Socioeconomic factors contributing to antibiotic resistance in China: a panel data analysis

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Abstract

Background

The relationship between socioeconomic factors and ABR remains a knowledge gap in China. In this study, our aim was to examine the association between ABR proportion and socioeconomic factors across 30 provinces in mainland China.

Methods

We used two measures of ABR: the proportion of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), 3rd generation cephalosporin-resistant *Klebsiella pneumoniae* (3GCRKP), 3rd generation cephalosporin-resistant *Escherichia coli* (3GCREC), methicillin-resistant *Staphylococcus aureus* (MRSA); and the aggregate resistance. ABR proportion, education, gross domestic product (GDP) per capita, out-of-pocket (OOP) health expenditure, physician density, hospital bed density, access to water source, and number of public toilets per 10,000 population data during 2014 and 2018 in 30 provinces in mainland China were included. We examined the association between ABR level and potential contributing factors using panel data modelling. In addition, we explored this relationship from eastern, central, and western economic zone, respectively.

Results

Our results indicated that higher hospital bed density and physician density were significantly associated with lower levels of ABR. The issue of ABR was also related to socioeconomic factors such as GDP per capita, OOP health expenditure, education, which might depend on different resistant bacteria or different economic zones. GDP per capita was negatively associated with CRPA level, but positively associated with MRSA level. Higher OOP health expenditure was associated higher CRPA level. In addition, we only found that ABR prevalence was significantly negatively associated with education, and positively associated with OOP health expenditure in central economic zone, but not found in eastern and western economic zone.

Conclusions

Our study highlights that measures increasing hospital beds and physicians allocation to curb ABR should be implemented. Besides, intervention measures tackling the development and spread of ABR in China must better recognize and address the importance of social and economic determinants.

Introduction

Antibiotic resistance (ABR) occurs when bacteria develop the ability to defeat the antibiotics that were previously effective. ABR poses a threat to public health and hinders to progress to achieve sustainable development goals (SDGs)[1]. Infections caused by ABR are associated with longer hospital stays, higher medical costs, and increased mortality compared with infections with antibiotic susceptible organisms[2-5]. It has been estimated that $100 trillion in economic loss and ten million deaths every year by 2050 could be attributable to antimicrobial resistance (AMR) around the globe, and there would be $20 trillion in economic burden and one million deaths every year by 2050 in China due to AMR[6]. Multidrug resistant (MDR) bacteria, as the major therapeutic challenge both in hospital and community settings[7], are leading us into a “post-antibiotic era”, in which common infections and minor injuries could be fatal[8].

The World Health Organization (WHO) developed a global priority list of MDR bacteria, in which carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), 3rd generation cephalosporin-resistant *Klebsiella pneumoniae* (3GCRKP), 3rd generation cephalosporin-resistant *Escherichia coli* (3GCREC), methicillin-resistant *Staphylococcus aureus* (MRSA) were regarded as the most problematic and highly MDR bacteria, they have the capabilities for developing resistance mechanisms to a wide range of antibiotics[9]. The situation of ABR, especially the above MDR bacteria mentioned in China is severe[10]. Reports from China Antimicrobial Resistance Surveillance System (CARSS) showed that the proportion of CRPA, 3GCRKP, 3GCREC, MRSA were 20.7%, 33.0%, 54.2%, and 32.2%, which were higher than those in some high-income countries[11].

Some studies have explored drivers of the emergence and transmission of AMR[12]. Inappropriate antibiotic use is one of the main drivers of ABR[13, 14]; however, previous studies demonstrated that interventions solely focusing on regulating antibiotic consumptions had limited effectiveness[13, 15-18]. Emergence and spread of ABR is influenced by socioeconomic determinants, such as political factors, economic drivers, and socio-cultural influences[15]. For example, economic status affected antibiotic prescriptions, further influence ABR. Higher ABR rates and lower per capita antibiotic consumption were observed in several high- and low/mid-income countries[16, 18]. Quality of governance, education, out of pocket (OOP) health expenditure, health facilities, and sanitation have been shown to be as closely associated with differences in ABR and antibiotic consumption patterns between regions[13, 14, 17-20]. Antibiotic consumptions in animal, agriculture, and aquaculture also play underappreciated roles in the development and spread of resistant bacteria[21, 22].

China has vast territory that is characterized by regions with diversity in environmental, economic and socio-cultural contexts, and disparity in medical resource distribution and population literacy[23]. However, the relationship between these socioeconomic factors and the level of ABR remains largely univestigated in China. In this study, we examined the association between provincial ABR level and socioeconomic factors across 30 provinces in mainland China.

Methods

2.1 Data sources

We created a dataset on ABR for 30 provinces in mainland China using data from 2014 to 2018. ABR data were obtained from CARSS, which covered 1,353 hospitals, including 349 secondary hospitals and 1,004 tertiary hospitals in 2018. According to the global priority list of MDR bacteria from WHO and the completeness and availability of resistant organisms from each province in mainland China, we included the following bacteria: CRPA, 3GCRKP, 3GCREC, and MRSA in this study. ABR combinations were aggregated by use of the average resistance prevalence of the above bacteria. We excluded Tibet autonomous region due to missing data[24].

There are many possible contributing socio-economic factors influencing ABR level, however, provincial data coverage of all factors were incomplete, therefore, we captured some main probable factors. We used the China Statistical Yearbook for data on education (finishing secondary education), gross domestic product (GDP) per capita, access to water source, and number of public toilets per 10,000 population[25] between 2014 and 2018. We took data for OOP health expenditure, physician density (number of physicians per 1,000 population), and hospital bed density (number of beds per 1,000 population) from China Health Statistical Yearbook during 2014 and 2018[26].

In this study, finishing secondary education is defined as the percentage of people finishing education level in junior high school in total population aged six and over. GDP per capita is a measure of the output of a province that takes GDP and divides it by the number of people in the province in China. Access to water source is measured by the percentage of the population having access to and using improved water sources. Number of public toilets per 10,000 population is calculated as number of public toilets divided by total population in a province, and adjusts this ratio to per 10,000 population; public toilets are the rooms or small building with toilets and sinks that are available for use by the general public, customers etc. OOP health expenditure is defined as payments made by individuals to healthcare providers for health service. Number of physicians per 1,000 population or number of beds per 1,000 population is calculated as number of physicians or number of hospital beds divided by total population in a province, and adjusts the ratios to per 1,000 population, respectively.

2.2 Statistical analysis

The dataset for the main analysis was panel data modelling of different bacteria at the provincial level. To explore the association between ABR level and the confounding factors, we used two provincial-level measures of ABR: the proportion of CRPA, 3GCRKP, 3GCREC, and MRSA; and the aggregate resistance. Resistance could vary from 0-100[18].

Fixed or random effects panel data modellings were conducted to analyze the effect of confounding factors on the ABR level. First, we estimated provincial-level regression models with aggregate resistance in 30 provinces as the outcome. In addition, we conducted regression model from eastern, central, and western economic zone, which were divided according to economic development and geographical location in China[27] (Fig. 1). Then, we ran separate regression models with resistance isolates for each bacterial group (CRPA, 3GCRKP, 3GCREC, and MRSA) as the dependent variable.

The independent variables in the regression analyses were selected according to our hypothesis and previous research[13, 14, 16-20]. We assumed that ABR level was associated with finishing secondary education, GDP per capita, OOP health expenditure, number of beds per 1,000 population, number of physicians per 1,000 population, access to water source, and number of public toilets per 10,000 population.

GDP per capita in 2018 US dollars was log transformed to account for non-linearity. All tests were two-tailed, and *P*-values less than 0.05 were considered significant. All statistical analyses were conducted using STATA version 14.

Results

The mean prevalence of ABR for the dependent variable aggregate resistance in 30 provinces was 36.0% (standard deviation (SD): 6.3%), and for CRPA, 3GCRKP, 3GCREC, and MRSA were 20.8% (6.5%), 33.8% (9.5%), 56.4% (5.4%), and 32.9% (8.4%), respectively. The mean aggregate resistance in eastern, central, and western economic zone were 38.5% (5.8%), 37.2% (7.2%), and 32.5% (4.4%), respectively. The average percentage of population finishing secondary education GDP per capita, percentage of OOP health expenditure, number of beds per 1,000 population, number of physicians per 1,000 population, percentage of population access to water source, and number of public toilets per 10,000 in 30 provinces were 69.0% (8.6%), \$14,813 (\$1.5), 29.2% (4.9%), 5.4 (0.8), 6.3 (1.2), 98.0% (1.9%), and 2.9 (1.1), respectively, in eastern economic zone were 75.0% (7.6%), \$21,306 (\$1.5), 27.2% (5.8%), 5.1 (0.8), 6.8 (1.5), 99.4% (0.8%), and 2.7 (0.8), respectively, in central economic zone were 70.6% (3.9%), \$12,305(\$1.2), 32.6% (3.5%), 5.5 (0.7), 5.7 (0.7), 97.3% (2.1%), and 2.9 (0.8), respectively, and in western economic zone were 61.8% (6.7%), \$11,787(\$1.4), 28.6% (3.4%), 5.8 (0.7), 6.3(0.9), 97.0% (1.8%), and 3.3 (1.4), respectively (Table 1).

Table 2 shows estimates from regression with percent aggregate resistance in 30 provinces and in three different economic zones as the dependent variables. First, we noted a significantly negative correlation between ABR and hospital bed density (95% confidence interval (CI): -4.679~-4.581, P<0.000), and between ABR and physician density (95% CI: -3.073~-0.477, P=0.008). None of other variables were significant. Then, we found an inverse relation between hospital bed density and ABR level in eastern economic zone; an negative correlation between education and ABR level but an positive correlation between OOP health expenditure in central economic zone; and an inverse relation between physician density and ABR and an positive relation between access to water source and ABR level in western economic zone (Table 2).

Table 3 shows estimates from regression with percent resistant isolates for each separate bacteria as the outcome variables. We found that an increase in hospital bed density resulted in significantly decreases in 3GCRKP, 3GCREC, and MRSA prevalence, and an increase in physician density resulted in significantly decrease in CRPA prevalence. An increase in GDP per capita resulted in a decrease in CRPA level, however, an increase in MRSA level. In addition, we explored a positive relation between OOP health expenditure and CRPA level, and between access to water source and 3GCRKP level (Table 3).

Discussion

Our results indicated that higher hospital bed density and physician density were significantly associated with lower levels of ABR. Surprisingly, higher GDP per capita was significantly associated with lower CRPA level, however, lower GDP per capita was associated with lower MRSA level. Higher OOP health expenditure was associated higher CRPA level, but no significant associations between OOP expenditure and other resistant bacteria were found. Also surprising was that ABR prevalence in central economic zone was significantly negatively associated with education, and positively associated with OOP health expenditure, however, these associations were not found in eastern economic zone and western economic zone. To our best of knowledge, it is the first cross-regional examination of the societal economic determinants of level of ABR using panel data modelling within countries, including China[15]. It is also the first study to compare the predictors of ABR in in different bacteria and three different economic zone in mainland China.

This study found that increasing the number of physicians could significantly reduce ABR prevalence, which was similar to the finding from previous studies[28]. It was reported that non-prescription antibiotic dispensing at pharmacies was an issue with 48.5% for diarrhoea and 70.1% for adult acute upper respiratory tract infection nationwide in China[29], therefore, increasing number of educated physicians might help curb non-prescription of dispensing of antibiotics, further decrease ABR. It was also reported that physician-targeted interventions were effective to decrease antibiotic prescription[30] and irrational use of antibiotics by physicians[31], therefore, the increased allocation of physicians could better optimize antibiotic therapy, which were conducive to containing of ABR.

We found that number of hospital beds was significantly associated with lower ABR rate, which was not reported in other studies. However, it was well known that hospital beds were potential reservoirs of bacteria in hospitals, and preventing bed contamination might help prevent dissemination of ABR[32]. It was noted that patients either colonized or infected with ABR bacteria must be isolated to prevent spread of the ABR to other patients and the closer the contact the easier acquired[32]. Larger number of hospital beds per 1,000 population denoted that more patients could timely receive health service with physicians' prescription, and it was also associated with better environmental sanitation and better health infrastructure, which might reduce the prevalence of ABR.

There were no previous studies exploring the association between GDP per capita and ABR level within countries, but it was reported that a negative and significant correlation between GDP per capita and ABR prevalence existed at the global level[16]. Surprisingly, this study showed that there was a negative relation between GDP per capita and CRPA level but a positive relation between GDP per capita and MRSA level. Poor environmental sanitation, inappropriate antibiotic usage, low vaccination rates, poor laboratory and infection control capacity in the low/mid-income region might ignore the problem of ABR and lead to increased ABR level[16, 19]. However, some studies reported that population with higher GDP were associated with higher antibiotic usage, which further resulted in higher ABR level[13, 33]. These different findings might be related to antibiotic stewardship and surveillance of antibiotic use on different levels.

OOP health expenditure were positively associated with CRPA level in mainland China, which was similar with the findings that a higher proportion of OOP health expenditure was associated with higher levels of ABR across countries[13, 14, 17]. Unsurprisingly, supplier-induced demand was an important determinant factor for excess use of health care[34, 35]. Patients with higher OOP health expenditure might consume expensive and advanced antibiotics, such as carbapenems, which resulted in higher CRPA prevalence.

Education level could reduce the self-medication and over-the-counter antibiotic consumption, further to decrease ABR prevalence[36], which was consistent with our finding. However, why education was a positive factor for ABR only in central economic zone needed further exploration, in addition, the effect of access of water source on ABR also needed to be studied in the future.

There is no one comprehensive, universally agreed definition of governance[37], and practices defined as governance might vary depending on country and context[38]. Because of data gaps, the indicator of governance was difficult to measure, so we did not include it. In the previous studies, the focus had been mainly on antibiotic consumption as the most important factor contributing to ABR[14, 18]. Although we did not assess the association between antibiotic consumption and ABR in this study, because adequate data is lacking, the findings in other studies confirmed that many social and economic factors are of more importance than the antibiotic consumption in explaining the diversity in the level of ABR in different region[14, 18].

There are some limitations in our study. First, some confounding factors both in the human, agricultural sectors and the environment that might correlate with ABR level could not be collected from each province, such as temperature, antibiotic consumption, governance, due to inadequate data. Relevant studies including the above socioeconomic factors using real-world data are needed in the future. Second, it was presented with a relationship between ABR level and socio-economic factors, but not a definitive evidence of ABR mechanism. In addition, we acknowledge the ABR level from CARSS as the better data to represent the provincial level presently, however, it could not apply to primary care facilities.

Conclusion

Our study found that higher hospital bed density and physician density were significantly associated with lower levels of ABR. The issue of ABR was also related to socioeconomic factors such as GDP per capita, OOP health expenditure, education, which might depend on different resistant bacteria or different economic zones. Our study highlights that measures increasing hospital beds and physicians allocation to curb ABR should be implemented. Besides, intervention measures tackling the development and spread of ABR in China must better recognize and address the importance of social and economic determinants.

Declarations

Ethics approval, guidelines and consent to participate

Our data were collected from China Antimicrobial Resistance Surveillance System and China Statistical Yearbook, so ethics approval, guidelines and consent to participate were not applicable.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in Tables, Figures.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

XZ and JC participated in the conception and design of this study, data collection, data analysis, and interpretation of data, drafted and revised the manuscript. XS participated in the conception and design of the study and helped in the revising the manuscript. SG and CSL performed the data analysis, and interpretation of data, drafted and revised the manuscript. QS participated in the conception, design of the study, data collection and interpretation of data, and drafted and revised the manuscript. All authors read and approved the final manuscript.

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Abbreviations

ABR: Antibiotic resistance; SDGs: Sustainable development goals; AMR: Antimicrobial resistance; MDR: Multidrug resistant; WHO: World Health Organization; 3GCRKP: 3rd generation cephalosporin-resistant *Klebsiella pneumoniae*; 3GCREC: 3rd generation cephalosporin-resistant *Escherichia coli*; MRSA: Methicillin-resistant *Staphylococcus aureus*; CARSS: China Antimicrobial Resistance Surveillance System; OOP: Out of pocket; GDP: Gross domestic product; CI: Confidence interval

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Tables

Table 1. Variables and measures

Variables	30 provinces		Eastern economic zone		Central economic zone		Western economic zone	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CRPA, %	20.8	6.5	25.0	5.5	19.8	5.6	17.3	5.8
3GCRKP, %	33.8	9.5	37.0	7.8	37.3	10.2	28.0	7.7
3GCREC, %	56.4	5.4	56.5	5.2	58.7	6.0	54.6	4.5
MRSA, %	32.9	8.4	35.6	8.5	32.9	9.2	30.2	6.9
Aggregate resistance, %	36.0	6.3	38.5	5.8	37.2	7.2	32.5	4.4
Education, % of finishing secondary education	69.0	8.6	75.0	7.6	70.6	3.9	61.8	6.7
GDP per capita, $ log	14813	1.5	21306	1.5	12305	1.2	11787	1.4
OOP health expenditure, % of total health expenditures	29.2	4.9	27.2	5.8	32.6	3.5	28.6	3.4
Hospital bed density, number of beds per 1,000 population	5.4	0.8	5.1	0.8	5.5	0.7	5.8	0.7
Physicians density, number of physicians per 1,000 population	6.3	1.2	6.8	1.5	5.7	0.7	6.3	0.9
Access to water source, % of population	98.0	1.9	99.4	0.8	97.3	2.1	97.0	1.8
Number of public toilets per 10,000 population	2.9	1.1	2.7	0.8	2.9	0.8	3.3	1.4

CRPA: carbapenem-resistant *Pseudomonas aeruginosa*; 3GCRKP: 3rd generation cephalosporin-resistant *Klebsiella Pneumoniae*; 3GCREC: 3rd generation cephalosporin-resistant *Escherichia coli*; MRSA: methicillin-resistant *Staphylococcus aureus*; SD: standard deviation; CI: confidence interval; GDP gross domestic product; OOP: out-of-pocket

Table 2. Effect of variables on the aggregate resistance (including CRPA, 3GCRKP, 3GCREC, and MRSA) among 30 provinces, eastern economic zone, central economic zone, and western econo zone in mainland China (excluding Tibet autonomous region)

Variables	30 provinces					Eastern economic zone					Central economic zone					Western economic zone				
	B	SE	P-value	95% CI		B	SE	P-value	95% CI		B	SE	P-value	95% CI		B	SE	P-value	95% CI	
Education, % of finishing secondary education	-0.08	0.12	0.500	-0.31	0.15	-0.02	0.18	0.893	-0.38	0.33	-1.92	0.36	<0.000	-2.62	-1.22	0.07	0.12	0.559	-0.17	0.3
GDP per capita, log	0.74	1.78	0.679	-2.79	4.28	-1.09	3.03	0.718	-7.03	4.84	-15.89	11.28	0.159	-38.00	6.22	1.30	2.41	0.593	-3.58	6.1
OOP health expenditure, % of total health expenditures	0.10	0.10	0.324	-0.10	0.29	-0.06	0.22	0.795	-0.49	0.38	0.73	0.29	0.013	0.16	1.31	0.09	0.13	0.484	-0.17	0.3
Hospital bed density, number of beds per 1,000 population	-3.13	0.78	<0.000	-4.68	-1.58	-3.20	1.28	0.012	-5.70	-0.70	-3.24	2.21	0.143	-7.57	1.10	1.44	0.83	0.092	-3.12	0.2
Physician density, number of physicians per 1,000 population	-1.78	0.66	0.008	-3.07	-0.48	-1.35	1.16	0.244	-3.62	0.92	5.48	3.12	0.079	-0.63	11.58	-3.25	0.71	<0.000	-4.69	-1.
Access to water source, % of population	0.26	0.18	0.145	-0.09	0.60	1.15	0.78	0.143	-0.39	2.68	-0.23	0.43	0.585	-1.07	0.60	0.56	0.20	0.009	0.15	0.9
Number of public toilets per 10,000 population	0.14	0.25	0.574	-0.35	0.63	0.16	0.46	0.727	-0.75	1.07	0.65	1.31	0.620	-1.92	3.22	0.06	0.32	0.851	-0.59	0.7
(Constant)	37.60	20.98	0.076	-3.96	79.17	-41.75	77.67	0.591	-193.98	110.48	231.06	77.90	0.003	78.38	383.74	-6.68	24.11	0.783	-55.53	42
P-value	<0.000					0.74					<0.000					<0.000				
R^2	0.746					<0.000					0.456					0.842				
Hausman (P-value)	10.23 (P=0.1762) Random effect model					14.81 (P=0.0386) Fix effect model					213.67 (P<0.000) Fix effect model					8.86 (P=0.2626) Random effect model				

CRPA: carbapenem-resistant *Pseudomonas aeruginosa*; 3GCRKP: 3rd generation cephalosporin-resistant *Klebsiella Pneumoniae*; 3GCREC: 3rd generation cephalosporin-resistant *Escherichia c* MRSA: methicillin-resistant *Staphylococcus aureus*; SE: standard error; CI: confidence interval; GDP gross domestic product; OOP: out-of-pocket

Table 3. Effect of variables on the CRPA, 3GCRKP, 3GCREC, and MRSA among 30 provinces in mainland China (excluding Tibet autonomous region)

Variables	CRPA					3GCRKP					3GCREC					MRSA				
	B	SE	P-value	95% CI		B	SE	P-value	95% CI		B	SE	P-value	95% CI		B	SE	P-value	95% CI	
Education, % of finishing secondary education	0.03	0.16	0.872	-0.28	0.33	0.11	0.20	0.577	-0.28	0.51	-0.22	0.14	0.111	-0.49	0.05	-0.15	0.15	0.338	-0.44	0.15
GDP per capita, log	-6.97	2.43	0.005	-11.77	-2.16	1.56	3.10	0.616	-4.58	7.70	0.84	2.13	0.695	-3.38	5.05	8.34	3.28	0.011	1.91	14.78
OOP health expenditure, % of total health expenditures	0.28	0.14	0.043	0.01	0.54	-0.34	0.17	0.052	-0.68	0.00	0.03	0.12	0.835	-0.21	0.26	0.29	0.17	0.077	-0.03	0.62
Hospital bed density, number of beds per 1,000 population	-1.33	1.06	0.213	-3.43	0.78	-5.76	1.36	<0.000	-8.45	-3.07	-3.94	0.93	<0.000	-5.79	-2.10	-3.57	1.10	0.001	-5.72	-1.42
Physician density, number of physicians per 1,000 population	-2.12	0.89	0.019	-3.89	-0.36	-0.88	1.14	0.441	-3.13	1.38	-1.37	0.78	0.083	-2.92	0.18	-1.24	1.04	0.231	-3.27	0.79
Access to water source, % of population	0.28	0.24	0.241	-0.19	0.75	0.62	0.30	0.044	0.02	1.22	-0.14	0.21	0.518	-0.55	0.28	0.36	0.31	0.245	-0.24	0.96
Number of public toilets per 10,000 population	-0.17	0.34	0.614	-0.84	0.50	0.08	0.43	0.862	-0.78	0.93	0.04	0.30	0.893	-0.55	0.63	0.41	0.45	0.358	-0.47	1.29
(Constant)	38.21	28.51	0.183	-18.29	94.70	4.47	36.42	0.903	-67.69	76.63	110.00	25.03	<0.000	60.40	159.59	-14.41	33.82	0.670	-80.70	51.89
P-value	<0.000					<0.000					<0.000					<0.000				
R^2	0.598					0.473					0.717					0.492				
Hausman (P-value)	8.78 (P=0.2686) Random effect model					11.14 (P=0.1328) Random effect model					5.39 (P=0.6125) Random effect model					27.68 (P=0.0003) Fix effect model				

CRPA: carbapenem-resistant Pseudomonas aeruginosa; 3GCRKP: 3rd generation cephalosporin-resistant Klebsiella Pneumoniae; 3GCREC: 3rd generation cephalosporin-resistant Escherichia coli MRSA: methicillin-resistant Staphylococcus aureus; SE: standard error; CI: confidence interval; GDP gross domestic product; OOP: out-of-pocket

Figures

Figure 1

Three economic zones in China. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.