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Colonization with resistant bacteria in hospital employees: an epidemiological surveillance and typing study

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ABSTRACT The objective of this study was to determine the prevalence, molecular epidemiology, and risk factors for gut colonization with extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), carbapenemase-producing Enterobacterales (CPE), and vancomycin-resistant enterococci (VRE) in healthcare workers (HCWs). In September/October 2022, we performed a cross-sectional study among HCW from 14 institutions in Northeastern Switzerland. HCWs reported risk factors for antimicrobial resistance (covering the last 12–24 months) and provided rectal swabs. Swabs were screened for ESBL-E, CPE, and VRE; whole-genome sequencing (WGS) was performed to assess the genetic relatedness. Logistic regression was used to identify occupational and non-occupational risk factors. Among approximately 22,500 employees, 1,209 participated (median age 46 years, 82% female). Prevalences of ESBL-E (n = 65) and CPE (n = 1) were 5.4% [95% confidence interval (CI) 4.2–6.8] and 0.1% (95% CI 0.0–0.5), respectively; no VREs were detected. In the multivariable analysis, non-European ethnicity [adjusted odds ratio (aOR) 7.0, 95% CI 1.4–27.3], travel to high-risk countries (aOR 4.9, 95% CI 2.5–9.3), systemic antibiotics (aOR 2.1, 95% CI 1.1–3.7), antibiotic eye drops (aOR 4.7, 95% CI 1.7–11.9), and monthly sushi consumption (aOR 2.4, 95% CI 1.4–4.3) were positively associated with ESBL-E colonization, whereas alcohol consumption (aOR 0.5 per glass/week, 95% CI 0.3–0.9) was negatively associated with ESBL-E colonization. Occupational factors showed no association. Among ESBL-*Escherichia coli*, ST131 (15 of 61, 25%) and $bla_{\text{CTX-M-15}}$ (37/61; 61%) were most common; one isolate co-harbored $bla_{\text{OXA-244}}$. WGS data did not show relevant clustering. Occupational exposure is not associated with ESBL-E colonization in HCW. Given the potential public health and antibiotic stewardship implications, the role of sushi consumption and antibiotic eye drops as risk factors should be further elucidated.

KEYWORDS antibiotic resistance, ESBL, prevalence, epidemiology, colonization, healthcare workers, occupation, sushi, risk factors

Antimicrobial resistance (AMR) represents an ongoing global health challenge, contributing to an estimated disease burden of 4.95 million deaths in 2019, with 1.27 million directly attributed to AMR (1). Healthcare workers (HCWs) have been identified as carriers and vectors of resistant bacteria, mainly methicillin-resistant *Staphylococcus aureus* (2). Systematic reviews concluded that for resistant bacteria such as extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E), carbapenemase-producing Enterobacterales (CPE), or vancomycin-resistant enterococci (VRE), the occupational infection risk for HCWs is unclear, and more research is needed (3, 4). The available literature shows a large geographic variation of ESBL-E colonization among

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HCW, ranging from 2.6% in Europe to 65% in Vietnam (3, 5). CPEs are very rarely detected in HCWs (6), and the sparse literature available suggests that VRE prevalence in HCW ranges from 0% to 5.3% (7, 8).

In this study, we assessed the prevalence of ESBL-E, CPE, and VRE rectal colonization in HCWs, both with and without patient contact. Furthermore, we sought to identify occupational and non-occupational risk factors influencing ESBL-E, CPE, and VRE colonization. Additionally, we aimed to interpret the molecular epidemiology of the detected resistant bacteria within a national context.

MATERIALS AND METHODS

Study design and participants

We performed a cross-sectional study nested within the prospective SURPRISE+ cohort. SURPRISE+ was launched in 2020 to study coronavirus disease 2019 and related topics and comprises over 3,000 participants at least 16 years of age affiliated with 14 healthcare institutions in Northeastern Switzerland. The cohort includes HCWs with and without direct patient interaction such as administrative personnel, information technology specialists, and facility management. The cohort comprises acute care hospitals, rehabilitation clinics, and geriatric and psychiatric institutions. Infection control measures are mostly identical across institutions, with patients carrying CPE, ESBL-non-*Escherichia coli*, or VRE being contact isolated. In August 2022, cohort participants were approached to engage in this subproject on AMR. In September/October 2022, consenting participants completed an electronic questionnaire elucidating risk factors for resistant bacteria. Additionally, participants self-collected rectal swab samples.

Questionnaire and definitions/data collection

Using REDCap, we collected baseline characteristics, potential exposures to and risk factors for resistant bacteria (Table S1). Risk factors included healthcare interactions within the preceding 12 months (or 24 months for endoscopies and hospitalizations), comorbidities, and medication usage. A specific emphasis was placed on systemic or topical antibiotic treatments. Work-related factors included profession, work field, patient contact within the last 12 months (work in patient room or administrative patient contact), and caring for patients with known colonization with resistant bacteria. Travel history over the preceding 12 months was collected. Northern Africa and Asian countries were considered as high-risk travel areas (9). Additional non-occupational factors included dietary practices (i.e., preferred diet, at least monthly consumption of raw milk products, raw meat, sushi, or seafood); household characteristics (i.e., presence of household members with known colonization with resistant bacteria, household size, pets, and residence on a farm); and recreational activities (i.e., swimming in lakes or rivers, animal contacts, and visits to high-risk settings such as long-term care facilities, intensive care units, or asylum centers) (10–12) (Table S1).

Sample processing, screening for resistant bacteria, and whole-genome sequencing

Participants were requested to submit a self-collected rectal eSwab (COPAN ITALIA). The swab was accompanied by instructions detailing the proper methodology for sample collection (Fig. S1). Swabs were sent to the Centre for Laboratory Medicine in St. Gallen following standard operating procedures under ISO 17025 accreditation. Processing of the samples was performed via WASPLab (COPAN ITALIA). Screening for ESBL-E, CPE, and VRE was accomplished applying an enrichment protocol, starting with the inoculation of 10-µL liquid of eSwab in tryptic soy broth or brain heart infusion broth, respectively. After enrichment, chromogenic media chromID ESBL, CHROMID OXA-48, and chromID VRE (bioMérieux, Marcy l'Etoile, France) were used to screen for colonies of interest. Further workup was performed with matrix-assisted laser desorption/ionization-time of flight

mass spectrometry (Bruker Daltonics Inc., Billerica, MA, USA) for identification followed by standard susceptibility tests using BD Phoenix M50 (NMIC-474 and PMIC-88 panel). Additional confirmatory tests were performed if required [RAPIDEC CARBA NP, ETEST (bioMérieux), and Xpert Carba-R (Cepheid, USA) where appropriate]. The antimicrobial susceptibility data were interpreted according to EUCAST guidelines (version 12.0).

Whole-genome sequencing (WGS) was performed on all ESBL-E and CPE isolates at the Institute of Microbiology (University of Zurich) under ISO 17025 accreditation (see Supplemental Methods). Sequencing data of *E. coli* ST131 isolates (the most identified sequence type [ST] in our study) from other Swiss studies were retrieved from the National Center for Biotechnology Information (see Table A2 for accession numbers). These comprised clinical urine or blood culture isolates collected between 2018 and 2020 at the University Hospital Basel (n = 147) (13), municipal wastewater and river water isolates collected between 2020 and 2022 in Central Switzerland (n = 57) (14), and rectal swabs collected in 2019 from long-term care facility residents in Eastern and Western Switzerland (n = 40) (15) (see Supplemental Methods).

Statistical analysis

Prevalence of colonization was calculated as percentage of participants with detection of ESBL-E, CPE, or VRE, respectively; binomial proportion confidence intervals (CIs) were calculated using the Clopper-Pearson exact method. We used descriptive statistics to compare baseline characteristics and risk factors between colonized and non-colonized participants. Students' t-test was used for continuous variables with equal variance assumption. For non-normal continuous variables, we used the Mann-Whitney U test. Chi-square test and Fisher exact test, as appropriate, were used for categorical variables. Subjects with incomplete data were excluded from the examination of the corresponding variable; no data imputation was performed. To determine the independent association between risk factors and colonization with resistant bacteria, multivariable logistic regression analysis was conducted, and adjusted odds ratios (aORs) with corresponding 95% CIs were computed. After fitting the full model, forward and backward stepwise variable selections were applied to obtain a simplified predictive model. We performed three sensitivity analyses: (i) we corrected our multivariable analysis for multiple testing using the Bonferroni-Holm correction; (ii) we performed a random-effect model treating the healthcare institution as random effect; and (iii) we combined adjustment for multiple testing and the random-effect model. Statistical analyses were performed using R statistical software (version 4.2.1). This article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

RESULTS

Study population

In total, 3,731 individuals, constituting 17% of the approximately 22,500 approached hospital employees, participated in the SURPRISE+ study. Thereof, 1,878 (50.3%) completed the questionnaire on AMR and 1,218 (32.6%) submitted a self-collected rectal swab sample. Of these samples, 1,209 correlated with the corresponding participant; 9 samples could not be matched with any participant and were therefore excluded. The subset of these 1,209 participants exhibited baseline characteristics comparable to the 2,522 cohort participants who did not participate in this substudy (Table S3). The median age was 46 years (range 16–69); 82% identified as female.

ESBL-E, CPE, and VRE colonization and risk factors

Among the 1,209 participants, prevalence for ESBL-E (n = 65) was 5.4% (95% CI 4.2–6.8); one of the ESBL-E carriers co-harbored a CPE, corresponding to a prevalence of 0.08% (95% CI 0.004–0.41). No VREs were detected. ESBL-E prevalence in HCWs ranged from 0.0% to 16.0% per institution (Fig. S2). Institutions with presumably sicker patients

(i.e., acute care and geriatrics) did not show a higher prevalence (5.2%) compared to rehabilitation and psychiatric clinics (7.1%).

In the univariable analysis, ESBL-E/CPE carriers (n = 65) differed from non-carriers (n = 1,144) regarding body mass index (25.8 vs 23.1 kg/m^2, $P \leq 0.001$), ethnicity (non-European) (4.6% vs 0.7%, $P \leq 0.005$), use of systemic antibiotics (29.2% vs 18.2%, P = 0.033), use of antibiotic eye drops (12.3% vs 3.2%, P = 0.001), and at least monthly sushi consumption (43.1 vs 23.8%, P = 0.004). Patient contact (66.2% vs 78.0%, P = 0.037) was negatively associated, and exposure to patients carrying resistant bacteria (37.0% vs 41.1%, P = 0.66) was not associated with colonization in HCW (Table 1).

In the multivariable analysis, previous systemic antibiotic treatment (aOR 2.07, 95% CI 1.12–3.73), antibiotic eye drops (aOR 4.74, 95% CI 1.70–11.9), travel risk (aOR 4.91, 95% CI 2.50–9.33), and at least monthly sushi consumption (aOR 2.44, 95% CI 1.40–4.25) showed an independent positive association with ESBL-E colonization, whereas alcohol consumption (aOR 0.50, 95% CI 0.27–0.88) was negatively associated (Fig. 1; Table S4). Results of forward and backward variable selections were identical. After adjustment for multiple testing, the variables ethnicity, alcohol consumption, and systemic antibiotics were no longer statistically significant, whereas accounting for the cluster effect of the institution in the random-effect model did not significantly change our estimates (Table S5).

Microbiology and molecular epidemiology

Among the 65 HCW with ESBL-E, we identified 69 isolates: 61 *E. coli*, 4 *Klebsiella variicola*, 1 *Klebsiella pneumoniae*, 1 *Klebsiella aerogenes*, 1 *Citrobacter amalonaticus*, and 1 *Citrobacter farmeri* (Table S2). Among ESBL-*E. coli*, the most common STs were ST131 (n = 15) and ST69 (n = 6); $bla_{\text{CTX-M-15}}$ (n = 37) was the most frequently detected β-lactamase followed by $bla_{\text{CTX-M-27}}$ (n = 10, thereof 9 in ST131). All ESBL-*K. variicola* were ST981 carrying $bla_{\text{CTX-M-14}}$. One HCW with a recent trip to Northern Africa carried a $bla_{\text{OXA-244}}$/$bla_{\text{CTX-M-15}}$-positive *E. coli* (i.e., co-colonization of carbapenemase and ESBL). Ciprofloxacin resistance was 34% (21 of 61) in *E. coli* and 50% (4 of 8) in non-*E. coli*; sulfamethoxazole/trimethoprim resistance was 59% (36 of 61) and 63% (5 of 8), respectively. In contrast, all tested isolates were susceptible against fosfomycin and nitrofurantoin (Table S2).

No genomic relatedness of ESBL-*E. coli* was observed, either within individual institutions or across multiple institutions (Fig. 2). Nevertheless, two cases with closely related ESBL-*E. coli* ST131 (showing identical core genome multilocus sequence typing [cgMLST] profiles) were identified, and subsequent investigation revealed that these individuals were living together as a couple. Additionally, four instances of ESBL-*K. variicola*, originating from three distinct institutions, exhibited genetic relatedness within a range of five allele differences (Fig. S3). Further investigations did not show any obvious commonalities, except that all four individuals reported at least monthly consumption of sushi (at different restaurants) and of raw milk products.

Phylogenomic characteristics of ST131 isolates

Compared to *E. coli* ST131 from other Swiss studies, our isolates differed by at least 13 cgMLST alleles, suggesting no genetic relatedness. Most HCW isolates belonged to ST131 clades A (n = 6, 40.0%) or C1 (n = 7, 46.7%) (Fig. 3). All isolates within clade C1 could be attributed to the C1M27 subclade, which is defined by a specific M27PP1 (+M27PP2) prophage-like region and often harbors $bla_{\text{CTX-M-27}}$ on an F1:A2:B20 plasmid (16).

Two isolates (13.3%) belonged to clade C2, which is associated with increased virulence (18). All clade C ST131 were resistant to ciprofloxacin, whereas clade A and B ST131 were not (Table S2). The virulence gene *papGII* was detected in 2 of the 15 ST131 isolates (13%). Both isolates belonged to an internationally circulating clade A sublineage characterized by a $bla_{\text{CTX-M-27}}$ transposition unit chromosomally integrated into the *gspD* gene and a pathogenicity island containing *papGII* and *cnf1* (encoding cytotoxic necrotizing factor 1), among other virulence genes (19).

TABLE 1 Baseline characteristics and risk factors of healthcare workers with and without ESBL-E[e]

	Overall *N* = 1,209	Missing	ESBL-E positive *n* = 65	ESBL-E negative *n* = 1,144	*P* value
Female gender	995	0	57	938	0.315
Age, median (IQR)	46.0 (18)	0	48.0 (13)	46.0 (18)	0.638
Body mass index, median (IQR)	23.2 (5.2)	0	25.8 (4.7)	23.1 (5.1)	<0.001
European (vs other)	1,188	10	62	1,126	0.011
Active smoker/ex-smoker (vs never)	429	2	18	411	0.352
Alcohol (glasses/week)	1.77	0	1.44	1.79	0.178
Education		12			0.295
Mandatory/high school	76		7	69	
Vocational training	401		24	377	
University of applied sciences	534		23	511	
University	186		10	176	
People in household, median (IQR)	1 (2)	0	2 (1)	1 (2)	0.876
Household with known colonization with resistant bacteria	7	20	0	7	1.000
Comorbidities[a]		2	–	–	–
Immunological/allergic disease	409		19	390	0.496
Cardiovascular disease/diabetes	109		8	101	0.468
Respiratory disease	79		5	74	0.899
Other disease	166		4	162	0.100
Proton-pump inhibitor[b]	377	21	21	356	0.888
Other regular medication	389	2	27	362	0.130
Hospitalization[c]	164	120	7	157	0.655
Endoscopies[c]	145	20	4	141	0.208
Systemic antibiotics[b]	227	21	19	208	0.033
Topical antibiotics		0	–	–	–
Antibiotic eye drops[b]	45		8	37	0.001
Antibiotic ear drops[b]	14		0	14	0.763
Antibiotic cream[b]	73		5	68	0.758
Working percentage, median (IQR)	80 (40)	0	80 (30)	80 (40)	0.736
Hospital workspace		6	–	–	0.311
Internal medicine/pediatrics	259		11	248	
Intensive care/emergency	144		6	138	
Surgery/orthopedics	139		6	133	
Other workspaces	390		29	361	
No workspace assigned	271		13	258	
Profession		2	–	–	0.206
Doctors	108		4	104	
Nurses/assistants	619		36	583	
Other professions	350		20	330	
Therapeutical services	70		0	70	
Research workers	60		5	55	
Patient contact[b]	935	2	43	892	0.037
Contact with patients carrying resistant bacteria[b]	494	19	24	470	0.664
Work in asylum center/ living with asylum seekers[b]	33	0	3	30	0.553
Work/visit in elderly home/ nursing home[b]	112	38	6	106	1.000
Travel abroad[b]	882	18	52	830	0.152
Travel risk[d]	93	18	18	75	<0.001
Swimming in lake/river at least monthly	795	20	46	749	0.353
Swimming in pool, at least monthly	450	20	24	426	0.052
Any pet at home	440	22	24	416	0.969
Living on farm	23	23	2	21	0.794
Eating meat	1,097	20	60	1,037	0.505

(*Continued on next page*)

TABLE 1 Baseline characteristics and risk factors of healthcare workers with and without ESBL-E[e] (*Continued*)

	Overall *N* = 1,209	Missing	ESBL-E positive *n* = 65	ESBL-E negative *n* = 1,144	*P* value
Eating raw meat at least monthly	268	104	17	251	0.600
Drinking raw milk at least monthly	735	24	32	703	0.079
Eating seafood at least monthly	420	69	26	394	0.409
Eating sushi at least monthly	300	69	28	272	0.001

[a]Multiple selection answers possible; result does not add up to 100% (1,209).
[b]In the last 12 months.
[c]In the last 24 months.
[d]Visit to Northern Africa or Asia at least once in the last 12 months, multiple answers possible; results do not add up to 100% (1,209).
[e]ESBL, extended-spectrum β-lactamase-producing Enterobacterales.

DISCUSSION

In this cross-sectional multicenter study involving 1,209 HCW in Switzerland, we found a rectal ESBL-E colonization rate of 5.4%. We identified potentially novel risk factors for ESBL-E colonization, namely, frequent sushi consumption and exposure to antibiotic eye drops. Notably, patient contact was not associated with ESBL-E colonization, and no genetic relatedness of ESBL-E was detected among HCWs from the same institution or among ESBL-Es from other Swiss studies. The study's main strengths are the uniquely large sample size, the comprehensive risk factor questionnaire, and the thorough molecular workup.

Our ESBL-E colonization rate aligns with the documented colonization rates observed among HCWs in other Western countries (3, 20, 21). ESBL-E prevalence in the general population of Switzerland ranges from 3% in pregnant women up to 10% in travelers (before travel) (4). These figures, which are similar to the prevalence of 5.4% in our HCWs, are in line with our finding that patient contact was not associated with an increased ESBL-E colonization risk, as shown by others (7, 21). In contrast, the prevalence of CPE

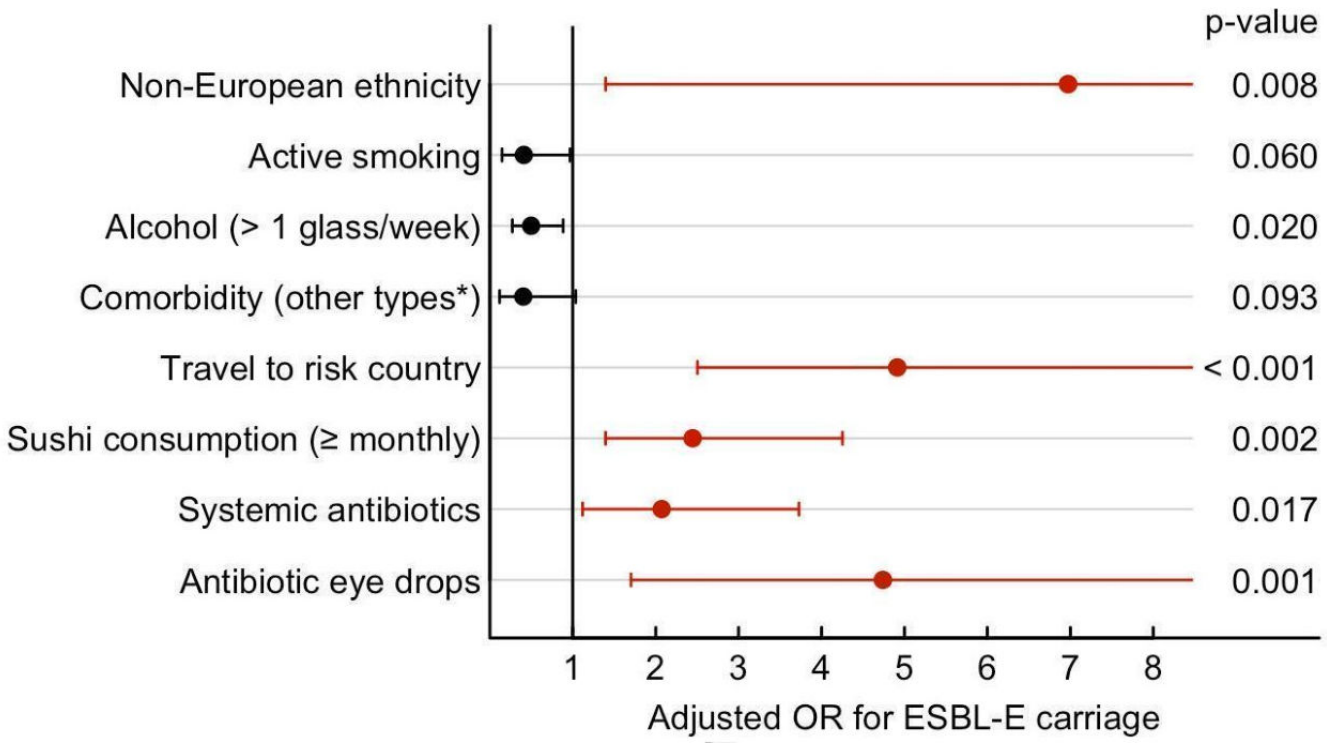

FIG 1 Results of multivariable logistic regression of factors independently associated with extended-spectrum β-lactamase-producing-Enterobacterales (ESBL-E) colonization shown as forest plot, including adjusted odds ratios (ORs) and corresponding 95% confidence intervals (red, factors with significant positive association).

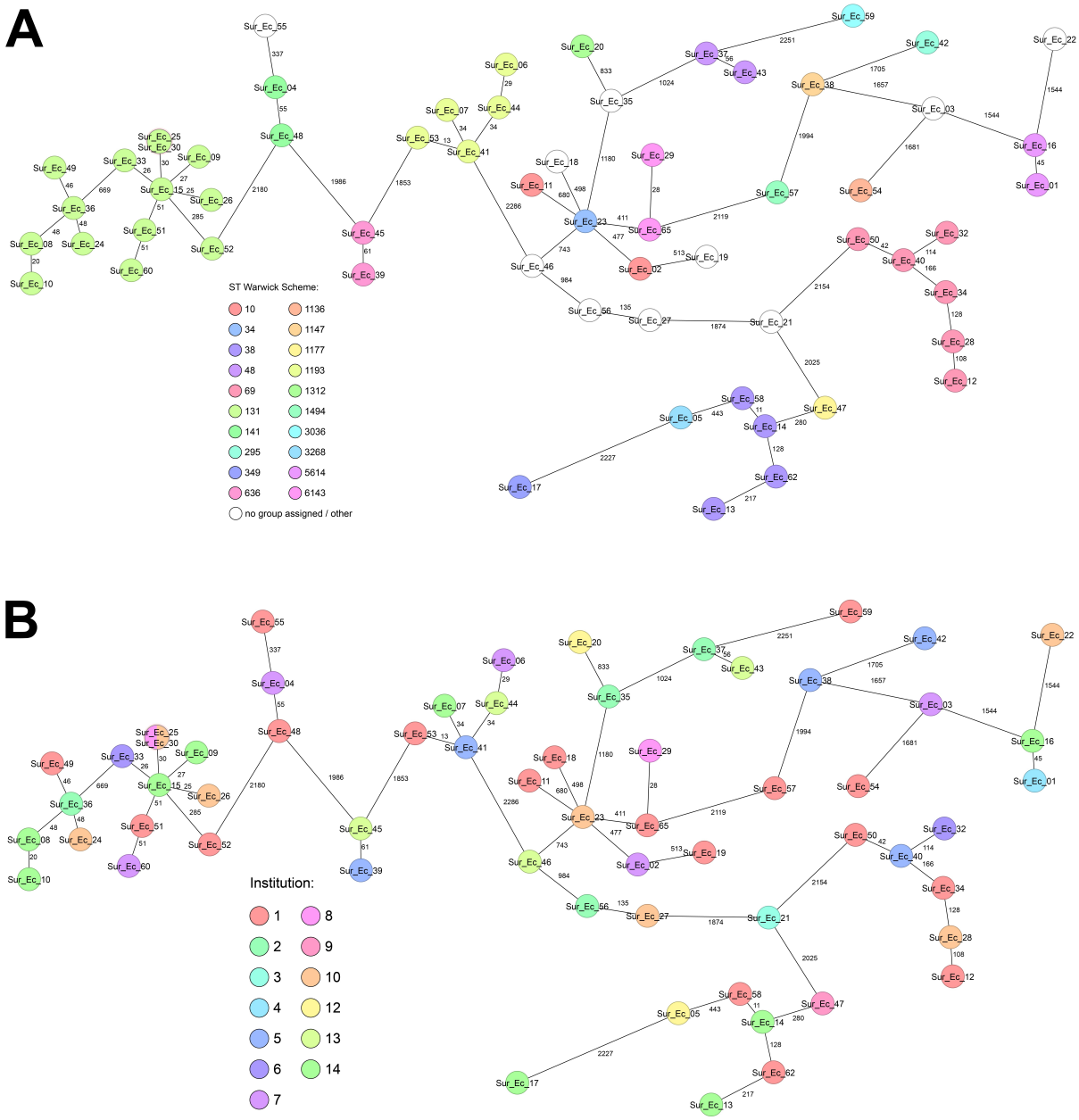

FIG 2 cgMLST analysis of extended-spectrum β-lactamase-producing *Escherichia coli* (*n* = 61), according to sequence type Warwick (a) and according to institution (b).

and VRE is negligible, which is in line with other data from Switzerland and Germany (4, 20).

Our study revealed a novel association between sushi consumption and ESBL-E colonization. Indeed, ESBL-*E. coli* has previously been identified in samples of fish used in sushi preparation (22). Additionally, investigations have revealed the presence of ESBL-E—mainly *Enterobacter cloacae*—in nearly one-fifth of raw fish from Northern Spain (10). Although other sources have to be kept in mind (e.g., colonization of other ingredients used for sushi and contamination of hands of fishmongers or sushi chefs), these data reinforce the conclusion from a literature review, suggesting that further research is needed in evaluating the potential contamination with resistant bacteria of raw fish (23). Of note, given that sushi fish is consumed raw as opposed to most chicken products, the risk of ESBL-E acquisition from contaminated sushi fish might potentially be much

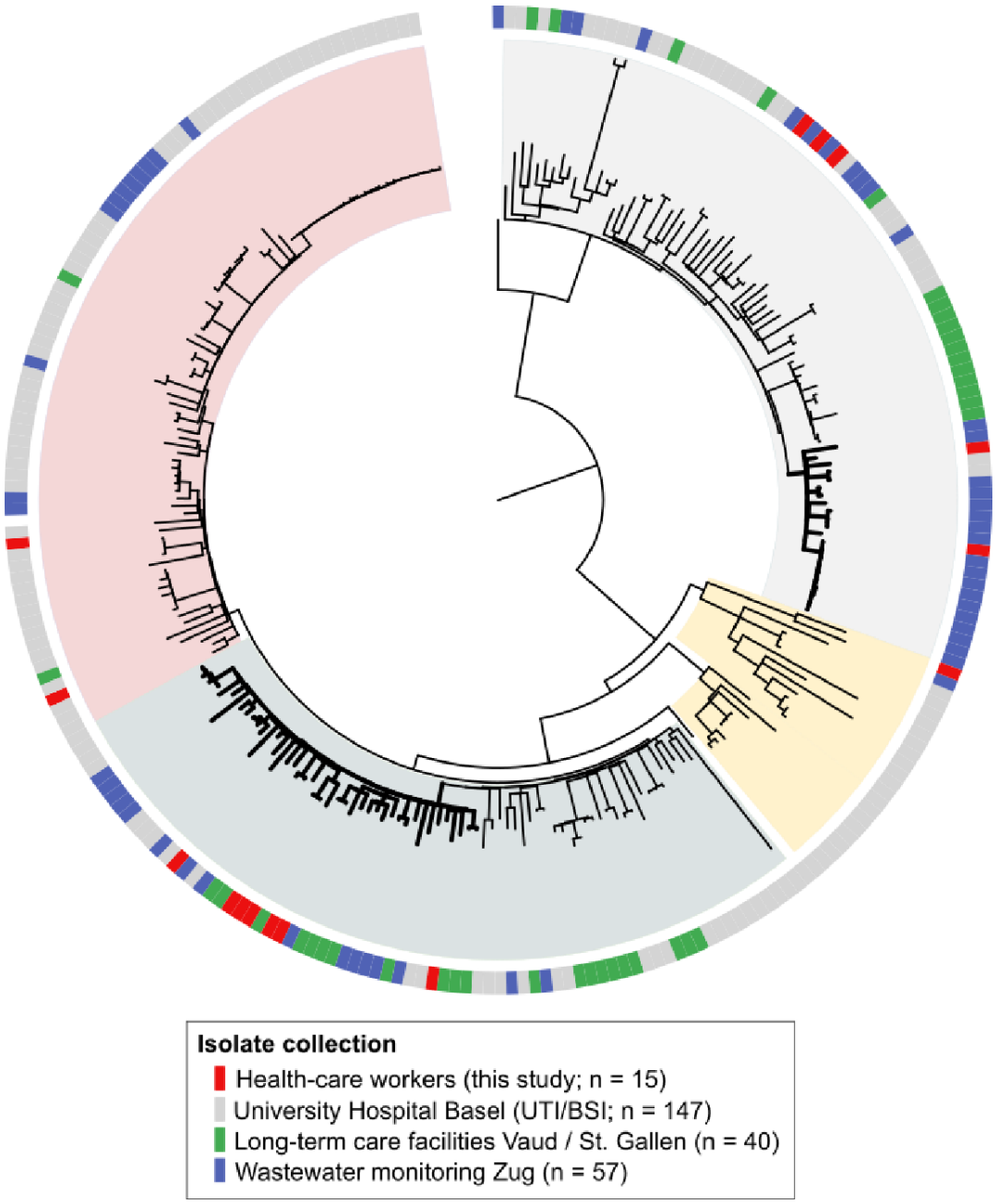

FIG 3 Maximum-likelihood phylogenetic tree of 259 Swiss *E. coli* ST131 isolates. In addition to 15 isolates from this study, 244 isolates from three other collections were included (annotated in the outer ring). ST131 clades A, B, C1, and C2 are labeled. Bold branch lines indicate international sublineages mentioned in the main text. The tree is based on 4,585 variable sites identified in a 3.6-Mb core genome alignment and was visualized using iTOL (17). UTI, urinary tract infection; BSI, bloodstream infection.

higher. Interestingly, current food regulations for sushi fish in the European Union and Switzerland include freezing to a temperature of at least −20°C to prevent parasitic infections, including anisakidosis (24). However, this measure cannot reduce the risk of contamination with resistant bacteria.

Traveling to high-risk countries is a well-known risk factor for ESBL-E (25), but also for CPE acquisition, as demonstrated in a participant with recent travel to Northern Africa colonized with an OXA-244 carrying *E. coli*. Antibiotic exposure was associated with ESBL-E colonization, consistent with previous reports (26). Notably, our study revealed

another novel association, wherein the use of antibiotic eye drops was linked to ESBL-E colonization. There is a proposition that eye drops may traverse the nasal cavity through the nasolacrimal duct, potentially entering the gastrointestinal tract (27). Importantly, antibiotic eye drops are frequently prescribed, yet they remain outside the focus of awareness for most antibiotic stewardship programs.

Further findings of our study include a presumptive protective effect of alcohol consumption. Given the direct toxic effects of ethanol on bacteria, this association is not completely implausible (28). However, the association was no longer significant after adjusting for multiple testing.

WGS analyses revealed a heterogeneous landscape in the molecular epidemiology of ESBL-*E. coli*, indicating the involvement of multiple acquisition sources within the community. The most frequently identified sequence type/β-lactamase combination was ST131 carrying $bla_{\text{CTX-M-27}}$. ST131 is responsible for substantial morbidity globally and is divided into four clades (A, B, C1, and C2), each comprising multiple sublineages. Multiple isolates belonged to the ST131 C1M27 subclade, whose emergence has been reported from other countries, such as Japan and France (29). Clade C2 isolates were rarely detected in our young and healthy population but were dominant in a collection of clinical isolates from a Swiss hospital (13), supporting an enhanced virulence potential of this clade as suggested in previous studies (19). Similarly, the *papGII* gene, a key determinant of invasive uropathogenicity encoding the P-pili tip adhesin, was detected in only two (13%) of our isolates, compared to 31% of the above-mentioned clinical isolates (13).

An important limitation of our study is that HCWs who were motivated to participate may be systematically different from those not participating. Indeed, certain behavior variables such as adherence to hand hygiene or to recommendations on how to safely prepare and handle potentially contaminated food were not included in our survey. Self-collection of rectal swabs may have resulted in an underestimation of the prevalence due to the potential of low-quality swabs (30). Although the association of sushi consumption and antibiotic eye drops remained significant after correction for multiple testing, we cannot fully exclude any type I error in our results.

These data suggest that patient contact does not increase the risk of ESBL-E colonization in HCWs, indicating the adequacy of current protective measures for HCWs against acquisition of resistant bacteria in our hospitals. The detection of a single case with community-acquired CPE reveals the potential circulation of these pathogens even in the absence of previous healthcare exposure.

Future research should be directed toward a more profound understanding of the role of sushi and antibiotic eye drops as potential risk factors for human ESBL-E colonization.

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DATA AVAILABILITY

For links to sequence records, visit https://www.ebi.ac.uk/ena/browser/view/PRJEB71832. The raw data and statistical codes are available from the authors upon reasonable request.

ETHICS APPROVAL

The study was approved by the Ethics Committee of Eastern Switzerland (#2020-00502).

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplemental material (AAC00985-24-s0001.docx). Supplemental methods, Tables A1 to A5, and Figures A1 to A3.

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