



## Taeniosis and cysticercosis in Serbia, 1990–2018: Significance of standard of living

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### ABSTRACT

**Objectives:** As is the case for all of Southeast Europe, Serbia is an area traditionally endemic for *Taenia saginata* and *Taenia solium* infections. This study was performed to analyse the epidemiological data on taeniosis and cysticercosis in Serbia for the period 1990–2018.

**Methods:** Data on cases of *T. saginata* and *T. solium* infection were collected via a systematic search of published articles, the grey literature, and official reports, as well as by performing clinical observational studies of patients treated in the departments for infectious diseases of hospitals and university clinics in Serbia.

**Results:** A total of 212 cases of taeniosis were reported, all between 1997 and 2004 when taeniosis was notifiable (incidence range 0.04–0.9/100 000 population/year). From 1990 to 2018, 170 cases of cysticercosis (all but one of neurocysticercosis), were registered (incidence range 0–0.29/100 000 population/year), with a strong decrease since 2000 and a single case in the last 9 years. The annual number of cases of both taeniosis (Pearson's  $r = 0.914$ ,  $p = 0.001$ ) and cysticercosis (Pearson's  $r = 0.582$ ,  $p = 0.014$ ) correlated with the consumer price index.

**Conclusions:** In Serbia, *T. saginata* and *T. solium* infections are autochthonous but occur only sporadically. However, the potential for re-emergence exists, depending on the socio-economic state of the country.

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### Introduction

In terms of health and economic burden, *Taenia solium* has been ranked as the first, and *Taenia saginata* as the nineteenth food-borne parasite at the global level (FAO/WHO, 2014). Both organisms are parasitic tapeworms for which humans are the definitive host. Following the consumption of undercooked meat from infected animals, parasite larvae evaginate from tissue cysts and mature into adult tapeworms in the intestines, causing taeniosis. Parasite eggs are excreted with the host faeces and the infection of the intermediate hosts (pigs and cattle, respectively) then occurs via faecal–oral transmission, resulting in the formation of tissue cysts – cysticerci – and the development of cysticercosis. For *T. solium*, humans can also be the intermediate hosts.

Taeniosis is usually mild and therefore can remain undetected for a long time, but can occasionally cause gastrointestinal symptoms and complications (Murrell, 2005). *T. saginata* taeniosis is globally widespread, with a significant incidence in Europe (Dorny and Praet, 2007). As a mild or asymptomatic infection, its clinical significance is small, but it may be a significant cause of economic losses in the meat industry.

*T. solium* is either endemic or emerging in most developing countries of South and Central America, Sub-Saharan Africa, and Asia and the Pacific Region, except in Islamic countries (Del Brutto, 2012a). Cysticerci can occur in any organ, and the severity of symptoms depends on the localization. Whereas in animals cysts are commonly found in muscles and the brain (Murrell, 2005) but the infection is rarely associated with clinical symptoms (García et al., 2003), the most common site for cysticerci in humans is the brain, resulting in neurocysticercosis (NCC), a clinically serious disease with potentially severe consequences and even fatal outcomes (Del Brutto, 2005; García et al., 2014).

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Moreover, NCC is globally the most common cause of preventable epilepsy. In countries where the parasite is endemic, it is estimated to cause 30% of all cases of epilepsy (García et al., 2014). *T. solium* can also be carried by infected hosts to non-endemic areas and therefore has international health implications (Pawlowski et al., 2005). Indeed, in the USA, where the parasite is not endemic, at least one cysticercosis-related death of a US-born person was reported in each year between 1990 and 2002 (Sorvillo et al., 2007). In Europe, the number of NCC cases is on the rise, presumably as a result of human migration and travel to endemic areas (Del Brutto, 2012b; Fabiani and Bruschi, 2013; Devleeschauwer et al., 2017). Moreover, the parasite is traditionally endemic in Central, Eastern, and South Eastern Europe, including Serbia (Trevisan et al., 2018).

Recent Serbian history is marked by political turmoil accompanied by the socio-economic crisis that followed the violent dissolution of the former Yugoslavia in the 1990s, which jeopardized all parts of Serbian society, including health and veterinary services. In the nineties, Serbia was a lower middle-income country with a gross national income (GNI) per capita value of less than 3000 USD (World Bank Data). After political changes in 2000, the country entered a period of economic and social recovery. Since 2006, Serbia has been a higher middle-income country, with GNI per capita since 2008 in the range of 5000–6000 USD. The population today is 7.2 million, of which 59.4% live in urban areas, with 16.1% living in the area of the capital Belgrade. More than 90% of the population are Christian and 3% are Muslim (Statistical Office of the Republic of Serbia, 2014).

To analyse the influence of the socio-economic crisis on the incidence of taeniosis and cysticercosis, an epidemiological study was performed of *T. saginata* and *T. solium* infection in Serbia between 1990 and 2018, a timeframe encompassing periods of economic crash and recovery.

## Materials and methods

This study was comprehensive in that epidemiological data on *T. saginata* and *T. solium* infection in Serbia from January 1, 1990 to December 31, 2018, were obtained by two different approaches, as follows: (1) a systematic review of major databases and other sources of publications, including the grey literature (meeting abstracts, theses), as well as a search of official reports. Notably, taeniosis was notifiable between 1997 and 2004, which is therefore the only period for which official reports are available. (2) Two clinical observational studies. The first study was of patients diagnosed with NCC. The data were collected through a questionnaire sent by e-mail to the four university clinical centres in Serbia. Although NCC is indeed treated only at the tertiary level, in order not to miss a single case, questionnaires were also sent to all 29 secondary level health facilities with infectious disease departments. The second study was of patients diagnosed with taeniosis. Data were collected by reviewing patient charts at Belgrade University Clinical Centre (Clinic for Infectious and Tropical Diseases (CITD), the largest tertiary infectious disease institution in the country).

### Systematic review of published sources

For data published on the epidemiology of *T. saginata* and *T. solium* in Serbia, a search was conducted of three international databases (PubMed, ISI Web of Science, Google Scholar) and two Serbian databases (Serbian Citation Index, a repository of articles from Serbian scientific journals <http://scindeks.ceon.rs/Default.aspx>; and doiSerbia national electronic database of doctoral dissertations <http://www.doiserbia.nb.rs/phd/>). The following search phrases were used: (cysticerci\* OR taenia\* OR tenia\* OR

*solium* OR *saginata* OR pork tapeworm OR beef tapeworm OR neurocysticercosis) AND Serbia (for Serbian databases: same terms in Serbian).

Eligibility of the database search results was evaluated with reference to the steps recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) (Moher et al., 2009). All references resulting from the database search were screened first by title, for duplicates, and then by abstract, for eligibility. Exclusion criteria included: (1) if the study only referred to parasites other than *T. saginata* or *T. solium*; (2) if the study did not apply to Serbia; (3) if the data presented in the study did not refer to the study period; (4) if the data presented in the study did not deal with the epidemiological characteristics of *T. saginata* or *T. solium*; and (5) if the study was just a general review of the topic but without original data. The full text of the publications that passed to this stage was evaluated against the same criteria.

Official data on human taeniosis were obtained from the annual reports on infectious diseases, published by the Institute for Public Health of Serbia.

### Clinical observational studies

The data on the NCC patients collected by means of the questionnaire included patient age, sex, profession (for assessing occupational exposure), information about travelling abroad, place of residence (for grouping by region), date of first hospitalization (for distribution by year), diagnostic methods applied, and possible referral to another clinical centre (in order to avoid duplication of records). NCC patients from neighbouring countries who were referred for treatment in Serbia were excluded.

The CITD patient charts reviewed for data on taeniosis included data on year of testing, age, and sex.

### Data generation and analysis

To avoid duplication of NCC cases, patient cases extracted from the literature survey were compared with those obtained by the questionnaires, and if already detected by the questionnaires were excluded from the analysis (as more data were derived from the questionnaires).

If the incidence of infection was given (such as in official reports for taeniosis), it was used directly. When only the number of cases was collected, the incidence was calculated based on the official census data.

To assess the relationship between the incidence of infection and the economic situation, the consumer price index (CPI) was used as a parameter of the socio-economic status. CPI values were obtained from official documents (Statistical Office of the Republic of Serbia, 2010).

### Statistical analysis

Changes in the incidence of NCC over time, as well as differences in the distribution of patients among groups formed according to modalities of individual variables (age, sex, number of cases per year), were analysed by univariate analysis of variance.

The relationship between the incidence of infection and the economic situation was analysed by correlation analysis. The number of cases of taeniosis in each year was correlated with the CPI value for the same year. For NCC, the annual number of cases was correlated with the CPI value of 5 years before, due to a latency period of infection of 4–6 years (Del Brutto and García, 2012); i.e., cases from 1990 were correlated with the CPI value for 1985.

The level of statistical significance was a *p*-value of <0.05.

## Results

Database searches identified 12 relevant peer-reviewed papers, all concerning NCC, of which seven were excluded due to duplicating cases from the questionnaires (Figure 1). All eight official reports (published annually during the 8 years of notification) were included in the analysis.

Completed questionnaires on NCC were received from three of the four clinical centres (Belgrade, Novi Sad, and Niš, but not from Kragujevac) and from a single secondary hospital.

### Taeniosis

Taeniosis in Serbia was notifiable only between 1997 and 2004 (Institute of Public Health of Serbia, 1998–2005). During this period, a total of 212 cases of taeniosis were officially reported, all diagnosed by microscopic examination of stool samples without distinction between *T. saginata* and *T. solium*. A wide variation in the number of cases per year was noted, ranging between 0.04 and 0.9 cases/100 000 population/year. Interestingly, the number of cases increased continually between 1997 and 2000 (from 0.29/100 000 population/year in 1997 to 0.9/100 000 population/year in 2000), when 146 (68.9%) cases were registered, and decreased

between 2001 and 2004 (from 0.61/100 000 population/year in 2001 to 0.04/100 000 population/year in 2004), when there were only 66 (31.1%) cases. Overall, the greatest number of cases (77.7%) involved patients below 14 years of age (Figure 2A). The majority of cases – 63.2% – were registered during the autumn and winter (Figure 2B), compared to 36.8% during spring and summer ( $p = 0.016$ ). There was no significant difference in sex distribution (male 52.4%, female 47.6%,  $p > 0.05$ ).

In comparison, the CITD observed few cases, i.e. a total of 22 over the whole 29-year study period. Still, a decreasing trend was noted after 2000, with 12 (54.5%) cases in the first 10 years (1990–1999) and 10 cases (45.5%) in the next 19 years (2000–2018). The sex distribution was identical to that in the official reports. However, patient age (mean  $38.8 \pm 12.9$  years, range 9–66 years) differed considerably, reflecting the fact that the CITD generally does not treat children. Proglottids were detected in stool samples of 10 patients. *T. saginata* was identified in nine of these based on morphological characteristics, while only immature proglottids were found in the remaining sample, thus precluding species determination.

Correlation analysis of official data on the number of cases of taeniosis and CPI by year showed a strong relationship between the number of cases and the price index (Pearson's  $r = 0.914$ ,  $p = 0.001$ ).

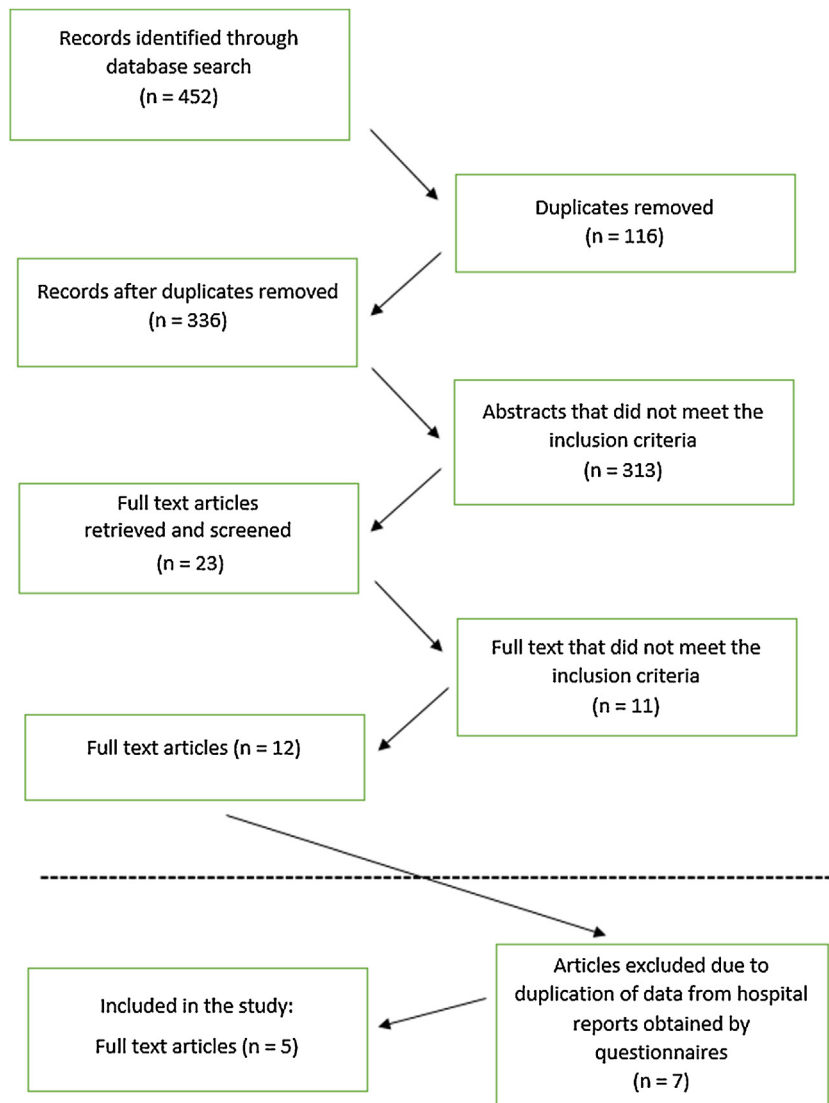
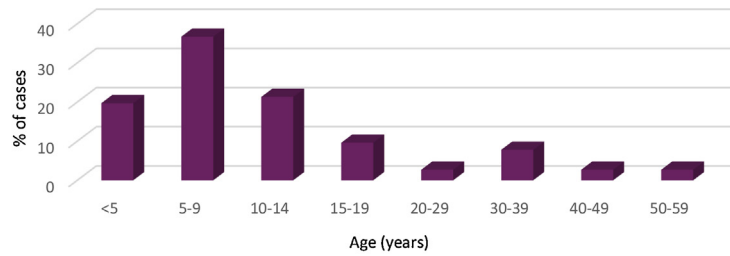
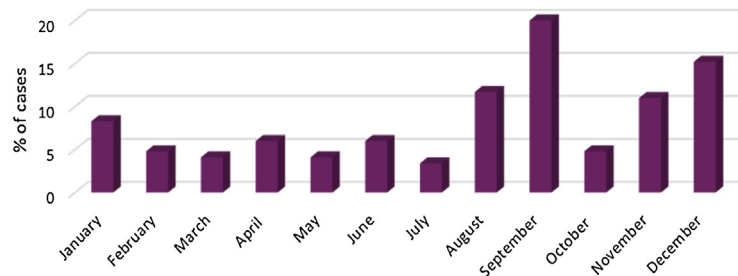


Figure 1. Flow diagram of the search strategy steps.

A



B

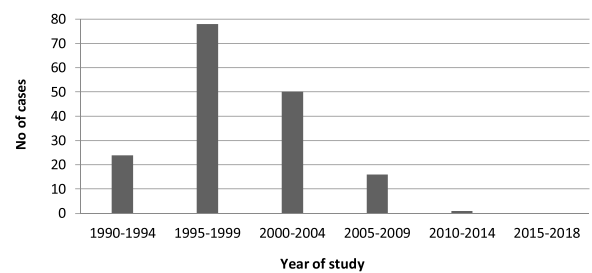


**Figure 2.** Patients with taeniosis in Serbia from 1997 to 2004 according to (A) age, and (B) month of reporting.

### Cysticercosis

A total of 170 cases of cysticercosis were identified during the whole 29-year study period, with all but one being cases of NCC. Of these, data on 165 NCC cases were collected from the questionnaires; this figure did not include 26 NCC patients from Bosnia and Herzegovina (B&H) and one from Croatia, because although these patients were treated in Serbian hospitals, they were only referred to them (ergo, the infection did not occur in Serbia). The diagnosis of NCC was based on clinical presentation, neuroimaging, serology, and response to treatment with cysticidal drugs. In addition, another five cases were identified by the systematic literature review, including a case of cysticercosis of the kidney (Potić et al., 2013) and four additional cases of NCC, missed by the questionnaires since the patients were treated in hospital units other than infectious diseases ones. These cases were reported in the literature as clinically interesting; for instance, NCC was accompanied by generalized cysticercosis in one case (Babić et al., 1996), and with ocular cysticercosis in another (Aksentijević et al., 2005). One was a case with a fatal outcome, as NCC caused cerebral infarction (Nožić et al., 1995). Interestingly, cysticercosis-related epilepsy was described in only one case (Kostić et al. 2019).

Overall, the incidence of NCC ranged between 0 and 0.29 cases/100 000 population/year (Figure 3). However, it increased significantly ( $F_{(1, 10)} = 18.041$ ,  $p = 0.002$ ) during the 1990s, followed by a significant decrease thereafter. More specifically, the incidence was on the decrease between 2000 and 2009 ( $F_{(1, 10)} = 17.578$ ,



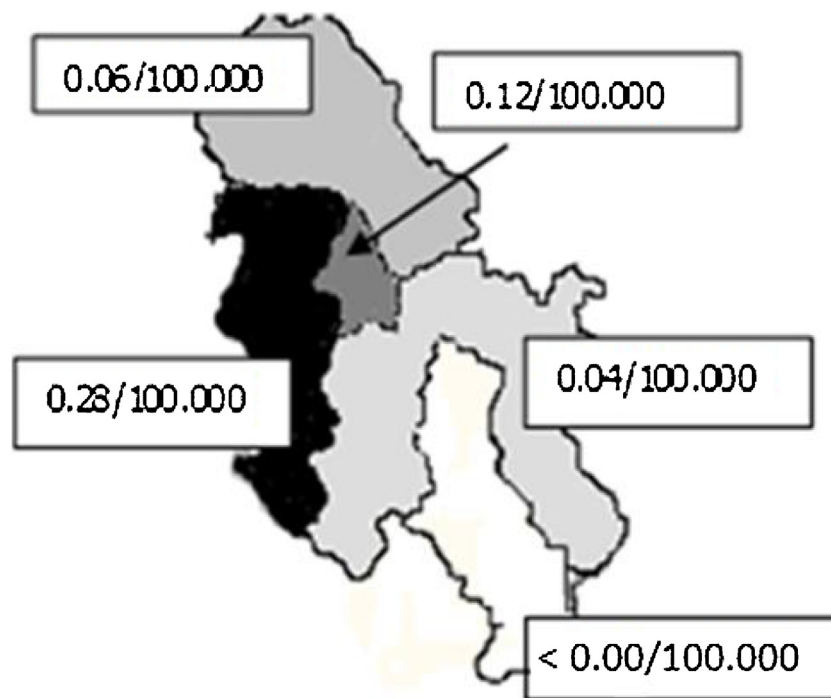
**Figure 3.** Distribution of cysticercosis patients in Serbia between 1990 and 2018 over time (in five-year intervals).

$p = 0.002$ ), while NCC practically disappeared in the last 9 years (when only one case was reported).

Correlation analysis of the number of cases of NCC and CPI by year showed that the number of cases was proportional to the price index (Pearson's  $r = 0.582$ ,  $p = 0.014$ ).

Analysis of the geographic distribution of patients (Figure 4) according to the place of residence revealed that although they came from almost all parts of the country, there was an uneven distribution. Infection was the most frequent in western Serbia, along the Sava and Drina rivers, and very frequent in Belgrade, the capital and the largest city in Serbia, while it was most rarely diagnosed in southern Serbia.

The age range of the patients was 7–73 years, with a mean of  $46.2 \pm 1.1$  years. The majority (67.2%) of the patients were aged



**Figure 4.** Geographic distribution of cysticercosis patients in Serbia between 1990 and 2018 12 (number of cases / 100.000 population).

between 30 and 59 years, while only 3.5% were younger than 20 years of age. There was no sex-related difference in the infection incidence (female, 48.7%; male, 51.3%;  $p > 0.05$ ).

No patient acknowledged visits or stays in endemic areas of South America, Africa, or Asia. Data on travel to neighbouring countries, similarly endemic for *Taenia* infection, have not been collected. Only 6.5% of patients were considered professionally exposed, 10 as farmers and one as a forest worker. It is interesting that six of the patients were Muslim, indicating specific epidemiological circumstances in ethnically mixed areas. A previous taeniosis episode was reported in only 3.5% of cases.

## Discussion

This study spanning 29 years showed the occurrence of both taeniosis and cysticercosis in Serbia, but at a low incidence. Taeniosis was present during all of the 8 years it was notifiable, but unfortunately without distinguishing between the species. However, an earlier study showed that *T. saginata* taeniosis was much more frequent than *T. solium* infection (Petrović, 1977). The predominance of *T. saginata* infection in the study period was indicated by the data from the CITD. These findings are in line with the continuous presence of *T. saginata* in cattle (although in sporadic cases, decreasing in numbers) and extremely rare *T. solium* infections in pigs. Cysticercosis in food animals is notifiable in Serbia, and based on official data from the veterinary services, 12 infected beef carcasses and a single infected pork carcass were registered from 2005 to 2017 (Ministry of Agriculture, Forestry and Water Management). On the other hand, the presence of *T. solium* taeniosis in people in Serbia is corroborated by cases of cysticercosis in humans and pigs.

The highest number of registered cases of taeniosis in the youngest age groups is primarily the result of the systematic examination of schoolchildren. The higher incidence of infection during the autumn and winter is not surprising, as such seasonality has also been shown for toxoplasmosis and trichinellosis in Serbia

and is associated with the more frequent consumption of undercooked/raw meat or meat products (homemade sausages and smoked meat) during those seasons (Bobić et al., 2010; Ofori-Belić et al., 2010).

Interestingly, although notifiable during only 8 years, an increase followed by a decrease in the incidence of taeniosis was observed, in parallel with the CPI. A high CPI, indicating high inflation and a drop in the population standard of living, coincided with a higher incidence of infection (and vice versa). A similar trend during the years of crisis was also observed in the incidence of trichinellosis (Čuperlović et al., 2005; Sofronić-Milosavljević et al., 2013). Structural and economic reforms during the transition from socialized to market economy and the economic crisis deepened by the conflicts in the nineties led to the collapse of large companies in the Serbian meat industry with in-house inspection, which were replaced by small slaughterhouses, too small for in-house veterinary services, and an increasing number of small farms with lower zootechnical and zoohygiene standards. As could be expected, traditional home slaughter became prevalent in the country (Bobić et al., 2012); furthermore, it was not always reported to the veterinary services. With the subsiding of the political and economic crisis, conditions of animal breeding as well as veterinary control of animal slaughter started to improve.

The study also detected a low presence of NCC. The fact that no NCC patients acknowledged travelling to endemic areas of South America, Africa, or Asia means that the cases registered in Serbia were autochthonous. Similarly to taeniosis, the number of NCC cases per year changed in parallel with the CPI. Taking into account that the incubation period for NCC is between 4 and 6 years (Del Brutto and García, 2012), it can be inferred that 55% of the patients were infected between 1990 and 1995 (CPI range from 170 to  $117 \times 10^{12}$ ), which was the period of the deepest economic crisis (which peaked on the eve of 1994 with an inflation of  $5 \times 10^{15}\%$  when prices doubled every 16 h). The crisis led to the deterioration of hygiene and sanitary conditions in general (e.g., maintenance of community utility systems) and at a personal level. A higher

incidence during the years of crisis was observed for another faecal–oral transmitted parasitic infection, echinococcosis (Džuričić et al., 2010).

In addition to the economic crisis, the war in the former Yugoslavia, accompanied by an influx of refugees (internally displaced persons) from war zones to Serbia, led to an increase in the number of patients. During the 1990s, more than half a million refugees (UNHCR, 1996) came to Serbia from Croatia and B&H, countries also endemic for *T. solium* (Meštrović et al., 2011; Trevisan et al., 2018). In this context, two of the NCC patients in this study were confirmed to be refugees from B&H, who were living in Serbia when they presented with disease symptoms. All of the other patients were Serbian citizens at the time of hospitalization, but it cannot be excluded that some may have been refugees who had recently obtained Serbian citizenship. Conversely, the literature review revealed two cases of Serbian citizens living and diagnosed abroad, one each in Austria and Slovenia (Finsterer et al., 2001; Šoba et al., 2014).

Despite the number of NCC cases, only one case of NCC-related epilepsy was reported. In addition, the leading institutions for the treatment of epilepsy in children and adults in Serbia confirmed that there were no cases of cysticercosis among patients with epilepsy in the last 25 years, although all patients were examined by computed tomography (CT) and/or magnetic resonance imaging (MRI) (personal communication with Milena Djurić, Institute for Health Protection of Mother and Child “Dr Vukan Čupić”, Belgrade, and Dragoslav Sokić, Clinic for Neurology, Clinical Centre of Serbia, Belgrade). Earlier studies described a rather large number of epilepsy cases associated with NCC. A single study by Umičević et al. (1989) described 50 cases of NCC in military trainees who had been recruited from all parts of the former Yugoslavia.

The geographic distribution of the patients showed that the infection was most frequent in western Serbia, along the Sava and Drina rivers, which are natural borders with B&H and Croatia. These countries are both known to be endemic for *T. saginata* and *T. solium*, which is supported here by the 26 patients from B&H and one from Croatia detected in the questionnaires. The above-average incidence in Belgrade is likely to be the result of a steady population influx from rural areas. The diagnosis of NCC in six Muslim patients points out that in multiethnic areas, regardless of ethnic or religious customs, NCC must be considered in the differential diagnosis of patients with neurological symptoms.

The cases described in this study once again remind us of the importance of reducing environmental contamination by *Taenia* eggs, and point to improving sanitation as a basic measure in the prevention of infection. Both *T. solium* and *T. saginata* taeniosis may last for up to 25 years in untreated persons, who continue to excrete proglottids with tens of thousands of eggs. These eggs may remain viable for several weeks or months in sewage, water, or on pastures (Flisser et al., 2005). Therefore, measures to break the transmission cycle of the taeniosis/cysticercosis disease complex should include treatment for taeniosis in diagnosed cases and subsequent control of treated patients, coupled with health education. This health education should focus on heightening personal and communal hygiene, the importance of consuming only meat controlled by a veterinarian during slaughter, and proper food preparation practices. In addition, as the results presented here show that the infection occurred sporadically and with a spatially uneven distribution, the mandatory reporting of taeniosis cases would appear to be a useful and inexpensive prevention measure. By comparing public health and veterinary services data, disease hotspot areas can be defined, and control through active surveillance and targeted treatment of taeniosis can be conducted.

Despite the lack of comprehensive epidemiological data, it can be concluded that in Serbia *T. saginata* and *T. solium* infections are autochthonous but currently occur only sporadically. However, the

potential for re-emergence exists, depending on the socio-economic state of the country.

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## Ethical approval

Not required.

## Conflict of interest

The authors declare that they have no conflicts of interest whatsoever.

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