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

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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.

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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

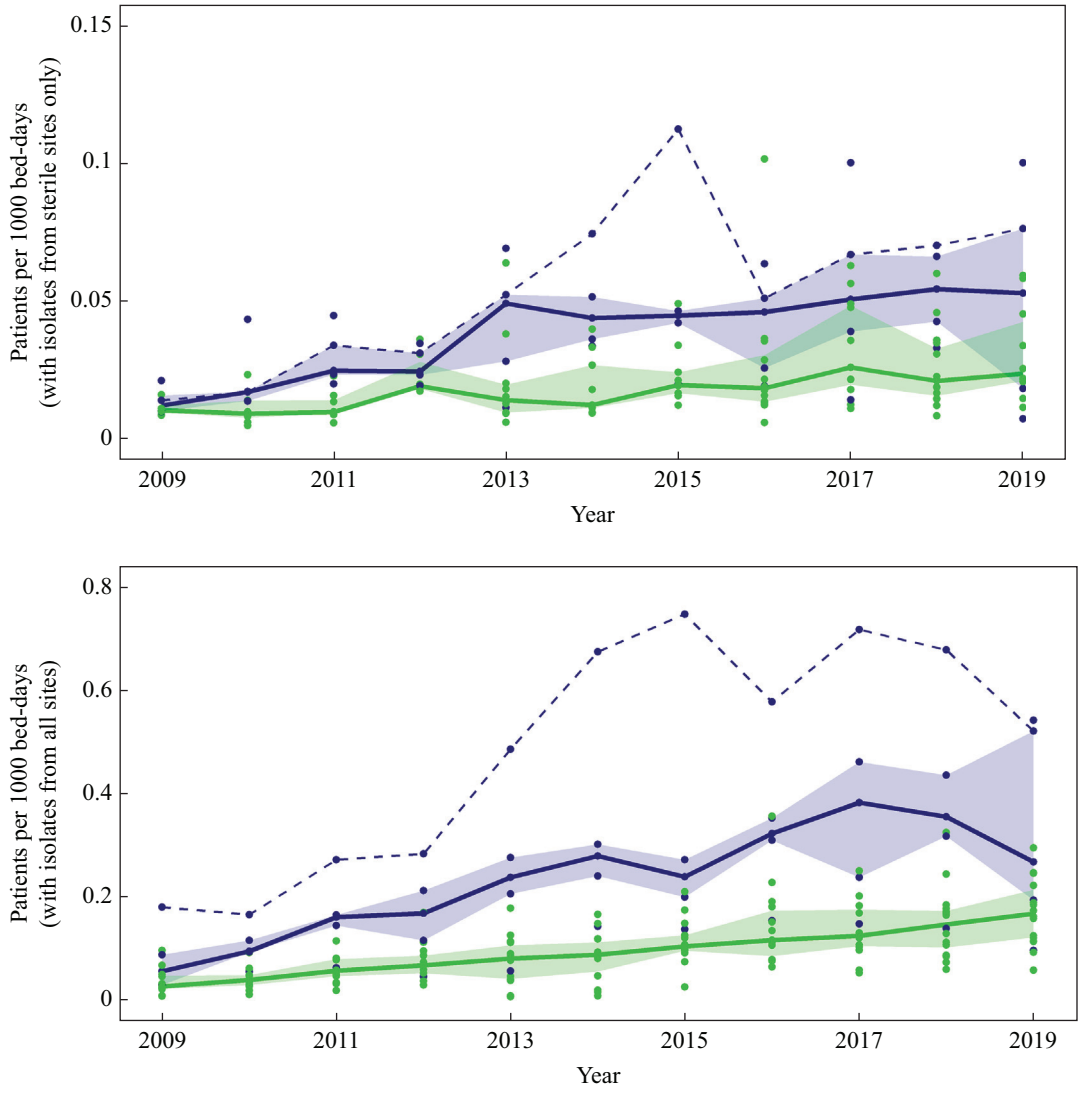

Figure 1. Incidence of invasive ESCR-KP infections (upper panel) and overall ESCR-KP incidence (all sample sites, lower panel) in 21 Swiss hospitals (points), including Geneva University Hospital (dashed line). The median (solid line) and interquartile range (shaded area) of university hospitals (blue) 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, $P > 0.05$).

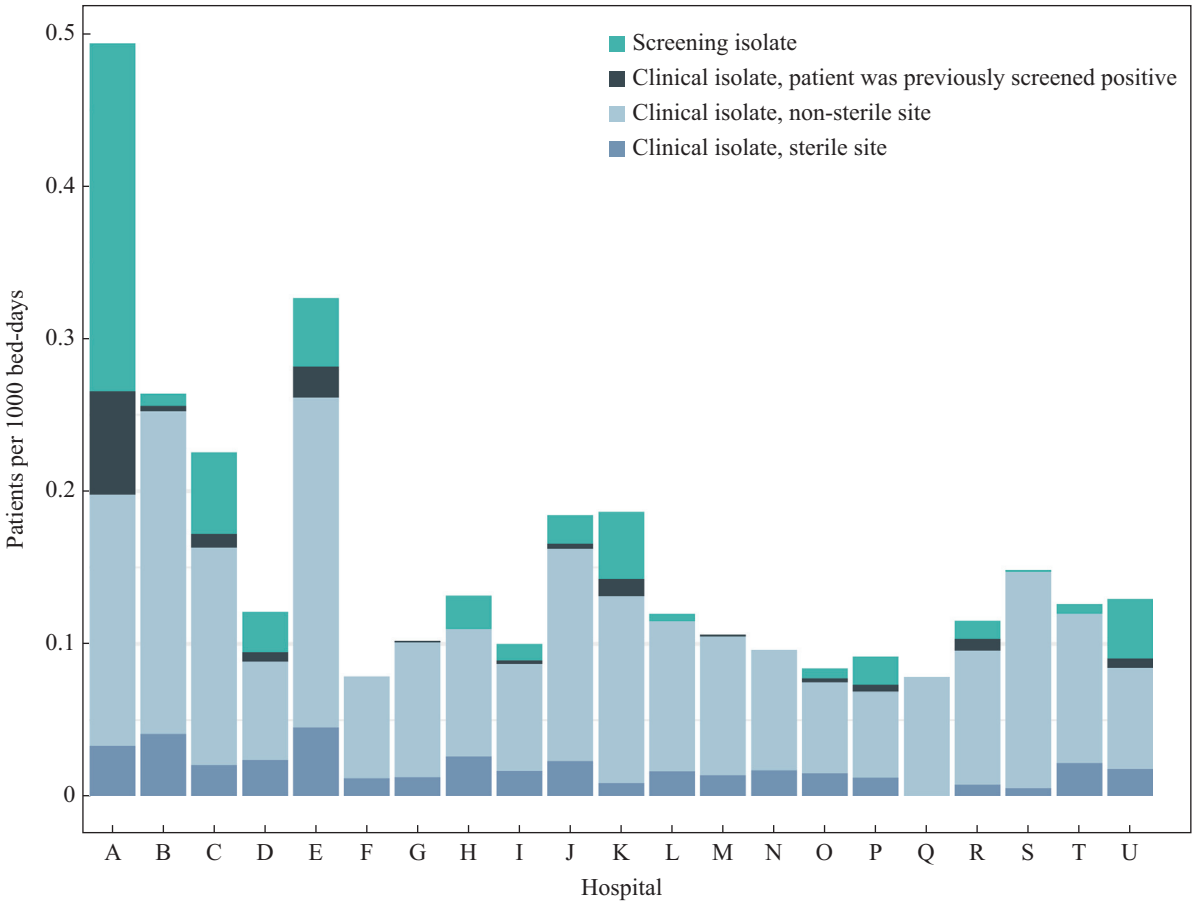

Figure 2. Comparison of sample sites of patients with ESCR-KP in university hospitals (A to E), including Geneva University Hospital (A), and non-university hospitals (F to U) from 2009–2019.

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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