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From Hospital-Level to Patient-Level Antibiotic Consumption Data:

How Can We Improve Surveillance of Antibiotic Use in the Frame of Antibiotic Stewardship Programmes?

PhD Thesis submitted by

Luzia Renggli

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Thesis advisor

Prof. Andreas Kronenberg,
Institute for Infectious Diseases,
Faculty of Medicine, University of Bern

Co-thesis advisor

Dr. Michael Gasser
Institute for Infectious Diseases,
Faculty of Medicine, University of Bern

Co-referee

Dr. med. Beat Sonderegger
Lucerne Cantonal Hospital

Accepted by the Faculty of Medicine and the Faculty of Human Sciences of the University of Bern

Bern, Dean of the Faculty of Medicine

Bern, Dean of the Faculty of Human Sciences

Content

Abstract

Background

Infections with antimicrobial-resistant bacteria caused approximately 4.95 million deaths worldwide in 2019 and are, thus, one of the major threats to public health [1, 2]. Antimicrobial resistance is the ability of a microorganism to withstand antimicrobial treatment and occurs naturally [3]. However, its spread has been driven by the extensive use of antibiotics in agriculture, and human and veterinary medicine during recent decades [4]. Improving the adequate use of antibiotics in order to slow antimicrobial resistance, treat patients effectively and enhance patient safety is referred to as antibiotic stewardship [5]. Surveillance of antibiotic consumption is a crucial element in antibiotic stewardship programmes in defining interventions to optimise antibiotic use [6, 7].

The quantity of antibiotic consumption is analysed routinely in Switzerland. The Swiss Centre for Antibiotic Resistance (ANRESIS) has collected and analysed antimicrobial resistance data and antibiotic consumption data from an increasing number of microbiology laboratories and hospital pharmacies throughout Switzerland since 2006 [8]. Antimicrobial resistance data are provided at the patient-level while antibiotic consumption data are aggregated at the department or hospital-level per year or month. The results of the analyses are sent back to individual hospitals in the form of feedback and benchmark reports. The purpose of these reports is to support local antibiotic stewardship teams when defining interventions.

The quality of antibiotic use has been analysed only sporadically in Switzerland [9, 10]. Recently, a consensus on quality indicators for antibiotic use was published [11]. This consensus includes antibiotic stewardship indicators that assess antibiotic treatment decisions. In recent years, most of the larger Swiss hospitals have implemented electronic medical record systems. Hence, patient-level antibiotic prescription data are increasingly available that could improve the monitoring of antibiotic use and provide better support for antibiotic stewardship programmes.

Aims

The overall aims of this PhD thesis were, first, to evaluate the benefits of extracting patient-level antibiotic prescription data compared to hospital-level data and, second, to propose a method for incorporating these data into future surveillance of antibiotic use.

The purpose of the first part was to assess whether associations between AMR and antibiotic consumption can be investigated using hospital-level data generated for routine surveillance. Three epidemiological projects aimed to investigate the temporal trends including explanatory variables of 1) consumption of antibiotics active against methicillin-resistant *Staphylococcus aureus* (MRSA), 2) the incidence of *Staphylococcus aureus* bloodstream infections and 3) extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (ESCR-KP). The objective of the fourth project was to develop an interactive dashboard to improve data visualisation for routine surveillance.

In the second part, we aimed to assess 5) the feasibility of converting patient-level antibiotic prescription data of the electronic medical record into antibiotic stewardship indicators. The last project (6) aimed to identify risk factors for the occurrence of extended-spectrum cephalosporin resistance in *Escherichia coli* and *Klebsiella pneumoniae*.

Methods

Data from the ANRESIS database were used to analyse trends and risk factors for 1) consumption of anti-MRSA antibiotics (glycopeptides, daptomycin, linezolid) and 2) incidence of ESCR-KP in 21 hospitals between 2009 and 2019. The same data source was used for analysing 3) the incidence of *Staphylococcus aureus* bloodstream infections in 70 hospitals over time (2008-2021). Trends and risk factors were analysed by applying multiple linear regression models. 4) A dashboard visualising antibiotic consumption of hospitals participating in the ANRESIS surveillance system was developed using the R software environment and packages such as Shiny and Plotly.

For projects 5 and 6, patients hospitalised between 1 October 2019 and 30 September 2021 at Lucerne cantonal hospital and who received at least one dose of a systemic antibiotic were included. Antibiotic prescription data were obtained from the electronic medical record Epic software® and linked with microbiological data from the ANRESIS database. Antibiotic stewardship indicators proposed by the literature were collected and, if needed, rephrased or specified to be calculable (project 5). Algorithms were programmed in R to convert electronic medical record data into antibiotic stewardship indicators. These were calculated, and the validity of each output value was assessed and categorised as either good quality data, missing data due to incomplete documentation or data processing issues or not computable.
For the resistance models with patient-level data, the dataset was restricted to patients with possibly nosocomial *Escherichia coli* and *Klebsiella pneumoniae* (project 6). A multiple logistic regression model was applied to investigate risk factors for the occurrence of extend-spectrum cephalosporin resistance in *Escherichia coli* and *Klebsiella pneumoniae*.

Results

Analysis of hospital-level antibiotic consumption data revealed an increase in the consumption of anti-MRSA antibiotics in Switzerland between 2009 and 2019 (project 1). Hospitals with lower levels of consumption of anti-MRSA antibiotics were associated with having an antibiotic stewardship group and restrictions for prescriptions of anti-MRSA antibiotics.

The MRSA incidence decreased significantly in the French-speaking region while increasing significantly in the German-speaking region, although at a low incidence level (project 2). The incidence of *Staphylococcus aureus* bloodstream infections increased in Switzerland between 2008 and 2021, mainly due to the increasing incidence of methicillin-susceptible *Staphylococcus aureus* bloodstream infections in elderly males. The increase was more pronounced in the German-speaking than in the French-speaking region.

Project 3 described a significant increase in the incidence of invasive ESCR-KP infections in Switzerland between 2009 and 2019. The incidence was higher in university than in non-university hospitals and in the French-speaking compared to the German-speaking region. However, the incidence was not associated with antibiotic consumption. Analysing the overall ESCR-KP incidence (all sample sites) revealed high variability between university hospitals, mainly due to a high proportion of patients with screening isolates at Geneva University Hospital (50% of patients with ESCR-KP).

A dashboard was developed that visualised antibiotic consumption of the user's hospital (project 4). The hospital-specific login provides free access to interactive graphics and interactive tables for the 71 hospitals that are part of the ANRESIS surveillance system. Antibiotic consumption is depicted graphically over ten years and the graphics can be adjusted according to selection criteria. A benchmark boxplot enables users to compare antibiotic consumption of their hospital with other hospitals of comparable size or in the same linguistic region.

Project 5 demonstrated the feasibility of converting electronic medical records data into antibiotic stewardship indicators. In total, data from 25,338 hospitalisations from 20,723 individual patients were analysed and visualised in an interactive dashboard. Data extraction allowed us to program algorithms for 89% (25/28) of the indicators assessing treatment decisions, and data quality was classified as good in 46% (13/28).
According to the data quality observed, the most important issues were A) missing (58% of hospitalisations) or meaningless (37% of hospitalisations) information on indication (*e.g.* general indication, infection) and B) data processing issues such as insufficiently categorised metadata.

The result of the resistance model with patient-level data was not meaningful since the number of patients with ESCR isolates was too low (project 6).

Conclusion

Our studies revealed that several national trends in antibiotic consumption and resistance were mainly caused by subpopulations. This demonstrates the need for stratifying surveillance analyses to formulate appropriate target measures at the right intervention level. Higher resolution data on antibiotic use are essential to provide better decision support to policy makers in hospitals and on regional and national committees.
To improve surveillance analysis for hospitals, we developed a procedure that converts electronic medical record data into antibiotic stewardship indicators. The routine monitoring of these indicators would be very useful for local antibiotic stewardship teams when defining and measuring the effectiveness of interventions. This PhD project has demonstrated the benefit of patient-level antibiotic data and is therefore the first step towards integrating patient-level antibiotic prescription data into routine surveillance.

Lay Summary

Infections due to antimicrobial-resistant bacteria caused approximately 4.95 million deaths worldwide in 2019 and are, thus, one of the major threats to public health [1, 2]. Antimicrobial resistance is the ability of a microorganism to withstand antimicrobial treatment and occurs naturally [3]. However, the spread of resistance has been driven by the extensive use of antibiotics in agriculture, and human and veterinary medicine during recent decades [4]. As a measure to limit the spread of resistance, the World Health Organization (WHO) recommends using antibiotics only when unavoidable and according to its current guidelines [2]. Surveillance of antibiotic resistance and antibiotic consumption is a crucial element in defining preventive measures and appropriate interventions to optimise antibiotic use.

The Swiss Centre for Antibiotic Resistance (ANRESIS) has collected and analysed antibiotic resistance data from microbiology laboratories and antibiotic consumption data from hospital pharmacies throughout Switzerland since 2006 [8]. The participating hospital pharmacies report the number of antibiotics used at the hospital level. In recent years, most of the larger Swiss hospitals have implemented electronic medical record systems. Hence, the antibiotic prescription is recorded at the patient level.

The purpose of this PhD project was to evaluate the benefits of analysing patient-level antibiotic prescription data compared to hospital-level data and, thereafter, propose a method to include these data in the future surveillance of antibiotic use.

In the first project, we analysed aggregated data from the ANRESIS database. Our study revealed an increase in the consumption of highly effective antibiotics used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) over the last decade in Switzerland. However, during the same period, MRSA incidence remained at a low level. We were unable to evaluate, if the use of these anti-MRSA antibiotics had been appropriate, since corresponding data were unavailable. As this limitation applies to hospital-level data in general, we assessed the feasibility of computing metrics evaluating antibiotic prescription in a further project. We demonstrated the technical feasibility of converting patient-level antibiotic prescription data from the electronic medical records into antibiotic stewardship indicators. Moreover, we devised a procedure for routine monitoring of antibiotic stewardship indicators. This can be applied to every Swiss hospital that provides data in the format required for our database. The routine monitoring of antibiotic stewardship indicators would be very useful for antibiotic stewardship teams to define and measure interventions.

Another aim was to investigate risk factors for resistance against extended-spectrum cephalosporins. First, we analysed the number of infections with extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (ESCR-KP) using hospital-level data. The incidence of ESCR-KP increased in Switzerland over the last decade. This was only partly explained by our model. Moreover, we did not find an association with antibiotic consumption. We hypothesised that data aggregation at the hospital level may not be sufficient to detect a correlation. Therefore, we built a model with patient-level data. While, the number of patients with resistant isolates was too low for meaningful model results, the continuous collection of these data would allow us to identify which variables in antibiotic therapy are associated with the occurrence of antimicrobial resistance. Several other research projects could also be initiated using these data generated during clinical routines.

These findings indicate that the next step in improving the surveillance of antibiotic use should be to extend routine surveillance to patient-level antibiotic prescription data. A corresponding network of participating hospitals must be established to achieve this aim.

Summary of Practical Implications

- Monitoring of patient-level antibiotic prescription data should be part of quality control programmes to provide better decision support to policy makers in hospitals, regional and national committees.
- The introduction of electronic medical records allows the calculation of new, meaningful antibiotic stewardship indicators. These can be used to implement targeted interventions.
- For implementing antibiotic stewardship indicators into routine surveillance, prioritisation according to clinical relevance, precise definitions and the setting of target values are needed at an early stage. The development of national guidelines is needed for the comparison between hospitals, plausibility checks and saving resources.
- Integrating a computerised decision-support system (*e.g.* containing a trigger to re-assess therapy after three days) should be considered in parallel with the introduction of antibiotic stewardship indicators.
- Data quality should be improved for parameters that have a strong impact on data analysis, *e.g.* standardised and complete recording of the indication for antibiotic therapy, complete data transmission of the hospitalisation date and correct labelling of screening samples.
- To implement, promote and coordinate these activities, the establishment of local antibiotic stewardship groups should be guided and supported at national level.
- National surveillance should stratify analyses to detect diverging trends in subgroups. Furthermore, the monitoring should be extended to incidence rates of bloodstream infections (in addition to the proportion of resistant microorganisms).
- Screening activities within Swiss hospitals should be extended, harmonised and monitored continuously.

Abbreviations

AB	Antibiotic
ABS	Antibiotics stewardship
ABS-I	Antibiotic stewardship indicators
AMR	Antimicrobial resistance
ANRESIS	Swiss Centre for Antibiotic Resistance
Anti-MRSA antibiotics	Vancomycin intravenous, teicoplanin, daptomycin and linezolid, referred to as anti-methicillin-resistant *Staphylococcus aureus* antibiotics
AST	Antimicrobial susceptibility testing
AWaRe classification	Classification in the groups Access, Watch and Reserve
BD	Bed-days
BSI	Bloodstream infection
CDS	Clinical decision support
CI	Confidence interval
CIS	Clinical information systems
CRP	C-reactive protein
CR-PA	Carbapenem-resistant *Pseudomonas aeruginosa*
DDD	Defined daily doses
DNA	Deoxyribonucleic acid
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
EEA	European Economic Area
EMR	Electronic medical record
ESBL	Extended-spectrum β-lactamases
ESCR	Extended-spectrum cephalosporin-resistant
ESCR-KP	Extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae*
EU	European Union
Gen.	Generation
ICU	Intensive care unit
IT	Information technology
K. pneumoniae	*Klebsiella pneumoniae*
MDR	Multidrug-resistant
MIC	Minimal inhibitory concentration

MRSA	Methicillin-resistant S*taphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
P. aeruginosa	*Pseudomonas aeruginosa*
S. aureus	*Staphylococcus aureus*
PCT	Procalcitonin
PPB	Penicillin-binding protein
PPS	Point prevalence study
TDM	Therapeutic drug monitoring
VRE	Vancomycin-resistant enterococci
WGS	Whole genome sequencing
WHO	World Health Organization

1. Introduction

1.1. Antimicrobial Resistance (AMR)

Infections with antimicrobial-resistant bacteria caused approximately 4.95 million deaths worldwide in 2019 and are, thus, one of the major threats to public health [1, 2]. Around a quarter of these deaths may have been preventable, if the antimicrobial-resistant infections had been caused by antimicrobial-susceptible bacteria, and are therefore referred to as deaths attributable to antimicrobial resistance (AMR). AMR is the ability of a microorganism to withstand antimicrobial treatment [3]. In Switzerland, approximately 290 deaths were attributed to AMR in 2019 [12]. AMR can affect anyone, but especially vulnerable are critically ill, immune-compromised and patients with prior antibiotic (AB) therapy.

Particularly difficult to treat are infections with bacteria, which are resistant to various AB classes, referred to as multidrug-resistant (MDR) bacteria. Treatment options for infections with MDR bacteria are limited since resistance is occurring faster than new antibiotics are developed. Besides the need for reserve antibiotics, patients with critical MDR bacteria require isolation measures and hospitalisation is often prolonged. Hence, multidrug resistance leads to increased medical costs.

At present, Switzerland is less affected by AMR than many other countries within and outside of Europe [13]. The most common human pathogen causing bloodstream infections (BSI) is *Escherichia coli (E. coli)* [14, 15]. A key resistance mechanism in *E. coli* is the production of extended-spectrum β-lactamases (ESBL). A surrogate marker for ESBL is the phenotypic resistance against 3rd or 4th generation (gen.) cephalosporins, referred to as extended-spectrum cephalosporin-resistant (ESCR). The percentage of ESCR-*E. coli* was 11% in Switzerland in 2019 [16]. Whereas the proportion of 3rd gen. cephalosporin-resistant *E. coli* ranged worldwide between 6% in Norway to over 80% in India in 2019 (Figure 1) [17]. However, bacteria are not stopping at national borders and the prevalence of gram-negative MDR bacteria such as ESCR-*E. coli* and ESCR-*Klebsiella pneumoniae* (ESCR-KP) are increasing in Switzerland (Figure 2) [16]. For treating BSI caused by ESCR bacteria, reserve antibiotics such as carbapenems are needed [18]. But, resistance against carbapenems is increasing worldwide [17, 19-22].

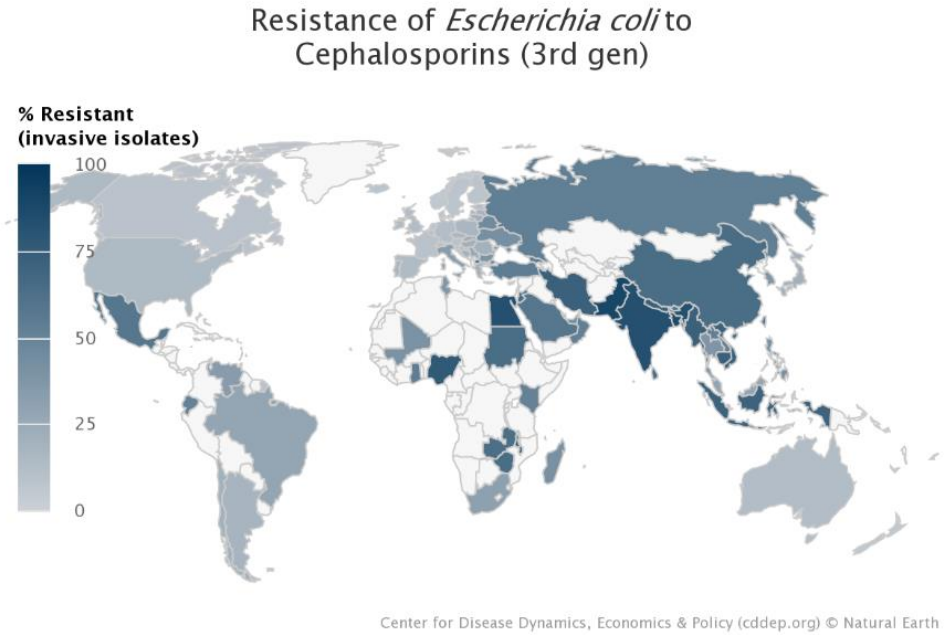

Figure 1: Prevalence of 3rd generation cephalosporin-resistant *Escherichia coli* [23].

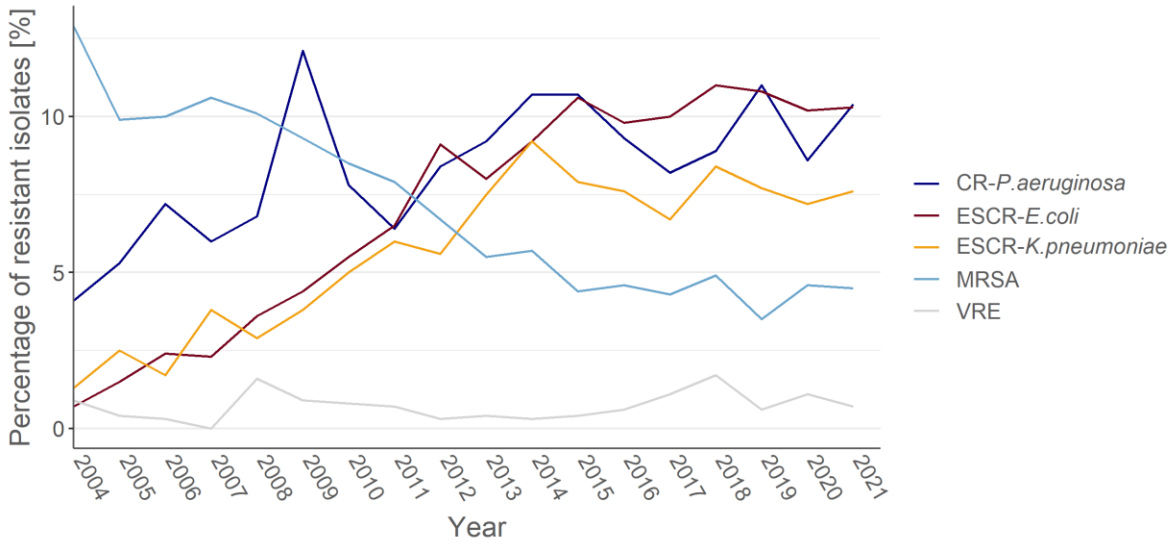

Figure 2: Temporal trends of selected highly resistant pathogens in Switzerland between 2004 and 2021 (adapted from [8])

CR-*P. aeruginosa*, carbapenem-resistant *Pseudomonas aeruginosa*; ESCR, extended-spectrum cephalosporin-resistant; *E. coli*, *Escherichia coli*, *K. pneumoniae*, *Klebsiella pneumoniae*, MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci

Mechanisms of AMR are diverse and include drug inactivation, drug alteration, modification of drug binding site, target modification, target overproduction, changes in cell permeability and biofilm formation [24]. One resistance strategy used by several bacteria is the production of enzymes, that hydrolyse and thus inactivate antibiotics, such as β-lactamases and carbapenemases. Another strategy is to reduce intracellular drug accumulation by mechanisms such as porin loss or the production of efflux pumps, which can result in carbapenem resistance too.

Short profiles of five highly resistant hospital pathogens are described below to introduce the microorganisms, which are mentioned in this PhD thesis. These AB-resistant bacteria pose the greatest threat to human health and were thus all listed as one of the high-priority pathogens for the research and development of new antibiotics by the World Health Organization (WHO) [25].

Escherichia coli

Family Enterobacterales

Characteristics	Gram-negative, facultative anaerobic, flagellated, fimbria, frequently polysaccharide capsules [26]
Occurrence	Gut of humans and animals
Disease	Urinary tract infections, abdominal infections, sepsis, meningitis in newborns, wound infections, diarrhea (enterotoxins)
Transmission	Direct and indirect contact, contaminated food, endogenous
Significance	Most frequent human pathogen [15]
Therapy	Amoxicillin, ceftriaxone, cefuroxime, levofloxacin [27]
Resistance	Switzerland 2021: amoxicillin (46%), amoxicillin-clavulanic acid (26%), piperacillin-tazobactam (7%), 2nd gen. cephalosporins (12%), carbapenems (< 0.1%), aminoglycosides (9%), trimethoprim/sulfamethoxazole (24%), fluoroquinolones (17%), nitrofurantoin (1%), fosfomycin (2%) [15]

Extended-spectrum cephalosporin-resistant *Escherichia coli (ESCR-E. coli)*

ESCR refers to resistance against 3rd or 4th gen. cephalosporins. The highest burden of AMR in Europe including Switzerland was caused by ESCR-*E. coli* [12, 28]. ESCR comes often along with co-resistance to aminoglycosides, fluoroquinolones and trimethoprim/sulfamethoxazole [29].

Prevalence	Switzerland 2021: 10% [15] EU/EEA mean (range) 2020: 15% (6% – 42%, 3rd gen. cephalosporin resistance) [30]
Mechanism	Production of ESBL and AmpC β-lactamases which inactivate β-lactam antibiotics by hydrolysis.
Risk factors for ESCR-*E. coli*	Global warming [31], prior treatment with carbapenems [32], 3rd and 4th gen. cephalosporins [33, 34], aminoglycosides, fluoroquinolones [35], trimethoprim/sulfamethoxazole, duration of total prior AB therapy [33]

Klebsiella pneumoniae

Family Enterobacterales

Characteristics	Gram-negative, facultative anaerobic, rods, thick polysaccharide capsule, fimbria [26]
Occurrence	Gut and upper respiratory tract in 30% of the healthy population, soil, plants, water
Disease	Respiratory tract infections inclusive pneumonia, urinary tract infections, sepsis, soft tissue infections
Transmission	Direct and indirect contact
Significance	Frequent hospital-acquired pathogen
Therapy	Amoxicillin, cefuroxime
Resistance	Switzerland 2021: amoxicillin-clavulanic acid (12%), piperacillin-tazobactam (10%), 2nd gen. cephalosporins (10%), 3rd and 4th gen. cephalosporins (8%), carbapenems (0.8%), aminoglycosides (5%), trimethoprim/sulfamethoxazole (13%), fluoroquinolones (9%) [15]

Extended-spectrum cephalosporin-resistant *K. pneumoniae* (ESCR-KP)

ESCR refers to resistance against 3rd or 4th gen. cephalosporins and comes often along with co-resistance to aminoglycosides, fluoroquinolones and trimethoprim/sulfamethoxazole [29].

Prevalence	Switzerland 2021: 8% [15] EU/EEA mean (range) 2020: 34% (0% – 79%, 3rd gen. cephalosporin resistance) [30]
Mechanism	Production of ESBL and AmpC β-lactamases which inactivate β-lactam antibiotics by hydrolysis, ESBL is much more frequent.
Risk factors for ESCR-KP	Global warming [31], prior treatment with carbapenems [32], 3rd and 4th gen. cephalosporins [33, 34, 36, 37], aminoglycosides, fluoroquinolones[35], trimethoprim/sulfamethoxazole, duration of total prior AB therapy [33], duration of hospitalisation [36]

Staphylococcus aureus

Family Staphylococcaceae

Characteristics	Gram-positive cocci, facultative anaerobic, catalase and coagulase positive, some strains with capsule formulation [38]
Occurrence	Skin and mucosa of humans and animals, 50% of the human population are nasal carriers [39], in the environment [40]
Risk factors for *S. aureus* carriage:	older age, male sex, HIV-infection, obesity, diabetes, rheumatoid arthritis, skin disease, patients undergoing hemodialysis [39, 41, 42]
Disease	Sepsis, endocarditis, joint, bone, wound and soft tissue infections [43] Toxin caused syndromes: SSSS (staphylococcal scaled skin-syndrome), TSS (toxic shock syndrome), food intoxication
Transmission	Mainly by direct contact [38], airborne [39], endogenous
Significance	Frequent hospital-acquired pathogen but also frequent in the outpatient setting (*e.g.* wound infections)
Therapy	Flucloxacillin, cefazolin, ceftriaxone, clindamycin, trimethoprim/sulfamethoxazole, vancomycin, daptomycin [44]
Resistance	Switzerland 2021: penicillin (83%), aminoglycosides (3%), trimethoprim/sulfamethoxazole (0.7%), tetracycline (4%), macrolides (14%), clindamycin (12%), vancomycin (<0.1%), ciprofloxacin (6%), fusidic acid (4%), linezolid (<0.1%), rifampicin (0.5%), daptomycin (0.8%) [15]

Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA is defined as resistant against to at least one of the following antibiotics: methicillin, oxacillin, flucloxacillin or cefoxitin. Hospital-acquired MRSA is often resistant against several other AB classes including fluoroquinolones, tetracyclines, aminoglycosides, erythromycin, trimethoprim/sulfamethoxazole and clindamycin.

Prevalence	Switzerland 2021: 5% [15] EU/EEA mean (range) 2020: 17% (1% – 49%) [30]
Mechanism	A modified structure of penicillin-binding protein (PBP), the target structure of β-lactams, referred to as PBP2a, is up-regulated [45]. PBP2a is not inhibited by β-lactam antibiotics and thus secures the survival of the cells.

Risk factors for MRSA: Treatment with fluoroquinolones was suggested to favour MRSA colonization by promoting colonization with *S. aureus* and simultaneously eradicating methicillin-susceptible *S. aureus* (MSSA) strains [46]. An association between MRSA and use of fluoroquinolones, 3rd gen. cephalosporins, amoxicillin-clavulanic acid and inverse relationship with hospital use of alcohol-based hand rub was reported by Lopez-Lozano *et al.* [47]. Whereas most studies investigating risk factors for MRSA did not find any relationship between AB use and resistance [48]. Further, an increase in minimum temperature of 10°C was associated with an increase of 5.8% in percentage of MRSA [31].

Enterococcus species

Family Enterococcaceae

Characteristics	Gram-positive, facultative anaerobe [49]
Occurrence	Gut of humans and animals
Disease	Sepsis, endocarditis, urinary tract infection, peritonitis, cholecystitis, cholangitis, skin and soft tissue infections, catheter-associated infections
Transmission	Endogenous, gut as source, nosocomial transmission is possible
Significance	Target immunocompromised patients
Therapy	Amoxicillin, vancomycin (+ gentamicin), daptomycin [44]
Resistance	Switzerland 2021 (*E. faecalis, E. faecium*): amoxicillin (0.3%, 65%), gentamicin high level resistance (11%, 33%), tetracycline (78%, 57%), linezolid (0.7%, 0.6%) [15]

Vancomycin-resistant enterococci (VRE)

Enterococcus faecalis (*E. faecalis*) is the most common species.

Prevalence	Switzerland 2021: *E. faecalis* <0.1%, *E. faecium* 2%, EU/EEA mean (range) 2020: *E. faecalis* no mean available *(0% – 7%) [50], E. faecium: 17% (0% – 56%) [30]*
Mechanism	The terminal D-amino acid in Lipid II, the target structure of vancomycin, is modified [51]. Vancomycin cannot form hydrogen bonds with the modified Lipid II and thus not interfering with the peptidoglycan maturation process.

Pseudomonas aeruginosa

Family Pseudomonadaceae

Characteristics	Gram-negative, rod-shaped, facultative anaerobe, flagellated [52]
Occurrence	Human gut, skin flora, soil, water, plants
Disease	Pneumonia, skin and soft tissue infections, urinary tract infections, sepsis
Transmission	Nosocomial, endogenous, contact with an environmental source
Therapy	Cefepime, ceftazidime, piperacillin-tazobactam, ciprofloxacin, meropenem [44]
Resistance	Switzerland 2021: piperacillin-tazobactam (11%), ceftazidime (9%), cefepime (8.5%), aminoglycosides (14%), ciprofloxacin (7%) [15]
Significance	Opportunistic pathogen, frequent hospital-acquired, intrinsic reduced susceptibility, fast occurrence of resistance under AB therapy

Carbapenem-resistant *P. aeruginosa* (CR-PA)

Cross-resistance of CR-PA to fluoroquinolones, aminoglycosides, colistin and cefepime was described, prior treatment with these antibiotics may be risk factors for carbapenem resistance [53-55].

Prevalence	Switzerland 2021: 10 % in 2021 [15] EU/EEA mean (range) 2020: 18% (4% – 49%) [30]
Mechanisms	Carbapenem resistance can result due to production of carbapenemases, which are hydrolysing carbapenems or the overexpression of efflux pumps or porin loss [56].

Risk factors for CR-PA: Prior treatment with carbapenems [57-61], recent institutional transfer [62]

During multiplication, mutations occur readily in bacteria. Some of them result in AMR by chance and can be transferred to subsequent generations of bacteria, referred to as *vertical gene transfer.* Resistance mechanisms that require only small genetic alteration are associated with the rapid occurrence of resistance, such as point mutations, rearrangements or deletion of bigger deoxyribonucleic acid (DNA) fragments [63, 64]. Other routes of AMR acquisition include the uptake of naked DNA (transformation) or the transfer of genetic material between bacteria, termed *horizontal gene transfer*, by conjugation (plasmids, integrative conjugative elements), bacteriophages (transduction), encapsulate DNA or nanotubes (non-conjugative plasmids) [65].

Antibiotics in the bacterial environment exert evolutionary pressure on selecting resistant strains (Figure 3). Furthermore, some bacteria respond by increasing the mutation frequency and sub-lethal AB concentrations were shown to induce the modulation of gene transcription [66].

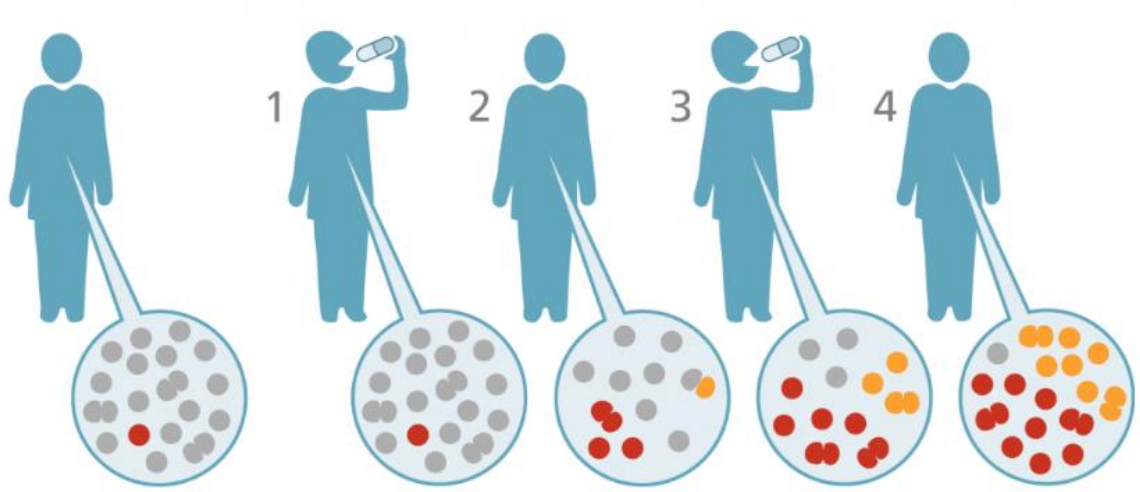

Figure 3: Selection of antibiotic-resistant isolates [67].
- Bacterium sensitive to the drug
- Antibiotic-resistant bacterium present before initiation of treatment
- Antibiotic-resistant bacterium appearing during treatment (by mutation)

Nowadays, the natural reservoir of resistance mechanisms is extensive [66, 68]. The evolution of resistance has been promoted by the presence of antibacterial compounds in the environment for millions of years [69]. In parallel, resistance mechanisms were evolved by the producers and their microbiological neighbours for self-protection [69]. Resistant genes including encodings for β-lactamases were found in ancient DNA of Beringian permafrost sediments dated 30'000 years ago. Multiple drug resistance may even be the default state in most environmental bacteria [66]. A corresponding study found that strains of spore-forming soil bacteria were resistant to seven or eight antibiotics (on average) including antibiotics that these bacteria have not been exposed to previously [68]. Furthermore, multidrug resistance is frequent in opportunistic human pathogens that commonly occur in soil and water such as *Acinetobacter* species and *Pseudomonas aeruginosa*. The association of various resistance mechanisms in the same bacteria are termed co–resistance. ESBL-producing organism exhibit frequently co–resistance to aminoglycosides, fluoroquinolones and trimethoprim/sulfamethoxazole [29]. Cross–resistance occurs when a single resistance mechanism confers resistance to several other antibiotics with comparable mechanisms of action [40, 70].

Due to cross–resistance or co–resistance, clinically and naturally AB agents can result in expression of resistance against other AB agents.

Besides antibiotics, other biocides can co–select for AMR genes and may stimulate horizontal gene transfer such as heavy metals (industrial pollutants, used as animal food supplements) and microplastics [4, 71]. Another driver for AMR is climate change [31]. *Mc Fadden et al.* proposed that increasing temperature may facilitate horizontal gene transfer or uptake of free DNA. Moreover, the optimal temperature for bacterial growth rate is around 30°C [72]. Consequently, the carriage and transmission of resistant strains between humans and animals may increase. The spread of resistant bacteria is further driven by increasing population density [31], poor sanitation, travel, human and animal migration, the globalization of food production, animal–human contacts and weather phenomena (Figure 4) [4]. The concept of optimizing the health of humans, animals and the ecosystem in a unified approach is referred to as *One Health* and integrating global aspects as *One Health One World* [73].

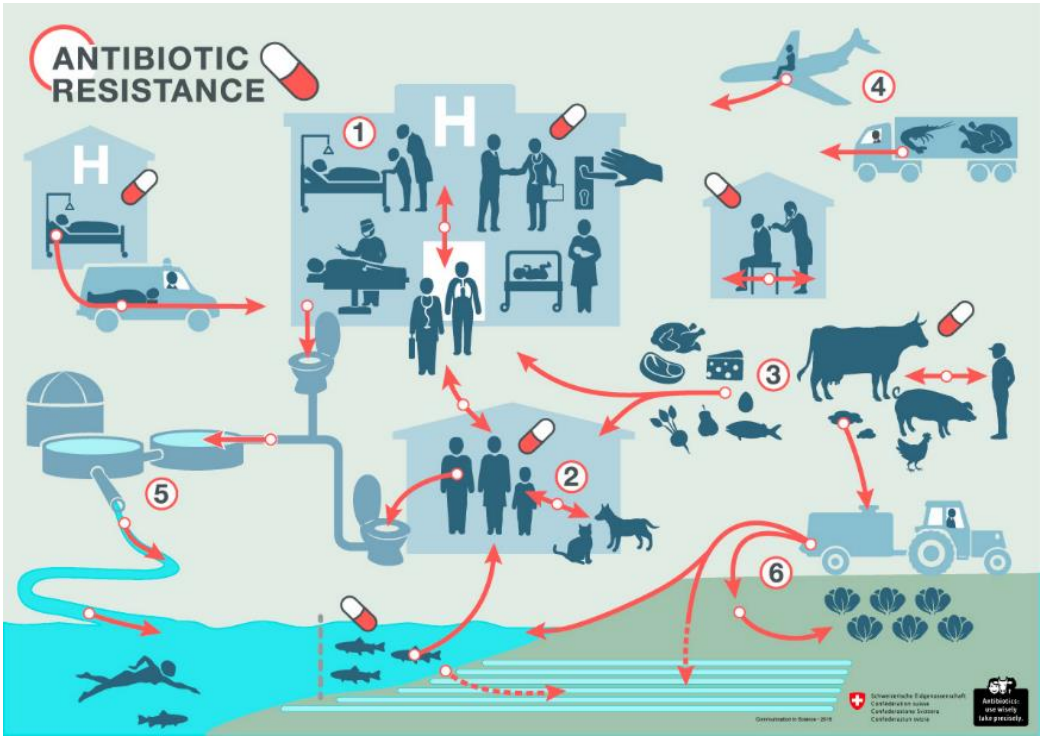

Figure 4: Sources and transmission routes of antibiotic-resistant bacteria [67]. 1) Transmission in health care facilities. 2) Transmission from humans to animals or vice versa. 3) Food contamination. 4) Spread through tourism and food imports. 5) Transmission in water. 6) Spread through the application of manure.

1.2. Antimicrobial Resistance and Antibiotic Use

AMR occurs naturally, however its spread in human pathogens has been driven by the extensive use of antibiotics in agriculture, and human and veterinary medicine during recent decades [4]. As measures to slow AMR, the WHO first recommends discontinuing the use of antibiotics in healthy animals for infection prevention and growth promotion [74]. Secondly, it suggests that antibiotics in veterinary and human medicine should be prescribed only when unavoidable and according to its current guidelines [2].

Using the right substance, the right dosage, the right application frequency, the right duration and the right route of administration are crucial for efficacy of treatment, to minimise adverse effects and resistance development. Several studies showed that previous AB treatment is a risk factor for resistance development [32, 33, 35-37, 57-61, 75]. However, to tackle AMR, it is crucial to understand which components of AB therapy are risk factors for the occurrence of resistance [76]. Since sub-lethal concentrations have been shown to promote resistance development, therapy efficacy is one important consideration. As part of the studies for drug approval, the spectre of activity is evaluated and an efficient and safe dosing schema is proposed. Clinical trial data are limited in patients with altered physiology such as pregnant and elderly patients [77, 78]. Further, most drug approval studies did not evaluate the resistance potential or the effect on the commensal bacteria. To control AMR, it was proposed to restrict antibiotics with high resistance potential [79]. Cunha suggested defining low resistance potential as resistance not occurring within the first years of general use [79]. His classification was discussed controversially [80-82]. The WHO classified the antibiotics as *Access, Watch* or *Reserve* (AWaRe), based on their impact on AMR and their activity against MDR organisms [83]. Access antibiotics are intended to be first-line therapy, as these have a lower resistance potential [84]. Watch antibiotics are recommended only for a limited group of syndromes. Reserve antibiotics should be applied as last resort, as these are the last effective antibiotics against MDR organisms. The criteria used for estimating the impact of the antibiotics on AMR were not published and studies assessing the resistance potential are limited. The AWaRe classification was supported by the meta-analysis of Sulis *et al.*, who found that multidrug resistance was more likely to occur after prior exposure to Watch or Reserve compared to Access antibiotics [85]. However, prior exposure to Access antibiotics was associated with the incidence of MDR infections as well. Information concerning resistance potential would be a useful criterion to decide between substances with the same indication.

Historically, the guiding principle was to treat until all pathogens were eliminated to prevent the development of resistance, but the recommended duration was often arbitrary [86]. For clinically stable patients, recent studies favour shorter courses due to non-inferiority to long courses and fewer gastrointestinal side effects [86, 87]. A shorter treatment duration may further reduce resistance rates. Teshome *et al.* demonstrated recently that duration of therapy with cefepime, meropenem or piperacillin-tazobactam in septic patients is associated with an increased risk of new resistance development [88]. Such large studies investigating the effect of treatment duration on the occurrence of resistance are limited. Most studies that examined prior AB treatment as a risk factor for resistance considered AB treatment as a binary variable (yes/no). In addition to reducing resistance rates, it was further hypothesised that shorter AB treatment may be favourable for the species diversity in the gut microbiome. Recently, a first study investigated these relationships but did not find a significantly different effect between long and short AB treatment neither on the resistome nor on the species diversity of the intestinal microbiota of 55 patients [89]. However, larger studies need to investigate the effect of treatment duration on commensal bacteria and the occurrence of resistance.

1.3. Antimicrobial Susceptibility Testing (AST)

In routine clinical practice, the susceptibility of bacteria to antibiotics is tested in microbiological laboratories to support physicians in AB treatment decisions. The oldest and most frequently used approach is the disc diffusion methodology [90]. A sample from the site with suspected infection is taken, cultivated overnight and used to prepare a suspension with standardised turbidity. An agar plate is inoculated with the bacterial suspension, disks impregnated with antibiotics are applied on the agar surface and the plates are incubated. After incubation, the diameter of the zone around the AB disc, where bacterial growth is inhibited, is measured by hand or with an automated zone reader (Figure 5).

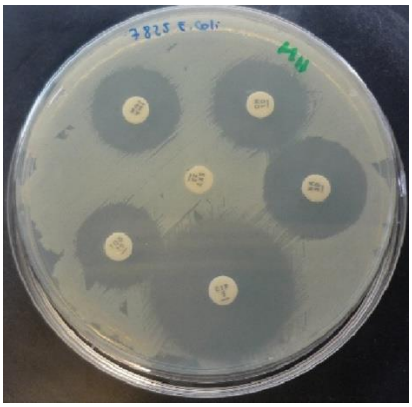

Figure 5: Disc diffusion test on an agar plate [91].

Another method is to determine the minimal inhibitory concentration (MIC) of an AB substance for the isolated pathogen. Based on clinical breakpoint tables, the results are categorised and reported to physicians in an antibiogram as *susceptible*, *susceptible with increased dose* or *resistant*. The antibiogram describes the phenotypic resistance patterns, which may be indicators for resistance mechanisms. For the detection of clinically or epidemiologically relevant resistance mechanisms in routine use, algorithm and additional phenotypic tests were elaborated [92]. Genetic markers for resistance mechanisms can be identified by molecular methods such as whole genome sequencing (WGS), performed by reference or other expert laboratories [93].

1.4. Antibiotic Consumption

In Switzerland, AB consumption decreased slightly between 2012 and 2021 from 11.6 to 8.6 defined daily doses (DDD) [94] per 1,000 inhabitants per day in 2021 [15, 95]. AB consumption in Switzerland was lower than the mean total consumption in the European Union and European Economic Area (EU/EEA) of 16.4 DDD per 1,000 inhabitants per day in 2020. Compared to other European countries, Switzerland was one of the countries with the lowest AB consumption in the outpatient setting with 7.5 DDD per 1,000 inhabitants per day compared to EU/EEA mean consumption of 15 DDD per 1,000 inhabitants per day (range 7.1–26.4). Whereas AB consumption in the Swiss inpatient setting was with 1.5 DDD per 1,000 inhabitants per day only slightly below the mean consumption of the EU/EEA countries (1.6 DDD per 1,000 inhabitants per day, range 0.8–22, Figure 6). Differences in AB consumption between the linguistic regions within Switzerland were noted [15, 96]. The linguistic regions represent geographical and cultural regions.

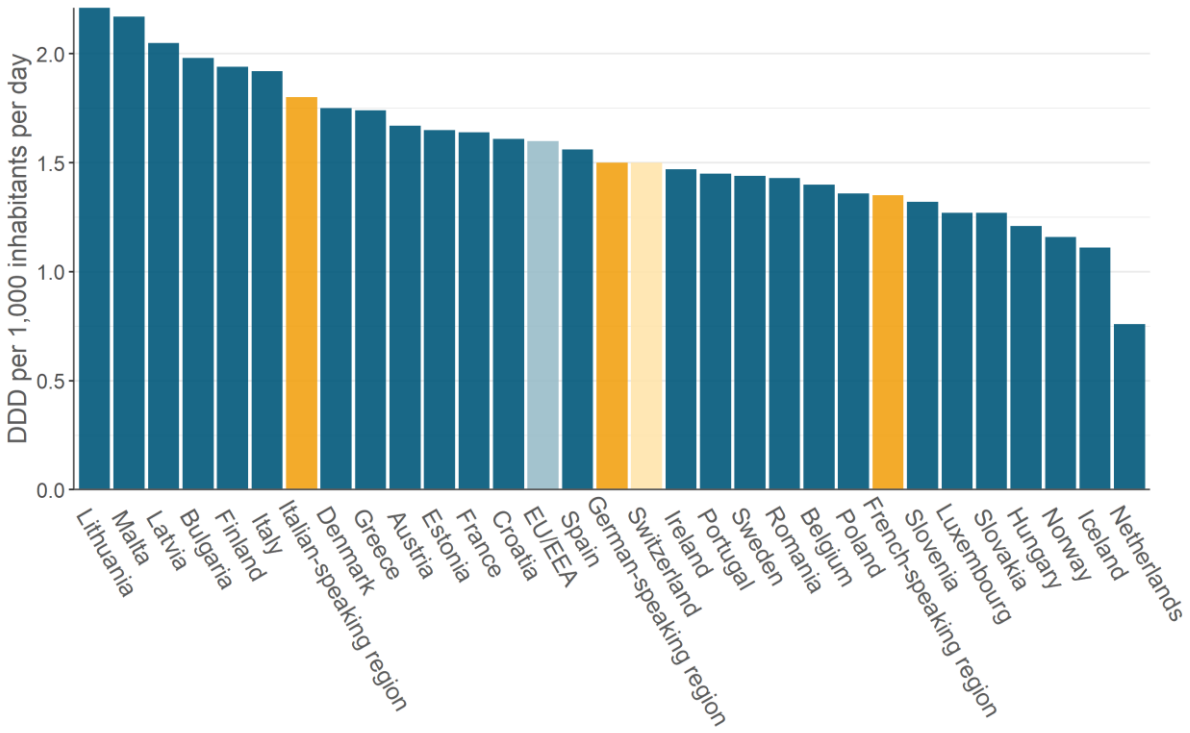

Figure 6: Inpatient antibiotic consumption in the European Union (EU) and European Economic Area (EEA) overall *(light blue),* in European countries *(turquoise)* including Switzerland *(light orange)* and the different linguistic regions within Switzerland *(dark orange)* in 2020 (adapted from [15]).

DDD, defined daily doses [94]

1.5. Antibiotic Stewardship (ABS)

Antibiotic stewardship (ABS) is the effort to measure and improve the adequate use of antibiotics in health care [5]. ABS is crucial to slow AMR, treat patients effectively and enhance patient safety.

Globally, 42% of AB prescriptions in the hospital setting were incongruent with the local guidelines according to a point prevalence study (PPS) including 335 hospitals [97]. While in a Swiss hospital, 33% of prescriptions were not appropriate [10]. This demonstrates the need for ABS programmes to assist physicians in the appropriate prescribing of AB treatment [5]. Numerous studies have proven the value of local ABS programmes in reducing AB use, AMR, mortality, length of hospitalisation and readmission rates, resulting in reduced health care costs [98-102]. In 2017, 29 % (18/63) of Swiss hospitals stated in a survey to have an official ABS programme implemented [103]. Core strategies of ABS programmes are the implementation of guidelines, education, surveillance, reporting and interventions such as prospective audit and feedback or pre-authorisation [5].

Before targeted measures can be defined, the current state must be assessed. Hence, surveillance of AMR and AB consumption is a crucial element in ABS programmes to define interventions [6, 7]. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) and the European Antimicrobial Resistance Surveillance Network (EARS-Net) are collecting resistance data for selected pathogens and data on AB consumption at national level [17, 104]. The standard proceeding to quantify AB consumption is to convert the number of packages into DDD, a technical unit of measurement defined by the WHO [94]. This allows the monitoring of trends in the quantity of AB use and a comparison between AB substances and countries. However, to optimise prescription, metrics evaluating the

quality of AB use are needed. For this purpose, a consensus of quality indicators for AB use in the inpatient setting was elaborated by van den Bosch *et al.* [105] and Monnier *et al.* [11]. The more comprehensive set of quality indicators by Monnier *et al.* encompassed i) structural indicators reflecting organisational aspects of health care, ii) process indicators describing AB treatment and iii) outcome indicators such as death or resistance. To measure process indicators, data on AB prescribing is needed. The continuous monitoring of patient-level AB prescription data are not yet done in the majority of countries worldwide as being too resource-intensive [106]. Alternatively, many countries are using the point prevalence methodology, referring to the collection of patient-level prescription data at a specific point in time [106].

The analysis of quantity of AB consumption is part of routine surveillance in Switzerland. The Swiss Centre for Antibiotic Resistance (ANRESIS) has collected and analysed AMR data and AB consumption data from an increasing number of microbiology laboratories and hospital pharmacies throughout Switzerland since 2006. In 2021, 39 microbiology laboratories and 71 hospital pharmacies participated in the surveillance network. AMR data are provided at the patient level while AB consumption data are aggregated at the department or hospital level and year or month. The results of the analyses are sent back to individual hospitals in the form of feedback and benchmark reports. The purpose of these reports is to support local antibiotic stewardship teams. Quality of AB use was analysed only sporadically; in 2017 and 2022, national PPS were performed by the National Center for Infection Control (swissnoso) [9].

2. Hypothesis & Aims

The current standard for routine surveillance of inpatient AB use is to measure quantity of AB consumption aggregated at the hospital level. In recent years, most of the larger Swiss hospitals have implemented electronic medical record (EMR) systems. Hence, patient-level AB prescription data are increasingly available that could improve the monitoring of AB use and provide better support for ABS programmes.

The overall aims of this PhD thesis were, first, to evaluate the benefits of extracting patient-level AB prescription data compared to hospital-level AB consumption data and, second, to propose methods to include these data in future surveillance of AB use.

Throughout six projects we aimed to assess the benefits and limitations of both, patient-level AB prescription and hospital-level AB consumption data for providing decision support for ABS programmes (Figure 7).

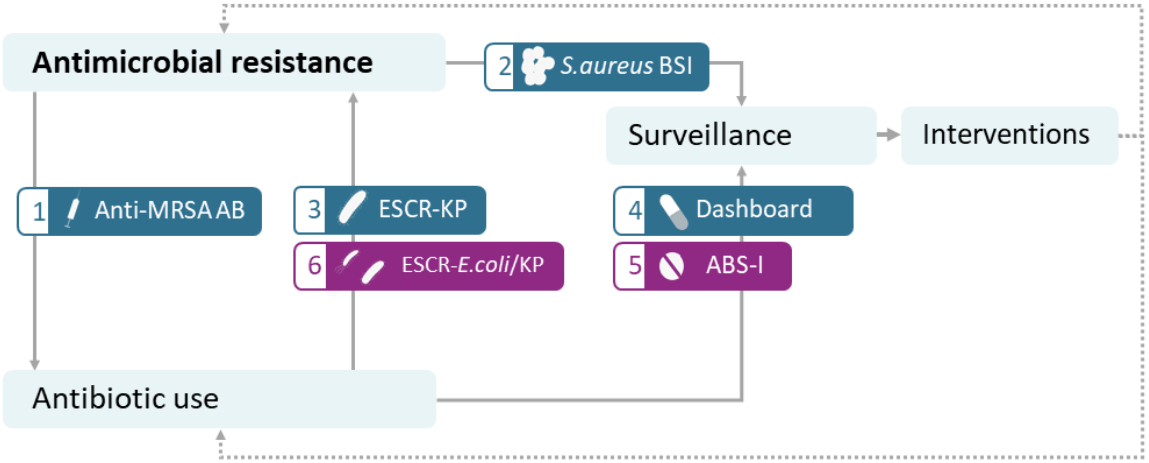

Figure 7: In the projects of this PhD thesis we aimed to analyse predictors for antibiotic use including antimicrobial resistance (project 1), predictors for antimicrobial resistance including antibiotic use (project 3 and 6) and how to improve surveillance (project 2, 4 and 5) in order to define targeted interventions to reduce antimicrobial resistance and antibiotic use. For project 1–4, routine surveillance data from the Swiss Centre for Antibiotic Resistance *(turquoise blue)* were used, while for projects 5 and 6, the electronic medical records from Lucerne Cantonal hospital *(purple)* were the main data source.

Project 1: Consumption of Anti-Methicillin-Resistant *Staphylococcus aureus* Antibiotics in Swiss Hospitals Is Associated with Antibiotic Stewardship Measures

Anti-MRSA AB

As the percentage of MRSA decreased since 2004 [107], it was assumed that consumption of anti-MRSA antibiotics was decreasing simultaneously.

The aims of project 1 were: (i) to describe the consumption of anti-MRSA antibiotics in 21 Swiss hospitals from 2009 to 2019; (ii) to identify underlying predicting parameters; and (iii) to include hospital policy-dependent predictors such as antibiotic stewardship policies in a second model for 2019 only.

Project 2: Increase in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections in Switzerland: A Nationwide Surveillance Study (2008-2021)

S.aureus BSI

An increasing burden of absolute numbers of *S. aureus* BSI despite a decrease in the percentage of MRSA was recently described for the EU and EEA [108]. It was proposed that Switzerland may mirror the epidemiological situation of the other European countries.

The main aim of project 2 was to analyse recent temporal trends of *S. aureus*, MSSA and MRSA BSI for Switzerland and the different linguistic regions within Switzerland. An additional aim was to estimate potential differences among patient–based and epidemiological risk factors for MRSA or MSSA [41, 42, 109].

Project 3: Temporal and Structural Patterns of Extended-Spectrum Cephalosporin-Resistant *Klebsiella pneumoniae* Incidence in Swiss Hospitals

Routine surveillance revealed an increase in the proportion of ESCR-KP in Switzerland, from 1.3% in 2004 to 8.5% in 2019 [16]. As previous studies described prior AB use as a risk factor for the occurrence of extend-spectrum cephalosporin resistance, it was hypothesised that AB consumption may be associated with the incidence of ESCR-KP.

The main aim of project 3 was to describe incidence rates of invasive ESCR-KP infections in Switzerland over time from 2009 to 2019 and to identify underlying predictors, such as AB consumption, hospital type and linguistic region. Overall ESCR-KP incidence (all sample sites) is of interest for infection control purposes, especially since contact isolation is recommended for patients with ESCR-KP in Switzerland, to prevent the nosocomial spread and for epidemiological understanding [110]. An additional aim was therefore to analyse overall ESCR-KP incidence (all sample sites) in a separate model.

Project 4: Dashboards

ANRESIS collects and analyses AB consumption data for routine surveillance. The results are sent back as feedback and benchmark reports to individual hospitals. Project 4a aimed to develop an interactive dashboard to supplement the AB consumption reports with customised visualisations according to the hospital-specific needs.

Analogue to project 4a, the purpose of project 4b was to develop an interactive AB resistance dashboard to supplement the resistance statistics, which are sent upon request to the laboratories. Another aim was to support the data manager in monitoring the data deliveries.

The objective of project 4c was to build an interactive dashboard to support the veterinary medicine AMR surveillance team in analysing the resistance data from veterinary pathogens.

Project 5: Assessing the Conversion of Electronic Medical Record Data Into Antibiotic Stewardship Indicators

The quality of AB use in Switzerland was evaluated only limited and sporadically so far. We assume that analysing the quality of AB use would provide improved support for ABS programmes.

The aim of project 5 was to assess the technical feasibility of converting EMR data into antibiotic stewardship indicators (ABS-I), which have been proposed in the literature. A second aim was to calculate a first estimate of these ABS-I.

Project 6: Resistance Models with Patient-Level Data

Several studies showed that prior AB treatment is a risk factor for resistance development [32, 33, 35-37, 57-61, 75]. However, to tackle AMR, it is crucial to understand which components of AB therapy are risk factors for the occurrence of resistance [76].

In project 6 we aimed to identify risk factors for the occurrence of a) extend-spectrum cephalosporin resistance in *Escherichia coli* and *Klebsiella pneumonia,* b) carbapenem-resistance in *Pseudomonas aeruginosa* and c) methicillin resistance in *Staphylococcus aureus*.

3. Methods & Results

3.1. Published Manuscripts, Main Projects

Project 1: Consumption of Anti-Methicillin-Resistant *Staphylococcus aureus* Antibiotics in Swiss Hospitals Is Associated with Antibiotic Stewardship Measures

L.Renggli*[1], M.Gasser*[1], C.Plüss-Suard[1], A.Kronenberg[1]

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

* contributed equally

My contribution: I extracted the data, performed the analysis, drafted the manuscript and applied the suggested revisions after reviews from co–authors and peer–review from the Journal of Hospital Infection.

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Consumption of anti-meticillin-resistant *Staphylococcus aureus* antibiotics in Swiss hospitals is associated with antibiotic stewardship measures

L. Renggli*[,1], M. Gasser[1], C. Plüss-Suard, A. Kronenberg

Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

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SUMMARY

Background: Consumption of antibiotics active against meticillin-resistant *Staphylococcus aureus* (MRSA) has been described in numerous European studies. However, the underlying predictors of consumption are still poorly understood.

Aim: To describe the consumption of anti-MRSA antibiotics (daptomycin, intravenous glycopeptides, linezolid) in Switzerland over time and to identify underlying predictor variables.

Methods: A retrospective observational multi-centre study was conducted in 21 Swiss hospitals over a period of 11 years (2009–2019). Multiple linear regression models were built to identify regional and hospital-specific predictor variables affecting the consumption of anti-MRSA antibiotics.

Findings: Consumption of anti-MRSA antibiotics increased between 2009 and 2019 from 12.7 to 24.5 defined daily doses per 1000 bed-days (+93%). In the first model presented, which includes data of the whole study period, the following variables were associated with higher anti-MRSA antibiotic consumption: number of MRSA cases ($P < 0.01$), year ($P < 0.01$), hospital type (tertiary care university hospitals vs others, $P < 0.01$), hospital department (intensive care unit vs others, $P < 0.01$) and linguistic region (French vs German and German vs Italian, $P < 0.01$). In a second model including data from a query on hospital policies in place in 2019, the presence of an antibiotic stewardship group ($P < 0.01$) and prescription restrictions ($P < 0.01$) were associated with consumption of anti-MRSA antibiotics.

Conclusion: Our study shows that both the presence of an antibiotic stewardship group and the implementation of prescription restrictions, i.e. factors that can be controlled by the hospital itself, were associated with a lower consumption of anti-MRSA antibiotics.

* Corresponding author. Address: Friedbühlstrasse 51, Bern, 3010, Switzerland. Tel.: +41 31 632 98 80.
E-mail address: luzia.renggli@ifik.unibe.ch (L. Renggli).

[1] Authors contributed equally to this work.

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Introduction

Staphylococcus aureus was reported to be the second most frequent micro-organism causing healthcare-associated infections in Europe in 2017, causing sepsis, cardiac valve infection, and joint, bone, wound, and soft tissue infections [1]. Approximately 50% of the population are nasal carriers, and they are widely disseminated [2]. Infections with meticillin-resistant *Staphylococcus aureus* (MRSA), resistant against all classical β-lactams, including combinations with β-lactam inhibitors, represent a high risk, especially for seriously ill and immunocompromised patients, and are therefore a serious threat in hospitals worldwide. Despite decreasing MRSA rates, deaths attributable to MRSA infections increased by a factor of 1.38–6810 yearly deaths in Europe between 2007 and 2015 [3]. By causing 32.6 disability-adjusted life-years (DALYs) per 100,000 individuals, MRSA ranked second of all DALYs attributed to infections with antimicrobial-resistant bacteria in the European Union (EU) and European Economic Area (EEA) and ranked third in Switzerland (8.9 DALYs per 100,000 individuals [4]). For different linguistic regions in Switzerland, both decreasing and slightly increasing MRSA rates were described [5]. In 2019, the MRSA rate in Switzerland was 3.4%, with slightly higher rates in southern and western Switzerland [6].

The emergence and spread of antimicrobial resistance are favoured by antibiotic therapy through evolutionary pressure [7–9]. Surveillance of antibiotic consumption is a crucial element in 'antibiotic stewardship', and it has been shown that optimizing the use of antibiotics may prevent the spread of resistant bacteria [10].

Daptomycin, glycopeptides (vancomycin and teicoplanin), linezolid, tigecycline, clindamycin, trimethoprim–sulfamethoxazole, fosfomycin, ceftobiprole, and ceftaroline are known to be biologically active against MRSA [11,12]. However, intravenous glycopeptides and the reserve antibiotics daptomycin and linezolid are the only effective options for the treatment of MRSA bacteraemia. While intravenous glycopeptides are mainly used against MRSA, daptomycin and linezolid may also be used against vancomycin-resistant enterococci (VRE). Due to these properties, we restrict our analysis to the glycopeptides daptomycin and linezolid, referred to hereinafter as 'anti-MRSA antibiotics'.

Therapy with intravenous glycopeptides, which are known for their relatively complex handling and toxicity, was the only effective treatment against MRSA bacteraemia until the introduction of linezolid in Switzerland in 2001. The introduction of daptomycin followed in 2007. Daptomycin and linezolid are comparable in their effectiveness, whereas the incidence of thrombocytopenia is higher under linezolid [13,14]. The potential effect of the introduction of daptomycin on the consumption of glycopeptides and linezolid has not yet been studied in Switzerland.

For different European countries, both increasing and decreasing trends in consumption of anti-MRSA antibiotics have been described for the period from 2010 to 2019 [15]. However, to the best of our knowledge, the underlying predictors of these long-term processes have only been studied to a limited extent for glycopeptides.

The aims of this study were: (i) to describe the consumption of anti-MRSA antibiotics in 21 Swiss hospitals from 2009 to 2019; (ii) to identify underlying predicting parameters; and (iii) to include hospital policy-dependent predictors such as antibiotic stewardship policies in a second model for 2019 only.

Methods

Design and study population

A retrospective observational multi-centre study was conducted with data from 21 Swiss hospitals over a period of 11 years (2009–2019). To homogenize the dataset, analysis was restricted to hospitals with more than 200 beds and data availability for at least two years within the study period.

Data collection and processing

Antibiotic consumption and resistance data were obtained from the Swiss Centre for Antibiotic Resistance (ANRESIS) database. ANRESIS is a representative surveillance system that continuously collects national data on antibiotic use and antibiotic resistance.

Yearly antibiotic consumption was described in defined daily doses (DDD) per 1000 bed-days (BD) and reflects the amount of antibiotics delivered from the hospital pharmacy to individual departments [16].

MRSA was defined as *Staphylococcus aureus* non-susceptible to at least one of the following antibiotics: meticillin, oxacillin, flucloxacillin, or cefoxitin. VRE was defined as *Enterococcus faecalis* or *Enterococcus faecium* non-susceptible to vancomycin. Analyses were restricted to isolates from sterile sites, surrogating invasive infections. Isolates obtained within 30 days after the first positive result for the same patient at the same hospital were considered duplicate and were excluded. Incidence is given by the number of invasive infections per 1000 bed-days. To obtain data on the 2019 hospital policies (i.e. availability of guidelines for the treatment of MRSA infections and restrictions for the use of daptomycin, glycopeptides and linezolid), a short online questionnaire (Survs®, https://survs.com/) was sent to the infectious diseases specialists at participating hospitals).

Statistical models

A multiple linear regression model was developed to identify predictor variables contributing to the consumption of anti-MRSA antibiotics (DDD/1000 BD) from 2009 to 2019 ('model 1'). The following predictor variables were included in the initial model: MRSA incidence, VRE incidence, time (i.e. the years), hospital type (university vs non-university hospital), linguistic region (see details below) and intensive care unit (ICU) vs non-ICU department. The initial model, which included all predictor variables, was transformed logarithmically to meet the assumptions for linear regression. The likelihood ratio test (χ^2 statistics) was then used in a backwards elimination process ($P < 0.05$ to retain) to select the set of independent variables for the final model.

The German-speaking region was used as a reference in comparisons of the three-level factor linguistic region. To analyse differences between the French- and Italian-speaking regions, the French-speaking region was additionally used as a reference.

Analysis of hospital policies in 2019

To improve the regression model, we included parameters of the hospital policies into an additional model ('model 2'). Data for this model were restricted to the year 2019, as data on hospital policies were available for this year only. Additional dichotomous ('yes'/'no') predictor variables included in this model were the presence of an antibiotic stewardship group (ABS group), meeting at least three times yearly, availability of internal guidelines for treatment of MRSA infections, pre-existing written restrictions in prescription of anti-MRSA antibiotics, recommendation of glycopeptides as the first choice for empirical treatment of severe skin and soft-tissue infections, and routine testing of daptomycin resistance. The questions which led to these variables where added to the supplement (Survey Questions for Analysis 2019). The initial model, which included all predictor variables, was transformed logarithmically to meet the assumptions for linear regression. The likelihood ratio test (χ^2 statistics) was then used in a backwards elimination process ($P < 0.05$ to retain) to select the set of independent variables for the final model.

All analyses and visualizations were performed with R software (version 3.6.1, R Core Team, Vienna, Austria).

Results

Temporal and regional patterns from 2009 to 2019

Total consumption of anti-MRSA antibiotics increased significantly ($P < 0.01$) from 2009 to 2019 in Switzerland (Table I). Consumption increased from 12.7 to 24.5 DDD/1000 BD (+93%) between 2009 and 2019, with the highest increase observed between 2009 and 2013 (up to 22.2 DDD/1000 BD, +75%). Increases were observed for all anti-MRSA antibiotics (glycopeptides 11.2 to 16.9 (+51%), daptomycin 1.4 to 7.9 (+400%), and linezolid 0.51 to 0.67 DDD/1000 BD (+31%)) (Figure 1). The percentage of daptomycin in the total consumption of anti-MRSA antibiotics increased from 9% in 2009 to 28% in 2019, whereas the proportion of glycopeptides decreased from 87% to 70% and that of linezolid decreased slightly from 4% to 2.7%.

The results of model 1 showed that the number of MRSA infections was positively associated with the consumption of anti-MRSA antibiotics ($P < 0.01$, Table I). Consumption was significantly higher in ICU departments than in non-ICU departments ($P < 0.01$, Figure 2). Conversely, the effect of MRSA incidence on consumption was lower in ICU departments than in non-ICU departments ($P < 0.01$). Further predictor variables were hospital type ($P < 0.01$) and linguistic region ($P < 0.01$). VRE incidence was not associated with the consumption of anti-MRSA antibiotics.

Consumption increased in all settings over time, with the exception of French-speaking university hospitals (Supplementary Table A1, Figure 2).

MRSA incidence decreased from 0.085 to 0.076 invasive infections/1000 BD (−11%) between 2009 and 2019, with the largest decrease between 2009 and 2013 (−22%). Remarkably, the incidence of MRSA decreased in university hospitals in the French-speaking region only (from 0.26 to 0.11 invasive infections/1000 BD, −58%), whereas increasing incidences were observed in the other linguistic-hospital type combinations (Supplementary Table A2, Figure 2). In ICU departments, MRSA incidence was consistently higher than that in non-ICU departments.

Table I
Predictor variables of a model describing the consumption of anti-MRSA antibiotics [$\log_{10}$(DDD/1000 BD)] in Switzerland from 2009 to 2019

Variable	Estimate[a]	95% CI	*P*-value
Year	0.04	(0.02, 0.05)	<0.001
MRSA incidence	1.02	(0.89, 1.16)	<0.001
ICU vs non-ICU	0.68	(0.51, 0.84)	<0.001
University vs non-university hospital	0.39	(0.25, 0.53)	<0.001
French vs German	1.34	(1.21, 1.46)	<0.001
Italian vs German	2.22	(0.88, 3.55)	0.001
MRSA and ICU interaction	−0.78	(−1.01, −0.55)	<0.001
University and French interaction	−1.88	(−3.2, −0.55)	0.006
VRE incidence	No association[b]		
R^2/adjusted R^2	0.731/0.725		
F-statistic	130.2		<1 E-15

MRSA, meticillin-resistant *Staphylococcus aureus*; DDD, defined daily doses; BD, bed-days; CI, confidence interval; ICU, intensive care unit; VRE, vancomycin-resistant enterococci.
[a] Negative sign indicates a negative association.
[b] Variable does not improve the model (likelihood ratio χ^2-statistic, $P > 0.05$).

Survey results for hospital policies in 2019

Nineteen out of 21 hospitals sent consumption data for 2019; 15 (79%) responded to the 2019 survey on hospital policies (11/13 from the German-, 4/4 from the French- and 0/2 from the Italian-speaking region). An infectious disease (ID) specialist was on-site at each participating hospital, and antibiotic stewardship groups who met at least three times yearly existed in eight (53%) of all hospitals. Guidelines concerning antibiotics in general were available in 14 out of 15 (93%) hospitals, whereas specific guidelines on MRSA and VRE

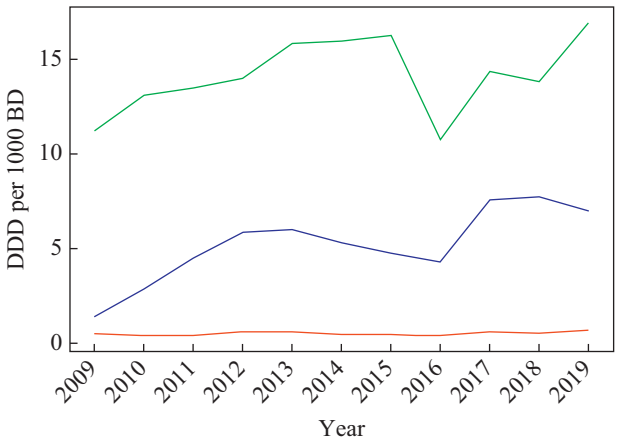

Figure 1. Consumption of the anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days) daptomycin (blue), glycopeptides (intravenous vancomycin, teicoplanin, green) and linezolid (red) in 21 Swiss hospitals between 2009 and 2019.

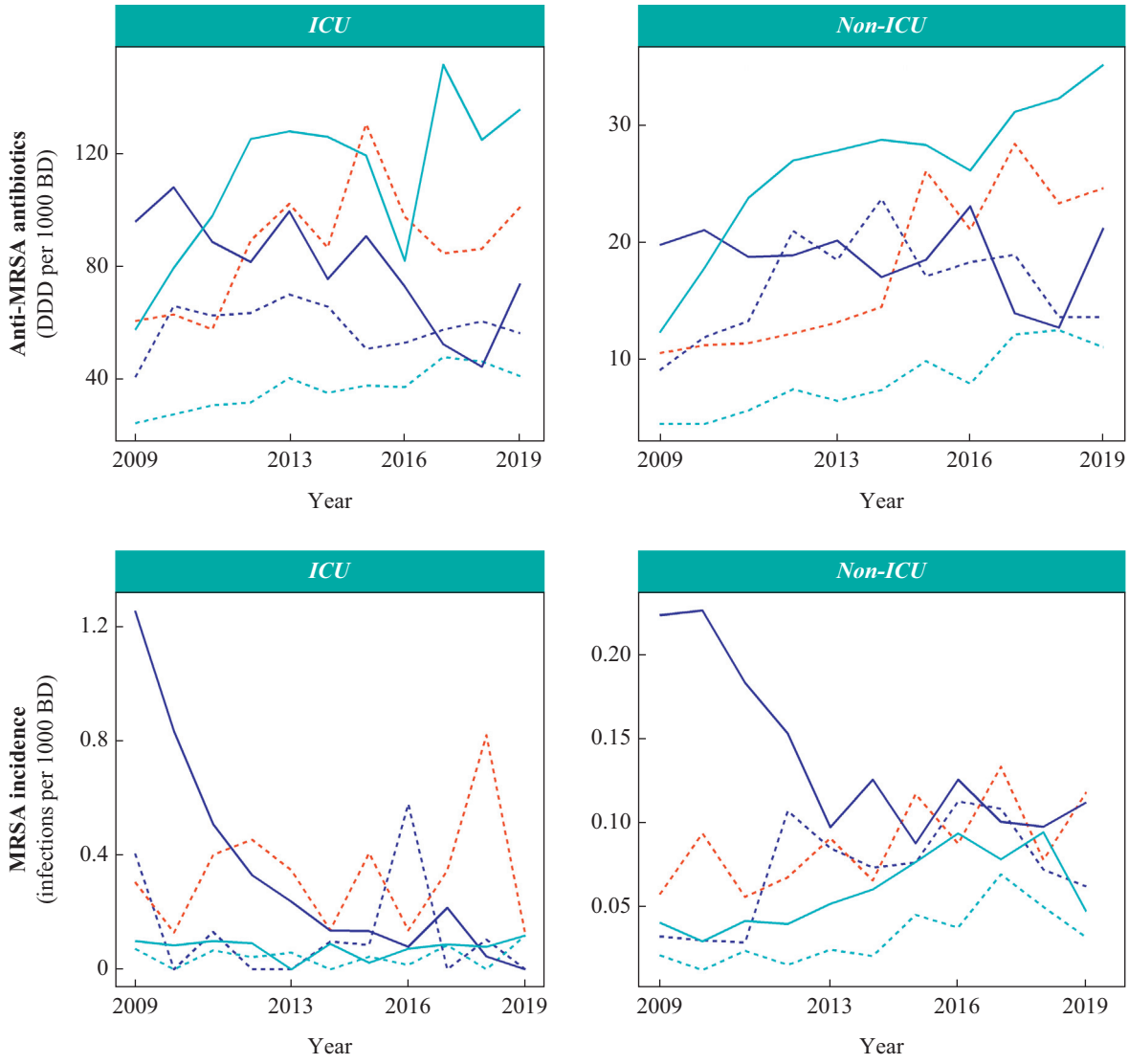

Figure 2. Median consumption of anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days (BD), upper panels) and MRSA incidence (invasive infections per 1000 bed-days, lower panels) in university (solid line) and non-university (dashed line) hospitals of the French-speaking (dark blue), German-speaking (light blue) and Italian-speaking (red) regions of Switzerland between 2009 and 2019 in intensive care unit (ICU) (left panels) and non-ICU departments (right panels).

treatments were available in eight (53%) and four (27%) of all hospitals, respectively. However, in four out of 11 (36%) hospitals without MRSA/VRE guidelines, a consultation from an ID specialist was automatically triggered after an MRSA or VRE infection. In one out of 15 hospitals (7%) a limitation in treatment days for intravenous glycopeptides was in place. More hospitals had restrictions on prescriptions for daptomycin (87%) than on those for linezolid (80%) or glycopeptides (27%). Common restrictions included an obligation to consult an ID specialist or the chief physician before prescription of anti-MRSA antibiotics or automatic limitation of the treatment duration. Other restrictions were the consultation of an ID specialist or validation by a clinical pharmacist. The recommended daily daptomycin doses for the treatment of skin and soft tissue infections ranged between 4 and 10 mg/kg body weight (BW). The recommended dosage in university hospitals was higher, with a median of 8 mg/kg BW (interquartile range: 6–8 mg/kg BW), than that in non-university hospitals, with a median of 6 mg/kg BW (interquartile range: 4.5–6 mg/kg BW).

The hospital policy-dependent predictor variables, namely, existing antibiotic stewardship group meeting at least three times yearly and pre-defined restrictions on prescriptions, were significantly (each $P < 0.01$) associated with lower consumption of anti-MRSA antibiotics in 2019 (Table II, Figure 3). Overall, the hospital policy-dependent factors explained 44% of the variability explained by this model.

All hospitals had either an existing antibiotic stewardship group, restrictions in prescription of anti-MRSA antibiotics, or both. Restrictions could not be specified further due to multicollinearity of different restriction types.

Except for hospital type and ICU vs non-ICU department, none of the predictors included in the initial model, including linguistic regions and MRSA incidence, were significantly associated with consumption of anti-MRSA antibiotics (Table II).

Table II
Predictor variables, including hospital policies, of a model describing the consumption of anti-MRSA antibiotics [$\log_{10}$(DDD/1000 BD)] in Switzerland in 2019

Variable	Estimate[a]	95% CI	*P*-value
University vs non-university hospital	1.15	(0.71, 1.6)	<0.001
ICU vs non-ICU	1.01	(0.62, 1.4)	<0.001
ABS group vs none	−0.71	(−1.15, −0.26)	0.003
Restrictions[b] vs none	−0.97	(−1.59, −0.36)	0.003
French vs German	No association[c]		
MRSA incidence	No association[c]		
VRE incidence	No association[c]		
Internal MRSA guidelines vs none	No association[c]		
Daptomycin resistance testing routinely vs not	No association[c]		
First choice for empirical therapy[d] (yes vs no)	No association[c]		
Physicians in hospital hygiene/500 beds	No association[c]		
R^2/adjusted R^2	0.73/0.687		
F-statistic	16.93		<1 E-06

MRSA, meticillin-resistant *Staphylococcus aureus*; DDD, defined daily doses; BD, bed-days; CI, confidence interval; ICU, intensive care unit; VRE, vancomycin-resistant enterococci.
ABS group: antibiotic stewardship group present with regular meetings (>3 times a year).
[a] Negative sign indicates a negative association.
[b] Restrictions on the prescription of anti-MRSA antibiotics.
[c] Variable does not improve the model (likelihood ratio χ^2-statistic, $P > 0.05$).
[d] Glycopeptides as the first choice for empirical therapy of skin and soft-tissue infections.

Discussion

Increasing consumption was observed for all anti-MRSA antibiotics, despite decreasing MRSA incidences in Switzerland between 2009 and 2019. Remarkably, the use of daptomycin, which was introduced in 2007, did not replace the use of glycopeptides (Figure 1). This finding is in contrast to observations from France and Italy, where decreased glycopeptides consumption was observed after the introduction of daptomycin [17]. Similar trends as in Switzerland, i.e. no reduction in glycopeptides consumption despite increasing consumption of new MRSA antibiotics (daptomycin, linezolid) and stable MRSA rates, were described in Spain between 2007 and 2012 [18]. However, according to stratified Swiss data, the overall decrease in MRSA incidence was caused solely by French-speaking university hospitals, in which consumption of anti-MRSA antibiotics was stable. In other regions, both the MRSA incidence and consumption of anti-MRSA antibiotics increased.

The finding that the consumption of anti-MRSA antibiotics in the French- and Italian speaking parts of Switzerland was higher than that in German-speaking regions may be explained by socio-cultural factors and by higher MRSA rates in neighbouring countries (2019: Italy 35.6%, France 11.6%, Germany 6.7%), as patients and medical staff exchange across the national borders [19–21]. Different MRSA rates, as well as different background of treating physicians, both influence prescription of anti-MRSA antibiotics which always is a balance between avoiding risks for the patient and avoiding resistance development. Development and advertisement of own national guidelines could help to further reduce these differences. Similar consumption patterns within Switzerland were described by Plüss-Suard *et al.* for vancomycin between 2004 and 2008 [22].

The consumption of anti-MRSA antibiotics in university hospitals was higher than that in non-university hospitals. In addition to the higher MRSA rates observed in French university hospitals only, the higher consumption in university hospitals is probably caused by the more severe and complex cases accommodated in higher-level-of-care hospitals, assuming that critically ill patients are more likely to be treated with anti-MRSA antibiotics [23]. This also holds true for the higher consumption in Swiss ICU compared to non-ICU departments observed in our study. These findings are consistent with those of previous studies in Germany, which described higher glycopeptide consumption in ICU compared to non-ICU departments and in university compared to non-university hospitals [24,25].

Our data reveal large variations in both MRSA incidence and consumption of anti-MRSA antibiotics at the regional, hospital, and even departmental levels (Supplementary Figure A1). Seventy-three percent of the variance in consumption was explained by different predictor variables, including MRSA incidence and the interaction between MRSA incidence and department. An analogous positive association between MRSA incidence and consumption of glycopeptides was observed in France during a single year in 2002, but the interaction between MRSA incidence and department type was not analysed [26].

In our study, the effect of the number of MRSA infections on the consumption of anti-MRSA antibiotics was more pronounced in non-ICU departments than in ICU departments. This could be explained by the early transfer of patients to the non-ICU department for prolonged antibiotic therapy after initial stabilization in the ICU. Further considering the critical condition of ICU patients, it is likely that they more frequently receive anti-MRSA antibiotics while awaiting microbiological results.

The VRE incidence in Switzerland is low. The absence of a significant association between VRE incidence and the consumption of anti-MRSA antibiotics should therefore be interpreted with care.

Since our data still showed considerable differences in the consumption of anti-MRSA antibiotics within otherwise comparable hospitals, we developed an advanced model including data on hospital policies. This model was restricted to data from 2019, as hospital policy data were available for this year only. In this model, 44% of the explained variability in consumption was due to prescription restrictions and the establishment of regular meetings of an antibiotic stewardship group. This positive effect is in line with the findings of Borde *et al.*, who reported a decline and optimization in the use of daptomycin after starting an antibiotic stewardship

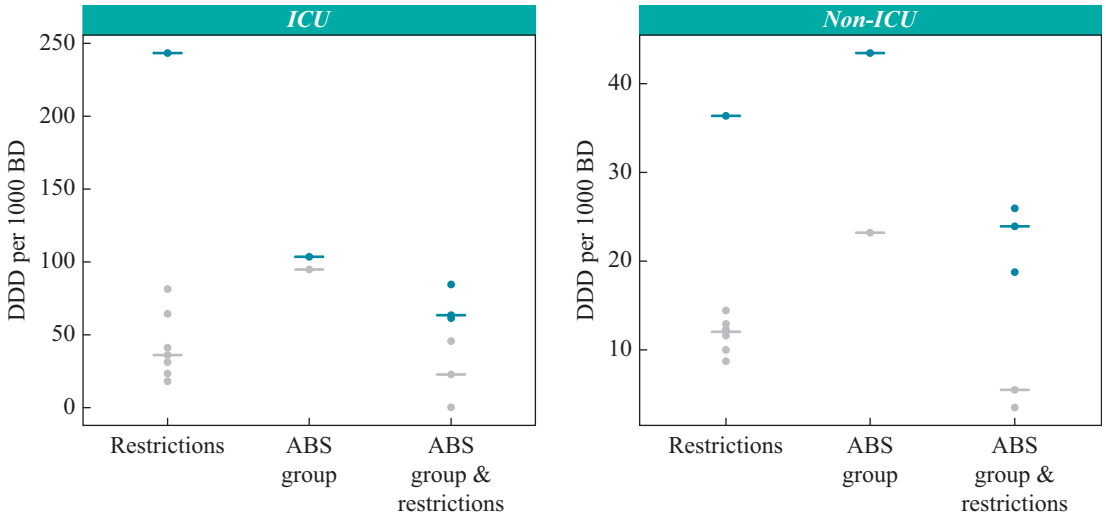

Figure 3. Association of antibiotic stewardship group (ABS), restrictions on the prescription of anti-MRSA antibiotics (Restrictions) or both (ABS group & Restrictions) with the consumption of anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days) in 15 Swiss university (turquoise) and non-university (grey) hospitals in 2019. Both individual data points and group medians (lines) are shown. Consumption data were grouped per intensive care unit (ICU) (left panel) and non-ICU department (right panel).

programme [27]. In our study, we did not analyse the effects of the optimized use of anti-MRSA antibiotics, but, as suggested by other studies, these interventions may not only reduce resistance rates but also decrease patient harm due to side-effects, mortality, and costs [27,28].

In contrast to the whole study period, variability in consumption of anti-MRSA antibiotics between hospitals was not explained by MRSA incidence in 2019. This may be explained by lower MRSA incidence and especially lower variance in MRSA incidence but comparable variance in consumption of anti-MRSA antibiotics compared to the whole study period. In addition, in model 1 the difference to the previous year was considered by the variable time (year) which could not be considered in model 2. Further, the statistical power was weaker in model 2, due to smaller dataset.

Our study has several limitations. First, the two models are not directly comparable, as only data from 2019 could be included in model 2. However, both models fit well ($R^2 = 0.73$ each), and we assume that continuous surveillance of hospital policies could even improve our model. Second, data were grouped by department level. The inclusion of patient-specific data could essentially improve these models. With the introduction of electronic prescriptions, such an analysis will be possible in the future. Third, MRSA cases were not confirmed by a central laboratory; however, all participating laboratories use Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing guidelines and are accredited by the Swiss government.

The main strength of our study is the extensive data collection, covering 11 years and all university and tertiary hospitals in Switzerland. In addition, Switzerland uniquely allows stratification into different linguistic and socio-cultural regions within a single country. To the best of our knowledge, this is the first multi-centre study investigating hospital policy-dependent predictors for the use of anti-MRSA antibiotics.

In conclusion, we found that daptomycin, when introduced, did not replace glycopeptides, since consumption of all anti-MRSA antibiotics examined in this study increased in Switzerland. It can also be concluded that, in addition to MRSA incidence, both regional factors and hospital type affect anti-MRSA antibiotic consumption, as significantly higher values were found in the French- and Italian-speaking regions than in the German-speaking region and in university hospitals than in non-university hospitals. Considering antibiotic stewardship policies, the presence of an antibiotic-stewardship group and the implementation of prescription restrictions were associated with a lower consumption of anti-MRSA antibiotics. Therefore, appointing an antibiotic stewardship group in addition to implementing restrictions in prescription for anti-MRSA antibiotics should be recommended.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.08.019.

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Supplementary Material Project 1

Supplementary Tables

Table A1: Consumption of anti-MRSA antibiotics in the different combinations of linguistic region and hospital type

	2009	2019	Difference [%]
German and non-university	5.1	13.4	160
French and non-university	11.1	15.4	38
Italian and non-university	12.4	28.7	132
German and university	15.5	41.5	168
French and university	22.5	23.1	3

Table A2: MRSA incidence in the different combinations of linguistic region and hospital type

	2009	2019	Difference [%]
German and non-university	0.02	0.05	133
French and non-university	0.04	0.15	246
Italian and non-university	0.07	0.12	78
German and university	0.05	0.05	21
French and university	0.26	0.11	-58

Supplementary Figure

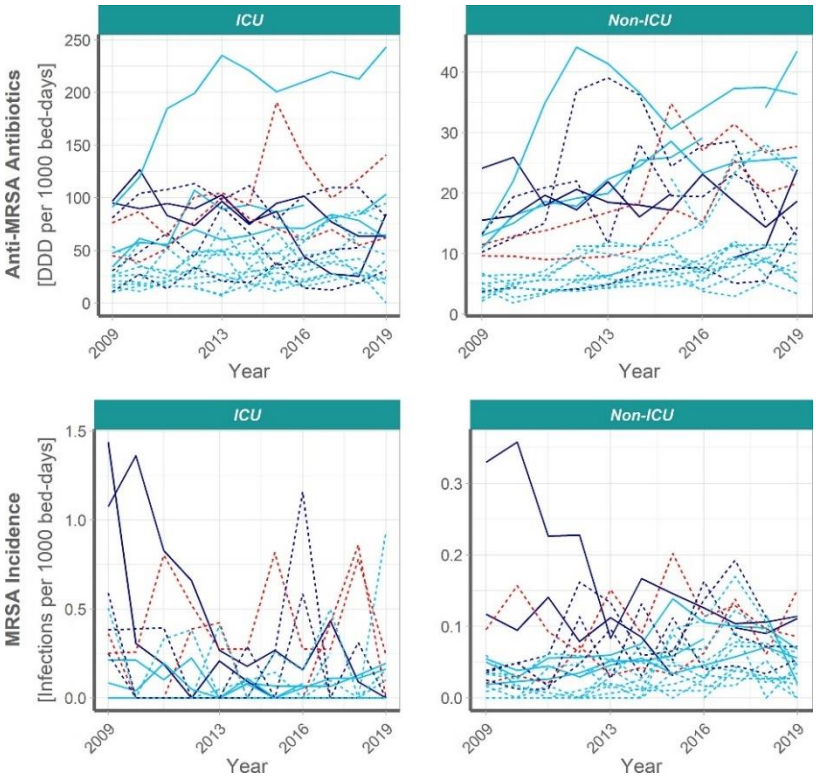

Figure A1: Consumption of anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days, upper panels) and MRSA incidence (invasive infections per 1000 bed-days, lower panels) between 2009 and 2019 in ICU (*left panels*) and non-ICU departments (*right panels*) of 21 Swiss university (*solid line*) and non-university hospitals (*dashed line*) in the French-speaking (*dark blue*), German-speaking (*clear blue*) and Italian-speaking (*red*) region. Please note the use of different units on the y-axes.

Supplementary Data

Survey Questions for Analysis 2019

1. Was in your hospital in 2019 a defined, regularly meeting (more than three times per year) antibiotic steward ship group existing?
    - Yes / no
2. Was there an infectious disease specialist or another physician responsible for hospital hygienic questions in 2019?
    - Yes /no
3. Were written guidelines for treatment of i) MRSA, ii) VRE infections available in your hospital in 2019?
    - Yes/no
4. Which antibiotic was the treatment of first choice in case of infection and i) MRSA confirmed, ii) MRSA suspected, iii) VRE confirmed, iv) VRE suspected, v) empirical in case of severe skin and soft tissue infections, vi) empirical for severe sepsis?
    - Daptomycin (except of pneumonia)
    - Glycopeptides (vancomycin, teicoplanin)
    - Linezolid
    - Others, please specify
5. Were there restrictions in prescription of i) daptomycin, ii) intravenous glycopeptides (vancomycin, teicoplanin), iii) linezolid in 2019?
    - Only after consultation of the chief physician
    - Only after consultation of the infectious disease specialist
    - Maximal defined number of days without consultation of the chief physician or infectious disease specialist
    - Others, please specify
    - No restrictions
6. Which is the normally used dosage of daptomycin for adults (without co-morbidities) in case of i) skin and soft tissue infection, ii) invasive infection with *Staphylococcus aureus* (e.g. bacteraemia), ii) invasive infections with Vancomycin-resistant *Enterococcus* (*e.g.* bacteraemia)? [mg/kg/d]
    - Open response in number

Project 3: Temporal and Structural Patterns of Extended-Spectrum Cephalosporin-Resistant *Klebsiella pneumoniae* Incidence in Swiss Hospitals

L.Renggli*[1], M.Gasser*[1], C.Plüss-Suard[1], S.Harbarth[2], A.Kronenberg[1]

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[2] Infection Control Programme, University of Geneva Hospitals and Faculty of Medicine, WHO Collaborating Centre, Geneva, Switzerland

*contributed equally

My contribution: I extracted the data, performed the analysis, drafted the manuscript and applied the suggested revisions after reviews from co–authors and peer–review from the Journal of Hospital Infection.

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Temporal and structural patterns of extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* incidence in Swiss hospitals

L. Renggli [a,*,†], M. Gasser [a,†], C. Plüss-Suard [a], S. Harbarth [b], A. Kronenberg [a]

[a] *Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland*
[b] *Infection Control Programme, University of Geneva Hospitals and Faculty of Medicine, WHO Collaborating Centre, Geneva, Switzerland*

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SUMMARY

Background: Routine surveillance data revealed increasing rates of invasive extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (ESCR-KP) in Switzerland, from 1.3% in 2004 to 8.5% in 2019.

Aim: The main aim of this study was to understand the causes of this recent trend, specifically to identify predictors affecting the incidence of invasive ESCR-KP infections in Switzerland.

Methods: A retrospective observational multi-centre study was conducted in 21 Swiss hospitals over a period of 11 years (2009–2019). Potential predictor variables for the incidence of invasive ESCR-KP infections were studied with a multiple linear regression model. In an additional analysis, the overall ESCR-KP incidence (all sample sites) was investigated.

Findings: An increasing incidence of invasive ESCR-KP infections from 0.01 to 0.04 patients per 1000 bed-days was observed between 2009 and 2019 and confirmed by multiple linear regression analysis ($P < 0.01$). ESCR-KP incidence was higher in university hospitals ($P < 0.01$) and in the French-speaking region than in the German-speaking region ($P < 0.01$). There was no association with antibiotic consumption. Analysing the overall ESCR-KP incidence (all sample sites) revealed high variability between university hospitals, mainly due to a high proportion of patients with screening isolates at Geneva University Hospital (50% of patients with ESCR-KP).

Conclusion: The incidence of invasive ESCR-KP infections increased in Switzerland between 2009 and 2019 and was not associated with antibiotic consumption. Our findings indicate that, in this low-incidence setting, structural factors such as the hospital type and the linguistic region play a more important role in relation to ESCR-KP incidence than the hospital's antibiotic consumption.

* Corresponding author. Address: Universität Bern, Friedbühlstrasse 51, Bern, 3010, Switzerland. Tel.: +41 31 632 98 80.
E-mail address: luzia.renggli@ifik.unibe.ch (L. Renggli).
† Authors contributed equally to this work.

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Introduction

Extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (ESCR-KP) is a severe threat for hospitalized patients worldwide, causing bloodstream, intra-abdominal and urinary tract infections as well as severe pneumonia. In 2017, extended-spectrum β-lactamase (ESBL)-producing Enterobacterales were listed as one of the highest-priority pathogens for the research and development of new antibiotics by the World Health Organization [1]. ESCR-KP ranked third among the most prevalent antimicrobial-resistant bacteria in 2015, causing ~22.5 disability-adjusted life-years (DALYs) per 100,000 population in the European Union (EU) and European Economic Area (EEA) and ~7 DALYs per 100,000 population in Switzerland [2,3]. The percentage of invasive *K. pneumoniae* isolates with resistance to third-generation cephalosporins increased in the EU and EEA from 21.5% to 31.7% (2009–2019) [4–6]. Routine surveillance data in Switzerland revealed an increase in the percentage of extended-spectrum cephalosporin resistance in invasive *K. pneumoniae* isolates from 4% to 8.5% (2009–2019) [7].

Previous work in Spain, the USA and China identified prior use of third- and fourth-generation cephalosporins as one of the main risk factors for extended-spectrum cephalosporin resistance in *K. pneumoniae* [8–12]. Further risk factors described in the literature are prior use of fluoroquinolones, aminoglycosides, and trimethoprim/sulfamethoxazole since extended-spectrum cephalosporin resistance frequently accompanies cross-resistance to these antibiotics [9,13–15]. To date, it has not been investigated whether these factors are relevant in Switzerland, representing a low-incidence setting.

The main aim of this study was to describe incidence rates of invasive ESCR-KP infections in Switzerland over time from 2009 to 2019 and to identify underlying predictors such as antibiotic consumption, hospital type (university vs non-university), and linguistic region.

Overall ESCR-KP incidence (all sample sites) is of interest for infection control purposes, especially since contact isolation is recommended for patients with ESCR-KP in Switzerland to prevent nosocomial spread and for epidemiological understanding [16]. An additional aim was therefore to analyse overall ESCR-KP incidence (all sample sites) in a separate model. By a comparison of this model with the main model based on invasive ESCR-KP infections only, it was then aimed to estimate a potential source of sampling bias.

Methods

Design and study population

A retrospective observational multi-centre study was conducted in 21 Swiss acute-care hospitals over a period of 11 years (2009–2019). To homogenize the dataset, the analysis was restricted to hospitals with more than 200 beds and data availability for at least two years within the study period. Positive samples from patients admitted to a hospital or who attended an emergency department were included. Samples from patients attending the outpatient clinic only were excluded.

Data collection and processing

Antibiotic consumption and resistance data were obtained from the Swiss Centre for Antibiotic Resistance (ANRESIS) database. ANRESIS is a representative surveillance system that continuously collects national data on antibiotic use and antibiotic resistance [17].

Yearly antibiotic consumption was described in defined daily doses (DDD) per 1000 bed-days (BD) and reflects the amount of antibiotics delivered from the hospital pharmacy to individual departments [18]. The consumption of third- and fourth-generation cephalosporins, fluoroquinolones, trimethoprim/sulfamethoxazole, and aminoglycosides was aggregated at the hospital level.

ESCR-KP was defined as *K. pneumoniae* non-susceptible (resistant or intermediately susceptible) to at least one of all third- or fourth-generation cephalosporins tested. Participating laboratories and hospitals are distributed all over Switzerland; laboratories are accredited by national authorities and use CLSI or EUCAST guidelines for antibiotic susceptibility testing. Deduplication was performed at the level of bacterial species by keeping only the most invasive isolate of all samples for a given year from the same patient. Incidence is given by the number of patients affected per 1000 bed-days.

For invasive infections, only samples from sterile sites were considered. Screening samples were defined as samples that were labelled as such by the hospitals or as samples from faeces, anal swabs, or intact skin. Isolates from non-screening sites (including invasive samples) were summarized as 'clinical isolates'. Clinical isolates were divided into three categories: isolates from patients who were screened as positive any time before a sample of a non-screening location was taken were described as 'clinical isolate, patient previously screened positive'. The remaining clinical isolates were categorized depending on their sample site as 'clinical isolate, sterile site' and 'clinical isolate, non-sterile site' (for details see Supplementary Figure A1).

Statistical models

A multiple linear regression model was developed to identify predictor variables, which are potentially associated with the yearly incidence of invasive ESCR-KP infections (patients per 1000 BD). The following predictor variables were included in the initial model: yearly consumption of third- and fourth-generation cephalosporins (DDD per 1000 BD), fluoroquinolones, trimethoprim/sulfamethoxazole or aminoglycosides; time (the year of isolate collection and antibiotic consumption, respectively); hospital type (university vs non-university hospital); and linguistic region (German-, French- and Italian-speaking regions). The dependent variable (patients per 1000 BD) was transformed logarithmically to meet the assumptions for linear regression. The likelihood ratio test (χ^2-statistics) was then used in a backwards elimination process ($P < 0.05$ to retain) to select the set of independent variables for the final model.

The German-speaking region was used as a reference in comparisons of the three-level factor linguistic region. To

analyse differences between the French- and Italian-speaking regions, the French-speaking region was additionally used as a reference.

Additional analyses

An additional analysis was performed by studying the association of invasive ESCR-KP incidence with antibiotic consumption of the year before to consider the time lag between antibiotic use and resistance development. In another exploratory analysis, the overall ESCR-KP incidence (all sample sites) was investigated separately in an analogous model.

Results

On a national level, an increase was observed in the incidence of infections with invasive ESCR-KP from 0.01 to 0.04 patients per 1000 BD between 2009 and 2019 (Figure 1, Supplementary Table A.I). Incidences with invasive ESCR-KP infections were higher in university hospitals than in non-university hospitals (range of the yearly median 0.01–0.05 vs 0.01–0.03 patients per 1000 BD) and in the French-speaking region than in the German-speaking region (range of the yearly median 0.01–0.05 vs 0.01–0.04 patients per 1000 BD). These observations were confirmed by multiple linear regression analysis (each $P < 0.01$, Table I). No significant differences were found between the German- and Italian-speaking regions. No association was observed between incidence of invasive ESCR-KP infections and antibiotic consumption of the same year, nor with the consumption of the year before (data not shown).

An increase in ESCR-KP was also observed if all samples were considered (Figure 1, Supplementary Table A.II). The distribution of sample types is shown in Supplementary Table A.III. In this additional analysis with isolates from all sample sites (Table II) the predictor variables were mostly consistent with those of the model with clinical isolates from sterile sites. However, incidence was higher in French-speaking university

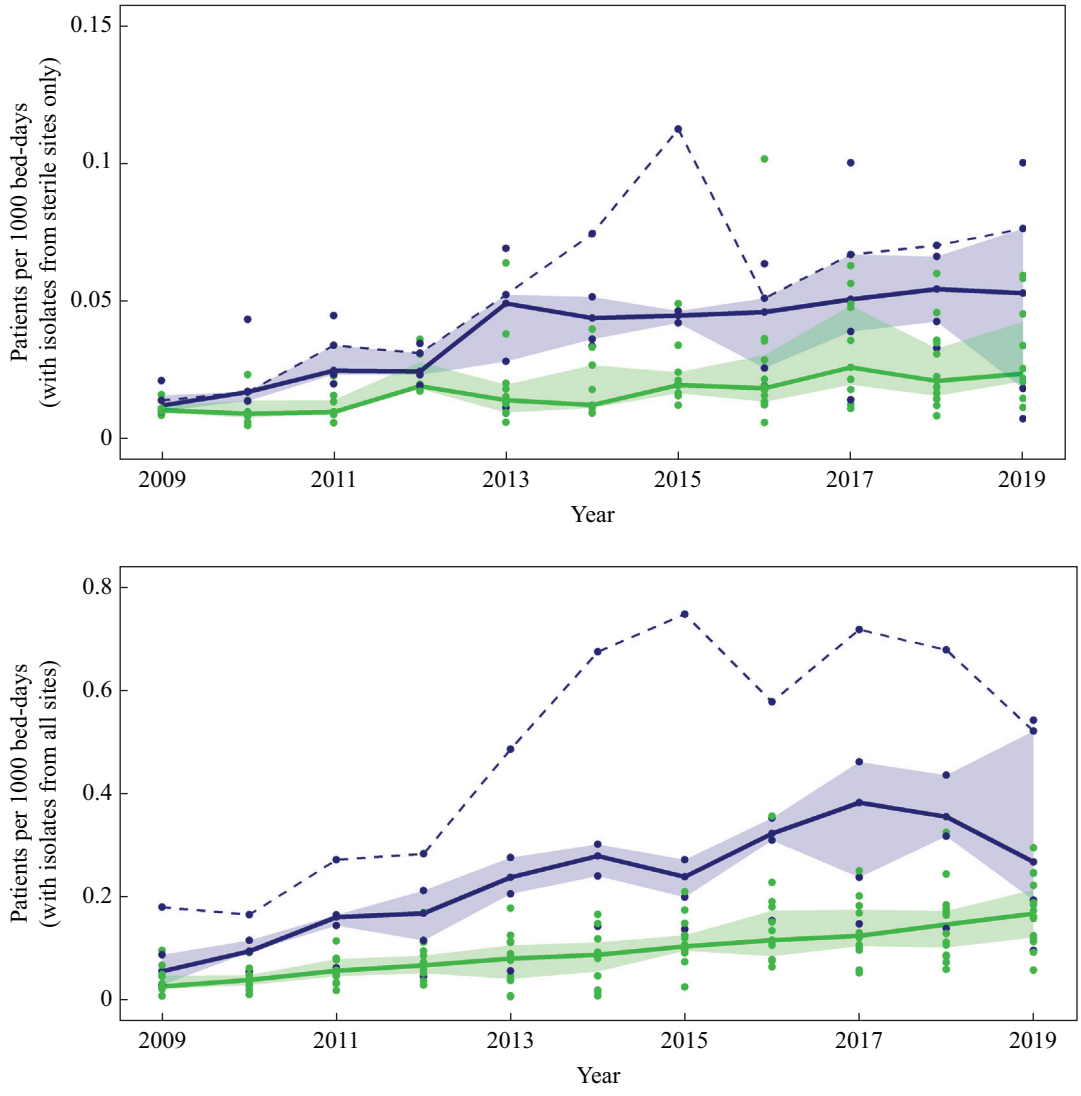

Figure 1. Incidence of invasive ESCR-KP infections (upper panel) and overall ESCR-KP incidence (all sample sites, lower panel) in 21 Swiss hospitals (points), including Geneva University Hospital (dashed line). The median (solid line) and interquartile range (shaded area) of university hospitals (blue) and non-university hospitals (green) are compared.

Table I
Predictor variables of a model describing the incidence of invasive ESCR-KP infections (logarithmus naturalis (log e or ln) (patients per 1000 BD)) in Switzerland from 2009 to 2019

Variable	Estimate[a]	95% CI	*P*-value
Year	0.1	(0.07, 0.12)	<0.001
University vs non-university hospital	0.54	(0.35, 0.72)	<0.001
French vs German	0.4	(0.21, 0.59)	<0.001
Italian vs German	−0.06	(−0.35, 0.24)	0.7
3rd- and 4th-generation cephalosporins	No association[b]		
Fluoroquinolones	No association[b]		
Trimethoprim/sulfamethoxazole	No association[b]		
Aminoglycosides	No association[b]		
R^2/adjusted R^2	0.41/0.40		
F-statistic	26.89		<0.001

ESCR-KP, extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae*; BD, bed-days; CI, confidence interval.
[a] A negative sign indicates a negative association.
[b] Variable does not improve the model (likelihood ratio χ^2-statistic, $P > 0.05$).

hospitals compared to university hospitals in the German-speaking region (see interaction of the variables 'University' and 'French' in Table II); thus, variability between university hospitals became larger (Figure 1, lower panel). The percentage of screening isolates was considerably higher in university compared to non-university hospitals (median 22% vs 9%). In this dataset, the overall incidence at Geneva University Hospital was clearly the highest (0.49 patients per 1000 BD). However, in 50% of all inpatients at Geneva University Hospital, ESCR-KP was detected in screening isolates only, and 15% were detected in clinical isolates from patients who were previously screened as positive (Figure 2).

Discussion

Our study showed that the incidence of invasive ESCR-KP infections in Switzerland increased fourfold between 2009 and 2019. These findings are consistent with increasing extended-cephalosporin resistance rates of invasive *K. pneumoniae* in Switzerland over the last 15 years and parallel the increasing resistance rates in other European countries [7,4–6]. According to literature the spread of ESCR-KP may be affected by tourism to endemic regions and migration, nosocomial transmission, household transmission of discharged patients, increasing population densities, and climate change [19–24].

The higher incidence of invasive ESCR-KP infections in university hospitals than in non-university hospitals may be caused by a higher risk for hospital-acquired infections in these environments along with more severe and complex cases accommodated [25,26].

In the French-speaking region, the incidence of invasive ESCR-KP infections was higher than that in the German-speaking region. This finding may be partially explained by a high cross-border traffic of individuals including patients and medical staff from these regions to neighbouring countries with higher ESCR-KP prevalence levels (i.e. France in 2019, 30.2%; Germany, 12.2%) [6]. By contrast, a similar effect was not observed for the Italian-speaking region. ESCR-KP incidence rates in this area were not significantly higher than those in the German-speaking region despite an ESCR-KP rate of 57.6% in Italy (2019). However, data from the Italian-speaking region of Switzerland were sparse, as the area is relatively small and has only two hospitals with more than 200 beds.

Table II
Predictor variables of a model describing overall ESCR-KP incidence (all sample sites) (logarithmus naturalis (log e or ln) (patients per 1000 BD)) in Switzerland from 2009 to 2019

Variable	Estimate[a]	95% CI	*P*-value
Year	0.16	(0.13, 0.18)	<0.001
University vs non-university hospital	0.70	(0.47, 0.92)	<0.001
French vs German	0.17	(−0.06, 0.4)	0.15
Italian vs German	−0.18	(−0.44, 0.09)	0.19
University and French interaction	0.46	(0.08, 0.85)	0.02
3rd- and 4th-generation cephalosporins	No association[b]		
Fluoroquinolones	No association[b]		
Trimethoprim/sulfamethoxazole	No association[b]		
Aminoglycosides	No association[b]		
R^2/adjusted R^2	0.58/0.57		
F-statistic	55.82		<0.001

ESCR-KP, extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae*; BD, bed-days; CI, confidence interval.
[a] A negative sign indicates a negative association.
[b] Variable does not improve the model (likelihood ratio χ^2-statistic, $P > 0.05$).

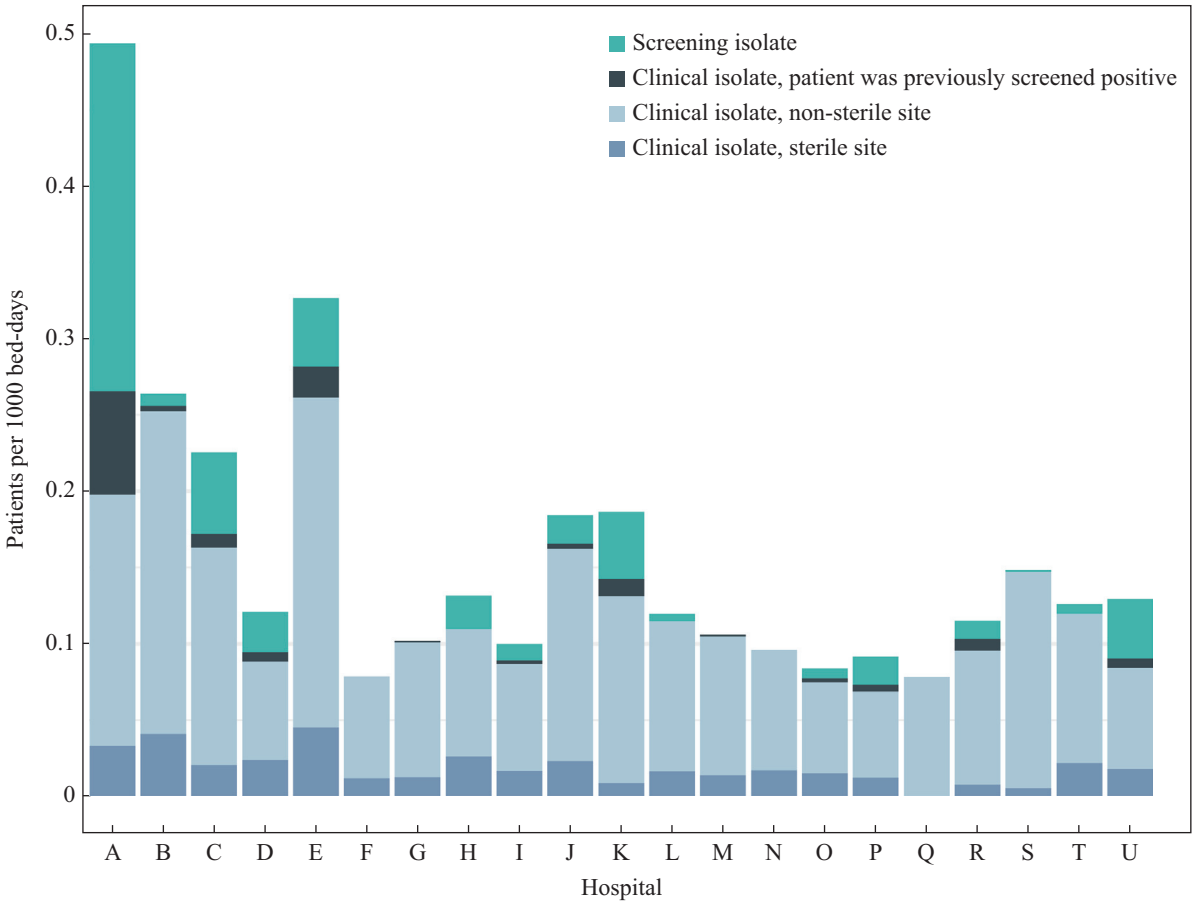

Figure 2. Comparison of sample sites of patients with ESCR-KP in university hospitals (A to E), including Geneva University Hospital (A), and non-university hospitals (F to U) from 2009–2019.

No association was found between the incidence of invasive ESCR-KP infections and the consumption of third- and fourth-generation cephalosporins, fluoroquinolones, aminoglycosides, or trimethoprim/sulfamethoxazole. On the one hand, these negative results are congruent with those of a local Swiss study, where no association between ESCR-KP and consumption of third- and fourth-generation cephalosporins was found [27]. On the other hand, they are in contrast to the findings of several other studies that identified antibiotic consumption as a risk factor for the occurrence of ESCR-KP [8,9,12,14,23,28,29]. Reasons for these discrepancies with other studies may be the comparatively low incidence and low total antibiotic use in Switzerland [27,30–33]. This presumption is supported by the result of the population-based mathematical modelling study of ESCR-KP of Kachalov *et al.*, showing that the import of resistant pathogens was a key factor in low-prevalence countries (defined as an ESCR-KP resistance rate <15%) compared to countries with medium prevalence where antibiotic consumption was the main driver of resistance [23]. Ecologic bias may be another explanation for these discrepancies, i.e. that data aggregation at the hospital level may not be sufficient to detect these correlations [34].

The approach of analysing overall ESCR-KP incidence, including isolates from all sample sites (which is frequently considered for infection control purposes), has led to additional important findings. Although the overall increase in ESCR-KP incidence was comparable, we noted highly variable incidence rates, especially among university hospitals. In our setting, this was mainly due to high total incidence rates observed in Geneva University Hospital, which is known for an extensive screening strategy, and therefore detecting unknown carriers more frequently. Screening activity at Geneva University Hospital was even substantially increased temporarily due to several clinical studies during the study period [35,36]. Indeed, Geneva University Hospital had the highest percentage of patients with screening isolates (50%) and of clinical isolates from patients previously screened as positive (15%). These differences disappeared when considering invasive isolates only. This finding indicates that different screening activities may bias overall ESCR-KP incidence even within a single country, which has to be considered if data are compared between hospitals. This interpretation is in line with the results of a previous study that described heterogeneity in screening recommendations among different Swiss hospitals for multiresistant bacteria [37]. It is important not to brand hospitals due to high resistance rates, which result from active screening policies, as early detection is important and may prevent nosocomial spread and thus additional costs. This is especially the case for microorganisms, where contact isolation is recommended, as is the case in Switzerland for patients with ESCR-KP [16].

This study has several limitations. (i) The data were aggregated at the hospital level and year. Inclusion of patient-specific data may essentially improve the models. With the

use of data from electronic prescriptions, which are currently implemented in several Swiss hospitals, such an analysis will be possible in the future. (ii) A separate analysis of nosocomial samples only was not possible due to incomplete labelling of these samples by the hospitals. Hence, it cannot be excluded that the data may also contain samples with community-acquired ESCR-KP. This circumstance might attenuate a potential association between inpatient antibiotic consumption and ESCR-KP incidence. (iii) Not all screening samples were correctly labelled. However, including typical screening sample sites in our algorithm probably reduced this bias. (iv) A further possible source of error was that not all laboratories sent the results of screening samples. Possible approaches to improve ESCR-KP surveillance include more rigorous labelling of screening samples, measuring the screening activity and nationwide implementation of screening guidelines.

The main strength of our study is the extensive data collection, covering 11 years and all university and tertiary hospitals in Switzerland. In addition, the analysis of Swiss data allowed stratification into different linguistic and socio-cultural regions due to the country's heterogeneity.

In conclusion, the incidence of invasive ESCR-KP infections increased in Switzerland between 2009 and 2019 and was not associated with antibiotic consumption. Our findings indicate that, in this low-incidence setting, structural factors such as the hospital type and the linguistic region play a more important role in relation to ESCR-KP incidence than the hospital's antibiotic consumption. However, further analyses using patient-specific data are needed to investigate this relationship.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.11.006.

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Supplementary Material Project 3

Supplementary Figure

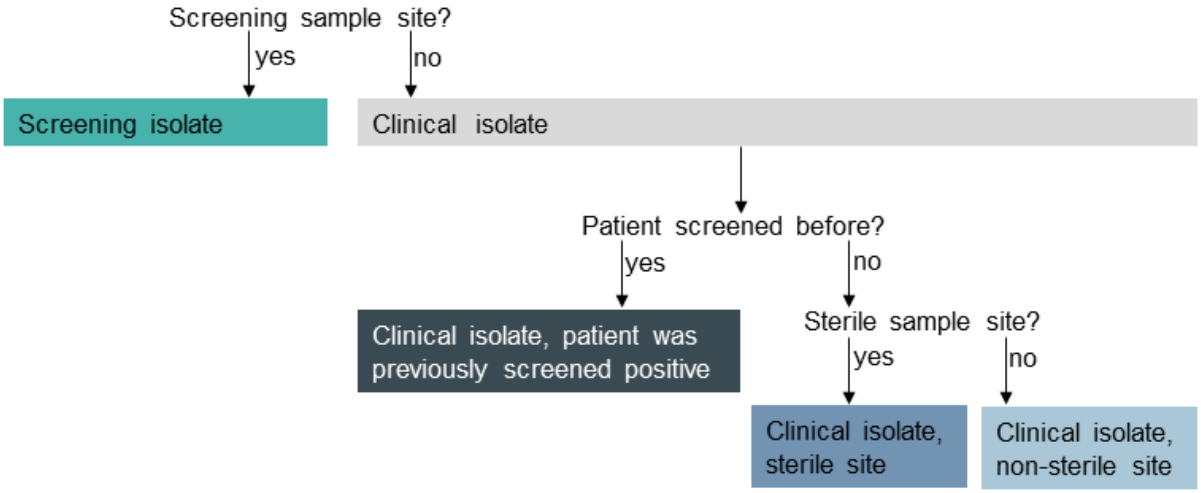

Figure A1: Flowchart describing the definition of the three categories of clinical isolates and the screening isolates.

Supplementary Tables

Table A I: Patients invasively infected with ESCR-KP per 1000 bed-days in 2009 and 2019 overall and stratified by hospital type and linguistic region.

	2009	2019	Increase [%]
Total	0.013	0.043	222
University hospital	0.014	0.053	279
Non-university hospital	0.012	0.03	142
German-speaking region	0.015	0.037	153
French-speaking region	0.012	0.057	371
Italian-speaking region	0.01	0.032	219

Table A II: All patients with ESCR-KP (including screening and clinical isolates) per 1000 bed-days in 2009 and 2019 overall and stratified by hospital type and linguistic region.

	2009	2019	Increase [%]
Total	0.061	0.256	323
University hospital	0.079	0.333	323
Non-university hospital	0.04	0.179	342
German-speaking region	0.049	0.222	357
French-speaking region	0.091	0.35	286
Italian-speaking region	0.03	0.181	499

Table A III: Sample characteristics

	Variable	Blood	Resp	Uro	GIT	Other	Total	%
Sample site	Screening	0	1	3	1213	147	1364	25
	Clinical, previously screened positive	67	70	171	10	73	391	7
	Clinical, sterile	453	16	95	57	196	817	15
	Clinical, non-sterile	0	488	1815	1	668	2972	54
Age group	0-15	28	48	111	215	188	590	11
	16-65	265	306	978	676	578	2803	51
	>65	227	221	994	388	315	2145	39
	Unknown	0	0	1	2	3	6	0
Sex	Female	162	144	1117	509	419	2351	42
	Male	358	431	965	772	664	3190	58
	Unknown	0	0	2	0	1	3	0

Resp, respiratory tract; Uro, urogenital tract; GIT, gastrointestinal tract;

3.2. Published Manuscripts, Other Projects

Echtzeit-Resistenzstatistik: Bekämpfung von Antibiotika-resistenzen in der Schweiz

Renggli Luzia[1], Gasser Michael[1], Frey Pascal M.* [2], Kronenberg Andreas[1]

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[2] Department of General Internal Medicine, Inselspital, Bern University of Bern, Bern, Switzerland

* For the core development team: Brugger S.D., Frey P.M., Steiner F., van der Weg L.M.

My contribution: I had the main responsibility in drafting the manuscript.

Echtzeit-Resistenzstatistik

Bekämpfung von Antibiotikaresistenzen in der Schweiz

Luzia Renggli[a], Michael Gasser[a], Pascal M. Frey[b,*], Andreas Kronenberg[a]

[a] Schweizerisches Zentrum für Antibiotikaresistenzen (ANRESIS)[1], Institut für Infektionskrankheiten, Universität Bern
[b] Departement für Allgemeine Innere Medizin, Inselspital, Universitätsspital Bern, Universität Bern
* Für das Core-Entwicklerteam: Brugger S.D., Frey P.M., Steiner F., van der Weg L.M.

Dank der neuen INFECT App mit Daten des Schweizerischen Zentrums für Antibiotikaresistenzen erhalten Ärztinnen und Ärzte einen Überblick über die aktuelle Resistenzsituation und werden bei der Therapieauswahl unterstützt.

Multiresistente Bakterien kennen keine Landesgrenzen und wurden im Bericht «Biologische Risiken Schweiz» der eidgenössischen Fachkommission für biologische Sicherheit und Umwelt vom November 2019 als grösstes biologisches Sicherheitsrisiko in der Schweiz bezeichnet. Durch einen angemessenen Umgang mit Antibiotika kann allerdings die weitere Verbreitung resistenter Bakterien verlangsamt werden. Die interaktive Applikation INFECT (INterface For Empirical antimicrobial ChemoTherapy), die vom Verein INFECT in Zusammenarbeit mit dem Schweizerischen Zentrum für Antibiotikaresistenzen (ANRESIS) und der Klinik für Allgemeine Innere Medizin des Inselspitals als Open-Source-Lösung entwickelt wurde, will mit seinen Echtzeit-Resistenzdaten einen Beitrag zur korrekten Antibiotikatherapie leisten.

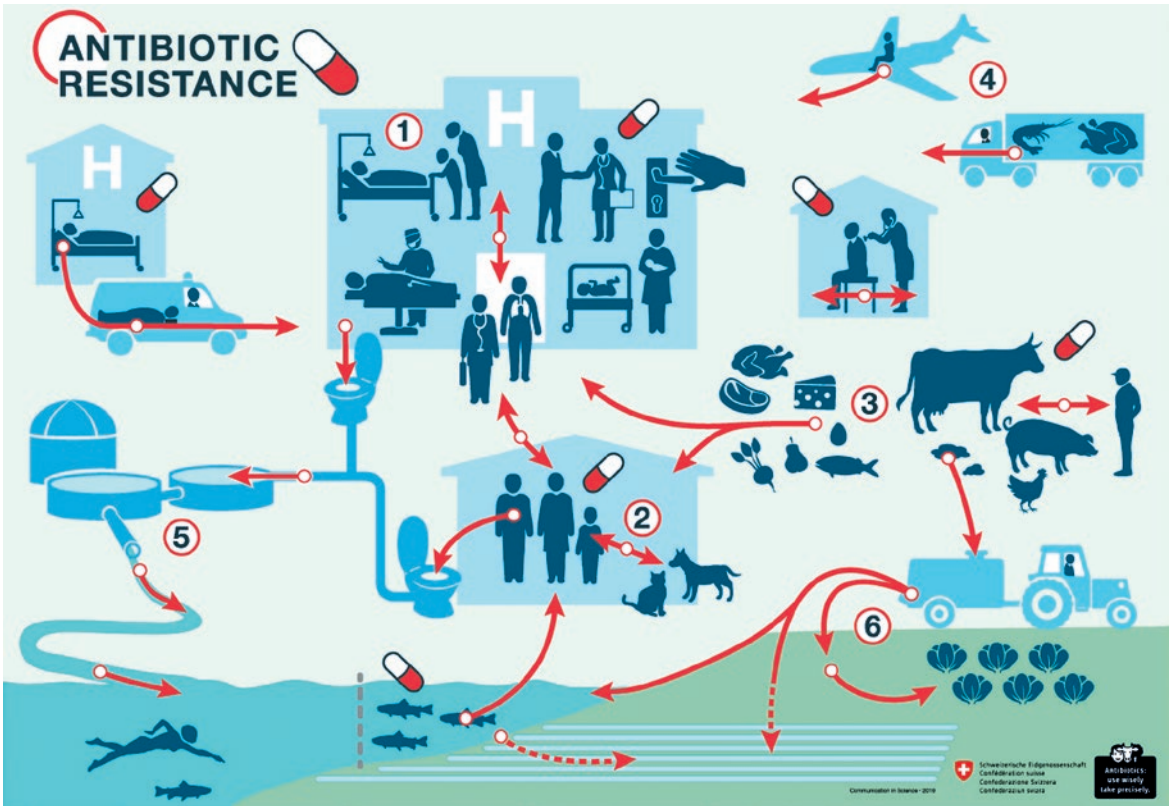

Abbildung 1: Ursachen und Übertragungswege von antibiotikaresistenten Bakterien [2].
1) Übertragung in Gesundheitseinrichtungen. 2) Übertragung von Menschen auf Tiere oder umgekehrt. 3) Kontamination von Lebensmitteln. 4) Verbreitung durch Tourismus und Lebensmittelimporte. 5) Übertragung in Gewässern. 6) Verbreitung durch das Ausbringen von Tierdünger (Gülle).
Nachdruck mit freundlicher Genehmigung von CiS (Communication in Science) und Schweizerische Eidgenossenschaft.

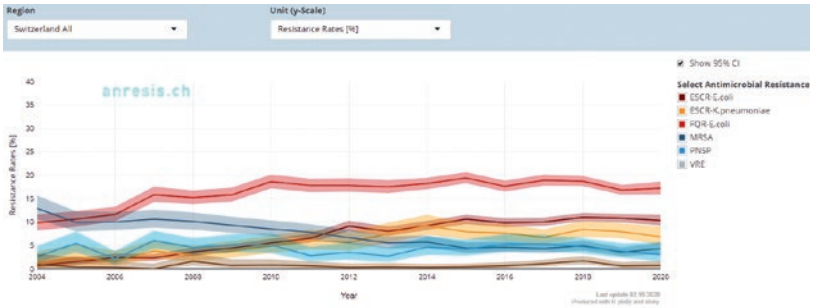

Abbildung 2: Resistenztrends multiresistenter Mikroorganismen in der Schweiz (www.anresis.ch). Dargestellt werden die [%] Anteile nicht empfindlicher Mikroorganismen (Linien) sowie die entsprechenden 95% Konfidenzintervalle (semitransparente Flächen) von Fluoroquinolonresistenten *Escherichia coli* (FQR-*E.coli*), Extended-spectrum Cephalosporin-resistenten *Escherichia coli* (ESCR-*E.coli*, Surrogat für ESBL-*E.coli*), Extended-spectrum Cephalosporin-resistenten *Klebsiella pneumoniae* (ESCR-KP, Surrogat für ESBL-KP), Penicillin-resistenten *Streptococcus pneumoniae* (PNSP) und Vancomycin-resistenten Enterokokken (VRE).

Antibiotikaresistenzen – ein globales Problem

In Europa sterben jährlich über 30 000 Menschen durch Infektionen mit antibiotikaresistenten Bakterien [1]. Besonders betroffen sind schwerkranke und immungeschwächte Personen, und Personen mit vorgängigen Antibiotikatherapien. Infektionen mit resistenten Erregern machen den Einsatz von Reserveantibiotika oder die Kombination mehrerer Antibiotika gleichzeitig notwendig. Die Behandlungskosten sind in solchen Fällen höher, nicht nur aufgrund der höheren Medikamentenkosten, sondern auch bedingt durch teure Isolationsmassnahmen und längere Hospitalisationsdauer. Kritisch wird es, wenn die Bakterien über Resistenzmechanismen gegen verschiedene Antibiotikaklassen verfügen, wobei man von multiresistenten Bakterien spricht. Ein Beispiel sind Extended Spectrum Betalactamase (ESBL) produzierende *Escherichia coli*: Invasive Infektionen mit diesen Erregern können oft nur durch Reserveantibiotika wie Carbapeneme behandelt werden. In Indien, Italien, Griechenland und Zypern werden, bedingt durch den vermehrten Einsatz von Carbapenemen als Reserveantibiotika, nun jedoch zunehmend Infektionen mit Carbapenem-resistenten Bakterien beobachtet, die kaum mehr behandelt werden können. Die resistenten Erreger kolonisieren oder infizieren Touristen und in besonderem Masse auch «Medizintouristen», die für günstigere Operationen in diese Länder reisen, und verbreiten sich somit über die ganze Welt.

One Health in der Strategie Antibiotikaresistenz Schweiz (StAR)

Neben der globalen Mobilität («One World»), spielen viele weitere Mechanismen in der Verbreitung der Antibiotikaresistenzen eine wichtige Rolle (Abb. 1). Deshalb haben sich 2015 das Bundesamt für Gesundheit (BAG) sowie weitere Bundesämter aus den Bereichen Lebensmittelsicherheit Landwirtschaft und Umwelt in der Strategie Antibiotikaresistenz Schweiz (StAR) zusammengeschlossen, um gemeinsam in einem «One Health»-Ansatz dieses wichtige Problem anzugehen. StAR definiert Handlungsfelder von der Überwachung über die Prävention bis hin zum sachgemässen Einsatz von Antibiotika, der Resistenzbekämpfung, Forschung und Entwicklung, Kooperation sowie der Information und Bildung. Dazu gehört das propagieren von Impfungen zur Verhütung von viralen und bakteriellen Infektionen, das Erarbeiten von Guidelines bezüglich Abgabe, Verschreibung und Anwendung von Antibiotika, das Unterstützen von Betrieben mit andauernd hohem Antibiotikaverbrauch zur Senkung dessen, Massnahmen zur Reduktion der Verbreitung in Lebensmittelketten und im Abwasser, das Optimieren von Betriebsabläufen in Tierhaltung sowie die Kooperation mit anderen Ländern und das Unterstützen von Entwicklungsländern im Bereich Antibiotikaresistenz. Die einzelnen Massnahmen sind im StAR-Strategiedokument zu finden (star.admin.ch).

Auch in der Schweiz nehmen gewisse Antibiotikaresistenzen kontinuierlich zu, während bei gewissen Resistenzen aber auch ein gegenläufiger Trend beobachtet wird. Insgesamt rechnen wir in der Schweiz mit jährlich knapp 300 durch Antibiotikaresistenzen bedingten Todesfällen pro Jahr [3].

Für zahlenmässig am meisten dieser tödlichen Infektionen sind ESBL-produzierenden *Escherichia coli* verantwortlich, auch, da *E. coli* zu den häufigsten Infektionserregern gehören, sowohl im ambulanten, als auch im stationären Bereich (häufig wird die Resistenz gegenüber Cephalosporinen der dritten Generation, z.B. Ceftriaxon, als Surrogat für ESBL-Produktion verwendet, auch wenn in 5–10% dieser Isolate andere Resistenzmechanismen wie z.B. AmpC vorliegen können). Diese Resistenz hat sich in den letzten zehn Jahren in etwa verzehnfacht (von 1% auf 10%), daneben ist bei *E. coli* aber auch die kontinuierliche Zunahme der Fluoroquinolon-Resistenz beunruhigend (Abb. 2), weshalb Fluroquinolone dementsprechend zurückhaltend und zum Beispiel für die unkomplizierte Zystitis nicht mehr eingesetzt werden sollten [4]. Während in der Schweiz Resistenzen bei gramnegativen Bakterien wie *E. coli* stark zunehmen, kann über einen Rückgang von Infektionen

Antibiotic Stewardship

Unter Antibiotic Stewardship wird das Optimieren der Verwendung und Verschreibung von Antibiotika verstanden, mit dem Ziel, die Entwicklung resistenter Bakterien zu vermindern [9]. Hauptelemente von Antibiotic Stewardship-Programmen sind:

- Analyse von Antibiotikaresistenztrends
- Implementieren von lokalen und nationalen Guidelines
- Prospektives Audit und Rückmeldungen
  - Einschränkung in der Verordnung für Reserveantibiotika (z.B. nur nach Rücksprache mit Kaderarzt oder Infektiologe)
- Optimierung der Therapie
  - Dauer nur so lange wie nötig
  - Wechsel von intravenöser auf orale Applikation sobald als möglich
  - Automatische Warnung, wenn sich das antibiotische Spektrum von mehreren Antibiotika überlappt
  - Automatischer Therapiestopp nach 48-72 Stunden zur Reevaluation der Therapie anhand des mikrobiologischen Befundes
- Organisation in einem multidisziplinären Team aus den Bereichen Infektiologie, Mikrobiologie, Pharmazie und Pflege

mit Methicillin-resistenten *Staphylococcus aureus* (MRSA) berichtet werden (Abb. 2). Diese Abnahme ist vor allem auf einen Rückgang der «Spital-MRSA» (hospital-aquired MRSA, HA-MRSA) zurückzuführen, wobei hier den erzielten Fortschritten in der Infektprävention, wie frühzeitiger Detektion und Isolation infizierter oder kolonialisierter Patienten sowie verbesserter Händehygiene, eine wichtige Rolle zukommt [5, 6].

Erste Erfolge der Aufklärung und Präventionsmassnahmen zeigen sich im abnehmenden Einsatz von Antibiotika im Veterinärwesen. Von 2014 bis 2017 konnte der Einsatz um 29% gesenkt werden, damit liegt die Schweiz in diesem Bereich im unteren europäischen Mittelfeld [7].

Detaillierte Analysen der wichtigsten Resistenztrends finden Sie in einem *Swiss Medical Forum*-Artikel [8] und im *Swiss Antibiotic Resistance Report* (anresis.ch/publication-category/anresis-publications).

Überwachung der Resistenzsituation in der Schweiz

Zur Überwachung der Resistenzsituation in der Schweiz wurde bereits in den Jahren 2000–2004 im Rahmen des nationalen Forschungsprojekts NRP49 eine repräsentative, schweizweite Datenbank zur Erfassung der Antibiotikaresistenzen und des Antibiotikakonsums aufgebaut. Diese Datenbank ist seither das zentrale Element des Schweizerischen Zentrums für Antibiotikaresistenzen (ANRESIS) und damit auch ein zentrales Element von StAR und wird im Auftrag des BAG vom Institut für Infektionskrankheiten der Universität Bern weitergeführt.

ANRESIS sammelt und analysiert anonymisierte Resistenzdaten von 30 Mikrobiologielabors im Human- und neun Labors im Veterinärbereich. In der Humanmedizin liegt die Abdeckung im stationären Bereich bei knapp 90%; im ambulanten Bereich bei etwa 40%. Die aktualisierten Daten können jederzeit auf anresis.ch mittels interaktiver Datenbankabfrage abgerufen werden. Auf der Website sind zudem interaktive Grafiken der wichtigsten, Resistenzentwicklungen (Abb. 2) sowie alle ANRESIS Publikationen abrufbar.

Neben Resistenzdaten sammelt ANRESIS aggregierte Antibiotikaverbrauchsdaten von 70 Spitälern und über 1000 Apotheken. Die analysierten Daten werden in

Abbildung 3: Die App INFECT by anresis existiert als Web-Applikation (www.infect.info) und als mobile App (Download via Google Play Store und Apple App Store). Sie zeigt die aktuellen Resistenzdaten (Punkte) und enthält nationale Guidelines (blaues Panel rechts) der Schweizerischen Gesellschaft für Infektiologie (SSI). Konfidenzintervall und Probeanzahl werden beim Anwählen der Punkte angezeigt (links unten).

SSI Guidelines

Die Schweizerische Gesellschaft für Infektiologie (SSI) entwickelt und aktualisiert infektiologische Guidelines durch Evaluation internationaler Guidelines und deren Anpassung an die nationale Resistenzsituation und anderen spezifischen Bedingungen in der Schweiz. Jede Guideline wird durch ein individuelles Autorenteam geschrieben und revidiert und nach Möglichkeit mit den entsprechenden weiteren Fachgesellschaften abgestimmt. Bemerkungen zu SSI Guidelines, Vorschläge für zukünftige Guidelines oder auch die Mitarbeit an spezifischen Guidelines sind erwünscht und können der SSI direkt mitgeteilt werden.

Form von Feedback- und Benchmarkreports an die Spitäler zurückgegeben. Sie ermöglichen das Erkennen von überproportionalem Antibiotikaverbrauch und helfen, Ziele für die lokalen *Antibiotic Stewardship*-Programme (s. Kasten) zu definieren.

INFECT zeigt die wichtigsten Resistenzdaten auf einen Blick

Mit den Zielen, Resistenzdaten übersichtlich und interaktiv darzustellen und damit insbesondere klinisch tätige Ärztinnen und Ärzte bei der Wahl einer optimalen antibiotischen Therapie zu unterstützen, wurde die Applikation INFECT entwickelt. Die App ist sowohl als Web-Version (infect.info) wie auch als mobile App («INFECT by anresis» im Google Play Store und Apple App Store) kostenlos verfügbar.

In einer Kreuztabelle sind für die häufigsten Bakterienspezies deren Empfindlichkeit gegenüber dem entsprechenden Antibiotikum angegeben (Abb 3). Farbverläufe von grün (100% Empfindlichkeit) nach hellrot (0% Empfindlichkeit) und Grösse der Punkte in Abhängigkeit der Anzahl Proben vereinfachen die Interpretation der Resistenzlage. Dank den Möglichkeiten nach Region, ambulant oder stationär entnommenen Proben sowie Altersklassen zu filtern, kann die Darstellung an spezifische Fragestellungen angepasst werden. Die Applikation erlaubt zudem, nach einzelnen Bakterienspezies, nach der Gram-Färbung, Form und Metabolismus der Bakterien, Antibiotikaklassen sowie nach einzelnen Wirkstoffen zu filtern. Die zugrundeliegenden Daten stammen von ANRESIS und werden monatlich aktualisiert.

Da gute Sensibilitätsdaten für eine Substanz nicht unbedingt eine gute Wahl in der klinischen Medizin implizieren, wurden zur besseren Anwendbarkeit – zum Beispiel auch in der Grundversorgung – und zur Optimierung der empirischen Therapien die nationalen Guidelines der Schweizerische Gesellschaft für Infektiologie (SSI) in die Applikation integriert (Abb. 3). Sie beschreiben Erst- und Zweitwahlantibiotika, sowie deren übliche Dosierungen und Anwendungsdauer bei Kindern und Erwachsenen. Beim Anwählen einer Guideline werden die relevanten Bakterien und die zur Therapie vorgeschlagenen Antibiotika hellblau markiert. SSI-Guidelines sind für die häufigsten bakteriellen Infektionskrankheiten verfügbar und werden kontinuierlich erweitert (ssi.guidelines.ch); neue SSI-Guidelines werden laufend in INFECT integriert (s. Kasten).

Dank dem modularen Aufbau der Applikation kann diese nach Bedarf angepasst und erweitert werden. Seit kurzem steht zudem auch «INFECT VET by anresis», eine Version mit veterinärmedizinischen Daten zur Verfügung (vet.infect.info).

Die Applikation INFECT fördert somit einen optimierten Einsatz von Antibiotika und kann damit einen wichtigen Beitrag zur Verminderung von Antibiotikaresistenzen und zur Verbesserung der Patientensicherheit in der Schweiz leisten. Rückmeldungen zu INFECT sind jederzeit willkommen (E-Mail an info[at]infect.info) und leisten einen wertvollen Beitrag zur Weiterentwicklung der Applikation.

Korrespondenz:
Luzia Renggli
PhD Studentin, Pharmazie
Friedbühlstrasse 51
CH-3010 Bern
luzia.renggli[at]ifik.unibe.ch

Fazit für die Praxis

- Antibiotikaresistenzen nehmen weltweit zu und führen zu erhöhter Morbidität, Mortalität und Kosten.
- Sachgemässer Einsatz von Antibiotika hilft die Entwicklung von Antibiotikaresistenzen zu vermindern.
- Das Schweizerische Zentrum für Antibiotikaresistenzen (ANRESIS) sammelt und analysiert Daten zur Resistenzsituation und zum Antibiotikaverbrauch in der Schweiz und stellt diese interessierten Personen in aggregierter Form zur Verfügung.
- Benchmarking- und Feedbackreports von ANRESIS sind ein wichtiges Element von Antibiotic Stewardship-Programmen.
- Die INFECT-Applikation stellt Resistenzdaten interaktiv dar und unterstützt mittels implementierter Guidelines Ärztinnen und Ärzte bei der optimalen Wahl der antibiotischen Therapie.

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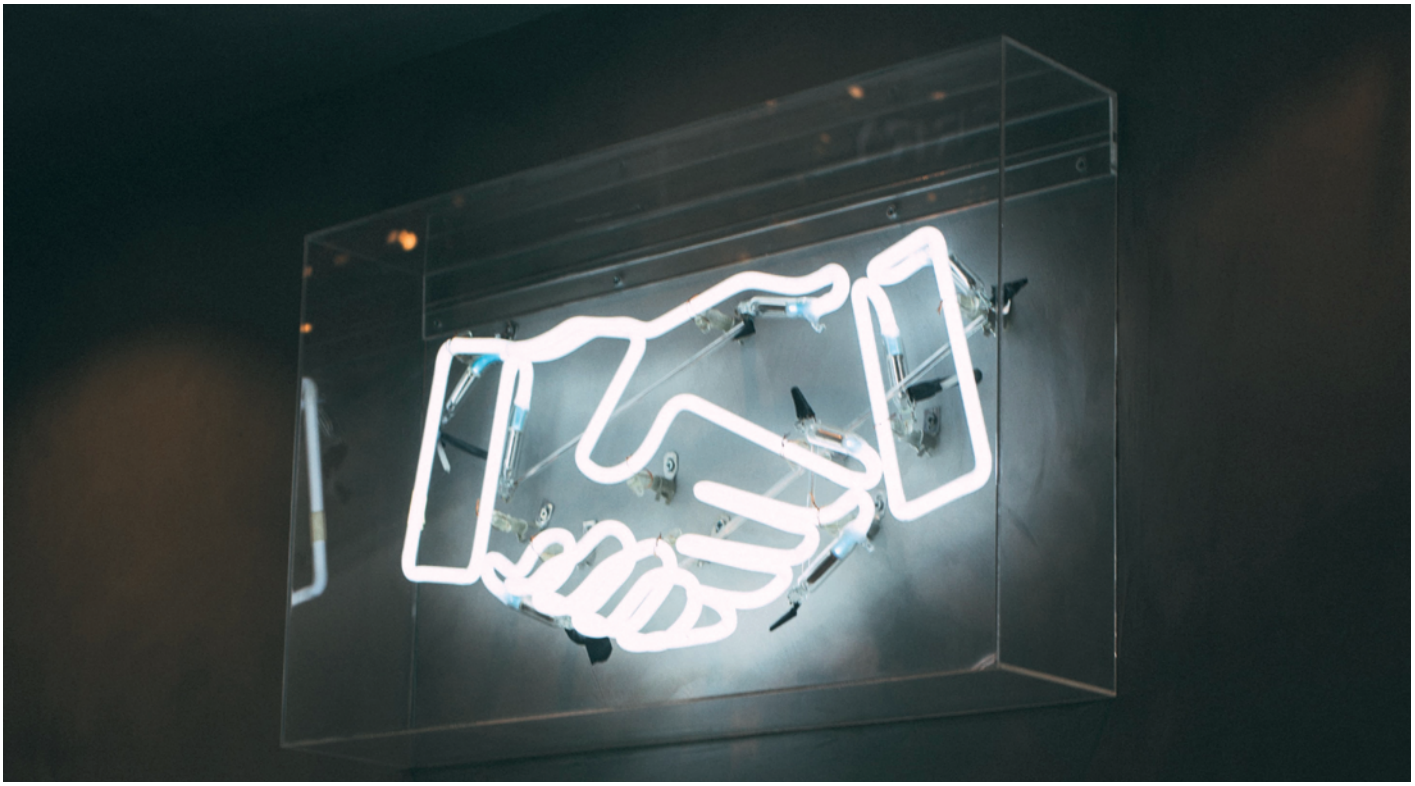
Hygieneregeln nach COVID-19 Handschlag – ja oder nein?

Andreas Kronenberg[1,2], Luzia Renggli[2] and quality circle Bern mediX Bern

[1] Praxis Bubenberg, Bern, Switzerland

[2] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

My contribution: I performed the statistical analysis, created the figures and revised the manuscript.



Schütteln wir wieder Hände? Nach Aufhebung der Massnahmen zur Bekämpfung von COVID-19 muss der Umgang mit den Patientinnen und Patienten neu ausgehandelt werden (charlesdeluvio / Unsplash).

Hygieneregeln nach COVID-19

Handschlag – ja oder nein?

Andreas Kronenberg[a], Luzia Renggli[b] und Qualitätszirkel Bern1 mediX Bern

[a] Prof. Dr. med., Praxis Bubenberg, Bern und Institut für Infektionskrankheiten, Universität Bern; [b] M. Sc., Institut für Infektionskrankheiten, Universität Bern

Wie gestaltet sich der Umgang im täglichen Miteinander nach Aufhebung der Corona-Massnahmen? Das wollten Hausärztinnen und -ärzte aus dem Kanton Bern mit einer Umfrage herausfinden. Sie haben in ihren Praxen nachgefragt, wie gross die Bereitschaft zum Verzicht auf die Begrüssung per Handschlag und zum Tragen einer Maske ist.

Die Begrüssung per Handschlag geht bis in die Antike zurück und ist in vielen europäischen Ländern die traditionelle Begrüssungsformel. Man vermutet, dass sie initial eine Geste des Friedens darstellte. Man zeigte dem Gegenüber, dass man keine Waffe trägt: Durch das Schütteln wurde sicherstellt, dass das Gegenüber nichts im Ärmel versteckt [1].

Auch in Schweizer Arztpraxen ist die Begrüssung per Handschlag sicherlich weit verbreitet, obwohl sich einzelne Ärztinnen und Ärzte, wie zum Beispiel augenärztliche Fachpersonen, bereits vor der COVID-Pandemie davon distanzierten. Genauere Angaben dazu

Mitglieder Qualitätszirkel mediX Bern

Dr. med. Andreas Gerber, Praxis Egghölzli; Dr. med. Christine Gerber Rihs, Praxis Bubenberg 11; Dr. med. Stefan Henzi, Ärztezentrum Fellergut; Dr. med. Daniel Horat, Gemeinschaftspraxis Brunnmatt; Dr. med. Marianne Kämpf, Gemeinschaftspraxis Könizsstrasse, Liebefeld; Prof. Dr. med. Andreas Kronenberg, Praxis Bubenberg 11; Dr. med. Gianni Melideo, Ärztezentrum Fellergut; Dr. med. Madeleine Mosimann, Ärztezentrum Fellergut; Dr. med. Véronique Rigamonti, Gemeinschaftspraxis Morillon; Dr. med. Alexandra Röllin, Gemeinschaftspraxis Brunnmatt; Dr. med. Thomas Staub, Praxis Schlossgraben; Dr. med. Marianne Wendel-Beck, Praxis Bubenberg 11; Dr. med. Urs Wiprächtiger, Praxis Egghölzli.

Tabelle: Merkmale der Studienpopulation

Variable		Kategorie[1]		
		Arzt/Ärztin (n = 11)	MPA (n = 50)	Patient/in (n = 706)
Alter	<20	–	16%, N = 8	2%, N = 12
	20–34	–	50%, N = 25	15%, N = 105
	35–49	9%, N = 1	8%, N = 4	16%, N = 115
	50–65	91%, N = 10	26%, N = 13	25%, N = 178
	65–75	–	–	19%, N = 134
	>75	–	–	23%, N = 159
	Keine Angabe	–	–	0%, N = 3
Geschlecht	Männlich	45%, N = 5	–	39%, N = 272
	Weiblich	55%, N = 6	100%, N = 50	61%, N = 429
	Andere	–	–	0%, N = 2
	Keine Angabe	–	–	0%, N = 3
Gesundheit	Leide an immunsupprimierender Erkrankung	–	4%, N = 2	10%, N = 68
	Nehme immunsupprimierende Medikamente	–	2%, N = 1	6%, N = 39
	Immunsystem schwächer (subjektiv)	–	–	12%, N = 86
	Gutes Immunsystem	100%, N = 11	94%, N = 47	69%, N = 487
	Keine Angabe	–	–	4%, N = 26
Impfstatus	Mindestens 1x geimpft	–	10%, N = 5	4%, N = 29
	Vollständig geimpft	45%, N = 5	46%, N = 23	63%, N = 446
	Genesen	–	4%, N = 2	7%, N = 48
	Genesen und vollständig geimpft	55%, N = 6	38%, N = 19	22%, N = 157
	Nicht geimpft und nicht genesen	–	2%, N = 1	2%, N = 17
	Keine Angabe	–	–	1%, N = 9
Ausbildung	Berufslehre	–	78%, N = 39	35%, N = 249
	Fachmittelschule/Gymnasium	–	12%, N = 6	17%, N = 119
	Grundschule	–	2%, N = 1	9%, N = 61
	Höhere Fachschule/Uni	100%, N = 11	8%, N = 4	36%, N = 251
	Keine Angabe	–	–	4%, N = 26

[1] In zehn Fragebogen fehlte die Angabe zu Kategorie und zu den *Denominator*-Daten (hier nicht aufgeführt).

lassen sich nicht finden. In der Hausarztpraxis dient der Handschlag auch der ersten körperlichen Kontaktaufnahme und hat einen gewissen diagnostischen Wert, werden doch Kräftigkeit, Feuchtigkeit und Hauttemperatur intuitiv erfasst.

Pandemie veränderte Gepflogenheiten

Mit dem Ausbruch der COVID-19-Pandemie [2] wurde vieles anders. Zwei Tage nach der Meldung des ersten Falles in der Schweiz am 25. Februar 2020 [3] wurde mit der Lancierung der schweizweiten Informationskampagne «So schützen wir uns» des Bundesamts für Gesundheit von der Begrüssung per Handschlag abgeraten. Diese Empfehlung wurde beibehalten bis zur Aufhebung aller Massnahmen ab 1. April 2022, wobei im Kanton Bern empfohlen wurde, in Praxen weiterhin eine Gesichtsmaske zu tragen. Völlige Unklarheit bestand im Mai 2022 bezüglich der vorgesehenen Dauer der Massnahmenaufhebung, der Haltung bezüglich Begrüssung per Handschlag und der Ansichten der Patientinnen und Patienten zu diesem Thema. Mittels einer Umfrage wollten wir deshalb die aktuellen Meinungen und Haltungen gegenüber Maskentragpflicht und Begrüssung per Handschlag in der Phase der allgemeinen Lockerungen erfragen.

In der Hausarztpraxis hat der Handschlag auch einen diagnostischen Nutzen.

Umfrage in der eigenen Praxis

Im Rahmen des MediX Qualitätszirkels (QZ) führten die Mitglieder im April 2022 eine Umfrage unter den Ärztinnen und Ärzten, den medizinischen Praxisassistentinnen (MPA) und den Patientinnen und Patienten in den Praxen zu diesen Themen durch. Alle QZ-Teilnehmenden hatten Anfang April 2022 konsekutiv den nächsten 50 Patienten und Patientinnen einen Fragebogen zu deren Einstellung bezüglich Maskentragpflicht (Mehrfachantworten möglich)

und Begrüssung in der Hausarztpraxis (Einfach-Antwort) abgegeben.

Die Teilnahme war freiwillig und anonym, erfasst wurden zusätzlich einige demografische Daten (Tabelle 1). Nach einer deskriptiven Analyse führten wir eine logistische Regression zur Identifizierung von erklärenden Variablen zu den *Outcomes* «Handschlag» und «Maskentragpflicht» durch. Variablen, welche das Modell nicht signifikant verbessert haben (Likelihood Test, Signifikanzniveau $P < 0.05$) wurden für das finale Modell schrittweise rückwärts eliminiert. Die Auswertung erfolgte mit R vers. 4.1.2.

Insgesamt nahmen 16 Ärztinnen und Ärzte aus 9 Praxen an der Umfrage teil. Es wurden 777 Personen befragt (11 ärztliche Fachpersonen, 50 MPA, 706 Patientinnen und Patienten, 10 ohne Angabe der Kategorie). Da die Umfrage freiwillig war, sind die Resultate indikativ, aber nicht zwingend repräsentativ (*selection bias*). Die Gruppen unterschieden sich bezüglich Alter, Geschlecht und Ausbildung (Tabelle 1).

64% der Ärzteschaft und MPA würden in Zukunft auf den Handschlag verzichten.

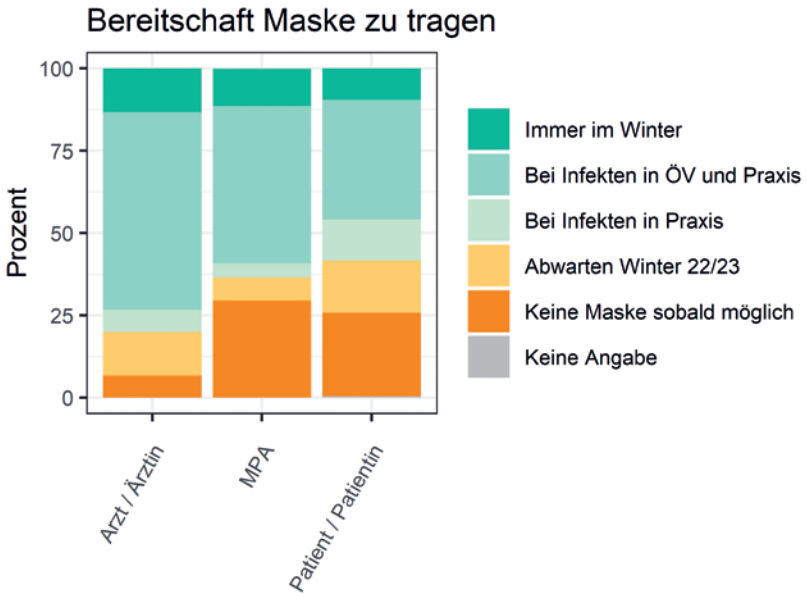


Abbildung 1: Wie steht es um die Bereitschaft, Maske zu tragen (Angaben in Prozent).

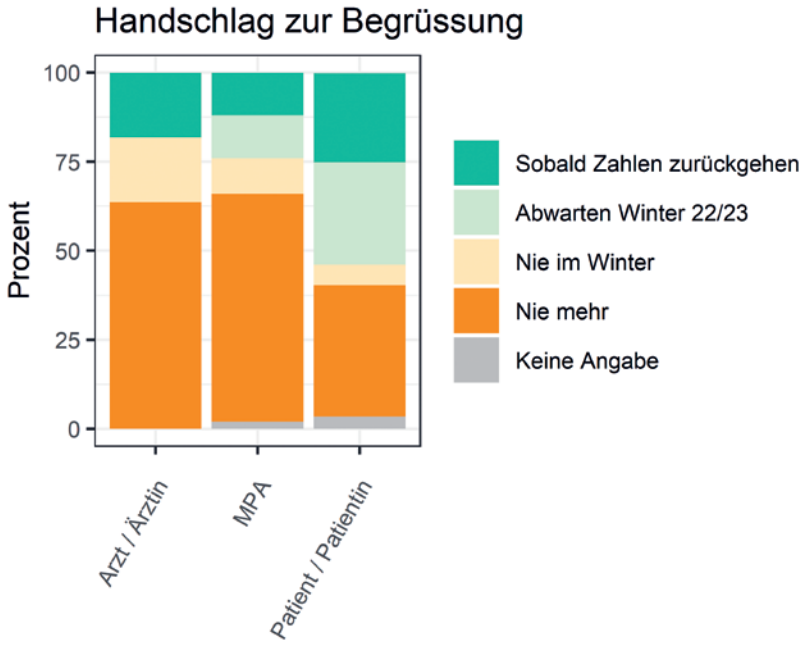


Abbildung 2: Wie steht es um den Handschlag? (Angaben in Prozent).

Grosse Bereitschaft zum Maskentragen

In der Bereitschaft, auch in Zukunft eine Maske zu tragen, waren sich die Gruppen der MPA und der Patientinnen und Patienten ähnlich (Abbildung 1). In allen Gruppen war die Mehrheit der Personen bereit, die Maske zumindest situativ (in Wintermonaten oder während eines Infekts des oberen Atemwegs) weiterhin zu tragen (ärztliche Fachpersonen 100 %, MPA 80 %, Patientinnen und Patienten 80 %). Sobald möglich keine Maske mehr zu tragen, war nur für 9 % der Ärztinnen und Ärzte, jedoch für 42 % der MPA und 32 % der Patientinnen und Patienten zumindest eine valable Option. Der Grossteil der Personen, die bereit wären, bei Infekten der Atemwege eine Maske in der Praxis zu tragen, würde dies auch im öffentlichen Verkehr so handhaben.

Zurückhaltung beim Handschlag

Bezüglich der Wiedereinführung der Begrüssung per Handschlag in der Praxis waren sich ärztliche Fachpersonen und MPA ähnlicher und deutlich zurückhaltender als Patientinnen und Patienten (Abbildung 2). 64 % der Ärztinnen und Ärzte und MPA würden in Zukunft auf eine Begrüssung per Handschlag verzichten und immerhin 37 % der Patientinnen und Patienten würden ebenfalls generell davon absehen. Deutlich mehr Patientinnen und Patienten (29 %) scheinen in dieser Frage aber noch verunsichert und würden vorerst die nächste Wintersaison abwarten, während keine der ärztlichen Fachpersonen diese Option wählte.

In der logistischen Regression korrelierte die Bereitschaft, die Begrüssung mit Handschlag wieder aufzunehmen, mit dem Anliegen, die Maske nicht mehr zu tragen ($P < 0.01$). Alle anderen untersuchten Variablen zeigten keine signifikante Assoziation, weder mit dem Wunsch eines Handschlags zur Begrüssung noch mit der Bereitschaft, eine Maske zu tragen.

Maske nicht nur bei COVID-19 effektiv

Die Umfrage zeigt, dass die Bereitschaft, unter bestimmten Bedingungen weiterhin eine Gesichtsmaske zu tragen, auch bei Patientinnen und Patienten im April 2022 mit 58,5 % Ja-Anteil bei den Antworten hoch war. Die Mehrheit dieser Personen wäre weiterhin bereit, bei Symptomen einer Atemwegsinfektion auch im öffentlichen Verkehr freiwillig eine Maske zu tragen. Die Propagation des freiwilligen Maskentragens bei Atemwegsinfekten könnte somit auch in Zukunft durchaus auf eine wesentliche Resonanz stossen. Dies hätte nicht nur Auswirkungen auf die COVID-Infektionsrate, führten die Massnahmen während der COVID-Pandemie doch auch zu einem signifikanten Rückgang anderer Atemwegsinfektionen [4] und der Antibiotikaverschreibungen im ambulanten Setting. (In der Schweiz konnte zwischen 2019 und 2021 ein Rückgang der Antibiotikaverschreibungen im ambulanten Bereich von 9 auf 7,4 (–18 %) *defined daily doses* (DDD) pro 1000 Einwohner beobachtet werden [5]). Allerdings ist noch nicht geklärt, wie viel die Maskentragpflicht zu diesem Effekt beiträgt.

Die neue «alte» Normalität

Während die Empfehlungen zum Maskentragen bisher stets recht klar von der öffentlichen Hand bestimmt wurden, fehlen klare Leitlinien bezüglich Begrüssung per Handschlag nach Aufhebung aller Massnahmen vollständig. Obwohl eine Übertragung von COVID-19 per Hand oder über Oberflächen möglich ist, bleibt die Übertragung per Tröpfchen sicherlich der Hauptübertragungsweg. Reinigung und Desinfektion schützen gut vor Übertragung durch direkten Kontakt mit Oberflächen [6]. Zudem ist die gründliche Händedesinfektion vor und nach dem Patientenkontakt auch ausserhalb der COVID-Pandemie medizinischer Standard [7].

Die Begrüssung mit Handschlag hat vor allem in der Schweiz eine hohe Tradition und wird von vielen Ärztinnen und Ärzten als erste (auch körperliche) Kontaktaufnahme geschätzt und teilweise auch diagnostisch genutzt. Trotzdem war in unserer Umfrage die Mehrheit von ihnen bereit, in Zukunft generell auf dieses Begrüssungsritual zu verzichten. Dies wohl auch, weil sich zwischenzeitlich andere Begrüssungsformen wie Nicken oder leichte Berührung an der Schulter beim Geleiten ins Sprechzimmer etabliert haben.

Die Autorinnen und Autoren sind der Meinung, dass allen Patientinnen und Patienten mit oberen Atemwegsinfektionen das Tragen einer Atemschutzmaske in den Praxisräumlichkeiten weiterhin nahegelegt werden sollte. Zudem sollte ihnen empfohlen werden, die Maske auch im öffentlichen Verkehr zu tragen. Dies sollte selbstverständlich auch für das Praxispersonal gelten. Im Sprechzimmer sollten individuelle Entscheidungen möglich sein, zum Beispiel wenn aus nachvollziehbaren Gründen bei älteren Personen auf die Maske verzichtet wird oder wenn bei nahem Kontakt zu immunsupprimierten Personen trotz fehlender Infektzeichen eine Maske getragen wird. Eine Berührung im individuellen Gespräch erscheint situativ nach wir vor von grosser Wichtigkeit und – bei entsprechender Händedesinfektion – auch unbedenklich.

Literatur
Vollständige Literaturliste unter www.saez.ch oder via QR-Code

redaktion.saez[at]emh.ch

Das Wichtigste in Kürze

- Die Mitglieder des MediX Qualitätszirkels Bern haben ärztlichen Fachpersonen, medizinischen Praxisassistentinnen (MPA) sowie Patientinnen und Patienten zu deren Haltung gegenüber Handschlag in der Arztpraxis und Tragen von Masken befragt.
- In allen Gruppen war die Mehrheit bereit, die Maske zumindest situativ trotz Aufhebung der Corona-Massnahmen weiterhin zu tragen. Beim Handschlag waren ärztliche Fachpersonen und MPA zurückhaltender als Patientinnen und Patienten.
- Gemäss den Autorinnen und Autoren sollte Personen mit oberen Atemwegsinfektionen empfohlen werden, in der Arztpraxis und den öffentlichen Verkehrsmitteln eine Maske zu tragen. Der Handschlag erscheint ihnen jedoch bei richtiger Händedesinfektion unbedenklich.

L'essentiel en bref

- Les membres du cercle de qualité MediX de Berne ont interrogé les professionnels de la santé, les assistants médicaux (AM) ainsi que les patients sur leur attitude vis-à-vis du port du masque et de la poignée de main dans le cabinet médical.
- Dans tous les groupes, la majorité était prête à continuer de porter le masque, du moins dans certaines situations, malgré la levée des mesures sanitaires. En ce qui concerne la poignée de main, les professionnels de la santé et les AM étaient plus réticents que les patients.
- Selon les auteurs, il faudrait recommander aux personnes souffrant d'infections des voies respiratoires de porter un masque au cabinet médical et dans les moyens de transport. La poignée de main leur semble toutefois sans danger si les mains sont correctement désinfectées.

Bactériémie à *Staphylococcus aureus* sensible à la méticilline

Louise Gueissaz[1], Noëmi Hauri [1], Juliane Kocher[1], Marc-André Lavallée [1], Manon F Munday[3], Luzia Renggli [4], Charles Béguelin[1,5]

[1] Department of Internal Medicine, Spitalzentrum Biel, Biel/Bienne, Switzerland

[2] Department of Emergency, Spitalzentrum Biel, Biel/Bienne, Switzerland

[3] Department of Internal Medicine, University of Geneva Hospitals, Geneva, Switzerland

[4] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[5] Department of Infectious Diseases, Inselspital, Bern University of Bern, Bern, Switzerland

My contribution: I performed the trend analysis including data extraction and created the figure visualising the incidence of *Staphylococcus aureus* bacteraemia over time.

Bactériémie à *Staphylococcus aureus* sensible à la méticilline

LOUISE GUEISSAZ[a], NOËMI HAURI[a], JULIANE KOCHER[b], MARC-ANDRÉ LAVALLÉE[a], MANON F. MUNDAY[c], LUZIA RENGGLI[d] et Dr CHARLES BÉGUELIN[a,e]

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Les bactériémies à *Staphylococcus aureus* sensibles à la méticilline sont fréquentes et en constante augmentation en Suisse. Elles sont associées à des morbidité/mortalité élevées, malgré les traitements antibiotiques. À la lumière de deux cas cliniques, nous présentons ici l'épidémiologie, la pathophysiologie, la clinique et le traitement de cette « maladie » dont l'anamnèse et l'examen clinique restent centraux afin de garantir une prise en charge optimale.

Methicillin-susceptible Staphylococcus aureus bacteraemia

Methicillin-susceptible staphylococcus aureus bacteremia is frequent and constantly increasing in Switzerland. It is associated with a high morbidity/mortality, despite antibiotic treatments. Through two clinical cases we discuss the epidemiology, pathophysiology, clinical presentation and treatment of this "disease", for which the history and clinical examination remain central in order to guarantee an optimal management.

INTRODUCTION

Staphylococcus aureus représente la deuxième cause de bactériémies en Suisse. Les bactériémies à *Staphylococcus aureus* (BSA) sont en constante augmentation ces dernières années. Une BSA ne peut jamais être considérée comme une contamination mais doit mener à la recherche d'un ou de plusieurs foyers infectieux. En effet, les *Staphylococcus aureus* se multiplient localement mais ont également la capacité de se propager dans l'organisme avec une prédilection particulière pour le matériel prothétique. Une prise en charge précoce et multidisciplinaire est requise afin qu'un traitement puisse être débuté dans les plus brefs délais, comprenant un antibiotique ciblé, souvent combiné à un traitement chirurgical.

CAS DE BSA NON COMPLIQUÉE

Une patiente de 65 ans est hospitalisée en médecine interne pour une décompensation cardiaque. Aux urgences, une voie veineuse périphérique lui a été posée pour l'administration d'un traitement diurétique IV. Cinq jours après son hospitalisation, elle développe un état fébrile à 38,5 °C, sans plainte particulière. Des hémocultures sont alors prélevées et la recherche étiologique met en évidence une phlébite au lieu d'insertion de la voie veineuse, qui est alors retirée. Un ultrason ne montre pas de thrombose. Une antibiothérapie empirique par amoxicilline/acide clavulanique est débutée. Par la suite, les résultats des cultures sanguines s'avèrent positifs pour un SASM (*Staphylococcus aureus* sensible à la méticilline) et le traitement antibiotique est changé pour de la céfazoline. La patiente est régulièrement réévaluée cliniquement, sans qu'une dissémination métastatique ne soit mise en évidence. Après 24 heures de traitement antibiotique adapté, elle devient apyrétique et les hémocultures de suivi prélevées à 48 heures sont négatives. L'antibiothérapie est poursuivie pour une durée de 2 semaines et l'évolution est favorable.

CAS DE BSA COMPLIQUÉE

Un homme de 54 ans se présente aux urgences avec une baisse de l'état général. L'anamnèse révèle une grande fatigue depuis quelques jours et des douleurs à la jambe droite. Le patient est connu pour un diabète et porteur d'une prothèse du genou gauche et d'un pacemaker. Il est fébrile à 38,6 °C, tachycarde et hypotendu. L'examen clinique révèle une jambe droite douloureuse, rouge et œdématiée, avec un ulcère au niveau du talon. L'épaule droite est douloureuse et la radiographie effectuée ne montre pas de fracture. On suspecte alors une contusion dans le cadre d'une chute il y a peu de temps. Des hémocultures sont prélevées, une antibiothérapie par amoxicilline/acide clavulanique est débutée pour une suspicion d'érysipèle sur un mal perforant plantaire. La plaie est débridée et une IRM permet d'exclure une ostéomyélite.

Les hémocultures reviennent positives pour un SASM. L'antibiothérapie est adaptée avec de la céfazoline. Le patient demeure cependant fébrile après 48 heures d'antibiothérapie adéquate et de nouvelles hémocultures 48 heures après le début du traitement sont toujours positives. Devant des douleurs progressives au niveau de l'épaule droite, les orthopédistes effectuent une ponction de l'épaule qui démontre une arthrite septique avec mise en évidence d'un SASM. Le patient bénéficie de rinçages répétés de l'articulation. Une échocardiographie transœsophagienne montre la présence de végétation sur une sonde du pacemaker. Le patient développe également des douleurs dorsales et une IRM montre une spondylodiscite de L3-L4 avec un abcès paravertébral s'étendant jusqu'au muscle psoas.

[a] Service de médecine interne, Centre hospitalier de Bienne, 2501 Bienne, [b] Service des urgences, Centre hospitalier de Bienne, 2501 Bienne, [c] Service de médecine intensive, Hôpitaux universitaires de Genève, 1211 Genève 14, [d] Centre suisse pour le contrôle de l'antibiorésistance ANRESIS, Institut de maladies infectieuses, Université de Berne, 3001 Berne, [e] Service des maladies infectieuses, Inselspital, Hôpital universitaire de Berne, 3010 Berne
louise.gueissaz@szb-chb.ch | noemi.hauri@szb-chb.ch | juliane.kocher@szb-chb.ch
marc-andre.lavallee@szb-chb.ch | manon.munday@hcuge.ch | luzia.renggli@ifik.unibe
charles.beguelin@szb-chb.ch

Après débridement opératoire de la spondylodiscite et de l'abcès du psoas ayant nécessité de multiples révisions, puis le remplacement du pacemaker sous poursuite de l'antibiothérapie, les hémocultures itératives se négativent finalement. L'antibiothérapie est poursuivie pour 6 semaines supplémentaires puis le patient est transféré dans un centre de réadaptation.

DÉFINITION ET PATHOPHYSIOLOGIE

Une bactériémie est définie comme la présence de bactéries circulant dans le sang. Il est important de différencier une bactériémie nosocomiale (hémocultures positives prélevées > 48 heures après l'admission) d'une bactériémie acquise en communauté (hémocultures positives prélevées < 48 heures après l'admission).[1]

À l'origine de chaque bactériémie, il y a pénétration des bactéries dans la circulation par une porte d'entrée. Celle-ci peut être évidente dans le cadre d'une phlébite après pose d'un cathéter veineux mais n'est très souvent plus identifiable au moment où une BSA est détectée. Le laps de temps entre l'inoculation, l'apparition des symptômes et le début du traitement mène à la multiplication des bactéries au niveau local ainsi qu'à la dissémination systémique, avec un risque de sepsis.

Les BSA sont caractérisées par une morbidité et une mortalité élevées. Dans l'ère «préantibiotique», la mortalité s'élevait à 90%. Grâce à la découverte des antibiotiques et à une meilleure compréhension de la maladie, la mortalité a progressivement diminué jusqu'en 2000 pour atteindre environ 20% dans les pays industrialisés. Depuis lors, elle reste stable à ce taux élevé.

ÉPIDÉMIOLOGIE

Avec une incidence de 29 cas/100 000 habitants, les *Staphylococcus aureus* sont la deuxième cause de bactériémie en Suisse (16,5%), précédés uniquement par *Escherichia coli* (29%).[2,3] Selon le centre suisse pour le contrôle de l'antibiorésistance ANRESIS, le nombre de BSA est en constante augmentation depuis 2010. Cette évolution est due principalement à l'augmentation des bactériémies à SASM alors que, durant la même période, celles à *Staphylococcus aureus* résistant à la méticilline (SARM) sont à la baisse (**figure 1**). Les causes de l'augmentation de l'incidence des BSA sont encore mal connues. Une population vieillissante et polymorbide (diabète, maladie tumorale, immunosuppression, dialyse), ainsi que l'implantation plus fréquente de matériel prothétique, jouent certainement un rôle.

BSA AVEC OU SANS COMPLICATIONS

Une BSA non compliquée est définie comme suit:[4]

- Une infection associée à un cathéter intravasculaire que l'on retire.
- Des hémocultures de suivi négatives à 48 heures.
- Une résolution de la fièvre dans les 72 heures.
- L'absence de matériel prothétique.
- L'absence de site d'infection secondaire.

Toute autre BSA ne remplissant pas ces critères sera définie comme compliquée. Ces complications peuvent se présenter sous différentes formes: une dissémination métastatique, une propagation locale ou le développement d'un sepsis. Elles sont fréquentes, survenant dans 10 à 50% des cas, et entraînent une morbidité et mortalité importantes.[5] Le *Staphylococcus aureus* peut se disséminer dans n'importe quel organe et conduire au développement d'arthrites septiques, de spondylodiscites ou d'abcès épiduraux, d'atteintes cérébrales, musculaires, rénales ou pulmonaires.[6] Il a également une prédilection pour le matériel prothétique, notamment les prothèses orthopédiques et valvulaires, les défibrillateurs ou les pacemakers. Une des complications les plus redoutées, et qui est également la plus fréquente, est l'endocardite infectieuse qui survient dans 5 à 17% des cas de BSA et augmente jusqu'à 30-50% en présence de matériel prothétique intracardiaque.[5,7]

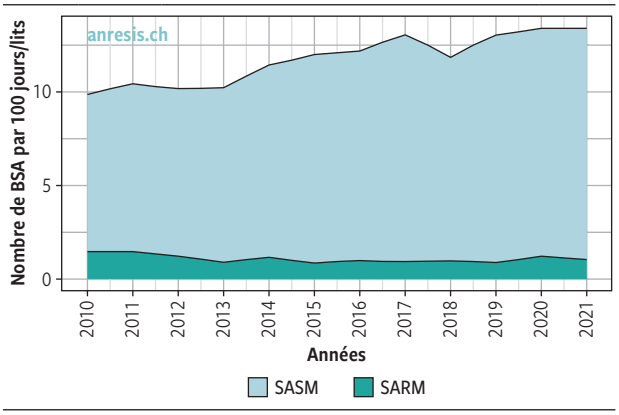
SCORES EN LIEN AVEC LES COMPLICATIONS ET UNE MORTALITÉ AUGMENTÉE

Actuellement, il n'y a pas de score validé à large échelle permettant de prédire la mortalité liée à une BSA. Néanmoins, plusieurs études ont permis de définir certains facteurs de risque aidant le clinicien à évaluer la probabilité qu'un patient développe des complications.

Les personnes atteintes d'une BSA d'origine communautaire ont une mortalité deux fois plus élevée que celles atteintes d'une BSA acquise en milieu hospitalier.[8] Ceci s'explique par le fait que dans le cas d'une BSA d'origine communautaire, les personnes atteintes sont probablement déjà bactériémiques depuis plusieurs jours avant d'être hospitalisées, ce qui permet à la bactérie de se multiplier et de circuler plus longtemps dans le corps. En revanche, une acquisition nosocomiale est souvent remarquée de façon précoce, les patients étant monitorés. Un traitement antibiotique empirique est souvent débuté rapidement en cas de fièvre.

FIG 1 **Situation épidémiologique en Suisse de 2010 à 2021**

BSA : bactériémies à *Staphylococcus aureus* ; SARM : *Staphylococcus aureus* résistant à la méticilline ; SASM : *Staphylococcus aureus* sensible à la méticilline.



Critère de Fowler

Ce score comprend 4 paramètres cliniques et permet d'estimer le risque de développer des complications lors d'une BSA. Ces 4 facteurs sont des cultures sanguines de suivi positives à 48 heures, une infection acquise en communauté, une fièvre persistant à 72 heures ainsi que la présence de lésions cutanées évocatrices d'une infection disséminée. Parmi ceux-ci, la persistance d'hémocultures positives est la caractéristique présentant la plus forte association avec le développement de complications et compte ainsi pour 2 points. Les 3 autres critères valent 1 point chacun. Ainsi, la probabilité de développer des complications est de 30% en présence de 1 point, elle passe à 45% à 2 points, 70% à 3 points, 80% à 4 points et à 90% si tous les critères sont remplis. Même en l'absence de tous ces critères, le risque de complication s'élève à 16%,[9] ce qui est non négligeable.

Score PREDICT-SAB

Ce score comprenant 3 paramètres cliniques permet d'estimer le risque qu'un pacemaker soit infecté lors d'une BSA. Ces 3 critères sont la présence d'un pacemaker permanent (a contrario d'un défibrillateur seul), la réalisation de plus d'une procédure sur cet appareil (par exemple, le changement de sonde), ainsi que la persistance d'une bactériémie de plus de 4 jours. Chez les patients ne présentant aucun des 3 critères suivants, le risque d'infection du pacemaker est < 10% et on peut envisager d'observer l'évolution clinique au lieu de retirer le pacemaker en première intention.[10]

PRISE EN CHARGE

La découverte d'une BSA doit mener à une anamnèse et un examen clinique approfondi. Il est primordial de rechercher une porte d'entrée et des symptômes et signes d'un éventuel foyer secondaire, tel un souffle cardiaque ou des stigmates d'endocardite. On doit questionner la présence de matériel prosthétique (valve, pacemaker, prothèse, etc.). La présence de douleurs articulaires ou dorsales nouvelles devrait mener à la recherche d'arthrite septique ou de spondylodiscite. Un haut niveau de suspicion doit être constamment maintenu et un examen clinique consciencieux doit être continuellement répété afin de repérer d'éventuels nouveaux foyers qui se seraient développés malgré l'antibiothérapie. Un infectiologue devrait également être impliqué précocement.[11,12]

Traditionnellement, l'échocardiographie transœsophagienne (ETO) était recommandée d'emblée dans tous les cas de BSA.[13] Récemment, des scores ont été développés, permettant de définir des BSA à bas risque ne nécessitant pas d'échocardiographie.[14,15] De ces scores, le VIRSTA présente la meilleure valeur prédictive négative (98%). Finalement, si une échocardiographie est jugée nécessaire, il est possible de l'effectuer initialement par la voie transthoracique, la visualisation d'une végétation posant déjà le diagnostic et rendant l'ETO superflue. Il faut cependant garder en tête qu'environ 10% des végétations ne seront pas visualisées à l'échographie thoracique (ETT).

Les autres imageries et examens doivent être ajustés à la suspicion clinique, comme résumé dans le **tableau 1**. Un CT thoraco-abdominal peut également être utile en cas d'endocardite confirmée afin d'exclure des sites d'embolies septiques subcliniques, tels un infarctus rénal ou splénique, des abcès pulmonaires ou du psoas.

Il faut porter une attention particulière à la présence de matériel prothétique qui est volontiers infecté par le *Staphylococcus aureus*. Les orthopédistes doivent être rapidement impliqués en cas de doute sur une infection de prothèse. De même, les abcès doivent être traités chirurgicalement. Le matériel endovasculaire (par exemple, un cathéter périphérique ou central, un port-à-cath ou un pacemaker) doit être considéré comme infecté jusqu'à preuve du contraire et retiré par le spécialiste concerné. Si le risque d'infection est jugé très bas par les infectiologues et les spécialistes impliqués, le matériel peut éventuellement être laissé en place.[10]

Une fois le traitement antibiotique débuté, des hémocultures de suivi toutes les 24 à 48 heures jusqu'à stérilité sont recommandées. La fièvre devrait cesser après 72 heures, sans quoi un foyer d'infection métastatique subclinique ou une endocardite devraient être suspectés. Récemment, l'utilisation du PET-CT à la recherche de foyers métastatiques a montré une réduction de la mortalité,[16] mais l'évidence à ce sujet est faible et l'accès à l'imagerie limité. Il pourrait être intéressant de le considérer en cas de fièvre persistant sans foyer clinique évident ainsi que dans certains cas de suspicion d'infection de prothèse valvulaire ou de pacemaker.

TRAITEMENT DE LA BACTÉRIÉMIE À SASM

Un traitement antibiotique précoce est extrêmement important en cas de suspicion de BSA. La durée du traitement et la voie d'administration seront établies selon le type d'infection.

TABLEAU 1 **Prise en charge d'une bactériémie à *Staphylococcus aureus***

[a] Peut éventuellement être omise en cas de bactériémie non compliquée.
ETO : échocardiographie transœsophagienne ; ETT : échocardiographie transthoracique.

Pour tous les patients	Selon la clinique	
• Réévaluation clinique régulière et anamnèse approfondie • Suivi de la fièvre • Hémocultures de suivi à 24-48 h • Consultation infectiologique • ETT[a]	Stigmates d'endocardite ou score PREDICT/VIRSTA positif ou embolie septique	ETO, éventuellement CT thoraco-abdominal
	Fièvre persistante	ETO, CT thoraco-abdominal, éventuellement PET-CT
	Arthralgies	Ponction articulaire
	Dorsalgies	IRM vertébrale
	Céphalées, atteinte de la conscience, signes neurologiques focaux	IRM cérébrale
	Présence de matériel endovasculaire (pacemaker, Picc-Line, cathéter)	Retrait du matériel prothétique
	Abcès	Drainage

TABLEAU 2 **Antibiotiques de choix pour le traitement IV d'une bactériémie à *Staphylococcus aureus***

ASP : pénicilline antistaphylococcique ; BSA : bactériémie à *Staphylococcus aureus* ; SA : *Staphylococcus aureus* ; SARM : *Staphylococcus aureus* résistant à la méticilline ; SASM : *Staphylococcus aureus* sensible à la méticilline.

Antibiotiques	Dosages	Avantages	Désavantages
Pénicilline G	4 mio UI/4 h IV	Traitement de choix en cas de BSA à SA sensible à la pénicilline	Peu de germes sensibles à la pénicilline (18 %)[3]
Flucloxacilline (ASP)	2 g/4-6 h IV	Efficace contre la plupart des staphylocoques en Suisse (92 %).[3] Disponible en Suisse	Effets secondaires menant à l'interruption du traitement
Céfazoline	2 g/8 h IV	Non inférieure et moins coûteuse que les ASP Peut être administrée si allergie de type IV aux pénicillines	Contre-indiquée si allergie de type I aux pénicillines
Vancomycine	15 mg/kg/12 h IV	Efficace contre les SARM. Peut être administrée si réaction allergique de type I aux pénicillines	Moins bonne efficacité contre les SASM
Daptomycine	6-10 mg/kg/24 h IV	Efficace contre SARM Peut être administrée si réaction allergique de type I aux pénicillines	Inactivée par surfactant pulmonaire. Pas de meilleur résultat si combiné avec ASP

Quel antibiotique?

Le choix de l'antibiotique est essentiel pour traiter correctement les BSA. Il est guidé par l'antibiogramme du germe identifié. 18% des staphylocoques dorés en Suisse ne produisent pas de pénicillinase[3] et sont ainsi sensibles aux pénicillines, dont l'efficacité est identique à celle de la flucloxacilline et qui provoquent moins d'effets secondaires.

Jusqu'à peu, les antibiotiques de choix pour le traitement des staphylocoques dorés produisant une pénicillinase étaient les pénicillines antistaphylococciques (ASP), dont font partie la flucloxacilline et la méticilline. À noter qu'en Suisse, la seule ASP disponible est la flucloxacilline. Toutefois, de nombreuses études récentes ont démontré la non-infériorité de la céfazoline, une céphalosporine de première génération, comparée aux ASP, avec l'avantage d'engendrer moins d'effets secondaires tels que des réactions cutanées (13,9 vs 4,2%), des dysfonctions rénales (11,4 vs 3,3%) ou hépatiques (8,1 vs 1,6%), menant ainsi à moins d'interruptions prématurées du traitement (33,8 vs 6,7%).[17] La céfazoline peut être administrée à des intervalles plus espacés et est globalement moins coûteuse que les ASP. Deux points négatifs sont à relever: la faible diffusion de la céfazoline dans le LCR, ce pour quoi elle n'est pas indiquée en cas d'atteinte du système nerveux central (une bonne alternative étant la flucloxacilline) ainsi qu'une probable corrélation entre une concentration de bactérie élevée et une évolution défavorable, aussi appelée «inoculum effect».[18]

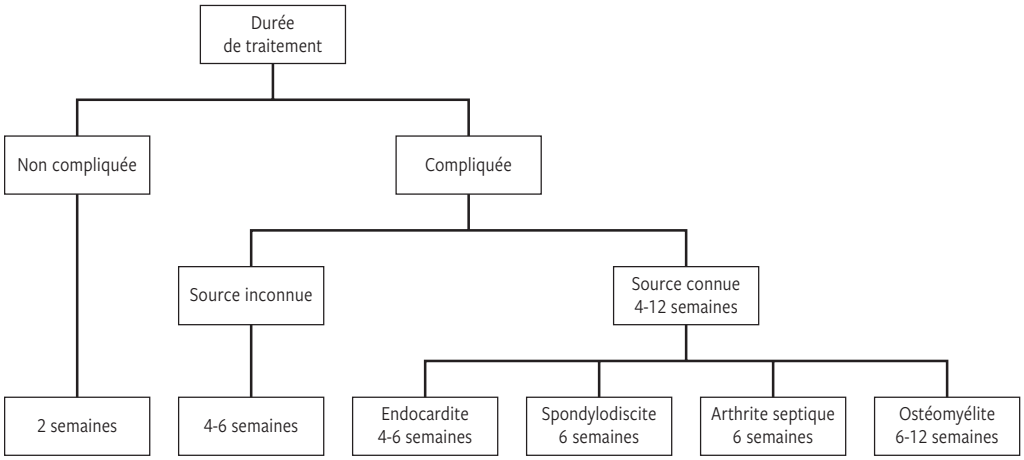
La vancomycine, utilisée lors d'infections à SARM, est moins efficace contre les SASM que les antibiotiques précédemment mentionnés et devrait donc être utilisée seulement dans certains cas d'allergies sévères à la pénicilline.[19]

Une antibiothérapie combinée n'est pas indiquée lors d'une BSA. Des études randomisées n'ont pas démontré d'efficacité supérieure lors de l'adjonction de la daptomycine ou de la rifampicine (**tableau 2**).[20]

Durée du traitement

La durée du traitement d'une BSA est définie par différents facteurs cliniques de l'infection. Une infection non compliquée peut être traitée pendant seulement 14 jours, les compliquées le seront sur une durée plus longue, qui dépend de la source d'infection (**figure 2**).

FIG 2 **Durée du traitement de la bactériémie à *Staphylococcus aureus***



Voie d'administration

La voie d'administration préférentielle est intraveineuse car la plupart des données sont basées sur ce mode d'administration. Toutefois, la recherche sur les traitements oraux progresse. Des études anciennes montraient déjà de bons résultats avec l'administration orale combinée de quinolones et rifampicine, par exemple lors d'endocardites droites à *Staphylococcus aureus*.[21] Plus récemment, une étude randomisée a démontré la non-infériorité d'un relais PO chez les patients stables après au moins 10 jours de traitement IV comparé à un traitement uniquement IV lors d'endocardites gauches, dont celles provoquées par des *Staphylococcus aureus*.[22] D'autres agents antimicrobiens oraux également utilisés sont le cotrimoxazole, la clindamycine ou le linézolide. Les traitements PO suscitent beaucoup d'intérêts du fait de la réduction importante de la durée d'hospitalisation et la diminution des risques liés à un traitement IV. Toutefois, certains effets secondaires sont non négligeables, comme la photo et la neurotoxicité des quinolones ou les effets gastro-intestinaux du linézolide. En somme, l'oralisation de l'antibiothérapie dans certains cas de BSA bien sélectionnés montre des résultats prometteurs et facilite la prise en charge mais les données sont encore insuffisantes pour émettre des recommandations officielles à large échelle.

CONCLUSION

Malgré l'évolution des options diagnostiques et thérapeutiques, la mortalité liée à la BSA reste élevée. La tendance épidémiologique montre une augmentation constante des BSA, raison pour laquelle une bonne compréhension de cette «maladie» et une prise en charge multidisciplinaire précoce sont cruciales.

Conflit d'intérêts: Les auteurs n'ont déclaré aucun conflit d'intérêts en relation avec cet article.

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IMPLICATIONS PRATIQUES

- Une hémoculture positive pour un staphylocoque doré ne doit jamais être considérée comme une contamination
- La distinction entre une bactériémie compliquée et non compliquée se fait sur des critères cliniques stricts et impacte la durée du traitement
- En cas de bactériémie à staphylocoques dorés, un foyer doit être recherché de manière systématique
- Une prise en charge multidisciplinaire avec traitement précoce est essentielle

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3.3. Manuscript in Press

Project 2: Increase in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections in Switzerland: A Nationwide Surveillance Study (2008-2021)

Renggli L[1], Gasser M[1], Buetti N [2,3], Kronenberg A[1]

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[2] Infection Control Programme, University of Geneva Hospitals and Faculty of Medicine, WHO Collaborating Center, Geneva, Switzerland

[3] UMR 1137, IAME, INSERM, Université de Paris, 75018, Paris, France

My contribution: I extracted the data, performed the analysis, drafted the manuscript and applied the suggested revisions after reviews from co–authors and peer–review from the journal Infection.

Increase in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections in Switzerland: A Nationwide Surveillance Study (2008-2021)

Renggli L[1], Gasser M[1], Buetti N [2,3], Kronenberg A[1] and the Swiss Centre for Antibiotic Resistance

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[2] Infection Control Programme, University of Geneva Hospitals and Faculty of Medicine, WHO Collaborating Center, Geneva, Switzerland

[3] UMR 1137, IAME, INSERM, Université de Paris, 75018, Paris, France

Abstract

Purpose

An increasing burden of *Staphylococcus aureus* bloodstream infections (BSI) despite a decrease in the percentage of methicillin-resistant *S. aureus* (MRSA) was described recently for other European countries.

The main aim of this study was to analyse recent temporal trends of *S. aureus*, methicillin-susceptible *S. aureus* (MSSA) and MRSA BSI for Switzerland as well as the different linguistic regions within Switzerland. An additional aim was to estimate potential differences among patient-based and epidemiological risk factors.

Methods

A retrospective observational study was conducted in Switzerland over a period of 14 years (2008-2021). Trends in *S. aureus*, MSSA and MRSA BSI were analysed by applying linear regression models.

Results

S. aureus BSI increased by +30% from 19.7 to 25.6 cases per 100,000 inhabitants between 2008 and 2021 (P<0.01) in Switzerland. Thereof, MSSA increased by +37% from 17.8 to 24.4 cases per 100,000 inhabitants (P<0.01). MRSA decreased from 1.9 to 1.2 cases per 100,000 inhabitants (P<0.01), which was driven by decreasing incidence in the French-speaking region.

MSSA BSI increased significantly (P<0.01) in both linguistic regions. A further stratification revealed that incidence increased the most in male patients of the age group ≥ 80 years of the German-speaking region.

Conclusion

The increasing health burden of MSSA BSI in Switzerland indicates that not only proportions of resistant microorganisms but also total BSI incidences should be monitored. In addition, data stratification revealed that the increase was mainly driven by an increasing incidence in elderly males of the German-speaking region.

Introduction

Bloodstream infections (BSI) are associated with increased mortality, with *Staphylococcus aureus* being one of the most common pathogens [41, 111-113]. An increasing burden of absolute numbers of *S. aureus* BSI despite a decrease in the percentage of methicillin-resistant *S. aureus* (MRSA) was recently described for the EU and European Economic Area (EEA) between 2005 and 2018 [108]. Switzerland is not an EU or EEA country and thus was not part of this project. In two earlier epidemiologic analyses of *S. aureus* BSI in Switzerland (2008-2014), a stable incidence was reported [114], with a decreasing percentage of MRSA (2004-2014)[109]. For the incidence of MRSA BSI, decreasing trends were described more recently for Switzerland overall, with different trends between the Swiss linguistic regions [115]. In addition to location in the French and Italian linguistic regions of Switzerland, Olearo *et al.* reported inpatient status and elderly age as risk factors for MRSA (compared with MSSA) [109]. Further studies identified older age and male sex as risk factors for *S. aureus* BSI [41, 42]. To target possible future prevention strategies, a timely analysis of the epidemiological situation in Switzerland is needed.

The main aim of this study was to analyse recent temporal trends of *S. aureus*, MSSA and MRSA BSI for Switzerland as well as the different linguistic regions within Switzerland. An additional aim was to estimate potential differences among patient-based and epidemiological risk factors for MRSA or MSSA [41, 42, 109].

Methods

Design and Study Population

A retrospective observational study was conducted in Switzerland over a period of 14 years (2008-2021). *S. aureus* BSI from 70 acute care hospitals that reported data in 2008 and 2021 and for more than half of the years within this period to the Swiss Centre for Antibiotic Resistance (ANRESIS) database were included (see map Supplementary Figure 1).

Data Collection and Processing

Data on *S. aureus* BSI were obtained from the ANRESIS database [8]. The participating laboratories are accredited by national authorities. During the study period, guidelines for antibiotic susceptibility testing changed from CLSI to EUCAST guidelines; however, breakpoints for methicillin did not change. MRSA BSI was defined as a blood culture containing *S. aureus* resistant to at least one of the following antibiotics: methicillin, oxacillin, flucloxacillin, or cefoxitin. The first blood culture with resistance testing for at least one of these antibiotics per patient per year was considered.

The number of cases per 100,000 inhabitants was extrapolated by the yearly bed-days covered by ANRESIS (coverage in Switzerland overall in 2014, 53%; French-speaking region, 75%; and German-speaking region, 51%).

In the main analysis, data were stratified by linguistic region (German-speaking *versus* French-speaking region), patient age group (<2 years, 2–24 years, 25–49 years, 50–64 years, 65–79 years and ≥ 80 years), sex (male or female) or hospital unit (ICU *versus* outpatient department *versus* other departments). The number of inhabitants was used as the denominator except for the analysis of the hospital unit, as inhabitants cannot be allocated to a hospital unit. For Switzerland overall, the incidence in 2008 and 2021 was additionally calculated using bed-days.

An explanatory analysis was performed differing between community- and hospital-onset BSI. Samples taken within the first 48 hours after admission were considered community-onset BSI. As this

information was not available for 38% of the samples, they could not be included. Therefore, the absolute number of BSI was analysed.

Two further explanatory analyses were performed with datasets for methicillin-susceptible *S. aureus* that used non-blood specimens. Samples from bone or prosthetic joints containing *S. aureus* were used as surrogate marker for bone and joint infections. Moreover, samples from wound samples and biopsies were used as surrogate markers for skin and soft tissue infections.

Statistical Analysis

The statistical plan comprised three steps. First, temporal trends in *S. aureus*, MSSA and MRSA BSI per 100,000 inhabitants for Switzerland overall and for each linguistic region were analysed by applying a linear regression model for Switzerland overall and for each linguistic region separately. Second, a logistic regression model was used to analyse the proportions of MRSA among *S. aureus* BSI over time. Third, to analyse trends in MSSA bone and joint infections as well as MSSA skin and soft tissue infections, a linear regression model was applied for each linguistic region. The results were considered significant when the model fit an R-square above 0.4 and the p value of the explanatory variable was below 0.05. All analyses were performed using R software (version 4.1.2., R Core Team, Vienna, Austria).

Results

During the study period, 17,012 blood cultures containing *S. aureus* were reported to ANRESIS (Supplementary Table 1). *S. aureus* increased by +30% from 19.7 to 25.6 cases per 100,000 inhabitants between 2008 and 2021 in Switzerland (Table 1). Thereof, MSSA BSI increased by +37% from 17.8 to 24.4 cases per 100,000 inhabitants (P<0.01), while MRSA BSI decreased from 1.9 to 1.2 cases (P<0.01). This resulted in a significant (P<0.01) decrease in the proportion of MRSA on *S. aureus* BSI over time (Fig.8).

Temporal trends in MRSA BSI differed between the linguistic regions within Switzerland: the incidence of MRSA BSI decreased significantly in the French-speaking region (P<0.01), whereas a slight increase (P<0.01) was observed in the German-speaking region, although it remained at a low level (Fig.9, Supplementary Table 2).

The number of MSSA BSI increased significantly (P<0.01) in both linguistic regions, but the increase was more pronounced in the German-speaking region (+58%) than in the French-speaking region (+13%). A significant increase was observed for MSSA bone and joint infections in the German-speaking region (P<0.01), while the increase was not significant in the French-speaking region (Supplementary Table 6, Supplementary Figure 6). Inpatient skin and soft tissue infections did not change significantly in the German-speaking region and decreased (P<0.01) in the French-speaking region (Supplementary Figure 7).

Table 1 Temporal course of *Staphylococcus aureus* bloodstream infections (BSI): total, MSSA, MRSA and the percentage of MRSA among *S. aureus* BSI, Switzerland (2008-2021)

	BSI per 100,000 inhabitants				BSI per 1,000 bed-days		
S. aureus BSI	2008	2021	Change	Trends	2008	2021	Change
Total	19.7	25.6	+30%	↑ (P<0.01)	0.277	0.412	+49%
MSSA	17.8	24.4	+37%	↑ (P<0.01)	0.251	0.393	+57%
MRSA	1.9	1.2	-37%	↓ (P<0.01)	0.026	0.019	-28%
% MRSA	9.5%	4.6%	- 52%	↓ (P<0.01)	9.5%	4.6%	- 52%

ns, not significant; BSI, bloodstream infections; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

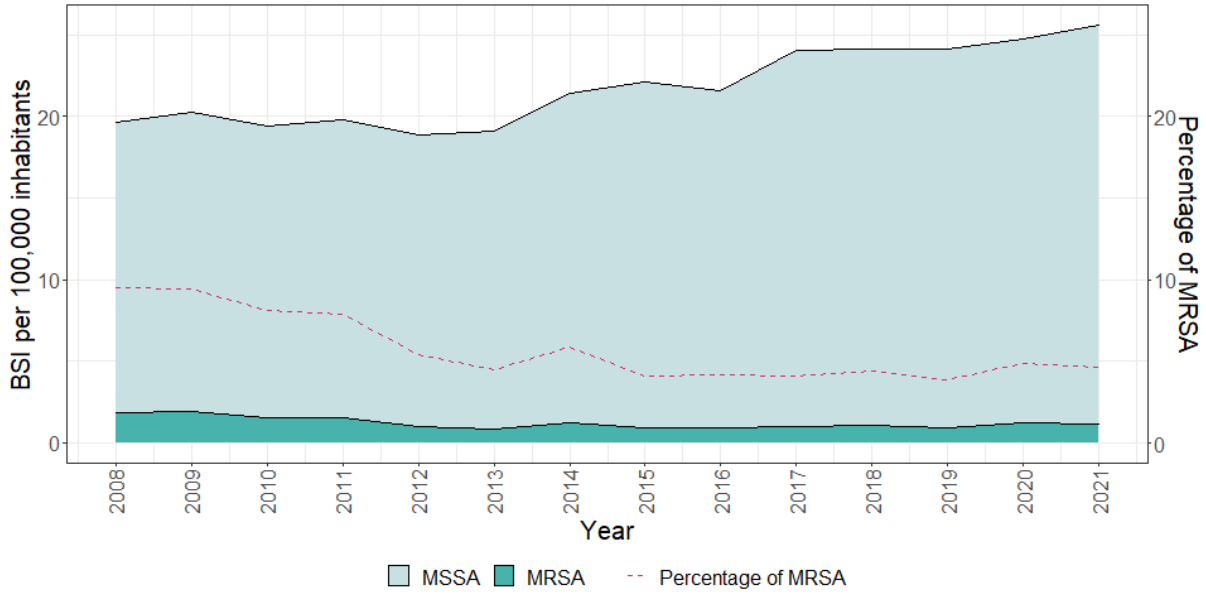


Fig.8 Incidence of MSSA and MRSA bloodstream infections (BSI) and percentage of MRSA among *S. aureus* BSI, Switzerland (2008-2021)

BSI, bloodstream infections; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

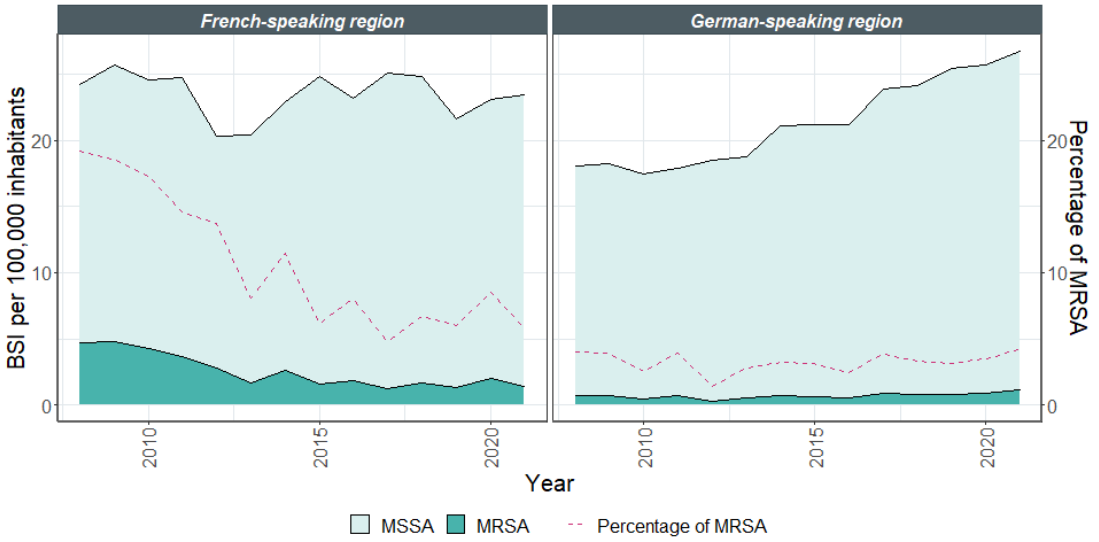


Fig.9 Incidence of methicillin-susceptible (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSI) and percentage of MRSA among *S. aureus* BSI in the different linguistic regions of Switzerland (2008-2021)

BSI, bloodstream infections; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

Further stratifications by age and sex revealed that the increase in incidence was mainly driven by patients of the German-speaking region in the age categories of 50-64 years, 65-79 years and ≥ 80 years (Fig.10, Supplementary Table 3). The proportional increase was highest in the age category of ≥80 years, followed by 50-65 years and 65-79 years, with a stronger increase in males than in females.

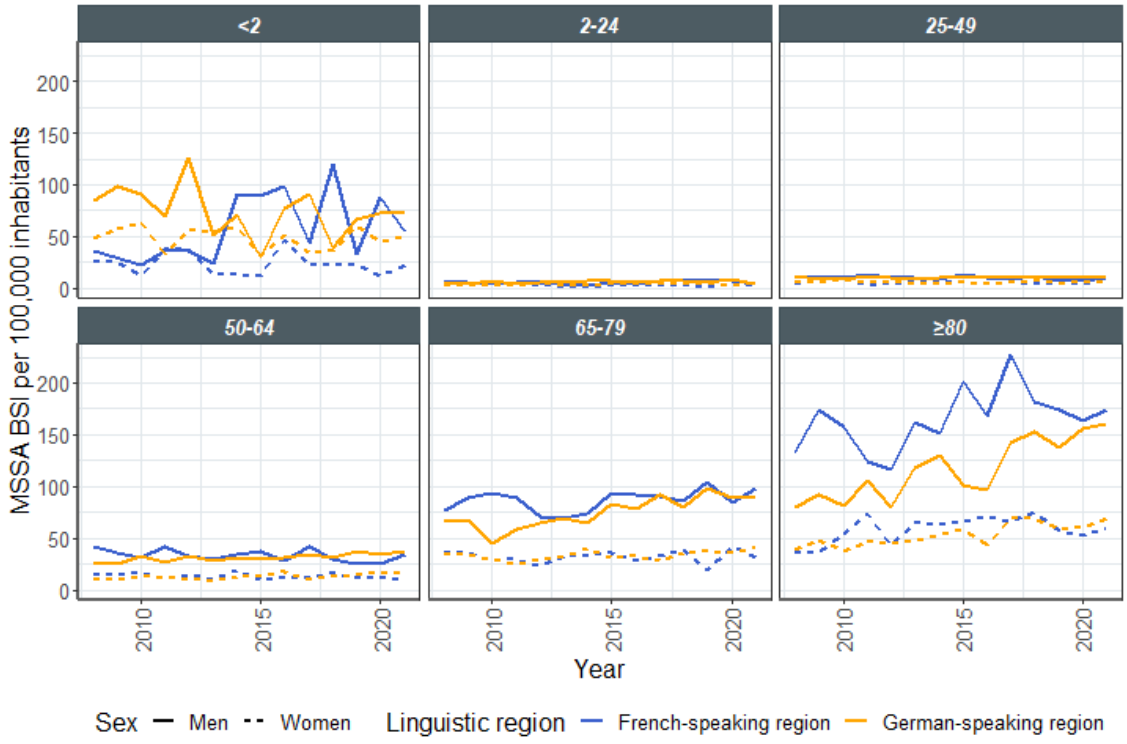


Fig.10 Temporal course of bloodstream infections (BSI) caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) in the different linguistic regions stratified by age group and sex, Switzerland (2008-2021)

MSSA BSI increased in all hospital types (university *versus* non-university ≥200 beds *versus* non-university <200 beds) in both linguistic regions. The variability in the proportional increase was high, especially among non-university hospitals with less than 200 beds (Supplementary Figure 5).

The increase in absolute MSSA BSI numbers was higher in the outpatient department than in the ICU and the other non-ICU departments (Supplementary Figure 4). The sub-analysis with the restricted dataset of samples labelled with the hospitalisation date showed a higher increase in community-onset MSSA BSI than in hospital-onset MSSA BSI (Supplementary Table 5, Supplementary Figure 8).

Discussion

The health burden of *S. aureus* BSI increased in Switzerland between 2008 and 2021: +30% from 19.7 to 25.6 cases per 100,000 inhabitants caused by an increasing incidence of MSSA BSI. Conversely, the incidence of MRSA BSI was slightly decreasing, which resulted in a decreased percentage of MRSA. These trends mirror the situation in most EU or EEA countries [108]. The incidence of *S. aureus* BSI in Switzerland was lower than that in northern Europe, although higher than that in Spain (Finland, 2015: 35.2 cases/100,000 inhabitants [116]; Denmark, mean for 2008-2015: 24.9 cases/100,000 inhabitants [117]; Spain, mean for 2013-2017: 9.3 cases/100,000 inhabitants[117]).

Surprisingly, the increasing trend in MSSA BSI was more pronounced in the German-speaking region than in the French-speaking region. The same patterns were observed for bone and joint infections. During the same time period, the number of surgical procedures for implementing or changing pacemakers increased in the German-speaking region while remaining constant in the French-speaking region [118] and may thus partly explain these regional differences, as devices are a common source of *S. aureus* BSI, and previous hospitalisation is a known risk factor [119]. In future studies, the relationship between device placements and *S. aureus* BSI over time considering possible changes in perioperative procedures must be analysed. Another possible reason for these regional discrepancies of MSSA may be that prevention measures to control MRSA have been implemented more in the French-speaking region [120, 121] since MRSA incidence was more than six-fold higher in the French-speaking compared to the German-speaking region to begin of the study period (discussed further below). This may have impacted the spread of MSSA. Superficial injuries are another important source of BSI [122], but MSSA skin and soft tissue infections did not increase during the study period. However, the incidence of MSSA skin and soft tissue infections mirrored the differences between the linguistic regions, with no significant trend in the German-speaking region and a significant decrease in the French-speaking region.

Finer stratifications revealed that increases in MSSA BSI as well as MSSA bone and joint infections were mainly driven by elderly males of the German-speaking region. This is in line with observations in most EU or EEA countries where the increase in *S. aureus* BSI was also more pronounced in males and in elderly individuals [108, 123]. Among others, age and male sex are well-described risk factors for *S. aureus* BSI [41, 42]. Although the elderly population was growing during the study period, this risk factor by itself may not explain the observed increase in incidence, as age-stratified populations were considered denominators. Other known risk factors for *S. aureus* BSI, such as diabetes mellitus and immunosuppression, probably increased slightly during the study period and could at least in part explain the overall increase [41, 124]. However, we were not able to quantify these factors, and we do not expect relevant differences between the French- and German-speaking regions. Further hypothetical explanations, such as the association between changes in smoking habits and *S. aureus* colonisation, are controversial [42].

The increase in MSSA BSI was higher in the outpatient department than in the ICU department as well as in community-onset MSSA BSI than in the hospital-onset MSSA BSI. The finding that an increase in

MSSA BSI was likely to be driven by community-onset BSI was not in contrast to the previous hypothesis of increasing device placements as a source of *S. aureus* BSI, because community-onset was defined as a microbiology sample taken within 48 hours after admission. As early prosthetic joint infection is defined as occurring within 3 months after surgery and the onset of *S. aureus* infection after hip or knee arthroplasty was described to have a median of 28 days (interquartile range 18-63 days) [125], these infections are likely to be defined as community-onset. Recent studies have reported an increasing incidence and virulence of the *S. aureus* CC398 lineage, a strain that originates from livestock, in the community setting [126]. Further studies need to investigate whether a more virulent and transmissible strain is the reason behind the increasing MSSA BSI incidence in Switzerland.

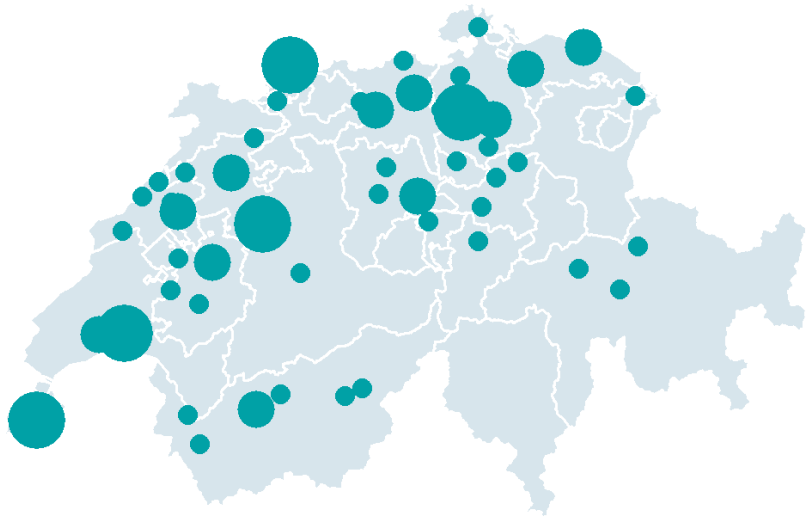
The decrease in MRSA BSI on a national level was caused solely by decreasing incidence in the French-speaking region, as the incidence even increased slightly in the German-speaking region. However, in 2008, the incidence of MRSA BSI was higher in the French-speaking region and converged during the study period to the levels of the German-speaking region, which may be explained by health care measures and an evolution of MRSA towards clones with reduced fitness [127-130]. These regionally differing trends for MRSA BSI were consistent with previous results [109, 115].

This study has some limitations, mainly due to its observational nature. First, we performed an epidemiological study using data from a microbiological surveillance system: several clinical individual patient data (e.g., baseline comorbidities, reasons for admission, and source of BSI) were not available. Although hospital coverage (53%) was achieved at the national level, no hospital from the Italian-speaking region was included due to inconsistent reporting. However, all Swiss university hospitals were included in this analysis. In addition, the hospitalisation date was available for only 62% of the samples, thus reducing the validity of this explanatory analysis. As the geographical distribution of samples with the hospitalisation data available was uneven and whether the labelling was performed thoroughly was unknown, the results of this analysis need to be interpreted with caution. However, the results seem plausible, as trends in analyses comparing outpatient, ICU and other departments could be confirmed.

The main strength of our study is the extensive data collection covering 14 years and all university hospitals in Switzerland. In addition, the analysis of Swiss data allowed stratification into different linguistic and sociocultural regions due to the country's heterogeneity.

In conclusion, the increasing health burden of MSSA bloodstream infections (BSI) in Switzerland indicates that surveillance should consider not only proportions of resistant microorganisms but also, more importantly, incidence rates of BSI. In addition, a stratification by linguistic region, sex and age group revealed that the increase in MSSA BSI was heterogeneous and mainly driven by an increasing incidence in elderly males of the German-speaking region. To formulate appropriate regionally targeted measures for this population, further investigations examining the underlying reasons for the growing incidence are needed.

Supplementary Material Project 2



Supplementary Figure 1: Swiss map with the included hospitals. The hospital size is visualised by the size of the points (university *versus* non-university ≥ 200 beds *versus* non-university < 200 beds).

Supplementary Table 1: Sample characteristics of all positive blood cultures included in the study

		Proportion during total study period (N isolates=17,012)
MRSA		5.6%
French-speaking region		32.3%
Hospital type:	university	43.8%
	non-university ≥200 beds	30.1%
	non-university <200 beds	26.1%
Department:	ICU	8.9%
	outpatient	35.8%
	other departments	55.3%
Men		66.5%
Age	<2	2.6%
	2-24	5.4%
	25-49	13.3%
	50-64	22.0%
	65-79	34.2%
	≥80	22.4%

N, number; MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit

Supplementary Table 2: Temporal course of *S. aureus*, MSSA and MRSA BSI stratified by linguistic region in percentage and cases per 100,000 inhabitants, Switzerland, 2008-2021

S. aureus BSI	French-speaking region				German-speaking region			
	2008	2021	Change	Trends	2008	2021	Change	Trend
Total	24.22	23.44	-3%	ns	18.06	26.76	+48%	↑(P<0.01)
MSSA	19.56	22.09	+13%	↑(P<0.01)	17.33	25.64	+48%	↑(P<0.01)
MRSA	4.66	1.35	-71%	↓(P<0.01)	0.72	1.11	+54%	↑(P<0.01)
% MRSA	19.24%	5.77%	-70%	↓(P<0.01)	4.01%	4.16%	+4%	ns

ns, not significant; *S. aureus*, *Staphylococcus aureus*; BSI, bloodstream infections; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*

Supplementary Table 3: Temporal change in bloodstream infections caused by methicillin-susceptible *Staphylococcus aureus* stratified by linguistic region, sex and age category in percentage and cases per 100,000 inhabitants (2008-2021)

Sex	Age category	French-speaking region			German-speaking region		
		2008	2021	Change	2008	2021	Change
Men	<2	36.52	55.12	51%	84.94	73	-14%
	2-24	5.78	3.5	-39%	6.1	4.41	-28%
	25-49	10.76	9.65	-10%	11.37	11.73	3%
	50-64	41.25	34.25	-17%	24.63	37.15	51%
	65-79	77.03	98.08	27%	66.76	90.67	36%
	≥80	133.15	174.79	31%	79.99	160	100%
Women	<2	25.63	23.21	-9%	47.69	51.13	7%
	2-24	4.02	3.22	-20%	2.3	4.25	85%
	25-49	4.94	6.43	30%	6.38	5.39	-16%
	50-64	15.21	8.21	-46%	10.33	15.73	52%
	65-79	35.27	31.94	-9%	34.77	40.5	16%
	≥80	35.98	58.06	61%	39.02	69.42	78%

Supplementary Table 4: Temporal changes in MSSA bone and joint infections and MSSA skin and soft tissue infections stratified by percentage and cases per 100,000 inhabitants (2008, 2021)

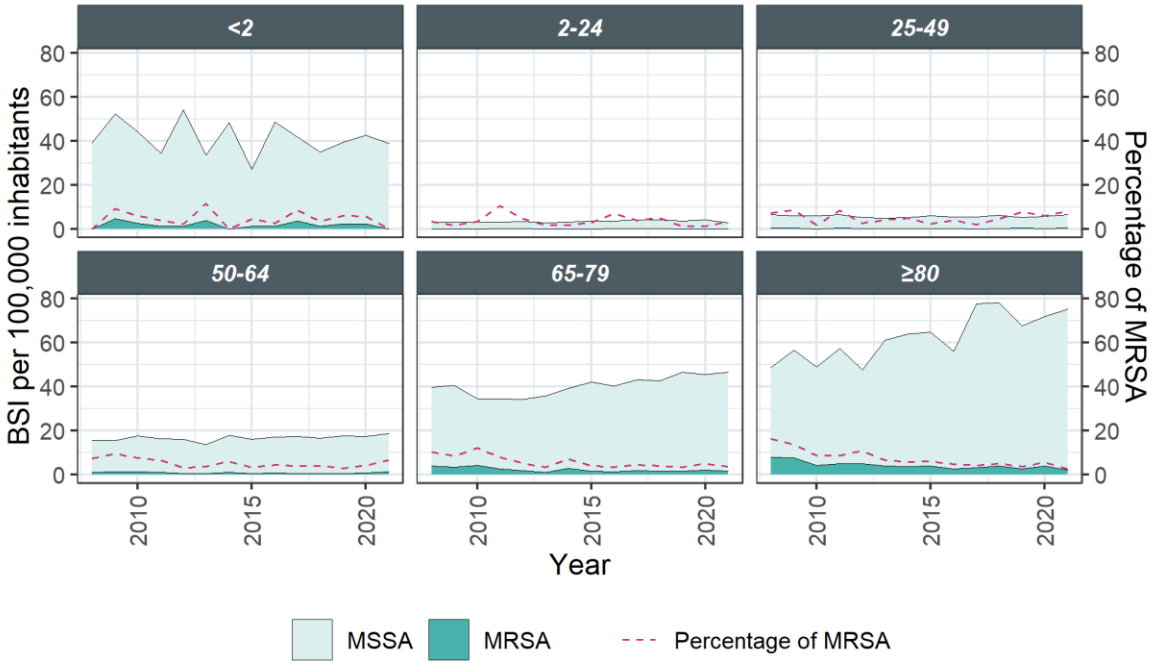
MSSA	French-speaking part				German-speaking part			
	2008	2021	Chang	Trend	2008	2021	Chang	Trend
Bone and joint	1.51	1.97	+31%	ns	1.78	3.37	+88%	↑(P<0.01)
Skin and soft	114.61		-24%	↓(P<0.01)	98.31	76.0	-22%	ns

MSSA, methicillin-susceptible *S. aureus*; ns, not significant

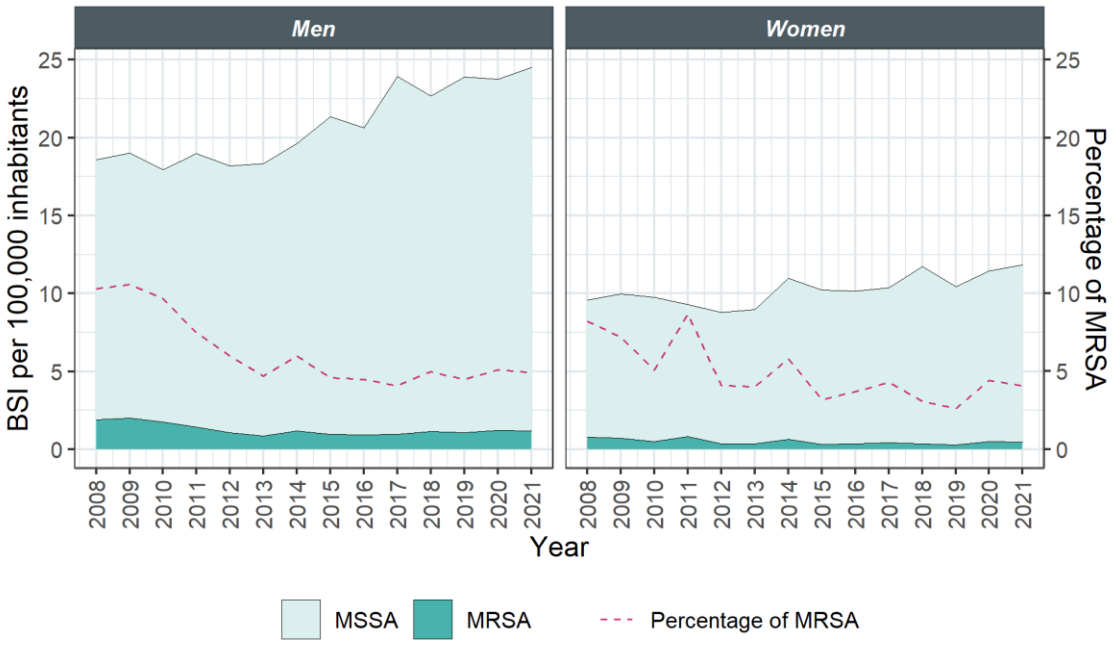
Supplementary Table 5: Temporal changes in *S. aureus*, MSSA and MRSA BSI stratified by community-onset *versus* hospital-onset in percentage and absolute number of cases (2008, 2021)

S. aureus BSI	Community-onset			Hospital-onset		
	2008	2021	Change	2008	2021	Change
Total	447	660	+48%	283	319	+13%
MSSA	421	637	+51%	22	305	+37%
MRSA	26	23	-11%	61	14	-77%

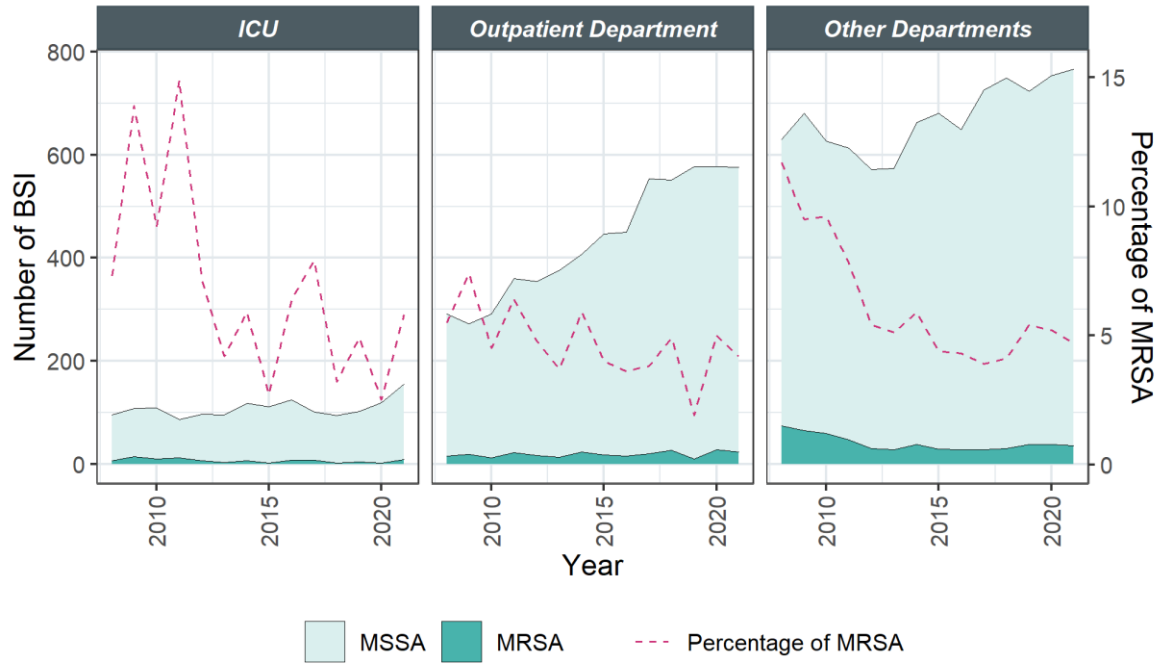
BSI, bloodstream infection; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*



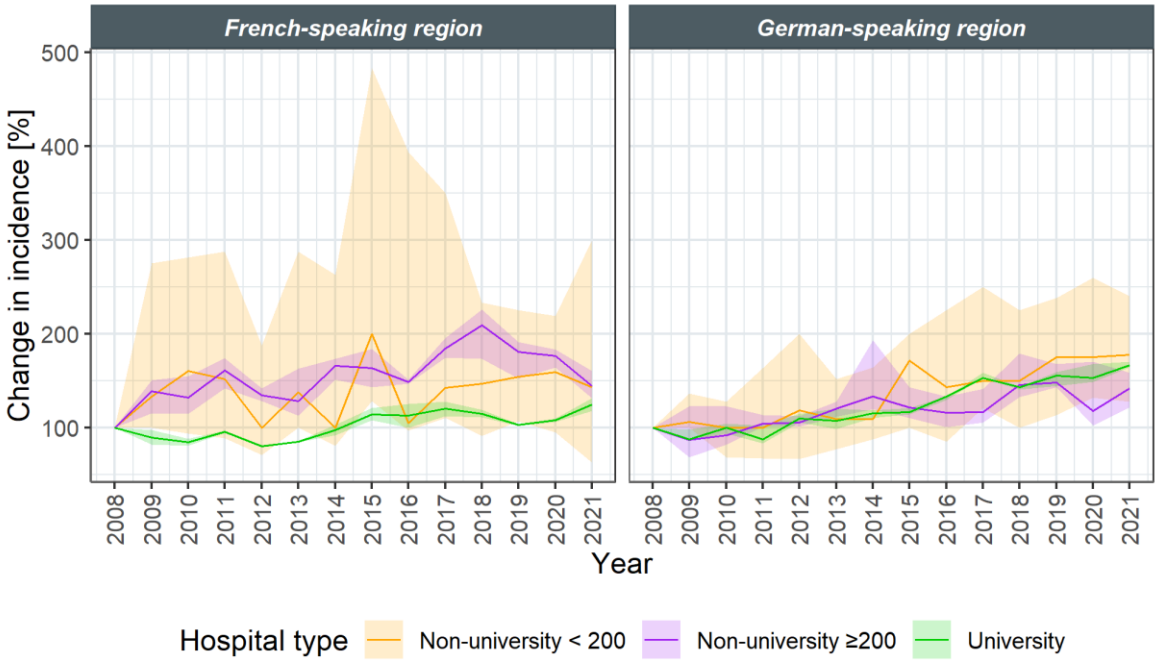
Supplementary Figure 2: Incidence in MSSA and MRSA bloodstream infections (BSI) and percentage of MRSA among *Staphylococcus aureus* BSI stratified by age category (2008-2021)



Supplementary Figure 3: Incidence in MSSA and MRSA bloodstream infections (BSI) and percentage of MRSA among *Staphylococcus aureus* BSI stratified by sex (2008-2021)

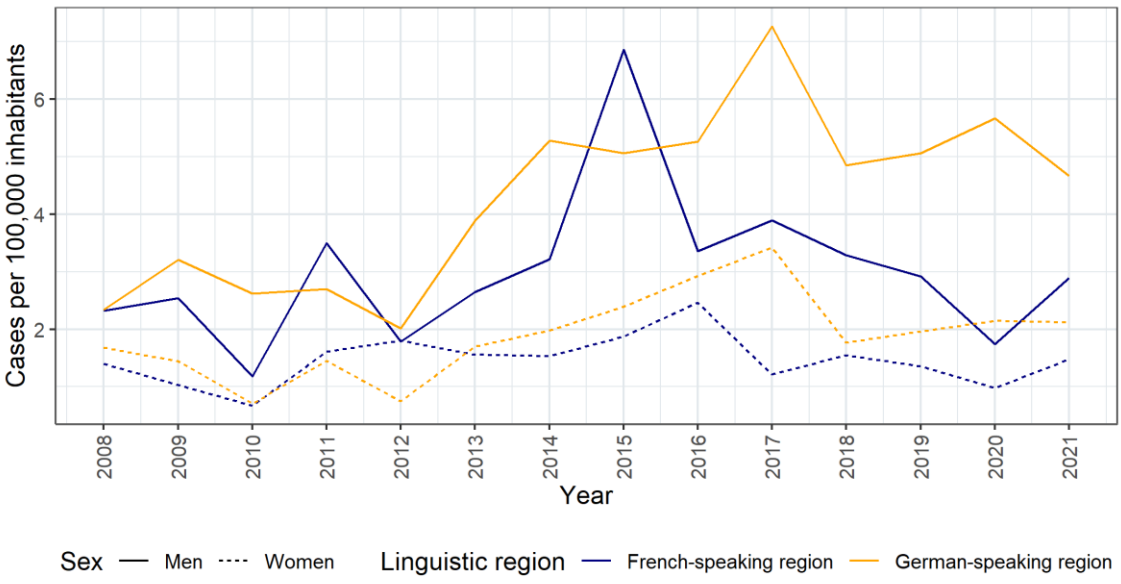


Supplementary Figure 4: Number of MSSA and MRSA bloodstream infections (BSI) and percentage of MRSA among *Staphylococcus aureus* BSI stratified by hospital unit (2008-2021)



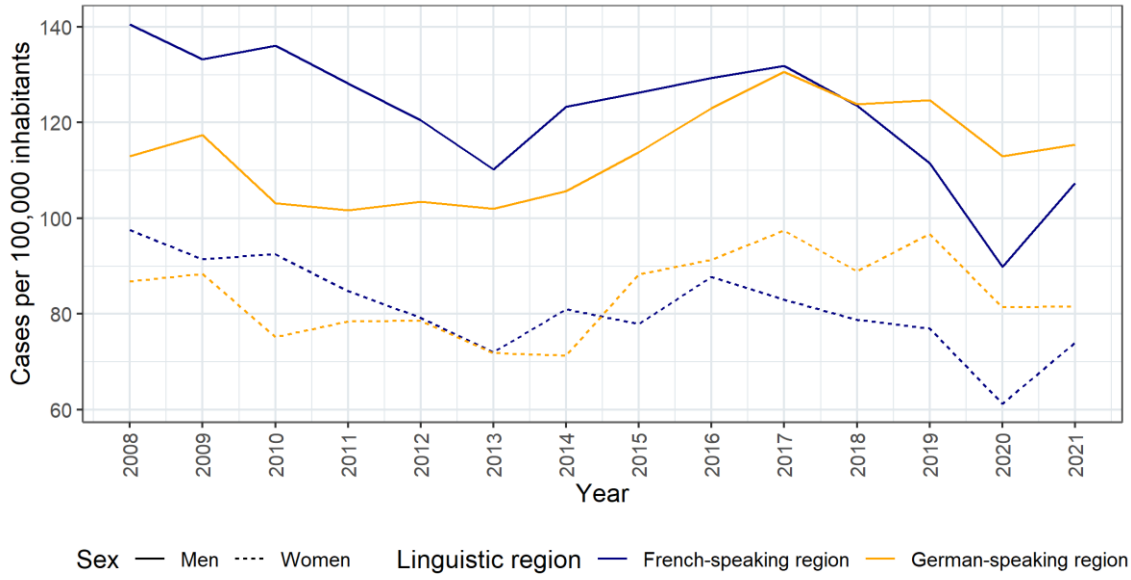
Supplementary Figure 5: Median (*bold line*) and interquartile range (*shaded area*) of proportional change in absolute numbers of MSSA BSI compared to 2008 grouped by hospital type and linguistic region (2008-2021)

MSSA BSI, methicillin-susceptible *Staphylococcus aureus* bloodstream infections



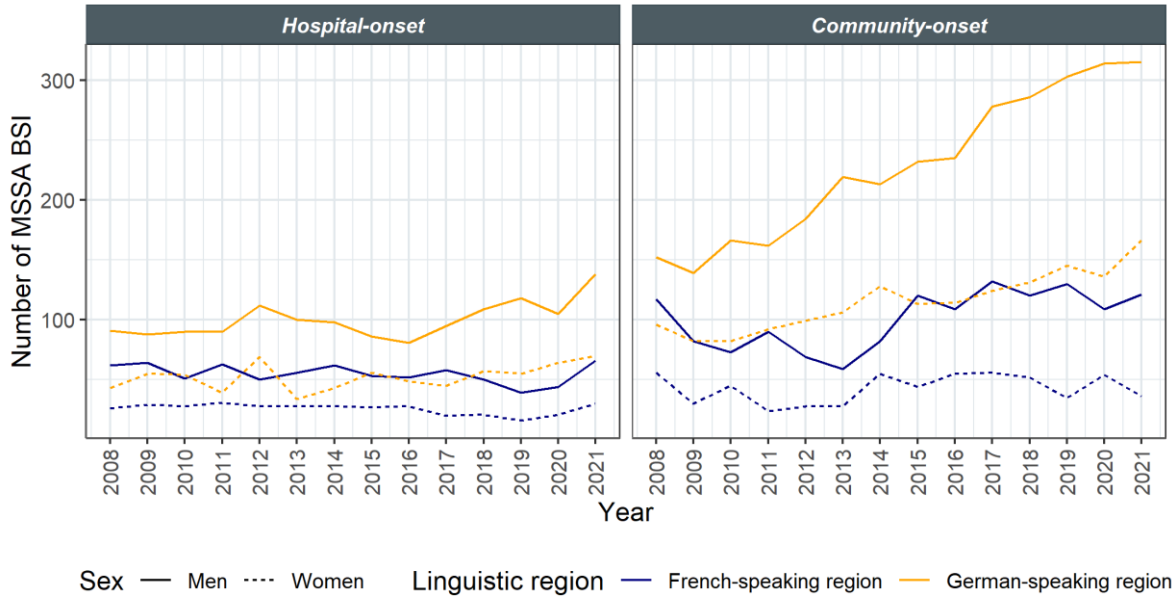
Supplementary Figure 6: Incidence of MSSA bone and joint infections stratified by linguistic region and sex (2008-2021)

MSSA, methicillin-susceptible *Staphylococcus aureus*



Supplementary Figure 7: Incidence of MSSA skin and soft tissue infections stratified by linguistic region and sex (2008-2021)

MSSA, methicillin-susceptible *Staphylococcus aureus*



Supplementary Figure 8: Number of community-onset and hospital-onset MSSA BSI stratified by linguistic region and sex (2008-2021)

MSSA BSI, methicillin-susceptible *Staphylococcus aureus* bloodstream infections

3.4. Manuscript Under Revision

Project 5: Assessing the Conversion of Electronic Medical Record Data Into Antibiotic Stewardship Indicators

Renggli L[1], Plüss-Suard C[1], Gasser M[1], Sonderegger B[2], Kronenberg A[1]

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[2] Institute for Infectious Diseases, Cantonal Hospital Lucerne, Lucerne, Switzerland

My contribution: I had the main responsibility in programming the algorithms, performing the analysis and drafting the manuscript.

Assessing the Conversion of Electronic Medical Record Data Into Antibiotic Stewardship Indicators

Renggli L[1], Plüss-Suard C[1], Gasser M[1], Sonderegger B[2], Kronenberg A[1]

[1] Swiss Centre for Antibiotic Resistance (ANRESIS), Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[2] Institute for Infectious Diseases, Cantonal Hospital Lucerne, Lucerne, Switzerland

Summary

Background

Measuring the appropriateness of antibiotic use is crucial for antibiotic stewardship programs to identify targets for interventions to improve antibiotic prescription. The introduction of electronic medical record (EMR) systems facilitates continuous monitoring of antibiotic use.

The aim of this project was to assess the technical feasibility of converting EMR data into antibiotic stewardship indicators (ABS-I), which have been proposed in the literature. A second aim was to calculate a first estimate of these ABS-I.

Methods

In this observational feasibility study, the health records of patients hospitalised between 1 October 2019 and 30 September 2021 at Lucerne Cantonal Hospital and receiving at least one dose of a systemic antibiotic were included.

ABS-I measuring steps in the process of antibiotic prescription proposed by the literature were collected and rephrased or defined more specifically to be calculable, if needed. Algorithms were programmed in R to convert EMR data into ABS-I. The ABS-I were calculated, and the validity of each output value was assessed and categorised as either good quality data ("1"), missing data due to incomplete documentation ("2A") or data processing issues ("2B") or not computable since the data were not considered in the application for ethical approval ("3A") or due to data processing issues ("3B").

Results

In total, data from 25,338 hospitalisations from 20,723 individual patients were analysed and visualised in an interactive dashboard. Data extraction allowed us to program the algorithm for 89% (25/28) of all preselected indicators assessing treatment decisions. Forty-six percent (13/28) of ABS-I data were classified as good quality.

According to the data quality observed, the most important issues were A) missing (58%) or meaningless (37%) information on indication (e.g., general indication, infection) and B) data processing issues such as insufficiently categorised metadata.

Conclusion

The calculation of indicators assessing treatment decisions from electronic medical records was feasible. However, better data structure and processing within EMR systems are crucial for improving the validity of the results.

Introduction

Improving the adequate use of antibiotics is critical to slow the spread of antimicrobial resistance, treat patients effectively and enhance patient safety [5]. Globally, 42.4% of antibiotic prescriptions in the hospital setting were incongruent with the guidelines according to a point prevalence study including 335 hospitals, while 33% of prescriptions were not appropriate in a Swiss hospital [10, 97]. Antibiotic stewardship (ABS) programmes aim to support clinicians in improving antibiotic therapy [5]. Numerous studies have proven the value of ABS programmes in reducing antibiotic use, antimicrobial resistance, mortality, length of hospitalisation and readmission rates, resulting in reduced health care costs [98-101]. Swiss hospitals, which had already established an ABS group as well as restrictions in the prescription of anti-MRSA antibiotics, showed lower consumption of anti-MRSA antibiotics [115]. Surveillance of antibiotic resistance and antibiotic consumption is a crucial element in ABS programmes, and it has been shown that optimising the use of antibiotics may prevent the spread of resistant bacteria [6, 7]. To date, surveillance of antibiotic use has been mainly based on quantitative measures, converting pharmacy sales data into defined daily doses (DDDs), a technical unit of measurement defined by the WHO [94], or on prescription data from point prevalence studies [9]. However, to optimise therapy, metrics evaluating the quality of antibiotic use are needed. For this purpose, a consensus of quality indicators for antibiotic use in the inpatient setting was elaborated by van den Bosch *et al.* [105] and Monnier *et al.* [11]. The more comprehensive set of QI by Monnier *et al.* encompassed i) structural indicators reflecting organisational aspects of health care, ii) process indicators describing the care delivered to patients and iii) outcome indicators such as death or resistance. To measure process indicators, data on AB prescribing are needed. The continuous monitoring of patient-level antibiotic prescription data is not yet done in the majority of countries worldwide as being too resource-intensive [106]. The implementation of electronic medical record (EMR) systems in an increasing number of Swiss hospitals leads to assisting physicians in the appropriate prescription of antibiotics due to the integration of clinical decision support systems directly in the electronic prescribing system and to increasing the availability of patient-level antibiotic prescription data, which could improve the quality of antibiotic consumption monitoring [131].
The aim of this project was to assess the technical feasibility of converting EMR data into ABS-I, which have been proposed in the literature. A second aim was to calculate a first estimate of these ABS-I.

Methods

Design and Study Population

A retrospective observational study was conducted at Lucerne Cantonal Hospital over a period of two years. It is a 730-bed acute care hospital with three locations: a tertiary care hospital, including the ICU, a long-term and a paediatric facility, but no department of psychiatry, and two smaller primary care hospitals. Health records of patients admitted to Lucerne Cantonal Hospital between 1 October 2019 and 30 September 2021 and receiving at least one antibacterial for systemic use (ATC codes J01 and P01AB01) were included. Patients who were discharged after 30 September 2021 or patients refusing general consent were excluded. Patient data were anonymised before analysis. The study was approved by the Swiss Ethics Commission of Northwest and Central Switzerland (EKNZ) reference number 2021-00059.

Selection and Categorisation of Antibiotic Stewardship Indicators (ABS-I)

Antibiotic stewardship indicators (ABS-I) were selected in four steps. First, a literature search was performed, summarising commonly used antibiotic stewardship process indicators. Second, we exclude ABS-I that do not measure the steps of the process of antibiotic therapy (*e.g.,* ABS-I measuring the IT process), analyse the administration of antibiotics or describe unspecific targets. Third, the ABS-I

definitions were rephrased or specified to be calculable by using EMR data, if needed (see supplementary data Table 1). In the process of specifying, some ABS-I of the literature were split into several new ABS-. In the fourth step, the ABS-I were categorised into treatment decision indicators and documentation quality indicators.
Metrics for analysing antibiotic consumption patterns were added (see supplementary data Table 2) [9, 16, 132].

Data Collection and Processing

Antibiotic prescription data were obtained from the EMR Epic software® and linked with microbiological data from the Swiss Centre for Antibiotic Resistance (ANRESIS) database. ANRESIS is a representative surveillance system that continuously collects national data on antibiotic consumption and antibiotic resistance [8], including microbiological data from Lucerne Cantonal Hospital. Data were generated during the daily clinical routine, independent of the study. The algorithms for converting the EMR data into ABS-I were written in Rstudio® version 2022.2.0.443 (RStudio: Integrated Development Environment for R. RStudio, PBC, Boston).

Calculation and Validation of Indicators

Only the first therapy per patient and hospitalisation wasanalysed (restart of therapy within two days was included in the first therapy). Prescriptions for surgical prophylaxis (according to the field "*indication*") were excluded from the analysis of ABS-I measuring the treatment decisions, except for the ABS-I assessing surgical prophylaxis itself. If an antibiotic was administered before it was prescribed, the time of the first administration was used as the prescription start time, assuming late documentation.
The output values of the indicators were quantified as the number of patients receiving an antibiotic and meeting the criterion of the indicator divided by all patients receiving antibiotics (expressed as a proportion). Validity of the output values was assessed by the study team including the local infectious diseases specialist and categorised as data complete (data quality category 1) or missing information possible due to incomplete documentation (data quality category 2A) or data processing issues (data quality category 2B), i.e., some information was not stored in a structure allowing (systematic) extraction. The third category was an indicator not computable as not considered in the application for ethical approval (data quality category 3A) or due to data processing issues (data quality category 3B). Rstudio® was used to quantify the selected ABS-I and to visualise the ABS-I in an interactive dashboard.
As there was no indication documented for numerous prescriptions and the plausibility of results were doubted, a post hoc sub-analysis was performed excluding patients with a duration of total antibiotic therapy less than 24 hours assuming prophylaxis, regardless of staying in the surgery or another ward. In another sub-analysis cefuroxime and cefazolin were excluded, as these substances were mainly used for surgical prophylaxis according to a local infectious disease specialist.

Results

Definition of Antibiotic Stewardship Indicators (ABS-I) (Figure 11)

The first selection of ABS-I consisted of 43 ABS-I, comprising 38 ABS-I described by Monnier *et al.* in their latest review on quality indicators for antibiotic use in the inpatient setting and 5 additional quality indicators used in the Swiss point prevalence study [9, 11]. As the review of Monnier *et al.* summarised almost completely all process indicators found in the literature, it was used as a basic list and supplemented when the wording in other studies was more specific (see supplementary data Table 1).

In the second step, 23 ABS-I were excluded, as 4 measured IT procedures, 2 analysed the mismatch between medical prescription and administration, and the terminology of 17 lacked the specificity to be rephrased as computable ABS-I. Of the remaining 19 ABS-I, 2 ABS-I were selected unchanged, 13 ABS-I were rephrased, and the last 6 ABS-I were split into 18 more specific and computable ABS-I. This resulted in a dataset of 32 process indicators, which were categorised into 28 indicators assessing treatment decisions and 4 indicators assessing documentation quality. Details for each indicator are given in supplementary data Table 1.

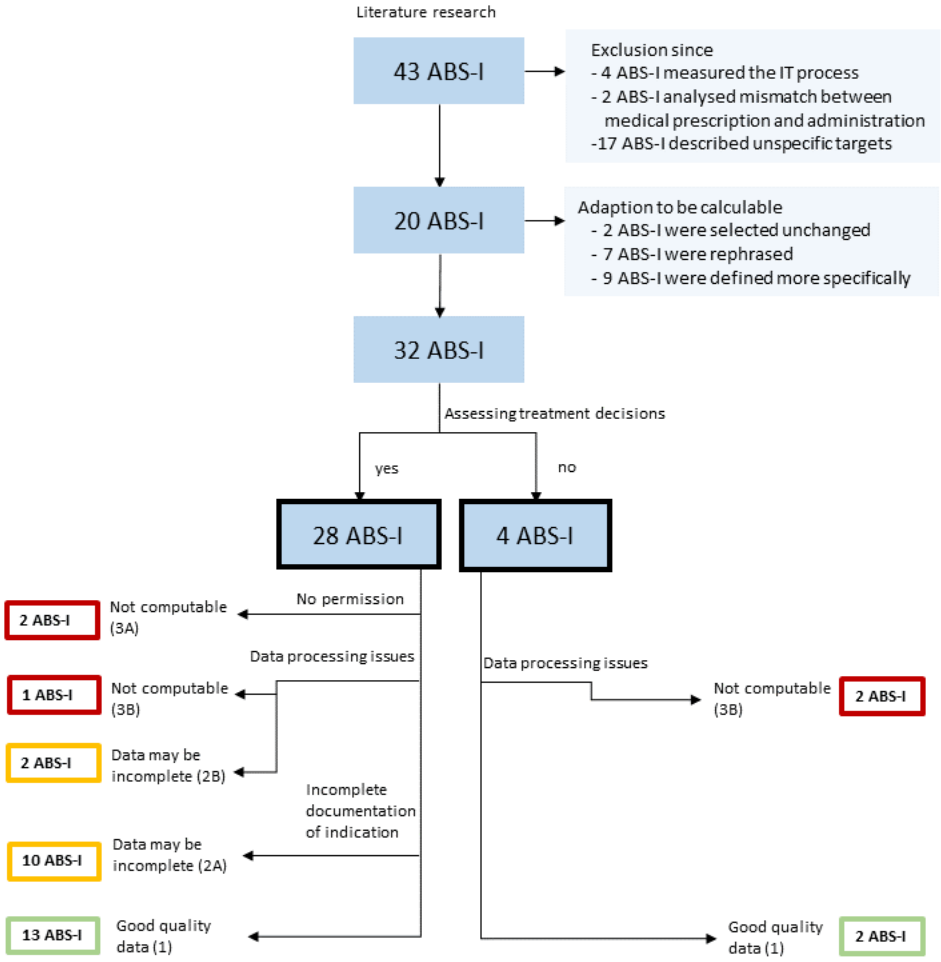


Figure 11: Selection process of selecting, coding and analysing antibiotic stewardship indicators (ABS-I). Data quality was categorised as good data quality (category 1, *green*), missing data (*orange*) due to incomplete documentation (category 2A) or data processing issues (category 2B) and data not computable *(red)* extracted as not considered in the application for ethical approval (category 3A) or due to data processing issues (category 3B).

Analysing Antibiotic Stewardship Indicators (ABS-I)

Data extraction allowed us to program algorithms for 89% (25/28) of the preselected ABS-I assessing treatment decisions (Table 2) and for 50% (2/4) of the ABS-I assessing documentation quality (Table 3). The two ABS-I that evaluate therapeutic drug monitoring could not be measured, as these data had not been considered in the application for ethical approval (data quality 3A). The proportion of patients with a documented severe allergic reaction against penicillin yet nonetheless treated with a beta-lactam could not be measured since documentation of the allergy could not be evaluated due to data processing issues (data quality 2B). More specifically, allergies to antibiotics could not systematically be distinguished from other recorded allergens.

Forty-eight percent (13/28) of treatment decision indicators and 50% (2/4) of the documentation quality indicators were considered good quality data (category 1, Figure 11, Figure 12). Data may be incomplete for the two ABS-I "*prescription was edited within 3 days*" and "*prescription was edited within 24 h after microbiological result*" (category 2B). Due to the data format, we could identify changes in therapy (including stopping therapy) or active new prescribing of the same therapy (which technically led to a new prescription number); however, if the therapy was simply continued, we were unable to evaluate if this was an active decision.

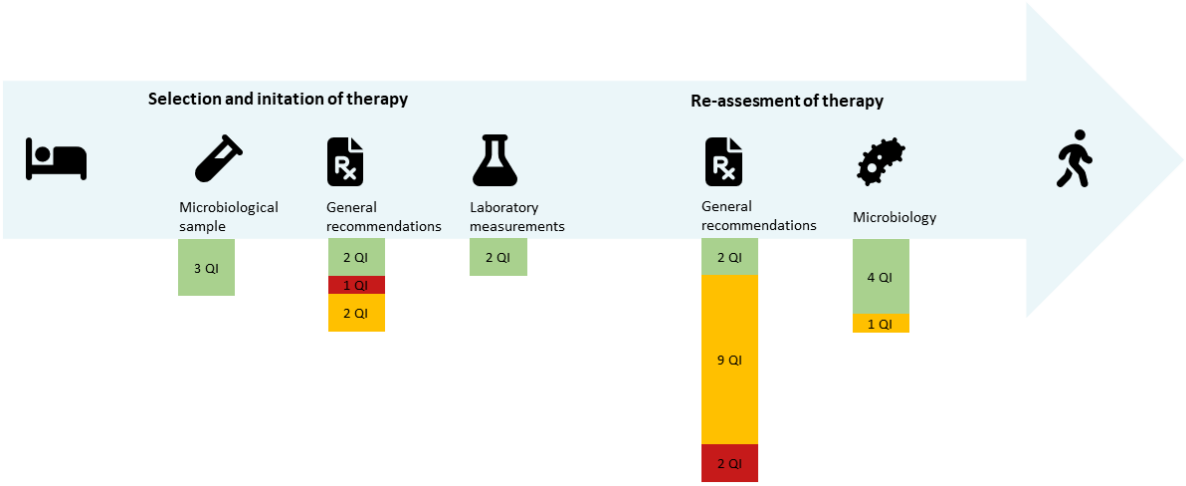


Figure 12: Antibiotic stewardship indicators (ABS-I) assessing treatment decisions classified based on data quality categorised as good data quality (category 1, *green*), missing data possible (category 2A, 2B, *orange*) due to incomplete documentation or data processing issues and data not systematically available (*red*).

A major issue was the incomplete documentation of the indication for antibiotic therapy, which affected 9 ABS-I (data quality 2A). In fact, meaningful documentation of the indication was available only in 5% of the hospitalisations. In 58% of the cases, it was completely missing, and in 37% it was meaningless (e.g., general indication, infection). Therefore, antibiotics given for surgical prophylaxis could not be properly excluded using the field "*indication*". To assess the impact of the incomplete exclusion of surgical prophylaxis for some ABS-I we performed two sub-analyses, defining surgical prophylaxis either as antibiotic therapy for less than 24 hours or excluding all antibiotic prescriptions with cefazolin of cefuroxime, the antibiotics used mainly for surgical prophylaxis in this hospital. The number of excluded patients in these sub-analyses was 9,113 (36%) and 5,721 (23%) patients, respectively. A total of 5,532 patients received cefazolin, and 267 received cefuroxime. Consequently, higher proportions were measured for the following ABS-I: edited prescription within 3 days, duration of (initial) therapy, antibiotic therapy despite low initial CRP, microbiological sample taken during hospitalisation and all ABS-I describing the first adjustments in antibiotic therapy (see supplementary data Table 3). As CRP is generally not measured before an invasive procedure, the corresponding ABS-I was judged as unlikely to be biased by incomplete documentation of surgical prophylaxis. In total, 32% (9/28) of treatment decision indicators were presumed to be affected by incomplete documentation of surgical prophylaxis (data quality 2A). In addition, it affected the two antibiotic consumption pattern indicators duration of therapy and proportion of patients receiving antibiotics for surgical prophylaxis (Table 4). The other 78% (7/9) of the metrics assessing antibiotic consumption patterns were considered good-quality data (data quality 1).

Table 2: Antibiotic stewardship process indicators assessing treatment decisions (for the entire study period).

Process indicator	Proportion of patients receiving antibiotics	Data quality category[1]
1) Selection and initiation of therapy		
A. Microbiological sample		
Microbiological sample taken during hospitalisation	51 % (N=25214)	1
Thereof microbiological sample taken before start of therapy	85 % (N=15200)	1
Thereof BC: % patients with at least two blood samples	85 (N=7119)	1
B. General recommendations		
Start of AB therapy for patients with bacteraemia at admission		
≤ 3h	69% (N=661)	1
> 3 and ≤ 24 h	24% (N=661)	
> 24 h	8% (N=661)	
% of patients with bacteraemia and start of AB therapy intravenously	98% (N=661)	1
Surgical prophylaxis: % patients with AB therapy < 24 hours	81 % (N=190)	2 A
Surgical prophylaxis: % patients with one administration	39 % (N=190)	2 A
Patients with a severe allergic reaction against penicillin documented and nonetheless treated with a beta-lactam	Not computable	3 B
C. Laboratory measurements		
Initial PCT < 0.25 µg/L and continuation of AB therapy > 24 h	32 % (N=3481)	1
Initial CRP < 20 mg/L and continuation of AB therapy > 24 h	19 (N=17156)	1
2. Re-assessment of therapy		
A. General recommendations		
Prescription was not adapted to impaired renal function[2]	30 % (N=997)	1
Thereof prescriptions should have been stopped due to impaired renal function[2]	8 % (N=301)	1
Serum level measurements performed when the treatment duration is more than 3 days for aminoglycosides or more than 5 days for vancomycin	Not computable	3 A
Thereof prescription was not adapted to measured serum level concentrations	Not computable	3 A
Prescription was edited within 3 days	31 % (N=25214)	2 B
Duration of initial therapy		2 A
< 24h	58 % (N=25214)	
1–3d	24 % (N=25214)	
3–7d	15 % (N=25214)	
>7d	3 % (N=25214)	
B. Types of first adjustments in antibiotic therapy		
Step-down to oral therapy within 3 days	10 % (N=16252)	2 A
Switch of substance within 3 days	10 % (N=25214)	2 A
Escalation: At least one AB added within 3 days	3 % (N=25214)	2 A
Narrow to broad-spectre[3] within 3 days	1 % (N=25214)	2 A
De-escalation: At least one AB less within 3 days	7 % (N=25214)	2 A
Broad[3] to narrow-spectre within 3 days	1 % (N=25214)	2 A
Stop of therapy within 3 days	59 % (N=25214)	2 A

C. Microbiology (considering antibiotic therapy >24h after arrival of microbiological result)		
Prescription was edited within 24h after microbiological result	31 % (N=15200)	2 B
ESCR-Enterobacterales BSI treated with piperacillin-tazobactam	34 % (N=82)	1
MSSA treated with anti-MRSA antibiotics	8 % (N=771)	1
Carbapenem-susceptible *P. aeruginosa* treated with substances reserved for multi-drug resistant organisms[4]	0 % (N=293)	1
VSE treated with daptomycin / linezolid	0.8 % (N=364)	1

AB, antibiotic; PCT, procalcitonin; CRP, C-reactive protein; BC, blood culture; ESCR-Enterobacterales BSI, bloodstream infection with extended-spectrum cephalosporin-resistant Enterobacterales; MSSA, methicillin-susceptible *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; VSE, vancomycin-susceptible enterococci

[1] Data quality category: 1, complete data; 2 A, incomplete data due to incomplete documentation of indication; 2 B, incomplete data due to data processing issues; 3 A, not computable since the data was not considered in the application for ethical approval; 3 B, not computable due to data processing issues

[2] Only antibiotics with dosing (measured in daily dose) independent of body-weight or indication and clearly recommended dose reduction according to eGRF were considered [133].

[3] Carbapenems, cefepime, ceftazidime, piperacillin-tazobactam

[4] Ceftolozane-tazobactam, ceftazidime-avibactam, cefiderocol, colistin

Table 3: Antibiotic stewardship process indicator assessing documentation quality (for the entire study period).

Process indicator	Proportion of patients receiving antibiotics	Data quality category[1]
Indication documented	42 % (N=25338)	1
Thereof meaningful	12 % (N=10537)	1
Antibiotic allergy documented	Not computable	3 B
Severity of antibiotic allergy documented	Not computable	3 B

Data quality category: 1, complete data; 3 B, not computable due to data processing issues

Table 4: Indicators assessing antibiotic consumption patterns (for the entire study period).

Indicator	Proportion of patients receiving antibiotics	Data quality category[1]
Intravenous therapy	83 % (N=25338)	1
Broad-spectre antibiotics[2]	10 % (N=25338)	1
Carbapenems	1 % (N=25338)	1
Fluoroquinolones	7 % (N=25338)	1
Per AWaRe group[3]		1
Access	61 % (N=25338)	
Watch	38 % (N=25338)	
Reserve	0.2 % (N=25338)	
Number of different antibiotics per patient and hospitalisation		
1	67 % (N=25338)	1
2	22 % (N=25338)	
>2	11 % (N=25338)	
Surgical prophylaxis	0.7 % (N=25338)	2 A
Restart of therapy (defined as interval of at least 2 days)	32 % (N=25338)	1
Duration of therapy (excluding prophylaxis and restarted therapies)		2 A
<24h	36 % (N=25214)	
1–3d	22 % (N=25214)	
3–7d	28 % (N=25214)	
>7d	15 % (N=25214)	

[1] Data quality category: 1, complete data; 2 A, incomplete data due to incomplete documentation of indication; 2 B, incomplete data due to data processing issues; 3 A, not computable since the data was not considered in the application for ethical approval; 3 B, not computable due to data processing issues

[2] Carbapenems, cefepime, ceftazidime, piperacillin-tazobactam

[3] According to 2021 AWaRe WHO classification [83]

Estimation and Visualisation of Antibiotic Stewardship Indicators (ABS-I)

In total, data from 25,338 hospitalisations from 20,723 individual patients were analysed. The estimated numbers are given in Tables 1, 2, and 3 and are presented in an interactive dashboard. Selected ABS-I were visualised as tacho graphics in the first tab of the interactive dashboard (Figure 13). In addition, all ABS-I were depicted in tables allowing comparison between location and departments. The ABS-I could be filtered according to location, department, year, month and age category.

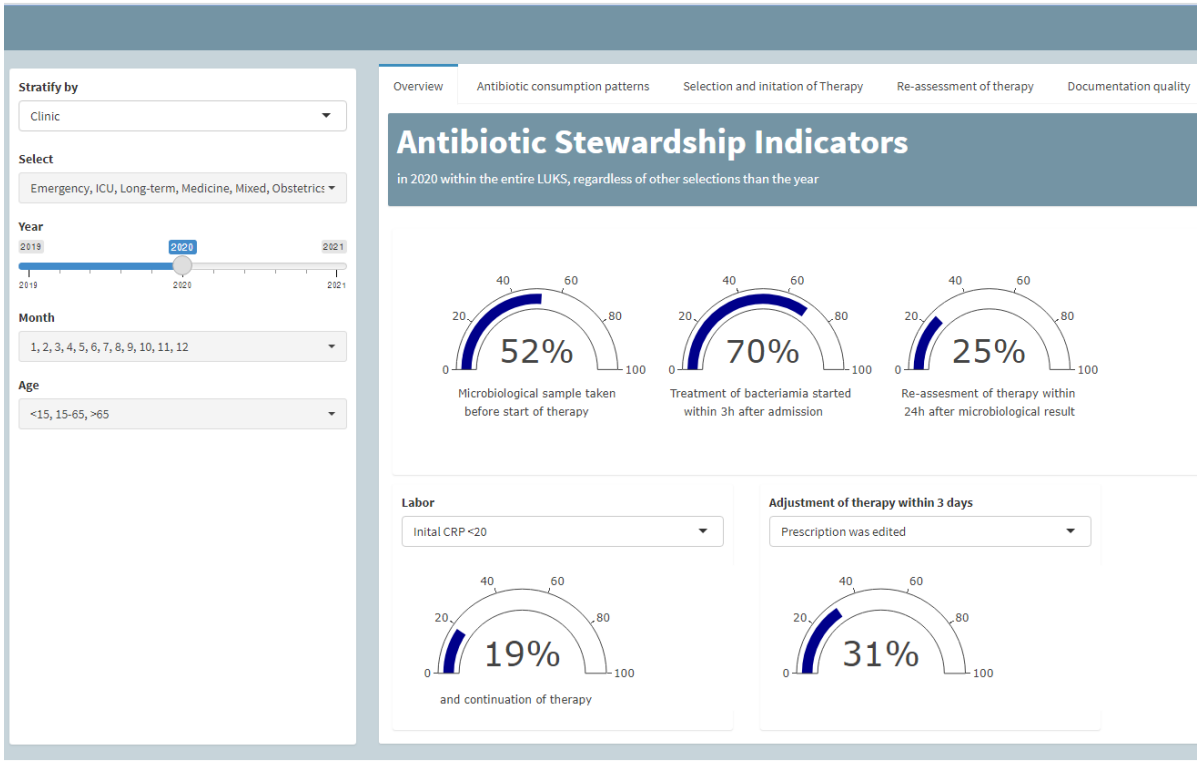


Figure 13: Screenshot of the antibiotic stewardship overview panel of the dashboard for 2020.

Based on this feasibility study, format specifications were elaborated to enable the incorporation of patient-level antibiotic prescription data into the surveillance database (Supplementary Table 5 – 7). In addition, an indication recording format was defined based on the indication-registration tool of Van den Broeak *et al.* (Supplementary Table 4) [134].

Discussion

Coding algorithms to convert EMR data into indicators assessing the treatment decisions was feasible for 25 ABS-I. The feasibility of using EMR data for analysing a narrowed list of antibiotic stewardship metrics was recently demonstrated as well in the UK [135].
Prior to the coding, most ABS process indicators described in the literature needed to be rephrased or specified to be calculable. This resulted in the exclusion of 17 ABS-I from the literature on the one hand and splitting of 6 ABS-I from the literature into 18 more specific ABS-I for our study on the other hand. In particular, the ABS-I referring to the implementation of guidelines would have to be adapted locally to be helpful for defining ABS measures, even if international comparability/benchmarking is hampered. In our setting, three main issues impaired data analysis. First, ABS-I that evaluate documentation of antibiotic allergies were not calculable since the allergens recorded were not systematically classifiable as antibiotic substances. To implement this, the predefined allergen list within the EMR needs to be adapted to a uniform labelling of drugs, and the preselection of "*unknown*

antibiotic" and "*no allergy*" should be added. Second, documentation of an active decision to prolong a given antibiotic therapy in the EMR should be improved. Actually, the two ABS-I "*prescription was edited within 3 days*" and "*prescription was edited within 24 h after microbiological result*" could only be calculated if therapy was adapted, stopped or reordered. Reviews and extensions were not recorded systematically. An automated stop rule after three days of antibiotic therapy could increase the performance in this ABS-I. Third, meaningful documentation of the indication was available only in 5% of the hospitalisations; in 58%, it was completely missing, and in 37%, it was meaningless. Hence, a more complete, well-structured and mandatory recording of the indication would be helpful not only to exclude (and analyse separately) the surgical prophylaxis but also to better survey choices and dosing of antibiotic therapies according to the indication. Van den Broeck *et al*. proposed a mandatory indication-registration tool using Epic systems®, which was not considered too burdensome by the prescribers [134]. Implementing these three main restrictions would have increased the number of good quality data from 13 to 26. In general, the data quality issues could easily be solved by implementing this simple, tailored suggestion to improve the data recording in the specific EMR.
Previous studies allowing a comparison and plausibility check of the ABS-I were scarce. A lower value for the step-down to oral therapy was found in our study than those reported in the UK, the Netherlands or within other Swiss hospitals (10% vs. 36% vs. 32% vs. 82%) [131, 135, 136]. Our ABS-I described the step-down within three days, while the Dutch study analysed the switch within 48—72 hours. The time frame considered was longer in the two other studies mentioned — seven days or not restricting it at all. In addition, all three other studies took the clinical condition into account manually, according to Catho *et al*. For the indicator microbiological sample taken before the start of therapy (51%), large differences were also observed in comparison to the UK (22%) and the Netherlands (94%). Again, differences in methodology may be the reason why in our study, samples taken on the same day as therapy was started were considered "samples taken before the start of therapy", since the sampling date but not the time was available. However, in the Netherlands, only patients with targeted therapy were considered. The lower adaptation of the antibiotic therapy after receipt of the microbiological result in our study (31% vs. 91% vs. 50%), however, could be explained by technical issues as described above [131, 136].
The percentage of antibiotics prescribed for surgical prophylaxis was much lower (0.7%) than reported in the Swiss point prevalence study (34%) [9]. Relying on the correct indication only, the proportion would be 0.3% (N=79/25338). However, in our first approach, antibiotic treatments given the first time in the operating room were also considered surgical prophylaxis, which elevated the proportion to 0.7% (N=190/25338). Considering all patients with antibiotic therapy for less than 24 hours or all patients treated with antibiotics nearly exclusively for surgical prophylaxis in this setting would have resulted in 37% and 28%, respectively. The correct classification of surgical prophylaxis not only affects the estimation of the percentage of prophylaxes but — as these prescriptions should be excluded from the analysis of antibiotic therapies — also for many other ABS-I, too. For example, excluding probable prescriptions for surgical prophylaxis in the sub-analysis yielded higher values for numerous ABS-I such as *edited prescription within 3 days* and *the duration of therapy*. This highlights the significance in differentiating between prescriptions for surgical prophylaxis vs. therapy and considering the documentation quality when comparing these ABS-I between hospitals in the future.
Analysing the overall prescription data revealed a high correlation with hospital-level data from ANRESIS (delivered by hospital pharmacists) in proportion to antibiotic use of intravenous therapy, fluoroquinolones, carbapenems and per AWaRe group [16]. However, the total antibiotic use of the pilot hospital summarising patient-level data was much lower than the consumption in comparable Swiss cantonal hospitals calculated by hospital-level data (data not shown). A small fraction of this difference was explained by antibiotic treatment of patients not included in the study due to rejection of the general consent. As this is the case for only approximately 500 patients, other explanations are

needed, such as the disposal of opened packages or give away of limited numbers of antibiotics after discharge. These differences need clarification in the future.
The most important limitation lies in the plausibility control. There are no satisfactory explanations for the differences in total antibiotic use calculated by patient-level data compared to the consumption of similar hospitals computed by hospital-level pharmacy data. Conversely, the proportion of antibiotic use per AWaRe group was comparable. Another constraint was the low documentation quality on indication, which limited the selection of ABS-I as well as the proper exclusion from surgical prophylaxis from most analyses [134]. In general, quantitative data on this ABS-I are very sparse in the literature and highly dependent on methodological issues, which differ essentially between studies, making comparison/validation impossible. This implies that our results should be validated by extending the analysis to other Swiss hospitals. Moreover, international antibiotic stewardship study groups should elaborate a set of unambiguously defined ABS-I assessing treatment decisions considering computability.
Despite these limitations, we were able to establish a continuous, automated monitoring system relying on EMR data and devised a procedure enabling all interested Swiss hospitals that provide data in the required format, to monitor patient-level data and conduct a systematic analysis of ABS-I in the future. In addition, we were able to formulate a few important steps, which essentially improve the data quality. Displaying data on an interactive dashboard enables us to give an overview, to compare the ABS-I within departments or patient groups and to filter the data according to user-specific needs. The dashboard technology will be developed further to handle patient-level data from several hospitals, which will also allow inter-hospital benchmarking. Monitoring of continuous patient-level prescription data would be very useful for antibiotic stewardship teams to define and measure interventions. In addition, research projects could be initiated, e.g., by analysing which ABS-I are associated with patient outcomes, costs and resistance. It was demonstrated by Van den Bosch *et al.* that an appropriate step down to oral therapy was associated with a shorter length of hospitalisation and, thus, reduced health care costs [137].
In conclusion, the calculation of antibiotic stewardship indicators reflecting the treatment decisions from electronic medical records was feasible. However, a better data structure within the electronic medical records and data from other hospitals is crucial for improving the validity of the results.

Supplementary Table 1: Selection process and technical definition of antibiotic stewardship process indicators

Process indicator	Decision	Rephrasing and *definition*, respectively
1) Selection and initiation of therapy **A. Microbiological sample** Microbiological investigations should be performed according to guidelines	Rejected[1]	
When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started. (Cultures should be taken until a maximum of 24 h after antibiotics are started.) [11, 105].	Specified	**Microbiological sample taken during hospitalisation.** **Thereof microbiological sample taken before start of therapy.** *Def. For the QI microbiological sample taken before therapy start, samples which were taken >= 3 days before the admission date were excluded. The date but not the time when the sample was ordered was available. It was assumed that the sample was taken at the same day as it was ordered. Samples ordered at the same day as the day of therapy start or the day before were considered as taken before therapy start. A more precise naming of the QI would be "Microbiological sample taken before 24 h of therapy".*
Before starting systematic antibiotic therapy, at least 2 sets of blood cultures should be taken [11, 105].	Rephrased	**Blood cultures: Proportion of patients with at least two blood cultures taken.**
B. General recommendations Patients with a history of anaphylaxis after penicillin therapy should pe prescribed and alternative drug class [11].	Rephrased	**Patients with a severe allergic reaction against penicillin documented and nonetheless treated with a beta-lactam.**
Antibiotic therapy in adult patients with sepsis should be started intravenously [11].	Rephrased	**% of patients with bacteraemia and start of AB therapy intravenously.**
	Specified	**% of patients with bacteraemia and start of AB therapy within 3 hours after admission [138].** *Def. Patient with bacteraemia at admission were defined by a positive blood culture (BC) taken at the admission day or the day before the admission. If more than 2 BC were taken but only 1 BC was positive, it was not considered as bacteraemia supposing contamination.*
Surgical prophylaxis: % patients with AB therapy < 24 hours [9]	Selected	*Def. Surgical prophylaxis was defined as indication surgical prophylaxis or therapy started the operation room with a substance which was not already administered before.*
Surgical prophylaxis: % patients with one administration [9, 132]	Selected	

C. Laboratory measurements Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection [11].	Specified	Initial PCT < 0.25 µg/L and continuation of AB therapy > 24 h [139-143] *Def. Measurement below 0.25 µg/L and duration of antibiotic therapy more than 24 hours after measurement was defined as antibiotic therapy despite low PCT values. PCT measurement within 2 days before or 1 day after start of therapy were considered.* Initial CRP < 20 mg/L and continuation of AB therapy > 24 h [144, 145] *Def. Measurement below 20 mg/L and duration of antibiotic therapy more than 24 hours after measurement was defined as antibiotic therapy despite low CRP values. CRP measurement within 2 days before or 1 day after start of therapy were considered.*
2) Re-assessment of therapy A. General recommendations Dose and dosing interval of systemic antibiotics should be adapted to renal function [11, 105].	Specified	*Def. For all indicators described below the first therapy was considered only. Meaning that prescriptions after a restart of therapy were excluded. Prescription with the indication surgical prophylaxis were excluded as well.* Prescription was not adapted to impaired renal function Thereof prescriptions should have been stopped due to impaired renal function *Def. Renal impairment was defined as estimated glomerular filtration rate (eGFR) below "eGFR ok". Patients with age >= 15 were considered. The smallest eGFR value during hospitalisation and the first date with this value was considered for the corresponding QI. Substances were only considered if the adaptation is independent of bodyweight and indication. Based on the guidelines used at Lucerne cantonal hospital (namely, the KSSG guidelines [17]), a table was created defining the "eGFR ok", the lowest eGFR which does not require dosage adaptation, and the "DDD ok" the maximal dosage per day in DDD for this substance at the "eGFR ok". The prescription data was aggregated on given DDD per day and order. Not adapted was defined as the given DDD per day higher than the "DDD ok". Therapy stopped due to impaired renal function was defined as therapy started before the eGFR measurement and stopped within 24 h after the measurement. Only antibiotics with dosing independent of body-weight or indication and clearly recommended dose reduction according to eGRF were considered.*

TDM should be performed for antibiotics with a narrow therapeutic spectrum and an increased risk of toxicity (such as gentamicin and vancomycin) according to guidelines [11]. Therapeutic drug monitoring should be performed when the treatment duration is > 3d for aminoglycosides and > 5 d for vancomycin [105].	Rephrased	**Serum level measurements performed when the treatment duration is more than 3 days for aminoglycosides or more than 5 days for vancomycin.**
If antibiotic TDM levels are not in the reference range, doses should be adjusted appropriately after the results become available [11]	Rephrased	**Thereof prescription was not adapted to measured serum level concentrations**
Antibiotics for empirical therapy should be reviewed after the third day of treatment or when microbiological results become available [11].	Specified	**Prescription was edited within 3 days.** *Def. Edited prescription within 3 days was defined as start date of a new order within 3 days but later than 6 hours after start of first prescription or if stop of therapy was within 3 days but later than 6 hours after start of first prescription. Prescription "edited" was defined by a change of therapy including therapy stop or by selecting the action "prescribe therapy again". Whereas the information of selecting the predefined action "prolonging therapy" was lost during data processing in the EMR system as this did not lead to a change in underlying "order id" and could not be considered for the QI regarding "editing" prescription.* **Duration of initial therapy (< 24 h vs. 1–3 d, vs. 3–7d vs. > 7d)** *Def. Duration of initial therapy was defined as the duration until the first adaptation of therapy excluding adaptations within the first 6 hours.*
B. Types of first adjustments in antibiotic therapy		*Def. Changes within the first 6 hours of therapy were not considered as "first switch of therapy" or "edited prescription" assuming that the change was caused by discussing the first therapy and not by re-evaluating it based on new information available [18].*
Switching from intravenous to oral antibiotic(s) should be performed according to guidelines [11]. Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate [11, 105].	Rephrased	**Step-down to oral therapy within 3 days** *Def. For the step-down to oral therapy, patients whose first treatment consisted of an intravenous therapy were considered only. The time when the intravenous therapy was stopped and therapy was continued with an oral antibiotic was described as duration until step-down to oral therapy. A total stop of therapy was not considered as step-down to oral therapy.*

Proportion of patients with a change in therapy regimen at the survey day: any change or escalation or de-escalation [9].	Specified	**Escalation: At least one AB added within 3 days** *Def. Combination therapy was defined as different antibiotic substances administered during the same time period and used for the QI "escalation: at least one AB added within 3 days", "de-escalation: at least one AB less within 3 days", respectively. Combination therapies within the same formulation such as amoxicillin clavulanic-acid were not considered as combination therapy. To match the definition, the first requirement was that the substances were different, second the order had to be started after/equal the start the other therapy. Third the order has to be started before before/equal the stop of the other therapy. The equal is important as there are antibiotics which are administered only once. For the de-escalation of number of antibiotics, the duration until the first stop of the combination therapy was considered.* **Escalation: Narrow to broad-spectre within 3 days** *Def. Following substances were defined as broad-spectre antibiotics: azetronam, carbapenems (meropenem, ertapenem, imipenem-cilastatin), cefepime, ceftazidime, piperacillin-tazobactam, ticarcillin-clavulanic acid.* **De-escalation: At least one AB less within 3 days** **De-escalation: Broad to narrow-spectre within 3 days** **Switch of substance within 3 days** **Stop within 3 days**
C. Microbiology (considering antibiotic therapy > 24 h after arrival of microbiological result) Antibiotics for empirical therapy should be reviewed after the third day of treatment or when microbiological results become available [11].	Rephrased	**Prescription was edited within 24 h after microbiological result** *Def. See definition of QI Prescription edited within 3 days*
Broad-spectre empirical antibiotic therapy should be changed to pathogen-directed therapy as soon as culture results become available [11]. Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available[105].	Specified	**ESCR-Enterobacterales BSI treated with piperacillin-tazobactam [18].** **MSSA treated with anti-MRSA antibiotics.** **VSE treated with daptomycin/linezolid.** **Carbapenem-susceptible *P. aeruginosa* treated with substances reserved for multidrug resistant organisms (ceftolozane-tazobactam, ceftazidime-avibactam, cefiderocol, colistin)** *Def. The bug-drug-mismatches were defined as corresponding therapy started within 24 hours after the microbiological result or therapy continued for more than 24 hours after the result was available.*

Documentation quality An antibiotic plan should be documented in the medical record at the start of the antibiotic treatment. (Antibiotic plan includes: indication, name, doses, duration, route, and interval of administration) [11, 105].	Specified	Indication documented Thereof meaningful *Def. Indications such as "severe infection", "general indication", "pain and inflammation" were considered as not meaningful.*
Allergy status (including nature and severity of the patient should be documented in the medical records when antibiotics are prescribed) [11].	Specified	Antibiotic allergy documented Severity of antibiotic allergy documented
Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics [11].	Rejected	Measures partly IT process
The results of bacteriological susceptibilities should be documented in the medical records [11].	Rejected	Measures IT process
TDM levels of antibiotics should be documented in the medical records [11]	Rejected	Measures IT process

AB, antibiotic; PCT, procalcitonin; CRP, C-reactive protein; BC, blood culture; ESCR-Enterobacterales BSI, bloodstream infection with extended-spectrum cephalosporin-resistant Enterobacterales; MSSA, methicillin-susceptible *Staphylococcus aureus*; VSE, vancomycin-susceptible enterococci

[1]The indicator is too general to be calculated. For example, a specification according to indication would be required to be computable.

[2] Measures IT process.

[3] The aim was to analyse medical prescription and not mismatch between medical prescription and actual administration.

[4] This is more a structural than a process QI.

Supplementary Table 2: Technical definitions of indicators assessing antibiotic consumption patterns

Antibiotic consumption patterns *[9, 16, 132]*	**Definition**
Intravenous therapy	*Proportion of patient receiving at least on prescription of an antibiotic for intravenous therapy.*
Broad-spectre antibiotics	*Proportion of patient receiving at least one prescription of a broad-spectre antibiotic. Following substances were defined as broad-spectre antibiotics: azetronam carbapenems (meropenem, ertapenem, imipenem-cilastatin), cefepime, ceftazidime, piperacillin-tazobactam, ticarcillin-clavulanic acid.*
Carbapenems	*Proportion of patient receiving at least on prescription of a carbapenem.*
Fluoroquinolones	*Proportion of patient receiving at least on prescription of a fluoroquinolone.*
Per AWaRe group	*The patients were categorised by receiving an antibiotic from the "access", "watch" and "reserve" group according to the WHO [83] . When a patient received several antibiotics, the most critical was counted.*
Number of different antibiotics per patient and hospitalisation 1 vs. 2 vs. > 2 substances	*For describing the number of different antibiotics per patient and hospitalisation, the number of different antibiotic substances given were counted, fixed combinations were counted as one substance. It was not differentiated if the substances were administered simultaneous or consecutively.*
Surgical prophylaxis	*Proportion of patients with an indication for surgical prophylaxis.*
Restart of therapy (defined as interval of at least 2 days)	*A restart of therapy was defined by a time difference between the stop of an order and start of new prescription >= 2 days. The "first restart" of therapy was considered only.*
Duration of therapy (excluding prophylaxis and restarted therapies, < 24 h vs. 1–3 d vs. 2–7 d vs. > 7d	*Duration of therapy was defined as the time between the first order of any antibiotic substance and the last stopped order of any antibiotic substance. Prescriptions for surgical prophylaxis or restart of therapy were excluded.*

Supplementary Table 3: Indicators assessing treatment decisions or duration of therapy excluding prophylaxis and number of patients receiving prophylaxis. Comparing results with the analysis excluding patients with a duration of therapy less than 24 hours and with the other sub-analysis excluding cefazolin and cefuroxime.

Indicator	Proportion of patients receiving antibiotics	Proportion of patients receiving antibiotics ≥ 24 h	Proportion of patients receiving antibiotics excluding cefazolin and cefuroxime
Antibiotic consumption patterns			
Surgical prophylaxis	0.7 % (N=25338)	37 % (N=25338)	28 % (N=25338)
Duration of total antibiotic therapy			
<24h	36 % (N=25214)	-	20 % (N=19493)
1–3d	22 % (N=25214)	34 % (N=16101)	26 % (N=19493)
3–7d	28 % (N=25214)	43 % (N=16101)	35 % (N=19493)
>7d	15 % (N=25214)	22 % (N=16101)	19 % (N=19493)
Treatment management decision			
1) Selection and initiation of therapy			
A. Microbiological sample			
Microbiological sample taken during hospitalisation	51 % (N=25214)	68 % (N=16101)	64 % (N=19493)
Thereof microbiological sample taken before start of therapy	85 % (N=15200)	88 % (N=12476)	87 % (N=14206)
Thereof BC: % patients with at least two blood samples	85 % (N=7119)	86 % (N=6560)	86 % (N=7077)
B. General recommendations			
Start of AB therapy for patients with bacteraemia at admission			
≤ 3 h	69% (N=661)	69 % (N=627)	69% (N=661)
>3h and ≤ 24 h	24% (N=661)	24 % (N=627)	24% (N=661)
> 24 h	8% (N=661)	8 % (N=627)	8% (N=661)
% of patients with bacteraemia and start of AB therapy intravenously	98% (N=661)	99 % (N=627)	98 % (N=661)
C. Laboratory measurements			
Initial PCT < 0.25 µg/L and continuation of AB therapy > 24 h	32 % (N=3481)	35 % (N=3181)	32 % (N=3454)
Initial CRP < 20 mg/L and continuation of AB therapy > 24 h	19 % (N=17156)	25 % (N=13113)	21 % (N=15458)

2) Re-assessment of therapy			
A. General recommendations			
Prescription was not adapted to impaired renal function[1]	30 % (N=997)	33 % (N=882)	31 % (N=930)
Thereof prescriptions should have been stopped due to impaired renal function[1]	8 % (N=301)	7 % (N=290)	8 % (N=292)
Prescription was edited within 3 days	31 % (N=25214)	46 % (N=16101)	38 % (N=19493)
Duration of initial therapy			
<24h	58 % (N=25214)	34 % (N=16101)	48 % (N=19493)
1–3d	24 % (N=25214)	37 % (N=16101)	29 % (N=19493)
3–7d	15 % (N=25214)	24 % (N=16101)	20 % (N=19493)
>7d	3 % (N=25214)	5 % (N=16101)	4 % (N=19493)
B. Types of first adjustments in antibiotic therapy			
Step-down to oral therapy within 3 days	10 % (N=16252)	10 % (N=16099)	10 % (N=15690)
Switch of substance within 3 days	10 % (N=25214)	15 % (N=16101)	11 % (N=19493)
Escalation: At least one AB added within 3 days	3 % (N=25214)	4 % (N=16101)	3 % (N=19493)
Narrow to broad-spectre[2] within 3 days	1 % (N=25214)	2 % (N=16101)	2 % (N=19493)
De-escalation: At least one AB less within 3 days	7 % (N=25214)	10 % (N=16101)	8 % (N=19493)
Broad[2] to narrow-spectre within 3 days	1 % (N=25214)	2 % (N=16101)	1 % (N=19493)
Stop of therapy within 3 days	59 % (N=25214)	37 % (N=16101)	48 % (N=19493)
C. Microbiology			
Prescription was edited within 24h after microbiological result	31 % (N=15200)	34 % (N=12476)	32 % (N=14206)
ESCR-Enterobacterales BSI treated with piperacillin-tazobactam	34 % (N=82)	35 % (N=81)	32 % (N=80)
MSSA treated with anti-MRSA antibiotics	8 % (N=771)	7 % (N=764)	7 % (N=761)
Carbapenem-susceptible *P. aeruginosa* treated with substances reserved for multi-drug resistant organisms[3]	0 % (N=293)	0 % (N=283)	0 % (N=287)
VSE treated with daptomycin / linezolid	0.7 % (N=364)	0.8 % (N=358)	0.8 % (N=357)

AB, antibiotic; PCT, procalcitonin; CRP, C-reactive protein; BC, blood culture; ESCR-Enterobacterales BSI, bloodstream infection with extended-spectrum cephalosporin-resistant Enterobacterales; MSSA, methicillin-susceptible *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; VSE, vancomycin-susceptible enterococci

[1] Only antibiotics with dosing independent of body-weight or indication and clearly recommended dose reduction according to estimated glomerular filtration rate (eGRF) were considered.

[2] Carbapenems, cefepime, ceftazidime, piperacillin-tazobactam

[3] Ceftolozane-tazobactam, ceftazidime-avibactam, cefiderocol, colistin

Supplementary Table 4: Indication recording format (adapted from [134])

Level 1	Level 2	Level 3
Prophylaxis	Perioperative CF SDD Other	
Pre-emptive therapy	Immuno-compromised Other	
Empirical therapy	Upper respiratory tract	GAS Otitis media Sinusitis Other
	Lower respiratory tract	CAP VAP HAP COPD Epyema Other
	Gastrointesintal	Enteritis/colitis Clostridium difficile Other
	Intra-abdominal	Biliary tract SBP/CAPD peritonitis Post-surgery/complication Perforation Appendicitis Other
	Urinary tract	Cystitis Pyelonephritis Prostatitis CAUTI Other
	Gynaecology/obstetrics	Obstetric infection PID/TOA Other
	STI	STI
	Central nervous system	Post-surgery Meningitis/encephalitis Brain abscess Other
	Sepsis	CLABSI Neutropenic fever Unknown cause
	Cardiovascular	Endocarditis native valve Endocarditis prosthetic valve PM/ICD Other
	Joint and bones	Prothesis joint infection Non-prothesis joint infection Osteomyelits Other
	Skin and soft tissue	Surgical site infection Cellulitis (incl. wound infections) Other
	Tropical disease	Malaria Other
	Other	Other
Targeted theray	(the same sub-categories as for empricial therapy)	

Supplementary Data: Format Specifications

These data specify the inpatient data on antibiotic prescription/ administration on patient-level.

Antibiotic prescription data ("p") consists of a single line per prescription including among others start and stop date/time of the prescription, the prescribed dosage and frequency.

Antibiotic administration data ("a") consist of a single line per each administration including time and dosage of the administration.

Data on administration level including information concerning prescription ("ap") consist on a single line per each administration including prescription id, start and stop date/time of the prescription, administration date/time and dosage of administration.

Supplementary Table 5: Data table for antimicrobial prescription data

Field Name	Description	Required	Type	Length
ATC Code	ATC code specific for antibiotic substance	ess if pharma code is empty (preferred)	number	
AD route	Route of administration (per oral, parenteral, topic or other)	ess if pharma code is empty (preferred)	text (pre-defined list)	
Pharma code	Code for the antibiotic-package (specific for antibiotic, dose and number of pills)	ess if ATC Code and AD route is empty	text	20
Data type	Differentiate between prescription data (p) administration data (a) and administration and prescription data (ap)	ess	Text (p or a or ap)	1
Prescription ID	Code for each prescription	ess for data type p or ap	text	
Prescription start date + time	Date and time of prescription	ess for data type p and ap	date + time [dd-mm-yyyyThh:mm]	
Prescription stop date + time	Date and time when prescription was stopped / expired	ess for data type p and ap	date + time [dd-mm-yyyyThh:mm]	
Date + time of administration	Date and time when antibiotic was administered	ess for data type a and ap	date + time [dd-mm-yyyyThh:mm]	
Dosage	Administered or prescribed dose	ess for data type a and ap	number	
Unit of dosage	[mg, Mio IU]	ess	text (pre-defined list)	
Unit of prescribed application frequency	Unit of the prescribed time interval between two administrations, together with the next data field - Single dose - Per day - Per week - Per month	ess for data type p	text (pre-defined list)	

Number of prescribed administrations per unit of application frequency	Prescribed duration between two administrations, depending on the data field before - Single dose -> 1 - Per days [hours] - Per week [days] Per month [days]	ess for data type p	number	
Patient ID	Laboratory specific patient ID. This can be an existing patient or a new one. RESISTANCE and ACD data can refer to the same patient IDs.	ess	text	80
Case number	Laboratory specific case number. This can be an existing case number or a new one. RESISTANCE and ACD data can refer to the same case numbers.	opt	text	30
Sex	Sex of patient. Permitted values are “m”, “f” and “u” (for ‘unknown).	mand	text	1
Age	Age in years, not known = -1	mand	number	1
Ward ID	Identifier of the ward This is a provider specific name which is defined in the ward mapping table.	ess	text (max 50 signs)	50
Hospitalisation date + time	Date of hospitalisation	mand if case number is not available	date + time [dd-mm-yyyyThh:mm]	
Discharge date + time	Date + time of discharge	mand	date + time [dd-mm-yyyyThh:mm]	
Therapeutic group	Prophylaxis Pre-emptive therapy Empirical therapy Targeted therapy	opt	text	15
Indication	Perioperative CF SDD Other Immune-compromised Upper respiratory tract Lower respiratory tract Gastrointestinal Intra-abdominal Urinary tract Gynaecology/obstetrics STI Central nervous system Sepsis Cardiovascular Joint and bones Skin and soft tissue Tropical disease	opt	text (pre-defined list)	

Indication specified	Perioperative CF SDD Other Immune-compromised GAS Otitis media Sinusitis Other VAP CAP HAP COPD Epyema Enteritis/colitis Clostridium difficile Biliary tract SBP/CAPD peritonitis Post-surgery/complication Perforation Appendicitis Cystitis Pyelonephritis Prostatitis CAUTI Obstetric infection PID/TOA STI Post-surgery Menigitis/encephalitis Brain abscess CLABSI Neutropenic fever Unknown cause Endocarditis native valve Endocarditis prosthetic valve PM/ICD Prothesis joint infection Non-prothesis joint infection Osteomyelitis Surgical site infection Cellulitis (incl. wound infections) Malaria	opt	text (pre-defined list)	

ess, essential; data type p, data on prescription level; data type ap, data on administration level including information concerning prescription; data type a, data on administration level; ACD, antibiotic consumption data; IU, international unit; mand, mandatory; opt, optional; CF, cystic fibrosis; SDD, selective decontamination of the digestive tract; STI, sexually transmitted infections; GAS, group A streptococcus; VAP, ventilator-associated pneumonia; CAP, community-acquired pneumonia, HAP, hospital-acquired pneumonia; COPD, chronic obstructive pulmonary disease; SBP, spontaneous bacterial peritonitis; CAPD, continuous ambulatory peritoneal dialysis; CAUTI, catheter-associated urinary tract infections; PID, pelvic inflammatory disease; TOA, tubo-ovarian abscess; CLABSI, central line-associated bloodstream Infection; PM, pacemaker; ICD, implantable cardioverter-defibrillator

Supplementary Table 6: Data table for microbiological data not send by laboratory but available

Field Name	Description	Required	Type	Length
Patient ID	Laboratory specific patient ID. This can be an existing patient or a new one. RESISTANCE and ACD data can refer to the same patient IDs.	ess	text	80
Case number	Laboratory specific case number. This can be an existing case number or a new one. RESISTANCE and ACD data can refer to the same case numbers.	mand if hosp date is not available	text	30
Ward ID	Identifier of the ward This is a provider specific name which is defined in the ward mapping table.	opt	text (max 50 signs)	50
Hospitalisation date/time	Date/time of hospitalisation	mand if case number is not available	date + time [dd-mm-yyyyThh:mm]	
sample Id	Identifier of the sample as it is used at laboratory. The identifier has to be unique for each laboratory. RESISTANCE and ACD data can refer to the same case numbers.	ess	text	30
Test type	Gram test, blood culture (positive/ negative), microorganism identification, resistance	ess	text (pre-defined list)	
Order date/time	Date/Time of ordering sample or sampling date of the test	ess	date + time [dd-mm-yyyyThh:mm]	
Result	From gram test, blood culture positivity and resistance: 0= negative, 1= positive For microorganism identification: name (pre-defined list)	ess	text	
Result date + time	Date/time when result is of the test is available	ess	date + time [dd-mm-yyyyThh:mm]	15

ID, identifier; ACD, antibiotic consumption data; ess, essential; mand, mandatory; opt, optional

Supplementary Table 7: Data table for prescription related data

Field Name	Description	Required	Type	Length
Patient ID	Laboratory specific patient ID. This can be an existing patient or a new one. RESISTANCE and ACD data can refer to the same patient IDs.	ess	text	80
Case number	Laboratory specific case number. This can be an existing case number or a new one. RESISTANCE and ACD data can refer to the same case numbers.	mand if hosp date is not available	text	30
Ward ID	Identifier of the ward This is a provider specific name which is defined in the ward mapping table.	opt	text (max 50 signs)	50
Hospitalisation date/time	Date/time of hospitalisation	mand if case number is not available	date + time [dd-mm-yyyyThh:mm]	
Parameter	Selected measured parameter - eGFR - CRP - PCT - allergy - TDM - bodyweight - leucocytes - granulocytes - placing or removing a device such as a catheter	ess	text (pre-defined list)	
Value	Value - eGFR [ml/min/1.73m²] - CRP [mg/L] - PCT [µg/L] - allergy [0-3], 0= none, 1= mild, 2= moderate, 3 = severe - TDM [mol/L] - bodyweight [kg] - leucocytes [%] - granulocytes [%] - device [0/1] 0= removal, 1= placing	ess	number	
Result date/time	Date/time when result of the measurement is available, respectively when allergy was documented or device was placed	ess	Mand if hosp date is not available	15
Parameter details	for allergy and therapeutic drug monitoring substance [atc_code including unknown AB], device [urinary catheter, central line catheter, incubation, prothesis, other]	opt	text	

ID, identifier; ACD, antibiotic consumption data; ess, essential; opt, optional; mand, mandatory; eGFR, estimated glomerular filtration rate; CRP, C-reaktive protein; PCT, procalcitonin; TDM, therapeutic drug monitoring; AB, antibiotic

3.5. Unpublished Data

Project 4: Dashboards

Project 4a: Interactive Access to Current Hospital-specific Antimicrobial Consumption Data: the ANRESIS Dashboard

The purpose of this project was to develop an interactive dashboard to supplement the PDF reports with customised visualisations according to hospital-specific needs.

Methods

The data source for the ANRESIS dashboard was AB consumption data, which was provided by the hospitals, that are part of the ANRESIS surveillance system. The dashboard was programmed by using the R software environment (Version 4.0.4, R core team, Vienna, Austria) and packages such as Shiny and Plotly (Version 1.7.1, 4.10.0, respectively).

Results

A dashboard was developed that visualises antimicrobial consumption of 71 Swiss hospitals (including 17 hospital groups). The ANRESIS dashboard is a web application with a hospital-specific login, which provides free access to interactive graphics and interactive tables to hospitals that are part of the ANRESIS surveillance system. The antimicrobial consumption of the user's hospital is depicted graphically over ten years and will be updated regularly. Data can be filtered by users according to antibiotics or antimycotics, antimicrobial categories and substances, departments, consumption units (DDD per 100 bed-days *vs.* DDD per 100 admissions) and additional parameters. A benchmark boxplot enables the user to compare the consumption of his hospital with other hospitals of comparable size or in the same linguistic region (Figure 14). For hospitals providing data at monthly basis or at the department level, corresponding supplementary visualisations are available. The dashboard was programmed with a flexible design, allowing adjustments of the beta version according to the users' needs and extension with further panels.

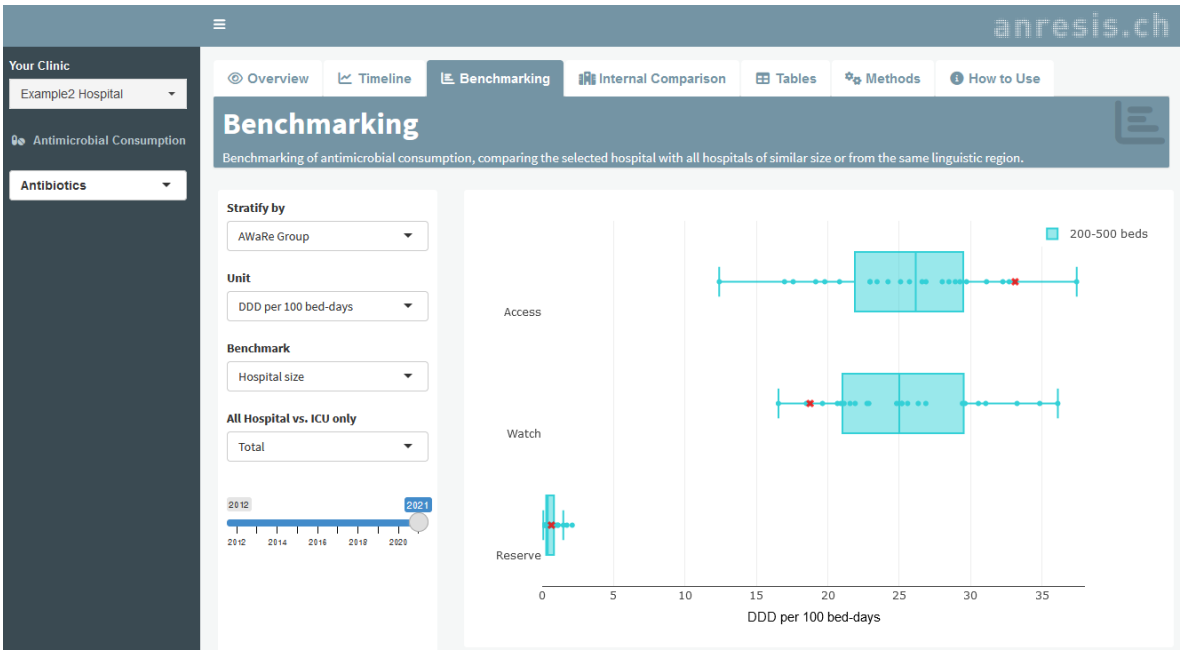


Figure 14: Screenshot of the benchmarking panel of the ANRESIS antibiotic consumption dashboard.

Project 4b: ANRESIS Laboratory Dashboard

The purpose of this project was to develop an interactive dashboard to supplement the resistance statistics, which are sent upon request to the laboratories. Another aim was to support the data manager in monitoring the data deliveries.

Methods

The data source for the dashboard was AMR data, which was provided by the laboratories, that are part of the ANRESIS surveillance system. The dashboard was programmed by using the R software environment (Version 4.0.4, R core team, Vienna, Austria) and packages such as Shiny and Plotly (Version 1.7.1, 4.10.0, respectively).

Results

A resistance dashboard was developed that visualises microbiological data from 39 laboratories. The temporal course of the number of delivered samples over ten years is depicted graphically and details of the data deliveries can be monitored. Resistance profiles and sample characteristics are depicted for the last complete calendar year. These include the ten most frequent microorganism for the selected sample provider, the proportion of sampling types and quality indicators such as percentage of samples with hospitalisation data available, with sampling type unknown and percentage of screening samples. For selected infection-control-organisms (IPC-organisms) such as MRSA, trends can be depicted over the last ten years or 24 months (Figure 15). The visualisations and tables can be filtered according to several variables including sample provider, sampling type and microorganism.

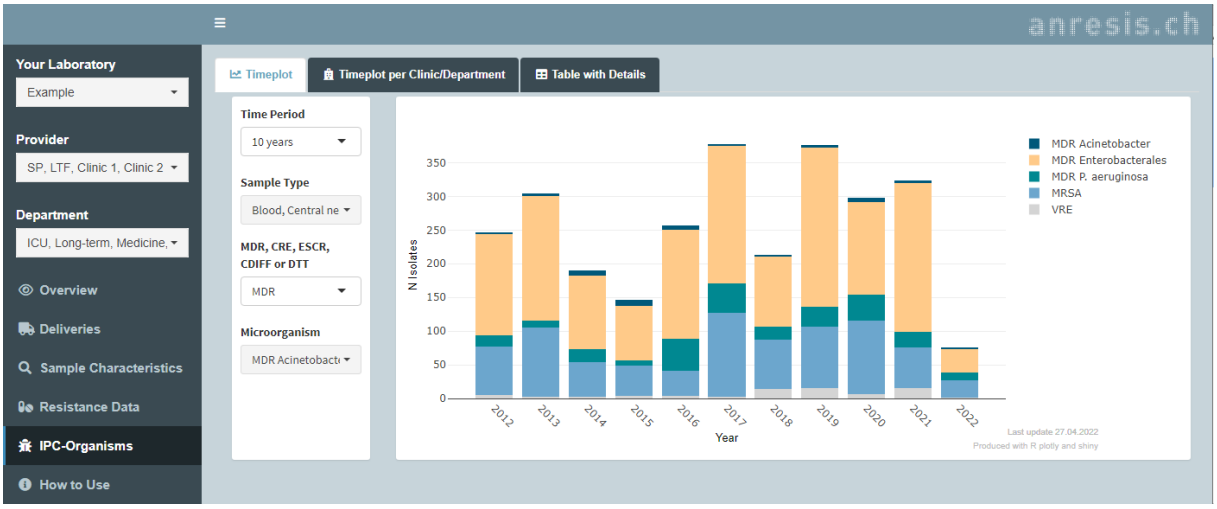


Figure 15: Screenshot of the infection-control-organisms (IPC-organisms) tab of the laboratory dashboard depicting the number of IPC-organism isolates over ten years.

Project 4c: ANRESIS Veterinary Resistance Dashboard

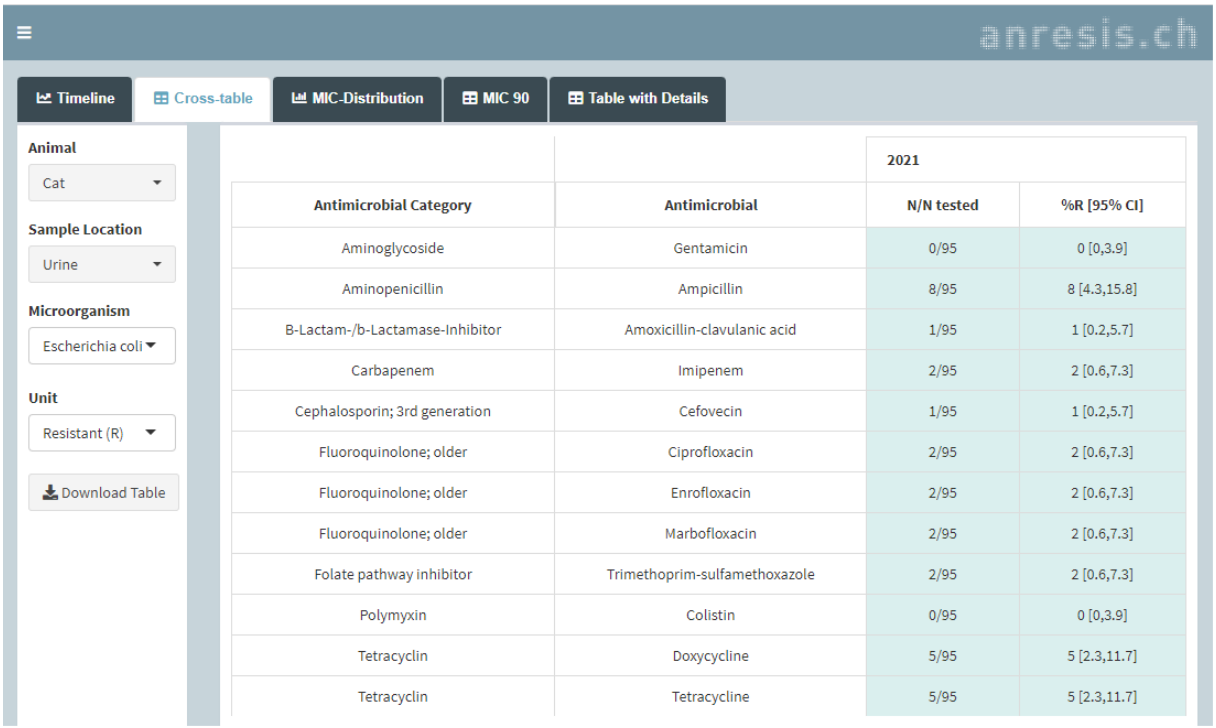
The purpose of this project was to develop an interactive dashboard to support the veterinary medicine AMR surveillance team of the Swiss Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA) in analysing the resistance data.

Methods

Data was provided by the Swiss Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA). AST results from isolates from veterinary diagnostic were processed. The dashboard was programmed by using the R software environment (Version 4.0.4, R core team, Vienna, Austria) and packages such as Shiny and Plotly (Version 1.7.1, 4.10.0, respectively).

Results

A dashboard was developed that depicts the proportion of resistant isolates from 11 veterinary medicine laboratories between 2019 and 2021 (Figure 16). In addition, resistance rates and MIC distributions are visualised. The graphics and tables can be stratified according to several selection criteria including sampling year, animal and microorganism. The tables can be downloaded and used for further analyses.



		2021	
Antimicrobial Category	Antimicrobial	N/N tested	%R [95% CI]
Aminoglycoside	Gentamicin	0/95	0 [0,3.9]
Aminopenicillin	Ampicillin	8/95	8 [4.3,15.8]
B-Lactam-/b-Lactamase-Inhibitor	Amoxicillin-clavulanic acid	1/95	1 [0.2,5.7]
Carbapenem	Imipenem	2/95	2 [0.6,7.3]
Cephalosporin; 3rd generation	Cefovecin	1/95	1 [0.2,5.7]
Fluoroquinolone; older	Ciprofloxacin	2/95	2 [0.6,7.3]
Fluoroquinolone; older	Enrofloxacin	2/95	2 [0.6,7.3]
Fluoroquinolone; older	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]
Tetracyclin	Doxycycline	5/95	5 [2.3,11.7]
Tetracyclin	Tetracycline	5/95	5 [2.3,11.7]

Figure 16: Screenshot of the cross-table panel of the veterinary resistance dashboard.

Project 6: Resistance Models with Patient-Level Data

Project 6a: Extended-Spectrum Cephalosporin-Resistance in *Escherichia coli* and *Klebsiella pneumoniae*

The purpose of this project was to investigate risk factors for the occurrence of extended-cephalosporin resistance in *E. coli* and *K. pneumoniae* including duration of prior AB therapy. Since a statistical discussion was needed for the interpretation of the result, this aspect was discussed in the result section below instead of the overall discussion.

Methods

Design and Study Population

A retrospective observational study was conducted at Lucerne cantonal hospital over a period of two years. Adult patients with possibly nosocomial *E. coli* or *K. pneumoniae* hospitalised at Lucerne cantonal hospital between 1 October 2019 and 30 September 2021 and who received at least one antibacterial for systemic use (ATC code J01 and P01AB01) were included. Patients discharged after 30 September 2021 or patients refusing the general consent were excluded. Patient data were anonymised before analysis. The study was approved by the Swiss Ethics Commission of Northwest and Central Switzerland (EKNZ) reference number 2021-00059.

Data Collection and Processing

AB prescription data was obtained from the EMR Epic software® and linked with microbiological data from the ANRESIS database. Laboratories participating in the ANRESIS surveillance system are accredited by national authorities and use AST guidelines from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) guidelines. Data were generated during daily clinical routine, independent of the study.

Each hospitalisation of a patient with a possibly nosocomial *E. coli* or *K. pneumoniae* was defined as one case. Isolates obtained within 30 days after the first positive result for the same patient were considered as duplicates and excluded. Possibly nosocomial was defined as sample take more than 48 hours after admission. If a sample of the same patient was taken before, the resistance pattern had to be different to be termed possibly nosocomial. All sampling types were included. Extended-spectrum cephalosporin-resistance was defined as *E. coli* or *K. pneumoniae* resistant to at least one of all 3rd or 4th gen. cephalosporins tested.

Duration of prior therapy was defined as duration between prescription start and prescription stop date measured in entire days. Therapy duration was aggregated by AB class. If the therapy period of two substances belonging to the same AB class overlapped, the start date of the first and the stop date of the last prescription were considered. In case of non-overlapping therapy periods, the duration of both therapies was summed up. If the sample with the possibly nosocomial bacteria was taken before the prescription stop date, the duration of therapy was defined as duration between prescription start and sampling order date. It was supposed that the sample was taken at the same day as the sample was ordered. Only prescriptions could be considered that belonged to the hospitalisation with the possibly nosocomial sample taken. The length of hospitalisation until sampling was defined as duration between hospitalisation date and sampling order date measured in entire days.

Statistical Model

Multiple logistic regression models were developed to identify risk factors for occurrence of extended-spectrum cephalosporin-resistance in *E. coli* and *K. pneumoniae*. The following potential risk factors were included in the initial model A: duration of prior therapy (days) with 3rd or 4th gen. cephalosporins, fluoroquinolones, carbapenems, aminoglycosides and trimethoprim/sulfamethoxazole, length of hospitalisation until sampling (days), age category (< 2 years, 2 – 65 years, > 65 years), sex, department and hospital location (three different cities: Lucerne, Sursee, Wohlhusen).

The department medicine was used as a reference in comparisons of the eight-level factor department (medicine, mixed, ICU, surgery, paediatrics, obstetrics/gynaecology, long-term, other). Collinearity was checked using the variance inflation factor (VIF). The likelihood ratio test ($\chi 2$ statistics) was then used in a backwards elimination process ($P < 0.05$ to retain) to select the set of independent variables for the final model. Model validity was assessed by confirming the superiority of the final model compared to a model without predictor variables (deviance-difference, $\chi 2$ statistics). Sensitivity and specificity were calculated and visualised by a Tukey-Anscombe Plot. It was checked for outliers using a leverage plot.

In an additional model (B) duration of prior AB therapy was considered per substance instead of aggregated per AB class. Model inclusion criterion for a substance was that at least ten patients received a prior treatment with this AB substance [146]. The other potential risk factors considered in the initial model were the same as in model A. Both models were compared to the corresponding models defining prior therapy as "yes" or "no" parameter instead of considering therapy duration in days (model C, model D).

Results

The proportion of extended-spectrum cephalosporin-resistance in possibly nosocomial *E. coli* and *K. pneumoniae* was 17% (98/569). In 9% (54/569) of the cases the patients were treated previously with ceftriaxone or cefepime (Figure 17). Thereof 36 cases were susceptible and 18 cases resistant against extended-spectrum cephalosporins.

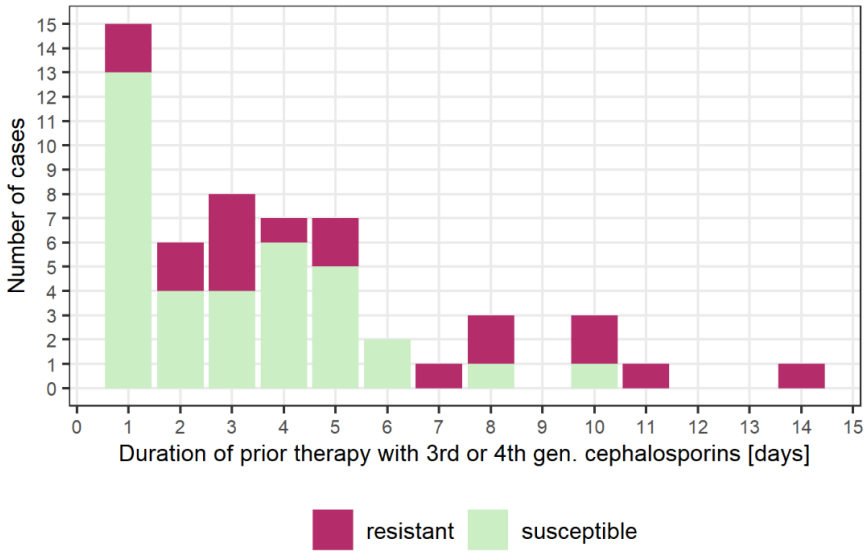


Figure 17: Distribution of duration of prior therapy with 3rd or 4th generation cephalosporins in possibly noscomial cases with extended-spectrum cephaloporin resistant (*red*) or susceptible (*green*) *Eschericia coli* and *Klebsiella pneumoniae*.

No final model could be chosen as the model fits of the four models were comparable. Among the risk factors significantly (P<0.05) associated with occurrence of resistance in at least one of the models were duration of prior therapy with 3rd or 4th gen. cephalosporins, ceftriaxone and cefepime, respectively, sex male, staying in the surgery compared to the medicine department and the location Sursee compared to Lucerne (Table 5, Table 6). Previous therapy with 3rd or 4th gen. cephalosporins was a significant risk factor in both models, the one investigating it as continuous variable (days) and the other considering it as categorical variable (yes/no). Previous treatment ("yes") with ciprofloxacin was a significant risk factor but not the duration of prior ciprofloxacin therapy.

Table 5: Risk factors for the occurrence of extended-spectrum cephalosporin-resistance in *E. coli* and *K. pneumoniae* (odds ratio) of models considering prior antibiotic therapy aggregated by antibiotic class (A: duration, C: yes/no).

Predictor	Model A AB class, duration [odds ratio]	Model C AB class, yes/no [odds ratio]
Sex: male *vs.* female	1.88 (P<0.01)	2.00 (P<0.01)
3rd or 4th gen. cephalosporins	1.31 (P<0.01)	2.92 (P<0.01)
Location: Sursee *vs.* Lucerne	ns	4.36 (P=0.02)
Wolhusen *vs.* Lucerne	ns	1.56 (P=0.48)
Department: Mixed	0.72 (P=0.32)	0.26 (P=0.03)
ICU	1.25 (P=0.61)	0.82 (P=0.68)
Surgery	2.09 (P=0.01)	2.08 (P=0.01)
Obstetrics/gynaecology	1.32 (P=0.73)	1.36 (P=0.70)
Long-term	1.30 (P=0.65)	1.05 (P=0.93)
Other	< 0.01 (P=0.98)	< 0.01 (P=0.98)
Model validity		
Chi-square test statistic	P<0.01	P<0.01
Sensitivity	7.1%	3.1%
Specificity	99.8%	99.8%

AB, antibiotic; gen., generation; ICU, intensive care unit; ns, not significant

Table 6: Risk factors for the occurrence of extended-spectrum cephalosporin-resistance in *E. coli* and *K. pneumoniae* (odds ratio) of models considering prior antibiotic therapy aggregated by substance (B: duration, D: yes/no).

Predictor	Model B Substance, duration [odds ratio]	Model D Substance, yes/no [odds ratio]
Sex: male *vs.* female	1.94 (P<0.01)	1.98 (P<0.01)
Ceftriaxone	1.31 (P=0.04)	31.50 (P=0.2)
Cefepime	1.22 (P<0.01)	3.39 (P<0.01)
Ciprofloxacin	ns	4.70(P=0.04)
Location: Sursee *vs.* Lucerne	ns	4.70 (P=0.01)
Wolhusen *vs*. Lucerne	ns	1.65 (P=0.44)
Department: Mixed	ns	0.25 (P=0.03)
ICU	ns	0.78 (P=0.62)
Surgery	ns	2.19 (P<0.01)
Obstetrics/gynecology	ns	1.46 (P=0.63)
Long-term	ns	1.08 (P=0.91)
Other	ns	< 0.01 (P=0.98)
Model validity		
Chi-square test statistic	P<0.01	P<0.01
Sensitivity	6.1%	5.1%
Specificity	99.8%	99.4%

Ns, not significant; ICU, intensive care unit

Statistical Interpretation

Specificity was for all models above 99% while sensitivity was 7.1% and lower. This was visualised in the Tukey-Anscombe Plot (Figure 18). In consequence, validity of the model results was doubted. This was underlined by the rule of thumbs regarding sample size for a valid logistic regression model [147]. Bujang *et al.* recommended a sample size of at least 500 and at least 50 events per number of explanatory variables for the poor outcome variable [147]. In the final model assessing duration by AB class three explanatory variables retained, suggesting that a sample size of at least 150 resistant cases would be required. But 98 cases were resistant only. Furthermore, only few patients were treated prior to the sampling with antibiotics. Data visualisation revealed a wide and overlapping data distribution of duration of prior therapy in resistant and susceptible cases. An outlier appeared in the residual analysis. This was a patient with a prior AB therapy of 10 days and a susceptible isolate. However, there was no good reason to exclude this patient of the analysis, as it seemed plausible. No recommendations concerning requirements of data distribution or numbers of poor outcome variables per category of explanatory variables were found in the literature. Given that our findings are based on a limited number of resistant cases, our results should thus be treated with considerable caution.

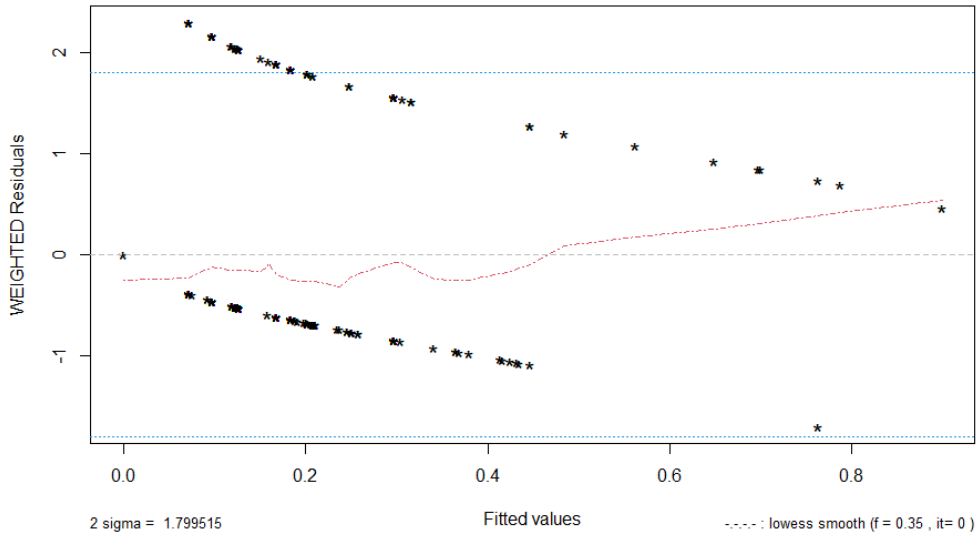


Figure 18: Tukey-Anscombe plot for the model investigating potential risk factors including duration of prior antibiotic therapy (aggregated by antibiotic class) for extended-spectrum cephalosporin-resistant *E. coli* and *K. pneumoniae.*

Project 6b: Carbapenem-Resistance in *Pseudomonas aeruginosa*

The purpose of this project was to investigate risk factors for the occurrence of carbapenem-resistance in *Pseudomonas aeruginosa* including duration of prior AB therapy.

Methods

The same methodology as in Project 6a was used and adapted to carbapenem-resistance in *Pseudomonas aeruginosa*. In addition, carbapenems, fluoroquinolones and aminoglycosides, were the only antibiotics considered in terms of duration of previous therapy. *P. aeruginosa* resistant to at least one carbapenem was defined as carbapenem-resistant *P. aeruginosa*.

Results

In 8% of 169 possibly nosocomial *P. aeruginosa* cases, the isolates were resistant to carbapenems. In consequence, the number of patients was too low for building a meaningful model.

Project 6c: Methicillin-Resistance in *Staphylococcus aureus*

The purpose of this project was to investigate risk factors for the occurrence of methicillin-resistance in *Staphylococcus aureus* including duration of prior AB therapy.

Methods

The same methodology as in Project 6a and 6b was used and adapted to *Staphylococcus aureus*. In addition, antibiotics considered in terms of duration of previous therapy were penicillins, 2nd gen. cephalosporins, 3rd or 4th gen. cephalosporins and carbapenems only. MRSA was defined as *S. aureus* resistant to at least one of the following antibiotics: methicillin, oxacillin, flucloxacillin, or cefoxitin.

Results

10% of 299 possibly nosocomial *Staphylococcus aureus* cases were MRSA. In consequence, the number of patients was too low for building a meaningful model.

4. Discussion & Outlook

This PhD project demonstrated the benefits of integrating patient-level AB prescription data in routine surveillance of AB use. In the first section, hospital-level AB consumption data and resistance data of the ANRESIS surveillance network were analysed. We investigated the opportunities and limitations of these data to improve surveillance and identified targets for ABS groups throughout four projects. In the second section, we analysed patient-level data and proposed a procedure to incorporate them into routine surveillance.

4.1. Hospital-Level Data

In this section, it was assessed whether associations between AMR and AB consumption can be investigated using hospital-level data generated for routine surveillance. We investigated the temporal course including explanatory variables of 1) the consumption of anti-MRSA antibiotics, 2) the incidence of *S. aureus* BSI and 3) ESCR-KP (Figure 19). To improve the data visualisation for routine surveillance of AB consumption, we developed an interactive dashboard (project 4).

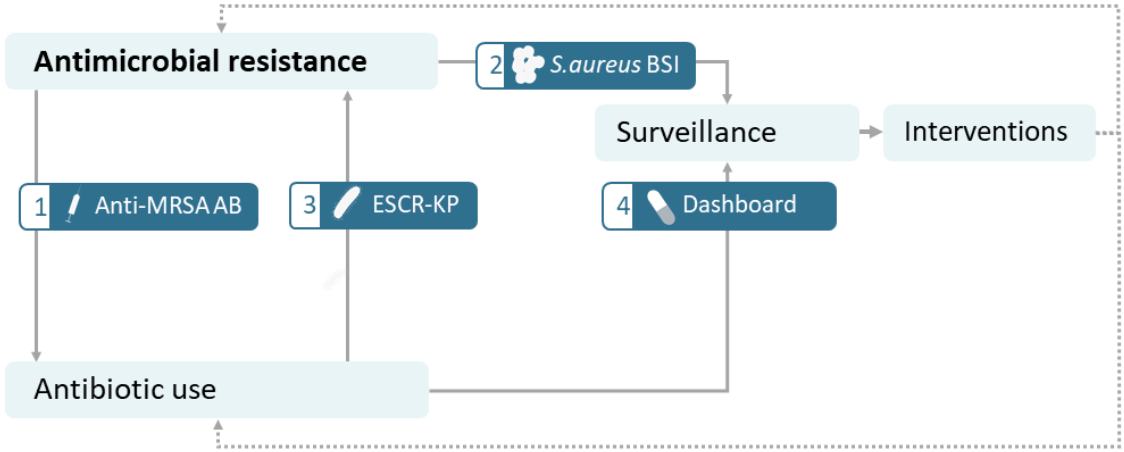


Figure 19: In the first part we aimed to analyse predictors for antibiotic use including antimicrobial resistance (project 1), predictors for antimicrobial resistance including antibiotic use (project 3) and how to improve surveillance (project 2 and 4) in order to define targeted interventions to reduce antimicrobial resistance and antibiotic use.

4.1.1. National Surveillance

Anti-MRSA AB

The analysis of hospital-level AB consumption data revealed an increase in the consumption of anti-MRSA antibiotics (glycopeptides, daptomycin, linezolid) in Switzerland between 2009 and 2019. The invasive MRSA infections decreased during this period, nonetheless, the consumption of anti-MRSA antibiotics was significantly associated with MRSA incidence. This was explained by the finding that MRSA infections did actually decrease only in the university hospitals of the French-speaking part, where consumption of anti-MRSA antibiotics was stable.

Stratifying by AB class showed that glycopeptides as well as daptomycin consumption increased. Hence, daptomycin, when introduced, did not replace glycopeptides in Switzerland.

These two findings indicate that the use of anti-MRSA antibiotics may be improvable. This was underlined by the results of our advanced model including data on hospital policies, which were available for the year 2019 only. First, MRSA incidence was not associated with the consumption of

anti-MRSA antibiotics in 2019. Second, hospitals with lower consumption were associated with having an ABS group and restrictions for prescriptions of anti-MRSA antibiotics. This positive effect is in line with the findings of Borde *et al.* and Yamaguchi *et al.* [148, 149]. Both reported a lower and more appropriate use of daptomycin, anti-MRSA antibiotics, respectively, after starting an ABS programme. The Japanese ABS group implemented a daily prospective audit and feedback regarding the time of de-escalation of anti-MRSA antibiotics, which shortened the time of de-escalation without affecting clinically important outcomes [148]. This may be a method to consider for Swiss hospitals in the upper range of consumption of anti-MRSA antibiotics.

Our study further implies that national measures on a political level are needed to optimise the prescription of these last remaining effective antibiotics for treating MRSA BSI. Concrete proposals are to provide national guidelines concerning the indication for anti-MRSA antibiotics, implement local ABS groups and restrict the prescription of anti-MRSA antibiotics.

We statistically evaluated the observation that trends in MRSA incidence differed between the linguistic regions in the next project.

The MRSA incidence decreased significantly in the French-speaking region while increasing significantly in the German-speaking region, although at a low incidence level. However, across Switzerland overall, the MRSA incidence and the percentage of MRSA decreased significantly. This mirrored the situation in the EU and EEA [108]. Gagliotti et *al.* reported an increasing incidence of *S. aureus* BSI in the EU and EEA due to the increasing incidence of MSSA. Therefore, we decided to extend our analysis to MSSA. *S. aureus* BSI increased also in Switzerland between 2008 and 2021, mainly due to the increasing incidence of MSSA BSI in elderly males. Male sex and age are well described risk factors for *S. aureus* BSI [41, 42]. The increase was more pronounced in the German-speaking than in the French-speaking region. One possible reason for these regional discrepancies may be that more prevention activities to control MRSA were implemented in the French-speaking region, which may have affected the spread of MSSA. In addition, during the same period, the number of surgical procedures for implementing or changing pacemakers increased in the German-speaking region while remaining constant in the French-speaking region [12]. Hence, this may be an explanation for these regional differences. Pacemakers and medical implants are a common source of *S. aureus* BSI and hospitalisation is known to be a risk factor for *S. aureus* BSI [13]. In future studies, the relationship between device placements and *S. aureus* BSI over time must be analysed, considering possible changes in perioperative procedures.

This increasing health burden indicates that surveillance should consider incidence rates of BSI too and not only the percentages of resistant microorganisms. Further, we demonstrated the need for data stratification in epidemiologic analyses as otherwise diverging trends in subpopulations may be lost due to data aggregation. However, to formulate appropriate regionally targeted measures for this population, further investigations examining the underlying reasons for the growing incidence are needed.

Following the *S. aureus* BSI project, we focused on another important hospital pathogen of the WHO priority pathogen list, ESCR-KP.

Our study showed that the incidence of invasive ESCR-KP infections increased fourfold, from 0.01 to 0.04 patients per 1,000 bed-days, in Switzerland between 2009 and 2019. This trend paralleled the increasing percentage of ESCR-KP isolates in Switzerland and other European countries [16, 150]. Although, the percentage of ESCR-KP isolates remained still at a lower level than in the neighbouring countries. An association between ESCR-KP incidence and AB use was reported in other countries [33, 37, 151-155]. However, this was not the case in Switzerland where incidence was associated with structural factors only. More specifically, the incidence was

higher in university than in non-university hospitals and in the French-speaking compared to the German-speaking region. The differences between the linguistic regions may be partly explained by a high cross-border traffic of individuals, including patients and medical staff to neighbouring countries with different ESCR-KP prevalence levels (*i.e.* France, 2019 30.2%, Germany 12.2%) [156]. This may either support the suggestion that the import of resistant pathogens may play a more important role than AB consumption in low prevalence settings, which was proposed by a population-based mathematical modelling study [154]. Or data aggregation at the hospital level may not be sufficient to detect such a correlation. Inclusion of patient-level AB prescription data would essentially improve our model. Further, it cannot be excluded that the data may also contain samples with community-onset ESCR-KP which may attenuate the potential association between inpatient AB consumption and ESCR-KP incidence. To distinguish between community-onset and hospital-onset infection, an algorithm is applied frequently. Based on the hospitalisation date, the algorithm classifies samples which are taken more than 48 hours after admission as hospital-onset infections. But, the hospitalisation date was missing in 59% of the cases and hence not analysed.

An additional finding was that variability in ESCR-KP incidence between hospitals became larger when isolates from all sample sites were included (which is frequently considered for infection control purposes). This was mainly due to high overall incidence rates at Geneva University hospital which is known for extensive screening activities and hence detecting unknown carriers frequently.

Our results indicate that different screening activities may bias overall ESCR-KP incidence even within a single country, which has to be considered if data are compared between hospitals. It is important not to brand hospitals due to the high resistance incidences that result from active screening policies: early detection is important and may prevent nosocomial spread and thus additional costs. A further implication of our study is that continuous providing of information regarding hospitalisation date and sample type would improve the data quality. This would not only improve surveillance of ESCR-KP but surveillance of other critical pathogens too. Further possible improvements for future are to implement screening guidelines nationwide and to measure the screening activity (*e.g.* the total number of screenings performed per 1,000 bed-days).

4.1.2. Surveillance for Local Antibiotic Stewardship Teams

In another approach to improve surveillance, we developed an interactive dashboard using the programming language R and packages such as Shiny and Plotly. The dashboard provides interactive and customisable visualisation of AB consumption for the 71 hospitals participating in the ANRESIS surveillance network. National surveillance networks in the USA and England provide hospital-specific AB consumption dashboards for participating hospitals as well [157, 158]. An open-source dashboard application for infection management and ABS, also using R and the package Shiny, was developed by Luz *et al.* based on the data structure of a Dutch hospital [159].

Our first version mainly contains graphics which are provided in the ANRESIS feedback and benchmark pdf reports. However, the dashboard technology allows adjustments to selection criteria including more detailed data stratification. Moreover, for hospitals providing data at monthly basis or at the department level, corresponding supplementary visualisations are available. In consequence, the user–friendly data visualisations enhance data communication and may be time-saving for the local ABS group that interprets the data.

We developed the first version of the dashboard within nearly six months. The process of implementing it into routine surveillance took almost two more years. Data security and legal issues had to be clarified with third parties, which had limited time resources and other priorities. This

demonstrated that close cooperation with various parties is necessary to successfully implement a new surveillance tool at the national level.

The dashboard was programmed with a flexible design, allowing adjustments of the beta version according to the users' needs and extension with further panels. A separate dashboard depicting resistance data was developed as well and will be integrated into the hospital dashboard after legal issues are clarified.

4.1.3. Benefits of Hospital-Level Data

Based on the dashboard, I illustrate hereinafter the use of hospital-level AB consumption data to set targets for local ABS programmes.

Analysis of AB consumption over time is useful for ABS programmes to assess the impact of interventions such as changes in guidelines or the implementation of restrictions. Further, unexplained increases can be targets for local ABS programmes. Targets may also be provided by the benchmark analysis that compares the annual AB consumption between hospitals of comparable size or the same linguistic region. For hospitals delivering data at the department level, we developed a dashboard panel doing an internal benchmark analysis. Based on this more detailed analysis, more targeted interventions can be defined.

Some hospitals provide data on a monthly basis. This allows to analyse seasonal trends and possibly the effect of AB drug shortages on AB consumption patterns. Further it allows to analyse effects assigned to specific periods such as during the waves of the COVID-19 pandemic, where increased consumption of broad-spectre antibiotics was observed [160].

The main strength of studies and surveillance with hospital-level data are the extensive data collection for more than ten years and the high coverage including all university hospitals in Switzerland. The high coverage allows a solid reflection of the epidemiological situation, to assess data plausibility and benchmark with other Swiss hospitals as well as with other countries. Concerning ABS programmes, the benefits of long-term data are that trend analyses may evaluate the impact of interventions on AB consumption and identify new targets.

4.1.4. Limitations of Hospital-Level Data

Since missing information concerning the microbiological samples was a limitation of the previous projects, metrics for sample quality and screening activity were included in the resistance dashboard. This refers to the metrics *percentage of samples with hospitalisation data available*, *percentage of sampling type unknown* and *percentage of screening samples*. In a further study, it should be investigated which process lost this information.

The available hospital-level AB consumption data do not allow to evaluate the appropriateness of AB consumption. In consequence, hospital-level data are of limited value in supporting local ABS programmes in defining targets for interventions. Additional information such as the indication would be required. A source of AB prescription data with indications are PPS. We intend to include these the dashboard, which may provide additional targets for ABS. However, PPS are snapshots only, the workload is high and hence, PPS should be a temporary solution only. EMR data are generated during clinical routine and may thus replace PPS, when they become increasingly available.

Another limitation of a previous project was that data aggregation at the hospital level may not be sufficient to detect correlations between AB use and AMR. The inclusion of patient-level data may essentially improve this type of model. The next projects assessed the opportunities and limitations of patient-level AB prescription data.

4.2. Patient-Level Data

The first project with patient-level AB prescription data assessed the feasibility of converting EMR data into indicators for ABS and proposed a method to include patient-level data into the future surveillance of AB use (Figure 20). The last project indicated which research question may be answered in future with patient-level AB prescription data and, hence, is discussed in the outlook section.

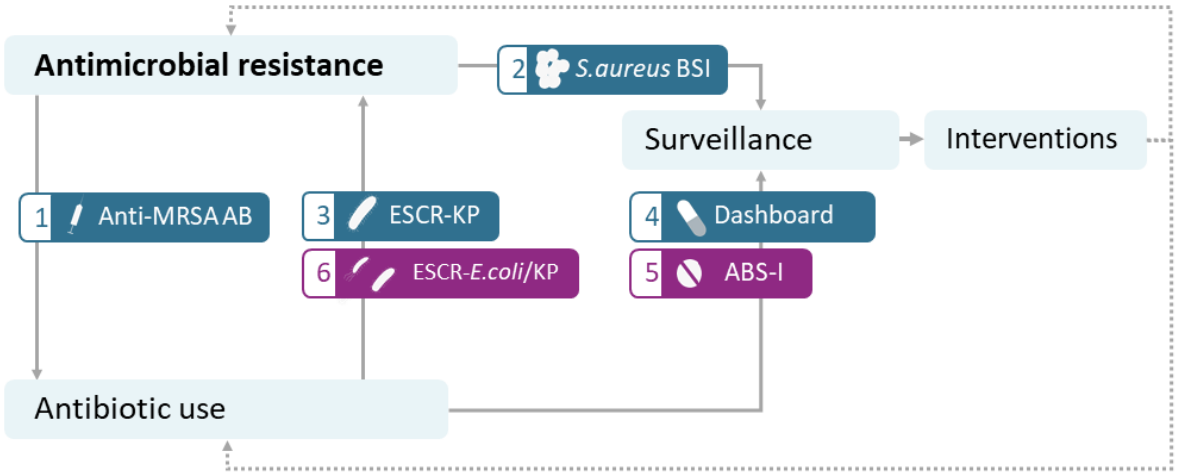


Figure 20: In the projects of this PhD thesis we aimed to analyse predictors for antibiotic use including antimicrobial resistance (project 1), predictors for antimicrobial resistance including antibiotic use (project 3 and 6) and how to improve surveillance (project 2, 4 and 5) in order to define targeted interventions to reduce antimicrobial resistance and antibiotic use. For project 1–4, routine surveillance data from the Swiss Centre for Antibiotic Resistance *(turquoise blue)* were used, while for projects 5 and 6, the electronic medical records from Lucerne Cantonal hospital *(purple)* were the main data source.

ABS-I Patient-level AB prescription data allowed a more detailed analysis of AB use than hospital-level data. AB use was stratified in a dashboard to different data levels including clinical ward and patient age group. In addition to DDD, patient-level AB prescription data could be used to calculate other standard metrics for quantifying the AB use in the inpatient setting, such as prescribed daily dose and days of therapy [161].

We linked patient-level AB prescription data out of the EMR system with resistance data from the ANRESIS database. Moreover, we showed that converting EMR data into ABS-I was feasible. We could program algorithms to compute 25 of 28 ABS-I assessing treatment decisions. Before the programming, most ABS-I described in the literature had to be rephrased or specified to be computable. Data were complete for 46% (13/28) of the ABS-I and, hence, assessed as good quality data. Technical difficulties in converting EMR data into ABS-I were described in detail in the manuscript *Manuscript Under Revision*

Project 5: Assessing the Conversion of Electronic Medical Record Data Into Antibiotic Stewardship Indicators. In summary, the number of ABS-I with good quality data could be increased from 13 to 26, if small modifications within the EMR system were applied to improve the data structure such as a more complete, well-structured and mandatory indication recording system.

4.2.1. Benefits of Patient-Level Data

The manuscript assessing the feasibility of converting EMR data into ABS-I focused on the technical feasibility of using EMR data for ABS. Evaluating the clinical relevance of the ABS-I was not part of the study and will be a task for expert committees. However, one purpose of this PhD project was to assess the benefits of including patient-level AB prescription data into future surveillance of AB use. ANRESIS aims to analyse the surveillance data in a format that is useful for local ABS programmes to define interventions. Hence, the clinical relevance of this ABS-I is discussed in the next paragraph.

Seventy-one percent (20/28) of the ABS-I assessing treatment decisions evaluated if the decisions were in line with general guidelines and recommendations. Thus, target values could be defined for this ABS-I. Local ABS programmes could set these as targets and implement appropriate measures. However, to successfully implement these ABS-I as tool for ABS programmes, first the corresponding treatment guidelines need to be implemented locally. Moreover, the development of national guidelines would facilitate the comparison and support the local implementation. The other 29% (8/28) of the ABS-I assessing treatment decisions described treatment duration and types of first adjustments in therapy such as step-down to oral therapy and de-escalation. These decisions depend on several variables such as the patient's condition and the suspected pathogen. As these data were not available, these indicators are not a quality measure, but describe treatment decision patterns. They allow a better understanding of AB prescribing, whereas no target values can be defined for these ABS-I. This may change, once the data and financial resources are available to program algorithms that encompass all case scenarios. In summary, computed ABS-I assessed treatment decision and described treatment patterns, whereas routine surveillance measures AB consumption patterns. In addition, patient-level AB prescription data including ABS-I could easily be stratified to different data levels including clinical ward, patient age group and month. To conclude, analysis of patient-level AB prescription data may provide more specific targets for defining and measuring interventions in ABS programmes than monitoring with hospital-level data. This may improve the quality of patient care and patient outcome.

4.2.2. Limitations of Patient-Level Data

The most important limitation of this study was that plausibility control was not possible. The methodology for ABS-I computed in the literature differed and most ABS-I were not calculated before. Data were available for one hospital group only, therefore benchmarking as plausibility check was not possible. Furthermore, total AB use calculated from patient-level data was much lower than the consumption in comparable hospitals computed by hospital-level pharmacy data. However, direct data comparison was not possible as Lucerne cantonal hospital has not participated anymore in the ANRESIS AB consumption surveillance since 2017. Another constraint was that in 78% of the hospitalisations, the indication was missing or not documented specifically (*e.g.* infection). Therefore, distinguishing between prophylaxis and treatment was only possible to a limited extent. This biased the estimates of several ABS-I. Furthermore, it limited the selection of ABS-I, since a lot of recommendations depend on the indication. Missing or unspecific documentation of indication was also reported by other studies using EMR data for ABS [135, 162]. To improve the documentation quality of indication, Van den Broeck *et al.* proposed an indication classification based on the main focus of the infection and tested it as a mandatory indication-registration tool [134]. Since their tool was not too burdensome for the prescribers and they also used Epic systems®, we propose to integrate a slightly modified version of their indication-registration format (Project 5: Supplementary Table 4).

In terms of data completeness, another issue is the lack of data from patients who refuse the general consent. Due to ethical concerns, it is not allowed to analyse these data for research purposes.

However, data completeness is important for the validity of the ABS-I and publication is important for plausibility and benchmarking between hospitals and countries. Moreover, it may affect guidelines and target values.

There are further limitations regarding patient-level data in general. Since recently implemented, EMR do not yet contain long-term data, but these are important for epidemiological analyses. At present, only a small number of hospitals are able to provide patient-level data. Therefore, patient-level AB prescription data should be incorporated into monitoring of AB use but currently not replace AB consumption data. Replacement may be discussed when long-term data are available and the coverage is comparable.

This project has demonstrated the benefit of patient-level data and is therefore the first step towards integrating patient-level AB prescription data into routine surveillance. To enable the incorporation into the surveillance database, we elaborated format specifications (Project 5: Supplementary Table 5 – 7).

4.3. Outlook

4.3.1. Antibiotic Stewardship Indicators (ABS-I)

The next step towards establishing the ABS-I as tool for ABS programmes is the validation of our results. We intend to extend the analysis to other hospitals and perform manual validation of a randomly selected data sample. In the application for ethical approval for the extended analysis, we will include serum level measurements of aminoglycosides and vancomycin to calculate the corresponding ABS-I. In addition, we aim to add additional parameters that may be of interest for ABS: time of catheter placement or intubation, time of arrival of intermediate microbiological results such as positivity of blood culture and results of gram-staining and additional laboratory parameters such as the leucocyte and granulocyte count. Creating a query for the EMR data is initially a high workload for the information technology (IT) specialists of the participating hospitals. But once they are set up, the data can be extracted automatically. Further, it may be established as part of the Swiss Personalized Health Network (SPHN) [163]. The SPHN is currently building an infrastructure to enable nationwide use and exchange of health data for research.

In parallel to establishing a network, we need to evaluate which ABS-I should be recommended for future monitoring. The selection should consider the clinical relevance, priority, computability and data availability and, hence, needs to be assessed in collaboration with a committee of clinical experts. Moreover, the committee should consider possible limited resources (data, IT, finances) in smaller hospitals while on the other hand capabilities in larger hospitals should be utilized. In consequence, I suggest defining a basic and an advanced list of ABS-I recommended for continuous monitoring. Furthermore, I would tag the most relevant ABS-I in both lists. To successfully implement the ABS-I as a tool for local ABS programmes, local monitoring should start with a selection of the most relevant ABS-I. Major issues regarding AB therapy are the use of antibiotics when not indicated and the lack of re-assessment of therapy. Therefore, I would consider the following ABS-I as most relevant:

- Stop of initial AB therapy, if it was decided initially to measure PCT or CRP and the values are below 0.25 µg/L, below 20 mg/L, respectively
- Re-assessment of AB therapy within 3 days
- Re-assessment of AB therapy within 24 hours after availability of microbiological result

An automated stop rule after three days of AB therapy could further increase the performance of these ABS-I. In addition to the selection of ABS-I, corresponding treatment decision recommendations and target values need to be defined at the local and national level. Target values for hospital-level AB consumption would be useful too. Official recommendations may provide political support for the implementation of ABS programmes and the monitoring of patient-level AB prescription data. Further, international ABS study groups should provide recommendations for the monitoring of ABS-I. Internationally accepted definitions of ABS-I may enhance consistency between the methodologies used and provide political pressure for the implementation of ABS-I in Switzerland.

ABS-I may be used in the future to measure the effect of interventions such as restrictions or implementation of clinical decision support (CDS) systems. Moreover, some ABS-I may be associated with resistance and in consequence be the most relevant targets for ABS programmes.

4.3.2. Local Antibiotic Stewardship Programmes

The ABS-I will be integrated into the ANRESIS dashboard. Future development of the dashboard could include data analysis at the clinical ward or prescriber level and real-time data analysis. One useful function would be the real-time monitoring of prescriptions for selected antibiotics, pathogens, and known bug–drug mismatches. This is already feasible in advanced clinical information systems (CIS). However, especially small hospitals with less advanced CIS would benefit from a nationally established solution. Additionally, the disease-specific microbiological spectre could be monitored continuously, if the indication is structurally documented. Such an analysis may lead to adaptions in the guidelines for empirical therapy. Another possible function may be the continuous monitoring of nosocomial infections. Furthermore, an outbreak detection algorithm might be integrated. However, such an algorithm must be developed first and may require the linkage of resistance data with WGS data, at least in the development phase [164]. Hence, a collaboration with the Swiss Pathogen Surveillance Platform is needed [165]. Real-time data analysis would require a direct connection between the EMR and the dashboard, which should technically be feasible using Shiny and R [159, 166]. Ideally, the dashboard would contain all information needed for the daily work of an antibiotic steward.

Available tools to assist physicians in the appropriate prescribing of antibiotics are among others the dose calculator for paediatric patients and several electronic guidelines, whereof infect.info includes the latest AMR rates [44, 167, 168]. Furthermore, CDS systems are under development that include functions for ABS. Such a CDS system was recently implemented in three Swiss hospitals [131]. It provided decision support for the therapy choice based on indication including treatment duration, alerts for self-guided re-evaluation of AB therapy and automated feedback reports on ABS-I. Despite that the implementation of this CDS system did not significantly reduce overall AB use, Catho *et al.* encourage to further explore CDS systems for ABS [131]. Future CDS systems may alert when prescriptions are not in line with guidelines, the AB spectre overlaps or bug–drug mismatches occur. But phenomena such as *"alert fatigue"* and treatment delays due to CDS need to be considered [169]. A possible alternative to alerts is the data visualisation in an ABS dashboard that triggers feedback and interventions of the Antibiotic Steward.

Another approach for local ABS teams may be to restrict the prescription of selected antibiotics such as reserve antibiotics. A further promising tool may be the selective reporting of AST results [170]. This implies that microbiologists perform AST according to standard practice but report only a limited number of AST results to the physicians. Selective reporting was associated with a reduction in inappropriate prescribing [170].

4.3.3. Additional Benefit of Patient-Level Antibiotic Prescription Data

Patient-level AB prescription data required for monitoring of the ABS-I may be used to conduct further studies. For example, serum level measurements of aminoglycosides and vancomycin need to be gathered for the ABS-I that assess whether the routine TDM was done for aminoglycosides and vancomycin. These serum level measurements may allow an analysis of the pharmacokinetic properties. Clinical trial data are limited in patient populations with altered physiological body proportions, such as elderly [78], pregnant [77, 171], critically ill pediatric [172] and obese patients [173]. Further parameters to consider for this analysis include the administered dosage, bodyweight and kidney function. However, these variables are measured during clinical routine, stored in the EMR and thus available. Pharmacokinetic analysis of vancomycin or aminoglycoside may improve the dosing scheme in specific patient populations and thus enhance the efficacy of AB therapy and minimize adverse events.

A second research question addressable with the data collected would be to assess the accordance between AB prescription and administration. This may be an issue as data analysis for computing the ABS-I revealed cases in which the time of administration was before the prescription time. Other aspects of treatment compared to the prescription could be evaluated, such as the actual duration of therapy, dosing interval and administered dose. This may result in further ABS-I.

ESCR-*E.coli*/KP

Third, the association between AB treatment and AMR can be examined. In project 6a, a model was built to investigate risk factors for extended-spectrum cephalosporin resistance in *K. pneumoniae* and *E. coli* including the duration of previous AB treatment. But sensitivity and the number of patients with resistant isolates were too low [147] and data distribution too wide for meaningful model results. Further limitations of this model were that first, information regarding antibiotic treatment before hospitalisation was not available. Second, it cannot be excluded that the Enterobacterales acquired resistance before the patient was hospitalised. However, including samples obtained at least 48 hours after admission probably reduced this bias. A larger study is needed to investigate this association. The larger the sample size, the more parameters can be considered. Relevant parameters may be dosage, indication, sample site and Charlson Comorbidity index.

A further study could be initiated that analyses the effect of antibiotic therapy on the natural microbiome [89]. However, this would require the regular collection of stool samples, which is generally not part of clinical routine practice.

When long-term patient-level AB prescription data are available, even more complex analyses will become feasible. Lopéz-Lozano *et al.* identified critical thresholds for AB consumption of selected AB categories (DDD per 1,000 bed-days) associated with resistance by performing a non-linear time-series approach at the population level [47]. The critical AB threshold for resistance development at the patient level might be identified in future. Such a model will require data regarding the occurrence of resistance, AMR incidence in the hospital environment, use of hand sanitiser, changes in recommendations including ABS policies *et cetera*. As a marker for AMR in the hospital environment, hospital wastewater could be analysed.

In summary, routinely collected patient-level AB prescription data offer great potential to address research questions ranging from pharmacokinetics to risk factors for AMR. The findings of such studies could result in further ABS-I, optimise treatment and reduce AMR.

4.3.4. One Health Model

Structured data about AMR and associated variables are also increasingly available in other areas such as veterinary medicine and environment. A one health model may enable a unified data analysis that integrates diverse AMR sources.

In veterinary medicine, it is mandatory to record AB prescriptions in a database in Switzerland since 2022. Sales data on vaccines against bacterial infections may be available as well. AB concentrations are measured in waste-, ground- and surface water [15]. Resistance data of veterinary pathogens generated during clinical routine and monitoring of MDR bacteria in fresh meat are part of routine surveillance [15]. In wastewater treatment plants, national monitoring of the COVID-19 viral load was established in January 2022 [174]. This may be extended to the surveillance of AMR. In water, further AMR risk factors may be measured, such as the concentration of microplastics, heavy metals and other biocides. Long-term data on other drivers for the increasing spread of AMR are already routinely collected for other purposes, such as temperature, moisture, population density and international travel (measured by the number of flights) [175].

Moreover, WGS data of resistant pathogens are increasingly collected by the Swiss Pathogen Surveillance Platform [165]. This includes isolates from human and veterinary medicine, environment and food and may be useful to explain spatiotemporal patterns of AMR transmission [164]. Long-term care facilities are a further setting where data on AMR and AB use may become increasingly available. Kohler *et al.* identified clusters of residents with identical pathogens [176] and Plüss *et al.* analysed AB use in a network of long-term care facilities in Switzerland [177]. Both studies concluded that long-term care facilities may benefit from targeted infection control interventions. Monitoring of AB use in these long-term care facilities is continued and more facilities may join the network. AMR data from long-term care facilities may already be routinely collected in the ANRESIS surveillance network, but most are unlikely to be identified as such since explicit labelling is required. However, a study has to assess the actual data situation and make tailored suggestions for improvement.

Efforts are being made to improve and extend the AMR surveillance networks in the fields of human and veterinary medicine, food and the environment in Switzerland. Hence, data on AMR and its potential risk factors are increasingly available for a combinatorial analysis in a one health model. More specifically, a model that investigates the occurrence of AMR and its transmission dynamics considering diverse settings throughout Switzerland.

4.3.5. Implications for Politics and Society

The worldwide digitalisation provides new opportunities for therapy decision management, research and quality control in the health care sector. However, digitalisation threatens the universal human right for informational self-determination, the right to control the terms under which personal data are processed [178]. To regulate the question of using data and samples generated during hospital stays for research purposes, the general consent was elaborated in 2018 in Switzerland [179]. Project 5 on ABS-I demonstrated the importance of data completeness for data plausibility and quality control. ABS-I may provide targets to optimise AB treatment decisions and thus improve patient safety and reduce AMR. In consequence, the population should be encouraged to consent to the use of data and samples generated during their hospital stay for research purposes. A written explanation of the significance of these data for research and society is part of the general consent. Nonetheless, the way the medical receptionist presents the general consent may be crucial for the patient's decision. Hence, medical receptionists need to be aware of the benefit of EMR data for research and quality control. Another approach may be the political discussion and education concerning the use of EMR data, comparable with the transplantation law in Switzerland. Thus, it could be proposed politically that the

data can be used for research purposes in the absence of a documented decision not to refuse the general consent. Actually, the act on human research law already deals with the data in this way. But an official discussion would promote the confrontation with the topic detached from being in a sick condition at the hospital. The main reason for rejecting the general consent is probably the fear of data misuse. Data security of health care data is essential for society. It should be the task of the government to ensure the protection of health care data, establish and support a secure infrastructure.

A national solution should be provided for another technical issue concerning ABS. Several Swiss hospitals are developing their own ABS dashboards. A national concept would save time and money for the Swiss health care system overall. Further, a harmonized concept would allow data comparability and benchmarking. The ABS-I feasibility study has demonstrated that small differences in definitions have a substantial impact on the results and, thus, impair comparability with other studies. In tangible terms, we need political and financial support for the development of a national ABS dashboard including local data extraction and data security. National guidelines are needed for ABS programmes, screening policies, use of reserve antibiotics, empirical and targeted therapy.

Preventing the spread of AMR is essential to ensure treatment efficacy for bacterial infections in future, reduce the burden of infections and health care costs. Thus, patients treated with antibiotics need to be educated on their part in preventing resistance by taking antibiotics exactly as instructed, returning leftovers to the pharmacy stores for correct disposal, and giving consent to the use of their data for research purposes.

4.4. Conclusion

Our studies revealed that several national trends in antibiotic consumption and resistance were mainly caused by subpopulations. This demonstrates the need for stratifying surveillance analyses to formulate appropriate target measures at the right intervention level. Higher resolution data on antibiotic use are essential to provide better decision support to policy makers in hospitals and on regional and national committees.
To improve surveillance analysis for hospitals, we developed a procedure that converts electronic medical record data into antibiotic stewardship indicators. The routine monitoring of these indicators would be very useful for local antibiotic stewardship teams when defining and measuring interventions. In addition to improving the quality of antibiotic treatment, collecting patient-level prescription data continuously would allow several research projects to be initiated. Our procedure can be applied to every Swiss hospital that provides data in the format required for our database.
For successful implementation into routine surveillance, we propose, firstly, that the clinically relevant antibiotic stewardship indicators should be selected in collaboration with a committee of clinical experts. Moreover, the committee should provide exact definitions of the indicators, because we have shown that standardisation is important for benchmarking the results and assessing plausibility. Secondly, small modifications within electronic medical records would improve data quality. Thirdly, a network of participating hospitals must be established.
Hopefully, this work encourages the implementation of the next steps for incorporating patient-level antibiotic prescription data and antibiotic stewardship indicators into routine surveillance.

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Curriculum Vitae including Publication List

PERSONAL INFORMATION

Luzia Renggli

Eidg. dipl. pharmacist

Winkelriedstr. 50, 3014 Bern

076 568 62 16

luzia_renggli@hotmail.com

linkedin.com/in/luzia-renggli-74158319a

Date of birth	August 31, 1994
Nationality:	Swiss

EDUCATION

01/2023 – today	**FPH clinical pharmacy**, University Department of Geriatric Medicine FELIX PLATTER and Basel University Hospital, Basel, Switzerland
04/2022 – today	**CAS clinical pharmacy**, University of Basel, Basel, Switzerland
11/2019 – today	Graduate School for Health Sciences (PhD studies, 18 ECTS), **specialisation in epidemiology, statistics, data analysis** University of Berne, Bern, Switzerland
10/2019	**Federal state examination pharmacy**
9/2017 – 7/2019	MSc Pharmacy, University of Basel, Basel, Switzerland Master's thesis data analysis and modelling: *Copeptin Kinetics and Its Relationship to Osmolality During Rehydration for Diabetic Ketoacidosis in Children*, **University Children's Hospital Basel**, Basel, Switzerland
9/2014 – 7/2017	BSc pharmaceutical science, University of Basel, Basel, Switzerland
12/2013	Gymnasium Oberwil (high school), Oberwil, Switzerland

WORK EXPERIENCE

11/2019 – 01/2023

PhD Student at the **Swiss Centre for Antibiotic Resistance (ANRESIS)**, Institute for Infectious Diseases, University of Bern, Bern, Switzerland
Project title: *From hospital-level to patient level antibiotic consumption data: How can we improve surveillance of antibiotic use for antibiotic stewardship programmes?*

- Analysis of antibiotic consumption and antibiotic resistance data
- Communication of results through presentations and scientific publications in peer reviewed journals
- Review activity
- Development of an interactive dashboard for visualising hospital-specific antibiotic consumption
- Supervision of tutorials on problem-based learning (PBL) for medical students about physiology of endocrine organs and the immune system

3/2019 – 8/2019	Temporary employee in the pharmacies Apotheke Hersberger and Goldene Engel, Basel, Switzerland - Custom service - Manufacture of medicine
2/2018 – 12/2018	Training as pharmacist in the pharmacies, Basel, Switzerland - Custom service - Manufacture of medicine
8/2014 – 12/2017	Waitress in the restaurant Papiermühle, Basel, Switzerland
6/2012 – 9/2014	Waitress in the Confiserie Bachmann, Basel, Switzerland

RESEARCH ACTIVITY

PUBLICATIONS, PEER-REVIEWD

7 **Renggli L**, Plüss-Suard C, Gasser M, Sonderegger B, Kronenberg A. Assessing the Conversion of Electronic Medical Record Data Into Antibiotic Stewardship Indicators, manuscript under revision.

6 **Renggli L**, Gasser M, Buetti B, Kronenberg A, Increase in Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections in Switzerland: A Nationwide Surveillance Study (2008-2021). J Infect, in press.

5 Gueissaz L, Hauri N, Kocher J, Lavallée M.A, Munday M.F, **Renggli L**, Béguelin C. Bactériémie à *Staphylococcus aureus* sensible à la méticilline. Rev Med Suisse, 2022 Oct 12;18(799):1889-1895. DOI: https://doi.org/10.53738/REVMED.2022.18.799.1889

4 **Renggli L***, Gasser M*, Plüss-Suard C, Harbarth S, Kronenberg A. Temporal and structural patterns of extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* incidence in Swiss hospitals. J Hosp Infect, 2022 Feb; 120:36-42.
DOI: https://doi.org/0.1016/j.jhin.2021.11.006
*contributed equally

3 **Renggli L***, Gasser M*, Plüss-Suard C, Kronenberg A. Consumption of anti-meticillin-resistant *Staphylococcus aureus* antibiotics in Swiss hospitals is associated with antibiotic stewardship measures. J Hosp Infect, 2021 Nov; 117:165-171.
DOI: https://doi.org/10.1016/j.jhin.2021.08.019
* contributed equally

2 **Renggli L**, Gasser M, Frey PM, Kronenberg A. Echtzeit-Resistenzstatistik. Bekämpfung von Antibiotikaresistenzen in der Schweiz. Prim Hosp Care Allg Inn Med, 2020;20(11):352-355.
DOI: https://doi.org/10.4414/phc-d.2020.10319

1 Burckhardt MA*, Gotta V*, Beglinger S*, **Renggli L**, Bachmann S, Hess M, Rentsch K, Pfister M, Koch G, Davis EA, Zumsteg U, Jones TW, Szinnai G. Copeptin Kinetics and Its Relationship to Osmolality During Rehydration for Diabetic Ketoacidosis in Children. J Clin Endocrinol Metab, 2020 Nov 1;105(11). DOI: https://doi.org/10.1210/clinem/dgaa568
* contributed equally

PUBLICATION, NON-PEER REVIEWED

Kronenberg A, **Renggli L**, quality circle mediX Bern. Hygieneregeln nach COVID-19 Handschlag– ja oder nein? Schweizerische Ärztezeitung, 2022 Aug; 103(35): 1110-1113

REVIEW ACTIVITY

05/2022	For the journal Antimicrobial Resistance & Infection Control

GRANT

04/2022	ESCMID attendance grant for *Pre-ECCMID postgraduate course on Antimicrobial Stewardship*, Carcavelos, Portugal

CONFERENCE CONTRIBUTIONS

09/2022	Poster and short oral presentation: *Assessing the conversion of electronic medical records data into antibiotic stewardship quality indicators,* Joint Annual Meeting of the Society for Infectious Diseases (SSI), Swiss Society for Hospital Hygiene (SSHH), Interlaken, Switzerland
08/2022	Poster presentation: *The increase in methicillin-susceptible Staphylococcus aureus bacteraemia in Switzerland (2008-2021) is mainly driven by elderly male of the German-speaking part,* Annual Congress of the Swiss Society for Microbiology, Lausanne, Switzerland
04/2022	Poster presentation: *Assessing the conversion of electronic patient records data into antibiotic stewardship quality indicators,* ECCMID (European Congress of Clinical Microbiology and Infectious Diseases), Lisbon, Portugal
09/2021	Poster and short oral presentation: *Interactive Access to Current Hospital-Specific Antimicrobial Consumption Data: The ANRESIS Dashboard*, Joint Annual Meeting of the Society for Infectious Diseases (SSI), Swiss Society for Hospital Hygiene (SSHH), Swiss Society for Tropical Medicine and Parasitology (SSTMP), Swiss Society of Tropical and Travel Medicine (SSTTM), Montreux, Switzerland
09/2020	Poster presentation: *Consumption of anti-methicillin-resistant Staphylococcus aureus antibiotics in Swiss hospitals is associated with antibiotic stewardship measures*, Joint Annual Meeting of the Society for Infectious Diseases (SSI), Swiss Society for Hospital Hygiene (SSHH), Geneva, Switzerland

ELECTRONIC DATA PROCESSING SKILLS

Microsoft Word, Excel	Very good expertise
PowerPoint	Very good expertise
R	Very good expertise
Python	Basic

LANGUAGES

German	Native
English	Written and oral very good (C1)
French	Fluent (B2)
Portuguese	Basic (A2)

Declaration of Originality

Last name, first name: Renggli, Luzia

Matriculation number: 14-051-627

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date Bern, 3.1.2023

Signature L. Renggli