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ORIGINAL ARTICLE

Patterns and trends of pediatric bloodstream infections: a 7-year surveillance study

N. Buetti[1] · A. Atkinson[1] · L. Kottanattu[1] · J. Bielicki[2] · J. Marschall[1] · A. Kronenberg[3] · the Swiss Centre for Antibiotic resistance (ANRESIS)

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Abstract We characterize the epidemiology of pediatric bloodstream infections (BSIs) in Switzerland. We analyzed pathogen distribution and resistance patterns in monomicrobial and polymicrobial BSIs in children from 2008 to 2014 using data from the Swiss antibiotic resistance centre (ANRESIS). A confirmatory statistical analysis was performed comparing pathogens and resistance across 20 acute care hospitals. We identified 3,067 bacteremia episodes, of which 1,823 (59 %) were considered true BSI episodes. Overall, *S. aureus* (16.5 %, 300) was the most frequent pathogen, followed by *E. coli* (15.1 %, 276), coagulase-negative staphylococci (CoNS, 12.9 %, 235), *S. pneumoniae* (11.1 %, 202) and non-*E. coli* Enterobacteriaceae (8.7 %, 159). *S. aureus* and *E. coli* showed similar frequencies in all of the variables analyzed (e.g., hospital acquisition, hospital type, medical specialty). The proportion of these microorganisms did not change over time, resistance rates remained low (4.3 % methicillin resistance in *S. aureus*; 7.3 % third-/fourth-generation cephalosporin resistance in *E. coli*), and no significant resistance trends were observed. We observed a 50 % increase of CoNS BSIs from 2008 (9.8 %, 27) to 2014 (15.2 %, 46, p value for trend = 0.03). *S. pneumoniae* decreased from 17.5 % (48) to 6.6 % (20) during that timeframe (p for trend = 0.007). *S. aureus* and *E. coli* remained the most significant pathogens among pediatric BSIs in Switzerland, exhibiting low resistance rates. CoNS accounted for a greater proportion of BSIs over time. The decrease in bacteremic pneumococcal infections can likely be attributed to the introduction of the 13-valent conjugate vaccine in 2011.

J. Marschall and A. Kronenberg contributed equally to this work

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✉ N. Buetti
niccolo.buetti@gmail.com

[1] Department of Infectious Diseases, University Hospital Bern, Freiburgstrasse 3010, Bern, Switzerland

[2] Paediatric Pharmacology Department, University of Basel Children's Hospital Basel, Basel, Switzerland

[3] Institute for Infectious Diseases, University of Bern, Bern, Switzerland

Introduction

Bloodstream infections (BSIs) in children are potentially life-threatening and require immediate and adequate antimicrobial treatment. Previous studies addressing the national epidemiology of BSIs have focused on adult populations [1–3]; thus, few studies of pediatric populations have been published [4–6].

Access to current epidemiological data is critically important for choosing empiric antibiotic therapy. There have been a number of developments in the last decade that may have had an influence on these data. First, as a consequence of advances in medical technology and the shift to outpatient treatment, there is a steady increase in healthcare-associated infections [5], the third most significant group besides community- and hospital-acquired

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infections. Second, the recent introduction of new vaccines may influence the epidemiology of pediatric BSIs. So far, the impact on children with BSIs of a 13-valent conjugate pneumococcal vaccine implemented in Switzerland in 2011 [7] has not been evaluated. Finally, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) suggest that the burden of bacterial BSIs is increasing, with a shift toward more resistant strains [8].

The need for recent data led us to perform the present study, which describes the patterns, trends, and resistance profiles for the major causative pathogen groups in pediatric BSIs in Switzerland from 2008 to 2014, using data from the national Swiss Antibiotic Resistance Surveillance System (ANRESIS).

Materials and methods

Data and setting

We conducted a national observational multicenter study on BSIs from neonates and children in Switzerland from 2008 to 2014. BSI data were analyzed retrospectively using the representative Swiss Antibiotic Resistance Surveillance System (ANRESIS) [9].

The ANRESIS program provides antibiotic resistance data for all routinely collected microbiological samples from 20 Swiss laboratories, each of them collecting microbiological data from different acute care hospitals distributed across the country. Species identification and antimicrobial susceptibility testing are performed at local laboratories according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) guidelines. Most of the participating laboratories switched from CLSI to EUCAST breakpoints between 2011 and 2013. All laboratories are participating in at least one external quality program of either National External Quality Assessment Service (NEQAS; www.uknegas.org.uk) or the Swiss quality control program from the Institute for Medical Microbiology, University of Zürich (http://www.imm.uzh.ch/services/qc.html).

For the present study, the dataset was restricted to positive blood or catheter tip cultures from children no older than 15 years. We further restricted data to those acute care hospitals that transferred data on a regular basis between 2008 and 2014, which yielded a subset of 20 acute care hospitals. The number of acute care beds from this sample of hospitals remained stable in relation to the overall number of acute beds in the country. In 2008, the acute care beds considered in our study accounted for 30.6 % (our study: 9,015 beds, Switzerland: 29,477), in 2014 for 31.0 % (our study 8,573, Switzerland 27,634) [10]. Two hospitals merged in 2011 and were analyzed as one hospital throughout the entire study period.

Definitions

We considered only positive blood cultures in the analysis; cultures from intravascular tips were interpreted as blood cultures (e.g., typical contaminants needed to be confirmed in another positive culture during the same episode, see below). Positive cultures were grouped into BSI episodes if they occurred no later than 7 days after the last positive culture in the same patient. If another set of cultures was found to be positive >7 days after the most recent BSI episode, it was considered a separate episode. Microorganisms commonly considered as skin contaminants (see Supplementary appendix) were included in the analysis only if they were isolated from two or more cultures within the same episode. In particular, episodes not including typical contaminants were considered to be *true* BSI episodes. Episodes including more than one different pathogen were classified as polymicrobial. If these pathogens were common contaminants, they were only considered if they were detected in ≥2 cultures.

The epidemiological data allowed stratification of isolates by sex, age group (0–2, 2–5, 5–10, and 10–15 years), hospital type (community hospitals [CH] vs university hospitals [UH]), hospital departments (newborn vs non-newborn departments, non-ICU vs ICU departments), linguistic/cultural regions (northeast vs southwest), and year of detection (2008–2014). The age group 0–2 years was further divided into newborns and 0 to 2-year-old non-newborns according to whether their admission was to a newborn or other unit. BSI episodes for which the hospitalization date was available (1,272, 70 %) were grouped into community-acquired (CA) BSIs (cultures positive <3 days after admission) and hospital-acquired (HA) BSIs. Detailed epidemiological analysis was undertaken for *E. coli*, non-*E. coli* Enterobacteriaceae, *S. aureus*, *S. pneumoniae*, CoNS, and *S. agalactiae*.

Analysis of resistance data was performed for *E. coli*, non-*E. coli* Enterobacteriaceae, and *S. aureus*. Duplicates, defined as isolates with identical antimicrobial resistance profiles isolated from the same patient within one calendar year, were excluded from this analysis. Resistance was defined as those who were resistant or had intermediate susceptibility against the antibiotic tested. Resistance against an antibiotic group (e.g., aminoglycosides/carbapenems), was defined as resistance against at least one antibiotic out of the corresponding group. Methicillin resistance was defined as resistance against at least one of the following: oxacillin, flucloxacillin, methicillin or cefoxitin.

This analysis was carried out on routinely collected, anonymous nongenetic surveillance data; ethical consent was not required according to the Swiss law for research on humans.

Statistical analysis

Group comparisons were performed using Student's *t* test for normally distributed continuous variables, with the Mann–Whitney/Wilcoxon tests for non-normally distributed continuous variables, or with Pearson's Chi-squared test for dichotomous variables. Bonferroni correction was used to correct for multiple comparisons on a family-wise basis, where appropriate. For linear time trends, tests of different slopes were based on standard ANOVA techniques. All analyses were conducted using SPSS 21 (SPSS, Chicago, IL, USA).

Results

Demographics

We identified 4,304 positive blood cultures constituting 3,067 bacteremia episodes collected between 2008 and 2014. Forty-one percent of episodes (1,244) were considered contaminant episodes, with CoNS (77 %, 962) being the predominant pathogen in this group, and were excluded from the analysis. The remaining 1,823 bacteremic episodes (59 %) were considered true BSIs and were included in the analysis.

The majority of BSIs occurred in male patients (60 %, 1,084 vs 40 %, 739, $p<0.001$) and in children between 0 and 2 years (59 %, 1,078 vs 41 %, 745, $p<0.001$).

Description of episodes

Overall, *S. aureus* (17 %, 300) was the most frequently occurring agent isolated, followed by *E. coli* (15 %, 276), CoNS (13 %, 235), *S. pneumoniae* (11 %, 202), and non-*E. coli* Enterobacteriaceae (8.7 %, 159; Fig. 1). *Klebsiella* spp. BSI episodes accounted for 3.3 % (60) of all BSI episodes in our study.

Relevant differences were observed among different age groups (Fig. 2). Although *E. coli* (21 %, 226) and CoNS (16 %, 175) predominated in children aged <2 years, *S. aureus* was more common in older children, being responsible for 37 % of BSI episodes in children aged between 10 and 15 years. For non-*E. coli* Enterobacteriaceae we observed higher rates in newborns (12 %, 35) and those 0–2 years of age (11 %, 113), and in patients aged 10–15 years (8.6 %, 19), whereas they were rare in children between 2 and 10 years of age. In this specific age group, *S. pneumoniae* was the leading pathogen, with a peak in children from 2 to 5 years of age (30 %, 80). *S. agalactiae* was almost exclusively isolated from newborns (7.9 %, 24) and children aged between 0 and 2 years (7.0 %, 55).

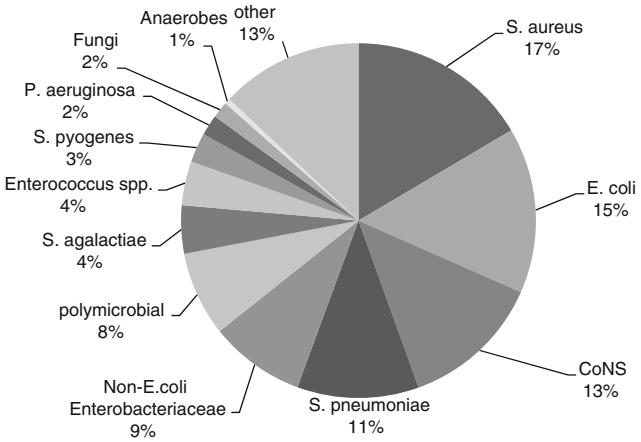

Fig. 1 Microorganisms causing pediatric bloodstream infection (BSI) episodes (total 1,823) in Switzerland, 2008–2014. *CoNS* coagulase-negative Staphylococci

Escherichia coli and *S. aureus* rates did not differ among the different epidemiological settings (such as the site of acquisition, hospital type, departments; Table 1). Regional differences were observed, with *E. coli* being more frequent in the northeastern part of Switzerland (16.5 % vs 11.9 %, $p=0.02$). In contrast, non-*E. coli* Enterobacteriaceae occurred more frequently in HA episodes (13 % vs 6.3 %, $p<0.001$), in ICU departments (13 % vs 9.0 %, $p<0.001$), and in the southwestern part of Switzerland (12.6 % vs 7.1 %, $p<0.001$). Similar epidemiological patterns were encountered for CoNS, being more frequently observed in HA episodes (25 % vs 5.6 %, $p<0.001$), newborn (22 % vs 11 %, $p<0.001$) and ICU departments (22 % vs 12 %, $p<0.001$). On the other hand, *S. pneumoniae* was typically observed among CA episodes (18 % vs 1.2 %, $p<0.001$) and in non-ICU departments (13 % vs 0.8 %, $p<0.001$).

Regarding the hospital setting the major differences emerged in the comparison of community hospitals (CHs) and university hospitals (UHs). CoNS (16 % in UHs vs 10 % in CHs, $p=0.006$) and non-*E. coli* Enterobacteriaceae (11 % in UHs vs 5.9 % in CHs, $p<0.001$) predominated in the academic setting, whereas *S. pneumoniae* dominated in community hospitals (14 % in CH vs 8.0 % in UH, $p=0.002$). The distribution of microorganisms by hospital type is illustrated in Table A of the Supplementary appendix. At the individual hospital level there were no significant differences in terms of patient demographics, but we noted considerable heterogeneity in terms of pathogen distribution ($p<0.001$).

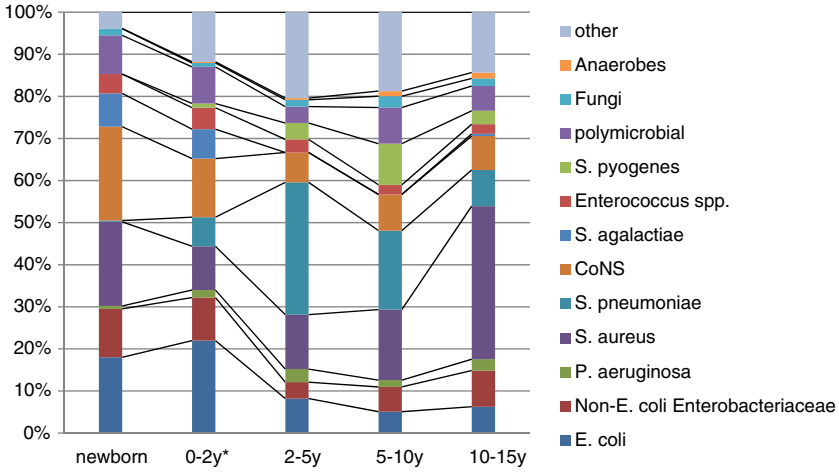

Fig. 2 Frequency of microorganisms causing pediatric BSI episodes by age group and in newborn departments, Switzerland 2008–2014. *Asterisk* patients from newborn departments excluded

Resistance

Resistance rates are shown in Table 2. For *E. coli*, resistance rates were below 10 % for aminoglycosides, third-/fourth-generation cephalosporins and piperacillin-tazobactam. Resistance against amoxicillin–clavulanic acid was observed in 27 % of cases. We did not detect any carbapenem-resistant *E. coli*. Resistance rates were significantly lower in newborns for aminoglycosides and third-/fourth-generation cephalosporins. Compared with *E. coli*, resistance rates in non-*E.coli* Enterobacteriaceae were higher for all antibiotics. Among Enterobacteriaceae, we detected only one carbapenem-resistant microorganism, which was isolated in a newborn (*Citrobacter freundii*, resistant to ertapenem, but susceptible to meropenem and imipenem).

The rate of methicillin-resistant *S. aureus* (MRSA) in children in Switzerland remains low at 4.3 %. No MRSA BSIs were observed in 2014 in the hospitals included (data not shown).

In all three microorganism groups, no significant resistance trends were observed during the study period (data not shown), despite the fact that most of the laboratories changed

Table 1 Number and proportion (%) of *E. coli*, non-*E. coli* Enterobacteriaceae, *S. aureus*, *S. pneumoniae*, and CoNS by site of acquisition, hospital type, and department, 2008–2014

	E. coli (n, %)		Non-*E. coli* Enterobacteriaceae (n, %)		*S. aureus (n, %)*		*S. pneumoniae (n, %)*		CoNS (n, %)		Total
Site of acquisition[a]	$p = 1$		$p < 0.001$		$p = 1$		$p < 0.001$		$p < 0.001$		
CA	165	17.5	59	6.3	161	17.1	171	18.2	53	5.6	942
HA	50	15.2	43	13.0	53	16.1	4	1.2	81	24.5	330
Hospital type	$p = 0.06$		$p < 0.001$		$p = 1$		$p = 0.002$		$p = 0.005$		
CH	162	18.1	53	5.9	155	17.4	128	14.3	90	10.1	893
UH	114	12.3	106	11.4	145	15.6	74	8.0	145	15.6	930
Department (ICU)	$p = 0.4$		$p < 0.001$		$p = 1$		$p < 0.001$		$p < 0.001$		
ICU	43	17.8	32	13.3	40	16.6	2	0.8	52	21.6	241
Non-ICU	233	14.7	127	8.0	260	16.4	200	12.6	183	11.6	1,582
Department (newborn)	$p = 0.2$		$p = 0.05$		$p = 0.07$		$p < 0.001$		$p < 0.001$		
Newborn	55	18.0	35	11.5	61	20.0	1	0.3	68	22.3	305
Non-newborn	221	14.6	124	8.2	239	15.7	201	13.2	167	11.0	1,518
Region	$p = 0.02$		$p < 0.001$		$p = 0.2$		$p = 0.03$		$p < 0.001$		
Northeast	211	16.5	90	7.1	224	17.6	125	9.8	191	15.0	1,275
Southwest	65	11.9	69	12.6	76	13.9	77	14.1	44	8.0	648

CoNS coagulase-negative staphylococci, *CA* community-acquired, *HA* hospital-acquired, *CH* community hospitals, *UH* university hospitals, *ICU* intensive-care unit

[a] Site of acquisition was identified in only 1,272 episodes (70%)

Table 2 Resistance pattern of *E. coli*, non-*E. coli* Enterobacteriaceae, and *S. aureus*, in newborn and non-newborn departments, 2008–2014

	Non-newborn	Resistant, *n* (%)	Newborn	Resistant, *n* (%)	*p* value	Total	Resistant, *n* (%)
E. coli							
Aminoglycoside	229	20 (8.7)	60	2 (3.3)	0.02	289	22 (7.6)
Carbapenem	229	0 (0)	60	0 (0)		289	0 (0)
3rd/4th generation cephalosporins	208	19 (9.1)	60	2 (3.3)	0.02	268	21 (7.3)
Tazobactam/piperacillin	216	14 (6.4)	59	4 (6.8)	0.85	275	18 (6.5)
Amoxicillin/clavulanic acid	225	62 (27.5)	63	15 (23.8)	0.46	288	77 (26.7)
Non-*E. coli* Enterobacteriaceae							
Aminoglycoside	132	20 (15.1)	43	4 (9.3)	0.16	175	24 (13.7)
Carbapenem	133	0 (0.0)	43	1 (2.3)	0.08	176	1 (0.6)
3rd/4th generation cephalosporins	144	15 (10.4)	43	4 (9.3)	0.71	187	19 (10.2)
Tazobactam/piperacillin	130	14 (10.8)	43	3 (7.0)	0.3	173	17 (9.8)
Amoxicillin/clavulanic acid	134	64 (47.8)	43	26 (60.5)	0.16	177	90 (50.6)
S. aureus							
MRSA	265	13 (4.9)	63	1 (1.6)	0.03	328	14 (4.3)

MRSA methicillin-resistant *S. aureus*

their analytical method from the CLSI to the EUCAST guidelines.

Trends

The absolute number of reported BSI episodes increased from 275 in 2008 to 303 in 2014. The proportion of contaminants remained stable between 2008 (41 %, 191) and 2014 (41 %, 210). No specific trends or abrupt increase/decreases in the total number of BSI episodes were observed in the individual hospitals (data not shown). Moreover, the number of records with the coding "unknown data sampling" did not change significantly between 2008 (70 out of 275 25.5 %) and 2014 (87 out of 303, 28.7 %, $p = 0.38$).

The proportion of *E. coli*, non-*E. coli* Enterobacteriaceae, and *S. aureus* varied somewhat over the study period; however, no significant trend between 2008 and 2014 was shown.

As shown in Fig. 3, *S. pneumoniae* decreased from 18 % (48) in 2008 to 6.6 % (20) in 2014 ($= 0.001$, p value for trend $= 0.007$), with the most prominent decrease between 2011 (14 %, 33) and 2012 (6.5 %, 17, $p = 0.006$). In addition, we observed a 50 % increase in CoNS BSI episodes from 2008 (9.8 %, 27) to 2014 (15 %, 46, $p = 0.06$, p for trend $= 0.032$), the increase being most pronounced among newborns, from 11 % (4) in 2008 to 19.3 % (11) in 2014 ($p = 0.22$).

The proportion of *S. agalactiae* doubled between 2008 (2.9 %, 8) and 2014 (5.6 %, 17, $p = 0.1$), with an increasing trend over time (p for trend $= 0.02$, data not shown). This increase was also detected among newborns (2.6 %, 1 in 2008 and 12.3 %%, 7 in 2014, $p = 0.059$).

Discussion

This study describes the epidemiology of BSIs in children in Switzerland between 2008 and 2014. The strength of the present study lies in its representativeness, incorporating 20 acute care hospitals across the country, corresponding with approximately 31 % of all acute care hospital beds nationwide in 2014, and data on 13 microorganism groups. To our knowledge, this is the first national study describing BSIs and their resistance patterns in children for the period up to and including 2014.

S. aureus (17 %), closely followed by *E. coli* (15 %), was the most commonly identified pathogen in our study. Although our data present similar results to those seen in a population-based study in Canada [5], others have reported *S. aureus* rates twice as high as those for *E. coli* [4, 6]. As described in other studies, *S. aureus* was more prevalent among adolescents [4] and newborns [11]; however, the proportion of *S. aureus* did not differ between different epidemiological subgroups (e.g., CA vs HA, ICU vs Non-ICU, UH vs CH) and therefore, as reported in a recent study from the USA [6], appeared to be largely independent of the healthcare exposure of children. This tendency seems to be more pronounced than that documented in a previous European study [11], and a more recent study from South Africa [12], which described an association between *S. aureus* and healthcare system exposure. Moreover, the MRSA proportion of *S. aureus* in Switzerland remained considerably lower compared with the surrounding countries [13, 14] and North America [6]. This probably reflects, amongst other factors, the impact of a national initiative aimed at reducing MRSA

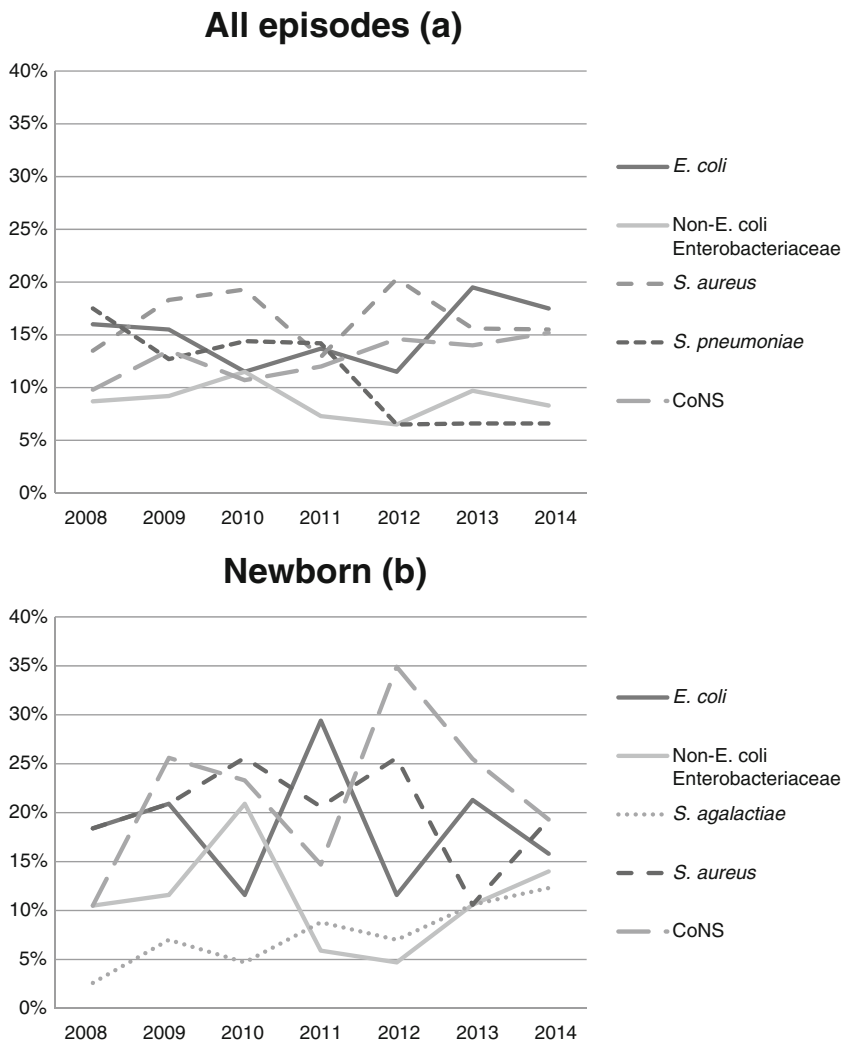

Fig. 3 Trends of *E. coli*, non-*E. coli* Enterobacteriaceae, *S. aureus*, *S. pneumoniae*, *S. agalactiae*, and CoNS in **a** all pediatric BSI episodes and in **b** newborn departments, Switzerland 2008–2014

infection [15]. In light of these considerations, and assuming CoNS infection is unlikely (e.g., in patients without vascular access or other devices in place), a reduced empirical use of glycopeptides may be considered desirable, irrespective of the information on the previous healthcare exposure of the child.

Escherichia coli was the second commonest pathogen identified in Switzerland and the most frequent Gram-negative microorganism. This is in line with other studies [5, 14], but contradicts results from a recent study from the USA, in which *E. coli* was surpassed by *K. pneumoniae* as the most frequent Gram-negative microorganism [6]. Increasing *K. pneumoniae* rates may be considered noteworthy, as intrinsic resistance rates in Europe are higher for *K. pneumoniae* compared with *E. coli* [14]. Therefore, we were encouraged to find stable, low rates of *K. pneumoniae* bacteremia (3.3 % of all BSI episodes) throughout the study period. In line with another study [16] and analogous to *S. aureus*, *E. coli* showed similar proportions regardless of the site of acquisition, hospital type, and department. In our data, the proportion of *E. coli* was stable between 2008 and 2014, which is in contrast to an upward trend described in a previous pediatric study from 1995 to 2005 [17]. Data from other countries are required to determine whether or not this trend is occurring elsewhere. We found very low resistance rates compared with other European [14] and North American countries [6, 18], with no significant temporal trends. It may be beneficial to integrate the epidemiological patterns and trends observed in Switzerland into a national antibiotic stewardship program, which would support the development of mechanisms for de-escalating to narrow-spectrum antibiotics when identifying an *E. coli* BSI.

Representing 13 % of all BSI episodes, CoNS ranked third among the pathogens detected in our study, which is of particular concern because of their intrinsic resistance to many antibiotics (e.g., beta-lactams) and their possible association with higher mortality rates in children [19]. A comparison with other surveillance data is difficult, because CoNS has either not been considered in analyses [20, 21] or contaminants were not properly excluded, resulting in high CoNS bacteremia rates [1, 4, 6]. In a

recent study, not restricted to the pediatric population [2], but using comparable methodology, the authors found CoNS rates of 10 %, which is similar to the 13 % described in our study. In the UK, an alarming increase in BSIs with CoNS was documented between 1998 and 2007 [4]. Unfortunately, our study confirmed this trend, showing a 50 % increase from 2008 to 2014. Besides changes in blood culture ordering techniques, we believe that the main reason for this increase was the growing use of vascular access devices in children [22]. Therefore, antibiotics for difficult-to-treat Gram-positive bacteria (e.g., glycopeptides) may play a role in the empiric treatment of Gram-positive BSIs in patients with vascular access, especially in newborn-, ICU-, and hospital-acquired infections.

Pneumococcal BSIs were typically observed in the community-acquired, non-ICU, and community hospital settings. As previously reported in the USA [23], in Spain [24], and in Switzerland [25], we observed a significant decrease in bacteremic pneumococcal infections after the introduction of the 13-valent conjugate vaccine in 2011. Our results appear to support the success of achieving high immunization coverage with public health programs.

In our study we observed an increase in *S. agalactiae* BSIs in children aged <2 years. This could be explained by increasing immigration from neighboring countries, where the prevalence of maternal colonization with *S. agalactiae* in pregnant women is known to be higher than in Switzerland [26, 27]. Although national gynecology guidelines recommend antibiotic prophylaxis in women with *S. agalactiae* in vaginal cultures 5 weeks before delivery [28], the adherence to guidelines appears to be low in Switzerland [29]. We hope that our data will contribute to the better implementation of these guidelines in the future.

Our study has several limitations. First, our surveillance was not population-based and, although 20 hospitals throughout the country were included, rendering results representative of Switzerland, we were unable to calculate the incidence rates. Second, clinical data were not included in the study and therefore differentiation between community- and hospital-acquired infections had to rely on the hospitalization date only. Third, according to data protection rules our database does not include the exact date of birth. Therefore, neonatal data were extrapolated from newborn departments, possibly missing neonatal BSIs in pediatric departments of smaller community hospitals. However, this would most probably lead to an underestimation of the difference between neonates and other children below 2 years of age. Finally, considering cultures from intravascular catheters to be equivalent to a blood culture makes comparisons with other studies more difficult. However, we believe that a better classification of CoNS into true BSI and contamination was achieved by using this approach. The significance of positive catheter tip cultures with negative concurrent blood cultures due to noncontaminant pathogens is still debated [30].

In conclusion, our study provides a timely picture of the pediatric BSI epidemiology in Switzerland. *S. aureus* and *E. coli* represent the most important pathogens causing pediatric BSI, with resistance rates remaining low. CoNS became more prominent over the period considered, especially in children with healthcare exposure, whereas *S. agalactiae* increased in newborn departments. The decrease in bacteremic pneumococcal infections may be attributable to the introduction of the 13-valent conjugate vaccine.

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Compliance with ethical standards

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Conflicts of interest The authors declare that they have no conflicts of interest

Ethical approval This analysis was carried out on routinely collected, anonymous, nongenetic surveillance data; thus, ethical consent was not required according to the Swiss law for research on humans.

Informed consent No clinical data were included

Swiss Centre for Antibiotic resistance (ANRESIS)

R. Auckenthaler, Synlab Suisse, Switzerland; A. Cherkaoui, Bacteriology Laboratory, Geneva University Hospitals, Switzerland; M. Dolina, Department of Microbiology, EOLAB, Bellinzona, Switzerland; O. Dubuis, Viollier AG, Basel, Switzerland; R. Frei, Clinical Microbiology Laboratory, University Hospital Basel, Switzerland; D.

Koch, Federal Office of Public Health, Bern, Switzerland; A. Kronenberg, Institute for Infectious Diseases, University of Bern, Switzerland; S. Leib, Institute for Infectious Diseases, University of Bern, Switzerland; S. Luyet, Swiss Conference of the Cantonal Ministers of Public Health, Switzerland; P. Nordmann, Molecular and Medical Microbiology, Department of Medicine, University Fribourg, Switzerland; V. Perreten, Institute of Veterinary Bacteriology, University of Bern, Switzerland; J.-C. Piffaretti, Interlifescience, Massagno, Switzerland; G. Prod'hom, Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; J. Schrenzel, Bacteriology Laboratory, Geneva University Hospitals, Geneva, Switzerland; A.F. Widmer, Division of Infectious Diseases and Hospital Epidemiology, University of Basel, Switzerland; G. Zanetti, Service of Hospital Preventive Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; R. Zbinden, Institute of Medical Microbiology, University of Zürich, Switzerland.

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