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Mathematical Basis for the Assessment of Antibiotic Resistance and Administrative Counter-Strategies

Hans H. Diebner[*†], Anna Kather[‡], Ingo Roeder[*], Katja de With[‡]

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[†]*Corresponding author:* hans.diebner@tu-dresden.de
[*]Carl Gustav Carus Faculty of Medicine, Technische Universität Dresden, Institute for Medical Informatics and Biometry, Fetscherstrasse 74, D–01307 Dresden, Germany.
ingo.roeder@tu-dresden.de
[‡]Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Klinische Infektiologie, Fetscherstrasse 74, D–01307 Dresden, Germany.
anna.kather@uniklinikum-dresden.de, katja.dewith@uniklinikum-dresden.de

Abstract

Background: Temporal changes of the proportional abundances of different antibiotics (e.g. mixing or cycling) is regarded as an effective administrative control strategy to reduce the prevalence of antibiotic-resistant pathogens in nosocomial infections. Although such a mixing strategy appears to be plausible, a rigorous assessment of its efficacy is lacking. In particular, a sound mathematical method that correlates temporal changes on both sides, i.e. the consumption of antibiotics and the prevalence of pathogens, is still pending.

Methods: We adopt diverse measures of heterogeneity and diversity based on the concept of entropy from other fields and adapt them to the needs in assessing antibiotic resistance. Most important, we extent the measures such that they optimally account for the temporal changes in heterogeneity of antibiotics consumption and pathogen prevalence. Furthermore, we introduce a scheme based on linear regression for the assessment of associations between changes of heterogeneities on the antibiotics and the pathogen side.

Results: A crucial part of our results is the derivation and provision of a sound mathematical basis to assess administrative control strategies against antibiotic resistance. As a showcase, we apply the derived methods to records of antibiotics consumption and prevalence of antibiotic-resistant germs from the University Hospital Dresden, Germany. Since the data has not been recorded in a controlled way, the application has to be understood as proof-of-concept. Besides the reasonable quantification of heterogeneities of antibiotics consumption and prevalence of pathogens, we show that a reduction of prevalence of antibiotic-resistant germs correlates with a change of heterogeneity of antibiotics consumption.

Conclusions: Although an interventional study is pending, our mathematical framework turns out to be a viable concept for the assessment and optimisation of control strategies intended to reduce antibiotic resistance. Provided that an interventional or comparative study yields different time courses of controlled mixing strategies, the method is potentially suitable to determine optimal counter-strategies by means of statistical learning, aka the maximum entropy method.

Keywords: antibiotic cycling; antibiotic mixing; antibiotic resistance; diversity, entropy; heterogeneity

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Background

The drastic increase of antimicrobial resistance worldwide resulting in an alarming increase in morbidity and mortality from clinical infections urges scientists and clinicians to develop counter-strategies. Designing new antiinfective agents is an option. However, the creation of new drugs is time-consuming and success is not guaranteed. Therefore, the control of consumption of available antibiotics or, more general, of antiinfectives, is obligatory. To refrain from administration of antibiotics is a preferred option, however, this decision should be both medically as well as ethically supported. No need to mention that a strict hygienic discipline is obligatory in order to avoid infections.

Due to limitations of the aforementioned strategies and the fact that a quick replacement of existing antibiotics is not feasible, the concepts of “antibiotic mixing”, “antibiotic cycling” or “antibiotic switching” gained evermore attention in the recent years ([6, 3]). All these recent concepts refer to a heterogeneity of antibiotic usage. For example, antibiotic cycling means to extract one or a subset of classes of antibiotics from administration in a temporarily alternating way whereas other strategies refer to a scheduled change of the dominantly used class of antibiotics. Frequently, mixing refers to a strategy where a fraction of patients receives drug (class) A and the remaining fraction receives drug (class) B in an alternating way. Although there is some evidence that the permutation of rates of consumption of different antiinfectives is able to reduce prevalence of resistant pathogens, there is a lack of rigorous quantification, which prevents optimisation.

Here, we present an analytical framework to quantify heterogeneity of both, time courses of antibiotic consumption as well as time courses of prevalence of antibiotic-resistant pathogens. This enables the assessment of associations between consumption and prevalence and, potentially, to optimise mixing or cycling counter-strategies. The analytic framework consists of adapted methods known in other areas ([13, 16]) and are applied to real data, i.e., to records of antibiotic consumption and prevalences of antibiotic-resistant pathogens of the University Hospital in Dresden, Germany. Unfortunately, there was no predefined protocol or rigorous guideline for the administration of antibiotics. Furthermore, completeness of records, particularly with respect to resistant germ variants, cannot be guaranteed. Thus, the application of the proposed methodological framework has to be understood as a proof-of-principle. Rigorous controlled interventional studies are planned, however, we regard the immediate provision of the analytical framework to have utmost priority.

Methods

Records of Antibiotic Consumption

The available data set contains 25 consecutive quarterly records of antibiotic consumption in the University Hospital Dresden starting from the first quarter 2012. Consumption has been recorded per cost centre. For operational reasons, some departments are divided into more than one cost centers. However, for our purpose, a grouping of the cost centres into departments or functional units is clinically more relevant. At the top of the divisional structure, of course, there is the whole hospital. The second and, henceforth, most relevant level is given by grouping the departments into the three top-level units: OP units, intensive care units, and normal care units. Consumption has also been recorded per active agent group, which is nested within antibiotic group. In total, 49 active agent groups have been

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observed, which are pooled to 12 antibiotic groups.

The consumption of an antibiotic is measured in standardised units according to the Defined Daily Dose system, DDD, in order to allow for comparisons of different active agents. In addition, the number of cases as well as patient days have been recorded on a quarterly basis. This allows to compute the consumption density DDD per 100 patient days in hospitals:

$$DDD_{density} = \frac{DDD}{100 \text{ patient days}}. \tag{1}$$

Please note, for the sake of completeness, consumption density sometimes refers to DDD per 100 or per 1000 cases, respectively. Some measures of diversity are functions of proportions of "species" within an "ecosystem", which is why we make use of proportions of consumption. If $DDD_i(t)$ denotes the consumption of antibiotics within the antibiotic group $i \in \{1,\dots,n\}$ at time t, the proportion is given by

$$ddd_i(t) = \frac{DDD_i(t)}{\sum_{i=1}^{n} DDD_i(t)} \tag{2}$$

Depending on the context, index i may also refer to the active agent group.

Descriptive Analysis

Figure 1a shows the 12 time courses of antibiotic consumption per antibiotic group, $DDD_i(t)$. The consumptions of 9 groups largely remain constant on a moderate level. One group, viz. "second-generation cephalosporins", is characterised by a high consumption at the outset but declines approximately monotonously by more than half towards the end of the observation period. The consumptions of two other groups, in contrast, viz. "aminopenicillin/beta-lactamase inhibitors" and "narrow-spectrum penicillins" increase approximately monotonously and roughly compensate for the aforementioned decline.

The time courses of the corresponding consumption densities, $100 \times DDD_i/$patient days, are depicted in fig. 1b. Apparently, these time courses exhibit only minor differences in shape when compared with fig. 1a. The same holds for the proportions, $ddd_i(t)$, shown in fig. 1c. More important, calculations based on DDD are hardly distinguishable from calculations based on the corresponding densities. Henceforth, due to these minor differences, we skip to report our results with respect to consumption densities since we here primarily deal with an introduction of a methodological concept. The distinction between DDD and the corresponding densities might become important in other contexts, though. The proportions, however, will be used in later sections where we introduce measures of diversity.

Figure 1d shows the time course of the quarterly sampled mean antibiotic consumption, $Mean(DDD(t))$, averaged over the 12 observed antibiotic groups (cf. 1a). The corresponding coefficient of variation

$$V(t) = \frac{SD(DDD(t))}{Mean(DDD(t))}, \tag{3}$$

is depicted in Figure 1e, where $SD(DDD(t))$ denotes the standard deviation.

The coefficient of variation, $V(t)$, can be used as a rough estimate of "homogeneity" in a properly defined sense. Unfortunately, analogous to the notion of "dispersion," "homogeneity"

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Figure 1: **Time course of antibiotic consumption by antibiotic group.** Time courses of a) consumption DDD per antibiotic group, b) consumption densities per antibiotic group, c) proportions of consumption ddd per antibiotic group, d) mean consumption averaged over the antibiotic groups, e) coefficient of variation with respect to the antibiotic groups.

is an ambiguous term which deserves clarification. In ecological analyses, the concept of "maximisation of statistical heterogeneity" refers to an approach by means of an entropy or a related diversity measure as discussed in the following section. In this context, an ecosystem is maximally heterogeneous if all species are equally abundant. In the latter case, V would be zero, i.e., the system has no variability and is thus without (statistical) dispersion. In

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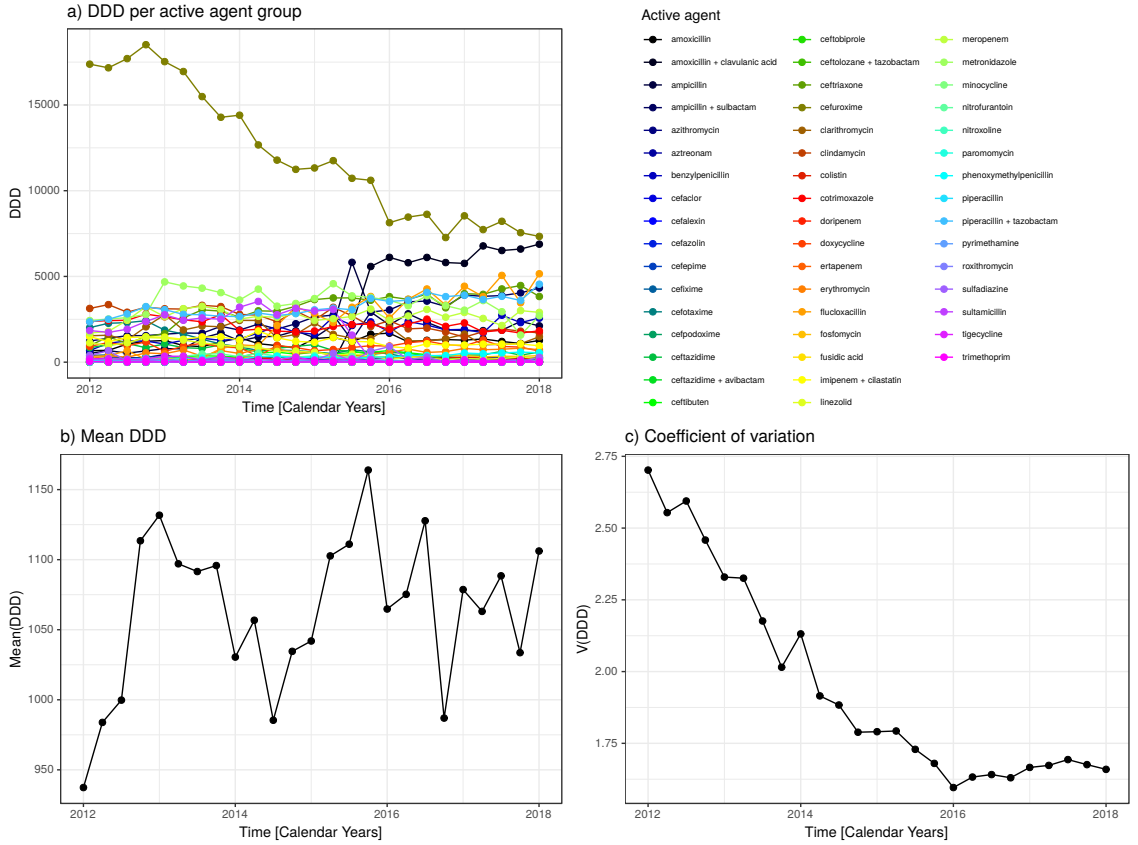

Figure 2: **Time course of antibiotic consumption by active agent.** Time courses of a) consumption DDD per active agent group, b) mean consumption averaged over the active agent groups, c) coefficient of variation with respect to the active agent groups.

contrast, physicists prefer to speak of a perfect dispersion, aka a perfect mixture, in such a situation. Thus, an ecosystem close to a monoculture is “homogeneous.” In a similar way, a multi-cultural society with equal proportions of all types of cultural backgrounds is intuitively called heterogeneous, and homogeneous, if only one cultural background is present. In other words, “heterogeneity” in the ecological sense is largely synonymous to “diversity.” In economics, the distribution of incomes, for example, is called homogeneous in the case of equal incomes of all individuals in accordance with the idea of a dispersion-free perfect mixture. Again, in the latter case, V would become zero. Due to compatibility, we stick with the ecological approach in the sequel. In this regard, the coefficient of variation is an inverse measure of heterogeneity. Arguably, heterogeneity in the ecological sense is better captured using the concept of diversity, as introduced in the following section. In order to provide compatibility with the terminology based on the notion of “heterogeneity” suggested in relevant publications on antibiotics resistance [10, 8], we cannot completely drop this term.

In the present case, variability thus homogeneity in the ecological sense is rather high during the first 4 to 6 quarters compared with the remaining time course. After an approximately monotonous decline until 2016, $V(t)$ slightly increases again during the final quarters. These results are consistent with the visual impressions from fig. 1a. Starting with a rather homogeneous distribution at the outset with an outstandingly large proportion of a single antibiotic group, we observe a trend towards a narrow distribution around the mean

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that starts to weakly widen towards the end. Equal proportions, thus $V(t) = 0$, means perfect heterogeneity, therefore, $V(t)$ can be interpreted as an inverse measure of heterogeneity.

In the same line, the descriptive analysis can be applied to consumption with respect to active agent groups. Figure 2a shows the 49 time courses of consumption per active agent group. We observe that a single active agent, viz. "cefuroxime", dominates consumption at the outset but declines approximately monotonously towards the end to a level still significantly above the bulk. This decline is compensated by an increase in consumption mainly of "amoxicillin + clavulanic acid" but also some other agents. The time courses of mean DDD and the coefficient of variation with respect to the active agent groups shown in figs. 2b-c reveal that variability remains on a high level during the time course. Thus, it turns out that pooling agents into antibiotic groups has a damping effect with respect to variability or homogeneity, respectively.

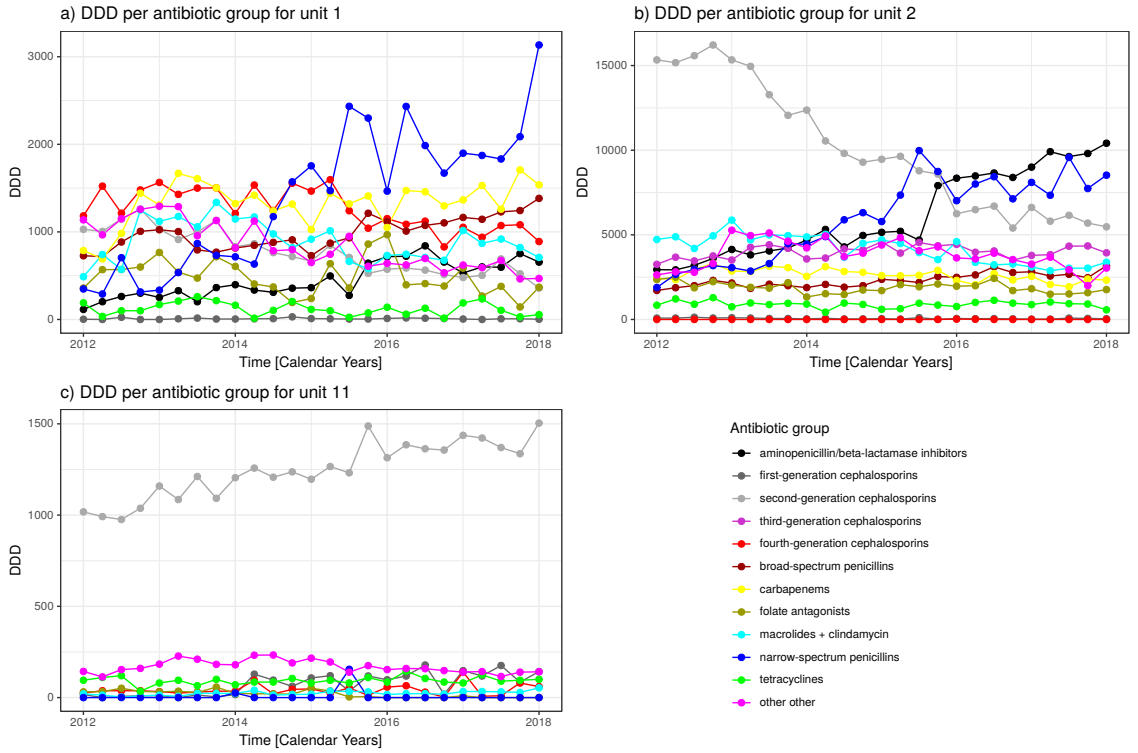

Figure 3: **Time courses of antibiotic consumption by antibiotic group separated by functional units.** Time courses of antibiotic consumption per antibiotic group shown separately for the functional units a) unit 1 = intensive care units, b) unit 2 = normal care units, c) unit 11 = OP units. Please note, the different scales of the y-axes reflect the different total amounts of consumption within each unit due to their different sizes. Important are the relative abundances within each unit.

Next step is to account for the Hospital's functional units. The three panels of fig. 3 show the time courses of antibiotic consumption per antibiotic group stratified by the three functional units: unit 1 = intensive care units, unit 2 = normal care units, unit 11 = OP units. Unit 1 consumed antibiotics out of 11 groups, whereas unit 11 consumed antibiotics out of only 8 different groups in at least one quarter during the whole observation period. Only unit 2 has non-zero consumption of antibiotics out of all 12 groups in at least one quarter.

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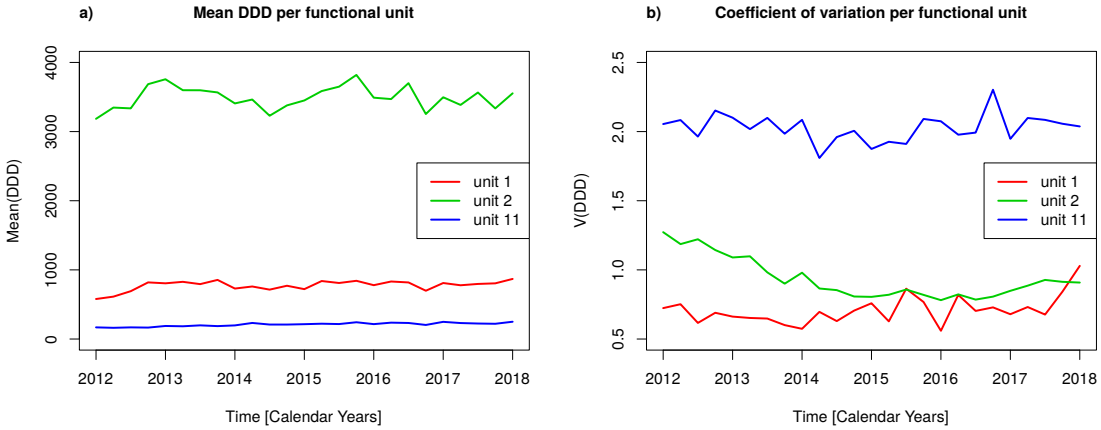

Figure 4: **Mean antibiotic consumptions and coefficient of variation by functional unit.** Time courses per functional unit of a) mean antibiotic consumption averaged over antibiotic groups, b) corresponding coefficient of variation, with unit 1 = intensive care units, unit 2 = normal care units, unit 11 = OP units.

Figure 4 shows the time courses of mean consumption averaged over the antibiotic groups per functional unit (fig. 4a) as well as the three corresponding coefficients of variation (fig. 4b). Unit 11 (the OP units) exhibits the lowest mean consumption but by far the highest coefficient of variation, both of which remain approximately constant over the time course. The explanation follows by throwing a glance on fig. 3c: Unit 11 has one absolutely dominating consumption of antibiotics out of the group “second-generation cephalosporins.” Units 1 and 2 both exhibit approximately temporarily constant mean consumption, however, unit 2 on a roughly 5-fold higher magnitude. Noteworthy, the variation of consumption of unit 2 approximately follows the variation for the whole clinic with a more or less monotonous decline during the first half of the observation period, whereas the coefficient of variation for unit 1 is approximately constant over the time course, with the exception of a marked rise at the final observation (first quarter of 2018), which can be explained by the sudden rise of consumption of “narrow-spectrum penicillins” antibiotics (cf. fig. 3a).

Heterogeneity and Entropy

Although the coefficient of variation can be interpreted as a rough measure of (inverse) heterogeneity, it has several inadequacies including the lack of uniquely capturing temporal changes. In the sequel, we harness methods known in ecological population modelling and other fields of research for an adequate quantification and assessment of antibiotic mixing behaviour and strategies as well as temporal patterns of prevalence of antibiotic resistance.

Let a_i and b_i with $i = 1,\ldots,n$ be the proportions of species of two $n-$species populations. Similarity of these two populations can be quantified by the similarity index

$$SI = 1 - 0.5 \sum_{i=1}^{n} \left| a_i - b_i \right|. \tag{4}$$

If $a_i = b_i, \forall i = 1,\ldots,n$, then $SI = 1$, i.e., the populations are identical in terms of their species distributions. If, on the contrary, the populations consist of disjoint sets of species, then $SI = 0$.

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Similarity index SI scales between 0 and 1. If we now fix say the first population to $a_i = \frac{1}{n}, \forall i = 1, \ldots, n$, which means maximum heterogeneity for this reference population, then, for the other population a heterogeneity index can be defined by

$$HI = 1 - \frac{n}{2(n-1)} \sum_{i=1}^{n} \left| \frac{1}{n} - b_i \right|. \tag{5}$$

Hereby, the slightly adapted factor $\frac{n}{2(n-1)}$ compared to 0.5 in SI (eq. 4) ensures $HI \in [0,1]$ independent from the concrete value of n. As far as we know, HI defined by eq. 5 has been used by Sandiumenge et al. [10] for the first time in the context of assessing antibiotic resistance and reapplied by Plüss-Suard et al. [8][1].

Diversity, a notion frequently used in ecology, is a more general concept than heterogeneity [13]. However, diversity is not uniquely defined. Thus, it depends on the specific context to which particular definition of diversity should be drawn on. An obvious somewhat simplistic way to quantify diversity is given by the so called richness, which is merely the number of species in a multi-species population (e.g. ecosystem). In terms of richness, a heterogeneous $n-$species population with equally frequent species has the same diversity as an $n-$species population with a minority of dominating and a majority of very rare species, that is to say n. It follows that an expedient diversity measure should be based on the distribution of species' abundances in some way.

A meaningful definition of diversity D_a is based on an "effective number of species" given by the species' proportions p_i and a weight parameter a by means of:

$$D_a = \left(\sum_{i=1}^{n} p_i^a \right)^{\frac{1}{1-a}}. \tag{6}$$

Setting $a = 0$ yields $D_0 = n$ independently from p_i, i.e. richness. Other special cases are:

$$\begin{aligned} D_1 &= e^{R_1} \\ D_2 &= \frac{1}{\sum_{i=1}^{n} p_i^2} \\ D_\infty &= \frac{1}{\max(p_i)} \end{aligned} \tag{7}$$

with $R_1 = -\sum_{i=1}^{n} p_i \ln(p_i)$ being the so called "Shannon entropy", sometimes also called "Shannon index." A unique name for D_1 itself, i.e. the exponential of the Shannon entropy, does not exist, however, in information science it is sometimes called "perplexity." Diversity measure D_2 is called "inverse Simpson index." The frequently used Gini-Simpson-Index derived from D_2 is given by: $GS = 1 - \frac{1}{D_2}$. The inverse of D_∞ is found in the literature named "Berger–Parker index," which is simply the proportional abundance of the most abundant type.

The Shannon entropy is a special case of a Renyi entropy defined by

$$R_a = \frac{1}{1-a} \ln \left(\sum_{i=1}^{n} p_i \right), \tag{8}$$

thus we have $D_a = e^{R_a}$. In other words, R_a is a monotonous function of D_a, thus, the two measures can be used interchangeably without loss of information since diversity has only a

[1] Please note that the typesettings of the formulas for HI in refs. [10, 8] are incorrect.

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relative meaning, anyway. The same holds for GS and other possible monotonous functions of D_a. Entropy R_a, thus D_a, independently of a reach their maximum for the fully heterogeneous situation $p_i = \frac{1}{n}(\forall i = 1,\ldots,n)$ and it then follows that $D_a = n$. From the latter result we conclude that richness might be a sufficient diversity measure for populations close to full heterogeneity. Having said that, heterogeneity HI itself, although it cannot be derived as a special case of a Renyi entropy, shares features of an entropy and is thus a legitimate measure of diversity.

Finally, the frequently used Gini coefficient deserves to be mentioned:

$$G = 1 - \frac{1}{2(n-1)} \sum_{i=1}^{n} \sum_{j=1}^{n} \left| p_i - p_j \right|. \tag{9}$$

The Gini coefficient is an interesting variant of the similarity index SI insofar as it can be interpreted as kind of a self-similarity. Once more, full heterogeneity (equal proportions) $p_i = \frac{1}{n}, \forall i = 1,\ldots,n$, implies $G = 1$, and maximally unequal proportions (e.g. $p_i = 1, p_{j\neq i} = 0$) implies $G = 0$.

For what follows, it is important to bring to mind that both heterogeneity, HI, as well as measures of diversity, D_a, GS, and G, are invariant under permutations of indices. In other words, if the proportions of two species are exchanged, diversity (heterogeneity) does not change. However, similarity index SI is capable to account for such a change. In order to assess the mixing behaviour of antibiotic administration or consumption, respectively, as well as prevalence of resistance, we present definitions of similarity tailored to our needs in the sequel.

Results

Heterogeneity of Antibiotic Consumption

The diversity measures introduced in the previous section are now calculated using the observed proportions p_i of antibiotic consumption with respect to antibiotic groups, thus $i = 1,\ldots,12$ refers to the 12 antibiotic groups. Figure 5 shows time courses of a) Renyi entropies, R_a, for 7 different values of weight parameter a (cf. figure legend), b) the corresponding diversities, $D_a = e^{R_a}$ for the same set of parameters a, c) the Gini-Simpson diversity, GS, and d) the Gini coefficient, G. Specifically, $a = 0$ yields $D_0 = n = 12$ (fig. 5b) in agreement with what we expected from theory.

Apparently, for all $a > 0$ the curves exhibit the same shape, i.e., they differ at each time point by a factor that seems to be a monotonous function of the values of a reference curve at these time points. A unique rule which specifies the best value of a does not exist. However, some researchers invoke a rule of thumb (e.g. [16]) which states that if one exactly observes such a monotonous relation between the different curves as we did, then the Renyi entropy is a robust measure and $a > 0$ can be chosen arbitrarily but consistently, since entropy does not have an absolute meaning, anyway. Apparently, the rule also holds for the Gini-Simpson diversity, GS, and the Gini coefficient G.

Figure 5 reveals that all diversity measures increase from 2012 until approximately 2016. Thereafter, this tendency is stopped and the data even suggest the initiation of a decrease in

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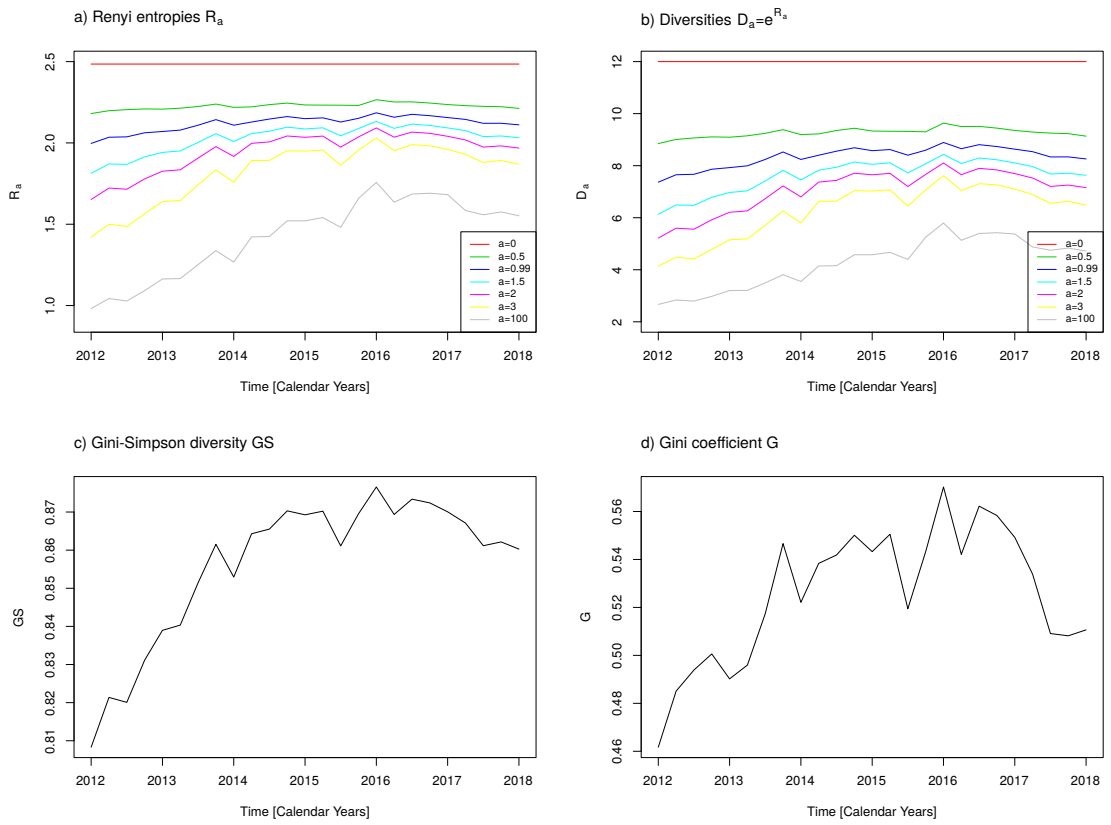

Figure 5: **Measures of diversity with respect to antibiotic groups.** a) Renyi entropies R_a for $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, b) Diversities D_a for $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, c) Gini-Simpson index GS, d) Gini coefficient G.

diversity. This behaviour coincides with the time course of the coefficient of variation (fig. 1).

Compared to the Renyi entropy, heterogeneity HI, defined in eq. 5, is easier to comprehend, which might explain that its application in the context of antibiotic resistance is unparalleled up to date ([10, 8]). However, the invariance under species permutations has not been taken into account thus far. A mixing strategy that dictates an occasional swap of consumption of two antibiotics leads to a temporarily constant heterogeneity and, therefore, to wrong conclusions if the assessment is merely based on HI. Since heterogeneity is nothing but a special case of similarity SI, we can now make use of SI to introduce a differential measure. Similarity with respect to the initial observation at the outset of a study

$$SI_0(t) = 1 - \frac{n}{2(n-1)} \sum_{i=1}^{n} \Big| p_i(t=0) - p_i(t) \Big|, \tag{10}$$

with $t = 0, 1, \ldots, 24$ being the number of elapsed quarters, captures changes with respect to the first observation. In the same line,

$$SI_\Delta(t) = 1 - \frac{n}{2(n-1)} \sum_{i=1}^{n} \Big| p_i(t-1) - p_i(t) \Big|, \quad \text{for } t > 0. \tag{11}$$

defines changes with respect to consecutive quarters, thus defines an approximation to a differential measure of similarity. The time courses of HI, SI_0, and SI_Δ are depicted in

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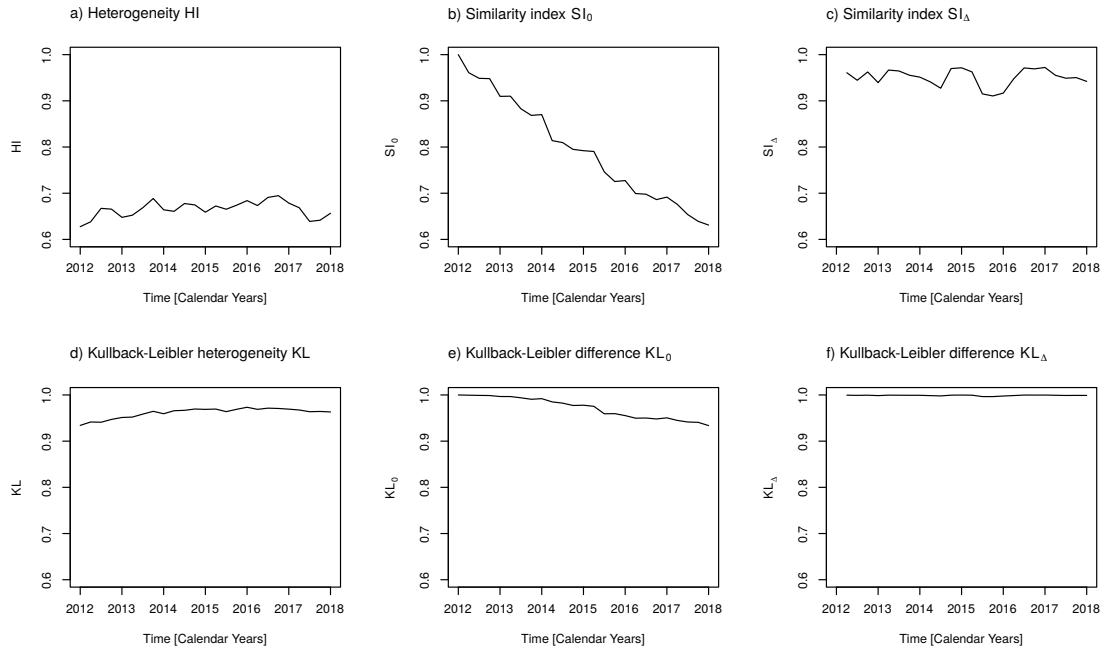

Figure 6: **Measures of heterogeneity and similarity with respect to antibiotic groups.** a) Heterogeneity index HI, b) Similarity index SI_0 with respect to proportions of the first observation, c) Similarity index SI_Δ with respect to proportions of the preceding observation, d) Kullback-Leibler heterogeneity KL e) Kullback-Leibler difference KL_0 with respect to proportions of the first observation, f) Kullback-Leibler difference KL_Δ with respect to proportions of the preceding observation. Confer text for definitions of these measures.

figs. 6a-c. Heterogeneity HI varies only within a small range from 0.63 to 0.69 (fig. 6a). However, we observe a monotonous, almost linearly increasing displacement from the first observation (fig. 6b), although the differential displacements are relatively small (fig. 6c). Obviously, the difference of the distribution of antibiotic abundances accumulates over the time course. Thus, we now have a sound basis for the evaluation of changing abundances and possibly related mixing strategies.

Within the scope of physics and information sciences, it is common to base measures of heterogeneity and diversity, respectively, on the Shannon entropy because it can be interpreted as the negative mean information that arises from averaging over the individual contributions $\ln(p_i)$ to information. In this context, the similarity index between two distributions given by a_i and b_i corresponds to the Kullback-Leibler divergence

$$KLD(a_i, b_i) = \sum_{i=1}^{n} a_i \log\left(\frac{a_i}{b_i}\right). \tag{12}$$

However, KLD is asymmetric, which is why the symmetric variant $KLD(a_i, b_i) + KLD(b_i, a_i)$, known as Kullback-Leibler difference, has been introduced. KLD is the mean information difference taken over the individual information differences $\log(a_i) - \log(b_i)$.

In order to harness KLD for our needs, we define the Kullback-Leibler heterogeneity

$$KL(t) = 1 - \frac{1}{2\ln(2)}\left(\sum_{i=1}^{n} a_i(t) \log\left(\frac{a_i(t)+1}{\frac{1}{n}+1}\right) + \sum_{i=1}^{n} \frac{1}{n} \log\left(\frac{\frac{1}{n}+1}{a_i(t)+1}\right)\right). \tag{13}$$

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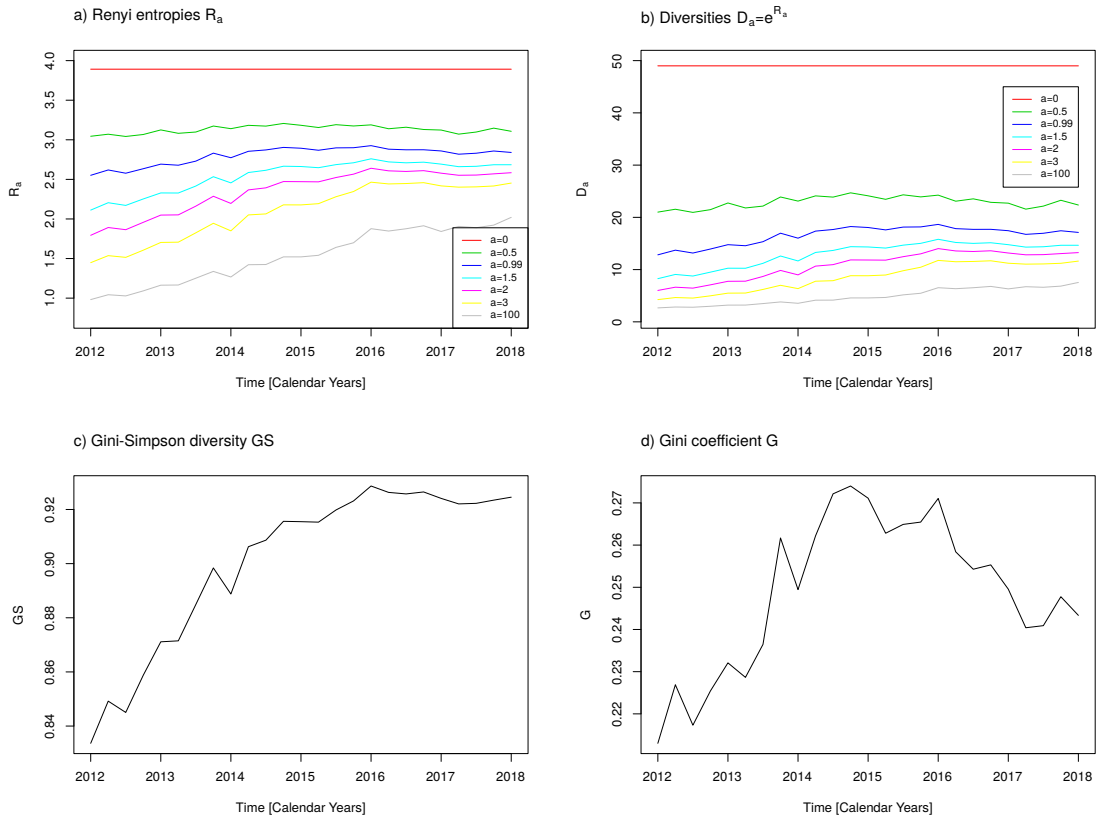

Figure 7: **Diversity measures with respect to active agent groups.** a) Renyi entropies R_a for $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, b) Diversities D_a for $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, c) Gini-Simpson index GS, d) Gini coefficient G.

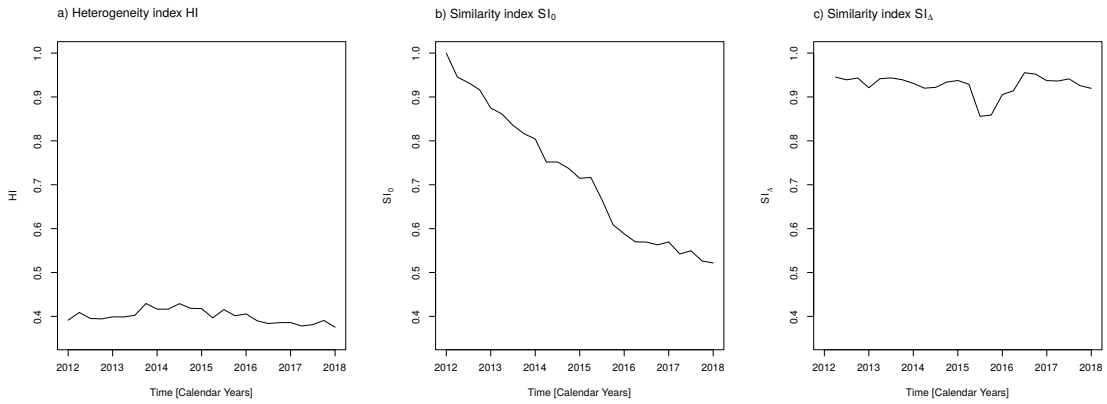

Figure 8: **Measures of heterogeneity and similarity with respect to active agent groups.** a) Heterogeneity index HI, b) Similarity index SI_0 with respect to proportions of the first observation, c) Similarity index SI_Δ with respect to proportions of the preceding observation. Confer text for the definitions of these measures.

Furthermore, the Kullback-Leibler similarity $KL_0(t)$ of distribution $a_i(t)$ at time t with the distri-

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bution at $t = 0$ (first observation) can be defined by

$$KL_0(t) = \sum_{i=1}^{n} a_i(t) \log\left(\frac{a_i(t)+1}{a_i(t=0)+1}\right) + \sum_{i=1}^{n} a_i(t=0) \log\left(\frac{a_i(t=0)+1}{a_i(t)+1}\right). \tag{14}$$

Finally, the Kullback-Leibler similarity $KL_\Delta(t)$ between two distributions observed at subsequent time points (here quarters) is given by

$$KL_\Delta(t) = \sum_{i=1}^{n} a_i(t) \log\left(\frac{a_i(t)+1}{a_i(t-1)+1}\right) + \sum_{i=1}^{n} a_i(t-1) \log\left(\frac{a_i(t-1)+1}{a_i(t)+1}\right). \tag{15}$$

Hereby, the $+1$ terms within the arguments of the logarithms ensure that situations with $p_i = 0$ remain well-defined.

Figures 6d–6f show time courses of KL, KL_0 and KL_Δ, respectively. A comparison with the ordinary heterogeneity and similarity measures of figs. 6a–6c reveals that the values of KL, KL_0 and KL_Δ are located within narrower intervals. In addition, KL appears to be smoother than HI and, noteworthy, the decreasing curve of $KL_0(t)$ has a concave shape. From these differences we conclude that measures based on information differences, due to their logarithmic dependence, weight larger differences in proportions stronger than small differences, whereas the ordinary measures exhibit a proportional weight.

In the same line, the time courses of measures of diversity and heterogeneity, respectively, with respect to active agent groups are depicted in figs. 7 and 8. Qualitatively, similar results as for the antibiotic groups are obtained. Once more, as already observed for the coefficient of variation, we see a damping effect of pooling the active agents into antibiotic groups. The variations of temporal changes of heterogeneity and related measures are larger for the active agent groups than for the more coarse grained antibiotic groups. No need to mention, the question of which stratification level should be prioritised is a matter of the concrete studies' objectives and the availability of adequate data. The usage of the more fine-grained level of active agents is advisable if records of prevalence of antibiotic resistance are available at the same fine-grained level.

Finally, we briefly report on the results obtained when the hospital's functional units are included as a second factor in addition to the antibiotic groups. Firstly, fig. 9 shows time courses of diversity measures stratified by the three functional units as previously defined. Secondly, heterogeneity HI and the similarity indexes SI_0 and SI_Δ are shown in fig. 10. Strikingly, diversities D_a and GS as well as heterogeneity HI remain approximately constant in the course of time for functional unit 11 and varies only very slightly for unit 1. To the contrary, the diversities for functional unit 2 resemble the corresponding curves for the whole hospital as shown in figs. 5 and 6, i.e., they exhibit an increase in the course of time. Apparently, the functional units have different policies of antibiotic administration. This becomes even more obvious when throwing a glance onto the curve $SI_0(t)$ shown in fig. 10b. The administration in unit 11 essentially remains constant with respect to the first observed administration in 2012. The administrations in unit 1 and unit 2, in contrast, show a cumulative difference with respect to the first observation.

So far, we conclude that neither of the diversity or heterogeneity measures D_a, GS, G, HI, and KL are capable to catch the policies or the observed mixing behaviours, respectively, without a concomitant assessment based on the newly introduced similarity indexes SI_0 and SI_Δ or, alternatively, KL_0 and KL_Δ.

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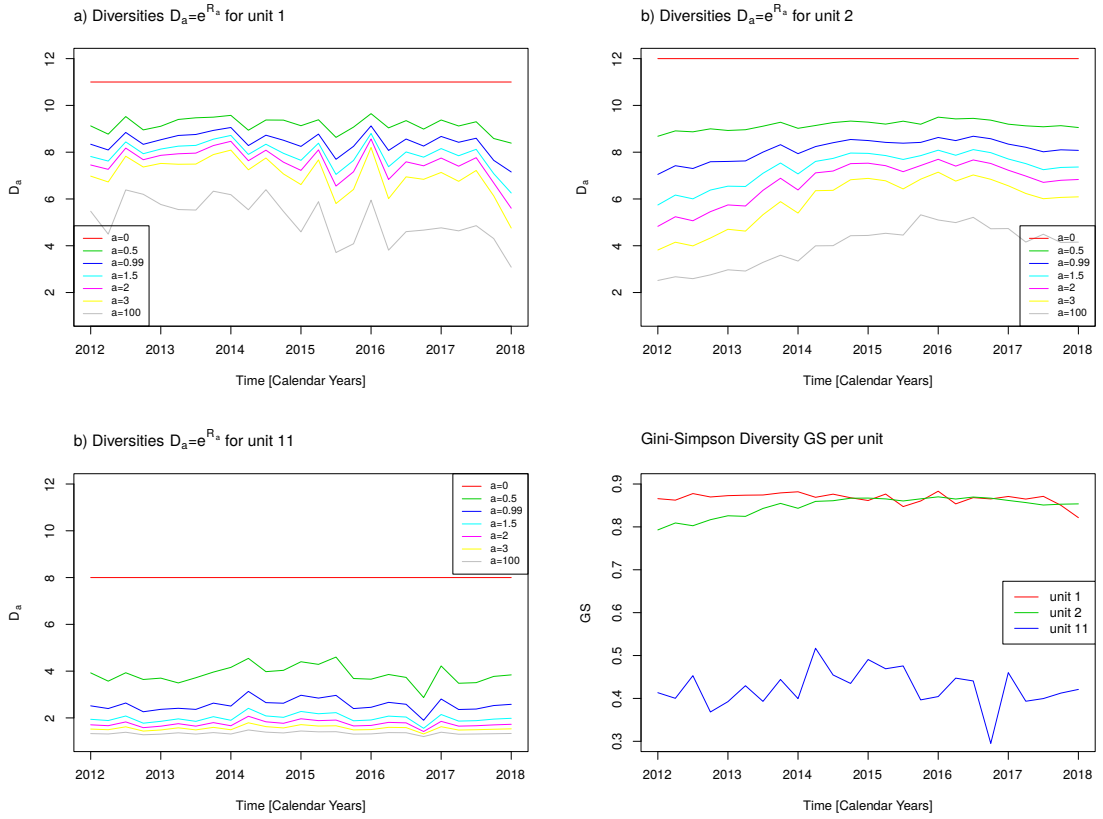

Figure 9: **Measures of diversity with respect to antibiotic groups stratified by functional units.** a) Diversities D_a for unit 1 with $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, b) Diversities D_a for unit 2 with $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, c) Diversities D_a for unit 11 with $a = 0, 0.5, 0.99, 1.5, 2, 3, 100$, d) Gini-Simpson Index GS. See text for definitions.

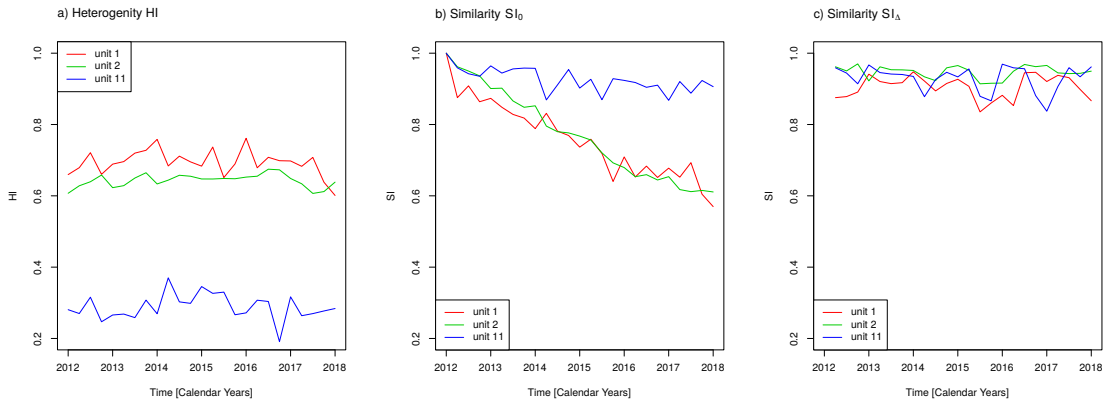

Figure 10: **Heterogeneity and similarities with respect to antibiotic groups stratified by functional units.** a) Heterogeneity HI. b) Similarity index SI_0 with respect to proportions of the first observation, c) Similarity index SI_Δ with respect to proportions of the preceding observation. Confer text for the definitions of these measures.

Correlation of Antibiotic Administration and Prevalence of Antibiotic Resistance

No need to emphasise, the most important and at the same time most challenging question is whether the mixing behaviour of antibiotic administrations correlates or even causally relates

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Figure 11: **Pathogen prevalence.** Sum of yearly registered number of cases of 9 observed pathogens stratified by resistance.

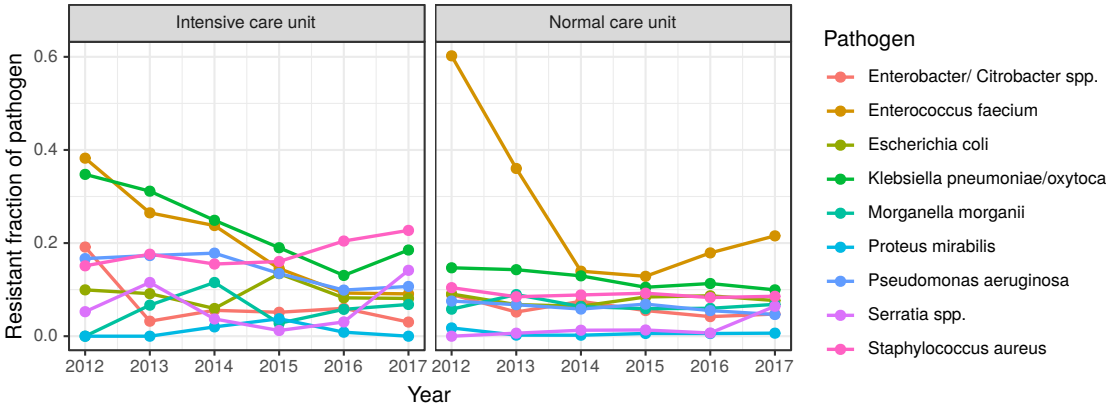

Figure 12: **Fraction of antibiotic-resistant germs.** Time courses of the fractions of resistance per pathogen plotted separately for units 1 and 2.

to the prevalence of antibiotic resistances. Only sufficient knowledge about existence and structure of such an association renders the design of administration policies that aim in minimising resistances meaningful. Unfortunately, recorded data on prevalence of antibiotic resistance are rare and often collected in a non-systematic way. Therefore, the following analysis should be viewed as paradigmatic rather than taking the results as credible.

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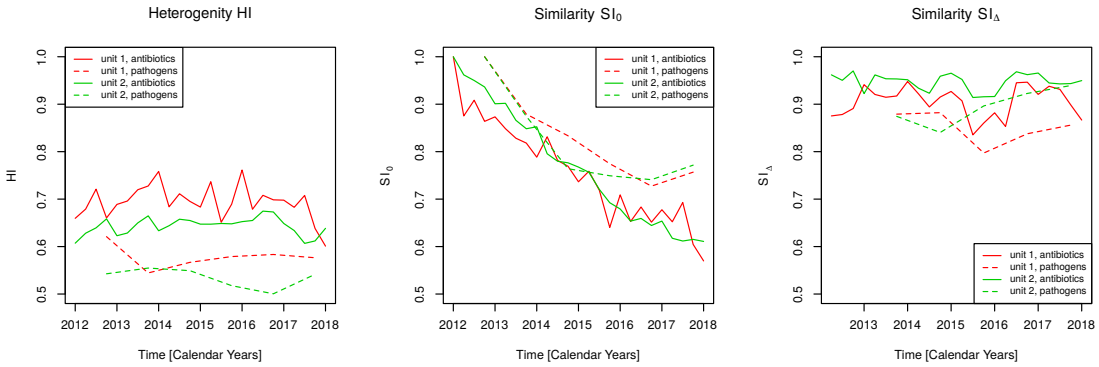

Figure 13: **Association of heterogeneities of antibiotic consumption and pathogen prevalence.** Time courses of heterogeneity, HI and similarity indexes, SI_0 and SI_Δ for antibiotic consumption with respect to antibiotic groups and prevalence of resistant pathogens stratified by the hospital's units 1 (intensive care) and 2 (normal care).

Nosocomial infections have been recorded on a yearly basis at the University Hospital of Dresden within intensive care units and normal care units, however, not in a controlled and regular way. Figure 11 shows the time courses of the number of registered cases per infectious agent (pathogen) stratified by resistance. Resistance, hereby, has been dichotomised in a yes/no-variable although for some cases a more detailed information on the type of resistance (the corresponding antibiotic agent, multiresistance, etc.) is available. The time courses of infection frequencies suggest a rising prevalence. However, since the awareness of the problem of antibiotic resistance and the commitment to corresponding guidelines are rather young, we suspect that the intention to rigorously record prevalence increased in the course of time, thus, the increase in prevalence could be a mock. The proportions of infections with resistant infectious agents per type of pathogen is perhaps more reliable than the total number of infections. Figure 12 shows the time courses of these proportions and it no longer appears as drastic as before. It appears natural to apply the measures of heterogeneity and similarity introduced above to the proportions of resistant pathogens with respect to the total population of resistant pathogens.

Figure 13 depicts the time courses of HI, SI_0, and SI_Δ both for the proportions of antibiotic consumption and for the proportions of resistant pathogens in order to allow for a direct comparison. Heterogeneity hardly changes in the time's course both for antibiotic consumption and resistant pathogens (fig. 13a). The slopes (denoted by mean (2.5%CI; 97.5%CI) in the following) resulting from linear regression are essentially zero (which is the null hypothesis of the linear model) with $-0.004(-0.012;0.004)$ and $p = 0.300$ (antibiotics, unit 1), with $0.001(-0.003;0.005)$ and $p = 0.705$ (pathogens, unit 1), with $-0.003(-0.021;0.016)$ and $p = 0.629$ (antibiotics, unit 2), and with $-0.006(-0.019;0.008)$ and $p = 0.300$ (pathogens, unit 2), respectively. However, heterogeneity of the population of resistant pathogens is slightly lower compared to antibiotic consumption.

The differential (quarter-by-quarter or year-by-year) changes of distributions are slightly greater for the distribution of resistant pathogens (fig. 13c), however, both are constant in essence for both units with $0.0002(-0.0078;0.0081)$ and $p = 0.968$ (antibiotics, unit 1), with $-0.0091(-0.0460;0.0279)$ and $p = 0.492$ (pathogens, unit 1), with $-0.0010(-0.0053;0.0034)$ and $p = 0.653$ (antibiotics, unit 2), and with $0.021(-0.002;0.045)$ and $p = 0.0637$ (pathogens,

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unit 2).

Most strikingly, the time series of the accumulated similarity index SI_0 for the resistant pathogens approximately follows the corresponding time series of antibiotic consumption, in fact in both units. The slopes significantly differ from zero with the concrete values $-0.055(-0.062;-0.047)$ per year (antibiotics, unit 1, $p < 10^{-3}$), $-0.049(-0.078;-0.021)$ per year (pathogens, unit 1, $p = 0.009$), $-0.067(-0.072;-0.063)$ per year (antibiotics, unit 2, $p < 10^{-3}$), and $-0.044(-0.088;-7.3e-04)$ per year (pathogens, unit 2, $p = 0.048$), respectively. It is appealing to speculate whether these coinciding changes are a result of correlations or even causal relations. For the time being, this speculation has to be treated with caution. However, this analysis gives directions to a proper controlled observational or experimental study design.

A further observation underpins our speculation. The total percentage of resistant pathogens reduces significantly from roughly 20% to 10% in functional unit 1. A linear regression gives a slope of $-0.017(-0.025;-0.008)$ per year for the proportion (significantly different from zero with $p = 0.005$). In functional unit 2 the proportion of resistant pathogens reduces non-significantly by $-0.007(-0.015;7.1e-05)$ per year, however, at the edge of significance ($p = 0.051$). We conclude that mixing of antibiotic consumption correlates with the prevalence of antibiotic-resistant bacteria by means of parallel slopes of similarity indexes SI_0. Whether mixing of antibiotic consumption has a direct causal impact is still speculative but gains additional evidence through the observed reduction of prevalent resistant bacteria. Controlled studies that allow comparisons with non-mixing or other types of mixing behaviours are needed to draw reliable inferences.

Discussion and Outlook

Applications of measures of heterogeneity and diversity are rare and unsatisfactory in the context of assessing antibiotic resistance. This is somewhat surprising since antibiotic administration policies that rely on mixing strategies in order to reduce antibiotic resistances have been promoted for quite some time [6, 3]. Mixing strategies, this is our claim, are best characterised by means of heterogeneity and diversity measures, respectively. Although some attempts to tackle antibiotic resistance by means of heterogeneity analyses exist [10, 8], a satisfactory mathematical framework is due.

We adopted diversity measures known in other fields of research [13] and adapted them to the needs within the scope of analysing antibiotic resistance. It is natural to seek for dependencies between the heterogeneity of consumption of antibiotics and the heterogeneity of the pattern of prevalence of antibiotic-resistant pathogens.

In order to provide a flexible methodological basis for the analysis of antibiotic resistance, we introduced and discussed a simple measure of heterogeneity as well as a general family of diversity measures, i.e., the so called family of Renyi diversities and derivatives thereof. It should be noted that the notions of “heterogeneity” and “diversity” do not refer to conceptually different measures, they merely reflect their emergence in different fields of application. As a novel aspect within the given context, we derived differential measures of similarity which are needed to capture temporal changes due to swapping proportions which leave moments like heterogeneity and diversity invariant.

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For many real-world applications, the simple heterogeneity measure HI and differential measures of similarity SI_0 and SI_Δ will suffice. However, showing that the whole family of diversity measures leads to the same conclusions supplies additional evidence ("We can regard a sample more diverse if all of its Renyi diversities are higher than in another samples.", [16]). Moreover, the smoothing and non-linear weighting effect of higher order measures like Shannon entropy and derivatives (Kullback-Leibler heterogeneity, etc.) might become important for damping spurious fluctuations by weighting larger deviations. A solid reason for the choice of entropies is the straightforward application of a maximum entropy method. Maximum entropy proved as the method of choice when it comes to learn dynamics of biological systems (e.g. [7]). With the aid of such an optimisation tool we expect that an optimal mixining/cycling strategy can be learned from the observed correlation patterns between antibiotics consumption and prevalences of antibiotic-resistance.

The presented inclusion of covariates and factors like clinical units and groupings of active agents has exemplary character. The concrete choice of covariates depends on their availability and, most important, on the specific questions that are raised. In the case of mixing with two (or more) subpopulations of patients that receive different drugs in a temporarily alternating way, it might be better to stratify for these subpopulations instead of functional units, unless these strata coincide. Needless to mention, that our analytical framework is flexible enough to account for such peculiarities. In addition, we point to the possibility to expand measures of heterogeneity and similarity to be applicable to joint probabilities of antibiotic consumption and resistance. This is beyond the scope of the present work, however, we paved the way for doing so.

It deserves to be mentioned, that some authors approached the problem by means of extended SIR-like epidemiological models [1, 14]. From a theoretical point of view, these models have benchmark character. However, the validation of these models necessitates recording of data on antibiotics consumption and pathogen load on an individual basis which is not feasible for most hospitals. As opposed to this, so called composite indices as "summary measures of the net impact of antibiotic resistance on empiric therapy" [5] are much more coarse-grained epidemiological measures based on the cumulative antibiogram [4], which reside on a higher population level. Our approach is compatible to both sides and bridges the gap. Moreover, due to its intermediate complexity it is able to serve as a performative boundary object [12], thence constituting a clinically relevant basis for a modelling for policy [15]. This holds all the more if implemented on a boundary infrastructure [11] as, for example, the modelling platform MAGPIE [2] that enables experts with different expertises to dock on.

Conclusions

To conclude, the presented analysis has paradigm character. We focused on setting up a methodological framework because the available data do not allow to assess mixing strategies in a controlled way. However, the performed applications of the suggested analytic methods to records of antibiotic consumption and prevalence of antibiotic-resistant bacteria definitely go beyond mere illustrations. That is to say, the results allow to raise hypotheses or at least to formulate conjectures. Specifically, we observe a strong positive correlation of time courses of similarity with respect to the initial observation of antibiotic consumption and prevalence of antibiotic-resistant pathogens. No need to mention, this correlation has to be confirmed in an experimental/interventional study. We are convinced that our mathematical framework provides a sound basis to substantially improve the determination of a viable roll back admin-

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istration policy to defeat antibiotic resistance.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HHD derived the mathematical framework, performed all calculations and drafted the manuscript. KdW initiated the study, is responsible for the data collection at the University Hospital and sketched a rough qualitative concept for the assessment of control strategies. AK managed the support with and quality of data. IR supervised the derivation of the mathematical framework, provided conceptual input, and assisted drafting the manuscript. All coauthors proofread the manuscript.

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Numerical calculations, statistics, and graphics have been performed with R [9].

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