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Highlights

- Immunity against BCG stops Mantoux tests directly identifying primary TB infections.
- Interferon-gamma release assay (IGRA) can mirror primary infection but it decays.
- An epidemiological model was devised to model the IGRA response and its decay.
- Annual risk of infection (ARI) was estimated to decline over time.
- ARI was found to be highly heterogeneous across geographic locations in Japan.

Estimating the annual risk of tuberculosis infection in Japan from interferon-gamma release assay data

Running title: ARI estimated from IGRA in Japan

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5 figures, 1 table.

ABSTRACT

To assess tuberculosis transmission frequency at a population level, the age-dependent Mantoux test has been used widely to estimate the annual risk of infection (ARI) with *Mycobacterium tuberculosis*. However, the widespread Bacille Calmette-Guerin (BCG) immunization program implemented in Japan in the 20th century has made natural infections with *M. tuberculosis* difficult to distinguish from immune responses against this vaccine. Consequently, a recognized alternative method for measuring the frequency of primary infections, the interferon-gamma release assay (IGRA), which partially decays as a function of time after infection, is used. We aimed to estimate the ARI in Japan from IGRA data along with its response decay information using mathematical modeling. Devising a partial differential equation system, we computed the probability of IGRA positivity as a function of time and age, accounting for the time-varying force of infection and decay function of the IGRA response. Jointly estimating the force of infection and the parameters governing the decay function of the IGRA response, we found that the age-dependent increasing pattern of the IGRA response was captured by the proposed simple model, yielding estimates of the time-dependent force of infection. ARI decreased as a function of time in the study subjects for all geographic locations. By the year 2030, our model showed that the median age of infection is predicted to be delayed by 40–50 years compared with that in 1940. The geographic variations in the ARI were striking, ranging from under 0.1% to 0.6% in 2018, which echoes the longstanding notion of highly heterogeneous geographical TB transmission in Japan.

Keywords: *Mycobacterium tuberculosis*; Statistical model; Likelihood function; Confidence interval; Japan

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1. Introduction

To assess the frequency of tuberculosis (TB) transmission at a population level, the annual risk of infection (ARI) with *Mycobacterium tuberculosis* calculation has been widely used in epidemiological studies (Rieder, 2005). ARI is particularly useful for assessing the transmission dynamics of TB, because it can reflect the frequency of primary infection, despite the intrinsic dynamics of TB being highly complex (Blower et al., 1995; Vynnycky & Fine, 1998; Trauer et al., 2014). To date, a multitude of methods have been proposed to estimate the ARI for TB and its variation over time, with the mainstream estimates relying on the national tuberculin survey data (i.e. Mantoux test results) or the mortality rates for infant meningitis (Styblo et al., 1969a; Styblo et al., 1969b; Sutherland et al., 1983; Sjogren & Sutherland, 1975; March-Ayuela, 1994; Vynnycky & Fine, 1997). The Bacille Calmette-Guerin (BCG) immunization

program was widely adopted in Japan during the 20th century, but the Mantoux test, which rests on the development of an effective memory T cell response in an individual, is unable to distinguish natural infections from other immune responses related to the BCG vaccine itself. Furthermore, meningitis mortality estimates only remain unbiased during the pre-chemotherapy era. Therefore, TB experts have sought alternative measures to accurately evaluate this disease epidemiologically, one of which is the TB prevalence survey (Trébucq et al., 2005; van't Hoog et al., 2012; Borgdorff et al., 2013; Pandey et al., 2017). Other methods that have been put into practice for Mantoux test-based ARI estimates include the so-called mirror method, the use of fixed cut-off values, and the imposition of certain recruitment restrictions on the observational study design has enabled continuous ARI monitoring to be conducted through the use of Mantoux test results (Kusano et al., 2005; Kritzinger et al., 2009; Shanaube et al., 2009; Christopher et al., 2011; Yadav et al., 2011; Chopra et al., 2012; Garyfalia et al., 2013; Haghdoost et al., 2014; Gao et al., 2016).

The ARI estimation studies that have taken place in both developing and developed countries include those spanning time periods, but such studies have been somewhat rare in Japan. The latest and only study from Japan was conducted by Mori in 1971 (published in Japanese) and employed the age-independent but time-dependent model of Stýblo et al. (1969a, 1969b). The study rested on the 1968 tuberculin survey data for Okinawa (the southernmost prefecture in Japan), which was politically under USA rule after World War II and did not implement a BCG vaccination program. ARI was estimated to be 0.3% in 1968 and was shown to decrease annually by 10–11% according to Stýblo's assumption (Mori, 1971). Subsequently, no explicit estimation

study has taken place, but many studies have adopted the 1971 study's estimate and have extended its exponential decline even into the 21st century (Ohmori, 1991; Ohmori et al., 2008). Although the TB notification rate has steadily decreased over a long time in Japan, to what extent the ARI has decreased over the last 50 years has not been properly evaluated.

Because the Mantoux test is disadvantaged by its inability to discriminate between a natural infection and reactivity against BCG components in its test outcome, as an alternative, the whole-blood interferon-gamma (IFN-γ) release assay (IGRA) was developed, which rests on the presence of an antigen-dependent immediate effector T cell response in an individual (Brock et al., 2001; Adetifa et al., 2013; Kruczak et al., 2014). Exclusive detection of natural infections by IGRA engenders the hope of directly capturing the frequency of primary infections through population-based cross sectional surveys, and this laboratory method was once used to measure the ARI among children in Spain (Diez et al., 2015). Consequently, the ability to identify latent TB infections has been eagerly awaited from the IGRA response data (Doan et al., 2017). Disappointingly, however, the IFN-γ response appears not to last as long as that of the Mantoux text, and it has been shown that both tuberculin and IGRA reactions wane as a function of time after TB exposure (Mori et al., 2007; Adetifa et al., 2010; Adetifa et al., 2013).

Although the IGRA response may wane over time after an individual becomes infected with TB, the waning response has been measured in an empirical follow-up study (Adetifa et al., 2013). This information offers a possible avenue towards explicitly estimating the ARI using IGRA data while addressing assay decay over time. Therefore, the present study aimed to estimate the ARI in Japan using a multitude of IGRA data

along with observations of the response decay, by employing a mathematical model.

2. Materials and Methods

2.1. IGRA response data

The present study used two published datasets. First, we collected the published observational study data from a seroepidemiological survey that used IGRA in Japan from 2005–15. The published seroprevalence data from 13 cities and a total of 18 different datasets were collected (Ohya et al., 2007; Suenaga et al., 2008; Miyano et al., 2010; Tsukiji et al., 2011; Kamijo et al., 2010; Uesugi et al., 2014; Inoue, 2011; Yoshikawa, 2012; Kimura, 2017; Seto & Ahiko, 2014; Fukushima et al., 2013; Fukushima et al., 2014; Fukushima et al., 2015; Fukushima et al., 2016; Sato et al., 2012; Yamada, 2017; Makishima et al., 2016; Kimura et al., 2016). These surveys were conducted as part of the case finding activities for active TB, and in two cities (Saitama and Hiroshima) the survey was conducted on four and three occasions, respectively, in different calendar years. The counts for the IGRA-positive and -negative individuals were provided as a function of the age groups.

Second, we reanalyzed the follow-up results for the IGRA responses from the randomized, double blinded, and placebo-controlled trials. Adetifa et al. (2013) examined the decay kinetics of TB-specific antigen T cell responses assessed by IGRA (in-house ELISPOT) among patients who experienced a primary infection, as identified by contact tracing practice. The IGRA response decay was followed for 12 months. The IGRA seroprevalence data and the decay data are available in Supplementary data 1.

2.2. Mathematical model

Here, we describe the epidemiological dynamics of primary infection with *M. tuberculosis* as well as the IGRA response. Fig. 1 shows the compartmental structure of our model. Susceptible individuals experience TB exposure at a rate corresponding to the force of infection $\lambda(t)$, which is assumed to be age-independent and time-dependent according to the method of Stýblo (1969a), after which they become infected and IGRA positive. Nevertheless, the IGRA response wanes at rate $\delta(\tau)$ as a function of time after infection τ. This process is described by the following equations:

$$\left(\frac{\partial}{\partial a}+\frac{\partial}{\partial t}\right)s(a,t) = -\lambda(t)s(a,t) \qquad (1)$$

$$\left(\frac{\partial}{\partial a}+\frac{\partial}{\partial \tau}+\frac{\partial}{\partial t}\right)i(a,\tau,t) = -\delta(\tau)\, i(a,\tau,t)$$

with boundary conditions

$$s(0,t) = 1 \qquad (2)$$

and

$$i(a,0,t) = \lambda(t)s(a,t). \qquad (3)$$

Analytically solving the McKendrick equation system (1) along characteristic lines, we have

$$s(a,t) = s(0,t-a)e^{-\int_{t-a}^{t}\lambda(x)\,dx}. \qquad (4)$$

Note that 1-$s(a,t)$ would give the cumulative distribution of primary infection at age a and time t. Similarly, we obtain

$$i(a,\tau,t) = \lambda(t-\tau)\, s(a-\tau,t-\tau)\, e^{-\int_0^{\tau}\delta(x)\,dx}. \qquad (5)$$

Let the survival probability of IGRA positivity as a function of time since exposure τ be

$$p(\tau) = e^{-\int_0^{\tau}\delta(x)\,dx}, \qquad (6)$$

we can rewrite (5) as

$$i(a,\tau,t) = \lambda(t-\tau)\, s(a-\tau, t-\tau)p(\tau), \qquad (7)$$

from which we obtain the expected value of IGRA positivity in year *t* at age *a* years as

$$j_t(a) = \int_0^\infty \lambda(t-\tau)\, s(a-\tau, t-\tau)p(\tau)d\tau. \qquad (8)$$

We extrapolated the decay function of the IGRA response with two different functional assumptions using a small number of parameters. First, the log-linear waning function is assumed to be

$$p(\tau) = -\gamma \ln(\pi\tau + 1) + 1, \qquad (9)$$

where γ scales the strength of decay and π is the steepness of decline over τ. Another functional assumption is the exponential function, which reads

$$p(\tau) = (1-\varphi)\, e^{-\omega\tau} + \varphi, \qquad (10)$$

where φ represents the fraction that remain positive and ω is the exponential waning rate. Loglinear model allows a long-lasting continuous decay over time since infection, while exponential model has the bottom level φ. While the latter assumption may be in line with the notion of decay in cellular immune response, we do not have empirical data of the long-term decay and thus examined both (9) and (10) as our assumptions. Equation (8) yields the model-based prediction of the probability of being IGRA positive at age *a* in year *t*, and the decay function can then be jointly fitted to the follow-up data using either (9) or (10) as the expected value still remains positive at time τ since infection.

We employed a maximum-likelihood estimation method to fit the abovementioned model to the data. To do so, we had to remember that the epidemiological TB dataset contains considerable heterogeneity, and thus, the range of

the IGRA-positive fraction can be broad. Thus, we considered the following three possible scenarios to capture the heterogeneity: (i) that no heterogeneity exists in Japan and an identical force of infection was shared among all cities, (ii) that heterogeneous transmission was classified into three discrete groups based on the tertile of the TB notification rate in 2010, and (iii) that all cities experience different forces of infection, while the decay rate is biologically determined and is thus a common function across the different cities.

Let D be the number of datasets (originally set at D=18). Since the individual IGRA positivity is Bernoulli sampling process, we assume that the population sample data follow a binomial distribution. Namely, given the sample size $n_{a,i}$, and the number of IGRA positives $x_{a,i}$ at age a in city i, the likelihood of estimating the parameters from the IGRA response data was

$$L_1(\theta; x_{a,i}, n_{a,i}) = \prod_{i=1}^{D} \prod_a \binom{n_{a,i}}{x_{a,i}} j_t\,(a)^{x_{a,i}} (1 - j_t\,(a))^{n_{a,i} - x_{a,i}}. \quad (11)$$

Similarly, given the sample size of the IGRA response decay study m_τ at time τ since exposure and y_τ being IGRA positivity, we have

$$L_2(\theta; y_\tau, m_\tau) = \prod_\tau \binom{m_\tau}{y_\tau} p\,(\tau)^{y_\tau} \left(1 - p\,(\tau)\right)^{m_\tau - y_\tau}. \quad (12)$$

The total likelihood is

$$L = L_1 L_2, \quad (13)$$

the negative log-likelihood of which we have minimized. The 95% confidence intervals for the parameters were obtained by profile likelihood. To compute the 95% confidence interval for the predicted IGRA positivity in each observed dataset, we employed the parametric bootstrap method; we resampled the parameter set based on the maximum likelihood estimates and the resulting covariance matrix (which is the inverse matrix of

the Hessian). Based on the parameter set, we obtain the predicted value of the model for 1000 times, and then, the densities of the IGRA positivity and IGRA decay were derived corresponding to the estimated parameters.

Once the force of infection was estimated, we computed the ARI in year t as

$$ARI(t) = 1 - e^{-\lambda(t)}. \quad (14)$$

It should be noted that the force of infection was parameterized as

$$\lambda(t) = e^{-\alpha t+\beta}, \quad (15)$$

following the method of Stýblo et al. (1969a).

3. Results

3.1. Descriptive epidemiology

In total, 18 IGRA response survey datasets were collected for 13 different cities in 2005–15 (Fig. 2). Of these, 17 datasets from 12 cities, which showed an age-specific monotonically increasing IGRA-positive fraction, were used for subsequent analyses. The data for Kanagawa were removed from the analysis, because the age-dependent increase in IGRA responsiveness turned out to have a declining pattern among the adults and we were not able to successfully derive the time-dependent force of infection estimates from this dataset. The data from Kinki represent the mixture of six different prefectures in this region, and for that reason, the sample size was larger than the other survey data and the uncertainty boundary was small. The observed datasets were classified as falling into three different categories of cities, according to the TB notification rate in 2010 (i.e., less than 12.6, from 12.6–18.4, and 18.4 and above per 100,000 people), as indicated by the x-marks and the filled and unfilled circles,

respectively, in Fig. 2.

3.2. Model fit

We examined three different heterogeneity scenarios for the force of infection, that is, (i) that no heterogeneity exists across geographic space (i.e., λ is common across cities), (ii) that there are three different λ values according to the tertile of the notification rate, and (iii) λ is city dependent, but the Akaike Information Criterion (AIC) specifically indicated that heterogeneity by city (i.e., scenario (iii)) appeared to yield the best fit of the data (Table 1). Note that the results with AICc did not vary from those with AIC. Using two different decay patterns (log-linear and exponential), the AIC for the log-linear and exponential decay models was 827.9 and 883.5, respectively, indicating that the log-linear model better explained the underlying decay pattern (Table 1). Fig. 3 compares the observed versus the predicted IGRA response based on the city-dependent force of infection (i.e. scenario (iii)). Supplementary data 2 shows parameter estimates. With the exception of Hiroshima and Saitam, in the majority of locations the observed data strongly overlapped with the 95% CI for the predicted IGRA positivity values. In Hiroshima and Saitama, the observed fractions for a small number of age groups fell outside of the uncertainty boundaries, perhaps because those age groups actually represented the exposed groups for which the IGRA surveys were triggered in the first place.

3.3. Exploring time-dependent estimates

Employing scenario (i) (i.e. that an identical λ exists across Japanese prefectures), we calculated the cumulative distribution for primary infections across the whole of Japan, using the log-linear and exponential decay models (Fig. 4A, B). A

tremendous right-wards shift in the cumulative frequency was observed in the models, such that while the median age at infection was estimated to be around 30 and 20 years of age in 1940 by the log-linear and exponential models, respectively, these were predicted to be delayed to 80 and 60 years of age, respectively, by 2030. Fig. 4C shows the time-dependent declining pattern of the ARI for scenario (i). The ARI, as based on the exponential decay of the IGRA, yielded a greater estimate over the same time period when compared with that of the log-linear decay model. Compared with Mori's 1960s dataset-based prediction, our estimates generated less steep ARI curves and, consequently, larger ARI estimates overall. The estimated decay functions of the IGRA response based on scenario (iii) are illustrated in Fig. 4D. The observed pattern by 6 months post-infection was well captured, and subsequently, the exponential decline was estimated to be faster than that of log-linear decay.

The ARI decay was also examined by prefecture (Fig. 5) using scenario (iii). In descending order, we found that Nishio, Adachi and Kinki experienced the three highest ARI estimates in 2018 estimated at 0.6% (95% CI: 0.2, 1.1), 0.5% (95% CI: 0.1, 0.7) and 0.4% (95% CI: 0.3, 0.4), respectively. The smallest ARI estimates in 2018 were obtained for Matsumoto, Miyazaki and Niigata at 0.1% (95% CI: 0.0, 0.2), 0.1% (95% CI: 0.0, 0.2) and 0.1% (95% CI: 0.1, 0.2), respectively. Highly diverse estimates of ARI were obtained, depending on the geographic survey location.

4. Discussion

The present study estimated the ARI for TB in Japan using the IGRA response data for time and age. Employing a mathematical model governed by partial differential equations, and jointly estimating the force of infection along with parameters governing the decay function of the IGRA response, we successfully estimated the ARI and characterized the frequency of primary TB infections in present day Japan. An age-dependent increasing pattern of IGRA response was captured by the proposed simple model, which yielded estimates of the time-dependent force of infection. Notably, our modelling predicted that the median age of infection will be delayed considerably by 40–50 years in 2030 as compared with the 1940 value. The highly heterogeneous nature of disease transmission was endorsed by the geographical estimate of the ARI.

Our findings have practical importance for the TB field in that our IGRA response data predicts that the annual rate of TB infection should decline over time. In a population with a high BCG vaccinated coverage, it has been difficult to estimate the incidence of primary infection with *M. tuberculosis* directly from Mantoux test results (Trebucg et al., 2005; Pandey et al., 2017), but this estimation was made possible in the present study by using IGRA results and their associated decay with a new mathematical model. Consequently, we have shown that the ARI has decreased as a function of time in all geographic locations for which we had data. It is worth noting that our estimated ARI is greater than that Mori (1971) predicted over 40 years ago, because that estimate was only based on the Mantoux test results for Okinawa, and

acted therefore as an unsupported measure of transmission for Japan in its entirety, even for the present day. Our exercise has helped with updating Mori's estimate.

Another important finding from the present study was that the ARI appears to be highly heterogeneous across the geographical locations that were studied. ARI in many cities was estimated to be 0.1% or lower (with greater precision), a finding consistent with published estimates from several decades ago in industrialized countries including the United Kingdom (March-Ayuela, 1994; Vynnycky & Fine, 1997). Here, we found that the estimates for relatively remote areas were typically low (e.g., Matsumoto and Miyazaki). However, the ARI estimates for urban locations such as Adachi and Nishio were as high as 0.5% and 0.7%, respectively. We believe that this level of heterogeneity has probably arisen for two different reasons. First, the presence of at-risk populations (e.g. unemployed persons, foreigners and the elderly) in some areas means that TB transmission in Japan is known to be highly heterogeneous geographically, and our ARI estimates reflect these actual heterogeneities. Second, it is more plausible, especially for Adachi and Nishio, that the subjects sampled for the IGRA survey included those at high risk of TB exposure. That is, it has frequently been the case that an IGRA survey at the local level is triggered by identifying infectious TB cases, and we cannot rule out the possibility that the sampled subjects were recruited from people with close contact to known cases. Heterogeneous exposure, the latter explanation, can also explain why the observed IGRA response data for Hiroshima and Saitama fluctuated irregularly with age.

Our approach has shown that the IGRA response can be used for estimating ARI by addressing its decay via a mathematical model, but we have to discuss the validity of

analyzing IGRA data for estimating the cumulative frequency of primary infections with TB. That is, our estimates of ARI rest on a model that makes certain assumptions on the decay function of the IGRA response. Depending on the functional assumption employed, the ARI appeared to differ. While our estimated decay function captured the observed decay data during the patients' follow-up (for up to 1 year post-infection), no empirical follow-up data are available covering longer time scales. Considering that Stýblo's model-based ARI assumption is very ambitious for estimating the time-dependent patterns for the force of infection, further longitudinal observation of the IGRA response is required for future validation of the ARI estimation method.

Our study was not free of limitations. First, the local survey sample sizes are quite limited, and thus, the uncertainty boundaries of our estimates are broad. Second, because of the heterogeneous nature of TB transmission, selection bias associated with the IGRA testing during sampling processing cannot be ruled out (as discussed above); therefore, the estimates for a single geographical area might not be applicable to the whole of Japan. In fact, it may not be a sound idea to aim to identify the representative value for the ARI across the whole of Japan in the present day; rather, perhaps it is better to explore the nature of heterogeneous transmission with greater spatial resolution and stratification in the at-risk populations. Third, as acknowledged above, the empirical data for IGRA decay was limited in its length of follow-up, making it difficult to currently identify the most appropriate functional pattern to fully describe the decay.

In conclusion, despite these remaining technical problems, we believe that our proposed model successfully estimated the ARI for TB from the IGRA response data for present day Japan without suffering from the complication of BCG vaccination. As

we aim to construct an accurate and reliable estimation method for TB infection frequency, we are open to any criticisms, comments or suggestions to bring about future improvements to ARI estimations.

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References

Adetifa, I., Ota, M., Walther, B, Hammond, AS, 2010. Decay kinetics of an interferon gamma release assay with anti-tuberculosis therapy in newly diagnosed tuberculosis cases. PLoS ONE 1, e12502.

Adetifa, Ota, M., Jeffries, 2013. Interferon-γ ELISPOT as a biomarker of treatment efficacy in latent tuberculosis infection: a clinical trial. American Journal of Respiratory and Critical Care Medicine 187, 439-445.

Blower, S.M., McLean, A.R., Porco, T.C., Small, P.M., Hopewell, P.C., Sanchez, M.A., Moss, A.R., 1995. The intrinsic transmission dynamics of tuberculosis epidemics. Nature Medicine 1, 815–21.

Borgdorff, M.W., Soolingen van, D., 2013. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? Clinical Microbiology and Infection 19, 889-901.

Brock, I., Munk, M.E., Kok-Jensen, A., Andersen, P., 2001. Performance of whole blood IFN-gamma test for tuberculosis diagnosis based on PPD or the specific antigens ESAT-6 and CFP-10. The International Journal of Tuberculosis and Lung Disease 5, 462–7.

Christopher, D.J., James, P., Daley, P., Armstrong, L., Isaac, B.T., Thangakunam, B., Premkumar, B., Zwerling, A., Pai, M., 2011. High annual risk of tuberculosis infection among nursing students in South India: a cohort study. PLoS ONE 6, e26199.

Chopra, K., Chadha, V.K., Ramachandra, J., Aggarwal, N., 2012. Trend in Annual Risk of Tuberculous Infection in North India. PLoS ONE 7(12), e51854.

Díez, N., Giner, E., Latorre, I., Lacoma, A., Roig, F.J., Mialdea, I., Díaz, J., Serra-Vidal, M., Escribano, A., Domínguez, J., 2015. Use of interferon-gamma release assays to calculate the annual risk of tuberculosis infection. Pediatr Infect Dis J 34, 219-21.

Doan, T.N., Eisen, D.P., Rose, M.T., Slack, A., Stearnes, G., McBryde, E.S., 2017. Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: A latent-class analysis. PLoS ONE 12, e0188631.

Fukushima, H., Hamamoto, N., Shimada, N., Aoki, A., 2016. Study of interferon-gamma release assays (IGRA) test in Saitama Prefecture. Annual Report of Saitama Prefectural Institute of Public Health 50, 95–97. (in Japanese)

Fukushima, H., Iida, Y., Shimada, N., Aoki, A., Kishimoto, T., Honda, A., 2015. Study of interferon-gamma release assays (IGRA) test in Saitama Prefecture. Annual Report of Saitama Prefectural Institute of Public Health 49, 31–36. (in Japanese)

Fukushima, H., Iida, Y., Shimada, N., Kishimoto, T., 2014. Study of interferon-gamma release assays (IGRA) test in Saitama Prefecture. Annual Report of Saitama Prefectural Institute of Public Health 48, 51–53. (in Japanese)

Fukushima, H., Shimada, N., Aoki, A., Kishimoto, T., 2013. Summary of QFT test in Saitama Prefecture (2012) and study on the fluctuation of results after doing retest for indeterminate in the TB Gold. Annual Report of Saitama Prefectural Institute of Public Health 47, 29–31. (in Japanese)

Gao, L., Bai, L., Liu, J., Lu, W., Wang, X., Li, X., Du, J., Chen, X., Zhang, H., Xin, H., Sui, H., Li, H., Su, H., He, J., Pan, S., Peng, H., Xu, Z., Catanzaro, A., Evans, T.G., Zhang, Z., Ma, Y., Li, M., Feng, B., Li, Z., Guan, L., Shen, F., Wang, Z., Zhu, T., Yang, S., Si, H., Wang, Y., Tan, Y., Chen, T., Chen, C., Xia, Y., Cheng, S., Xu, W., Jin, Q.; LATENTTB-NSTM study team., 2016. Annual risk of tuberculosis infection in rural China: a population-based prospective study. Eur Respir J 48, 168-78.

Garyfalia, V., Irini, G., Vasilios, S., Konstantinos, G., 2013. Annual Risk of Tuberculosis Infection in Hellenic Air Force Recruits. Open Respir Med J 7, 77-82.

Haghdoost, A.A., Afshari, M., Baneshi, M.R., Gouya, M.M., Nasehi, M., Movahednia, M., 2014. Estimating the annual risk of tuberculosis infection and disease in southeast of iran using the bayesian mixture method. Iran Red Crescent Med J 16, e15308.

Hoog, van't A., Meme, HK, Laserson, KF, one, A.-J., 2012. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. PLoS ONE 7, e38691.

Inoue, T., 2011. Epidemiological study on contact examinations done by Nishio Health

Centre using QFT from 2008 to 2010. Kekkaku 86, 709–715. (in Japanese)

Kamijyo, A., Nakano, M., Kondo, A., Ishida, S., Ichikawa, M., Ohguchi, K., Terai, N., 2010. QuantiFERON kensa wo motiita kekkaku sesshokusha kensin no ichi kousatsu [Discussion of tuberculosis contact examinations with QuantiFERON]. Shinshu Society of Public Health 5, 36-37. (in Japanese)

Kimura, H., Sakota, T., Sonoda, C., Nakamori, I., Kaneyuki, T., Miyauchi, M., Mikasa, M., Yamada, N., Sudo, A., Kyoraku, Y., Ito, Y., 2017. Kekkaku sesshokusha kenshin ni okeru QuantiFERON-TB kensa no ooureisha ni taisuru yuyousei no kento [Effectiveness of QuantiFERON-TB in the tuberculosis contact investigation of elderly people]. Miyazaki City Center of Public Health. http://www.msuisin.jp/upimg/20120626102606F_1.pdf (accessed 1st October 2017) (in Japanese)

Kimura, Y., Inomata, A., Kawase, M., Hosoya, M., Shichiku, M., 2016. An analysis of QFT results in tuberculosis contact examination (Ⅱ). Annual Report of Niigata Prefectural Institute of Public Health and Environmental Sciences 83‐86. (in Japanese)

Makishima, M., Hatano, R., Furukawa, Y., Ito, T., Yamazaki, S., Kato, Y., Abe, A., 2016. Heisei 27 nen QuantiFERON-TB wo motiita kekkaku kansen shindan no jisshi joukyou [QuantiFERON-TB in diagnosis of tuberculosis infection among tuberculosis contacts in 2015]. Annual Report of Suginami City Institute of Public Health 34, 32-33. (in Japanese)

Kritzinger, F.E., den Boon, S., Verver, S., Enarson, D.A., Lombard, C.J., Borgdorff, M.W., Gie, R.P., Beyers, N., 2009. No decrease in annual risk of tuberculosis infection in endemic area in Cape Town, South Africa. Trop Med Int Health 14, 136-42.

Kruczak, K., Duplaga, M., Sanak, M., Cmiel, A., Mastalerz, L., Sladek, K., Nizankowska-Mogilnicka, E., 2014. Comparison of IGRA tests and TST in the diagnosis of latent tuberculosis infection and predicting tuberculosis in risk groups in Krakow, Poland. Scand J Infect Dis 46, 649-55.

Kusano, M.S., Messias Mendes, I.J., Alves, E.D., de Assis, M.C., 2005. The annual risk

of tuberculosis infection in the Federal District (Brazil). Rev. Bras. Epidemiol. 8, 262-71.

March-Ayuela, de P., 1994. Trend in Tuberculous Meningitis in Barcelona in Children Aged 0-4 Years: Correlation with the Annual Risk of Tuberculous Infection. Tubercle and lung disease 75, 423–428.

Miyano, T., Tanaka, H., Suenaga, A., Kunii, E., Mouri Y,, Ishimura, K., Ikeda, Y., Kasama, Y., 2010. Heisei 21 nendo kekkaku-kanja sesshokusha-kenshin ni okeru QuantiFERON-TB 2G hou ni yoru kensa joukyou [QuantiFERON-TB 2G and Gold tests among tuberculosis contacts in 2009]. Annual Report of Hiroshima City Institute of Public Health 29, 101-102. (in Japanese)

Mori, T., 1971. Epidemiological analysis of tuberculosis in Okinawa, Report1. Trend of tuberculosis infection analyzed by Stýblo's model. Kekkaku (Tuberculosis) 46, 357–364 (in Japanese).

Mori, T., Harada, N., Higuchi, K., Sekiya, Y., Uchimura, K., Shimao, T., 2007. Waning of the specific interferon-gamma response after years of tuberculosis infection. The International Journal of Tuberculosis and Lung Disease 11, 1021–5.

Ohmori, M., 1991. Estimating the Year of Eradication of Tuberculosis in Japan. Kekkaku (Tuberculosis) 66, 819-828 (in Japanese).

Ohmori, M., Yoshiyama, T. and Ishikawa, N., 2008. Estimation of the Future Epidemiological Situation of Tuberculosis in Japan. Kekkaku (Tuberculosis) 83, 365–377 (in Japanese).

Ohya, H., Okazaki, N., Takahashi, C., Watanabe, Y., Onoue, Y., Nikkawa, T., Imai, M., 2007. Usefulness of QuantiFERON®TB-2G in diagnosis of tuberculosis infection among tuberculosis contacts. Bulletin of Kanagawa Prefectural Institute of Public Health 37, 6–8. (in Japanese)

Pandey, S., Chadha, V.K., Laxminarayan, R., Arinaminpathy, N., 2017. Estimating tuberculosis incidence from primary survey data: a mathematical modeling approach. The International Journal of Tuberculosis and Lung Disease 21, 366-74.

Reider, H., 2005. Annual risk of infection with Mycobacterium tuberculosis. Eur Respir J 25, 181-5.

Sato, N., Morita, H., Takahashi, M., Iwabuchi, K., Saito, K., 2012. QuantiFERON-TB kensa no jisshi joukyo (heisei 24 nendo) [QuantiFERON-TB tests among tuberculosis contacts in 2012]. Annual Report of Iwate Prefectural Research Institute for Environmental Science and Public Health 12, 74-75. (in Japanese)

Seto, J., Ahiko, T., 2014. Effectiveness of Interferon-gamma release assays in the tuberculosis contact investigation of elderly people. Kekkaku 89, 503–508 (in Japanese).

Shanaube, K., Sismanidis, C., Ayles, H., Beyers, N., Schaap, A., Lawrence, K-A., Barker, A., Godfrey-Faussett, P., 2009. Annual Risk of Tuberculous Infection Using Different Methods in Communities with a High Prevalence of TB and HIV in Zambia and South Africa. PLoS ONE 4(11), e7749.

Sjögren, I., Sutherland, I., 1975. The risk of tuberculous infection in Sweden. Tubercle 56, 97–112.

Stýblo, K., Meijer, J., Sutherland, I., 1969a. The transmission of tubercle bacilli: its trend in a human population. Bull. World Health Organ. 41, 137–178.

Stýblo, K., Meijer, J., Sutherland, I., 1969b. The transmission of tubercle bacilli: its trend in a human population. Bull. World Health Organ. 42, 5–104.

Suenaga, A., Kuniyori, K., Mouri, Y., Ishimura, K., Kasama, Y., 2008. Kekkaku kanja sesshokusha kenshin ni okeru QuantiFERON-TB 2G hou ni yoru kensa joukyo [QuantiFERON-TB 2G tests among tuberculosis contacts in 2007]. Annual Report of Hiroshima City Institute of Public Health 27, 45-48. (in Japanese)

Sutherland, I., Bleiker, M.A., Meijer, J., Stýblo, K., 1983. The risk of tuberculous infection in The Netherlands from 1967 to 1979. Tubercle 64, 241–53.

Trauer, J.M., Denholm, J.T., McBryde, E.S., 2014. Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-Pacific. J Theor Biol 358, 74-84.

Trébucq, A., Guérin, N., Ismael, H. Ali, Bernatas, J.J., Sèvre, J.P., Rieder, H.L., 2005. Prevalence and trends of infection with Mycobacterium tuberculosis in Djibouti, testing an alternative method. The International Journal of Tuberculosis and Lung Disease 9, 1097–104.

Tsukiji, Y., Tanaka, A., Suenaga, A., Hanaki, Y., Kunii, E., Miyano, T., Sato, M., Sakamoto, A., Kyozuka, A., Ito, F., Hashimoto, K., Kasama, R., 2011. Heisei 22 nendo kekkaku kanja sesshokusha kenshin ni okeru QuantiFERON-TB 2G hou oyobi QuantiFERON-TB Gold hou ni yoru kensa joukyo [QuantiFERON-TB 2G and Gold tests among tuberculosis contacts in 2010]. Annual Report of Hiroshima City Institute of Public Health 30, 95-96. (in Japanese)

Uesugi, H., Kohguchi, K., Kurokawa, Y., Kobashi, Y., Tohyama, K., 2014. Recent status and data analysis of examination for Mycobacterium tuberculosis-specific interferon-γ release assay, QuantiFERON (QFT) test. Japanese Association of Medical Technologists 63, 497-503. (in Japanese)

Vynnycky, E., Fine, P.E., 1997. The annual risk of infection with Mycobacterium tuberculosis in England and Wales since 1901. The International Journal of Tuberculosis and Lung Disease 1, 389–96.

Vynnycky, E., Fine, P.E., 1998. The long-term dynamics of tuberculosis and other diseases with long serial intervals: implications of and for changing reproduction numbers. Epidemiology and Infection 121, 309–24.

Yadav, R., Rao, V.G., Bhat, J., Gopi, P.G., Wares, D.F., 2011. Annual risk of tuberculosis infection among the tribal children of Jhabua, Madhya Pradesh. Indian Pediatrics 48, 43-45.

Yamada, Z., 2017. Kekkaku sesshokusha kensin ni okeru IGRA wo motiita senzaisei kekkaku kansenshou (LTBI) sindan no genjyo to seidokanri ni tsuite [Interferon-gamma release assay in diagnosis of latent tuberculosis infection among tuberculosis contacts and its accuracy]. Department of Public Health, Nara Medical University. http://www.naramed-u.ac.jp/~hpm/7th_summerseminar2015_0805.html (accessed 1st October 2017). (in Japanese)

Yoshikawa, H., 2012. Possible presence of a booster effect in people repeatedly exposed to Mycobacterium tuberculosis demonstrated in a Mycobacterium tuberculosis-specific interferon-gamma release assay. Kekkaku 87, 557–564. (in Japanese)

Figure legends

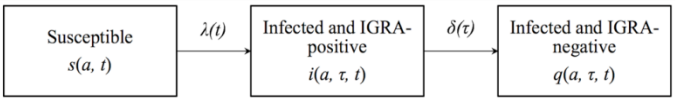

Fig. 1. Compartmental model for describing the interferon-gamma release assay (IGRA)-positive fraction as a function of time and age.

New infections take place at a rate $\lambda(t)$, which is referred to as the force of infection at time t, yielding an estimate of the annual risk of infection. Once becoming infected and IGRA-positive, the IGRA decay occurs at the rate $\delta(\tau)$ at the time τ since infection.

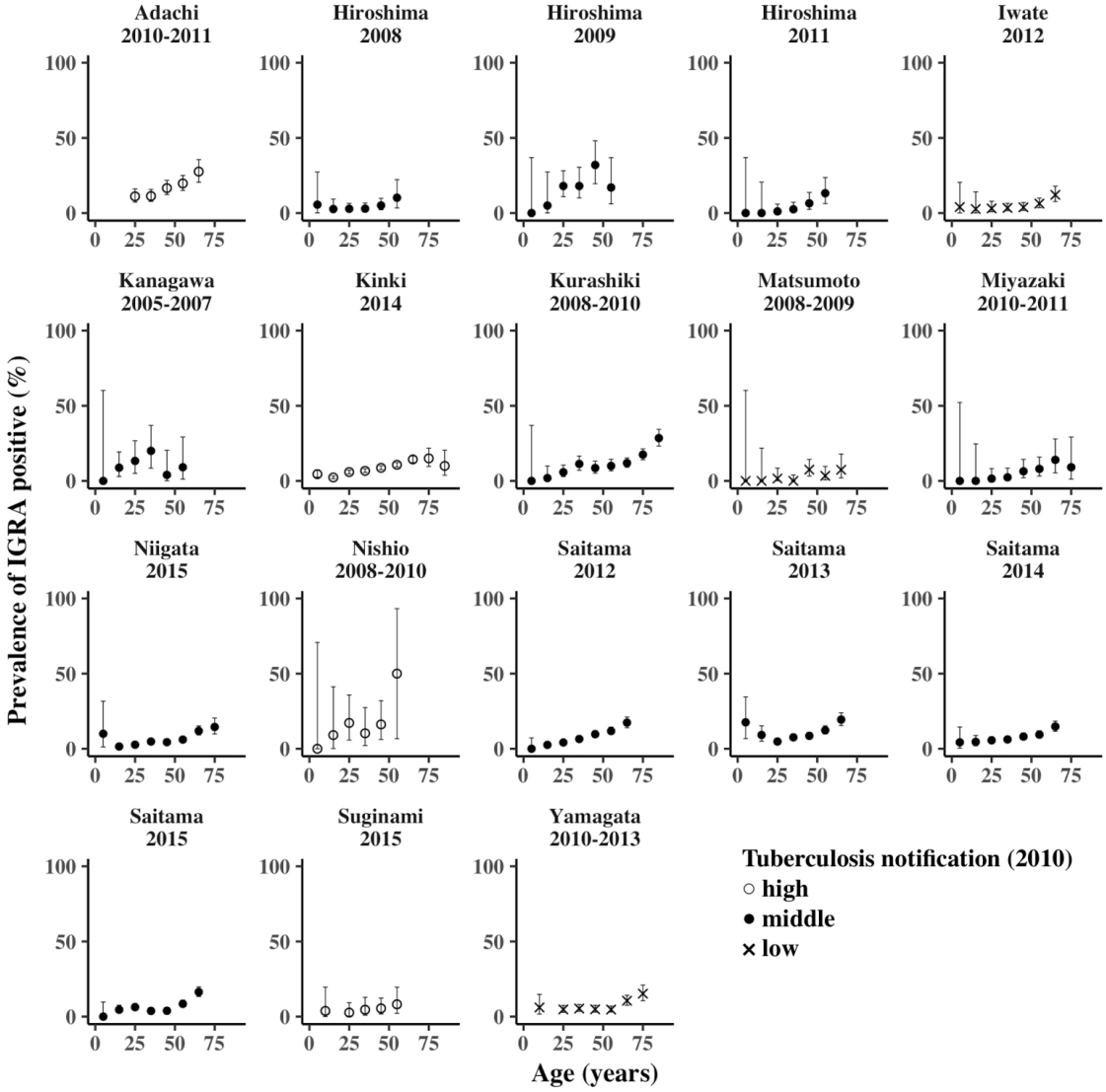

Fig. 2. Observed proportion of the study subjects that are interferon-gamma release assay (IGRA)-positive in Japan.

Observations took place from 2008–15 with a total of 18 different datasets from 13 different cities. City and year of observation are written on the top of each panel. In Hiroshima and Saitama, the survey was conducted a total of 3 and 5 times, respectively. The proportion of individuals that are positive in a given age group is represented by a mark, which is stratified into three groups according to the tertile (i.e., low, middle and high) of the tuberculosis notification rate in 2010 in the respective prefectures. Vertical error bars represent the 95% confidence intervals calculated from the binomial distribution. Because the observed pattern of IGRA-positivity in Kanagawa was not

captured well by our mathematical model, this dataset was excluded from our modeling study.

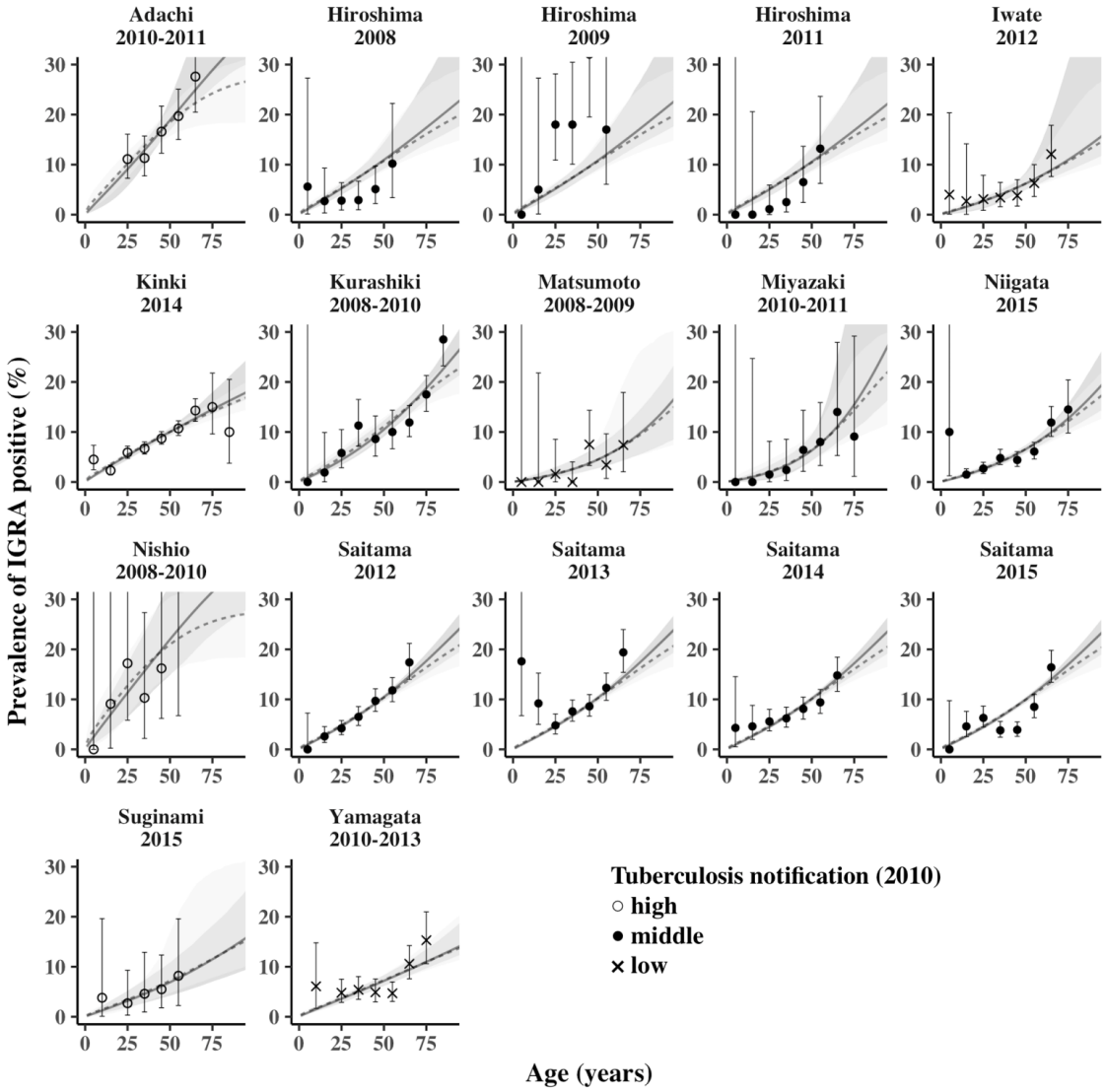

Fig. 3. Comparison between the observed and predicted proportion of individuals with interferon-gamma release assay (IGRA)-positivity in Japan.

The age-specific proportion of individuals with positive interferon-gamma release assays (IGRAs) was modeled, and comparisons between the observed and predicted frequencies were made for a total of 17 different datasets from 12 cities. It was assumed in the predicted model that the force of infection varied by city, while the decay function of the IGRA response was assumed to be common (i.e. shared across cities). The

observed proportion that were positive in a given age group is represented by a mark, which is stratified into three groups according to the tertile (i.e., low, middle and high) of the tuberculosis notification rate in 2010 in the respective prefectures. Vertical error bars represent the 95% confidence intervals calculated from the binomial distribution. The solid line represents the prediction based on the model that uses a log-linear decay of the IGRA response. The dashed line shows the prediction based on the model that uses an exponential decay of the IGRA response. The uncertainty boundaries (i.e. 95% confidence intervals) of the predicted log-linear and exponential decay models are shown as dark and light gray shaded areas, respectively, based on the bootstrapping method; the calculated AICs for these models were 827.9 and 883.5, respectively.

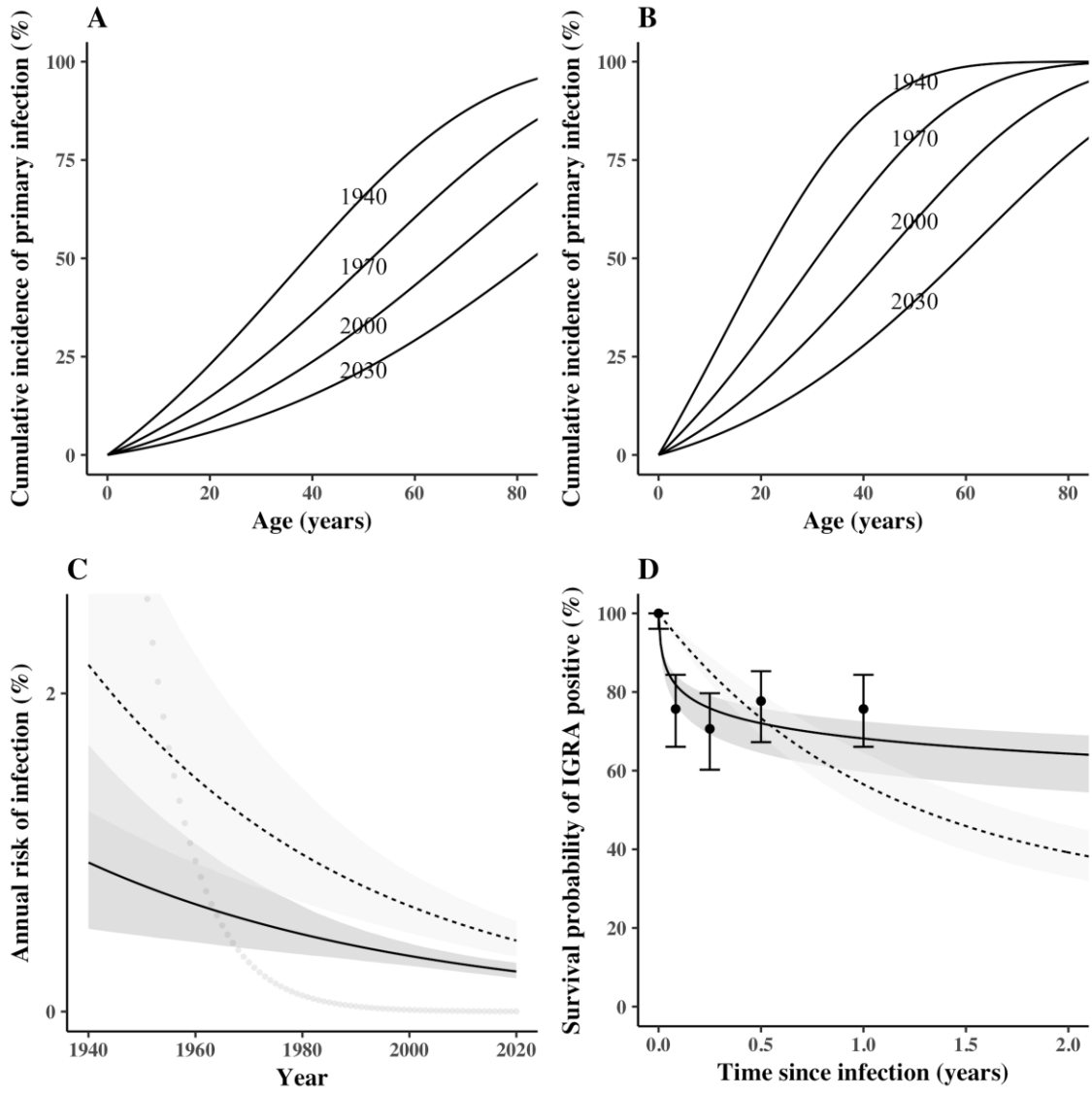

Fig. 4. Cumulative incidence, annual risk of infection and decay function of the interferon-gamma release assay (IGRA)

A. Predicted age-specific cumulative incidence of primary infection with tuberculosis (TB) by year based on our log-linear decay model of IGRA response. B. Predicted age-specific cumulative incidence of primary infection with TB by year based on our exponential decay model of IGRA response. C. Estimated annual risk of infection by year. The dashed line within light-colored shading shows the estimate from the exponential decay model, and the solid line within dark-colored shading shows the prediction from the log-linear decay model. Light and dark shaded areas represent the 95% confidence intervals calculated using the bootstrap method. Grey dots show the

estimate obtained from the national tuberculin survey in Okinawa, Japan, 1968 (Mori, 1971). D. Decay of the IGRA response as a function of time since infection. Dots and whiskers represent the observed data and their associated confidence intervals, respectively. The dashed line shows the estimate from the exponential decay model, while the solid line shows the prediction from the log-linear decay model. The shaded areas represent the 95% confidence intervals calculated using the bootstrap method. For panels A, B and C, these predictions were made by employing a model that assumed that the force of infection was identical across Japan. For panel D, the force of infection was assumed to vary by city, but an identical IGRA response decay was assumed.

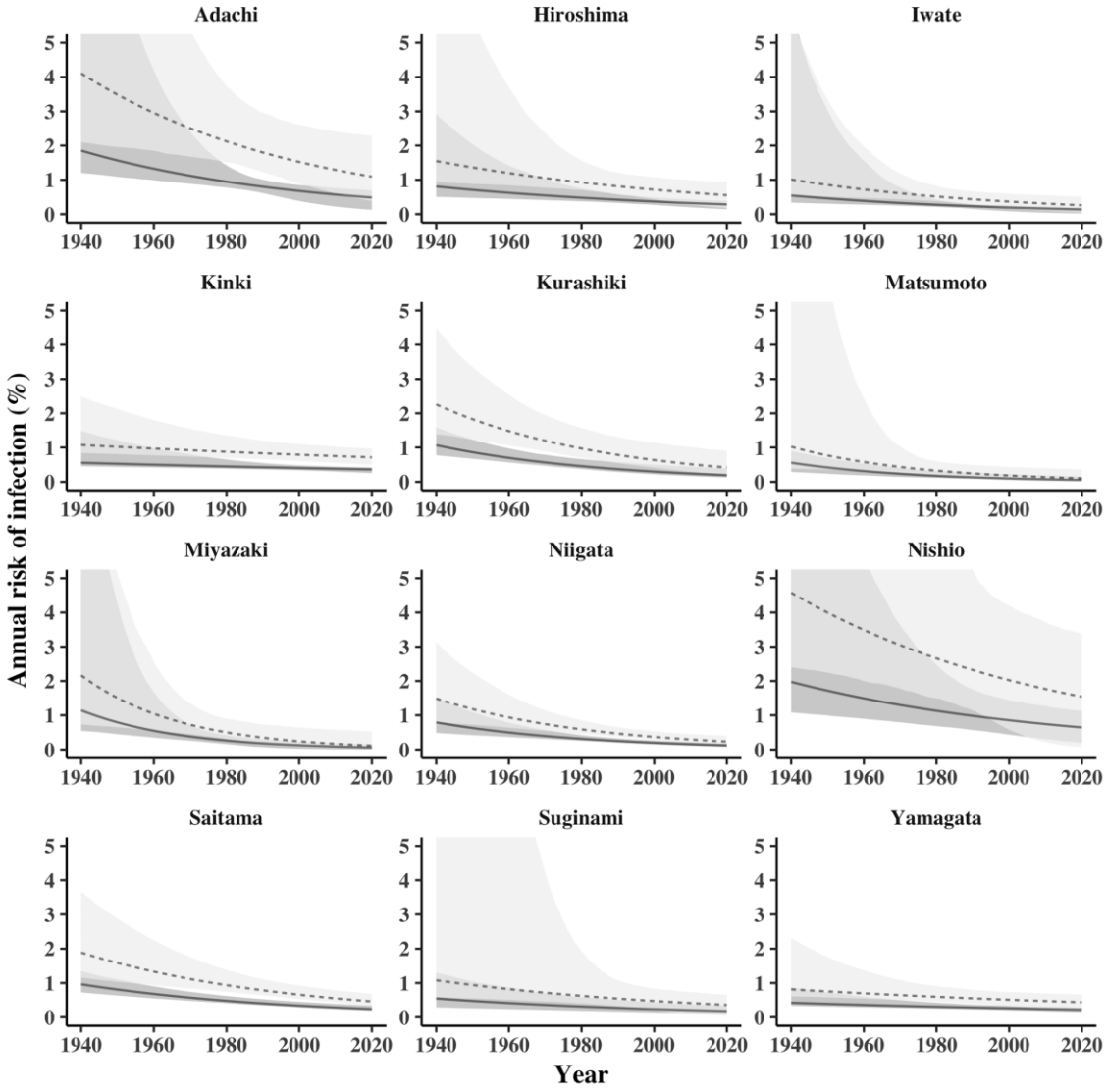

Fig. 5. Annual risk of infection among 12 cities

Estimated annual risk of infection among 12 different Japanese cities. The dashed line within light-colored shading shows the estimate from the log-linear decay model, whereas the solid line within dark colored-shading shows the prediction from the exponential decay model. The shaded areas represent the 95% confidence intervals calculated using the bootstrap method. The force of infection was assumed to vary by city, but an identical IGRA response decay was assumed.

Table 1. Estimated parameters for the different survival probability functions for IGRA-positive individuals and AIC value comparisons.

	Parameter: γ			Parameter: π			
Log-linear decay model	MLE	Lower	Upper	MLE	Lower	Upper	AIC
No heterogeneity in ARI	0.06	0.05	0.08	178.06	98.54	257.59	989
ARI in the three groups	0.08	0.08	0.08	97.25	97.01	97.48	910
Different ARIs by city	0.06	0.04	0.07	295.60	281.50	309.69	828
	Parameter: φ			Parameter: ω			
Exponential decay model	MLE	Lower	Upper	MLE	Lower	Upper	AIC
No heterogeneity in ARI	0.25	0.17	0.33	0.86	0.62	1.14	1039
ARI in the three groups	0.24	0.17	0.31	0.85	0.60	1.10	963
Different ARIs by city	0.28	0.20	0.36	0.92	0.65	1.19	884

MLE, maximum likelihood estimate. Lower and upper: 95% confidence intervals derived from the profile likelihood. AIC, Akaike Information Criterion.