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Toxoplasma gondii infection risk among pregnant people and congenital toxoplasmosis incidence in Japan

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Abstract

Acute infection with *Toxoplasma gondii* in pregnant people can lead to vertical transmission to the foetus and congenital toxoplasmosis. As part of risk assessment, the epidemiology of toxoplasmosis among pregnant people must be quantitatively elucidated. Herein, we investigated the risk of primary *T. gondii* infection during pregnancy in Japan, estimating the incidence of *T. gondii* infection among pregnant people as well as that of congenital toxoplasmosis. We used a compartment model that captured the infection dynamics in pregnant people, analysing prescription data for spiramycin in Japan, together with local serological testing results and the screening rate of primary *T. gondii* infection during pregnancy. The nationwide risk of *T. gondii* infection pregnant people in Japan was estimated to be 0.016% per month. Among prefectures investigated, the risk estimate was highest in Tokyo with 0.030% per month. Nationally, the number of *T. gondii* infections among pregnant people in the years 2019, 2020, and 2021 was estimated to be 1507, 1440, and 1388 infections, respectively. The nationwide number of cases of congenital toxoplasmosis in each year was estimated at 613, 588, and 567 cases, respectively. Our study indicated that *T. gondii* infection continues to place a substantial burden on public health in Japan.

Introduction

Toxoplasmosis is a protozoan disease caused by *Toxoplasma gondii*, the zoonotic parasite belonging to the phylum Apicomplexa. Members of the *Felidae* family are the definitive hosts of *T. gondii*. Any warm-blooded vertebrate can act as the intermediate host through ingestion of tissue cysts in other hosts or sporulated oocysts in contaminated environments [1]. Humans can be infected by ingesting *T. gondii* tissue cysts in undercooked meat of infected animals or oocysts in environments contaminated by the faeces of primarily infected cats. Once ingested, tissue cysts are formed in human muscle or brain tissue, and latent infection is established [2]. One-third of the world's population is generally assumed to have been infected with *T. gondii*. Infections are mostly asymptomatic and/or self-limited; however, severe consequences are more common in the developing foetus and immunocompromised individuals [1, 2].

Vertical transmission to the foetus via the placenta can occur in women with primary *T. gondii* infection during pregnancy or just before pregnancy and can lead to spontaneous abortion or congenital toxoplasmosis (CT) in some infants. Two meta-analyses on the risk of primary infection among pregnant people consistently reported that acute *T. gondii* infection in pregnant people, primarily determined by specific IgM detection or several serological criteria combined, is 1.9% and 1.1% worldwide, respectively [3, 4]. Globally, the annual CT number is estimated to be 190100 cases (95% confidence interval [CI]: 179300–206300), accounting for 1.2 million disability-adjusted life years (DALYs) annually (one DALY is equivalent to one year of healthy life lost) [5]. Pyrimethamine jointly used with sulfadiazine is approved for treatment of CT in several countries [6, 7]. Spiramycin is the only available medication to prevent vertical transmission of *T. gondii* among pregnant people with primary infection [2, 8].

The reported seroprevalence of *T. gondii* in the general Japanese population is 9.3%–16.4% [9–11]. Sakikawa et al. [12] reported a seroprevalence of 10.3% among pregnant people who received antenatal care in a private hospital during 1997–2004. Other studies in Japanese language have documented a seroprevalence from 2% to 10% among pregnant people [8, 13–16]. The risk of *T. gondii* during pregnancy has not been well studied. Sakikawa et al. [12] reported a 0.25% acute infection rate during pregnancy. A guideline for *T. gondii* screening and treatment for primary infection during pregnancy is available in Japan [8]. According to the guideline, when serum *T. gondii* IgG is positive in the first trimester, *T. gondii* IgM is measured. The *T. gondii* IgG avidity index may also be considered, although this is not mandatory. If *T. gondii* IgM is positive, primary *T. gondii* infection during pregnancy is suspected, and prompt therapy with spiramycin is strongly recommended. Amniocentesis may be performed based on the pregnant woman's preference.

If foetal infection is confirmed by detection of *T. gondii* DNA, maternal therapy with pyrimethamine, sulfadiazine, and folinic acid is administered between 16 and 27 weeks of gestation. Because pyrimethamine and sulfadiazine are not approved in Japan, their use is restricted to designated medical institutions. From 28 weeks of gestation, sulfadiazine is discontinued and pyrimethamine and folinic acid (or spiramycin) are given until delivery. If amniocentesis is not done or if foetal infection is not confirmed by polymerase chain reaction (PCR), spiramycin is given until delivery. For primary infections detected later in pregnancy, the same management with cases detected earlier is applied. Notification of CT is not mandated in Japan, and thus, it is unclear how many cases are present at a national level in Japan. Yamada et al. [17] reported the rate of CT at 1.5% (7/469) in Japanese women testing positive for *T. gondii* between April 2005 and July 2017. However, in a prospective study at two university hospitals from 2013 to 2020, Hijikata et al. [18] reported that among 73 newborns from 71 *T. gondii* IgM-positive mothers, none had clinical manifestations and *T. gondii*-specific IgM antibodies were detected in one (approximately 70% of participants had preventive therapy with acetylspiramycin or spiramycin). To address the number of CT cases at national level using a commercial claims database covering 17 million employed persons and their relatives, the yearly number of CT cases from 2010 to 2018 was recently estimated to be 295, corresponding to 2.9 cases per 10000 births [19]. In studies using International Classification of Diseases Tenth Revision (ICD-10) codes in claims databases, the validity of coding can be a limitation. Moreover, the generalizability of findings based only on employed workers relative to the entire Japanese population should be considered. The epidemiology of toxoplasmosis among pregnant people and CT in Japan remains to be quantitatively elucidated.

The National Database (NDB) is a Japanese database that stores and organises data such as medical receipt information and specific health checkup and health guidance information [20]. The NDB is an open data source on selected reimbursed health care services during particular fiscal years, including prescribed medications in all prefectures [21]. Spiramycin was approved for the prevention of CT in Japan in 2018 and it is the only approved drug for this indication. On the other hand, spiramycin is used only for the prevention of CT, and not for the treatment of other infections. The use of a mathematical modelling approach with local serological data, combined with the rate of detection of primary *T. gondii* infection during pregnancy, enables estimating the burden of disease caused by the parasite, including the number of primary *T. gondii* infections in pregnant people and CT cases. In the present study, we estimated the *T. gondii* infection risk during pregnancy using a compartment model capturing the infection dynamics in women during pregnancy, further assessing primary infections among pregnant people and vertical transmission of *T. gondii* in Japan.

Methods

Data collection strategy for estimation

The prescribed number of spiramycin doses is recorded, encompassing all treatment courses received by pregnant people following a first-ever diagnosis of *T. gondii* infection during pregnancy. We assumed that the risk of pregnant people acquiring the infection depends on the prefecture of residence (characterising the exposure); ascertainment of infection is also dependent on the local testing rate, such that the fraction of infected pregnant people receiving treatment with spiramycin also differs by prefecture. To describe the process of estimating the *T. gondii* infection rate based on spiramycin prescriptions, we used the datasets described below.

Number of new pregnancies

Data on pregnancies in Japan are reported on a yearly, not monthly, basis, except for specific periods shown later [22]. Rather than using these data, we leveraged the monthly reported number of births in each prefecture [23]. Assuming all reported births had a gestation period of 10 months, we used the number of births in (X + 9) calendar month as the number of new pregnancies in X calendar month. For the period January 2018 to October 2021, the number of pregnancies was mandated to be reported each month to investigate the impact of COVID-19 on pregnancy [24]. Most pregnancies (i.e., >90%) were reported by 11 weeks of gestation [24]. Thus, for this specific period, we used the monthly reported number of pregnancies in (X + 2) calendar month as the number of new pregnancies in X calendar month.

Seroprevalence of *T. Gondii* among pregnant people

Data on the seroprevalence of *T. gondii* among pregnant people, indicating previous *T. gondii* infection, are available for selected prefectures in Japan, i.e., Hokkaido (3.6%), Saitama (3.3%), Chiba (4%), Tokyo (6%), Osaka (6%), Hyogo (3.5%), Yamaguchi (5.3%), Nagasaki (2.1%), and Miyazaki (10%) [8, 12–16, 25]. Additionally, a nationwide multi-centre study by the Ministry of Health, Labour and Welfare of Japan reported that the seroprevalence at the national level during 2013–2015 was 6.1% [8]. Once infected with *T. gondii*, the host generally remains infected for life and develops life-long immunity against reinfection; therefore, only primary infection was taken into account and no reinfections were assumed in the model. We targeted the above prefectures in the following analysis, using the value (1 − seroprevalence) as the proportion of susceptible pregnant people.

Testing rate of *T. Gondii* in selected prefectures

Biennial national-level surveys targeting all hospitals offering obstetrics or gynaecology services in Japan are used to report the proportion of hospitals that routinely check for acute *T. gondii* infection during pregnancy in each prefecture [26]. The average proportion of testing in 2019 and 2021 was retrieved for our analysis. In sensitivity analyses to determine the impact of the testing rate on our estimate of the risk of infection, we calculated 95% CI of the proportion in both years, assuming a binominal distribution (Supplementary Table S1). The lower bound or upper bound of the 95% CI was used as the pessimistic or optimistic scenario of the testing conditions, respectively.

Spiramycin prescription in Japan

The prescribed number of spiramycin doses per fiscal year from 2018 (i.e., April 2018 to March 2019) to 2021 is available across Japan [21]. Because spiramycin treatment was initially set up in practice from August 2018 [8], and the adoption and procurement of newly approved medications require some time, the data for fiscal year 2018 were excluded in the following analysis.

Transmission model of *T. Gondii* infection in pregnant people

We used a simple catalytic susceptible–infected (SI) model to describe the transmission dynamics of *T. gondii* among pregnant

people over the course of time and by age [27]. Letting $S_i(t)$ be the time-dependent number of susceptible pregnant people at calendar time t and in prefecture i, the incidence of infection among pregnant people in gestational month a at calendar time t and in prefecture i is described as

$$i_i(t,a) = S_i(t-a)[\exp(-\lambda_i a)(1 - \exp(-\lambda_i))], \quad (1)$$

for $a = \{0, \ldots, 9\}$, where λ_i is the risk of endemic infection with *T. gondii* in prefecture i. Notably, infections estimated to occur one month before pregnancy (gestation month zero) were included among infections during pregnancy because 12 weeks are required for IgG to reach the peak value after infection [28], and infections acquired in the month prior to pregnancy will be detected in early pregnancy. Assuming that the number of women at calendar time $t-1$ who will eventually become pregnant at calendar time t is equal to the number of pregnant people at gestational month zero at calendar time $t+1$, we modelled infections 1 month prior to the pregnancy (i.e., $a = -1$) at calendar time t and in prefecture i as $S_i(t+1)(1 - \exp(-\lambda_i))$.

Modelling the number of infected women starting spiramycin

A nationwide survey of screening practice during pregnancy shows that the testing for *T. gondii* infection takes place only once during the course of pregnancy (789/803 hospitals, 98%) [29]. We let $g(\sigma|a)$ be the probability density function of the time delay from infection to testing σ, conditional on gestational month a of infection. Assuming that all infections, if tested for, would be judged as confirmed/suspected infection, and spiramycin is started in the month of testing, the number of infected women starting spiramycin in calendar month t and in prefecture i can be described as

$$c_i(t) = \sum_{\sigma=0}^{10} \sum_{a=-1}^{9-\sigma} \rho_i i_i(t-\sigma, a) g(\sigma|a), \quad (2)$$

where ρ_i is the testing rate for *T. gondii* in prefecture i. Considering that (1) anti-*T. gondii* IgM, indicative of acute infection, becomes positive 4 weeks after infection [28] and (2) nearly all testing occurs during the first trimester (i.e., gestational months 0–2) in Japan (752/753 hospitals) [29], only pregnant people infected in gestational months -1, 0, or 1 were considered to have a chance of being diagnosed and receiving spiramycin. For a time delay from infection to testing conditional on gestational month at infection -1, 0, or 1, we adopted the mid-point of possible values, i.e., 1, 2, or 2 months, respectively, to calculate the gestational month of testing positive.

Modelling the prescribed number of spiramycin doses

The Japanese guideline on toxoplasmosis during pregnancy recommends continuing treatment with spiramycin until delivery [8]. Spiramycin is not effective for an infected foetus confirmed by PCR and treatment is usually switched to pyrimethamine and sulfadiazine for foetal prenatal treatment between 16 and 27 weeks of gestation. Pyrimethamine and sulfadiazine are available in only four university hospitals in Japan as of this writing [8], and a report from one site among these four hospitals mentions that spiramycin or acetylspiramycin, which was used before approval of spiramycin in 2018, was given between 16 and 27 weeks in their routine practice (total of 52 pregnant people received treatment from 2013 to 2020) [18]. Thus, we assumed in our model that spiramycin would be continuously

administered until delivery, regardless of the amniocentesis results. Considering that the approved regimen of spiramycin is six tablets (1.5 M units/tablet) per day (such that, on average, 180 tablets are consumed per month), the total number of spiramycin doses prescribed in calendar month t and in prefecture i will be:

$$D_i(t) = 180 \sum_{\tau=0}^{9} c_i(t-\tau). \quad (3)$$

The total number of spiramycin doses prescribed in fiscal year y and in prefecture i can be written as $\sum_{t \in y} D_i(t)$. Assuming that infection with *T. gondii* among pregnant people is endemic during 2019–2021, the expected value of the total number of spiramycin doses in prefecture i during any fiscal year would be the arithmetic mean of $\sum_{t \in y} D_i(t)$ for all fiscal years (i.e., identical doses for 2019, 2020, and 2021), or $\frac{1}{3} \sum_y \sum_{t \in y} D_i(t)$. Letting the observed number of prescribed spiramycin doses in fiscal year y and in prefecture i follow a normal distribution, the likelihood of estimating λ_i, the risk of infection in prefecture i, is written as:

$$L(\theta|D) = L(\lambda_i, \sigma^2|D) = \prod_i \text{Normal}\left(\frac{1}{3}\sum_y \sum_{t \in y} D_i(t), \sigma^2\right), \quad (4)$$

where σ^2 is the variance of a normal distribution, assumed to be the same across fiscal years and prefectures. As a sensitivity analysis, we assumed that a number of people infected before pregnancy will start spiramycin if they had to be managed as suspected primary infection during pregnancy because of (1) detection of specific persistent IgM antibodies persisting from an earlier infection and (2) no IgG avidity test performed to rule out past infection, to determine the robustness of estimated infection risk in the base model. Owing to limited information on the rate of IgG avidity testing in Japan, this supplementary analysis was restricted to two prefectures (i.e., Tokyo and Hyogo) (see the Supplementary text).

Estimation of parameters

We used a Bayesian hierarchical model to estimate the parameters of interest. That is, the risk of infection in each prefecture was assumed to follow a gamma distribution, whose shape and rate parameters were assumed to follow the same normal distribution with mean = 0 and variance = 1. The prior variance of normal distribution for the number of spiramycin doses, σ^2, was assumed to follow a uniform distribution bounded by zero. The Bayesian inference was implemented in RStan [30]. Markov chain Monte Carlo (MCMC) with the No-U-Turn Sampler algorithm was used to estimate model parameters. The Gelman–Rubin (GR) statistic (R-hat) was used to judge MCMC convergence with a threshold of <1.1.

Prediction of CT in Japan

The incidence of CT per year was predicted using estimated parameters. To predict primary infections during pregnancy, we included the estimated risk of primary infection with *T. gondii* into equation (1). The transmission risk when treated with spiramycin is known to vary depending on the gestation period of the pregnant woman, i.e., 10% in the first trimester, 20% in the second, and 60%–70% in the third trimester [31]. Because spiramycin is suggested to reduce the risk of transmission by 50% according to

several observational studies [32], in our computations, we assumed that the risk of transmission without treatment is 20% in the first trimester, 40% in the second, and 100% in the third trimester.

All analyses were conducted using R version 4.3.1 [33]. The code is available from https://github.com/koudylan/toxoplasma_japan.

Ethical considerations

The present study used publicly available data. The datasets did not contain any individual identifying information; therefore, ethical approval was not required for this study.

Results

Infection risk of T. Gondii in Japan

The observed number of prescribed spiramycin doses in the selected prefectures is shown in Figure 1. The total number of doses prescribed nationally in fiscal years 2019, 2020, and 2021 was 252551, 353535, and 399522, respectively (Supplementary Table S2). No prescriptions were recorded in Yamaguchi Prefecture except for 2021, and thus, we excluded this prefecture from further analyses to ensure certainty in our estimates. Assuming that the risk follows a gamma distribution, the nationwide risk of infection was estimated to be 0.016% per month (95% credible interval [CrI]: 0.009–0.029) (Table 1). The risk estimates in selected prefectures ranged from 0.008% to 0.030% per month, with the largest value seen in Tokyo. The variance of normal distribution for spiramycin doses was estimated to be 0.48 (95% CrI: 0.35–0.72). The number of prescribed spiramycin doses in each fiscal year from 2019 to 2021 allowed our

Table 1. Infection risk of *Toxoplasma gondii* during pregnancy (median and 95% credible interval)

Location	Base scenario (%/month)	Pessimistic scenario (%/month)	Optimistic scenario (%/month)
All	0.016 (0.009–0.029)	0.017 (0.010–0.030)	0.015 (0.009–0.026)
Hokkaido	0.018 (0.010–0.032)	0.020 (0.011–0.037)	0.015 (0.009–0.027)
Saitama	0.024 (0.013–0.044)	0.038 (0.021–0.068)	0.017 (0.010–0.032)
Chiba	0.013 (0.007–0.022)	0.016 (0.009–0.029)	0.010 (0.006–0.018)
Tokyo	0.030 (0.017–0.053)	0.038 (0.021–0.068)	0.025 (0.014–0.044)
Osaka	0.008 (0.005–0.015)	0.013 (0.007–0.023)	0.006 (0.003–0.010)
Hyogo	0.010 (0.006–0.018)	0.013 (0.007–0.023)	0.008 (0.005–0.015)
Nagasaki	0.017 (0.010–0.032)	0.030 (0.017–0.054)	0.012 (0.007–0.022)
Miyazaki	0.012 (0.007–0.021)	0.019 (0.011–0.034)	0.008 (0.005–0.015)

model to be reasonably well fitted to the observed pattern (Figure 1). The estimates of rate/shape parameters are shown in Supplementary Tables S3 and S4. Under the pessimistic scenario with a low testing rate, the risk of infection was estimated at 0.017% per month (95% CrI: 0.010–0.030) nationwide and 0.013–0.038 at the prefectural level; under the optimistic scenario with a high testing rate, the risk of infection was 0.015% per month (95% CrI: 0.009–0.026) nationwide and ranged from 0.006 to 0.025 at the local level (Table 1). When considering the proportion of people infected before pregnancy, the risks in Tokyo and Hyogo were estimated to be 0.02% per month (95% CrI: 0.00–0.07) and 0% (95% CrI: 0.00–0.02), respectively.
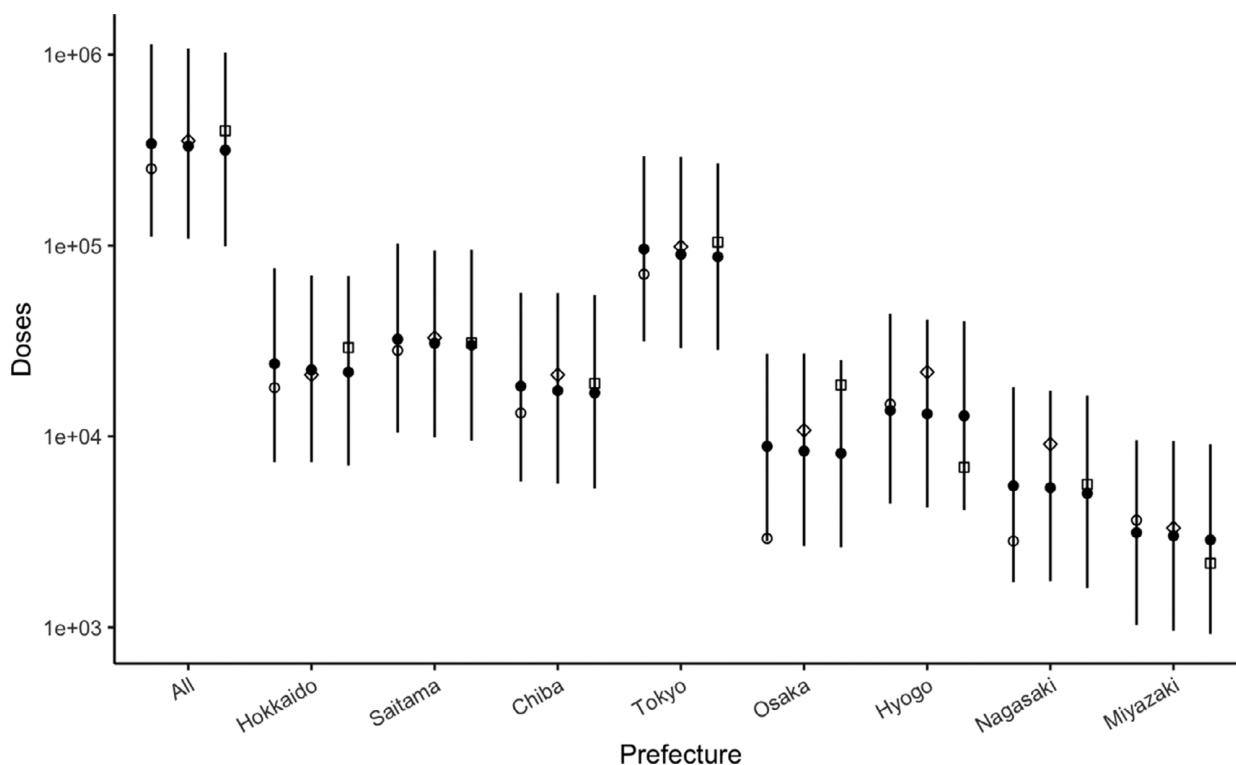

Figure 1. Prescribed spiramycin in Japan. Open circles, diamonds, and squares represent observed number of doses (in log-scale) in 2019, 2020, and 2021, respectively. Solid circles represent estimated number for the corresponding year. The line shows 95% credible interval for the corresponding year.

Number of T. gondii *infections in pregnant people*

The number of *T. gondii* infection among pregnant people nationwide in the years 2019, 2020, and 2021 was estimated to be 1507 (95% CrI: 851–2732), 1440 (95% CrI: 813–2611), and 1388 (95% CrI: 784–2517), respectively. Among selected prefectures, the highest number was seen in Tokyo (362 in 2019, 345 in 2020, 330 in 2021), followed by Saitama (134 in 2019, 128 in 2020, 124 in 2021), a prefecture neighbouring Tokyo. When scaled according to the population at risk in each prefecture, the incidence of *T. gondii* infection per 10000 pregnant people was highest in Tokyo with 32 (95% CrI: 18–55) in 2019, 32 (95% CrI: 18–56) in 2020, and 33 (95% CrI: 18–57) in 2021 (Figure 2a; Supplementary Table S5). Sensitivity analysis varying testing rates showed that the number of infections per 10000 pregnancies nationwide was 15–18 in 2019 and 16–18 in 2020/2021 (Figure 2b; Supplementary Tables S6 and S7). Under the pessimistic scenario, the incidence of infection per 10000 pregnancies in Tokyo and Saitama was similar (39 vs. 40 in 2019, 40 vs. 41 in 2020, 40 vs. 41 in 2021). Among all infected pregnant people, 13% were estimated to receive spiramycin nationwide during 2019–2021 under the base scenario. The proportion did not change substantially under the different testing scenarios (i.e., 12% and 14% for the pessimistic scenario and the optimistic scenario, respectively). In a model with people infected before pregnancy, the number of infections per 10000 pregnancies in Tokyo and Hyogo was estimated to be 17–18 and 0.01–0.02, respectively, during 2019–2021 (Supplementary Table S11).

CT cases in Japan

The estimated number of CT nationwide in the years 2019, 2020, and 2021 was estimated at 613 (95% CrI: 346–1110), 588 (95% CrI: 332–1067), and 567 (95% CrI: 322–1033) cases, respectively. The largest case number was seen in Tokyo with 146 (95% CrI: 82–256) in 2019, 141 (95% CrI: 79–246) in 2020, and 135 (95% CrI: 76–236) in 2021. Figure 3a shows the incidence of CT per 10000 pregnant people in each prefecture, with the largest number in Tokyo (13 in 2019, 13 in 2020, and 13 in 2021), followed by Saitama (10 in 2019, 11 in 2020, and 11 in 2021). The incidence of CT nationwide was shown to range from 6 to 7 per 10000 pregnant people during 2019–2021, even with varying testing rates. The number of CT cases per 10000 pregnancies in Tokyo and Saitama was found to be very close under the pessimistic scenario (16 vs. 16 in 2019, 16 vs. 17 in 2020, 17 vs. 17 in 2021) (Figure 3b; Supplementary Tables S8, S9, and S10). Using risk of primary infection estimated from the sensitive analysis, the numbers of CT cases per 10000 pregnancies in Tokyo and Hyogo were estimated to be 7 and 0.01, respectively, during 2019–2021 (Supplementary Table S12).

Discussion

We examined prescription data for spiramycin, which is uniquely and very specifically used for the prevention of CT during pregnancy in Japan, to estimate the infection risk of *T. gondii* nationwide and at prefectural level in selected prefectures. The nationwide risk was estimated to be 0.016% per month. The estimate was robust, even when we assumed two alternative testing scenarios (i.e., pessimistic and optimistic percentages of pregnant people undertaking testing), with estimates ranging from 0.015% to 0.017% per month. Among the prefectures investigated, the risk estimate was highest in Tokyo with 0.030% per month. Nationally, the number of *T. gondii* infections among pregnant people in 2019, 2020, and 2021 was estimated to be 1507, 1440, and 1388, respectively. We also estimated the nationwide number of CT in each year at 613, 588, and 567 cases, respectively. The number of CT per 10000 pregnant people at prefecture level was highest in Tokyo, estimated at 13 cases from 2019 to 2021.
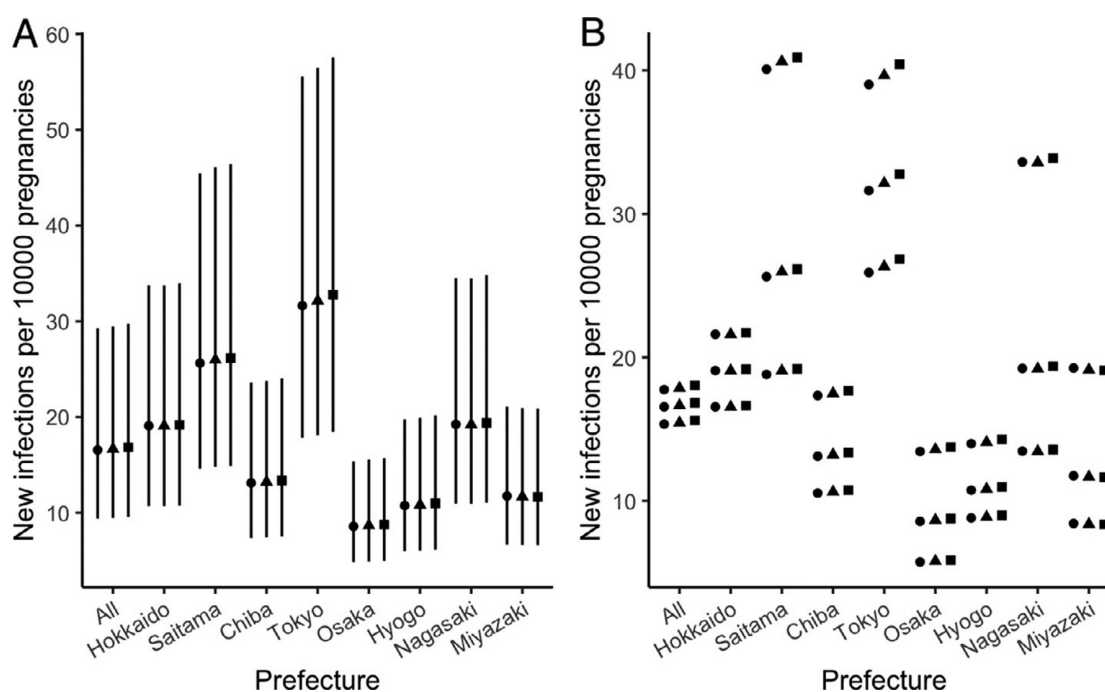

Figure 2. Incidence of *Toxoplasma gondii* infections during pregnancy. (a) Incidence in base scenario. Closed circles, diamonds, and squares represent estimated incidence in 2019, 2020, and 2021, respectively. The continuous black line shows 95% credible interval. (b) Incidence in base (centre), pessimistic (upper), and optimistic (lower) scenarios. Closed circles, diamonds, and squares represent estimated incidence in 2019, 2020, and 2021, respectively.
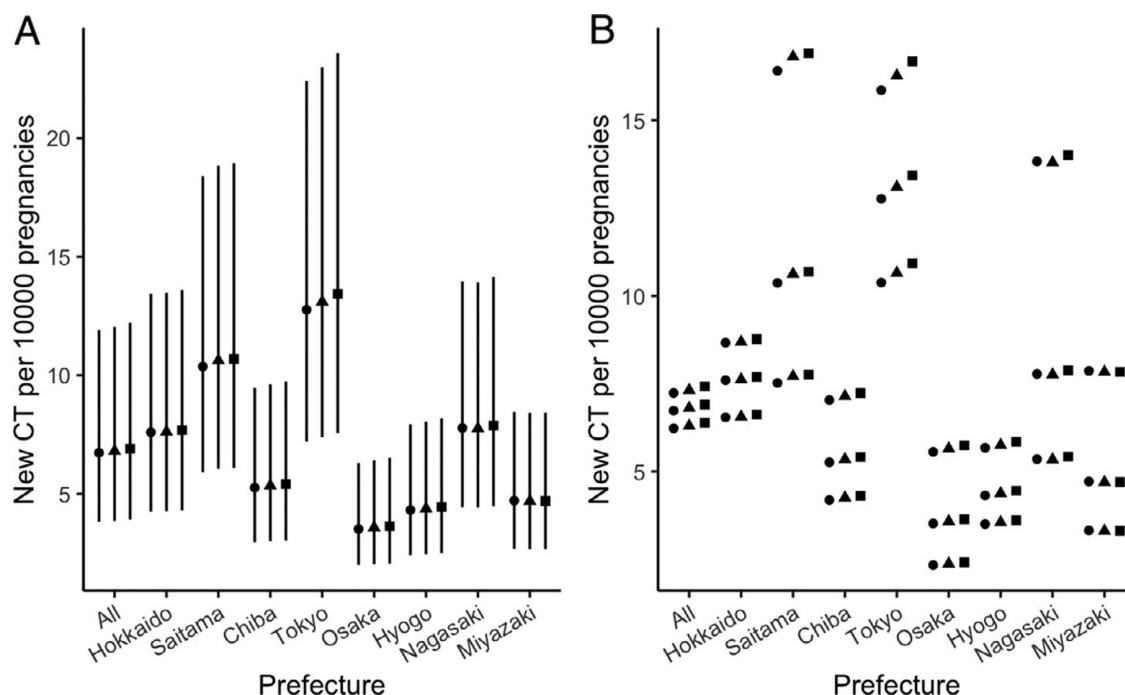
Figure 3. Incidence of congenital toxoplasmosis. (a) Incidence in base scenario. Closed circles, diamonds, and squares represent estimated incidence in 2019, 2020, and 2021, respectively. The continuous black line shows 95% credible interval. (b) Incidence in base (centre), pessimistic (upper), and optimistic (lower) scenarios. Closed circles, diamonds, and squares represent estimated incidence in 2019, 2020, and 2021, respectively.

To our knowledge, the present study is the first to explicitly quantify the risk of infection with *T. gondii* at national level as well as the incidence during pregnancy in Japan. Using a model-based approach, we predicted the number of primary infections in pregnancy, including those that could not be diagnosed and treated under the current testing rate and practice. In a modelling study focused on women of childbearing age in France, the incidence was estimated at 2.4/1000 cases in 2010 and was predicted to be 1.6/1000 in 2020 [34]. Using a healthcare claims database in Germany, the incidence of toxoplasmosis during pregnancy (defined as the first diagnosis in the study period but not in the pre-observational period) was reported to be 29.3 (95% CI: 16.7–56.4)/100000 in 2011 and 60.3 (95% CI: 33.0–107.5)/100000 in 2015 [35]. Our estimate of the incidence during pregnancy (16/10000 pregnancies) is comparable to the one in France and numerically higher than in Germany. Our estimated annual number of CT cases was consistently larger than that in a report based on diagnosed CT cases (with an ICD-10 code) using a claims database in Japan (295, 95% CI: 226–363) [19]. The database includes only health insurance claims for employees of large companies and does not cover other health insurance data, such as national health insurance [36]. The potential biased distribution in socioeconomic status of insured people in the database may lead to underestimation of CT cases. Although the study approaches differed, both studies indicate that CT constitutes a serious burden among neonates in Japan. Considering its magnitude as compared with the reported case number for congenital syphilis (i.e., 20–30 cases annually) in Japan [37, 38], greater effort is needed to ensure prevention (e.g., no exposure to undercooked meat) and proper screening of *T. gondii* during pregnancy.

Although the number of prefectures explored in this study was limited, our findings suggest possible spatial heterogeneities in the risk of *T. gondii*, at least among pregnant people, and consequently neonates. The incidence of both primary *T. gondii* among pregnant people and of CT was estimated to be consistently high in Tokyo and

Saitama, a prefecture bordering the northern end of Tokyo. In contrast, prefectures in western and southern Japan (i.e., Osaka, Hyogo, and Miyazaki) showed a lower incidence of primary infections and CT cases. The local differences in the T. gondii burden observed in our study may be attributed to differences in risky practices during pregnancy, such as eating raw meats or unwashed vegetables, but this remains to be elucidated. Several studies have assessed the spatial pattern of toxoplasmosis. By retrieving local seroprevalence data of *T. gondii*, Su et al. performed a geospatial analysis in mainland China and Taiwan, showing that the highest infection risk of *T. gondii* in humans was observed in Taiwan, followed by Xizang and Jilin provinces in mainland China [39]. Gotteland et al. applied an agent-based model to investigate the spatial distribution of *T. gondii* in soil, providing a risk map of infection in Europe [40]. To our knowledge, no modelling attempts have been made to explicitly link the spatial pattern of human infection to other intermediate or definitive hosts or the environmental load of *T. gondii*, which remains to be addressed in future studies [41]. Notably, Japan has a unique system of umbilical cord blood "banks" from which serological data on endemic infections could potentially be obtained [42]. The use of this resource should be considered to determine whether a spatial pattern exists in *T. gondii*-associated disease burden in order to implement an efficient preventive strategy for CT in Japan.

This study has limitations. First, we assumed that every infected pregnant woman undertaking testing was appropriately diagnosed as infected (or strongly suspected of being infected) and was receiving treatment with spiramycin. Under the Japanese guideline, detection of *T. gondii* IgG and IgM antibodies in early pregnancy is considered to be sufficient for starting treatment with spiramycin. IgG avidity testing may be used but it is not recommended as a standard practice in the guideline [8]. Considering the possibility of over-diagnosis of acute infection based solely on the results of the detection of specific IgM antibodies, the risk and incidence estimates may be lower than those reported in this study. In a

sensitivity analysis to determine the impact of over-diagnosis owing to longer persistence of specific IgM antibodies (which are therefore not markers of acute infection in pregnancy), we found that the estimate of risks and, consequently, numbers of new infections and CT cases in two prefectures were lower, with much uncertainty. *T. gondii* IgG avidity testing was approved in October 2024 [43]; we can estimate the parameters more robustly in the future when more precise diagnosis of acute infection during pregnancy is available across the country. Second, the serological surveys to which this study refers use various testing methods (three hemagglutination tests [13, 14]; one latex agglutination test [12]; one enzyme-linked immunosorbent assay [16]; three unknown [8, 25]); the most recent survey was conducted 10 years ago [25]. A national-level serological study using a uniform testing method is warranted to provide more reliable and updated information on the susceptible proportion of pregnant people in Japan. Third, except for January 2018 to October 2021 during which the number of pregnancies was mandated to be reported each month, the monthly number of reported live births was leveraged as the number of monthly pregnancies, i.e., we could not include pregnancies that ended with spontaneous or induced abortion. To calculate the exact risk, both risk conditional on delivery and conditional on no delivery are needed, although precisely quantifying pregnancy outcomes along with infection history is challenging. Fourth, in addition to CT being a consequence of primary infection in pregnancy, it can occur in cases of infection reactivation in immunocompromised pregnant people, whereas CT cases in previously immunised women reinfected with a more virulent strain have also been reported [44]; our model did not take into account cases of reactivation. Fifth, owing to the limited number of years for which the NDB provides open data, we could not investigate the dynamic trend of incident *T. gondii* infections and CT cases over a longer time scale. Lastly, but not the least, we assumed only one testing in early pregnancy based on nationwide survey from obstetric facilities in Japan. Motivated by regulatory approval of IgG avidity test last year, testing practice may be changed in future and an alternative model accounting for this revision would be warranted.

In conclusion, as an exercise in putting open health data in Japan to good use, we performed mathematical modelling of *T. gondii*, estimating the infection risk of *T. gondii* in pregnancy in Japan. The estimated incidence of infection among pregnant people as well as CT cases, at both national and selected local levels, indicates that toxoplasmosis continues to place a substantial burden on public health in Japan. Given that the magnitude of the burden was comparable to or greater than that of other notifiable congenital infections, far greater attention should be paid to this particular disease, and further studies to elucidate its epidemiology are required.

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