Although not ubiquitous, HTLV-1 is found worldwide, and clusters of high endemicity often exist near areas where the virus is rarely present. This could be explained by factors including a possible founder effect, predominance of mother-to-child transmission (MTCT), and cell-to-cell transmission mechanisms [13,14]. The estimated number of HTLV-1 carriers is 5–10 million people across the world [13]. This number may be underestimated because it does not include Russia, China, and India, countries with large populations. The most endemic regions are the southwestern part of Japan, sub-Saharan Africa, South America, the Caribbean region, and foci in the Middle East and Australo-Melanesia regions [13]. HTLV-1-infected individuals are often asymptomatic. Therefore, there is concern about the silent spread of mother-to-child and horizontal transmission.

Most ATL cases are attributed to MTCT [15,16]. The MTCT rate is estimated to be approximately 20% [11], and if we assume a 5% lifetime risk of developing ATL, it is estimated that 25% of cases of MTCT are at a risk of developing ATL. HTLV-1 is a latent virus. Because the host immune system cannot eliminate the virus, HTLV-1 persists in the host and poses a lifelong threat of the development of ATL, HAM/TSP, and other diseases [10,17]. Currently, there is no effective antiretroviral therapy (ART) in clinical use, and the only available measure is the prevention of infection. In this article, we review how HTLV-1 MTCT can be prevented and discuss the challenges in prevention measures.

2. Mechanisms of HTLV-1 Transmission

2.1. Cell-to-Cell Transmission

HTLV-1 virions are rarely detected in the extracellular environment [18]. Thus, HTLV-1 infection is believed to spread predominantly through direct cell-to-cell contact. Cell-to-cell transmission may enhance the multiplicity of infection and evade the host immune responses. It also aids rapid viral replication kinetics by directing virus assembly and budding to sites of cell-to-cell contact [19,20]. Although in vivo evidence has not been established yet, in vitro studies have suggested that HTLV-1 cell-to-cell transmission may occur through viral synapses [21], conduits [22], biofilm-like structures [23], and extracellular vesicles [24]. Recently, Hiyoshi et al. [25] reported that the host factor M-Sec, which induces membrane protrusion and establishes intercellular conduits, plays an important role in efficient viral infection. These modes seem to be favorable for the virus to escape immune elimination (HTLV-1-specific T-cell unresponsiveness) and efficiently reach contacted cells, resulting in increased proviral load (PVL) [26]. HTLV-1 predominantly infects CD4+ T cells via cellular receptors such as heparin sulfate (HS) proteoglycans and neuropilin 1 (NRP-1), which help in initial binding to the cell and glucose transporter 1 (GLUT1) [27–31].

Recent studies have shown that cell-free HTLV-1 can infect certain types of cells rather than being poorly infectious as previously thought [27]. In vitro studies have shown that HTLV-1 infection of T cells via dendritic cells (DCs) can occur in two different ways: In cis-infection, after infecting DCs, de novo produced HTLV-1 is transferred to T cells [32]. In trans-infection, uninfected DCs capture the virus produced by infected T cells and transfer it to T cells before becoming infected [32–34].

Because DCs, monocytes, epithelial cells, macrophages, and B cells express these receptors, they can also infect each other in individuals with HTLV-1 infection [27,35]. CD4+ T cells are the primary targets of HTLV-1 infection in vivo [36]. In addition, HTLV-1 proviral DNA can be detected in CD8+ T cells [37], DCs [38], plasmacytoid dendritic cells [39], and monocytes, including macrophages [35,40], albeit to a lesser extent.

2.2. HTLV-1 Life Cycle

Infected lymphocytes transmit HTLV-1 through intercellular contact with target cells, and viral components, including the single-stranded RNA genome of HTLV-1, are transferred to target cells through these junctions [41]. HTLV-1 genomic RNA (gRNA) is reverse-transcribed in the cytoplasm of target cells, resulting in double-stranded DNA of size 9 kb, which is inserted into the host genome in the target cell nucleus to form a provirus. The position at which the double-stranded DNA is inserted is not completely random. HTLV-1

is preferentially incorporated into characteristic regions; however, the underlying mechanism is currently unknown [42,43]. The provirus is transcribed by RNA polymerase II in the cell and is modified post-transcriptionally. Both full-length and spliced viral mRNAs are transported from the nucleus to the cytoplasm. Viral proteins are then translated by the translation machinery of the host cell, and Gag, Gag-Pol, and Env proteins are transported to the plasma membrane along with two copies of HTLV-1 gRNA. Immature viral particles are formed from these viral proteins and gRNAs, which release from the cell surface. Subsequently, viral proteases act on immature viral particles to form mature viral particles with infectious potential (see Martin's review [44] for a detailed description of this process).

2.3. HTLV-1 Replication

According to previous studies, immediately after infecting the cell, the HTLV-1 virus spreads from cell to cell. Later, during the chronic infection phase, the virus survives through clonal expansion as a provirus, which is incorporated into the host cell genome and replicates as the infected cells divide [27,45]. Replication of HTLV-1 occurs via (i) an infection cycle involving viral budding and infection of new target cells and (ii) mitosis of cells harboring an integrated provirus [46]. During HTLV-1 integration into the host genome, the 5′ and 3′ ends of HTLV-1 are duplicated to form long terminal repeats (LTRs). These regions constitute the promoter regions as transcription factor binding sites. The proviral genome comprises the structural genes gag, pol, and env flanked by LTR at both ends. The genome also contains the pX region, which has four partially overlapping open reading frames encoding p12, p13, p30, Rex, and Tax, which are regulatory or accessory proteins. The viral genes are transcribed from the 5′ LTR. HTLV-1 also expresses a minus-stranded RNA that encodes HTLV-1 bZIP factor (HBZ), a basic leucine zipper factor protein. *HBZ* is the only gene that is encoded in the antisense strand and is transcribed from the 3′ LTR. The HTLV-1 genome has the potential to express multiple products using various strategies, such as frameshifting and alternative mRNA splicing.

Tax and *Rex* are essential for viral replication. *Tax* promotes viral mRNA synthesis by transactivating the HTLV-1 promoter located in the 5′ LTR. Tax acts in a coordinated manner on various intracellular targets during cell transformation and is involved in immortalization, cell proliferation, and leukemogenesis. On the other hand, Tax is a major target antigen recognized by cytotoxic T lymphocytes (CTLs) [47]. Therefore, for HTLV-1-infected cells to survive, *Tax* expression must be tightly regulated to evade host immune surveillance. Tax expression is normally suppressed to escape CTLs, but at the same time Tax is transiently expressed to maintain and expand HTLV-1-infected cells [48]. The *HBZ* gene is the only HTLV-1 gene present in all infected individuals. Unlike Tax, HBZ is always expressed but is less immunogenic, and thus more likely to escape CTL clearance. Furthermore, HBZ may suppress the effects of Tax, leading to survival of infected cells and oncogenesis [49]. *Rex* regulates the synthesis of structural proteins at the post-transcriptional level [50]. The accessory proteins p12/p8, p13, and p30 are important for viral infectivity and persistence in vivo but are not essential for viral replication in vitro [51–53].

3. Modes of HTLV-1 Transmission

There are two modes of HTLV-1 transmission: horizontal infection and antenatal or postnatal MTCT [15,54]. In 2013, there were an estimated 1780 pregnant carriers in Japan [55]. In addition, the MTCT rate in a recent prospective cohort study in Japan was observed as 4.5% (95% confidence interval (C.I.) 2.6–7.4%) [56]. Based on these data, the number of new mother-to-child infections is estimated to be 70 (95% C.I. 41–115) per year. The number of new horizontal infections in Japan is estimated to be approximately 4000 per year, which is far larger than the number of new infections caused by MTCT.

3.1. Horizontal Transmission

The main sources of horizontal infection are sexual intercourse, blood transfusion, and parenteral transmission via contaminated needles. According to the WHO Technical

Report, 23 countries have implemented mandatory screening for HTLV-1 antibodies in all donated blood samples. However, despite being mandatory, HTLV-1 antibody screening is not always performed during blood donations by the same person in these countries [11]. Since donor blood screening for HTLV-1 infection is always performed at the time of blood collection [57], horizontal infection occurs mainly through sexual transmission in Japan [58]. Organ transplantation from an HTLV-1 carrier has also been identified as a cause of horizontal HTLV-1 infection, and the addition of HTLV-1 antibody testing to donor testing has been advocated [59].

The Miyazaki Cohort Study examined heterosexual HTLV-1 transmission in 534 couples over a five-year period from 1984 to 1989. This study showed that the infection rate was 3.9 times higher when the carrier spouse was male [60]. Satake et al. evaluated 3,375,821 repeat blood donors aged 16–69 years for new HTLV-1 infection over a 4.5-year period. Their results were as follows [58]: (i) at least 4000 adolescents and adults were estimated to be newly infected each year, (ii) the incidence density was significantly higher in women (6.88 per 100,000 person-years; 95% C.I. 6.17–7.66) than in men (2.29 per 100,000 person-years; 95% C.I. 1.99–2.62; $p < 0.0001$), (iii) the highest number of newly infected individuals were males in their 60s and females in their 50s, regardless of endemic area, (iv) a higher number of males in their 20s were newly infected in metropolitan areas (non-endemic areas) than in non-endemic areas. As new infections in adolescence and adulthood are primarily caused by sexual transmission in Japan, reports advocate the importance of preventing horizontal transmission from a public health perspective.

Factors related to sexual intercourse include non-use of contraceptives, numerous partners, and male-to-male intercourse [61]. Kaplan et al. found that high PVL and length of relationship played a role in viral transmission from male carriers to non-carrier women [7]. A higher PVL tends to be associated with HAM/TSP [62], ATL [63], HTLV-1-associated infectious dermatitis [64], and HTLV-1 uveitis [65]. In addition, PVL tends to be higher in patients co-infected with *Strongyloides stercoralis* than in the others [66]. Sexual transmission occurs more efficiently from men to women than women to men and might be enhanced by sexually transmitted diseases that cause ulcers and result in mucosal ruptures, such as syphilis, herpes simplex type 2 (HSV-2), and chancroid [67]. Other sexually transmitted diseases may result in the recruitment of inflammatory cells and increase the risk of HTLV-1 acquisition and transmission [61].

3.2. Mother-to-Child Transmission

The main reason for the focus on MTCT of HTLV-1 is that most ATL cases originate from MTCT [64], and ATL rarely develops in individuals infected during adulthood [6].

3.2.1. Transmission Routes of MTCT

The Nagasaki ATL Prevention Program found that exclusive formula feeding (ExFF) markedly reduced the HTLV-1 MTCT rate from 20.3% to 2.5% [68]. Accumulating evidence has shown that the HTLV-1 MTCT rate in children who were exclusively fed infant formula was significantly lower than in children who were breastfed for an extended period [68–71]. Therefore, the primary route of MTCT is through breastfeeding. However, MTCT has been observed in a small percentage of children (approximately 2.5–6.7%) exclusively fed infant formula [56,68,71]. This suggests the possibility of antenatal MTCT [54].

Antenatal Transmission

The presumed pathways for antenatal MTCT are intrauterine and the birth canal. A recent study showed that trophoblasts in pregnant carriers are highly susceptible to HTLV-1, suggesting that intrauterine infection may occur due to impairment of the blood–placental barrier [72]. However, there is little clinical evidence for intrauterine ascending infection, intrapartum infection due to exposure to contaminated maternal blood, or intrauterine infection [51].

Transmission through Breastfeeding

It is unclear which infected cells in breast milk are transmitted to the infant and how MTCT is established. It has been noted that viral uptake during lactation may occur in the tonsillar mucosa, the intestinal mucosa, or both sites [73], while postnatal infection is thought to occur when infected cells in ingested breast milk enter the infant's digestive tract [74,75]. The number of leukocytes in breast milk decreases to 0–2% of the total cell count within a few weeks of lactation. In addition to leukocytes, many other cell types are present in breast milk, including mammary luminal epithelial cells, mammary gland cells, and stem/progenitor breast cells, which vary with lactation period, maternal conditions, and infant feeding [76]. HTLV-1 MTCT has been thought to be primarily mediated by CD4+ T cells, but several studies have suggested that mammary epithelial cells and macrophages may be involved in the persistence and spread of HTLV-1 infection from the carrier mother [77–79]. However, it remains unclear which cells present in breast milk are the main players in breast milk infection. The process from the contact of infected cells with the mucosa to the spread of infection in the submucosal tissue has been described in detail in several reviews [27,46,80], and the following process has been postulated by Carpenter et al. [46]: (i) bilions incorporated into vesicles migrate from the apical surface of epithelial cells to the basal surface of the epithelial cell [73], (ii) newly produced virions are released from the basal surface of infected epithelial cells [80], (iii) HTLV-1-infected cells are bypassed through the injured mucosa [81], and (iv) macrophages pass through the epithelium, as seen with HIV [82]. The process by which infected cells in breast milk enter the infant's gastrointestinal tract and establish infection is not yet fully understood.

3.2.2. Risk Factors Associated with MTCT

Since the 1980s, it has been widely recognized that extended breastfeeding is a risk factor for MTCT, and as discussed below, avoidance of breastfeeding is an important measure for preventing MTCT [71,83]. However, the involvement of other factors should be considered when testing pregnant women, particularly in countries or regions where maternal HTLV-1 antibody screening is not routinely performed [84]. Furthermore, even if HTLV-1 screening tests are performed on all pregnant women, as in Japan [83], intervention measures considering the risk factors are desirable to minimize avoidance of breastfeeding. The risk factors for MTCT reported to date are shown in Figure 1. However, sensitivity and specificity of these factors, except the duration of breastfeeding, in predicting MTCT have not been sufficiently studied. Plancoulaine et al. detected chromosome 6q27 as the dominant gene that predisposes individuals to HTLV-I infection based on a large genetic epidemiological study on an HTLV-1 endemic population of African descent living in French Guiana [85–87].

There has long been an interest in whether the presence or transfer of antibodies in breast milk plays an effective role in preventing MTCT. Moreover, it has been reported that pregnant women infected with HTLV-1 have significantly increased levels of anti-HTLV-1 antibodies, although their PVL did not change during pregnancy [88]. This results in the transmission of more antibodies to the fetus through the placenta during pregnancy. This report is consistent with the hypothesis that infection may be prevented in fetuses and early postnatal infants.

Rosadas et al. measured anti-HTLV-1/2 IgG antibodies and PVL in paired blood and breast milk from HTLV-1/2-positive mothers and reported that HTLV-1 PVL and IgG binding ratios were similar in plasma and breast milk; however, the anti-HTLV-1/2 IgG antibody titer in plasma was approximately 1000 times higher than that in breast milk [89]. After delivery, HTLV PVL increased in the mother's blood [90]. Given the antepartum and postpartum changes in PVL and antibodies in infected mothers, as well as the lower antibody levels in breast milk, MTCT prevention with short-term breastfeeding (discussed below) may be less likely to involve IgG antibodies in breast milk. One reason for the increased risk of MTCT with prolonged breastfeeding may be related to lower levels of transitional antibodies during infancy and increased cumulative intake of infected cells

ingested through breast milk. High maternal PVL has also been identified as a risk factor for MTCT [91,92]. This was also reflected in elevated maternal antibody titers [93].

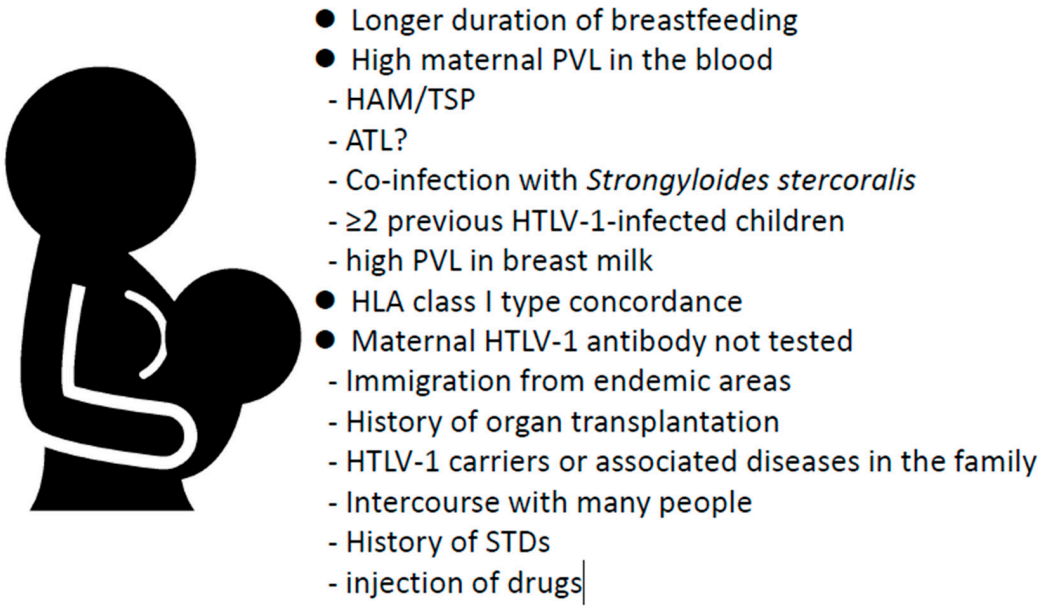

Figure 1. Risk factors associated with development of HTLV-1 mother-to-child transmission. Risk factors for mother-to-child transmission are broadly classified as long-term breastfeeding, high PVL in carrier mothers, HLA class type 1 concordance between mother and child, and mothers with untested HTLV-1 antibodies. HLA, human leukocyte antigen.

Other risk factors for carrier mothers include HAM/TSP complications [94], co-infection with *Strongyloides stercoralis* [94], ≥2 previous children with HTLV-1 infection [91], high PVL in breast milk [95], and human leukocyte antigen (HLA) class I type concordance between mother and child via breastfeeding [96]. Furthermore, in mothers with untested HTLV-1 antibodies from endemic areas, a lack of effective intervention may result in MTCT.

Substances present in breast milk, such as tumor growth factor (TGF)-β and lactoferrin, which are abundant in colostrum [92,97], promote HTLV-I replication [98,99]. Furthermore, lactoferrin expression has been shown to be elevated during HTLV-1 infection [100]. However, the levels of these components are not constant during lactation and vary from person to person. Therefore, it is unclear how they affect MTCT.

4. Strategies to Prevent HTLV-1 MTCT

Theoretical strategies to prevent the MTCT of HTLV-1 include avoidance of breastfeeding, reduction in infected cells in breast milk, and administration of vaccines, neutralizing antibodies, and antiretroviral drugs. These strategies are discussed in the following sections. Other important strategies include promoting the use of condoms to prevent transmission to uninfected women from male carriers. Furthermore, it is essential to disseminate knowledge about HTLV-1 infection not only to medical providers and health administrators but also to the general public.

4.1. Prevention of MTCT through Nutritional Regimens

Several nutritional regimens have been proposed to prevent the MTCT of HTLV-1 (Table 1) [54]. However, some methods provide limited evidence. Previous epidemiological and animal studies have shown that most HTLV-1 MTCT occurs through breast milk containing infected cells. Therefore, ExFF, which intercepts breast milk containing infected cells, is theoretically the most reliable method for postnatal prevention. As mentioned

above, a follow-up study by the ATL Prevention Program (APP), which started in 1987 in the Nagasaki Prefecture, showed that ExFF reduced the rate of MTCT to approximately 1/10 of that after long-term breastfeeding (≥6 months) [68]. However, it has been suggested that the longer a carrier mother breastfeeds her infant, the higher the MTCT rate [91].

Table 1. Effectiveness of feeding regimens in peventing mother-to-child transmission and their limitations.

Nutritional Regimens	Effectiveness on MTCT	Comments
Exclusive infant formula feeding (ExFF)	Widely used and well evaluated to block MTCT through breast milk	Prevents about 95% or more of MTCT No benefits from breastfeeding Concerns about increased risk of postpartum depression and impaired mother–child bonding
Short-term breastfeeding (≤3 months)	No apparent difference in the MTCT prevention effect (vs. ExFF) Majority of studies in Japan	Acquisition of some benefits of breastfeeding Approximately 18% of children exceed 4 months of breastfeeding Need to provide adequate support for weaning No data on the preventive effect of postpartum depression or impairment of mother–child bonding
Short-term breastfeeding (≤6 months)	Approximately three times increased risk of MTCT (vs. ExFF)	Better to avoid this regimen
Frozen–thawed breast milk feeding	No apparent difference in the MTCT prevention effect (vs. ExFF) Only three small case studies in Japan, with little confidence in preventive effects	Time-consuming Considered for use in infants admitted in the NICU No data on the preventive effect of postpartum depression or impairment of mother–child bonding
Mixed feeding	Unknown effectiveness of MTCT prevention due to lack of data (vs. ExFF)	Concerns about increased risk of MTCT due to damage to the intestinal mucosa Better to avoid this regimen
Banked human milk pasteurization	No data available, but expected to be as effective as ExFF in preventing MTCT	No use of breast milk from untested HTLV-1 donors No data on the preventive effect of postpartum depression or impairment of mother–child bonding

Note: It should be noted that ~5% of antenatal infections cannot be avoided regardless of which nutritional regimen is chosen. MTCT, mother-to-child transmission; NICU, neonatal intensive care unit. The table is reproduced from Itabashi et al. [54] with some modifications.

In Japan, methods such as limiting the duration of breastfeeding to three to six months or inactivating infected cells by freezing and thawing procedures (frozen–thawed breast milk feeding; FTBMF) have been proposed as alternatives to ExFF for carrier mothers who wish to breastfeed their babies [83]. In the Kagoshima Prefecture, an endemic area of Japan, short-term breastfeeding (STBF) has historically been promoted if mothers wish to breastfeed, and over 60% of mothers have opted for STBF [101]. This indicates that a significant number of HTLV-1 carrier mothers wished to breastfeed their infants. However, because the effectiveness of these interventions in preventing MTCT is based on small observational studies rather than randomized controlled trials, sufficient evidence is lacking.

In a recent technical report on HTLV-1, the WHO recommends that "available data should be further analyzed to better define the risk of HTLV-1 transmission associated with specific duration of breastfeeding, balanced with the risks of other adverse health outcomes that may result from reduced breastfeeding" [102]. In this context, Itabashi et al. conducted a prospective multicenter cohort study involving HTLV-1 carrier pregnant women and their infants as part of the Health, Labor, and Welfare Science Research Program in Japan

to determine the rate of MTCT by ExFF, STBF, and FTBMF [56]. Miyazawa et al. reported findings through a systematic review that integrated the results of the cohort study and previous studies [103].

4.1.1. Exclusive Formula Feeding (ExFF)

A meta-analysis of 12 studies by Rosadas et al. in 2022 showed that the risk of MTCT with breastfeeding (of any duration) was approximately four times higher than that with ExFF [84], supporting the effectiveness of avoiding breastfeeding for the prevention of infection. However, ExFF lacks the various positive effects of breastfeeding, such as nutritional and immunological benefits, long-term disease prevention, economic efficiency, promotion of mother–infant bonding, and promotion of maternal recovery after delivery. Many HTLV-1 carrier mothers are concerned that they cannot form mother–infant bonds because they cannot breastfeed their babies [104].

According to a review article by Millen et al., avoidance of breastfeeding is not an option in resource-limited areas or populations with few infected individuals [105]. In particular, in developing countries with high morbidity and mortality rates of serious gastrointestinal and other infections due to poor sanitation, which do not provide a stable supply of formula, baby bottles, and clean water, the advantages of the immunological benefits of breast milk may outweigh the disadvantages of the MTCT of HTLV-1. Therefore, the recommended level of breastfeeding avoidance to prevent HTLV-1 MTCT should be considered based on each local situation.

4.1.2. Short-Term Breastfeeding (STBF)

Although the precise mechanism of MTCT prevention by STBF is unknown, it is assumed to be due to the transplacental transfer of neutralizing antibodies from the mother to infant during pregnancy. The antibodies remain in the infant for several months after birth and may prevent MTCT during the first few months of life. The period of exposure to the infected cells is short, and the cumulative number of infected cells entering the digestive tract is small.

In the Nagasaki Prefecture, the duration of STBF has been set at six months or less since the late 1980s. During this period, the MTCT rate was 2.4% (23/962) for ExFF, while it was significantly higher for STBF ($\leq$6 months) at 8.3% (14/169) [106]. Since the late 1990s, when the duration of STBF was changed to three months or less, the MTCT rate was observed to be 3.7% (8/218) for ExFF versus 2.8% (1/36) for STBF, with no statistical difference between the two [106]. In the Kagoshima Prefecture, between 1986 and 2006, the MTCT rate for ExFF was 4.8% (16/331), whereas that for STBF ($\leq$3 months) was 1.6% (2/126) [107]. Based on these results, the recommended period of STBF is less than three months (less than 90 days after birth) in Japan [54].

In a Japanese prospective cohort study by Itabashi et al., the intention-to-treat (ITT) analysis showed that the MTCT rates for STBF (less than 90 days) and ExFF were 2.3% (4/172 children born to carrier mothers) and 6.4% (7/110), respectively, with no statistically significant difference between the two groups [56]. Among 172 mother–infant pairs who chose STBF, 33.5% were still breastfeeding at three months of age and 7.8% at six months, and the approximate formula suggests that 18.2% were still breastfeeding at 4 months of age [56]. Thus, even if a mother chooses STBF, it is difficult for her to terminate breastfeeding and make the transition to ExFF within $\leq$3 months (90 days) of age of the infant. In addition, there is a concern that prolonged breastfeeding may increase the risk of MTCT.

A 2021 systematic review included a meta-analysis of the risk of MTCT of STBF $\leq$ 3 months and STBF $\leq$ 6 months compared with that of ExFF [103]. The meta-analysis integrated five retrospective studies and the cohort study by Itabashi et al.; comparing STBF $\leq$ 3 months (including <90 days) with ExFF found no statistical difference in the risk of MTCT between the two groups (pooled risk ratio (RR): 0.72, 95% CI: 0.30–1.77) (Figure 2) [103]. In contrast, a meta-analysis integrating five retrospective studies and comparing STBF $\leq$ 6 months and ExFF showed that STBF $\leq$ 6 months was associated with an approximately 3-fold higher risk

of MTCT than that of ExFF (pooled RR: 2.91, 95% CI: 1.69–5.03) (Figure 3) [103]. Although there was no statistical difference in the MTCT rates between STBF ≤ 3 months and ExFF, Rosadas et al. documented that all studies included in the meta-analysis were observational studies in Japan [84].

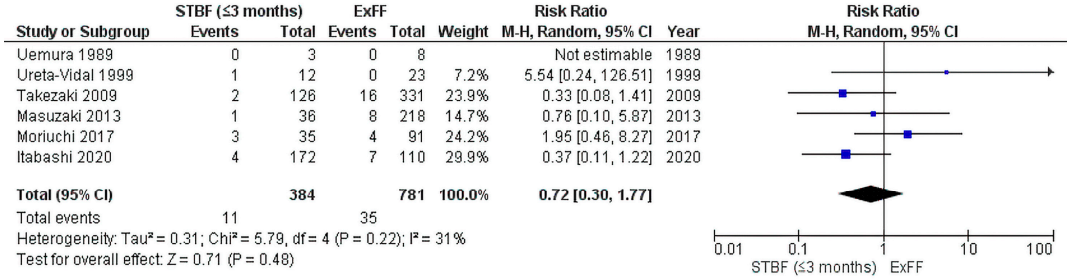

Figure 2. Forest plot of the risk ratios of HTLV-1 MTCT in the STBF ≤ 3 months group compared with that of the ExFF group. There is no statistical difference in the risk of MTCT between the two groups (pooled risk ratio (RR): 0.72, 95% CI: 0.30–1.77). Abbreviations: STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, risk ratio; MTCT, mother-to-child transmission; events, number of cases with mother-to-child transmission; total, number of children born to carrier mothers; weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [103].

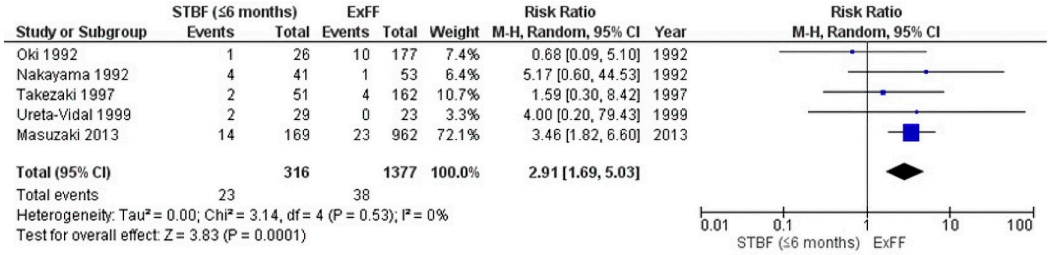

Figure 3. Forest plot of the risk ratios of HTLV-1 MTCT in the STBF ≤ 6 months group compared with that of the ExFF group. Comparing STBF ≤ 6 months and ExFF showed that STBF ≤ 6 months was associated with an approximately 3-fold higher risk of MTCT than that of ExFF (pooled RR: 2.91, 95% CI: 1.69–5.03). Abbreviations: STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, risk ratio; MTCT, mother-to-child transmission; events, number of cases with mother-to-child transmission; total, number of children born to carrier mothers; weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [103].

4.1.3. Frozen–Thawed Breast Milk Feeding (FTBMF)

It is speculated that freeze–thaw treatment of breast milk destroys infected cells, thereby inactivating its infectivity in the infant [54]. Specifically, the expressed breast milk is frozen in a home freezer at −20°C or lower for at least 24 h, thawed, and fed to the infant. Milk expression, freezing, and thawing are necessary and time-consuming processes. In a Japanese prospective cohort study, only 19 of 313 mothers opted for FTBMF, and MTCT was confirmed in one infant [56]. A meta-analysis integrating three prospective observational studies, including the cohort study by Itabashi et al., found no difference in the risk of MTCT between ExFF and FTBMF (pooled RR: 1.14, 95% CI: 0.20–6.50) [103]. However, the number of cases analyzed was small, the subjects were limited to Japan, and the duration of FTBMF was not constant, and included cases of a short duration (2–6 months) [108,109]. Therefore, it may be premature to conclude that FTBMF is an effective intervention to prevent MTCT. However, FTBMF is routinely administered to preterm infants born at less than 32 weeks of gestation who are at risk for infection, necrotizing enterocolitis, and

related deaths [110]. Thus, FTBMF would outweigh the risk of HTLV-1 MTCT while in the neonatal intensive care unit (NICU) for such infants.

FTBMF requires several work processes. If an infant born to an infected mother is admitted to the NICU, the mother's work involves expressing and freezing breast milk, and then bringing the frozen breast milk to the NICU. However, if not admitted to the NICU, two additional processes are required: thawing the frozen breast milk and transferring it to a bottle. It is difficult to repeat a series of work processes on a daily basis.

4.1.4. Milk Pasteurization and Banked Human Milk

When newborn infants cannot be fed with their mother's milk, such as preterm infants admitted to the NICU, human milk donated to human milk banks is an important resource for supporting their health. According to international guidelines [111], milk is pasteurized using the Holder method (62.5 °C for 30 min). According to a systematic review conducted by Pitino et al., all viruses studied, except parvoviruses, are susceptible to thermal killing [112]. Unfortunately, this review did not report any studies on HTLV-1. Yamato et al. reported that heat treatment (56°C for 30 min) eliminated HTLV-1 activity in an in vitro study [113], but no subsequent clinical studies have been conducted to date. Theoretically, this is sufficient to suppress transmission of infection through breastfeeding; however, further studies are required to clarify this issue.

Banked human milk should be screened for maternal HTLV-1 infections [114]. Theoretically, banked human milk could have the same preventive effect as ExFF in infants born to HTLV-1 carriers. However, while banked human milk may provide some health benefits for infants and children [115], it is unlikely to reduce carrier mothers' anxiety and/or impairment of mother–child bonding. This method would be available assuming that resources are abundant and a breast milk banking system exists; however, clinical studies must be conducted before this can be performed.

4.1.5. Mixed Feeding

The method of supplementing the deficiency with infant formula in the case of decreased breast milk secretion is called mixed feeding. Some carrier mothers intentionally choose mixed feeding immediately after birth to reduce the amount of breast milk ingested by their infants, thus reducing the amount of virus transferred to them. However, the effect of this approach on MTCT is unknown. In recent studies, the rate of MTCT of HIV was extremely high (approximately 20%) compared to normal breastfeeding or infant formula feeding [116]. Mixed feeding may cause gastrointestinal mucosal injury or dysbiosis, resulting in changes in intestinal permeability [117]. It is possible that the same concept can be applied to the MTCT of HTLV-1. However, there is a lack of evidence recommending mixed nutrition immediately after birth.

4.2. Prevention Methods Other Than Nutritional Regimens

To prevent the MTCT of HIV, antiretroviral prophylaxis, cesarean section, and avoidance of breastfeeding are now sentinel events in resource-rich countries [118]. These are expected to be effective in preventing the MTCT of HTLV-1, which belongs to the same Retroviridae family.

Bittencourt et al. reported that when elective cesarean sections were performed in 81% of 41 HTLV-1 carrier pregnant women who opted for ExFF, no MTCT was observed in any of the 41 infants [119]. Although elective cesarean sections are expected to be effective in minimizing an infant's exposure to mother's blood containing infected cells, no high-quality studies have been conducted to date, and no evidence exists to support elective cesarean sections [15,71,84]. Conclusively, carrier pregnant women should not be generally indicated for cesarean section, as it may increase the risk of complications for mothers and children.

To date, no clinical trials have been conducted on ART during pregnancy, although in vitro studies have suggested efficacy of ART [71]. In a case series published in the United

Kingdom in 2021, zidovudine was administered to four mothers who developed ATL during pregnancy and to their babies. The authors reported that MTCT was observed in one of the four mothers, but the outcomes of the other three were unknown because of the short follow-up period [120]. Since there have been no studies on asymptomatic carriers who have not developed ATL, further investigation is warranted. Despite promising in vitro data, clinical data on the efficacy of antiretroviral drugs in preventing the MTCT of HTLV-1 are scarce [84].

Previous animal experimental and pilot studies have suggested that immunotherapy, such as neutralizing antibodies and vaccination with the HTLV-1 gene product, may protect against infection [121–124]. The ideal candidates and methods of inoculation remain to be elucidated. Furthermore, the correlates of the immune response have not yet been elucidated. Even if clinically effective vaccines and neutralizing antibodies are developed, they may be targeted first to those at high risk of sexual transmission, followed by the prevention of MTCT (see the review article by Ratner [125]).

5. Screening Program and Strategies for Prevention of MTCT in Japan

5.1. Background

Introduction of an HTLV-1 antibody screening program for all pregnant women remains controversial [88,91,126]. HTLV-1 antibody screening tests for all pregnant women are currently unavailable in countries except Japan. A nationwide antenatal HTLV-1 antibody screening program was implemented in Japan since 2010 owing to the following reasons: (i) HTLV-1 carriers are spread throughout Japan by internal population movement from endemic areas to non-endemic areas [127]; (ii) more than 4000 adolescents and adults are newly infected through sexual contact [58]; (iii) no effective drug treatment has been developed against this virus [128]; (iv) reduction in the number of these children would also contribute to a reduction in horizontal sources of transmission.

5.2. Screening Program in Practice

HTLV-1 antibody screening is usually performed within 30 weeks of gestation, allowing carriers sufficient time to obtain more information from their healthcare providers before delivery and select the appropriate feeding regimen for their infants. Pregnant women with positive screening results undergo confirmatory antibody testing using an algorithm (Figure 4) [54,129]. If a pregnant woman is determined to be a carrier, the healthcare provider will explain the risks of MTCT and preventive measures to the extent possible before delivery. If the mother does not have strong concerns about the risks of HTLV-1 associated diseases and interventions for MTCT, infant and child health examinations are performed on the same schedule (at 1, 3–4, 7–10, 18, and 36 months) as for infants born to non-carrier pregnant women. Testing for HTLV-1 antibodies at the age of three years to assess MTCT is recommended, but not mandatory [83].

5.3. Nutritional Regimens in Japan

Since 2017, the Japanese nutrition protocol for the prevention of postnatal MTCT via breast milk has changed from the three previous options of ExFF, STBF, and FTBMF to ExFF as the first choice with the most reliable preventive effect [83]. Based on the results of a recent cohort study and meta-analysis by Itabashi and Miyazawa [56,103], it was concluded that the MTCT rate for STBF would not exceed the risk of MTCT for ExFF unless the duration of breastfeeding does not exceed 90 days after birth and that adequate maternal support by a medical care provider is a precondition for ensuring this. Sufficient evidence to prove the effectiveness of FTBMF has not yet been obtained; therefore, it is not recommended [130]. Medical providers should not uniformly recommend ExFF to mothers from the perspective of MTCT prevention, but should fully explain the advantages and disadvantages of each nutritional regimen from the perspective of pregnancy, delivery, and childcare and provide shared decision-making support so that mothers can make their

own decisions about nutritional methods, including STBF and other nutritional regimens (Table 1) [54].

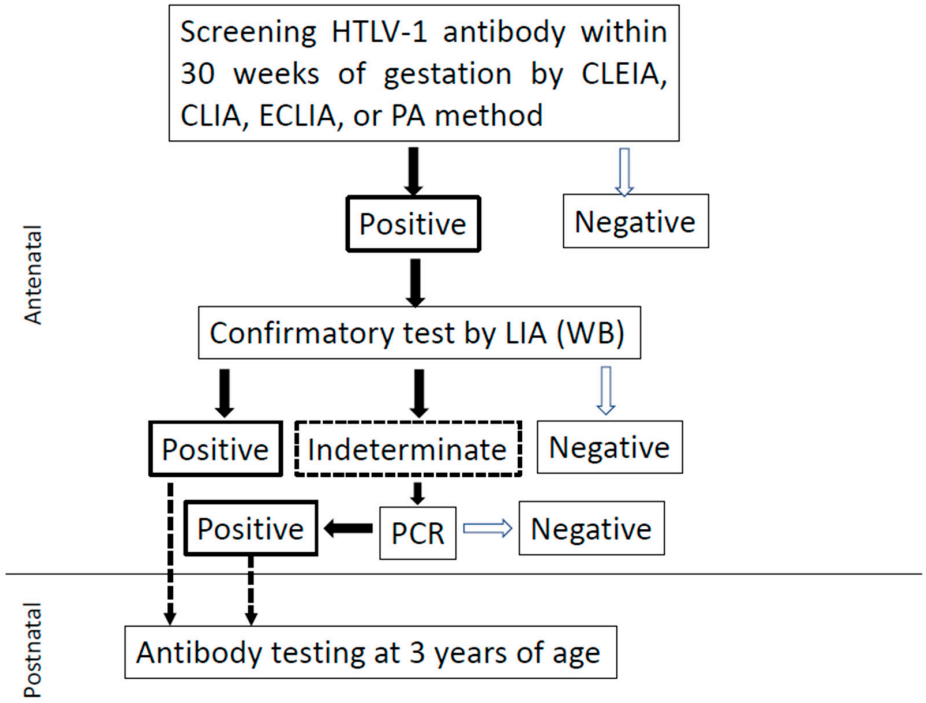

Figure 4. Algorithm for diagnosing HTLV-1 infection in Japan. Currently, no confirmatory tests using Western blotting are conducted in Japan. Flowchart for identifying HTLV-1 carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electrochemiluminescent immunoassay; PA, particle agglutination; WB, Western blotting; LIA, line immunoassay; PCR, polymerase chain reaction. The figure is reproduced from Itabashi et al. [54]. For further details, please refer to Okuma et al. [129].

5.4. Issues of Nationwide Antenatal Screening Program in Japan

5.4.1. Support for Carrier Mothers

More than 10 years have passed since the screening test for all pregnant women was introduced in Japan. However, carrier mothers were not satisfied with the status quo. Their main opinions were as follows: (i) it is difficult to say that medical providers adequately support carrier mothers' choice of nutritional regimen, and (ii) there are no medical facilities close by where mothers can discuss their concerns about the onset of the disease or their children's infection, and they do not know whom to consult. This might be due to limited experience and insufficient knowledge of obstetricians and pediatricians about HTLV-1 infection, as well as lack of collaboration among obstetricians, pediatricians, hematologists or neurologists, and local government officials. Therefore, establishment of a consultation and support system for carrier mothers and their families based on local medical resources, along with public awareness of HTLV-1 infection, is an urgent issue.

5.4.2. Selection of Nutrition Regimen Considering Risk Factors

It is unclear whether it is appropriate to select ExFF or STBF without considering risk factors for MTCT. Deprivation of long-term breastfeeding in infants at very low risk for MTCT may impact their future health [131]. In addition, there are concerns about the impact of the selection of a nutrition regimen on mothers' parenting behavior and mother–infant bonding [132]. Future studies should accumulate data on infants born to

carrier mothers to determine the association between MTCT and its risk factors and to minimize the avoidance of breastfeeding.

5.4.3. Follow-Up of a Child Infected via MTCT

Although HAM/TSP is generally considered an adult manifestation of HTLV-1, the possibility of early-onset HAM/TSP via MTCT has long been reported, mainly in South America [133–135]. Yoshida et al. reported a case of childhood HAM/TSP in Japan in 1993 [136]; however, only a few cases have been reported since then.

Dermatological lesions, such as infectious dermatitis, atopic dermatitis, seborrheic dermatitis, acquired ichthyosis, candidiasis, palmar erythema, dermatophytosis, crusted scabies, and folliculitis decalvans, may be associated with HTLV-1 infection [137]. Cutaneous involvement in an apparently asymptomatic carrier has been considered a premonitory indication for the future development of either ATL or HAM/TSP [137]. As PVL may slightly fluctuate in asymptomatic children, measurement of PVL on a regular basis may not be of much clinical significance [138]. However, as early-onset HAM/TSP and ATL may be associated with a variety of skin lesions in addition to infectious dermatitis [133,134], serological tests and PVL measurements may be useful in children with known MTCT in endemic areas [138]. Children with known MTCT and suspected of having neurological abnormalities, such as weakness, muscle stiffness, spasm, gait disturbance, and abnormal urination, should be considered for PVL measurements. Skin lesions are also observed in such cases. The association between skin lesions and early-onset HAM/TSP in children in Japan has rarely been discussed. Since atopic dermatitis and seborrheic eczema occur frequently in infants in Japan, regardless of HTLV-1 infection, pediatricians are not concerned about their appearance in HTLV-1-infected children via MTCT. Longitudinal follow-up is needed to determine whether the relationship between skin lesions and premature HTLV-1-related disease in infected mother and child pairs in Japan differs from that in South America.

If MTCT is obvious, parents should consider at what age the child will be informed and who will inform the child of this fact. Furthermore, if the child is anxious, counseling may be necessary.

6. Conclusions

The perception of HTLV-1 infection as a "silent disease" has recently given way to concern that its presence may be having a variety of effects. Therefore, measures to prevent mother-to-child and horizontal transmissions are becoming increasingly important. Currently, no antiretroviral drugs or immunotherapies can be used clinically. More than 90% of MTCT cases involve trans-breastfeeding; therefore, the main preventive measures are avoidance of breastfeeding or reduction in infected cells in breast milk. Our study indicated that the MTCT rate of STBF within 90 days of birth in infants born to carrier mothers did not exceed that of ExFF. However, it is estimated that approximately 20% of mothers who choose STBF are unable to discontinue it by 90 days; therefore, adequate support from healthcare providers is essential. ExFF and STBF are available only in resource-rich areas with good sanitation. On the other hand, breastfeeding has various advantages. Accurate prediction based on risk factors for MTCT may curb more over-intervention cases for infants born to carrier mothers in resource-rich countries and reduce cases where the benefits of breastfeeding are traded off. However, in countries with limited medical resources, ExFF may not be a realistic option, particularly because it is directly associated with increased infant mortality. If antiretroviral drugs and immunotherapy, such as vaccines and neutralizing antibodies, are introduced in the future, it is expected that they may contribute to the prevention of MTCT after birth without compromising the advantages of breastfeeding and may even be useful for prenatal prevention of infection.

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REVIEW
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A Nationwide Antenatal Human T-Cell Leukemia Virus Type-1 Antibody Screening in Japan

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Japan has been running a nationwide antenatal human T-cell leukemia virus type-1 (HTLV-1) antibody screening program since 2010 for the prevention of HTLV-1 mother-to-child transmission. As part of the program, pregnant women are invited to take an HTLV-1 antibody screening test, usually within the first 30 weeks of gestation, during regular pregnancy checkups. Pregnant women tested positive on the antibody screening test undergo a confirmatory test, either western blotting or line immunoassay. In indeterminate case, polymerase chain reaction (PCR) is used as a final test to diagnose infection. Pregnant women tested positive on a confirmatory or PCR test are identified as HTLV-1 carriers. As breastfeeding is a predominant route of postnatal HTLV-1 mother-to-child transmission, exclusive formula feeding is widely used as a postnatal preventive measure. Although there is insufficient evidence that short-term breastfeeding during $\leq$3 months does not increase the risk of mother-to-child transmission compared to exclusive formula feeding, this feeding method is considered if the mother is eager to breastfeed her child. However, it is important that mothers and family members fully understand that there is an increase in the risk of mother-to-child transmission when breastfeeding would be prolonged. As there are only a few clinical studies on the protective effect of frozen-thawed breastmilk feeding on mother-to-child transmission of HTLV-1, there is little evidence to recommend this feeding method. Further study on the protective effects of these feeding methods are needed. It is assumed that the risk of anxiety or depression may increase in the mothers who selected exclusive formula feeding or short-term breastfeeding. Thus, an adequate support and counseling for these mothers should be provided. In addition to raising public awareness of HTLV-1 infection, epidemiological data from the nationwide program needs to be collected and analyzed. In most cases, infected children are asymptomatic, and it is necessary to clarify how these children should be followed medically.

Keywords: human T-cell leukemia virus type-1, nationwide antenatal screening, confirmatory test, mother-to-child transmission, infection, prevention

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INTRODUCTION

While the majority of HTLV-1-infected individuals remain asymptomatic, the two well-recognized disease associations ATL and HAM/TSP are caused by the virus. HTLV-1 carriers are estimated to have a lifetime risk of 2–7% for the development of ATL (Iwanaga et al., 2012) and 0.25–3.8% for HAM/TSP (Yamano and Sato, 2012). Both these diseases exhibit serious clinical manifestations, and the associated prognosis remains poor despite therapeutic efforts (Katsuya et al., 2015; Willems et al., 2017). Numerous studies have demonstrated that MTCT through breastfeeding is the predominant route of HTLV-1 infection (Hino et al., 1987; Murphy et al., 1989; Hino, 2011), while HAM/TSP develops in both populations infected via vertical and horizontal routes (Bartholomew et al., 1998). Thus, antenatal HTLV-1 screening program is expected to play an important role, especially in reducing the number of ATL patients.

A first step in taking measures to prevent HTLV-1 MTCT is to determine whether the mother is infected. To date, there are no effective measures to prevent antenatal infection, but avoiding or restricting breastfeeding is expected to reduce the number of postnatal infections via MTCT. In turn, the prevalence of HTLV-1-associated diseases could be reduced, and the rising trend in the number of people with horizontal infection could be curbed to some extent. Non-endemic and endemic countries may have different views on the need to introduce a nationwide screening program, but in countries or areas where HTLV-1 is endemic, antenatal screening is likely to contribute to a reduction in the burden of associated diseases (Ribeiro et al., 2012; Rosadas et al., 2018).

In 2010, the Ministry of Health, Labor, and Welfare in Japan decided to conduct a nationwide HTLV-1 antibody screening program for all pregnant women (Nishijima et al., 2019). Japan is the first country in the world to conduct such a nationwide screening program. There are several factors to this— (1) Japan is the only developed country with >1 million HTLV-1 carriers (Satake et al., 2012); (2) HTLV-1 carriers are spreading throughout Japan due to internal population migration (Satake et al., 2012); (3) >4,000 adolescents and adults (77% female) are newly diagnosed annually (Satake et al., 2016); and (4) to date, no effective vaccines or antiviral regimens have been developed yet (Willems et al., 2017).

The United Kingdom National Screening Committee had considered antenatal HTLV-1 screening program three times, but the committee did not recommend introducing a screening program in the United Kingdom because of the low prevalence of HTLV-1 infection and the low risk for infected infants to develop a serious illness. The Committee maintained its conclusions after updating and reviewing the evidence in 2017 (UK National Screening Committee, 2017). However, Malik and Taylor (2019) analyzed the cost-effectiveness of a United Kingdom screening program using a highly conservative model of transmission and disease attribution. This analysis suggested that an antenatal screening program to identify HTLV-1 carriers and reduce transmission was potentially cost-effective in the United Kingdom.

In this review, we would like to introduce the nationwide antenatal screening program in Japan and discuss the associated issues.

Abbreviations: ATL, adult T-cell leukemia; CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent-immunoassay; electro-chemiluminescent immunoassay (ECLIA); ExFF, exclusive formula feeding; FTBMF, frozen-thawed breast milk feeding; HAM/TSP, HTLV-1 associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-cell leukemia virus type-1; LIA, Line Immunoassay; MTCT, mother-to-child transmission; PA, particle agglutination; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PVL, proviral load; STBF, short-term breastfeeding; WB, Western Blot.

ANTENATAL MOTHER SCREENING FOR HTLV-1 ANTIBODY

Algorithm for Virus Carrier Screening

The algorithm for HTLV-1 carrier screening during pregnancy in Japan is shown in **Figure 1**. HTLV-1 antibody screening is usually performed within the first 30 weeks of gestation to secure enough time for a carrier to gain access to the detailed information from healthcare providers and to select a suitable feeding method before labor. Confirmatory tests are performed for pregnant women with positive screening results. In indeterminate cases, PCR is used as a definite test to diagnose infection. Pregnant women who have either a positive confirmatory test or PCR-positive results are identified as HTLV-1 carriers.

Assays for HTLV-1 Antibody Screening

In Japan, laboratory screening for HTLV-1 infection has been routine practice for blood donors since 1986 (Inaba et al., 1989). Furthermore, following several cases of HAM/ TSP and ATL in donors and recipients after organ transplantation, HTLV-1 screening has been proposed for both transplant donors and recipients (Gallo et al., 2016; Kawano et al., 2018; Moreno-Ajona et al., 2018).

Several assays for HTLV-1 antibody screening are available, including PA (Fujino et al., 1991), CLEIA (Morota et al., 2009),

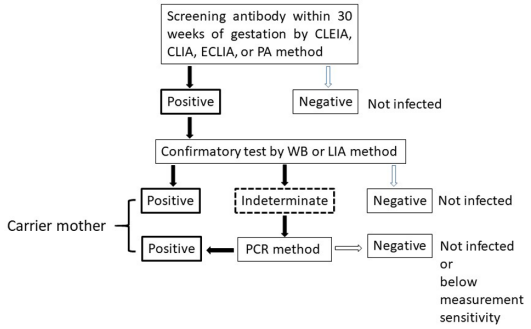

FIGURE 1 | Algorithm to determine HTLV-1 virus carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electro chemiluminescent immunoassay; PA, particle agglutination; WB, Western Blot; LIA, line immunoassay; PCR, polyclonal chain reaction.

CLIA (Qiu et al., 2008), and ECLIA (Laperche et al., 2017). These assays are available in Japan because they are capable of processing large numbers of samples in a relatively short time. A multicenter performance evaluation study in Europe and Japan was carried out with the new ECLIA for HTLV-I/II antibody detection (Laperche et al., 2017). This study demonstrated a specificity of 99.83% and sensitivity of 100% in routine diagnostic samples, regardless of the geographic origin of the samples, the virus type, or the location of the testing laboratory. This assay has the sensitivity and specificity to support its use as a routine screening assay for detecting HTLV infection. The development of screening assays with high sensitivity and specificity has contributed to HTLV-1 detection.

However, antibody screening tests use different antigens and have different measurement principles, and the test results often do not match between them due to the methods used. In addition, these tests have a high false-positive rate, especially in non-endemic areas. For this reason, a confirmatory test must be performed following a positive screening test.

Confirmatory Test

According to data collected retrospectively by the Japan Association of Obstetricians and Gynecologists, the prevalence rate of pregnant women tested positive on a PA or CLEIA screening test was 0.32% (2,259/707,711) in 2011. Among 2,259 pregnant women who screened positive, 1,894 women (83.8%) underwent a WB test as a confirmatory test. Thus, the screening program was still in its early days, and confirmatory tests were not performed on all cases.

The number of WB positive, indeterminate, negative, and missing cases was 942 (49.7%), 212 (11.1%), 660 (34.8%), and 80 (4.2%), respectively. The rate of false-positive results was 14.0% (88/629) in Kyushu and Okinawa prefecture, which are endemic areas in Japan, whereas it was 45.2% (572/1,265) in other areas (Suzuki et al., 2014). The results show that the positive predictive value of any screening assay is low in non-endemic areas and generates a substantial number of false-positive results, highlighting the need for a confirmatory test (Morrison et al., 2015).

Western Bolt is the approach that has been the most frequently used for the confirmatory test. WB measures the serological reaction to both Gag core proteins (p19, p24, and p53) and the Env protein gp46 (WHO News and Activities, 1991). Unfortunately, WB exhibits a high proportion of indeterminate results (Garin et al., 1994; Filippone et al., 2012; Suzuki et al., 2014). Kuramitsu et al. (2017) explored the reasons why WB methods show a high proportion of indeterminate results. They revealed that the maximum proviral load (PVL) in WB-indeterminate samples from pregnant women was 1 copy/100 peripheral blood mononuclear cells (PBMCs), and the median (0.01 copy/100 PBMCs) was approximately 100-fold lower than that of WB-positive samples, as determined by a PCR assay (Kuramitsu et al., 2017). They also reported that the proportion of HTLV indeterminates with detectable provirus was 16.5% (32/194) among pregnant women. Such carrier status may have a very low risk of developing ATL because the PVL is significantly lower than that necessary for the development of the disease (>4 copies/100 PBMCs) (Iwanaga et al., 2010). The authors also observed mutations in the provirus which would interfere with host recognition of HTLV-1 antigens. Thus, they suggested that WB-indeterminate carriers have a low production of viral antigens due to these mechanisms.

Recently, the LIA has been implemented in Japan in replacement of WB. LIA was developed for the serological confirmation and discrimination of HTLV-1 and -2 infection (Zrein et al., 1998). This assay performs well in confirming HTLV-1 seropositivity by exhibiting a low incidence of indeterminate results. Further, the results are in good agreement with PCR results (Sabino et al., 1999; Umeki et al., 2017). It was reported that the number of indeterminate results was reduced by up to 90% when LIA was introduced to replace the WB confirmatory test (Thorstensson et al., 2002). Thus, LIA may be expected to decrease the costs of diagnosis.

However, PCR should be conducted for determining PVL in those cases where the confirmatory tests show indeterminate results. Nowadays, both LIA and qualitative PCR test are covered by the Universal Health Insurance system in Japan as part of the antenatal HTLV-1 screening program. If the PCR qualitative test is negative, it means that there is no infection or that the PVL is below the sensitivity of measurement (<4 copies/10^5PBMCs).

HTLV-1 PREVALENCE AMONG PREGNANT WOMEN

The nationwide prevalence of HTLV-1 infection is generally estimated using blood donor data. Health studies on blood donors can be affected by a selection bias due to the healthy donor effect, in which donors are generally healthier than the general population (Atsma et al., 2011). Thus, the estimated number of HTLV-1 infected people might be underestimated. On the other hand, studies of pregnant women may have a bias in the opposite direction compared to studies of blood donors because of sexual intercourse with infected partner. The seroprevalence of HTLV-1 and HTLV-2 in Western Europe is 6-fold higher among pregnant women (4.4 per 10,000) than that among blood donors (Taylor et al., 2005). Although the two populations were surveyed at different times in Japan, the prevalence rate among women in a 2005–2006 study of blood donors was 6.88 per 10,000 (Satake et al., 2012) compared to 16 per 10,000 for pregnant women in 2011 (Suzuki et al., 2014). More detailed information on prevalence in several countries of HTLV-1 infection in pregnant women is summarized in the review written by Rosadas and Taylor (2019). However, many of these reports are limited to endemic countries and areas.

FEEDING METHODS AS A POSTNATAL PREVENTIVE MEASURE

To date, there have been no randomized controlled trials investigating HTLV-1 MTCT rates by feeding method. All previous reports are observational studies, and the number of cases per study is often small.

Exclusive Formula Feeding

Since the main infection route of HTLV-1 MTCT is breastfeeding, it is reasonable to recommend avoiding breastfeeding. The ATL Prevention Program in Nagasaki revealed a marked reduction of HTLV-1 MTCT by ExFF from 20.3 to 2.5% (Hino, 2011). Nowadays, ExFF has been considered as the most reliable method for MTCT prevention (Ribeiro et al., 2012; Rosadas and Taylor, 2019).

Short-Term Breastfeeding

In Japan, the debate on the use of STBF on MTCT prevention has continued since the 1990s. It has been pointed out that the risk of MTCT is lower in STBF than in longer term breastfeeding (Takahashi et al., 1991; Maehama et al., 1992; Oki et al., 1992; Takezaki et al., 1997; Wiktor et al., 1997; Ureta-Vidal et al., 1999; Takezaki, 2009; Hino, 2011). One of the reasons may be that antibodies against HTLV-1 are transferred from the carrier mother *in utero* and block MTCT for several months after birth (Takahashi et al., 1991). However, the presence of antibodies decreases over the first few postnatal months of life, so HTLV-1 infection may occur when breastfeeding is prolonged. Another reason may be that the cumulative number of infected cells entering the gastrointestinal tract is limited due to short-term breastfeeding. It has been proposed that an infant can ingest a total of 10^8 HTLV-1 infected cells before weaning (Yamanouchi et al., 1985). In contrast, substances contained in breastmilk such as tumor growth factor-β and lactoferrin, which are rich in colostrum (Albenzio et al., 2016; Morita et al., 2018), and prostagrandin E_2 have a promoting effect on HTLV-I replication (Moriuchi and Moriuchi, 2001, 2002; Moriuchi et al., 2001). If STBF could be effective to prevent postnatal MTCT, the antibodies transferred to the fetus *in utero* may overcome the enhanced viral replication during the first few months of life.

The ATL Prevention Program in Nagasaki from 1987 to 2004 showed an 7.4% (15/202) incidence of MTCT in children that were breastfed for <6 months. This was significantly higher than the rate of MTCT on ExFF (2.5%, 29/1,152; $P < 0.001$), but significantly lower than that on longer term (≥6 months) breastfeeding (20.3%, 74/365; $P < 0.001$) (Hino, 2011). Therefore, the ATL Prevention Program in Nagasaki has recommended ExFF for carrier mothers. According to previous studies, the rates of MTCT in children fed by short-term breastmilk during less than 7 months ranged from 3.4 to 9.8%, while ranged from 0 to 6.0% in children fed by exclusive formula. On the other hand, the MTCT rate tends to increase from 11.3 to 25% in longer-term breastfeeding (**Table 1** and **Supplementary Table S1**; Takahashi et al., 1991; Nakayama et al., 1992; Oki et al., 1992; Takezaki et al., 1997; Ureta-Vidal et al., 1999; Hino, 2011).

Several studies have shown that the rates of MTCT with ≤3 months of STBF ranged from 0 to 8.5% (**Table 2** and **Supplementary Table S2**; Hirata et al., 1992; Ureta-Vidal et al., 1999; Kashiwagi et al., 2004; Takezaki, 2009; Moriuchi et al., 2017), while ranged from 0 to 12.8% in children fed by exclusive formula. On the other hand, the MTCT rate ranged from tends to increase from 5 to 28.6% in longer-term breastfeeding. Hirata et al. showed that the prevalence of HTLV-l antibody among

TABLE 1 | Comparison of mother-to-child transmission rates by exclusive formula feeding, short-term breastfeeding (<7 months) and longer-term breastfeeding.

Author, year	Study area	Study period	Exclusive formula feeding	Short-term breast feeding		Longer-term breastfeeding		Study design
			Seroconversion n/N (%)	Inclusion	Seroconversion n/N (%)	Inclusion	Seroconversion n/N (%)	
Takahashi et al., 1991	Kagoshima, Japan.(13 hospitals)	1985–1990	0/0 (0%)	≤6 months	3/67 (4.5%)	>6 months	19/136 (14.0%)	Retrospective
Takahashi et al., 1991	Kagoshima, Japan.(13 hospitals)	1986–1990	9/151 (6.0%)	≤6 months	1/23 (4.3%)	>6 months	1/3 (33.3%)	Prospective
Nakayama et al., 1992	Kagoshima, Japan.(single center survey)	1986–1990	1/53 (1.9%)	≤6 months	4/41 (9.8%)	7–12 months	7/50 (14.0%)	Retrospective
Oki et al., 1992	Kagoshima and Miyazaki, Japan	1986–1990	0/7 (0%)	<7 months	3/67 (4.5%)	≥7 months	19/136 (14.0%)	Retrospective
Oki et al., 1992	Kagishima and Miyazaki, Japan	1986–1991	10/177 (5.6%)	<7 months	1/26 (3.8%)	≥7 months	1/4 (25.0%)	Prospectiver
Takezaki et al., 1997	Tsushima and Kamigoto, Nagasaki, Japan	1985–1991	4/162 (2.5%)	≤6 months	2/51 (3.9%)	>6 months	13/64 (20.3%)	Retrospective
Ureta-Vidal et al., 1999	French Guyana	1989-NA	0/23 (0%)	≤6 months	2/32 (3.4%)	>6 months	17/151 (11.3%)	Retrospective
Hino, 2011	Nagasaki, Japan	1987–2004	29/1,152 (2.5%)	<6 months	15/202 (7.4%)	≥6 months	74/365 (20.3%)	Retrospective

NA: not applicable.

children breastfed for over 3 months was significantly higher (16/28, 27.6%) than that of those breastfed for under 3 months (2/39, 5.1%; P = 0.012; Hirata et al., 1992). Based on these reports, some healthcare providers in Japan considered that STBF for up to 3 months is unlikely to increase the risk of MTCT and have therefore recommended STBF for ≤3 months if the carrier mother eager to breastfeed her infant. However, there is insufficient evidence for this speculation because almost these reports had the small sample size of studied children and the risk of bias due to selections of participants, confounding variables, and incomplete outcome data. And, it is unclear whether the risk of MTCT is clearly increased between 4 and 6 months. Further study is needed on the protective effects of STBF on MTCT.

As children with longer duration of breastfeeding have higher rates of MTCT (Rosadas et al., 2018), it should be noted that MTCT rate in the longer-term breastfeeding group depends on the distribution of breastfeeding duration in the included subjects.

Frozen-Thawed Breastmilk Feeding

There are very few studies evaluating the incidence of MTCT when using FTBMF. Ando et al. (1989) observed that infected cells in breast milk were effectively destroyed *in vitro* due to the process of freezing and thawing. The rate of MTCT on FTBMF in previous studies ranged from 0 to 7.1% (Ando et al., 1989, 2004; Maehama et al., 1992; Ekuni, 1997). Only two studies compare the effect of ExFF with that of FTBMF on the prevention of MTCT (**Table 3** and **Supplementary Table S3**; Maehama et al., 1992; Ekuni, 1997). It however remains unclear whether FTBMF is effective in preventing MTCT because of the limited number of studies and participants.

Other Feeding Methods

Regardless of its duration, breastfeeding may also be combined with the use of infant formula. In recent studies of MTCT of HIV, MTCT rates with ordinary breastfeeding and ExFF were 2.70 and 3.77%, respectively, compared to 20.0% with mixed feeding (Njom Nlend et al., 2018). It is speculated that mixed feeding may cause gastrointestinal mucosal injury or dysbiosis, which may involve changes in intestinal permeability (O'Sullivan et al., 2015). However, to date, there is no evidence to inform mixed feeding recommendations to HTLV-1 carrier women, and further studies on the impact of mixed feeding on HTLV-1 MTCT are warranted.

STRATEGY FOR PREVENTION AGAINST HTLV-1 MTCT

Even after the national antenatal HTLV-1 antibody screening test began in 2010, healthcare providers in each prefecture were instructing carrier mothers to choose among ExFF, STBF, and FTBMF for the next 5 years. However, within the same endemic area in Kyushu, Japan, STBF during ≤3 months or ExFF has been recommended in Kagoshima Prefecture (Nerome et al., 2014), while ExFF has been recommended mainly in Nagasaki Prefecture (Hino et al., 1994; Moriuchi et al., 2013). The selection

TABLE 2 | Comparison of mother-to-child transmission rates by exclusive formula feeding, short-term breastfeeding (≤3 months) and longer-term breastfeeding.

Author, year	Study area	Study period	Exclusive formula feeding	Short-term breastfeeding (≤3 months)		Longer-term breastfeeding		Study Design
			Seroconversion n/N (%)	Inclusion	Seroconversion n/N (%)	Inclusion	Seroconversion n/N (%)	
Ureta-Vidal et al., 1999	French Guyana	1989-NA	0/23 (0%)	≤3 months	1/12 (8.3%)	>3 months	18/168 (10.7%)	Retrospective
Hirata et al., 1992	Ishigaki island, Okinawa, Japan	1989–1991	10/78 (12.8%)	≤3 months	2/39 (5.1%)	>3 months	16/58 (21.6%)	Retrospective
Kashiwagi et al., 2004	Okinawa, Japan	1995–1999	1/31 (3.2%)	≤3 months	1/25 (4.0%)	>3 months	1/20 (5%)	Prospective
Takezaki, 2009	Kagoshima, Japan	1986–2006	16/331 (4.8%)	≤3 months	2/126 (1.6%)	>3 months	9/46 (19.6%)	Retrospective
Moriuchi et al., 2017	Nagasaki, Japan	2011–2017	4/91 (4.4%)	≤3 months	3/35 (8.5%)	>3 months	6/21 (28.6%)	Retrospective

NA: not applicable.

TABLE 3 | Comparison of mother-to-child transmission rates by exclusive formula feeding, frozen-thawed breastmilk feeding and breastfeeding.

Author, year	Study area	Study.period	Exclusive formula feeding	Frozen-thawed breast milk feeding		Breastfeeding		Study Design
			Seroconversion n/N (%)	Inclusion	Seroconversion n/N (%)	Inclusion	Seroconversion n/N (%)e	
Maehama et al., 1992	Okinawa, Japan	1986–1989	0/46 (0%)	12 h freezing in a home freezer	2/26 (7.7%)	0–4 months	4 (4.2%)	Retrospective
						5–8 months	2 (7.4%)	
						9–12 months	1 (4.2%)	
						≥13 months	3 (16.7%)	
Ekuni, 1997	Okinawa, Japan	1983–1984	5/108 (4.6%)	12 hfreezing at −20°C	0/33 (0%)	NA	13 (41.9%)	Retrospective

NA: not applicable.

of feeding methods by the carrier pregnant women is most likely influenced by the opinions of the healthcare providers. Therefore, we designated the strategies for prevention of HTLV-1 MTCT (**Figure 2**) in the manual of nationwide antenatal HTLV-1 screening program with the support of the Ministry of Health, Labor, and Welfare in 2016 (Itabashi, 2016). In this strategy, ExFF should be prioritized with the view to prevent postnatal MTCT. The STBF during ≤3 months rather than <7 months would be better to be selected if the mother is eager to breastfeed. However, it is important that mothers and family members fully understand an increase in MTCT risk with increased duration of breastfeeding and an insufficient evidence of this feeding method. Thus, a support system to help mothers to refrain from breastfeeding after 3 months of life may be necessary. There are few studies on the risk of MTCT by FTBMF compared to ExFF, and there is little evidence to recommend this feeding method. Considering the efforts needed by mothers in preparing frozen-thawed breastmilk represents every day, it may be better to use it only for preterm infants staying in newborn intensive care units. To date, there are no reports on the risk of MTCT by mixed feeding, which should be considered in the future.

ISSUES NEEDED TO MAXIMIZE THE EFFECTS OF THE NATIONWIDE SCREENING PROGRAM

In Japan, HTLV-1 antibody testing is mandatory along with testing for other infectious diseases during health checkups

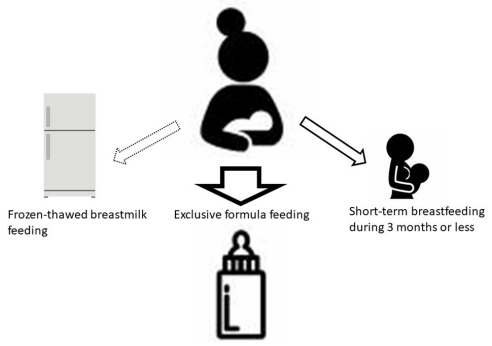

FIGURE 2 | Selection of feeding methods. Due to the well-established evidence, ExFF should be the first choice for postnatal prevention of MTCT. If a carrier mother strongly desires to breastfeed, STBF during 3 months or less would be better to be selected. Health care providers should support her to avoid longer-term breastfeeding because prolonged periods may increase the risk of MTCT. There are few studies on the effects of FTBMF compared to ExFF. For preterm low birth weight infants, FTBMF using own mother's milk during tube feeding would be better to be selected in consideration of reducing the risk of severe infections and necrotizing enterocolitis. Currently, the breast milk banking system is not available in Japan, but banked human milk is the best choice when it becomes available. ExFF, exclusive formula feeding; STBF, short-term breastfeeding; MTCT, mother-to-child transmission; FTBMF, frozen-thawed breastmilk feeding (Itabashi, 2016).

for pregnant women. Although there is no specific data on the implementation rate, it is likely that most pregnant women have been tested for HTLV-1 antibody screening, except for those who have never undergone a prenatal checkup. There are several issues not only selection of feeding methods to prevent HTLV-1 MTCT but also the others to succeed the nationwide antenatal screening program and need to be solved in the future (**Table 4**). We have already discussed the selection of feeding methods, so we will discuss other issues here.

Evaluation of Effect of Mother Screening on MTCT Prevention

It remains unknown whether the introduction of the screening program in Japan has contributed to a reduction in MTCT incidence at present. For this, it is necessary to examine whether children born to infected mothers become carriers. Our 2016 manual recommended to perform antibody testing in children born to carrier mothers at 3 years of age (Itabashi, 2016) because no seroconversion has been reported beyond that age (Kusuhara et al., 1987; Nyambi et al., 1996). Earlier diagnosis by serological or molecular method has been proposed (Rosadas and Taylor, 2019), but there may be little clinical advantage even if HTLV-1 infection is diagnosed.

Serological testing is not mandatory in the current screening program in Japan. A nationwide system for collecting and evaluating the results of MTCT rates in these children has not yet been established. From a public health perspective, antibody testing should be recommended for all children born to infected pregnant women. This will reveal more reliable data on the relationship between the selected feeding method and MTCT rates, and will allow us to verify the effects of introducing this screening program in Japan. On the other hand, the infected children are often asymptomatic during childhood and have difficulties predicting future HTLV-1 associated diseases at present. If future studies could predict the risk of HTLV-1-associated diseases and prevent these diseases in infected children, more children will be tested for antibodies. Healthcare providers explain the purpose of antibody testing at 3 years of age to carrier mothers using the following arguments: (1) Identification of children as carriers will allow minimization of transmission to sexual partners in the future; and (2) If you know that your child is a carrier, you will have immediate access to information when effective treatment strategies for ATL and HAM/TSP become available in the future.

TABLE 4 | Issues needed to maximize the effects of the nationwide screening program.

Issues	Countermeasures
Selection of feeding methods	Establishment of evidence on the prevention of MTCT by STBF and FTBMF
Evaluation of effect of mother screening on MTCT prevention	To increase the rate of antibody testing after 3 years of age
Public awareness	Necessary for patient groups, scientists, clinicians, and policy makers to work together to raise public awareness about HTLV-1 infection.
Support for carrier mothers	Establishment of adequate support system for carrier mothers in each prefecture
Elimination or reduction of the benefits obtained by breastfeeding	Establishment of evidence on the prevention of MTCT by STBF and FTBMF, and development of preventive measures except for feeding methods
Very low birth weight and/or very preterm infants	Banked human milk or FTBMF
Infection during pregnancy and breastfeeding after antenatal screening test	To use a contraceptive (condom)
Delivery of pregnant women who did not test antibodies during pregnancy	To test HTLV-1 antibody for these mothers as soon as possible. In the case there is an infected sibling due to MTCT, the use of infant formula may be an option to minimize the postnatal MTCT risk until the test results are obtained.

MTCT: mother-to-child transmission, STBF: short-term breastfeeding, FTBMF: frozen-thawed breastmilk feeding.

Public Awareness About HTLV-1 Infection

While a few patients have severe symptoms, most infected individuals remain asymptomatic throughout their lives and their infections may be unknown to many health providers. In addition, healthcare providers except for specialists have little experience with HTLV-1-associated diseases, and residents have little knowledge about the virus in non-endemic areas. However, as mentioned in an open letter to WHO, "HTLV-1 remains a strong threat to individual and community health, and even more so to global health because of the accelerated rate of human migration in recent times" (Martin et al., 2018). Although the nationwide antenatal HTLV-1 antibody screening program has been conducted, public awareness about HTLV-1 infection except in endemic areas still seems to be low in Japan.

Support for Virus Carrier Mothers

Rocha-Filho and Goncalves (2018) showed both symptomatic and asymptomatic patients with HTLV-1 experienced more anxiety and depression than uninfected patients. In contrast, a study comparing HTLV between antibody positive and negative individuals do not support a biologic role for HTLV in the pathogenesis of depression and anxiety (Guiltinan et al., 2013). There is no consensus on the cause of the elevated risk of these mental disorders in HTLV-1 infected patients.

According to an interview with thirteen infected people conducted by Zihlmann et al. (2012), they stated that HTLV-1 is a largely unknown infection to society and healthcare providers due to health care providers' inadequate responses.

These investigators speculated as follows: "The diagnosis of HTLV-1 can remain a stigmatized secret as patients deny their situations. As a consequence, the disease remains invisible and there are potentially negative implications for patient self-care and the identification of infected relatives" (Zihlmann et al., 2012). It is presumed that carrier mothers may be a similar situation when they could not have sufficient support.

Little is known about the impact of the diagnosis on the mother's emotional state (anxiety and depression), their delivery experience or the mother–infant bonding, and the relationship between the mother and her family (Rosadas and Taylor, 2019). Recent systematic review represents that breastfeeding duration is associated with postpartum depression in almost all studies. And, postpartum depression is predicted by breastfeeding cessation in several studies (Dias and Figueiredo, 2015). Therefore, it is assumed that the risk of anxiety or depression may increase in the mothers who selected ExFF or STBF not only during pregnancy but also postpartum. The Ministry of Health, Labor and Welfare has requested that prefectural governments establish a support system for carrier mothers. Carrier mothers are also concerned about their own risk for onset of ATL and HAM/TSP in the future. Carrier mothers with the risk of HTLV-1-associated diseases should be referred to a specialist physician (Ishitsuka et al., 2015).

Elimination or Reduction of the Benefits Obtained by Breastfeeding

In developed countries, it may be possible to adopt ExFF safely for MTCT prevention because the sanitation environment is up to date. On the other hand, infants and children who have received longer term breastfeeding have lower infectious morbidity and mortality, fewer dental malocclusions, and higher intelligence than those who have been breastfed for a shorter period, or not at all. This inequality persists until later in life. Growing evidence also suggests that breastfeeding might protect against a tendency to be overweight and to develop diabetes later in life (Victora et al., 2016). A meta-analysis concluded that breastfeeding duration of at least 2 months after birth is associated with half the risk of sudden infant death syndrome. Breastfeeding does not need to be exclusive to confer this protection (Thompson et al., 2017). However, infants and children fed exclusively by infant formula may not get these benefits provided by breastfeeding.

Several risk factors for HTLV-1 MTCT other than long-term breastfeeding are known, including high mother HTLV-1 antibody titers and PVL (Ureta-Vidal et al., 1999; Hisada et al., 2002; Paiva et al., 2018). Paiva et al. (2018) reported that breastfeeding ≥12 months, higher maternal PVL (≥ 100 copies/10^4 PBMC) and ≥ 2 previous HTLV-1-infected children were independently associated with MTCT in a multiple logistic regression. Hisada et al. (2002) suggests that mothers who have a high PVL (≥ 3%) should be encouraged not to breast-feed, while a risk of the transmission in low PVL less than 0.1% was negligible. Li et al. (2004) reported that PVL in breastmilk, which is correlates maternal PVL, is a strong predictor of risk of MTCT. However, Rosadas and Taylor (2019) mentioned that PVL in breastmilk may not be suitable because lymphocytes in breastmilk are not be main cellular population. If the infants born to only pregnant women with a high PVL would be subjected to complete formula feeding, the number of the infants fed by formula could be reduced. In order to prove this hypothesis, it would be better to conduct investigation using the antenatal HTLV-1 antibody screening program in Japan.

In the future, should it become possible to use risk factors to clearly predict the risk of MTCT, it may be possible to reduce the number of children recommended to have breastfeeding avoided or limited.

Preventive Measures Other Than Feeding Methods

Since the 1990s, ExFF has been used as the main method to prevent postnatal MTCT. Considering the psychosocial influences carrier mothers are subjected to and the potential health risks in their infants and children associated with either completely avoiding or restricting breastfeeding, the development of additional preventive MTCT strategies such as vaccine or antiviral regimens should be developed in the future.

In animal experiments, it was reported that the administration of HTLV-1 antibody (Kuo et al., 2011; Fujii et al., 2016; Murakami et al., 2017) and the use of polyanionic microbicides are effective in preventing MTCT (Romer et al., 2009), but they are not ready for human use yet.

Very Preterm and/or Very Low-Birth-Weight Infants Born to Carrier Mothers

The potential for viral transmission from mother to child presents a dilemma on how best to interpret the benefits and risks of breastfeeding in different settings (Prendergast et al., 2019). Meta-analysis has shown that feeding with the mother's own milk or banked human milk can reduce the risk of necrotizing enterocolitis and/or severe infections, especially for very low-birth-weight infants (<1,500 g birth weight) or very preterm infants (<32 weeks of gestation) (Corpeleijn et al., 2016; Miller et al., 2018). Therefore, the most rational approach would be to feed banked human milk to infants born to carrier mothers for preventing not only necrotizing enterocolitis and/or severe infections but also HTLV-1 MTCT. Unfortunately, to date no human milk bank system exists in Japan. Although there is little evidence on the effect of FTBMF on the prevention of MTCT after birth, FTBMF instead of banked human milk may be the second best option because of the risk of mortality and morbidities caused by formula feeding during newborn intensive care unit admission. HTLV-1 antibodies transferred *in utero* from carrier pregnant women may offer insufficient protection in very preterm and/or very-low-birth-weight infants. We assume that FTBMF may be safer than feeding with the mother's own milk without any treatment. However, there are few studies on MTCT in these infants to support this hypothesis.

Pitfalls of the Nationwide Screening Program

A pregnant woman with a negative result may become infected from sexual contact with a HTLV-1-infected partner after the screening test, in which case the child could become infected by long-term breastfeeding (Nerome and Kawano, 2017). If you already know that your sexual partner is an HTLV-1 carrier, you may use a contraceptive (condom), especially during pregnancy and breastfeeding.

Not all pregnant women may have been screened for HTLV-1 antibodies during pregnancy, in which case serological antibody testing for such a woman should be performed after delivery. It is unclear whether breastfeeding during a very short period of time before the mother's test results are obtained will increase the risk of MTCT after birth. In the case there is an infected sibling due to MTCT, the use of infant formula may be an option to minimize the postnatal MTCT risk to the newborn infant until the test results are obtained. Later, if the mother proves to be a carrier, the healthcare provider should discuss feeding methods with her.

Follow-up of the Infected Children

Adult T-cell leukemia is generally known to be occurred in individuals with vertical infection via mainly prolonged breastfeeding, and HAM/TSP to be occurred in individuals infected via sexual intercourse or blood transfusion during adulthood. Owing to the long latency of the virus, mean onset age in ATL is 66.0 years old (Iwanaga et al., 2012). The average age of HAM/TSP diagnosed is 40 years old (Nakagawa et al., 1995).

However, several studies suggested that children infected via MTCT present with higher risk of developing ATL and/or HAM/TSP in Latin America (Murphy et al., 1989; Kendall et al., 2009; Oliveira et al., 2017). Kendall et al. (2009) showed that abnormal neurological findings (clonus and lower extremity hyperreflexia) were common in Peruvian children infected with HTLV-1. The data also suggested that persistent hyperreflexia of the lower extremities may be an early sign of HTLV-1-associated neurological involvement in children. Additionally, several cases were coprevalent with infective dermatitis. Maloney et al. (2003) reported that the childhood skin diseases associated with HTLV-1 can include seborrheic dermatitis and eczema. Oliveira et al. (2017) reviewed studies about early onset HTLV-1-associated diseases that together included 27 HAM/TSP cases and 31 ATL cases. Age at diagnosis ranged from 3 to 18 years and from 2 to 18 years for HAM/TSP and ATL cases, respectively. Interestingly, about half of HAM/TSP cases were associated with infective dermatitis. Although how the incidence of symptoms varies by age in infected children remains unknown, skin abnormalities such as seborrheic dermatitis and eczema and neurological abnormalities may appear at as early as 2 to 3 years of age. Knowing in advance that a child is a carrier would allow healthcare providers to ensure early detection of HAM/TSP and ATL. Therefore, provision of such information to the carrier mother may be helpful in encouraging antibody testing at 3 years of age or regular visits to the clinic. In addition, follow-up of MTCT pediatric carriers may help elucidate the mechanisms underlying the future development of ATL and HAM/TSP.

It remains unclear whether the association of skin lesions with HAM/TSP in HTLV-1 infected children is unique to Latin America due to a lack of studies in Japan. Yoshida et al. reported that disease onset was before 15 years of age in 10% of HAM/TSP patients in Japan (Yoshida et al., 1993). These patients shared common features of short stature and slight intellectual disability, and three of them had pseudoparathyroidism. However, no obvious signs of childhood leading to the development of HAM/TSP or ATL have been observed after their report. Therefore, little attention has been paid to symptoms in MTCT-infected children in Japan. In the future, it is desirable that antibody testing at the age of 3 is more widely performed in children born to carrier pregnant women and allow early detection of HTLV-1-associated symptoms and diseases by follow-up study.

As most infected children are asymptomatic, clinic consultation intervals and points of attention at the time of the consultation are unclear. In addition, considering the psychological effects on children, there is some debate about how old it is to be notified them to be infected. Thus, discussions are needed on how to follow up the infected children.

CONCLUSION

In Japan, an antenatal HTLV-1 antibody screening program has been implemented on a nationwide scale for preventing MTCT of the virus. Pregnant women tested positive on a confirmatory or PCR test are identified as HTLV-1 carriers. Since the main infection route of HTLV-1 MTCT is breastfeeding, it is reasonable to recommend avoiding breastfeeding. Nowadays, ExFF has been considered as the most reliable method for MTCT prevention. The STBF during $\leq$3 months is considered if the mother is eager to breastfeed her child. However, it is important that mothers and family members fully understand not only an increase in MTCT risk with increased duration of breastfeeding but also having an insufficient evidence. As there are only a few clinical studies on the protective effect of frozen-thawed breastmilk feeding on MTCT of HTLV-1, there is little evidence to recommend this feeding method. Further study on the protective effects of STBF and FTBMF are needed.

It is assumed that the risk of anxiety or depression may increase in the mothers who selected ExFF or STBF not only during pregnancy but also postpartum. Thus, not only to provide an adequate support and counseling for these mothers in various fields but also to raise public awareness of the risks and prevention methods of HTLV-1 infection is urgently necessary. As most infected children are asymptomatic, further study is needed on how to follow up them.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, contributed to manuscript revisions, read and approved the submitted version. KI wrote the first draft of the manuscript.

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SUPPLEMENTARY MATERIAL

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Implementation of nationwide screening of pregnant women for HTLV-1 infection in Japan: analysis of a repeated cross-sectional study

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Abstract

Background: Screening of pregnant women carrying human T-lymphotropic virus type 1 (HTLV-1) has a crucial role in reducing the number of HTLV-1 carriers. A national HTLV-1 screening program for pregnant women was started in 2011 in Japan. The purpose of this study is to report on the implementation of this nationwide screening program.

Methods: This was a retrospective repeated cross-sectional study. We used datasets from surveys of HTLV-1-antibody-positive pregnant women performed by the Japan Association of Obstetricians and Gynecologists in 2011, 2013, and 2016. Outcomes for evaluation included the number of persons (pregnant women) who conducted the screening test, the number of positive persons (women) identified by these tests, and the proportion of positive persons to the number of persons (women) who conducted the tests.

Results: Numbers of target facilities changed yearly: 1857 in 2011, 2544 in 2013, and 2376 in 2016. The mean number of screening-test participants increased per facility, but the median increased or decreased. The mean number of positive individuals identified decreased. Multivariate analysis results revealed the number of screenings was slightly reduced yearly, although areas (Kanto and Kinki) and high volume in facility types increased. Regarding the positive rates, some areas (Hokkaido/Tohoku, Kanto, and Chugoku/Shikoku) exhibited decreases or increases by facility type. The number of western blotting (WB) implementations decreased in 2016, positive rates identified by WB decreased in 2016 in all areas, and the number of facility types increased. The number of PCR participants increased in 2016 in Kanto and Kinki, but a decrease in facility type was observed. Positive rates were decreased in all areas (except the central region) but facility types were increased.

Conclusions: The nationwide screening program for HTLV-1 in Japan was almost fully implemented. However, regional variations in screening tests were observed during this implementation. Thus, some incentives are needed to encourage proper implementation across all regions.

Keywords: Human T-lymphotropic virus type 1, Pregnant, Screening

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Background

Human T-lymphotropic virus type 1 (HTLV-1) infects lymphocytes, a type of white blood cell. HTLV-1 causes adult T-cell leukemia/lymphoma, HTLV-1-associated myelopathy, HTLV-1 uveitis [1], and infective dermatitis [2]. Although these HTLV-1-related diseases can develop in HTLV-1-infected persons, most patients are asymptomatic carriers [1].

HTLV-1 is endemic in areas such as southwestern Japan, the Caribbean, Central and South America, intertropical Africa, and the Middle East [3]. HTLV-1 is sexually, parenterally, and vertically transmissible [4]. Detection of pregnant women carrying HTLV-1 is crucial for reducing the number of HTLV-1 carriers because HTLV-1 is primarily transmitted vertically from mother to child. If this epidemiological trend remains, the implementation of a prenatal screening program will be an important public policy in Japan. This must be reinforced by the authors. Mother-to-child transmission (MTCT) of HTLV-1 occurs mainly via breast milk and refraining from breastfeeding was shown to be effective at reducing MTCT [5–8]. An epidemiological study in Japan reported that breastfeeding was the main route of HTLV-1 transmission [9]. Indeed, the expected outcome of withholding breastfeeding is a reduction of the MTCT rate from 15 to 20% to 2–3% [6]. Because ATL likely develops after a long incubation period of more than 20 years in HTLV-1 carriers via MTCT, the prevention of milk-borne transmission is the most efficient and feasible way to reduce the disease burden.

In Japan, HTLV-1 carriers and individuals with related diseases are particularly prevalent in the southwest region, including Kyushu and Okinawa. However, surveys performed in 2006 and 2007 revealed that carriers have migrated to areas within large cities [10–13]. In response, the Ministry of Health, Labour and Welfare (MHLW), Maternal and Child Health Section passed a notice in November 2010 for an HTLV-1 antibody screening test for pregnant women, which was initiated in 2011.

The purpose of this study was to report on the implementation of the nationwide screening for HTLV-1 in pregnant women conducted since 2011.

Methods

Nationwide screening and tests

The Japanese MHLW decided to financially support blood testing for the screening of HTLV-1 in pregnant women in 2010. Specifically, the migration of Japanese people from Kyushu to metropolitan areas was thought to contribute to a significant decrease in HTLV-1 carriers in Kyushu and an increase in Kanto (including Tokyo). Local prefectural governments were responsible for the implementation of the screening. The local governments collaborated with stakeholders and endorsed the screening program. Japanese Clinical Guidelines for Obstetric Practice (edited in 2011 by the Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists) recommended carrying out a screening test for anti-HTLV-1 antibody using particle agglutination (PA) or chemiluminescent enzyme immunoassay (EIA) with western blotting (WB) and/or polymerase chain reaction (PCR) confirmation in all pregnant women [14, 15]. The screening test is performed during early-to-middle pregnancy (up to around 30 weeks of pregnancy). If the screening test is negative, the pregnant woman is judged to be a non-infected person. If the screening test is positive, the individual might be a carrier; therefore, a confirmation test via WB method is always performed. It is recommended that the PCR method be performed if the WB method is suspended, and it was listed as part of the national health insurance in April 2016. The PCR-positive rate of the decision holder was estimated to be about 20%.

Serological screening via EIA or PA tests has been used to detect HTLV-1 antibodies in all pregnant women in Japan at the expense of the Japanese public fund since September 2010. If the result of the screening is positive, confirmatory testing by WB can be performed to eliminate false-positive reactions, which is covered by the Universal Health Insurance system. This is important because a considerable number of tests had a false-positive result by EIA or PA screening tests. Diagnosis as an HTLV-1 carrier can be determined only after a confirmatory test (WB test); however, a polymerase chain reaction (PCR) test is also available (at one's own expense) to further refine the diagnosis. In uncertain serological consultations, PCR analysis can provide a definitive diagnosis of infection.

Diagnosis as an HTLV-1 carrier can usually be determined after the confirmation test (WB test) following a serological screening test performed for all women during pregnancy in Japan since September 2010. According to the Guidelines for Obstetrical Practice in Japan published in 2011, these methods are advised for HTLV-1-positive pregnant women to prevent vertical transmission [14, 15].

Study design and data collection

This was a retrospective repeated cross-sectional study. We used data from three surveys for HTLV-1-antibody-positive pregnant women performed by the Japan Association of Obstetricians and Gynecologists (JAOG) [16–18]. The three questionnaire surveys were administered in 2011, 2013, and 2016 (April 2016–March 2017) by the Japanese Association of Gynecologists including head obstetrics and gynecologists in all 47 prefectures in Japan (Fig. 2). Target medical facilities that performed

the screening test certified by the Japanese Association of Gynecologists were included in the survey. Data from hospitals included information of the region, not the prefecture, to protect the hospital information. Japan had six regions as follows; Hokkaido and Tohoku, Kanto (including Tokyo), Chubu and Tokai, Kinki, Chugoku and Shikoku, and Kyusyu. Three questionnaire surveys were conducted by the JAOG in 2011, 2013, and 2016 (April 2016 to March 2017). All medical facilities that handled the delivery of the questionnaire surveys were included in the survey. Analyses from each survey were reported elsewhere [16–18]. Outcomes for evaluation included the coverage of screening (number of persons who conducted the screening test/number of total pregnant cases), the number of positive persons identified by these tests, and the proportion of positive persons to the number of persons who performed the tests. Unfortunately, the survey contained no data regarding the total number of pregnant women in a hospital. Alternatively, we calculated the total number of pregnant women by region from vital statistics (supplement file 1) [19]. Then, we calculated the coverage of screening by region but not by hospital. We originally drew the map in Japan with our survey data and vital statistics in public by free license software. (Shirochizu nuri-nuri: https://n.freemap.jp/) (figure1) The study was approved by the ethics committee of the JAOG. We have reported this report in accordance with STROBE statement (supplement file 2) [20].

Statistical analysis

The number of target facilities, number of screening facilities, number of people who carried out the test method, and number of positive individuals are summarized according to annual regional area and type of units. We performed multivariate Poisson's regression with a generalized estimating equation to examine the impact on these covariates [21]. Rate ratios, 95% confidence intervals, and *p*-values were calculated. Denominator of the outcome variable as pregnant women or number of people who carried out the test method were included as the offset in the model. Because this research was exploratory, the priorities of outcomes were not set in the analysis. The significance level of *p*-values was set to 5% on both sides as supplementary information. All data were analyzed using SAS version 9.4.

Results

Numbers of target facilities changed yearly: 1857 in 2011, 2544, in 2013, and 2376 in 2016 (Fig. 1). However, the configuration of facilities was similar in the 2013 and 2016 surveys. Moreover, the regional composition was similar in all surveys. The numbers of facilities that implemented screening changed yearly: 1779 facilities (95.8%) in 2011, 1367 (53.7) in 2013, and 1742 (73.3) in 2016 (Table 1). The change in screening coverage is shown by regions on a map of Japan (Fig. 2). The mean number of screening test participants increased per facility, but the median increased or decreased. The number of positive individuals was similar. For the WB method, the number of practitioners and number of positive individuals tended to decrease after 2011, with approximately one positive person per center. The PCR method had a high mean number of practitioners in 2016, but because only one facility performed PCR with many practitioners, the median did not change. The number of positive individuals identified by PCR was approximately 0.5 at this facility (Table 2).

By multivariate analysis, areas (Kanto and Kinki) and facility types showed slightly increased screening

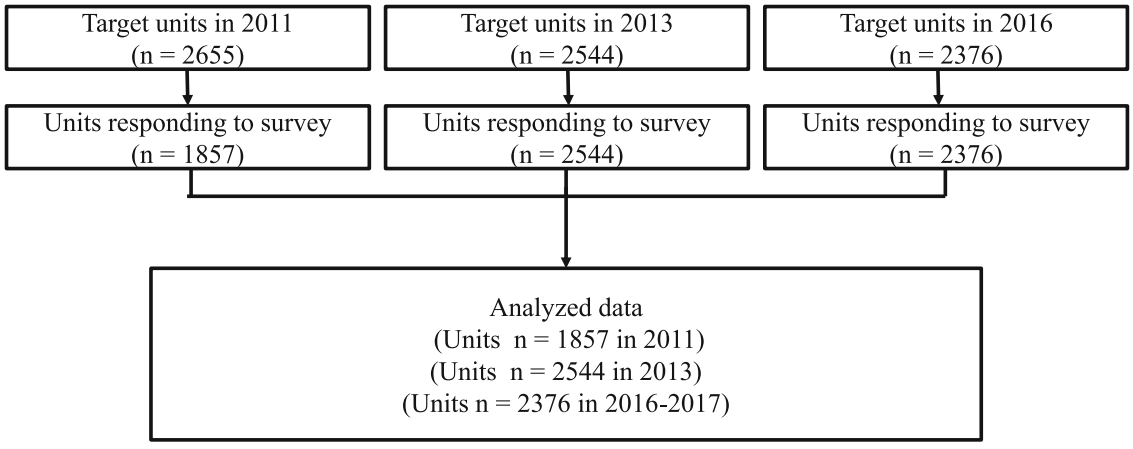

Fig. 1 Study data flow

Table 1 Characteristics of hospitals and clinics, n (%)

Year	2011			2013			2016		
	Target	Screening	S/T (%)[a]	Target	Screening	S/T (%)[a]	Target	Screening	S/T (%)[a]
Total of units	1857	1779	95.8	2544	1367	53.7	2376	1742	73.3
Units									
High-volume hospital	258 (13.9)	252	97.7	1091 (42.9)	572	52.4	1041 (43.8)	731	70.2
Middle- and low-volume hospitals and clinics	1599 (86.1)	1527	95.5	1453 (57.1)	795	54.7	1335 (56.2)	1011	74.6
Region									
Hokkaido, Tohoku	225 (12.1)	217	96.4	305 (12.0)	156	51.1	275 (11.6)	190	69.1
Kanto	459 (24.7)	443	96.5	661 (26.0)	314	50.5	634 (26.7)	441	69.6
Chubu, Tokai	367 (19.8)	352	95.9	494 (19.4)	273	55.3	456 (19.2)	340	74.6
Kinki	284 (15.3)	274	96.5	412 (16.2)	236	57.3	385 (16.2)	286	74.3
Chugoku, Shikoku	209 (11.3)	198	94.7	270 (10.6)	154	57.0	247 (10.4)	182	73.7
Kyusyu, Okinawa	313 (16.9)	295	94.2	402 (15.8)	234	58.2	379 (16.0)	296	78.1

[a]S/T (%): (n of screening hospitals and clinics/n of target hospitals and clinics) × 100

coverage although screening coverage in other areas (Kanto and Chubu) decreased. Positive rates were decreased in some areas (Hokkaido/Tohoku, Kanto, and Chugoku/Shikoku) and positive identification increased by facility type. Numbers of WB performed were decreased in 2016 and the positive identification rate was lower in 2016 for all areas; however, facility types were increased. The number of PCR participants was markedly increased in 2016 in Kanto and Kinki; however, the facility types were decreased. The positive identification rate for PCR decreased in all areas (except the Chubu region) but facility types were increased (Tables 3, 4 and 5).

Discussion

The study evaluated the national implementation of HTLV-1 screening in Japan. To the best of our knowledge, this is the first nationwide routine screening of pregnant women for HTLV-1 infection. The HTLV-1

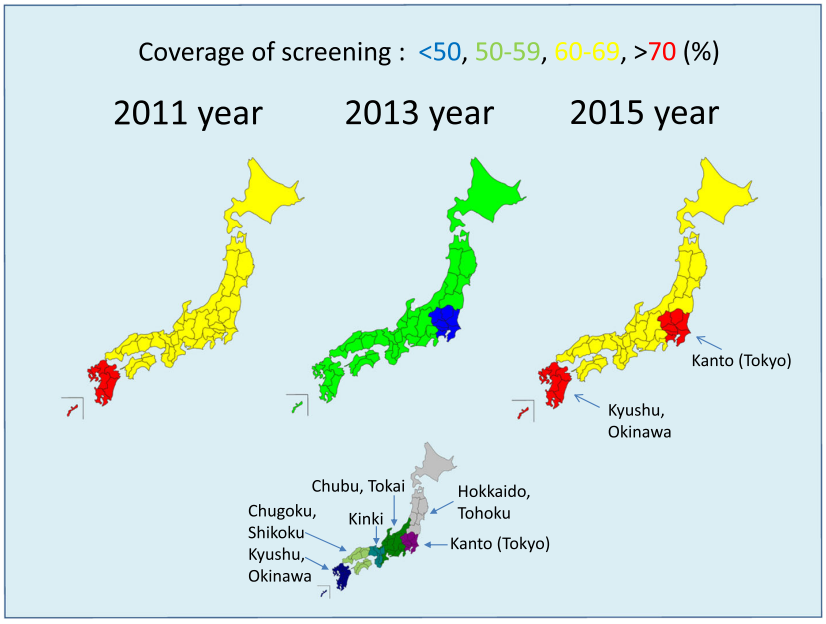

Fig. 2 Map of screening proportion of pregnant women by region in Japan (%). The map was created by software (Shiro-chizu nuri-nuri) using our survey data and public vital statistics in Japan

Table 2 Annual change in the number of positive individuals by test per unit

Target	n of units	2011	2013	2016
		1857	2544	2375
Screening	n of units (%)	1779 (95.8)	1367 (53.7)	1742 (73.3)
Tested	Mean (SD) Median (interquartile)	388.9 (387.0) 309.0 (175–502)	397.8 (311.6) 286 (194–502)	400.2 (348.2) 320.5 (195–509)
Positive	Mean (SD) Median (interquartile)	2.0 (20.4) 0 (0–1)	1.7 (14.7) 0 (0–2)	1.6 (12.2) 0 (0–2)
WB	n of units (%)	803 (43.2)	860 (33.8)	1699 (71.5)
Tested	Mean (SD) Median (interquartile)	13.1 (73.1) 1 (1–3)	5.9 (47.2) 1 (0–3)	5.9 (44.2) 0 (0–2)
Positive	Mean (SD) Median (interquartile)	1.2 (3.9) 1 (0–1)	1.0 (1.7) 1 (0–1)	0.5 (1.4) 1 (0–1)
PCR	n of units (%)	816 (43.9)	78 (3.1)	255 (10.7)
Tested	Mean (SD) Median (interquartile)	2.5 (28.5) 0 (0–0)	2.4 (2.5) 1 (1–3)	20.5 (112.0) 0 (0–1)
Positive	Mean (SD) Median (interquartile)	0.2 (3.6) 0 (0–0)	0.5 (0.9) 0 (0–1)	0.6 (6.3) 0 (0–0)

screening program in Japan was almost fully implemented but variations in screening tests were observed. Endemic or non-endemic countries or areas might have different perspectives regarding the need to introduce a nationwide screening program, but in countries or areas where HTLV-1 is endemic, antenatal screening is likely to contribute to a reduction in associated diseases. Most previous reports of nationwide screening estimated the incidence or prevalence for research purposes but not the implementation of screening as a routine health service program [22, 23].

The National Screening Committee in the UK previously discussed a national HTLV-1 screening program but the committee did not recommend implementing the screening because the UK had a low prevalence of HTLV-1 infection and there was a low risk for infected infants to develop a serious illness. The Committee reiterated its previous conclusions in 2017 [24]. Recently, a cost-effectiveness study of HTLV-1 screening in the UK was reported [25]. The analysis used a highly conservative model of transmission and disease attribution. They reported that a screening program to identify HTLV-1 carriers to reduce transmission was potentially cost-effective in the UK. Therefore, our study findings might provide information useful for implementing a national screening program in other countries.

The implementation of HTLV-1 screening was conducted nationwide after its introduction in 2011. There was no consistent overall trend because differences were observed by region and facility type for each examination. The number of people per facility varied widely. There were about 200–500 people per facility per quartile in the analysis. This may have been influenced by the local infection rate [11, 12] and local government's commitment to HTLV-1. Kyushu area was the most endemic area in Japan [15, 16]. Facility types were

Table 3 Screening, rate ratio (95% CI), *p*-value

	Screening				Screening positive			
	Rate ratio	95%CI		*P*-value	Rate ratio	95%CI		*P*-value
Year								
2011	Reference				Reference			
2013	0.96	0.91	1.02	0.1781	0.74	0.42	1.30	0.2876
2016	1.00	0.95	1.05	0.9242	0.69	0.38	1.27	0.2329
Regions								
Hokkaido, Tohoku	1.20	1.04	1.37	0.0119	0.21	0.13	0.33	<.0001
Kanto	0.55	0.48	0.62	<.0001	0.30	0.17	0.52	<.0001
Chubu, Tokai	0.77	0.68	0.87	<.0001	0.43	0.17	1.06	0.0670
Kinki	0.89	0.79	1.02	0.0928	0.54	0.25	1.16	0.1142
Chugoku, Shikoku	1.33	1.15	1.53	0.0001	0.22	0.14	0.35	<.0001
Kyusyu, Okinawa	Reference				Reference			
Units								
High-volume hospital	1.18	1.11	1.26	<.0001	1.56	1.02	2.38	0.0386
Middle- and low-volume hospitals and clinics	Reference							

Table 4 Western blot, rate ratio (95% CI), *p*-value

	WB				WB positive			
	Rate ratio	95%CI		*P*-value	Rate ratio	95%CI		*P*-value
Years								
2011	Reference				Reference			
2013	0.57	0.27	1.21	0.1435	0.87	0.66	1.14	0.3168
2016	0.54	0.33	0.88	0.0145	0.59	0.45	0.77	<.0001
Regions								
Hokkaido, Tohoku	1.00	0.46	2.20	0.9982	0.30	0.22	0.40	<.0001
Kanto	0.66	0.34	1.27	0.2140	0.29	0.22	0.39	<.0001
Chubu, Tokai	0.88	0.36	2.12	0.7744	0.25	0.19	0.33	<.0001
Kinki	0.85	0.46	1.59	0.6198	0.35	0.27	0.46	<.0001
Chugoku, Shikoku	0.67	0.29	1.52	0.3385	0.27	0.21	0.36	<.0001
Kyusyu, Okinawa	Reference				Reference			
Units								
High-volume hospital	0.63	0.36	1.08	0.0907	1.59	1.19	2.13	0.0019
Middle- and low-volume hospital and clinic	Reference							

associated with the implementation of the screening and testing. Local governments might the change role of facilities for screening and testing to optimize medical resources. 2013 year was a time of transition on the implementation. It is hoped that the dissemination, inspection, and follow-up of this study will consider regional and facility characteristics. To the best of our knowledge, this is the first evaluation of a nationwide HTLV-1 screening program. Our findings are relevant to the implementation of similar screening programs.

Limitations

This study performed an integrated analysis of three questionnaires and had some limitations. First, the survey was institutional and there was no information about individuals (pregnant women or children). The data only provided counts of categories by individuals. Data of pregnant women were obtained from vital statistics and only by region. Second, some unmeasured confounders and bias effects of individual factors could not be adjusted for. Third, because the questionnaire was a survey

Table 5 PCR, rate ratio (95% CI), *p*-value

	PCR				PCR positive			
	Rate ratio	95%CI		*P*-value	Rate ratio	95%CI		*P*-value
Years								
2011	Reference				Reference			
2013	2.44	0.81	7.32	0.1121	0.96	0.17	5.50	0.9645
2016	16.06	6.02	42.84	<.0001	1.54	0.29	8.23	0.6137
Regions								
Hokkaido, Tohoku	5.36	0.71	40.40	0.1032	0.13	0.03	0.55	0.0051
Kanto	1.40	0.41	4.79	0.5908	0.09	0.03	0.35	0.0004
Chubu, Tokai	1.83	0.34	9.77	0.4819	0.93	0.14	6.16	0.9410
Kinki	3.68	1.10	12.26	0.0340	0.12	0.04	0.43	0.0011
Chugoku, Shikoku	3.42	0.70	16.78	0.1297	0.10	0.02	0.44	0.0022
Kyusyu, Okinawa	Reference				Reference			
Units								
High-volume hospitals	0.14	0.04	0.54	0.0045	10.93	2.94	40.59	0.0004
Middle- and low-volume hospitals and clinics	Reference							

of the facility, there was the potential for response bias. Fourth, the time intervals for each survey were different. Finally, HTLV-1 infection rates vary by region, which may be reflected in the results. Although information on the infection rate in each region is limited, previous studies reported that the infection rate of HTLV-1 was high in Kyushu and Okinawa. Multivariate analysis assumes that the factors evaluated have been adjusted from the observed information; thus, changes are only reported for the reference group.

Conclusion

The nationwide screening program for HTLV-1 in Japan was almost fully implemented. However, variations in screening tests were observed during its implementation. Thus, some incentives are needed to encourage proper implementation across all regions.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12889-020-09258-4.

Additional file 1. Screening and pregnant women by region in Japan, n (%).Number of screening and Birth and still birth in population by region (Hokkaido and Tohoku, Kanto, Chubu and Tokai, Kinki, Chugoku and Shikoku, Kyusyu and Okinawa) and by year (2011, 2013, 2015).

Additional file 2. STROBE statement. Checklist table of STROBE statement for the manuscript.

Abbreviations

EIA: Enzyme immunoassay; HTLV-1: Human T-lymphotropic virus type 1; JAOG: Japan Association of Obstetricians and Gynecologists; MHLW: Ministry of Health, Labor and Welfare; MTCT: Mother-to-child transmission; WB: Western blotting; PA: Particle agglutination; PCR: Polymerase chain reaction; STROBE: Strengthening the reporting of observational studies in Epidemiology; UK: United Kingdom

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Authors' contributions

NY, AS, and KI developed the ideas for this research. NY drafted the initial report. NY analyzed the data. NY and AS wrote the final version of the report. SS, SH, and YS collected and checked the data. NY and AS interpreted the data. All authors reviewed and approved the final version.

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Availability of data and materials

The data in this study are not publicly available due to data security agreements with JAOG, but data are available from the corresponding author upon reasonable request with permission from JAOG.

Ethics approval and consent to participate

The study was approved by the ethics committee of the Japan Association of Obstetricians and Gynecologists. The survey was institutional and contained no individual information (pregnant women or children).

Consent for publication

Not applicable.

Competing interests

NY is a member of Editorial Board. SS, AS, SH, YS, and KI declare that they have no competing interests.

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Review

Mother-to-Child Transmission of Human T-Cell Leukemia Virus Type 1: Mechanisms and Nutritional Strategies for Prevention

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Simple Summary: Mother-to-child transmission (MTCT) of human T-cell leukemia virus type 1 (HTLV-1) is a major cause of adult T-cell leukemia (ATL). Owing to the poor prognosis of ATL and the fact that more than one million people have been infected with this virus, the HTLV-1 antibody screening test was established in Japan in 2010 for all pregnant women to detect carriers and prevent MTCT. Because breastfeeding is the most common route of postnatal MTCT, exclusive formula feeding is widely used as a measure to prevent MTCT. Recently, it was reported that there is no obvious difference in the efficacy of short-term breastfeeding for ≤3 months in preventing MTCT compared to that in exclusive formula feeding, and that a duration of breastfeeding that does not exceed four months can be effective for preventing MTCT.

Abstract: Approximately 95% of mother-to-child transmission (MTCT) of human T-cell leukemia virus type-1 (HTLV-1) is derived from prolonged breastfeeding, which is a major cause of adult T-cell leukemia (ATL). Exclusive formula feeding (ExFF) is therefore generally used to prevent MTCT. A recent cohort study revealed that 55% of pregnant carriers chose short-term breastfeeding for ≤3 months in Japan. Our meta-analysis showed that there was no significant increase in the risk of MTCT when breastfeeding was carried out for ≤3 months compared with ExFF (pooled relative risk (RR), 0.72; 95% confidence interval (CI), 0.30–1.77), but there was an almost threefold increase in risk when breastfeeding was carried out for up to 6 months (pooled RR, 2.91; 95% CI, 1.69–5.03). Thus, short-term breastfeeding for ≤3 months may be useful in preventing MTCT. Breastmilk is the best nutritional source for infants, and any approach to minimizing MTCT by avoiding or limiting breastfeeding must be balanced against the impact on the child's health and mother–child bonding. To minimize the need for nutritional interventions, it is necessary to identify factors that predispose children born to carrier mothers to MTCT and thereby predict MTCT development with a high degree of accuracy.

Keywords: human T cell leukemia virus type 1; mother-to-child transmission; exclusive formula feeding; short-term breastfeeding; frozen and thawed breastmilk feeding; transplacental transmission

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1. Introduction

Early-life exposure to infectious agents may be involved in the development of future cancers. Well-known pathogens include the human papillomavirus, hepatitis B and C viruses, Epstein–Barr virus, and human T-cell leukemia/lymphoma virus type-1 (HTLV-1) [1]. Among these pathogens, the number of HTLV-1 carriers in Japan is by far the largest among developed countries, estimated to be at least 1.1 million based on data from first-time blood donors in 2006 and 2007 [2]. While the majority of HTLV-1-infected individuals remain asymptomatic, it is well known that adult T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) are

caused by this virus. HTLV-1 carriers are estimated to have a lifetime risk of 2–7% for the development of ATL [3] and 0.25–3.8% for the development of HAM/TSP [4]. The pathogenesis of HAM/TSP and other HTLV-1-associated diseases, such as infective dermatitis and myositis, are derived from inflammation due to HTLV-1 infection [4,5]. HTLV-1 uveitis, which has long been recognized in the field of ophthalmology, is also associated with inflammation caused by HTLV-1 [6]. Infective dermatitis associated with HTLV-1 (IDH) is a recurrent eczema that affects vertically infected children [7,8]. Although IDH disappears in adulthood, it may predispose individuals to the early development of HAM/TSP and ATL [9,10].

A recent meta-analysis demonstrated that the risk of all-cause death was higher in people with HTLV-1 infection than that in people without the infection [11]. The analysis indicated that many of the diseases associated with HTLV-1 are not fatal, and those that are fatal (e.g., ATL) occur too rarely to account for the observed mortality effect. Thus, HTLV-1 infection is likely to affect human health in more ways than is currently unknown, and with increasing globalization, it has the potential to spread from endemic to non-endemic areas and become a global burden.

Diverse clinical features, including lymphadenopathy, skin lesions, increased abnormal lymphocytes, frequent blood and bone marrow involvement, hypercalcemia, and lytic bone lesions characterize ATL [12]. The diagnosis of ATL often involves the detection of ATL cells ('flower cells') in the peripheral blood. ATL has been divided into four clinical subtypes based on the Shimoyama classification system: acute, lymphoma, smoldering, and chronic [13]. The smoldering and chronic subtypes, also known as indolent ATL, are characterized by rashes and minimal blood involvement. The acute and lymphoma subtypes, also known as aggressive ATL, are characterized by a large tumor burden, lymph node and blood involvement, and hypercalcemia. Classification of ATL subtypes greatly influences the treatment regimen and prognosis of patients [14].

ATL has been associated with HTLV-1 mother-to-child transmission (MTCT) [1] owing to the following reasons: (1) ATL develops after a long incubation period of more than 20–30 years [3]; (2) the majority of ATL patients are infected during childhood [15]; (3) the development of ATL is extremely rare in people infected in adulthood [3]; (4) breast milk containing infected cells is the main route of transmission during this period [16–19]; and (5) family history is a risk factor for developing ATL [20]. Numerous studies have demonstrated that MTCT through breastfeeding is the predominant route of HTLV-1 infection [15,16,21], and HAM/TSP develops in populations infected through vertical and horizontal routes [22]. Recently, a case of HTLV-1-associated uveitis caused by horizontal transmission was reported [23].

In Japan, there has been a nationwide antenatal HTLV-1 antibody screening program since 2010 to prevent HTLV-1 MTCT [24,25]. Because infected children are often asymptomatic during childhood, it is not clear whether MTCT is involved in the development of HTLV-1-associated diseases other than ATL. It is expected that an antenatal HTLV-1 screening program will reduce the number of infected children via MTCT, which in turn will reduce the number of ATL cases. Furthermore, the reduction in the number of these children may also contribute to a reduction in the sources of horizontal transmission. The following are the justifications for nationwide screening in Japan: (1) HTLV-1 carriers are widespread throughout Japan because of internal population migration from endemic areas such as Kyusyu to non-endemic areas [2]; (2) more than 4000 adolescents and adults (77% women) are newly diagnosed annually with HTLV-1 (mainly caused by sexual contact) [26]; and (3) no effective vaccine or antiviral regimens have been developed against this virus [27].

However, despite the implementation of nationwide antenatal HTLV-1 antibody screening, there is no consensus among healthcare providers, especially regarding prevention by nutritional regimens. In this review, the mechanisms of MTCT and evidence for preventive measures through nutrition will be discussed along with the latest findings.

2. Nationwide Antenatal HTLV-1 Antibody Screening

2.1. International Trends in the Implementation of Nationwide Antenatal Screening

The implementation of nationwide HTLV-1 antibody screening tests in all pregnant women is controversial. Although the United Kingdom National Screening Committee considered the antenatal HTLV-1 screening program three times, the committee did not recommend introducing a screening program in the United Kingdom because of the low prevalence of HTLV-1 infection and the low risk for infected infants developing serious illness [28]. Although antenatal HTLV-1 screening is performed in some Brazilian cities and states, such as Salvador, the city with the highest reported HTLV-1 prevalence, it is not included among the tests currently offered to pregnant women by the Brazilian health system [29]. Nevertheless, it has been emphasized by several groups that screening tests for pregnant women are necessary in endemic areas and countries [29–31]. However, Japan is the only country to have a nationwide screening program for pregnant women.

2.2. Screening Program in Japan

The flowchart for HTLV-1 carrier screening during pregnancy in Japan is shown in Figure 1. HTLV-1 antibody screening is usually performed within the first 30 weeks of gestation to secure enough time for a carrier to receive detailed information from healthcare providers and to select a suitable feeding regimen for their infants before labor. Confirmatory tests are performed on pregnant women with positive screening results. Line immunoassay (LIA) has demonstrated superior performance to that of Western blotting (WB), resulting in fewer indeterminate results [32,33]. Thus, WB has recently been replaced by LIA in Japan [33]. If the result of the confirmation test is indeterminate, a polymerase chain reaction (PCR) test is used to determine the presence or absence of infection. As shown in Table 1, pregnant women who had either a positive confirmatory test or PCR-positive results were identified as HTLV-1 carriers [25]. When a pregnant woman is identified as a carrier, the healthcare provider explains the risk of MTCT and preventive measures as much as possible before delivery. Our retrospective surveys conducted in 2011, 2013, and 2016 confirmed that a nationwide screening program for HTLV-1 was almost fully implemented in Japan [34]. Even if a child is born to a carrier pregnant woman, a regular infant's health check-up schedule is appropriate unless the mother is highly anxious. Testing for HTLV-1 antibody at the age of 3 years to assess MTCT is recommended but not mandatory [25].

Table 1. Interpretation of test results for pregnant women.

	Positive	**Negative**
Primary screening test	Pregnant woman cannot be confirmed as infected: a confirmatory test must be conducted.	Uninfected
Confirmatory test	Infected	Uninfected
PCR (To be performed when the confirmation test is indeterminate)	Infected	Probably uninfected

PCR, polymerase chain reaction.

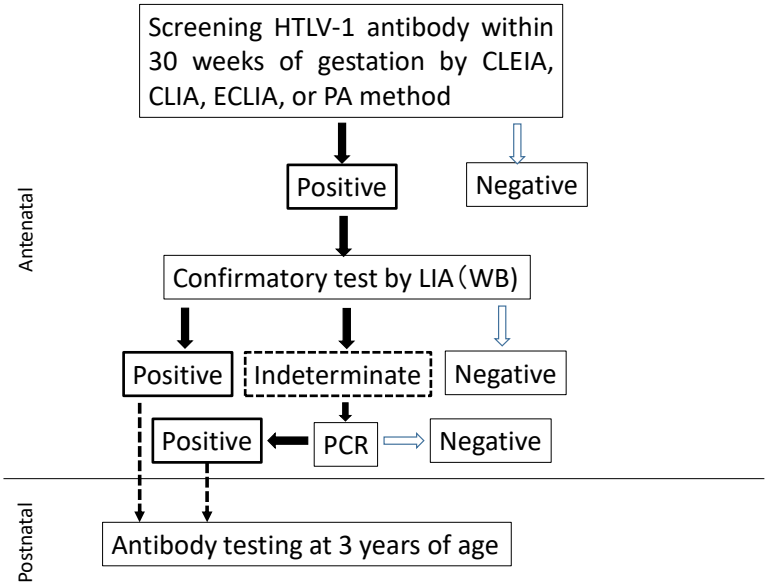

Figure 1. Flowchart to determine HTLV-1 carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electrochemiluminescent immunoassay; PA, particle agglutination; WB, Western blot; LIA, line immunoassay; PCR, polymerase chain reaction.

2.3. Prevalence among Pregnant Women in Japan

The prevalence of HTLV-1 carriers among pregnant Japanese women in 2011 and 2013 was 0.15% and 0.18%, respectively [35]. In 2019, the prevalence determined using the LIA and PCR was 0.10%. Among them, 10.7% had negative test results in their previous pregnancies, and the infections were therefore assumed to be due to horizontal transmission [36]. In Kyushu and Okinawa, which are endemic areas in Japan, the prevalence was 0.60%, 0.66%, and 0.30% in 2011, 2013, and 2019, respectively. The prevalence of HTLV-1 in pregnant women in 2019, both nationally and in the Kyushu and Okinawa areas, was lower than that in 2011 and 2013, but the reasons for this are not fully understood.

2.4. Worldwide Prevalence of HTLV-1 in Pregnant Women

Based on available data in 2012, Gessain and Cassar reported that the most endemic regions for HTLV-1 are the Southwestern part of Japan, sub-Saharan Africa and South America, the Caribbean region, and foci in the Middle East and Australo-Melanesia. They also reported the prevalence of HTLV-1 in pregnant women in these regions [37]. Rosadas and Tayler added to the published data regarding the prevalence of HTLV-1 infection among pregnant women after the report by Gessain et al. [18]. In South America, the prevalence among pregnant women was reported to be 0.1–1% in Brazil, 4% in French Guyana, and 1–4% in Peru. In the Caribbean area, the prevalence ranged from 2–4%. In sub-Saharan Africa, the prevalence was above 1% in all countries, and in Gabon, it was 5% in some areas [38]. As already mentioned, in Eastern Asia, Japan had a prevalence of 0.1% in 2019. In Europe, the prevalence in most countries was less than 0.1% (see Rosadas et al. for details on country data [18]).

3. Mechanisms of HTLV-1 MTCT

3.1. Cell-to-Cell Transmission

Human immunodeficiency virus (HIV), mouse mammary tumor virus (MMTV), and HTLV-1 are transmitted from mother to child through breast milk. HIV MTCT can occur before, during, and after delivery, with postnatal transmission through breastfeeding accounting for one-third to one-half of all cases of HIV MTCT [39]. Both cell-free and cell-

associated viruses are present in the breast milk of HIV-infected mothers [40]. Ndirangu et al. reported that the role of cell-free viruses is more dominant than that of cell-associated viruses in MTCT through breast milk during the early postnatal period (6 weeks of life) [41]. MMTV is usually transmitted via breastmilk to the offspring, and neonatally infected mice of susceptible strains usually develop mammary tumors after only 5 months of life [42]. The MMTV-infected mother's breastmilk contains cell-free viruses.

In contrast to HIV and MMTV, HTLV-1 cell-free viruses are rarely detected extracellularly [43,44]. Cell-free viruses are thought to be less involved in the spread of HTLV-1 infection. Thus, the spread of HTLV-1 infection is thought to occur predominantly through direct cell-to-cell contact. Subsequent experimental studies have shown that when dendritic cells (DCs) are exposed to cell-free viruses, the infection spreads to CD4+ T cells, but they may not be the main players for the spread of the infection [44–47].

In vitro studies have speculated that HTLV-1 cell-to-cell infection may spread through viral synapses [48], conduits [49], biofilm-like structures [50], and extracellular vesicles [51]. These modes allow the virus to escape elimination by the immune system (HTLV-1-specific T cell unresponsiveness) and efficiently deliver virions to contacted cells, resulting in an increased proviral load (PVL) [44,52,53]. HTLV-1 preferentially infects $CD4^+$ T cells via their cellular receptors such as heparin sulfate (HS) proteoglycans and neuropilin 1 (NRP-1), which are used for the initial binding to the cell, and glucose transporter 1 (GLUT1) for entry [44,45,47,54,55]. However, Tanaka et al. found that the cellular susceptibility to HTLV-1 infection did not correlate with the expression of GLUT1, HS, or NRP-1 alone [56]. Cell-to-cell transmission of HTLV-1 can occur frequently after interactions between DCs and T cells, as well as between T cells [46,57]. Because DCs, monocytes, macrophages, and B cells express these receptors, they can also be infected with each other in individuals with HTLV-1 [44,58].

3.2. Modes of HTLV-1 Transmission

There are two modes of HTLV-1 transmission: horizontal infection due to sexual intercourse and blood transfusion, and antenatal or postnatal MTCT [59]. The most common mode in Japan is horizontal infection, with a prevalence of more than 4000 people infected per year [26]. The predominant horizontal infection is estimated to be related to sexual intercourse because donor screening for HTLV-1 infection is always tested at the time of blood donation [60]. Organ transplantation has also been identified as a mode of horizontal transmission of HTLV-1 [61]. Screening for HTLV-1 infection in donors of organ transplantation is recommended. Additionally, it is necessary to test whether the recipient is a carrier because the use of immunosuppressants may increase the risk of developing HTLV-1-associated diseases [62–64].

3.3. Routes of MTCT in HTLV-1 Infection

Currently, HTLV-1 MTCT is mainly attributed to prolonged breastfeeding based on the findings of epidemiological [65–68] and animal studies [69,70]. The ATL Prevention Program in Nagasaki revealed a marked reduction in HTLV-1 MTCT from 20.3% to 2.5% through exclusive formula feeding (ExFF) [16]. Previous studies revealed that the rate of HTLV-1 MTCT in children who were exclusively fed infant formula was significantly lower than that in children who were breastfed over a prolonged period. However, MTCT was observed in a small proportion of children who were exclusively fed infant formula [18,25]. This suggests the possibility of MTCT through antenatal routes. However, no evidence has been established for ascending HTLV-1 infection in utero, birth canal infection due to contaminated maternal blood exposure, or transplacental transmission. It is thought that more than 95% of MTCT cases are derived from prolonged breastfeeding, but even if antenatal routes constitute a small proportion of MTCT cases, it is necessary to elucidate the alternative infection route to prevent MTCT.

3.3.1. Transplacental HTLV-1 Transmission

In in vitro experiments, exposure of the cell-free HTLV-1 virus to trophoblasts did not result in infection [71]. Recently, Tezuka et al. demonstrated that during pregnancy of HTLV-1 carriers, HTLV-1 was highly expressed in placental villous tissues, and villous trophoblasts showed high HTLV-1 sensitivity compared to that in other component cells (mesenchymal fibroblasts and placental vascular endothelial cells) of the blood–placental barrier. These results suggest that MTCT of HTLV-1 occurs through the placenta when the blood–placental barrier is impaired [72] (e.g., in preeclampsia [73]). However, the study could not directly investigate transplacental transmission because the authors did not have data on MTCT rates in children born to carrier pregnant women. Nevertheless, the study brings us one step closer towards understanding antenatal HTLV-1 MTCT.

3.3.2. Transmission through Breastfeeding

It is not fully understood how HTLV-1-infected cells in breastmilk enter the infant and establish MTCT. Virus uptake during breastfeeding may occur in the tonsil mucosa or intestinal mucosa or in both of these sites in infants [74]. Although a recent in vitro study suggested that co-infection with HIV and cytomegalovirus can disrupt the mucosal barrier and allow HIV to spread to the tonsils [75], it is not clear whether it is involved as a transit pathway for HTLV-1.

Currently, postnatal infection in children born to carrier pregnant women is thought to occur primarily when infected cells in ingested breastmilk enter the infant's digestive tract [70,76]. Animal studies have shown that breastmilk leucocytes survive passage through the infant's digestive tract, and then translocate from the gastrointestinal tract to the blood and distant sites such as the lymph nodes, spleen, and liver [77,78]. The leukocyte count in breastmilk is highest in the colostrum and decreases to 0–2% of the total cell count within several weeks of lactation [79]. However, the rapid response of breastmilk leukocytes to infections of the mother and infant in healthy mother/infant dyads involves a tightly regulated process aimed at conferring additional immunological support to the infant [80]. Furthermore, there are many types of breastmilk cells other than leukocytes, including mammary luminal epithelial cells, lactocytes, and stem/progenitor breastmilk cells, whose relative proportions can change depending on the lactation period, maternal conditions, and infant feeding [79].

It was initially thought that HTLV-1 MTCT is mainly caused by $CD4^+$ T cells [69,70], but the involvement of macrophages and mammary epithelial cells has also been considered because $CD4^+$ T cells are not predominant in breastmilk. Southern et al. reported that basal mammary epithelial cells were susceptible to HTLV-1 infection and capable of transferring HTLV-1 infection to normal peripheral blood lymphocytes in an in vitro experiment [81,82]. Takeuchi et al. showed that breastmilk macrophages might be an appropriate HTLV-I reservoir involved in MTCT through breastfeeding [83]. These studies suggest that mammary epithelial cells and macrophages may be involved mainly in the persistence and transmission of HTLV-1 infection from carrier mothers. At present, it is not clear which cells present in breastmilk are the main players in transmission through breastmilk. It is necessary to longitudinally investigate the types and numbers of infected breast milk cells secreted by the carrier mother in the future.

The process from the contact of infected cells with the mucosa to the spread of infection in submucosal tissues has been described in detail in several reviews [44,84,85]. However, the process by which infected cells in breastmilk enter the infant's digestive tract and establish infection has not been fully elucidated. After the HTLV-1-infected cells enter the digestive tract, infection likely involves the transfer of HTLV-1-infected cells and/or cell-free HTLV-1 produced by infected cells across the epithelium in the oral or gastrointestinal mucosa. In their review, Carpenter et al. summarized the process of establishment of HTLV-1 transfection after contact between mucosa and infected cells [84]. This could occur in the following ways: (1) the transit of a virion incorporated into a vesicle from the apical to the basal surface of an epithelial cell (transcytosis) [74]; (2) release of newly produced virions

from the basal surface of an infected epithelial cell [86]; (3) bypass of HTLV-1-infected cells through a damaged mucosa [87]; and (4) transmigration of macrophages through an intact epithelium, as observed for HIV [88]. However, this has not yet been formally demonstrated [84].

4. Strategies to Prevent MTCT of HTLV-1

4.1. Prevention of MTCT by Measures Other Than by Nutrition

The strategies to prevent MTCT ideally involve the administration of neutralizing antibodies, vaccines, and antiviral drugs. An early study indicated the importance of conformational epitopes within HTLV-1 gp46 in mediating a neutralizing antibody response to HTLV-1 infection [89]. Fujii et al. evaluated the effects of passive immunization using an anti-gp46 neutralizing monoclonal antibody (LAT-27) in mice as part of their research to develop a vaccine. They found that neonatal mice born to mother mice pre-infused with LAT-27 showed complete resistance to intraperitoneal infection with HTLV-I. [90] However, if breastfeeding is continued after the period in which the antibody transferred to the newborn decreases or disappears, it is questionable whether it is effective in preventing mother-to-child infection. Therefore, an active vaccine that can elicit or boost anti-HTLV-I gp46 neutralizing antibody titers should be developed.

4.2. Prevention of MTCT by Nutritional Regimens

Shortly after the discovery of HTLV-1 approximately 40 years ago [91,92], it became clear that breastfeeding was the main route of MTCT. Therefore, prevention strategies have focused on either refraining from breastfeeding or reducing the infectivity of the carrier mother's breastmilk. To date, the main nutritional strategy for the prevention of HTLV-1 MTCT is through ExFF [18,93]. In addition to ExFF, either short-term breastfeeding (STBF) or frozen and thawed breastmilk feeding (FTBMF) has been proposed in Japan [25,94].

The duration of breastfeeding is an important risk factor for MTCT and PVL in carrier pregnant women [31]. However, it is not clear after how many months of breastfeeding the MTCT rate increases significantly compared to ExFF. In previous studies, the duration of breastfeeding was arbitrarily determined to be $\leq$3 months, $\leq$6 months, etc. Among breastfed children in Nagasaki (included in the ATL Prevention Program in Nagasaki), the prevalence of MTCT was lower among children who were breastfed for $\leq$6 months than that among children who were breastfed for $\geq$6 months [16]. However, many healthcare providers have recently limited STBF to $\leq$3 months, partly because of a higher MTCT rate when carrier mothers breastfed for >3 months than when mothers breastfed for $\leq$3 months, as shown in the study by Hirata et al. [95].

The mechanism of MTCT prevention by STBF may involve the presence of neutralizing antibodies against HTLV-1 transferred from the carrier mother in utero, which may block MTCT for several months after birth [96]. Another mechanism may involve the lower cumulative number of infected cells entering the gastrointestinal tract due to STBF. MTCT prevention by FTBMF is thought to be caused by the destruction of the infected cells in breastmilk by the freezing and thawing process [97].

In Japan, healthcare providers and mothers are speculated to be interested in STBF and FTBMF as nutritional regimens for MTCT prevention because of their potential to prevent HTLV-1 MTCT while taking advantage of the benefits of breastfeeding [98,99] (e.g., reduction in postpartum anxiety in mothers, formation of mother–infant bonding, and biological effects of the components in breastmilk). A recent systematic review reported that breastfeeding duration is associated with postpartum depression. In addition, postpartum depression was shown to be predicted by breastfeeding cessation in several studies [100]. However, the causes and effects of postpartum depression and short breastfeeding duration are unclear. Screening for depression during pregnancy may be useful in evaluating both aspects [100]. Rocha-Filho et al. showed that both symptomatic and asymptomatic patients with HTLV-1 experienced more anxiety and depression than those experienced

by uninfected patients [101]. Thus, it is believed that carrier mothers may have similar experiences.

Even with the implementation of a nationwide antenatal HTLV-1 antibody screening program, the choice of postnatal nutritional regimens varied among regions and healthcare providers. Because of concerns that this situation could cause anxiety for carrier mothers and their families, in 2016, the Ministry of Health, Labour and Welfare (MHLW) of Japan recommended ExFF as the first choice among nutritional regimens for MTCT prevention [102], for which clear evidence had been established. However, evidence for the effectiveness of STBF and FTBMF in preventing MTCT is insufficient because of the small sample sizes and/or methodological issues reported in previous studies. Therefore, we conducted a cohort study, systematic review, and meta-analysis to establish evidence for the effectiveness of STBF and FTBMF in preventing MTCT.

4.2.1. Prospective Cohort Study in Japan

We conducted a prospective cohort study on MTCT prevention using nutritional regimens. Carrier pregnant women were recruited from 92 centers in Japan for 3 years beginning in 2012, and MTCT rates with nutritional regimens were evaluated in their children at 3 years of age. Our study was initiated before the recommendation of the MHLW in Japan [102]. The results were as follows: (1) among 313 HTLV-1 carrier mothers, the proportion of mothers that chose STBF ($\leq$3 months), ExFF, FTBMF, and long-term breastfeeding was 55.0%, 35.1%, 6.1%, and 3.8%, respectively; (2) despite the selection of STBF, 18% of mothers continued to breastfeed for 4 months, and 8% of mothers continued to breastfeed for six months; (3) the MTCT rate in children for whom STBF was selected was 2.3% (4/172), and the risk ratio compared to ExFF was not significantly different (0.365, 95% confidence interval (CI): 0.116–1.145); (4) FTBMF was selected in fewer cases, and the MTCT rate was statistically unreliable. Our study suggests that STBF can be a valid option for the prevention of MTCT. However, as it is not always easy to refrain from breastfeeding within 3 months, both mothers and healthcare providers should be aware of this issue while choosing STBF [94]. In addition, more than half of the children born to the recruited carriers dropped out of follow-up, indicating that a low follow-up rate in children born to pregnant carriers was a major flaw in the screening program.

4.2.2. Systematic Review and Meta-Analysis

In previous reports, there has been insufficient evidence on the effectiveness of STBF and FTBMF in preventing MTCT compared to ExFF because of the small number of subjects. Therefore, we conducted a systematic review and meta-analysis that incorporated both English and Japanese reports. The definition of STBF varies across articles. In the present study, we defined STBF as breastfeeding for no more than 3 months (STBF $\leq$ 3 months) or 6 months of life (STBF $\leq$ 6 months). MTCT was confirmed by the detection of HTLV-1 antibodies in infants after 12 months of life. Finally, 11 articles (i.e., 10 previous studies and our prospective cohort study [94]) were included in the meta-analysis. Six articles on the effect of STBF $\leq$ 3 months [94,103–107], five articles on STBF $\leq$ 6 months [104,106,108–110], and three articles on FTBMF [94,111,112] were included for the systematic review and meta-analysis [113]. The pooled relative risks of STBF $\leq$ 3 months, STBF $\leq$ 6 months, and FTBMF compared with ExFF were 0.72 (95% CI: 0.30–1.77; p = 0.48), 2.91 (95% CI: 1.69–5.03; p = 0.0001), and 1.14 (95% CI: 0.20–6.50; p = 0.88), respectively (Figures 2–4) [113]. The results suggest that STBF $\leq$ 3 months does not increase the risk of MTCT compared to ExFF, but the risk of MTCT may increase by approximately threefold if the duration of STBF is up to 6 months. Although the preventive effect of FTBMF is not significantly different from that of ExFF in MTCT, the number of reports and the number of subjects were small, and the results may not be reliable.

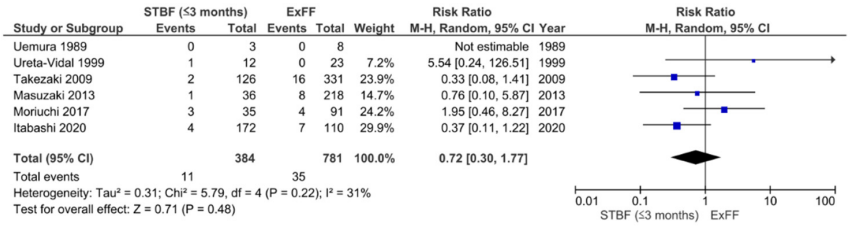

Figure 2. Forest plot of the risk ratios of HTLV-1 MTCT in the 'STBF ≤3 months' group compared with that of the ExFF group. STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, risk ratio; MTCT, mother-to-child transmission; Events, number of cases with mother-to-child transmission; Total, number of children born to carrier mother; Weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [112].

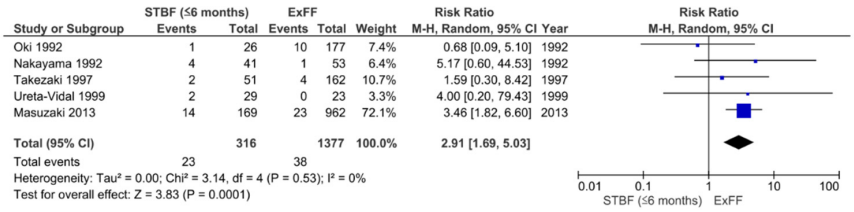

Figure 3. Forest plot of the risk ratios of HTLV-1 MTCT in the 'STBF ≤6 months' group compared with that of the ExFF group. STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, relative risk; MTCT, mother-to-child transmission; Events, number of cases with mother-to-child transmission; Total, number of children born to carrier mother; Weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [112].

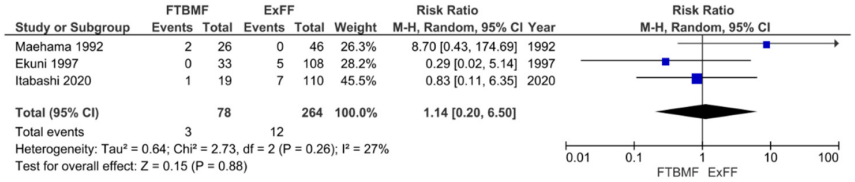

Figure 4. Forest plot of the risk ratios of HTLV-1 MTCT in the FTBMF group compared with that of the ExFF group. FTBMF, frozen-thawed breastmilk feeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, relative risk; MTCT, mother-to-child transmission; Events, number of cases with mother-to-child transmission; Total, number of children born to carrier mother; Weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [112].

4.2.3. Which Nutritional Regimen Is Best for MTCT Prevention Currently?

In our cohort study and meta-analysis, there was no obvious difference in the MTCM rate between ExFF and STBF ≤ 3 months. In addition, data on FTBMF are lacking. Therefore, from the perspective of preventive effects alone, either ExFF or STBF may be acceptable for postnatal MTCT prevention. However, there are some considerations and issues that need to be addressed when choosing between these nutritional approaches (Table 2).

Table 2. Evidence-based selection of nutritional regimens for MTCT prevention.

Nutritional Regimens	Effectiveness on MTCT Prevention	Comments
Exclusive infant formula feeding (ExFF)	Widely used and well evaluated to block MTCT through breastmilk	Approximately 95% or more MTCT prevention No benefits from breastfeeding Concerns about increased risk of postpartum depression and impaired mother–child bonding
Short-term breastfeeding (≤3 months)	No apparent difference in the MTCT prevention effect (vs. ExFF)	Acquisition of some benefits of breastfeeding Approximately 18% of children exceed 4 months of breastfeeding Need to provide adequate support for weaning No data on the preventive effect of postpartum depression or impairment of mother–child bonding
Short-term breastfeeding (≤6 months)	Approximately three times increased risk of MTCT (vs. ExFF)	Better to avoid this regimen
Frozen–thawed breastmilk feeding	Unknown effectiveness of MTCT prevention due to lack of sufficient case accumulation (vs. ExFF)	Time-consuming Considered for use in infants admitted in the NICU No data on the preventive effect of postpartum depression or impairment of mother–child bonding
Mixed feeding	Unknown effectiveness of MTCT prevention due to lack of data (vs. ExFF)	Concerns about increased risk of MTCT due to damage to the intestinal mucosa Better to avoid this regimen
Banked human milk	No data available, but expected to be as effective as ExFF in preventing MTCT	No use of breast milk from untested HTLV-1 donors No data on the preventive effect of postpartum depression or impairment of mother–child bonding

Note: It should be noted that ~5% of prenatal infections cannot be avoided regardless of which nutritional regimen is chosen. MTCT, mother-to-child transmission; NICU, neonatal intensive care unit.

Exclusive Infant Formula Feeding (ExFF)

It is less challenging to perform ExFF than it is to perform STBF, but a major drawback of ExFF is that it does not offer the benefits of breastfeeding. In addition, there are issues regarding the risk of postpartum depression due to low self-esteem owing to not being able to breastfeed and anxiety about the development of HTLV-1-associated diseases [25]. Therefore, counseling should be provided as needed.

Short-Term Breastfeeding (STBF)

STBF for ≤3 months appears to offer the advantages of breastfeeding over ExFF, in that the carrier mother can feed her own milk even if it is only for a few months. However, it may not always be easy to refrain from breastfeeding after 3 months, as evidenced by the results of our cohort study [94]. This may be due to problems with the weaning technique and psychosocial conflicts of the mother. If a carrier pregnant woman chooses STBF, then

she needs the support of midwives and lactation consultants to minimize stress due to refraining from breastfeeding.

Frozen–Thawed Breastmilk Feeding (FTBMF)

FTBMF is very time-consuming when performed at home. Even in our cohort study, only 6.1% of carrier pregnant women opted for it [94]. Given the lack of evidence on its efficacy in preventing MTCT, if it is to be performed, a better indication would be for infants admitted to the neonatal intensive care unit.

Other Nutritional Regimens

Regardless of its duration, breastfeeding may also be combined with the use of infant formulas. In recent studies, the rate of MTCT of HIV was extremely high, at approximately 20%, compared with normal breastfeeding or infant formula feeding [114]. It is speculated that mixed feeding may cause gastrointestinal mucosal injury or dysbiosis, which may involve changes in intestinal permeability [115]. However, to date, there is no evidence to inform HTLV-1 carrier women with mixed feeding recommendations, and further studies on the effects of mixed feeding on HTLV-1 MTCT are warranted.

Human milk donated to breast milk banks should be screened for maternal HTLV-1 infection [116]. In theory, feeding banked human milk donated by HTLV-1-uninfected mothers could have the same preventive effect as that of ExFF for infants born to HTLV-1 carriers. However, while banked human milk may provide partial health benefits of ordinary breastfeeding to infants and children [117], it may be unlikely to reduce carrier mothers' anxiety and/or impairment of mother–child bonding.

4.2.4. Factors Associated with HTLV-1 MTCT

The selection of a feeding regimen is an important factor associated with MTCT of HTLV-1, but the involvement of other factors should also be considered.

Plancoulaine et al. conducted a large genetic epidemiological survey in an HTLV-1-endemic population of African origin from French Guiana. They found the presence of a dominant major gene that predisposes to HTLV-I infection, in addition to the expected familial correlations (mother–offspring and spouse–spouse) due to the virus transmission routes. The authors concluded that this gene appears to account for most infections occurring in children through breastfeeding and can explain, at least in part, the reason why MTCT of HTLV-I only occurs in a certain proportion of children fed by infected mothers [118,119]. A following study by the same group identified a major locus conferring a predisposition to childhood HTLV-1 infection on chromosome 6q27 [120].

An immunological issue that has long been of interest is whether transfer antibodies or antibodies contained in breastmilk play an effective role in preventing mother-to-child infection. Pregnant women infected with HTLV-1 have significantly increased levels of anti-HTLV-1 antibodies, although PVL does not change during pregnancy [121]. This is consistent with the hypothesis that more antibodies are transmitted through the placenta during pregnancy, which may protect against infection in the fetus and early postnatal infants. Rosadas et al. measured anti-HTLV-1/2 IgG antibodies and PVL in paired blood and breastmilk samples from HTLV-1/2-positive mothers and reported that the HTLV-1 PVL and IgG binding ratio were similar in plasma and breastmilk, but that the titer of anti-HTLV-1/2 IgG antibodies in plasma was about 1000 times higher than that in breastmilk [122]. After delivery, HTLV PVL increases in the blood of the mother [123]. Considering the low levels of antibodies in breast milk in addition to the pre- and post-partum trends of PVL and antibodies in infected mothers, it is believed that the preventive effect of STBF on MTCT may not involve IgG antibodies in breastmilk. One of the reasons for the increased risk of MTCT with prolonged breastfeeding may be related to the decrease in transfer antibodies during infancy and the increase in the cumulative intake of infected cells ingested through breastmilk. High maternal PVL has been cited as a risk factor for MTCT [31,124]. This is also reflected in an increase in maternal antibody titer [104].

Substances contained in breastmilk, such as tumor growth factor-β and lactoferrin, which are rich in colostrum [125,126], promote HTLV-I replication [127,128]. Furthermore, lactoferrin expression has been shown to be upregulated during HTLV-1 infection [129]. However, since the respective levels of these components are not constant during lactation and vary from person to person, it is unclear how they actually affect MTCT.

5. Conclusions

Since the discovery of HTLV-1 almost 40 years ago, much has been learned about the associated disease and its pathogenesis. MTCT of HTLV-1 became evident within a short time after its discovery, and epidemiological studies and animal studies have shown that prolonged breastfeeding is an important risk factor for MTCT. However, symptoms are rarer in infected infants and children than in adults, and for this reason, there have been no vigorous studies of MTCT, and the detailed mechanisms underlying MTCT remain unknown. Our recent cohort studies and meta-analyses have shown that STBF $\leq$ 3 months is not significantly different from ExFF in preventing MTCT, which may provide reassurances that STBF can be successfully implemented. However, STBF and ExFF may not be optimal interventions for carrier pregnant women and their children. Breastmilk is the best source of nutrition for infants, and any approach to preventing MTCT by avoiding or limiting breastfeeding must be balanced against the impact on the child's health and mother–child bonding. In the absence of commercially available vaccines, antivirals, and neutralizing antibodies, to minimize the need for nutritional interventions, it is necessary to identify factors that predispose children born to carrier mothers to MTCT and to thereby predict the development of MTCT with a high degree of accuracy. In addition, further research is needed on the mechanisms underlying prenatal MTCT and its prevention.

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Original Article

Issues of infant feeding for postnatal prevention of human T-cell leukemia/lymphoma virus type-1 mother-to-child transmission

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Abstract ***Background*:** Nationwide antenatal human T-cell leukemia/lymphoma virus type-1 (HTLV-1) antibody screening has been conducted in Japan. The purpose of our study was to clarify the issues related to feeding options to prevent postnatal mother-to-child transmission.

***Methods*:** Of the pregnant carriers at 92 facilities in Japan between 2012 and 2015, 735 were followed prospectively. Among the children born to them, 313 (42.6%) children were followed up to the age of 3 and tested for HTLV-1 antibodies. The mother-to-child transmission rate was calculated for each feeding option selected before birth.

***Results*:** Among the 313 pregnant carriers, 55.0, 35.1, 6.1, and 3.8% selected short-term breast-feeding (≤3 months), exclusive formula feeding, frozen-thawed breast-milk feeding, and longer-term breast-feeding, respectively. Despite short-term breast-feeding, 8–18% of the mothers continued breast-feeding for 4–6 months. The mother-to-child transmission rate with short-term breast-feeding was 2.3% (4/172), and its risk ratio compared with that of exclusive formula feeding was not significantly different (0.365; 95% CI: 0.116–1.145). Because of the small number of children who were fed by frozen-thawed breast-milk, their mother-to-child transmission rate was not statistically reliable.

***Conclusions*:** Pregnant HTLV-1 carriers tended to select short-term breast-feeding in Japan. While short-term breast-feeding was not always easy to wean within 3 months, it may be a viable option for preventing postnatal mother-to-child transmission because the vertical transmission rate with short-term breast-feeding was not significantly higher than that with exclusive formula feeding. Increasing the follow-up rates for children born to pregnant carriers may provide clearer evidence of preventative effects by short-term breast-feeding and frozen-thawed breast-milk feeding.

Key words feeding options, HTLV-1, mother-to-child transmission, nationwide antenatal screening, prevention.

Human T-cell leukemia/lymphoma virus type-1 (HTLV-1) is widely known as the causative agent of adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Carriers of HTLV-1 are estimated to be at a lifetime risk of 2–7% for the development of ATL[1] and 0.25–3.8% for HAM/TSP.[2] Both of these diseases exhibit serious clinical manifestations, and their associated prognoses remain poor despite therapeutic efforts.[3,4] Mother-to-child transmission (MTCT) can theoretically occur during the intrauterine period or during labor; however, it primarily occurs via breast-feeding.[5,6] A previous study has shown that children infected via MTCT are predominant risk of developing ATL.[6]

In 2010, the Ministry of Health, Labor, and Welfare (MHLW) of Japan decided to conduct a nationwide HTLV-1 antibody screening program for all pregnant women to prevent postnatal MTCT.[7] The following were the justifications for this screening: (i) Japan is the only developed country with more than 1 million HTLV-1 carriers;[8] (ii) they are more widespread throughout Japan due to internal population migration from endemic area such as Kyusyu, Japan to non-endemic area;[8] (iii) more than 4,000 adolescents and adults (77% women) are newly diagnosed annually with HTLV-1 (mainly caused by sexual contact),[9] and (iv) neither an effective vaccine nor antiviral regimens have been developed against this virus.[3]

The ATL Prevention Program (APP) in the Nagasaki Prefecture revealed a marked reduction in MTCT of HTLV-1,

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from 20.3% to 2.5%, by relying on exclusive formula feeding (ExFF).[10] This program also showed that the rate of MTCT with breast-feeding for less than 6 months was higher than that with ExFF, but significantly lower than that with longer term breast-feeding.[10] Hirata *et al*. showed that the prevalence of HTLV-1 antibody among children breast-fed for over 3 months was significantly higher than that of those breast-fed for under 3 months.[11] Thus, in Japan, short-term breast-feeding (STBF) is generally defined as breast-feeding up to 3 months of age.[12]

While some healthcare providers in Japan have recommended STBF[11,13] or frozen-thawed breast-milk feeding (FTBMF)[14,15] as alternatives to ExFF, there is insufficient evidence regarding the effects of STBF and FTBMF on the incidence of MTCT.[12] Despite the increased risk of MTCT from longer term breast-feeding,[11,13] the proportion of mothers who select STBF and refrain from breast-feeding by 3 months remains unknown. Serological testing for the children born to pregnant carriers is not mandatory under the screening program, so we do not know what proportion of the children will undergo serological antibody testing. Our study purpose is to clarify these issues related to feeding options for postnatal prevention of HTLV-1 MTCT.

Methods

Algorithm used for the antenatal HTLV-1 antibody screening test

Human T-cell leukemia/lymphoma virus type-1 antibody screening is usually performed within the first 30 weeks of gestation to ensure that a carrier pregnant woman has enough time to obtain detailed information from healthcare providers and to enable the selection of a suitable feeding option before labor. A confirmatory test by western blotting (WB) was performed for pregnant women with positive screening results. In indeterminate cases, the polymerase chain reaction (PCR) is used as a definite test to diagnose the infection. Its sensitivity of measurement is less than 4 copies/10^5 peripheral bold mononuclear cells.[16] Pregnant women who have either a positive confirmatory test or PCR-positive results are defined as being HTLV-1 carriers.

Study population

From April 2012 until December 2015, we prospectively recruited a cohort of carrier pregnant women at 92 facilities, both inside and outside endemic areas in Japan. The testing statuses of the subjects are shown in Figure 1. Western blot testing was performed for pregnant women with positive screening tests. Of these women, 757 were WB positive and 223 were WB indeterminate. Forty-five of the 757 WB-positive and 108 of the 223 women with a WB-indeterminate result did not participate in the study. Of the 115 women with indeterminate tests, 23 were PCR-positive and 92 were negative; this left 735 carrier mothers who were either WB-positive or PCR-positive were enrolled in the study. After delivery, 313 (42.6%) of the children born to the 735 identified carriers were followed up to the age of 3 and tested for HTLV-1 antibodies. Of the 313 children, there were 29 and 30 preterm and low-birthweight infants, respectively.

Feeding options

Pre-trained healthcare providers at each facility provided subjects with a thorough explanation of ExFF, STBF (≤3 months), and FTBMF. The 27 pregnant carriers selected long-term breast-feeding (>3 months).

Assessment of MTCT

Infants born to carriers were checked at a pediatric clinic at 1, 3, 6, 12, 18, 24, and 36 months after birth. A serum antibody test was performed at the final 36-month visit, because no seroconversion has been reported beyond that age.[17,18] The MTCT rates for the feeding options were calculated based on antenatal feeding selection.

Data collection

The following information was requested by researchers at each facility for database entry: the mother's age, number of births, WB and/or PCR results, antenatal selection of feeding option, gestational age, birthweight, sex, actual feeding methods at 1, 3, and 6 months of life, and the results of the child's serum antibody test at 36 months. This study was carried out in accordance with the recommendations of the Ethical Committee of Showa University (No. 1109, October 7, 2011). The protocol was also approved by the ethics committee at each facility. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Statistical analysis

Continuous variables were expressed as means ± standard deviations. Categorical variables were expressed as number and percentages. We used the unpaired *t*-test for continuous data and χ^2 tests for categorical data, except when the expected cells were less than 5; in such cases we used Fisher's exact test. All tests were two-tailed and it was determined that there was a significant difference if $P < 0.05$. Risk ratios (RRs) of MTCT on STBM or FTBMF to ExFF are expressed as medians with 95% confidence intervals (CI). SPSS Statistics version 26 (IBM Japan, Tokyo, Japan) was used for the statistical analysis.

Results

Feeding options selected by carrier pregnant women

The distribution of feeding options selected by pregnant women is shown in Table 1. As approximately 41% of the data originated from subjects residing in Kagoshima prefecture

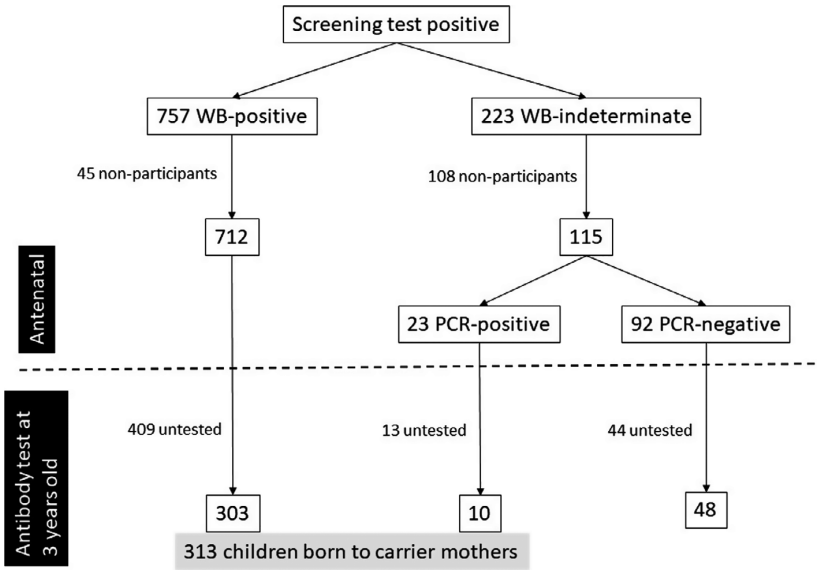

Fig. 1 Subject inclusion based on HTLV-1 testing. WB, western blotting

located in the Japanese endemic area of Kyushu, it is also shown separately for this and other regions. Among the 313 carrier pregnant women whose children was followed up to 3 years of age, the distribution of STBF and ExFF was 55.0% and 35.1%, respectively. It was significantly different between Kagoshima prefecture and other regions (P = 0.001). The selection rate of STBF in Kagoshima prefecture was 77.0%, which was about twice that in other regions.

MTCT rates with respect to the feeding option

The total number of infected children was identified as 14 (4.5%). The clinical characteristics of the children with and without MTCT are shown in Table 2. There were no significant differences between the two groups except for gestational age. The MTCT rates on feeding options selected before labor, not on the actual feeding options, are shown in Table 3. The incidences of MTCT on ExFF and STBF were 6.4% (7/110) and 2.3% (4/172), respectively. Infants with confirmed MTCT in the ExFF group were never breast-fed. The risk ratio (RR) of MTCT for the children born to the women who selected STBF relative to those who selected ExFF was not significant (RR 0.365; 95% CI: 0.116–1.145). The number of subjects who opted for long-term breast-feeding and FTBMF was very small, so those MTCT rates were not reliable.

Breast-feeding changes in the STBF group

Percentages of the infants fed breast milk up to 6 months of age are shown in Figure 2. Approximately 8% of the mothers continued breast-feeding at 6 months of life. We did not have data on what percentage of the mothers in the STBF group

Table 1 The distribution of selected feeding options

	Kagoshima prefecture**			Other regions			F/U n = 313	Lost to F/U n = 422	Total n = 735
	F/U n = 135	Lost to F/U n = 166	Total n = 301	F/U n = 178	Lost to F/U n = 256	Total n = 434			
Long-term breast-feeding (>3 months), n (%)	2 (1.5)	4 (2.4)	6 (2.0)	10 (5.6)	11 (4.3)	21 (4.8)	12 (3.8)	15 (3.6)	27 (3.7)
Short-term breast-feeding, n (%)	104 (77.0)	120 (72.3)	224 (74.4)	68 (38.2)	96 (37.5)	164 (37.8)	172 (55.0)	216 (51.2)	388 (52.8)
Frozen-thawed breast-milk feeding, n (%)	1 (0.7)	0 (0)	1 (0.3)	18 (10.1)	18 (7.0)	36 (8.3)	19 (6.1)	18 (4.3)	37 (5.0)
Exclusive formula feeding, n (%)	28 (20.7)	42 (25.3)	70 (23.3)	82 (46.1)	131(51.2)	213 (49.1)	110 (35.1)	173 (41.0)	283 (38.5)

The distribution of selected feeding options was not significantly different between follow up (F/U) and lost to F/U groups not only in Kagoshima prefecture but also in other regions.

**The distribution of feeding-option selection was significantly different between Kagoshima prefecture and other regions (P = 0.001).

Table 2 Comparison between the clinical characteristics of infected and non-infected children

	Infected children (n = 14)	Non-infected children (n = 299)	P
Mother's age (years old)	33.2 ± 4.9	32.8 ± 4.8	0.751
Primipara (n, %)	9 (64.3%)	150 (50.2%)	0.593
Gestational age (weeks)	38.1 ± 2.3	39.2 ± 1.6	0.021
Birthweight (g)	2,818 ± 403	2,976 ± 417	0.170
Sex (boy) (n, %)	8 (57.1%)	151 (50.5%)	0.627

continued breast-feeding at 4 and 5 months of age. Thus, in order to estimate the rate of breast-feeding at 4 and 5 months, the relationship between postnatal months of life and the proportion of the breast-fed infants was evaluated with second-order polynomial analysis. According to this equation, the rate of breast-feeding at 4 months and 5 months was estimated to be 18.2% and 9.6%, respectively.

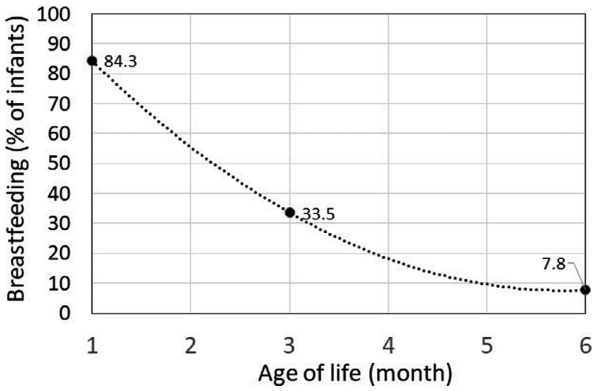

Fig. 2 Longitudinal changes of percentages of infants fed breast-milk in the short-term breast-feeding (STBF) group. The relationship between postnatal months (x) and the rate of breast-feeding (y) in the STBF group was shown by the second-order polynomial analysis. The equation obtained is as follows: $y = 3.3639x^2 - 38.858x + 119.83$, ($R^2 = 1.0$).

Discussion

Exclusive formula feeding (ExFF) has been given priority as a means of preventing postnatal HTLV-1 MTCT.[19,20] Nevertheless, approximately half of all pregnant carriers selected STBF, although there were regional variations of 38–74%. One of the reasons may be that not only healthcare providers but also carrier mothers want to obtain the benefits of breast milk.[21,22] Second, there is concern about the psychological consequences for mothers of having to avoid or restrict breast-feeding despite the general promotion of breast-feeding.[23] However, our study indicates that it is not always easy to refrain breast-feeding within 3 months after delivery and healthcare providers should explain this fact to pregnat carriers who select STBF.

Previous studies of HTLV-1 MTCT have been retrospective observational studies, mostly conducted in endemic areas.[10,13-15,18,24-27] In most cases, infants' dietary reports could be inaccurate because the data were obtained retrospectively. There is an additional defect in that the timing of antibody testing for the children varies within and between studies. On the other hand, ours is the first nationwide and prospective study in Japan after the introduction of a nationwide antenatal screening program. Our study suggests that STBF may be a viable option for preventing postnatal MTCT. However, if carrier mothers select STBF without obtaining appropriate support, there is a concern that an increase in the proportion of longer term breast-feeding infants would lead to an increased incidence of MTCT. To minimize MTCT risk, a support system to help mothers to refrain from an extended period of breast-feeding is necessary. The MTCT rate for ExFF (6.4%) in this study appears to be higher than was stated by the APP in the Nagasaki Prefecture (2.5%).[10] The reason for this is not clear, but it may be related to the fact that the number of children born to carrier mothers who selected ExFF was 1/10 in our study compared to that of the ATL prevention program.

Although the detailed mechanisms by which STBF prevents postnatal MTCT remain unknown, antibodies transferred from mother to child *in utero* may have an important role.[24] Frozen-thawed breast-milk feeding (FTBMF) may be associated with the destruction of infected cells by freezing and thawing.[14] It is theoretically an attractive alternative, its effect on the incidence of MTCT could not be evaluated because of the small number of cases in this study. The reason that fewer carrier mothers selected FTBMF may be due to an assumption that daily feeding would be too time-consuming.

The enrolled carriers were told about the serological antibody tests for their children at 3 years of age at each facility but the rate of antibody testing was only about 42%. There are several reasons for this. Most likely, this may be because serological antibody testing is not mandatory in the screening program in Japan. Unlike Latin American reports,[28] the infected children in Japan seem to have few symptoms during

Table 3 Mother-to-child transmission rates with respect to feeding options

	Long-term breast-feeding (n = 12)	Short-term breast-feeding (n = 172)	Frozen-thawed breast-milk feeding (n = 19)	Exclusive formula feeding (n = 110)
Infected children (n, %) (95% CI)	2 (16.7%) (−4.4%–37.8%)	4 (2.3%) (0.0%–4.6%)	1 (5.3%) (−4.8%–15.3%)	7 (6.4%) (1.9%–10.9%)

childhood. Thus, there may be little motivation for mothers to have their children tested for antibodies. From a public health perspective, we argue that antibody testing should be recommended for all children born to the infected pregnant women. This would provide more reliable data on the relationship between the selected feeding options and MTCT rates, allowing us to verify the effects of introducing this screening program in Japan. Moreover, a recent systemic review shows that people with HTLV-1 are at a higher risk of death due to other than two diseases (ATL and HAM/TSP) than their HTLV-1-negative counterparts.[29] This report leads to the recognition of various risks of HTLV-1 infection which have not been given close attention due to the low incidence of ATL and HAM/TSP. Although this article does not mention the timing of infection (MTCT or horizontal transmission), such results may contibute to promote antibody testing of children born to pregnant women in carriers.

Our study suggested that a low follow-up rate for children born to pregnant carriers was a major flaw in the screening program. The limitation in our study is associated with this. More than half of the children born to carriers were not available for follow up, resulting in an antibody testing rate of about 42%. Less confidence can therefore be given to the MTCT rates on feeding options obtained by this cohort study. In particular, it was difficult to evaluate the effects of FTBMF on the prevention of MTCT.

The results of this cohort study showed no statistically significant differences in MTCT rates between STBF and ExFF. It also became clear that STBF does not make it easy to wean within 3 months, so it is necessary to understand this if a pregnant woman desires STBF. Whether a mother selects ExFF or STBF, adequate information and support from healthcare providers is essential. However, there is little evidence to recommend FTBMF at present.

In conclusion, our study revealed that the MTCT rate for STBF was not significantly higher than that for ExFF. There is a concern that it is not always easy to wean within 3 months. In addition, the low rate of postnatal antibody testing is a major issue. To clarify not only reliable feeding options to prevent MTCT but also to evaluate the effects of the screening, antibody testing should be recommended for all children born to infected pregnant women.

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Disclosure

The authors declare no conflict of interest.

Author contributions

All of the authors contributed to the conception, design, and execution of the study. K.I. wrote the first draft of the

manuscript and all of the authors contributed to the manuscript revisions. All authors read and approved the submitted version.

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