SYPHILIS RESURGENCE IN BELGRADE, SERBIA, IN THE NEW MILLENNIUM: AN OUTBREAK IN 2014

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SUMMARY

Objective: A worldwide syphilis incidence increase was recorded at the beginning of the new millennium, occurring primarily among men who have sex with men (MSM). The aim of this study was to analyse the epidemiological situation of syphilis in the Belgrade population between 2005 and 2014 and to examine the characteristics of an early syphilis outbreak among MSM in Belgrade in 2014.

Method: Reporting of syphilis is compulsory in Serbia. Routinely reported data were analysed along with data collected from patients' charts.

Results: During the period observed, syphilis incidence increased from 1.07 per 100,000 in 2005 to 4.1 per 100,000 in 2014 (383.2%). From 2005 to 2009, syphilis rates in Belgrade were low, around 1 case per 100,000 people. The first outbreak was registered in 2010. The new incidence increase happened in 2012, and again in 2014 when it was the highest. These incidence changes were registered mainly in men, where the frequency of syphilis was much higher than in women. In 2014, primary syphilis was diagnosed in 20 cases, secondary syphilis in 42, and early latent syphilis in 9 patients. Fifty-seven were MSM, 10 were heterosexual men and 4 were women. Twenty-four cases, all MSM were co-infected with HIV. Majority of patients acquired infection in Belgrade, while in 42/71 cases oral sex was the only risk factor. In comparison with HIV negative, HIV positive syphilis patients were older, more frequently unemployed and MSM. They also more frequently had sex with unknown partners and were diagnosed in the secondary stage of infection.

Conclusions: Study results underline the need for coordinated and expeditious surveillance, partner services, enhanced screening of population at risk, health education, as well as early diagnosis and treatment.

Key words: syphilis, incidence, outbreak, oral sex, men who have sex with men

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INTRODUCTION

A worldwide syphilis incidence increase was recorded at the beginning of the new millennium, occurring primarily among men who have sex with men (MSM). Several outbreaks of infectious syphilis cases have been reported in major European cities (1–5). The outbreaks were associated with high rates of partner change and an increasing predominance of transmission among MSM with a high proportion of HIV co-infection among incident cases (5–7).

During the late 1990s, increasing rates of syphilis were reported in Belgrade (8). The highest incidence of syphilis in men and women was in 1998 (4.22/100,000) and 1997 (1.82/100,000), respectively. This may be attributed to the changes in the country caused by war, the break-up of former Yugoslavia, economic sanctions and resulting socioeconomic difficulties as well as syphilis importation from the former Soviet Union countries (8). From 2001 to 2009, infectious syphilis rates in Belgrade remained below 1.5 per 100,000 people. An upsurge of syphilis incidence began in 2010 (9). The new increase was recorded in 2012 and again in 2014.

The purpose of this study was to analyse epidemiological situation of syphilis in the Belgrade population (about 1.5 million inhabitants) between 2005 and 2014 and to examine the characteristics of an early syphilis outbreak among MSM in Belgrade in 2014. We also compared HIV-positive and HIV-negative syphilis cases registered from 2010 to 2014 in order to identify any distinct need with regard to prevention, screening or other public health measures for these groups of patients.

MATERIALS AND METHODS

Reporting of syphilis is compulsory in Serbia, in Belgrade all reports are sent to the City Institute for Public Health. These reports were used as data sources to calculate incidence rates. Incidence rates for syphilis were calculated using data from the 2011 Serbian census for the Belgrade population (785,826 men and 873,614 women).

Primary, secondary and early latent syphilis (referred to as early syphilis) were defined using the generally accepted criteria (10). Requirements for syphilis were as follows: for primary syphilis (PS), ulcers and reactive treponemal (Treponema pallidum hemagglutination assay – TPHA) and nontreponemal (Venereal Disease Research Laboratory – VDRL) serologic tests; for secondary syphilis (SS), clinical manifestations of this stage with both reactive treponemal test and a nontreponemal titre ≥ 4; for early

latent syphilis, both reactive treponemal and nontreponemal tests and any of the following criteria within the past 12 months: documented seroconversion or fourfold or greater increase in titre of nontreponemal test, documented seroconversion on a treponemal test, a history of symptoms consistent with PS or SS diagnosis, sexual exposure to a person with PS, SS or early latent syphilis, and sexual debut within the last 12 months.

Case-note reviews of patients with early syphilis were undertaken in the City Institute for Skin and Venereal Diseases and in the Institute for Infectious and Tropical Diseases in Belgrade. Basic demographic characteristics of syphilis cases between 2010 and 2014 were retrospectively abstracted from their charts. Data about possible source of infection as well as sexual orientation provided on the official syphilis notification form were also analysed.

Data proportions and Fischer's exact test or χ^2 test were used throughout the analysis.

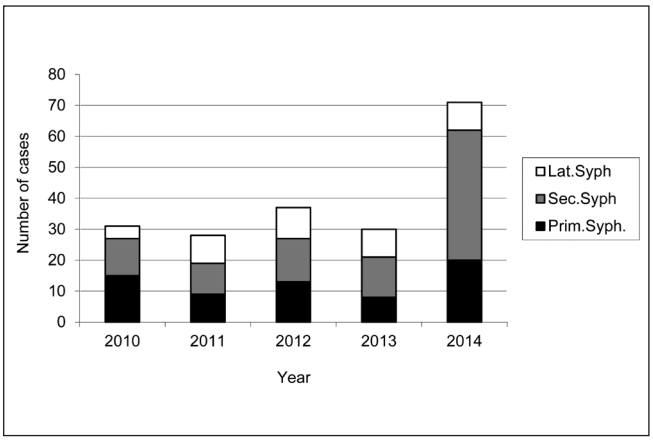

Fig. 2. *Distribution of 196 reported syphilis cases by stage of infection, Belgrade, 2010–2014.*

RESULTS

Between 2005 and 2014, syphilis incidence increased by 383.2% from 1.07 per 100,000 in 2005 to 4.1 per 100,000 in 2014 (Fig. 1). From 2005 to 2009, syphilis rates in Belgrade were low, around 1 case per 100,000 people. The first outbreak occurred in 2010 with the rate of 2.25 per 100,000. The new incidence increase was recorded in 2012 (2.9 per 100,000), and again in 2014 (4.1 per 100,000). From 2013 to 2014 syphilis incidence increased by 308.3%. These incidence changes were registered mainly in the male population. Syphilis incidence in women was much lower than in men and it was almost the same during the entire period observed.

There were no registered syphilis cases in age groups under 9 years of age and over 70 years of age. The youngest male and female patients were aged 17 years and 19 years, respectively. In all age groups the incidence rates were higher among males than among females. Average syphilis incidence in Belgrade between 2005 and 2014 was the highest in men aged 30–39 years (6.61/100.000) and 20–29 (6.54/100.000) and in women aged 40–49 years (0.07/100.000).

From 2010 to 2014, a total number of 196 cases of early syphilis (185 men and 11 women) were registered in Belgrade (Fig. 2). There were 65 (33.2%) cases of primary syphilis, 91 (46.4%) of secondary syphilis and 40 (20.4%) cases of early latent infection.

Characteristics of syphilis cases by HIV status in Belgrade in the period 2010–2014 are shown in Table 1. There were 154 (78.6%) HIV-negative and 42 (21.4%) HIV-positive syphilis cases. Comparisons of socio-demographic characteristics between HIV-negative and HIV-positive revealed several statistically significant differences. HIV positive patients were older ($p = 0.013$), more frequently unemployed ($p < 0.001$) and MSM ($p < 0.001$). A significantly greater percentage of HIV-positive patients reported unknown source of infection ($p = 0.022$) and were diagnosed in the secondary stage of infection ($p < 0.001$). However, only 2.4% of them had an early latent infection. A comparison of sex, marital status and education revealed no statistically significant differences between HIV-positive and HIV-negative patients.

During an early syphilis outbreak in 2014, a total of 71 cases were reported in Belgrade. There were 67 male patients (43 HIV-negative and 24 HIV-positive) among whom 57 (85.1%) were MSM while 4 were female patients. However, all HIV-positive patients were MSM. The patients' average age was 32.4 years (range 19–61 years). Primary syphilis was diagnosed in 20 cases, 42 patients had secondary syphilis, and 9 cases were classified as early latent syphilis.

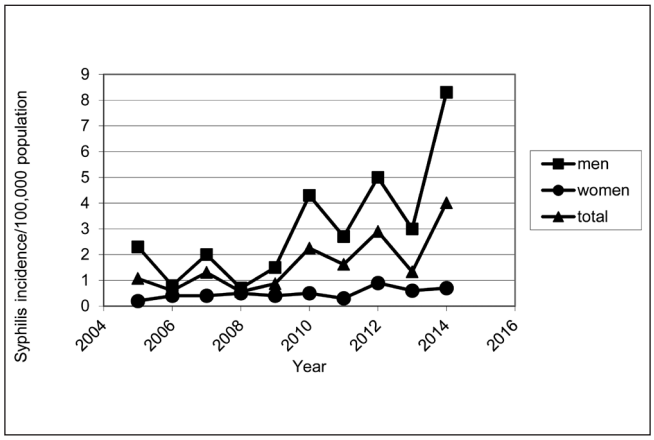

Fig. 1. *Incidence of early syphilis cases by sex, Belgrade, 2005–2014.*

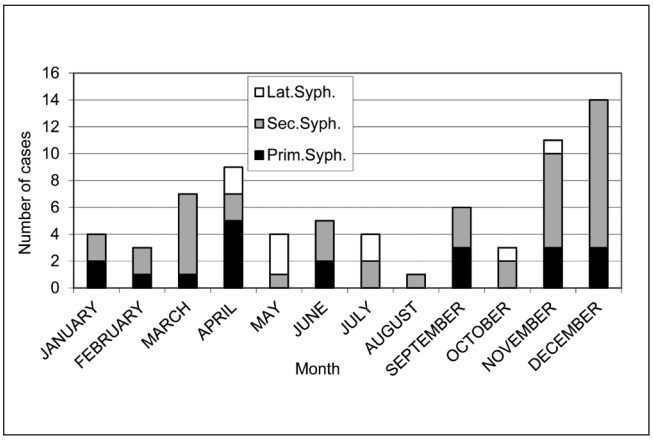

Fig. 3. *Distribution of 71 reported syphilis cases by stage of infection, Belgrade, 2014.*

Table 1. *Characteristics of 196 early syphilis cases by human immunodeficiency virus status, Belgrade, 2010–2014*

Variable	HIV negative n (%)	HIV positive n (%)	Total n (%)	p-value[a]
Gender				
Male	143 (92.9)	42 (100.0)	185 (94.4)	0.075
Female	11 (7.3)	0 (0.0)	11 (5.6)	
Age (years)				
≤ 19	5 (3.2)	0 (0.0)	5 (2.6)	0.013
20–29	58 (37.7)	5 (11.9)	63 (32.1)	
30–39	65 (42.2)	25 (59.5)	90 (45.9)	
40–49	20 (13.0)	9 (21.5)	29 (14.8)	
50+	6 (3.9)	3 (7.1)	9 (4.6)	
Marital status				
Never married	131 (85.1)	41 (97.6)	172 (87.8)	0.061
Married	18 (11.7)	0 (0.0)	18 (9.2)	
Divorced	5 (3.2)	1 (2.4)	6 (3.0)	
Education				
≤ Elementary	9 (5.9)	1 (2.4)	10 (5.1)	0.660
Secondary	118 (76.6)	33 (78.6)	151 (77.0)	
High	27 (17.5)	8 (19.0)	35 (17.9)	
Working status				
Employed	84 (54.5)	11 (26.2)	95 (48.5)	< 0.001
Unemployed	46 (29.9)	26 (61.9)	70 (35.7)	
Supported person	22 (14.3)	2 (4.8)	24 (12.2)	
Retired	2 (1.3)	3 (7.1)	5 (2.6)	
Sexual orientation				
Heterosexual	59 (38.3)	0 (0.0)	59 (30.1)	< 0.001
Homosexual	93 (60.4)	41 (97.6)	134 (68.4)	
Bisexual	2 (1.3)	1 (2.4)	3 (1.5)	
Source of infection				
Known	54 (35.1)	7 (16.7)	61 (31.1)	0.022
Unknown	100 (64.9)	35 (83.3)	135 (68.9)	
Syphilis stage				
Primary	53 (34.4)	12 (28.6)	65 (33.2)	< 0.001
Secondary	62 (40.3)	29 (69.0)	91 (46.4)	
Early latent	39 (25.3)	1 (2.4)	40 (20.4)	
Total	154 (78.6)	42 (21.4)	196	

p-value, according to Fischer's exact test or to χ^2 test, for differences between HIV positive and HIV negative patients

Seasonal variation in disease frequency during 2014 is presented in Figure 3. A peak was observed during November–December when 25 syphilis cases (35%) were diagnosed. Moreover, 72% of them were diagnosed in the secondary stage of infection.

Eighteen patients with PS had penile lesions associated with non-tender regional lymphadenopathy and reported unprotected oral sex with unknown partners one-month before referral to dermatologist. Anal chancres were found in two cases. Among all 20 male cases with PS, 80% were MSM and 4 patients were also HIV-positive.

There were 42 patients with SS: 39 male patients (36 were MSM while more than half of them – 55.6% were HIV-positive) and 3 female patients. Rash was identified in the majority of cases (95.2%), while condylomata lata were revealed in two women. In 24 cases, the only risk factor for SS among MSM was unprotected oral sex, with unprotected oral and anal sex in 12 cases. Three heterosexual men, as well as 3 women reported unprotected oral and vaginal sex.

There were nine patients (12.7%) with early latent syphilis at the referral: 8 men (75% were MSM) and 1 woman.

The majority of patients reported to have acquired syphilis in Belgrade. Actually, only 6 patients were infected abroad. Out of all 71 patients, 9 were referred to physicians due to information provided by their sexual partners.

Almost all patients were treated with a single intramuscular dose of 2.4 million units of benzathine penicillin G, except 10 penicillin-allergic patients, who were treated with 14-day course of oral doxycycline (100 mg twice a day).

DISCUSSION

During the observed period 2005–2014, early syphilis incidence in Belgrade increased by 383.2%. Belgrade is the capital of Serbia, and the largest city with a population of approximately 1.5 million. Syphilis incidence increase began in 2010 (9) and continued, with ups and downs, until 2014 when the rate was the highest (4.1 per 100,000). Men accounted for the most cases of syphilis between 2010 and 2014, with the vast majority of such cases occurring among MSM.

Syphilis incidence in Serbia in the new millennium was below 1.5 per 100,000 people (11). The exception was the year 2001 (2.7 per 100,000) when an outbreak occurred among heterosexual people in an institution for the care of adults with mental disorders (12). Low syphilis incidence has also been reported in other neighbouring countries. Rates below 1.5 per 100,000 population were observed in Albania (13), while syphilis incidence in Croatia in 2012 was below 2.5 per 100,000 (14). In the same year, the highest syphilis rate (8.5 per 100,000) in the South-East Europe was observed in Romania (14).

Critical feature of this analysis is data accuracy. There are reasons to believe that syphilis incidence is underestimated, since it is possible that some patients do not visit physicians. Syphilis is also well known as a great imitator and could be overlooked especially among non-experienced physicians, whereas some physicians do not report all cases.

HIV infection is strongly associated with syphilis especially among MSM. This association results from the common modes of transmission but also from the increase of unsafe sexual behaviour among HIV infected MSM (15). Moreover, there are significant statistical associations between syphilis infection and HIV acquisition, as genital ulcers can facilitate HIV transmission (16, 17). Several studies have reported that the rate of HIV and syphilis co-infection were as high as 50% (18, 19). However, in the study conducted in Israel (20), the majority of syphilis cases (96%) were co-infected with HIV. Such data indicate that HIV-infected patients with syphilis may be among the most important transmitters of HIV infection based on their continuous risky behaviour as well as biologic effects of genital ulcerations.

According to our results, between 2010 and 2014, more than 20% of syphilis cases were co-infected with HIV, nonetheless in 2014 this co-infection was revealed in 1/3 of cases. In our study, in comparison with HIV negative, HIV-positive syphilis patients were significantly older and more frequently unemployed and were MSM. They also significantly more frequently had sex with unknown partners and were diagnosed in the secondary stage of infection. Our results are in accordance with other studies where the majority of HIV-positive syphilis cases were MSM and diagnosed in the secondary stage of disease (6, 20, 21). In our study, almost 90% of HIV-positive patients were older than 30 years. In an outbreak of syphilis in London, the majority of HIV-positive patients were also older than 35 years (6).

We compared HIV-positive cases with HIV-negative cases in order to determine whether there were any distinct needs for these groups with regard to prevention, screening or other public health measures. There were no great differences between these two groups of patients in socio-demographic characteristics except for age and employment status. As already stated, HIV positive patients were older and much more of them (61.9% vs. 29.9% of HIV-negative cases) were unemployed. People who struggle financially are often experiencing life circumstances that increase their risks for sexually transmitted infections (22).

A significantly greater percentage of HIV-positive cases reported sex with unknown partners, making contact tracing ineffective. The majority of HIV-positive cases were diagnosed in the most contagious secondary stage of infection and only 2.4% in the early latent stage. Based on the fact that syphilis is a great imitator, that it is often overlooked, and that contact tracing is not possible when sexual partners are unknown, the number of syphilis co-infected cases could be underestimated and routine screening for syphilis and other sexually transmitted infections is highly recommended in this group. Given that HIV-positive patients are more often in contact with healthcare professionals (i.e. regular controls and taking prescriptions for anti-retroviral therapy) than HIV-negative individuals, this highlights the importance of counselling and risk reduction messages for this group.

During an early syphilis outbreak in Belgrade in 2014, the majority of patients acquired syphilis infection through oral sex. These data correlate with other reported outbreaks of syphilis such as the one reported in London, where 44% of MSM acquired syphilis through oral sex (6). This sexual practice is usually mistaken for "safe" sexual behaviour. MSM have low awareness of transmission of other sexually transmitted infections due to diverse types of sexual behaviour other than anal intercourse. Condom use for oral sex should be an important part of patient counselling.

Syphilis acquisition in our outbreak mainly occurred in Belgrade, Serbia's largest city. MSM choose to live in large cities which provide more anonymity, less stigma and more meeting places (i.e. sex venues such as parks and public toilets) for sexual contacts (23). For primary and secondary syphilis, a peak was observed during November–December. In this period, 72% of cases were diagnosed in the secondary stage of infection. Based on the mean incubation period of *Treponema pallidum* infection at 2–3 months (24), these data suggest an annual increase in syphilis acquisition from July to August. This could be explained by the fact that an increase in sexual activity and unsafe sex was linked with the increased leisure time during the summer vacation (25). Another potential explanation is that during the summer months there are more places where MSM can practice outdoor sex (i.e. parks, cruising area near the largest Belgrade's beach on Lake Ada Ciganlija).

In this outbreak, only 12.7% of syphilis cases were identified by their sexual partners. However, identification of potentially infected persons by their sexual partners was a limited contribution to epidemiological data, as the majority of partners were casual, anonymous or untraceable.

CONCLUSIONS

An early syphilis outbreak in Belgrade was mainly transmitted among men, out of whom more than a half were MSM. In

addition, all HIV positive patients in this outbreak were MSM. These findings underline the need for coordinated and expeditious surveillance, partner services, enhanced screening of population at risk, health education, as well as early diagnosis and treatment.

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Conflict of Interests

None declared

REFERENCES

1. Fenton KA, Lowndes CM. Recent trends in the epidemiology of STI in the European Union. Sex Transm Infect. 2004; 80(4):255-63.
2. Lacey HB, Higgins SP, Graham D. An outbreak of early syphilis: cases from North Manchester General Hospital. Sex Transm Infect. 2001; 77(5):311-3.
3. Halsos AM, Edgardh K. An outbreak of syphilis in Oslo. Int J STD AIDS. 2002; 13(6):370-2.
4. Giuliani M, Palamara G, Latini A, Maini A, Di Carlo A. Evidence of an outbreak of syphilis among men who have sex with men in Rome. Arch Dermatol. 2005; 141(1):100-1.
5. Cowan S. Syphilis in Denmark – outbreak among MSM in Copenhagen, 2003-2004. Euro Surveill. 2004; 9(12):25-7.
6. Righarts AA, Simms I, Wallace L, Solomou M, Fenton KA. Syphilis surveillance and epidemiology in the United Kingdom. Euro Surveill. 2004; 9(12):21-5.
7. Cronin M, Domegan L, Thornton L, Fitzgerald M, O'Lorcain P, Creamer E, et al. The epidemiology of infectious syphilis in the Republic of Ireland. Euro Surveill. 2004; 9(12):14-7.
8. Bjekić M, Vlajinac H, Šipetić S, Kocev N. Trends of gonorrhea and early syphilis in Belgrade 1985-1999. Sex Transm Infect. 2001; 77(5):387-8.
9. Bjekić M, Šipetić S. An outbreak of early syphilis in patients registered at City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2012: a case series of 86 patients. Serb J Dermatol Venereol. 2013; 5(2):65-71.
10. Centers for Disease Control and Prevention (CDC). STD Surveillance case definitions. Available at: http:/www.cdc.gov/std/stats/casedefinitions-2014.pdf [accessed 19.9.17]
11. Institute of Public Health of Serbia „Dr Milan Jovanovic Batut". Center for disease control and prevention: Report of infectious diseases in the Republic of Serbia. Belgrade: Institute of Public Health of Serbia „Dr Milan Jovanovic Batut"; 2012:39-50. Serbian
12. Vlajinac H, Šipetić S, Bjekić M, Savčić G, Marinković J. Outbreak of early syphilis in an institution for the care of adult with mental disorders. Epidemiol Infect. 2006; 134(3):585-8.
13. Harxhi A, Kraja D, Shehu E, French P. Multiple ulcers in primary syphilis with negative rapid plasma reagin and Venereal Disease research Laboratory tests: an unusual presentation during the re-emergence of syphilis in Albania. Int J STD AIDS. 2010; 21(3):211-2.
14. European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2012. Stockholm: ECDC; 2014:25-29.
15. Dougan S, Evans BG, Elford J. Sexually transmitted infections in Western Europe among HIV-positive men who have sex with men. Sex Transm Dis. 2007; 34(10):783-90.
16. Zeltser R, Kurban AK. Syphilis. Clin Dermatol. 2004; 22(6):461-8.
17. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis. 2001; 28(10):579-97.
18. Paz-Bailey G, Meyers A, Blank S, Brown J, Rubin S, Braxton J et al. A case-control study of syphilis among men who have sex with men in New York City: association with HIV infection. Sex Transm Dis. 2004; 31(10):581-7.
19. Wong W, Chew J, Kent C, Klausner J. Risk factors for early syphilis among gay and bisexual men seen in an STD Clinic: San Francisco, 2002-2003. Sex Transm Dis. 2005: 32(7):458-63.
20. Brosh-Nissimov T, Mor Z, Avramovich E, Katchman E, Avidor B, Mor O, et al. Syphilis outbreak among men who have sex with men, Tel Aviv, Israel, 2008-2009. Isr Med Assoc J. 2012: 14(3):152-6.
21. Rompalo AM, Joesoef MR, O'Donnell JA, Augenbraun M, Brady W, Radolf JD, et al. Clinical manifestations of early syphilis by HIV status and gender. Sex Transm Dis. 2001; 28(3):158-65.
22. Laumann EO, Youm Y. Racial/ethnic group differences in the prevalence of sexually transmitted diseases in the United States: a network explanation. Sex Transm Dis. 1999; 26(5):250-61.
23. Velicko I, Arneborn M, Blaxhult A. Syphilis epidemiology in Sweden: re-emergence since 2000 primarily due to spread among men who have sex with men. Euro Surveill. 2008;13(50): pii=19063.
24. Garnett GP, Aral SO, Hoyle DV, Cates W, Anderson RM. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex Transm Dis. 1997; 24(4):185-200.
25. Gillies P, Slack R, Staddard N, Connay S. HIV-related risk behaviour in UK holiday makers. AIDS. 1992; 6(3):339-41.

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