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Higher Incidence of Syphilis among Patients with HIV Infection: Population Study using Surveillance Data of Tokyo, Japan

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In Japan, the reported cases of syphilis have been increasing since 2011 especially in large cities such as Tokyo. The objective of this study was to evaluate the risk of HIV infection for syphilis co-infection on the population of Tokyo, Japan. We analyzed data of syphilis cases obtained from additional surveillance by the Tokyo Metropolitan Government in 2018, including those with human immunodeficiency virus (HIV) infection as well as data of HIV/acquired immunodeficiency syndrome (AIDS) cases during 1985-2017. We calculated the incidence of symptomatic syphilis cases among HIV-infected or non-HIV-infected individuals. Similarly, we calculated the incidence of syphilis, including asymptomatic cases, among each population. The relative risk of HIV infection for syphilis, including or excluding asymptomatic syphilis cases, was estimated. The relative risk was calculated by dividing the incidence of syphilis in the HIV-infected population by that in the non-HIV-infected population. Of the 1,775 syphilis cases reported in 2018, 172 cases were infected with HIV, 575 cases were uninfected, and the remainder were either unknown or not reported. The cumulative number of HIV/AIDS cases during 1985-2017 in Tokyo was 9,629; among them, 172 were co-infected with syphilis. The relative risk of HIV infection for syphilis was estimated as 423.29 if asymptomatic syphilis cases were included, and 372.37 if they were excluded. These results showed an extremely high risk of HIV infection. Since many syphilis cases have unknown or unreported HIV infection status, reduction of these cases might contribute to more reliable estimation of HIV infection risk.

Keywords: HIV; men who have sex with men; population-based study; relative risk; syphilis
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Introduction

In Japan, the reported cases of syphilis have been increasing since 2011, especially in large cities such as Tokyo and Osaka, and surrounding areas (National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare, Japan 2015; Takahashi et al. 2018). Reported cases of primary and secondary syphilis in Tokyo increased during 2011-2013 (Sugishita et al. 2016), with the rate of sexual transmission among men who have sex with men (MSM) being a contributing factor. However, since 2015, cases among heterosexual men and women have also been increasing rapidly (Sugishita et al. 2019). As of 2016, heterosexual transmission is dominant, although infection among MSM has continued.

In the USA, reported cases of primary and secondary syphilis have been increasing since 2011, and in 2017, MSM accounted for approximately 60% of cases (Centers for Disease Control and Prevention 2019). It is noteworthy that the incidence of human immunodeficiency virus (HIV) infection among MSM primary and secondary syphilis cases reached as high as 45.4% in 2017. Since both HIV and syphilis are sexually transmitted infections (STIs), the risk of co-infection is expected to be high.

To date, there have been numerous case reports of syphilis in HIV-infected patients (Shulkin et al. 1988; Tosca et al. 1990; Don et al. 1995; Tucker et al. 1997; D'Amico and Zalusky 2005; Weis et al. 2010; De Socio et al. 2011; Rajan et al. 2011; Yanagisawa et al. 2011; dos Santos et al. 2015; Mena Lora et al. 2017; Centers for Disease Control and Prevention 2019). However, since these studies did not use a control group (a non-HIV-infected population), the findings did not represent the relative risk of HIV infection

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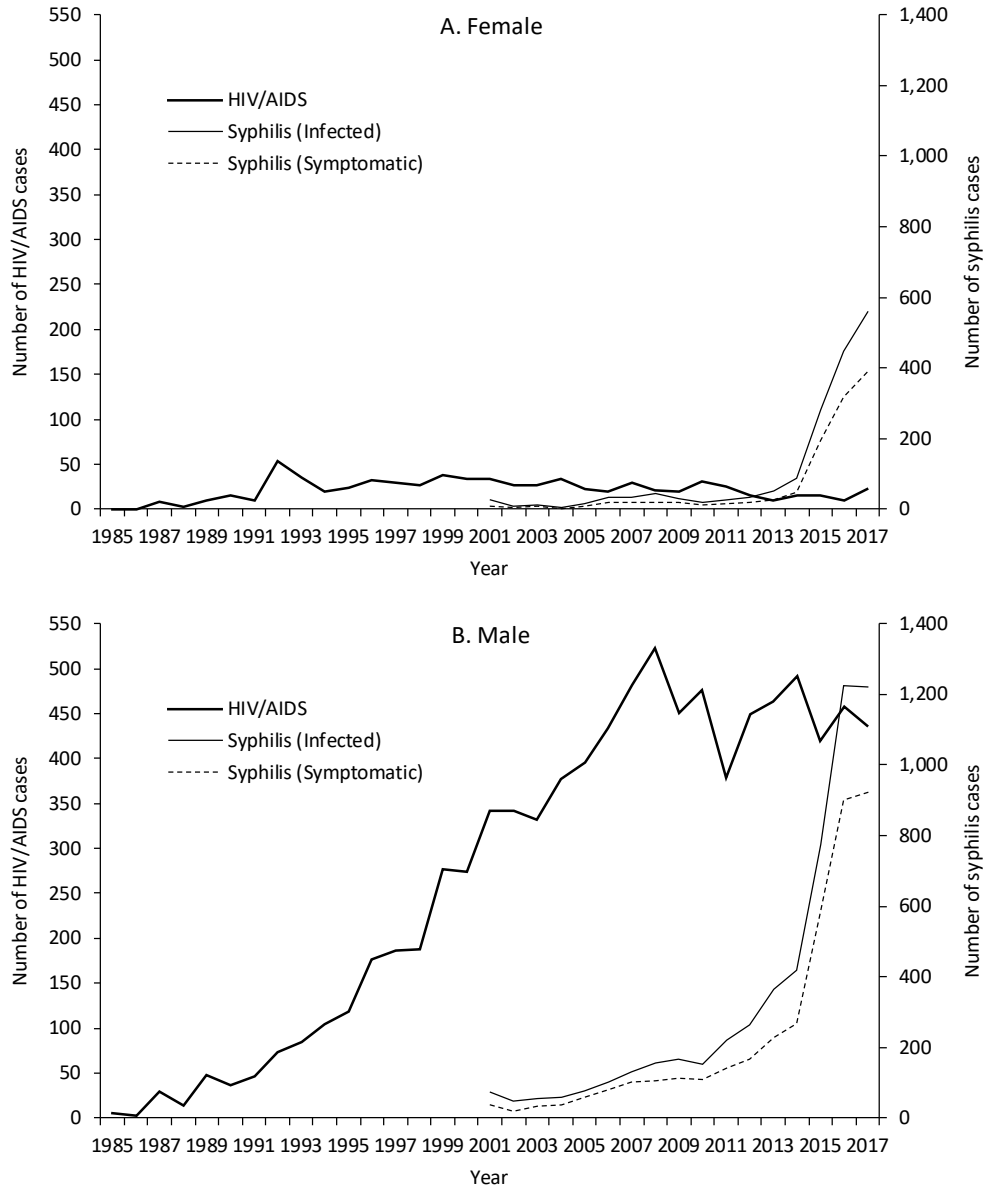

Fig. 1. Epidemic curve of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and syphilis-infected and symptomatic cases by sex in Tokyo.
Data sources are National Official Surveillance of Infectious Diseases in Tokyo, Japan, reported from doctors who diagnosed syphilis in Tokyo, based on the Law Related to the Prevention of Infectious Diseases and Medical Care for Patients of Infections in Japan. The data source is surveillance; therefore, the cases were defined as newly diagnosed cases each year. Syphilis-infected cases, including asymptomatic cases and symptomatic cases have been recorded separately since 2001; shown here are syphilis-infected and symptomatic cases after 2000 only. The upper panel shows the epidemic curve of HIV/AIDS and syphilis-infected and symptomatic cases in women, while the lower panel shows the same for men. The bold black line represents HIV/AIDS, the thin black line represents syphilis-infected cases, including asymptomatic cases, and the broken line represents syphilis-infected cases, excluding asymptomatic cases.

to syphilis. Moreover, because these were case reports, the data were collected from single or only a few medical facilities; thus, it may have a bias that fail to represent the risk to the population accurately. Moreover, one report specifically examined only MSM (Centers for Disease Control and Prevention 2019), and not the entire population. Even among heterosexual men and women, co-infection of HIV and syphilis might pose a high risk. Therefore, the relative risk in a population-based study must be considered, and to the best of our knowledge, has not been previously examined.

Fig. 1 demonstrates the number of cases of HIV/acquired immunodeficiency syndrome (AIDS) and syphilis in females and males in Tokyo, Japan. Since the data source was surveillance, the cases were defined as newly diagnosed cases each year. The data show that the reported number of HIV/AIDS cases had been increasing, but had remained at a high level recently. By contrast, the reported

number of syphilis cases has been increasing rapidly.

Tokyo Metropolitan Government (TMG) started to collect HIV infection history data from syphilis cases in 2018. The objective of this study was to evaluate the risk of HIV infection to syphilis on the population base using unique data collected by the TMG.

Methods

We used data of syphilis cases in 2018 and HIV/AIDS cases during 1985-2017 in Tokyo from surveillance based on the Law Related to the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law) in Japan. The Infectious Diseases Control Law in Japan requires all physicians to report early symptomatic (primary and secondary) syphilis, late symptomatic syphilis, asymptomatic syphilis, and congenital syphilis to the public health center within 7 days of diagnosis, using a designated reporting form (National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare, Japan 2015). The case definition of symptomatic syphilis, excluding congenital syphilis, was patients who showed syphilitic symptoms and were positive for both non-treponemal test and specific treponemal test. Asymptomatic syphilis is defined as syphilis characterized by seroreactivity without the symptoms of syphilis. Information related to nationality, sexual services, and co-infection of HIV among the syphilis cases were obtained through additional surveillance in Tokyo in 2018. The Tokyo population was based on 2017 population estimated from the 2015 Census in Tokyo. Since the syphilis antibody does not prevent reinfection (Fantry and Tramont 2002), we ignored the past history of syphilis prevalence before 2018. We also assumed that there were no HIV/AIDS cases before 1985, when surveillance for HIV/AIDS in Japan started.

We calculated the respective incidence of syphilis-infected cases, including asymptomatic and symptomatic cases among cumulative HIV/AIDS cases during 1985-2017 or the non-HIV-infected population. Incidence was defined as cases per 100,000 population. We then calculated the relative risk of HIV infection to syphilis among all people, and by sex. The relative risk was calculated by dividing the incidence of syphilis in the HIV-infected population divided by that in the non-HIV-infected population. We first estimated the relative risk while excluding syphilis cases for which the HIV infection status was unknown or not reported. Secondly, we applied sensitivity analysis to cases of unknown HIV infection status or for unreported HIV infection status among syphilis cases. We performed analysis under the assumption that the "HIV positive" rate among syphilis cases with unknown HIV infection status or no report was twice that of the "HIV positive" rate among syphilis cases with known HIV infection status. Furthermore, we performed analysis under the assumption that the "HIV positive" rate among syphilis cases with unknown HIV infection status or no report was half or quarter that of the "HIV positive" rate among syphilis cases with known HIV infection status.

Statistical inference was made through Fisher's exact test, and we adopted the significance level at 5%.

Ethical considerations

We asked the Ethical Committee in Tokyo Metropolitan Institute of Public Health for ethical review. However, because this study was an investigation based on the Infectious Diseases Control Law, the committee decided in August 2018 that the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare [MHLW] [22 December 2014, revised in 28 February 2017]) were not applicable.

Additional information was collected based on Chapter 15 of the Infectious Diseases Control Law, by asking doctors to provide information to the TMG following patient consent. The MHLW reviewed the associated legal aspects and approved the study.

Results

Characteristics of syphilis cases

In 2018, 1,775 syphilis cases were reported, of which, infection in males accounted for 66.48% (1,180) of them. The median age of the patients was 35 years old (range, 0-94 years), and the age distribution by sex is shown in Fig. 2. The dominant group was 20-24 years old among females, and 40-44 years old among males. In total, 1,303 cases were symptomatic syphilis (Table 1); among the female cases, 417 were symptomatic syphilis, and 886 cases were symptomatic in male cases. Among symptomatic syphilis cases, 555 cases had primary syphilis, 717 had secondary syphilis, 30 had late symptomatic syphilis, and one case had congenital syphilis.

Table 2 shows the background information of syphilis cases obtained from additional surveillance. In total, 1,053 (430 female cases and 623 male cases) were Japanese, which accounted for 59.32% of all syphilis cases. With regards to sexual services, 234 (222 female cases and 12 male cases) had provision of sexual services and 210 (one female case and 209 male cases) had accessed to them in the last 6 months, accounting for 13.18% and 11.83% of all syphilis cases, respectively. In terms of HIV co-infection, 171 cases (99.42%) were male. The 369 syphilis cases in MSM, which is homosexual contact in male, accounted for 20.79% of all syphilis cases and 31.27% of male syphilis cases. Among the MSM syphilis cases, 156 were HIV positive, and 69 were HIV negative. HIV co-infection in MSM was significantly higher than male non-MSM.

Relative risk of HIV infection

HIV infection status known cases only: Regarding HIV infection among syphilis-infected cases, 172 cases were

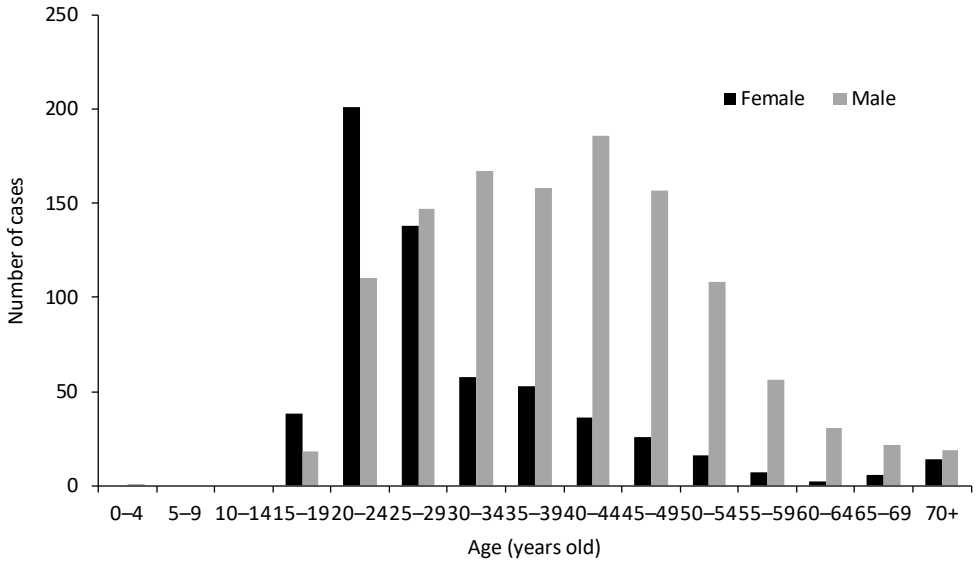

Fig. 2. Age distribution of syphilis cases by sex in Tokyo, 2018.
Data sources are National Official Surveillance of Infectious Diseases in Tokyo, Japan, reported by doctors who diagnosed syphilis in Tokyo, based on the Law Related to the Prevention of Infectious Diseases and Medical Care for Patients of Infections in Japan. The data source is surveillance, and the cases were defined as newly diagnosed cases each year. Black bars represent the age distribution of syphilis cases among women, and the gray bars represent the distribution among men.

Table 1. Disease stage of syphilis cases in Tokyo (2018).

	Number of cases		
	Total	Female	Male
Syphilis cases	1,775	595	1,180
Symptomatic syphilis	1,303	417	886
Early symptomatic syphilis (primary)	555	131	424
Early symptomatic syphilis (secondary)	717	278	439
Late symptomatic syphilis	30	8	22
Congenital syphilis	1	0	1
Asymptomatic syphilis	472	178	294

positive, 575 cases were negative, and the remaining cases were unknown or not reported as shown in Table 3. Of the symptomatic syphilis cases, 109 cases were HIV positive, 415 cases were HIV negative. Among female syphilis cases, one case was HIV positive, and 285 cases were HIV negative. Of the symptomatic syphilis cases among females, one case was HIV positive, and 200 cases were HIV negative. Among males, 171 cases were HIV positive, and 290 cases were HIV negative. Of male symptomatic syphilis cases, 108 cases were HIV positive, and 215 cases were HIV negative. The remaining cases in each category were unknown or not reported.

The cumulative incidence of HIV/AIDS cases during 1985-2017 in Tokyo was 9,629. Of these, in 2018, 172 cases were syphilis-infected cases, and 109 cases were symptomatic syphilis (Table 3). The respective incidence per 100,000 people was 1,786.27 for syphilis-infected cases and 1,132.00 for symptomatic syphilis cases.

In 2018, the Tokyo population was 13.65 million; thus, the non-HIV-infected population was inferred as 13.64 million. With regards to non-HIV-infected syphilis cases in 2018, 575 cases were syphilis-infected, and 415 cases were symptomatic syphilis (Table 3). The incidence was 4.22 for syphilis-infected cases and 3.04 for symptomatic syphilis cases per 100,000. Therefore, the relative risk was 423.29 for syphilis-infected cases and 372.37 for symptomatic syphilis cases (Table 4).

Among HIV/AIDS cases, 715 cases were female, including one case with symptomatic syphilis. Consequently, the incidence for both syphilis-infected and symptomatic syphilis cases was 139.86 per 100,000. In Tokyo in 2018, the female population was 6.92 million, and the non-HIV-infected population was 6.92 million. Regarding female non-HIV-infected syphilis cases, 285 cases were syphilis-infected cases, and 200 cases were symptomatic; the incidence was 4.12 for syphilis-infected

Table 2. Background information of syphilis cases by sex and human immunodeficiency virus (HIV) infection status in Tokyo (2018).

		Female (n = 595)				Male (n = 1,180)			
		Total	HIV positive	HIV negative	Unknown or unreported	Total	HIV positive	HIV negative	Unknown or unreported
Nationality	Japan	430	1	283	146	623	151	262	210
	Other than Japan	3	0	2	1	31	15	10	6
	Unknown	162	0	0	162	526	5	18	503
Provision of sexual services in the last 6 months	No	150	1	84	65	404	95	187	122
	Yes	222	0	171	51	12	1	7	4
	Unknown	223		30	193	764	75	96	593
Access to sexual services in the last 6 months	No	345	1	238	106	235	88	97	50
	Yes	1	0	1	0	209	8	110	91
	Unknown	249		46	203	736	75	83	578
Sexual activity	Homosexual contact	1	0	0	1	369	156	69	144
	Heterosexual contact	535	1	268	266	518	7	172	339
	Bisexual contact	1	0	0	1	7	2	3	2
	Unknown	58	0	17	41	286	6	46	234
Age (years)	0-9	0	0	0	0	1	0	0	1
	10-19	38	0	18	20	18	0	8	10
	20-29	339	0	160	179	257	22	73	162
	30-39	111	0	51	60	325	63	70	192
	40-49	62	1	31	30	343	59	74	210
	50-59	23	0	13	10	164	25	41	98
	60-69	8	0	3	5	53	2	18	33
	70+	14	0	9	5	19	0	6	13
Total		595	1	285	309	1,180	171	290	719

In total, 1,775 syphilis cases were reported. "Unknown" in "sexual activity" represents cases in whom the contact type was unknown. In total 172 cases were HIV positive and 575 cases were HIV negative.

Table 3. Human immunodeficiency virus (HIV) infection status among syphilis cases in Tokyo (2018).

	Both		Female		Male	
	Infected	Symptomatic	Infected	Symptomatic	Infected	Symptomatic
HIV positive	172	109	1	1	171	108
HIV negative	575	415	285	200	290	215
Unknown or unreported	1,028	779	309	216	719	563
Total	1,775	1,303	595	417	1,180	886

"Infected" consists of cases who were diagnosed with both symptomatic and asymptomatic syphilis. "Symptomatic" consists of syphilis cases that were diagnosed as syphilis infection with symptoms of syphilis.

cases and 2.89 for symptomatic cases. The relative risk was 33.95 for syphilis-infected cases and 48.39 for symptomatic cases (Table 4).

Among the 8,914 male HIV/AIDS cases, 171 cases were syphilis-infected cases, in which 108 cases were symptomatic; their respective incidences were 1,918.33 and 1,211.58. In Tokyo in 2018, the male population was 6.73 million; thus, the non-HIV-infected male population was inferred to be 6.72 million. Regarding male non-HIV-infected syphilis cases, 290 were syphilis-infected cases, and 215 cases were symptomatic; thus, their respective incidences were 4.32 for syphilis-infected cases and 3.20 for symptomatic cases. Their relative risks were 444.06 for syphilis-infected cases and 378.62 for symptomatic cases (Table 4).

Sensitivity analysis: The relative risks of HIV infection were estimated as 808.02 for syphilis-infected cases and 704.83 for symptomatic syphilis cases if we assumed that the "HIV positive" rate of the unknown/not reported cases

Table 4. Estimated relative risk of human immunodeficiency virus (HIV) infection to syphilis-infected or symptomatic cases.

	Both		Female		Male	
	Infected	Symptomatic	Infected	Symptomatic	Infected	Symptomatic
HIV infection status known cases only	423.29	372.37	33.95	48.39	444.06	378.62
Sensitivity analysis						
Twice	808.02	704.83	49.02	70.16	1,115.49	907.97
Half	276.56	241.81	32.64	46.62	261.53	222.60
Quarter	211.93	184.35	16.28	23.27	190.44	159.82

"Infected" consists of cases who were diagnosed with both symptomatic and asymptomatic syphilis. "Symptomatic" consists of syphilis cases that were diagnosed as syphilis infection with symptoms of syphilis. "HIV infection status known cases only" represents syphilis cases in which the HIV infection status was unknown or unreported were excluded from calculations. "Twice/half/quarter" in sensitivity analysis indicates relative risk under the assumption that the HIV positive rate among syphilis cases whose HIV infection status was unknown or unreported was twice/half/quarter that of the HIV positive rate among syphilis cases whose HIV infection status was known.

of HIV infection among syphilis cases was twice that of the rate among syphilis cases with known cases of HIV infection. Conversely, assuming that the "HIV positive" rate of syphilis cases with unknown or not reported HIV infection was half or a quarter that of the rate among syphilis cases with known cases of HIV infection, then the relative risks of HIV infection can be estimated as 276.56 or 211.93 for syphilis-infected cases, and 241.81 or 184.35 for symptomatic syphilis cases.

If we assumed that the "HIV positive" rate of the unknown/not reported cases of HIV infection among syphilis cases was twice/half/quarter that of the rate among syphilis cases with known cases of HIV infection, for females, the relative risks of HIV infection were estimated as 49.02/32.64/16.28 for syphilis-infected cases and 70.16/46.62/23.27 for symptomatic syphilis cases. For males, the relative risks of HIV infection were estimated as 1,115.49/261.53/190.44 for syphilis-infected cases and 907.97/222.60/159.82 for symptomatic syphilis cases.

The results of sensitivity analysis are presented in Table 4. The relative risk in sensitivity analysis was 16.28 to 1115.49, as shown in the lower panel of Table 4. The risk to males was much higher than the risk to females. In both sexes, and to males, the relative risk for syphilis-infected cases was higher than that for symptomatic syphilis cases. However, to females, the relative risk for syphilis-infected cases was lower than that for symptomatic syphilis cases.

Sensitivity analysis, shown at Table 4, revealed that, for the case of "twice," the relative risks were more than twice to males but lower than twice to females or to both sexes. Conversely, for the case of "half," relative risks were slightly lower to females, but approximately 40% or 35% lower to males or to both sexes. For the case of "quarter," the relative risks were approximately half lower to females or to both sexes and approximately 60% lower to males.

Discussion

Although many case reports have described the rate of syphilis infection among HIV-infected patients (Shulkin et al. 1988; Tosca et al. 1990; Don et al. 1995; Tucker et al. 1997; D'Amico and Zalusky 2005; Weis et al. 2010; De Socio et al. 2011; Rajan et al. 2011; Yanagisawa et al. 2011; dos Santos et al. 2015; Mena Lora et al. 2017) or among MSM with HIV infection (Centers for Disease Control and Prevention 2019), in the current study, we present the relative risk of HIV infection to syphilis for a population base. This report is the first to describe the relative risk in a general population. The estimated results show the relative risks to be large and irrespective of sex, for syphilis-infected cases or symptomatic syphilis cases. Even the smallest relative risk was 16.28, which represents an extremely high risk. Moreover, the risk to males is higher than that to females, and the substantial differences between sexes might be attributable to MSM cases. The relative risk for syphilis-infected cases and for symptomatic syphilis cases was different between sexes. Careful interpretation of these results is necessary since there was only one case of symptomatic syphilis in female HIV co-infection cases.

We analyzed data of syphilis cases in 2018 and HIV/AIDS cases during 1985-2017 in Tokyo. By the Infectious Diseases Control Law, both syphilis and HIV/AIDS are notifiable diseases, and all doctors who diagnose syphilis or HIV/AIDS must report it to the public health center of the appropriate jurisdiction. Therefore, information on the number of syphilis cases was available even before 2018 as shown in Fig. 1; however, the HIV/AIDS status among syphilis cases was not reported until 2018. Data on HIV co-infection among syphilis cases were obtained from additional surveillance in Tokyo in 2018. Conversely, syphilis co-infection among HIV-infected cases has not yet been reported, even in Tokyo; therefore, we cannot evaluate the opposite risk.

HIV/AIDS patients were carefully monitored for co-

infection with syphilis, even in cases without symptoms of co-infection, as recommended by the guideline (Centers for Disease Control and Prevention et al. 2014). For non-HIV-infected people, the presence of syphilis was checked before surgery or during pregnant, but its frequency is considered to be low, compared to HIV/AIDS patients. It is therefore considered that the detection rates of asymptomatic syphilis cases will differ among HIV-infected and non-infected patients. If this is correct, then the risk of HIV infection to syphilis might be different among asymptomatic and symptomatic cases of syphilis, and they must be divided for risk assessment.

Using sensitivity analysis, we estimated the relative risks of HIV infection under three hypothetical situations for unknown or non-reported HIV infection cases: We assumed that the HIV positive rate among syphilis cases with unknown HIV infection status was twice that of the rate among syphilis cases with known HIV infection status; we assumed that the HIV positive rate among syphilis cases with unknown HIV infection status was half or quarter that of the rate among syphilis cases with known HIV infection status. We consider the true relative risk to be among three hypothetical situations, which is more plausible likely depends on the reasons that the disease remains unknown or unreported. If infected people hesitate to declare their HIV carrier or AIDS status, then the HIV positive rate among unknown or unreported groups might be higher. The assumption of twice is therefore probably the more plausible. Alternatively, if the dominant reason was due to lack of testing, then the assumption of quarter might be more plausible because they might feel less responsibility to report their HIV infection status and have less interest in the test. If we assume that the HIV positive rate among syphilis cases with unknown or non-reported HIV infection status is the same among syphilis cases with known HIV infection status, then the relative risks would be the same as those calculated by excluding syphilis cases with unknown or non-reported HIV infection status by definition (Table 4).

We treated HIV infection cases as the sum of HIV-infected cases and AIDS cases. Logically, the cumulative number of HIV-infected cases and AIDS cases might include twice the number of the same cases with AIDS. Therefore, one must avoid double-counting when estimating the HIV-infected population.

Since the data were sourced by surveillance, HIV-infected cases or AIDS cases could not be identified. Therefore, we cannot exclude the possibility of the same cases being included with AIDS from the list of HIV-infected cases in the past. Indeed, patients might be diagnosed as HIV carriers and recorded in surveillance at a location other than Tokyo, even in Japan. We ignored the possibility of double-counting and assumed for simplicity that AIDS cases were not recorded by surveillance in Tokyo as HIV carriers to date. We cannot currently evaluate this assumption; therefore, as the next challenge for related research, we must check its robustness using other information for surveillance.

These results suggest that HIV testing for syphilis cases, especially for male cases, should be mandatory. Conversely, testing for syphilis should be mandatory for newly diagnosed cases of HIV infection. If such policies were to be followed, the known syphilis cases would increase considerably, especially in asymptomatic cases of syphilis. Moreover, if testing for syphilis or HIV infection was to be extended to all newly diagnosed STI cases instead of being routinely limited to syphilis or HIV-infected cases, then more precise data for epidemics of STIs, including syphilis and HIV/AIDS, could be obtained; thus, the development and spread of disease from symptomatic cases would be avoided.

Additionally, enhancement of surveillance might be another suitable policy to control syphilis. For example, we can suppose that a public health center is notified of newly diagnosed HIV-infected cases, the public health center should confirm whether they also receive test results for syphilis. As a result, the performance rate of testing for syphilis, as well as the rate of positive results could represent a policy target to implement change. At any rate, the feasibility of policy reform, including testing costs and effectiveness, as a control policy is our next challenge.

This study has a number of limitations that should be considered. First, only 1 year of data was available for HIV infection among newly diagnosed syphilis cases. We were therefore unable to estimate the variance of our estimated relative risk and applied statistical tests, as several years must have passed to accumulate sufficient data. Second, we did not consider movement into or from Tokyo; although the population in each year was examined, HIV-infected or syphilis cases were assumed not to change residence to or from Tokyo. The third limitation, which is closely related to the second, is that we assumed that HIV-infected or syphilis-infected cases never died. That is a strict assumption; however, surveillance data do not include information of outcomes after reported to surveillance and thus information of surveillance was limited to condition at the time of diagnosis. Fourth, the surveillance for syphilis in Tokyo provides the number of newly diagnosed cases of syphilis at medical facilities in Tokyo and does not consider people who may reside outside Tokyo, but visit a doctor in Tokyo. Probably the most important limitation is that more than half of the cases of syphilis had unknown or unreported HIV infection status. We conducted sensitivity analysis of the HIV positive rate among them, and we expected the true relative risk to reside among three hypothetical situations. However, the true positive rate might not be among the assumptions. This could be resolved by accumulation of data for more than 1 year, and this point remains a challenge for future research. Finally, as described above, the detection rates of asymptomatic syphilis cases were expected to be significantly different among HIV-infected patients and non-HIV-infected persons, and it is impossible to evaluate such a difference quantitatively. On the other

hand, the detection rates of symptomatic syphilis cases were considered to be the same among HIV-infected patients and non-HIV-infected persons. The calculation of relative risk of HIV infection to asymptomatic syphilis in the present study assumed to ignore this difference in detection rates, implicitly. Therefore, the estimated relative risk of HIV infection for syphilis-infected cases, including asymptomatic cases, might be less credible than that for symptomatic cases.

In conclusion, we used surveillance data of HIV/AIDS and syphilis in Tokyo, Japan to examine the risk of HIV infection to syphilis. The results showed a very high relative risk of HIV infection, and even the smallest risk was more than 16. Furthermore, we demonstrated that males are at considerably more risk than females, presumably because of male homosexual activity in addition to the risk of heterosexual activity. Many syphilis cases had unknown or unreported HIV infection status, and a reduction of this unknown or unreported proportion might contribute to a more plausible estimator of the risk of HIV infection.

From January 2019, the MHLW expanded the gathering of information from syphilis cases to add "history of engaging in sexual services or access to sexual services," "history of HIV co-infection," "site of occurrence of lesions such as external genitals, anus, lips, oral cavity, oropharynx, or other place," "presence or absence of pregnancy," and "history of treatment for syphilis." Of these items, the first two items were introduced by TMG from January 2018 and were analyzed in this study. We therefore propose that the trial of TMG in 2018 contributes to public health policies nationwide.

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Conflict of Interest

The authors declare no conflict of interest.

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