95%) is much higher than that found in Swiss isolates (24%). Interestingly, the non-susceptibility rate against tetracycline is lower in European isolates than the non-susceptibility rates of Swiss isolates. Based on these results, the antibiotics recommended, especially gentamicin, can still be recommended for the treatment of *E. coli* mastitis, and there is no need to use critical antibiotics such as third- and fourth-generation cephalosporins in non-complicated cases.

Noteworthy is the fact that Swiss isolates were included 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" [6].

Table 11. a: Number of isolates by animal, indication, microorganism and sample origin of the monitoring of antimicrobial resistance in veterinary pathogens 2019–2021.

Animal	Indication	Microorganism	Sample origin	Number of isolates 2019	Number of isolates 2020	Number of isolates 2021
Cattle	Mastitis	*Staphylococcus aureus*	milk	60	33	113
Cattle	Mastitis	*Streptococcus uberis*	milk	61	54	130
Cattle	Mastitis	*Escherichia coli*	milk	51	42	79
Dog	Urinary tract infection	*Escherichia coli*	urine	36	30	102
Dog	Skin infections	*Staphylococcus pseudintermedius*	skin	22	15	45
Cat	Urinary tract infection	*Escherichia coli*	urine	35	31	95
Horse	Skin infections	*Streptococcus equi subsp. zooepidemicus*	skin	6	1	7
Small ruminants	Enterotoxemy	*Clostridium perfringens* (Types B, C, D, E)	–	1	3	10
Small ruminants	Abscess	*Corynebacterium pseudo-tuberculosis*	abscess	8	5	11
Poultry	All indication	*Escherichia coli*	faeces	102	101	94
Cattle	Respiratory tract infection	*Pasteurella multocida*	respiratory	2	3	16
Cattle	Diarrhea	Pathogenic *Escherichia coli*	faeces	2	3	1
Pig	Diarrhea	Pathogenic *Escherichia coli*	faeces	7	20	19
Total				**393**	**341**	**722**

Table 11. b: Non-susceptibility rates of *Staphylococcus aureus* isolates from bovine mastitis from 2019 to 2021.

Antimicrobial class	Antimicrobial	*Staphylococcus aureus* 2019			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycosides	Gentamicin	0	60	0	[0,6]
3rd-generation cephalosporins	Ceftiofur	0	60	0	[0,6]
Fluoroquinolone	Ciprofloxacin	1	60	2	[0.3,8.9]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	0	60	0	[0,6]
Glycopeptides	Vancomycin	0	60	0	[0,6]
Lincosamides	Pirlimycin	0	60	0	[0,6]
Macrolides	Erythromycin	0	60	0	[0,6]
Penicillinase-sensitive penicillins	Penicillin	5	60	8	[3.6,18.1]
Tetracycline	Tetracycline	2	60	3	[0.9,11.4]

Antimicrobial class	Antimicrobial	*Staphylococcus aureus* 2020			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycosides	Gentamicin	0	33	0	[0,10.4]
3rd-generation cephalosporins	Ceftiofur	2	33	6	[1.7,19.6]
Fluoroquinolone	Ciprofloxacin	1	33	3	[0.5,15.3]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	0	33	0	[0,10.4]
Glycopeptides	Vancomycin	0	33	0	[0,10.4]
Lincosamides	Pirlimycin	1	33	3	[0.5,15.3]
Macrolides	Erythromycin	1	33	3	[0.5,15.3]
Penicillinase-sensitive penicillins	Penicillin	7	33	21	[10.7,37.8]
Tetracycline	Tetracycline	1	33	3	[0.5,15.3]

Antimicrobial class	Antimicrobial	*Staphylococcus aureus* 2021			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycosides	Gentamicin	1	113	1	[0.2,4.8]
3rd-generation cephalosporins	Ceftiofur	1	113	1	[0.2,4.8]
Fluoroquinolone	Ciprofloxacin	1	113	1	[0.2,4.8]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	0	113	0	[0,3.3]
Glycopeptides	Vancomycin	0	113	0	[0,3.3]
Lincosamides	Pirlimycin	2	113	2	[0.5,6.2]
Macrolides	Erythromycin	2	113	2	[0.5,6.2]
Penicillinase-sensitive penicillins	Penicillin	8	113	7	[3.6,13.4]
Tetracycline	Tetracycline	5	113	4	[1.9,9.9]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

Table 11. c: Non-susceptibility rates of *Streptococcus uberis* isolates from bovine mastitis in 2019 to 2021.

Antimicrobial class	Antimicrobial	*Streptococcus uberis 2019*			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
3rd-generation cephalosporins	Ceftiofur	9	61	15	[8,25.7]
Lincosamide	Clindamycin	16	61	26	[16.8,38.4]
Lincosamide	Pirlimycin	13	61	21	[12.9,33.1]
Macrolide	Erythromycin	15	61	25	[15.5,36.7]
Penicillinase-sensitive penicillins	Penicillin	27	61	44	[32.5,56.7]
Tetracycline	Tetracycline	17	61	28	[18.2,40.2]

Antimicrobial class	Antimicrobial	*Streptococcus uberis 2020*			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
3rd-generation cephalosporins	Ceftiofur	3	54	6	[1.9,15.1]
Lincosamide	Clindamycin	5	54	9	[4,19.9]
Lincosamide	Pirlimycin	3	54	6	[1.9,15.1]
Macrolide	Erythromycin	6	54	11	[5.2,22.2]
Penicillinase-sensitive penicillins	Penicillin	17	54	31	[20.7,44.7]
Tetracycline	Tetracycline	16	54	30	[19.1,42.8]

Antimicrobial class	Antimicrobial	*Streptococcus uberis 2021*			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
3rd-generation cephalosporins	Ceftiofur	2	130	2	[0.4,5.4]
Lincosamide	Clindamycin	20	130	15	[10.2,22.6]
Lincosamide	Pirlimycin	14	130	11	[6.5,17.3]
Macrolide	Erythromycin	13	130	10	[5.9,16.4]
Penicillinase-sensitive penicillins	Penicillin	18	130	14	[8.9,20.8]
Tetracycline	Tetracycline	37	130	28	[21.4,36.8]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

Table 11. d: Non-susceptibility rates of *Escherichia coli* isolates from bovine mastitis in 2019 to 2021.

Antimicrobial class	Antimicrobial	*Escherichia coli* 2019			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	3	51	6	[2,15.9]
Aminopenicillin	Ampicillin	10	51	20	[11,32.5]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	51	4	[1.1,13.2]
Carbapenem	Imipenem	0	51	0	[0,7]
3rd-generation cephalosporins	Ceftiofur	0	51	0	[0,7]
Fluoroquinolones	Ciprofloxacin	4	51	8	[3.1,18.5]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	6	51	12	[5.5,23.4]
Polymyxin	Colistin	0	51	0	[0,7]
Tetracycline	Tetracycline	6	51	12	[5.5,23.4]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2020			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	42	0	[0,8.4]
Aminopenicillin	Ampicillin	5	42	12	[5.2,25]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	1	42	2	[0.4,12.3]
Carbapenem	Imipenem	0	42	0	[0,8.4]
3rd-generation cephalosporins	Ceftiofur	0	42	0	[0,8.4]
Fluoroquinolones	Ciprofloxacin	0	42	0	[0,8.4]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	3	42	7	[2.5,19]
Polymyxin	Colistin	0	42	0	[0,8.4]
Tetracycline	Tetracycline	5	42	12	[5.2,25]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2021			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	2	79	3	[0.7,8.8]
Aminopenicillin	Ampicillin	19	79	24	[16,34.5]
Beta-lactam/ Beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	79	3	[0.7,8.8]
Carbapenem	Imipenem	0	79	0	[0,4.6]
3rd-generation cephalosporins	Ceftiofur	0	79	0	[0,4.6]
Fluoroquinolones	Ciprofloxacin	0	79	0	[0,4.6]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	12	79	15	[8.9,24.7]
Polymyxin	Colistin	0	79	0	[0,4.6]
Tetracycline	Tetracycline	19	79	24	[16,34.5]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

11.2 Pathogenic *Escherichia coli* from poultry

Escherichia (E.) coli in poultry can cause localized or systemic infections. Colibacillosis is caused by avian pathogen *E. coli* (APEC). It manifests in diverse ways, including acute fatal septicemia, subacute pericarditis, airsacculitis, salpingitis, peritonitis, and cellulitis. It is one of the most common economically important bacterial diseases of poultry worldwide. Results on molecular characterization of strains regarding possible identification of avian pathogenic *E. coli* (APEC) were not available.

In 2021, 94 avian *E. coli* isolates were investigated. In 2021, moderate non-susceptibility rates against enrofloxacin (17%), ampicillin (13%) and tetracyclines (13%) were detected. Low non-susceptibility rates were detected for sulfamethoxazole/trimethoprim (4%) as well as for gentamicin (2%) and amoxicillin/clavulanic acid (1%) (Table 11. e). No resistance against colistin, third- and fourth-generation cephalosporines and carbapenems was detected.

Discussion

Compared to the data from 2019 and 2020, there are no indications of a changed resistance situation in pathogenic *E. coli* in poultry in 2021. Considering that aminopenicillins are recommended as first-line antibiotics in poultry, it is important to at least maintain moderate resistance rates to aminopenicillins in the future. Although resistance rates to the critical antibiotics enrofloxacin and colistin are low and 0% respectively, these antibiotics should only be used in selected cases.

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 [8]. Therefore, antimicrobial resistance in companion animals has become a focus in the One Health perspective [1].

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 [9]. *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% [10]. However, 22% of all clinically healthy dogs can also be carriers of MRSP [11]. 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 [12–13]. Colonization and/or infection may therefore not only be a concern for veterinarians treating the infected animals, but also represent a risk for companion animal owners.

In 2021, 45 canine *S. pseudintermedius* isolates were investigated. In 2021, high rates of non-susceptibility were found against aminopenicillins (40%), macrolides (31%), lincosamides (27%) and tetracyclines (24%). Moderate non-susceptibility rates were found against fluoroquinolones (enrofloxacin 20%, marbofloxacin 16%) and gentamicin (11%). Five isolates were confirmed as methicillin-resistant *S. pseudintermedius* (MRSP), resulting in resistance rates of 11% to amino-penicillins/beta-lactamase inhibitors and cefovecin.

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 [14]. Antimicrobial treatment is in many cases the therapy of choice.

***Escherichia coli* from canine urogenital tract infections (UTI)**

In 2021, 102 canine *E. coli* isolates were investigated. A high non-susceptibility rate to ampicillin (21%) and a moderate non-susceptibility rate to amoxicillin/clavulanic acid (12%) was found. Low rates of non-susceptibility were found to fluoroquinolones (8–10%), tetracyclines (8%), third-generation cephalosporins (7%), doxycycline (7%) and sulfamethoxazole/trimethoprim (5%) (Table 11. g). All isolates were susceptible to colistin. No resistance against carbapenems was detected.

***Escherichia coli* from feline urogenital tract infections (UTI)**

In 2021, 95 feline *E. coli* isolates were investigated. Overall, low non-susceptibility rates were found in 2021 for ampicillin (8%), tetracyclines (5%), sulfamethoxazole/trimethoprim (2%), and amoxicillin/clavulanic acid (2%) (Table 11. h). One isolate was resistant to cefovecin. Resistance to fluoroquinolones was detected for the first time in 2021 (2–3%). In addition, two isolates were found to be resistant to imipenem (carbapenem). All isolates were susceptible to gentamicin and colistin.

11.3.3 Discussion

Resistance rates of *E. coli* from UTI in Swiss companion animals showed slightly varying non-susceptibility patterns. Canine isolates generally expressed slightly higher non-susceptibility rates against several antimicrobials, such as ampicillin, amoxicillin/clavulanic acid, fluoroquinolones and tetracyclines, than feline *E. coli* from UTI. Moreover, seven out of 102 canine *E. coli* isolates were confirmed to be ESBL/AmpC producers (6.8%). In contrast, Zogg *et al.* (2018) detected a much higher prevalence of ESBL/AmpC producers (20.8%) among *Enterobacterales* isolated from Swiss clinical cases of dogs and cats [14]. 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. In veterinary clinics, the selective pressure on bacteria due to increased antimicrobial use is higher than in veterinary practices. Moreover, it is not known whether multiple isolates from the same animal were excluded, due to repeated (control) sampling over time. High resistance rates against ampicillin and only sporadically detected multidrug-resistant *E. coli* were also described in a comparable European study of canine and feline UTI *E. coli* [15].

The non-susceptibility rate of *E. coli* from UTI in dogs for aminopenicillins, as first-line antibiotics, is still high at 21% in 2021, but there does not appear to be an increasing trend. Moderate or low rates of non-susceptibility to second-line antibiotics such as combinations of aminopenicillins and beta-lactamase inhibitors, as well as to sulfamethoxazole/trimethoprim, have been found. Therefore, these antibiotics can still be recommended.

Compared to the data from 2019 and 2020, there are no indications of a significant change in pathogenic *E. coli* in cats in 2021 with regard to the favorable non-susceptibility situation. However, the first-time detection of imipenem-resistant *E. coli* shows that the occurrence of such resistant bacteria must be expected in the small animal sector.

The non-susceptibility situation of *E. coli* from UTI in cats for aminopenicillins, as antibiotics of first choice, is favorable, as is that for combinations of aminopenicillins and beta-lactamase inhibitors as well as for sulfamethoxazole/trimethoprim. Therefore, these antibiotics can still be recommended.

11.4 Summary and outlook

In 2021, more than 700 isolates were sent by Swiss university, cantonal and private veterinary diagnostic laboratories to the ZOBA and tested for antimicrobial resistance using the broth microdilution method. All isolates originated from clinically ill animals. In 2019, only isolates from animals that had not received antimicrobial treatment were examined. However, as it turned out to be very difficult for the laboratories to obtain information on the antimicrobial pre-treatment status, isolates have been accepted regardless of their pre-treatment status since 2020. However, in 2020, the number of isolates sent in was sometimes very low, as the laboratories were forced to work with reduced personnel resources due to the COVID-19 pandemic. This situation improved significantly in 2021.

Already in its third year of implementation, the antibiotic resistance monitoring in animal pathogens is proving to be a useful tool for reviewing antibiotic treatment recommendations for various animal species and indications. For the future, it is important to optimize and expand the completeness and presentation of the data collected. Facilitating the access of involved veterinarians and laboratories to these data will be a task for the next monitoring period.

Table 11. e: Non-susceptibility rates of *Escherichia coli* isolates from poultry in 2019 to 2021.

Antimicrobial class	Antimicrobial	*Escherichia coli* 2019			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	102	0	[0,3.6]
Aminopenicillin	Ampicillin	19	102	19	[12.3,27.3]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	1	102	1	[0.2,5.3]
Fluoroquinolones	Enrofloxacin	29	102	28	[20.6,37.8]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	9	102	9	[4.7,15.9]
Polymyxin	Colistin	1	102	1	[0.2,5.3]
Tetracycline	Tetracycline	22	102	22	[14.7,30.5]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2020			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	4	101	4	[1.6,9.7]
Aminopenicillin	Ampicillin	18	101	18	[11.6,26.4]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	101	2	[0.5,6.9]
Fluoroquinolones	Enrofloxacin	19	101	19	[12.4,27.5]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	9	101	9	[4.8,16.1]
Polymyxin	Colistin	2	101	2	[0.5,6.9]
Tetracycline	Tetracycline	15	101	15	[9.2,23.1]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2021			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	2	94	2	[0.6,7.4]
Aminopenicillin	Ampicillin	12	94	13	[7.5,21]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	1	94	1	[0.2,5.8]
Fluoroquinolones	Enrofloxacin	16	94	17	[10.8,25.9]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	4	94	4	[1.7,10.4]
Polymyxin	Colistin	0	94	0	[0,3.9]
Tetracycline	Tetracycline	12	94	13	[7.5,21]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

Table 11. f: Non-susceptibility rates of *Staphylococcus pseudintermedius* isolates from canine skin infections in 2019 to 2021.

Antimicrobial class	Antimicrobial	*Staphylococcus pseudintermedius 2019*			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	1	22	5	[0.8,21.8]
Aminopenicillin	Ampicillin	11	22	50	[30.7,69.3]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	22	9	[2.5,27.8]
3rd-generation cephalosporins	Cefovecin	1	22	5	[0.8,21.8]
Fluoroquinolones	Enrofloxacin	0	22	0	[0,14.9]
Fluoroquinolones	Marbofloxacin	0	22	0	[0,14.9]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	1	22	5	[0.8,21.8]
Lincosamide	Clindamycin	7	22	32	[16.4,52.7]
Macrolide	Erythromycin	6	22	27	[13.2,48.1]
Tetracycline	Tetracycline	5	22	23	[10.1,43.4]

Antimicrobial class	Antimicrobial	*Staphylococcus pseudintermedius 2020*			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	2	15	13	[3.7,37.9]
Aminopenicillin	Ampicillin	8	15	53	[30.1,75.2]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	1	15	7	[1.2,29.8]
3rd-generation cephalosporins	Cefovecin	1	15	7	[1.2,29.8]
Fluoroquinolones	Enrofloxacin	0	15	0	[0,20.4]
Fluoroquinolones	Marbofloxacin	0	15	0	[0,20.4]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	1	15	7	[1.2,29.8]
Lincosamide	Clindamycin	2	15	13	[3.7,37.9]
Macrolide	Erythromycin	3	15	20	[7,45.2]
Tetracycline	Tetracycline	3	15	20	[7,45.2]

Antimicrobial class	Antimicrobial	*Staphylococcus pseudintermedius 2021*			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	5	45	11	[4.8,23.5]
Aminopenicillin	Ampicillin	18	45	40	[27,54.5]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	5	45	11	[4.8,23.5]
3rd-generation cephalosporins	Cefovecin	5	45	11	[4.8,23.5]
Fluoroquinolones	Enrofloxacin	9	45	20	[10.9,33.8]
Fluoroquinolones	Marbofloxacin	7	45	16	[7.8,28.8]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	3	45	7	[2.3,17.9]
Lincosamide	Clindamycin	12	45	27	[16,41]
Macrolide	Erythromycin	14	45	31	[19.5,45.7]
Tetracycline	Tetracycline	11	45	24	[14.2,38.7]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

Table 11. g: Non-susceptibility rates of *Escherichia coli* isolates from canine urogenital tract infections in 2019 to 2021.

Antimicrobial class	Antimicrobial	*Escherichia coli* 2019			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	36	0	[0,9.6]
Aminopenicillin	Ampicillin	5	36	14	[6.1,28.7]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	36	6	[1.5,18.1]
3rd-generation cephalosporins	Cefovecin	2	36	6	[1.5,18.1]
Fluoroquinolones	Enrofloxacin	6	36	17	[7.9,31.9]
Fluoroquinolones	Marbofloxacin	6	36	17	[7.9,31.9]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	5	36	14	[6.1,28.7]
Polymyxin	Colistin	0	36	0	[0,9.6]
Tetracycline	Doxycycline	7	36	19	[9.8,35]
Tetracyclin	Tetracycline	7	36	19	[9.8,35]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2020			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	30	0	[0,11.3]
Aminopenicillin	Ampicillin	10	30	33	[19.2,51.2]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	5	30	17	[7.3,33.6]
3rd-generation cephalosporins	Cefovecin	2	30	7	[1.8,21.3]
Fluoroquinolones	Enrofloxacin	0	30	0	[0,11.3]
Fluoroquinolones	Marbofloxacin	0	30	0	[0,11.3]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	3	30	10	[3.5,25.6]
Polymyxin	Colistin	0	30	0	[0,11.3]
Tetracycline	Doxycycline	4	30	13	[5.3,29.7]
Tetracycline	Tetracycline	4	30	13	[5.3,29.7]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2021			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	2	102	2	[0.5,6.9]
Aminopenicillin	Ampicillin	21	102	21	[13.9,29.4]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	12	102	12	[6.9,19.4]
3rd-generation cephalosporins	Cefovecin	7	102	7	[3.4,13.5]
Fluoroquinolones	Enrofloxacin	10	102	10	[5.4,17.1]
Fluoroquinolones	Marbofloxacin	8	102	8	[4,14.7]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	5	102	5	[2.1,11]
Polymyxin	Colistin	0	102	0	[0,3.6]
Tetracycline	Doxycycline	7	102	7	[3.4,13.5]
Tetracycline	Tetracycline	8	102	8	[4,14.7]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

Table 11. h: Non-susceptibility rates of *Escherichia coli* isolates from feline urogenital tract infections in 2019 to 2021.

Antimicrobial class	Antimicrobial	*Escherichia coli* 2019			
		Number of non-susceptible isolates	Number of isolates tested	Non-Susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	35	0	[0,9.9]
Aminopenicillin	Ampicillin	7	35	20	[10,35.9]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	35	6	[1.6,18.6]
3rd-generation cephalosporins	Cefovecin	2	35	6	[1.6,18.6]
Fluoroquinolones	Enrofloxacin	0	35	0	[0,9.9]
Fluoroquinolones	Marbofloxacin	0	35	0	[0,9.9]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	2	35	6	[1.6,18.6]
Polymyxin	Colistin	0	35	0	[0,9.9]
Tetracycline	Doxycycline	3	35	9	[3,22.4]
Tetracycline	Tetracycline	3	35	9	[3,22.4]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2020			
		Number of non-susceptible isolates	Number of isolates tested	Non-susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	31	0	[0,11]
Aminopenicillin	Ampicillin	1	31	3	[0.6,16.2]
Beta-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	0	31	0	[0,11]
3rd-generation cephalosporins	Cefovecin	0	31	0	[0,11]
Fluoroquinolones	Enrofloxacin	0	31	0	[0,11]
Fluoroquinolones	Marbofloxacin	0	31	0	[0,11]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	0	31	0	[0,11]
Polymyxin	Colistin	0	31	0	[0,11]
Tetracycline	Doxycycline	3	31	10	[3.4,24.9]
Tetracycline	Tetracycline	3	31	10	[3.4,24.9]

Antimicrobial class	Antimicrobial	*Escherichia coli* 2021			
		Number of non-susceptible isolates	Number of isolates tested	Non-Susceptibility (%)	95%CI
Aminoglycoside	Gentamicin	0	95	0	[0,3.9]
Aminopenicillin	Ampicillin	8	95	8	[4.3,15.8]
B-lactam/ beta-lactamase inhibitors	Amoxicillin-clavulanic acid	2	95	2	[0.6,7.3]
3rd-generation cephalosporins	Cefovecin	1	95	1	[0.2,5.7]
Fluoroquinolones	Enrofloxacin	3	95	3	[1.1,8.9]
Fluoroquinolones	Marbofloxacin	2	95	2	[0.6,7.3]
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole	2	95	2	[0.6,7.3]
Polymyxin	Colistin	0	95	0	[0,3.9]
Tetracycline	Doxycycline	5	95	5	[2.3,11.7]
Tetracycline	Tetracycline	5	95	5	[2.3,11.7]

CI: Confidence interval; Interpretation according to CLSI Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th ed. CLSI supplement VET01S. Wayne, PA: Clinical and Laboratory Standards Institute; 2020

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12

Antibiotics and antimicrobial resistance in the water cycle

12 Antibiotics and antimicrobial resistance in the water cycle

12.1 Sources of antibiotics to the environment

Antibiotics are consumed in high quantities in human as well as veterinary medicine. Approximately 27,000 kg were sold in human medicine in Switzerland in 2021, with penicillins, tetracyclines and macrolides-lincosamides being the main used substance groups (see Chapter 5). Sales data of veterinary antibiotics are in the same range as human antibiotics, with sulfonamides, penicillins, and tetracyclines being the main applied substance groups (see Chapter 6). However, a decline of 18% in human use of antibiotics and 48% in veterinary usage is observed as compared to 2012. After intake, humans and animals excrete antibiotics partly unchanged, so that they end up in wastewater or soils via application of manure. Beside these routes, production facilities as well as aquaculture can also be a source of antibiotics to the aquatic environment.

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 in the aquatic environment. 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 activated carbon) eliminate a large spectrum of micropollutants to varying extents. Most antibiotics are very well eliminated (>90%). The upgrade of the WWTPs must be completed by 2040 at the latest, at which time approximately 70% of all Swiss municipal wastewater 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 biological degradation. However, certain mobile and persistent antibiotics are not removed during riverbank filtration and thus ultimately reach the groundwater. In addition, manure application to soils may lead to a contamination of groundwater with antibiotics used in veterinary medicine by direct leaching from soils into groundwater. Since 2006, the application of sewage sludge to fields is no longer allowed.

12.2 Available Monitoring Data 2020

Wastewater (WW) and wastewater treated against micropollutants (WW-MP)
For wastewater, data on effluent concentrations of antibiotics are available from cantonal measurement campaigns of the cantons VD and ZH as well as from the WWTPs performance surveillance that is required after the upgrade. Effluent samples (24 h to 48 h composite samples) were collected between January and December 2020 at 62 municipal WWTPs, of which 8 were equipped with an additional treatment step for the elimination of micropollutants.

Surface water (SW)
Surface water is regularly analyzed within the National Surface Water Quality Monitoring Program (NAWA). This network of monitoring sites enables the Federal Office for the Environment (FOEN) and the cantonal authorities to document and evaluate the water quality of surface waters across Switzerland. Since 2018, this network is enhanced to monitor micropollutants, including pharmaceuticals. In 2020, data on 13 antibiotics and 4 metabolites were obtained from 33 different NAWA monitoring sites. Not all the compounds are analyzed at each station. These NAWA monitoring sites are mainly located on the Swiss plateau and cover different land use types and sources of micropollutants. Approximately half of the sites contain treated wastewaters. Refrigerated 2-week composite samples are collected continuously throughout the year.

The Rhine Monitoring Station (RMS), located in Weil am Rhein near Basel, allows monitoring of the antibiotics originating from the whole Swiss Rhine catchment before they are exported to downstream countries. Representing waters from 68% of the Swiss land surface, the samples taken at the RMS are of particular importance. Therefore, antibiotic concentrations found at the RMS, along with the flow measurements, allow the calculation of the load of the substances that are annually exported from Switzerland to the North Sea.

Groundwater (GW)
Groundwater is monitored for selected pharmaceuticals by the National Groundwater Monitoring (NAQUA) since 2013. NAQUA is operated by the FOEN in close collaboration with the cantonal authorities (FOEN 2022a). It comprises approximately 550 groundwater quality monitoring sites representing different typical hydrogeological settings and anthropo-

genic 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.

12.3 Antibiotics in municipal wastewater, surface water and groundwater

Figure 12. a shows the distribution of different antibiotic concentrations as boxplots according to the water type: wastewater (WW), wastewater treated against micropollutants (WW-MP), surface water (SW) and groundwater (GW). In the effluent of conventional WWTPs, without an additional treatment step against micropollutants, antibiotics were detected in almost every sample (mean detection frequency 95%). Their concentrations quantified in treated wastewater ranged mainly from 0.001 to 0.77 µg/l, with some outliers above 1 µg/l (Figure 12. a). The median value of clarithromycin, sulfamethoxazole, sulfapyridine and trimethoprim ranged from 0.05 to 0.29 µg/l, whereas the median value of sulfamethazine is one order of magnitude lower (0.005 µg/l). Other antibiotics, such as clindamycin, were also found (data not shown).

In the effluent of WWTPs equipped with an additional treatment step for micropollutants (mainly ozonation or activated carbon treatment), antibiotics were less frequently detected than in conventional WWTPs (mean detection frequency of 41%). Their concentrations were significantly lower than in conventional WWTPs and ranged from 0.005 to 0.16 µg/l, with median concentrations between 0.007 µg/l (trimethoprim) and 0.08 µg/l (sulfamethoxazole; Figure 12. a). Concentrations of sulfamethazine and sulfapyridine were below the limit of quantification. The data clearly show the efficient elimination of antibiotics by an additional treatment step against micropollutants.

In surface water, the detection frequencies were lower than in wastewater: sulfapyridine was found in 50% of all samples, followed by sulfamethoxazole (35%), clarithromycin (23%), trimethoprim and sulfamethazine (13%). Other antibiotics such as azithromycin (4%) and erythromycin (2%) were only rarely detected (data not shown). Concentrations in surface water ranged mainly from 0.001 to 0.26 µg/l (Figure 12. a). The median concentrations of the detected antibiotics ranged between 0.005 µg/l (trimethoprim) and 0.05 µg/l (sulfamethoxazole). With the exception of sulfamethazine, these concentrations are 2 to 20 times below the medians of conventionally treated wastewater due to dilution with uncontaminated river water. The median concentration of sulfamethazine is 2 times higher in surface water than in wastewater (Figure 12. a). However, sulfamethazine was detected less frequently in surface water (13%) than in wastewater (100%). Sulfamethazine is only authorized in veterinary usages and, thus, can enter rivers through WWTPs but also by diffuse transfer (runoff) from agricultural soils after manure application.

Sulfapyridine is no longer authorized in human nor in veterinary usages in Switzerland. Therefore, its presence in wastewater and surface water is probably due to the metabolization of another drug (sulfasalazine, an anti-inflammatory drug used in human medicine for the treatment of ulcerative colitis and rheumatoid arthritis).

These results clearly show that antibiotics in surface water originate from both human and veterinary medicine. In addition, they may also appear as metabolites of other pharmaceuticals. Rivers containing high antibiotic concentrations were mainly the ones with a significant fraction of treated wastewater in their discharge, such as the Glatt, Vedeggio or Landgrabe rivers.

Moreover, two antibiotics (azithromycin and clarithromycin) exceeded their ecotoxicological numerical requirements, as defined in the Annex 2 of the Waters Protection Ordinance. This implies that with concentrations above 0.12 µg/l and 0.019 µg/l for azithromycin and clarithromycin, respectively, negative effects on aquatic organisms cannot be excluded.

At the Rhine Monitoring Station (RMS), the antibiotic annual load of clarithromycin and sulfamethoxazole decreased from 2013 to 2020 (Figure 12. b). Loads of sulfamethoxazole decreased mainly between 2013 and 2015, while those of clarithromycin decreased sharply after 2018. These changes are influenced both by the decline in antibiotic consumption and by the implementation of the supplementary micropollutants elimination step in some WWTPs from 2014 onwards. Indeed, on the one hand, clarithromycin consumption was reduced by half between 2013 and 2020 in human medicine (Plüss, pers. comm.). Additionally, the proportion of wastewater treated with a micropollutant elimination step within the Rhine catchment increased from 0% in 2013 to 13.4% in 2020. The combination of these two factors add to the strong reduction of clarithromycin loads at the RMS in the last years (Figure 12. b). On the other hand, sales of sulfamethoxazole for human and veterinary purposes have increased (Plüss/Léger, pers. comm.), explaining the relative stagnation of loads found at the RMS between 2015 and 2020.

Figure 12. a: Antibiotic concentrations (2020) in wastewater (WW) of conventional WWTPs, wastewater treated with an additional treatment step against micropollutants (WW-MP), surface water (SW) and groundwater (GW). National statistics on GW are only available for sulfamethoxazole. Boxes represent 50 % of the quantified values, and the white line their median value. The number of quantified samples above the Limit of Quantification (n > LOQ) used for each box plot are indicated below, as are the total analyzed samples (n TOTAL) per antibiotic and water type. The 2020 authorization status of the substances is indicated at the bottom: Human Medicines (HM), Veterinary Medicines (VM) or no longer authorized (–).

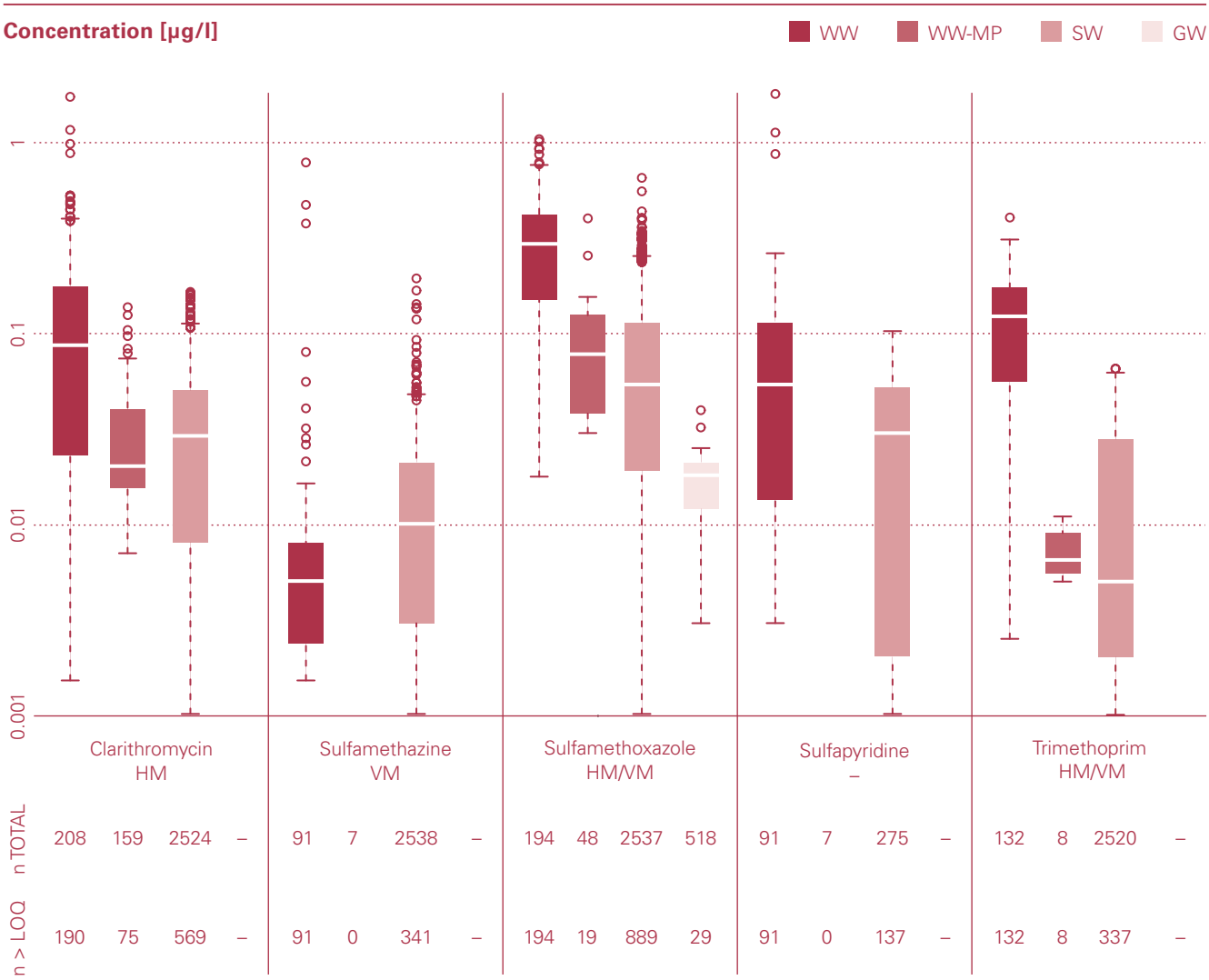
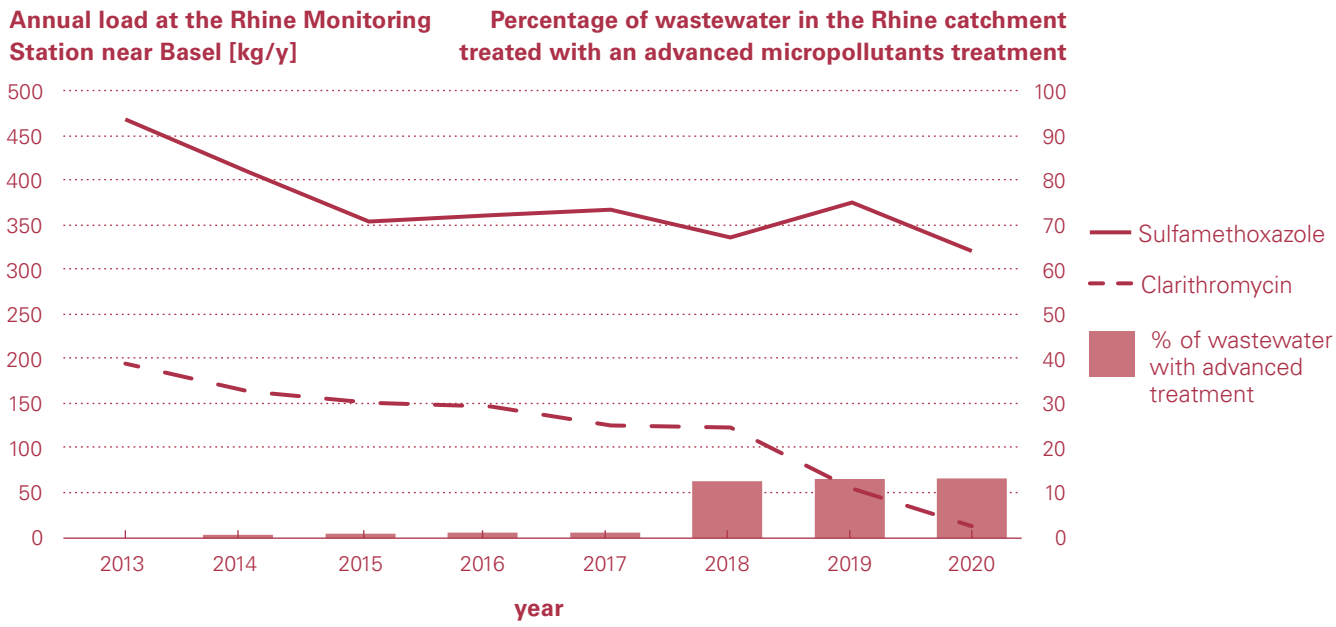


Figure 12. b: Decrease of the annual load of two antibiotics at the Rhine Monitoring Station near Basel from 2013 to 2020 (primary Y-axis), in relation to the proportion of wastewater in the Rhine catchment area that is treated with an additional treatment step for the elimination of micropollutants (secondary Y-axis).



Mobile and persistent antibiotics enter groundwater mainly via infiltration of river water into the subsoil. Manure may also be a source of antibiotics in groundwater. However, antibiotics exclusively used as veterinary pharmaceuticals are only rarely detected in groundwater. Sulfamethoxazole is by far the antibiotic appearing most frequently in groundwater (FOEN 2022b). In 2020, it was detected at 13% of the groundwater monitoring sites near rivers. Its median concentration was approximately 0.02 µg/l (Figure 12. a), which is 2.5 times lower than in river water. Most affected are groundwater monitoring sites near adjacent rivers containing more than 5% of domestic wastewater discharge, such as the Birs, Glatt or Thur rivers. In the coming years, groundwater resources will benefit from the upgrade of the WWTPs and the consequent improvement of river water quality. Significant effects in groundwater will however be visible with a delay, due to long renewal rates of groundwater.

12.4 Conclusions

Antibiotics are present in treated wastewater, surface water and groundwater. Their concentrations decrease from wastewater to surface water due to dilution, and further decrease to groundwater due to degradation and sorption during riverbank filtration or soil passage. Nevertheless, some antibiotics exceed the numerical requirements of the Annex 2 of the WPO in surface water, indicating possible negative effects on aquatic organisms.

Whether these concentrations directly promote the development of antibiotic resistance in the environment is currently unknown. However, recent findings indicate that antibiotics, often in addition to other pollutants, probably add to the selection pressure for antimicrobial resistance (AMR) in the water environment (Lyautey *et al.*, 2021, Murray *et al.*, 2021, Haenni *et al.*, 2022). Recent results of the National Research Program 72 on antimicrobial resistance provide a good overview of the presence of AMR in Swiss waters and the dynamics of AMR environmental spreading (see Textbox at the end of this chapter). Although many questions remain unanswered, emissions of antibiotics to the environment should be minimized 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, and in 2020, 12 WWTPs treating approximately 11% of Switzerland's wastewater were already equipped with an additional treatment step against micropollutants. The elimination effect of more than 90% for most antibiotics is clearly visible in the treated wastewater concentrations (Figure 12. a). This effect is also visible through the general decrease of the total loads calculated for the Rhine River (Figure 12. b). Until 2040, approximately 70% of all Swiss wastewater will be treated against micropollutants; this should lead to a significant reduction of the load of antibiotics being released from WWTPs to the environment. Therefore, in the coming years, the trend seen in the Rhine River should be further confirmed across Switzerland in surface (NAWA) as well as in groundwater (NAQUA) monitoring.

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Textbox

Antimicrobial resistance in wastewater, mixed overflows and surface water: insight into the results of the NRP 72

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Antibiotic-resistant bacteria in the environment, in agriculture, outside of livestock production and meat processing, e.g., in slurry, soil or on crops, but also in aquatic systems such as wastewater, surface water and groundwater are currently not part of the regular monitoring of antimicrobial resistance (AMR) – neither in Switzerland nor internationally. However, in line with the One Health strategy against AMR (https://www.star.admin.ch/star/en/home.html), these aspects remain a focus of research. Within the framework of the National Research Program 72 "Antibiotic Resistance" (NRP 72; www.nfp72.ch), various research projects were carried out with the aim of better understanding the occurrence and spread of AMR in environmental reservoirs, including wastewater and water bodies (NRP72, Module 1).

Detection and characterization of resistant isolates

In one of the NRP 72 projects, the sources and transmission pathways of extended spectrum beta-lactamase (ESBL)-producing Enterobacterales were investigated using detailed genome analyses (https://p3.snf.ch/project-167060). For this purpose, isolates originating from the wastewater system of Basel and from food purchased from local stores were analyzed and compared to clinical isolates from the University Hospital Basel. ESBL producers were detected in more than 94% of all wastewater samples. Comparisons between the distribution of ESBL genes, plasmid replicon types and bacterial strains revealed significant similarities with strains from clinical samples. These results demonstrate the wide distribution of ESBL-producing Enterobacterales in the community, and show that wastewater samples reflect this distribution. In the future, wastewater monitoring could therefore be a useful instrument for general surveillance of AMR, similar to the successful wastewater-based surveillance of COVID-19 (Fernandez-Cassi *et al.*, 2021).

Given the prevalence of antimicrobial resistance in wastewater, and the good, but by no means complete removal of resistant bacteria in biological wastewater treatment plants (WWTPs) (Lee *et al.*, 2022), it is not too surprising that the detection of problematic AMR in water bodies has been repeatedly reported. Recently, for example, *Enterococci* with resistance to the reserve antibiotic linezolid (Biggel *et al.*, 2021) and carbapenemase-producing Enterobacterales (Bleichenbacher *et al.*, 2020) were found in several Swiss rivers. Several similar reports had been published previously, e.g., on the finding of plasmid-localized *mcr1* colistin resistance (Zurfuh *et al.*, 2016) and several other problematic resistance types in surface waters.

Sources and behavior of antimicrobial resistance in surface waters

In the NRP 72 project Swiss River Resistome (https://p3.snf.ch/projects-167116), different aspects of the environmental behavior of AMR entering water bodies with wastewater were investigated. One focus was an environmental fate analysis of resistance determinants (resistance genes or counts of resistant bacteria) suitable as indicators of resistance contamination in the environment. For the first time, a mass-flow approach was applied to study the environmental fate of AMR indicators. The study concluded that much of the rapid decrease of concentrations of resistance indicators observed downstream of WWTPs is due merely to dilution, but that other losses can be observed and quantified over longer transport distances (Lee *et al.*, 2021).

The Swiss River Resistome team also provided data on the impact of combined sewer overflows and wastewater bypass (Lee *et al.*, 2022). These mechanisms lead to the discharge of untreated or minimally treated sewage when heavy rainfall exceeds the capacities of combined sewers and WWTPs. The monitored events led to an up to 100-fold increase of indicator genes and counts of AMR bacteria in river water. Metagenomic sequencing showed that abundant and diverse multiresistant genotypes reach the river in this way. Considering the frequency of such events, and the high removal in WWTPs, these inputs probably amount to a substantial input of antimicrobial resistance into Swiss surface waters.

As part of the Swiss River Resistome project, a first attempt was made to develop country-scale models for indicators of contamination with AMR bacteria (e.g., the *sul1* and *intI1* genes), similar to those previously developed for the mass-flow analysis of micropollutants (Ort *et al.*, 2009). The developed model considers only the input of wastewater treatment plants and calculates the expected levels (concentration) and mass flow of two indicator genes for acquired AMR (Lee, 2021). The researchers tested model variants with or without distance-dependent decomposition of the resistance indicators as well as consideration of the background concentration, which is also present in the case of resistance in non-polluted waters. The model validation allowed the identification of a model variant without degradation, but with consideration of the background contamination, as the best variant. For the mass flux, this model achieved a good correlation with measured data (R^2 adj. 0.71 and 0.75 for the sul*1* and intl*1* gene, respectively). The predicted concentrations correctly reproduced the trends

($p < 0.01$), but with larger deviations (R^2 0.20 and 0.33, respectively). For the first time, the model allows an overview of expected loads of AMR and shows that high abundances of resistances are to be expected especially in the tributaries of the main river systems in the heavily populated Swiss Plateau (Figure 1).

The synthesis report on Module 1 of the NRP 72 recommends establishing wastewater-based surveillance of AMR and making genomic surveillance a cornerstone of future AMR surveillance. Hot-spot-oriented surveillance (e.g., at airports, hospitals or long-term care facilities) could directly support risk management and interventions. Regular population-oriented monitoring of resistance indicators or even the overall resistance profile of wastewater in the influents of municipal wastewater treatment plants (e.g., in larger Swiss cities) could provide important data for the assessment of public health that is complementary to and independent of clinical case reports. Similar measurements in effluents would provide important data on the efficiency of AMR removal in wastewater treatment plants and dissemination into the environment. These measures would thus complement existing surveillance and fill gaps in the One Health concept of combatting AMR.

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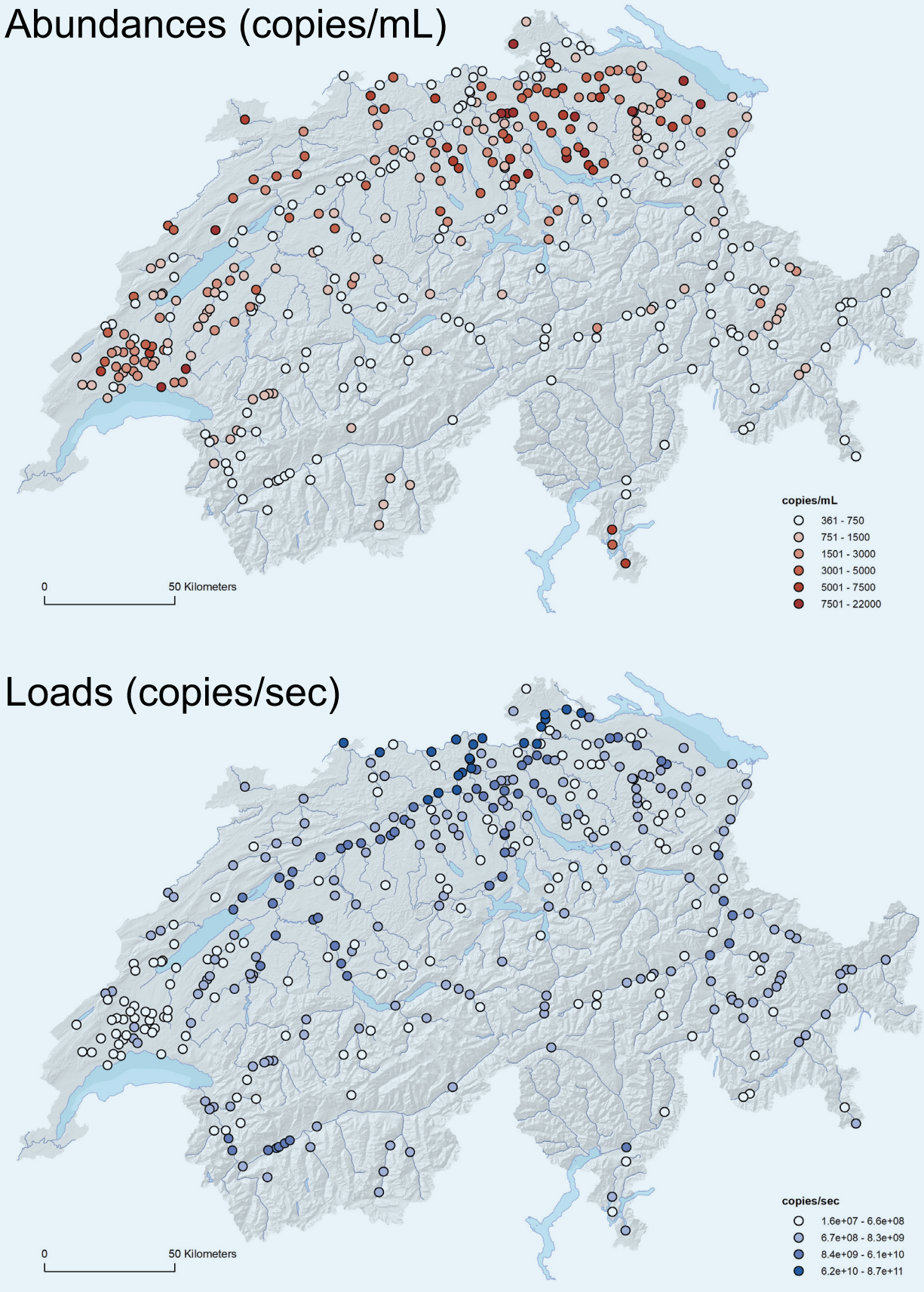
Figure 1: Modelled sulfonamide resistance gene (*sul1*) abundances (top) and loads (i. e., mass-flow, bottom) in the Swiss river network.



13

One Health spotlight: New methods allow new insights into the spread of antibiotic resistance

13 One Health spotlight: New methods allow new insights into the spread of antibiotic resistance

13.1 Introduction

Antimicrobial resistance (AMR) is increasing worldwide and is one of the major challenges for the 21st century. AMR is associated with increased morbidity and mortality for individual patients, but also the societal impact is tremendous, with a severe economic burden due to increased healthcare costs and reduced economic productivity. In 2015, it was estimated that 671,689 infections in Europe were caused by antimicrobial-resistant bacteria with 33,110 attributable deaths [1]. For Switzerland, 7,156 infections and 276 attributable deaths were estimated [2]. Since then, these numbers have further increased, especially in cephalosporin-resistant Enterobacterales [3]. A more recent publication showed that in 2019 1.27 million deaths were attributable to bacterial AMR, with the highest burden in western sub-Saharan Africa [4]. In addition, the O'Neill report estimated that by 2050, 10 million people will die every year and the cumulative costs will be 100 trillion USD of lost economic output due to AMR [5].

In 2014, the WHO recognized the danger of antimicrobial resistance [6] and proposed a global action plan, providing a framework for national action. In 2015, the Swiss Federal Council adopted the Swiss strategy on Antibiotic Resistance (StAR), which aims to preserve the effectiveness of antibiotic therapies for humans and animals. A One Health concept with the involvement of four federal offices (Federal Office of Public Health [FOPH], Federal Food Safety and Veterinary office [FSVO], Federal Office for Agriculture [FOAG] and Federal Office for the Environment [FOEN]) was developed and future measures were divided into eight fields of action (surveillance, prevention, prudent use of antibiotics, resistance control, science and development, cooperation, information and education, and framework conditions).

Several concrete outputs have already been achieved within the StAR project:

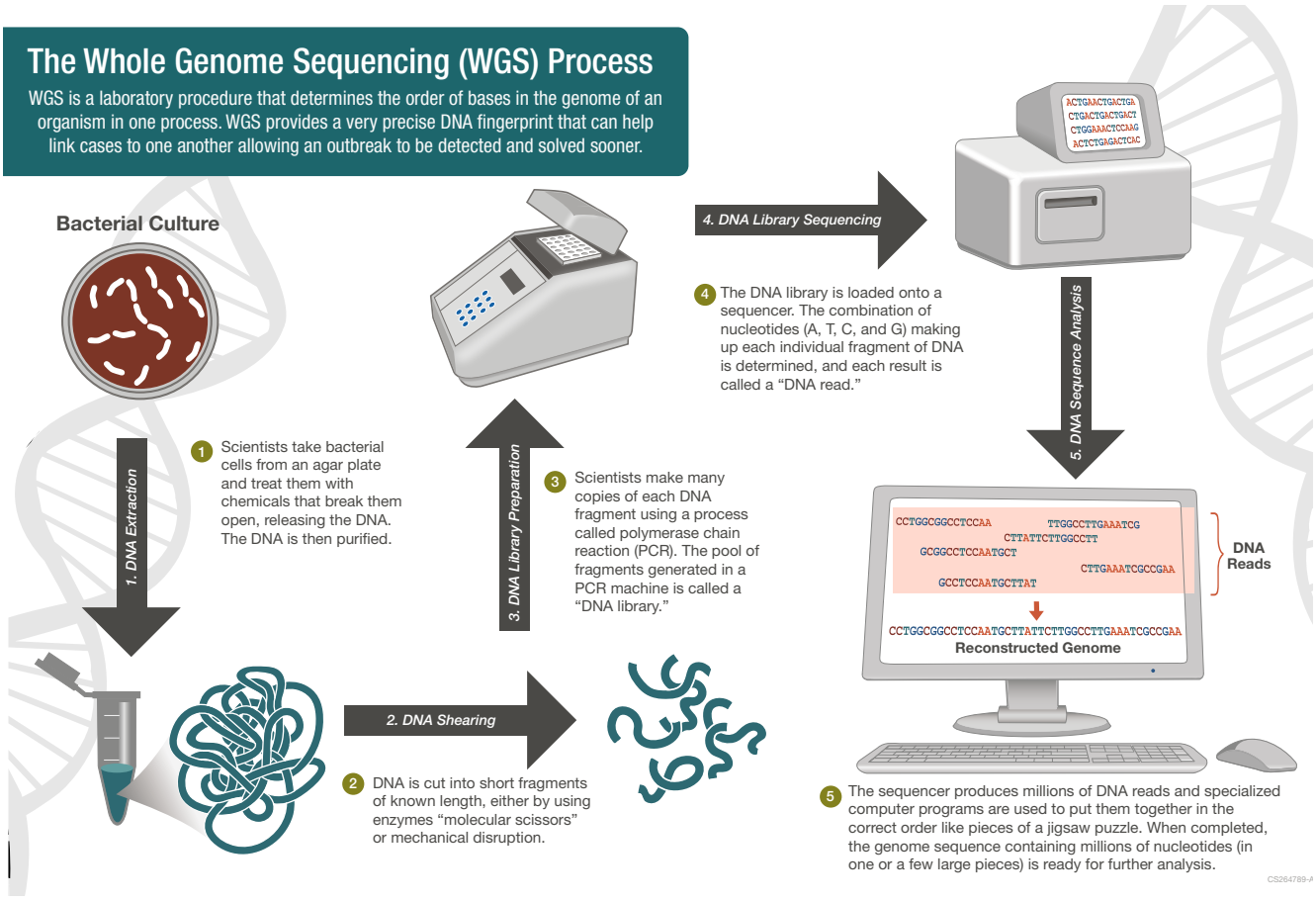
- In the human sector, the surveillance database ANRESIS for phenotypic antibiotic resistances has been further developed. Current resistance trends are published continuously on the website (www.anresis.ch). Physicians can access actual resistance data and treatment guidelines on www.infect.info and www.ssi.guidelines.ch. In addition, hospitals are regularly informed on their antibiotic use, benchmarked to other hospitals in their group. Future tools include unrestricted institutional access to their data by means of interactive dashboards.
- In the veterinary sector, monitoring data on antibiotic use and resistance data of indicator bacteria, zoonotic bacteria and animal pathogens are published regularly. In addition, a database registering all antibiotic use in animals was established in 2019 (IS ABV, "Informationssystem Antibiotika in der Veterinärmedizin"). Treatment guidelines for several bacterial infections are available online at www.blv.admin.ch. Tools concerning prevention and biosecurity on farms (www.gesunde-nutztiere.ch) and a manual for infection control in small animals practices (www.kltmed.uzh.ch/de/Handbuch-IPK.html) have been developed.
- In the environmental sector, the focus was placed on wastewater treatment and sewage overflow management as possible sources of dissemination of resistance determinants into lakes and rivers. Wastewater treatment plants are continuously upgraded to increase elimination of micropollutants, including antibiotics, as well as to reduce the number of resistant bacteria in the effluent, e.g., through ozonation. Whether wastewater surveillance may in future provide a new way to monitor the spread of resistance in the population still has to be clarified (see below).

In this chapter, we focus on the newest scientific developments and achievements, illuminating the transfer of antibiotic resistance within and between different compartments. In recent years, new gene-sequencing methods have evolved very rapidly, resulting in technologies such as whole-genome sequencing (WGS), plasmid sequencing, and metagenomics (sequencing of genetic material directly from humans, animals or the environment, without the cultivation of microorganisms). These technical advances make it possible to determine rapidly and at highest resolution the content of microbes. Single bacterial isolates and more complex samples can be analyzed and compared with each other in a short time. This provides valuable information about their genetic relationship (relatedness and phylogeny) and potentially the transmission route or source. In addition, functions can be elucidated from genome or plasmid content, allowing to predict phenotypes. Importantly, the spread of antibiotic resistance can be studied at the genomic level with substantially higher (spatiotemporal) resolution. Additionally, the transfer of mobile resistance genes, such as plasmids, can be studied between different bacterial species. This horizontal gene transfer is the reason why resistance and multiresistance genes are not only passed on by means of reproduction, but also transferred between living bacteria of the same or different species. This means that even non-pathogenic bacteria can be involved in the spread

Figure 13. a: Spread of antibiotic resistance in a One Health context.

Applying new gene-sequencing technologies, recent research in the frame of the National Research Programme "Antimicrobial Resistance" (NRP 72) uncovered important interfaces in the spread of antibiotic resistance between humans, animals, and the environment. Among other things, the transmission of multidrug-resistant *Escherichia coli* bacteria from hospitalized animals to employees of small animal clinics was shown for the first time. Furthermore, elevated levels of antibiotic resistance genes have been detected near the discharge of treated water from sewage treatment plants in rivers. In many cases, these results provide the basis for concrete measures that prevent or limit transmission chains. In addition, the new technologies hold great potential for continuous monitoring of antibiotic resistance in a One Health context.

Figure 13. b: Whole-Genome Sequencing (WGS).



Source: National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED), from www.cdc.gov/pulsenet/pathogens/wgs.html (last access 4.8.2022)

of clinically significant antibiotic resistance, and so-called reservoirs of resistance genes emerge in the environment (e. g., in soil or water) or in human and animal hosts.

13.2 NRP 72 projects reveal the potential of new sequencing technologies

Over the past five years, several research projects of the National Research Program "Antimicrobial Resistance" (NRP 72, www.nrp72.ch) applied whole-genome sequencing, plasmid sequencing, and metagenomics to investigate critical interfaces in the spread of antibiotic resistance across humans, animals and the environment. These studies provided new and crucial insights and highlighted the potential and impact of the new technologies.

13.3 Humans as spreaders of resistance: International travel and home care

As part of the project "Whole-Genome and Plasmid Sequencing for MDR Enterobacteriaceae Simultaneously Isolated from Multiple Human and Non-Human Settings: Deciphering Impact, Risks, and Dynamics for Resistance Transmission and Spread" (Prof. Endimiani, Principal Investigator), researchers collected stool samples from Swiss Zanzibar travelers, each before departure and after their return. The *Escherichia coli* strains isolated from the stools were compared to those found in local residents in Zanzibar and also locally retailed chicken meat or poultry. It was found that at least one-third of the travelers, upon return, were newly colonized with resistant strains clearly originating from Zanzibar [7]. In another study conducted in Laos, the same research group showed that most of the ESBL-carrying plasmids found in *E. coli* strains colonizing Swiss travelers were identical to those found in many other countries; this

indicates that horizontal gene transfer play an important role in the global dissemination of antimicrobial resistance [8]. The researchers conclude that travelers returning from countries with a high prevalence of multidrug-resistant pathogens often introduce new resistant bacteria and resistance genes that originate from animal foodstuff consumed in the visited countries. However, as they usually do not show any signs of illness, but are merely colonized by the pathogens, appropriate screening measures should be considered. The researchers also recommend developing new strategies for the decolonization of the intestinal tract from resistant germs.

In the project "Understanding and Modelling Reservoirs, Vehicles and Transmission of ESBL-Producing Enterobacteriaceae in the Community and Long-Term Care Facilities," research teams in four countries investigated different transmission pathways of multiresistant bacteria that link medical and home care. In Switzerland, researchers at the University Hospital of Geneva (HUG) (Prof. Harbarth, Principal Investigator) focused on patients discharged from hospital, in whom multidrug-resistant Enterobacterales had been detected in the hospital. They followed up 71 patients carrying ESBL-producing Enterobacterales and 102 contact persons at home for four months after hospital discharge. In this period, 13 clonally related household transmissions occurred from patients to other household members, and 6 transmissions from family contacts to patients, whereby the risk of such an event was highest during the first 2 months after hospital discharge [9]. As Enterobacterales are enteric pathogens, the fecal-oral route played an important role in the transmission chain, namely in the context of assistance with intimate care of frail patients. The findings highlight that general hygiene measures, rather than more appropriate handling of contaminated food items, may become an important preventive measure to reduce transmission within households, especially if family members have to assist a patient. This would be in line with experience in healthcare settings, where hand hygiene has been shown to be a key factor in reducing pathogen transmission. While for the part on long-term care facilities no Swiss institutions were included in this project, a recent study (not part of NRP 72) assessed the burden of ESBL-producing Enterobacterales in Swiss long-term care facilities and identified independent institution- and resident-level factors associated with colonization [10]. The study was performed among residents from 16 long-term care facilities in Western and Eastern Switzerland (8 per region) from August to October 2019. It showed that the prevalence of ESBL-producing Enterobacterales in Swiss facilities is comparable to that of other middle-European countries, with *E. coli* ST131, and its subclone H30R1, being the predominant strains. The researchers observed multiple clusters of residents with identical pathogens in certain institutions, calling for targeted interventions to revise and improve infection control policies in affected institutions. Such interventions may include efforts to increase adherence to hand hygiene, instructions for the correct use of personal protective equipment, and strategies to reduce prescription of antibiotics. And since use of proton-pump inhibitors (medicines to reduce the production of acid in the stomach) was identified as an independent risk factor for the carriage of ESBL-producing Enterobacterales, reducing the use of this kind of drugs should be considered as part of any antibiotic stewardship program in long-term care.

13.4 Transmission from animals to humans

In another part of the the above-mentioned project "Whole Genome and Plasmid Sequencing for MDR Enterobacteriaceae Simultaneously Isolated from Multiple Human and Non-Human Settings: Deciphering Impact, Risks, and Dynamics for Resistance Transmission and Spread" (Prof. Endimiani, Principal Investigator), researchers sequenced multidrug-resistant enterobacteria from patients, foodstuffs, farmed animals, wild animals and wastewater in Switzerland. By linking the data obtained with each other and with epidemiological data on the patients concerned, the researchers obtained information on how certain resistances spread across humans, animals, the food chain and environmental domains. They found multidrug-resistant *Escherichia coli* bacteria in two stool samples from employees of veterinary clinics that were clearly identical to strains they had previously detected in dogs and cats at these clinics [11]. Furthermore, they discovered high-risk clones of highly resistant *Klebsiella pneumoniae* in the immediate vicinity of a veterinary clinic. The genetic analysis also revealed that these strains were identical to those causing infections in companion animals hospitalized at the clinic. Interestingly, no transmission was observed between animal keeper and animal in this study [12]. However, in a more recent analysis, it was shown that human and non-human settings may share high-risk clones of multidrug-resistant *K. pneumoniae* strains [13]. Overall, the results suggest that the infection control procedures already implemented in the human clinics should be implemented in the veterinary clinics as well. In addition, in the interests of early outbreak detection, it would be important to report to the Federal Institutions the detection of certain resistant pathogens (e. g., those producing carbapenemases) in companion animals, as is already the case in human medicine.

In the project *Resistome in the Pig Farms: Comparison of the Breeding and Fattening Units with a One Health Approach* (Dr. Hilty, Principal Investigator), researchers investigated how resistance burden evolves in fattening pigs over their life cycle. The primary bacteria of concern in pigs are *Escherichia coli* that are resistant to colistin or to extended spectrum cephalosporin (ESC). As for the latter, the researchers found the highest prevalence of these resistant pathogens in rectal swabs of suckling piglets [14]. Just over 6% of these samples contained ESC-resistant *E. coli*, while just over 5% of all samples contained colistin-resistant enterobacteria [15]. These numbers declined once the pigs started eating regular feed and fell even further during the final (fattening) phase of their lives. Less than 2% and 4% of the samples taken from animals in this phase of life respectively contained ESC-resistant and colistin-resistant *Escherichia coli*.

The researchers conclude that these low percentages are little cause for concern regarding the potential transmission to farmers.

However, since enterobacteria primarily colonize the intestines, the researchers also investigated the composition of the microbial community – what is known as the intestinal microbiota – in pig farmers' intestines. Samples of the farmers' stools tested by 16S rRNA sequencing were found to contain an elevated proportion of bacteria that are typically found in pigs [16]. This indicates that coming into close contact with pigs for work purposes affects the intestinal microbiota. Provisional data analyses show that the situation is similar for antibiotic-resistant pathogens. However, further studies will have to investigate whether this represents a direct health risk. Despite this, it would be relatively simple to improve preventive measures. For example, the researchers found that a large number of microorganisms are transmitted by aerosols. Farmers could avoid inhaling these aerosols by wearing FFP2 face masks, something they rarely do so far.

13.5 Reservoirs and transmission routes connected to the environment

In the project "Transmission of ESBL-Producing Enterobacteriaceae and Their Mobile Genetic Elements – Identification of Sources by Whole Genome Sequencing" (Prof. Tschudin Sutter, Principal Investigator), researchers collected and analyzed numerous samples from various sources in the city of Basel. At the University Hospital Basel, they collected all ESBL-producing bacteria recovered from patients colonized or infected over a period of two years. During the same period, they examined wastewater samples from the sewage system of every district of the city of Basel, as well as poultry meat, herbs, sprouts and salads, which they bought once a month in a large supermarket and a small shop in each district. The analyses of these samples showed that ESBL-producing enterobacteria are very widespread in the population: they were found in over 94% of all wastewater samples [17]. By far the most common species was *Escherichia coli*. The researchers conclude that in the future wastewater monitoring could therefore make a decisive contribution to the general monitoring of antibiotic resistance. Of the food samples, up to 17% of the poultry and 2% of the vegetable samples contained ESBL-producing bacteria. Here, too, *Escherichia coli* was the most common type. The analysis of the genetic sequencing showed a large genetic diversity of bacterial strains, i. e., few relationships overall. This indicates that a variety of different sources must be involved in the spread of this specific antibiotic resistance mechanism. However, the data showed that while resistant bacteria are rarely transferred from food to humans, this occasionally may occur (although transfer of resistant bacteria could be avoided thanks to proper food preparation) [18]. In a follow-up project, the researchers are now evaluating which mobile genetic elements occur in different unrelated bacterial strains. By doing this, they are clarifying the role that horizontal gene transfer contributes to the spread of resistance between humans, food and wastewater.

In the project "Swiss River Resistome – Identity, Fate, and Exposure" (Dr. Bürgmann, Principal Investigator), researchers analyzed how antibiotic resistant microorganisms and resistance genes which enter wastewater with feces spread in natural waters even after wastewater treatment. They first analyzed and compared different habitats in the river ecosystem, both upstream and downstream of wastewater treatment plants. This study showed that the discharge of treated wastewater not only increases the antibiotic resistance load of river water, but that resistant organisms and resistance genes from wastewater are also found in sediments, on biofilms on stones and in the intestines of freshwater crustaceans, among other places [19, 20]. While the contamination is strongest immediately after the wastewater discharges, it is already significantly reduced over a distance of a few kilometers. The reasons for this are primarily dilution and, secondarily, degradation processes. However, the researchers also found exceptions: in one river, they detected temporarily increased concentrations of resistance genes far downstream. While this indicates that antibiotic-resistant organisms and resistance genes can accumulate and multiply in certain habitats in river systems, the exact underlying conditions and processes could not be clarified in the frame of this project and need further investigation.

The researchers also analyzed river water samples during heavy rain events, which regularly lead to an overflow of a mixture of excess rainwater and untreated wastewater from wastewater treatment plants into rivers, bypassing conventional treatment processes. They found that such events lead to a rapid and strong increase in antibiotic-resistant organisms and resistance genes in receiving rivers. In each case, the high levels subside after several hours. Despite this, the researchers estimate that, over the course of a year, such extreme events account for about half of the total input of antibiotic resistance to rivers, although only about 3% of municipal wastewater is discharged untreated into rivers in this way. They therefore suggest that the retention capacity of wastewater treatment plants and retention basins should be increased. Similarly, stormwater and wastewater should be better separated, and improved infiltration in the catchment areas of wastewater treatment plants could reduce the volume of water entering the sewer system during heavy rainfall.

In the project "Tracking Antibiotic Resistance from Environmental Reservoirs to the Food Chain" (Dr. Hummerjohann, Principal Investigator), using lettuce as an example, researchers investigated how resistant bacteria are transferred to plants in vegetable production, e. g., from the soil or from liquid manure. The researchers conducted experiments with both outdoor and greenhouse lettuce. They grew the lettuce by the conventional method, but in different soils – with and without slurry, with river water and with sterilized water. Regardless of the soil or water type during

the early growth phase, the outdoor lettuce plants all presented similarly low levels of antibiotic-resistant bacteria and resistance genes [21]. Furthermore, these levels declined as the plants grew. Using slurry made a difference, since it resulted in higher resistance gene loads. However, these also declined over time, falling to similar values detected in plants that had not been manured.

With the greenhouse plants, the researchers also investigated the effect of slurry and water that had first been contaminated with multidrug-resistant (ESBL-producing) *E. coli* bacteria. In both cases, the resistant bacteria were transferred to the seedlings [22]. While intact bacteria were only detectable for a few days, their clinically most significant resistance genes were still detectable on the plants up to four weeks after transmission. The researchers therefore recommend observing strict waiting times if non-potable water or slurry is applied to plants, since both may contain multidrug-resistant *E. coli* bacteria of the type investigated in the project. This preventive measure is important for growers of crops such as lettuce that are eaten raw, because, unlike products that are cooked, any antibiotic-resistant bacteria that might be present are not killed off during preparation.

13.6 How new technologies could complement antimicrobial resistance surveillance in future

The examples given show that, thanks to new technical methods, it is possible to identify important control and possible intervention points that are significant in the spread of antibiotic resistance between humans, animals, and the environment. The interfaces investigated are generally not surprising, as they have already been the focus of previous research. What is new is that interrelationships can now be demonstrated with sufficient evidence and unprecedented spatiotemporal resolution, resulting in a very detailed tracing of the spread of antibiotic resistance. The high quality of evidence and the high degree of resolution of this work are important prerequisites for developing targeted measures, the effects of which can be verified.

Beyond insights into individual critical control points, the new technologies also hold great potential for uncovering the routes of AMR dissemination in a One Health context including humans, animals and the environment: in principle, the recording of all resistance genes can provide unlimited correlations, of geographic nature and across the entire biological system. However, despite these excellent new research tools, estimation of the quantitative effects of different modes of transmission still remains difficult. In addition, these new technologies will expand our tools for surveillance and monitoring (e. g., routine analysis of wastewater). At the European level, the European Food Safety Agency (EFSA) and the European Centers for Disease Control strongly recommend the usage of whole-genome sequencing and the building of platforms for surveillance. In Switzerland, however, in contrast to already established surveillance systems using data generated in routine clinical care (ANRESIS), these high-resolution genomic technologies are as yet rarely applied outside of research, and in a limited number of samples only. Therefore, in future, it will become important to combine broad surveillance, based on routinely generated data, with deeper but narrower insights using whole-genome sequencing data. While such a system should be open to compare data from as many sources as possible, which would be of great benefit for research projects, it has to be examined carefully at which points of the AMR transmission chain the collection of whole-genome sequencing data will have most added value to design more targeted measures.

Although human, veterinary and environmental laboratories as well as scientific studies generate increasing volumes of such genetic data, the scope for using them to monitor and investigate antibiotic resistance on a systemic level has as yet been limited by the need to collate and analyze data centrally. Furthermore, patterns of spread of antibiotic resistance can only be traced if what is happening at the genetic level is put into context with epidemiological and other information (metadata), e. g., the isolation date, place of destination, type of infection, etc. Research to date shows that this linking of genetic and contextual data requires specific and detailed studies on individual aspects.

The data generated by new sequencing technologies hold great additional potential if they can be merged and combined with other data sources. The requirements for doing so are high: the large amounts of high-resolution data and the high complexity of different data from the human, animal and environmental fields require corresponding computing capacities, bioinformatic competences and a high level of data security for sensitive information. Appropriate interfaces and legal frameworks for the use and dissemination of data are required for the input of data from different institutions. These must comply with national and international standards, since important processes in the spread of antibiotic resistance take place on a global level. From a legal point of view, it is particularly important that patient-related metadata be included in analyses that are intended to provide information on the spread of AMR relevant to human medicine, such as date of pathogen isolation or geographical details. However, these are particularly sensitive and are subject to their own legal provisions (in Switzerland, the Data Protection Act and the Human Research Act are central in this respect).

In this regard, in the NRP 72 project "Development of a Swiss Surveillance Database for Molecular Epidemiology of Multi-Drug Resistant Pathogens" (Prof. Adrian Egli, Principal Investigator), researchers developed a database for collating and analyzing data centrally that address the mentioned challenges: the Swiss Pathogen Surveillance Platform (SPSP – www.spsp.ch) was built in a step-by-step process,

in close consultation with health authorities and potential data providers and users. The functionality of the platform was proven during the SARS-CoV-2 pandemic: the SPSP is currently being used extensively to exchange more than 140,000 SARS-CoV-2 sequenced genomes, and provides the authorities with automated, timely reports for virus lineage analyses. With respect to One Health AMR surveillance, the platform could provide an additional benefit if additional datasets were linked, e.g., samples from food, agriculture, and the environment to reveal patterns of AMR spread across the entire human-animal-environment biological system. As the SPSP uses internationally established data standards, it enables connectivity with international AMR surveillance networks, which increasingly include WGS data.

In summary, current research shows that new technologies enable deeper insights into the spread of AMR in a One Health context. In many cases, they provide the basis for concrete measures that prevent or limit transmission chains, not least at the interfaces between humans, animals and the environment. In addition, these technologies hold great potential for continuous monitoring of antibiotic resistance, which also covers One Health contexts. As a complement to existing surveillance systems, they hold the potential to enable faster and more targeted interventions in the future.

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Textbox

Whole-genome sequence-based pilot study for One Health surveillance of carbapenemase-producing Enterobacterales in animals and humans

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In Switzerland, carbapenemase-producing Enterobacterales (CPEs) were reported for the first time in animals in 2018. Whole-genome sequencing (WGS) was used to determine their genetic characteristics and to permit genomic comparison with strains from other sources following a One Health approach. In February 2018, an *Escherichia coli* sequence type (ST) 167 carrying the carbapenemase NDM-5 was associated with a wound infection of a dog in a veterinary hospital [1]. During the summer of 2018, a major outbreak of *E. coli* ST410 producing the carbapenemase OXA-181 occurred in another veterinary clinic, where one quarter of the hospitalized companion animals acquired this pathogen during their stay [2]. Over the same period, employees of both veterinary clinics were screened for the presence of CPEs, revealing that one employee of each clinic was colonized with the same *E. coli* as the one detected in the hospitalized animals [3]. Nevertheless, CPEs were not detected among owners of CPE-positive animals [4]. During the same period, OXA-48-producing *Klebsiella pneumoniae* of the high-risk lineages ST11 and ST307 also emerged in infection sites of companion animals hospitalized in one of the above-mentioned veterinary clinics [5].

The emergence of CPEs in veterinary settings raised the question whether they are related to the strains causing infections in humans in Switzerland. Human cases of CPE infection have to be notified to the Federal Office of Public Health (FOPH) since 2016, and isolates are sent for confirmation or identification to the National Reference Center for Emerging Antibiotic Resistance (NARA) at the University of Fribourg, where they are analyzed from biochemical and molecular points of view and archived [6]. Human OXA-181 *E. coli* strains were made available from NARA, and human OXA-48 *K. pneumoniae* strains were obtained from a collection of the Institute of Infectious Diseases, University of Bern [7]. These strains served as a baseline for the WGS-based pilot study and were compared to the strains circulating in the veterinary settings.

WGS comparative analysis of the *E. coli* ST410-OXA-181 from companion animals with those from humans revealed several sublineages of *E. coli* ST410-OXA-181. Of note, the *E. coli* ST410-OXA-181 associated with the veterinary clinic outbreak in 2018 belonged to the same sublineage as some of the human strains and was very close to one of them. Similarly, WGS analysis revealed that *K. pneumoniae* ST11 of animal and human origin were closely related [7]. However, to date, the link between animals and humans carrying CPEs cannot be made due to the lack of available epidemiological data, and whether transmission occurs from humans to animals or vice versa is therefore still an open question.

This approach provided a first One Health insight into the genomic relatedness between human and animal CPEs in Switzerland, and indicated that exchange is likely to occur. However, WGS-based continuous surveillance as well as availability of WGS data and metadata are crucial for modern molecular epidemiology. This study also highlighted the need for an extension of the Swiss Pathogen Surveillance Platform (SPSP) database, which would enable real-time sharing of WGS of CPEs and their associated clinical and epidemiological metadata [8]. Altogether, a One Health and WGS-based surveillance will contribute to the rapid identification of new emerging CPEs and their potential reservoirs, and routes of dissemination in animals, humans and the environment.

Funding

This study is financed by grant no. 1.21.07 of the Federal Food Safety and Veterinary Office FSVO "Whole-genome-sequencing of cephalosporinase- and carbapenemase-producing Enterobacteriaceae from animals: a baseline for a One Health molecular epidemiology" to V.P., and by the Swiss National Science Foundation (SNSF) grant no. 177378 "Whole genome and plasmid sequencing for MDR Enterobacteriaceae simultaneously isolated from multiple human and non-human settings: deciphering impact, risks, and dynamics for resistance transmission and spread" within the National Research Program NRP72 "Antimicrobial Resistance" to A.E. and V.P.

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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 (code J01 of the ATC classification), antibiotics for treatment of tuberculosis (ATC code J04AB) and agents against amoebiasis and other protozoal diseases (ATC code P01AB) [1]. Since 2018, we have also collected data regarding intestinal anti-infectives (ATC code A07AA, including vancomycin oral and fidaxomicin). Antibiotic consumption (in grams or millions of international units) was converted into defined daily doses (DDD) using the 2022 release of the DDD by the World Health Organization Collaborating Centre for Drug Statistics Methodology (see Annex I). Of note, 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].

14.1.2 Data sources in the hospital setting

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

(i) IQVIA™ sales Data (Sell-In) from pharmaceutical industries to hospitals

2012–2021 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 covered the antibiotics sold to hospitals (IQVIA™ channel: SPI), including acute care hospitals, as well as rehabilitation, geriatric, and psychiatric clinics, and some nursing homes. As IQVIA™ follows the EphMRA classification, we accordingly collected antibacterial use data from the J01 (systemic antibiotics), D10B (minocycline, doxycycline oral, lymecycline), G01A1 (metronidazole oral, ornidazole oral), G04A1 (fosfomycin), G04A9 (nitrofurantoin), and J08 (metronidazole parenteral) classes [3]. This allowed us to measure antibiotic consumption at the national level and by linguistic region (German-speaking, French-speaking and Italian-speaking parts of Switzerland).

For the calculation of the consumption in DDD per 1,000 inhabitants per day, the permanent resident population of Switzerland on 31 December of the corresponding year was used [4]. Of note, the population used for the year 2021 is a provisional number and is subject to change once the definitive number is released. This may lead to changes in results between reports.

(ii) A network of voluntary acute care hospitals participating in the surveillance system ANRESIS

The sentinel network being set up in 2004 is mainly composed of somatic public hospitals and some private clinics.

Table 14. a: Number of hospitals and intensive care units contributing to ANRESIS, 2012–2021.

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of participating hospitals per hospital size										
<200 beds	39	37	31	33	42	42	33	36	42	42
200–500 beds	15	15	17	18	21	19	21	22	23	23
>500 beds	9	7	7	9	6	9	8	8	7	6
Total	**63**	**59**	**55**	**60**	**69**	**70**	**62**	**66**	**72**	**71**
Number of intensive care units per hospital size										
<200 beds	18	20	15	15	19	18	14	16	18	18
200–500 beds	14	14	15	16	17	18	20	21	23	21
>500 beds	9	7	7	9	6	8	8	8	6	6
Total	**41**	**41**	**37**	**40**	**42**	**44**	**42**	**45**	**47**	**45**

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, since their activity might bias the results. To measure the representativeness, we used the number of hospitals, number of beds (activity type A), and number of bed-days (without days of discharge) from general acute care hospitals (typology K111–K123 from FOPH) [5]. Data were collected from the entire hospitals, and separately from the adult intensive care units (ICU) when available. In this report, we describe the antibiotic consumption for the period 2012 to 2021. 63 hospital sites participated in 2012 and 71 in 2021, of which 42 were small-size (<200 beds), 23 medium-size (200–500 beds) and 6 large-size hospitals (>500 beds, which includes four Swiss university hospitals) (Table 14. a). In 2020, the hospital network represented 45% of the total number of acute somatic care hospitals and 75% of all bed-days in this category in Switzerland. In 2021, 45 hospital sites (41 in 2012) also provided data on adult ICUs (18 small-size, 21 medium-size and 6 large-size hospitals), representing 64% of the hospitals equipped with ICU beds in Switzerland.

When interpreting the hospital data from ANRESIS, structural and patient characteristics can vary greatly depending on the size or typology of a hospital. New participating hospitals may provide retrospective data, which may slightly change the values included in previous Swiss Antibiotic Resistance Reports. In the regional comparisons, it should be noted that there is no university hospital in Italian-speaking Switzerland.

The major difference between datasets is that the network of sentinel hospitals only includes acute care hospitals, whereas the IQVIA™ dataset is not restricted to acute care, also including data from rehabilitation, geriatric, and psychiatric clinics, as well as some nursing homes. Administrative data collected from the sentinel network allow us to use the number of bed-days and admission as denominators.

The measurement units for reporting antibiotic consumption in the inpatient setting were DDD per 1,000 inhabitants per day (DID), DDD per 100 bed-days and DDD 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 three sources of data:

(i) IQVIA™ sales Data (Sell-In) from pharmaceutical industries to public pharmacies and self-dispensing physicians

Data for the years 2012 to 2021 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 antibacterials 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 (systemic antibiotics), D10B (minocycline, doxycycline oral, lymecycline), G01A1 (metronidazole oral, ornidazole oral), G04A1 (fosfomycin), G04A9 (nitrofurantoin), J08 (metronidazole parenteral) classes [3]. 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).

For the calculation of the consumption in DDD per 1,000 inhabitants per day, the permanent resident population of Switzerland on 31 December of the corresponding year was used [4]. Of note, the population used for the year 2021 is a provisional number and is subject to change once the definitive number is released. This may lead to changes in results between reports.

(ii) Prescriptions orders from the pharmaSuisse database

We herein report data from pharmaSuisse for the years 2019 to 2021. These data were provided 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 50% of all pharmacies in 2021 in Switzerland (52% in 2020, 53% in 2019). 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). Relative consumption was measured using the quantity in DDD.

(iii) Prescriptions orders from the Sentinella network

We analyzed all antibacterial prescriptions reported from practitioners from general and internal medicine and pediatricians during 2019–2021 using the representative Swiss Sentinel Surveillance Network "Sentinella" [6]. 134 practitioners from general and internal medicine contributed to Sentinella in 2021 (n = 134 in 2019, n = 137 in 2020). The number of contributing pediatricians was 27 in 2021 (n = 22 in 2019, n = 24 in 2020). The network covers all regions of Switzerland. Extrapolation on the population level was performed by attributing the estimated covered population to each Sentinella physician.

The major difference between datasets is that prescriptions from self-dispensing physicians were included in the IQVIA™ database but not in the pharmaSuisse database. The pharmaSuisse database allowed us to calculate the proportion of antibacterial use by age group, where antibacterial use by indication was given by the Sentinella database. The Sentinella data allowed us to calculate the use in numbers of prescriptions per 100,000 inhabitants or per 1,000 consultations.

In Switzerland, principally all antibacterials are dispensed with a prescription. The Federal Act on Medicinal Products and Medical Devices mentions that medicinal products subject to prescription may be dispensed without a prescription

when the pharmacist has direct contact with the person concerned and the dispensing is recorded, and if the medicines and indications are designated by the Federal Council [7]. The dispensing of antibacterials for patients with simple urinary tract infections (e. g., fosfomycin) by pharmacists may therefore be allowed in justified exceptional cases, and therefore is missed in this dataset.

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

The WHO Expert Committee on Selection and Use of Essential Medicines recommends the categorization of antibiotics into the following categories: Access, Watch and Reserve (AWaRe) [8, 9]:

- The Access group contains first- and second-choice antibiotics for empirical treatment of common infections.
- The Watch group contains antibiotic classes 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.

Of note, benzathine phenoxymethylpenicillin, which is unclassified, has been classified in the Access group for the analysis of the present report.

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

References

[1] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2020. Oslo, 2021. Available from: www.whocc.no/atc_ddd_index/ (accessed until 21 July 2022)

[2] WHO Collaborating Centre for Drug Statistics Methodology, DDD alterations 2005–2021. Oslo, 2022. Available from: https://www.whocc.no/atc_ddd_alterations__cumulative/ddd_alterations/ (accessed until 21 July 2022)

[3] European Pharmaceutical Market Research Association (EphMRA), Comparison of WHO ATC Classification with EphMRA/Intellus Anatomical Classification – updated for 2021. Available from: https://www.ephmra.org/anatomical-classification (accessed 21 July 2022)

[4] Federal Statistical Office, Effectif et évolution. Available from: https://www.bfs.admin.ch/bfs/fr/home/statistiques/population/effectif-evolution.html [French, German, Italian] (accessed 21 July 2022)

[5] Federal Office of Public Health, Chiffres-clés des hôpitaux suisses, 2020. Available from: www.bag.admin.ch/cchs [French, German, Italian] (accessed 21 July 2022)

[6] Système de surveillance Sentinella. Available from: www.sentinella.ch [French, German] (accessed until 21 July 2022)

[7] Fedlex, Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA). Available from: https://www.fedlex.admin.ch/eli/cc/2001/422/en (accessed 21 July 2022)

[8] WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2021. Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.04). License: CC BY-NC-SA 3.0 IGO.

[9] WHO Antibiotic Categorization. Available from: https://adoptaware.org (accessed until 21 July 2022)

14.2 Antimicrobial consumption in veterinary medicine

The information system for antibiotics in veterinary medicine (IS ABV) was set up in 2019 to collect sales and prescription data of antibiotics for animals in Switzerland. For sales data, all marketing authorization holders deliver their data at least annually to the database. Concerning prescriptions, the notifications to IS ABV became mandatory in Switzerland in early 2019 for production animals, followed by companion animals in October 2019. Veterinarians have to register all their prescriptions of antimicrobials to animals in the database, with detailed information about the animal (e. g., average weight, batch number, production type), the diagnosis, the prescription (e. g., preparation name, doses, dates, and treatment duration), and the farmer's identification (only for production animals). Veterinarians can register four different types of prescriptions: individual animals (only possibility for companion animals), oral group therapies, non-oral group therapies, and delivery on stock. IS ABV is an integrated part of the StAR strategy and provides a wide range of actions and incentives at the veterinarian, farmer and owner levels to improve the use of antibiotics in Switzerland. IS ABV is constantly updated and improved in order to widen the potential impact of the database. Some features are already implemented and others will be in the coming months, e. g., regular feedback to farmers, veterinarians and cantonal authorities, benchmarking.

14.2.1 Sales of antimicrobials in veterinary medicine

The list of veterinary products which had or were granted marketing authorization during the years under review in this report has been entered and maintained manually in the information system for antibiotics in veterinary medicine (IS ABV). Marketing authorization holders regularly submit sales figures for their products to IS ABV. Products authorized for export only are excluded. They cannot be used in Switzerland and do not contribute to the development of resistance in Switzerland.

In IS ABV, 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 species. 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. Each marketing authorization holder checked and approved their data, summarized by preparation and year. Finally, the data was assessed by Swissmedic before publication.

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. The only distinction possible is between "livestock," "companion animals" and "mixed" according to the marketing authorizations. Specific animal species or age groups could only be recorded if these were clearly mentioned in the marketing authorization (e. g., intramammary injectors for cows or products to treat piglets).

14.2.2 Prescriptions of antimicrobials in veterinary medicine

For veterinary practitioners, obligatory reporting of antibiotic prescriptions in the IS ABV database is possible via the practice software or a local IS ABV application. Reports of group therapies are only possible via the local IS ABV application. For veterinarians, reporting via the practice software has the advantage that the prescriptions only have to be recorded once in the veterinary practice or clinic. For the evaluation, however, this means that two reporting channels have to be taken into account, which is also a possible source of errors. Most veterinarians and veterinary clinics use the practice software reporting channel.

Furthermore, it was found that it is absolutely necessary for the reporting veterinarians to be able to check their prescription reports stored on the IS ABV server. Regular feedback of the data transmitted by the practices has been received since May 2021. Data quality is continuously updated via monthly feedback to veterinarians and continuous access for farmers to their consumption. Only veterinarians can update their own data on the IS ABV software. Since the implementation of such feedback, improvements in the frequency of errors have been observed.

Ultimately, the responsibility for correct reporting to IS ABV lies with the veterinarian. IS ABV is constantly being improved to make the correct reporting of prescriptions as easy as possible.

A data-cleaning process was implemented in three steps that allowed the identification and subsequent exclusion of outliers. The first and second exclusion criteria are based on the median of the given amount per day and animal per antimicrobial class, preparation and group of production. Prescriptions with a given amount per day and animal above 15 times the median and/or the 99% percentile were excluded. Finally, all prescriptions were manually reviewed using a four eyes principle to exclude, if needed, evident errors in the database. Only penicillins, tetracyclines and sulfonamides were affected by the cleaning process. In total, 6,557 prescriptions (0.8% of all prescriptions) were excluded for the analyses on the quantities of active substances. This procedure was not possible for the prescription type "dispensing on stock," as neither the use category nor the number of treated animals had to be recorded.

References

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

[2] European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, sales of veterinary antimicrobial agents in 31 European countries in 2019 and 2020; European Medicines Agency, 2021.

14.3 Antimicrobial susceptibility testing of human isolates and data analyses

14.3.1 Data collection and resistance testing

ANRESIS (www.anresis.ch) collects and analyses anonymous antibiotic resistance data provided on a regular basis (weekly or monthly) by 35 Swiss clinical microbiology laboratories, distributed all over Switzerland. All laboratories providing data for this report are approved by Swissmedic and are enrolled in at least one external quality control program. Most laboratories use semi-automated systems, generally based on EUCAST guidelines. However, there are no mandatory Swiss guidelines for antibiotic resistance testing, and individual laboratories are free to use other guidelines than EUCAST. Resistance data are validated by the primary laboratories only and not by ANRESIS.

In 2019, EUCAST changed the interpretation of the susceptibility category "I" from "intermediate" to "susceptible, increased dose," and suggested reporting this category together with susceptible ("S"). In addition, breakpoints for several difficult-to-treat microorganisms have changed in a way that there is no susceptible category left at all. Due to these changes, ANRESIS decided to adapt its reporting as well, and now thoroughly reports percentages of resistant isolates (R) instead of non-susceptibility rates (I+R) as in earlier reports. Numbers and percentages may therefore slightly differ from earlier reports. Changing breakpoints over time may affect the proportion of resistant isolates. This is always an important issue in *S. pneumoniae*, for which, in addition to changing breakpoints, different breakpoints are used for different types of infections.

14.3.2 Data processing

In contrast to most other surveillance systems, ANRESIS collects all antimicrobial resistance results, i. e., the data set is neither restricted to invasive isolates nor to a predefined set of microorganisms. Nevertheless, all main analyses in this report were performed on isolates from blood cultures or cerebrospinal fluid only, to allow comparison with international data. For *Salmonella* spp. and *Campylobacter* spp., isolates from all materials (e. g., stool) were analyzed. 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. Isolates from foreign countries were excluded. Doubles were defined as identical microorganisms from the same patient during the same calendar year (i. e., only the first isolate per patient and calendar year was 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 this analysis, interpreted, qualitative data (SIR) from all samples as defined above were extracted from the ANRESIS database using the KNIME Analytics Platform. An isolate was considered resistant (R) to an antimicrobial agent when tested and interpreted as resistant in accordance with the breakpoint used by the local laboratory. An isolate was considered resistant to an antibiotic group if it was tested resistant to at least one antibiotic of this group. Multiresistance was analyzed in accordance with the EARS-Net methodology, to allow comparability with European data. In most cases, quantitative resistance data were not provided by the laboratories and therefore could not be used in this report, although such data would be beneficial for the comparison of resistance testing results from different origins.

14.3.3 Statistical analyses

The Wilson score method was used for the calculation of the 95% confidence interval of proportions of resistant isolates. 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-value < 0.05 of the likelihood ratio test (G2) measuring the goodness of fit of the model and a p-value < 0.05 of a z-test for the predictor variable "time" (i. e., the years) were considered as significant and are represented by arrows. Statistical analyses were performed using R, version 4.1.2.

14.4 Antimicrobial susceptibility testing of veterinary isolates and data analyses

14.4.1 Sampling of livestock at slaughterhouse and meat thereof

Stratified random samples were taken in the years 2020 and 2021 (Table 14. b and Table 14. c). Sampling was spread evenly throughout each year, based on a sampling plan established for meat inspections. Samples were collected at the five largest poultry slaughterhouses as well as the six largest pig and seven largest cattle slaughterhouses. Every slaughterhouse taking part in the program collected a number of samples proportional to the number of animals of the species slaughtered per year. This procedure ensured that at least 60% of all slaughtered animals belonging to the species in question were part of the sample. In 2020, samples were taken from 808 broiler flocks. Random cecum samples were taken from 5 broilers per flock and 1 pig or calf per

Table 14. b: Antimicrobial resistance monitoring in livestock, 2020.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cecum – broilers	808	*Campylobacter jejuni/coli*	247
Cecum – broilers	217	Indicator *E. coli*	208
Cecum – broilers	612	ESBL/AmpC-prod. *E. coli*	61
Cecum – broilers	612	Carbapenemase-prod. *E. coli* & *Klebisella* spp.	0
Meat – broilers	296	*Campylobacter jejuni/coli*	128
Meat – broilers	296	ESBL/AmpC-prod. *E. coli*	87
Meat – broilers	269	Carbapenemase-prod. *E. coli* & *Klebsiella* spp.	0
Clinical material / hen, turkey, pig, cattle	–	*Salmonella* spp.	138

Table 14. c: Antimicrobial resistance monitoring in livestock, 2021.

Type of sample	Number of samples	Bacteria tested	Number of resistance tests
Cecum – fattening pigs	298	*Campylobacter coli*	191
Cecum – fattening pigs	188	Indicator *E. coli*	170
Cecum – fattening pigs	289	ESBL/AmpC-prod. *E. coli*	17
Cecum – fattening pigs	288	Carbapenemase-prod. *E. coli* & *Klebsiella* spp.	0
Nasal swab – fattening pigs	289	MRSA	155
Cecum – calves	294	*Campylobacter jejuni*	143
Cecum – calves	191	Indicator *E. coli*	180
Cecum – calves	294	ESBL/AmpC-prod. *E. coli*	70
Cecum – calves	294	Carbapenemase-prod. *E. coli* & *Klebsiella* spp.	0
Nasal swab – calves	294	MRSA	18
Meat – fattening pigs	309	ESBL/AmpC-prod. *E. coli*	0
Meat – fattening pigs	307	Carbapenemase-prod. *E. coli* & *Klebsiella* spp.	0
Meat – beef	307	ESBL/AmpC-prod. *E. coli*	0
Meat – beef	307	Carbapenemase-prod. *E. coli* & *Klebsiella* spp.	0
Clinical material / hen, turkey, pig, cattle	–	*Salmonella* spp.	150

slaughter batch. In 2021, 289 cecum samples and nasal swab samples were collected from fattening pigs, and 294 cecum samples and 294 nasal swab samples from calves. Samples were sent to the national reference laboratory for antimicrobial resistance ZOBA, Vetsuisse Faculty, University of Bern, for further analyses.

For *Salmonella*, monitoring at slaughter is not feasible due to the very low prevalence of *Salmonella* spp. in Swiss livestock. Therefore, *Salmonella* isolates sent to ZOBA in 2020 and 2021 in connection with its function as a reference laboratory for *Salmonella* spp. at the primary production level were included in the monitoring (Table 14. b and Table 14. c). 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).

In accordance with European legislation, 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 the 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 was included in the sampling plan.

In 2020, 296 chicken meat samples (186 samples of Swiss origin and 110 of foreign origin), and in 2019, 309 pork (all Swiss origin) and 307 beef samples (266 samples of Swiss origin, 41 samples of foreign origin) were collected (Table 14. b, Table 14. c).

14.4.2 Processing of samples from livestock at slaughterhouse 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.

Since 2019, MRSA have been isolated using the one-step enrichment method, following recommendations of the European reference laboratory for antimicrobial resistance (EURL, The National Food Institute, Lyngby, Denmark). 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 multiplex real-time PCR, as previously published [1].

Since 2015, detection of ESBL/AmpC-producing *E.coli* and carbapenemase-producing *E. coli and Klebsiella spp.* is 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 of broth was plated onto MacConkey agar with 1 µg/ml cefotaxime (CTX) (Tritium, The Netherlands). For carbapenemase-producing *E. coli* and *Klebsiella* spp., 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* and *Klebsiella* spp. colonies were identified by MALDI TOF MS (Biotyper 3.0, Bruker Daltonics, Bremen, Germany). Confirmation of ESBL/AmpC-producing *E. coli* and carbapenemase production was carried out phenotypically by MIC determination on EUVSEC2 plates and the Carba blue test [2], respectively.

14.4.3 Antimicrobial susceptibility testing and data processing

Isolates were cryo-conserved 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* spp.) or without lysed horse blood, using Sensititre susceptibility plates (Trek Diagnostics Systems, Thermo Fisher, Scientific, UK) according to CLSI guidelines [3]. 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 cut-off (ECOFF) values. The ECOFF distinguishes between wild type and non-wild type MIC distributions of bacteria. 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). ECOFFs 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 2020/1729/EU (Table 14. d).

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 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.

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				
	Penicillin				0.125
	Temocillin		16		
Cephalosporins	Cefotaxime		0.25[c] / 0.5[d]		
	Cefotaxime / Clavulanic acid		0.25[c] / 0.5[d]		
	Ceftazidime		0.5[c] / 2[d]		
	Ceftazidime / Clavulanic acid		0.5[c] / 2[d]		
	Cefepime		0.125[c]		
	Cefoxitin		8		4
Carbapenems	Ertapenem	0.5	0.06		
	Imipenem		0.5[c] / 1[d]		
	Meropenem		0.125		
Amphenicol	Chloramphenicol	16	16	32	16
Tetracyclines	Tetracycline	1[a] / 2[b]	8	4	1
Glycylcyclines	Tigecycline		0.5	0.25	
(Fluoro-)quinolone	Ciprofloxacin	0.5	0.06	4	1
	Nalidixic acid	16	8		
Sulfonamids	Sulfamethoxazole		64[c] / 256[d]		128
Lincosamides	Clindamycin				0.25
Aminoglycosides	Amikacin		8[c] / 4[d]		
	Gentamicin	2	2	64[e] / 32[f]	2
	Kanamycin				8
Polymyxins	Streptomycin	4			16
Macrolides	Colistin		2		
	Erythromycin	4[a] / 8[b]		4	1
Cyclic lipopeptides	Azithromycin		16		
Glycopeptides	Daptomycin			4[e] / 8[f]	
	Vancomycin			4	2
Diaminopyrimidins	Teicoplanin			2	
Oxazolidons	Trimethoprim		2		2
Streptogramins	Linezolid			4	4
Ansamycins	Quinupristin/Dalfopristin			0.5[e] / 1[f]	1
Pleuromutilins	Rifampin				0.03
Monocarbolic acid	Tiamulin				2
Fusidans	Mupirocin				1
	Fusidic acid				0.5

[a] *C. jejuni*, [b] *C. coli*, [c] *E. coli*, [d] *Salmonella* spp., [e] *E. faecalis*, [f] *E. faecium*; CLSI-clinical breakpoint (EUCAST clinical breakpoint not defined or outside test range)

14.4.4 Collection of isolates from diseased animals

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 plans of 2019–2021 include pathogens/animals and indication combinations which are of relevance in veterinary medicine (Table 14. e). All strains were isolated from clinical submissions of diseased animals by Swiss veterinary laboratories (university, cantonal, private) across Switzerland and sent to ZOBA.

14.4.5 Antimicrobial susceptibility testing and data processing

At ZOBA, re-identification of the bacterial species was performed by MALDI TOF MS (Biotyper 3.0, Bruker Daltonics, Bremen, Germany).

Isolates were cryo-conserved 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 [3]. 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 current clinical breakpoints published by the Clinical and Laboratory Standards Institute [3]. 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 are transmitted to the database of the Swiss Centre for Antimicrobial Resistance (ANRESIS), which is a nationwide system for resistance data for both human and veterinary medicine (www.anresis.ch).

References

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[2] Poirel L, Nordmann P. Rapidec Carba NP test for rapid detection of carbapenemase producers. J Clin Microbiol. 2015;53(9):3003–3008.

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Table 14. e: Antimicrobial resistance monitoring in veterinary pathogens, 2019–2021.

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	Urogenital tract infection	*Escherichia coli*	100
Dogs	Skin infection	*Staphylococcus pseudintermedius*	100
Cats	Urogenital tract infection	*Escherichia coli*	100
Cats	Skin infection	*Streptococcus equi subsp. zooepidemicus*	30
Small ruminants	Enterotoxemia	*Clostridium perfringens* (Types B, C, D, E)	30
Small ruminants	Abscess	*Corynebacterium pseudotuberculosis*	30

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]
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
	Tigecycline	parenteral	0.1	R
J01B	Chloramphenicol	parenteral	3	A
	Thiamphenicol	parenteral	1.5	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]
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
	Cefetamet	oral	1	W
	Cefiderocol	parenteral	6	R
	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
	Meropenem-vaborbactam	parenteral	3	R
J01E	Sulfadiazine	oral	0.6	A
	Sulfadiazine	parenteral	0.6	A
	Trimethoprim	oral	0.4	A
	Trimethoprim-sulfamethoxazole	oral (tablets)	4 UD (= 4 tabl.)	A
	Trimethoprim-sulfamethoxazole	oral (suspension)	8 UD (= 40 ml)	A
	Trimethoprim-sulfamethoxazole	parenteral	20 UD (= 20 ml)	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	1	W
	Erythromycin (ethylsuccinate tablets)	oral	2	W
	Erythromycin	parenteral	1	W
	Quinupristin-dalfopristin	parenteral	1.5	R
	Roxithromycin	oral	0.3	W
	Pristinamycin	oral	2	W
	Spiramycin	oral	3	W

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Access [A], Watch [W], Reserve [R]
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 (inhal. powder)	inhaled	0.112	W
	Tobramycin (inhal. solution)	inhaled	0.3	W
	Tobramycin	parenteral	0.24	W
J01M	Ciprofloxacin	oral	1	W
	Ciprofloxacin	parenteral	0.8	W
	Delafloxacin	oral	0.9	W
	Delafloxacin	parenteral	0.6	W
	Fleroxacin	oral	0.4	W
	Levofloxacin	oral	0.5	W
	Levofloxacin	parenteral	0.5	W
	Levofloxacin (inhal.solution)	other	0.24	W
	Lomefloxacin	oral	0.4	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	A
	Polymyxin B	parenteral	0.15	R
	Tedizolid	oral	0.2	R
	Tedizolid	parenteral	0.2	R
	Teicoplanin	parenteral	0.4	W
	Vancomycin	parenteral	2	W

ATC Group	Antibiotic Name	Administration Route	DDD [g]	Groups Access [A], Watch [W], Reserve [R]
J04AB	Rifabutin	oral	0.15	W
	Rifampicin	oral	0.6	W
	Rifampicin	parenteral	0.6	W
	Rifamycin	parenteral	0.6	W
P01AB	Metronidazole	rectal	2	A
	Metronidazole	oral	2	A
	Ornidazole	oral	1.5	A
A07AA	Vancomycin	oral	2	W
	Rifaximin	oral	0.6	W
	Fidaxomicin	oral	0.4	W

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