

Mass Drug Distribution Strategy Efficacy for Schistosomiasis Control in Mali (West Africa)

Abdoulaye Dabo (✉ adabo@icermali.org)

Department of Epidemiology of Infectious Diseases, Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako

Mouctar Diallo

Department of Epidemiology of Infectious Diseases, Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako

Privat Koba Agniwo

Laboratoire de Parasitologie et d'Ecologie Parasitaire, Faculté des Sciences et Techniques, Université Abomey-Calavi

Salim Danté

Department of Epidemiology of Infectious Diseases, Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako

Assitan Traoré

Department of Epidemiology of Infectious Diseases, Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako

Sidy Diawara

Department of Epidemiology of Infectious Diseases, Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako

Boubou Doucouré

Department of Epidemiology of Infectious Diseases, Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako

Research

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Abstract

Background -Schistosomiasis is a water-based parasitic disease caused by blood flukes of the genus *Schistosoma*. Mass Drug Distribution (MDD) with Praziquantel is periodically recommended in schistosomiasis-endemic countries to prevent morbidity. In Mali, schistosomiasis still remains endemic, especially in Senegal and Niger rivers basin, although the strategy has been adopted since 2005. Our study aimed to assess the impact of annual school-based MDD.

Materials and methods – The study was conducted at twelve sentinel sites across Kayes and Koulikoro regions. A cross-sectional study design was performed in April 2018 after four-or five-years post treatment with praziquantel (PZQ) depending on the statute of sites. At baseline (2014-2015) and for the control year (2018), 734 (386 boys and 347 girls) and 1708 (844 boys and 864 girls) school children of 7-14 years of age, were successfully examined respectively. Infections with *Schistosoma haematobium* and *S. mansoni* were diagnosed with the urine filtration and the Kato-Katz method respectively.

Results – From eight schools treated in 2014, the four annual rounds of MDD with PZQ were associated with a significant decrease in *S. haematobium* prevalence in five sites ($p<0.001$) and a significant increase in one site ($p<0.001$). Of them, the prevalence of high-intensity (≥ 50 eggs/10mL of urine) significantly decreased in four previous sites but not in Diakalele where it increased ($p<0.001$). In all the four sites treated in 2015, *S. haematobium* prevalence increased significantly in Kokoun and Samaya ($P<0.05$). The heavy infection increased slightly in Dougourakoro and Samaya ($P>0.05$). The prevalence of *S. mansoni* significantly decreased in three sites ($p<0.001$), increased in three and remains zero in the six others sites.

Conclusion – Our findings show that five of the twelve sentinel sites have achieved the criterion of elimination of schistosomiasis due to *Schistosoma haematobium* as a major public health problem (Prevalence of heavy infection $<1\%$); three have achieved the criterion of morbidity control (Prevalence of heavy infection $<5\%$), whereas two sites remain confined below the control criterion. These results call for a strong improvement in the therapeutic coverage associating, education and provision of safe water, sanitation and hygiene to interrupt the transmission cycle of the schistosome.

Introduction

Schistosomiasis is one of the most important human helminthiasis in terms of morbidity and mortality [1]. The disease is endemic in many developing countries mainly affecting children, farmers, and women who are frequently in contact with waters where live snail intermediate hosts. The disease affects more than 250 million people and it is estimated to have caused 1.4 million disability-adjusted life years in 2017 [2, 3].

Referring to the results of the national surveys carried out by the PNLSH in 1984–1989, then in 2004–2006, schistosomiasis due to *Schistosoma mansoni* and *S. haematobium* and Soil-transmitted helminths (STH) are endemic throughout the territory [4]. Recommended by WHO from 1970–1980 [5, 6], large-scale chemotherapy to control morbidity with 75% of coverage rate in school-age children have been formally considered as an essential public health strategy to combat schistosomiasis by the fifty Fourth World Health Assembly (WHA 54.19) in 2001 [7]. As indicated in the WHO guidelines, mass drug distribution strategy with PZQ and Albendazole targeting school-aged children (SAC) and at-risk adults has been implemented in Mali since 2004 to attain the WHA54.19 recommendation with technical and financial support from the Schistosomiasis control Initiative (SCI), USAID/RTI/HKI, Organization for the development of the Senegal River (OMVS) and Sight savers in all endemic regions [8, 9]. Since that date, an annual or bi-annual treatment campaign carried out in endemic areas (Ségou, Mopti, Koulikoro and Kayes regions) based on the current threshold of prevalence as recommended by WHO. However, it is appropriate to regularly assess its impact particularly in sentinel sites. The current study was carried out with a view to a global fight against malaria and schistosomiasis to accelerate the achievement of the WHO-advocated sustainable development goals adopted in 2015. It aimed to assess the impact of drug mass distribution (DMM) on the prevalence and intensity of schistosomiasis and STH in sentinel sites identified by Schistosomiasis National Control Program (PNLSH).

Materials And Method

Study site

The study was carried out in twelve villages spread over six districts: Bafoulabé, Diéma and Kayes (in Kayes region); Kalabancoro, Koulikoro and Nara (in Koulikoro region) (Figure 1) [10]. The river system consists of Senegal River and its tributaries in Kayes region, and Niger River and its tributaries in Koulikoro region. It was also composed by the lacustrine systems including Lac Magui and the pools of Doro and Goumbaye. The economic life in the study area is dominated by agricultural and pastoral activities which occupy more than 80% of the population. The health system is precarious and characterized by high infant and maternal mortality, low life expectancy, chronic malnutrition of children and inadequate infrastructure and equipment [11]. The study site is recognized as a schistosomiasis highly-endemic area [12, 13, 14].

We carried out an observational cross sectional study with two passages: the first basic pass was conducted in December 2014-2015 and the second in April 2018. All these passages were devoted to the analysis of stool and urine analysis.

The school-aged children (6-14 years old), were primarily identified as study population.

Sampling design and sample size calculation

Sample size was calculated based on *Schistosoma haematobium* prevalence (the most frequent schistosome species) described in 2009. The assumed precision around the prevalence rates to be measured was 6% with an alpha risk of 5%. We added 10% to this sample size to compensate for the loss sight. Schwartz formula was used to calculate the minimum sample size.

Techniques and Data Collection Procedures

All urine samples were collected between 10 h and 14 h in the field, by trained laboratory technicians to determine prevalence and intensity of *Schistosoma haematobium* infection. From each subject, urine was collected in a properly labeled specimen container. Filtration technique was employed to analyze the samples. A total of 10 mL urine was taken from each specimen bottle after mixing it. The mixed sample was filtered through a Whatman filter (CAT N° 1001-025, 25 mm) which was stained with 3% ninhydrin solution, before sending them in Bamako to be examined under a microscope using $\times 10$ magnifications for *S. haematobium* egg characteristics. One single stool sample from each child was collected and examined immediately on fields with the standard Kato-Katz method for *Schistosoma mansoni* and STH eggs. The intensity of *S. haematobium* infection was expressed as number of eggs per 10 ml of urine and was classified into three categories : i) no egg ; ii) slight (1–49 eggs per 10 ml of urine); and iii) heavy (≥ 50 eggs per 10 ml of urine). The intensity of *S. mansoni* intensity was expressed as eggs per gram of faeces (pg) and classified into four classes: i) no egg; ii) 1–99 EPG (eggs per gram of stool); iii) 100–399 EPG; and iv) ≥ 400 EPG [11]. To ensure quality control, 10% of the filters and slides were randomly selected and recounted by another senior biologist. At the end of the study, all the positive children were treated with PZQ (40 mg/kg body weight) according to the Schistosomiasis and STH National Control Program in Mali (PNLSH).

Mass drug administration

The preventive chemotherapy strategies recommended by WHO has been adopted by the Mali's national schistosomiasis control program since 2004 [11, 12]. To perform this strategy, a MDD campaign is designed each year and school and health authorities at regional, district and community school personal are mobilized. Drugs are distributed through the school-based delivery in schools targeting school-going children. This drug delivery strategy is carried out by trained school teachers. PZQ tablets (600 mg) were delivered using the WHO dose pole method to determine the dosage for each child [13].

Statistical analysis

Data were double entered using Access and Prevalence, and the intensity of infection with 95% confidence intervals was calculated using SPSS (IBM, version 19). Differences in proportions were tested using the chi-square test or Exact Fisher test depending on the data. P values less than 0.05 were considered to be significant.

Ethical approval

Before doing the survey at each sentinel school, informed verbal consent was first obtained from the school teachers at schools prior to the recruitment of children. These were recorded by the survey team leader. During recruiting, informed verbal consent was obtained from each child with the presence of school teachers. Any children who did not want to participate were free to leave without prejudice to its support for the treatment. The proposal was reviewed and approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Pharmacy and Dentistry, University of Bamako.

Results

In April 2018, 1836 schoolchildren were successfully examined with 733 girls. They were aged from 7 to 14 years with an average age of 9 ± 1.970 years.

As shown in the table I, *Schistosoma haematobium* prevalence in 2014 varied from zero in Boudjiguire to 96.8% in Babaroto. In 2018, the prevalence increased to 11% in Boudjiguire while it significantly decreased to 33.95% in Babaroto ($p < 0.001$). Globally, from 2014 to 2018, the prevalence significantly decreased in Babaroto, Saorane, Dianguirde, Torodo and Koussane ($p < 0.001$), significantly increased in Dianguirde ($p = 0.004$) and in Torodo ($p < 0.001$), but not significantly in Kolly ($p = 0.28$) and Boudjiguire ($p = 0.011$). From In 2015 to 2018, the prevalence increased but not significantly except in Samaya ($p = 0.006$) and Kokoun ($p = 0.02$).

Between 2014 to 2018, there was a significant reduction in *S. haematobium* prevalence of heavy infection in the districts of Bafoulabe (Babaroto and Saorané) and Diéma (Dianguirde et Torodo) ($p < 0.001$) (Table II). In Diakalele, the prevalence of heavy infections raised to 19.21% from 2014 to 2018 ($p < 0.001$). In Kolly and Bougoudjire, prevalence remained zero. From 2015 to 2018, the prevalence of heavy infections slightly increased in Dougourakoro and Samaya, slightly decreased in Kokoun. In terms of the results obtained after the treatment campaigns on the intensity of disease, five sentinel sites (Saorané, Kéniégué, Samaya, Kolly and Boudjiguiré) have achieved the criterion of elimination of the schistosomiasis as Major public health problem (prevalence of heavy infection $< 1\%$); five sites (Dianguirde, Torodo, Koussane, Dougourakoro and Kokoun) have achieved the criterion for the control of morbidity (prevalence of high excretors $< 5\%$) and that two sites (Babaroto and Diakalele) remain confined below the control criterion.

As shown by table II, the prevalence of *S. mansoni* significantly decreased in three sites (Babaro, Dougourakoro and kokoun) ($p < 0.001$), but it increased in Keniege, Samaya and Kolly ($p > 0.05$).

Discussion

The study of the impact of repeated mass distribution of Praziquantel at sentinel sites in the two regions (Kayes and Koulikoro) covered children aged 6 to 14 years. This target population has been chosen in regard to the peak prevalence and intensity of schistosomiasis and STH observed in this age group [11]. The priority given to this age group is based on the fact that the level of infection observed in this population reflects the impact of several repeated PZQ mass treatment rounds after the implementation of a control program. In relation to the participation rate in study, highly infected children were more involved in the study hoping to be treated. On the other hand, children with poor memories of side effects of PZQ were reluctant to provide stool or urine samples.

Regardless of the increased prevalence of *S. haematobium* in the site of Diakalele (Table I), significant reduction in both overall prevalence of infection was seen in 2018 in five sites (Babaroto, Saorane, Dianguirde, Torodo and Koussane) ($p < 0.001$), and in intensity of infection in the previous sites except in Koussane (Tables I & II). One concern is the MDD coverage and quality both in 2014-2015 and in general the result of the positive evolution of MDD-PZQ

coverage in Mali, particularly among school-age children. That means the sites associated with high prevalence and/or ovular excretion rates were those where the MDD coverage was zero or very low at baseline. Indeed, the WHO guidelines in force recommend an annual frequency of mass distribution of praziquantel in areas of high endemicity against a frequency of treatment every two years for areas of medium prevalence [12]. This trend is confirmed by the results of Malian Schistosomiasis Control Program which showed a significant reduction from 26.4 to 6.8% in 1999; 14.2 to 4.8% in 2004 and 5.4 to 2.4% in 2010 [13] and also to Sotuba where it went from 86.77; 100 and 94% respectively in 2005, 2008, 2009 to 8.7% in 2010 [14].

In the Sahelian environment such as Burkina Faso and Niger, one round of MDD significantly reduced *S. haematobium* prevalence to a very low level, which remained low for 2–3 years [15, 16, 17]. However, along the Niger River in Segou district (Mali), one year after treatment the *S. haematobium* prevalence bounced back to nearly the pre-treatment level [18], suggesting high level of transmission and frequent water contact activities in such locations. A similar situation was seen in Uganda where *S. mansoni* prevalence also showed less reduction in highly endemic areas along the lake shores after repeated MDD [19]. On other hand, in the urban area of Bamako district, one round of MDD has resulted in mitigated results in reducing or increasing *S. haematobium* prevalence [20].

As stated by WHO guidelines [21], five sites Saorane, Kéniégue, Samaya, Kolly and Boudjiguire have achieved the criterion of elimination of the schistosomiasis as major public health problem (prevalence of high excretors < 1%). It should be noted, however, that four of these sites already had zero prevalence in 2014; four sites (Dianguirde, Torodo, Koussane et Kokoun) have achieved the criterion for the control of morbidity (prevalence of high excretors < 5%). The reduction of the prevalence of heavy infection is important as it is well known that the severity of morbidity caused by schistosomiasis is closely related to the intensity of infection. In many national control programs, cases of significant morbidity were avoided or reverted due to MDD. This is in line with what was achieved in other national MDD programs especially in both East and West Africa through preventive chemotherapy [15, 19, 22,23, 24]. However, beside the heavier infections, there still exist a significant proportion of children with relatively low intensity of infections (1-49 eggs per 10 ml of urine), not including those undetected due to the low sensitivity of the urine filtration technique. This is the case of the four sites we described above (Kéniégue, Samaya, Kolly and Boudjiguire) where no egg excretory child was observed in 2014-2015. Such light infections have long been overlooked in terms of the morbidity consequences, while recent findings suggest that light infections can cause considerable morbidity due to anaemia, chronic pain, diarrhoea, exercise intolerance and undernutrition [25, 26].

The objective in all cases was to reduce or even to prevent morbidity due to schistosomiasis by regular treatment according to the WHO recommendations [11, 27] as it was conducted in the sentinel sites. However, the persistent infection in many sites (Table 1) emphasizes the need for a more effort associating with comprehensive control measures including preventive chemotherapy, intensified case management, vector and intermediate host control, veterinary public health at the human-animal interface, education and provision of safe water, sanitation and hygiene [28, 29]. Another hypothesis in addition to the low impact of treatment would be to the presence of hybrid strains of *Schistosoma haematobium* /*S. bovis* or *S. haematobium*/*S. curassoni*) which have been found to influence parasite establishment, growth, maturation, reproductive success, and/or drug efficacy [30, 31]. Indeed, the first cases of a human infection by *Schistosoma haematobium*/*S. bovis* hybrid have just been observed from Belgian tourists returning from the Plateau Dogon in central Mali [32]. Cases of schistosome hybridizations had already been described in Niger, Benin, Senegal and Côte d'Ivoire [33-37], and all these cases are linked to the cohabitation of animal and human schistosomes made possible by the breeding, a widely practiced activity that increases the genes crossing across the human or animal definitive host. The study area especially the Kayes region, an endemic for *Schistosoma haematobium* and also an excellent breeding area of cattle, sheep and goats offers optimal conditions for genes crossing. These together suggest that molecular and epidemiological studies are needed to identify the strains of schistosomes circulating there and what role they play in human and animal pathology. It should be noted that current results are limited due to the lack of the results of MDD coverage rate and data from intensity of *Schistosoma mansoni* infections from the Schistosomiasis National Control Program in Koulikoro region involving Dougourakoro, Kokoun, Keniegué, Samaya, Boudjiguire and Kolly.

Conclusion

MDD with PZQ has been conducted in Mali since 2005 and several rounds of treatment have been delivered. Sentinel site surveys in Kayes and Koulikoro regions showed that one site in the endemic area of Kayes region has achieved the criterion of elimination of the schistosomiasis as Major public health problem; five sites have achieved the criterion for the control of morbidity and two sites remain confined below the control criterion. These results call for a strong improvement of the therapeutic coverage in addition to intensified case management, vector and intermediate host control, veterinary public health at the human-animal interface, awareness, education and provision of safe water, sanitation and hygiene to interrupt the transmission cycle of the parasite.

List Of Abbreviations

EPG : Egg per gram

HKI : Helen Keller international

IBM : International Business Machines Corporation

IRB : International Review Borad

MDD : mass drug distribution

OMVS : Organization of for the Development of the Senegal River

PLNSH : Schistosomiasis National control Program

PZQ : Praziquantel

RTI : Research Triangle Institute

SAC : School Age Children

SCI : Schistosomiasis Control Initiative

STH : Soil Transmitted Helminth

SPSS : Statistical Product and Service Solutions

USAID : US Agency for international Development

WHA : World Health Assembly

WHO : World Health Organization

Declarations

Ethics Approval and consent for participation

An ethics approval is attached as file to the manuscript.

Consent for publication

No applicable

Availability of data and materials

Data and materials are available.

Competing interests

the authors assure that they have no competing interests with regard to this article.

Funding

The authors are from Mali (West Africa), a low-income country.

Authors' contributions

Author AD, DM participated in the conception and design of the study, data analysis, and interpretation. They also contributed to the writing of the paper, and assured the coordination of the trial. They have reviewed the final version. Authors AP, DS, DS, and DB participated in the design of the study and onsite execution by collecting and analyzing the data. They also assisted in praziquantel distribution and the assessment of side effects.

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Tables

Table I: Variation *Schistosoma haematobium* prevalence in the sentinel schools/Villages in the regions of Kayes and Koulikoro from 2014- 2015 to 2018.

Périodes / Sites sentinelles	2014	2015	2018	Diff. (%)	p
Babaroto	96.8 (62)		62.8 (78)	33.95	<0.001
Saorané	70.0 (60)		31.5 (108)	38.51	<0.001
Dianguiré Torodo	76.7 (60)		54.3 (184)	22.32	0.004
	80,0 (60)		39.6 (169)	40.36	<0.001
Diakalèle Koussané	31.7 (63)		84.1 (226)	- 50.55	<0.001
	65.0 (60)		32.1 (109)	32.89	<0.001
Dougourakoro Kokoun		5.0 (60)	7.7 (65)	- 0.03	0.8036
		16.7 (60)	34.4 (160)	- 17.71	0.02
Kéniégué Samaya		1.6 (63)	7.4 (214)	- 5.89	0.16
		1.6 (63)	15.9 (183)	- 14.26	0.006
Kolly Boudjiguiré	8.3 (60)		15.5 (103)	- 7.2	0.28
	0 (63)		11.9 (109)	- 11.9	0.011

* Diff. (%): Difference

Table II: Variation of the intensity of heavy infections of *Schistosoma haematobium* in sentinel sites of Kayes and Koulikoro between 2014- 2015 and 2018.

Période Sites sentinelles	2014	2015	2018	Diff. (%)*	p
Babaroto	29.0 (18/62)		9.0 (7/78)	20.06	0.004
Saorané	13.3 (8/60)		0 (0/108)	13.0	0.0004
Dianguiré Torodo	26.7 (16/60)		3.3 (6/184)	23.41	<0.001
	25.0 (15/60)		4.7 (8/169)	20.27	<0.001
Diakalèle Koussané	1.6 (1/63)		20.8 (47/226)	- 19.21	0.0007
	8.3 (5/60)		1.8 (2/109)	6.5	0.10
Dougourakoro Kokoun		0.0 (0/60)	1.1 (1/65)	- 1.5	1
		3.3 (2/60)	1.9 (3/160)	1.46	0.89
Kéniégué Samaya		0.0 (0/63)	0 (0/214)	0	–
		0.0 (0/63)	0.5 (1/183)	- 0.55	1
Kolly	0.0 (0/60)		0 (0/103)	0	–
Boudjiguiré	0.0 (0/60)		0 (0/109)	0	–

* Diff. (%): Difference

Figures

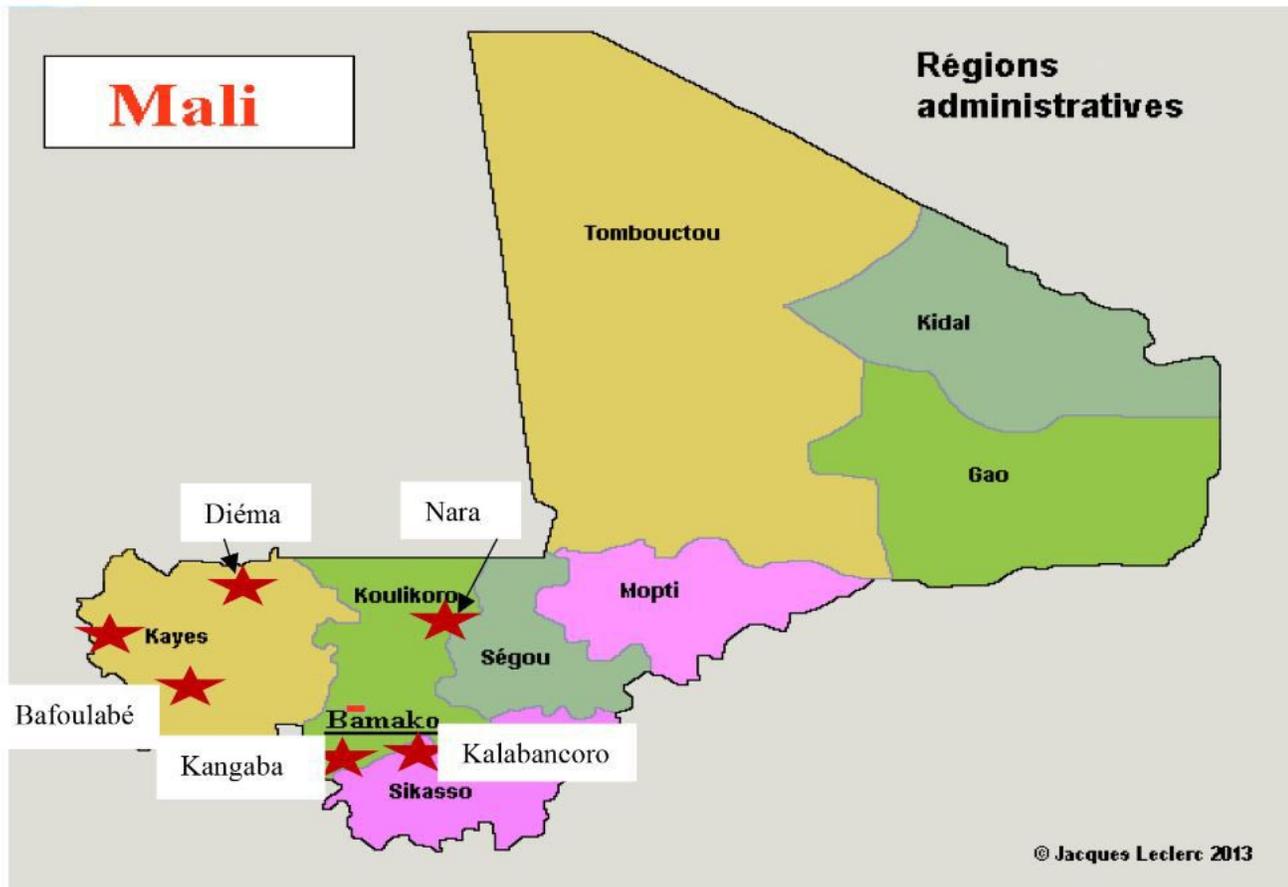


Figure 1

The map of Mali modified showing the localization of study sites (*), with the modified image (10. <https://www.google.ml/search?q=le+Mali:+climattett+régions+naturelles>, consulted 11/02/2020) 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.