Environmental Research 215 (2022) 114146

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

# Air temperature and incidence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae

Lukas Bock, MD [a,**], Lisandra Aguilar-Bultet [a], Adrian Egli [b,c], Manuel Battegay [a], Andreas Kronenberg [d], Roland Vogt [e], Carole Kaufmann [f], Sarah Tschudin-Sutter [a,g,*]

[a] Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel, University Basel, Basel, Switzerland
[b] Division of Clinical Bacteriology and Mycology, University Hospital Basel, University of Basel, Switzerland
[c] Applied Microbiology Research, Department of Biomedicine, University of Basel, Switzerland
[d] Swiss Centre for Antibiotic Resistance, Institute for Infectious Diseases, University of Bern, Switzerland
[e] Department of Environmental Sciences, Atmospheric Sciences, Basel, Switzerland
[f] Division of Hospital Pharmacy, University Hospital Basel, University Basel, Basel, Switzerland
[g] Department of Clinical Research, University Hospital Basel, Basel, Switzerland

ARTICLE INFO

*Keywords:*
Air temperature
Incidence
Extended-spectrum beta-lactamase
ESBL-producing Enterobacteriaceae
Time-series analyses

ABSTRACT

*Background:* Higher outdoor temperature may be related to an increase in antibiotic resistant bacteria. We investigated the association between local outdoor air temperature and the incidence of extended-spectrum betalactamase (ESBL)-producing Enterobacteriaceae (ESBL-PE) correcting for known drivers of antibiotic resistance.

*Methods:* We performed a time-series regression study using prospectively collected weekly surveillance data on all ESBL-PE isolated from in- and outpatients of the University Hospital Basel, a tertiary care center in Switzerland, between 01/2008–12/2017. Temperature was measured hourly at the meteorological institute of the University Basel next to our institution over this time period. A time-series approach using a Poisson regression model and different lag terms for delayed exposure effects was performed to assess associations between minimal, mean and maximal weekly temperature and the number of ESBL-PE recovered.

*Results:* Over 10 years, recovery of ESBL-PE increased (annual incidence rate ratio [IRR] 1.14, 95%CI 1.13–1.16), while mean weekly temperature measures remained stable. In multivariable analyses, increasing temperature was associated with higher recovery rates of ESBL-PE after three to four weeks, correcting for potential confounders, such as the number of admissions, proportion of long-term nursing facility- and ICU-admissions, age, Charlson comorbidity index and consumption of antimicrobials (IRRs per 10 °C ranging from 1.14 to 1.22, 95% CIs 1.07–1.33). These trends remained when analyzing correlations between temperature with the proportion of extended spectrum cephalosporin resistance of all recovered Enterobacteriaceae.

*Conclusions:* Higher outdoor temperature may be associated with an increase of ESBL-PE-incidence, independent of important confounders, such as antimicrobial consumption and thus should be considered for future resistance-trajectories.

## 1. Introduction

Antimicrobial resistance is a pressing public health concern, posing a serious threat to human health and limiting effective treatment options for a wide range of infections. *Klebsiella pneumoniae* and *Escherichia coli* producing extended-spectrum beta-lactamases (ESBLs) have been ranked among the top five most important antibiotic-resistant bacteria in terms of mortality, health-care and community burden, prevalence and 10-year trend of resistance, transmissibility, preventability, and treatability by the World Health Organization (Tacconelli et al., 2018). Antimicrobial use is an important driver, but it has recently been shown to only explain a minor part of the occurrence of antimicrobial resistance worldwide (Hendriksen et al., 2019). There is emerging evidence that environmental factors might also contribute to increasing

* Corresponding author. Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031, Basel, Switzerland.
** Corresponding author. Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031, Basel, Switzerland.
*E-mail addresses:* bock.lukas@gmail.com (L. Bock), sarah.tschudin@usb.ch (S. Tschudin-Sutter).

https://doi.org/10.1016/j.envres.2022.114146
Received 24 May 2021; Received in revised form 24 July 2022; Accepted 16 August 2022
Available online 19 August 2022
0013-9351/

drug-resistance. Infections with gram-negative pathogens are more frequent during warmer months, with some studies even noting an association with increased air humidity (Alcorn et al., 2013; Anderson et al., 2008; Eber et al., 2011; McDonald et al., 1999; Perencevich et al., 2008; Retailliau et al., 1979; Richet, 2012). A suggested link between outdoor air temperature and antibiotic resistance in the United States (MacFadden et al., 2018) and studies reporting a rise in ESBL-producing Enterobacteriaceae (ESBL-PE) during summer (Kaier et al., 2010) have been of particular interest. Yet, previous studies have been heterogeneous in their design, some not differentiating between clinically relevant infections and asymptomatic colonization, not accounting for potential confounders and frequently not performing time series analyses, which is the most appropriate design to investigate associations between environmental factors and incidence over time.

Further insights into associations between seasonal patterns, outdoor air temperature and the emergence of resistant pathogens are of high relevance to inform estimates of resistance trajectories, especially as temperatures are expected to rise in response to climate change (Solomon and LaRocque, 2019). In line with global trends, ESBL-PE have steadily increased over the last decade in Switzerland (anresis.ch, 2018). As outdoor air temperature was systematically measured at the meteorological institute located in close proximity to our institution over the last decade, we investigated the association between local outdoor air temperature and the incidence of ESBL-PE correcting for known important drivers of antibiotic resistance over a 10-year time period.

## 2. Methods

### 2.1. Study design

We performed a time-series regression study at the University Hospital Basel, Switzerland, a 735-bed tertiary academic care center admitting approximately 35'000 adult patients annually. It primarily provides acute care and hospital services in the city of Basel (approximate population: 200'000) and serves as a referral center for patients requiring specialized medical care for the north-western part of Switzerland. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies (Vandenbroucke, 2009) (Supplementary Table 1).

### 2.2. Data collection

All reports of ESBL-producing *E. coli* and *K. pneumoniae* recovered between 01/2008 and 12/2017 at the University Hospital Basel were extracted from the electronic database of the Clinical Bacteriology and Mycology Laboratory. We choose to only include the species *E. coli* and *K. pneumoniae* as other ESBL-producing Enterobacteriaceae are rarely recovered at our institution (Emmanuel Martinez et al., 2019). Only the first sample per pathogen per individual hospital stay for inpatients and only the first sample per pathogen per patient per 365 days for pooled analyses of outpatients and inpatients were included. Both recovery of ESBL-producers from screening and routine clinical samples were considered.

Identification of ESBL-producing *E. coli* and *K. pneumoniae,* as well as screening strategies are detailed in the supplementary file.

Hourly outside air temperature measurements were included from December 1st, 2007 to December 31st, 2017 (supplementary file).

To account for changes in the hospital's case-mix over the study period, data regarding weekly number of admissions, the proportion of patients admitted from a long-term nursing facility, the proportion of admitted patients requiring intensive care and the average age at admission were collected. Furthermore, ICD-10 coded diagnosis lists of all inpatients were provided by the hospital's Finances & Accounting Department to calculate hospital-wide weekly averages of the Charlson Comorbidity Index (Charlson et al., 1987) (CCI), applying the original International Classification of Diseases (ICD) 10 Charlson comorbidity algorithm by Quan et al. (2005) for all diagnosis codes of each inpatient using the package "comorbidity" 0.2.019 for R (Gasparrini, 2018).

To correct for the consumption of antibiotics during the study period, monthly amounts of antibiotic agents delivered by the hospital pharmacy were converted into Defined Daily Doses (DDD) using the 2019 edition of the German ATC/DDD-Index (GKV-Arzneimitelindex im Wissenschaftlichen Institut der AOK (WIdO), 2018). To assign the respective amount of DDDs to each week, we fitted a Hermite monotone cubic spline function interpolating the cumulative monthly DDD amounts using the Hyman method (Dougherty et al., 1989). The respective weekly amount of DDDs corresponded to the integral of the spline function's first derivation for the respective period.

### 2.3. Definitions

All ESBL-producing *E. coli* and *K. pneumoniae* recovered from samples collected from inpatients and sent to the microbiological laboratory as of the third day after admission were defined as hospital-onset (HO) (Center for Disease Control, 2019). All other isolates collected from inpatients, were classified as present on admission (POA).

### 2.4. Outcomes

The outcome measure was incidence risk ratio for ESBL detection per 10 °C change in outside air temperature. Detection of ESBL-producing *E. coli* or *K. pneumoniae* in any specimen collected from all in-and outpatients of the University Hospital Basel (including each detection once per patient, species and year) and detection of ESBL-producing *E. coli* or *K. pneumoniae* in any specimen collected from all inpatients (including each detection once per hospitalization per patient per species) were considered as primary outcomes. We predefined subgroups for stratified analyses according to bacterial species (*E. coli* and *K. pneumoniae*), detection in respect to hospital admission (POA and HO) and detection in blood cultures.

### 2.5. Statistical analyses

We followed published principles for time series regression studies in environmental epidemiology for all statistical analyses (Bhaskaran et al., 2013). Considerations regarding sample size are outlined in the supplementary file.

Kruskal-Wallis-test was applied to compare annual distributions of ESBL-detection rates, minimum, mean and maximum air temperature measures (reported as medians and interquartile ranges) and potential confounders over the study period. Potential confounders were defined *a priori* considering important risk factors for ESBL-PE, (i.e. antimicrobial use, weekly number of admissions, the proportions of patients admitted from a long-term nursing facility or requiring intensive care, hospital-wide weekly averages of the CCI and average age of admitted patients) which may be related to weekly fluctuations of the exposure of interest (i.e. outdoor air temperature) as well as the outcome (i.e. incidence risk ratios for ESBL-recovery).

We performed a time series analysis with a time interval of one week using uni- and multivariable Poisson regressions corrected for overdispersion with a scale parameter estimated by the Pearson chi-square statistic divided by the residual degrees of freedom (Bhaskaran et al., 2013) to calculate incidence risk ratios. For multivariable analyses, all potential confounders were included by forced entry to obtain corrected estimates. To explore delayed exposure effects of air temperature, the most significant of 0–4 weeks lagged exposure terms was selected for each model by stepwise forward and backward selection.

For model comparisons and selection, statistical significance was set at 0.001515 (Bonferroni correction of significance level 0.05 for 33 comparisons, considering the three different outdoor temperature exposure variables and all pre-defined outcome variables and subgroups).

*2.5.1. Model checking*

All models passing the defined significance level were checked for autocorrelation and distribution of deviance residuals. Autocorrelation coefficients of the original outcome series and of the deviance residuals of the multivariable regression models were calculated for lags 1–200 (i.e. up to 4 years). Only models with correlation coefficients of the deviance residuals <0.3 were retained. Deviance residuals of a Poisson regression should furthermore be approximately normally distributed,

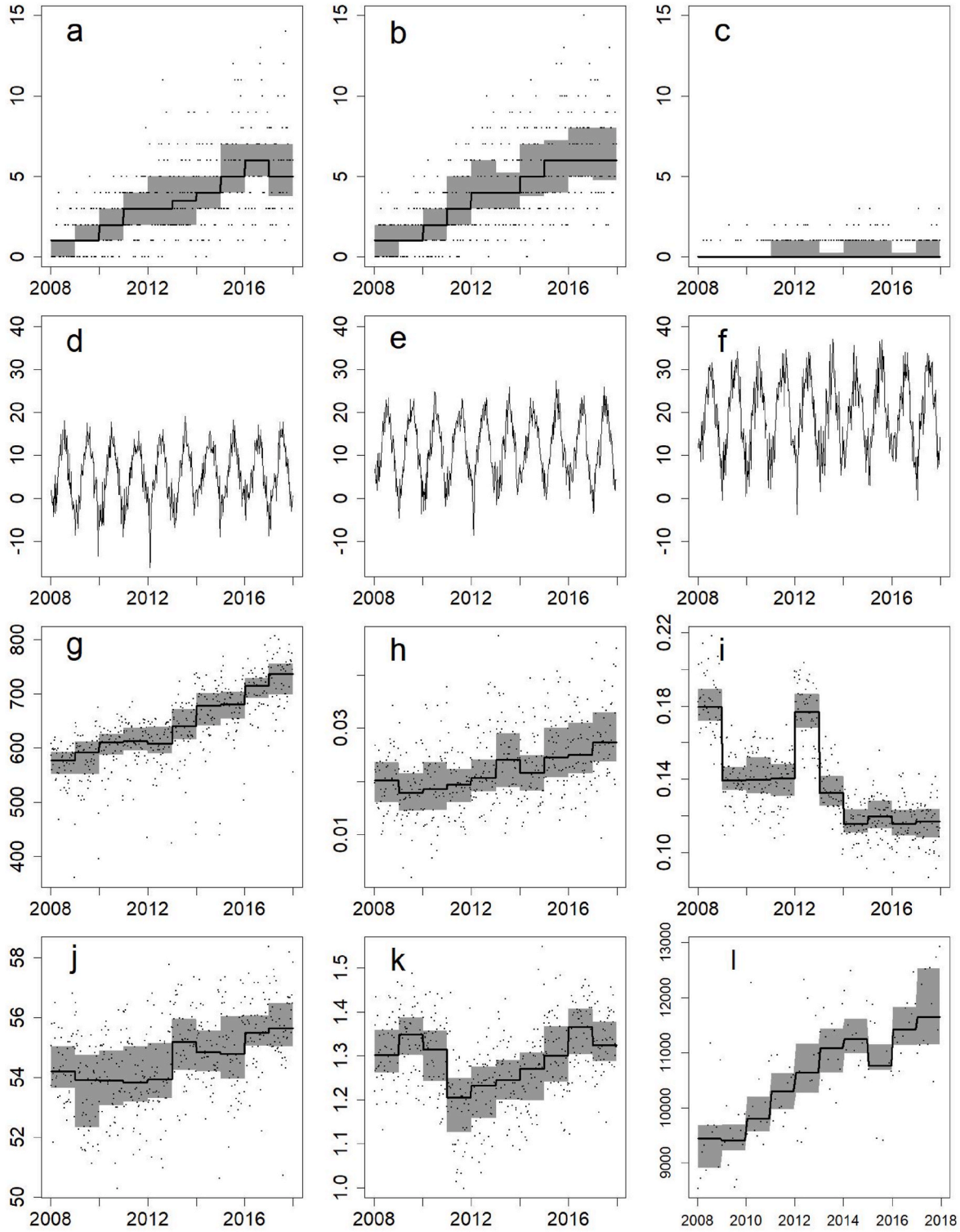


**Fig. 1.** Weekly number of recovered ESBL-producing *E. coli* and *K. pneumoniae* (a–c), weekly outdoor air temperature values (d–f) and confounding variables (g–l) (y-axis) during the study period (x-axis). Recovery of ESBL-producing *E. coli* and *K. pneumoniae* from in-and outpatients (including only the first sample per pathogen per patient per 365 days) (a), inpatients (including only the first sample per pathogen per individual hospital stay) (b) and bloodcultures (c). Weekly minimum (d), mean (e) and maximum (f) outdoor air temperature values. Number of all admissions (g) percentage of admissions from long-term care facilities (h) percentage of ICU-admissions (i) age of admitted patients (j), hospital-wide weekly averages of the Charlson comorbidity index (CCI) (k), antimicrobial usage expressed as defined daily doses (DDD) per month (l). Single data points with yearly median (line) and interquartile ranges (grey shaded area).

hence only models for which the Shapiro-Wilk-test supports a normal distribution (i.e. a p-value $> 0.05$) were retained.

#### 2.5.2. Sensitivity analyses

To confirm or refute the robustness of our findings, all models passing our model checking criteria were subjected to subsequent sensitivity analyses. First, the national trend regarding the proportion of third generation cephalosporin-resistance during the 10-year study period was included into the models to assess the independence of our exposures with baseline national trends (www.anresis.ch). Second, we re-calculated all associations after excluding all isolates of ESBL-PE recovered from screening samples. Third, as recovery of Enterobacteriaceae may be associated with outdoor air temperature regardless of their respective resistance profiles, we examined associations between the temperature measures and the proportion of extended spectrum cephalosporin resistance in all clinical isolates (excluding screening samples) by applying linear regression models.

All statistical and graphical analyses were perfomed using R 3.5.2 (https://www.R-project.org/) and RStudio 1.0.143 (http://www.rstudio.com/), as well as STATA 15.0 (Stata Corp., College Station, Texas, USA).

## 3. Results

During the 10-year study period, 1855 unique reports of ESBL-producing *E. coli* or *K. pneumoniae* were identified in the combined analyses of in- and outpatients (including one recovery per patient per species per year). Among the 1855 unique reports of ESBL identified, 1389 derived from inpatients (74.9%) and 466 from outpatients (25.2%), 744 represent screening samples (40.1%) and 1111 (59.9%) represent clinical samples. *E. coli* was isolated more frequently (84.6%) than *K. pneumoniae* (15.4%). Among inpatients (considering one recovery per hospitalization and species), 2090 unique identifications of ESBL-producing *E. coli* (83.9%) or *K. pneumoniae* (16.1%) were documented. Of the 2090 unique identifications of ESBL, 1376 were classified as POA (65.8%) and 714 as HO (34.2%), 1180 represent screening samples (56.5%), while 910 (43.5%) represent clinical samples. Bloodstream infections (BSIs) were identified in 153 inpatients (*E. coli* accounting for 128, *K. pneumoniae* accounting for 25). Fig. 1 a to c summarizes recovery rates over time. Weekly ESBL recovery rates increased during the study period and differed between years ($p < 0.001$) in the combined analyses of in-and outpatients, as well as in all predefined subgroup analyses (Supplementary Table 2).

Minimum, mean and maximum weekly outdoor air temperature measures did not change significantly during the same time period (Fig. 1 d to f and Supplementary Table 3).

All confounding variables (i.e. weekly number of admissions, the proportions of patients admitted from a long-term nursing facility or requiring intensive care, hospital-wide weekly averages of the CCI of admitted patients, age, antimicrobial use) differed between years ($p < 0.001$). Weekly number of admissions, the proportions of patients admitted from a long-term nursing facility, average age at admission and antimicrobial use showed ascending trends over time (Fig. 1 g-l).

Univariable analyses revealed trends for a temperature-dependent effect for all models; only the model for HO-ESBL-PEs and minimum temperature reached the adjusted significance level (Table 1) with minimum temperature appearing to have the strongest effect. Including confounders into the models increased effect sizes and statistical significance. Seven models reached the adjusted significance level, with IRRs between 1.15 and 1.24 per 10 °C: the analyses performed on the whole dataset (for minimum, mean and maximum weekly temperature), as well as the analyses only including inpatients or HO-ESBL-PE (for minimum and mean temperature). Effect sizes were strongest for HO-ESBL-PE and generally stronger for minimum temperature (Table 1).

Automated stepwise forward and backward selection with forced entry for all confounding variables including lag terms for temperature exposures from zero to four weeks resulted in selection of the most significant lag term for 25 models (for eight models, no significant exposure lag term existed). Minimum weekly temperature was most strongly associated with the different outcomes and delayed exposure effects of three to four weeks were most frequently selected (Table 2).

Model checking was performed on all 17 models with significant exposure effects applying the predefined criteria assessing underlying model assumptions, residual autocorrelation and abnormalities in the data. Autocorrelation analysis of deviance residuals showed significant autocorrelation at shorter time lags, however, no correlation coefficient of deviance residuals was greater than 0.2, which represents a substantial reduction from initial autocorrelation of the univariable

**Table 1**
Uni- and multivariable analyses of associations between different outdoor air temperature measurements and different outcome measures. Multivariable analyses were adjusted for the number of admissions, proportion of admissions from long-term nursing facilities, proportion of patients requiring an ICU admission, age at admission, Charlson comorbidity Index and consumption of antimicrobials.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| Temperature | IRR per 10 °C | 95% CI | p-value | IRR per 10 °C | 95% CI | p-value |
| **Overall** | | | | | | |
| *E. coli* and *K. pneumoniae* combined | | | | | | |
| Minimum | 1.16 | 1.05–1.28 | 0.0025 | 1.19 | 1.09–1.31 | **0.0001** |
| Mean | 1.12 | 1.02–1.22 | 0.0131 | 1.16 | 1.07–1.26 | **0.0002** |
| Maximum | 1.08 | 1–1.16 | 0.0432 | 1.12 | 1.05–1.19 | **0.0011** |
| *E. coli* | | | | | | |
| Minimum | 1.13 | 1.02–1.25 | 0.0217 | 1.17 | 1.06–1.28 | 0.002 |
| Mean | 1.09 | 0.99–1.19 | 0.0792 | 1.14 | 1.04–1.24 | 0.004 |
| Maximum | 1.05 | 0.98–1.14 | 0.1877 | 1.09 | 1.02–1.17 | 0.0144 |
| *K. pneumoniae* | | | | | | |
| Minimum | 1.16 | 0.95–1.4 | 0.1424 | 1.21 | 0.99–1.49 | 0.0655 |
| Mean | 1.15 | 0.96–1.37 | 0.1195 | 1.22 | 1.02–1.46 | 0.033 |
| Maximum | 1.13 | 0.98–1.31 | 0.1016 | 1.19 | 1.02–1.38 | 0.0253 |
| **Inpatients only** | | | | | | |
| *E. coli* and *K. pneumoniae* combined | | | | | | |
| Minimum | 1.13 | 1.03–1.25 | 0.0088 | 1.18 | 1.08–1.29 | **0.0002** |
| Mean | 1.1 | 1.01–1.2 | 0.0359 | 1.15 | 1.07–1.25 | **0.0003** |
| Maximum | 1.06 | 0.99–1.14 | 0.0963 | 1.11 | 1.04–1.18 | 0.0016 |
| *E. coli* | | | | | | |
| Minimum | 1.09 | 0.99–1.2 | 0.0793 | 1.14 | 1.05–1.25 | 0.0033 |
| Mean | 1.05 | 0.96–1.15 | 0.2613 | 1.11 | 1.03–1.2 | 0.0092 |
| Maximum | 1.03 | 0.96–1.1 | 0.4669 | 1.08 | 1.01–1.15 | 0.0281 |
| *K. pneumoniae* | | | | | | |
| Minimum | 1.19 | 0.99–1.43 | 0.0684 | 1.25 | 1.03–1.52 | 0.0254 |
| Mean | 1.21 | 1.02–1.43 | 0.0282 | 1.28 | 1.08–1.53 | 0.0048 |
| Maximum | 1.17 | 1.02–1.35 | 0.0285 | 1.23 | 1.06–1.42 | 0.0053 |
| Present on admission | | | | | | |
| Minimum | 1.07 | 0.96–1.19 | 0.23 | 1.12 | 1.01–1.24 | 0.039 |
| Mean | 1.05 | 0.95–1.16 | 0.3558 | 1.11 | 1.01–1.22 | 0.0262 |
| Maximum | 1.03 | 0.95–1.12 | 0.5145 | 1.08 | 1–1.17 | 0.0452 |
| Hospital-onset | | | | | | |
| Minimum | 1.27 | 1.12–1.45 | **0.0003** | 1.32 | 1.15–1.51 | **0.0001** |
| Mean | 1.2 | 1.06–1.35 | 0.0033 | 1.24 | 1.1–1.4 | **0.0005** |
| Maximum | 1.13 | 1.03–1.25 | 0.0141 | 1.17 | 1.05–1.29 | 0.0028 |
| Bloodstream infections, *E. coli* and *K. pneumoniae* combined | | | | | | |
| Minimum | 1.19 | 0.91–1.55 | 0.1999 | 1.28 | 0.96–1.7 | 0.0971 |
| Mean | 1.17 | 0.92–1.49 | 0.2134 | 1.26 | 0.98–1.63 | 0.0749 |
| Maximum | 1.12 | 0.92–1.38 | 0.2593 | 1.2 | 0.97–1.48 | 0.0886 |
| Bloodstream infections, *E. coli* | | | | | | |
| Minimum | 1.12 | 0.84–1.49 | 0.4329 | 1.22 | 0.9–1.66 | 0.2023 |
| Mean | 1.08 | 0.84–1.41 | 0.5417 | 1.19 | 0.9–1.56 | 0.2201 |
| Maximum | 1.05 | 0.84–1.3 | 0.68 | 1.13 | 0.9–1.41 | 0.3059 |
| Bloodstream infections, *K. pneumoniae* | | | | | | |
| Minimum | 1.66 | 0.88–3.14 | 0.1207 | 1.61 | 0.82–3.14 | 0.1634 |
| Mean | 1.75 | 0.97–3.17 | 0.0645 | 1.78 | 0.98–3.23 | 0.0608 |
| Maximum | 1.67 | 1.01–2.76 | 0.0447 | 1.73 | 1.06–2.82 | 0.03 |

Bold print indicates significant p-values (Bonferroni adjusted threshold of 0.001515).

**Table 2**
Automated stepwise forward and backward selection of lag terms for temperature exposures from zero to four weeks with forced entry for all confounding variables (number of admissions, proportion of admissions from long-term nursing facilities, proportion of patients requiring an ICU admission, age at admission, Charlson comorbidity Index and consumption of antimicrobials).

| Temperature | Model # | Lag term (weeks) | IRR per 10 °C | 95% CI | p-value |
|---|---|---|---|---|---|
| **Overall** | | | | | |
| *E. coli* and *K. pneumoniae* combined | | | | | |
| Minimum | 1 | 3 | 1.23 | 1.13–1.35 | **<0.0001** |
| Mean[a] | 2 | 3 | 1.21 | 1.12–1.31 | **<0.0001** |
| Maximum[a] | 3 | 3 | 1.15 | 1.07–1.23 | **0.0001** |
| *E. coli* | | | | | |
| Minimum | 4 | 3 | 1.19 | 1.08–1.31 | **0.0003** |
| Mean | 5 | 3 | 1.18 | 1.08–1.28 | **0.0003** |
| Maximum | 6 | 1 | 1.14 | 1.06–1.22 | **0.0005** |
| *K. pneumoniae* | | | | | |
| Minimum | 7 | 3 | 1.34 | 1.09–1.64 | 0.0053 |
| Mean | 8 | 3 | 1.29 | 1.07–1.55 | 0.0071 |
| Maximum | 9 | 3 | 1.19 | 1.02–1.39 | 0.0232 |
| **Inpatients only** | | | | | |
| *E. coli* and *K. pneumoniae* combined | | | | | |
| Minimum[a] | 10 | 3 | 1.22 | 1.12–1.33 | **<0.0001** |
| Mean[a] | 11 | 4 | 1.21 | 1.12–1.31 | **<0.0001** |
| Maximum[a] | 12 | 4 | 1.14 | 1.07–1.22 | **<0.0001** |
| *E. coli* | | | | | |
| Minimum | 13 | 4 | 1.19 | 1.09–1.3 | **0.0001** |
| Mean | 14 | 4 | 1.18 | 1.09–1.28 | **0.0001** |
| Maximum | 15 | 4 | 1.13 | 1.06–1.21 | **0.0004** |
| *K. pneumoniae* | | | | | |
| Minimum | 16 | 3 | 1.31 | 1.08–1.59 | 0.0066 |
| Mean | 17 | 0 | 1.28 | 1.08–1.53 | 0.0048 |
| Maximum | 18 | 0 | 1.23 | 1.06–1.42 | 0.0053 |
| **ESBL-PE detection** | | | | | |
| *Present on admission* | | | | | |
| Minimum | 19 | 3 | 1.19 | 1.08–1.32 | **0.0008** |
| Mean | 20 | 4 | 1.18 | 1.07–1.29 | **0.0008** |
| Maximum | 21 | 3 | 1.13 | 1.04–1.22 | 0.0024 |
| *Hospital-onset* | | | | | |
| Minimum | 22 | 4 | 1.31 | 1.14–1.5 | **0.0001** |
| Mean | 23 | 4 | 1.27 | 1.13–1.44 | **0.0001** |
| Maximum | 24 | 4 | 1.2 | 1.09–1.33 | **0.0004** |
| **Bloodstream infections** | | | | | |
| *E. coli* and *K. pneumoniae* combined | | | | | |
| Minimum | 25 | *N/A* | *N/A* | *N/A* | *N/A* |
| Mean | 26 | *N/A* | *N/A* | *N/A* | *N/A* |
| Maximum | 27 | *N/A* | *N/A* | *N/A* | *N/A* |
| *E. coli* | | | | | |
| Minimum | 28 | *N/A* | *N/A* | *N/A* | *N/A* |
| Mean | 29 | *N/A* | *N/A* | *N/A* | *N/A* |
| Maximum | 30 | *N/A* | *N/A* | *N/A* | *N/A* |
| *K. pneumoniae* | | | | | |
| Minimum | 31 | *N/A* | *N/A* | *N/A* | *N/A* |
| Mean | 32 | *N/A* | *N/A* | *N/A* | *N/A* |
| Maximum | 33 | 0 | 1.73 | 1.06–2.82 | 0.03 |

Bold print indicates significant p-values (Bonferroni adjusted threshold of 0.001515).

[a] Models fulfilling all predefined model checking criteria.

outcome series (up to 0.48, Supplementary Figs. 1 and 2). No model was hence excluded due to autocorrelation. Applying the Shapiro-Wilk-test to assess the distribution of the deviance residuals of all 17 models revealed a normal distribution in five final models (Table 2), revealing significant associations between mean and maximum outdoor air temperature and the detection of ESBL-PE after 3 weeks in the complete data set, as well as between minimum, mean and maximum outdoor air temperature and the detection of ESBL-PE after 3 or 4 weeks in inpatients.

### 3.1. Sensitivity analyses

We first included the national trend of the proportion of third generation cephalosporin-resistance during the 10-year study period into the models. The delayed exposure effects for mean outdoor air temperature after three weeks (IRR 1.07, 95%CI 1.01–1.02, p = 0.034) and maximum outdoor air temperature after three weeks (IRR 1.01, 95%CI 1.00–1.01, p = 0.020) on overall ESBL-PE recovery rate, minimum outdoor air temperature after three weeks (IRR 1.12, 95%CI 1.05–1.19, p = 0.001), mean outdoor air temperature after four weeks (IRR 1.11, 95%CI 1.04–1.17, p = 0.001), and maximum outdoor air temperature after four weeks (IRR 1.07, 95%CI 1.02–1.13, p = 0.008) for ESBL-PE-recovery among inpatients yielded slightly smaller effect sizes.

Second, as recovery of Enterobacteriaceae may be associated with outdoor air temperature regardless of their respective resistance profiles, we examined associations between the temperature measures identified in our five final models and the proportion of extended spectrum cephalosporin resistance in all clinical isolates (including samples from in-and outpatients and excluding screening samples), again including the same confounders into the multivariable regression models. Mean outdoor air temperature with delayed exposure effects of three and four weeks (regression coefficient [RC] 0.01, 95%CI 0.00–0.02, p = 0.003 and RC 0.01, 95%CI 0.01–0.02, p = 0.001), maximum outdoor air temperature with delayed exposure effects of three and four weeks (RC 0.01, 95%CI 0.00–0.01, p = 0.006 and 0.01, 95%CI 0.00–0.02, p = 0.002) and minimum outdoor air temperature with delayed exposure effects of three weeks (RC 0.01, 95%CI 0.00–0.02, p = 0.013) were all associated with the proportion of extended spectrum cephalosporin resistance.

Finally, we re-calculated all associations after excluding all isolates of ESBL-PE recovered from screening samples. Mean outdoor air temperature with delayed exposure effects of three and four weeks (IRR 1.09, 95%CI 1.01–1.18, p = 0.027 and IRR 1.09, 95%CI 1.00–1.02, p = 0.035), maximum outdoor air temperature with delayed exposure effects of three and four weeks (IRR 1.07, 95%CI 1.00–1.01, p = 0.052 and IRR 1.07, 95%CI 1.00–1.14, p = 0.050) and minimum outdoor air temperature with delayed exposure effects of three weeks (IRR 1.11, 95%CI 1.02–1.21, p = 0.021) were all associated with the proportion of extended spectrum cephalosporin resistance.

## 4. Discussion

Our study supports that higher outdoor air temperature may be associated with an increase in the incidence of ESBL-PE, independent of important confounders reflecting changes in patient populations and antimicrobial consumption over time.

First, an increase of 10 °C outside air temperature was associated with a relative increase in ESBL-PE incidence of 14–22%. Second, this effect was more pronounced for minimum or mean temperature than for maximum temperature. Third, the effect of temperature on incidence seems to be delayed by three to four weeks. Fourth, including risk factors for ESBL infections did not reduce, but increase the association between ESBL-PE incidence and temperature, indicating negative confounding. Risk factors for ESBL-infections appeared not to have seasonal patterns and hence to conceal the true influence of temperature upon ESBL.

ESBL-rates increased during the study period, whereas minimum, mean and maximum temperature did not change significantly over the entire 10-year period. Incidence risk ratios per 10 °C are more relevant for temperature changes within a year or between different geographic regions than for temperature changes in the context of global warming, which should be limited to 2 °C according to the Paris agreement (https://unfccc.int/process-and-meetings/the-paris-agreement/the-paris-agreement). Taking the tenth root of 10°C-IRRs results in IRRs per 1 °C temperature change; for the final models, this would result in 1°C-IRRs

between 1.013 and 1.020. The contribution of climate change to the rise of multiresistant bacteria is hence smaller than the already ongoing trend of increasing antimicrobial resistance. However, this does not exclude that antimicrobial resistance might develop quicker at warmer temperatures, since accelerated replication and enhanced survival might increase the speed at which antimicrobial resistance develops. Furthermore, even a small effect can have a relevant impact on a global scale further adding to the extent of health-related challenges related to global warming (Haines and Ebi, 2019). Rates of antimicrobial resistance differ substantially between different regions of the world with higher rates commonly seen in warmer climates. Our findings may indicate that a part of these differences may be attributable to higher outdoor temperature, especially as antimicrobial resistance gene abundance has been recently correlated with socioeconomic, health and environmental factors and to a lesser extent with antimicrobial use (Hendriksen et al., 2019).

A general increase in gram-negative bacteria during warmer months (Alcorn et al., 2013; Eber et al., 2011; McDonald et al., 1999; Perencevich et al., 2008; Retailliau et al., 1979; Richet, 2012), an increase of urinary tract infections during warmer periods (Gonçalves-Pereira et al., 2013), facilitated plasmid transfer between bacteria or increased survival (Walsh et al., 2011), development of resistance and replication in environmental niches (Walsh et al., 2011) might all be keys to explain the seasonal pattern of ESBL-PEs. While the exact mechanism for the effect of outdoor temperature on the incidence of ESBL-PE remains to be investigated in further detail, the finding that this effect is delayed by three to four weeks suggests the causing mechanism to lie on the pathogen's side or in the environment some time before infection of the host. Temperature-dependent mechanisms on the host's side cannot be ruled out, however, these would likely not show a delayed exposure effect but would be expected to lead to a much faster increased susceptibility towards infection.

Strengths of our study include the time series regression approach analyzing weekly data, a so far unmatched temporal resolution, and assessment of different temperature measures (minimum, mean and maximum weekly temperature) systematically collected during the entire study period, which to the best of our knowledge have not been reported so far. Minimum temperature is a climatic variable commonly used for the description of survival of species within the environment, while the influence of mean temperature and maximum temperature is not well known. In contrast to previous studies investigating temperature-effects on rates of antimicrobial resistance (Kaier et al., 2010; MacFadden et al., 2018), ours included a wide array of established ESBL risk factors. While some of these had to be adapted to match the time series analysis format, this approach unites the need for a statistically valid model on a population level with the need to include patient-based risk factors. Removal of duplicates has reduced residual autocorrelation of the models and increased their validity. Our study used appropriate statistical analyses (i.e. time-series analyses) and a conservative approach to define significance. Overdispersion of the data was corrected, which resulted in wider confidence intervals and higher p-values. Additionally, an adjusted significance level and a structured model checking and selection process were applied – and yet, an effect of temperature upon ESBL incidence remained in the final models. The final models are robust and show a highly reliable and significant effect of temperature upon ESBL incidence. In line, the effect sizes reported in previous studies of seasonality and temperature on the occurrence of infections with gram-negative bacteria appear to be smaller than those that we now report for ESBL-PE (Alcorn et al., 2013; Chazan et al., 2011; Deeny et al., 2015; Fisman et al., 2014; Gradel et al., 2016; Perencevich et al., 2008; Schwab et al., 2014). The final models were subsequently further challenged by different sensitivity analyses. While the respective associations did not reach the adjusted significance level, they point to trends in terms of independence from the Swiss national trend of the proportion of third generation cephalosporin-resistance and from associations between the recovery of Enterobacteriaceae, regardless of their respective resistance profiles, with outdoor air temperature.

Some important limitations need to be considered when interpreting our results. Our study was conducted at a single center. While this leads to increased data quality (study conducted with raw data, no reporting errors, coherent laboratory standards and ESBL definitions), the generalizability of the results warrants confirmation. Time series analyses by definition investigate associations on the population level. Whether patients infected with ESBL-producing bacteria have indeed been exposed to the temperature measured next to the hospital is not clear. The city of Basel covers a limited area of 35.9 $km^2$ and temperature measurements were performed in its center at the weather station of the Department of Environmental Sciences of the University of Basel, located directly next to our institution (47°33′42″ N, 7°34′50″ E, 264 m above sea level), thus they are representative for the city. How much the individual risk for an ESBL infection changes with temperature cannot be answered and our results should hence not be interpreted as a patient-based risk prediction tool.

The number of blood stream infections with ESBL-PE and ESBL-*K. pneumoniae* was low during the 10-year study period, therefore, it is not surprising that no significant effect could be shown for the respective outcomes. The inclusion of screening samples might in part explain why the association of temperature with HO was stronger than with POA: The POA group likely contained a significant number of positive samples of continuously colonized patients, which made the detection of seasonal patterns in this group unlikely. To mitigate such an effect, only the first sample per pathogen per individual hospital stay for inpatients and only the first sample per pathogen per patient per 365 days for pooled analyses of outpatients and inpatients were included.

Further research is needed to investigate interactions between different bacterial species, resistance mechanisms and the climate. Our study supports that higher outdoor temperature may be associated with an increase of ESBL-PE-incidence, independent of important confounders, such as antimicrobial consumption and thus should be considered for future resistance-trajectories.

## Key points

This time-series regression study, performed over 10 years, revealed significant associations between higher outdoor temperature and an increase of the incidence of ESBL-producing Enterobacteriaceae, independent of important confounders, such as antimicrobial consumption and thus should be considered for future resistance-trajectories.

## Submission declaration

The manuscript has not been published and is not being considered for publication elsewhere, except for the abstract which was presented as an oral presentation at 29th ECCMID (European Congress of Clinical Microbiology and Infectious Diseases), Amsterdam, Netherlands, April 2019.

## Funding

This work was supported by the University Hospital Basel, Switzerland. No further funding was received for this study.

## Ethics

This study was approved by the local ethics committee (EKNZ, Project-ID ID 2017-00100).

## Credit author statement

Lukas Bock collected and analyzed the data and wrote the first draft of the manuscript. Lisandra Aguilar-Bultet supported collection and analyzes of the data and revised the manuscript. Adrian Egli contributed

data and revised the manuscript. Manuel Battegay revised the manuscript. Andreas Kronenberg contributed data and revised the manuscript. Roland Vogt contributed data and revised the manuscript. Carole Kaufmann contributed data and revised the manuscript. Sarah Tschudin-Sutter conceptualized the study analyzed the data and revised the manuscript.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Acknowledgements

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114146.

## References

Alcorn, K., et al., 2013. Seasonal variation in health care-associated bloodstream infection: increase in the incidence of gram-negative bacteremia in nonhospitalized patients during summer. Am. J. Infect. Control 41, 1205–1208.
Anderson, D.J., et al., 2008. Seasonal variation in Klebsiella pneumoniae bloodstream infection on 4 continents. J. Infect. Dis. 197, 752–756.
A.-V. anresis.ch, 2018. Usage of Antibiotics and Occurrence of Antibiotic Resistance in Bacteria from Humans and Animals in Switzerland. Joint Report 2018. Usage of Antibiotics and Occurrence of Antibiotic Resistance in Bacteria from Humans and Animals in Switzerland. Joint report 2013.
Bhaskaran, K., et al., 2013. Time series regression studies in environmental epidemiology. Int. J. Epidemiol. 42, 1187–1195.
Center for Disease Control, 2019. National Healthcare Safety Network (NHSN) Patient Safety Component Manual. 2019, pp. 2–7.
Charlson, M.E., et al., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chron. Dis. 40, 373–383.
Chazan, B., et al., 2011. Seasonal variation in Escherichia coli bloodstream infections in northern Israel. Clin. Microbiol. Infect. 17, 851–854.
Deeny, S.R., et al., 2015. Seasonal changes in the incidence of Escherichia coli bloodstream infection: variation with region and place of onset. Clin. Microbiol. Infect. 21, 924–929.
Dougherty, R.L., Edelman, A., Hyman, J.M., 1989. Positivity-, monotonicity-, or convexity-preserving cubic and quintic Hermite interpolation. Math. Comput. 52, 471–494.
Eber, M.R., et al., 2011. Seasonal and temperature-associated increases in gram-negative bacterial bloodstream infections among hospitalized patients. PLoS One 6, e25298.
Emmanuel Martinez, A., et al., 2019. ESBL-colonization at ICU admission: impact on subsequent infection, carbapenem-consumption, and outcome. Infect. Control Hosp. Epidemiol. 40, 408–413.
Fisman, D., et al., 2014. Geographical variability in the likelihood of bloodstream infections due to gram-negative bacteria: correlation with proximity to the equator and health care expenditure. PLoS One 9, e114548.
Gasparrini, A., 2018. Comorbidity: an R package for computing comorbidity scores. J. Open Source Softw. 3, 648.
GKV-Arzneimitelindex im Wissenschaftlichen Institut der AOK (WIdO), 2018. Anatomisch-therapeutisch-chemische Klassifikation mit Tagesdosen. Amtliche Fassung des ATC-Index mit DDD-Angaben für Deutschland im Jahre 2019.
Gonçalves-Pereira, J., et al., 2013. Bloodstream infections as a marker of community-acquired sepsis severity. Results from the Portuguese community-acquired sepsis study (SACiUCI study). Clin. Microbiol. Infect. 19, 242–248.
Gradel, K.O., et al., 2016. Seasonal variation of Escherichia coli, Staphylococcus aureus, and Streptococcus pneumoniae bacteremia according to acquisition and patient characteristics: a population-based study. Infect. Control Hosp. Epidemiol. 37, 946–953.
Haines, A., Ebi, K., 2019. The imperative for climate action to protect health. N. Engl. J. Med. 380, 263–273.
Hendriksen, R.S., et al., 2019. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nat. Commun. 10, 1124.
Kaier, K., et al., 2010. Seasonal and ascending trends in the incidence of carriage of extended-spectrum ß-lactamase-producing Escherichia coli and Klebsiella species in 2 German hospitals. Infect. Control Hosp. Epidemiol. 31, 1154–1159.
MacFadden, D.R., et al., 2018. Antibiotic resistance increases with local temperature. Nat. Clim. Change 8, 510–514.
McDonald, L.C., et al., 1999. Seasonal variation of acinetobacter infections: 1987-1996. Nosocomial infections surveillance system. Clin. Infect. Dis. 29, 1133–1137.
Perencevich, E.N., et al., 2008. Summer peaks in the incidences of gram-negative bacterial infection among hospitalized patients. Infect. Control Hosp. Epidemiol. 29, 1124–1131.
Quan, H., et al., 2005. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med. Care 43, 1130–1139.
Retailliau, H.F., et al., 1979. Acinetobacter calcoaceticus: a nosocomial pathogen with an unusual seasonal pattern. J. Infect. Dis. 139, 371–375.
Richet, H., 2012. Seasonality in Gram-negative and healthcare-associated infections. Clin. Microbiol. Infect. 18, 934–940.
Schwab, F., et al., 2014. The warmer the weather, the more gram-negative bacteria - impact of temperature on clinical isolates in intensive care units. PLoS One 9, e91105.
Solomon, C.G., LaRocque, R.C., 2019. Climate change - a health emergency. N. Engl. J. Med. 380, 209–211.
Tacconelli, E., et al., 2018. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect. Dis. 18, 318–327.
Vandenbroucke, J.P., 2009. STREGA, STROBE, STARD, SQUIRE, MOOSE, PRISMA, GNOSIS, TREND, ORION, COREQ, QUOROM, REMARK... and CONSORT: for whom does the guideline toll? J. Clin. Epidemiol. 62, 594–596.
Walsh, T.R., et al., 2011. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect. Dis. 11, 355–362.