Antibiotics to outpatients in Norway – assessing effect of latitude and municipality population size using quantile regression in a cross sectional study

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② Abstract

Background

High antibiotic consumption rates are associated to high prevalence of antimicrobial resistance. Geographical differences in dispensing rates of antibiotics are frequently analysed using statistical methods addressing the central tendency of the data. Yet, examining extreme quantiles may be of equal or greater interest if the problem relates to the extremes of consumption rates, as is the case for antimicrobial resistance.

The objective of this study was to investigate how geographic location (latitude) and municipality population size affect antibiotic consumption in Norway.

Methods

We analysed all outpatient antibiotic prescriptions (n>14 000 000) in Norway between 2004 and 2010 using quantile regression. Data were stratified by year and we aggregated individual data to municipality, county or latitudinal range. We specified the quantile regression models using Directed Acyclic Graphs and selected the model based on Akaike Information Criteria.

Results

Yearly outpatient antibiotic consumption in Norway varied up to tenfold at municipality level. We found geographical variation to depend on the number of inhabitants in a municipality and on latitude. These variables interacted, so that consumption declined with increasing latitude when municipality population sizes were small, but the effect of latitude diminished as the number of inhabitants increased. Aggregation to different levels of spatial resolution did not significantly affect our results.

Conclusion

In Norway, outpatient antibiotic dispensing rates decreases with latitude at a rate contingent on municipality population size. Quantile regression analysis provides a flexible and powerful tool to address problems related to high, or low, dispensing rates.

Keywords

Antibiotic consumption, municipality size, latitude, quantile regression.

Background

Geographic variation in outpatient antibiotic dispensing rates, a proxy for consumption rates, has important public health implications as high consumption rates increase the risk of antimicrobial resistance. It is imperative to identify where consumption is too high to guide targeted preventive measures. Typically, geographic differences are assessed using analytical methods addressing the central tendency of the dispensing rates.[1-9] Considering the public health implications of high vs low antibiotic use, examining the characteristics of the extreme quantiles may be of greater interest. Though an examination of determinants of high and low use we can not only investigate a potential over consumption. We can also draw conclusions on what determines patients (or prescribers) with a low rate of prescriptions. If we only focus on central tendencies we risk losing information on how our predictor variables behaves at the most interesting parts of our data.

Studies on regional antibiotic consumption often rely on different levels of aggregation of individual data. Firstly, several antibiotics may be aggregated to antibiotic groups to reduce the complexity of the dataset. Secondly, individuals may be aggregated to different geographical entities like municipality or county.[4, 10, 11] Aggregation may influence measures of consumption due to the Modifiable Areal Unit Problem (MAUP)[12], with unpredictable effects on regression parameters[13], and may increase variance heterogeneity, with geographical units (e.g. municipalities) with small population sizes displaying greater variance in consumption than units with high population size.

In Norway there are 428 municipalities, 19 counties and 4 health regions (5 health regions prior to 2007). The number of dispensed Defined Daily Doses/1000 inhabitants/day (DID) for outpatients at the county level in 2010 varied between 13.5 and 18.9.[14] The lowest DIDs at county level were in the North.

The objectives of this study were to investigate the effect of municipality latitude and municipality population size on antibiotic consumption, focusing on high and low consuming municipalities in Norway.

Methods

Data on dispensed antibiotics for the period 2004-10 and population estimates were provided by the Norwegian Prescription Database (NorPD) and Statistics Norway.[14, 15] A detailed description of NorPD is given by Furu.[16] The database contains information on all dispensed drugs to outpatients) in addition to demographic data. Patients are registered with an encrypted ID, month and year of birth (the same variables are recorded for death), gender and both municipality and county where they live. Likewise, the prescribers are registered with month and year of birth, gender and the same variables on residence. Prescriber profession and speciality is also recorded.

The prescribed drug is registered with ATC code, the DDD and the reimbursement code. Further, the prescription has a date, number of packages, a Nordic article number and a free text for area of application. Finally the pharmacy is registered with a name, licence and in which municipality and county it is located.From this database we extracted 14 132 020 individual prescriptions from ATC group J01, and prior to aggregation we excluded prescriptions for methenamine (J01XX05), and entries with erroneous ATC-codes and implausible values (e.g. age of prescribers or patients, unreasonably large amounts for single prescriptions, and erroneous ATC codes). Cases with missing or wrong data on municipality codes or cases dispensed on Svalbard were also removed.

We defined the outcome by aggregating the number of DDD for all antibiotics and calculated the age adjusted DID for each municipality and county.

Exposure variables

Latitude was assigned to municipalities in three different ways; a latitude ranking (South-North) according to the latitude of a municipality’s county (1 through 19), a rank based on latitude of the municipalities (1 through 428), and finally we divided the 428 ranks into 19 intervals with even number of municipalities and assigned a latitude rank to each cluster of municipalities. All ranks for latitude were based on administrative centre coordinates.[17, 18] The number of inhabitants in municipalities were log transformed.

Statistics

Prior to choosing statistical method and model, we inspected the data for heteroscedasticity and nonlinearity in the relationship between antibiotic consumption, population size and latitude. This revealed a data structure violating the assumption of constant variance of antibiotic consumption over municipality sizes, favouring the choice of quantile regression (QR). QR is suited for, but not limited to, data with heterogeneous variance.[19-21] An illustration of the data structure and the variation for 2010 is given in Supporting Information (SI) Fig. 1.

In order to control for confounding effects we used the Directed Acyclic Graphs (DAG) methodology suggested by Shrier and Platt[22] to identify covariates to include in the statistical model choosing the minimal adjustment set reported from this analysis. For our DAG model we explored the relationship between the following variables: Latitude, geographical entity,

Given the covariates from the DAG analysis, we investigated two models and used Akaike Information Criteria (AIC) for model selection.[23] The full model, where all variables are allowed to interact, was compared to a reduced model were municipality population size and latitude were included as main effects only. We included year as a categorical variable to estimate independent regression surfaces for each year. This variable interacts with all other variables in both models.

We set levels of antibiotic consumption for table and figures to the 80th, 50th and 20th percentile, and compared three versions of the chosen model; 1) municipalities ranked after the county latitude (1-19); 2) municipalities clustered in 19 areas constructed solely by latitude along a South-North axis; 3) municipalities ranked after municipality latitude (1-428). We estimated the p-values for the parameter estimates with a Markov chain marginal bootstrap with 500 replicates. [21, 24]

To create a suitable database for analysis, we used the statistical software SPSS (version 21.0.0).[25] We used the statistical software R (version 3.02) for all analytical purposes with the packages quantreg (version 5.05), rgl (version 0.03.935), and diagram (version 1.6.2). [24, 26-28] The DAG was created and analysed in DAGitty (version 2.0).[29] We used ImageJ (version 1.47) to construct a video for the SI.[30]

Results

Consumption of outpatient antibiotics declined with increasing latitude (South-North axis) (Fig. 1 and SI Video 1). Consumption also depended on the number of inhabitants in a municipality and variation was largest where population size was low. Over the study period we found 6-10-fold difference in consumption of antibiotics (measured in DIDs) among Norwegian municipalities. The main effect of municipality population size on antibiotic consumption was largest for the lower percentiles, decreasing for higher percentiles of consumption (Fig. 2).

The decline in antibiotic consumption with increasing latitude was contingent on municipality population size, and the effect of latitude was reduced as municipality population size increased. The curved regression surfaces for 2010 illustrate this interaction between latitude and municipality size detected at both the 20th and 80th percentile (SI video 1 displays surfaces for all years). The interaction effect was present from the 20th through the 80th percentile (Fig. 2, Table 1). However, below the 20th and above the 80th percentile the interaction effect was less pronounced and estimates were not statistically different from zero (Fig. 2).

The full model fitted the data best and had the lowest AIC (Δ AIC = 132, 116 and 24 for the 20th, 50th and 80th percentile respectively). The lowest antibiotic consumption, at both the 20th and 80th percentile, was found in Northern Norway, in municipalities with small population sizes (Table 1, Fig. 2, SI Video 1).

We found no evidence for MAUP effects when we aggregated the data at three different levels of spatial resolution (Table 1).

Discussion

We detected a 10-fold difference antibiotic consumption, measured in DID, among Norwegian municipalities. Consumption was highest at lower latitudes and in larger municipalities. The rate of reduction in consumption with increasing latitude was contingent on municipality population size. Lower DID in the northern counties correlates with an increasing number of municipalities with small population sizes in this part of the country. Our data are unsuitable for explaining any causal relation relationships behind these findings. Although we find an effect of latitude on the consumption of antibiotics this is most likely an proxy for other, unmeasured variables. If we allow ourselves to speculate; prescriber density, temperature, variations in infectious diseases and possibly different antibiotic resistance patterns along the latitude gradient can have an effect. Therefore, latitude is a devious variable for predicting drug consumption.

Highlighting differences in antibiotic consumption is important in the public health perspective. Low levels of consumption may reflect underuse resulting in negative health outcomes, and unnecessary high use is associated with high prevalence of antimicrobial resistance.

By addressing percentiles of antibiotic consumption, QR allows to model the higher, or lower, consumption rates, and is thereby a valuable inferential tool in pharmacoepidemiological studies,[20] providing essential information for antibiotic stewardship and conservancy. Further, in the context of geographical studies, aggregation often leads to strong variance heterogeneity, which can be effectively handled by the nonparametric QR.

We found no evidence for MAUP effects. The observed differences in parameter estimates between models 1 through 3 are expected, as the covariate latitude differs between the models. However, the tendency for parameter estimates does not change.

Strengths and weaknesses

The NorPD captures all prescriptions to outpatients in Norway, but contains limited information on underlying diseases. Possible differences in indications for treatment between regional units are not addressed in the present study.

For some years, the regression surfaces for the 20^{th} percentile and the 80^{th} percentile cross close to the highest values of population size. This reflects some bias in the regression estimates due to few observations for municipalities with the highest number of inhabitants.

By aggregating individual prescriptions to geographical levels information is inevitably lost. At the same time, individual data pose analytical challenges with respect to dependency of data connected to patients, prescribers and time.

A recent paper advised on selection criteria for geographical units.[31] Our study meets some of those criteria (biological relevance, how easily results are communicated, and missing values within geographical areas). MAUP is likely an issue when data were aggregated to county level. We have tried to assess whether different levels of aggregation affected our results and we conclude that we can exclude MAUP effects between the models we have investigated. However, we have not addressed a full aggregation of all variables, and we do not explore all possibilities of MAUP effects.

Comparing European studies on differences in geographical antibiotic consumption poses two challenges; firstly, variation between countries is substantial. [11, 32, 33] Secondly, the geographical effects on consumption within countries varies, and it is difficult to obtain predictors for this variation.[4]

The North-South differences found in Italy [34] and the east-west gradient in Germany [4] are comparable to the latitude gradient in Norway. The German, Italian and present Norwegian studies use different analytical approaches. The Italian study relies on the periodic prevalence of antibiotic consumption, whereas the German and our study rely on aggregated individual consumption.

A recent study revealed a large variation in periodic prevalence between districts and found an effect of area deprivation on odds of being prescribed antibiotics. In this study individual data were utilized in a multilevel statistical analysis.[9] Both the German and our study aggregate to the lowest political and administrative level. Our results show that this aggregation level is appropriate for summarizing and interpreting the data for regional consumption in Norway.

Conclusions

Antibiotic consumption, measured as DID, varies 10-fold between Norwegian municipalities. The decline in antibiotic consumption along latitude is associated with municipality size. Although geographical differences may exist, we do not consider latitude to be a good predictor of antibiotic use in Norway.

Municipality population size has a clear effect on consumption, and its interaction with latitude must be taken into account.

List of abbreviations

AIC	Akaike Information Criteria
ATC	Anatomical Therapeutic Chemical classification system
DAG	Directed Acyclic Graph
DDD	Defined Daily Dose
DID	DDD/1000 inhabitants/day
MAUP	Modifiable Areal Unit Problem
NorPD	Norwegian Prescription Database
OLS	Ordinary Least Squares regression
QR	Quantile Regression
REC	The Regional Committee for Medical and Health Research Ethics
SI	Supporting Information

Ethics and Consent statement

The Norwegian Directorate permitted access to NorPD data for Health and Social Affairs (project 06/4951), and The Regional Committee for Medical and Health Research Ethics (REC) (project 144/2006), in addition to the Data Protection Official for research at the University Hospital of North Norway (project 001/07), approved the study.

Competing interests

None.

Authors contributions

PH had the main responsibility for specifying research questions, data preparation, data analysis, figures, and interpretation of results. PH also had the main responsibility for writing the first draft of the manuscript.

RP supervised the statistical analysis and computer programming work.

GSS initiated the project.

ASF acquired the data.

LS supervised and complemented literature searches, and had main responsibility for completing the manuscript.

All authors contributed to discussions on study design, choice of DAG model, analytical approach, the interpretation of results and approved the final version of the manuscript.

Availability of data

All data are available from the NorPD.

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UiT – The Arctic University of Norway had no role in planning of the project, analysis of data, interpretation of results or writing of the manuscript.

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Table 1 Parameter estimates for the main effects and the interaction term in a linear QR for three quantiles in three different models

		Parameter estimates[1]		
Percentile	**Variable**	**Model 1**	**Model 2**	**Model 3**
20th percentile	South-North axis	**-0.77**	**-0.03**	**-0.70**
	Log (Inhabitants)	**1.41**	**1.65**	**1.52**
	South-North axis * Log (Inhabitants)	**0.17**	**0.01**	**0.15**

50th percentile	South-North axis	**-1.01**	**-0.05**	**-1.00**
	Log (Inhabitants)	0.31	0.69	0.50
	South-North axis * Log (Inhabitants)	**0.25**	**0.01**	**0.24**
80th percentile	South-North axis	**-0.85**	**-0.04**	**-1.01**
	Log (Inhabitants)	-0.30	-0.18	-0.42
	South-North axis * Log (Inhabitants)	**0.21**	**0.01**	**0.25**

[1] Bold figures are estimates which are significantly different from zero at the $\alpha=0.05$ level. Parameter estimates for intercept and interactions with year investigated are omitted. Model 1: Municipalities ranked along latitude based on county. Model 2: Municipalities ranked along latitude. Model 3: Municipalities ranked along latitude in 19 intervals. Data from the NorPD.