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Zusammenfassung des wissenschaftlichen Inhalts (Hani E. J. Kaba und Simone Scheithauer)

Hintergrund: Antimikrobielle Resistenzen (AMR) stellen eine große Herausforderung für Gesundheitssysteme weltweit dar. Neben bekannten Faktoren auf denen Interventionen beruhen (z. B. Antibiotikaeinsatz), könnten bislang unbekannte Einflussfaktoren zur Erklärung beitragen, warum Interventionen nur mäßig effektiv sind und warum es mit den bisher bekannten Faktoren die Unterschiede in der AMR Prävalenz (z. B. in Europa) nicht erklärt werden können. MacFadden et al. (*Nat. Clim. Change*, 2019) konnten erstmals zeigen, dass die (u. a. klimazonenbedingte) minimale lokale Temperatur mit der Prävalenz von AMR in den USA assoziiert war. Unsere Ziele waren zu überprüfen (1) ob diese Assoziation auch trotz unterschiedlicher Gesundheitssysteme (z. B. in Europa) existiert, (2) ob diese Assoziation auch für eine temporale Dimension (d. h. Klimawandel) vorhanden ist, und (3) vorherzusagen welche AMR Prävalenzveränderungen anhand von klimatischen Veränderungen in der Zukunft zu erwarten wären.

Methoden: Wir haben die 6-Jahres-Prävalenz von vier humanmedizinisch hoch relevanten Erreger-Antibiotika Kombinationen (methicillinresistente *Staphylococcus aureus* [MRSA], carbapenem-resistente *Klebsiella pneumoniae* [CRKP] und *Pseudomonas aeruginosa* [CRPA] sowie multiresistente *Escherichia coli* [MREC]) anhand von nationalen Daten (> $900 \cdot 10^3$ Isolaten) aus 30 Europäischen Ländern berechnet und modelliert. Als unabhängige Variablen wurden die saisonale kumulative Durchschnittstemperatur [wm_temp/ cm_temp] sowie die saisonale Nettoerwärmung [wm_net_warming/ cm_net_warming] für jedes Land berechnet. Wir haben für potentielle Confounder kontrolliert, z. B. den Korruptionswahrnehmungsindex [CPI] oder den totalen Antibiotikaverbrauch [DDD]. Die 30 Länder wurden nach geopolitischer Affiliation (Nordwest- vs. Südost-Gruppe) oder nach dem Gatekeeping Status im Gesundheitssystem (ja vs. nein) stratifiziert. Die Modellierung wurde mittels log-linearer Regressionsanalyse durchgeführt.

Ergebnisse: Die (u. a. klimazonenbedingte) Variable [wm_temp] war in der multivariaten Analyse mit [MRSA], [CRKP] und [MREC] signifikant assoziiert, was die Ergebnisse von MacFadden et al. in einem anderen Kontinent, gesundheitssystemunabhängig, bestätigen konnte. Somit würde eine Erhöhung von [wm_temp] um 1 °C in einer 1,02-fachen Erhöhung ($p = 0{,}0002$; $R^2 = 83\%$) von [MRSA], 1,01-fachen Erhöhung ($p = 0{,}003$; $R^2 = 75\%$) von [MREC] und 1,03-fachen Erhöhung ($p = 0.011$; $R^2 = 79\%$) von [CRKP] resultieren. Zusätzlich wurde die Assoziation der Klimawandel-Variable [wm_net_warming] für die warme Jahreszeit (Mai – Oktober) mit [CRPA] aufgezeigt. Demnach würde eine Erhöhung von [wm_net_warming] um 0,5 °C in einer 1,02-fachen Erhöhung ($p = 0{,}035$; $R^2 = 78\%$) von [CRPA] resultieren (*ceteris paribus*). Exponierte Länder (≥ 0,5 °C phasenweise Erhöhung) hatten eine doppelt so hohe Chance für das Erreichen des Outcomes einer kumulativen jährlichen [CRPA]-Erhöhung von mindestens 2% (OR = 2,03; CI [1,03 – 3,99]). Stratumsspezifische Analysen zeigten, dass sich speziell das [MRSA] Modell in der Gruppe ohne Gatekeeping (n = 13) verbessert hat ($R^2 = 97\%$), besonders nach dem Hinzufügen einer Variable welche die durchschnittliche Bettenzahl im stationären Bereich repräsentiert. Die Anpassungsgüte des [CRPA] Modells war in der Nordwest-Gruppe höher (n = 16; $R^2 = 71\%$) im Vergleich zur Südost-Gruppe (n = 14; $R^2 = 19\%$). Durch Einbeziehen von projizierten (erwarteten) Klimadaten, würde [CRPA] in 2039 entsprechend des Modells in 12 der 16 Nordwest Länder im Vergleich zu 2016 steigen (z. B. 2-fach in Großbritannien und Holland, um ca. 70% in Dänemark und 50% in Island).

Konklusionen: Diese Arbeit konnte zum ersten Mal einen Hinweis auf eine Assoziation zwischen Klimawandel und AMR liefern. Während es unbekannt (und eher unwahrscheinlich) ist das solch eine Assoziation kausal ist, liegt die Wichtigkeit dieser Erkenntnisse darin, dass beide Phänomene möglicherweise durch die gleichen Faktoren (gesundheits- und umweltpolitische Regularien, versorgungs- und umweltbezogene Verhaltensweisen) beeinflusst werden. Deren vollständige Identifikation und Adressierung in Strategiekonzepten könnten effizient (Kosten-Nutzwert) dabei helfen, das Fortschreiten von Klimawandel und AMR synergistisch zu minimieren.

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Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe – A 30 country observational study

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ABSTRACT

The association of antimicrobial resistance (AMR) with climatic factors gained higher attention since resistance increased with increasing local temperatures in the USA.

We aimed to investigate whether the explanatory strength of climatic factors holds true in a region encompassing diverse healthcare systems, like Europe. In particular, we determined whether exposure to temporal climate warming is associated with an increase in AMR prevalence for clinically relevant pathogens.

A 30-country cross-sectional study was conducted. The six-year prevalence of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), *Klebsiella pneumoniae* (CRKP), Multiresistant *Escherichia coli* (MREC), and Methicillin-resistant *Staphylococcus aureus* (MRSA) was determined based on > 900 k clinical isolates. Bi- and multivariate analysis were performed to identify associations with climatic variables using healthcare and socio-economic confounders.

CRPA was significantly associated with the warm-season change in temperature, which, alongside corruption perception, explained 78% of total CRPA variance. Accordingly, a 0.5 °C increase of year-wise temperature change (exposition) resulted in a 1.02-fold increase ($p = 0.035$) in CRPA prevalence (outcome). For a given country, exposition status doubled the odds of outcome attainment compared to non-exposition (OR = 2.03, 95%-CI [1.03–3.99]). Moreover, we found significant associations of CRKP, MREC, and MRSA with the warm-season mean temperature, which had a higher contribution to MRSA variance explanation than outpatient antimicrobial drug use.

We identified a novel association between AMR and climatic factors in Europe, which reveals two aspects: climatic factors significantly contribute to the explanation of AMR in different types of healthcare systems, while climate change (i.e. warming) might increase AMR transmission, in particular CRPA.

1. Introduction

Antimicrobial resistance (AMR) is a growing public health threat worldwide. AMR in bacteria occurs in many ways, including drug efflux, break down and modification of target structures. It can be acquired through mutations or horizontal gene transfer from one organism to another (Normark and Normark, 2002), which help to facilitate the spread of AMR in the host and the environment. Consequently, there might be multiple factors associated with the rise of AMR and this even increases through the variation of AMR patterns across species and drug classes.

One major factor identified to trigger AMR is the inadequate use of antimicrobials, including overuse, misuse and substandard use (Llor and Bjerrum, 2014; Harbarth et al., 2015). In European countries, AMR significantly correlated with outpatient antibiotic consumption levels, revealing higher consumption in the South and East of Europe compared to the North and West. Moreover, seasonal fluctuations of antibiotic prescription did exist, as prescription peaked in the winter season in countries with relatively high prescription levels (Goossens et al., 2005; McDonnell et al., 2017).

In recent years, research suggested that other factors than antimicrobial use might be involved, leading scientists to adopt an "out-of-the-box" thinking approach to elucidate such factors (Borg et al., 2012). Within this context, AMR of several drug-species pairs was found to be associated with corruption (Collignon et al., 2015), which can be considered as a cultural determinant of non-compliance to common rules. This observation was further strengthened by an association of corruption with antibiotic use (Rönnerstrand and Lapuente, 2017),

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indicating that corruption might confound the influence of antimicrobial use on AMR. A pan-continental study suggested that differences in the national economy account for a part of AMR variance, as AMR increased with increasing poverty (Alvarez-Uria et al., 2016). This result could not be reproduced for Europe, however (Collignon et al., 2015).

Cassini et al. showed that the burden due to infections with AMR bacteria has recently increased in European countries, in particular carbapenem-resistance. Remarkably, countries around the Mediterranean Basin, especially Italy and Greece, displayed a higher burden due to infections with AMR bacteria compared to Northern European countries (Cassini et al., 2019). Most recently, the role of climatic factors gained higher attention in AMR variance explanation. AMR in three bacterial species, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae*, was found to increase with increasing local temperature in the USA (MacFadden et al., 2018). This finding confirmed an association between AMR and the climate under the conditions of different climate zones, but (relatively) uniform social, economic and healthcare system conditions within a single country. The intriguing question is whether the AMR-climate association holds true when confronted with a variety of healthcare systems. Furthermore, it is of interest to estimate whether climate change would influence AMR prevalence, which requires additional variables that represent spatial developments in temperature in addition to local temperature variables.

As such, our present study aimed at answering the following questions:

1. Does spatial temperature (climate zone) partly explain AMR variance within diverse healthcare systems (e.g. in Europe)?
2. Does the exposure to temporal temperature warming (climate change) partly explain AMR variance in Europe? If true, for which resistance types and for which season(s)?

We investigated the influence of country-specific seasonal temperature as well as the year-wise change of temperature on the explanation of AMR variance, when they are confounded by cultural, socio-economic and healthcare system variables. We further compared the explanatory power of these predictors between Northern/Western (NWC) and Southern/Eastern (SEC) countries.

2. Material and methods

2.1. Study design

We conducted an observational study exploring the relationship between patterns of national AMR prevalence of four bacterial species (2011–2016) and recorded seasonal temperatures (1991–2015) in European countries.

2.2. Country sample

Our study sample comprised 30 countries from the European Union (EU) or the European Economic Area (EEA) and participating in the EARS-net surveillance program (European Center for Disease Prevention and Control (ECDC), 2017). These were Austria, Belgium, Bulgaria, Croatia, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, the Republic of Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, the Slovak Republic, Slovenia, Spain, Sweden, the United Kingdom (all EU and EEA members), in addition to Iceland and Norway (EEA members). We further divided this sample into two subgroups, one containing the Northern and Western countries (NWC) and the other the Southern and Eastern countries (SEC). Details on allocation criteria are given in the Supplementary Material. The affiliation of individual countries can be taken from Supplementary Table S2 (variable geo_2G) and Fig. 1.

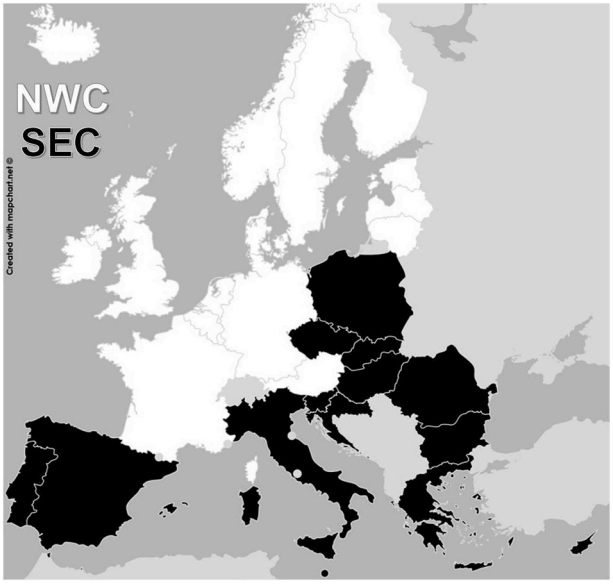

Fig. 1. Countries included in the sample (n = 30, EARS-net program, ECDC). Countries shown in black or white were included in the sample. Color code: white: Northern and Western countries (NWC), black: Southern and Eastern countries (SEC), grey: not included in the sample.

2.3. Dependent variables

In 2017, the WHO published a priority list of antibiotic-resistant pathogens for which new antibiotics are urgently needed WHO, (2017). According to this list, bacterial species-drug pairs of the Priority 1 (critical) and Priority 2 (high) categories were selected for analysis in this study. These were carbapenem-resistant gramnegative bacteria including *Pseudomonas aeruginosa* (CRPA) and *K. pneumonia* (CRKP), multidrug resistant *E. coli* (MREC), in addition to methicillin-resistant *S. aureus* (MRSA). MREC was selected rather than carbapenem-resistant *E. coli* (CREC) due to the relative low diversity of the latter entity. We calculated the 6-year prevalence of each AMR entity (2011–2016), which constituted the variables subjected to statistical analysis (see Supplementary Material for details).

2.4. Predictors and confounders

We used historical monthly mean temperatures (Harris et al., 2014, Climate Change Knowledge Portal, 2018a and b) and processed this data as defined in the Supplementary Material part for the warm (May–October) and cold (January–April, November and December) seasons. We created two variables, each representing a temperature change score (1991–2015) for the warm and cold seasons respectively. Temperature change projections were obtained from the same source. Equations used for calculation are provided in Table 2.

To control for potential confounders, we selected variables previously shown to be associated with AMR in Europe, while simultaneously known to vary in a similar way, as do AMR variables between colder (NWC) and warmer (SEC) countries. These variables included the gross domestic product per capita (GDP, log-transformed) as an economic indicator (The World Bank, 2018), the Corruption Perceptions Index (CPI) as an indicator of non-compliance to common rules (Transparency International, 2018), and the total antibiotic consumption in the primary care sector (DDD) (ECDC, 2018).

Recent research suggested an association between provider density and antibiotic prescribing in the USA, in particular in high-income areas due to competition between providers, including physicians (Klein

Table 1
Description of major variables used for statistical analysis.

Variable	Description
MRSA	MRSA proportion (%) (*Staphylococcus aureus* isolates (2011–2016) (ECDC, 2018)
MREC	*E. coli* proportion (%) with combined resistance (3rd generation cephalosporins, fluorquinolones and aminoglycosides) (2011–2016) (ECDC, 2018)
CRKP	*Klebsiella pneumoniae* proportion (%) resistant to carbapenems (2011–2016) (ECDC, 2018)
CRPA	*Pseudomonas aeruginosa* proportion (%) resistant to carbapenems (2011–2016) (ECDC, 2018)
DDD	Total antibiotic consumption in defined daily doses per day and 1000 population (primary care sector; mean of 2010–2015) (ECDC, 2018)
docs	Physician density (hlth_rs_phys) (Eurostat, 2018b) per 1000 population (demo_pjan) (Eurostat, 2018c), mean of 2010–2015
no_exp_smok	People (%) of the population not exposed to daily smoking (2014) (Eurostat file: hlth_ehis_sk4e) (Eurostat, 2018a)
GDP	GDP per capita (current US$) 2016, log-scale transformed (The World Bank, 2018)
CPI	Corruption Perceptions Index score, sum of points 2012–2015 (Transparency International, 2018)
wm_temp	Sum of temperature means [°C] (1991–2015) for the six warmest months (May, June, July, August, September and October) (Harris et al., 2014, Climate Change Knowledge Portal, 2018a)
cm_temp	Sum of temperature means [°C] (1991–2015) for the six coldest months (November, December, January, February, March and April) (Harris et al., 2014, Climate Change Knowledge Portal, 2018a)
wm_net_warming	Net year-wise increase/decrease in mean monthly temperatures [°C] (1991–2015) for May, June, July, August, September and October (Harris et al., 2014, Climate Change Knowledge Portal, 2018a)
cm_net_warming	Net year-wise increase/decrease in mean monthly temperatures [°C] (1991–2015) for November, December, January, February, March and April (Harris et al., 2014, Climate Change Knowledge Portal, 2018a)
tp_ensemble_rcp8.5	Projected changes in monthly temperature [°C] (2020–2039) for May, June, July, August, September and October, median of 16 climatic and earth system models under the RCP8.5 scenario (Harris et al., 2014, Climate Change Knowledge Portal, 2018b)
wm_net_warming_ph1-6	Six variables (wm_net_warming_ph1, …, wm_net_warming_ph6) each comprising the sum of 4 year-wise changes in warm months temperature according to EQ5.0.
warming_0.5	Binary variable, representing a cumulative difference in seasonal temperatures between consecutive 4-year phases (wm_net_warming_ph1-6), either true (difference ≥ 0.5 °C) or false (difference < 0.5 °C)
CRPAtrend	Binary (values true or false) variable, representing the yearly increase of in the cumulative CRPA prevalence compared to the year before, either true (increase ≥ 1.02-fold) or false (increase < 1.02-fold or no increase)
geo_2G	Binary variable, representing the geographic allocation of each country into either the “NWC” or the “SEC” groups

et al., 2015). Therefore, we introduced a health system related variable: density of physicians per population (docs) (Eurostat, 2018b, 2018c) as an indicator of healthcare human resource.

The variable (no_exp_smok) was the percentage of the population (%) not exposed to daily passive smoking (Eurostat, 2018a), which we regarded as compliance to public health measures of anti-indoor smoking policies. When applicable, data of these variables were collected considering a time lag of 1 year (2010–2015) compared to the AMR observation period. Table 1 provides further information on variables used in this study.

After initial analysis considering the variables mentioned above, the influence of specific health system variables (health spending, acute care beds and gate-keeping) and environmental (connection to tertiary waste water treatment plants) on the dependent variables was studied as indicated in the Supplementary Material (see section Additional Variables).

2.5. Modeling

We applied log-linear regression for multivariate modeling by transforming all dependent AMR variables using the natural logarithm “LN(AMR)” function (see Supplementary Material for further information on modeling and regression assumptions assessment).

2.6. Model validation

To investigate the validity of the models, we included four countries not covered by the EARS-net program in this analysis. These countries were Belarus, Serbia, Switzerland and Turkey (see Supplementary Material for details). AMR data on these countries were obtained from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network (WHO Regional Office for Europe, 2018). We compared predicted (fitted) and empiric AMR prevalence values for each model and country. To quantify the deviation of the fitted values, we calculated the “Index of Estimation Deviation” (IED). The lower the IED value is, the better the model fitted values for the respective country as compared to the empirically identified prevalence. This index was calculated as following: IED = 1 – Q, where Q is the quotient of PRE and AMR with AMR being any of the analyzed 6-year prevalence values (MRSA, MREC, CRKP or CRPA) and PRE the corresponding unstandardized estimated value by the respective model (e.g. PRE1.0 for MRSA, PRE2.0 for MREC, etc.). To neutralized positive and negative deviations around the empiric AMR value, Q was calculated using the Microsoft® Excel IF(condition; then; otherwise) function as follows: Q = IF(PRE < AMR; PRE/AMR; AMR/PRE), therefore resulting in standardized and intercomparable IED values for all four countries and resistance types.

Table 2
Equations used to calculate variable values in this work.

No.	Equation
EQ1	AMR prevalence = $\Sigma R_i/\Sigma B_i$
EQ2A	wm_temp = $\Sigma \bar{T}$ [May … October] $_{1991\text{-}2015}$
EQ2B	cm_temp = $\Sigma \bar{T}$ [January … April, November, December] $_{1991\text{-}2015}$
EQ3A	wm_net_warming = [Σ (May … October) $_{1992}$ – Σ (May … October) $_{1991}$] + … + [Σ (May … October) $_{2015}$ – Σ (May … October) $_{2014}$]
EQ3B	cm_net_warming = [Σ (January … April, November, December) $_{1992}$ – Σ (January … April, November, December) $_{1991}$] + … + [Σ (January … April, November, December) $_{2015}$ – Σ (January … April, November, December) $_{2014}$]
EQ4	tp_ensemble_rcp8.5 = [$\bar{\Sigma}$ $_{\text{Model 1 … Model 16}}$ (May … October)]
EQ5[a]	wm_net_warming_ph1 = [Σ (May … October) $_{1992}$ – Σ (May … October) $_{1991}$] + … + [Σ (May … October) $_{1995}$ – Σ (May … October) $_{1994}$]
	wm_net_warming_ph6 = [Σ (May … October) $_{2012}$ – Σ (May … October) $_{2011}$] + … + [Σ (May … October) $_{2015}$ – Σ (May … October) $_{2014}$]

[a] EQ5: only two examples for the calculation on the first and last phases are provided. The other phases were calculated in analogy to these two phases.

2.7. Supplementary Material

Detailed information on methods, including data collection and processing and Supplementary Figures/Tables is provided in the Supplementary Material.

3. Results

We found strong significant correlations of MRSA (methicillin-resistant *S. aureus*) with wm_temp (warm season mean temperature) and cm_temp (cold season mean temperature), using the Spearman rank correlation coefficient (r_s). The correlation with wm_net_warming (warm season net change in temperature) was weaker, although significant. MREC (multidrug resistant *E. coli*) similarly correlated with wm_temp and wm_net_warming, while showing a stronger association with CPI (Corruption Perceptions Index). CRKP (carbapenem-resistant *K. pneumoniae*) significantly correlated with wm_temp and to a lesser extent with CPI, wm_net_warming and cm_temp. In contrast, CRPA (carbapenem-resistant *P. aeruginosa*) showed a weaker correlation with wm_temp and stronger correlations with wm_net_warming, CPI and GDP (gross domestic product). No significant bivariate associations were found for any AMR variable with docs (physician density) (Tables 3A and 3B).

Multivariate analysis (Table 4) identified wm_temp as a significant predictor of MRSA, MREC and CRKP, but not CRPA. A cumulative increase of mean temperature of 1 °C between May and October would result in an increase of 1.02 (p = 0·0002), 1.01 (p = 0.003) and 1.03-fold (p = 0.011) in MRSA (Model M1.0), MREC (Model M 2.0) and CRKP (Model M 3.0) respectively (*ceteris paribus*). In contrast, cm_temp was not a significant predictor of any AMR variable. When the pair of wm_net_warming and cm_net_warming was added to regression, M1.0, M2.0 and M3.0 did not change. Consequently, neither warming variable had a significant contribution to variance explanation of the respective AMR variable.

Interestingly, wm_net_warming was retained by the log_CRPA model (M4.0) as a significant predictor together with CPI. Accordingly, an increase in the cumulative year-wise augmentation of seasonal temperature (wm_net_warming) by 0.5 °C leads to a 1.02-fold increase (p = 0.035) in CRPA prevalence (when CPI is kept constant).

We analyzed model M4.0 for each country group, NWC and SEC, separately with CPI and wm_net_warming as fixed predictors. Both variables had significant regression coefficients (p = 0.0002 and 0.03 respectively, adj.-R^2 = 71%) in NWC in contrast to SEC (p = 0.3 and 0.4 respectively, adj.-R^2 = 19%). This result indicates that M4.0 fitted the values better in NWC than in SEC and thus explained a higher proportion of CRPA variance in NWC compared to SEC.

As CRPA was the only variable that was significantly explained by wm_net_warming, we further validated this result using a different approach. We determined whether countries experiencing a warming of ≥0.5 °C (exposition) displayed higher odds for increase in CRPA prevalence (cut-off 1.02-fold increase; outcome) in the following years. At this stage of analysis, the time interval that is sufficient for outcome attainment cannot be accurately defined. Therefore, we paired the year-wise change in cumulative CRPA prevalence (binary outcome variable CRPAtrend) with the phase-wise change in seasonal temperature, where each phase corresponds to four years (binary exposition variable warming_0.5; see Supplementary Material for details on calculation), resulting in five binary values for each variable and country (n = 150 pairs in total). We found that exposed countries displayed a 2-fold higher odds of outcome attainment compared to unexposed countries (OR = 2.03, 95%-CI [1.03–3.99]). This result strengthens the association revealed through M4.0.

Next, we validated all four models by using them to estimate fitted values for the AMR variables in countries not present in the EU/EEA sample (Belarus, Serbia, Switzerland and Turkey), by calculating the Index of Estimation Deviation (IED, Table 5).

M1.0 could only estimate the MRSA prevalence in Switzerland and Turkey. We obtained a wrong estimation for Turkey, as the fitted value exceeded 100% (Supplementary Table S13). M2.0 estimated MREC in Switzerland at best. In contrast, the best estimation obtained by M3.0 was for Turkey; however, the 95%-CI of the estimation was broad and exceeded 100% (Supplementary Table S15). M4.0 underestimated CRPA prevalence in Belarus (Supplementary Table S16), but estimated all other three countries with a comparably higher accuracy (Table 5).

Finally, we aimed to estimate the effect of temperature change on future CRPA prevalence as calculated by M4.0. First, we calculated the expected change in warm season temperature by the end of 2039 (variable tp_ensemble_rcp8.5) and determined its relationship with wm_net_warming. The two variables showed a positive correlation (r_s = 0.74, p ≤ 0.0001), indicating that the majority of countries with a higher ranking in terms of historical increase in seasonal temperature are expected to rank higher in relation to future seasonal temperature increases. Additionally, tp_ensemble_rcp8.5 positively correlated with CRPA (r_s = 0.73, p ≤ 0.0001). Furthermore, NWC displayed a higher expected difference (variable Δ_warming_16_39) between historical and expected temperature in average, as compared to SEC (Supplementary Table S17).

Since M4.0 explained CRPA variance in a better way in NWC than in SEC, we calculated the expected CRPA prevalence by 2039 in these countries (assuming constant CPI values) by entering the values of tp_ensemble_rcp8.5 into wm_net_warming, although these two variables are not fully identical. According to the estimation (variable CRPA_est2039), most NWC are expected to observe an increased CRPA prevalence by 2039 because of the expected change in warming alone. For example, CRPA prevalence is expected to double in the UK and the Netherlands and to increase by ca. 70% in Denmark and 50% in Iceland (Fig. 2), although it remains low (≤10%) in those countries compared to currently observed prevalence in SEC.

Finally, we pondered whether distinct variables not retained by the models (e. g. docs, or GDP) were insufficient to represent the respective indicator, potentially leading to underfitting of values. We therefore subjected the obtained models to further analysis by adding additional, more health and eco-system specific variables.

These additional variables were health spending (hsp), acute care beds (ac_beds) and people connected to tertiary waste water treatment plants (ter_WWT). We added these variables into linear regression, yet none had a significant contribution to variance explanation of any of the analyzed AMR variables herein (Supplementary Table S18).

Next, we considered whether contrasting prescribing behavior, independent of physician density, is present between countries with a gate-keeping role of general practitioners (GPs) and those without gate-keeping. We particularly asked whether the total antimicrobial consume and AMR prevalence significantly differed between these two country groups. As a control we investigated the same phenomenon between NWC and SEC, expecting significant differences since north-to-south and west-to-east gradients in Europe are known to exist (European Center for Disease Prevention and Control, 2017).

Table 3a
Bivariate analysis. Association of antimicrobial resistance (AMR) with potential confounder variables using the Spearman correlation coefficient r_s in 30 countries. Statistical significance was assumed when p < 0.05 (95% level).

AMR variable		DDD	docs	no_exp_smok	GDP	CPI
MRSA	r_s	0.715	−0.088	−0.483	−0.531	−0.699
	p	0.000	0.643	0.007	0.003	0.000
CRPA	r_s	0.391	−0.061	−0.584	−0.841	−0.865
	p	0.033	0.750	0.001	0.000	0.000
CRKP	r_s	0.617	0.026	−0.556	−0.543	−0.726
	p	0.000	0.894	0.002	0.002	0.000
MREC	r_s	0.442	−0.102	−0.536	−0.698	−0.822
	p	0.015	0.593	0.002	0.000	0.000

Table 3b
Bivariate analysis. Association of antimicrobial resistance (AMR) with climatic variables using the Spearman correlation coefficient r_s in 30 countries. Statistical significance was assumed when $p < 0.05$ (95% level).

AMR variable		wm_temp	cm_temp	wm_ net_warming	cm_ net_warming	tp_ensemble_ rcp8.5
MRSA	r_s	0.826	0.691	0.542	−0.067	0.435
	p	0.000	0.000	0.002	0.724	0.016
CRPA	r_s	0.671	0.224	0.748	0.247	0.727
	p	0.000	0.233	0.000	0.187	0.000
CRKP	r_s	0.798	0.543	0.546	−0.074	0.469
	p	0.000	0.002	0.002	0.704	0.010
MREC	r_s	0.718	0.446	0.617	0.115	0.540
	p	0.000	0.014	0.000	0.545	0.002

After applying the Mann-Whitney (MW)-Test, no significant differences, neither in DDD nor in any AMR variable were found between the two gate-keeping (Yes; No) groups however. This result indicates that the values of these variables were on average similar independent of the gate-keeping status. In contrast, significant differences for all tested variables (DDD, MRSA, MREC, CRKP and CRPA) were found between NWC and SEC (Supplementary Tables S19a and b) as previously assumed.

Gate-keeping not only influences prescription behavior, it has also impacts on patient choice and access to care, including acute care (Reibling and Wendt, 2012). Thus, we expected a higher average number of acute care beds in the No-group compared to the Yes-group, taking into account that additional factors also influence this number.

Indeed, countries without gate-keeping displayed a higher median of ac_beds than countries with gate-keeping (409 vs. 329 per 100,000 population). However this difference was not significant (MW-test: $U = 76$, $p = 0.145$).

To determine whether ac_beds eventually contributes to AMR variance explanation within countries with or without gate-keeping, we reran linear regression in each gate-keeping group separately, using fixed predictors as obtained by models M1.0, M2.0, M3.0 and M4.0, with ac_beds forced into each model.

In the Yes-group, ac_beds had no significant contribution to variance explanation of any AMR variable. Furthermore, the introduction of ac_beds into each model rendered some regression-coefficients that have been previously significant, not significant anymore (Supplementary Table S20a). Similarly, ac_beds had no significant contribution to variance explanation of log_MREC, log_CRKP and log_CRPA in the No-group (Supplementary Table S20b). Interestingly, b_{ac_beds} was significant when ac_beds was introduced into M1.0, with all other regression coefficients of fixed predictors remaining significant (Supplementary Table S20a and Table 4). Strikingly, the adj. R^2 of this Model (M1.5) was 97.4% with fitted values very close to the empirical MRSA prevalence. Removal of ac_beds from the model reduced adj. R^2 to 77.5%, indicating that ac_beds improved the previous model by ca. 20%. However, not all assumptions for linear regression were met probably due to the small sample size of this subgroup (n = 13) (See Supplementary Material for detailed information).

Table 5
Assessment of estimation deviation. Model estimations in four countries (not present in the EU/EEA sample) were compared to empirical data determined through the CAESAR project (WHO Regional Office for Europe, 2018). The values represent the Index of Estimation Deviation (IED; see Supplementary Material for calculation). IED range [0–1]. The higher the IED the higher is the deviation.

Country	IED				
	M1.0 (MRSA)	M2.0 (MREC)	M3.0 (CRKP)	M4.0 (CRPA)	M1.5 (MRSA)
Belarus	–	0.61	0.93	0.45	–
Serbia	–	0.35	0.76	0.01	–
Switzerland	0.66	0.23	0.94	0.20	0.67
Turkey	0.83	0.37	0.21	0.11	0.63

4. Discussion

The present study contributes novel results to the debate about AMR and climate factors, suggesting an association between temporal climatic developments and carbapenem-resistance in *P. aeruginosa* in Europe. Furthermore, the exposition to temporal warming in seasonal temperature was associated with an increase in CRPA year-wise prevalence.

This association is the major finding of the present study and to our best knowledge is shown here for the first time.

Our results suggest an influence of spatial temperature variability in Europe, which partly explains AMR variance in three bacterial species, including carbapenem-resistance (*K. pneumoniae*), methicillin-resistance (*S. aureus*) and multidrug resistance (*E. coli*). This is in line with recent results from another region, showing an association between minimum local temperatures and AMR in the same three species in the

Table 4
Summary of the multivariate models obtained in this study. Adj.-R^2: adjusted coefficient of determination, $ß_0$: intercept, b: regression coefficient, ß: standardized regression coefficient. Only variables with significant regression coefficients were retained by the respective model through step-wise selection.

Model	adj.-R^2	Dependent variable		$ß_0$	DDD	no_exp_ smok	CPI	wm_ temp	wm_net_ warming	ac_beds
M1.0	83%	log_MRSA	b	−4.788	0.068	2.501	−0.011	0.022	–	–
			ß		0.347	0.261	−0.542	0.444		
M2.0	75%	log_MREC	b	−2.232	–	–	−0.007	0.011	–	–
			ß				−0.598	0.377		
M3.0	79%	log_CRKP	b	−6.213	0.106	–	−0.012	0.025	–	–
			ß		0.376		−0.409	0.321		
M4.0	78%	log_CRPA	b	0.007	–	–	−0.008	–	0.039	–
			ß				−0.693		0.263	
M1.5[a]	97%	log_MRSA	b	−6.505	0.066	2.424	−0.009	0.020	–	0.004
			ß		0.430	0.309	−0.478	0.474		0.416

[a] M1.5 valid only for countries without full gate-keeping role for general practitioners (n = 13/30).

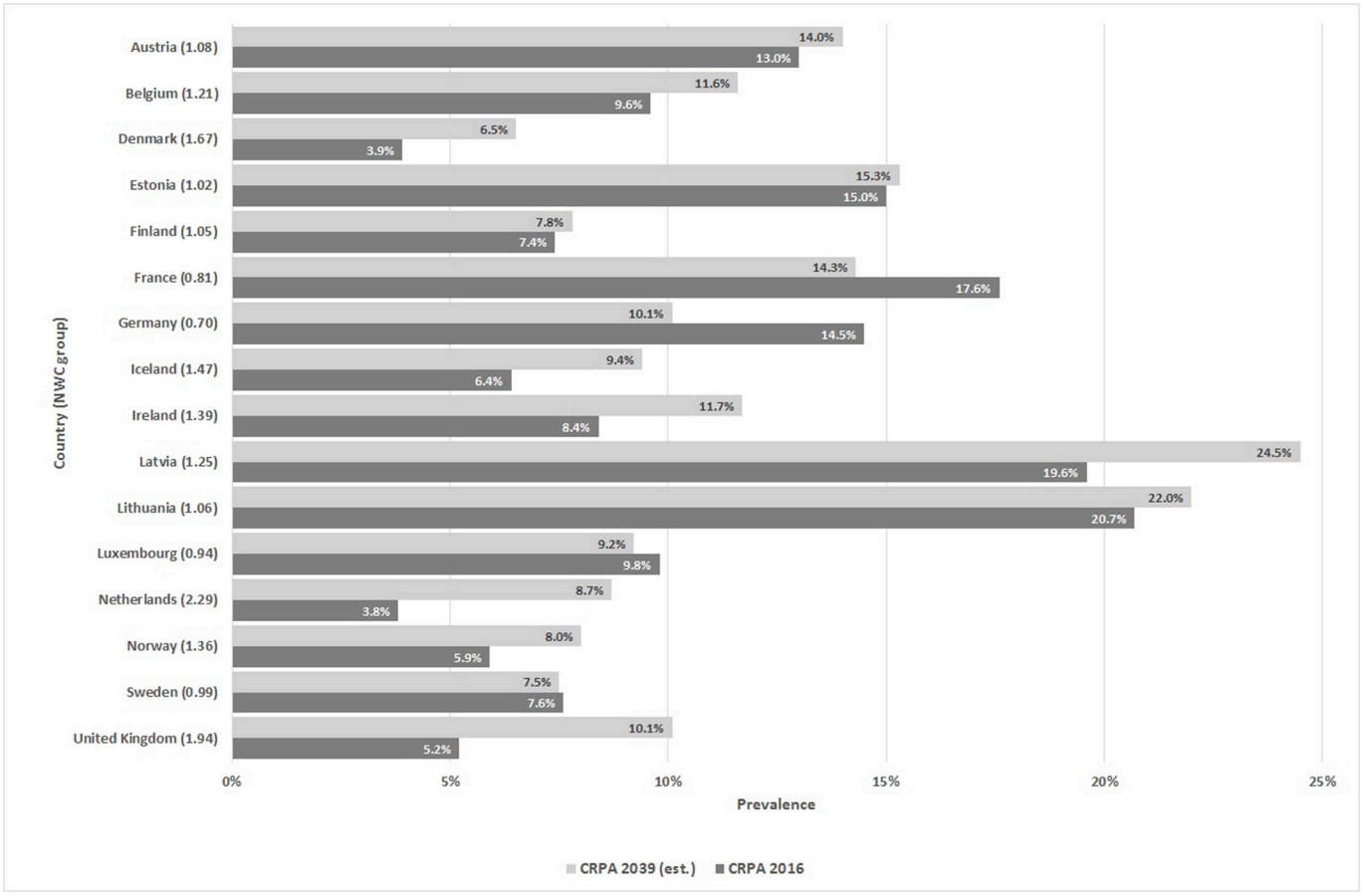

Fig. 2. CRPA prevalence by 2039 (light bars) as estimated by M4.0 (with constant CPI) and tp_ensemble_rcp8.5 (ensemble of 16 climatic models) for NWC. Empirical prevalence by 2016 (dark bars) is given for comparison. The fold change in estimated CRPA is given between brackets.

USA (MacFadden et al., 2018). This phenomenon might thus be of global validity and not restricted to a single continent.

We selected different confounders of AMR by using a health system related variable and socio-economic indicators, given the higher diversity of these factors in a multi-country European landscape compared to the USA as a single country. In accordance with Collignon et al. (2015), we identified corruption perception (CPI) as a major predictor that is negatively associated with AMR. Furthermore, its contribution to variance explanation was always higher than that of antimicrobial consumption in the outpatient sector (DDD). CPI can be regarded as an indicator of compliance to common rules and guidelines. Projected on the healthcare system, this concerns for instance infection control practices in hospitals or prescription practices, most notably in the outpatient sector.

The national economy, represented by GDP, had no major influence on any AMR variable, again confirming previous observations (Collignon et al., 2015). GDP is a significant explanatory factor of AMR variance at a global level, for instance, when comparing countries from different continents (Alvarez-Uria et al., 2016) but it does not hold true within Europe.

Physician density was not related to any AMR variable under the selected test conditions. This could be due to the aggregated nature of data, however. An association might still occur at the sub-regional level, where an interaction with antimicrobial consumption might exist.

Interestingly, the density of acute care beds significantly contributed to variance explanation of MRSA, although only in the subgroup of countries without gate-keeping system. Gate-keeping is a regulatory element to control patient choice of consuming healthcare goods and services. Thus, it affects access to specialized and/or secondary care facilities, but might also impact physicians' behavior, i. e. in terms of prescription.

Our results suggest no significant differences in total antimicrobial use between countries with or without a gate-keeping system, yet there are some remaining queries.

Increased access to secondary care facilities would result in an increased risk of transmission per se. This would partly explain why only log_MRSA prevalence was associated with ac_beds in contrast to the other AMR variables, since *S. aureus* (and therefore MRSA) is a common colonizer of the skin flora, which increases the risk of transmission.

However, ac_beds encodes only for the density of hospital beds, that means independent from whether they are occupied or not. It is rather the occupancy rate of hospital beds that was found to be associated with hospital acquired infections, most notably MRSA infection/colonization (Kaier et al., 2012), something which limits the previous assumption. We should also note that transmission risk depends on the type of patient groups admitted, but the distribution of this variable within the analyzed group of countries is unknown.

Although these results confirm previous findings and since temperature is known to facilitate both *in vitro* bacterial growth and horizontal gene transfer (Lorenz and Wackernagel, 1994), they do not mandatorily mean the presence of a causal association between environmental temperatures and AMR. These findings rather indicate a kind of geographic and therefore climate zone "pre-disposition" that seems to influence AMR. A similar indication was recently found, where the distance to the equator was associated with a lower risk of AMR in *Acinetobacter* spp. (Alvarez-Uria and Midde, 2018).

The reason of such associations is still unknown. If a causal relationship indeed exists, a potential explanation could be that warmer climates might influence concentrations of heavy metals or biocides in soil or water or their uptake by different organisms, including bacteria

(Marques et al., 2010). These potentially toxic substances are at the same time known to trigger AMR through co- or cross-selection (Singer et al., 2016). This could partly explain why the association with AMR was exclusively found during the European warm season. However, the relationship could be non-causal, as both variables are associated with common confounders, such as CPI. Furthermore, MRSA was also significantly, although weakly, associated with no_exp_smok, further indicating a role of community related behavioral practices (i.e. compliance to non-indoor smoking rules) with the spread of MRSA. Again, such behaviors could be related to hand hygiene practices of healthcare personnel or antimicrobial prescribing habits of providers. What strengthens this assumption is the reported association of MRSA with cultural determinants in Europe (Borg et al., 2012).

No evidence of an association between warming (i.e. temporal increase in temperatures) and AMR in the three species mentioned above could be drawn from our findings.

In contrast, an association between seasonal warming, and carbapenem-resistance in *P. aeruginosa* was present. CRPA prevalence was higher in those countries that have experienced higher increases in seasonal temperatures over the recent years. This was true for the warm season (May–October), but not for the cold season (November–April). Furthermore, an increase of 0.5 °C in the mean seasonal temperature over a phase of 4 years was associated with 2-fold higher odds of year-wise increase in cumulative CRPA prevalence. These results link the recent climate developments to the spread of AMR, in particular carbapenem-resistance in *P. aeruginosa*.

The intriguing question is why such association was found only for CRPA and not for other AMR variables investigated in this study. There is no final answer, yet one possible explanation may emerge if two phenomena are combined. Associations between elevated outdoor temperatures during the warm season and infections have been reported for *P. aeruginosa* (Psoter et al., 2013). Therefore, an increase of *P. aeruginosa* infections can be expected with rising temperatures. Since carbapenems are so-called reserve antibiotics, the increase in *P. aeruginosa* infections could have triggered the use of carbapenems. Since *P. aeruginosa* is a bacterium known to quickly react to selective pressure resulting from the application of antibiotics (Lister et al., 2009), this could have facilitated the rise in CRPA proportions of *P. aeruginosa* isolates due to selection mechanisms. Another possible explanation may be related to the usual habitats of this ubiquitous bacterium as *P. aeruginosa* is frequently found in water (Mena and Gerba, 2009). As mentioned above, environmental warming might influence concentrations of toxic substances in the waters and, therefore, induce AMR by co-resistance mechanisms. However, a causal relationship might not exist at all, and both AMR and climate change may be influenced by a common strong confounder.

The variable wm_net_warming significantly explained a part of CRPA variance, yet its explanatory power diminished when the regression was exclusively performed within SEC, in contrast to NWC. This explains the higher deviation in estimations for SEC compared to their NWC counterparts. Because M4.0 estimations for distinct adjacent SEC (e.g. Croatia, Slovenia and Serbia) were surprisingly accurate, distinct geographical regions might exist where M4.0 is an accurate estimator and others where it is not (e.g. Poland, Czech and Slovak Republic or Greece, Romania and Bulgaria; see Supplementary Table S16). The conclusion is that other factors, not identified through this study, exist in such sub-regions (largely SEC) that have a stronger influence on CRPA than wm_net_warming, something that might also be true for MRSA and CRKP with wm_temp.

Our study has a number of strengths, including the combination of various indicators in the analysis, the reproduction of previous results using different datasets and models as well as the validation of obtained models by estimating AMR variance values outside the country sample by the obtained models.

We consider the reproduction of previously known associations by using different modeling methods as well as different datasets as a requirement when performing modeling. By this, we confirmed previous findings on one hand and strengthened the validity of additional results obtained by our methodological approach in this study, on the other.

However, a number of limitations must be considered. First, the analysis was not based on a random sample. However, as the selection of countries under observation was restricted by data availability, there was no alternative than selecting all European countries for which coherent data was available.

Another limitation of our study was that bacterial isolates were restricted to invasive bloodstream infections and cerebrospinal fluid samples and do not contain, for example, samples of urinary tract, superficial skin infections or bacterial colonization of mucosal surfaces. Furthermore, the number of reporting laboratories from each country is variable, potentially leading to some bias in the data source. We utilized the currently best available data source (EARS-net data). Additionally, data on antibiotic consumption in humans were not coherent, with some countries reporting total healthcare data including the hospital sector, while the majority reported data of the primary care sector only. However, the risk of overestimating primary care consumption in those countries should be low, as primary care antibiotic consumption on average accounts for 90% of the total consumption (McDonnell et al., 2017).

The use of a carbapenem specific (J01DH) consumption variable might have been more accurate to estimate carbapenem-resistance in ecological studies rather than a universal antibiotic (J01) consumption variable. Including J01DH was not possible due to a high missing proportion in the country sample.

Furthermore, only aggregated (national) data were available, which have prevented the use of different regression methods and forced the application of mathematical transformations. This is while neither climate, nor AMR or use of antibiotics is national. This could have biased the data in some way.

Finally, while we used a complex selection of various indicators, some important factors were missing from the analysis. Most notably antibiotic use in the animal sector, due to missing and inconsistent country data for the observation period. The inclusion of other factors might have added explanatory value to the models or on the other hand, altered their composition.

5. Conclusions

The present study provides the first evidence on the association between increased temperatures and AMR in invasive bacterial isolates in Europe. Our data highlight future increases in carbapenem-resistant *P. aeruginosa* (CRPA) under exposure to a warming climate. In particular, the CRPA prevalence might double by 2039 in some NWC, which are likely to experience stronger climate change. We further recommend the use of socio-economic variables other than GDP (e.g. CPI) in AMR modeling of European countries.

While these results remain hypothetical, we believe that further research is necessary to better understand the nature of the association between AMR and climate change. Our findings suggest to consider regional level variations, cross-border patterns and multi-factor effects to build new knowledge on the potential effects of temperature change on bacterial resistance mechanisms, which may inform future policy strategies in Europe.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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