厚生労働科学研究費補助金

成育疾患克服等次世代育成基盤研究事業

（健やか次世代育成総合研究事業）

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HTLV-1母子感染対策および支援体制の課題の検討と対策に関する研究

令和２年度～４年度　総合研究報告書

研究代表者　内丸　薫

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Ⅰ．総合研究報告書

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HTLV-1 母子感染対策および支援体制の課題の検討と対策に関する研究

研究代表者
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研究要旨：HTLV-1 キャリア妊婦の現状・支援体制・ニーズに関する課題を整理し、HTLV-1 キャリア妊産婦の授乳法として、原則を完全人工乳とし、乳房管理など人工乳への移行を支援する体制が整うのを前提として短期授乳を選択肢として挙げる母子感染予防対策マニュアルの改定を行った。改定マニュアルの付録として動画コンテンツなどの研修資材を作成した。児の抗体検査体制、内科との連携体制の不足を明らかにし、これらも含めて対応するための地域連携モデルとして東京プログラムを構築して運用を開始した。

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A.研究目的

わが国に 100 万人程度感染者が存在すると考えられる HTLV-1 は、成人 T 細胞 白血病（ATL）や HTLV-1 関連脊髄症（HAM）などの原因となることから、その感染予防は極めて重要である。感染ルートの一つである母子感染予防の手段として授乳介入が有用であり、妊婦 HTLV-1 抗体検査が HTLV-1 総合対策の一環として実施されている。2017 年先行研究班である厚生労働行政推進調査事業「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（板橋班）」による改訂授乳指導マニュアルでは完全人工栄養を推奨し（HTLV-1 母子感染予防マニュアル（板橋家頭夫 2017））ているが、改訂以降も短期授乳選択者の比率にあまり動きはなく、現場における栄養指導が必ずしも統一されていない可能性も推定される（板橋班平成 30 年度総括分担研究報告書）。さらに同班の調査では現状の対策が不十分とするキャリア経産婦が 70%以上に及び、心理的なサポートまで含めた支援体制、キャリアとしての母親への相談体制が不十分であることが指摘されている（同報告）。また、総合対策の推進体制の一環とされる都道府県母子感染対策協議会の状況について厚生労働科学研究「HTLV-1 キャリア・ATL 患者に対する相談機能の強化と正しい知識の普及の促進（内丸班）」および前記板橋班の研究により必ずしも十分機能していない可能性が明らかになった（内丸班総合研究報告書、板橋班平成 29 年度総括分担報告書）。

本研究は、これらの研究成果を踏まえ、HTLV-1 キャリア妊婦の現状・支援体制・ニーズに関する情報収集と課題整理を行い、自治体と連携した支援体制の構築、および授乳指導の標準化の推進を目的とする。そのために、初年度産婦人科医会の実態調査なども含む調査研究により、キャリアマザーの授乳指導の実態、ニーズなどの課題を整理するとともに、板橋班研究データをもとにした標準授乳指導法を検討、確立する。また、都道府県との連携の実態を調査し、高浸淫地域、大都市圏など地域ごとの課題を抽出する。これらの情報を統合し、標準化された指導や支援、自治体と連携した支援体制構築の取り組みについて提言を行うことを目的とする。

B.研究方法

本研究の遂行のため、本課題開始時に以下の 5 つの大課題を設定し、その中をさらにいくつかの小課題に分け、課題ごとに分担研究者を配置して研究を遂行した。

1. HTLV-1 キャリア妊婦の現状・支援体制・ニーズに関する情報収集、課題整理

1-1) HTLV-1 キャリア登録ウェブサイト「キャリねっと」を用いたアンケート調査と分析

HTLV-1 キャリア登録ウェブサイト「キャリねっと」の登録者を対象に、妊娠出産の経験のある登録者に登録者向けメールマガジン、ニュース欄などでアンケート機能を用いた追加調査として「アンケート 1」への入力の協力要請を 2017 年 12 月 27 日に開始した。設問項目は資料 1 に示す通りである。さらにキャリアマザーの授乳に対する意識、およびおもに 3 歳時点における児の抗体検査についての考え方について調査するために「アンケート 2」へ

の追加入力要請を 2021 年 12 月 2 日に開始した。設問項目は資料 2 に示す通りである。アンケート 1 については、2022 年 2 月 7 日現在で集計してデータを固定した。全登録者 768 名のうちアンケート回答者は 310 名で、そのうち妊娠出産を経験していない 54 名を除き 256 名を対象に解析を実施した。アンケート 2 については 2023 年 2 月 10 日現在でデータを固定した。キャリねっと登録者のうち、アンケート 2 回答者：78 名から男性 1 名を除いた 77 名について集計、解析した。

1-2）産婦人科医による授乳指導の実態調査

日本産婦人科医会に登録されている全国の分娩を取扱う 2214 施設を対象に 2020 年 8 月～9 月に妊婦の HTLV-1 キャリアのスクリーニング検査の状況および HTLV-1 キャリアのケアについての実態を把握することを目的に調査票（資料 3）を送り、研究に同意したものが返信する形式でのアンケート調査を実施した。返信のあった回答施設数は 1468 施設であり、回収率は 66.3%であった。

2. 自治体と連携したキャリア妊婦、家族の相談支援体制の検討

2-1）東京地区の実態調査

東京都の保健所を対象に育児支援の現状、キャリアマザーに対する対応についての実態調査を行う。

2-2）東京プログラムの運用と問題点の検討

先行研究班（板橋班）で構築された産婦人科、小児科、内科の連携システム東京ネットワーク（産婦人科拠点 6 施設、小児科 16 施設、内科拠点 1 施設）をベースに、より広く東京地区をカバーする東京プログラムを構築し、周産期中核センターをハブとした地域における連携システムを構築し課題を抽出して検討を行った。東京産婦人科医会や東京小児科医会の支援が必要であり、両会の協力を得て、段階的に取り組むことについて了承いただいた。その上で、東京プログラムの産婦人科基幹病院となる都内の全総合周産期医療センターと日本医科大学多摩永山病院の合計 15 施設の代表者に集まっていただき、趣旨説明をしたのちに、参加するための要望を聴取した。その結果、産科の一次医療機関で HTLV-1 キャリアと診断された妊婦に配布するチラシの作成、東京プログラムで使用する説明資料の作成、東京産婦人科医会のホームページから妊婦が情報を得られるようにするシステムの構築などの要望があり、それら課題に順次取り組んだ。一方小児科側では、東京小児科医会公衆衛生委員会を中心に検討を行い、キャリア妊産婦から生まれた児に対する小児科側の役割について検討した。

2-3）事例検討

HTLV-1 キャリアマザーへの体制が運用されている事例として、神奈川県、大阪府、鹿児

島県、長崎県、富山県をとりあげ、高浸淫地域、大都市圏、非浸淫地域ごとに先行事例の体制、課題などを検討した。

2-4）内科側からの検討

日本 HTLV-1 登録医療機関の年次調査データをベースに産婦人科領域との連携の実態を検討した。

3. 児のフォローアップ体制の検討

小児フォローアップシステムの必要性、小児期キャリアの問題点、必要なシステムについて年齢ごとに検討する。

4. HTLV-1 母子感染予防法の科学的エビデンスの収集と標準化した指導法(キャリア妊婦の心理的支援を含むニーズに対応した内容)の確立と普及啓発

以下の通り検討を進めた。

母子感染予防対策マニュアル改訂に関する小グループ検討会の開催

産婦人科領域、小児科領域、内科領域、助産領域の有識者による web 会議を複数回開催し、「出生後の母子感染予防のための栄養方法の選択」を中心としたマニュアルの改訂、ならびに「キャリアおよびキャリアからの出生児に対する継続的な支援体制」の在り方について検討した。

鹿児島県・長崎県における支援体制の現状および問題点の抽出

母児に対する継続的支援の在り方については、HTLV-1 流行地域である鹿児島県および長崎県における母子感染予防対策の現状での問題点、さらにはマニュアル改訂により短期母乳栄養を選択する母親が増加した場合に想定される問題点を抽出するため、両県の実務担当者および有識者を交えた web ミーティングを開催した。

「HTLV-1 母子感染予防対策マニュアル（第 2 版)」の作成

小グループ検討会での検討内容を踏まえて、本研究班および関連する研究班の分担研究者を中心に改訂版マニュアルの執筆者を決定し、執筆を依頼した。マニュアルの内容については、電子メールによる協議を経て、各章ごとに web での検討会を開催し、執筆者全体でピア・レビューを行い、執筆者全員のコンセンサスを得て作成した。

5. HTLV-1 母子感染予防に関する研修会の開催・研修資材の作成

東京プログラムの実施に必要な資材の作成と行うとともに、HTLV-1 母子感染予防マニュアルの改訂第 2 版の付録動画コンテンツとして研修に役立つ資材の作成を行った。また、日本助産師会を対象に HTLV-1 母子感染予防に関する研修会をオンデマンド講習も含めて開催した。

（倫理面への配慮）

人を対象とする医学系研究に関する倫理指針を遵守の上で研究を遂行した。キャリねっとを用いたアンケート調査については東京大学ライフサイエンス委員会倫理審査専門員会による審査を受け承認されている（審査番号 18-36)。日本産婦人科医会による実態調査に当たっては、日本産婦人科医会の倫理委員会において倫理審査を行い、その承認のもとで行われた。また、本アンケート調査の回答は日本産婦人科医会の施設情報とリンクさせ、施設情報のリンクによって、施設の所在地情報をえて、解析を行ったものの、解析後には施設情報は切り離すことで、個別の施設の情報の漏洩が起こらないように配慮した。

C.研究結果

1. HTLV-1 キャリア妊婦の現状・支援体制・ニーズに関する情報収集、課題整理

1-1) HTLV-1 キャリア登録ウェブサイト「キャリねっと」を用いたアンケート調査と分析

令和２～4 年度報告書　（担当　内丸　薫、齋藤　滋、関沢昭彦、森内浩幸、根路銘安仁、宮沢篤生、時田彰史、山野嘉久、高　起良、井村真澄　研究協力者　板橋家頭夫、渡邉俊樹）

アンケート 1 の継続調査の対象 256 例の背景を図 1 に示す。キャリねっと登録者が首都圏、関西圏に多いことを反映して、首都圏、関西圏居住者が全体の半数を占める。最終分娩時期により 2011 年の総合対策開始前、総合対策開始後授乳指導マニュアルが変更された 2017 年まで、それ以降の 3 群に分けたところ、2011 年以前が 46.1%、2011 年以降 2017 年までが 27.3%、2017 年以降が 25.8%であった（図 2)。2017 年以降妊娠出産の 66 例を対象に HTLV-1 母子感染予防法について説明を受けた医療者を尋ねたところ、産婦人科医が 70%と最も多かったが、誰からも説明を受けられなかったと回答した母親が 9%存在した（図 3)。説明を受けた母親の理解度の自己評価は次第に向上してきており 2017 年以降の妊産婦では約 9 割がほぼ理解できたと回答しており（図 4)、次第に適切な説明がなされるようになってきていることが推測される。選択する授乳法では人工乳がもっとも多く、2017 年以降の出産、妊娠中の母親では約 6 割が人工乳を選択していたが、短期授乳を選択した母親も 30%存在していることは注目すべきと考えられた。(図 5)。選択した授乳法の困難さについて、授乳法毎の区別をせずに集計をしたところ、2017 年以降のグループでも 40%が容易ではなかったと回答していたが、困難さの理由としては、「母乳を与えられないことの罪悪感にさいなまれた」とするものがもっとも多く、続いて「周囲から人工栄養にしていることを指摘され肩身が狭かった」というもので（図 6)、この傾向は 2017 年以降においても変わっていなかった。いずれも人工乳を選択した母親が多く指摘した結果であると推定された。

これらを踏まえて現在の HTLV-母子感染予防対策の医療的な支援についての満足度については約 70%が不十分であると回答している。2017 年以降の妊産婦に限っても十分と回答したのは 62%であった。母親に対する支援が不十分と考える理由については、「母親の気持ちに寄り添って指導してほしい」という回答が非常に多く、上記の通り人工乳を選択した母親がもっとも多いことを反映していると考えられた。また、これとほぼ同数でもっとも多か

った回答は「相談先がわからなかった」というものであった（図 7）。これらの調査結果から、完全人工乳を選択するキャリア妊産婦に対しても支援対策が必要であることが示唆される。

アンケート 2 回答者の背景として、回答者の 83.2%が 30 代～50 代で、居住地域については関東地方在住者、近畿地方在住者それぞれ 31.2%、九州地区在住者は 14.3%であった。資料 2 の通り、回答の背景知識としてキャリア妊産婦には人工乳哺育が推奨されていること、一方、まだ調査数は十分とは言えないが、3 か月以下の短期授乳と人工乳哺育を比べた場合赤ちゃんの感染率は増加しないという調査結果もあることを提示して上で、「もし 3 か月以下の授乳であれば赤ちゃんの感染率が上がらないのであれば、3 か月以下の母乳哺育を望みますか（すでに授乳を終えた母親に対しては、もしそうであれば望んだか？）」という質問で、授乳の希望と授乳による感染リスクのバランスについての考え方を質問したところ「3 か月以下であれば赤ちゃんの感染率が変わらないのなら、3 か月以下の母乳哺育をした」と回答したのが 42.9%、「少しでも感染のリスクがあることはしたくないので、人工乳哺育にしたい」と回答したのが 48.1%とほぼ拮抗するデータであった。

次いで、児の抗体検査についての考え方についての質問を行った。通常児の抗体検査を受ける年齢として 3 歳以上をあげていることから、77 名の対象者のうち、3 歳以上の子どもがいると回答した 62 名を対象に集計を行ったところ、3 歳以上の子どもの抗体検査を行ったと回答したのは 38.7%であった。抗体検査を受けさせていないと回答した母親に検査をしなかった理由を複数回答可で尋ねたところ、「子どもの抗体検査について聞いたことがなかったから」が 39.5%、「検査をできる場所がなかったから（どこで検査を受けられるかわからなかったから）」が 42.1%とこの 2 つの理由が最も多く、それぞれ全体の約 40%を占めていた。

1-2）産婦人科医による授乳指導の実態調査

令和 2 年度報告書　（担当　関沢明彦、齋藤　滋　研究協力者　小出馨子、鈴木俊治　日本医科大学（教授）・日本産婦人科医会）

回答のあった施設で 2019 年度に 568、626 件の抗 HTLV-1 抗体スクリーニング検査が行われた。そこでの陽性数は 1、466 例であり、陽性率は 0.26%であった。地域別では、九州での陽性率は 0.57%と最も高く、続いて中国・四国 0.28%、関西 0.26%、中部・東海 0.19%、関東 0.18%、北海道・東北 0.15%と西高東低の分布であった。確認検査（LIA 法）は 1、274 例で行われ、陽性者は 581 例で、陽性率は 45.6%であった。また、PCR 検査は 104 例で行われ、陽性率が 24%で判定保留が 7.7%に発生していた。今回の調査では確認検査陽性と PCR 検査陽性を合わせた 606 人が HTLV-1 キャリアであることが判明した。606 人の新規感染者のうち 65 人(10.7%)が前回の妊娠時の検査で抗 HTLV-1 抗体陰性であり、前の出産から今回の妊娠までの間に水平感染があったと推定された。

各施設で推奨する栄養法についても複数回答で聞いた。その結果、90.6%の施設では人工栄養、29.9%では短期母乳、27.9%では凍結母乳を推奨しており、3 分の 1 の妊婦が選択肢の中から選択している実態が確認できた(図 8)。実際に HTLV-1 キャリアと診断された女性

がどのような選択した栄養方法については、71.9%が人工栄養を選択し、短期母乳を選択した女性は 18.4%、凍結母乳を選択した女性は 4.0%と推定された(図 9)。短期母乳を選択した場合には、3 か月で断乳する必要があるので、そのサポートは必要である。ケアの継続時期については 1 か月健診までが 45.1%、断乳終了まで（3〜4 か月まで）が 31.9%、断乳後も必要に応じて継続的に実施が 23.0%という結果であった(図 10)。児のフォローアップについては小児科等に紹介するが 70.0%と最多であり、妊婦に委ねる(15.0%)、フォローはしていない(12.9%)、自院でフォローする(2.1%)と続いた。3 歳ころの抗体検査については、かかりつけの小児科医に紹介する(42.8%)、地域の HTLV-1 専門施設に紹介する(7.7%)を合わせて 50.5%であり、その他は、必要性について説明している(26.5%)、特に考慮していない(21.3%)という結果であった。

2. 自治体と連携したキャリア妊婦、家族の相談支援体制の検討

2-1）東京地区の実態調査

（担当　内丸　薫）

本研究開始と同時に新型コロナウイルスによるパンデミックとなり、調査を延期した。2022 年度末になり、パンデミックの終息が見えてきたため、調査項目の検討をメール稟議などを研究班内で実施し調査用紙を作成した。一方、この間の議論から、行政のサポートとして、包括的子育て支援との関連など、より広い視点からの調査の行うべきと判断されたため、あらたに今後の継続課題として検討することになった。

2-2）東京ネットワークの運用と問題点の検討

令和 2 〜4 年度報告書　（担当　関沢明彦、時田章史、宮沢篤生、内丸　薫　研究協力者　小出馨子、谷垣伸治、板橋家頭夫）

東京地区における周産期領域連携ネットワークとして、都内の 15 の総合周産期母子医療センターを中心に HTLV-1 相談窓口となる基幹施設を設置し、小児科側の窓口として東京小児科医会と協議した結果、その相談窓口となる小児科クリニック 21 施設を選定し、東京プログラム参加施設群の構築を終えた（図 11、12)。産婦人科側を中心として運用上の問題点などの検討を行い、妊婦に正確な基本的な情報をいつでも振り返って確認できるように、キャリア妊婦に説明する際に配布するフライヤーを作成するとともに、各施設における説明内容の統一化が必要であり、また、説明に実際に使用する妊婦さんが見て理解しやすいような資料が必要と判断し、妊産婦への説明用に「HTLV-1　東京プログラム説明用資料」を作成した。資料には HTLV-1 の基礎的な説明、児への母乳投与の問題点、母子感染を防止するための栄養法などが図をまじえてキャリア妊婦に説明しやすいように記載した。必要な資材や東京産婦人科医会のホームページの準備など概ね完了した。2023 年 4 月から運用を開始した。

2-3）事例検討

令和 2〜3 年度報告書　（担当　齋藤　滋、森内浩幸、根路銘安仁、山野嘉久、高　起良）

神奈川県、大阪府、鹿児島県、長崎県、富山県をとりあげ、高浸淫地域、大都市圏、非浸淫地域ごとに先行事例の体制、課題などを検討した。

長崎県（森内）

長崎県で HTLV-1 抗体陽性妊婦から生まれ、2011 年 1 月から 2020 年 12 月に受診し HTLV-1 抗体検査を実施した 3 歳以降の児と母親を対象に、児の乳汁栄養法を聴取し、又母子双方の HTLV-1 proviral DNA (PVL)の定量を行った。285 人中 19 人（6.7 %）の児が感染しており、栄養方法別に見てみると、長期母乳（3 か月以上）が 33 例中 9 例（27%)、短期母乳（3 か月未満）が 55 例中 3 例（5.5%)、完全人工栄養が 195 例中 7 例（3.6%）だった。児では PVL が cut-off 値未満のものが 12 名だったが、母親の PVL は高かった。注目すべき点の一つは、長期母乳によって感染した 9 事例のうち、少なくとも 2 名は短期母乳を勧められたがどうしても母乳を途中で止めることが出来ずに長期に及んでしまったものである。少数例での検討であるが、長期母乳のリスクが再確認された。また、短期母乳の場合には、離乳の難しさを説明した上で自己決定してもらうことと、離乳指導の重要性についても再認識する事例を経験した。また、3 歳以降で児の抗体検査が実施されたのは、全体の 3 分の 1 程度と推測され、フォロー率向上のための対策が必要とされる。

鹿児島県（根路銘）

鹿児島県は endemic area に属し、1985 年に ATL 調査研究委員会を設置し調査研究を行い 1997 年に「HTLV-1 感染対策マニュアル」を作成するとともに、鹿児島 ATL 制圧 10 カ年計画を実施した。2010 年に国が「HTLV-1 総合対策」を策定したことに併せて、2011 年に鹿児島県 HTLV-1 対策協議会を立ち上げ体制整備を行ってきた。今回、鹿児島県 HTLV-1 対策協議会が県医師会・県産婦人科医会・県小児科医会の協力を得て、両医会に加盟する医療機関に調査を行った。鹿児島県の HTLV-1 母子感染対策として、産科医療機関での妊婦への HTLV-1 検査、保健所への情報提供、栄養法の選択は十分に機能していることが明らかとなったが、一方で産科医療機関から小児医療機関との連携は十分でなく、保護者に 3 歳以降の抗体検査の情報も伝わっていない可能性が考えられた。産科医療機関から小児医療機関への情報提供書式の作成や小児医療機関や行政からの 3 歳以降の抗体検査の情報提供方法など更なる体制整備が必要であることが明らかになった。

富山県（斎藤）

富山県では 2011 年 11 月に HTLV-1 母子感染対策検討部会を設置し、2012 年 1 月には富山県 HTLV-1 母子感染対応マニュアルを作成し、HTLV-1 抗体検査から児のフォローアップについてまとめた。2020 年以新生児のフォローアップを集計したところ、調査できた 24 名中、3 歳時に抗体検査を施行したのは 9 名（37%）に留まり、フォローアップ途中での脱落が 5 名（21%)、産科病院同士での紹介状はあったが、フォローアップする小児科病院が不明なものが 9 名（37%）であった。フォローアップできた症例では、予防接触や小児アレルギー等で通院していた例が大半であった。フォローアップ率を向上させるためには①産科側か

ら小児科への紹介状を徹底する、②小児科ではワクチン接種等継続的なフォローアップを心がける事が必要と考えられた。

神奈川県（山野）

平成 22 年に「HTLV-1 総合対策」が開始され 10 年が経過した。この 10 年の間に 5 つの重点施策である、1.感染予防対策、2.相談支援（カウンセリング）、3.医療体制の整備、4.普及啓発・情報提供、5.研究開発の推進について様々な取り組みが行われてきた。

HTLV-1 感染者が比較的多い地域では、HTLV-1 について、ある程度の認知度が期待されるが、神奈川県では、医療者や医療支援者であっても HTLV-1 に対する認知度が低いのが現状である。近年では、人の移動に伴い首都圏においても HTLV-1 感染者が増加していることから、神奈川県でも医療者・医療支援者の HTLV-1 の認知度を高め、HTLV-1 感染者に正しく適切な支援を行うことができる体制の基盤づくりを進める必要がある。そこで本研究では、神奈川県における普及啓発活動を行うことを目的とした活動を行った。

2011 年より、神奈川県が主催する研修会で、HTLV-1 の基礎知識、HTLV-1 感染が原因となって起こる疾患の解説、HTLV-1 感染検査方法、HTLV-1 キャリア妊婦への説明方法等についての講演を行い、普及啓発活動を推進させた。また、それと同時に日本 HTLV-1 学会登録医療機関の紹介を行い、より専門的な支援のニーズに対する対応策の普及活動を行った。これにより、HTLV-1 感染者にとってより満足のいく相談支援が受けられることが期待された。今後の課題としては、日本 HTLV-1 学会登録医療機関数が少ないことがあげられ、この解決策として、オンライン相談の導入等により一定の成果が得られることが期待される。

大阪府（高）

大阪府の HTLV-1 母子感染予防対策事業の内容を分析することでキャリア妊婦の支援に不可欠な相談体制と周産期領域との連携のありかたについて検討した。その結果、大阪府では母子保健運営協議会が HTLV-1 母子感染対策協議会の役割を担っており、その中で産婦人科と小児科の周産期領域および HTLV-1 学会登録医療機関（血液内科）の連携の枠組みは形成されているが、キャリア妊婦に関する情報が十分共有されている訳ではないことが明らかになった。キャリア妊婦と直接つながりを持つ母子保健担当者（保健師、助産師）が把握した情報が大阪府母子感染対策協議会へ集約され、関係医療機関で共有されると同時に、必要とする情報がキャリア妊婦にフィードバックされるような体制作りが望ましいと考えられた。「子育て世代包括支援センター」と呼ばれる既存のシステムを HTLV-1 母子感染予防対策に活用すれば、全てのキャリア妊婦の把握が可能となり、そこで得られた情報を共有することで出生児のフォローも含めたキャリア妊婦に対する相談体制の整備につながる可能性が考えられた。

2-4）内科側からの検討

令和 2〜3 年度報告書　（担当　内丸　薫、山野嘉久、高　起良　研究協力者　渡邉俊樹）

毎年 4 月末締め切りで全国の日本 HTLV-1 学会登録医療機関から活動実績の年次報告書が提出され、5 月末に集計されている。昨年度分については、令和 3 年 3 月 31 日現在日本 HTLV-1 学会登録医療機関認定されている 16 施設が対象であった。令和 3 年（2021）年度の登録医療機関における HTLV-1 キャリア対応の年次報告書の集計を表 1 に示す。16 施設合わせて通常の初診が 216 例、相談センター、院内他科からの紹介が 124 例、合わせて 340 例の HTLV-1 キャリアへの初診対応を行っていた。周産期施設からの紹介は 16 施設合わせても 14 例と非常に少なかった。保健所からの紹介はわずか 2 例でやはり少なく、今年度は保健所からの相談件数は全体で 0 件であった。日赤からの紹介例は 27 例であった。2022 年度分日本 HTLV-1 学会登録医療機関年次報告書は現在集計中であるが、報告対象 17 施設中 14 施設からの報告時点で周産期領域からの紹介が 0 であった施設が 6 施設で、残りも一部を除いて 1〜2 件と、周産期領域施設からの紹介数は今年度も低調であった。

3. 児のフォローアップ体制の検討

令和 2 年度報告書　（担当　根路銘安仁、時田章史、森内浩幸）

児の年齢（月齢）区分におけるフォローアップ上の現状と課題について検討した。

１）出生〜 1 か月（健診時）

現行マニュアルで「原則として完全人工栄養を勧める」ことになっているが、HTLV- 1 キャリア登録サイトの「キャリねっと」に登録されたキャリア妊産婦の調査では、マニュアル改訂後でも母親の栄養法選択に大きな変化はなく、一定数の短期母乳選択者がいる。選択栄養法支援の方法について産科医療機関の後の断乳支援について課題がある。

２）1 か月（健診後）〜（3 〜 4 か月健診時）〜3 歳時

通常 1 か月健診後は 2 か月目から定期予防接種（ロタウイルス・Hib・PCV・HBV）が開始になるため児のフォローアップ主体が小児科へ変更になる。児に関しては、原則として通常の乳幼児健診のスケジュールでよい。総ての母親に対し不安を訴える場合への対応と、短期母乳栄養を選択した母親に対しては、生後 2 か月時点で母乳を中断するための準備について指導を行い、さらに 3 か月時点で中断できたかどうかを確認するなどの対応が必要である。現状では産科医療機関から小児科への紹介（情報共有）がうまくいっていない可能性が示唆されていること、子育て期の親は移動も多く、またかかりつけ医も変更があるのでその時の連携が途切れる可能性があること、母親が不安を訴えた場合の対応が慣れない小児科医では難しいことなどが課題としてあげられた。また短期母乳を選択した母親が一定数いるので、体制整備が必要である。マニュアル改訂についても検討が必要であり、断乳をしっかり守るためのリーフレットや視聴覚教材が必要である。支援体制については、看護職（助産師）の参画が必要と考えられる。

３）3 歳以降

3 歳以降児の抗体検査が可能となるが、必要性については現時点ではコンセンサスが得ら

れていない。また、母子感染が確定した場合の対応として、感染させてしまったとの悩みや、子に対してキャリアとなったことをいつ説明するか悩むことも多いため精神的ケアが必要となるが、体制は未整備である。HTLV-1 キャリア登録サイトの「キャリねっと」に登録されたキャリア妊産婦の調査では、子どもの抗体検査をしたお母さん 21.4%　していないお母さん 69.4%のうち抗体検査をしようと思っているお母さんが 46.9%。21.4%＋69.4%X46.9%＝53.9%で、迷っているというお母さんを入れると 60%～70%くらい。板橋班でのフォローアップを経験した医師からも 6 割程度が実施する意向があると考えられる。一方で、実際に抗体検査を受けた児の数は 30%程度であり、検査をしなかった方への「しなかった理由」をキャリネットで調査して、検査に対する不安を取り除ける説明が必要である。そのほか、母子感染が確定した場合の母親への精神的ケアはどうすべきか？母子感染が確定した場合の児のフォローアップはどうすべきか？母親自身の HTLV-1 関連疾患のリスクに対する不安にどうするか？ 3 歳時に抗体検査をしない場合のリスクへの対処は？などの課題が抽出された。これらの検討結果は事項の母子感染予防対策マニュアル改定の中に取り込まれた。

4. HTLV-1 母子感染予防法の科学的エビデンスの収集と標準化した指導法(キャリア妊婦の心理的支援を含むニーズに対応した内容)の確立と普及啓発

令和 3 年度報告書参照　（担当　宮沢篤生、関沢明彦、齋藤　滋、森内浩幸、根路銘安仁、井村真澄、三浦清徳　研究協力者　板橋家頭夫、武市洋美、下敷領須美子、小杉純子、柘植薫）

母子感染予防マニュアル改訂に関する小グループ検討会において検討した結果、以下の方針を決定した。

マニュアル改訂の必要性について

前研究班（板橋班）によるコホート研究は、必ずしも十分な症例数とは言えないものの、ITT 解析された質の高いエビデンスである。国内外の報告をまとめたメタ解析でも「3 か月以内の短期母乳栄養」と「完全人工栄養」では母子感染率に差があるとは言えないことが示されている。これらは前回マニュアルが作成された 2017 年以降に明らかになった最新のエビデンスであることから、これらを反映させた形でのマニュアル改訂を行う必要がある。

産婦人科診療ガイドラインとの整合性について

現行のガイドライン（2020 年版）では板橋班による母子感染予防対策マニュアルの内容を踏まえて完全人工栄養を推奨、短期母乳・凍結解凍母乳については解説文にのみ記載されている。次回の改訂は 2023 年版が予定されており、2021 年 12 月までに推奨レベルを決定、2022 年 5 月から 9 月にコンセンサスミーティングの開催、9 月・11 月にパブリックコメントの募集が行われる予定である。産婦人科診療ガイドライン作成委員会との連携を図るため、同委員長の三浦清徳先生に本研究班の分担研究者としての参画を依頼した。

母子感染予防のための栄養法選択（「90 日以内の短期母乳）容認の是非）

コホート研究では解析対象 313 名のうち、172 名が短期母乳を選択したが、生後 3 か月時点で 33.5%、6 か月時点で 7.8%の母親が母乳栄養を継続していた。計算上、4 か月時点で約 20%の母親が母乳栄養を終了できていない可能性があることから、完全人工栄養と短期母乳栄養を同列として良いのかについては慎重な議論が必要である。また短期母乳栄養を選択肢として容認するのであれば、母乳栄養の期間が 3 か月を超えて長期化しないようにするための方策（助産師による乳房ケアなど）が必須である。また母親に対しては、3 か月で短期母乳栄養から完全人工栄養に移行することの難しさについても十分に説明すべきである。2020 年に日本産婦人科医会が実施した調査では、キャリアと診断された母親のうち、18.4%が短期母乳栄養を選択しており、完全人工栄養推奨に変更された 2017 年以降も短期母乳栄養を希望する母親は一定の割合で存在している。栄養方法の選択においては「母子感染予防」の観点だけでなく「妊娠・出産・育児」の視点からも短期母乳・人工乳それぞれのメリット・デメリットを十分に説明したうえで、母親自身による意思決定を支援する必要があると考えられた。

母児に対する継続的な支援体制

短期母乳栄養を選択した母親に対しては、母乳栄養を終了するまで助産師による乳房ケアを提供し、3 か月で母乳栄養が終了していることを確認するための体制を整備することが必要である。鹿児島県では歴史的に短期母乳を選択する母親が多いが、出産後 3 か月までは分娩した施設の産科医・助産師に対応してもらう体制が構築されている。一方、完全人工栄養を以前から推奨している長崎県では現在でも年間約 60 名のキャリアマザーがいるが、マニュアル変更により短期母乳を選択する母親が増えた場合、保健師などのマンパワーの確保が課題になる可能性がある。助産師や臨床心理士が中心的な役割を担うことが必要であり、多職種連携の支援体制の構築が課題となる。現状では助産師による乳房ケア（母乳外来など）は自費診療となっていることから、診療報酬（管理料など）の設定についても検討が必要と考えられる。

鹿児島県支援体制ワーキンググループ会議では乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）において助産師を雇用し、キャリア妊婦への対応を行っており、またキャリア妊婦に対するミルク代の女性を行っているなどの対応が示された。長崎県支援体制ワーキンググループ会議では妊婦キャリアは年間 100 名で 9 割は完全人工栄養を選択していること、出産した分娩施設から 3 歳抗体検査の時期にご家族に連絡するシステムを検討している。乳児全戸訪問事業はほぼ 100%実施されているが、助産師の対応が難しい地域があるため、各地域の医療機関との連携が必要になることなどが報告された。

以上の検討を経て、「HTLV-1 母子感染予防対策マニュアル（第 2 版）」の作成に着手した。小グループ検討会ならびに鹿児島県・長崎県支援体制ワーキンググループでの検討内容を踏まえ、本研究班として 2017 年版「HTLV-1 母子感染予防対策マニュアル」の改訂を行うこととした。「出生後の母子感染予防のための栄養方法」の概要は以下の通りである。

① 医療者は母親に対して母子感染予防のための栄養方法（完全人工栄養および短期母乳栄養）のメリット、デメリットについて、妊娠・出産・育児の視点から中立的に説明し、母親自身が望む栄養法を選択できるように支援するとともに、母親の選択を最大限に尊重する姿勢が求められる。

② 母乳栄養を希望する母親に対しては、下記の条件をみたしたうえで、90 日未満の短期母乳栄養を考慮する。

・　母乳を与える期間が長期化すると児への感染リスクが上昇することを十分に説明し、理解を得る。

・　助産師外来等において、適切な乳房ケアおよび生後 90 日までに確実に完全人工栄養に移行するための支援体制が整備されている。

・　里帰り分娩などで自施設でのフォローが困難な場合には、母児のフォローが可能な適切な医療機関に紹介する。

③ 完全人工栄養、短期母乳栄養いずれを選択した母児に対しても、医療機関、各自治体（HTLV-1 母子感染予防対策協議会など）、関連する学会および職能団体が連携し、母児に対する適切な支援を提供できる体制の構築が必須である。

④ 凍結解凍母乳栄養は理論的には有効な可能性があるが、現状では十分なエビデンスが存在しないため、壊死性腸炎のリスクが高い超早産児など特殊なケースを除いては推奨しない。

以上の方針により分担執筆により 2022 年 1 月までに原稿を完成、2 月に全章について研究班メンバー全員によるウェブによるピア・レビューを行って修正を加え、3 月に第 1 稿として取りまとめた。2022 年 7 月～8 月にかけて、日本 HTLV-1 学会、日本産科婦人科学会、日本産婦人科医会、日本小児科医会に対してパブリックコメントの募集を依頼した。各学会から多数のコメントが寄せられ、それぞれのコメントを全班員で共有し、メール稟議にて、各コメントに対する対応の必要性の有無、修正などを行い、10 月までに確定した。本研究班版マニュアルと 2023 年改訂版日本産科婦人科学会産婦人科診療ガイドライン産科編とも文言の記載の整合性の確認を行い、最終的な確認・合意に至ったので、2022 年 12 月 19 日、厚生労働省子ども家庭局母子保健課より HTLV-1 母子感染予防対策マニュアルの改訂等についてとして事務連絡発出により都道府県母子保健主管部への周知が行われた。発行された「厚生労働科学研究班による母子感染予防対策マニュアル（第 2 版）」を資料 4 に示す。

5. HTLV-1 母子感染予防に関する研修会の開催・研修資材の作成

令和 4 年度報告書参照　（担当　井村真澄、宮沢篤生　研究協力者　柘植　薫、下敷領須美子、武市洋美、納富理絵、谷口光代）

厚生労働科学研究班による母子感染予防対策マニュアル（第 2 版）に対する付録として動画コンテンツによる研修資材の作成を行った。コンテンツのテーマとして

1. HTLV-1 母子感染の基礎知識

2.共有意思決定支援

3.心理的カウンセリング

4. 出生した児のフォローアップ

5. 授乳と乳汁産生抑制 授乳の支援

6.ロールプレイ　キャリ妊婦編

7.ロールプレイ　短期母乳栄養編

を取り上げ、それぞれ制作担当者、グループを決定して作成した。制作過程で、内容について班内で意見交換を行うとともに、完全人工乳を選択したキャリア妊産婦に対する支援についての資材の追加作成が必要と判断し、ロールプレイ　完全人工栄養編を追加することになった。2022 年 12 月 23 日デジタルナレッジ社スタジオにて動画の収録を行い、班内で動画を共有して内容の確認と修正を行い、2023 年 3 月に最終版の動画を完成した。

また、東京プログラムで用いる資材として、参加施設の研修、および妊産婦への説明用に説明内容の統一化、妊婦にもわかりやすい資料が必要であることから妊産婦への説明用に「HTLV-1　東京プログラム説明用資料」を作成した（資料 5)。資料には HTLV-1 の基礎的な説明、児への母乳投与の問題点、母子感染を防止するための栄養法などが図をまじえてキャリア妊婦に説明しやすいように記載した。またキャリア妊産婦に配布するためのフライヤーを作成した（資料 6)。

これらの内容を中心に日本助産師会を対象に「感染症と母乳育児/HTLV-1 母乳育児支援」「助産師による HTLV-1 母乳育児支援」のテーマで講習会、およびオンデマンド研修を実施した。

D.考察

2017 年に本研究班の先行研究班である厚生労働行政推進調査事業「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（板橋班)」による改訂授乳指導マニュアルが作成され、同マニュアルの中では HTLV-1 キャリア妊産婦の授乳法として完全人工栄養を推奨し（HTLV-1 母子感染予防マニュアル（板橋家頭夫 2017)）ているが、改訂以降も短期授乳選択者の比率にあまり動きはなく、現場における栄養指導が必ずしも統一されていない可能性も推定されていた（板橋班平成 30 年度総括分担研究報告書)。また同研究班の 3 期 9 年にわたる HTLV-1 母子感染予防に関する前向きコホート研究が終了して､90 日未満の短期授乳では完全人工乳と比較して児の感染率は上昇しないという結果がでていた。これらを踏まえて、改めて HTLV-1 キャリア妊婦の現状・支援体制・ニーズに関する情報収集・課題整理、自治体との連携下での HTLV-1 キャリア妊婦、家族、出生した児のフォロー・相談支援体制の構築、HTLV-1 母子感染予防法の科学的エビデンスの収集と標準化した指導法の確立と普及啓発などを課題として開始された。キャリねっとによる調査、日本産婦人科医会の調査を実施し､2017 年以降も 30%程度の HTLV-1 キャリア妊産婦が 90 日未満の短期授乳を選択していると改めて推定された。日本産婦人科医会調査によると HTLV-1 キャリア妊産婦に対する授

乳法の指導について、複数選択で完全人工乳を推奨していると回答した施設が 90%であったが、100%ではなかったという見方もできる。一方、短期授乳、凍結母乳を推奨するとした施設が約 30%存在していた。どのような推奨レベル（完全人工乳を推奨してもなお母乳を授乳することをキャリア妊産婦が望んだ場合なのか、単純に並列で示したのかなど）で説明したかは不明なので解釈は難しいが、現場でもキャリア妊産婦に対する授乳指導がやや混乱していた可能性も推測される。いずれにせよ、現実に 30%程度のキャリア妊産婦が短期授乳を選択しているとすれば、それにどのように対応するかという対策の検討が必要と考えられる。

上記のように板橋班の研究成果によれば、90 日未満の短期授乳では完全人工乳と比較して児の感染率は上昇しないという結果が出ていた。キャリねっとなどのウェブ調査の結果では、完全人工乳を選択することによる HTLV-1 キャリア妊産婦の心理的苦痛はかなり大きいと推定され、栄養方法の選択においては「母子感染予防」の観点だけでなく「妊娠・出産・育児」の視点からも短期母乳・人工乳それぞれのメリット・デメリットを十分に説明したうえで、母親自身による意思決定を支援する必要があると考えられた。今回の研究による調査結果でも、90 日未満の短期授乳であれば完全人工乳と比べて児の感染率が上昇しないのであれば短期授乳を選択したいと回答した母親が 42.9%おり、感染予防の観点から差がないのであれば短期授乳を選択したいというニーズが存在する。一方、板橋班研究では、短期授乳を選択したキャリア妊産婦のうち、生後 3 か月時点で 33.5%、6 か月時点で 7.8%の母親が母乳栄養を継続していた。計算上、4 か月時点で約 20%の母親が母乳栄養を終了できていない可能性があることから、短期授乳を選択する場合には、確実に人工乳へ移行できる支援体制が重要であること、逆に言えば、支援体制がなければ安易に短期授乳を選択肢に挙げてはならないことが明らかになった。本研究における日本産婦人科医会の調査結果によれば短期授乳を選択したキャリア妊産婦のうち 45.1%は母乳育児のケアは 1 か月検診までしか受けられておらず（図 9)、短期授乳を選択したキャリア妊産婦の多くが、乳房ケアなどの支援なしに一人で完全人工乳への移行に取り組んでいることがわかり、現状で無条件に短期授乳を選択肢に挙げることはできないことが示唆される。伝統的に短期授乳選択者が多い鹿児島県の先行事例研究では、乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）において助産師を雇用し、キャリア妊婦への対応を行っており、またキャリア妊婦に対するミルク代の女性を行っているなどの対応が示された。

これらを踏まえて HTLV-1 母子感染予防マニュアル（板橋家頭夫 2017）を改定して、新たな HTLV-1 キャリア妊産婦に対する標準的指導法を示す必要があると判断され、厚生労働科学研究班による母子感染予防対策マニュアル（第 2 版）を作成した（資料 4)。主要なポイントは

① 母乳感染を予防する上で最も確実な方法は、理論的にも完全人工乳として母乳を与えないことを明記すること

この点はウェブアンケート調査で仮に 90 日未満の短期授乳であれば児の感染率は上昇しな

いとしても、少しでもリスクのあることはしたくないので完全人工乳を選択すると回答したキャリア妊産婦が 48.1%と短期授乳を選択すると回答した母親よりも多かったことを考慮すると重要であり、きちんと明示するべきである。

② 母乳栄養を希望する母親に対しては、助産師外来等において、適切な乳房ケアおよび生後90日までに確実に完全人工栄養に移行するための支援体制が整備されていることを必須条件として 90 日未満の短期母乳栄養を考慮する。

栄養方法の選択においては「母子感染予防」の観点だけでなく「妊娠・出産・育児」の視点からも選択肢を検討するべきであるが、そのためには確実に人工栄養へ移行が可能となる支援体制の整備が必須であり、今後の周産期医療・行政の重要な課題であることを明記した。

③ 完全人工栄養、短期母乳栄養いずれを選択した母児に対しても、医療機関、各自治体（HTLV-1 母子感染予防対策協議会など）、関連する学会および職能団体が連携し、母児に対する適切な支援を提供できる体制の構築が必須である。

完全人工乳を選択したキャリア妊産婦も支援の対象であり、医療機関、自治体などが連携して支援体制を構築することが課題であることを明記した。

などである。行政における HTLV-1 キャリア妊婦支援体制の調査については今後の研究班への継続課題となったが、子育て支援包括支援センターなどの子育て支援制度への組み込みなど、より広い視点からの支援体制の検討が必要と考えられる。今後本改訂マニュアル、および付録動画コンテンツを関連学会なども通じて医療機関における対応の標準化を図っていくことが必要である。また、この付録動画コンテンツなどを有効活用し、研修などを進めていく必要がある。今後、助産師を中心とした母乳ケアの支援体制が非常に重要になることから日本助産師会を対象として研修を進めてきており、今後とも継続の予定である。

先行事例研究においても、キャリア妊産婦の児のフォローアップにうまくつながっていないことが示唆されている。児のフォローアップの必要性については現状でも様々に意見があり、必ずしも統一した見解はいまだ形成されていない。児の抗体検査についても同様であるが、今回のキャリねっとなどによる調査からは 60%程度のキャリア妊産婦が児の抗体検査について希望している一方、実際の児の抗体検査実施率は 30%程度と推定され、地域によってはもっと低いと考えられる。抗体検査を受けさせていないとして、本研究班の調査により児の抗体検査について聞いたことがなかった、どこで検査を受けられるかがわからなかったからという回答がいずれも半数近く、最も多いことが明らかになった。この結果は、児の抗体検査が必ずしも十分行われていないのは、児の抗体検査を行う体制が整っていないことが大きな理由であることが強く示唆され、児の抗体検査を実施する体制まで含めて整備すべきであることがわかる。児のフォローアップについての検討を行う上での必要な基盤として児の抗体検査の体制の整備を合わせて進めていく必要がある。

妊婦検診に限らず HTLV-1 キャリアと判明した時の相談体制の不備は以前から指摘されているところであるが、妊婦検診で抗体陽性と判明した HTLV-1 キャリア妊産婦に対する相談

対応のための連携の構築が依然不十分であることが明らかになった。日本 HTLV-1 学会登録医療機関年次報告集計では、1 施設平均で年間 2 件に満たない状況である。登録医療機関そのものが設置地域にまだ偏在があるものの、設置地域においても周産期領域との連携が十分とられていないものと推測される。連携を推進するためには、関連学会同士の連携による相談対応施設の周知とともに、地域における連携システムの構築が求められる。このため、HTLV-1 総合対策で設置が求められている都道府県母子感染対策協議会などにおいて、地域ごとの連携システムの構築について検討することが求められる。下記の東京プログラムでは血液内科の相談施設が組み込まれており、地域における連携システムのモデルケースとしてその検証が期待される。そのほか厚生労働科学研究渡邉班において HTLV-1 ポータルサイト

東京地区では、総合周産期医療センターと東京小児科医会、東京大学医科学研究所附属病院血液内科の連携システムのモデルとしての東京プログラムが立ち上げられた。拠点となる施設のみではなく、産科医療一般のキャリア妊産婦に対する対応レベルを上げていくためにも、キャリア妊産婦による直接のアプローチのみではなく、一般産科施設からの相談、妊産婦の紹介システムとして機能することが重要である。さらに短期授乳を選択したキャリア妊産婦に対する授乳支援体制を各施設ごとに構築することで、その体制整備を進めるとともに、小児科医会との連携により児の抗体検査に関する相談対応も可能にするなど、周産期中核センターを中心とした HTLV-1 キャリア妊産婦対応システムの実証モデルとして機能することが求められる。妊産婦自身が HTLV-1 キャリアであることに対する相談のためには、内科領域との連携も重要であるが、日本 HTLV-1 学会登録医療機関における周産期医療機関との連携はまだまだ低調であり、この間の連携強化についても検討を進める必要がある。このプログラムの運用の過程で様々な課題が抽出されるものと期待される。一般の HTLV-1 キャリア外来においても同様であるが、HTLV-1 キャリア妊婦に対する相談支援は保険診療で点数がつけられているわけではないので、その対応については施設ごとに対応を決定するところから始めざるを得ない。同様に授乳に関して乳房管理などが保険点数化されていないので、どのようにこれらの対応を進めていくのかが大きな課題となってくることが予測される。今後の検討課題である。

E.結論

2017 年の厚生労働行政推進調査事業「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（板橋班)」による授乳指導マニュアルが作成後の HTLV-1 キャリア妊産婦の現状・支援体制・ニーズに関して調査を実施し、課題を整理した。2017 年以降も 20～30%のキャリア妊産婦が 90 日未満の短期授乳を選択しており、一方板橋班研究の結果を整理し、90 日未満の短期授乳では完全人工乳と比較して児の感染率が上昇ないこと、短期授乳選択者のうち 20～30%が人工乳に移行できずに長期の母乳哺育となっているなどの結果を踏まえて HTLV-1 母子感染予防マニュアルの改訂を行った。同改訂マニュアルでは完全人工乳を原則とするとともに、助産師による乳房管理など、人工乳への移行支援が得られることを条件に

90 日未満の短期授乳を選択肢に挙げた。今後、短期授乳選択者に対する乳房管理支援体制を確立していくことが強く求められる。

F.健康危険情報

本研究に関連しては特にない。

G.研究発表

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40. 中野和民、田部亜季、高橋良明、山本菜央佳、津本浩平、渡邉俊樹、内丸薫、「新規 CADM1 抗体-FoxM1 阻害剤複合体による ATL 細胞への標的治療の試み」、第８回日本 HTLV-1 学会学術集会、一橋講堂、東京、2022 年 11 月 5 日（2022 年 11 月 4 日～6 日）口演

41. 田部亜季、高橋良明、那須智博、由井杏奈、中木戸誠、内丸薫、渡邉俊樹、津本浩平、中野和民、「新規抗 CADM 1 抗体を用いた成人 T 細胞白血病・リンパ腫細胞に対する抗体薬物複合体の開発」、第８回日本 HTLV-1 学会学術集会、一橋講堂、東京、2022 年 11 月 5 日（2022 年 11 月 4 日～6 日）ポスター
42. 佐藤知雄、斎藤益満、和田悠作、長谷川寛雄、松平崇弘、今泉芳孝、内丸薫、渡邉俊樹、山野嘉久、「HTLV-1 クロナリティ定量検査 RAISING-CLOVA を用いた ATL 発症リスク評価法の開発」、第８回日本 HTLV-1 学会学術集会、一橋講堂、東京、2022 年 11 月 5 日（2022 年 11 月 4 日～6 日）口演
43. 田部亜季、田中勇悦、那須智博、内丸薫、中野和民、津本浩平、中木戸誠、由井杏奈、渡邉俊樹、「成人 T 細胞白血病リンパ腫を標的とした新規抗体薬物複合体の開発」、日本レトロウイルス研究会 2022、2022 年 7 月 15 日
44. Asami Yamada A, Jun-ichirou Yasunaga, Junya Sunagawa, Shinji Nakaoka, Shingo Iwami, Yasunori Kogure, Keisuke Kataoka, Masanori Nakagawa, Masako Iwanaga, Kaoru Uchimaru, Atae Utsunomiya, Ki-ryang Koh, Toshiki Watanabe, Kisato Nosaka, Masao Matsuoka, “Evaluation of the risk of HTLV-1-associated diseases by analyzing the host immune responses and provrial load”, 第 84 回日本血液学会学術集会, 福岡国際会議場、福岡、2022 年 10 月 15 日（2022 年 10 月 14 日～10 月 16 日）（口演）
45. 中島誠、宇都宮與、渡邉俊樹、堀江良一、内丸薫、「CD30 シグナルが誘導する染色体不安定性の促進機構」、第 81 回日本癌学会学術集会、パシフィコ横浜、横浜、2022 年 9 月 29 日（2022 年 9 月 29 日～10 月 1 日）（口演）
46. Yamauchi J, Sato T, Yagishita N, Araya N, Nakagawa M, Matsuura E, Tsuboi Y, Tamaki K, Sakima H, Ishihara S, Araujo A, Jacobson S, Grassi MFR, Galvão-Castro B, Bland M, Taylor GP, Martin F, Yamano Y. A randomized controlled trial on corticosteroid therapy for HTLV-1-associated myelopathy/tropical spastic paraparesis in Japan (HAMLET-P trial). 20th International Conference on Human Retrovirology: HTLV and Related Viruses(HTLV22), 8 - 11 May 2022, 国外, 口頭.
47. Sato T, Yagishita N, Araya N, Yamauchi J, Takahashi K, Kunitomo Y, Hasegawa Y, Higashikuse Y, Miyachi K, Yamano Y. Evaluation of quantification method of HTLV-1 proviral load in white blood cells using whole blood. 20th International Conference on Human Retrovirology: HTLV and Related Viruses(HTLV22), 8 - 11 May 2022, 国外,口頭.
48. 新谷奈津美, 荒谷聡子, 八木下尚子, 山内淳司, 佐藤知雄, 山野嘉久. HTLV-1 関連脊髄症（HAM）の病態形成機構. 第 63 回日本神経学会学術大会, 2022 年 5 月 19 日, 国内, 口頭.
49. 伊佐早健司, 柴田宗一郎, 飯島直樹, 平川経晃, 伊藤歩, 西村直, 福田隆浩, 佐々木諒, 藤井伸治, 佐藤知雄, 山野嘉久. 成人 T 細胞白血病移植後の神経障害例 2 例の検討. 第 63 回日本神経学会学術大会, 2022 年 5 月 21 日, 国内, ポスター.
50. 山野嘉久. HTLV-1 の基礎知識とキャリア妊産婦・患者への支援. 令和 4 年度山梨県 HTLV-1 母子感染予防対策研修会, 2022 年 7 月 6 日　Web 開催, 国内, 口頭.
51. 山野嘉久. 難病の全ゲノム解析等実証事業の現状と展望. 第 7 回クリニカルバイオバンク学会シンポジウム, 2022 年 7 月 9 日, ハイブリッド開催, 国内, 口頭.
52. 山野嘉久. HAM 病態研究の最近の知見と今後の展望. 第 34 回日本神経免疫学会学術集会, 2022 年 10 月 21 日, 国内, 口頭.
53. 山野嘉久. 難病領域におけるリアルワールドデータ活用の動向～難病プラットフォームを例に～. 第 40 回日本神経治療学会学術集会, 2022 年 11 月 4 日, 国内, 口頭.
54. 伊佐早健司, 柴田宗一郎, 飯島直樹, 平川経晃, 伊藤歩, 福田隆浩, 佐々木諒, 藤井伸治, 佐藤知雄, 山野嘉久. 成人 T 細胞白血病移植後の神経障害例 2 例の検討. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, ポスター.
55. 鷹尾直誠, 佐藤知雄, 山内淳司, 八木下尚子, 新谷奈津美, 荒谷聡子, 山野嘉久. HAM の排尿障害における臨床症状評価と治療効果判定の標準化スケールの確立. 第８回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, ポスター.
56. 菅田謙治, タン ベンジージェックヤン, ホサイン ベラル, ラジブ サミウルラジ, レダ オムニア, 徳永雅仁, 野村隼也, 増田曜章, 佐藤知雄, 植田光晴, 宇都宮與, 山野嘉久, 佐藤賢文. HAM 患者末梢血および脳脊髄液のシングルセル解析による HAM 病態解明と疾患サロゲートマーカーの探索研究. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, 口頭.

57. 新谷奈津美, 荒谷聡子, 八木下尚子, 山内淳司, 鷹尾直誠, 佐藤知雄, 山野嘉久. HTLV-1 関連脊髄症(HAM)の神経障害機構の解析. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, ポスター.
58. 倉光球, 石塚賢治, 久保田龍二, 佐藤知雄, 山野嘉久, 橋倉悠輝, 梅北邦彦, 野坂生郷, 長谷川寛雄, 三浦清徳, 宇都宮與, 高起良, 相良康子, 蕎麦田理英子, 佐竹正博, 浜口功. イムノクロマト法による新規 HTLV-1 抗体検査法の性能評価―多施設共同研究. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, 口頭.
59. 相良康子, 中村仁美, 堀部恵梨佳, 入田和男, 山野嘉久, 渡邉俊樹. ウェブサイト・トラフィック -HTLV-1 ウェブサイトの検証と解析-. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, ポスター.
60. 堀部恵梨佳, 相良康子, 山野嘉久, 内丸薫, 浜口功, 渡邊俊樹. JSPFAD アンケート調査による HTLV-1 水平感染の現状. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 4 日, 国内, ポスター.
61. 山野嘉久. HTLV-1 関連脊髄症（HAM）の病態生理に基づく治療. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 5 日, 国内, 口頭.
62. 松浦英治, 野妻智嗣, 田代雄一, 安藤匡宏, 平松有, 樋口雄二郎, 崎山雄介, 橋口昭大, 道園久美子, 東桂子, 松﨑敏男, 兒玉大介, 田中正和, 山野嘉久, 久保田龍二, 高嶋博. HAM/TSP の運動障害に対する L-アルギニンの効果を評価する第 2 相臨床試験（特定臨床研究）. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 5 日, 国内, 口頭.
63. 佐藤知雄, 斎藤益満, 和田悠作, 長谷川寛雄, 松平崇弘, 今泉芳孝, 内丸薫, 渡邉俊樹, 山野嘉久. HTLV-1 クロナリティ定量検査 RAISING-CLOVA を用いた ATL 発症リスク評価法の開発. 第 8 回日本 HTLV-1 学会学術集会, 2022 年 11 月 5 日, 国内, 口頭.
64. 山野嘉久. 難病領域におけるレジストリ活用の動向 ～難病プラットフォームについて～. 第 43 回日本臨床薬理学会学術総会, 2022 年 11 月 30 日, 国内, 口頭.
65. 山野嘉久. 患者レジストリを活用した医療イノベーションへの挑戦～治療そして予防まで～, 令和 4 年度第 3 回聖マリア病院特別講演会, 2023 年 3 月 20 日, 国内, 口頭.
66. 関西地区における HTLV-1 水平感染の解析 高 起良、南野 智、手塚健太、倉光球、浜口功. 第 8 回日本 HTLV-1 学会学術集会、東京、2022/11/4-6、国内、ポスター

3. 講演会・シンポジウム

1. 内丸薫、2022 年長崎県 ATL ウイルス母子感染防止に関する講演会 「HTLV-1 キャリアマザーに対する授乳指導～厚生労働科学研究板橋班/内丸班の研究紹介」2022 年 2 月 23 日 名麻危険医師会館・オンライン
2. 内丸薫、ウェブ調査から見えてくるキャリアマザーの思い、第 36 回日本母乳哺育学会学術集会 シンポジウム 家族ぐるみで考える HTLV-1 2022.9.18 長崎
3. 山野嘉久. 「難病プラットフォームについて. リアルワールドデータ（RWD）の利活用と課題（第 5 回）」, 2022 年 3 月 22 日, Web 開催.
4. 山野嘉久. 「HTLV-1 母子感染の予防と対策」. 令和 3 年度不妊・不育 HTLV-1 相談に関するオンライン研修, 2022 年 2 月 24 日, オンライン配信.
5. 山野嘉久. 「難病レジストリの構築と重要性」. 2021 年度 AMED 村山班 小坂分担班・集中 TR 会議, 2022 年 2 月 20 日, Web 開催 ＜特別講演＞
6. 山野嘉久. 「HTLV-1 関連脊髄症（HAM）の病態生理に基づく個別化医療の展望」. 第 7 回 Kyoto Neurology Forum. 2021 年 9 月 4 日, Web 開催.
7. 山野嘉久. 「難病領域での展望. デジタルトランスフォーメーションの挑戦」. 2021 年 8 月 30 日, Web 開催.
8. 山野嘉久. 「HTLV-1 の基礎知識と最新情報について」 キャリア妊産婦・患者の支援について. 令和 3 年度 山梨県 HTLV-1 母子感染予防対策研修会, 2021 年 7 月 7 日, Web 開催.
9. 山野嘉久. 「HAM の病態理解に基づく個別化医療の展望」. 第 32 回山梨神経先端セミナー, 2021 年 6 月 9 日, web 開催.

10. 高起良、「HTLV-1 全国ネット研修交流会で講演、HTLV-1 キャリア外来での取り組みについて」令和３年度特定非営利活動法人　HTLV-1 全国ねっと 第２回 研修交流会、令和４年３月 26 日　姫路市国際交流センター＋ZOOM
11. 齋藤滋：HTLV-1 の母子感染予防対策．令和 4 年度 富山県 HTLV-1 母子感染対策研修会．2022.10.13．富山．
12. 根路銘安仁．HTLV-1 母子感染予防マニュアルの主な変更点について．鹿児島県令和４年度 HTLV-1 対策講習会　2023 年 1 月　鹿児島県医師会
13. 宮沢篤生．感染症と母乳育児　HTLV-1 母乳育児支援．日本助産師会研修会．2022 年 7～9 月．Web 配信
14. 宮沢篤生．母子感染対策マニュアル改訂版の紹介．2022 年世界 HTLV-1 デー記念講演．2022 年 11 月 6 日、一橋講堂（東京）
15. 山野嘉久. HTLV-1 関連脊髄症．第 1 回神経免疫疾患診療医育成セミナー, 2022 年 6 月 18 日, 一橋大学一橋講堂
16. 山野嘉久. HTLV-1 母子感染の予防と対策．令和 4 年度性と健康の相談支援者研修（神奈川県主催）, 2023 年 2 月 8 日, オンライン開催.
17. 山野嘉久. HTLV-1 基礎知識と相談支援について．令和 4 年度北海道 HTLV-1 母子感染予防対策研修会（北海道主催）, 2023 年 1 月 28 日, オンライン開催.
18. 山野嘉久．これからの難病医療と産学連携. RDD medU-net フォーラム（世界希少・難治性疾患の日）, 2023 年 3 月 19 日, オンライン開催.
19. 令和４年度　大阪府母子保健コーディネーター育成研修（スキルアップ編）にて講演「HTLV-1 母子感染予防対策マニュアル第２版」の理解と最新の知見、高　起良、大阪、2023/2/10
20. 井村真澄・武市洋美：助産師による HTLV-1 キャリアの母親への授乳支援．日本助産師会勤務部会集会研修会．2023 年 1 月 28 日
21. 井村真澄：授乳支援．長野県看護協会助産師支援研修会．2023 年 2 月 17 日
22. 井村真澄：千葉大学大学院看護学研究科健康増進看護学講座．Confederation of Maternity Nursing 勉強会．助産政策と研究－乳腺炎重症化予防ケア・指導料、母子感染予防対策マニュアル(第 2 版)と助産師による HTLV-1 キャリアの母親への授乳支援．2023 年 3 月 12 日
23. 関沢明彦、令和 4 年度三重県 HTLV-1 研修会「HTLV-1 母子感染予防対策～新しいマニュアルではどう変わる？」2022 年 10 月 1 日

H.知的財産権の出願・登録状況

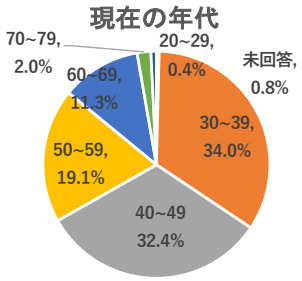
該当なし

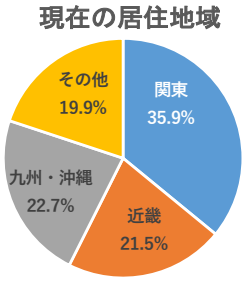
図1

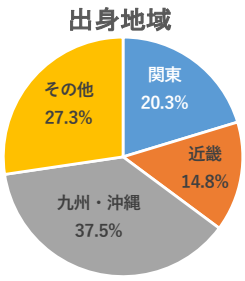
アンケート回答者の基本属性① (n =256)

		全体				九州・沖縄				それ以外			
		n	%	平均	SD	n	%	平均	SD	n	%	平均	SD
現在の年齢※				46.1	10.5			31.9	11.6			46.51	10.6
現在の年代※	20~29	1	0.4			0	0.0	4.0		1	0.5		
	30~39	87	34.0			23	39.7			64	32.3		
	40~49	83	32.4			17	29.3			66	33.3		
	50~59	49	19.1			11	19.0			38	19.2		
	60~69	29	11.3			5	8.6			24	12.1		
	70~79	5	2.0			1	1.7			4	2.0		
	未回答	2	0.8			1	1.7			1	0.5		
性別	女性	256	100.0			58	100.0			198	100.0		
診断時年齢				31.7	11.1			30.9	9.3			44.6	10.2
居住地域	関東	92	35.9							92	46.5		
	近畿	55	21.5							55	27.8		
	九州・沖縄	58	22.7							0	0.0		
	その他	51	19.9							51	25.8		
出身地域	関東	52	20.3			1	1.7			51	25.8		
	近畿	38	14.8			0	0.0			38	19.2		
	九州・沖縄	96	37.5			54	93.1			42	21.2		
	その他	70	27.3			3	5.2			67	33.8		

※年齢、年代は2022年2月7日時点で算出。





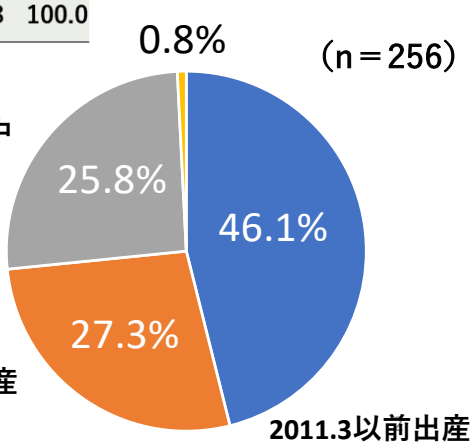


1

図2　最終分娩時期

現在妊娠中の妊婦さん<Ⅰ>/すでに出産されたお母さん<Ⅱ>（n＝ 256）

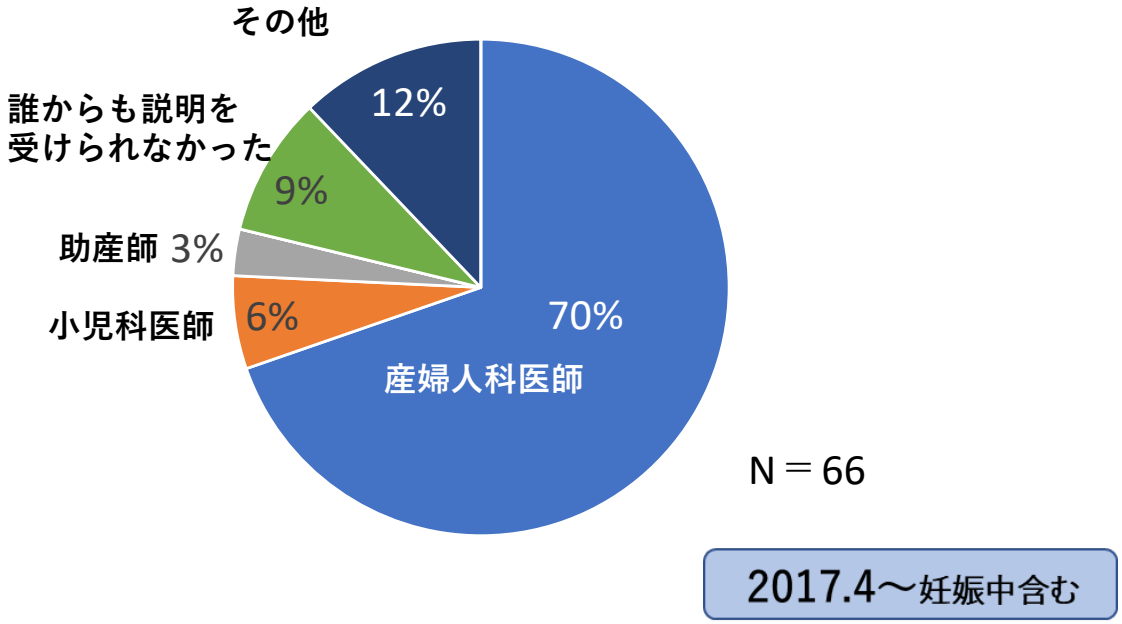
	全体		九州・沖縄		それ以外	
	n	%	n	%	n	%
a.2011年3月31日以前	118	46.1	24	41.4	94	47.5
b.2011年4月1日～2017年3月31日	70	27.3	13	22.4	57	28.8
c.2017年4月1日以後	66	25.8	21	36.2	45	22.7
未回答	2	0.8	0	0.0	2	1.0
合計	256	100.0	58	100.0	198	100.0



妊娠出産時期については、比較的いい
バランスの集団

図3　HTLV-1母子感染や予防法について説明を受けた医療者

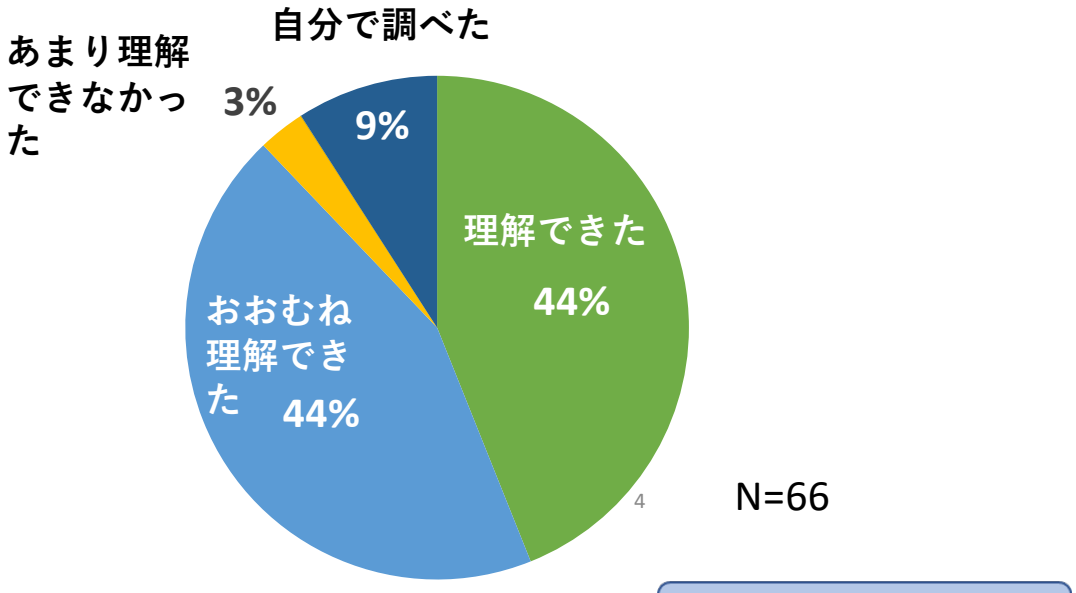
現在妊娠中の妊婦さん<Ⅰ>/すでに出産されたお母さん<Ⅱ>
2017~（n＝ 66）



2017.4～妊娠中含む

図4　HTLV-1母子感染や予防法について説明の理解度

現在妊娠中の妊婦さん<Ⅰ>/すでに出産されたお母さん<Ⅱ>（n＝ 218）



2017.4～妊娠中含む

図5　キャリアマザーの授乳法の変化(妊娠中のお母さん含む)

現在妊娠中の妊婦さん<Ⅰ>/すでに出産されたお母さん<Ⅱ>（n＝ 256）

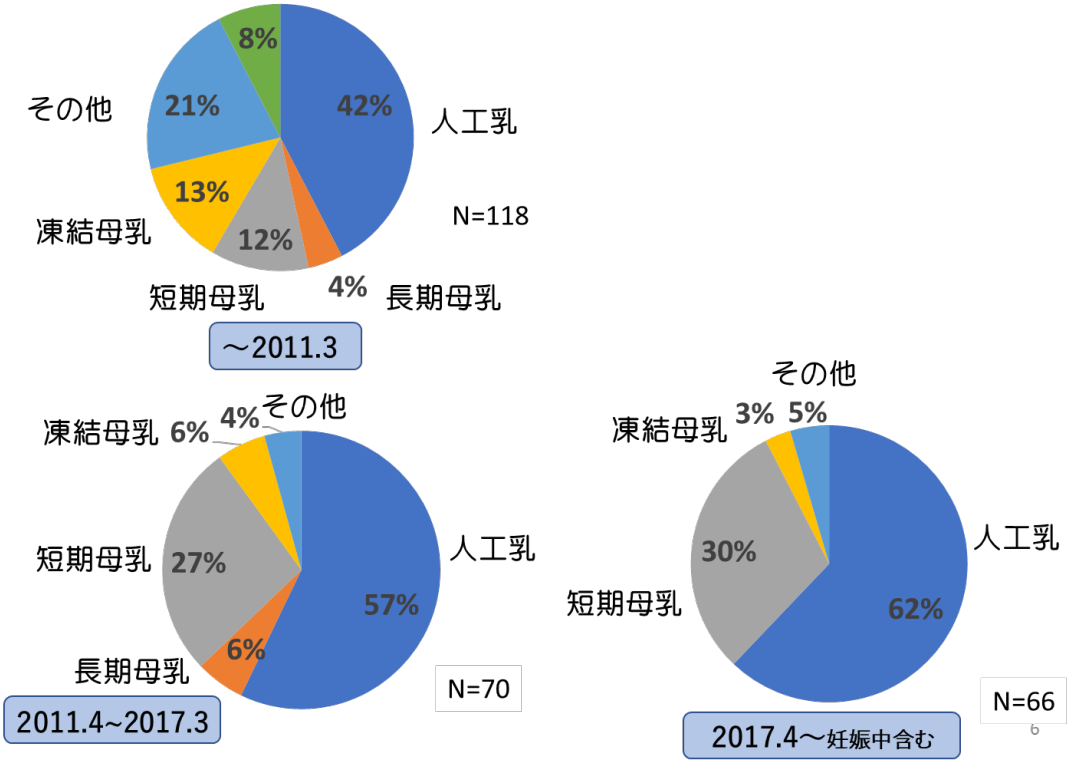
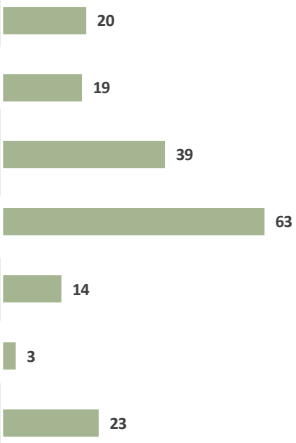


図6　困難さの理由（複数回答）

すでに出産されたお母さん<Ⅱ>（n＝ 232）

	全体					九州・沖縄		それ以外	
	①	②	③	合計	%	n	%	n	%
a.　母乳を中断することが難しかった	8	9	3	20	23.5	6	37.5	14	20.3
b.　母乳の凍結・解凍が煩雑であった	12	7	0	19	22.4	2	12.5	17	24.6
c.　周囲から人工栄養にしていることを指摘され肩身が狭かった	12	17	10	39	45.9	11	68.8	28	40.6
d.　母乳を与えられないことの罪悪感にさいなまれた	23	25	15	63	74.1	12	75.0	51	73.9
e.　医療者の支援が不十分であった	5	6	3	14	16.5	1	6.3	13	18.8
f.　家族の協力が得られなかった	2	1	0	3	3.5	0	0.0	3	4.3
g.　その他	12	9	2	23	27.1	2	12.5	21	30.4
合計	41	27	17	85	100.0	16	100.0	69	100.0



※子の生年月日　①2011年3月31日以前 ②2011年4月1日～2017年3月31日 ③2017年4月1日以後

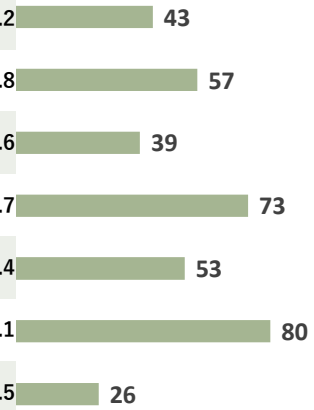
※子の生年月日別の合計と地域別の合計は、無回答があるため一致しない

※設問10にて「b.容易ではなかった」と回答した85名を母数として%算出

図7　支援が不十分と考える理由（複数回答）

すでに出産されたお母さん＜Ⅱ＞（n＝ 232）

	全体					九州・沖縄		それ以外	
	①	②	③	合計	%	n	%	n	%
a.　母子感染予防についての説明が不十分である	22	15	6	43	27.9	11	40.7	32	25.2
b.　医療者がHTLV-1母子感染についてよくわかっていない	30	20	7	57	37.0	9	33.3	48	37.8
c.　具体的な栄養法の支援が欲しい	17	13	9	39	25.3	9	33.3	30	23.6
d.　母親の気持ちに寄り添って指導して欲しい	33	25	15	73	47.4	15	55.6	58	45.7
e.　産婦人科から小児科への連携がほとんどない	17	22	14	53	34.4	8	29.6	45	35.4
f.　相談先がわからなかった	47	20	13	80	51.9	10	37.0	70	55.1
g.　その他	14	11	1	26	16.9	5	18.5	21	16.5
合計	83	45	26	154	100.0	27	100.0	127	100.0



※子の生年月日　①2011年3月31日以前 ②2011年4月1日～2017年3月31日 ③2017年4月1日以後

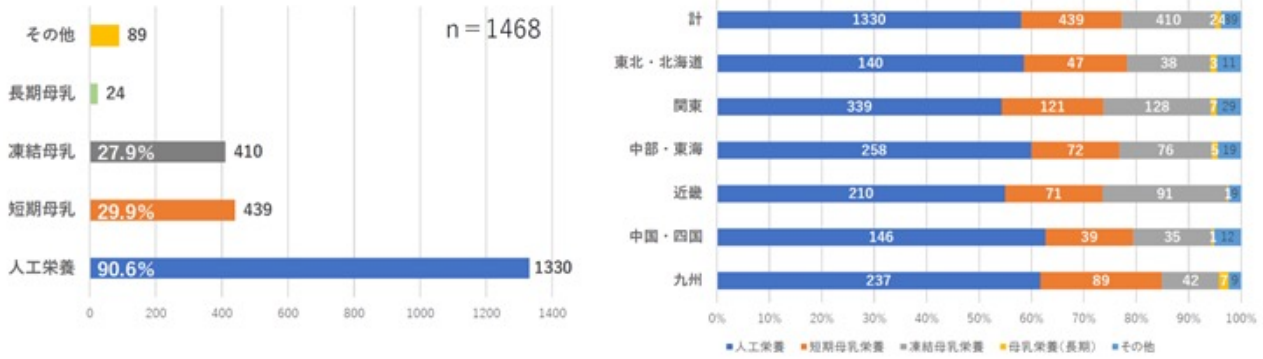
※子の生年月日別の合計と地域別の合計は、無回答があるため一致しない

※設問12にて「b.不十分である」と回答した154名を母数として%算出

図8

実際にHTLV-１キャリアと診断された女性に 貴施設ではどのような授乳法を原則的に勧めますか

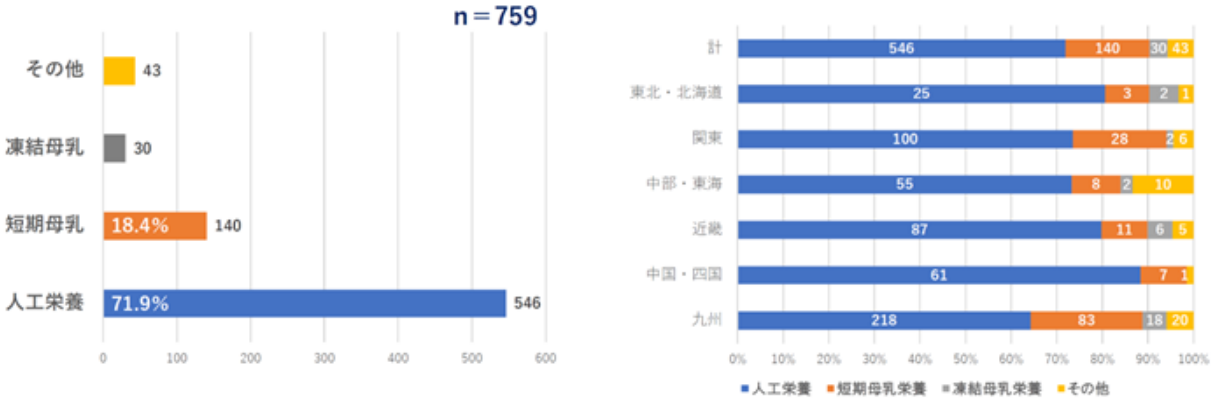
（複数回答）



施設ごとにみると、90%で人工栄養、30%で短期母乳、28%で凍結母乳が推奨されていた。

図9

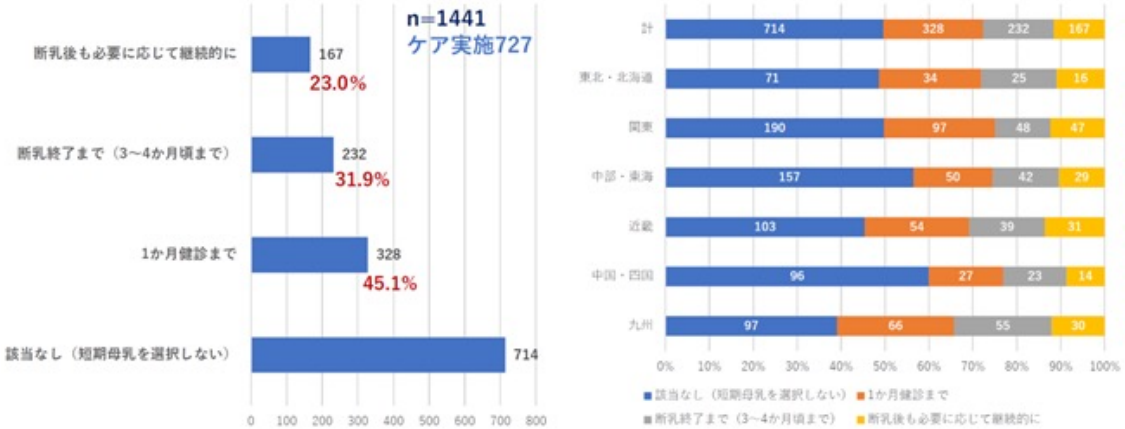
実際にHTLV-１キャリアと診断された女性の栄養方法の選択
（複数回答）



キャリアの授乳方法として
- 全体では70%以上が人工栄養、18%が短期母乳を選択していた。
- 九州では短期母乳が選択される割合がやや多めであった。

図10

HTLV-1キャリアが短期母乳を選択した場合、貴施設は母乳育児中のケアはいつ頃まで行っていますか



産科施設での母乳育児中のケアは45%は1か月健診までで、断乳が必要な時期までのケアを行っているのは54.9%にとどまった。

図11　産婦人科HTLV-1診療の基幹施設の分布

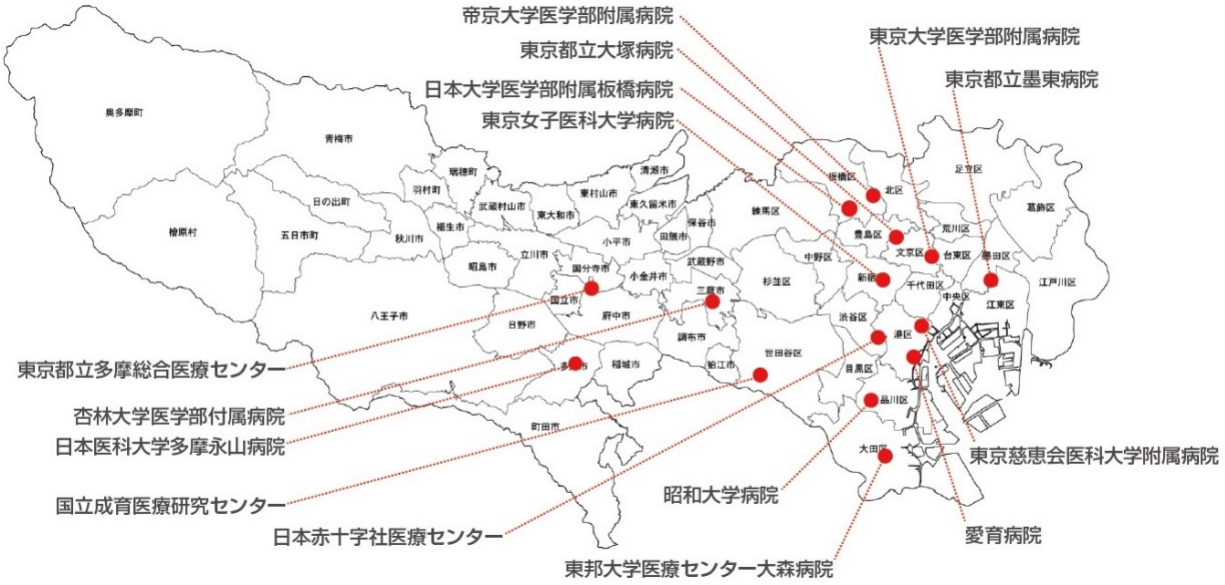


図12　東京プログラムでの小児相談窓口の分布

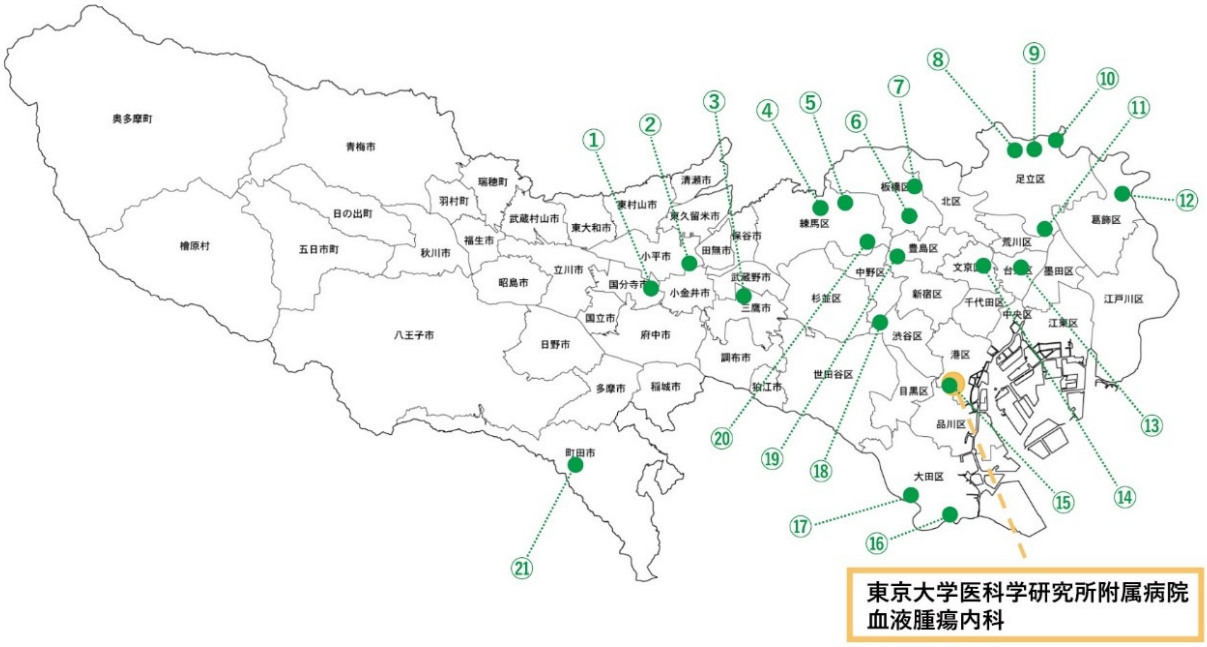


表1　日本HTLV-1学会登録医療機関一覧令和3年度年次報告集計

施設番号	施設名	初診数						保健所からの相談件数	相談センターのち院内他科対応件数	再診件数	近隣施設研修
		日赤からの紹介	周産期施設からの紹介	保健所からの紹介	他医療機関からの紹介	紹介無し	合計				
1	東大医科研病院	3	1	0	9	19	32	0	0	120	0
2	聖マリアンナ医大病院	1	1	0	1	4	7	0	4	157	2
3	JR大阪鉄道病院	0	2	1	10	0	13	0	0	181	1
4	佐賀大学病院	3	5	0	2	15	25	0	10	127	0
5	今村総合病院	2	1	1	27	18	49	0	8	180	1
6	鹿児島大学病院	0	0	0	12	0	12	0	1	35	1
7	宮崎大学病院	2	1	0	11	3	17	0	4	65	1
8	大分大学病院	0	0	0	1	3	4	0	3	30	0
9	熊本大学病院	2	0	0	10	0	12	0	0	37	0
10	琉球大学病院	7	0	0	0	2	9	0	15	55	0
11	九州がんセンター	7	0	0	5	0	12	0	36	285	0
12	京都大学病院	0	0	0	3	0	3	0	9	45	1
13	長崎大学病院	0	0	0	3	0	3	0	16	6	0
14	岩手医大病院	0	0	0	5	1	6	0	5	48	0
15	山形大学病院	0	0	0	3	0	3	0	0	0	0
16	佐世保市総合医療センター	0	3	0	6	0	9	0	13	40	0
	計	27	14	2	108	65	216	0	124	1411	7

Ⅱ．研究成果の刊行物に関する一覧表

HTLV-1母子感染対策および支援体制の課題の検討と対策に関する研究

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
根路銘 安仁	HTLV-1母子感染予防での小児保健関係者の役割	小児保健研究	81(3)	189-197	2022
Komatsu N, Iwanaga M, Hasegawa Y, Miura S, Fuchi N, Moriuchi H, Yanagihara K, Miura K	Frequency of HTLV-1 seroconversion between pregnancies in Nagasaki, Japan	Front Microbiol	2022;13	1036955	2022
Itabashi K, Miyazawa T, Uchimaru K	How Can We Prevent Mother-to-Child Transmission of HTLV-1?	J Mol Sci	9;24(8)	6961	2023
Kazuo Itabashi, Tokuo Miyazawa, Akihiko Sekizawa, Akifumi Tokita, Shigeru Saito , Hiroyuki Moriuchi, Yasuhito Nerome, Kaoru Uchimaru, Toshiki Watanabe	Nationwide Antenatal Human T-Cell Leukemia Virus Type-1 Antibody Screening in Japan.	Front Microbiol	9;11	595	2020
Yonemoto N, Suzuki S, Sekizawa A, Hoshi S, Sagara Y, Itabashi K	Implementation of nationwide screening of pregnant women for HTLV-1 infection in Japan: analysis of a repeated cross-sectional study	MC Public Health	22;20(1)	1150	2020
Kazuo Itabashi, Tokuo Miyazawa	Mother-to-Child Transmission of Human T-Cell Leukemia Virus Type 1: Mechanisms and Nutritional Strategies for Prevention.	Cancers (Basel)	14;13(16)	4100	2021
Itabashi K, Miyazawa T, Nerome Y, Sekizawa A, Moriuchi H, Saito S, Yonemoto N.	Issues of infant feeding for postnatal prevention of human T-cell leukemia/lymphoma virus type-1 mother-to-child transmission.	Pediatr Int	63(3)	284-289	2021

Ⅲ．研究成果の刊行物・別刷

HTLV-1母子感染対策および支援体制の課題の検討と対策に関する研究

総　　説

HTLV-1 母子感染予防での小児保健関係者の役割

根路銘安仁

はじめに

HTLV-1 の感染と起因する疾患群への対策に総合的に取り組むため，2010 年 9 月に内閣総理大臣の指示により「HTLV-1 特命チーム」が設けられ，「HTLV-1 総合対策」が開始された。小児保健分野では，母子感染予防のために全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになった。それに伴い，医師向け手引き[1]および保健指導マニュアル[2]が作成され，2017 年に厚生労働研究事業（代表　板橋家頭夫）により「HTLV-1 母子感染予防対策マニュアル」[3]が作成された。

本年，前研究班でのコホート研究で短期母乳栄養法と完全人工栄養法を選択した場合に母子感染率に有意な差はなかったエビデンス[4,5]をうけて厚生労働科学研究（代表者　内丸薫）が 2022 年にマニュアル改訂を行った[6]。今回の改訂でも人工栄養が最も確実な方法である。一方，短期母乳栄養は「母親が母乳を与えることを強く希望する場合」に限り選択肢として考慮することであったが，90 日未満で完全人工栄養に移行する支援を行うことで完全人工栄養とともに選択肢として含められることになった。短期母乳を選択するには支援する体制を整備することが必須である。短期母乳選択者への支援において小児保健関係者も産科医療施設，小児医療施設，行政機関に所属しており，連携するため互いの支援内容の理解を深める必要がある。今回，マニュアル改訂を機会に HTLV-1 母子感染予防について概説する。

Ⅰ．我が国の HTLV-1 母子感染対策のあゆみ

1．HTLV-1 と母子感染対策の歴史

1977 年に高月清らにより成人 T 細胞白血病（Adult T cell leukemia：ATL，以後 ATL）が報告された[7]。1981 年には日昭賴夫が ATL と関連するウイルスとして HTLV-1 を報告した[8]。1985 年に日野茂男らが母乳を介した感染の成立を証明し，母子感染の対策のきっかけを作った[9]。

HTLV-1 流行地域で，それぞれ率先して研究対策が行われ成果を上げてきた。長崎県では 1987 年には ATL ウイルス母子感染防止研究協力事業（ATL Prevention Program Nagasaki：APP）を開始し現在まで継続している[10]。鹿児島県でも 1985 年から鹿児島大学と共同研究を行い，短期母乳栄養法を確立し，1997 年から鹿児島 ATL 制圧 10 ヵ年計画を実施[11]して完全人工栄養法と短期母乳栄養法から選択することを臨床で確立した。しかし，1991 年に厚生省心身障害研究重松班でキャリア率の高い地域でのみの対策で十分であり，全国一律の検査や対策は必要ないと提言され[12]，全国的な対策はとられることは無かった。

その後，20 年ほど全国的な研究対策は低迷したが，2009 年厚生労働科学研究山口班報告で，HTLV-1 キャリア（以降キャリア）が全国に拡散している事が明ら

The Role of Child Health Personnel in the Prevention of HTLV-1 Mother-to-child Transmission
Yasuhiro Nerome
鹿児島大学医学部保健学科看護学専攻成育看護学講座

かとなり[13]，研究者や患者団体等の働き掛けもあって，「HTLV-1 総合対策」が開始され，全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになった。

2. HTLV-1 に関連する疾病

HTLV-1 は，関連する疾患は多くあるが，主なものとして ATL，HTLV-1 関連脊髄症（HTLV-1-associated myelopathy：HAM，以降 HAM）があげられる。しかし，キャリアだからといって多くの人は発症せず，妊娠出産で問題になることは少ない。

ATL は 40 歳以前の発症は珍しく，キャリアのうち年間 1,000 人に 1 人，生涯で約 5% 発症するとされている[14]。しかし，最近では，新薬の登場や骨髄移植により治療成績も改善されつつあるが，発症すると予後不良であり寿命ロスを引き起こす疾患である。

HAM は，キャリアのうち生涯で約 0.25% 発症するとされている[15]。歩行障害や膀胱直腸障害が緩徐に進行することが多く，治療で進行することを遅らせることはできるが止めることはできず，生活の質（QOL）を損ね健康ロスを引き起こす疾患である。

このように，HTLV-1 は私たちの健康寿命を短くする原因になるため，感染予防対策が重要である。

Ⅱ．HTLV-1 感染経路と対策

HTLV-1 はＢ型肝炎ウイルスやヒト免疫不全ウイルス（HIV）のように血漿中や体液中のウイルス自体で感染するのと異なり，感染リンパ球が生きたまま体の中に入り自分の中のリンパ球と細胞同士の接触によりおこる。感染力は弱く，主な感染経路は，1 母子感染，2 性行為による水平感染，および，3 輸血や臓器移植による感染があげられる。

1. 母子感染

母子感染は，1 年程度母乳を与えた場合の母子感染率は約 15-20% とされている。

ⅰ．母乳以外を介した感染

これまでの研究より，母乳を与えない完全人工栄養法でも約 3% 母子感染が成立する[1~5]。母乳以外を介した感染経路が考えられてきたが，経胎盤感染の存在が示唆されている[16]。この経路を防止する有効な手段は現在ない。

ⅱ．母乳を介した感染

母乳中には感染リンパ球が多く含まれる[17]，母乳を介した感染が証明され[9]，感染予防のため，完全人工栄養法[18]，短期母乳栄養法[19]，凍結解凍母乳法[20]が行われてきた。わが国で初めてのコホート研究で，短期母乳栄養法 2.3%（95% 信頼区間：0.0-4.6%），完全人工栄養法 6.4%（95% 信頼区間：1.9-10.9%）と両者に統計学的な差は認められなかった[4]。母乳以外を介した感染率を考慮すると母乳を介した感染は栄養法を選択することで防止することが可能であると考えられる。

2. 性行為による感染

精液中に多くの感染リンパ球が含まれており[17]，傷ついた粘膜に精液や血液のリンパ球が接触することで感染すると考えられている。男性から女性が優位な経路になる。献血者のデータから HTLV-1 陽転化割合は女性が 10 万人あたり 6.88 人，男性が 10 万人あたり 2.29 人であった[21]。この経路を防止するのは，HTLV-1 に限らず他の性行為感染症と同様に挙児希望無い場合には，エビデンスは乏しいがコンドームの使用が有効と考えられる。

3. 輸血，臓器移植による感染

血液や臓器中の感染リンパ球を介しての感染である。1986 年以降献血での HTLV-1 抗体検査が実施されているため安全に輸血が可能である。2000 年以降，臓器移植後早期に HAM を発症した症例が報告された[22]。キャリアをドナーとした移植には制限がある。

Ⅲ．母子感染対策での支援

1. 産科施設での支援（妊婦健康診査でのスクリーニング検査から栄養法選択と達成まで）

ⅰ．スクリーニング検査からキャリアの確定まで（図 1）

スクリーニング検査陽性の場合に確認検査をしなければキャリアであると判定できないことを伝え，ラインブロット（LIA）法の確認検査を行う。流行地であった鹿児島でも 2018 年には，スクリーニング検査陽性者 69 人のうち確認検査での陽性者は 47 人（68.1%）にとどまっている[23]（**図 2**）。スクリーニング抗体が陽性で確認検査が陰性となる割合は，キャリアが少ない地域では高くなり，非流行地域では 7 割以上陰性とも報告されている[3]。

確認検査が陽性であればキャリアとして，母子感染

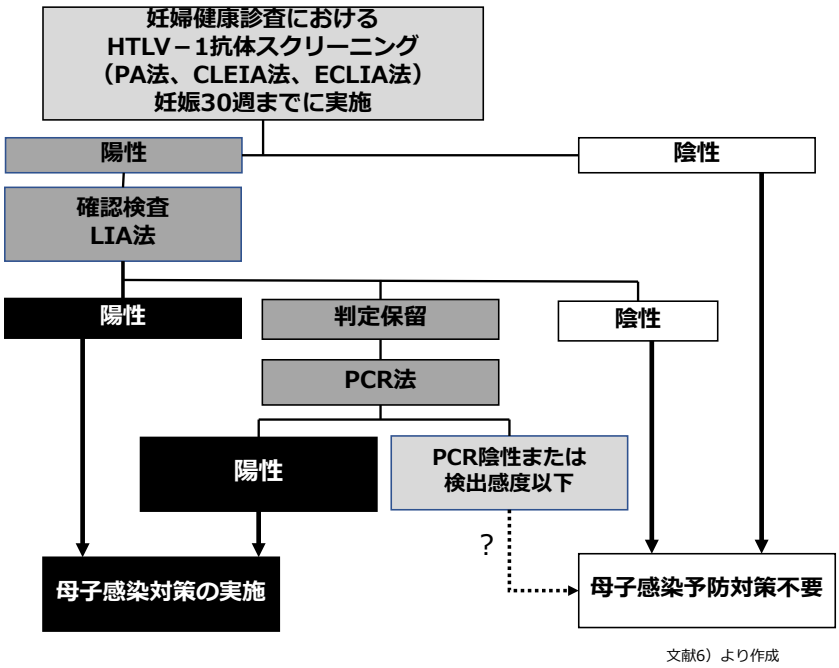


図１　妊婦健診における HTLV-1 抗体検査の流れ

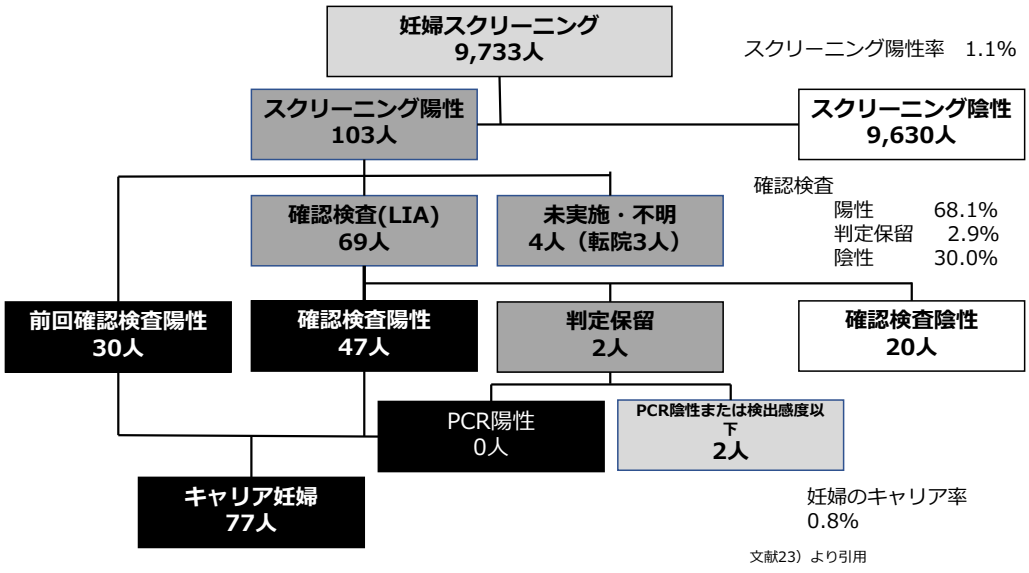


図２　鹿児島県における妊婦への HTLV-1 検査実施状況（令和元年度）

対策を含め情報提供を行う。キャリアは児への感染防止と共に自身が将来発病する可能性で不安となるため[24]，心理的サポートを開始することが必要である。多くのキャリアマザーが相談できずに悩みを抱えている現状がある[25]ため，保健医療者から話しやすい環境を作っていくことが求められる。

一方，確認検査で「判定保留」となる確率は減ったが一定数存在する。2016 年から「判定保留」であった妊婦に限り PCR 法が保険適用された。PCR 法で「陽性」であればキャリアとして扱う。「陰性もしくは検出感度以下」の場合には母子感染の可能性は低いと推定されるがエビデンスが確立していない[6]。授乳で感染症例もあった[26]ため，キャリアではないとはいえず対応が難しい。

ⅱ．キャリアの確定から栄養法選択と達成への支援

キャリアであった場合，感染防止のため栄養法の選択を行う。充分な説明や栄養法選択の意志決定支援を受けた母親では，産後 1 か月，および 3 か月のエジンバラ産後うつ病評価尺度（EPDS）は差を認めず，また EPDS が 9 点以上を示す割合も一般的な妊婦に比

	母乳	人工栄養（ミルク）
児	最適な成分組成で少ない代謝負担 感染症の発症および重症度の低下 小児期の肥満や2型糖尿病の発症リスクの低下 乳児突然死症候群のリスクが下がる 喘息やアトピー性皮膚炎のリスクの低下	ビタミンD,Kや鉄分などが不足しにくい
母親	産後の母体の回復の促進 衛生的、経済的で手間もかからない	父親も授乳に参加できる 授乳量が測定しやすい

図３　母乳と人工栄養（ミルク）の児と母親のメリット

栄養方法	完全人工栄養	短期母乳栄養（90日未満）	凍結解凍母乳栄養	長期母乳栄養
母子感染予防効果	母乳を介した母子感染を予防するためには最も確実な方法（母子感染率約3%）	完全人工栄養と比較して明らかな差がない 達成できる環境では母子感染予防対策として推奨できる	エビデンスとしては少ない （早産児に対して考慮する）	母子感染率約15～20%。 母子感染予防対策としては推奨されない
メリット	最も確実である	母乳のメリットをある程度得ることができる 直接授乳が可能	母乳のメリットをある程度得ることができる 母乳が出る限り与えることができる	母乳のメリットが得られる
デメリット	完全人工栄養購入費がかかる（約10万円） 母乳のメリットが得られない 直接授乳ができない	90日未満しか与えることができない 完全人工栄養に90日未満で移行完了するのに困難がある 助産師等の支援が必要である	パック購入費がかかる（約10万円） 凍結解凍の手間がかかる 直接授乳ができない	感染する確率が上がる

図４　各栄養法の母子感染予防効果とメリット・デメリット

べて高くなかったことから，十分な説明や支援が重要であると考えられる[27]。

母乳を介した感染を防ぐ意味では完全人工栄養法が最も確実である。しかし，母乳育児は母子ともに多くのメリットがある[28]（図３）。そのため短期母乳栄養法が検討され，コホート研究でのエビデンスより今回のマニュアル改訂で短期母乳栄養法も選択肢として含むことになった[6]。また，凍結解凍母乳栄養法も検討されたが，症例数が少なくエビデンスが不十分とし選択肢には含められなかったが早期産児などが選択する可能性がある。母子感染予防よりも母乳栄養のメリットから長期母乳栄養法を選択する母親も存在する。母親および家族が何を重視するかによって選択肢は変わってくる。

そのため保健医療従事者は，自身の価値観にとらわれることなく，感染防止についての情報と共に，各栄養法のメリットと困難さなどのデメリットの情報（図４）を提供し，母親と家族から何を重視するかを聞いて，どの栄養法を選択するかの意思決定支援をおこなう。

どの栄養法を選択しても母親は選択後も自分の選択が正しかったのかと揺れ動いている。出産まではいつでも変更できることを伝える。出産後は栄養法変更が難しいため，正しい選択であったと支持的な対応を行い，選択した栄養方法を達成できるように支援を行う。栄養法を実施するにあたり，選択栄養法によらず約３割が困難を抱えていた[29]。

選択をするにあたり，出生時に児の検査を行い感染していたら母乳を与えたいという希望があることもある。抗体検査は移行抗体により陽性となり，PCR 検査も陰性であっても感染する可能性があるため出生時に検査での判断はできない。

a. 完全人工栄養法

困難を感じた理由の多くは「周囲の理解不足」だった[29]。産婦人科外来には，母乳育児を推奨するポスターも多く，母親学級で授乳指導や出産後授乳する人との同室などがストレスであった。産科スタッフはそのようなストレスがあることを知り配慮することが望まれる。

また，退院後にキャリアであることを知らない人から「母乳がでないの？」といわれストレスだったと言うこともあったため，一般の方への啓発活動が重要であるが難しい。せめて身近な人から言われないように，キャリアであることをどこまで伝えるかも栄養法選択と共に相談して決めていくことが必要である。栄養法選択時点では伝えることができなくても，出産後に関係性をつくり家族の理解と協力を得られるように母親の気持ちに寄り添いながら支援することも重要である。

一方，完全人工栄養法と決定していた場合に早産となった場合，壊死性腸炎の予防などで母乳を与えることを検討することがある。早産児に人工栄養を与えての壊死性腸炎発症など生命的リスクと，凍結母乳栄養

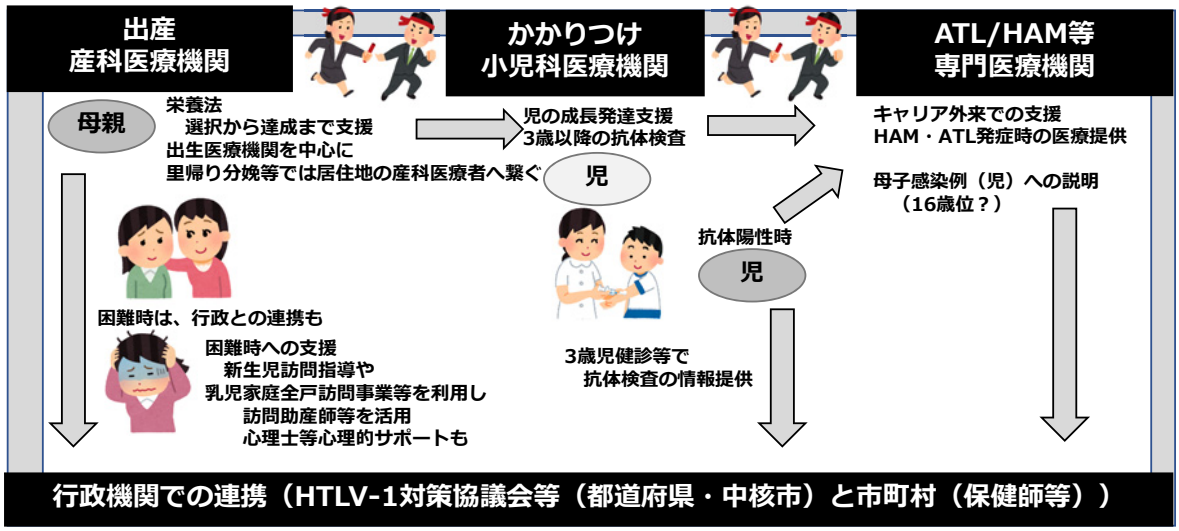


図 5　母子保健分野での医療機関および行政支援体制

法のエビデンスは少ないが理論的には HTLV-1 感染のリスクをよく説明して母親に納得の上，選択してもらう。

b. 短期母乳栄養法

本栄養法の困難は，やはり 90 日未満で人工栄養への完全な移行の達成である。ひとりで達成するのは困難で，支援が無ければ 5 人に 1 人やめられない可能性がある[4]。その理由は乳房トラブルなど技術的支援不足であった[29]。産後 1 か月健診で支援が途切れていることが多かったが，鹿児島県では短期母乳栄養法を選択した場合に，約半数が「3 か月後の断乳を確認した」と回答していた[23]。出産した産科施設で母親も慣れているため 1 か月以降も継続して，人工栄養への完全移行達成の確認まで支援を続けるのが望ましい。もしも，里帰り分娩等の場合で難しい場合には，本人の同意のもと居住地近くの産科医療機関や開業助産師へ紹介するか，居住地の保健師につなぎ，新生児訪問指導や乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）で助産師の活用を依頼することを検討し，途切れることがない支援体制を作る。

また，「そんなに泣くならあげたら」と夫に言われ心が折れたと話す方もいたので，移行時に家族の支援も重要であり，理解と協力が得られるように事前に話し合いを持ち準備しておくことが重要である。移行後は，完全人工栄養と同じように他者からの授乳に関するストレスは生じうる。

完全人工栄養法も含め短期母乳栄養法も移行後，約 1 年間で人工栄養購入費が 10 万円ほどかかる。経済的理由から長期母乳を選択する家族もいた。鹿児島県では 2019 年以降の一部助成が行われている[30]。健康社会格差解消のために HTLV-1 キャリアだけでなく，本人の意思によらない理由で母乳を与えることができない方への支援を検討する必要がある。

c. その他の栄養法

母親と家族に説明後，十分考え抜いた末に「長期母乳栄養法」や「凍結母乳栄養法」を選択することもある。自身がアレルギー体質で悩んでこられ，母乳をあげないことで HTLV-1 関連疾病の発症するリスクと母乳をあげることでのアレルギー発症のリスク軽減から，長期母乳栄養法を選択された母親がいた。絶対に正しい栄養法はなく，本人の価値観により正しい選択肢は変わってくる。本人が納得できる選択をした際に達成できるよう支援することが重要である。

ⅲ．切れ目ない支援へ（図 5）

2010 年に妊婦スクリーニング検査が開始後，産科施設での支援は充実してきている。しかし，産後 1 か月健診以降は途切れること[23]の課題がある。そのため，次項にある小児医療施設での支援と行政機関での支援に診療情報提供書等でつないでいく。母体・児の一般的な情報以外に，抗体検査の情報，選択栄養法，キャリアであることを知っている家族の範囲が有効な情報になる。

2. 小児医療施設での支援（産科医療施設からの紹介から内科医療施設紹介まで）（図 5）

キャリア妊婦より出生した児を産科医療機関等から

の紹介を受ける。小児期において南米でHTLV-1関連の神経症状[31]や皮膚症状[32]の報告があるが，我が国ではほぼ報告がない。人種差なのかその差を説明する要因は不明である。他の小児と同じように定期予防接種や健診をすすめていくが，母子感染の有無の確認についての説明が必要になる。

母子感染の確認は，3歳以降に妊婦健診と同様の方法でスクリーニング検査を実施する。移行抗体消失後3歳までに抗体が陽転することから[33]，それ以前に検査して陰性であってもその後陽性になる可能性があるため，勧められない。

3歳以降に検査を実施すれば，約97%の確率で母子感染していなかったと判断できる。母親も自分が行った感染対策の成果があったことを確認でき満足度も高く，母親の不安を取るという大きなメリットがある。しかし，母乳以外の経路での感染が約3%あり，母子感染したことを知った母親のショックは大きい。十分なカウンセリングと児が理解できる年齢に達したときに，告知と情報提供の機会を確保する必要がある。HTLV-1は妊娠・母乳をあげる・性行為・臓器移植など特別な関係での行為以外の日常生活で他の人に感染させることはないため，性活動期が始まるまでは特別な感染防止策は必要ない。そのため児の所属する施設・学校等へのキャリアであることの情報提供は必要ない。

児がキャリアであることを知るメリットは，性活動期前に男女ともパートナーを守るためにHTLV-1に限らず性感染予防のためにコンドームの使用の重要性の教育，女性は妊娠後限られた時間ではなく事前に情報を得て判断する時間の確保ができることが考えられる。偶発的に児が感染を知る機会として献血がある。献血時希望すればHTLV-1感染には親展郵便で通知される[34]。著者の経験であるが妊婦健診で分かる前に，1割ほどが献血で既に知っていた。しかし，多くは同封の資料では理解できず，かつ親を含め誰にも相談せず一人で悩み，中にはHIVと勘違いして自殺を考えたものがいたため，事前に告知し説明する機会を確保することができるのはメリットになるかもしれない。しかし，HTLV-1に関しての国民の理解が十分でないためキャリアへの負担が多く，3歳時に検査をして陽性であればその後に告知を行うことは，約3%と少数ではあるが「知らされない」という児の自己選択権を侵害する可能性もあり，判断が難しい。

3歳児に理解して自己決定してもらうことが難しいため，一つの方法として本人がHTLV-1感染のことを理解できるようになった時，目安として性活動期が活発化や献血をすることができる16歳よりも前に，「母親がキャリアであり，子どものことを考えて栄養法を選択した」，「その栄養法を選択しても，一定の割合で母子感染してしまう」，「検査でキャリアであるかは知ることができる」，「キャリアである場合には性行為の際にコンドームの使用でパートナーに感染するのを減らすことができる」，「将来子どもに関しては栄養法を選択することで母子感染リスクを下げることができる」等の事柄を伝え，児に選択してもらう方法もあると考える。母子感染の有無の確認の検査は，母親および家族の価値観で検査の時期，実施するかしないかを決めることになる。

母子感染予防のため栄養法を達成した後，安堵と共に自身がキャリアであることの不安が再度湧き上がってくることがある。日本HTLV-1学会では登録医療機関制度を設けて，HTLV-1に関連した相談対応が可能な施設を認定して公開している[35]。2021年5月時点で16機関中九州・沖縄に10機関と偏在しているが，現在も登録募集を行っているので今後増えていくことが期待される。また，登録されている医療機関がない場合には，厚生労働省は各都道府県や政令指定都市に対して，HTLV-1母子感染対策協議会を設置し体制整備を推進している[36]ので，問い合わせてみるとよい。

3. 行政機関（各都道府県や政令指定都市，市町村）での支援（医療機関との連携）（図5）

各都道府県や政令指定都市はHTLV-1母子感染対策協議会を設置し，妊婦に対するHTLV-1抗体検査の適切な実施，相談窓口，母子感染に関する普及啓発，医療機関連携，体制整備，評価などを行うことになっている。産科医療機関でキャリアと判明した場合には，本人の同意を得て，富山県[37]をはじめ未熟児等出生連絡票を用いたり，鹿児島県[38]のように専用の情報提供書を用いたりして連携をとっている地域もある。

各都道府県や政令指定都市は，自治体内の出生数と妊婦の感染率から，年間のキャリア妊婦の数，母子感染者数，将来の発症者数を推定し母子感染対策の体制整備が必要である。例えば，鹿児島県では令和元年度11,977出生数で感染率が0.8%から，年間のキャリア妊婦の数は約100人，3年後の母子感染者は3人，

HTLV-1 関連疾患の発症者は 5 人と推定される。流行地であった鹿児島県でも数が減っているため，非流行地域では更に少ないと考えられる。そのため各都道府県や政令指定都市を中心とした整備が重要である。

産科医療機関より情報提供があった際には，市町村の保健師による支援を行う。新生児訪問指導や乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）など既存の事業を利用し，短期母乳栄養法で乳房のことで不安を抱えている場合には助産師など産科医療関係者，心理的な不安に関しては臨床心理士など精神医療関係者など専門職を活用し，必要なサービスにつなげる。

3 歳児健診時には，3 歳以降検査が可能であり，そのメリット・デメリットを含め情報提供を行い，母親および家族の選択を支援する。決して検査実施を強制してはならない。また，キャリアであることの不安や母子感染した症例やキャリアである母親を各都道府県や政令指定都市が整備したカウンセリングや診療体制へ適切につなぐことも必要である。

おわりに

HTLV-1 総合対策として全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになり 10 年が経過した。産科医療施設での支援体制は整備されつつあるが，今回のマニュアル改訂で短期母乳栄養法選択者への支援を新たに整備する必要がある。今後，小児保健関係者は所属機関は異なっても互いの支援内容を理解し，産科医療施設から小児医療施設，内科等専門医療施設への医療機関同士の連携，また都道府県と市町村の行政機関内同士での連携を行うことが求められる。医療機関と行政機関を中心に社会での総合的な HTLV-1 キャリア支援を多方面から行うことで，キャリアマザーと児が脱落しない体制が構築されることを期待したい。

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Frequency of HTLV-1 seroconversion between pregnancies in Nagasaki, Japan, 2011–2018

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Background: Human T-cell leukemia virus type-1 (HTLV-1) is transmitted vertically from an infected mother to her child *via* breastfeeding during infancy or horizontally *via* sexual contact. However, little information is available on the HTLV-1 seroconversion rate in pregnant mothers and the impact of new HTLV-1 infection on mothers and babies during the perinatal period.

Methods: From the database of a prefecture-wide antenatal adult T-cell leukemia prevention program in Nagasaki, Japan, we extracted data on 57,323 pregnant women who were screened for anti-HTLV-1 antibody during 2011–2018. Data on the 16,863 subjects whose HTLV-1 proviral load (PVL) was measured more than twice were included in our analyses.

Results: In total, 133 (0.79%) pregnant women were HTLV-1-positive during their first pregnancy and nine (0.05%) seroconverted before or during subsequent pregnancies (between pregnancies). The median PVL (per 100 peripheral blood mononuclear cells) was significantly lower in the seroconverted mothers (0.10%) than in the initially seropositive mothers (0.15%). A repeated measures correlation analysis for the individual PVLs of the HTLV-1-positive pregnant women showed that PVL increased with parity number (rrm=0.25) with no perinatal problems.

Conclusion: The HTLV-1 seroconversion rate between pregnancies was 0.05%, and their HTLV-1 PVL increased annually but no perinatal problems were noted.

KEYWORDS

HTLV-1, pregnant woman, carrier, screening test, seroconversion, horizontal transmission, proviral load, adult T-cell leukemia-lymphoma

Introduction

Human T-cell leukemia virus-1 (HTLV-1) is a retrovirus that causes adult T-cell leukemia (ATL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and a variety of HTLV-1-associated inflammatory disorders (Watanabe, 1997). Globally, HTLV-1 infects at least 5–10 million people (Gessain and Cassar, 2012), particularly in southwest Japan, Brazil, the Caribbean islands, Central and South America, sub-Saharan Africa, and central Australia (Gessain and Cassar, 2012; World Health Organization, 2020). HTLV-1 infects mainly CD4-positive T-cells and is known to transmit from person-to-person *via* cell-to-cell contact between HTLV-1-infected cells and uninfected cells through three modes (Bangham, 2003; Matsuoka and Jeang, 2007; Pique and Jones, 2012): vertical mother-to-child transmission from HTLV-1-infected mothers *via* breastfeeding (Hino et al., 1985), horizontal transmission from HTLV-1-infected partners *via* sexual intercourse (Stuver et al., 1993; Kaplan et al., 1996; Roucoux et al., 2005; Satake et al., 2016; Paiva et al., 2017), and iatrogenic transmission *via* HTLV-1-infected donated blood or organs. However, the risk of iatrogenic transmission through transfusion can be reduced by performing leukoreduction prior to transfusion (Okochi et al., 1984; Armstrong et al., 2012).

The first scientific evidence of vertical transmission from a HTLV-1-infected mother to their infant *via* prolonged breastfeeding by the infected mother was presented in 1985 by researchers from Nagasaki University, located in southwest Japan (Hino et al., 1985; Figure 1). They presented the following findings: (1) the first nationwide survey of HTLV-1 infection in Japan identified Nagasaki Prefecture as one of the regions with the highest prevalence of HTLV-1-infected individuals (Tajima et al., 1982); (2) HTLV-1-infected cells are present in breastmilk from HTLV-1-carrier mothers, and infection through breastfeeding is associated with a higher probability of developing ATL (Kinoshita et al., 1984); and (3) experimentally, HTLV-1 can be transmitted *via* intraoral inoculation among common marmosets (Kinoshita et al., 1985; Yamanouchi et al., 1985). Soon after, a prefecture-wide, multidisciplinary, antenatal intervention program, known as the "ATL Prevention Program (APP)," was established in 1987 in Nagasaki (APP Nagasaki; Hino et al., 1987) through collaboration with virologists, obstetric gynecologists, hematologists, pediatricians, and clinical laboratory scientists at Nagasaki University, obstetric gynecologists throughout Nagasaki Prefecture, and public health officers of the Maternal and Child Health Division (MCHD) of the Nagasaki Prefectural Government. The purpose of APP Nagasaki was to reduce the vertical transmission of HTLV-1 *via* breastfeeding and to reduce the future development of HTLV-1-associated diseases through systematic screening for anti-HTLV-1 antibodies in pregnant women and the avoidance

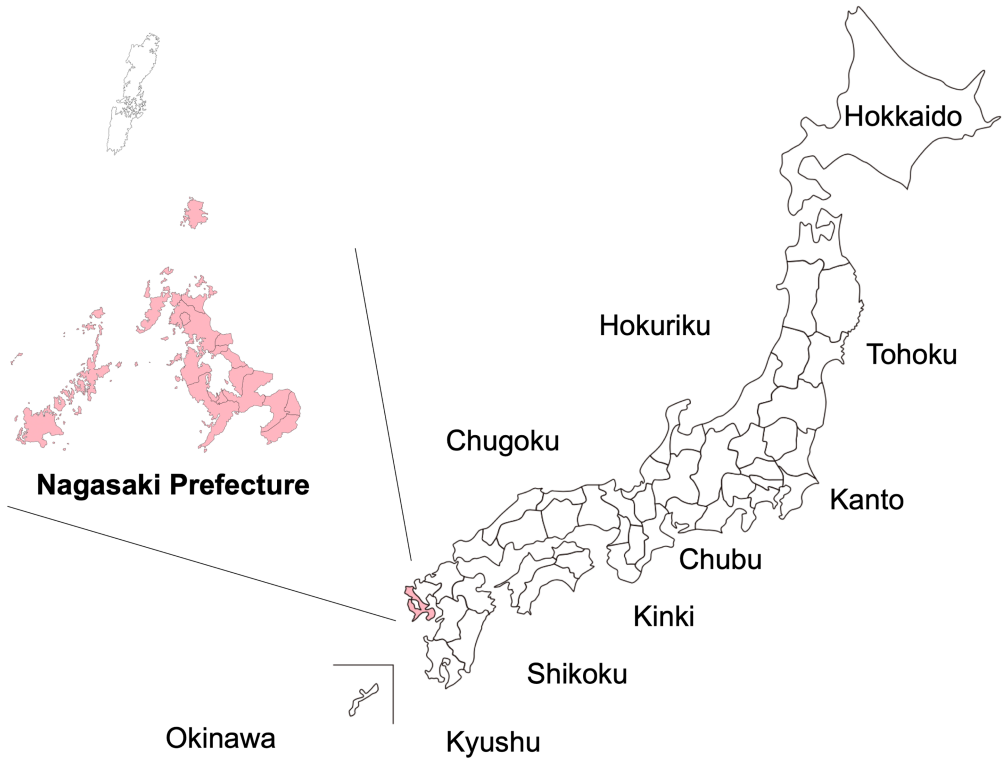

FIGURE 1
Location of the study area in Nagasaki Prefecture, Japan. The present study was carried out in Nagasaki Prefecture, which is located in the most western part of Japan. Only the part of Nagasaki Prefecture colored pink is included in this study. (Tsushima islands are not included).

of breastfeeding in identified HTLV-1-infected mothers, in Nagasaki Prefecture.

As previously reported, APP Nagasaki led to a marked reduction in mother-to-child HTLV-1 transmission rates from 20.5% before the APP began to 2.4% after its implementation (Hino et al., 1997; Katamine, 1999; Hino, 2011; Moriuchi et al., 2013; Miura and Masuzaki, 2017). Other intervention programs similar to APP Nagasaki have been implemented in several areas endemic for HTLV-1 in Japan (Takahashi et al., 1991; Kashiwagi et al., 2004). However, HTLV-1 infection is currently widespread across geographical regions (Watanabe, 2011; Satake et al., 2012), and the number of HTLV-1 carriers in the metropolitan areas in Japan has increased. This situation probably reflects the migration of individuals from HTLV-1-endemic areas (Watanabe, 2011). A nationwide antenatal screening program for HTLV-1 was introduced in Japan in 2011 (Itabashi et al., 2020). Currently, it is estimated that each year ~1,600 HTLV-1-infected pregnant mothers in Japan (almost 0.16% of all pregnant mothers in Japan; Suzuki et al., 2014) are recommended to refrain from breastfeeding to avoid mother-to-child HTLV-1 transmission by methods similar to that of APP Nagasaki.

Recently, researchers from APP Nagasaki reported that the HTLV-1 proviral load (PVL), induced regulatory T-cell population, and soluble interleukin-2 receptor (sIL-2R) levels of HTLV-1-infected pregnant mothers remained stable during pregnancy but became elevated after delivery (Fuchi et al., 2018). However, many questions regarding the impact of HTLV-1 infection on pregnant mothers remain unanswered. For example, the number of pregnant mothers who seroconvert from HTLV-1 negative to positive between pregnancies, how the HTLV-1 PVL changes in HTLV-1-infected pregnant mothers through delivery (between pregnancies), and the specific risks to pregnancy outcomes for HTLV-1-infected and HTLV-1-seroconverted mothers are not currently known.

The present study therefore aimed to assess the HTLV-1 seroconversion status in multiparous mothers who participated in APP Nagasaki, the individual changes of the HTLV-1 PVL between pregnancies in HTLV-1-positive mothers, and the impact of HTLV-1 positivity on pregnancy outcomes.

Materials and methods

Study area and database

From its initiation in July 1987 to April 2018, the APP Nagasaki database included information on ~330,000 pregnant mothers, from almost all areas of Nagasaki Prefecture, who were tested for HTLV-1 infection (Figure 1). The database is managed by the Department of Obstetrics–Gynecology at Nagasaki University Hospital (Miura and Masuzaki, 2017).

Protocol employed for APP Nagasaki

Figure 2 shows the protocol employed for APP Nagasaki (Miura and Masuzaki, 2017). Briefly, any pregnant mothers who were ~30 weeks of gestation and living in most areas of Nagasaki Prefecture were asked to participate in APP Nagasaki when visiting their obstetric gynecologists. After providing consent to participate in the project, each pregnant mother was required to provide a blood sample for an anti-HTLV-1 antibody test. From 2011 onwards, such blood samples were sent to one of five commercial clinical laboratory companies (see Acknowledgment) where a screening test for anti-HTLV-1 antibody was performed using either a particle agglutination (PA) assay, a chemiluminescent immunoassay (CLIA), or a chemiluminescent enzyme immunoassay (CLEIA). The definition of "HTLV-1-positive" as a result of the screening test is a titer of 8 or higher in the PA assay or a cutoff index (COI) of ≥1.0 in the CLEIA or CLIA, in accordance with the manufacturer's criteria (Fujirebio, Japan).

All of the negative screening test results from the clinical laboratory companies were sent back to the respective obstetric gynecologists, for them to inform the respective pregnant mothers. From 2011 onward, in the case of a positive or suspected positive screening test result, the residual blood sample was forwarded to the APP Nagasaki office at Nagasaki University Hospital where a confirmatory test was performed by western blotting and the HTLV-1 PVL was quantified by a real-time polymerase chain reaction (RT-PCR) assay in the Department of Laboratory Medicine. The final test results were reported to the respective obstetric gynecologists, who then informed the respective mothers by 35 weeks of gestation (Figure 2). The obstetric gynecologists also asked their public health nurses to explain to HTLV-1-positive pregnant mothers how to prevent HTLV-1 mother-to-child transmission, preferentially through exclusive bottle-feeding or alternatively by freeze–thawing breast milk or only short-term breastfeeding for no more than 3 months. According to the APP Nagasaki report, the majority of HTLV-1-positive pregnant mothers chose the first choice option of exclusive bottle-feeding to prevent mother-to-child transmission (Miura and Masuzaki, 2017).

Quantification of the HTLV-1 PVL

In APP Nagasaki, a quantitative RT-PCR assay was routinely performed from 2011 onward to quantify the HTLV-1 PVL in peripheral blood mononuclear cells (PBMCs) from anti-HTLV-1 antibody-positive pregnant mothers and those with indeterminate western blotting results. The details of the method used to quantify the HTLV-1 PVL have been previously published (Kamihira et al., 2003; Sasaki et al., 2010), and the resulting value was expressed as the copy number per 100 PBMCs. All measurements were performed by the Department of Laboratory Medicine at Nagasaki University Hospital. Coefficient variation (CV) of HTLV-1

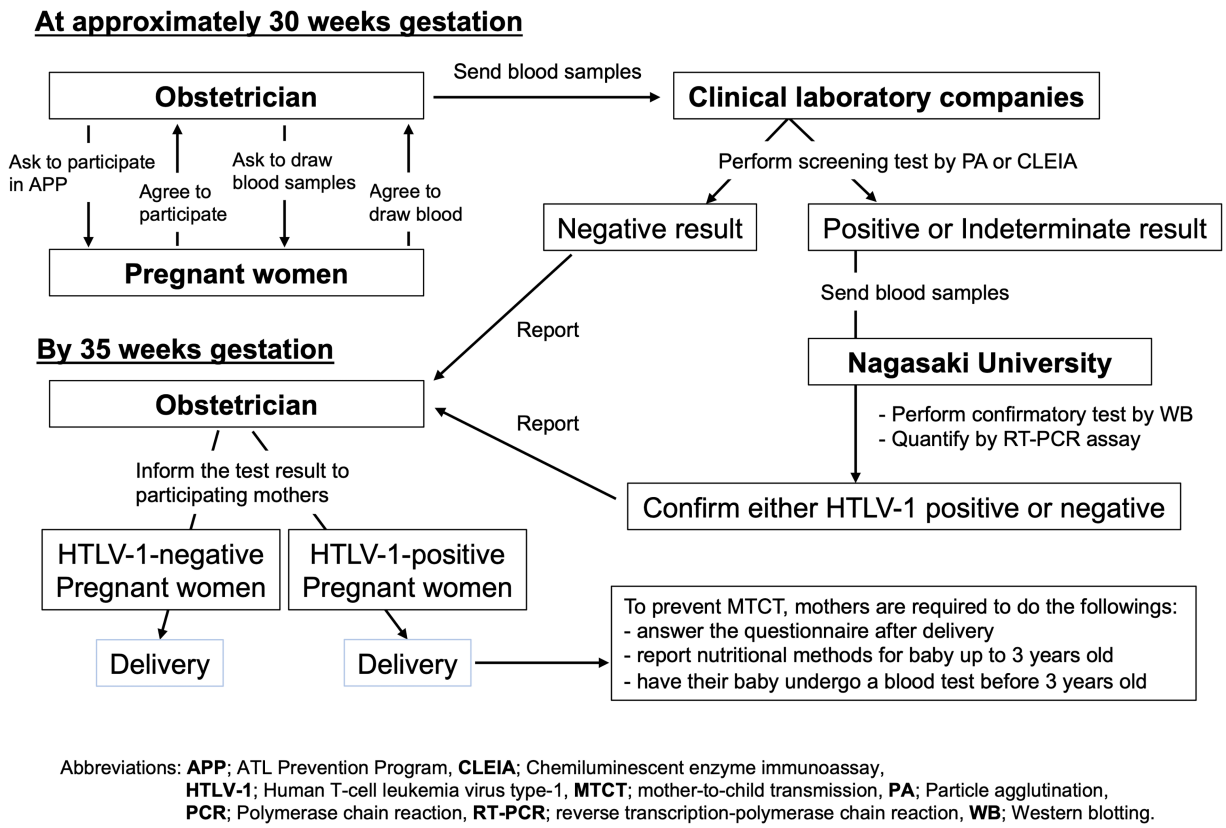

FIGURE 2
Study protocol of the APP Nagasaki project. By 30weeks of gestation, blood samples were obtained from the pregnant mothers who participated in APP Nagasaki to screen for anti-HTLV-1 antibody. Negative test results were reported directly to the respective obstetrician. For positive or indeterminate test results, confirmatory tests were performed. All of the test results were scheduled to be returned to the respective obstetricians by 35weeks of gestation.

quantitative PCR test in Nagasaki university hospital was 13.3% (Kuramitsu et al., 2015).

Questionnaires for HTLV-1-positive mothers and their doctors after delivery

Within 1 week of delivery, each of the HTLV-1-positive mothers who participated in APP Nagasaki was required to answer questions about their birthplace, pregnancy history, the feeding method chosen by their own mother (i.e., the grandmother) during their infancy, and the feeding method that they chose for their own baby. Their obstetric gynecologist was also required to answer questions regarding pregnancy/delivery complications, the health condition of the baby, and the medical history of the pregnant mother (Supplementary material S1).

Data extraction for analysis

The dataset used for analysis in this study was extracted from the APP Nagasaki database after obtaining approval from the Ethics Committee of the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (approval number: 20051810, September 2019). The APP Nagasaki was initiated in 1987, and modern techniques to measure the HTLV-1 PVL using an RT-PCR assay have been applied to participating mothers only since 2011 (Kamihira et al., 2003; Sasaki et al., 2010). Therefore, for the present analysis, we limited our data extraction to the years 2011–2018.

Statistical analysis

We analyzed the available data on pregnant mothers who were tested for HTLV-1 infection at least twice during pregnancy. The demographic data were summarized with standard descriptive statistics, such as frequencies (percentages) for categorical variables, and median (min–max) or median (interquartile range, IQR) values for continuous variables. The pregnant mother age at enrollment in the APP was treated as a continuous variable or categorized into four groups (<25, 26–30, 31–35, and >36 years old). The

method of feeding that the pregnant mothers themselves received from their own mothers was categorized into three groups: long-term breastfeeding (6 months or longer), short-term breastfeeding (shorter than 6 months), and formula feeding alone. The mothers were also categorized into subgroups based on their history of gravidity (the number of pregnancies), parity (the number of live births), and divorce. Continuous variables were compared using Wilcoxon rank-sum tests. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. All of the basic statistical analyses were performed using OpenEpi Statistical Software version 3.01 (http://www.openepi.com, Atlanta, GA, United States; Sullivan and Dean, 2009) and R package version 3.4.2 (R-Project for Statistical Computing, https://CRAN.R-project.org). To analyze changes over time in the HTLV-1 PVL by age and by parity of the HTLV-1-positive mothers, we conducted repeated measures correlation (rmcorr) analyses using the R package version 0.3.0 (R-Project for Statistical Computing, https://CRAN.R-project.org; Bakdash and Marusich, 2017) and calculated the correlation coefficient for repeated measures (*rrm*). All statistical tests were performed at the two-tailed 5% level of significance.

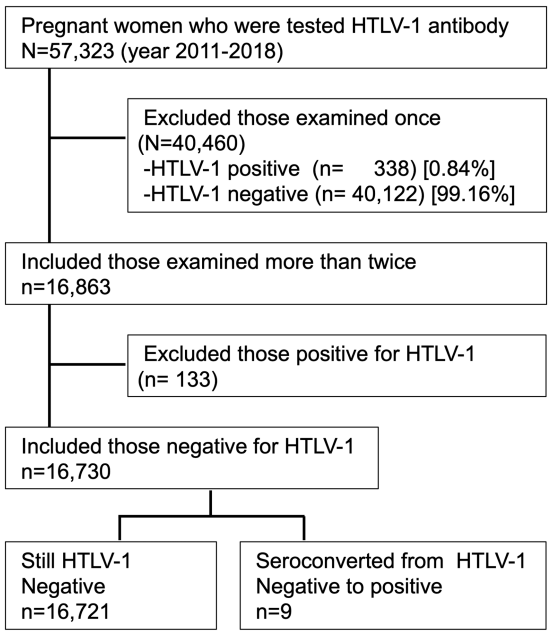

FIGURE 3
Study flowchart for the present analysis. Of the 57,323 pregnant mothers who were screened for anti-HTLV-1 antibody during 2011–2018, the 16,863 mothers who were examined more than twice were included in the study. Of those included, the 16,730 mothers who tested negative for anti-HTLV-1 antibody were included in the analysis. Nine of these women later seroconverted to HTLV-1-positive.

Results

HTLV-1 seropositive status

Figure 3 shows the flowchart for the present analysis. In the years 2011–2018, a total of 57,323 pregnant mothers were screened for anti-HTLV-1 antibody, and 471 (seropositive rate of ~0.82%) were identified as being HTLV-1-positive. Among the 57,323 screened women, 40,460 (70.6%) were examined only once, and the remaining 16,863 (29.4%) were examined more than twice. Of those examined only once, 338 (0.84%) were HTLV-1-positive; of those examined more than twice, 133 (0.79%) were HTLV-1-positive. Among the 133 HTLV-1-positive pregnant mothers screened during their first pregnancy, 61 (45.9%) had already been diagnosed as asymptomatic HTLV-1 carriers in a hospital before their enrollment with APP Nagasaki, but the remaining 72 had no prior HTLV-1 diagnosis information. To date, there have been no reports about ATL, HAM/TSP, or other HTLV-1-associated diseases from their obstetric gynecologists.

HTLV-1 seroconversion rate

During the period between January 2011 and December 2018, nine (0.054%) of the 16,730 pregnant mothers who were found to be negative for HTLV-1 during the initial screening subsequently seroconverted to HTLV-1 positive (Figure 3). Thus, the incidence rate of HTLV-1 seroconversion among HTLV-1-negative pregnant mothers was 17.5 (95% confidence interval: 11.4–26.0) per 100,000 person-years at follow-up.

Background characteristics

Table 1 summarizes the characteristics of pregnant mothers who were already known to be HTLV-1 seropositive before their entry into the study ($n = 133$) and those of mothers who were HTLV-1 seronegative at study entry but later seroconverted to anti-HTLV-1 antibody-positive ($n = 9$). The median age at first entry to APP Nagasaki was 30 years old (range, 17–47 years old) in mothers of known HTLV-1-seropositive status and 31 years old (range, 23–38 years old) in HTLV-1-seroconverted mothers. Although there was no statistically significant difference in the age distribution between the two groups, approximately half of those already known to be HTLV-1-seropositive were in their late 20 s at their first pregnancy, whereas approximately half of the HTLV-1-seroconverted mothers were in their 30 s at their first pregnancy. There was also no significant difference in the proportions of mothers with a family history of ATL, a divorce history, or particular screening test values or in the proportion of western blot-positive or -indeterminate individuals between the two groups.

In contrast, there were significant differences between the two groups regarding the feeding method that the participating

TABLE 1 The characteristics of HTLV-1-positive or HTLV-1-seroconverted pregnant women.

Characteristic	Mothers HTLV-1-positive at first pregnancy ($n = 133$)	Mothers seroconverted to HTLV-1-positive ($n = 9$)	*p*-Value
Age (year) at entry to APP Nagasaki			
Median (min, max), year	30 (17, 41)	31 (23, 38)	0.42
Age category, *n* (%)			
<25	19 (14.3)	2 (22.2)	
26–30	58 (43.6)	1 (11.1)	
31–35	44 (33.1)	5 (55.6)	
>36	12 (9.0)	1 (11.1)	
Nutrition method that participant mothers received from their mothers, *n* (%); [unknown = 22]			
Long-term breastfeeding	85 (63.9)	4 (44.4)	
Short-term breastfeeding	14 (10.5)	2 (22.2)	
Formula feeding	14 (10.5)	1 (11.1)	
Family history of ATL, *n* (%)			
Yes	9 (6.8)	1 (11.1)	
No	124 (93.2)	8 (88.9)	
Gravidity history, *n* (%); [unknown = 6]			
Once	61 (45.9)	0	
Twice	39 (29.3)	3 (15.8)	
Three or more	27 (20.3)	6 (31.6)	
Parity history, *n* (%); [unknown = 5]			
Once	76 (59.4)	0	
Twice	36 (28.1)	4 (44.4)	
Three or more	16 (12.5)	5 (55.6)	
Divorce history, *n* (%)			
Yes	10 (7.5)	1 (11.1)	
No	123 (92.5)	8 (88.9)	
Screening test values			
PA, titer	1,024 (16–8,192)	1,024 (16–8,193)	0.69
CLEIA, COI	34.4 (2.5–45)	34.4 (2.5–46)	0.47
WB test result, *n* (%); [unknown = 53]			
Positive	72 (90)	8 (88.9)	0.99
Indeterminate	8 (10)	1 (11.1)	
Quantified PVL, % per 1,000 PBMCs			
Median (min, max)	0.15 (0–7.05)	0.10 (0–1.09)	0.024

HTLV-1, human T-cell leukemia virus-1; APP, ATL Prevention Program; PA, particle agglutination; CLEIA, chemiluminescent enzyme immunoassay; COI, cutoff index; PVL, proviral load; PBMCs, peripheral blood mononuclear cells.

mothers themselves received from their mothers (i.e., the grandmothers), gravidity history, parity history, and HTLV-1 PVL. In brief, compared with the group of those already known to be HTLV-1-positive before pregnancy, the group of mothers that underwent HTLV-1 seroconversion between pregnancies had lower HTLV-1 PVL (0.15% vs. 0.10% per 100 PBMCs; $p < 0.024$).

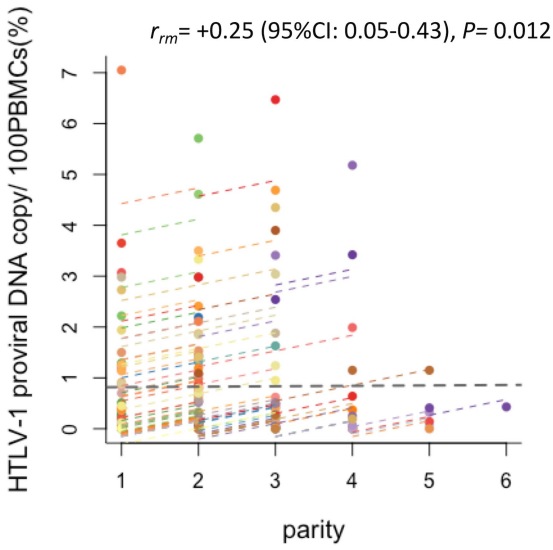

FIGURE 4
Changes in the HTLV-1 PVL of HTLV-1-positive pregnant women by parity. Plots of the correlation between the HTLV-1 PVL and parity of HTLV-1-positive pregnant women. Of the study participants, the 87 who were HTLV-1 seropositive and had their PVL measured more than twice were analyzed by repeated measures correlation (rmcorr). Each colored plot line shows the chronological change in HTLV-1 PVL of an individual HTLV-1-carrier pregnant woman. Positive correlations were found between increased HTLV-1 PVL and increased parity (r=0.25, p=0.012, 95% CI 0.05, 0.43).

Regarding whether the mothers had known about the HTLV-1 infection status of their husband or sexual partner, only two pregnant mothers reported HTLV-1 infection in their partner; the rest of the study participants did not know their partner's HTLV-1 infection status.

Sequential changes in the HTLV-1 PVL in HTLV-1-positive pregnant mothers

An analysis of the HTLV-1-positive mothers revealed a statistically significant positive correlation between an increase in parity number and an increase in HTLV-1 PVL ($rrm = +0.25$, $p = 0.012$; Figure 4).

Sequential changes in the HTLV-1 PVL In HTLV-1-seroconverted pregnant mothers

Among the nine HTLV-1-seroconverted pregnant mothers, there was only one mother (No. 2 in the Supplementary material S2) for whom the HTLV-1 PVL had been measured more than twice after HTLV-1 seroconversion. Her HTLV-1 PVL increased from 1.09 at her second delivery to 3.90 at her third delivery, which suggests that, even in

HTLV-1-seroconverted pregnant mothers, the HTLV-1 PVL increased over time.

Pregnancy outcomes

Table 2 summarizes the pregnancy outcomes of mothers of known HTLV-1-positive status and mothers that seroconverted to HTLV-1 between pregnancies. There was no statistically significant difference between the two groups in the frequency of any complications that occurred during pregnancy, the length of delivery time, or the sex distribution or birth weight of the babies.

Discussion

This is the first report on the HTLV-1-positive and -seroconversion status of pregnant mothers that participated in APP Nagasaki, and the first to report HTLV-1 PVL chronological data. Our main findings were that: (1) the proportion of those who underwent seroconversion from anti-HTLV-1 antibody negative to positive among pregnant mothers was 0.054%, with a seroconversion incidence rate of 17.5 per 100,000 person-years during the period 2011–2018, (2) HTLV-1 infection had no adverse effect on pregnancy outcomes in either the HTLV-1-infected or HTLV-1-seroconverted mothers; however, (3) the HTLV-1 PVL increased with increased parity number, and this showed a statistically significant positive correlation in both the HTLV-1-infected and the HTLV-1-seroconverted pregnant mothers.

TABLE 2 Pregnancy outcomes in mothers with known HTLV-1-positive status and mothers with HTLV-1 seroconversion during pregnancy.

Characteristic	Mothers HTLV-1-positive at first pregnancy ($n = 133$)	Mothers seroconverted to HTLV-1-positive ($n = 9$)	p-Value
No. of deliveries	265	10	–
Complications during pregnancy, *n* (%)			
No	222 (83.8%)	9 (90.0%)	0.67
Yes	43 (16.2%)	1 (10.0%)	
Length of delivery time, *n* (%)			
<34 weeks of gestation	222 (83.8%)	9 (90.0%)	0.37
34–36 weeks of gestation	11 (4.2%)	1 (10.0%)	
After 36 weeks of gestation	32 (12.1%)	0	
Sex of child, *n* (%)			
Unknown	7 (2.6%)	0	0.25
Male	130 (49.1%)	7 (70%)	
Female	128 (48.3%)	3 (30%)	
Birth weight, *n* (%)			
LFD	18 (6.8%)	1 (10.0%)	0.51
AFD	217 (81.9%)	9 (90.0%)	
HFD	30 (11.3%)	0	

LFD, light for dates; AFD, appropriate for dates; HFD, heavy for dates.

The estimated incidence rate (17.5 per 100,000 person-years) of HTLV-1 seroconversion among pregnant mothers aged 17–41 years in this analysis was higher than that for female blood donors aged 16–49 years (2.03–8.54 per 100,000 person-years) in Kyushu-Okinawa, where HTLV-1 is endemic (Satake et al., 2016), despite the similar age range of these groups. A possible explanation for this difference might be the eligibility criteria for blood donation, because pregnant women or recently postpartum mothers are not eligible to donate blood in Japan. Instead, the estimated crude incidence rate in this analysis was close to the HTLV-1 seroconversion rate in female repeated blood donors aged over 50 years in Kyushu-Okinawa (11.8–17.0 per 100,000 person-years; Satake et al., 2016). One possible explanation for the HTLV-1 seroconversion rate similarity in these two groups might be related to unprotected sexual contact with HTLV-1-infected partners—the majority of pregnant mothers in our study did not know the HTLV-1 infection status of their partner.

Regarding the PVL in HTLV-1-positive pregnant mothers, we previously reported that the PVL was the highest during the postpartum period (i.e., the period just after delivery) as compared with that during pregnancy terms (i.e., the first, second, and third trimesters; Fuchi et al., 2018). The present study supported the previous report by performing time-sequential analyses of the individual PVL of both HTLV-1-positive and HTLV-1-seroconverted pregnant mothers. In other words, we hypothesize that the positive correlation between the number of deliveries and HTLV-1 PVL found in this study indicates that the elevated HTLV-1 PVL that occurs during the first postpartum period is maintained and then the HTLV-1 PVL increases further during the second postpartum period. Thus, the individual HTLV-1 PVL increased with increased parity number among multiparous women (Figure 4). Alternatively, this finding could suggest that these women are continuously exposed to HTLV-1 from their HTLV-1-positive partners (Stuver et al., 1993; Sullivan et al., 1993; Kaplan et al., 1996). Therefore, they require regular medical check-ups and monitoring of the HTLV-1 PVL for the early detection of HTLV-1-associated diseases, not only by obstetric gynecologists, but also by hematologists. This is primarily because it has been well-established that the higher the PVL in HTLV-1-infected asymptomatic carriers, the higher their risk of developing HTLV-1-associated diseases (Nagai et al., 1998; Iwanaga et al., 2010), but also because a number of case reports have indicated the development of ATL in HTLV-1-positive pregnant mothers with a high PVL (Ohba et al., 1988; Utsumi et al., 1996; Safdar et al., 2002; Amor et al., 2013; Motedayen Aval et al., 2020; Ramassamy et al., 2020). In APP Nagasaki, one asymptomatic HTLV-1-positive pregnant woman developed ATL (Fuchi et al., 2016).

We also report here, for the first time, that even in a HTLV-1-seroconverted mother, the PVL increased between her second and third pregnancies with her increase in age (the second case in Supplementary material S2). This finding supports the idea that the HTLV-1 PVL increases with parity (or age) even in HTLV-1-seroconverted pregnant mothers. Therefore, we recommend that all HTLV-1-positive women of reproductive age be checked regularly for their HTLV-1 PVL and HTLV-1-associated diseases.

Regarding pregnancy complications in HTLV-1-positive pregnant mothers, previous studies reported no difference in the degree of pregnancy complications between those who were positive and those who were negative for anti-HTLV-1 antibody (Kusuhara et al., 1987; Rosadas et al., 2019). In the present study, among the 10 deliveries from nine HTLV-1-seroconverted pregnant mothers, only one baby (10% of all deliveries) was born prematurely at 29 weeks of gestation. Although only one premature case occurred, and therefore the sample size was small, the proportion (10%) was greater than the national average for premature cases (5.6%–5.7%) in Japan during 2015–2018 (Vital Statistics of Japan, 2015–2018). Further large-scale analyses are required to determine whether the occurrence of preterm/premature birth/delivery/labor is higher in HTLV-1-infected and/or HTLV-1-seroconverted pregnant mothers than in uninfected individuals.

Regarding the babies born from HTLV-1-positive mothers, Kusuhara et al. reported that such babies may acquire their own anti-HTLV-1 antibodies by the age of 3 years and continue to acquire such antibodies until the age of 18 (Kusuhara et al., 1987). Therefore, the obstetric gynecologists participating in APP Nagasaki advised each of the HTLV-1-positive mothers to have their children tested for HTLV-1 antibodies when they reach 3 years of age. In APP Nagasaki, 10 children were born from HTLV-1-seroconverted mothers; of these, one baby girl was given artificial nutrition and tested HTLV-1-negative, while no information was available on the other nine babies.

The major limitation of this study is that the findings were based on a single area of Nagasaki Prefecture; therefore, the results may not apply to other regions of Japan. Another limitation is that our analyses were based only on healthy pregnant women; as such, information on pregnant mothers with possible HTLV-1-associated diseases was lacking. Furthermore, our method was not capable of identifying cases in which a pregnant mother is HTLV-1-negative at the screening date but seroconverts to positive after the screening date. Therefore, our results might be an underestimation. Furthermore, we have little information on the HTLV-1-infection status of the partners of the pregnant mothers. Taking these limitations into account, the actual number of pregnant mothers horizontally infected with HTLV-1 might be higher than what we observed in this study. Also, since our APP project is a kind of a public-health project to avoid mother-to-child HTLV-1-transmission rather than a research-oriented project, the accuracy of data collection may not be perfect and only peripheral blood test and HTLV-1 PVL are regularly measured. Therefore, even if we are willing to perform a multivariate analysis, it is possible to include only factors such as age and the number of deliveries. However, since aging and the number of deliveries are almost proportional, therefore it is difficult to perform a multivariate analysis as another limitation of our study.

In conclusion, this is the first report on the individual change in HTLV-1 PVL of HTLV-1-positive and HTLV-1-seroconverted pregnant mothers and the infection status of their babies in APP Nagasaki. Although there were no serious adverse effects in the HTLV-1-infected pregnant mothers and their babies, we found that the HTLV-1 PVL of the mothers increased with parity (or age), which suggests that HTLV-1-infected women of reproductive age are continuously exposed to HTLV-1 horizontally from their HTLV-1-infected partners. Therefore, further careful follow-up is needed for both HTLV-1-positive pregnant mothers and their babies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (approval number: 20051810, September 2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NK and NF analysis the data of HTLV-1 test among pregnant women. MI and KM organized the study protocol. NK, MI, and KM wrote the manuscript. YH, SM, NF, and KM collected the data of HTLV-1 tests among pregnant women. HM collected the data regarding Mother to Child transmission of HTLV-1. KY and KM performed the HTLV-1 screening test of pregnant women in Nagasaki. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2022.1036955/full#supplementary-material

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Review

How Can We Prevent Mother-to-Child Transmission of HTLV-1?

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Abstract: The perception of human T-cell leukemia virus type 1 (HTlV-1) infection as a "silent disease" has recently given way to concern that its presence may be having a variety of effects. HTLV-1 is known to cause adult T-cell leukemia (ATL), an aggressive cancer of peripheral CD4 T cells; however, it is also responsible for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Most patients develop ATL as a result of HTLV-1 mother-to-child transmission. The primary route of mother-to-child transmission is through the mother's milk. In the absence of effective drug therapy, total artificial nutrition such as exclusive formula feeding is a reliable means of preventing mother-to-child transmission after birth, except for a small percentage of prenatal infections. A recent study found that the rate of mother-to-child transmission with short-term breastfeeding (within 90 days) did not exceed that of total artificial nutrition. Because these preventive measures are in exchange for the benefits of breastfeeding, clinical applications of antiretroviral drugs and immunotherapy with vaccines and neutralizing antibodies are urgently needed.

Keywords: human T-cell leukemia virus type 1 (HTlV-1); adult T-cell leukemia (ATL); mother-to-child transmission; antenatal screening; prevention; nutritional regimens

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1. Introduction

There are seven known carcinogenic viruses: Epstein–Barr virus (EBV; also known as human herpesvirus 4 (HHV4)), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell leukemia/lymphotropic virus type 1 (HTLV-1), human papilloma virus (HPV), Kaposi's sarcoma herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)), and Merkel cell polyomavirus (MCV). These viruses are responsible for approximately 15% of all human cancers [1]. Among these viruses, HTLV-1 was the first retrovirus discovered to be carcinogenic [2,3], and the patients showed unique clinical characteristics. HTLV-1 is known to cause adult T-cell leukemia (ATL), an aggressive cancer of peripheral CD4 T cells; however, it is also responsible for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [4,5]. HTLV-1 carriers have an estimated lifetime risk of 2–5% for the development of ATL [6] and 0.25–1.8% for HAM/TSP [7,8]. Both diseases exhibit serious clinical manifestations and poor prognosis despite therapeutic efforts. In addition to these two diseases, HTLV-1-associated uveitis is widely known [9]. Although ATL and HAM/TSP have been recognized as major outcomes of HTLV-1 infection, they account for less than 10% of the infected population. A recent meta-analysis showed that disease outcomes (morbidity and mortality) for which HTLV-1 is not a necessary diagnostic criterion are clearly associated with HTLV-1 infection (10). This analysis showed a 57% increased risk of early mortality, independent of ATL or HAM/TSP. As ATL and HAM/TSP are present in less than 10% of cases, increased mortality cannot be explained by these two diseases alone [10]. Thus, HTLV-1 infection is likely to affect human health in more ways than currently known and is a global burden [11,12].

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].

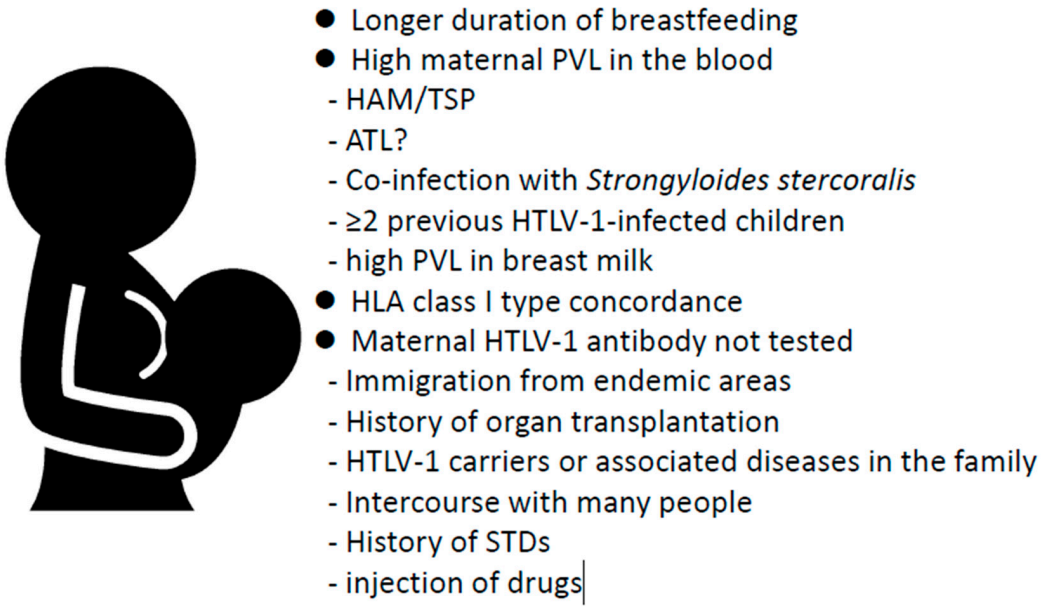

Figure 1. Risk factors associated with development of HTLV-1 mother-to-child transmission. Risk factors for mother-to-child transmission are broadly classified as long-term breastfeeding, high PVL in carrier mothers, HLA class type 1 concordance between mother and child, and mothers with untested HTLV-1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

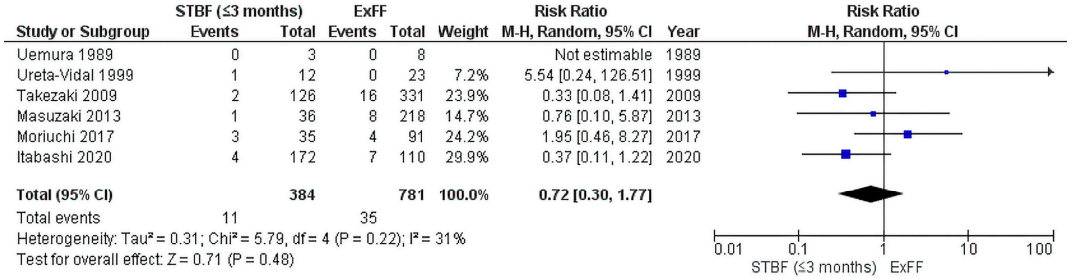

Figure 2. Forest plot of the risk ratios of HTLV-1 MTCT in the STBF ≤ 3 months group compared with that of the ExFF group. There is no statistical difference in the risk of MTCT between the two groups (pooled risk ratio (RR): 0.72, 95% CI: 0.30–1.77). Abbreviations: STBF, short-term breastfeeding; ExFF, 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].

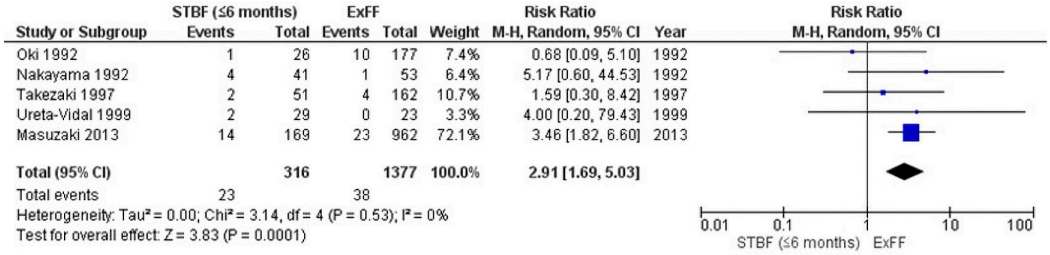

Figure 3. Forest plot of the risk ratios of HTLV-1 MTCT in the STBF ≤ 6 months group compared with that of the ExFF group. Comparing STBF ≤ 6 months and ExFF showed that STBF ≤ 6 months was associated with an approximately 3-fold higher risk of MTCT than that of ExFF (pooled RR: 2.91, 95% CI: 1.69–5.03). 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].

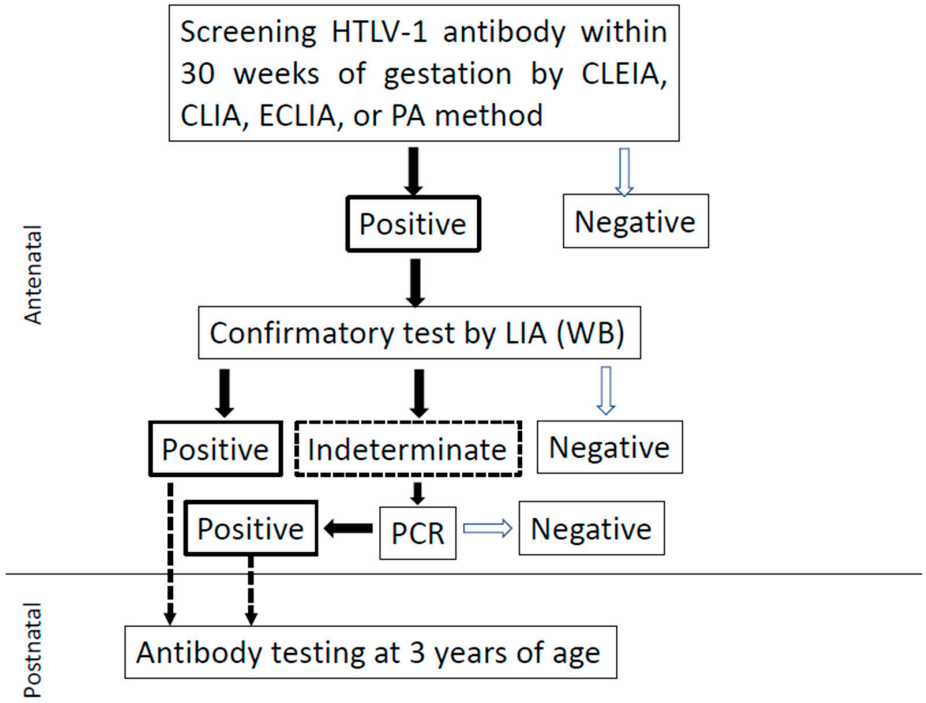

Figure 4. Algorithm for diagnosing HTLV-1 infection in Japan. Currently, no confirmatory tests using Western blotting are conducted in Japan. Flowchart for identifying HTLV-1 carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electrochemiluminescent 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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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Showa University (No.1109, 7 October 2011).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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. The data presented in this study are available on request from the corresponding author.

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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),

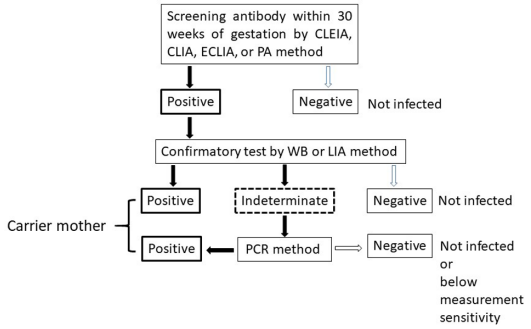

FIGURE 1 | Algorithm to determine HTLV-1 virus carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electro chemiluminescent immunoassay; PA, particle agglutination; WB, Western Blot; LIA, line immunoassay; PCR, polyclonal chain reaction.

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

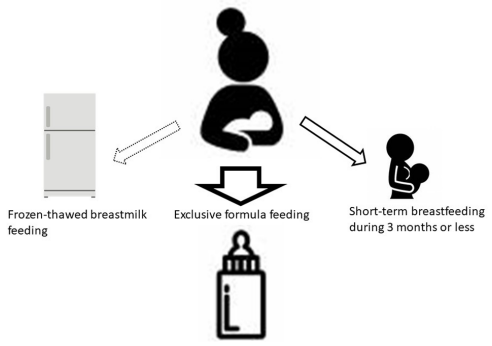

FIGURE 2 | Selection of feeding methods. Due to the well-established evidence, ExFF should be the first choice for postnatal prevention of MTCT. If a carrier mother strongly desires to breastfeed, STBF during 3 months or less would be better to be selected. Health care providers should support her to 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

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

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RESEARCH ARTICLE Open Access

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

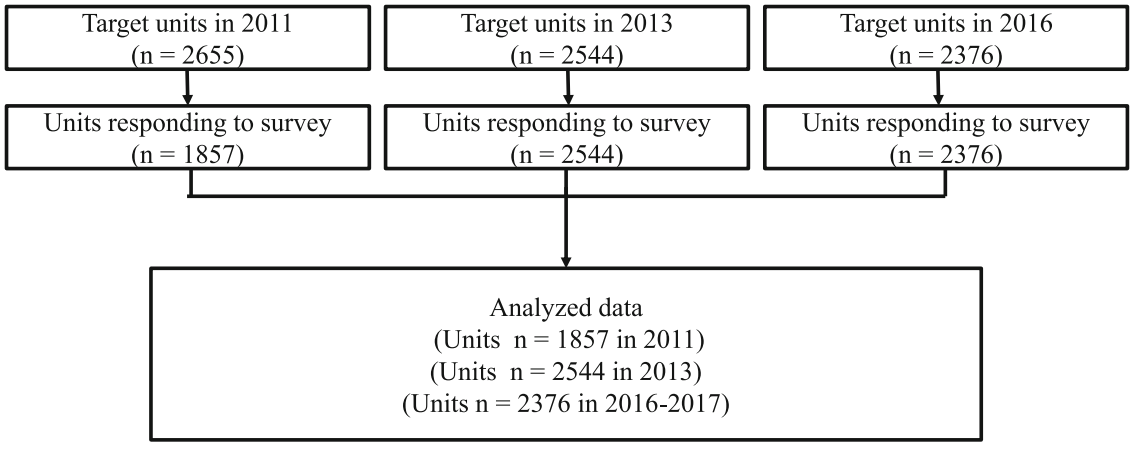

Fig. 1 Study data flow

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

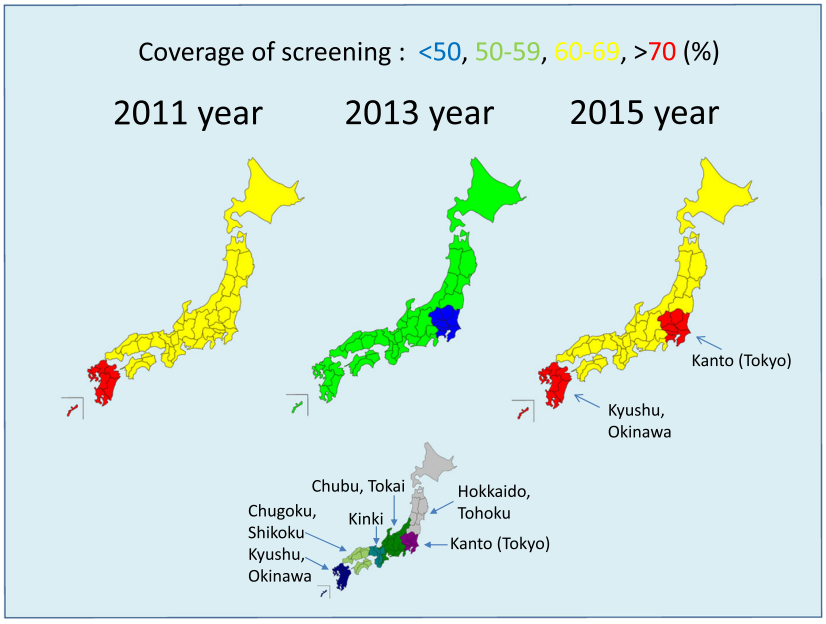

Fig. 2 Map of screening proportion of pregnant women by region in Japan (%). The map was created by software (Shiro-chizu nuri-nuri) using our survey data and public vital statistics in Japan

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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Publisher's Note

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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.

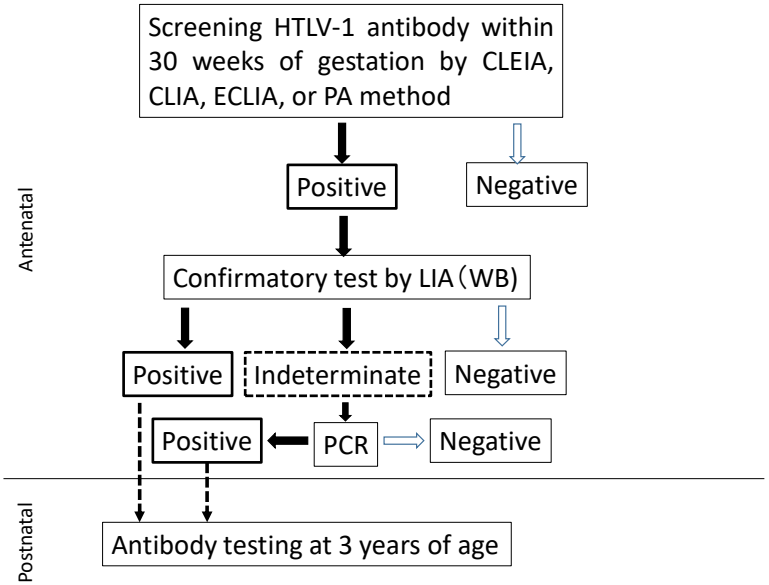

Figure 1. Flowchart to determine HTLV-1 carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electrochemiluminescent immunoassay; PA, particle agglutination; WB, Western blot; LIA, line immunoassay; PCR, polymerase chain reaction.

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.

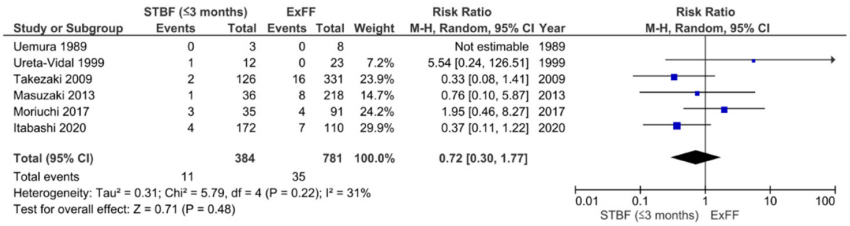

Figure 2. Forest plot of the risk ratios of HTLV-1 MTCT in the 'STBF ≤3 months' group compared with that of the ExFF group. STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, risk ratio; MTCT, mother-to-child transmission; Events, number 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].

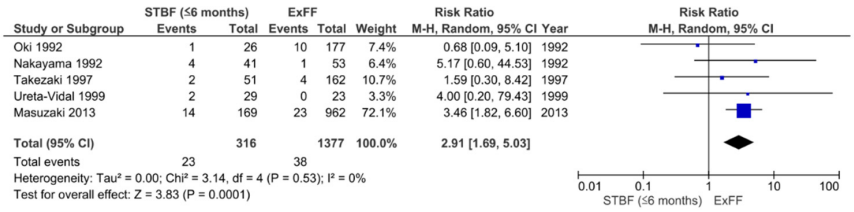

Figure 3. Forest plot of the risk ratios of HTLV-1 MTCT in the 'STBF ≤6 months' group compared with that of the ExFF group. STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, relative risk; MTCT, mother-to-child transmission; Events, number 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].

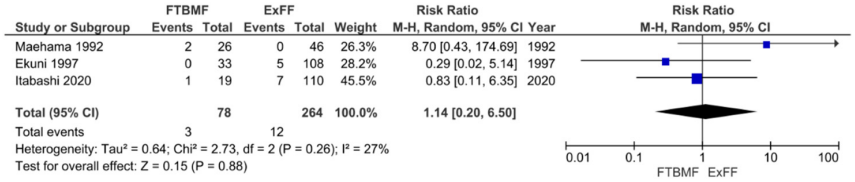

Figure 4. Forest plot of the risk ratios of HTLV-1 MTCT in the FTBMF group compared with that of the ExFF group. FTBMF, frozen-thawed breastmilk feeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, relative risk; MTCT, mother-to-child transmission; Events, number 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

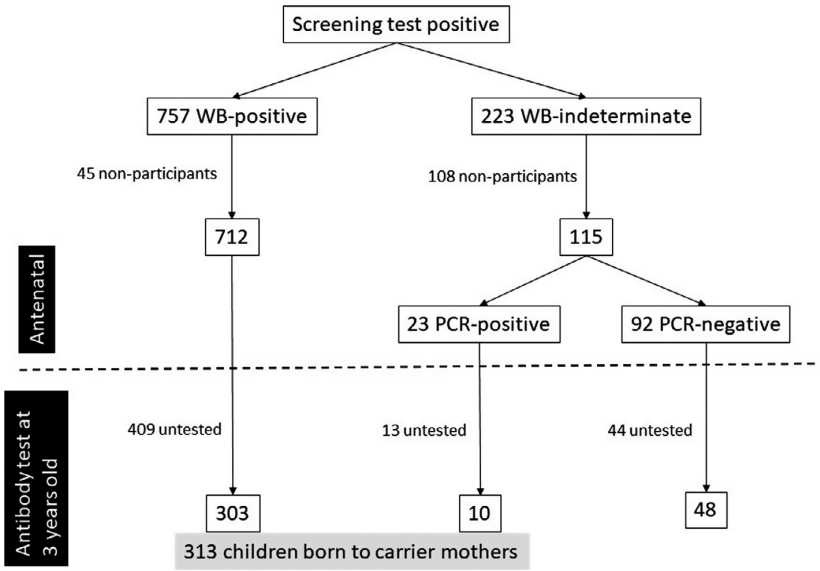

Fig. 1 Subject inclusion based on HTLV-1 testing. WB, western blotting

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.

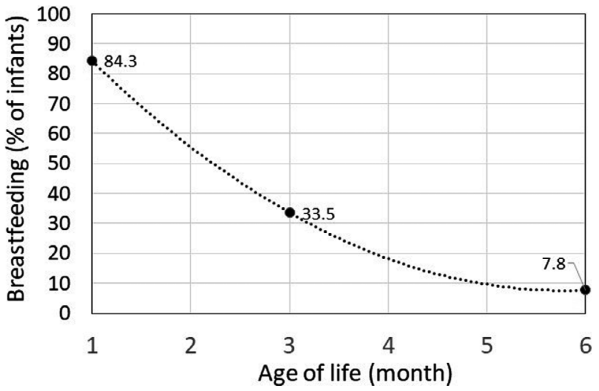

Fig. 2 Longitudinal changes of percentages of infants fed breast-milk in the short-term breast-feeding (STBF) group. The relationship between postnatal months (x) and the rate of breast-feeding (y) in the STBF group was shown by the second-order polynomial analysis. The equation obtained is as follows: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

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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