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Original Article

Tuberculosis and associated risk factors among children and adolescent population in Serbia: 12 year's retrospective study

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Abstract

Introduction: Recognition and epidemiological control of childhood and adolescent tuberculosis (TB) is essential to achieve effective control of TB in general as it presents high risk for transmission in the community. The aim of the study is to provide a descriptive and analytic overview of the trends in childhood and adolescent TB notifications and treatment outcomes and to identify factors associated with treatment success in a twelve-year period in Serbia.

Methodology: We performed a retrospective trend analysis and analysis of treatment outcomes of 596 child and adolescent TB cases notified in Serbia in the period 2005–2016 from all health facilities, as well as logistic regression analysis to identify predictors of treatment success.

Results: Factors independently associated with treatment success were: new TB (OR=2.60; 95% CI: 1.45–3.74), male sex (OR=2.55; 95% CI: 2.09–3.00), pulmonary TB (OR=3.34; 95% CI: 2.34–4.34), comorbidities (OR=2.58; 95% CI: 2.24–2.91), age below 5 years (OR=0.37; 95% CI: 0.32–0.43), and social vulnerability (OR=0.40; 95% CI: 0.34–0.46).

Conclusions: In order to improve TB treatment outcomes among children and adolescent population in Serbia, it is important to focus on female, age group 5-18, EPTB, retreatment cases and socially vulnerable groups.

Key words: tuberculosis; children; adolescents; risk factors; Serbia.

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Introduction

Even in the twenty-first century, tuberculosis (TB) remains the one of the main causes of morbidity and mortality worldwide. There were an estimated 1.1 million new cases of childhood TB and an estimated 205,000 TB deaths in children in 2018 [1,2]. Tuberculosis in children is often under-diagnosed as they experience a variety of symptoms and therefore are a particularly vulnerable population. In early childhood, immature immune systems make children more susceptible to develop severe disseminated forms of the disease, such as TB meningitis, miliary TB, and TB of the bones and joints [3]. Moreover, conventional diagnostic tests, such as sputum smear microscopy and culture, have low sensitivity in children due to difficulties in obtaining adequate samples [4]. Challenges in microbiological confirmation and clinical diagnosis in children often lead to missing cases, delayed and ineffective treatment, disease progression and increased risk of death [5]. In addition, social determinants and underlying factors, such as overcrowding, malnutrition and poverty contribute to childhood TB in the communities [6]. Previous studies identified that risk factors for negative treatment outcomes in children with TB include HIV positivity [7,8], age below 5 years [7,9], low body weight [10], and smear positivity of the source of infection [11]. In the period 2005–2016, TB notification rate in Serbia decreased from 32 per 100,000 in 2005 to 11 per 100,000 in 2016. The proportion of TB cases among children under 14 years of age was 1% [12]. An in-depth analysis of notification and treatment outcomes of childhood TB has not been undertaken before in Serbia. Previous studies in Serbia have focused on trends in TB incidence and mortality among children and highlighted the need to further describe the trends to improve our understanding of the TB burden and performance of the TB control programme [13]. This analysis aims to provide a descriptive and analytic overview of the trends in childhood and adolescent TB notifications and treatment outcomes and to identify factors associated with treatment success in a twelve-year period in Serbia.

Methodology

Source population

Within the descriptive study design, we performed trend analysis of case notifications and analysis of treatment outcomes of all TB cases (child and adolescent) diagnosed in the period 2005–2016 from all health facilities in Serbia, based on the data derived from the national electronic data collection system for TB of the Ministry of Health and Institute of Public Health of Serbia. We analyzed notified child and adolescent TB cases by age, sex, bacteriological confirmation, anatomical site of the disease, history of previous treatment, risk factors (such as: being contact with confirmed TB case, having comorbidities and social vulnerability defined as potential harm to people involving combination of factors that determine the degree to which someone's life and livelihood are put at risk by a discrete and identifiable event in nature or in society), HIV status (recorded since 2010), multidrug resistance and bacille Calmette-Guerin (BCG) vaccination coverage. Internal consistency of the data was analyzed using WHO checklists [14,15]. Treatment results included: cured, treatment completed, defaulted (lost to follow-up), died, failed and not evaluated [16,17]. TB diagnosis and case definitions were used from the National guidelines for TB control in Serbia developed in line with WHO guidelines [18].

Diagnosis

TB diagnosis in children was based on clinical and radiological findings and was confirmed bacteriologically and/or histologically. Laboratory confirmation was performed by detection of *Mycobacterium tuberculosis complex* from a clinical specimen, either by culture or by a newer molecular technique [18].

Case definition and classification

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. PTB also includes cases that affect the lung with additional extra-pulmonary manifestations. Extra-pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones or meninges. New patients are defined as those who have never been treated for TB or have taken anti-TB drugs for less than one month. Previously treated patients are defined as those who have received 1 month or more of anti-TB drugs in the past. Multidrug resistance (MDR) refers to resistance to at least isoniazid and rifampicin together. Treatment outcomes were categorized according to the latest WHO definitions and reporting framework for tuberculosis [15].

Statistical analysis

Analyses of trends of TB notification rates and treatment outcomes during the 12-year study period were performed for all cases. National Statistical Office

Table 1. Demographic characteristics of child and adolescent TB cases notified in Serbia 2005-2016.

Characteristics	Year N (%)												
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total (N)**
Number of cases	60	63	64	58	65	52	39	53	47	44	21	30	596
Notification rate (per 100.000)	3.7	3.7	3.8	3.8	3.9	3.9	4.0	4.2	4.2	4.3	4.3	4.4	
Gender													
Male	25	30	38	25	36	25	16	29	18	23	14	15	294
	41.7	47.6	59.4	43.1	55.4	48.1	41.0	54.7	38.3	52.3	66.7	50.0	
Female	35	33	26	33	29	27	23	24	29	21	7	15	302
	58.3	52.4	40.6	56.9	44.6	51.9	59.0	45.3	61.7	47.7	33.3	50.0	
Age category													
0 to 4	6	7	8	7	8	3	6	4	1	5	3	0	58
	10.0	11.1	12.5	12.1	12.3	5.8	15.4	7.5	2.1	11.4	14.3	0.0	
Notification rate (per 100.000)	2.3	2.7	3.1	2.7	3.1	1.2	2.5	1.7	0.4	2.2	1.3	0.0	
5 to 14	14	17	21	15	13	14	7	14	13	16	5	0	149
	23.3	27.0	32.8	25.9	20.0	26.9	17.9	26.4	27.7	36.4	23.8	0.0	
Notification rate (per 100.000)	1.4	1.7	2.4	1.7	1.5	1.6	0.8	1.8	1.6	2.0	0.6	0.0	
15-18	40	39	35	36	44	35	26	35	33	23	13	30	389
	66.7	61.9	54.7	62.1	67.7	67.3	66.7	66.0	70.2	52.3	61.9	100.0	
Notification rate (per 100.000)	11	11	8	8	10	8	6	9	9	6	4	8	305

TB: tuberculosis.

provided population data for each year [18]. Trends were analyzed for case notification by age, sex, bacteriological confirmation, anatomical site of the disease, history of previous treatment, risk factors (such as being contact with confirmed TB case, having comorbidities and social vulnerability), HIV status (recorded since 2010), multidrug-resistance and BCG vaccination coverage. To identify factors associated with treatment success we used a logistic regression analysis. The variables age, sex, bacteriological confirmation, anatomical site of the disease, history of previous treatment, contact with confirmed TB case, comorbidities, social vulnerability, HIV status, multidrug resistance and BCG vaccination coverage were entered in univariate logistic regression analysis (ULRA) model. The outcome of the model was dichotomized as treatment success (cured or completed) vs negative treatment outcome (failed, died, lost to follow-up or not evaluated).

The variables that showed statistically significant association at p value ≤ 0.05 in ULRA were entered in multivariable logistic regression analysis (MLRA) models. Statistical Package for Social Sciences (IBM SPSS) version 24 was used for data analysis and p values ≤ 0.05 were considered statistically significant.

Ethics statement

This analysis used routine comprehensive surveillance data collected programmatically, no one provided informed consent. All data were completely de-identified prior to the analysis. Review Board (RB) of the Institute of Public Health of Serbia determined the study exempt from ongoing review and waived the requirement for informed consent.

Results

Characteristics of the cases

There were almost the same representatives from both genders (male to female ratio = 0.97:1). The most patients belonged to the age group 15-18 years (389, 65.3%) (Table 1).

Most of the cases, (473, 79.4%) had PTB. A total of 583 cases (97.8%) were new. Among all 305 (51.2%) cases were bacteriologically confirmed whereas 60% (N = 284) were PTB cases and 17.1% (N = 21) EPTB cases. MDR TB was notified and recorded in 3 out of 225 cases (37.8%) covered by drug-susceptibility testing (DST). HIV status has been recorded in TB register since 2010. From 2010 to 2016, there were no HIV positive cases among 12 (4.2%) TB cases tested, while for 274 cases (95.8%) HIV status was unknown. Social vulnerability was notified in 85 (14.3%) and comorbidities in 13 (2.2%) cases. Over the observed period, BCG vaccination coverage ranged from 98-99% (Table 2).

Trends analysis of tuberculosis case notifications among child and adolescent population

Between 2005 and 2016 the proportion of child and adolescent cases among all TB cases significantly increased from 2.5% in 2005 to 4.0% in 2016 (p value for trend < 0.05). Bacteriological confirmation of cases significantly increased during the observed period, from 46.6% in 2005 to 73.3% in 2016 (p value for trend < 0.05). The proportions of PTB increased significantly from 71.7% in 2005 to 96.7% in 2016, while EPTB decreased over time (p value for trend < 0.05). Social vulnerability of cases significantly increased during the observed period, from 8.3% in 2005 to 33.3% in 2016 (p value for trend < 0.05). There was a significant decrease in unknown DST results from 86.7% in 2005 to 40.0% in 2016 (p value for trend < 0.05). The proportions of HIV testing results increased significantly (p value for trend < 0.05), from 0.0% in 2010 to 10.0% in 2016.

Trends in tuberculosis treatment outcomes among child and adolescent population

Treatment outcome was available for all 596 cases. Treatment success significantly increased among retreatment cases (p value for trend < 0.05), from 0% in 2005 to 100% in 2016. The proportion of patients lost to follow-up decreased significantly among PTB cases, from 11.6% in 2005 to 3.5% in 2016 and among previously treated cases from 50.0% in 2005 to 0.0% in 2016 (p value for trend < 0.05). The proportion of child and adolescent TB patients' deaths remained stable over time at the level of zero to one death per year (p value for trend > 0.05) (Table 4).

Factors associated with treatment outcomes

In the multivariable logistic regression analysis (Table 3), factors independently associated with treatment success were: new TB (OR = 2.60; 95% CI: 1.45–3.74), male sex (OR = 2.55; 95% CI: 2.09–3.00), pulmonary TB (OR = 3.34; 95% CI: 2.34–4.34), and comorbidities (OR = 2.58; 95% CI: 2.24–2.91). Factors independently associated with negative treatment outcomes were age below 5 years (OR = 0.37; 95% CI: 0.32–0.43), and social vulnerability (OR = 0.40; 95% CI: 0.34–0.46).

Table 2. Clinical and microbiological characteristics of cases of child and adolescent TB notified in Serbia 2005-2016.

Characteristics	Year N (%)												
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total (N)**
Bacteriological confirmation (%)	46.7	55.6	35.9	60.3	44.6	55.8	53.8	52.8	55.3	50.0	33.3	73.3	
Anatomic site of the disease													
PTB	43	47	49	49	50	40	31	43	39	35	18	29	473
	71.7	74.6	76.6	84.5	76.9	76.9	79.5	81.1	83.0	79.5	85.7	96.7	
EPTB	17	16	15	9	15	12	8	10	8	9	3	1	123
	28.3	25.4	23.4	15.5	23.1	23.1	20.5	18.9	17.0	20.5	14.3	3.3	
EPTB localization													
Pleura	13	8	10	6	14	9	6	6	5	7	2	0	86
	21.7	12.7	15.6	10.3	21.5	17.3	15.4	11.3	10.6	15.9	9.5	0.0	
Extra-thoracic lymph nodes	2	7	4	0	0	2	0	2	1	0	1	1	20
	3.3	11.1	6.3	0.0	0.0	3.8	0.0	3.8	2.1	0.0	4.8	3.3	
TB meningitis	0	0	0	1	1	0	1	1	0	1	0	0	5
	0.0	0.0	0.0	1.7	1.5	0.0	2.6	1.9	0.0	2.3	0.0	0.0	
Disseminated TB	0	0	0	1	0	0	0		0	0	0	0	1
	0.0	0.0	0.0	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Osteoarticular TB	2	1	1	1	0	1	1	1	2	1	0	0	11
	3.3	1.6	1.6	1.7	0.0	1.9	2.6	1.9	4.3	2.3	0.0	0.0	
History of previous treatment													
New	58	62	63	58	64	52	39	52	44	43	19	29	583
	96.7	98.4	98.4	100.0	98.5	100.0	100.0	98.1	93.6	97.7	90.5	96.7	
Previously treated	2	1	1	0	1	0	0	1	3	1	2	1	13
	3.3	1.6	1.6	0.0	1.5	0.0	0.0	1.9	6.4	2.3	9.5	3.3	
Risk groups													
Contacts	23	15	23	17	22	16	12	23	17	18	9	6	201
	38.3	23.8	35.9	29.3	33.8	30.8	30.8	43.4	36.2	40.9	42.9	20.0	
Co-morbidity (immunosuppression)	0	2	1	0	0	2	1	3	3	1	0	0	13
	0.0	3.2	1.6	0.0	0.0	3.8	2.6	5.7	6.4	2.3	0.0	0.0	
Social vulnerability	5	8	13	9	9	7	8	2	4	10	0	10	85
	8.3	12.7	20.3	15.5	13.8	13.5	20.5	3.8	8.5	22.7	0.0	33.3	
HIV status[1]													
Positive						0	0	0	0	0	0	0	0
						0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Negative						0	1	2	3	2	1	3	12
						0.0	2.6	3.8	6.4	4.5	4.8	10.0	
Unknown						52	38	51	44	42	20	27	274
						100.0	97.4	96.2	93.6	95.5	95.2	90.0	
Multidrug resistance													
No	8	11	14	23	37	30	16	24	21	15	5	18	222
	13.3	17.5	21.9	39.7	56.9	57.7	41.0	45.3	44.7	34.1	23.8	60.0	
Yes	0	0	0	0	1	0	0	0	0	2	0	0	3
	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	4.5	0.0	0.0	
Unknown	52	52	50	35	37	22	23	29	26	27	16	12	371
	86.7	82.5	78.1	60.3	56.9	42.3	59.0	54.7	55.3	61.4	76.2	40.0	
BCG vaccination coverage (%)	98.0	99.0	98.0	98.0	98.0	98.0	98.0	98.0	98.0	98.0	98.0	98.0	

TB: tuberculosis; PTB: pulmonary TB; EPTB: extra-pulmonary TB; BCG: bacillus Calmette-Guerin. [1]Data on HIV status are available in TB register from 2010.

Table 3. Treatment outcomes of child and adolescent tuberculosis cases in Serbia, 2005-2016.

Treatment outcome	Year N (%)												
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total (N)**
New cases													
PTB[1]													
Cured + Completed	37	42	48	45	43	39	29	39	35	32	17	28	434
	86.05	89.36	97.96	91.84	86.00	97.50	93.55	90.70	89.74	91.43	94.44	96.55	
Negative treatment outcomes	6	5	1	4	7	1	2	4	4	3	1	1	
	13.95	10.64	2.04	8.16	14.00	2.50	6.45	9.30	10.26	8.57	5.56	3.45	
Total	43	47	49	49	50	40	31	43	39	35	18	29	473
EPTB[2]													
Cured + Completed	17	16	13	9	15	11	8	10	7	9	3	1	119
	100.00	100.00	86.67	100.00	100.00	91.67	100.00	100.00	87.50	100.00	100.00	100.00	
Negative treatment outcomes	0	0	2	0	0	1	0	0	1	0	0	0	
	0.00	0.00	13.33	0.00	0.00	8.33	0.00	0.00	12.50	0.00	0.00	0.00	
Total	17	16	15	9	15	12	8	10	8	9	3	1	123
All new TB cases													
Cured+Completed	54	56	60	54	60	50	37	49	40	40	17	28	545
	93.10	90.32	95.24	93.10	93.75	96.15	94.87	94.23	90.91	93.02	89.47	96.55	
Negative treatment outcomes	4	6	3	4	4	2	2	3	4	3	2	1	
	6.90	9.68	4.76	6.90	6.25	3.85	5.13	5.77	9.09	6.98	10.53	3.45	
Total	58	62	63	58	64	52	39	52	44	43	19	29	583
Previously treated cases													
Cured+Completed	0	0	1	0	0	0	0	1	2	1	1	1	7
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	100.00	66.67	100.00	50.00	100.00	
Negative treatment outcomes	2	1	0	0	1	0	0	0	1	0	1	0	
	100.00	100.00	0.00	0.00	100.00	0.00	0.00	0.00	33.33	0.00	50.00	0.00	
Total	2	1	1	0	1	0	0	1	3	1	2	1	13

TB: tuberculosis; PTB: pulmonary TB; EPTB: extra-pulmonary TB.

Table 4. Factors associated with treatment success among notified child and adolescent TB cases in Serbia. 2005-2016 according to the multivariable logistic regression analysis.

N = 596	**Treatment success**	**P-value**
Characteristics	**OR (95% CI)**	
Gender		
Male	2.55 (2.09-3.00)	0.000
Female		
Age category		
0-4	0.37(0.32-.0.43)	0.000
5 to 18		
TB localization		
PTB[1]	3.34 (2.34-4.34)	0.000
EPTB[2]		
Registration category		
New	2.60 (1.45-3.74)	0.000
Retreatment		
Comorbidities		
Yes	2.58 (2.24-2.91)	0.000
Social vulnerability		
Yes	0.40 (0.34-0.46)	0.000

TB: tuberculosis; PTB: pulmonary TB; EPTB: extra-pulmonary TB.

Discussion

Over the twelve-year study period, we found a stable trend in child and adolescent TB notification rate, while significantly increasing trend of proportions of child and adolescent cases among all TB cases. These proportions correspond to EU/EEA surveillance data [2], less than proportions presented in WHO standards and benchmarks for childhood TB (5–15%) for middle-income countries where Serbia belongs [19], reflecting some improvements in case detection. However, it is reasonable to assume that country is still facing challenges in TB control in child and adolescent population such as: sub-registration [20], under diagnosis and misdiagnosis due to difficulties in obtaining adequate samples, especially in children aged <5 years, as illustrated by a recent review where between 1% and 23% of pneumonia cases also had TB [23,24].

We found that the proportions of bacteriological confirmation of cases and drug susceptibility testing significantly increased during the observed period. It might be a result of programmatic improvements in Serbia and support of the Global Fund to fight AIDS, TB and malaria since 2005 when TB laboratory diagnostic capacities were expanded that provided an opportunity to improve both diagnosis and surveillance in the country [12]. In our study, there was no notified HIV-positive case among children and adolescents; the rate was lower than in EU/EEA countries [2]. Despite there was significant increase in HIV testing over the time in Serbia, the proportion of TB cases with known HIV status is still very low compared to EU/EEA countries [12], since there is no routine offering of HIV testing for TB patients [24]. BCG vaccination coverage in our study was higher than globally [25] and in the EU/EEA countries implementing national BCG vaccination policy for all [26]. In Serbia, BCG vaccine is mandatory and administered to newborn children as a single dose [27]. While most experts agree that BCG is efficacious against severe forms of childhood TB, little is known about how long the BCG vaccine protects against TB. A new scientific insight from Norway suggests that vaccine could be more cost effective than has been previously estimated [28].

The TB treatment success rate among child and adolescent population in Serbia was higher than the EU/EEA treatment success rate [2] at the level of the global target [1] due to decrease of patients lost to follow up and low mortality. The progress made during the study period could be the result of the continuous efforts invested in capacity building of the health professionals for diagnosis, treatment and follow up of the patients.

We identified new TB, male sex, PTB and comorbidities and as independent factors associated of treatment success, while age below 5 years and social vulnerability as independent factors associated with unsuccessful treatment among child and adolescent TB cases.

Many studies reported retreatment as a predictor of negative treatment outcomes [29,4]. One of the fundamental strategies in TB control is early case detection, rapid initiation of adequate treatment, treatment adherence and prevention of disease recurrence, in order to achieve treatment success and avoid toxic effects of re-treatment cycles [30].

We identified male sex as independent predictor of treatment success. In the last two decades, very few studies analyzed trends and treatment outcomes in childhood TB considering the gender of the patients [31,32]. Since the majority of our patients were adolescents and having in mind there studies, findings may suggest a role of hormones, as initial difference in male and female TB trends and treatment outcomes after puberty is observed, due to role of androgens and estrogens in modulating immune system synthesis of pro-inflammatory and immunosuppressive cytokines, as well as antibody production [32,33]. Gender should be further considered not only from an epidemiological point of view but also from a clinical one, being an important factor in the pathogenesis, management and prognosis of this infection [33].

In our study PTB and comorbidities were identified as factors associated with treatment success. Other studies identified comorbidities [31,4] and HIV positivity [32] as factors associated with unsuccessful treatment due to increased mortality. The reason might be the fact that patients with infectious forms of PTB and comorbidities are likely to be hospitalized and under direct supervision of the health worker, unlikely to be lost to follow up. On the other hand, EPTB forms of the disease in children are often severe, towards unfavorable treatment outcomes [23,24].

We find that age below 5 year was an independent predictor of negative treatment outcome, consistent with other studies [34,35]. In children under 5 years of age, primary TB infection frequently progresses to severe forms of the disease. Development of fatal miliary TB or meningeal TB is a significant concern. Osteoporosis, sclerosis, and bone involvement are more common in children with TB than in adults with the disease. The epiphyseal bones can be involved because of their high vascularity [35,36]. Effective early

intervention in this age group would have the potential to reduce the mortality [37].

Furthermore, we identified social vulnerability as a factor associated with negative TB treatment outcomes. People living in unfavorable circumstances have worse health at all ages. The linkage between TB and poverty has long been noted but studies have only recently been undertaken to identify socioeconomic burden of TB. Increased probability of becoming infected with TB, developing active TB and poor adherence to treatment are associated with malnutrition, crowding, poor air circulation, and poor sanitation - all associated with poverty [38]. Social vulnerability is often connected to perception of stigma. Many studies have identified bad cooperation and communication with the health service due to stigma, resulting in delays in medical care, affecting adherence to treatment leading to interruptions, prolonged treatment and drug resistance [39,40]. These circumstances have public health implications in ongoing disease transmission and the risk of drug resistance in the community [39].

Data related to latent tuberculosis infection (LTBI) and chemoprophylaxis were not available for the study period since national Law on population protection against infectious diseases recommends recording and reporting on TB disease, not TB infection. In addition, data on cases from contacts were missing for two thirds of the cases. Despite its limitations, this study is the first in-depth analysis of childhood TB epidemiology in Serbia and provides evidence on the risk factors associated with treatment outcomes.

Conclusions

In the period 2005-2016, stable trend of tuberculosis is notified in child and adolescent population. Although case detection, bacteriological confirmation, drug susceptibility testing and HIV testing among child and adolescent population are improved in Serbia, the values are still below the global targets. During the study period, treatment success rate remain the same. To further improve TB treatment outcomes, it is important to focus on female, age group 5-18, EPTB, and socially vulnerable groups.

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Authors' Contributions

Concept and design (MS), statistical analysis (MS), interpretation of the data (MS, LS, DS, TAV) drafting the manuscript (MS) and critical revision of the manuscript for important intellectual content (MS, LS, DS, VJ, VR, TAV).

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