Investigation of Relations between Epidemiological Factors and Antibiotic Resistance Data

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Introduction

The origin and spread of antibiotic resistance in populations is complex. Hypotheses generation & analysis can be done by **risk factor assessment with MIC data as outcome** (MIC=minimum inhibitory concentration). Among antibiotic use and dissemination of antibiotic resistance genes, epidemiological factors may have an impact.

Due to the phenomenon of **multi-drug resistance** it is important to analyse antimicrobial agents of interest simultanously to involve the relations between them (multivariate analysis). The challenge is that MIC data is quantitative but not normal distributed and ties may occure.

Objective: develop a method, which is easy to apply and interpret, to handle multi-dimensional resistance data and link them with epidemiological host data for risk factor assessment

Data

Within an ongoing German research network on food borne zoonotic infections, epidemiological studies on animals and humans are conducted. Bacteria isolates are used both for microbiological as well as for epidemiological research.

In a case-control study on sporadic *Salmonella* infections in humans 204 *S.* Typhimurium strains were isolated and antibiotic susceptibility tests were conducted.

Antimicrobial agent	MIC Ranges in µg/ml		
Ampicillin	1	-	16
Mezlocillin	2	-	32
Mezlocillin / Sulbactam	2	-	32
Cefotiam	0.5	-	8
Cefotaxime	1	-	16
Ceftazidime	2	-	32
Nalidixic acid	4	-	32
Ciprofloxacin	0.06	-	64
Streptomycin	4	-	64
Kanamycin	2	-	32
Gentamicin	0.5	-	8
Amikacin	2	-	32
Oxytetracycline	0.5	-	8
Trimethoprim / Sulfamethoxazole	4	-	128
Chloramphenicol	4	-	32

MIC data was determined by broth microdilution method following the recommendations of the Clinical Laboratory and Standards Institute (CLSI).

Resistance Score: Definition & Application

Idea

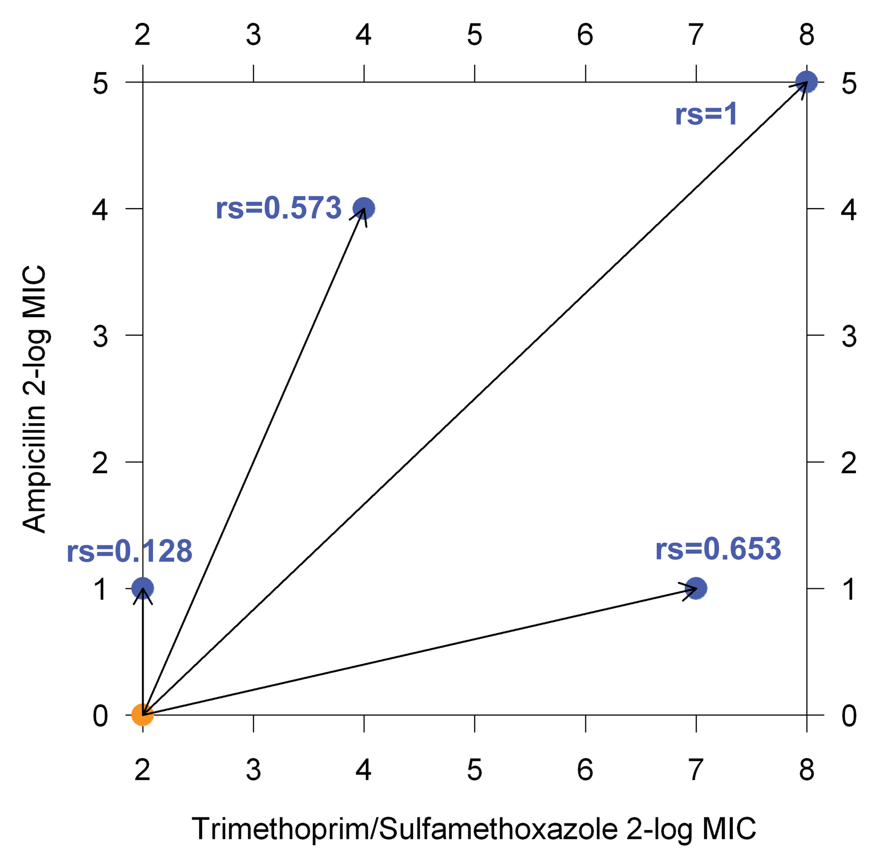
To use the multi-dimensional resistance data as an outcome, we suggest dimension reduction by summarising the resistance profile of an isolate i to one resistance score rs_i (i=1,...,n).

Score definition

- based on the 2-log MICs
- Euclidean distance between each isolate and a fictive isolate which has minimum 2-log MIC values (lowest 2-log concentration levels) for all susceptibility tests of interest
- standardised by its maximum, which ensures that it is between 0 and 1

Score interpretation

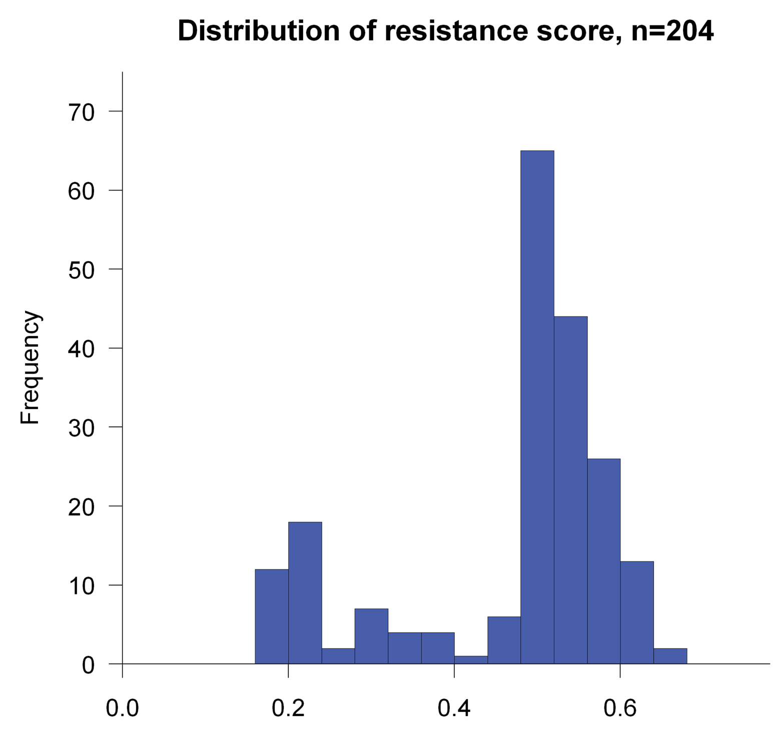
- **measure of global resistance**
  - at a higher score a higher multi-resistance is found
- a high score quantifies generally the increase of the MICs
  - not explicit for which antimicrobial agent

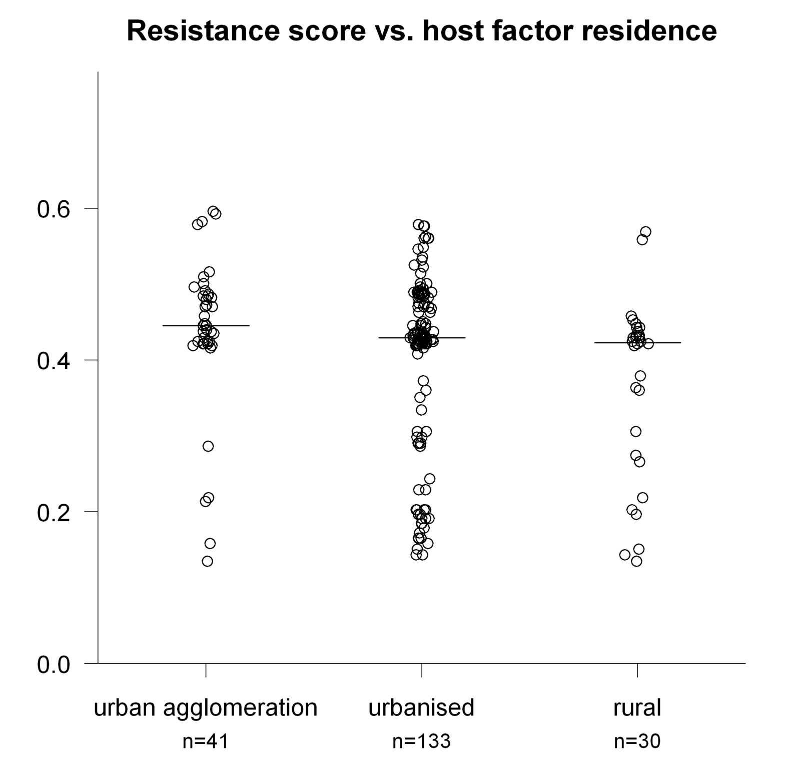


The figure demonstrates the graphical meaning of calculating the Euclidean distance between points exemplified in a two-dimensional space (i.e. two antibiotics). Displayed are 4 isolates ●, the fictive isolate with min. values ● and the distances →.

Results

- resistance scores, based on MIC data of 14 susc. tests, distribute bimodal separating the isolates in less resistant isolates and more resistant (multi-resist.) isolates
- due to cross-resistance to Ampicillin, Mezlocillin has been excluded from the analysis
- patients with different types of residence (by population density) have significant different resistance scores ($p=0.026$, Kruskal-Wallis-test)





Conclusion & Outlook

The resistance score enables a simultaneous analysis of resistance data and epidemiological factors.

Subgroups of antimicrobial agents can be selected to investigate specific scores, e.g. a score summarising therapeutical relevant antimicrobial agents.

Comparisons with other strategies to handle multi-dimensional resistance data [1,2] is ongoing.

References
[1] Berge A.C., Atwill E.R. and W. M. Sischo: Assessing antibiotic resistance in fecal Escherichia coli in young calves using cluster analysis techniques, Preventive Veterinary Medicine 2003; 61(2), p. 91-102
[2] Stegeman J. A., Vernooij J. C., Khalifa, O. A. and J. Van den Broek: Establishing the change in antibiotic resistance of Enterococcus faecium strains isolated from Dutch broilers by logistic regression and survival analysis, Preventive Veterinary Medicine 2006; 74(1), p. 56-66

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