研究成果の刊行物・別刷

frontiers in Microbiology

REVIEW
published: 09 April 2020
doi: 10.3389/fmicb.2020.00595

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

Kazuo Itabashi[1], Tokuo Miyazawa[2], Akihiko Sekizawa[3], Akifumi Tokita[4], Shigeru Saito[5], Hiroyuki Moriuchi[6], Yasuhito Nerome[7], Kaoru Uchimaru[8] and Toshiki Watanabe[9]*

[1] Showa University Hospital, Tokyo, Japan, [2] Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan, [3] Japan Association of Obstetricians and Gynecologists, Tokyo, Japan, [4] Japanese Pediatric Association, Tokyo, Japan, [5] The University of Toyama, Toyama, Japan, [6] Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [7] Faculty of Medicine, School of Health Sciences, Kagoshima University, Kagoshima, Japan, [8] Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan, [9] Future Center Initiative, and Research Hospital of the Institute of Medical Science, The University of Tokyo, Tokyo, Japan

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 ≤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

OPEN ACCESS

Edited by:
Akio Adachi,
Kansai Medical University, Japan

Reviewed by:
Antoine Gessain,
Institut Pasteur, France
Edward Murphy,
University of California,
San Francisco, United States

****Correspondence:***
Kazuo Itabashi
kitaba@med.showa-u.ac.jp

Specialty section:
This article was submitted to Virology, a section of the journal Frontiers in Microbiology

Received: *31 December 2019*
Accepted: *18 March 2020*
Published: *09 April 2020*

Citation:
Itabashi K, Miyazawa T, Sekizawa A, Tokita A, Saito S, Moriuchi H, Nerome Y, Uchimaru K and Watanabe T (2020) A Nationwide Antenatal Human T-Cell Leukemia Virus Type-1 Antibody Screening in Japan. Front. Microbiol. 11:595. doi: 10.3389/fmicb.2020.00595

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),

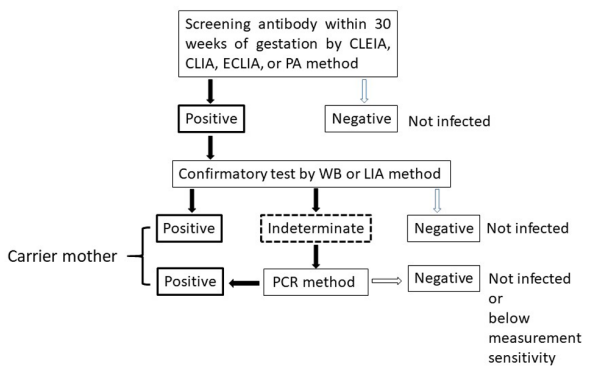


FIGURE 1 | Algorithm to determine HTLV-1 virus carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electro chemiluminescent immunoassay; PA, particle agglutination; WB, Western Blot; LIA, line immunoassay; PCR, polyclonal chain reaction.

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 $\geq$12 months, higher maternal PVL ($\geq$ 100 copies/10^4 PBMC) and $\geq$ 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 ($\geq$ 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.

FUNDING

This work was supported by the Ministry of Health, Labor and Welfare (Grant number: H29-Sukoyaka-Shitei 3).

ACKNOWLEDGMENTS

We would like to thank the HTLV-1 carrier mothers and doctors cooperated with our survey. And, we also would like to thank Editage (www.editage.com) for English language editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2020.00595/full#supplementary-material

REFERENCES

Albenzio, M., Santillo, A., Stolfi, I., Manzoni, P., Iliceto, A., Rinaldi, M., et al. (2016). Lactoferrin levels in human milk after preterm and term delivery. *Am. J. Perinatol.* 33, 1085–1089. doi: 10.1055/s-0036-1586105

Ando, Y., Ekuni, Y., Matsumoto, Y., Nakano, S., Saito, K., Kakimoto, K., et al. (2004). Long-term serological outcome of infants who received frozen-thawed milk from human T-lymphotropic virus type-I positive mothers. *J. Obstet. Gynaecol. Res.* 30, 436–438. doi: 10.1111/j.1447-0756.2004.00227.x

Ando, Y., Kakimoto, K., Tanigawa, T., Furuki, K., Saito, K., Nakano, S., et al. (1989). Effect of freeze-thawing breast milk on vertical HTLV-I transmission from seropositive mothers to children. *Jpn. J. Cancer Res. Gann.* 80, 405–407. doi: 10.1111/j.1349-7006.1989.tb02327.x

Atsma, F., Veldhuizen, I., Verbeek, A., de Kort, W., and de Vegt, F. (2011). Healthy donor effect: its magnitude in health research among blood donors. *Transfusion* 51, 1820–1828. doi: 10.1111/j.1537-2995.2010.03055.x

Bartholomew, C., Jack, N., Edwards, J., Charles, W., Corbin, D., Cleghorn, F. R., et al. (1998). HTLV-I serostatus of mothers of patients with adult T-cell leukemia and HTLV-I-associated myelopathy/tropical spastic paraparesis. *J. Hum. Virol.* 1, 302–305.

Corpeleijn, W. E., de Waard, M., Christmann, V., van Goudoever, J. B., Jansen-van der Weide, M. C., Kooi, E. M., et al. (2016). Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the early nutrition study randomized clinical trial. *JAMA Pediatr.* 170, 654–661. doi: 10.1001/jamapediatrics.2016.0183

Dias, C. C., and Figueiredo, B. (2015). Breastfeeding and depression: a systematic review of the literature. *J. Affect. Disord.* 171, 142–154. doi: 10.3389/fmicb.2018.01879

Ekuni, Y. (1997). Prevention of HTLV-1 vertical infection: usefulness of frozen-thawed breast milk. *Adv. Obstet. Gynecol.* 49, 171–179. doi: 10.11437/sanpunosinpo1949.49.171

Filippone, C., Bassot, S., Betsem, E., Tortevoye, P., Guillotte, M., Mercereau-Puijalon, O., et al. (2012). A new and frequent human T-Cell leukemia virus indeterminate western blot pattern: epidemiological determinants and pcr results in central african inhabitants. *J. Clin. Microbiol.* 50, 1663–1672. doi: 10.1128/JCM.06540-11

Fujii, H., Shimizu, M., Miyagi, T., Kunihiro, M., Tanaka, R., Takahashi, Y., et al. (2016). A Potential of an Anti-HTLV-I gp46 neutralizing monoclonal antibody (LAT-27) for passive immunization against both horizontal and mother-to-child vertical infection with human T Cell leukemia virus type-I. *Viruses* 8:41. doi: 10.3390/v8020041

Fujino, R., Kawato, K., Ikeda, M., Miyakoshi, H., Mizukoshi, M., and Imai, J. (1991). Improvement of Gelatin Particle Agglutination Test for Detection of Anti-HTLV-I Antibody. *Jpn. J. Cancer Res.* 82, 367–370. doi: 10.1111/j.1349-7006.1991.tb01856.x

Gallo, R. C., Willems, L., and Hasegawa, H. (2016). Htlv-1 the GVNTF on. screening transplant donors for HTLV-1 and -2. *Blood* 128, 3029–3031. doi: 10.1182/blood-2016-09-739433

Garin, B., Gosselin, S., de Thé, G., and Gessain, A. (1994). HTLV-I/II infection in a high viral endemic area of Zaire, Central Africa: comparative evaluation of serology, PCR, and significance of indeterminate Western blot pattern. *J. Med. Virol.* 44, 104–109. doi: 10.1002/jmv.1890440119

Guiltinan, A. M., Kaidarova, Z., Behan, D., Marosi, C., Hutching, S., and Kaiser, M. (2013). Major depression and generalized anxiety disorder among human T-lymphotropic virus Types I– and II–infected former blood donors. *Transfusion* 53, 60–68. doi: 10.1111/j.1537-2995.2012.03677.x

Hino, S. (2011). Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL prevention program nagasaki. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 87, 152–166. doi: 10.2183/pjab.87.152

Hino, S., Katamine, S., Kawase, K., Miyamoto, T., Doi, H., Tsuji, Y., et al. (1994). Intervention of maternal transmission of HTLV-1 in nagasaki. *Jpn. Leukemia* 8(Suppl. 1), S68–S70.

Hino, S., Sugiyama, H., Doi, H., Ishimaru, T., Yamabe, T., Tsuji, Y., et al. (1987). Breaking the cycle of Htlv-I transmission via carrier mothers' milk. *Lancet* 330, 158–159. doi: 10.1016/S0140-6736(87)92358-0

Hirata, M., Hayashi, J., Noguchi, A., Nakashima, K., Kajiyama, W., Kashiwagi, S., et al. (1992). The effects of breastfeeding and presence of antibody to p40tax protein of human T cell lymphotropic virus type-I on mother to child transmission. *Int. J. Epidemiol.* 21, 989–994. doi: 10.1093/ije/21.5.989

Hisada, M., Maloney, E. M., Sawada, T., Miley, W. J., Palmer, P., Hanchard, B., et al. (2002). Virus markers associated with vertical transmission of human T lymphotropic virus type 1 in Jamaica. *Clin. Infect. Dis.* 34, 1551–1557. doi: 10.1086/340537

Inaba, S., Sato, H., Okochi, K., Fukada, K., Takakura, F., Tokunaga, K., et al. (1989). Prevention of transmission of human T-lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus one-year experience. *Transfusion* 29, 7–11.

Ishitsuka, K., Yamano, Y., Utsunomiya, A., and Uchimaru, K. (2015). A survey of HTLV-1 carrier clinics in Japan. *Rinsho. Ketsueki.* 56, 666–672.

Itabashi, K. (2016). *HTLV-1 Boshikansen Yobo Taisaku Manyuaru-HTLV-1 母子感染予防対策マニュアル*. Available online at: https://www.mhlw.go.jp/bunya/kodomo/boshi-hoken16/dl/06.pdf (accessed November 13, 2019).

Iwanaga, M., Watanabe, T., Utsunomiya, A., Okayama, A., Uchimaru, K., Koh, K.-R., et al. (2010). Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. *Blood* 116, 1211–1219. doi: 10.1182/blood-2009-12-257410

Iwanaga, M., Watanabe, T., and Yamaguchi, K. (2012). Adult T-cell leukemia: a review of epidemiological evidence. *Front. Microbiol.* 3:322. doi: 10.3389/fmicb.2012.00322

Kashiwagi, K., Furusyo, N., Nakashima, H., Kubo, N., Kinukawa, N., Kashiwagi, S., et al. (2004). A decrease in mother-to-child transmission of human T lymphotropic virus type I (HTLV-I) in Okinawa, Japan. *Am. J. Trop. Med. Hyg.* 70, 158–163.

Katsuya, H., Ishitsuka, K., Utsunomiya, A., Hanada, S., Eto, T., Moriuchi, Y., et al. (2015). Treatment and survival among 1594 patients with ATL. *Blood* 126, 2570–2577. doi: 10.1182/blood-2015-03-632489

Kawano, N., Yoshida, S., Kawano, S., Kuriyama, T., Tahara, Y., Toyofuku, A., et al. (2018). The clinical impact of human T-lymphotrophic virus type 1 (HTLV-1) infection on the development of adult T-cell leukemia-lymphoma (ATL) or HTLV-1–associated myelopathy (HAM) / atypical HAM after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and renal transplantation. *J. Clin. Exp. Hematop.* 58, 107–121. doi: 10.3960/jslrt.18011

Kendall, E. A., Gonzalez, E., Espinoza, I., Tipismana, M., Verdonck, K., Clark, D., et al. (2009). Early neurologic abnormalities associated with human T-cell lymphotropic virus type 1 infection in a cohort of Peruvian children. *J. Pediatr.* 155, 700–706. doi: 10.1016/j.jpeds.2009.05.027

Kuo, C.-W. S., Mirsaliotis, A., and Brighty, D. W. (2011). Antibodies to the envelope glycoprotein of human t cell leukemia virus type 1 robustly activate cell-mediated cytotoxic responses and directly neutralize viral infectivity at multiple steps of the entry process. *J. Immunol.* 187, 361–371. doi: 10.4049/jimmunol.1100070

Kuramitsu, M., Sekizuka, T., Yamochi, T., Firouzi, S., Sato, T., Umeki, K., et al. (2017). Proviral features of human T cell leukemia virus type 1 in carriers with indeterminate western blot analysis results. *J. Clin. Microbiol.* 55, 2838–2849. doi: 10.1128/JCM.00659-17

Kusuhara, K., Sonoda, S., Takahashi, K., Tokugawa, K., Fukushige, J., and Ueda, K. (1987). Mother-to-child transmission of human T-cell leukemia virus type I (HTLV-I): a fifteen-year follow-up study in Okinawa. *Jpn. Int. J. Cancer* 40, 755–757. doi: 10.1002/ijc.2910400607

Laperche, S., Sauleda, S., Piron, M., Mühlbacher, A., Schennach, H., Schottstedt, V., et al. (2017). Evaluation of sensitivity and specificity performance of elecsys HTLV-I/II assay in a multicenter study in europe and Japan. *J. Clin. Microbiol.* 55, 2180–2187. doi: 10.1128/JCM.00169-17

Li, H.-C., Biggar, R. J., Miley, W. J., Maloney, E. M., Cranston, B., Hanchard, B., et al. (2004). Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I. *J. Infect. Dis.* 190, 1275–1278. doi: 10.1086/423941

Maehama, T., Nakayama, M., Nagamine, M., Nakashima, Y., Takei, H., and Nakachi, H. (1992). Studies on factor affecting mother-to-child HTLV-I transmission. *Acta Obst. Gynaec. Jpn.* 44, 215–222.

Malik, B., and Taylor, G. P. (2019). Can we reduce the incidence of adult T-cell leukaemia/lymphoma? Cost-effectiveness of human T-lymphotropic virus type 1 (HTLV-1) antenatal screening in the United Kingdom. *Br. J. Haematol.* 184, 1040–1043. doi: 10.1111/bjh.15234

Maloney, E. M., Wiktor, S. Z., Palmer, P., Cranston, B., Pate, E. J., Cohn, S., et al. (2003). A Cohort study of health effects of human T-Cell lymphotropic virus type I infection in jamaican children. *Pediatrics* 112, e136–e142. doi: 10.1542/peds.112.2.e136

Martin, F., Tagaya, Y., and Gallo, R. (2018). Time to eradicate HTLV-1: an open letter to WHO. *Lancet* 391, 1893–1894. doi: 10.1016/S0140-6736(18)30974-7

Miller, J., Tonkin, E., Damarell, R. A., McPhee, A. J., Suganuma, M., Suganuma, H., et al. (2018). A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants. *Nutrients* 10:707. doi: 10.3390/nu10060707

Moreno-Ajona, D., Yuste, J. R., Martín, P., and Gállego Pérez-Larraya, J. (2018). HTLV-1 myelopathy after renal transplant and antiviral prophylaxis: the need for screening. *J. Neurovirol.* 24, 523–525. doi: 10.1007/s13365-018-0627-3

Morita, Y., Campos-Alberto, E., Yamaide, F., Nakano, T., Ohnisi, H., Kawamoto, M., et al. (2018). TGF-β concentration in breast milk is associated with the development of eczema in infants. *Front. Pediatr.* 6:162. doi: 10.3389/fped.2018.00162

Moriuchi, H., Masuzaki, H., Doi, H., and Katamine, S. (2013). Mother-to-child transmission of human T-cell lymphotropic virus type 1. *Pediatr. Infect. Dis. J.* 32, 175–177. doi: 10.1097/INF.0b013e31827efc39

Moriuchi, H.森内浩幸, Takeda, K.武田敬子, and Nakajma, Y.中嶋有美子. (2017). Kyaria botai kara umareta ji no tsuiseki chôsa (Nagasaki-ken) キャリア母体から生まれた児の追跡調査 (長崎県). *Health Lab. Sci. Res. Grant* 19–25.

Moriuchi, M., Inoue, H., and Moriuchi, H. (2001). Reciprocal interactions between human T-lymphotropic virus Type 1 and prostaglandins: implications for viral transmission. *J. Virol.* 75, 192–198. doi: 10.1128/JVI.75.1.192-198.2001

Moriuchi, M., and Moriuchi, H. (2001). A milk protein lactoferrin enhances human T cell leukemia virus type I and suppresses HIV-1 infection. *J. Immunol.* 166, 4231–4236. doi: 10.4049/jimmunol.166.6.4231

Moriuchi, M., and Moriuchi, H. (2002). Transforming growth factor-β enhances human T-cell leukemia virus type I infection. *J. Med. Virol.* 67, 27–30. doi: 10.1002/jmv.10074

Morota, K., Fujinami, R., Kinukawa, H., Machida, T., Ohno, K., Saegusa, H., et al. (2009). A new sensitive and automated chemiluminescent microparticle immunoassay for quantitative determination of hepatitis C virus core antigen. *J. Virol. Methods* 157, 8–14. doi: 10.1016/j.jviromet.2008.12.009

Morrison, B. J., Labo, N., Miley, W. J., and Whitby, D. (2015). Serodiagnosis for tumor viruses. *Semin. Oncol.* 42, 191–206. doi: 10.1053/j.seminoncol.2014.12.024

Murakami, Y., Hasegawa, A., Ando, S., Tanaka, R., Masuda, T., Tanaka, Y., et al. (2017). A novel mother-to-child human T-cell leukaemia virus type 1 (HTLV-1) transmission model for investigating the role of maternal anti-HTLV-1 antibodies using orally infected mother rats. *J. Gen. Virol.* 98, 835–846. doi: 10.1099/jgv.0.000733

Murphy, E. L., Hanchard, B., Figueroa, J. P., Gibbs, W. N., Lofters, W. S., Campbell, M., et al. (1989). Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. *Int. J. Cancer* 43, 250–253. doi: 10.1002/ijc.2910430214

Nakagawa, M., Izumo, S., Ijichi, S., Kubota, H., Arimura, K., Kawabata, M., et al. (1995). HTLV-I-associated myelopathy: analysis of 213 patients based on clinical features and laboratory findings. *J. Neurovirol.* 1, 50–61. doi: 10.3109/13550289509111010

Nakayama, H.中山英樹, Take, H.武弘道, Umemoto, M.梅本正和, Seki, S.関修一郎, and Kuraya, K.蔵屋一枝 (1992). HTLV-I no boshikansenritsu ni tsuite -bonyû eiyô to jinkô eiyô no hikaku- HTLV-Iの母子感染率について–母乳栄養と人工栄養の比較–. *J. Jpn. Pediatic. Soc.* 96, 2092–2096.

Nerome, Y., and Kawano, Y. (2017). Failure to prevent human T-cell leukemia virus type 1 mother-to-child transmission in Japan. *Pediatr. Int.* 59, 227–228. doi: 10.1111/ped.13165

Nerome, Y., Kojyo, K., Ninomiya, Y., Ishikawa, T., Ogiso, A., Takei, S., et al. (2014). Current human T-cell lymphotropic virus type 1 mother-to-child transmission prevention status in Kagoshima. *Pediatr. Int.* 56, 640–643. doi: 10.1111/ped.12385

Nishijima, T., Shimada, S., Noda, H., and Miyake, K. (2019). Towards the elimination of HTLV-1 infection in Japan. *Lancet Infect. Dis.* 19, 15–16. doi: 10.1016/S1473-3099(18)30735-7

Njom Nlend, A. E., Motaze, A. C. N., Sandie, A., and Fokam, J. (2018). HIV-1 transmission and survival according to feeding options in infants born to HIV-infected women in Yaoundé, Cameroon. *BMC Pediatr.* 18:69. doi: 10.1186/s12887-018-1049-3

Nyambi, P. N., Ville, Y., Louwagie, J., Bedjabaga, I., Glowaczower, E., Peeters, M., et al. (1996). Mother-to-child transmission of human T-cell lymphotropic virus types I and II (HTLV-I/II) in gabon: a prospective follow-up of 4 years. *J. Acquir. Immun. Defic. Syndr. Hum. Retrovirol.* 12, 187–192. doi: 10.1097/00042560-199606010-00013

Oki, T., Yoshinaga, M., Otsuka, H., Miyata, K., Sonoda, S., and Nagata, Y. (1992). A sero-epidemiological study on mother-to-child transmission of HTLV-I in southern Kyushu, Japan. *Asia Ocean. J. Obstet. Gynaecol.* 18, 371–377. doi: 10.1111/j.1447-0756.1992.tb00333.x

Oliveira, P. D., Kachimarek, A. C., and Bittencourt, A. L. (2017). Early onset of HTLV-1 associated Myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATL): systematic search and review. *J. Trop. Pediatr.* 64, 151–161. doi: 10.1093/tropej/fmx039

O'Sullivan, A., Farver, M., and Smilowitz, J. T. (2015). The influence of early infant-feeding practices on the intestinal microbiome and body composition in infants. *Nutr. Metab. Insights* 8(Suppl. 1), 1–9. doi: 10.4137/NMI.S29530

Paiva, A. M., Assone, T., Haziot, M. E. J., Smid, J., Fonseca, L. A. M., Luiz, O. D., et al. (2018). Risk factors associated with HTLV-1 vertical transmission in Brazil: longer breastfeeding, higher maternal proviral load and previous HTLV-1-infected offspring. *Sci. Rep.* 8:7742. doi: 10.1038/s41598-018-25939-y

Prendergast, A. J., Goga, A. E., Waitt, C., Gessain, A., Taylor, G. P., Rollins, N., et al. (2019). Transmission of CMV, HTLV-1, and HIV through breastmilk. *Lancet Child Adolesc. Health* 3, 264–273. doi: 10.1016/S2352-4642(19)30024-0

Qiu, X., Hodges, S., Lukaszewska, T., Hino, S., Arai, H., Yamaguchi, J., et al. (2008). Evaluation of a new, fully automated immunoassay for detection of HTLV-I and HTLV-II antibodies. *J. Med. Virol.* 80, 484–493. doi: 10.1002/jmv.21083

Ribeiro, M. A., Martins, M. L., Teixeira, C., Ladeira, R., Oliveira, M., de, F., et al. (2012). Blocking vertical transmission of human T cell lymphotropic virus

type 1 and 2 through breastfeeding interruption. *Pediatr. Infect. Dis. J.* 31, 1139–1143. doi: 10.1097/INF.0b013e318263215e

Rocha-Filho, P. A. S., and Goncalves, L. R. (2018). Depression and anxiety disorders among patients with human T-cell lymphotropic virus type-1: a cross-sectional study with a comparison group. *Rev. Soc. Bras. Med. Trop.* 51, 357–360. doi: 10.1590/0037-8682-0365-2016

Romer, D., Brighty, D. W., Robson, C. L., and Sattentau, Q. J. (2009). Candidate polyanionic microbicides inhibit human T-Cell lymphotropic virus type 1 receptor interactions, cell-free infection, and cell-cell spread. *Antimicrob. Agents Chemother.* 53, 678–687. doi: 10.1128/AAC.01550-07

Rosadas, C., Malik, B., Taylor, G. P., and Puccioni-Sohler, M. (2018). Estimation of HTLV-1 vertical transmission cases in Brazil per annum. *PLoS Negl. Trop. Dis.* 12:e0006913. doi: 10.1371/journal.pntd.0006913

Rosadas, C., and Taylor, G. P. (2019). Mother-to-Child HTLV-1 transmission: unmet research needs. *Front. Microbiol.* 10:999. doi: 10.3389/fmicb.2019.00999

Sabino, E. C., Zrein, M., Taborda, C. P., Otani, M. M., Ribeiro-Dos-Santos, G., and Sáez-Alquézar, A. (1999). Evaluation of the INNO-LIA HTLV I/II assay for confirmation of human T-cell leukemia virus-reactive sera in blood bank donations. *J. Clin. Microbiol.* 37, 1324–1328.

Satake, M., Iwanaga, M., Sagara, Y., Watanabe, T., Okuma, K., and Hamaguchi, I. (2016). Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: a nationwide retrospective cohort analysis. *Lancet Infect. Dis.* 16, 1246–1254. doi: 10.1016/S1473-3099(16)30252-3

Satake, M., Yamaguchi, K., and Tadokoro, K. (2012). Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. *J. Med. Virol.* 84, 327–335.

Suzuki, S., Tanaka, M., Matsuda, H., Tsukahara, Y., Kuribayashi, Y., Gomibuchi, H., et al. (2014). Current status of HTLV-1 carrier in Japanese pregnant women. *J. Matern. Fetal Neonatal Med.* 27, 312–313. doi: 10.3109/14767058.2013.814631

Takahashi, K., Takezaki, T., Oki, T., Kawakami, K., Yashiki, S., Fujiyoshi, T., et al. (1991). Inhibitory effect of maternal antibody on mother-to-child transmission of human. *Int. J. Cancer* 49, 673–677. doi: 10.1002/ijc.2910490508

Takezaki, T.嶽崎俊郎. (2009). Kagoshima-ken ni okeru HTLV-I kyaria haha karano shuseiji ni okeru tuiseki kenkyū 鹿児島県における HTLV-Iキャリア母からの出生児における追跡研究. *Health Lab. Sci. Res. Grant* 59–61.

Takezaki, T., Tajima, K., Ito, M., Ito, S., Kinoshita, K., Tachibana, K., et al. (1997). Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. The Tsushima ATL Study Group. *Leukemia* 11(Suppl. 3), 60–62.

Taylor, G. P., Bodéus, M., Courtois, F., Pauli, G., del Mistro, A., Machuca, A., et al. (2005). The Seroepidemiology of human T-lymphotropic viruses: types I and II in europe: a prospective study of pregnant women. *J. Acquir. Immun. Defic. Syndr.* 38:104. doi: 10.1097/00126334-200501010-00018

Thompson, J. M. D., Tanabe, K., Moon, R. Y., Mitchell, E. A., McGarvey, C., Tappin, D., et al. (2017). Duration of breastfeeding and risk of SIDS: an individual participant data meta-analysis. *Pediatrics* 140:e20171324.

Thorstensson, R., Albert, J., and Andersson, S. (2002). Strategies for diagnosis of HTLV-I and -II. *Transfusion* 42, 780–791. doi: 10.1046/j.1537-2995.2002.00114.x

UK National Screening Committee (2017). *Antenatal Screening for HTLV Infection*. Available online at: https://legacyscreening.phe.org.uk/policydb_download.php?doc=704 (accessed August 28, 2019).

Umeki, K., Umekita, K., Hashikura, Y., Yamamoto, I., Kubo, K., Nagatomo, Y., et al. (2017). Evaluation of line immunoassay to detect HTLV-1 infection in an endemic area, southwestern japan; comparison with polymerase chain reaction and western blot. *Clin. Lab.* 63, 227–233. doi: 10.7754/Clin.Lab.2016.160501

Ureta-Vidal, A., Angelin-Duclos, C., Tortevoye, P., Murphy, E., Lepere, J. F., Buigues, R. P., et al. (1999). Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: implication of high antiviral antibody titer and high proviral load in carrier mothers. *Int. J. Cancer* 82, 832–836.

Victora, C. G., Bahl, R., Barros, A. J. D., França, G. V. A., Horton, S., Krasevec, J., et al. (2016). Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 387, 475–490. doi: 10.1016/S0140-6736(15)01024-7

WHO News and Activities (1991). AIDS: proposed WHO criteria for interpreting western blot assays for HIV-1, HIV-2, and HTLV-I/HTLV-II. *Bull. World Health Organ.* 69, 127–133.

Wiktor, S. Z., Pate, E. J., Rosenberg, P. S., Barnett, M., Palmer, P., Medeiros, D., et al. (1997). Mother-to-child transmission of human T-cell lymphotropic virus type I associated with prolonged breast-feeding. *J. Hum. Virol.* 1, 37–44.

Willems, L., Hasegawa, H., Accolla, R., Bangham, C., Bazarbachi, A., Bertazzoni, U., et al. (2017). Reducing the global burden of HTLV-1 infection: an agenda for research and action. *Antivir. Res.* 137, 41–48. doi: 10.1016/j.antiviral.2016.10.015

Yamano, Y., and Sato, T. (2012). Clinical pathophysiology of human T-lymphotropic virus-type 1-associated myelopathy/tropical spastic paraparesis. *Front. Microbiol.* 3:389.

Yamanouchi, K., Kinoshita, K., Moriuchi, R., Katamine, S., Amagasaki, T., Ikeda, S., et al. (1985). Oral transmission of human T-Cell leukemia virus Type-I into a common marmoset (Callithrix Jacchus) as an experimental model for milk-borne transmission. *Jpn. J. Cancer Res. Gann.* 76, 481–487. doi: 10.20772/cancersci1985.76.6_481

Yoshida, Y., Sakamoto, Y., Yoshimine, A., Maruyama, Y., Ikegami, N., Inose, M., et al. (1993). Three cases of juvenile onset HTLV-I-associated myelopathy with pseudohypoparathyroidism. *J. Neurol. Sci.* 118, 145–149.

Zihlmann, K. F., de Alvarenga, A. T., and Casseb, J. (2012). Living invisible: HTLV-1-infected persons and the lack of care in public health. *PLoS Negl. Trop. Dis.* 6:e1705. doi: 10.1371/journal.pntd.0001705

Zrein, M., Louwagie, J., Boeykens, H., Govers, L., Hendrickx, G., Bosman, F., et al. (1998). Assessment of a new immunoassay for serological confirmation and discrimination of human T-cell lymphotropic virus infections. *Clin. Diagn. Lab. Immunol.* 5, 45–49.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

260 妊娠中にHTLV-1抗体が陽性といわれました。母乳を飲ませても大丈夫ですか？

宮沢篤生

Key words
HTLV-1，母乳，母子感染，成人T細胞白血病，HTLV-1関連脊髄症

回答のポイント

1)成人T細胞白血病（ATL）の大部分は母子感染から40～50年を経て発症することから，母子感染予防が重要である。
2)母子感染の主要な経路は経母乳感染であり，予防には完全人工栄養が最も確実な方法である。
3)母乳栄養を強く希望する場合には3カ月未満の短期母乳栄養や凍結解凍母乳による栄養方法を選択することもできるが，十分なエビデンスは確立していない。
4)短期母乳栄養を選択する場合には，3カ月で確実に母乳を中止できるように母児を支援する必要がある。

○解　説

1．HTLV-1とは

HTLV-1（human T-cell lymphotrophic virus）はレトロウイルスの一種であり，ヒトTリンパ球（$CD4^+$）に感染後，逆転写酵素の働きでDNAを合成し，宿主細胞の染色体DNAに組み込まれるプロウイルスとして存在する。HTLV-1キャリアは通常無症状であるが，5%でATL，0.3%でHTLV-1関連脊髄症（HAM）を発症する。HTLV-1キャリアは世界で500万～1,000万人と推測されるが，日本，西アフリカおよび中央アフリカ，カリブ海地域，南米など特定の地域に偏在している。我が国は先進諸国ではキャリア数が最も多く100万人を超えている。従来，キャリアは流行地域である西日本（九州，沖縄など）に集中していたが，近年では東京，愛知，大阪といった大都市を抱える地域にも拡大しつつある。

MIYAZAWA Tokuo　昭和大学医学部小児科学講座
〒142-8666　東京都品川区旗の台1-5-8
Email address：miyazawa.t@med.showa-u.ac.jp

HTLV-1の感染力は弱く，感染リンパ球を介した細胞同士の接触により感染が伝播する。主な感染経路は，母子感染，性行為感染（主に男性から女性），輸血による感染である。我が国では母子感染が60%以上，性行為感染（主に男性から女性への感染）が20%，輸血による感染はスクリーニング検査が行われているため皆無であると考えられている。成人期の感染によりATLを発症することは稀であり，ATLのほとんどが母子感染から40～50年を経て発症することから，母子感染の予防が最も重要である。これまでの疫学研究や動物実験などから，母子感染の主体は感染したリンパ球を含む母乳を介した感染であることが明らかになっている。

2．妊婦に対するスクリーニング検査

我が国では2010年11月の厚生労働省母子保健課長通達を経て，全妊婦に対するHTLV-1抗体スクリーニング検査への公費助成が行われるようになった。『産婦人科診療ガイドライン産科編2017』においても，妊娠30週頃までにスクリーニング検

表　母子感染予防のための栄養方法

	母子感染率（1990～2009）※	機序	利点	課題
完全人工栄養（推奨）	3.3%（51/1,553）	・感染細胞への曝露がない	・最も確実な予防方法	・母親の満足が得られにくい ・母乳栄養の利点が得られない ・費用がかかる
短期母乳栄養（3カ月未満）	1.9%（3/162）	・母由来の中和抗体の存在 ・感染細胞への曝露が短期間	・短期間であるが母乳の利点が得られる ・直接授乳が可能	・現時点では十分なエビデンスがない ・結果的に母乳栄養が長期化すると感染リスクが高くなる ・2カ月ごろから母乳遮断に向けた準備と支援が必要
凍結解凍母乳（−20℃，24時間以上）	3.1%（2/64）	・感染細胞の破壊・死滅	・ある程度は母乳栄養の利点が得られる	・現時点では十分なエビデンスがない ・手技が煩雑 ・母乳パックなどの費用がかかる ・直接授乳ができない ・Cell Alive Systemの冷蔵庫は使用不可
長期母乳栄養	17.7%（93/525）			

※厚生労働科学研究費補助金・特別研究事業「HTLV-1の母子感染予防に関する研究」（研究代表者：齋藤 滋），平成21年度総括・分担報告書

査（CLEIA法，CLIA法，ECLIA法，PA法）を行うことが推奨されている（推奨レベルA）。スクリーニング検査には偽陽性が一定の割合で存在することから，スクリーニング陽性者に対しては必ずウエスタンブロット法（WB法）もしくはラインブロット法（LIA法）による確認検査が必要である。確認検査が陰性であれば妊婦は感染していないと判定される。2011年の調査ではスクリーニング検査陽性妊婦の発生率は0.3%であり，このうちWB法陽性は51.6%，陰性は36.7%。判定保留は11.7%であった。WB法で判定保留の場合には，HTLV-1核酸検出法（PCR法）による評価が推奨されている（2016年4月保険収載）。近年開発された新しい確認検査であるLIA法は，WB法に比べ判定保留率が低減することが期待されている（2017年10月保険収載）。

3．母子感染予防のための乳準選択

母子感染の主要な経路である経母乳感染を予防するためには，感染したTリンパ球を含む母乳を与えないこと，すなわち完全人工栄養が理論的には最も確実な方法である。我が国では完全人工栄養以外の手段として，3カ月未満の短期母乳栄養や凍結解凍母乳による栄養法が選択されることがあるが（**表**），現時点でこれらの方法による母子感染予防効果について十分なエビデンスは確立していない（註：2011年より厚生労働科学研究班によるコホート研究が進行中である）。短期母乳栄養を選択した場合であっても，3カ月で母乳を中止することが困難となり，母乳栄養期間が長期化すると母子感染のリスクが高くなる可能性がある。このような背景から，2017年に改訂された『HTLV-1母子感染予防対策マニュアル』[1]ではキャリア妊婦に対しては「原則として完全人工栄養を勧める」と記載されている。一方で完全人工栄養であっても，経母乳感染以外の経路により3.3%で母子感染が起こり得る。栄養方法については分娩前に母親に対して十分な情報提供を行った上で事前に決定しておくことが望ましい。

4．キャリアから出生した児の評価

母子感染の有無を確認するための抗体検査の時期は，母体からの移行抗体が消失し，感染による抗体が確実に出現する3歳以降に実施することが推奨される。

文献

1）　平成28年度厚生労働行政推進調査事業費補助金・成

育疾患克服等次世代育成基盤研究事業HTLV-1母子感染予防に関する研究：HTLV-1抗体陽性妊婦からの出生児のコホート研究（研究代表者：板橋家頭夫）：HTLV-1母子感染予防対策マニュアル，2017（https://www.mhlw.go.jp/bunya/kodomo/boshi-hoken16/dl/06.pdf（2019年7月17日アクセス））

実際の回答モデル

我が国ではすべての妊婦さんに対してHTLV-1感染のスクリーニング検査が公費負担で実施されています。スクリーニング検査が陰性であれば感染を否定することができますが，陽性であってもHTLV-1に感染していると診断することはできません。確認検査が陽性であった場合にはじめてHTLV-1に感染していると判定することが可能です。HTLV-1に感染しても通常自覚症状はありませんが，HTLV-1は血液中のTリンパ球のDNAに組み込まれるため，感染が成立するとHTLV-1のキャリアとなります。キャリアとなった方の大部分は生涯にわたって疾患を発症することはありませんが，およそ5%がATL，0.3%がHAMを発症するといわれています。

HTLV-1の主要な感染経路は母乳を介した母子感染であり，ATLの大部分は母子感染から40～50年以上の潜伏期間を経て発症することから，母子感染の予防が最も重要です。母子感染の予防には感染したリンパ球を含む母乳を与えないこと，すなわち人工乳（育児用ミルク）のみを与えることが最も確実な方法です。しかし完全人工栄養であっても母子感染が3%程度は起こり得ることがわかっています。また，この方法では母乳によるメリット（栄養学的な利点，免疫成分の付与，母子愛着形成の促進など）を生かすことができないといった問題があります。母乳栄養を強く希望される場合には，3カ月未満の短期母乳栄養を行い，その後は人工乳栄養に切り替える方法，あるいは一度凍結させた母乳を解凍して与える方法を選択することも可能です。完全人工栄養と同程度の予防効果が期待されていますが，どちらも小規模の検討しか行われていないため，現時点では十分なエビデンスが確立されていません。特に短期母乳栄養を選択した場合には，3カ月で母乳を中止することが困難となり，結果として母乳栄養が長期化すると母子感染のリスクが高くなるため，生後2カ月あたりから母乳中止に向けた準備が必要です。お子さんへの母子感染の有無を評価するためには3歳以降で抗体検査を実施する必要があります。

特集　母子感染症の必修知識―エキスパートに学び予防につなげる

各病原体の母子管理―最新の疫学情報を含めて　HTLV-1 関連疾患

HTLV-1 母子感染の現状と課題

宮沢篤生*　板橋家頭夫**

はじめに

HTLV-1（human T-cell lymphotropic virus）はレトロウイルスの一種であり，ヒトTリンパ球（$CD4^+$）に感染後，逆転写酵素の働きでDNAを合成し，宿主細胞の染色体DNAに組み込まれるプロウイルスとして存在する。HTLV-1キャリアは通常無症状であるが，5%で成人T細胞性白血病（ATL），0.3%でHTLV-1関連脊髄症（HAM）を発症する。HTLV-1キャリアは世界で500万～1000万人と推測されるが，日本，西および中央アフリカ，カリブ海地域，南米など特定の地域に偏在している[1]。わが国は先進諸国ではキャリア数がもっとも多く100万人をこえている。従来，キャリアは流行地域である西日本（九州，沖縄など）に集中していたが，近年では東京，愛知，大阪といった大都市を抱える地域にも拡大しつつある（図1）[2]。

HTLV-1 の感染経路

HTLV-1の感染力は弱く，感染リンパ球を介した細胞同士の接触により感染が伝播する。主な感染経路は，母子感染，性行為感染（主に男性から

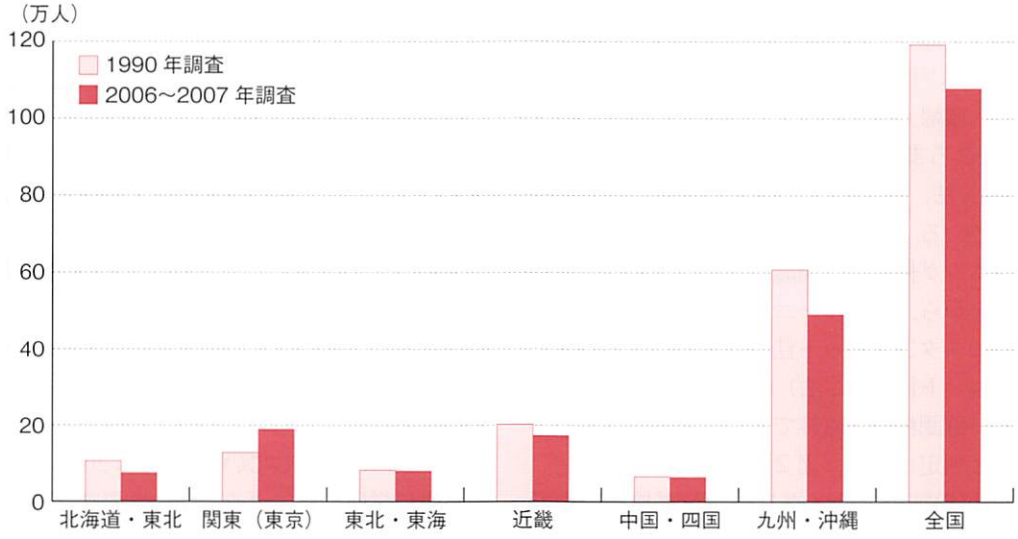


図1　献血者の陽性数から推測したHTLV-1キャリアの国内動向
〔文献2)〕

MIYAZAWA Tokuo　ITABASHI Kazuo
* 昭和大学医学部小児科学講座〔〒142-8555　東京都品川区旗の台1-5-8〕
TEL 03-3784-8000　E-mail：miyazawa.t@med.showa-u.ac.jp
** 昭和大学病院病院長

女性への感染），輸血による感染である。わが国では母子感染が60%以上，性行為感染が20%，輸血による感染はスクリーニング検査が行われているため皆無であると考えられている。成人期の感染によりALTを発症することはまれであり，ATLのほとんどが母子感染から40～50年を経て発症することから，母子感染の予防がもっとも基本的な対策となる。

これまでの疫学研究や動物実験などから，母子感染の主体は感染したリンパ球を含む母乳を介した感染であることが明らかになっている。キャリアの母親から出生した児の乳汁栄養法別の母子感染率は完全人工栄養児で3.3%であるのに対して，生後3か月以上母乳栄養を続けた児では17.7%であり，母乳を遮断することで1/5～1/6に減らすことが示されている[2]。一方で完全人工栄養児であっても母子感染例が存在することから，母乳以外の感染経路，すなわち経胎盤感染や産道感染が存在する可能性が示唆されるが，現時点では明らかになっていない。

母子感染予防対策の現状

わが国では2010年11月の厚生労働省母子保健課長通達を経て，全妊婦に対するHTLV-1抗体スクリーニング検査への公費助成が行われるようになった。産婦人科診療ガイドラインにおいても妊娠30週ごろまでにスクリーニング検査（CLEIA法，CLIA法，ECLIA法，PA法）を行うことが推奨されている（推奨レベルA：強く推奨する）。スクリーニング検査には偽陽性が一定の割合で存在することから，スクリーニング陽性者に対しては必ずウエスタンブロット法（WB法）もしくはラインブロット法（LIA法）による確認検査が必要である。確認検査が陰性であれば妊婦は感染していないと判定される（図2）[3]。

2011年の調査ではスクリーニング検査陽性妊婦の発生率は0.3%であり，このうちWB法陽性は51.6%，陰性は36.7%。判定保留は11.7%であり，WB法陽性は全対象者の0.16%であった[4]。WB法で判定保留の場合には，HTLV-1核酸検出法（PCR法）による評価が推奨されており（2016年4月保険収載），およそ20%がPCR法陽性となる。近年開発された新しい確認検査であるLIA法は，WB法に比べ判定保留率が低減することが期待されている（2017年10月保険収載）[5]。

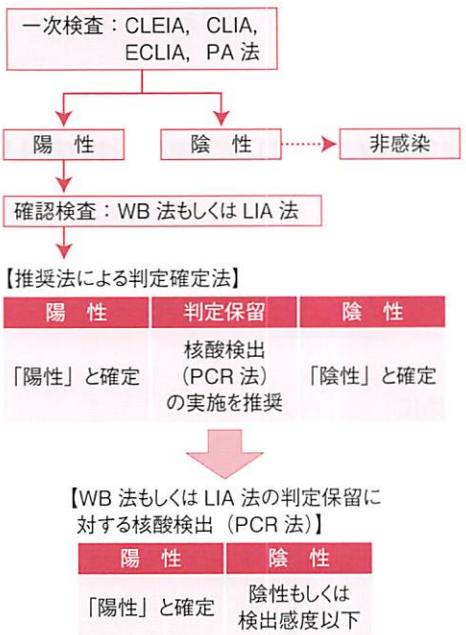


図2　HTLV-1感染の診断のためのフローチャート　〔文献3)〕

母子感染予防のための乳汁選択

母子感染の主要な経路である経母乳感染を予防するためには，感染したTリンパ球を含む母乳を与えないこと，すなわち完全人工栄養が理論的にはもっとも確実な方法である。わが国では完全人工栄養以外の手段として，3か月未満の短期母乳栄養や凍結解凍母乳による栄養法が選択されることがあるが（表），これらの方法による母子感染予防効果に関する報告はいずれも症例数の少ない小規模な研究によるものであり，現時点では十分なエビデンスは確立していない（註：2011年より厚生労働科学研究班によるコホート研究が進行中である）。短期母乳栄養による感染予防は，母親からの移行抗体による効果や感染細胞への曝露が短期間であることが機序として考えられている。一方，3か月で母乳から人工乳（あるいは凍結解凍母乳）への切り替えは必ずしも容易ではなく，母乳栄養期間が長期化すると母子感染のリスクが高

表　母子感染予防のための栄養方法

	母子感染率（1990～2009）*	機　序	利　点	課　題
完全人工栄養（推奨）	3.3%（51/1553）	・感染細胞への曝露がない	・もっとも確実な予防方法	・母親の満足が得られ難い ・母乳栄養の利点が得られない ・費用がかかる
短期母乳栄養（3 か月未満）	1.9%（3/162）	・母由来の中和抗体の存在 ・感染細胞への曝露が短期間	・短期間であるが母乳の利点が得られる ・直接授乳が可能	・現時点では十分なエビデンスがない ・結果的に母乳栄養が長期化すると感染リスクが高くなる ・2 か月ごろから母乳遮断に向けた準備と支援が必要
凍結解凍母乳（−20℃，24 時間以上）	3.1%（2/64）	・感染細胞の破壊・死滅	・ある程度は母乳栄養の利点が得られる	・現時点では十分なエビデンスがない ・手技が煩雑 ・母乳パックなどの費用がかかる ・直接授乳ができない ・Cell Alive System の冷蔵庫は使用不可
長期母乳栄養	17.7%（93/525）			

〔*文献 2)〕

くなる可能性がある。短期母乳栄養を選択した母親に対しては，事前にいつからどのように授乳を減らしていくのかについて相談しておくとともに，乳房トラブルへの対処方法など，きめ細かい支援が必要となる。

このような背景から，2017 年に改訂された「HTLV-1 母子感染予防対策マニュアル」ではキャリア妊婦に対しては「原則として完全人工栄養を勧める」と記載されている[6]。完全人工栄養であっても，経母乳感染以外の経路により 3.3%で母子感染が起こりうる。栄養方法については分娩前に母親に対して各栄養方法のメリット・デメリットについて十分な情報提供を行ったうえで事前に意思決定できるように支援する必要がある。

早産児や極低出生体重児に対しては人工乳を与えることによる壊死性腸炎のリスク，母体からの免疫成分を付与することができないといったデメリットを考慮する必要がある。母親と十分に相談したうえで，直接授乳を開始する時期までは凍結母乳を使用することも考慮すべきであろう[6]。

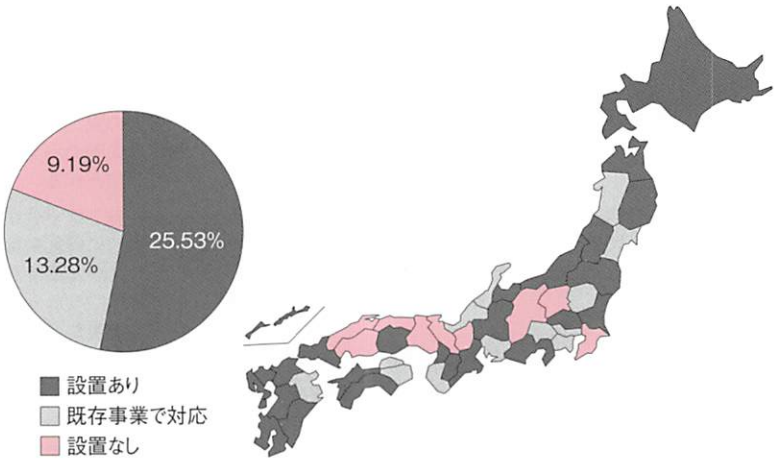
キャリアから出生した児のフォローアップ

乳幼児期に HTLV-1 関連疾患を発症することはないことから，キャリア妊婦から出生した児のフォローアップは，原則として通常の乳幼児健診のスケジュールで実施すればよい。予防接種に関しても一般的なスケジュールどおりに実施する。短期母乳栄養を選択した母親に対しては，生後 2 か月時点で授乳を中止する準備について指導を行い，3 か月時点で中止できていることを確認する。

母子感染の有無を評価するための児の抗体検査の必要性については現時点でコンセンサスは得られていない。児の検査を医療者側から強制すべきではないが，検査を実施することにより① 将来，妊娠や献血などの際に突然キャリアであることを告知される精神的負担の軽減，② HTLV-1 関連疾患に対する新薬や治療方法が開発された際の医療へのアクセスの確保，③ 周囲への感染伝播（とくに性感染）の抑制，といった利点が挙げられる。生後早期には母親由来の移行抗体が存在するため，生後 1 年以内の検査は不適切である。一般的には移行抗体が消失し，児への感染によって抗体が確実に出現する 3 歳以降の検査が推奨されている[6]。

HTLV-1 母子感染対策協議会の現状

2010 年より妊婦に対する HTLV-1 抗体スクリーニング検査が開始されたことに伴い，厚生労



設置なし：**群馬県**，千葉県，長野県，**滋賀県**，京都府，鳥取県，兵庫県，島根県，広島県
実質的な活動なし：山形県，福島県，埼玉県，岡山県，佐賀県，大分県

※下線は「設置予定あり」と回答した県

図3　HTLV-1 母子感染予防対策協議会の設置状況（平成 29 年 11 月）

働省は各都道府県に対して，HTLV-1 母子感染対策協議会の設置を認めている。母子感染予防対策協議会の機能としては① HTLV-1 抗体スクリーニングの実施体制の整備，② HTLV-1 抗体スクリーニングの実施状況の把握，③ 出生した児のフォローアップ体制の整備，④ キャリア妊婦への支援・連携体制の整備，⑤ 相談窓口の設置，⑥ 母子保健担当者や医療関係者に対する研修や講習の開催．などが挙げられる。

全国 47 都道府県を対象に 2017 年に実施された調査[2]では，母子感染対策協議会が設置されていたのは 25 府県，既存の保健事業などで対応しているのが 13 都県であり，残りの 9 県ではとくに対応が行われていなかった（図 3）。また協議会が設置されていた 25 府県のうち，6 県は調査時点で実質的な活動は行われていなかった。協議会の事業としても母子感染に関する啓発活動や相談窓口の設置が大部分であり，具体的なキャリアの支援や地域における母子感染の把握，フォローアップ体制の整備などを行っている地域はごくわずかであった。

おわりに

全妊婦に対するスクリーニング検査によりキャリア妊婦が発見されたとしても，HTLV-1 母子感染対策協議会が十分な機能を果たさなければ母子に対する支援は行き届かず，有効な母子感染対策事業とはなりえない。今後早急な対応が求められる。

Key Points

1. HTLV-1 キャリア妊婦に対しては原則として完全人工栄養を勧める。
2. 母乳栄養を強く希望する場合には 3 か月以内の短期母乳栄養や凍結解凍母乳栄養が選択肢となるが，現時点でこれらの栄養法の予防効果について十分なエビデンスは確立していない。
3. 分娩前に母親に対して各栄養方法のメリット・デメリットについて十分な情報提供を行ったうえで事前に意思決定できるように支援する。
4. 出生した児の抗体検査は 3 歳以降に実施することが推奨される。

文　献

1) Gessain A, Cassar O : Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 3 : 388, 2012
2) 齋藤　滋：厚生労働科学研究費補助金・特別研究事業「HTLV-1 の母子感染予防に関する研究」平成 21 年度総括・分担報告書

3) 平成29年度日本医療研究開発機構委託研究開発費（AMED補助金）新興・再興感染症に対する革新的医薬品等開発推進研究事業「HTLV-1の疫学研究及び総合対策に資する研究」班（研究代表者：浜口　功）：HTLV-1感染の診断指針　第1.1版（2018年6月）http://htlv.umin.jp/data/HTLV-1_guidelines201806.pdf（2019年11月25日アクセス）
4) 板橋家頭夫：厚生労働科学補助金（成育疾患克服等次世代育成基盤研究事業）「HTLV-1抗体陽性妊婦からの出生児コホート研究」平成24年度総括・分担研究報告書
5) Umeki K, Umekita K, Hashikura Y, et al：Evaluation of line immunoassay to detect HTLV-1 infection in an endemic area, southern Japan：Comparison with polymerase chain reaction and western blot. Clin Lab **63**：227-233, 2017
6) 平成28年度厚生労働行政推進調査事業費補助金・成育疾患克服等次世代育成基盤研究事業「HTLV-1母子感染予防に関する研究：HTLV-1抗体陽性妊婦からの出生児のコホート研究」（研究代表者：板橋家頭夫），HTLV-1母子感染予防対策マニュアル，2017
7) 板橋家頭夫：厚生労働行政推進調査事業費補助金・成育疾患克服等次世代育成基盤研究事業「HTLV-1母子感染予防に関するエビデンス創出のための研究」平成29年度総括・分担研究報告書

3) 平成29年度日本医療研究開発機構委託研究開発費（AMED補助金）新興・再興感染症に対する革新的医薬品等開発推進研究事業「HTLV-1の疫学研究及び総合対策に資する研究」班（研究代表者：浜口　功）：HTLV-1感染の診断指針　第1.1版（2018年6月）http://htlv.umin.jp/data/HTLV-1_guidelines201806.pdf（2019年11月25日アクセス）
4) 板橋家頭夫：厚生労働科学補助金（成育疾患克服等次世代育成基盤研究事業）「HTLV-1抗体陽性妊婦からの出生児コホート研究」平成24年度総括・分担研究報告書
5) Umeki K, Umekita K, Hashikura Y, et al：Evaluation of line immunoassay to detect HTLV-1 infection in an endemic area, southern Japan：Comparison with polymerase chain reaction and western blot. Clin Lab **63**：227-233, 2017
6) 平成28年度厚生労働行政推進調査事業費補助金・成育疾患克服等次世代育成基盤研究事業「HTLV-1母子感染予防に関する研究：HTLV-1抗体陽性妊婦からの出生児のコホート研究」（研究代表者：板橋家頭夫），HTLV-1母子感染予防対策マニュアル，2017
7) 板橋家頭夫：厚生労働行政推進調査事業費補助金・成育疾患克服等次世代育成基盤研究事業「HTLV-1母子感染予防に関するエビデンス創出のための研究」平成29年度総括・分担研究報告書

SY4-3　HTLV-1の母子感染

森内　浩幸
長崎大学大学院医歯薬学総合研究科　小児科学

母乳はHTLV-1の主要な感染経路であり、キャリアとなった児の約5%が中高年以降に成人T細胞白血病（ATL）を発症する。今なお予後不良であり、二次予防（キャリアからの発症予防）法がないATLに対する基本対策は一次予防（母子感染予防）によるキャリア化の阻止であり、流行地長崎県では1987年より全妊婦のHTLV-1抗体スクリーニング、キャリア母親を対象とした母乳回避介入、出生児の追跡調査を行ってきた。その成果は、以下の二点にまとめられる。
（1）母子感染率は人工栄養2.4%、短期（6か月未満）母乳8.3%、長期（6か月以上）母乳20.5%であった（$p<0.01$）。つまり、授乳期間が長いほど感染率が高くなるが、母乳が唯一の感染経路ではない。
（2）妊婦の抗体陽性率を出生コホート別に解析すると、1971~85年では1.32%であったのが、1986~90年には0.63%、1991年以降では0.30%と減少した。

この介入事業の対象年齢（1987年以降に生まれた女性）におけるHTLV-1キャリア率が非流行地に近いレベルにまで減少したことで、将来のATL患者数の減少に大きく貢献できたと推定している。

しかし全国的には今なお百万人を越すキャリアが居り、また近年キャリア分布が西南日本だけではなく全国的に拡がったことを受けて、平成23年度から全国的に公費補助の元で妊婦のHTLV-1抗体検査が行われることになった。しかし予防対策にはまだまだ問題点が数多く残されている。例えば、栄養方法についてのきめ細かな指導と継続的なサポートやキャリアの抱える悩みに応えるカウンセリング体制が整っていないこと、完全人工栄養にしてもなお2~3%の児がキャリアになってしまうこと、妊娠中の抗体検査で陰性であったがその後パートナーから水平感染した母親が授乳して垂直感染が起こる事例があること、そしてもう一つの主要なHTLV-1関連疾患であるHTLV-1関連脊髄症は水平感染でキャリアとなった場合にも発症すること等が挙げられる。現状の問題点を整理して発表する。

森内　浩幸（もりうち　ひろゆき）

経歴：

1984年　長崎大学医学部卒業、長崎大学医学部小児科入局
1988年　国立仙台病院　臨床研究部　レジデント
1990～99年　NIAID 研究員（Visiting Fellow, Visiting Associate, Staff Scientist）
（この間1994～99年　NIH Clinical Center 臨床スタッフも併任）
1999年　長崎大学医学部小児科学教室 主任教授（長崎大学病院 小児科長 併任：現在まで続く）
2002年　長崎大学大学院医歯薬学総合研究科 教授（現在まで続く）
2015年　長崎大学大学院熱帯医学・グローバルヘルス研究科　教授併任（現在まで続く）

専門領域：

小児感染症、特に母子感染

所属学会（役職）：

American Academy of Pediatrics (International Fellow)
Asian Society for Pediatric Infectious Diseases (President, ACPID 2018; Standing Committee)
日本小児科学会（理事）
日本小児感染症学会（理事）
日本HTLV-1学会（理事）
日本臨床ウイルス学会（幹事）、他

受賞歴：

1996年　Dade MicroScan Young Investigator Award (American Society for Microbiology)
1997年　Special Recognition Award (NIAID)
1999年　Staff Recognition Award (NIAID)
2001年　The Taiwanese Society of Neonatology Lecture Award
2002年　Travel Award (International Symposium on Infections in the Immunocompromised Society)