

**Trends in the Incidence of Syphilis in the Middle-aged and Older Adults in Japan: A Nationwide
Observational Study, 2009–2019**

Short title: Syphilis in the middle/elderly in Japan

Misa Takahashi^a, Hideharu Hagiya^{a*}, Toshihiro Koyama^b, Fumio Otsuka^a

^aDepartment of General Medicine, Okayama University Graduate School of Medicine, Dentistry and
Pharmaceutical Sciences, Okayama, 7008558, Japan

^bDepartment of Pharmaceutical Biomedicine, Okayama University Graduate School of Medicine,
Dentistry, and Pharmaceutical Sciences, Okayama, 7008558, Japan

***Corresponding author**

Hideharu Hagiya, M.D., Ph.D.

Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and
Pharmaceutical Sciences

2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Phone: +81-86-235-7342 Fax: +81-86-235-7345

E-mail: hagiya@okayama-u.ac.jp

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T. Koyama and F. Otsuka.*

Abstract

Aim: Sexually transmitted infections remain a neglected area of research in geriatrics. However, in the global aging societies, sexual health among the middle-aged and the older adults is an emerging public concern. High-income countries are facing a resurgence of syphilis cases among young generations, but little is known about its prevalence in older population. We aimed to investigate the national trend of syphilis cases in Japan. **Methods:** This nationwide observational study used the publicly-available database (2009–2019) to calculate crude and age-adjusted incidence rates of syphilis per 100,000 population by age, sex, and clinical stage. We collected data of patients aged 50 years or older and performed joinpoint regression analysis to estimate long-term trends and average annual percentage changes (AAPCs). **Results:** The total number of syphilis patients increased about 8-fold from 165 in 2009 to 1,280 in 2019. AAPCs of crude incidence rates significantly increased in every age category; 33.2% in 50–59 years, 23.8% in 60–69 years, and 20.9% in ≥ 70 years. Age-adjusted incidence rates have surged at AAPCs of 28.7% in men and 23.1% in women, reaching 4.09 in men and 0.71 in women in 2019. By clinical stage, marked increases were observed in primary (AAPCs, 42.3% in men and 41.6% in women) and secondary syphilis (AAPCs, 24.9% in men and 24.2% in women). **Conclusions:** An up-toward trend of syphilis among people aged 50 years or older was observed. The importance of sexual health among older people should be highlighted in this aging Japanese society.

Keywords: aging; sexual health; sexually transmitted infection; spirochete; syphilis

INTRODUCTION

Sexual health among the older population is an emerging public concern, especially in views of sexually transmitted infections (STIs).¹ Due to less attention in this field, geriatric research on this area remained neglected. However, globally, the current aging population has become a springboard for further investigations on STIs among the **middle-aged and older adults**. Syphilis is one of the most common STIs caused by *Treponema pallidum*, which is renowned for its invasiveness and immune-evasiveness.² Clinical manifestations result from an inflammatory response elicited by the spirochete replicating within tissues, varying from a lesion at the infectious site to systemic involvement potentially imitating those of other diseases. Owing to its diverse manifestations, syphilis has earned the names of the great imitator or the great mimicker,³ prompting Dr. William Osler to say “He who knows syphilis knows medicine”.

According to the World Health Organization, an estimated 6 million new cases of syphilis are diagnosed annually worldwide.^{4,5} Based on an observational study using the Global Burden of Disease, disability-adjusted life-years of STIs decreased from 1990 to 2019 worldwide, excepting syphilis showing an upward trend from 2010 (347.65 per 100 000 person-years) to 2019 (423.16 per 100 000 person-years).⁶ This suggests that syphilis still represents a global public burden that needs more attention to be tackled with. In low- and middle-income countries syphilis incidence remains high; unfortunately, neonatal syphilis is still common, and several hundred thousands of births result in death due to this preventable disease yearly.⁷ In contrast, high-income countries have had declining syphilis incidence among heterosexual young population, although it has re-emerged notably among men who have sex with men.^{8–10} Japan has also been experiencing a marked upsurge in syphilis prevalence. According to a nationwide surveillance in 2016, the annual cases of syphilis in Japan increased almost 7-fold compared to those reported in 2010.^{11,12} Particularly noteworthy is the increase in the case number among young adult women.¹³ Also, approximately half of young male syphilis patients were identified as a heterosexual orientation,¹² rather than men who have sex with men.

Reports on the rising trend of syphilis among young populations have accumulated, but those among the **middle-aged and older adults** remain under-investigated. To our knowledge, recent data

suggest elevating trends of syphilis in patients aged 50 years or older in high-income countries, such as North America,¹ the United Kingdom,¹⁴ Australia,¹⁵ Korea,¹⁶ and China.^{17,18} Thus, it is a pressing issue faced by many advanced countries as the life span of people increases. However, little is known about Japan, one of the most aging countries worldwide, and there is no guideline available for prevention or intervention targeting this geriatric population. The aim of this study is to reveal the recent trend of syphilis incidence by age and sex in a population aged 50 years and older in Japan.

METHODS

Data sources

This was an 11-year retrospective observational study covering national data between 2009 and 2019. We used the publicly available data published by the Japanese Ministry of Health, Labour and Welfare, which is known as the Annual Report of the National Epidemiological Surveillance of Infectious Diseases.¹⁹ In Japan, in accordance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law), which was established in 1999 and updated in 2007, syphilis has been registered as one of the notifiable diseases, classified under Category V Infectious Diseases that should be reported within 1 week after diagnosis.²⁰ The reportable case definition of syphilis requires a positive result by both a specific treponemal test (*e.g.*, *T. pallidum* hemagglutination assay and *T. pallidum* latex agglutination) and a nonspecific treponemal test (*e.g.*, rapid plasma reagin and latex agglutination), or laboratory identification of *T. pallidum* (detection by India ink or Giemsa staining method and/or polymerase chain reaction detection of the bacterial genome from skin lesions). Physicians are required to report all such cases to the local public health centre, who in turn report the data to the national level through the National Epidemiologic Surveillance of Infectious Disease system, which is made publicly available as an online material.¹⁹ As a notifiable disease, any physician, regardless of the sector (*e.g.*, public or private), is legally required to report all cases meeting the reporting criteria.

Data analysis

Data on patients aged 50 years and older were stratified by age and sex, and crude incidence rates (CR) and age-adjusted incidence rates (AAR) per 100,000 population were calculated. The age groups were categorized as follows: 50–59 years, 60–69 years, and 70 years and older. For those aged ≥ 70 years, details in the patient age were unavailable in the open database; thus, we treated the data for those aged ≥ 70 years as a combined number. To determine the AAR of syphilis incidence, we used the direct age-standardization method with the 2009 (the first year of the study period) Japanese population as the standard population. Since this study focused on the older population, patients younger than 50 years were excluded from the analysis. For comparison with other STIs, we extracted the incidence data of *Neisseria gonorrhoeae* infection, Condyloma acuminatum, Genital herpes virus infection, and Genital chlamydial infection from the identical database.

Statistical analyses

A joinpoint regression model was implemented with the Joinpoint Regression Program (version 4.8.0.1, April 2020, Statistical Research and Applications Branch, National Cancer Institute, USA).²¹ The analysis is supposed to identify the year (joinpoint) when the significant trend changes occurred and estimated the magnitude of the increase or decrease. The annual percentage changes (APCs) between trend-change points were determined as well. To compare the differences in the incidence trends between population subgroups, the average annual percentage change (AAPC) was computed for the entire period. The threshold for statistical significance was defined as p -value < 0.05 , which indicated the level at which the slope differed from zero.

Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the institutional review board of Okayama University Hospital with a waiver for informed consent because the study intended to

retrospectively analyse open data (No. 1910-009).

RESULTS

Number of syphilis cases

In the past 11 years, 6,527 syphilis cases were reported from patients aged 50 years or more in Japan, of which 5,276 cases (80.8%) accounted for men. The annual numbers increased from 165 in 2009 to 1,280 in 2019, suggesting that the case number increased about 8-fold in the past 11 years (Supple Fig. 1). By the age group, each of the case numbers in 50–59 years, 60–69 years, and ≥ 70 years remarkably increased, reaching at 715 cases, 276 cases, and 289 cases in 2019, respectively. On the other hand, other STIs showed plateau levels during the study period (Supple Fig. 2).

Trends in CRs by age groups and sex

CRs per 100,000 population by 10-year age groups and sex were investigated (Supple Table 1). The overall CR in 50–59 years increased about 9.3-fold, ranging from 0.47 in 2009 to 4.39 in 2019. Comparing between sex, CR among men remained higher than that of women during the study period, which reached 7.63 among men and 1.13 among women in 2019. Similarly, the overall CR in 60–69 years increased about 6.1-fold; 0.28 in 2009 and 1.70 in 2019. CRs in men and women were greatly different as well; 3.18 among men and 0.29 among women in 2019. Additionally, the overall CR in 70 years or more also increased about 6.2-fold; 0.17 in 2009 to 1.06 in 2019. The difference between sex was comparatively smaller than other age groups.

Trends of CRs over time by the age groups and sex, and the results of joinpoint regression analysis were provided in Fig. 1 and Table 1. Overall, including men and women, the AAPCs (95% CI) of CRs significantly increased in every age category across the entire period; 33.2% (30.0–48.0) in 50–59 years, 23.8% (17.7–30.3) in 60–69 years, and 20.9% (16.3–25.6) in ≥ 70 years. The increasing trend was much significant in 50–59 years age group than the others in both men (AAPC 31.3%, 95% CI: 22.8–40.4) and women (AAPC 39.7%, 95% CI: 19.4–50.2).

Trends in AARs by sex and clinical stages

The overall trends in AARs by sex are depicted in **Fig. 2**. Comparing between sex, AAR among men were continuously higher than that of women, reaching 4.09 among men and 0.71 among women in 2019 (**Supple Table 2**). The results of the joinpoint regression analysis by sex were as follows: overall (AAPC 28.3%, 95% CI: 21.5–35.6), men (AAPC 28.7%, 95% CI: 21.7–36.2), and women (AAPC 23.1%, 95% CI: 16.2–30.5) (**Table 2**). AARs in both sex have surged over the study period without any trend change points.

Trends of AARs by the clinical stage (primary, secondary and late syphilis) were finally analyzed (**Fig. 3** and **Supple Table 2**). Numerically, the annual case numbers of primary and secondary syphilis in 50-59 years have drastically increased in comparison with other categories (**Supple Fig. 3**). AAR in primary syphilis have remarkably risen; the total AAR increased about 16-fold, ranging from 0.05 in 2009 to 0.80 in 2019. Between sexes, AAR among men in primary syphilis increased about 14-fold, ranging from 0.11 in 2009 to 1.59 in 2019, in comparison with that among women (0 in 2009 to 0.11 in 2019). Those of secondary syphilis have also increased about 8-fold from 0.05 in 2009 to 0.41 in 2019. Similar to the primary syphilis, AARs among men were higher than women during the study period, going up to 0.79 and 0.07, respectively, as of 2019. However, the rising trend appeared to reach its peak in recent years. In contrast, we observed slight upward trends for late syphilis in both sexes; the total AAR only doubled in the past 11 years (from 0.06 to 0.14). The joinpoint regression analysis revealed that the primary, secondary, and late syphilis increased with the total AAPCs (95% CI) of 42.3% (27.7–58.7), 32.4% (19.0–47.3), and 12.0% (8.5–15.6), respectively (**Table 2**). Although APC of primary syphilis among women was not calculable, no large difference was observed between sexes in the secondary and late syphilis.

DISCUSSION

The number of syphilis cases among 50 years or older have been increasing by nearly 8-fold in Japan in the past 11 years, even among those aged ≥ 70 years. The increasing trends were remarkable in men

than in women, especially among those in the 50–59 years of age with an average APC of over 30%. By clinical stage, there was a marked increase in primary syphilis in both men and women. This indicates that new syphilis infections are increasing among the middle-aged and older people in Japan. Compared with the constant trends of other STIs, the case number of syphilis has been indeed surging. This could be associated with an improved awareness of the disease, advances in diagnostic tools, and a law revision to report all cases of syphilis. In comparison with younger generations,^{11–13} the total number of syphilis is still quite lower; however, our data cast a new concern in this aging Japanese society.

The underlying reasons for the increasing trends among the middle-aged and older population should be discussed. Previous literature raised inadequate understanding of STIs, unsafe sexual practices (they may no longer care for pregnancy), shortage of sexual health services, and prolonged life span as potential causes.^{14,22} In addition to these, sexual activity among the older population should be considered. In Brazil, the prevalence of sexual activity among adults aged 60 years or over was reportedly 48%, of whom men were more sexually active than women.²³ In China, those among women aged 55 to 85 years were reportedly sexually active (12.5%) one month prior the time of investigation.²⁴ Another report from China suggested nearly half of syphilis cases reported in 2019 were those from aged ≥ 50 years.¹⁷ To the best of our knowledge, there is no such data among the Japanese older population. However, through the advancement in medicine and public health, an increasing number of people age healthily. Thus, the sexual behaviour of older Japanese individuals may have also changed over time, leading to a higher risk of STIs among them.

Indeed, STIs, including syphilis, are underdiagnosed in older people. However, if left untreated, the disease will progress over the years through a sequence of clinical stages or may even present as a latent disease, finally causing irreversible cardiovascular or neurological complications.²⁵ Syphilis may remain undeveloped for decades, and thus, most of the reported cases in the older population are in its tertiary stage. Patients with neurosyphilis manifest varied symptoms encompassing cognitive impairment, general paresis, uveitis, and hearing loss, all of which can be misdiagnosed as a primary psychiatric or neurologic disease especially in the older population.^{26,27} However, neurosyphilis

is known as one of the treatable dementia diseases,²⁸ and thus, in the context of an increasing case of syphilis in the older people in Japan, geriatric clinicians should be aware of the disease more carefully. Moreover, a further complication is that older patients can also develop an acute phase of syphilis. For instance, a recent report illustrated a case of a man over 80 years suffering from syphilis-induced dermatologic lesions who had sexual intercourse over the past few months.²⁹ Difficulty in the interpretation of serological tests for the diagnosis of syphilis makes the matter more complicated.³⁰

To attenuate the high incidence rate of syphilis among the elderly, several strategies can be considered. First, it may be of help in diagnosing latent cases by incorporating the serologic tests for annual medical check-up. For that, however, cost-effectiveness should be carefully investigated because the total number of syphilis cases would not be higher than expected. Second, repeated education on the management of syphilis to geriatric clinicians would be warranted. If no test was submitted, no appropriate diagnosis would be given. Thirdly, public education targeting older population should include syphilis as their own healthcare issue.

The strength of the present study is the presentation of the recent trends of syphilis cases among middle-aged and older populations in the most aging country in the world through a joinpoint regression analysis. This study also has some limitations. First, our study lacked age information on the incidence among those aged ≥ 70 years because the detailed data was not open to public. Second, under-diagnosis, as well as under-reporting, is a big issue to be addressed. Third, multiple reporting from identical individuals might be counted because people getting STIs tend to conduct the similar high-risk behaviour. Despite these challenges, this study provides prominent findings to deeply understand the prevalence of syphilis among the aging population in Japan.

In summary, we statistically demonstrated the up-toward trend of syphilis cases among patients aged 50 years or older, particularly among men. However, the unavailability of clinical and background data restricted us in identifying their sources of infection. Although an increasing awareness of the disease among clinicians may have contributed to the increase of notification reports, in both positive and negative light, this trend might suggest healthy aging in Japan. However, syphilis is a latent disease-causing various manifestations in systemic organs, possibly resulting in a fatal outcome.

Therefore, including social education on sexual health as one aspect of aging-related problems, efforts to outline multifaceted approaches to reduce the incidence of syphilis among the middle-aged and older people, are needed in Japan.

Declarations

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Conflict of Interest Disclosure: All authors have no conflicts of interest to declare.

Consent for publication: The need for informed consent was waived because this was a retrospective study using anonymized data.

Data availability statement

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. Trends in crude incidence rates of syphilis per 100,000 population among patients aged ≥ 50 years, by sex and 10-year age groups, 2009-2019.

Figure 2. Overall age-adjusted incidence rates (AAR) of syphilis per 100,000 population among patients aged ≥ 50 years in Japan, by sex.

Figure 3. Age-adjusted incidence rates (AAR) of primary, secondary and late syphilis per 100,000 population among patients aged ≥ 50 years in Japan, by sex.

Due to a small number of data on primary syphilis in women, the joinpoint analysis was not applicable.