

Sociodemographic characteristics and clinical description of congenital syphilis patients and their mothers in Japan: a qualitative study, 2016

Mizue Kanai^{A,B}, Yuzo Arima^{C,G}, Tomoe Shimada^C, Narumi Hori^D, Takuya Yamagishi^C, Tomimasa Sunagawa^C, Yuki Tada^E, Takuri Takahashi^C, Makoto Ohnishi^F, Tamano Matsui^C and Kazunori Oishi^C

^AField Epidemiology Training Program, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan.

^BDivision of Global Infectious Diseases, Department of Infection and Epidemiology, Graduate School of Medicine, Tohoku University, Sendai 980-8575, Japan.

^CInfectious Disease Surveillance Center, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan.

^DDisease Control and Prevention Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.

^ETravellers' Medical Center, Tokyo Medical University Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

^FDepartment of Bacteriology I, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan.

^GCorresponding author. Email: arima@niid.go.jp

Abstract. *Background:* In Japan, congenital syphilis (CS) notifications have increased recently. However, little is known about the CS cases or the clinical and sociodemographic characteristics of the patients' mothers. *Methods:* Twelve cases of CS were reported through national surveillance in the period March–December 2016, and the mothers of seven patients were included in this study. The patients' mothers and physicians completed a self-administered questionnaire, providing sociodemographic and clinical information of the patients and their mothers. In addition, we explored the awareness and knowledge of, attitudes towards and practices regarding CS occurrence through semistructured interviews with the mothers. *Results:* Of the seven CS patients, three were asymptomatic, with a range of non-specific clinical manifestations in the rest. The mothers tended to be of young age, unmarried and to have a history of commercial sex work, other sexually transmissible infections (STIs) and no or irregular prenatal care visits during pregnancy. Of the four mothers who had had regular prenatal care visits, two had tested negative for syphilis at the first trimester antenatal screening. Themes emerged that indicated challenges in preventing CS, including a lack of guidance or guidelines for physicians to consider testing for syphilis after the first trimester, lack of physicians' awareness or experience of syphilis or CS and a lack of awareness or knowledge in pregnant women regarding STIs. *Conclusions:* Key characteristics of recent CS patients and their mothers in Japan were revealed, identifying previously reported factors as well as new challenges. A holistic approach, designed to address challenges at the level of the healthcare system, healthcare provider and the pregnant woman and her partner will be important in preventing CS.

Additional keywords: Asia, social context, surveillance.

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Introduction

With the global re-emergence of syphilis, congenital syphilis (CS) has become a public health concern.¹ Approximately 70% of pregnant women with untreated syphilis can have

poor pregnancy outcomes in the infant, including CS, stillbirth, neonatal death and low birthweight.² However, CS is preventable with effective antepartum syphilis screening and appropriate treatment.³ In fact, in Japan, through local

government funds, a syphilis screening test is conducted in all pregnant women at the first prenatal care visit, normally in the first trimester of pregnancy, likely contributing to low CS occurrence.¹

However, since 2010, cases of syphilis notified through the national surveillance system have increased sharply,⁴ reaching 4564 cases in 2016.⁵ A large proportion of cases are notified from urban areas. This increase was initially associated with men who have sex with men (MSM), but reports of infections acquired through heterosexual contact subsequently increased, with cases of primary and secondary syphilis among men who have sex with women ($n = 1390$) and women who have sex with men (WSM; $n = 696$) surpassing MSM ($n = 488$) in 2016.⁵ Reports of syphilis cases in WSM have increased yearly, with 137 cases in 2013 increasing to 253 in 2014, 548 in 2015 and 1077 in 2016; the increase was particularly notable among women in their teens and 20s.⁵ Concomitantly, CS reports also increased; from four cases each in 2012 and 2013 to nine cases in 2014, 13 in 2015 and 14 in 2016. Per 100 000 live births, the CS notification rate was 0.4, 0.9, 1.3 and 1.4 in 2012 and 2013, 2014, 2015 and 2016 respectively.^{4,5} Although CS reports are still rare in Japan, these trends have raised concerns. Although the current surveillance system requires that basic information be reported for CS patients (e.g. age, sex, time of diagnosis, place of report), information regarding the mother is limited. Such information is crucial to better understand potential risk factors and to assess possible entry points for prevention.

Based on previous studies from overseas, maternal risk factors for CS include inadequate prenatal care visits, being unmarried, low maternal education, low income, having sex during pregnancy and a prior history of syphilis.^{6,7} In Japan, two case series studies have also indicated low income, inadequate prenatal care visits, commercial sex work and unmarried status as potential risk factors for CS.^{8,9} However, there has been no study comprehensively evaluating the social, demographic and clinical characteristics of CS patients and their mothers in Japan. Furthermore, no such investigation has been conducted since 2014, when syphilis notifications among women of reproductive age started to increase. Importantly, the clinical spectrum of recent CS patients, and current methods for the diagnosis and treatment of CS in Japan, remain mostly undescribed.

Therefore, we conducted a qualitative study of CS case patients and their mothers to describe: (1) the sociodemographic characteristics of CS patients' mothers to help shed light on potential risk factors for CS; (2) the clinical characteristics, including treatment details, of CS patients; and (3) key themes that emerged regarding CS occurrence.

Methods

Study design

We conducted a prospective case series study among CS patients reported through Japan's National Epidemiological Surveillance of Infectious Diseases (NESID) system; notification of all CS cases is mandatory by law,¹⁰ and no sampling was involved. For each case notified, information about the patients and the mother was collected from: (1) the mother, based on

a questionnaire and interview; and (2) the physician who reported the case, based on a questionnaire. We created an interview guide to facilitate discussion and to minimise interviewer bias, and pretested it with simulated subjects for refinement. The questionnaire was also piloted among a convenience sample of clinicians to evaluate its acceptability and feasibility.

The information collected was analysed to identify emergent themes regarding CS occurrence and prevention.

Case definition

Eligible subjects were CS patients reported through NESID in the period March–December 2016. The surveillance case definition for CS was a patient who fulfilled any of the following:¹⁰ (1) antibody levels substantially higher than those of the mother; (2) persistent antibody titres at levels substantially higher than the titres expected from maternal antibodies; (3) IgM antibodies against *Treponema pallidum* (TP) derived from the infant; (4) the presence of signs or symptoms of early CS; and (5) the presence of signs or symptoms of late CS.

In the case of the first two criteria above, 'antibody levels' can refer to TP or non-TP antibodies. Although one case did not fulfil the above criteria, the patient was included in the study because the mother had tested positive in both TP and non-TP serological tests at the time of delivery and the placenta also tested positive for TP by polymerase chain reaction (PCR).

Data collection

Following case notification, the study coordinator, based at the National Institute of Infectious Diseases (NIID), contacted the local public health centre (PHC) that verified and reported the case to inform them of the study. The PHC then assisted in coordinating communication between the study coordinator and the physician who reported the case; information regarding the study, along with informed consent forms, was mailed to the physician. An explanation of the study was then provided by the physician to the mother of the patient (based on the materials sent), and the mother was invited to participate in the study. Mothers who provided written consent were enrolled in the study, and scheduling for the questionnaire and interview was arranged, based on the most convenient time for the patient and mother. After the scheduling was arranged, at least two study team investigators went to the medical facility caring for the patient to conduct the investigation. Prior to the visit, the facility was requested to prepare a private room for conducting the investigation, including the option of a physical partition between the interviewer and interviewee for privacy. During the interview, one investigator performed the interview while the other took notes; when given permission by the interviewee, interviews were audio taped. Separately, the physician who reported the case also completed a questionnaire.

Self-administered questionnaire: mothers of CS patients

In each case, information regarding the patient, mother and, when disclosed, the father was provided by the mother. Information collected included the mother's socioeconomic status, marital status, social welfare assistance status, education

status, any commercial sex work (including participation in commercial exchange for sexual practices), awareness and knowledge of sexually transmissible infections (STIs), including whether information was provided by physicians at the prenatal care visit, prior infection with STIs, prenatal care visits, signs or symptoms during pregnancy and sexual partner's diagnosis and treatment for syphilis.

Self-administered questionnaire: physicians

In each case, the physician also provided medical information regarding the patient, mother and, when known, the father through a self-administered questionnaire. The following information was collected: clinical and treatment history of the patient and mother, including details regarding diagnosis, treatment and care; the mother's infection status with other STIs (e.g. chlamydia, genital herpes, condyloma acuminatum, gonorrhoeae, HIV, hepatitis B or C); and information regarding diagnosis and treatment of the father.

Physicians were also requested to provide comments about any clinical challenges they faced regarding CS.

Face-to-face semistructured interviews

Following the questionnaire, an interview was conducted with the mother in which we inquired about her pregnancy and the context surrounding CS diagnosis. Specifically, the following key areas were explored:

1. Awareness and/or knowledge of STIs (e.g. content and source of information, prevention measures) before and during pregnancy
2. Diagnosis and treatment status of the mother's sexual partner believed to be the patient's father, and details regarding the relationship with the partner
3. Context and situation regarding the pregnancy, healthcare access and utilisation practices, experience related to CS occurrence and opinions and hopes about the diagnosis and/or treatment of syphilis.

Ethics

The NIID Ethics Committee approved this study (Registration no. 658) and written informed consent was obtained from all participants. The participating mother and physician each received 1000 Japanese yen as compensation.

Results

Twelve cases of CS were reported during the study period, seven of which were included in the present study (Table 1). The mothers of the other five patients did not provide written informed consent. The mother of Case 2 discontinued medical follow-up and was unable to be reached; therefore, only comments of the physician based on the information reported to NESID were analysed. These seven cases of CS were all reported from different prefectures, including some non-urban areas.

Clinical characteristics of CS

All cases were diagnosed during the neonatal period (Table 1) and the median age at the time of study investigation was

Table 1. Description of clinical characteristics of the patients with congenital syphilis (n = 7)

| | Case number 1 | | Case number 2 | | Case number 3 | | Case number 4 | | Case number 5 | | Case number 6 | | Case number 7 | |
|-------------------------------|--|---|---|---|---|---|--|---|--|---|--|---|--|--|
| | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male |
| Sex | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Age at diagnosis (months) | 2 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 3 |
| Age at time of study (months) | 33 | Unknown | 36 | 28 | 36 | 28 | 28 | 28 | 27 | 40 | 27 | 40 | 27 | Unknown |
| Weeks gestation | 2058 | Unknown | 2875 | 1264 | 2875 | 1264 | 2875 | 1264 | 1106 | 2956 | 1106 | 2956 | 1106 | 2844 |
| Birthweight (g) | | | | | | | | | | | | | | |
| Clinical manifestations | Elevated inflammatory response, hepatosplenomegaly, cholestatic liver function abnormality, hypoglycaemia, purpura, thrombocytopenia | | Elevated inflammatory response, cholestatic liver function abnormality, hypoglycaemia | Hepatomegaly, renal function abnormality, PPHN, anaemia, thrombocytopenia, enlargement of the ventricle | Elevated inflammatory response, cholestatic liver function abnormality, hypoglycaemia | | | | RDS, ascites, anaemia, DIC | | | | | |
| Laboratory diagnosis | FTA-ABS IgM+ Penicillin G (i.v., 10 days) | PCR+ in placenta Penicillin G (i.v., 10 days) | FTA-ABS IgM+ Penicillin G (i.v., 10 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) plus penicillin G (i.v., 10 days) | FTA-ABS IgM+ Penicillin G (i.v., 10 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) plus penicillin G (i.v., 10 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) | FTA-ABS IgM+ Penicillin G (i.v., 10 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) | FTA-ABS IgM+ Penicillin G (i.v., 10 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) | FTA-ABS IgM+ Penicillin G (i.v., 10 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) | FTA-ABS IgM+ Ampicillin (i.v., 14 days) |
| Treatment | | | | | | | | | | | | | | |

PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; DIC, disseminated intravascular coagulation; FTA-ABS, fluorescent treponemal antibody absorption; PCR, polymerase chain reaction

2 months (range 1–5 months). Four cases were preterm (<37 weeks gestation), and three had a low birthweight (<2500 g). Although four had a wide spectrum of non-specific manifestations, three were asymptomatic at birth and were detected because their mothers were diagnosed with syphilis at delivery or in the third trimester of pregnancy.

Most cases were laboratory confirmed by the fluorescent treponemal antibody absorption (FTA-ABS) IgM antibody assay; Case 1 also had a higher non-treponemal (rapid plasma reagin (RPR)) titre than the mother. Case 7 tested weakly positive for FTA-ABS IgM, and was diagnosed based on the mother's untreated syphilis status.

Most cases of CS were treated with intravenous injection of benzylpenicillin (penicillin G (PCG)) for 10 days. One of the two patients treated with intravenous injection of ampicillin for 14 days had relapsed, and was treated afterwards with intravenous injection of PCG for 10 days (Table 1). None of the cases of CS was fatal at the time of our investigation.

Sociodemographic and clinical characteristics of the mothers

The mothers' ranged in age from the teens to early 40s (median age 25 years), and all but one were Japanese (Table 2). Five were unmarried, and three had a history of commercial sex work. Although five had received a high school education, two were receiving social welfare assistance. Three mothers also had *Chlamydia trachomatis* infections.

Two mothers did not receive prenatal care and were diagnosed with syphilis when tested at delivery. In addition, one mother reported that her first prenatal visit was at 25 weeks gestation; although she received a screening test soon after where the result was positive, she delivered at 28 weeks gestation and timely treatment was not possible. Notably, four mothers had a history of regular prenatal visits and, of these, two had a previous history of syphilis (Table 2).

We were able to conduct interviews with six mothers, which lasted for a median of 29 min (range 22–47 min). We also gathered opinions and comments from all physicians who cared for the patients (six paediatricians and two internists specialising in infectious disease). Based on the information obtained, we categorised the challenges in CS prevention that emerged into three levels: health systems, healthcare provider and individual (Table 3).

Structural health systems-level challenges

Challenges related to the structural public health and medical systems were identified, including: (1) a lack of policies or guidance for syphilis testing after the first trimester of pregnancy; (2) a lack of comprehensive information regarding clinical descriptions of CS and guidance or guidelines for clinical treatment and follow-up of CS patients; and (3) a complicated surveillance case definition for CS.

First, there is no official policy or guidance for CS testing after the first trimester of pregnancy in Japan. Of the four mothers who had had regular prenatal care visits, two tested negative at the first trimester antenatal screening. The other two mothers had a history of previous syphilis infection, and the test results at the first trimester screening were difficult

Table 2. Sociodemographic and clinical characteristics of mothers of patients with congenital syphilis (n = 7) STIs, sexually transmissible infections

| | Case number | | | | | | |
|---|----------------------------|-------------|---------------------------------|------------------------------|------------------------------|------------------------------|-------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Age group (years) | 25–29 | 20–24 | 15–19 | 25–29 | 15–19 | 40–44 | 30–34 |
| Japanese nationality | Yes | Yes | Unknown | Yes | Yes | Yes | Yes |
| Married | + | - | - | - | - | + | - |
| History of commercial sex work | - | + | + | - | - | - | + |
| Highest level of education | High school | Unknown | High school | High school | High school | University/Graduate school | High school |
| Social welfare assistance | - | Unknown | + | - | - | - | + |
| Other STIs | - | - | <i>Chlamydia trachomatis</i> | <i>Chlamydia trachomatis</i> | <i>Chlamydia trachomatis</i> | - | - |
| Prenatal care visit history | Regular | None | Regular | Irregular ^A | Regular | Regular | None |
| Prenatal screening result (first trimester) | Indeterminant ^B | Not done | - | Not done | - | Indeterminant ^C | Not done |
| Time diagnosis confirmed | After delivery | At delivery | After delivery | After delivery | After delivery | Third trimester of pregnancy | At delivery |
| Prior syphilis infection | + | Unknown | - | - | - | + | - |
| Signs or symptoms during pregnancy | - | Unknown | Fever, exanthema, pubic prurigo | - | Exanthema | - | - |

^AFirst visit at 25 weeks gestation.

^BRapid plasma reagin test positive.

^C*Treponema pallidum* haemagglutination test positive.

Table 3. Challenges in preventing congenital syphilis (CS) that emerged from interviews with mothers and comments from physicians
STIs, sexually transmissible infections

| Level | Challenges |
|---|--|
| Structural or systems | No policy or guidance for CS test after the first trimester of pregnancy Lack of comprehensive information regarding clinical descriptions of CS and very limited domestic guidance or guidelines for clinical treatment and follow-up of CS patients Surveillance case definition of CS, including the diagnostic criteria, is complicated, not easily understood by physicians |
| Healthcare provider (paediatrics, obstetrics and gynaecology) | Lack of awareness or knowledge regarding the epidemiological situation of syphilis and CS Lack of experience in diagnosis and treatment of syphilis and CS Lack of communication or encouragement regarding testing of the sexual partner |
| Individual (pregnant woman and her sexual partner) | Lack of prenatal care visit (especially for high-risk mothers) Low awareness, knowledge and education regarding STIs, especially regarding risks during pregnancy |

to interpret (Table 2). Thus, these four mothers missed possible opportunities for intervention despite having regular prenatal care visits. The importance of additional testing for syphilis in the second and third trimester of pregnancy was suggested by some physicians after considering the mother's socioeconomic profile or context.

The mother of Case 4 also mentioned the possibility of acquiring syphilis during pregnancy, and thus the importance of testing later in pregnancy, and the need for timely treatment if detected (Table 4, Quote 1). Another mother (of Case 6) mentioned the value of retesting later in pregnancy, especially for mothers who have a prior history of syphilis (Table 4, Quote 2). In fact, given her previous infection and treatment 7–8 years ago (with a different partner then), she was told by her physician at the time that the test result at the first trimester was a reflection of her past infection and that she did not need to worry. However, based on the hospital's policy of testing all pregnant women at a later stage of pregnancy, an additional test conducted at 35 weeks gestation revealed reinfection, based on a large increase in her TP antibody titre. Antibiotic treatment was initiated 1 day before delivery. Such occurrence of CS among mothers who received first trimester screening highlights the challenges concerning the lack of guidance for considering additional tests later in the pregnancy.

Second, regarding diagnosis and treatment of CS, all the physicians universally voiced their opinions regarding the lack of comprehensive information in Japan regarding the clinical description of CS and guidance or guidelines for treatment and follow-up. One physician mentioned that he was confused regarding the interpretation of the infant's antibody titre results when there was a time lag between the mother's and infant's results. Other physicians felt that deciding the course of treatment and follow-up of patients was difficult because of a lack of domestic guidance or guidelines. Of two physicians who decided to treat with ampicillin, reasons for this choice included use noted in previous case reports, advice from other physicians and familiarity of use in neonates compared with penicillin.

Finally, physicians mentioned that the surveillance case definition, including the diagnostic criteria, is complicated

and not easily understandable. One physician requested simpler explanations for the definition, especially regarding laboratory diagnostic methods.

Healthcare provider (physician)-level challenges

Certain challenges at the provider level also emerged: (1) a lack of awareness or knowledge regarding the syphilis situation in Japan; (2) a lack of experience in the diagnosis and treatment of syphilis and CS; and (3) limited communication to the mother, including encouraging testing for the mother's sexual partner.

First, some physicians were unaware of the recent increase in CS reports in Japan, let alone the increase in total syphilis notifications or in women of reproductive age. The fact that these were the very physicians who made a CS notification revealed the possibly low awareness level for syphilis among physicians in general. In Japan, because syphilis testing is not conducted universally for all unwell newborns and depends on the physician's decision (or the hospital's policy), low awareness was deemed to be an important provider-level challenge.

Second, three physicians reported having had previous experience with CS, including suspected cases. One of these physicians commented that his past experience caring for a symptomatic infant born from a mother with syphilis helped him suspect CS and test the newborn (Case 3) when he saw multiple abnormal signs at birth. Conversely, another three physicians without experience (one physician's previous experience unknown) expressed mixed attitudes regarding improving diagnosis. One mentioned that photographs of typical signs would be useful for diagnosis, but another pointed out the difficulty in diagnosing atypical CS for infants born prematurely because the clinical signs are similar to prematurity associated with other causes. Maternal information appeared to be an important trigger: although both patients were symptomatic, Case 1 was tested because of the physician's knowledge regarding the mother's past history of syphilis and Case 5 was tested because the mother and her partner were both diagnosed with syphilis after delivery.

Table 4. Select quotes from mothers regarding their feelings, opinions and experience regarding congenital syphilis (CS)

| Level | Quotes |
|---|---|
| Structural or systems | Quote 1 (mother of Case 4): Even if the syphilis test was negative in early pregnancy, some women could become infected with syphilis during the middle or late stage of pregnancy. If the test is positive, physicians should call the pregnant woman soon after the result is known, and tell her to come to the clinic. Waiting for the next regular prenatal visit day would be too late because premature birth could occur especially in the late stage of pregnancy, and miss opportunities for treatment before delivery. Quote 2 (mother of Case 6): Every hospital should conduct a syphilis test in the late stage of pregnancy for pregnant women with antibody against syphilis like me. |
| Healthcare provider (paediatrics, obstetrics and gynaecology) | Quote 3 (mother of Case 1): When I got pregnant with my eldest child [with syphilis infection], none of the physicians advised me to let my husband come to the hospital, so he did not get checked for syphilis. I wonder if physicians advised so for us at that time, it would have been better. When I got pregnant with this child [current CS patient], the obstetrics and gynaecology physicians and dermatologist advised me to let my husband come to the hospital. Quote 4 (mother of Case 3): Although the physician did not advise me to do so, I voluntarily told my [partner of my syphilis infection], and advised him to come to the hospital to check his status. However, I'm not sure whether he went to the hospital or not. Quote 5 (mother of Case 1): It would have been better if I was told that reinfection is possible for my second child [current CS patient]. If I knew, I would have asked for more testing. |
| Individual (pregnant woman and her sexual partner) | Quote 6 (mother of Case 4): Normal women visit prenatal care regularly. I think that women who do not visit prenatal care have some reason that they cannot go. Some may not because they cannot pay the fee. Women learn that there is a public subsidy for the fee only after visiting the hospital. Quote 7 (mother of Case 3): If mothers know the risks of syphilis infection during pregnancy, including the risk to their child, I think they will take action because they love their child. Quote 8 (mother of Case 3): I think if mothers get the knowledge regarding syphilis or preventive measures for sexually transmitted infections in the early stage of pregnancy, they will practice these preventive measures, like using a condom during pregnancy. Quote 9 (mother of Case 3): Now I am 18 years old, but syphilis and chlamydia infection are [common] around me. They work as commercial sex workers. Everyone thinks that syphilis infection is a mild illness. I hope they know the importance of preventing syphilis infection. Quote 10 (mother of Case 4): I think that syphilis infection will not be realised without pregnancy because few people go to the clinic to check for sexually transmitted infections. So, I think that prenatal care visit is important for the diagnosis of syphilis. |

In addition, there were potential opportunities for intervention that were missed for three mothers who were diagnosed only after CS diagnosis in their infants. The mothers of Cases 3 and 5, who acquired syphilis infection during pregnancy, experienced suspected signs or symptoms of early syphilis (severe itching and/or eczema) at 30 and 20 weeks gestation respectively, but were not diagnosed; they reportedly consulted their respective physicians at the time (obstetrics and gynaecology) regarding their manifestations, but no additional tests were conducted. Another mother (Case 1), previously diagnosed with syphilis during an earlier pregnancy (older sibling of Case 1), tested positive by RPR in the first trimester but did not receive further examination by her provider at the time (obstetrics and gynaecology), because he considered it to be a sign of past infection.

Third, there was an apparent lack of proactive communication by the attending physicians at the time, including encouraging testing for the sexual partner (Table 4, Quotes 3 and 4). Such situations indicated the value of good rapport and communication between physicians and mothers, given the risk of reinfection (Table 4, Quote 5) and the need to test and treat their partners. At the same time, the lack of such communication indicated barriers, such as inexperience or discomfort in dealing with such situations. At the time of investigation, only three mothers were able to confirm their respective partners' status regarding

syphilis testing: one had tested positive and was receiving treatment, another was also positive but of unknown treatment status and the third reported that he had tested negative based on a self-test kit.

Individual-level challenges (pregnant women and their sexual partners)

We identified particular challenges at the individual level: (1) a lack of prenatal care visits by some mothers; and (2) the mothers' low awareness, knowledge and education regarding STIs.

First, both mothers who did not have prenatal care visits were unmarried with a history of commercial sex work. One commented that she did not realise she was pregnant until close to delivery, and that without an initial prenatal care visit infection cannot be detected. Another mother mentioned that there are contextual reasons for not making visits and commented that she only had irregular visits and delayed her first visit because she could not disclose her pregnancy to her family. However, she also mentioned cost as another possible reason, and that some mothers do not know about financial assistance (i.e. some women are not aware of available subsidies; Table 4, Quote 6).

Second, all but one of the mothers answered that they did not know about the risk of syphilis infection during pregnancy,

including for CS (Table 4, Quotes 7 and 8); this is an individual-level concern because an STI involves the mother's partner. In addition, all the mothers commented that they did not recall receiving information about STI prevention during pregnancy, whether through education at school, the media, women's magazines or from providers at their perinatal care visit. Given the apparent low awareness and knowledge regarding STIs (Table 4, Quotes 9 and 10), many mothers suggested ways to distribute this information to pregnant women, such as inserting a pamphlet in the 'Mother and Child Health Handbook' (a record book shared by Japanese parents and health providers in order to monitor maternal health throughout the perinatal period, track the child's health and to provide relevant educational information¹¹). Because a considerable quantity of information is provided at prenatal care visits, a few also felt that having pictures (e.g. infographics) regarding STI prevention would help catch the mother's attention. Another suggestion was to use modern tools, such as smartphone or tablet applications, because many commented that this is the primary mode of obtaining information.

Discussion

This descriptive case series and qualitative investigation, while ongoing, highlights some of the challenges in preventing CS in Japan. Along with detailed clinical and sociodemographic pictures of CS patients and their mothers, salient themes emerged concerning recent CS cases.

First, for appropriate CS treatment, PCG is recommended by the Centers for Disease Control and Prevention,¹² and most cases in this study were treated with PCG. However, a few were treated with ampicillin, including one patient who subsequently relapsed. Importantly, a recent report noted that treatment with ampicillin for 14 days was ineffective against CS with meningitis.¹³ Although information is limited, taken together these recent findings would favour the continued recommendation of PCG for CS. Collecting follow-up information of CS cases will be important for further evaluation.

Similar to previous reports, both domestic and elsewhere,⁶⁻⁹ our results indicated that mothers of CS patients tended to have certain demographic and socioeconomic characteristics, namely young age, being unmarried, having other STIs, commercial sex work and/or inadequate prenatal care visits. Although the reasons for the resurgence of syphilis in Japan remain unclear,⁵ and syphilis epidemiology could change over time or differ by birth cohort, the consistent findings indicate that potential risk factors for recent CS occurrence in Japan remain similar to what has been reported in the past. In fact, a recent report noted that the proportion of pregnant Japanese women who screened positive for syphilis tended to increase with decreasing age, with the highest among teenage women.¹⁴ Such findings have important implications for prevention and early treatment. For example, although physicians admitted the difficulty of suspecting CS because of the non-specific clinical manifestations, by considering such maternal characteristics the index of suspicion can be raised.

However, the occurrence of CS among mothers who received first-trimester screening presents a new challenge. Importantly, a similar situation was recently reported from

England, where four CS cases caused by maternal infection after a negative screening in the first trimester occurred.¹⁵ From our interviews, key themes emerged suggesting challenges at the structural or health systems, provider and individual levels. Certain measures could help address such challenges. For example, at the structural level, creation of guidance or guidelines for clinicians could help physicians make informed decisions regarding retesting for syphilis in the second or third trimester or for testing unwell newborns (e.g. for pregnant women with certain characteristics, especially when syphilis prevalence is high¹). Given the complicated surveillance case definition, such material could also point out key aspects regarding clinical diagnosis, along with explanations of the reporting criteria. In addition, while acknowledging provider discomfort in discussing STIs,¹⁶ the importance of communicating to a pregnant woman with syphilis the need to have her partner tested and treated should also be strongly emphasised. Such guidance would be particularly beneficial for providers without experience in syphilis or CS. Furthermore, given the apparent low knowledge, awareness and practice regarding STI prevention during pregnancy among the mothers (and understanding that there are possible adverse outcomes for her newborn from her infection; Table 4), more user-friendly communication tools could be considered (e.g. pamphlets or smartphone applications), which was recently also suggested in England.¹⁵ Thus, to prevent CS and syphilis infection throughout the duration of pregnancy, our findings suggest that a multifaceted, holistic approach may be important.

This study has several limitations. First, as a small, qualitative case series, we cannot explicitly assess for risk factors for CS and the small numbers do not permit stratified assessments. However, overall, the findings were consistent with those reported previously and there was plausibility in the sociodemographic patterns and the themes that emerged. Second, five mothers did not provide consent to participate in the study at the time of this assessment, and CS cases manifesting as stillbirths, those that were aborted or asymptomatic cases at delivery whose mothers tested negative at the first-trimester screening would be missed by the surveillance system. Although such missed cases could differ with regard to the mothers' characteristics, again, our findings are similar to what has been reported elsewhere where CS surveillance is more sensitive. Third, some of the information provided by the respondents may have been affected by social desirability and/or recall bias. Finally, we were unable to collect specific information regarding factors that could have affected maternal infection risk, such as condom use; however, because this is an important modifiable behaviour, we recommended condoms during pregnancy as a prevention message after the interview.

This study was able to uncover key characteristics of recently reported CS patients and their mothers in Japan. In particular, knowing the maternal characteristics could help physicians in their decision making regarding the diagnosis of and testing for syphilis, for both the mother and infant. A holistic public health approach, designed to address the challenges at the health system, provider and individual levels, will likely be important in preventing CS cases in

Japan. With limited domestic guidance regarding CS and syphilis testing in pregnant women and newborns, the findings of this study will contribute to the development of such decision-making tools.

Conflicts of interest

The authors declare no conflicts of interest.

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