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Title page

Syphilis testing among spouses of patients with syphilis in Japan: an epidemiological study using an administrative claims database

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Introduction

Incidence rates of syphilis, a sexually transmitted infection (STI) caused by Treponema pallidum, is increasing in high-income countries.\cite{1,2} In the United States and Western Europe, there has been a sharp increase in cases of primary and secondary syphilis primarily among men who have sex with men.\cite{1,2} In Japan, the incidence of syphilis increased from 883 in 2012 to 4564 in 2016, and the majority of syphilis cases were among heterosexual men and women.\cite{3} In addition, among young women, the number of primary and secondary syphilis cases reported in Japan has increased rapidly since 2014, with the proportion of women among those aged 20–29 years increasing from 31.1% in 2014 to 54.5% in 2018.\cite{4,5} Syphilis in women of reproductive age, especially those in their 20s and 30s, can lead to mother-to-
child transmission during pregnancy and adverse pregnancy outcomes, including stillbirth,
neonatal death, low birth-weight, and prematurity. Therefore, public health strategies need to
be strengthened to prevent the spread of syphilis, especially through heterosexual contact
among women of reproductive age.

Partner notification (PN) is one of the most critical public health interventions for
prevention of the spread of STIs. PN is a means for informing the sex partners of patients
diagnosed with an STI that they have been exposed to an STI and for providing testing and
treatment. There are five main PN strategies: (1) patient referral, (2) assisted partner
notification, (3) expedited partner therapy, (4) provider referral, and (5) contact referral.\textsuperscript{6} To
eradicate infection and prevent re-infection, many high-income countries adopt multiple
types of PN in their programs for syphilis control.\textsuperscript{7–10} However, of these strategies, only simple patient referral, which entails a physician advising patients that their partner should be tested, is available in Japan. This is primarily because personal information that can identify patients with syphilis is not included in the items reported by physicians to local public health centres under the Infectious Diseases Act. As a result, staff working in local public health centres cannot interview patients or notify their partners. With the substantial increase in the incidence of syphilis, PN has become a more critical means of controlling syphilis; therefore, public health policymakers need to understand the effectiveness of simple patient referral in Japan. However, it remains unclear, whether contacts of patients with syphilis are notified that they are at risk of syphilis transmission, and whether contacts receive
treatment for syphilis.

Infection control policies should be reorganised in response to the growing syphilis epidemic. If investigations reveal that few contacts with syphilis have been screened through simple patient referral, Japanese policymakers may try to modernise current infection control strategies to provide a more practical partner service. In the present study, we aimed to determine the proportion of patients whose spouses, particularly women of reproductive age, underwent syphilis testing after their partners were diagnosed with syphilis, using an administrative claims database.
Materials and methods

Study design and data source

We conducted a retrospective descriptive study that used a large administrative claims database maintained by the Japan Medical Data Center (JMDC, Tokyo, Japan). The analysis covered claims between January 2010 and December 2017. The JMDC collects data regarding inpatient, outpatient, and pharmacy insurance claims of members of various health insurance associations that cover employees in large companies, and the spouses and dependents of these members. The database includes clinical and procedural information with an encrypted personal identifier, sex, year and month of birth, medical diagnosis codes according to the International Classification of Diseases 10th Revision (ICD-10), the drug
codes according to the World Health Organization (WHO) Anatomical Therapeutic
Chemical system, and the medical procedure codes. The database also includes anonymised
family identification codes and insurance coverage periods, which enabled us to identify
husband-wife relationships according to the time period. Due to the JMDC’s privacy policy,
medical diagnosis codes, drug codes, and medical procedure codes linked with human
immunodeficiency virus infections were not stored in the database and were not provided to
the investigators.

The study was conducted in accordance with the Declaration of Helsinki, and was
approved by the Institutional Review Board of the University of Kyoto (No. R1563). Due to
the anonymous nature of the data, the requirement for informed consent was waived in
accordance with the Japanese ethical guidelines.

Syphilis testing in Japan

Syphilis testing in Japan is divided into those tests that are covered by health insurance and those that are not. The tests covered by health insurance are performed at medical institutions on patients with symptoms or suspected infection. In addition, tests for infection, including syphilis testing, are performed before invasive treatment, such as surgery. Conversely, the tests not covered by health insurance include free tests conducted at local public health centres and universal prenatal syphilis screening at an early gestational age. Routine annual general health check-ups do not include syphilis testing.
Selection of index patients with syphilis and their spouses

We identified index patients who were newly treated for syphilis between January 2010 and December 2017. The dates of syphilis treatment were determined based on the month of the first prescription of antibiotics for syphilis. New treatment of syphilis was defined as (1) having a definitive diagnosis of syphilis (ICD-10 code: A51, A52, or A53); (2) prescription of antibiotics for syphilis; and (3) performance of syphilis testing as both nontreponemal and treponemal tests in the month of antibiotic prescription, or in the month preceding antibiotic prescription. Antibiotics for syphilis were defined according to the guidelines of the Japanese Society for Sexually Transmitted Infections (amoxicillin, ampicillin, minocycline,
doxycycline, azithromycin, acetylsalicylamycin, ceftriaxone, and benzylpenicillin). The guidelines suggest using amoxicillin or ampicillin 500 mg three times daily orally.

Benzathine penicillin G, which is recommended by the WHO guidelines for the treatment of Treponema pallidum infection, was not included in the list because it has not been available in Japan.

We excluded patients aged <20 years because this database only identified married pairs, and adolescents are unlikely to be married. To increase the accuracy of the definition of newly treated syphilis by excluding patients treated previously, we required continuous enrolment in the health insurance plan for at least 6 months before the syphilis treatment started. We also excluded patients who underwent surgery, blood transfusion, gastrointestinal
endoscopy, or coronary angiography during the index month because syphilis testing may be performed as a screening test for these procedures.

We identified the spouses of index patients using anonymised family identification codes. If both the husband and wife were treated for syphilis, we chose the spouse who was treated first as the index patient. To determine whether the spouse was tested after treatment of the index patient, we included only spouses who were enrolled in the health insurance plan for at least three months after the index patient started treatment.

Outcomes

The outcome of interest was spousal syphilis testing within three months of the index patient
starting syphilis treatment. Spousal syphilis testing was defined as either nontreponemal or
treponemal testing for syphilis according to the medical procedure codes. Because the dataset
used in this study did not include information on whether the index patient notified his or her
spouse, spousal notification was not an outcome of this study.

Other variables

We extracted information on index patient demographic characteristics, including age (20–
44 and 45–74 years), sex, and clinical characteristics of previous STI diagnoses according to
the ICD-10 codes (including gonorrhoea (A54), chlamydia (A55–A56), genital herpes (A60)),
and psychiatric disorders (schizophrenia, schizotypal and delusional disorders: F20–F29 and
mood disorders: F30–F39). Clinical data within 3 months preceding the index month were also assessed. We also recorded the provider type (clinic and hospital) and the year of syphilis treatment (2010–2011, 2012–2013, 2014–2015, and 2016–2017). In Japan, clinics are defined as medical institutions with 19 beds or fewer, and hospitals as those with 20 beds or more. Spousal demographic characteristics included age (20–44 and 45–74 years) and sex.

Statistical analyses

Firstly, descriptive statistics were calculated for the basic demographic and clinical variables of the index patient. Secondly, male-female and female-male contacts were analysed separately. We calculated the proportion of patients with newly treated syphilis during the
study period whose spouses had undergone syphilis testing within 3 months of treatment initiation. Associations between the characteristics of index patients and their spouses and performance of spousal syphilis testing were evaluated using Fisher’s exact test. The trend in the proportion of spousal syphilis testing during the study period was assessed using the Cochran-Armitage trend test. Thirdly, to evaluate the prevention of congenital syphilis, we determined the proportion of men married to women aged 20–44 years who had undergone a spousal syphilis test. This age range was chosen because approximately 99% of mothers in Japan gave birth when they were between the ages of 20 and 44 years. Probability values for statistical tests were two-tailed, and p-values <0.05 were considered to be statistically significant. All statistical analyses were performed using SAS version 9.4 for Windows (SAS
Second edition

130 Institute, Cary, NC, USA).
Results

During the study period, 217 pairs of patients with syphilis and their spouses met the inclusion criteria (Figure 1). The characteristics of the index patients with syphilis are shown in Table 1. Between 2010 and 2013, 10 or fewer index patients were diagnosed with syphilis per year; however, during the period 2014–2017, the number of index patients increased each year from 23 in 2014 to 75 in 2017.

Overall, 29 of 217 spouses (13.3%) underwent syphilis testing within 3 months of the index patient’s new syphilis treatment (Table 2). The proportion of spousal syphilis testing was 12.6% among the wives of male index patients, and 17.1% among the husbands of female index patients, respectively. Among male index patients, the proportion whose
wives were tested was higher among those aged 20–44 years than among those aged 45–74 years, whereas among female index patients, the proportion whose husbands were tested did not differ by age group. The proportion of spouses tested did not differ significantly according to STI history or psychiatric disease history. The spouses of all 12 index patients who were treated at a hospital were tested for syphilis.

Although not significant, among male index patients, the wives of those aged 20–44 years were more likely to undergo syphilis testing than those aged 45–74 years. Similarly, the wives aged 20–44 years were more likely to undergo syphilis testing than those aged 45–74 years. The proportion of spousal syphilis testing declined from 37.5% in 2010–2011 to 9.5% in 2016–2017 ($P$ for trend = 0.01).
Table 3 shows the proportion of wives aged 20–44 years who underwent spousal syphilis testing. The proportion of spousal syphilis testing was higher among index patients aged 20–44 years than among those aged 45–74 years. The proportion of spousal syphilis testing decreased significantly between 2010–2011 and 2016–2017 ($P$ for trend = 0.03).
Discussion

To the best of our knowledge, the present study is the first in Japan to describe partner syphilis testing using an administrative claims database. Less than one in seven spouses of index patients with syphilis underwent syphilis testing within three months after their spouse was treated. In the subgroup of wives aged 20–44 years, who constitute women of reproductive age, approximately one-fifth of underwent syphilis testing within three months, and the proportion tested decreased significantly between 2011–2012 and 2016–2017. Another unique feature of our study is the use of existing health insurance claims data without the collection of primary data. We determined whether partners were tested using claims data which identified married couples.
In a questionnaire survey of physicians conducted in Japan in 2006, 17.5% of partners of patients, who were diagnosed with an STI such as chlamydia or gonorrhoea, were examined or treated for STIs. Recent studies conducted in the United States reported that 63–81% of named partners were tested for syphilis as a result of disease intervention specialist investigations. In randomised controlled trials of patients with gonorrhoea or chlamydial infection, conducted in the United States, 35–52% of named partners either tested negative or were treated through simple patient referral. Another previous randomised controlled trial among men and women with chlamydial infection found that 45% of named partners were treated by simple patient referral. Our study found that in Japan the proportion of partners tested through simple patient referral was only 13% among married couples. This
result is similar to the result of the previous study conducted in Japan, but is lower than those of studies conducted in other countries. One possible reason for this difference may be that physicians in Japan may not explain the necessity of spousal testing to patients more carefully compared with those in other countries. Because PN services involving public health sectors have not been implemented in Japan, there may be a difference in physicians’ interest and practice in caring for partners. As a result, some physicians may not adequately inform patients regarding the need for partner testing. In addition, because the present study was conducted among married couples, disclosing a diagnosis of syphilis to a partner would have revealed infidelity; therefore, patients may have been reluctant to disclose the diagnosis to their spouse. These factors may partially explain the differences in the proportion of partners...
tested in our study and previous studies.

Patients may have difficulty in referring their partner for syphilis testing if the physician advises, "Tell your partner that he/she needs to be tested." because patients are hesitant to notify their partner due to guilt and stigma.\textsuperscript{25} Therefore, public health specialists need to support patients’ efforts to communicate with their partners by helping them understand the need to notify their partners and the possible adverse health effects of having an untreated STI. In a retrospective observational study of PN of syphilis conducted in Switzerland, patients diagnosed at a public university hospital were less likely to notify their partner than those diagnosed at other institutions.\textsuperscript{26} This difference may have been due to differences in patient characteristics between institutions. In contrast, in our study, all 12
spouses of index patients treated at hospitals were tested for syphilis. Because the health care setting in Japan allows patients to visit any medical institution, it may be due to differences between hospitals and clinics in the quality of PN, rather than differences in the characteristics of the patient population.

Despite increased public interest in syphilis due to the increase in reported syphilis cases, the present study showed that the proportion of wives aged 20–44 years who were tested for syphilis declined during the study period. The Japanese Ministry of Health, Labour, and Welfare has strengthened its prevention programs in order to increase public awareness. This effort has included new types of health campaigns that use manga cartoons to target the public in their 20s to 40s and increase opportunities for people to undergo STI testing.
However, health information campaigns and a population-based intervention approach are only effective among those who consider themselves to be at risk. Therefore, the decrease in spousal testing, despite health campaigns, may be due to an increased incidence of syphilis in populations previously at low risk.

Our study has several limitations. Firstly, information about the syphilis stage of the index patients was unavailable. Unlike the high infectivity of primary and secondary syphilis, the transmission of late syphilis is unlikely; thus, screening contacts of patients with late syphilis is generally unnecessary. However, even in patients with late-latent syphilis, it is appropriate to screen long-term sex partners for syphilis. Because our study used marital data, screening of spouses was advisable regardless of the syphilis stage of the index patient.
Secondly, the nature of the marital relationship during the infectious period was unclear. If the patient did not have sexual contact with the spouse during the infectious period, the outcomes of spousal syphilis testing might be underestimated as the spouse did not need to be tested for syphilis. In particular, it was estimated that more older couples had not had sexual contact in the preceding two years compared with younger couples. Thirdly, selection bias may limit the generalisability of our findings because the population of employees and their spouses in the present study had a higher socioeconomic status than the overall population at risk of syphilis. However, given that patients with syphilis are less likely to notify casual partners than long-term stable partners,\textsuperscript{29} the contacts of patients with syphilis in Japan overall may be less likely to undergo screening than the population of our study.
Fourthly, the small sample size of index patients precludes a multivariate analysis of partner testing according to variables such as sex, age, clinical characteristics, or provider type.

However, the data used in the present study were from the largest database of information on married couples that is currently available in Japan. To address the public health concern of the rapid increase in the incidence of syphilis, our study provides timely results to public health policymakers from a current database. Finally, spouses may have undergone syphilis testing that was not covered by health insurance. People can visit specialised medical institutions at relatively low prices under the Japanese health insurance system. Although some local public health centres are trying to improve access to free syphilis testing, the accessibility to free testing is generally poor. In addition, most syphilis cases have been
reported from clinics and hospitals rather than from local public health centres.

Despite public health interventions to increase syphilis testing of contacts in Japan, only approximately one-seventh of spouses of patients who start syphilis treatment undergo testing. The present study provides evidence that syphilis testing among contacts has been low and has declined over the past eight years. Although surveillance and awareness-raising have been intensified in Japan due to the recent surge in the incidence of syphilis, there is a need to coordinate surveillance and field services that remain fragmented. Our findings highlight the importance of introducing PN services that will result in higher partner testing rates.
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Second edition

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341 Figure legends

342

343 Figure 1. Flow diagram of the participant selection process

344
Table 1. Characteristics of the index patients (n = 217).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>89</td>
<td>(41.0)</td>
</tr>
<tr>
<td>45–74</td>
<td>128</td>
<td>(59.0)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>35</td>
<td>(16.1)</td>
</tr>
<tr>
<td><strong>STI history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>6</td>
<td>(2.8)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>12</td>
<td>(5.5)</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>19</td>
<td>(8.8)</td>
</tr>
<tr>
<td><strong>History of psychiatric disorders</strong></td>
<td>12</td>
<td>(5.5)</td>
</tr>
<tr>
<td><strong>Age of spouse, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>101</td>
<td>(46.5)</td>
</tr>
<tr>
<td>45–74</td>
<td>116</td>
<td>(53.5)</td>
</tr>
<tr>
<td><strong>Provider type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>205</td>
<td>(94.5)</td>
</tr>
<tr>
<td>Hospital</td>
<td>12</td>
<td>(5.5)</td>
</tr>
<tr>
<td><strong>Year of syphilis treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010–2011</td>
<td>14</td>
<td>(6.5)</td>
</tr>
<tr>
<td>2012–2013</td>
<td>15</td>
<td>(6.9)</td>
</tr>
<tr>
<td>2014–2015</td>
<td>58</td>
<td>(26.7)</td>
</tr>
<tr>
<td>2016–2017</td>
<td>130</td>
<td>(59.9)</td>
</tr>
</tbody>
</table>

STI, sexually transmitted infection
Table 2. Number and proportion of index patients whose spouses underwent syphilis testing according to patient characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male index patients</th>
<th>Female index patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 182 (%)</td>
<td>n = 35 (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>23 (12.6)</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>13 (19.4)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>45–74</td>
<td>10 (8.7)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>History of STIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (13.9)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (6.5)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>History of psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (12.2)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (20.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Age of spouse, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>14 (16.5)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>45–74</td>
<td>9 (9.3)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Provider type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>14 (8.1)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Hospital</td>
<td>9 (100.0)</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>Years of syphilis treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010–2011</td>
<td>3 (37.5)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>2012–2013</td>
<td>3 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2014–2015</td>
<td>6 (13.0)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>2016–2017</td>
<td>11 (9.5)</td>
<td>2 (14.3)</td>
</tr>
</tbody>
</table>

*Fisher’s exact test
†Cochran-Armitage test
STI, sexually transmitted infection
Table 3. Syphilis testing among wives aged 20–44 years, according to the characteristics of the index patient

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of spouses</th>
<th>Syphilis testing (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>85</td>
<td>14 (16.5)</td>
<td></td>
</tr>
<tr>
<td>Age of the index patient, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>65</td>
<td>13 (20.0)</td>
<td>0.171*</td>
</tr>
<tr>
<td>45–74</td>
<td>20</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>History of STIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69</td>
<td>13 (18.8)</td>
<td>0.290*</td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>1 (6.3)</td>
<td></td>
</tr>
<tr>
<td>History of psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>13 (18.8)</td>
<td>0.520*</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>1 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Provider type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>80</td>
<td>9 (11.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hospital</td>
<td>5</td>
<td>5 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Years of syphilis treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010–2011</td>
<td>3</td>
<td>2 (66.7)</td>
<td>0.026†</td>
</tr>
<tr>
<td>2012–2013</td>
<td>6</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>2014–2015</td>
<td>21</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>2016–2017</td>
<td>55</td>
<td>7 (12.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher’s exact test
†Cochran-Armitage test
STI, sexually transmitted infection
Figure 1. Flow diagram of the participant selection process.

426x299mm (300 x 300 DPI)