Original Article

CHRONOLOGICAL DECREASE OF TUBERCULOSIS INCIDENCE RATES BY ORGAN CLASSIFICATION BASED ON A BIRTH COHORT STUDY IN JAPAN, 1975–2005

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Abstract [Background and objective] The incidence and annual risk of infection of tuberculosis (TB) have decreased rapidly in Japan because of the development of anti-TB medicines and nutritional and hygienic improvements after World War II. The incidence of tuberculosis is currently high among elderly people, reflecting the fact that the prevalence rate of TB infection had been extremely high during their youth. This would suggest that most current cases of TB in the elderly are reactivation of infections acquired in their youth. TB reactivation in various organs have both common and unique aspects. We evaluated the frequency of endogenous reactivation of TB in various organs by examining the TB incidence rate over a 30-year period (1975–2005) in Japan. [Methods] The incidence rate of TB in each organ was obtained for each 10-year birth cohort, using reports of newly registered TB patients in Japan in 1975, 1985, 1995, and 2005. Specifically, the incidence rates of pulmonary TB, lymph node TB, bone-joint TB, kidney TB, and meninges TB were analyzed. [Results] Chronological changes in TB incidence rates in each organ were characterized by a rapidly declining phase followed by a stationary phase in every organ TB except pulmonary TB. Incidence rates among the already infected population in the stationary phase were 3.0 (lymph node TB), 1.2 (bone-joint TB), 0.5 (kidney TB), and 0.3 (meninges TB) per 100,000 cases, respectively. [Conclusions] Once infected with TB, the incidence rate of TB in these organs does not decrease below the above-mentioned values.

Key words: Tuberculosis, Incidence rate, Reactivation, Extra-pulmonary TB

Introduction

The interval from infection with mycobacteria to the onset of tuberculosis (TB) has been studied before the advent and spread of antibiotic therapy. For example, a study on the trends in the incidence rate of TB after infection was conducted by Chiba[1)] by following 1,192 railway workers (15- to 29-year-old males) for 30 years who had had a positive conversion in the tuberculin reaction. The incidence rate was reported to be 16% within 1 year, 1% after 10 years, 0.3% after 20 years, and 0.1% after 30 years.[1)] Taken together with the reports by Ferebee[2)] and Hart and Sutherland[3)] who studied chronological changes in the incidence rate of the disease among contacts of TB patients, a pattern was observed in which occurrences were concentrated in the first 1–2 years after positive conversion and became sporadic over the longer term as illustrated in Fig. 1A where the logarithm of the incidence rate was plotted on the y-axis.[1)~3)] However, long-term trends in the incidence rate were unclear due to the limited numbers of cases. For example, the incidence rate after 30 years was 0.1% in Chiba's report[1)]; this would indicate that there was only one incident, considering that there were originally 1,192 cases. It was unclear whether this particular case was actually reactivation from infection 30 years prior or re-infection. Despite these shortcomings, the incidence rate decreased almost linearly on the logarithmic graph (i.e., exponentially) for 10 years or longer after infection. The decline rate is approximately −0.11/year (Fig. 1A) on the logarithmic scale.

Different from pulmonary TB, chronological changes in the incidence rate of extra-pulmonary TB after the initial infection have rarely been reported. Wallgren[4)] reported that the incidence of bone-joint TB was high in the first one year and then decreased gradually, and was very low after 4 years. His data, illustrated on a logarithmic scale in Fig. 1B, demonstrated a linear decrease (slope −0.38/year) in the incidence of bone-joint TB.

What would be the ultimate incidence rate more than 10 years after the initial infection, which was not described in the above reports? Will the incidence rate continue to decrease exponentially with time, or will other features appear? It is

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almost impossible to answer these questions with prospective studies now. However, by using the national statistics of new TB cases in Japan, it might be possible to obtain some answers to these questions.

National statistics of new TB cases have been published in Japan, classified by year of birth in 10-year intervals. By using the data of these groups, we studied the chronological changes in the incidence rate in each 10-year birth cohort for 30 years, of evaluable organ TB (specifically, pulmonary, lymph node, bone-joint, kidney, and meninges TBs).

Methods

We used data from the national registry of new TB patients in 1975[5], 1985, 1995[6], and 2005[7]. Based on the incidence rate in each birth cohort, grouped in 10-year intervals, the chronological changes in the incidence rate of newly registered

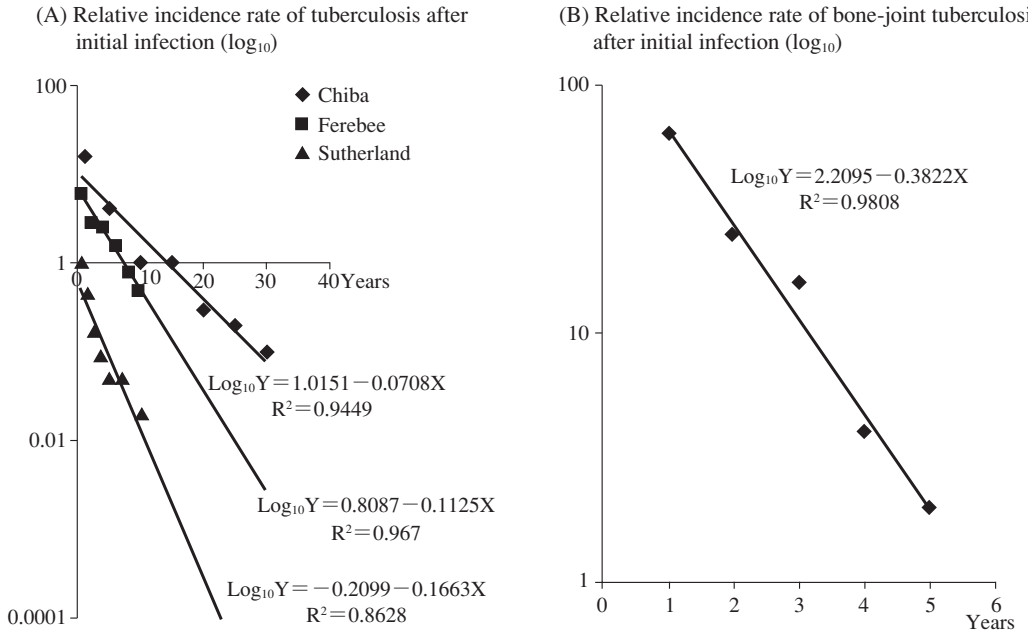

Fig. 1 Time dependency of the relative incidence rates after initial tuberculosis infection
(A) Relative incidence rates of all forms of tuberculosis after initial infection reported by Chiba[1], Ferebee[2] and Hart and Sutherland[3]
(B) Relative incidence rate of bone-joint tuberculosis after initial infection reported by Wallgren[4]

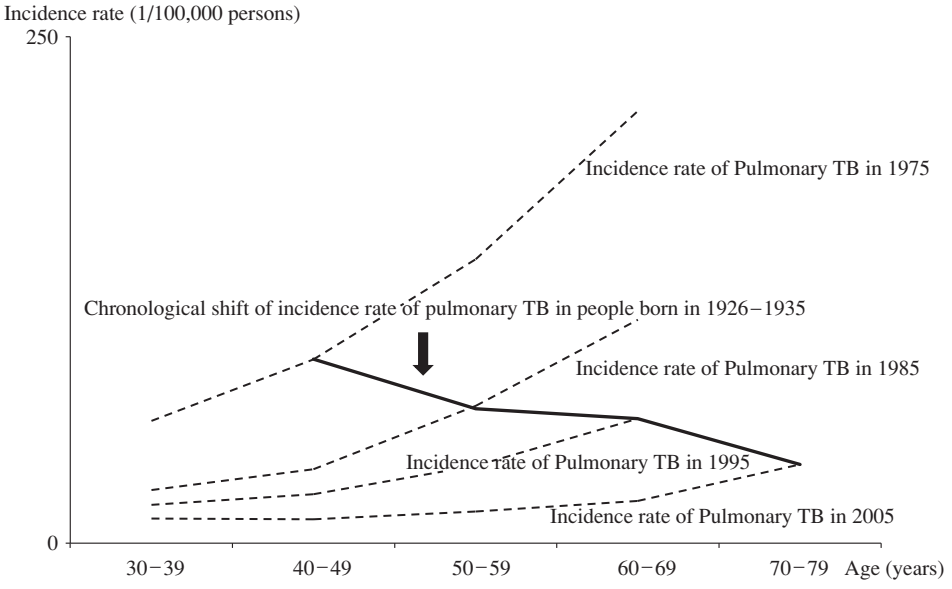

Fig. 2 Illustration of how we determined the chronological shift in the incidence rate of pulmonary tuberculosis among people born in 1926−35

pulmonary and extra-pulmonary TB (lymph node, bone-joint, kidney and meninges) were determined. The number of newly registered patients in each birth cohort was divided by the population in the same birth year to obtain the annual incidence rate of newly registered TB (Fig. 2). In the national registry of TB, the number of new TB cases was reported for ten-year age groups. Those who were born between 1926 and 1935 were categorized in the age group of 70−79 in 2005, in the group of 60−69 in 1995, and in the group of 50−59 in 1985. This method has also been used to predict the near future incidence rate of TB.[8)]

In the data of 1975, pulmonary TB, or rather thoracic TB, included tuberculous pleurisy, empyema, and hilar lymphadenopathy in addition to pulmonary TB. Since the incidences of empyema (ratio to pulmonary TB being 0.006) and hilar lymphadenopathy (0.003) were small compared to that of tuberculous pleurisy (0.122), the incidence rate of pulmonary TB in 1975 was estimated based on the ratio of the number of cases of pulmonary TB to the number of cases of tuberculous pleurisy in 2005 and in 1995. The data from 1985 and 1986 were not obtainable. Therefore, the average was obtained from the data of 1983[9)] and 1987[10)] for each birth year group and used as the data for 1985. This method was valid since most people born in Japan would live and die in Japan. Actually, the rate of foreign-born TB patients was less than 4%[11)]. Therefore, this study was deemed to be a cohort study. This method may not be used in countries where people frequently move in and out of the country, such as in European countries. It should be noted that the rate of HIV/TB co-infection was less than 0.5% among the TB cases[11)].

First, the chronological changes in the incidence of TB in each birth cohort were illustrated using a regular graph for

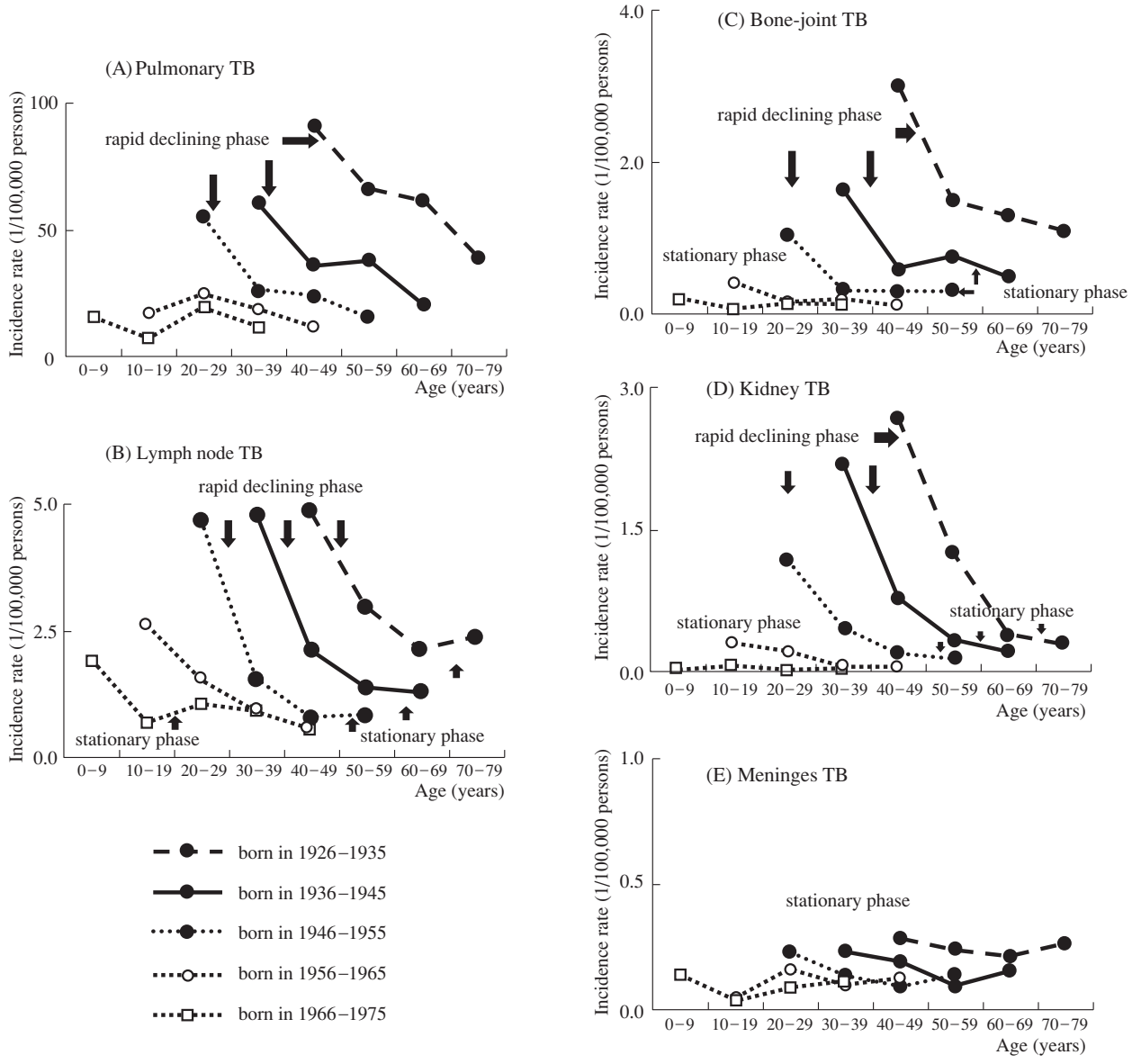

Fig. 3 Age dependency of the incidence rate of tuberculosis in various organs classified by birth year

each organ TB (see Fig. 3). We defined the "rapid declining phase" as the period when the gradient of the declining slope was more than 5×10^{-10} persons/persons • years and the "stationary phase" as the period when the rate of decrease was less than 1×10^{-10} persons/persons • years. Then, on a semi-logarithmic graph, the average of the decline rate (i.e., the slope of the curve in the rapid declining phase) in each birth cohort for each organ TB was obtained and compared to see whether there was a difference in the slope among birth cohorts and also among organs. The incidence rate of each organ TB at the time of the stationary phase was calculated and evaluated.

According to the report by Ohmori[12], the prevalence rate of TB infection in Japan in 2005 was 4.6%, 9.8%, 23.2%, 48.4%, and 72.9% among those aged 35, 45, 55, 65, and 75 years, respectively. These were plotted on the x-axis and the incidence rate of each organ TB in the stationary phase was plotted on the y-axis. Using each regression line, the incidence rates of each organ TB at the estimated prevalence rate of 100 % (i.e., in the group of already infected people) and of 0 % (i.e., in the group without previous TB infection) were obtained.

This study was performed based on data released by public agencies and ethical approval was therefore not required.

Results

In this birth cohort study, the chronological decrease in the incidence rate of TB in each organ showed one of the following three patterns when limited to individuals older than 20 years of age. The first pattern, a rapid declining phase only

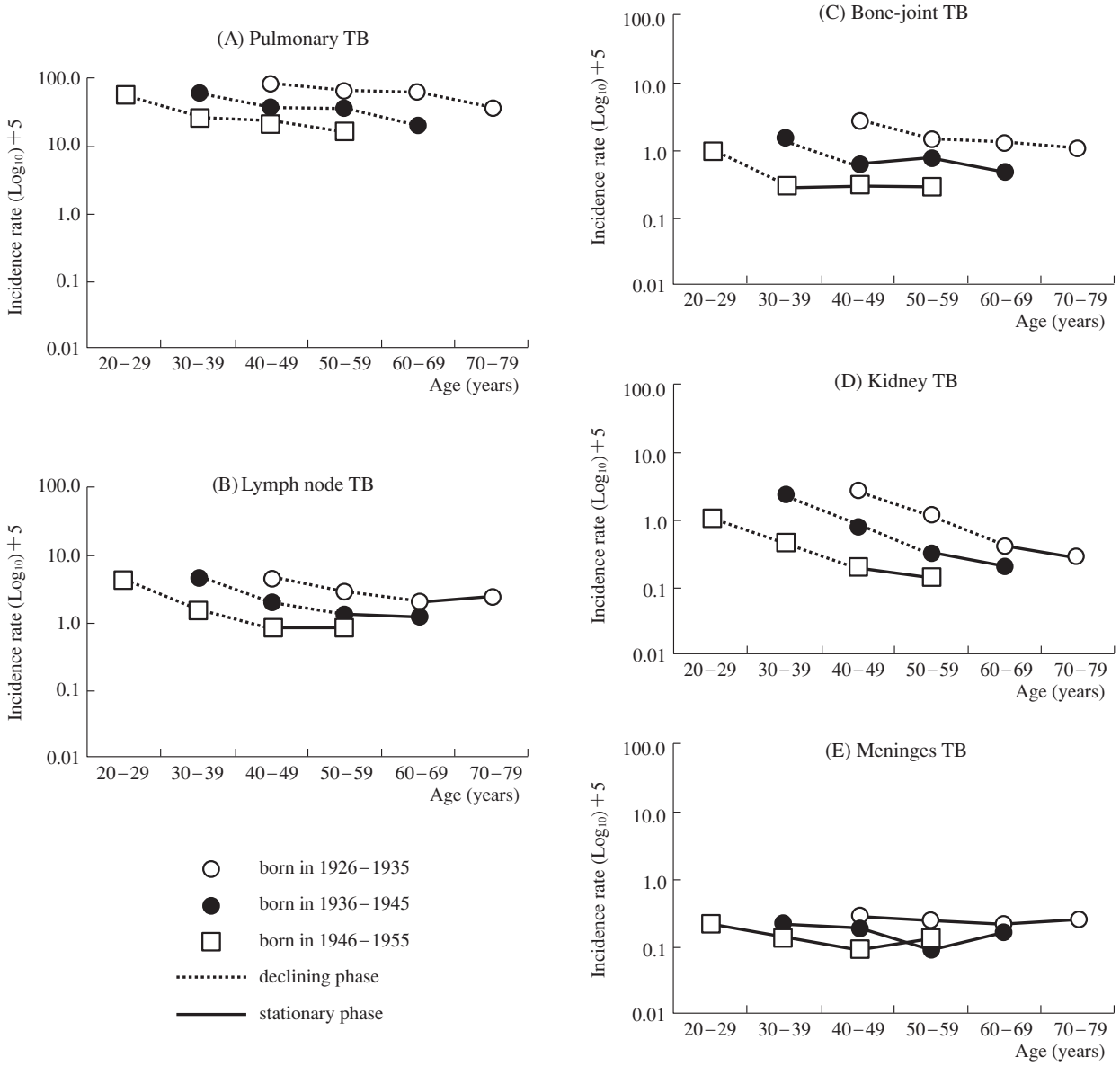

Fig. 4 Age dependency of the incidence rate of tuberculosis on a logarithmic scale classified by both birth year and organ in Japan plus 5 on the ordinate comes from the unit of incidence rate ($1/10^5$) persons.

over the 30-year period examined, was demonstrated in cases of pulmonary TB in each birth cohort (Fig. 3A). The second pattern was a rapid declining phase followed by a stationary phase, as detected in cases of lymph node, bone-joint and kidney TB in people born in 1926−1955 (Fig. 3-B, C, D)]. The third pattern was a stationary phase only, observed in the incidence rate of lymph node TB in people born in 1966−1975, bone TB in people born in 1956−1975, kidney TB in people born in 1966−1975, and meninges TB in every birth year group (Fig. 3-B, C, D, E). The chronological changes were characterized by a rapid declining phase and/or a stationary phase in the various organ TBs.

When the incidence rate was graphed logarithmically on the y-axis against the various age groups on the x-axis, it could be seen more clearly that the incidence rate decreased linearly (i.e., exponentially) in the rapid declining phase (see below), and that a transition from the rapid declining phase to the stationary phase occurred (Fig. 4). In Fig. 4 the stationary phase is drawn by solid lines.

In organ TBs with a high incidence rate, such as pulmonary TB, only a rapid declining phase was observed, while in organs with a sufficiently low incidence, such as meninges TB, only a stationary phase was seen. In TB affecting organs such as the lymph nodes, bone-joint and kidney with an incidence rate between the two extremes, a rapid declining phase followed by a stationary phase was observed (Fig. 4).

In order to study further the chronological changes described above, the changes in the rapid declining phase and mean incidence rates in the stationary phase were examined.

The mean rates of decline of the incidence of each organ TB in the three birth year groups (born in 1926−1935, 1936−1945 and 1946−1955) calculated from Fig. 4 are shown in Table 1. The rates of decline of lymph node, bone-joint, and kidney TBs were almost the same (−0.0035 to −0.0042/year) among the different birth year groups. The decline rate of pulmonary TB (−0.0014/year) was about one-third of the decline rates of lymph node, bone-joint, and kidney TBs.

Table 1 Decline rate of the logarithmic incidence rate of tuberculosis in various organs (/10 years)

Organ	Pulmonary	Lymph node	Bone-joint	Kidney
MEAN	−0.014	−0.035	−0.042	−0.041
SEM	0.002	0.007	0.006	0.001

SEM, standard error of the mean

On the other hand, the incidence rates in the stationary phase were dependent on the year of birth in TBs affecting all four organs. The groups born in the era of higher TB prevalence showed a higher rate (Table 2). The incidence rate in the stationary phase was the highest for lymph node TB followed by bone-joint, kidney, and meninges TBs.

In Fig. 5, the relationships between the incidence rate in the stationary phase (y-axis) of each cohort for each organ TB and the estimated prevalence rate of TB (x-axis) in the corresponding cohort are shown. These two variables showed clear proportional relationships. When extrapolated to an estimated prevalence rate of 100% (i.e., the group that is already infected), the annual incidence rates of lymph node, bone-joint, kidney, and meninges TB were 3.0, 1.2, 0.5, and 0.3/100,000 persons, respectively, and when extrapolated to an estimated prevalence rate of 0% (i.e., the group that is not infected), the annual incidence rates of lymph node, bone-joint, kidney, and meninges TB were 0.13, 0.04, 0.04, and 0.09/100,000 persons, respectively.

Discussion

We cannot distinguish reinfection from reactivation in each case of organ TB. However, more than 50% of TB cases in Japan in 2005 occurred in elderly people aged 60 and older[7]. The rapid reduction in annual risk of TB infection or reinfection after World War II spotlighted TB reactivation in the elderly. Although we still experience TB outbreaks in nursing homes, the high TB incidence in the elderly, compared with the younger generations, would be primarily due to reactivation of TB in the population with a high prevalence of TB infection during their youth.

In this birth cohort study, the TB incidence rate for various organs demonstrated a rapid declining phase where the incidence rate decreased exponentially, followed by a stationary phase where the incidence rate became nearly constant. The former phenomenon appeared to reflect the fact that the incidence rate of secondary TB in pulmonary TB or extrapulmonary TB such as bone-joint TB decreases exponentially with time[1)~4)] after the initial infection, as noted in the Introduction section of this report.

However, the rate in the rapid declining phase obtained from

Table 2 Incidence rates in the stationary phase among patients with lymph node, bone-joint, kidney or meninges tuberculosis classified by year of birth

Born in	Lymph node	Bone-joint	Kidney	Meninges
1926−35	2.25 (2)		0.35 (2)	0.25±0.03 (4)
1936−45	1.35 (2)	0.63±0.09 (3)	0.25 (2)	0.18±0.03 (4)
1946−55	0.85 (2)	0.30±0.00 (3)	0.15 (2)	0.13±0.03 (4)
1956−65		0.17±0.03 (3)	0.10 (2)	0.13±0.03 (3)
1966−75	1.00 (2)	0.10 (2)	0.03 (2)	0.10 (2)

Numbers in the parentheses show number of points used to calculate incidence rates (1/100,000 persons) in the stationary phase.

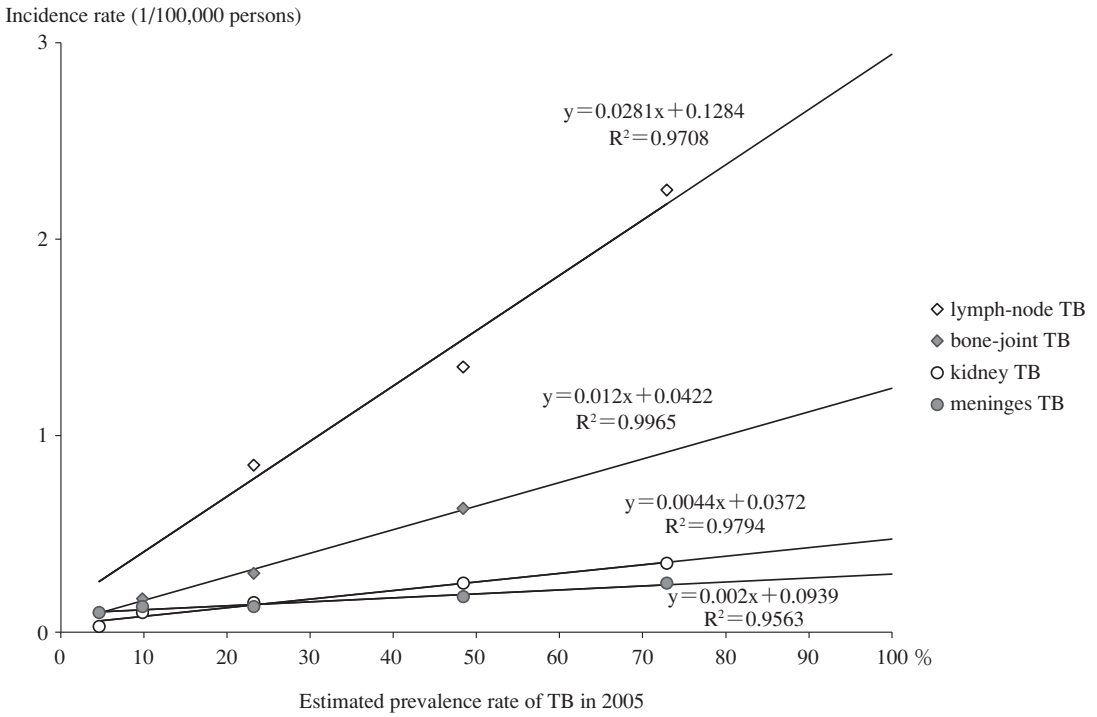

Fig. 5 Relationships between the estimated prevalence rate of tuberculosis in 2005 and the incidence rate of tuberculosis (per 100,000) in the stationary phase in various organs. The prevalence rates of TB infection in Japan in 2005 were 4.6%, 9.8%, 23.2%, 48.4%, and 72.9% among those aged 35, 45, 55, 65, and 75 years, respectively, according to the report by Ohmori[12].

the national statistics was very different from the decline rate in patients whose initial infection period could be specified[1)~3)]. For pulmonary TB, the former decline rate was 0.0014/year (Table 1) and the latter decline rate was 0.11/year[1)~3)]. In the cases of kidney TB, the former decline rate was 0.0041/year (Table 1) and the latter was 0.38/year[4)]. In both situations, the decline rate differed by 100-fold between the national statistics and the cases in which the time of the initial infection could be specified. We suspect three reasons for the difference in the decline rate between the national statistics and the cases in which the time of the initial infection could be specified: in the national registry, "the time of infection was unknown", "people born within a 10-year range were included in one group", and "cases of re-infection and new infection were included".

Meanwhile, Comstock et al.[13)] reported that the age-specific incidence of TB was bimodal with peaks in infancy and adolescence. Our study observed the incidence in ten-year intervals; therefore, details of age-specific TB incidence were not elucidated.

The declining slopes were almost the same in lymph node, bone-joint and kidney TBs. Although the reason is not clear, it seems to reflect that the pattern of infection in these organs and occurrence of TB disease are similar in extra-pulmonary organs including the lymph nodes, bone-joint and kidneys.

As illustrated in Fig. 3A, the trend of pulmonary TB incidence indicated a rapid declining phase over the age of 20 years. The exponential decrease in TB incidence rate reflected a decrease in endogenous reactivation and also a decrease in annual risk of infection. It was impossible to determine which of the two was more contributory to the rapid declining phase.

As shown in Fig. 4, the stationary phase was reached at an earlier age in more recent birth cohorts. This probably occurred because it took a longer period of time for a birth cohort with higher infection rate to reach the stationary phase.

On the other hand, as indicated in Fig. 5, we might be able to discuss the endogenous reaction of organ TBs, such as kidney and bone-joint TB, in the stationary phase. In the population with estimated prevalence rate of TB infection being 100% (i.e., the already TB-infected group), all occurrences of organ TB were considered as either endogenous reactivation or reinfection, while in the population without previous TB infection (0% in Fig. 5) all organ TBs were caused by recent infection. The reinfection rate was thought to be equal to or less than the new infection rate. Therefore, the approximate endogenous reactivation rate in the already TB-infected group was obtained by subtracting the incidence rate at 100% from the incidence rate at 0%. As is clearly seen in Fig. 5, the incidence of organ TB was much higher in the former group, indicating that in the stationary phase reactivation was more significant than recent infection and reinfection.

The fact that there was a stationary phase in extra-pulmonary TB (lymph node, bone-joint, kidney, meninges) from the national statistics suggests that the onset of TB in that phase occurs at a constant rate in the population already infected,

regardless of the latent time. This result may be directly related to how the disease develops after the initial infection with mycobacteria. After a certain period of time, the incidence rate might become constant without further decreases or increases. This may also be true for pulmonary TB in the future.

These results raise thought-provoking questions. If the incidence rate of TB is assumed to be proportional to the total number of viable bacteria in the body, the fact that the incidence rate decreased exponentially could mean that the number of viable bacteria decreases exponentially. The decrease in the number of viable bacteria is considered to be the result of cell-mediated immunity of the individual. After the incidence rate becomes constant, the number of viable bacteria may remain unchanged. This may indicate that the cell-mediated immunity against *Mycobacterium tuberculosis* is no longer mobilized. In other words, it is suggested that the cell-mediated immunity may act bacteriostatically and not bactericidally when the number of bacteria becomes less than a certain threshold level in each organ.

Among various organ TBs, the incidence rate in the stationary phase varied by organ. We suspect that the rate was low in the meninges because the number of bacteria originally disseminated to the meninges was small. The rate was relatively high in lymph nodes probably because the number of bacteria originally disseminated to the lymph nodes was high or the immunity against TB was weak in the lymph nodes.

In this study, we reported the TB incidence rates in various organs in the stationary phase. The TB reactivation rate seemed to be constant in each organ TB independent of the length of the latent period after the rapid declining phase was over.

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