Economic analysis of antenatal screening for human T-cell lymphotropic virus type 1 in Brazil: an open access cost-utility model

Carolina Rosadas, Kátia Senna, Milene da Costa, Tatiane Assone, Jorge Casseb, Youko Nukui, Lucy Cook, Lívia Mariano, Bernardo Galvão Castro, Maria Fernanda Rios Grassi, Augusto Cesar Penalva de Oliveira, Adele Caterino-de-Araujo, Bassit Malik, Ney Boa-Sorte, Paula Peixoto, Marzia Puccioni-Sohler, Marisa Santos, Graham Philip Taylor

Summary

Background Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that causes severe diseases, such as aggressive cancer or progressive neurological disease. HTLV-1 affects mainly people in areas with low human development index and can be transmitted from mother to child, primarily through breastfeeding. Refraining from breastfeeding is an effective intervention to reduce the risk of infection in infants. However, HTLV-1 antenatal screening is not offered globally. According to WHO, the scarcity of cost-effectiveness studies is considered one of the major barriers to the implementation of policies to prevent HTLV-1 infection. Therefore, this study aimed to assess the cost-effectiveness of antenatal screening and postnatal interventions to prevent HTLV-1 mother-to-child transmission in Brazil and to develop an open-access, editable, mathematical model that can be used by other countries and regions to assess different scenarios.

Methods In this cost-utility analysis, we constructed a decision tree and a Markov model to assess the cost-effectiveness of HTLV-1 antenatal screening and postnatal interventions (ie, avoidance of breastfeeding, by suppression of lactation with cabergoline, and provision of formula feed) to reduce transmission. For our model, we used data from Brazil and we took the perspective of the public health-care system to estimate costs.

Findings The implementation of both screening and interventions would result in the prevention of 1039 infections in infants every year in Brazil with an incremental cost-effectiveness ratio (ICER) of US$11 415 per quality-adjusted life-year (QALY). 88% of all probabilistic sensitivity analysis simulations had ICER values lower than the Brazilian cost-effectiveness threshold ($18 107·74 per QALY). HTLV-1 prevalence in pregnant women, the risk of HTLV-1 transmission when breastfeeding lasts for 6 months or more, and the cost of screening tests were the variables with the largest effect on ICER.

Interpretation HTLV-1 antenatal screening is cost-effective in Brazil. An open-access model was developed, and this tool could be used to assess the cost-effectiveness of such policy globally, favouring the implementation of interventions to prevent HTLV-1 mother-to-child transmission worldwide.

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For the Portuguese translation of the abstract see **Online** for appendix 1

For the Spanish translation of the abstract see **Online** for appendix 2

Section of Virology, Department of Infectious Disease, Imperial College London, London, UK (C Rosadas PhD, Prof G P Taylor DSc); **Núcleo de Avaliação de Tecnologias em Saúde, Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil** (K Senna MSc, Prof M da Costa PhD, Prof M Santos PhD); **Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil** (Prof M da Costa); **Departamento de Dermatologia, Instituto de Medicina Tropical, Faculdade de Medicina** (T Assone PhD, Prof J Casseb PhD) **and Hospital das Clínicas da Faculdade de Medicina** (Y Nukui PhD, L Mariano MD), **Universidade de São Paulo, São Paulo, Brazil; National Centre for Human Retrovirology, Imperial College Healthcare NHS Trust, London, UK** (L Cook PhD, Prof G P Taylor); **Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil** (Prof B Galvão Castro PhD, Prof N Boa-Sorte PhD); **Instituto Gonçalo Muniz, Fundação Oswaldo Cruz, Salvador, Brazil** (M F Rios Grassi PhD); **Instituto de Infectologia Emílio Ribas, São Paulo, Brazil** (A C Penalva de Oliveira PhD); **Centro de Imunologia, Instituto Adolfo Lutz, São Paulo, Brazil** (A Caterino-de-Araujo PhD); **Centre for Economics of Obesity, Institute of Applied Health Research, University of Birmingham, Birmingham, UK**

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that can be disseminated by horizontal (infected blood and unsafe sex) and vertical transmission. Mother-to-child transmission occurs primarily through breastfeeding. The risk of HTLV-1 transmission reduces from 20% to 2·5% if breastfeeding is avoided. The duration of breastfeeding is a major risk factor for HTLV-1 mother-to-child transmission.[1]

The pathogenesis of HTLV-1-associated diseases involves chronic inflammation triggered by the virus, which persistently infects the host. This type of pathogenesis results in several inflammatory diseases, depending on the affected site, such as HTLV-1-associated myelopathy (HAM), uveitis, pulmonary disorder, and infective dermatitis. A different type of pathogenesis involving the acquisition and accumulation of mutations in infected T lymphocytes, which favour the survival and replication of the infected cells and evasion of immune system surveillance, can result in adult T-cell leukaemia–lymphoma (ATLL), a severe neoplasm associated with poor prognosis and short survival.[1] The incubation period before HTLV-1-associated diseases manifest is commonly years to decades, which can explain, at least partly, why infection early in life is associated with a higher risk of developing disease. ATLL is observed almost exclusively in people infected during infancy, whereas infective dermatitis is mainly a paediatric disease. Children who develop infective dermatitis have a higher risk of developing HAM than children without infective dermatitis. Infection during infancy could result in disease during childhood and adulthood, reinforcing the need to

(B Malik MSc); **Health Technology Assessment Unit, Hospital Universitário Professor Edgar Santos, Universidade Federal da Bahia, Salvador, Brazil**
(Prof N Boa-Sorte); **Faculdade de Medicina Veterinária, Universidade Estácio de Sá, Rio de Janeiro, Brazil**
(P Peixoto BSc); **Departamento de Medicina Geral, Escola de Medicina e Cirurgia, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil**
(Prof M Puccioni-Sohler PhD); **Programa de Pós-graduação em Doenças Infecciosas e Parasitárias, Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil**
(Prof M Puccioni-Sohler)

Correspondence to:
Dr Carolina Rosadas, Section of Virology, Department of Infectious Disease, Imperial College London, London W2 1PG, UK
c.rosadas-de-oliveira@imperial.ac.uk

Research in context

Evidence before this study

WHO has included human T-cell lymphotropic virus type 1 (HTLV-1) infection in its strategic planning for sexually transmitted infections and considers the prevention of HTLV-1 mother-to-child transmission a priority in the response to this infection. However, the implementation of public policies is hampered by the scarcity of cost-effectiveness studies, as also shown by our literature search done on Dec 2, 2022. We searched PubMed for studies addressing cost-effectiveness of interventions related to HTLV-1 from database inception to Dec 2, 2022. We used a combination of the search terms for HTLV and cost-effectiveness: "((HTLV) OR (Human t lymphotropic virus) OR (Human t cell lymphotropic virus) OR (human t-cell leukemia virus)) AND (cost-effectiveness)", with no restriction for language. We identified ten manuscripts, of which nine focused on blood donors and were outdated. Only one study (from our group), which focused on the UK, assessed the cost-effectiveness of HTLV-1 antenatal screening. Since the publication of this study in 2019, key data have emerged, including data published by our group as we understood the limitations of our previous study, and data commissioned by WHO. These key data suggest a broader effect of HTLV-1 infections on health outcomes, including an increase in all-cause mortality and reduced quality of life. These new data have the potential to influence cost-effectiveness analyses.

Added value of this study

We developed a mathematical model to assess the cost-effectiveness of HTLV-1 antenatal screening followed by postnatal interventions to prevent transmission (avoidance of breastfeeding and provision of formula feed). This study is the first one to show the cost-effectiveness of such a strategy in a middle-income country. We found that this strategy would prevent HTLV-1 infection in more than 1000 babies every year in Brazil. Moreover, this strategy was considered cost-effective, with an incremental cost-effectiveness ratio of US$11 415 per quality-adjusted life-year (QALY), which is lower than the Brazilian cost-effectiveness threshold ($18 107·74 per QALY). Prevalence of HTLV-1 infection in pregnant women, probability of mother-to-child transmission if breastfeeding lasts for 6 months or more, and cost of the screening test were the variables that most influenced the model. Our model is open access and is available as an editable Microsoft Excel spreadsheet; it can therefore be used by users worldwide to assess the cost-effectiveness of policies to prevent HTLV-1 mother-to-child transmission in different scenarios.

Implications of all the available evidence

Effective interventions exist to prevent HTLV-1 mother-to-child transmission. The implementation of HTLV-1 antenatal screening is cost-effective in Brazil and should be implemented nationally. All countries might benefit from this study as they could use the model with their own data to assess the cost-effectiveness of this policy in their own setting. These findings should be applicable where country-specific data are limited but HTLV-1 prevalence, breastfeeding behaviour, and testing costs are similar. This study will support decision making and adequate allocation of resources, particularly in resource-poor areas, in which prevalence of people with HTLV-1 infection is usually the highest. Importantly, the cost of screening tests should be reduced because it strongly influences the cost-effectiveness of this policy.

prevent infections early in life. Some countries, such as Japan and Brazil, recommend exclusive formula feeding for babies born from mothers who are HTLV-1 seropositive. However, universal HTLV-1 antenatal screening has only been implemented in Japan (in 2010), and it was recommended nationally in Brazil only in April, 2022.[2]

Although HTLV-1 has a global distribution, affecting at least 5–10 million individuals worldwide, HTLV-1 is usually found in communities with a low human development index, with many social determinants of health contributing to the risk of HTLV-1 infection. Our research group has previously shown that HTLV-1 prevalence in pregnant women inversely correlates with gross domestic product per capita and becomes proportionally higher as the unequal distribution of income within a country increases.[3] In such scenarios, where demands in public health are many but resources are scarce, economic analyses are of utmost importance to ensure appropriate allocation of resources.

However, health economic studies are sporadic in the HTLV field, have focused mainly on testing blood banks, and are outdated. The scarcity of economic data is one of the major barriers to the implementation of policies designed to prevent new infections through vertical transmission. In the past 5 years, key data have emerged,[4–6] allowing the development of more accurate models.

The aim of the study was to assess the cost-utility of universal HTLV-1 antenatal screening in Brazil, one of the countries with the highest number of people living with HTLV-1 in the world (800 000–2·5 million). Additionally, our goal was to develop an open-access, user-friendly, cost-utility model to assess the implementation of HTLV-1 antenatal screening, which can be edited by users by inputting local data and thus adapting the model to different scenarios.

Methods

Study design

We did an economic evaluation to assess the cost-utility of the implementation of universal HTLV-1 antenatal screening in Brazil, followed by postnatal interventions for seropositive mothers to avoid HTLV-1 mother-to-child transmission. This scenario was compared to the status-quo scenario—ie, without HTLV-1 antenatal screening.

The analysis was based on a decision-analytical model combined with a Markov model constructed by considering the lifetime as time horizon. We took the perspective of the Brazilian unified public health system for the analysis, and we reported the analysis according to the Consolidated Health Economic Evaluation Reporting Standards.

Model structure

We built a decision tree combined with a Markov model using Microsoft Excel (2019). The decision tree captures the number of mother-to-child infections that occur in two different scenarios: with or without HTLV-1 antenatal screening, followed by postnatal interventions in women infected by HTLV-1 (figure 1). Screening was based on the detection of anti-HTLV-1 antibodies with ELISA as a screening test, followed by western blot in reactive samples to confirm infection, as per the Brazilian Ministry of Health HTLV guidelines.[7] Some laboratories in the country use chemiluminescence, instead of ELISA, but the costs that are covered by the Government are the same. Although the Brazilian Ministry of Health also recommends using PCR as an alternative to western blot depending on the laboratory facilities and the expertise available, we did not consider PCR in our model because there is no commercially available PCR for HTLV-1. According to the current recommendations of the Brazilian Ministry of Health,[7] cabergoline (1 mg as a single dose, by mouth) should be offered to women with confirmed HTLV-1 infection to suppress lactation, and formula feed should be given to the babies for 6 months.

The Markov model captures the long-term outcomes from HTLV-1 infection throughout the children's lifetime. We included six health states to represent the possible clinical states in the target population: asymptomatic infection, no infection, HAM, ATLL, ATLL developing in a patient with HAM, and death (figure 2). Each cycle length was 1 year.

Model parameters

All the parameters included in this analysis are described in the table.[4–18] Direct costs were valued according to the public health system perspective, whereas HTLV-1 prevalence in pregnant women, the rate of women who breastfeed for 6 months or more, mother-to-child

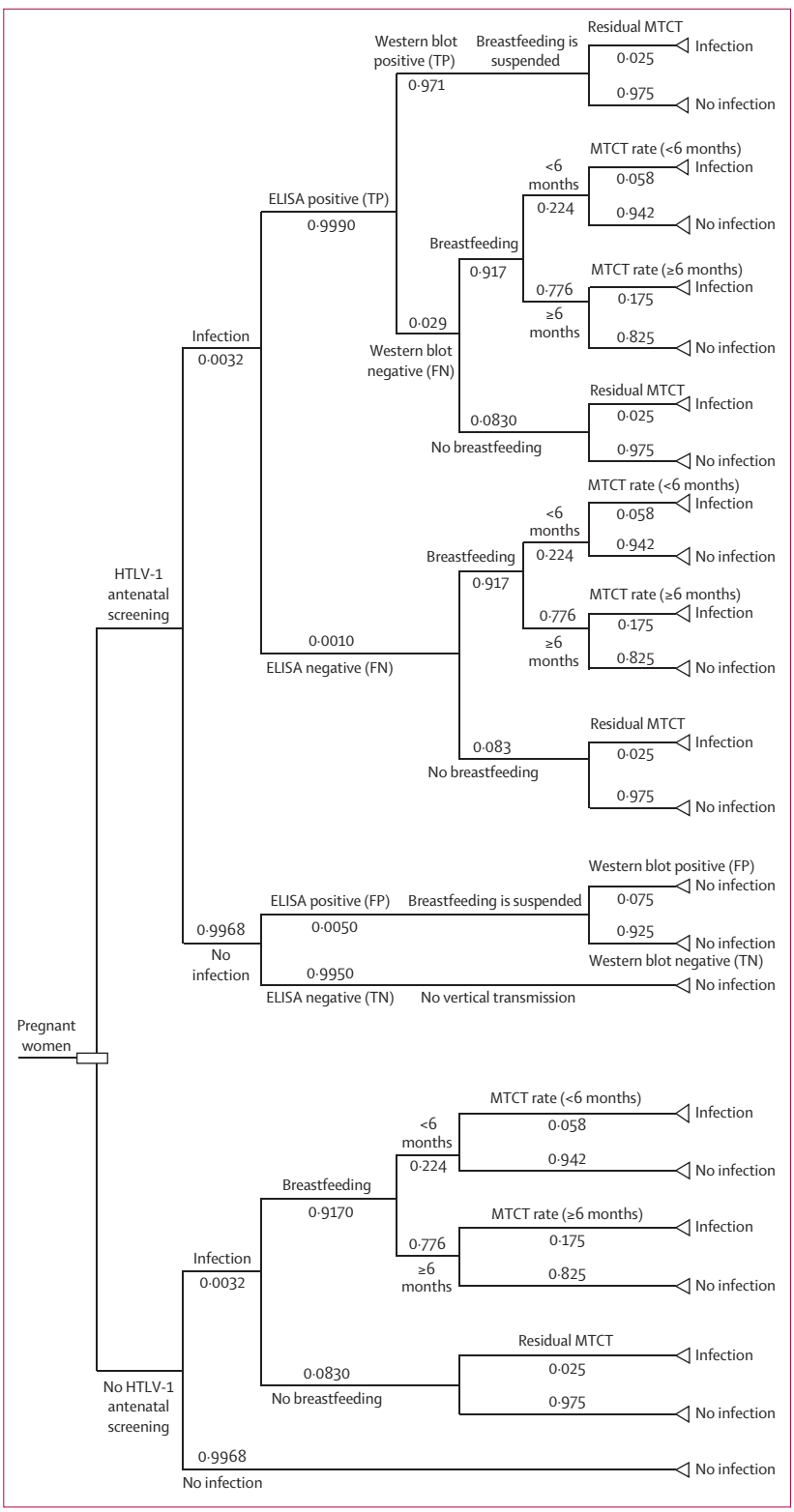

Figure 1: **Decision tree model diagram**
The model represents the number of mother-to-child infections that occur in two different scenarios: without HTLV-1 antenatal screening (status quo) and with HTLV-1 antenatal screening, followed by postnatal interventions in women with HTLV-1 infection. In the scenario alternative to the status-quo scenario, a population of pregnant women is screened for HTLV-1 with ELISA. Women with reactive samples are tested by western blot. Women with HTLV-1 infection refrain from breastfeeding. The model considers the effect of the performance of laboratory assays on the number of true positive, true negative, false positive, and false negative results. The risk of HTLV-1 transmission varies according to the duration of breastfeeding and the number of infant infections is linked to the breastfeeding pattern in the country. FN=false negative. FP=false positive. HTLV-1=human T-cell lymphotropic virus type 1. MTCT=mother-to-child transmission. TN=true negative. TP=true positive.

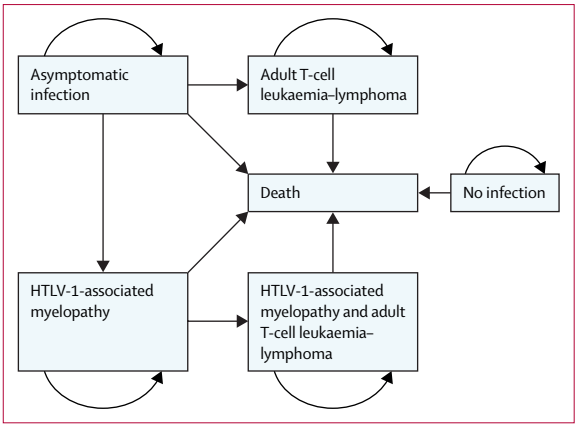

Figure 2: **Markov model diagram**
The model shows the long-term outcomes of HTLV-1 infection throughout the children's lifetime. Six health states were included to represent the possible clinical states in the target population. HTLV-1=human T-cell lymphotropic virus type 1.

transmission rates according to the duration of breastfeeding (including residual transmission that occurs despite exclusive formula feeding), the sensitivity and specificity of the diagnostic tests, and the transition probabilities and utilities of each health state were derived from existing literature, unless otherwise stated. When more than one reference was available for a particular input, the value used was decided via a Delphi method (with CR, TA, JC, YN, LC, LM, BGC, MFRG, ACPdO, AC-d-A, MP-S, and GPT involved in the discussion).

Measure of effectiveness

The outcome measure we used was quality-adjusted life-years (QALYs). QALY is the product of the utility value of a health state (preference-based measure of health quality of life) and the number of years spent in that state. Therefore, QALYs express life expectancy adjusted for the quality of life during those years. In this study, a utility value obtained from literature was attributed for each health state in the Markov model. The model calculates the total number of life-years spent in each health state weighed by their respective utility value (QALY). The use of QALY is important as HTLV-1 infection affects both the number of years lived and the quality of life. The incremental cost-effectiveness ratio (ICER; ie, cost per QALY gained) was calculated as the ratio of incremental costs to incremental QALYs between the proposed strategy and current practice.

See Online for appendix 3

For **SIGTAP** see http://sigtap.datasus.gov.br

For the **Painel de Preços** see https://paineldeprecos.planejamento.gov.br

The willingness-to-pay threshold was set as R$40 000 per QALY, or US$18 107·74 per QALY (with the conversion rate being true in 2022), in reference to the Brazilian cost-effectiveness threshold.[19] All clinical benefits were discounted at a fixed annual rate of 5% as recommended by the Brazilian Ministry of Health.

Model assumptions

The strategies simulated in the analytical model are based on the screening process and treatments recommended by the Brazilian Ministry of Health[7] and expert opinion as needed. We assumed that (1) western blot was used as a confirmatory test; (2) western blot results are not indeterminate; (3) HAM or ATLL onset occurs from age 18 years or older; and (4) costs and outcomes for the HAM associated with ATLL state are the same as the ATLL state; additionally, we did not take into account ATLL remission and maintenance treatment. Health outcomes and care costs related to mothers infected with HTLV-1 were not included in the model because they are assumed to be demands that will naturally arise in the public health system, independent of the adopted strategy. HTLV-1-associated diseases other than HAM and ATLL and the increase in overall mortality were not considered in the model because they are too complex to model and because of the uncertainty in the corresponding data. Infections by HTLV-2 were not considered because disease associations are rare.

Cost parameters

We considered the direct medical costs related to HTLV-1 screening, those arising from the follow-up of people living with HTLV-1, and those to support the diagnosis of HTLV-1-associated diseases. Each health state included the costs associated with the diagnosis and follow-up (medical visits, tests to diagnose HAM and ATLL, patient's monitoring, and treatment or medical procedure). We consulted a panel of specialists in HTLV infections to define the procedures and drugs necessary to patients' diagnosis, treatment, and appropriate follow-up. The specialist panel reached consensus agreement regarding the medical care for these diseases on the basis of the current practice and recommendations of the Brazilian Ministry of Health.[7] This consensus was used to establish the costs of patient care (appendix 3).

We valued the aforementioned costs according to data collected from an open-access information system (the Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos, Órteses, Próteses, e Materiais Especiais do Sistema Único de Saúde [SIGTAP]), which gives access to costs of medical procedures adopted by the Brazilian Ministry of Health. For drugs not included in SIGTAP, drug costs were based on purchases in 2021 by the Brazilian Ministry of Health, as retrieved from a different portal (Painel de Preços) recommended by the Brazilian Health Technology Assessment Agency. We adjusted values by a correction factor of 2·8 because these data refer to the federal government spending only. The correction factor of 2·8 is an adjustment recommended by the Brazilian Health Technology Assessment Agency to account for the remaining costs covered by local governments. We converted all costs to US$ using the International Monetary Fund purchasing power parity adjusted exchange rate via an online tool;[20] costs were discounted at a 5% fixed annual discount rate. The cost parameters are shown in the table and detailed in appendix 3.

	Point estimate	Lower limit	Upper limit	Reference
HTLV-1 prevalence in pregnant women	0·0032	0·0019	0·0054	Vieira et al[8]
Prevalence of breastfeeding	0·917	0·868	1·000	Brazilian Ministry of Health[9]
Probability of breastfeeding for ≥6 months	0·776	0·697	0·873	Brazilian Ministry of Health[9]
Sensitivity of ELISA	0·999	0·978	0·999	da Silva Brito et al[10]
Specificity of ELISA	0·995	0·991	0·999	da Silva Brito et al[10]
Sensitivity of western blot	0·971	0·923	0·999	Manufacturer's instructions
Specificity of western blot	0·925	0·860	0·975	Manufacturer's instructions
Probability of HTLV-1 mother-to-child transmission if breastfeeding lasts for <6 months	0·0580	0·0464	0·0696	Mean of the studies presented by Rosadas and Taylor[11]
Probability of HTLV-1 mother-to-child transmission if breastfeeding lasts for ≥6 months	0·175	0·140	0·210	Mean of the studies presented by Rosadas and Taylor[11]
Probability of residual HTLV-1 mother-to-child transmission (without breastfeeding)	0·025	0·020	0·030	Takezaki et al[12]
Relative risk of death in people living with HTLV-1 *vs* those without	1·57	1·37	1·80	Schierhout et al[5]
Hazard ratio of death for people with HTLV-1-associated myelopathy *vs* those without	5·03	1·96	12·90	Marcusso et al[6]
Probability of death in people with adult T-cell leukaemia–lymphoma	0·294	0·271	0·318	Imaizumi et al[13]
Probability of developing HTLV-1-associated myelopathy	0·0053	0·0026	0·0109	Romanelli et al[14]
Probability of developing adult T-cell leukaemia–lymphoma	0·000976	0·000606	0·001490	Arisawa et al[15]
Probability of progression to adult T-cell leukaemia–lymphoma for people with HTLV-1-associated myelopathy	0·00381	0·00305	0·00457	Nagasaka et al[16]
Utility value of asymptomatic infection	0·680	0·630	0·738	Rosadas et al[4]
Utility value of adult T-cell leukaemia–lymphoma	0·262	0·209	0·314	Stein et al[17]
Utility value of HTLV-1-associated myelopathy	0·340	0·273	0·399	Rosadas et al[4]
Utility value of no infection	0·858	0·840	0·876	Santos et al[18]
Cost of ELISA (individually; US$)	23·51	18·81	28·21	SIGTAP
Cost of western blot (individually; US$)	107·74	86·19	129·29	SIGTAP
Cost of breastfeeding interruption (cabergoline and formula feed; US$)	594·77	475·82	713·72	Brazilian Ministry of Health[7] and Painel de Preços
Cost of asymptomatic infection (US$)	903·40	722·72	1084·08	SIGTAP and Painel de Preços; Delphi method applied
Cost of HTLV-1-associated myelopathy (US$)	7842·10	6273·68	9410·52	SIGTAP and Painel de Preços; Delphi method applied
Cost of adult T-cell leukaemia–lymphoma (US$)	40 787·18	32 629·74	48 944·62	SIGTAP and Painel de Preços; Delphi method applied

Lower limit values are the decreased values from the point estimate; similarly, upper limit values are the increased values from the point estimate. Lower and upper limit values were chosen on the basis of confidence intervals reported in the literature or via the Delphi method. HTLV-1=human T-cell lymphotropic virus type 1. SIGTAP=Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos, Órteses, Próteses, e Materiais Especiais do Sistema Único de Saúde.

Table: **Parameters used in the model**

Sensitivity analysis

To identify the effects of the uncertainties of each parameter, we did a one-way deterministic sensitivity analysis and expressed the results as a tornado diagram. We did a probabilistic sensitivity analysis with 1000 simulations to test the robustness of results. We assumed a β probability distribution for prevalence, sensitivity and specificity of tests, and probabilities, whereas we applied a log-normal distribution to relative risks and hazard ratios and a γ distribution to costs.

Estimation of the number of infant deaths associated with avoidance of breastfeeding

Breastfeeding is associated with a decrease in infant mortality. Therefore, avoidance of breastfeeding might result in infant death that could be prevented. Data on the estimated number of pregnant women living with HTLV-1 in Brazil,[8] infant mortality in the country (1·3% mortality in children younger than 1 year),[21] the reduction in the rate of infant mortality associated with breastfeeding in Brazil (9·3%),[22] and the percentage of women who breastfeed in the country (96·2%)[23] were factored in to estimate the number of infant deaths that might occur as a consequence of women living with HTLV-1 and not breastfeeding.

Role of the funding source

There was no funding source for this study.

Results

Considering a hypothetic cohort of 1000 000 pregnant women, HTLV-1 antenatal screening would avert 353 childhood infections and produce a mean incremental health system cost of U$16·56 per pregnant woman tested. By considering the number of livebirths in Brazil in 2018 (2 944 932)[24] as the number of pregnant women, implementation of this policy would result in the prevention of 1039 (80%) of 1305 childhood infections every year. The incremental effectiveness was 0·00145 QALYs. The ICER of HTLV-1 antenatal screening

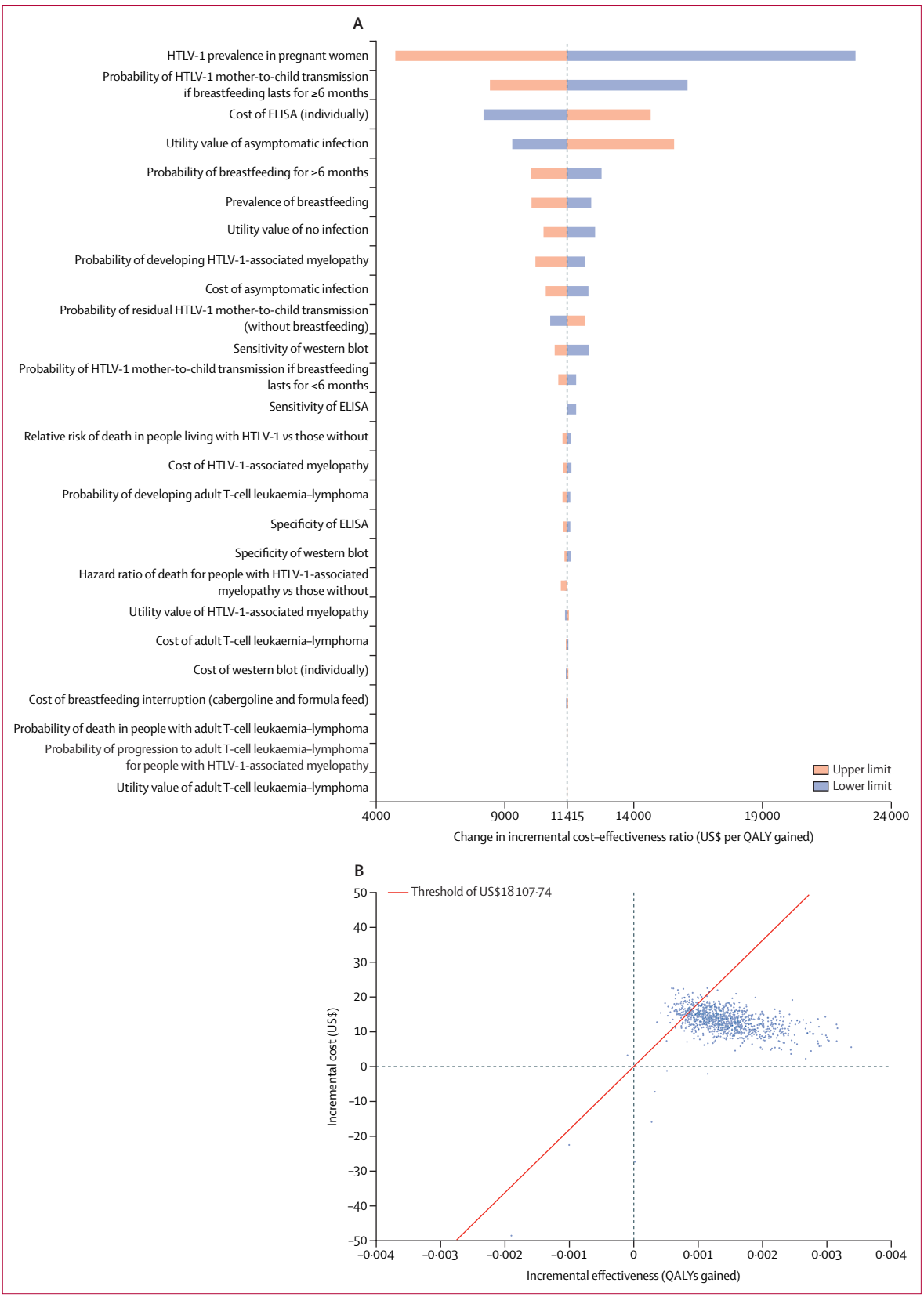

***Figure 3*: Sensitivity analysis**
Upper and lower limit values of each parameter are reported in the table. (A) Tornado diagram from the deterministic sensitivity analysis showing the effect of parameters on the incremental cost-effectiveness ratio. (B) Scatter plot of incremental cost-effectiveness ratios from the probabilistic sensitivity analysis; effectiveness was measured by QALY. HTLV-1=human T-cell lymphotropic virus type 1. QALY=quality-adjusted life-year.

was US$11 415 per QALY, and, considering the Brazilian threshold for ICER of $18 107·74 per QALY, HTLV-1 antenatal screening would be deemed a cost-effective intervention.

The one-way sensitivity analysis showed that the parameters with the largest effects on the model results are the prevalence of HTLV-1 infection in pregnant women, the probability of HTLV-1 mother-to-child transmission if breastfeeding lasts for 6 months or more, the cost of ELISA, and the health state utility value of asymptomatic infection (figure 3A). For all parameters, except for the prevalence of HTLV-1 in pregnant women, the ICER of HTLV-1 antenatal screening remained below the threshold of $18 107·74 per QALY (figure 3A), which is considered cost-effective by the Brazilian Ministry of Health. In nearly all simulations of the probabilistic sensitivity analysis, HTLV-1 antenatal screening was more effective than no screening (figure 3B). About 88% of the simulations were below the threshold, meaning an 88% probability of being cost-effective (figure 4).

By extrapolating the number of livebirths in Brazil in 2018 (2 944 932) as the number of pregnant woman and by using a prevalence of HTLV-1 of 0·32%,[8] we estimated that 9424 (2 944 932×0·0032) women infected with HTLV-1 would refrain from breastfeeding. The all-cause infant mortality (younger than 1 year) in Brazil is 1·3%, so we estimated that 122 of 9424 infants might die. Because breastfeeding can reduce infant mortality by 9·3%,[22] avoidance of breastfeeding to prevent HTLV-1 mother-to-child transmission could cause 11 infant deaths.

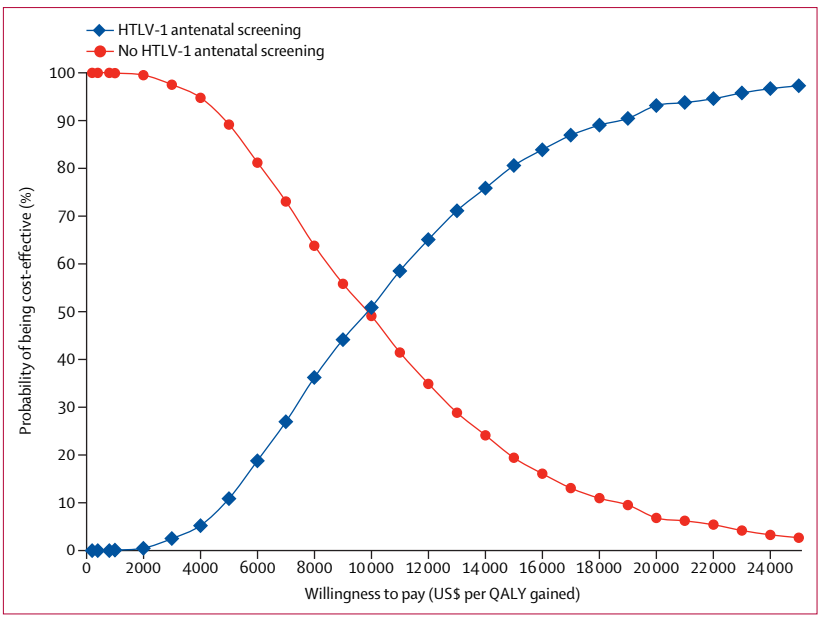

Figure 4: **Cost-effectiveness acceptability curve of HTLV-1 antenatal screening**
HTLV-1=human T-cell lymphotropic virus type 1. QALY=quality-adjusted life-year.

Discussion

Prevention of HTLV-1 mother-to-child transmission is considered a priority to tackle this lifelong infection, for which there is neither a curative treatment nor a vaccine.[1,25] However, the implementation of public health policies has been hampered by the scarcity of cost-effectiveness analyses.[1,25] Therefore, we developed a cost-utility model to assess the implementation of antenatal screening and postnatal interventions to prevent HTLV-1 mother-to-child transmission. The model showed that the proposed strategy is cost-effective, and the robustness of this finding was further substantiated by the sensitivity analysis. Although the model has used data from Brazil, the range of scenarios tested is broad; therefore, the findings can be potentially extrapolated to other countries with similar HTLV-1 prevalence, breastfeeding patterns, and costs (eg, many other Latin American countries). Additionally, a user-friendly version of the model is available; users can edit it, input local data, and derive cost-effectiveness data.

All predictive models have limitations and uncertainties. The major limitation of our model is that the negative effect of avoidance of breastfeeding was not considered. However, exclusive formula feeding is already the current recommendation for mothers who are HTLV-1 seropositive in several countries, including Brazil, Canada, Chile, Colombia, Japan, Uruguay, and the USA.[7,26] In Brazil, the policy includes the provision of complimentary formula feed for 6 months (or more, if needed) and counselling. We did an additional analysis to estimate the number of deaths that would not be prevented if breastfeeding was avoided. Although we have estimated that 11 infants might die because of the avoidance of breastfeeding in this cohort, 1039 HTLV-1 infections, 41–207 cases of ATLL (ie, an aggressive neoplasm associated with short survival), and 31–93 cases of the progressive neurological disease HAM (considering a risk of 4–20% for ATLL and 3–9% for HAM[27]) would be prevented. Moreover, secondary transmission during adulthood, which further disseminates HTLV-1 and contributes to the commonly observed familial aggregation of HTLV-1 infection, would be prevented. Notably, HTLV-1 antenatal screening has a high acceptance rate (>90%) and most seropositive mothers (>90%) opt to refrain from breastfeeding.[26] Some mothers feel guilty when transmitting the virus to their babies and some feel relieved when they learn that they can reduce the risk of transmission if they avoid breastfeeding.[26] Patients' representatives from different countries, including Argentina, Brazil, and the UK, unanimously identified HTLV-1 antenatal screening as a priority to ultimately prevent HTLV-1 mother-to-child transmission.[28]

Another limitation of this study is the uncertainty of the inputs. Most of the data used were based on a single-study analysis. However, the robustness of the results observed in the sensitivity analysis strengthens the findings and strongly supports the cost-effectiveness of

HTLV-1 antenatal screening. 88% of all scenarios considered in the analysis were cost-effective. Moreover, according to the Brazilian Ministry of Health, a higher than the recommended threshold could be adopted to guarantee innovation and health equity if a given condition strongly affects QALYs and (1) is endemic in low-income areas and has reduced availability of therapeutic interventions, (2) is severe, (3) is rare, or (4) affects children.[19] Although HTLV-1 could fulfil all these criteria, in this study we opted to use a conservative threshold of US$18 107·74, the one recommended for usual analysis by the Brazilian Ministry of Health.[19] Some other aspects of our model can also be considered conservative. For instance, we did not compute alternatives that could skew the results towards an increased cost-effectiveness (use of PCR instead of western blot, use of pooled samples, computation of other clinical manifestations of HTLV-1, etc). We used western blot as a confirmatory test instead of PCR, because PCR is not commercially available. However, PCR is about 25% less expensive than western blot[29] and use of in-house PCR assays is recommended by the Brazilian Ministry of Health to confirm a diagnosis of ATLL.[30] Another strategy that could be used to reduce the cost of screening by up to 75%, without affecting the sensitivity of the assay, is testing pooled samples.[31] The specificity of the assay is known to influence cost,[31] and therefore we opted to factor this aspect into the model. To test previously screened samples, we used a conservative estimate for the performance of western blot, based on the manufacturer's instructions; the estimate did not consider the performance of the assay as part of a diagnostic algorithm. However, assays used to screen blood banks in Brazil need to have sensitivity of 100% and specificity higher than 99%, and blood donors in Brazil have been routinely screened for HTLV-1 and HTLV-2 since 1993. Our analysis showed that the three most influential variables are the prevalence of HTLV-1 in pregnant women, the risk of HTLV-1 transmission (when breastfeeding lasts for ≥6 months), and the cost of the screening test. Therefore, strategies to reduce costs of HTLV-1 screening are important and could include sample pooling,[31] use of screening tests with increased specificity,[29] adjustment of assay cutoff values to assign positive and negative assay results,[32] and use of less expensive confirmatory tests, such as PCR assays.[29] The development of low-cost tests, such as point-of-care or multiplex assays that simultaneously test for different infections, would be beneficial, especially if these tests are relevant to antenatal screening programmes.

HTLV-1 antenatal screening would not only prevent HTLV-1 transmission but it would also allow for the identification of individuals with HTLV-2 infection, with no additional cost. In fact, screening assays detect both HTLV-1 and HTLV-2, and confirmatory tests such as western blot and PCR confirm infection and differentiate HTLV types. This parameter was not computed in the model, but it is another advantage of implementing this policy. Although HTLV-2-associated leukaemia has not been reported and HTLV-2-associated myelopathy has only been found rarely, individuals with HTLV-2 infection have higher rates of bladder and respiratory infection than uninfected individuals. HTLV-2 is both less common and less studied than HTLV-1; however, it can result in lifelong infection and integration of provirus into the host cell genome. Furthermore, mother-to-child transmission through breastfeeding is an important route of HTLV-2 infection.

In this analysis, we considered the two best characterised diseases that are associated with HTLV-1 infection (HAM and ATLL), and the effect of HTLV-1 on all-cause mortality.[5] We used the lifetime risk for all people living with HTLV-1—that is, we did not adjust the risk of ATLL for HTLV-1 infections that happen early in life, which would improve the ICER ratio. Indeed, if we consider an adjusted risk of developing ATLL, the intervention would become dominant (ie, more effective with a lower cost, with an ICER of US$–335·03). Moreover, we did not include the effect of other HTLV-1-associated inflammatory diseases, such as infective dermatitis, pulmonary disorder, uveitis, and mild neurological symptoms (eg, symptoms that suggest early neurogenic bladder or bowel disease, observed in up to 26% of patients with HTLV-1 infection in Brazil[33]), and we did not include the effect of HTLV-1 on several co-infections, such as the increase in prevalence, severity, and rates of treatment failure.[34,35] The societal costs of HTLV-1 infections are detrimental to society's welfare; however, we did not include them in the model because they are very difficult to quantify. HTLV-1-associated diseases affect patients' autonomy, cause premature death and, consequently, productivity loss, which is not restricted to patients only, but it could also affect their family members. The productivity loss is associated with early retirement, premature death, and loss of days at work for medical care.[3] We did not include the utility loss of caregivers because information in the literature on this topic is not yet available. Intangible costs, including the loss of loved ones and the psychological impact of having HTLV-1 are extremely important, and although they are difficult to measure, they should not be underestimated, and they should be considered when assessing the implementation of health-care policies and addressed in future research. To do so, future research would require in-depth analysis of patients and their families representing the spectrum of HTLV-1-associated diseases.

One of the most important variables that was not computed in the model is secondary transmissions. The prevention of infection of each baby results in the interruption of a chain of transmissions that would potentially happen. Although averted secondary transmissions would have a strong effect on the model results—ie, increasing the effectiveness of the

intervention at the same cost—we did not consider this variable because the exact number of further transmissions is too uncertain and difficult to predict. Additionally, antenatal screening could also be used for contact tracing to identify other individuals living with HTLV-1, such as sexual partners, parents, siblings, and other children of the newly diagnosed pregnant women. This aspect can be considered an added value of the antenatal screening programme, because familial aggregation of HTLV-1 infection is common. Cross-breastfeeding has been reported by about 20% of women in Brazil,[23] but we did not account for it because its contribution to transmission is unknown. A survey showed that this practice was more common in the North Region (36%), and among people who are black (25%) or from a mixed ethnic background (24%). This finding is important because these groups of people are usually most affected by HTLV-1 in Brazil.[23]

Our model is in accordance with the guidance of complete avoidance of breastfeeding to prevent HTLV-1 mother-to-child transmission as recommended by countries such as Brazil,[7] but it could also be easily adapted to assess the cost-effectiveness of short-term breastfeeding. Some researchers argue that short-term breastfeeding can be recommended to allow both mothers and babies to take advantage of the benefits of breastfeeding, even if restricted to a short period. The risk of HTLV-1 mother-to-child transmission increases with the duration of breastfeeding. Thus, short-term breastfeeding is associated with reduced risk of transmission compared with long-term breastfeeding;[26] however, the experience in Japan is that mothers find stopping breastfeeding at 3 months difficult.[26] The mechanism of HTLV-1 mother-to-child transmission is still unclear and alternatives should be developed to allow women living with HTLV-1 to breastfeed their babies safely. Meanwhile, avoidance of breastfeeding is still considered the safest alternative to prevent HTLV-1 mother-to-child transmission, avoiding 85% of transmissions, and, therefore, should be encouraged when formula feeding is acceptable, feasible, affordable, sustainable, and safe.[26]

In conclusion, the implementation of antenatal screening followed by postnatal interventions aimed at avoiding HTLV-1 mother-to-child transmission would not only prevent new incurable infections and avoid the health and socioeconomic burden of HTLV-1 in more than 1000 Brazilian families annually, but it would also be highly cost-effective. This new cost-utility model can be edited by users, allowing the evaluation of the cost-effectiveness of such policies in different settings worldwide.

Contributors

CR conceptualised this Article and wrote the original draft of the manuscript. CR, KS, MdC, MS, and GPT contributed to the study design, methodology, data analysis, and data interpretation. KS, MdC, TA, JC, YN, LC, LM, BGC, MFRG, ACPdO, AC-d-A, BM, MP-S, NB-S, MS, and GPT reviewed and edited the manuscript. CR, TA, JC, YN, LC, LM, BGC, MFRG, ACPdO, AC-d-A, BM, MP-S, and PP contributed to data collection. MS and GPT supervised the study group. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. CR and MS have directly accessed and verified the underlying data reported in the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

LC reports receipt of funding from AbbVie, Roche, and AstraZeneca for participation in advisory boards, outside of the submitted work. All other authors declare no competing interests.

Data sharing

All inputs used are available in the main text and in appendix 3. The mathematical model developed for this study is an open-access resource and is available at Mendeley Data (https://doi.org/10.17632/5wb25p9d5g.1).

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