

Long-term Projection of HTLV-1 Transmission Dynamics in Japan Through 2060

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Abstract

Background

Japan implemented a nationwide mother-to-child transmission (MTCT) prevention program for human T-cell leukemia virus type 1 (HTLV-1) in 2011. However, the long-term impact of this strategy on HTLV-1 epidemiology remains unclear. This study aimed to evaluate the long-term impact of Japan's nationwide MTCT prevention program by projecting HTLV-1 transmission dynamics and carrier numbers through 2060, 50 years after implementation.

Methods

Using nationwide epidemiological data, we developed a projection model with three components: newly infected individuals through MTCT, surviving HTLV-1 carriers from the 2020 population after adjustment for age-specific mortality, and newly infected individuals through horizontal transmission over the subsequent 50 years. Horizontal transmission was estimated using age-specific horizontal transmission coefficient (ATC) derived from nationwide seroconversion data among repeat blood donors, and the number of HTLV-1 carriers in 2060 was projected by integrating these three components.

Results

The number of HTLV-1 carriers in Japan was projected to decrease to 96,780 by 2060, representing an 85% reduction compared with the 2020 estimate. Between 2011 and 2060, approximately 1,611 new MTCT infections were projected, whereas over 100,000 new infections were expected to arise through horizontal transmission. The projected incidence of MTCT among children born after implementation of the nationwide prevention program was only 0.005%, indicating substantial success of the current prevention strategy. In contrast, horizontal transmission was projected to become the dominant route of new HTLV-1 infection, with the highest transmission potential observed among adolescents and young adults aged 16–29 years.

Conclusions

This study provides the first long-term quantitative projection of HTLV-1 transmission dynamics through 2060 using an ATC-based model. Although Japan's nationwide MTCT prevention program is expected to substantially reduce vertical transmission through 2060, the epidemiological burden of HTLV-1 infection is projected to shift from vertical to horizontal transmission. These findings highlight the need to expand future national HTLV-1 control strategies beyond MTCT prevention to include comprehensive interventions targeting horizontal transmission.

1. Background

HTLV-1 is the causative retrovirus of lifelong HTLV-1-associated diseases, such as adult T-cell leukemia, HTLV-1-associated uveitis, and HTLV-1-associated myelopathy. Although most carriers remain asymptomatic throughout their lives, approximately 5% develop HTLV-1-associated diseases with a 57% increase in all-cause mortality and a poor prognosis [1].

The number of HTLV-1 carriers is estimated to be approximately 5–10 million worldwide [2]. The global distribution of HTLV-1 carriers is regionally uneven. Japan, South America, Sub-Saharan Africa, and the Caribbean islands are endemic areas [3, 4]. Nationwide epidemiological surveys of HTLV-1 carriers in Japan have been performed by evaluating the seropositive rate among blood donors. In 1988, there were an estimated 1.2 million carriers [5], but this number has been gradually decreasing, with the 2006–2007 survey showing approximately 1.08 million [6] and our 2020 survey estimating 658,000 [7]. However, we previously suggested that these estimates of HTLV-1 carrier numbers based on data from blood donors were underestimated due to the healthy donor effect [7].

There are two main routes of HTLV-1 transmission: MTCT and horizontal transmission. The primary route of MTCT is through breast milk. HTLV-1-infected T cells have been identified in the breast milk of HTLV-1-carrier mothers [8], and experimental studies using a common marmoset model confirmed HTLV-1 transmission through breast milk [9, 10]. Based on these findings, in Nagasaki, Japan, preventive measures against MTCT were initiated in 1987. Hino et al. demonstrated the difference in the rate of MTCT depending on feeding protocol [11], and these findings were subsequently supported by independent studies [12–14]. Consequently, nationwide antenatal HTLV-1 antibody screening and preventive measures were introduced in Japan in 2011 [15, 16], followed by publication of a manual for MTCT prevention in 2017 [17] and national guidelines for the diagnosis of HTLV-1 infection in 2018 [18].

Increasing evidence suggests that transplacental transmission may also occur. Using RNA scope, we demonstrated the presence of HTLV-1-infected trophoblastic cells in the placentas of HTLV-1-carrier mothers and showed that placental trophoblastic cells are targets of HTLV-1 infection [19]. However, the mechanisms underlying transplacental transmission remain unclear and require further investigation.

On the other hand, horizontal transmission of HTLV-1 includes all routes other than MTCT, such as blood transfusion, organ transplantation, needlestick injuries, intravenous drug abuse, and sexual intercourse. After initiating prescreening of blood donors for infection in 1986, including HTLV-1, there are currently no new cases of HTLV-1 infection owing to blood transfusion in Japan. As an eligibility criterion for donation, organ transplant donors must be tested for infectious diseases, including HTLV-1. Recently, the World Health Organization (WHO) has recognized the importance of strengthening public health measures to prevent sexual transmission of HTLV-1 [20].

Epidemiological studies of horizontal HTLV-1 infection have been performed in Japan, with an investigation of the seroconversion rate of HTLV-1 antibodies among repeat blood donors. A first cohort study of 3,375,821 men and women aged 16–69 years who donated blood repeatedly between 2005 and

2011, with 2005–2006 as the registration period, reported 532 antibody seroconversions (0.2%) and an outbreak of more than 4,000 new HTLV-1 infections per year [21]. Subsequently, overall HTLV-1 seroprevalence in Japan has been reported to decline, with a substantial reduction in the estimated number of carriers [7]. However, despite this overall decline, a large cohort study of 5,017,916 repeat donors aged 16–69 years between 2013 and 2020 showed an increasing trend in new horizontal infections among AYA population [22]. In this second cohort study, we also reported that the number of horizontally-infected persons was increasing in suburban areas, suggesting that the infection was spreading nationwide with the movement of people into the metropolitan area and that nationwide measures are needed to prevent the spread of HTLV-1 infection [22].

Additionally, an epidemiological study of HTLV-1 screening testing for pregnant women in Nagasaki reported that approximately 94% of HTLV-1-carrier pregnant mothers were HTLV-1 seropositive at the time of their first pregnancy [23]. However, approximately 6% of pregnant women confirmed seronegative at their first pregnancies seroconverted between pregnancies, indicating that at least 6% of HTLV-1 carriers were horizontally infected [23]. These findings are supported by a recent nationwide survey, which suggested that 16.3% of newly identified HTLV-1-carrier pregnant women may have acquired infection through horizontal transmission, further highlighting the growing importance of preventing horizontal transmission in Japan [24].

A recent mathematical modelling study further highlighted the importance of quantitatively evaluating the contribution of multiple HTLV-1 transmission routes to the epidemiology of HTLV-1 across endemic settings. However, no previous study has evaluated the long-term impact of Japan's nationwide MTCT prevention program on future HTLV-1 transmission dynamics [25].

The aim of this study was to evaluate the long-term impact of Japan's nationwide MTCT prevention program by projecting HTLV-1 transmission dynamics and carrier numbers through 2060.

2. Methods

2 – 1. Projection model for estimating HTLV-1 carriers in 2060

In this study, the composition of HTLV-1 carriers in 2060 was set as follows: Group 1: New HTLV-1 infections through MTCT occurring over the next 50 years, Group 2: Surviving HTLV-1 carriers projected from the 2020 data, Group 3: New HTLV-1 infections through horizontal transmission occurring over the next 50 years. The total number of HTLV-1 carriers in 2060 was calculated as the sum of these three groups.

HTLV-1 carrier group1: New HTLV-1 infections through MTCT occurring over the next 50 years

The annual number of new HTLV-1 MTCT carriers was estimated using the selection rate of feeding protocols by HTLV-1 carrier mothers, MTCT rates for each feeding protocol, the estimated numbers of HTLV-1 carrier mothers, and birth statistics from the National Institute of Population and Social Security

Research. As previously reported, the proportions of infant-feeding protocols were as follows: Long-term (6%), Short-term (27%), Formula (57%), and Frozen/thawed milk (6%) from April 2011 to March 2017; and Long-term (0%), Short-term (30%), Formula (62%), and Frozen-thawed milk (3%) after April 2017 [26]. In addition, transmission rates for each feeding protocol were as follows: Long-term: 17.7%, Short-term: 1.9%, Formula: 3.3%, Frozen-thawed: 3.1% [27]. Note that 33.5% of short-term breastfeeding continued breastfeeding beyond 3 months, and were reclassified as long-term breastfeeding [28]. The ratio of carrier mothers were 1,560 persons until 2023 [29] and 718 persons after 2024 per million pregnant women [24]. Annual numbers of live births through 2023 were obtained from national vital statistics, whereas those for 2024–2060 were based on the medium-fertility and medium-mortality population projections published by the National Institute of Population and Social Security Research [30]. All births were assumed to be singleton births, therefore, the number of live births was equal to the number of pregnant women.

HTLV-1 carrier group 2: Surviving HTLV-1 carriers projected from the 2020 data

In 2023, Satake et al. estimated the age-specific number of HTLV-1 carriers in Japan in 2020 using first-time blood donor data [7]. These estimates were used as the baseline carrier population. The number of surviving HTLV-1 carriers was projected by applying age-specific mortality rates from the 2024 Vital Statistics published by the Ministry of Health, Labour and Welfare [31]. Age-specific annual survival rates were assumed to be 99%, 98%, 96%, 87%, and 59% for individuals aged 0–59, 60–69, 70–79, 80–89, and 90–99 years, respectively. Individuals aged ≥ 100 years were excluded from the analysis.

HTLV-1 carrier group 3: New HTLV-1 infections through horizontal transmission occurring over the next 50 years

To estimate future horizontal transmission, we applied a stepwise cohort-based approach. First, we defined the age-specific horizontal transmission coefficient (ATC) as the ratio of the number of horizontally infected individuals to the number of HTLV-1 carriers within each age group per 10-year period. Second, for Group 2 (Surviving HTLV-1 carriers projected from the 2020 data), we projected the surviving population at each 10-year interval using age-specific mortality rates. In the present study, age groups were defined in 10-year intervals, whereas the previous study by Sagara et al. used 5-year intervals [22]. This aggregation was performed to ensure consistency with the available demographic and mortality data, which were reported in 10-year age groups [31]. While this approach may reduce age-specific resolution, it was considered sufficient for estimating long-term trends in population-level transmission dynamics. The potential impact of this aggregation on the estimated ATC values and transmission patterns should be acknowledged as a limitation. New horizontal infections were then estimated by multiplying the number of carriers in each age group by the corresponding ATC. These newly infected individuals were added to the carrier population for the subsequent time period. Third, for Group 1 (MTCT-derived carriers), horizontal transmission risk was assumed to begin at age 16. The number of new infections was estimated based on the duration of exposure (from age 16 until 2060) and

the corresponding ATC. Finally, the total number of Group 3 carriers was calculated as the cumulative sum of new horizontal infections from both Group 1 and Group 2 over the next 50-year period.

2–2. Scenario and sensitivity analysis

To evaluate the robustness of the projection model, scenario and deterministic sensitivity analyses were performed for the three principal sources of uncertainty. First, uncertainty in future birth projections was assessed using alternative birth projection scenarios (low- and high-birth scenarios) together with the corresponding mortality assumptions published by the National Institute of Population and Social Security Research. Second, uncertainty in horizontal transmission and baseline HTLV-1 carrier prevalence was evaluated using one-way deterministic sensitivity analyses. Because confidence intervals or probability distributions were unavailable for both the estimated number of HTLV-1 carriers in 2020 and the derived age-specific horizontal transmission coefficients (ATCs), all ATC values and the age-specific baseline carrier population were varied independently by $\pm 10\%$ and $\pm 20\%$, while all other model parameters were held constant. These variation ranges were selected with reference to the nationwide estimates reported by Satake et al. [7], in which the number of HTLV-1 carriers in Japan was estimated to be 534,000 based on measured seroprevalence and 658,000 after adjustment using the birth cohort effect. This adjustment resulted in an approximately 20% variation in the estimated number of HTLV-1 carriers. Accordingly, a $\pm 20\%$ variation was adopted to evaluate the robustness of the projection model, whereas an additional $\pm 10\%$ variation was examined as a more conservative sensitivity analysis.

For each scenario and sensitivity analysis, the projected numbers of MTCT-derived infections, horizontally infected carriers, and total HTLV-1 carriers in 2060 were recalculated.

3. Results

3 – 1. Estimation of the number of HTLV-1 carriers in 2060

The number of HTLV-1 carriers in 2060 was estimated by summing Group 1: New HTLV-1 infections through MTCT occurring over the next 50 years, Group 2: Surviving HTLV-1 carriers projected from the 2020 data, and Group 3: New HTLV-1 infections through horizontal transmission occurring over the next 50 years.

HTLV-1 carrier group 1: New HTLV-1 infections through MTCT occurring over the next 50 years

Table 1 summarizes the estimated numbers of HTLV-1 MTCT cases per one million mothers according to infant-feeding protocols during each study period. After accounting for the finding that 33.5% of mothers who selected short-term breastfeeding continued breastfeeding beyond 3 months, the estimated numbers of MTCT cases per one million mothers were 79.1, 67.1, and 30.9 during 2011–2016, 2017–2023, and 2024–2060, respectively. Annual numbers of live births used in the projection model are

shown in Supplementary Fig. 1. The annual number of new MTCT cases was projected to fall below 50 in 2026, and the cumulative number of new MTCT cases between 2011 and 2060 was estimated to be 1,611 (Fig. 1).

Table 1

Estimated annual numbers of HTLV-1 MTCT cases per 1 million mothers during each study period

Nutrition protocol	Population (%)	Carrier mothers (n)	Transmission rate	Estimated MTCT cases	Total estimated MTCT cases
2011–2016 *1					
Long-term breast milk	6	93.6	17.7	16.6	79.1
Short-term to long-term breast milk*2	9	141.1	17.7	25	
Short-term breast milk	18	280.1	1.9	5.3	
Exclusive formula	57	889.2	3.3	29.3	
Frozen-thawed breast milk	6	93.6	3.1	2.9	
2017–2023 *1					
Long-term breast milk	0	0	17.7	0	67.1
Short-term to long-term breast milk*2	10.1	156.8	17.7	27.8	
Short-term breast milk	20	311.2	1.9	5.9	
Exclusive formula	62	967.2	3.3	31.9	
Frozen-thawed breast milk	3	46.8	3.1	1.5	
2024–2060*3					
Long-term breast milk	0	0	17.7	0	30.9
*1: Estimated number of carrier mothers: 1,560 per 1-million mothers					
*2: 33.5% of mothers who selected short-term breastfeeding subsequently continued breastfeeding beyond 3 months.					
*3: Estimated number of carrier mothers: 718 per 1-million mothers					

Nutrition protocol	Population (%)	Carrier mothers (n)	Transmission rate	Estimated MTCT cases	Total estimated MTCT cases
2011–2016 *1					
Short-term to long-term breast milk*2	10.1	72.2	17.7	12.8	
Short-term breast milk	20	143.2	1.9	2.7	
Exclusive formula	62	445.2	3.3	14.7	
Frozen-thawed breast milk	3	21.5	3.1	0.7	
*1: Estimated number of carrier mothers: 1,560 per 1-million mothers					
*2: 33.5% of mothers who selected short-term breastfeeding subsequently continued breastfeeding beyond 3 months.					
*3: Estimated number of carrier mothers: 718 per 1-million mothers					

HTLV-1 carrier group 2: Surviving HTLV-1 carriers projected from the 2020 data

The age-specific HTLV-1 carrier population estimated by Satake et al. for 2020 was projected by applying age-specific mortality rates. The surviving HTLV-1 carrier population gradually declined over time and was estimated to be 25,600 in 2060 (Supplementary Fig. 2).

HTLV-1 carrier group 3: New HTLV-1 infections through horizontal transmission occurring over the next 50 years

The number of horizontally infected individuals by age group in 2020, calculated after adjustment for the HTLV-1 seroprevalence among women of reproductive age, was 4,751 (men, 1,135; women, 3,616), indicating that the number of newly horizontally infected women was 3.19 times higher than that of men (Fig. 2). The estimated ATC were 0.0318 (16–19 years), 0.0234 (20–29 years), 0.0169 (30–39 years), 0.0121 (40–49 years), 0.0220 (50–59 years), 0.0088 (60–69 years), and 0.0043 (≥ 70 years), with the highest value observed among adolescents and young adults (AYA) (Table 2). Although the ATC value gradually decreased with advancing age, a second peak was observed in the 50–59-year age group (Fig. 3).

Table 2. Estimated Age-specific horizontal transmission coefficient (ATC)

Age group	Corrected numbers of HTLV-1 horizontally infected carriers in 2020			HTLV-1 carriers by age group reported in 2023	ATC values
	Man	Woman	Total		
16-19	20.2	24.0	44.2	1,389.5	0.0318
20-29	53.0	72.4	125.4	5,354.9	0.0234
30-39	93.5	306.0	399.6	23,703.2	0.0169
40-49	121.6	344.2	465.7	38,589.5	0.0121
50-59	370.4	1,444.0	1,814.4	82,428.5	0.022
60-69	402.2	876.7	1,278.90	145,617.2	0.0088
70-79	73.6	548.4	622.0	146,241.0	0.0043
Total	1,135	3,616	4,751	443,324	

The estimated number of new horizontal HTLV-1 infections arising from MTCT-derived carriers between 2011 and 2060 was 669 (Fig. 4). In addition, 99,857 new horizontal HTLV-1 infections were projected to arise from surviving HTLV-1 carriers in carrier group 2 over the subsequent 50 years, resulting in a cumulative total of 100,526 newly generated horizontal infections by 2060.

The numbers of horizontally infected individuals by age group in 2020 were estimated after adjusting for HTLV-1 seroprevalence among women of reproductive age. A total of 4,751 new horizontal infections were estimated (1,135 men and 3,616 women), indicating that the number of newly infected women was 3.19 times greater than that of men. The highest numbers of new horizontal infections were observed among the AYA population.

Age-specific horizontal transmission coefficient (ATC) values were shown. The ATC value was highest in the AYA population, gradually decreased with advancing age, and showed a second peak in the 50–59-year age group.

The projected numbers of new horizontal HTLV-1 infections arising from MTCT-derived carriers between 2011 and 2060 were calculated using the duration of exposure and ATC values. A total of 669 new horizontal infections were projected by 2060.

In this study, the total number of HTLV-1 carriers in 2060, calculated as the sum of HTLV-1 carrier groups 1–3, was estimated to be 96,780 (Fig. 5A). According to the 2023 population projections published by the National Institute of Population and Social Security Research, Japan's total population is projected to be 96.15 million in 2060 under the medium-fertility and medium-mortality scenario. Accordingly, the estimated HTLV-1 carrier prevalence in 2060 was approximately 0.1%, representing a substantial decline from that in 2020.

3 – 2. Evaluation of the effect of measures to prevent MTCT

The number of new MTCT during these five decades was 1,611 among 35,709,254 children born after 2011, resulting in a carrier incidence rate of 0.005% from MTCT. As no nationwide survey examining the selection rate of nutritional management for HTLV-1 carrier mothers prior to 2010 had existed, it was difficult to accurately assess the situation before the implementation of nationwide measures from 2011 to prevent MTCT. However, the total number of MTCT cases between 2011 and 2016, immediately after launch of these policies, was 79.1 per 1 million mothers. If this trend had continued until 2060, there would have been 2,826 new carriers via MTCT. The prevention measures prevented 1,216 new cases, representing a reduction of almost 43%, implementing that these nationwide measures to prevent MTCT demonstrated the high effectiveness.

3–3. Projected changes in HTLV-1 transmission dynamics

Figure 5B shows the projected numbers of newly generated HTLV-1 infections by transmission route during each 10-year period. The numbers of new infections through both MTCT and horizontal transmission decreased over time. However, newly generated horizontal infections consistently exceeded MTCT-derived infections throughout the projection period. The projected composition of the HTLV-1 carrier population is shown in Supplementary Fig. 3. After accounting for age-specific mortality, the proportion of cumulative horizontally infected carriers within the total HTLV-1 carrier population increased from 10.4% in 2030 to 37.8% in 2060, whereas the proportion of surviving carriers from the 2020 baseline population decreased from 89.3% to 60.5%. In contrast, cumulative MTCT-derived carriers consistently accounted for only a small proportion of the total carrier population throughout the projection period. As a supplementary quantitative measure of these temporal changes, the relative horizontal transmission (RHT) index increased from 0.000100 in 2030 to 0.000235 in 2060, representing an approximately 2.3-fold increase (Supplementary Table 2). These findings indicate an increasing relative contribution of horizontal transmission to the projected HTLV-1 carrier population.

3–4. Scenario and sensitivity analysis

Sensitivity analyses were performed to evaluate the effects of uncertainty in future birth projections, horizontal transmission, and baseline HTLV-1 carrier prevalence on the model outcomes. Under alternative birth projection scenarios, the cumulative number of MTCT-derived infections by 2060 ranged from 1,511.0 to 1,838.2, while the cumulative number of secondary horizontal infections generated from MTCT-derived carriers ranged from 651.6 to 704.8. The projected total number of HTLV-1 carriers in 2060 varied only modestly across the alternative birth projection scenarios.

One-way sensitivity analyses demonstrated that varying ATC values by $\pm 10\%$ and $\pm 20\%$ resulted in projected total HTLV-1 carrier numbers ranging from 88,254 to 105,897 in 2060, whereas varying the baseline HTLV-1 carrier prevalence by $\pm 10\%$ and $\pm 20\%$ resulted in projected carrier numbers ranging

from 77,880 to 115,680 (Supplementary Table 1). The tornado plot showed that baseline HTLV-1 carrier prevalence had the greatest influence on the projected carrier population, followed by ATC values, whereas future birth projections had the smallest impact (Supplementary Fig. 4). Despite these variations in the absolute number of projected HTLV-1 carriers, the overall epidemiological transition from MTCT-dominated transmission to horizontal transmission remained consistent across all scenarios.

4. Discussion

This study evaluated the long-term impact of Japan's nationwide HTLV-1 MTCT prevention program by projecting HTLV-1 transmission dynamics through 2060 using an ATC-based projection model.

The projected MTCT incidence of only 0.005% among more than 35 million births suggests that Japan's nationwide MTCT prevention program has achieved substantial control of vertical transmission. The estimated MTCT rate after April 2017 was 4.3%, which closely agrees with the previously reported rate of 4.5%, further supporting the validity of our model [28]. Our analysis also suggests that improved adherence to recommended infant-feeding practices could further reduce MTCT. If mothers who initially choose short-term breastfeeding were supported to discontinue breastfeeding within the recommended three-month period, MTCT-derived infections would decrease from 30.9 to 19.5 per one million pregnancies, reducing the projected cumulative number of MTCT-derived infections by 2060 from 1,611 to 1,340, an approximately 17% reduction.

Despite the successful implementation of nationwide MTCT prevention in Japan, antenatal HTLV-1 screening remains uncommon worldwide [32]. Previous studies have suggested that nationwide screening combined with appropriate interventions could be cost-effective in endemic countries such as Brazil [33], and the UK is also considering targeted antenatal HTLV-1 screening [34]. Our findings provide long-term epidemiological evidence supporting the public health value of nationwide MTCT prevention programs and may serve as a useful reference for countries considering similar strategies.

A major strength and novelty of the present study is that the projection model enables quantitative evaluation of the epidemiological transition from MTCT-dominated transmission to horizontal transmission following implementation of the nationwide MTCT prevention program. Unlike conventional cross-sectional epidemiological studies, this modelling approach provides long-term projections of future transmission dynamics, thereby generating quantitative evidence to support future HTLV-1 control strategies.

Our principal finding is that horizontal transmission is projected to become increasingly important in future HTLV-1 epidemiology despite the substantial decline in the overall HTLV-1 carrier population. This shift reflects the sustained effectiveness of nationwide MTCT prevention together with the persistence of horizontal transmission. Consequently, strategies focusing solely on MTCT prevention are unlikely to achieve long-term control or eventual elimination of HTLV-1 infection, highlighting the need for interventions targeting horizontal transmission.

These findings are consistent with a recent mathematical modelling study by Ochida et al., which quantitatively evaluated the relative contribution of multiple HTLV-1 transmission routes across endemic settings [25]. That study demonstrated that sexual transmission accounted for the majority of adult HTLV-1 infections, whereas vertical transmission contributed only a small proportion of new infections. Building on these observations, our model extends this concept by demonstrating the long-term impact of Japan's nationwide MTCT prevention program on future HTLV-1 transmission dynamics.

An important feature of the present projection model is the application of ATC, which enabled quantitative estimation of future horizontal transmission according to age-specific transmission potential. The highest ATC values were observed among the AYA population, particularly those aged 16–29 years, indicating that this population should be prioritized in future prevention strategies. In addition, the projected number of newly infected women was more than three times greater than that of men, further supporting the importance of sexual transmission in future HTLV-1 spread.

Interestingly, a second peak in ATC was observed among individuals aged 50–59 years. The mechanism underlying this finding remains unclear. Previous studies have suggested that age-related biological changes, including menopause-associated alterations in mucosal immunity and reactivation of latent retroviral infections, may influence susceptibility to retroviral infection. Although these mechanisms remain speculative, they may partially explain the second ATC peak observed in the present study. Further biological and epidemiological studies are needed to clarify its underlying mechanism [35–40].

Our findings underscore the importance of strengthening public health measures targeting horizontal transmission. The recent resurgence of syphilis in Japan illustrates how sexually transmitted infections can rapidly re-emerge in the absence of effective public health interventions [41]. Future HTLV-1 control strategies should therefore include public education to increase awareness that HTLV-1 is sexually transmissible [42], promotion of preventive measures such as condom use [43, 44], and education of healthcare professionals.

Despite these important public health implications, several knowledge gaps remain. Although nationwide cohort studies have demonstrated increasing numbers of horizontally infected individuals [22], the dynamics of sexual HTLV-1 transmission remain incompletely understood. In addition, approximately 6% of initially seronegative women seroconverted between pregnancies [23], highlighting the need to better understand transmission between sexual partners during the reproductive period. Further studies are needed to clarify the dynamics of sexual transmission, sex-specific transmission probabilities, the relationship between HTLV-1 proviral load and infectivity [42], and the epidemiology of HTLV-1 infection in men, thereby providing evidence for more effective prevention strategies.

This study has several limitations. First, the number of HTLV-1 carriers may have been underestimated because the data were derived from blood donors, a selected population of healthy individuals (healthy donor effect). Furthermore, individuals with high-risk behaviors, such as sex workers and men who have sex with men (MSM), were excluded according to blood donation eligibility criteria, which may have

further contributed to underestimation. Because the ATC values were also estimated from these blood donor data, the degree of horizontal transmission may likewise have been underestimated.

Second, the number of future HTLV-1 carriers may have been overestimated. The present model did not account for future improvements in public awareness that may further reduce prolonged breastfeeding among HTLV-1 carrier mothers. In addition, women born after implementation of the nationwide MTCT prevention program in 2011 will gradually enter their reproductive years from approximately 2031 onward. As this protected cohort replaces older generations, maternal HTLV-1 prevalence is expected to decline progressively, which may further reduce MTCT. Consequently, the present model may overestimate the future number of HTLV-1 carriers.

Third, ATC were estimated using 10-year age groups to ensure consistency with demographic data, national population projections, and mortality tables. Although appropriate for long-term projections, this approach may have reduced age-specific resolution compared with the original 5-year model reported by Sagara et al., potentially underestimating age-specific transmission patterns.

Fourth, the projected estimates are inherently dependent on several model assumptions, including future demographic projections, ATC values, and baseline HTLV-1 carrier prevalence. In addition, ATC values were assumed to remain constant throughout the projection period because no reliable evidence is currently available to predict long-term changes in HTLV-1 transmission dynamics. Although future changes in sexual behavior, demographic structure, or preventive interventions may influence horizontal transmission patterns, reliable long-term data to model these changes are currently unavailable. Sensitivity analyses demonstrated that, despite these assumptions, the projected carrier population consistently remained on the order of approximately 100,000 and that the principal epidemiological transition from mother-to-child to horizontal transmission remained unchanged across all plausible scenarios. These findings support the overall robustness of the present projection model. Nevertheless, because uncertainty arising from the simultaneous variation of multiple parameters was not evaluated, future studies incorporating probabilistic sensitivity analyses may provide a more comprehensive assessment of model uncertainty.

Despite these limitations, this study provides the first quantitative projection of the long-term population-level impact of Japan's nationwide HTLV-1 MTCT prevention program by integrating vertical transmission, horizontal transmission, and age-specific mortality into a single projection model extending through 2060. Our findings indicate that nationwide MTCT prevention has substantially reduced vertical transmission, whereas horizontal transmission will account for an increasingly greater proportion of future HTLV-1 infections. These findings support expanding future HTLV-1 control strategies beyond MTCT prevention to include comprehensive measures targeting horizontal transmission. Such strategies may ultimately reduce the long-term burden of HTLV-1-associated diseases, including adult T-cell leukemia/lymphoma, HTLV-1-associated myelopathy, and HTLV-1-associated uveitis [45–49], and may provide a useful framework for other HTLV-1-endemic countries considering nationwide prevention programs.

5. Conclusions

This study estimated future HTLV-1 transmission dynamics using an original ATC-based projection model, enabling quantitative estimation of HTLV-1 carrier numbers through 2060. Although the projected estimates remain subject to uncertainty because they are based on epidemiological assumptions and future demographic changes, the model consistently demonstrated the substantial long-term effectiveness of Japan's nationwide MTCT prevention program. At the same time, more than 100,000 new HTLV-1 infections were projected to occur through horizontal transmission during the same period. These findings indicate that a shift in the dominant transmission route of HTLV-1 infection in Japan from vertical transmission to horizontal transmission and support a transition from MTCT-centered prevention toward comprehensive national HTLV-1 control strategies targeting horizontal transmission.

Abbreviations

AYA: Adolescents and young adults

HTLV-1: Human T-cell leukemia virus type 1

MSM: Men who have sex with men

MTCT: Mother-to-child transmission

ATC: Age-specific horizontal transmission coefficient

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Nagasaki University Hospital (Approval No. 24101706-2) and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The requirement for individual informed consent was waived by the Institutional Ethics Committee because this retrospective study used existing anonymized data and was conducted using an approved opt-out procedure. Information about the study was publicly disclosed, allowing participants the opportunity to decline the use of their data. Blood donor data were included only from donors who had consented to research use, while clinical data from the ATL Prevention Program were used under the approved opt-out procedure.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are not publicly available because they contain sensitive personal information but are available from the corresponding author on reasonable request and with permission from the relevant ethics committee and data providers.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

KN and YS designed the study; KN, YS, HN, KM, and KT performed the formal analyses; KN, YS, HN, MK, KT, YH, NK, CE, MN, AN, SM and KM discussed the results; KN and YS designed the figures; KN, YS, HN, KM, and KT wrote the manuscript; YS and KM review and edit the manuscript; and KN, NK, AN, SM, and KM provided funding for this study. All authors approved the final version of the manuscript.

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Figures

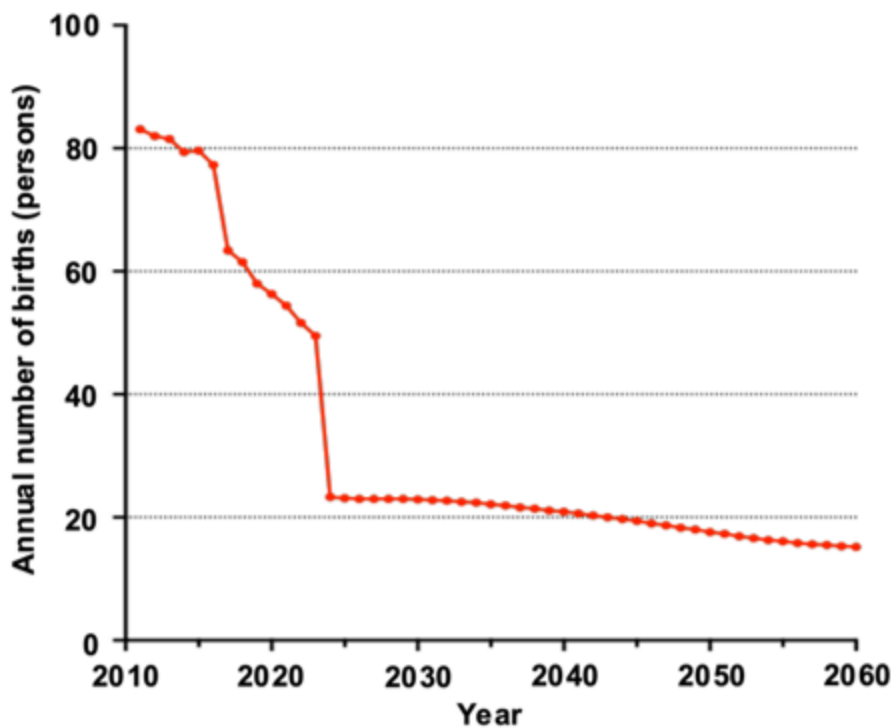


Figure 1

Estimated annual number of new HTLV-1 MTCT cases, 2011–2060

Estimated annual numbers of new HTLV-1 MTCT cases from 2011 to 2060 were derived using annual live births, maternal HTLV-1 seroprevalence, feeding practices, and MTCT risks according to feeding method. The estimated annual number of new MTCT cases declined steadily after implementation of the

nationwide MTCT prevention program, resulting in an estimated cumulative total of 1,611 new MTCT cases between 2011 and 2060.

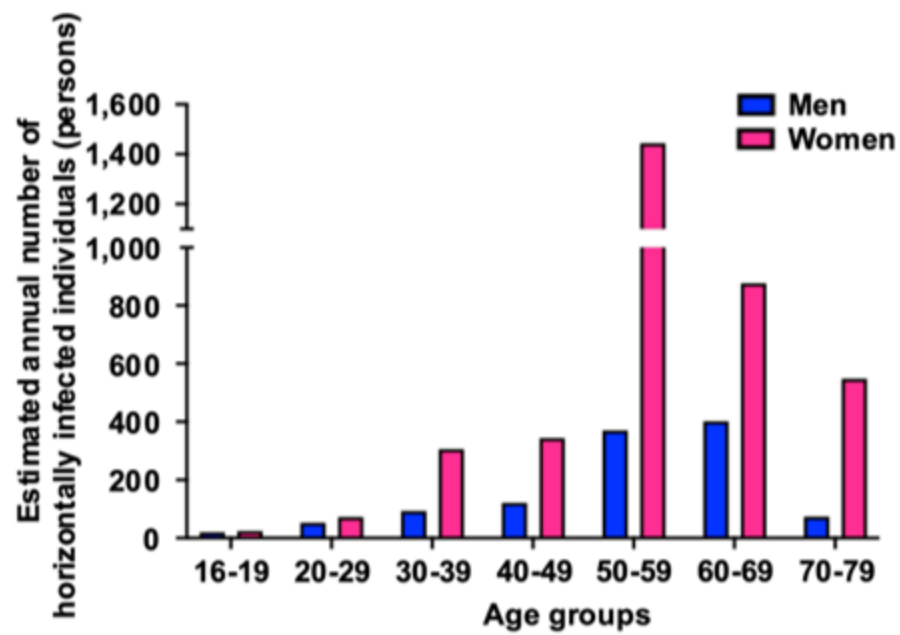


Figure 2

Estimated numbers of horizontally infected individuals by age group in 2020

The numbers of horizontally infected individuals by age group in 2020 were estimated after adjusting for HTLV-1 seroprevalence among women of reproductive age.

A total of 4,751 new horizontal infections were estimated (1,135 men and 3,616 women), indicating that the number of newly infected women was 3.19 times greater than that of men. The highest numbers of new horizontal infections were observed among the AYA population.

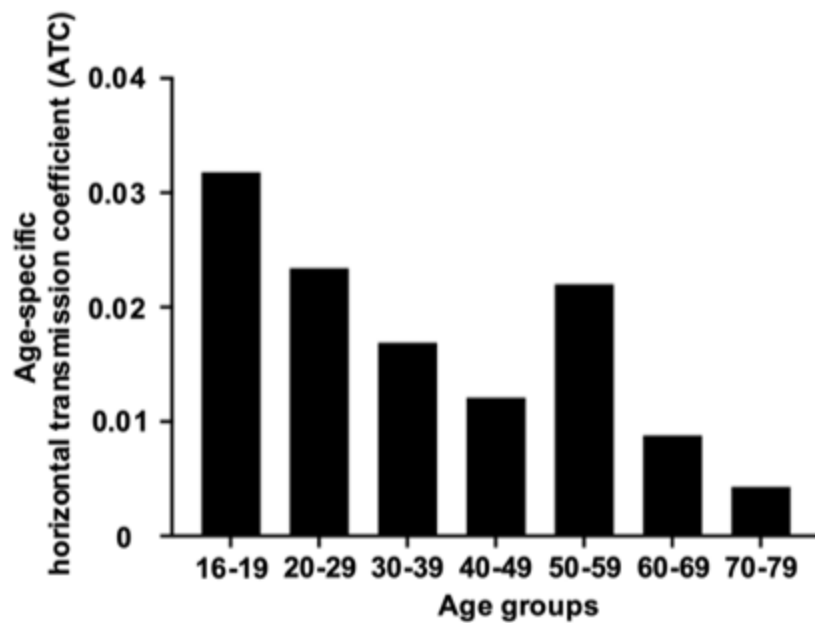


Figure 3

Age-specific horizontal transmission coefficient (ATC)

Age-specific horizontal transmission coefficient (ATC) values were shown. The ATC value was highest in the AYA population, gradually decreased with advancing age, and showed a second peak in the 50–59-year age group.

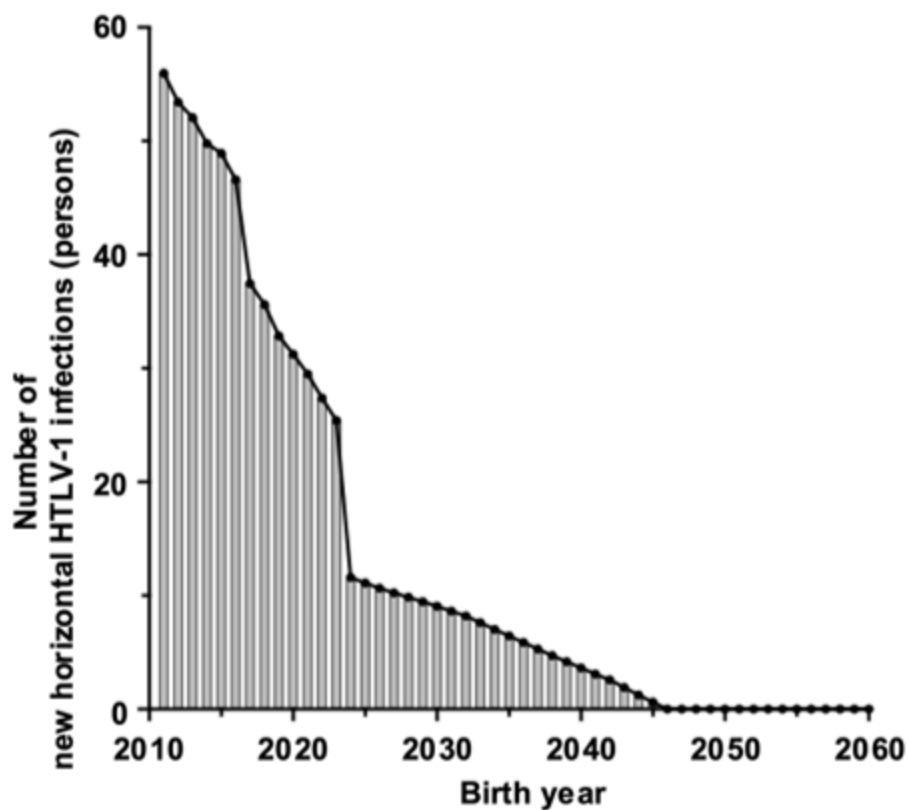


Figure 4

Projected horizontal HTLV-1 infections arising from MTCT-derived carriers

The projected numbers of new horizontal HTLV-1 infections arising from MTCT-derived carriers between 2011 and 2060 were calculated using the duration of exposure and ATC values. A total of 669 new horizontal infections were projected by 2060.

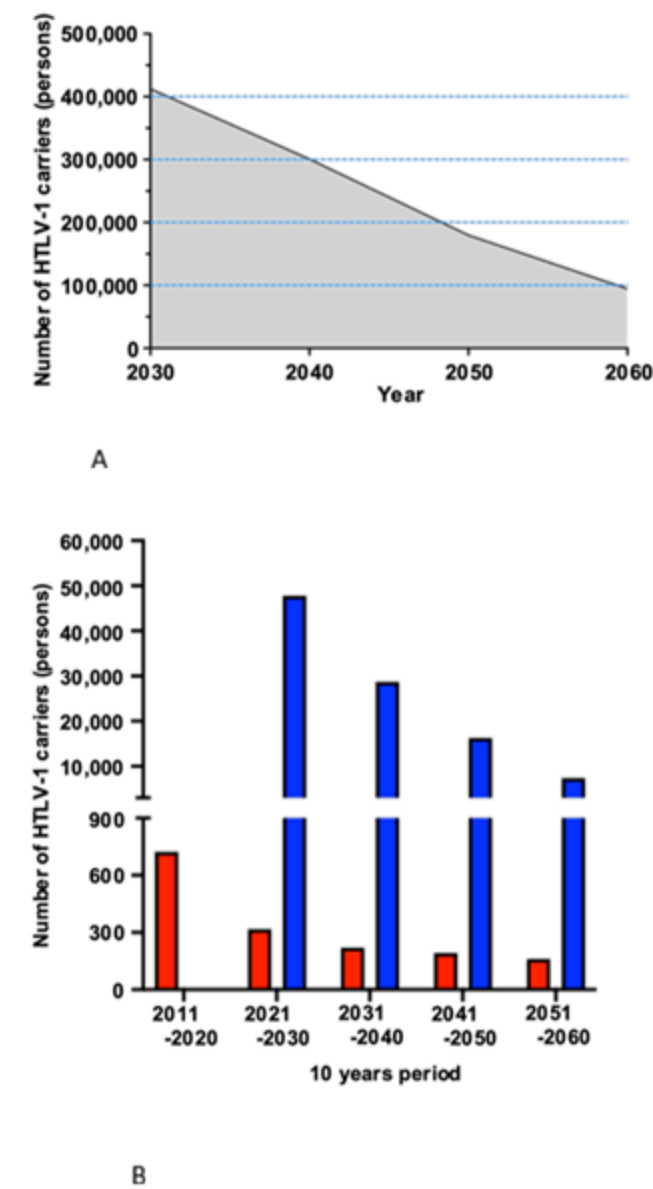


Figure 5

Projected changes in the HTLV-1 carrier population in Japan through 2060.

(A) Projected total number of HTLV-1 carriers in Japan in 2030, 2040, 2050, and 2060. (B) Projected numbers of newly generated HTLV-1 infections by transmission route during each 10-year period. Annual numbers of newly generated HTLV-1 infections through MTCT and horizontal transmission were

summed for each 10-year period. Both new MTCT- and horizontal infections declined over time; however, the number of newly generated horizontal infections consistently exceeded that of MTCT throughout the projection period.

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