UNIVERSIDADE FEDERAL DA BAHIA
FACULDADE DE MEDICINA DA BAHIA

PROGRAMA DE PÓS-GRADUAÇÃO
EM MEDICINA E SAÚDE

Ludy Alexandra Vargas Torres

PREVALÊNCIA E FATORES ASSOCIADOS À TRANSMISSÃO VERTICAL DE HIV, HTLV, HBV, HCV E SÍFILIS EM MATERNIDADES PÚBLICAS DE SALVADOR, BAHIA.

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UFBA, 2018

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Tese apresentada os Programa de Pós-graduação em Medicina e Saúde da Faculdade de Medicina da Bahia da Universidade Federal da Bahia, como requisito parcial para a obtenção do título de Doutor em Medicina e Saúde.

Orientador: Prof. Dr. Carlos Roberto Brites Alves.
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Tese de autoria de Ludy Alexandra Vargas Torres intitulada Prevalência e fatores associados à transmissão vertical de HIV, HTLV, HBV, HCV e Sífilis em maternidades públicas de Salvador- Bahia, apresentada na Universidade Federal da Bahia, como requisito parcial para a obtenção do título de Doutor em Medicina e Saúde.

Salvador, 27 de novembro de 2018

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Dedicatória

A Deus e a minha família:
A meu pai Jairo Vargas, que no céu intercede por mim.
A minha mãe Rosalba Torres por sempre ter me apoiado e pelo seu amor.
A meus filhos Paula e Juan Camilo por seu compressão e amor
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A meus irmãos Edwin e Carolina por sempre confiar e apoiar meus projetos de vida

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RESUMO

As infecções virais crônicas e suas complicações em recém-nascidos constituem-se um problema de saúde pública. Durante a gestação, estas infecções nem sempre são diagnosticadas e tratadas a tempo, levando à manutenção do ciclo de transmissão e elevação do risco de transmissão vertical (TV). **Objetivo**: Estimar a taxa da infecção materna e de transmissão vertical pelos vírus da Imunodeficiência Humana (HIV), vírus Linfotrópico de Células T Humanas (HTLV-1/2), vírus das hepatites (B/C), e da Sífilis assim como os fatores associados. **Metodologia:** Estudo de corte transversal, realizado com 2.099 parturientes atendidas nas maternidades de Referência Professor José Maria de Magalhães Neto (MRPJMMN) e Climério de Oliveira (MCO), em Salvador, entre abril de 2016 e junho de 2017. Parturientes foram testadas para estas infecções e foram coletados dados sociodemográficos, obstétricos, clínicos e do pré-natal, parto/nascimento e puerpério. As crianças filhas de mães soropositivas foram também testadas. Analise estatístico descritivo e analítico foi realizado usando o programa estatístico SPSS, versão 22. **Resultados:** Estimou-se uma prevalência

de 1,5% para HIV, 0,4% para HTLV, 0,4% para HBV, 0,1% para HCV e 4,7% para sifilis. A avaliação das crianças expostas desses vírus estimou uma taxa de TV de 6,2% para HIV, 40% para HTLV, 0% para HBV e não foi avaliada para HCV. Foram detectada uma taxa de prevalência de 3,7% de casos prováveis para sífilis congênita. Os fatores sociodemográficos, de comportamento e obstétricos das mães associados às infecções dos vírus estudados evidenciaram um contexto de vulnerabilidade individual e social. **Conclusão.** Existe ainda altas taxas de TV no Salvador, Bahia sugerindo a persistência de fatores como o diagnóstico tardio das infecções na gestação e baixa adesão às recomendações por parturientes em condição de vulnerabilidade.

Descritores: Transmissão Vertical, Soroprevalência HIV, HTLV-1/2, HBV e HCV e Fatores de risco

VARGAS, Ludy Alexandra T. **Prevalência e fatores associados à transmissão vertical de HIV, HTLV, HBV, HCV e Sífilis em maternidades públicas de Salvador, Bahia**. Faculdade de Medicina, Universidade Federal da Bahia, Salvador, 2018.

ABSTRACT

Chronic viral infections and their complications in newborns are a public health problem. During pregnancy, these infections are not always diagnosed and treated in time, leading to maintenance of the transmission cycle and elevation of the risk of vertical transmission (TV). **Objective**: To estimate maternal and vertical transmission rate of Human Immunodeficiency Virus (HIV), human T-cell lymphotropic virus (HTLV-1/2), hepatitis virus (B / C), and Syphilis and to assess the associated factors. **Methods**: This is a cross-sectional study with 2,099 parturient attended in two public maternity hospital in Salvador, Brazil, between April 2016 and June 2017. Parturients and child were tested for these infections, and sociodemographic, obstetrical, clinical and prenatal, childbirth and puerperium data were collected. **Results**: HIV prevalence rates was 1.5%, seroprevalence rates for HTLV, HBV and HCV were 0.4%,0.4% and 0.1% respectively. And 4,7% for Syphilis. The evaluation of the exposed children of

these viruses estimated a TV rate of 6.2% for HIV, 40% for HTLV, 0% for HBV and was not evaluated for HCV. We detected a high prevalence (3.7%) of probable cases of congenital syphilis. The sociodemographic, behavioral and obstetric factors of the mothers associated with the infections of the studied viruses evidenced a context of individual and social vulnerability. **Conclusion**. There are still high rates of TV in Salvador, Bahia suggesting the persistence of factors such as late diagnosis of infections during pregnancy and low adherence to recommendations by parturients in vulnerable conditions.

Keywords: Vertical Transmission, HIV Seroprevalence, HTLV-1/2, HBV, HCV, and Risk Factors

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LISTA DE SIGLAS E ABREVIATURAS

Aids	Síndrome de imunodeficiência humana (do inglês, Acquired imune deficiency syndrome)
Anti-VHC	Anticorpo contra o vírus da hepatite C
IC	Intervalo de confiança (do inglês, CI; confidence interval)
IHBlg	Imunoglobulina específica para o vírus da hepatite B

ITS	Infecção de transmissão sexual
HBeAg	Antígeno e do vírus da hepatite B
HBsAg	Antígeno de superfície do vírus da hepatite B
HBV	Vírus da Hepatites B
HCV	Vírus da Hepatites C
HIV	Vírus da Imunodeficiência Humana (do inglês, Human immunodeficiency vírus)
HTLV 1/2	Vírus Linfotrópico de Células T Humanas tipo 1 e tipo 2 (do inglês, Human T lymphotropic vírus)
LAPI	Laboratório de Pesquisa e Infectologia
MCO	Maternidade Climério de Oliveira
MRPJMMN	Maternidade de Referência Professor José Maria de Magalhães Neto
PCR	Reação em cadeia de polimerase
RN	Recém-nascido
SIH	Sistema de Informações Hospitalares
SIM	Sistema de Informações sobre Mortalidade
SINAN	Sistema de Informação de Agravos de Notificação
SINASC	Sistema de Informações sobre Nascidos Vivos
SISCEL	Sistema de Controle de Exames Laboratoriais
TCLE	Termo de Consentimento Livre e Esclarecido
TV	Transmissão Vertical
UFBA	Universidade Federal da Bahia

SUMÁRIO

1. INTRODUÇÃO

A transmissão vertical (TV) de infecções virais crônicas pode ocorrer na gestação, no trabalho de parto ou durante a amamentação. Estas infecções quando acometem gestantes nem sempre são diagnosticadas e tratadas a tempo, perpetuando o ciclo de transmissão e podendo culminar na transmissão vertical. Os agentes adquiridos por esta via podem causar efeitos sobre os fetos e causar

alterações patológicas, incluindo, abortos, nascimentos prematuros, mortes neonatais e anomalias fetais ou congênitas[1].

No Brasil, a incidência de casos de HIV em crianças menores de cinco anos foi reduzida em 34% (de 3,6 a 2,4 casos por 100 mil habitantes) entre 2006 a 2016. Durante o mesmo período, na região nordeste (NE) se observou um leve aumento de 8,7% na taxa de detecção da AIDS em menores de cinco anos, passando de 2,3 para 2,5 casos por 100 mil habitantes[2]. O programa para prevenção de transmissão vertical de HIV e sífilis da Secretaria de Vigilância em Saúde mostrou que 35% dos casos de TV do HIV ocorrem durante a gestação, 65% destes no periparto e 7-22% pela amamentação. As taxas de TV podem atingir 25% quando não são realizadas intervenções profiláticas[3].

No período de 1999 a 2017, foram notificados 218.257 casos de hepatites B no Brasil, sendo que 23.928 casos (10,9%) ocorreram em gestantes e a região NE foi responsável por 10,4% destes. Na Bahia, a taxa de detecção de hepatite B em gestantes em 2017 foi 0,4 por 1.000 NV, taxa inferior à nacional (0,5 por 1.000 NV). Em crianças menores de 10 anos se apresentaram 3.978 casos (1,8%)[4].

A partir de 2015, o critério para notificação de casos confirmados de hepatite C foi mais amplo, para qualquer um dos marcadores – AntiHCV ou HCV-RNA – reagentes. Por isso, houve uma tendência de elevação na taxa de detecção de infecção nas gestantes em todas as regiões do Brasil. Entre 2003 e 2016, 64,1% dos casos ocorreram no Sudeste, 24,5% no Sul e 5,5% no NE[5]. Em crianças a principal fonte de infecção é a transmissão vertical, com taxas que variam de 1 a 19,4%. Fatores geográficos, doença materna grave ou com altos títulos de HCV-RNA, coinfecção com HIV e a presença de monócitos infectados pelo HCV em sangue periférico estão associados a maior soroprevalência nesta faixa etária[6].

No que se refere a taxa de infecção pelo HTLV-1, a cidade de Salvador, capital do estado da Bahia, apresenta uma soroprevalência de 1,8% na população geral e 0,84% em gestantes[7-8]. Um recente estudo elaborado no Brasil, estimou que a taxa de transmissão vertical do HTLV é de 20,4% em bebês que foram amamentados[9].

A sífilis aumentou na população em geral, entre junho de 2010 e 2016 foram notificados quase 230 mil casos novos da doença, em 2015, no Brasil, foram reportados 33.365 casos de sífilis em gestantes no Sistema de Informação de Agravos de Notificação (Sinan), com uma taxa de detecção de 11,2 casos de sífilis em gestantes/mil nascidos vivos. Aumentando o risco de mortes fetais e neonatais por ano e um numero de crianças com risco de morte prematura[10]. Considerando esses dados e também que segundo estudos a taxa de transmissão vertical pode chegar a 100% quando não é feito o tratamento adequado, é dramática a situação que o Brasil está enfrentando[11,12].

Embora existam informações mais abrangentes sobre as taxas de TV para sífilis e HIV, pouco se sabe sobre a transmissão de outras viroses crônicas (HTLV, HBV e HCV) prevalentes em nosso meio, por esta via. O presente estudo visa avaliar as taxas de TV para estes agentes, e os fatores de risco para sua ocorrência.

2. OBJETIVOS

Geral ou primário

Estimar a taxa de transmissão vertical da sífilis e dos vírus HIV, HTLV-1/2, HBV e HCV, e analisar os fatores associados em parturientes do município de Salvador, atendidas nas maternidades: Maternidade de Referência Professor José Maria Magalhães Neto (MRPJMMN) e Maternidade Climério de Oliveira (MCO).

Específicos

1. Estimar a prevalência das infecções por sífilis e dos vírus HIV, HTLV-1/2, HBV e HCV em parturientes do município de Salvador, Bahia.

2. Determinar a frequência de transmissão vertical em crianças menores de 10 anos, nascidas de mães soropositivas para os agentes avaliados.

3. Determinar os fatores associados à transmissão vertical das infecções sífilis, dos retrovírus (HIV/HTLV) e vírus das hepatites (B/C).

3. REVISÃO DE LITERATURA

ARTIGO ORIGINAL Nº 1

Mother to child transmission of human T-cell lymphotropic virus (HTLV): rate, associated factors and fetal outcome: a systematic review and meta-analysis.

Mother to child transmission of human T-cell lymphotropic virus (HTLV): rate, associated factors and fetal outcome: a systematic review and meta-analysis.

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ABSTRACT

Background. HTLV vertical transmission increased the risk for developing of chronic diseases in adult life. We aim to estimate the pooled rate of mother to child transmission of HTLV, and to assess the risk factors and fetal outcomes of maternal HTLV infection, based on published studies accessible scientific databases. **Methods**. We conducted a systematic search in PubMed, EMBASE and Lilacs databases of original studies that providing HTLV-1/2 rates of infection in pregnant women and child using confirmatory test and studies evaluating the risk factor or the outcomes of HTLV infection. Meta-analysis for HTLV infection in pregnant women and mother to child transmission of HTLV was performed. **Results**. A total of 87 studies based on a prevalence rate defined by the confirmatory test were retained for the review. From the meta-analysis, we estimated a pooled prevalence rate of 1.3% (95%CI: 0.9-1.8) HTLV infection in 848.576 pregnant/parturient women, 14.1% (95%CI: 10.2-18.6) within a population of 11.039 breastfed children and 4.4% (95%CI: 3.3-6.0) in 1070 non-breastfest children. The associated factors with regards to increased o risk the VT were: high immunological markers in the HTLV carrier mother and in the breast milk, breastfeeding > 6 months, genetic predisposition and sociodemographic factors with maternal age > 30 years and lower maternal income. Few studies evaluated the fetal outcome of HTLV maternal infection, showed higher positive rate in newborns with mothers who have had a history of abortion. **Conclusion**. The prevalence of maternal HTLV infection and the vertical transmission of the same have the heterogeneous distribution, both globally and regionally. The studies analyzed allowed us to discern the reasons as to why there is still a high rate of vertical transmission in children born to HTLV seropositive mothers, despite taking preventive measures such as abstinence from breastfeeding.

Registration: It is registered in the Prospero database: (PROSPERO 2018:CRD42018089811).

KEYWORDS: HTLV transmission; mother to child transmission; pregnancy outcome; risk fact

Background:

When HTLV infection affects pregnant women, it is not always diagnosed on time. This will promote the transmission cycle and thus increase the risk of mother to child transmission. Harmful agents acquired by this route increased risk for developing of chronic diseases such as leukemia/lymphoma[1-4], infective dermatitis[4-6] and human T-lymphotropic virus-1 associated myelopathy in infantile-juvenile population[6].

HTLV-1 modes of transmission include sexual transmission[7] (predominantly from men to women[8-10]), mother to child transmission (vertical transmission), and transfusion of infected blood products[11,12] or by sharing of needles and syringes[13] (parenteral transmission). Vertical transmission (VT) occurs predominantly through prolonged breastfeeding[14] or by intrauterine[15]. In relation to HTLV-2, the transmission mechanism differs because it is clustered in families, especially among indigenous populations and intravenous drug users.

The estimation of the prevalence rate of the vertical transmission of HTLV 1/2 has several sources of information, principally scientific studies carried out with serological tests on populations and specific geographic spaces. This variability in the statistical data that leads to the scarce approximation of the problem.

Through this systematic review, we intend to arrive at an approximation of the prevalence rate, the associated factors that favor the spread of mother to child transmission of HTLV 1/2 virus and the fetal outcomes, based on the statistical data available in studies of Brazil and the world. In addition, the results will provide information on the interventions carried out to reduce the mother to child transmission

Methods:

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) statement. The protocol was registered on PROSPERO, number: CRD42018089811.

Study eligibility criteria

The specific study eligibility criteria were: (1) Observational and experimental studies; (2) the

study population was pregnant/parturient women or children; (3) maternal HTLV status was determined using confirmatory test, (4) study outcome: HTLV prevalence rate, VT rate or risk factor or pregnancy outcomes for HTLV vertical transmission and (5) The language was restricted to English, Portuguese and Spanish.

Data sources and searches

Studies were identified from large databases such as Embase, MEDLINE through PubMed library and LILACS database through BIREME library using search terms of Emtree, MeSH and DeCS. In addition, the references list of included studies were also evaluated to determine the eligibility. The search strategy is shown in Appendix S1

Study selection

Three researchers (Amaral S, Fausto T and Vargas L) assessed titles and abstracts of the identified publications and performed data extraction independently. Discrepancies were discussed and resolved by consensus. Studies were included without any limitation of the year of publication. We excluded studies with only abstracts, case reports, editorial, review literature and animal studies or those that were not relevant to the subject or did not discuss the prevalence rate or risk factors.

Data extraction and quality assessment

We extracted data based on the identification of study (first author, year of publication), location and date (city, country and year), study design (type of study, methodology, tests used and type of statistical analysis), population (sample size, pregnant women/parturient, children), and results (prevalence rate, associated factors, type of statistical analysis, fetal outcome).

The Newcastle – Ottawa Scale (NOS) for observational studies and Cochrane Handbook of systematic review for randomized controlled trials were used to assess the risk of bias (quality) of included studies.

Data synthesis and analysis

Study characteristics were summarized descriptively. Data were combined and expressed as prevalence rate with 95% confidence intervals (CIs) via the effects model, using Comprehensive Meta-Analysis (CMA) version 3.0 and MedCalc software version 15.1. Subgroup analyses was performed, according to the study geographical area. A value of I^2 statistic >50% indicated significant heterogeneity among studies. Analyze of risk factors was

performed for study when data were available. The publication bias were evaluated with funnel plots and Egger's test, p value <0.05 was considered indicative of statistically significant bias.

Results:

Study selection

In total, 450 articles were identified. Of these, 133 full-text articles that were reviewed, only 87 studies were included after applying the study criteria. We identified 55 studies providing quantitative data for meta-analysis of HTLV prevalence in pregnant women and 40 studies for meta-analysis of VT rate (Figure 1).

Study characteristics

The studies were conducted in different regions of the world, the highest percentage of studies were found in Japan (31.7%), the same number for Brazil and Africa (15.8%). Throughout the 1980s and 1990s, the largest number of studies was carried out (71.9%), and a decrease of 6.1% was observed since 2010. The studies characteristics are shown in detail in Table1 and Table 2.

The mean age of the pregnant women was 27.6 years (range 23- 37) and that of HTLV-infected pregnant women was 30.2 years (range 25.4-45.4). Regarding the children analyzed with HTLV infection, the average age was 12.7 months (range 10-14.1).

The Newcastle Ottawa Scale (NOS) scores were reported in Table 2, and the ranged from 4-8. There was an appropriate selection of patients in the included studies, since almost all were representative, however any cross-sectional study included non-respondents in the selection process. 60% of the studies were not comparative.

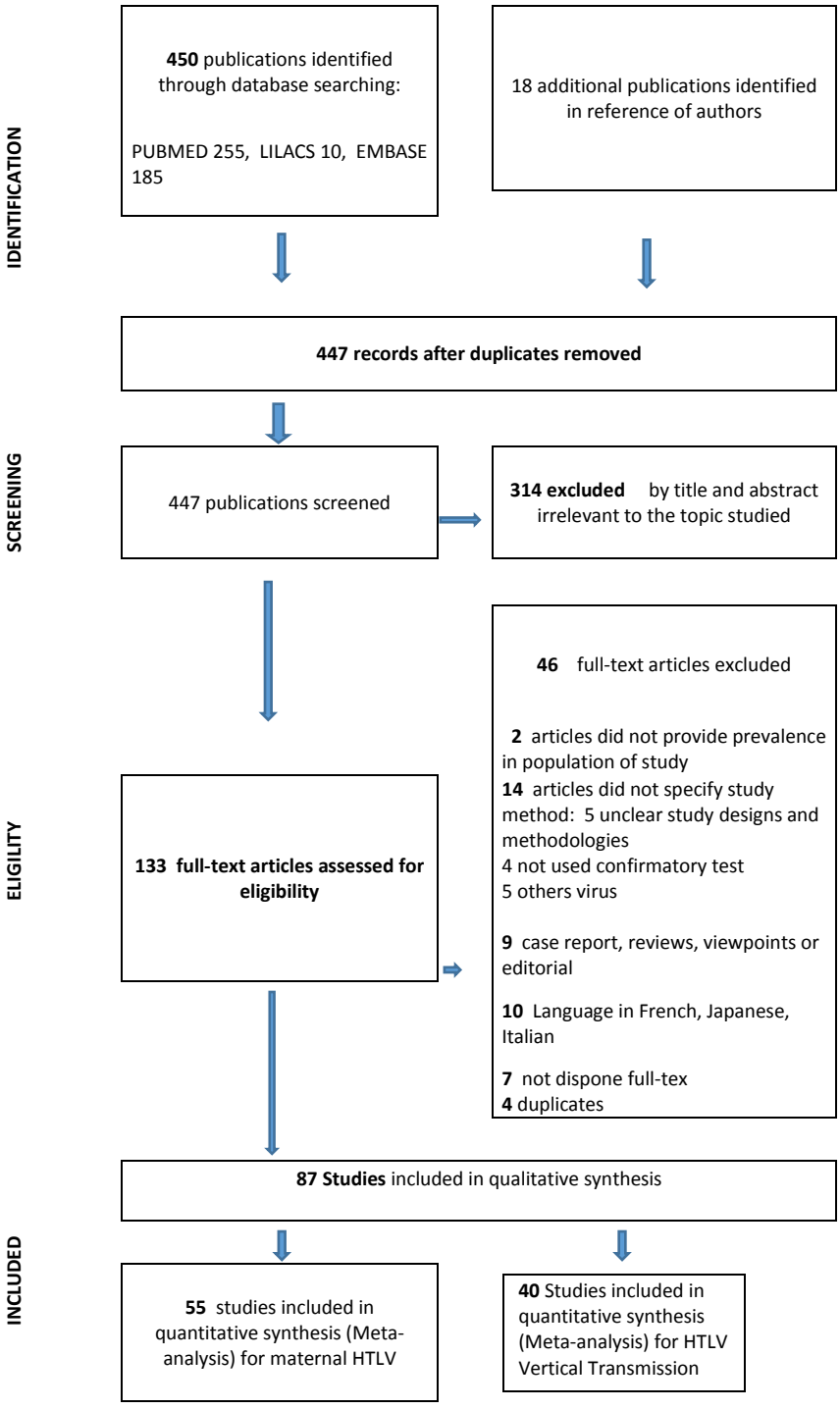

Figure 1 - PRISMA flow diagram of study selection process.

Table 1. Main characteristic of the included studies

Characteristic	Number studies	Percentage
Regions		
Japan	26	31.7
Brazil	13	15.8
Africa	13	15.8
Caribbean	11	13.4
Europe	10	12.2
South America (No Brazil)	5	6.2
United States	4	4.8
Study Period		
Before- 1989	32	39.0
1990-1999	27	32.9
2000 – 2009	18	21.9
2010 – Present	5	6.1
Participants		
Pregnant women	37	45.1
Parturient women	8	9.8
Children	14	17.1
Cluster familiar	12	14.6
Mother-child pair	11	13.4
Confirmatory test		
Western Blot (WB)	40	48.8
Indirect immunofluorescence (IFA)	14	17.1
PCR	9	10.9
Western Blot (WB) and PCR	10	12.2
Expression antigens in cultured cells	3	3.7
Multiple testing	6	7.3
Virus		
HTLV-1	48	58.5
HTLV-2	5	6.1
HTLV 1 and 2	29	35.4
Method study		
Cross-sectional study	54	65.8
Cohort	19	23.2
Case-control	9	11.0
Score NOS		
High risk of bias	55	63.2
Low risk of bias	32	36.7

Innogenetics line immunoassay (INNO-LIA) and Western Blot (WB) radioimmunoprecipitation (RIPA) + Western Blot + PCR Western Blot and PCR

NOS: Newcastle Ottawa Scale

Maternal HTLV Infection Prevalence and Vertical Transmission Rate

Meta-analysis was used for the pooled crude prevalence with 95% CI of maternal HTLV infection and vertical transmission by regions (continents). From random-effects models for meta- analysis, a HTLV-1 pooled prevalence of 1.3% (95%CI: 0.9-1.8) was estimated in 848.576 pregnant/parturient women. The prevalence of maternal HTLV-1 ranges from 0.05% in Europa to 4.4% in Asia (Figure 2).

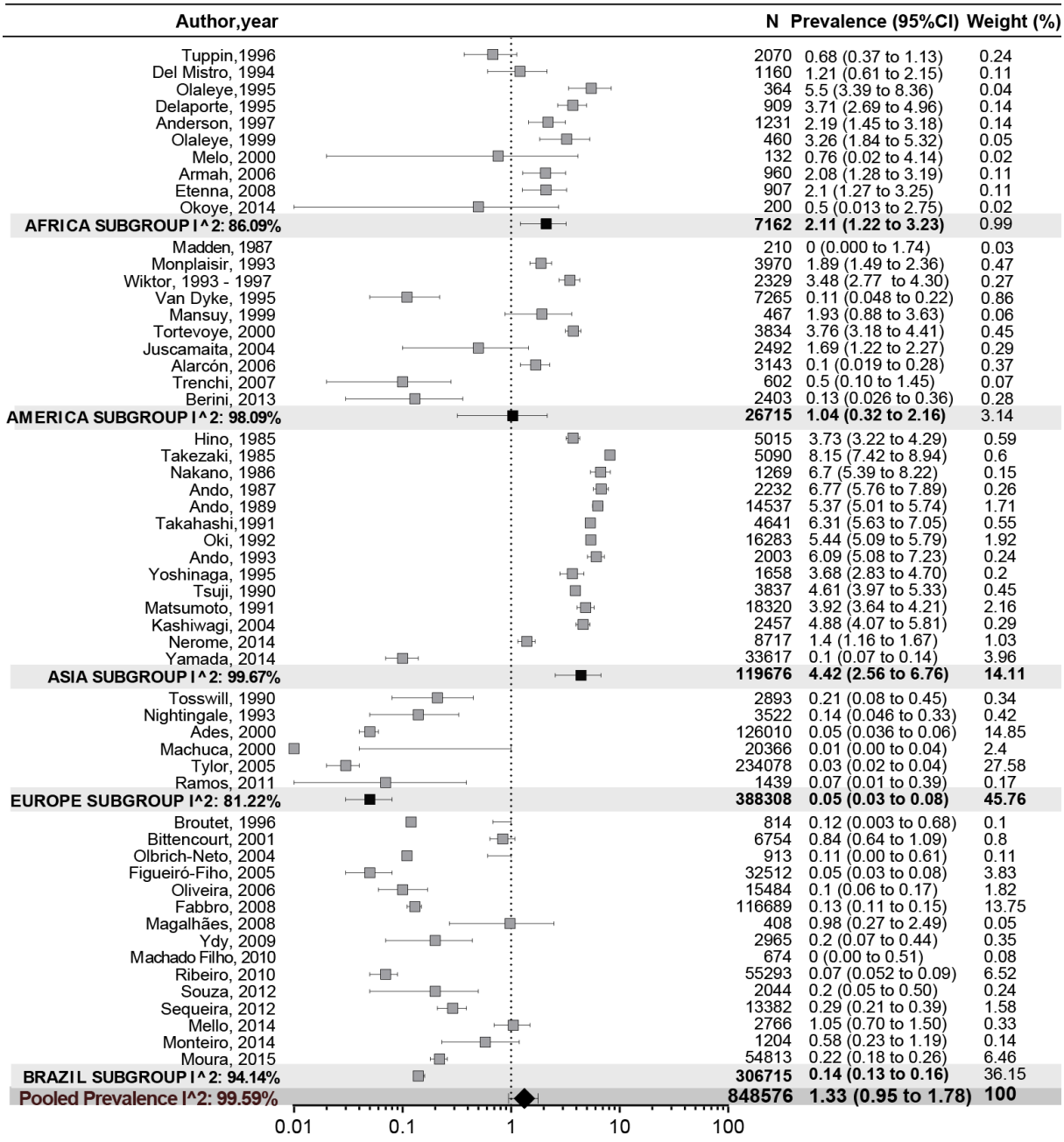

Figure 2. Forest Plot of HTLV-1 Prevalence in Pregnant Women

Among the regions studied, Japan had the highest number of maternal HTLV cases. The forest plot show decrease of prevalence from 1985 (8.2%)[16] to 2014 (0.1%)[17]. The weight considered for the studies was 14.1.

In Africa and America (excluding Brazil), the prevalence of HTLV in pregnant women was 2.1 and 1.0% respectively. African studies evidenced a prevalence decreased in Nigeria from 5.5% (Olaleye, 1999[18]) to 0.5% (Okoye, 2014[19]). In America, the prevalence is noted as being 3.8% in French Guayana[20] and 0.1% in USA[21] and Argentina[22-23]. Several large American regions have not been investigated for maternal HTLV-1 infection or no recent studies were found in regions already studied excepting Argentina.

The lowest prevalence rates (less than 1%) were found in Brazil and Europa. In Brazil, the seroprevalence in pregnant women ranging from 0.05%[24] to 1.1%[25-26], with the state of Bahia having the highest number of cases. The Brazilian studies reported highest population analyzed (306.715 pregnant women).

The prevalence and geographical distribution for HTLV-2 varied in relation to HTLV-1 (Figure 3). The pooled prevalence was 0.1% (IC95%:0.1-0.2) among 410.987 women pregnant. There are high prevalence in America Subgroup (0.86%); the population studied was women and their offspring of indigenous people of Argentina[22-23] and women pregnant drug users in USA[21, 27]. In Brazil, the highest prevalence was found in the state of Maranhão (0.15%)[28].

Several studies estimated indeterminate WB patterns in 320.452 women pregnant (Figure 4). It was found that indeterminate HTLV has a pooled prevalence (0.5%) similar to the prevalence of HTLV-2. The highest prevalence of 2.6% was seen in Africa subgroup.

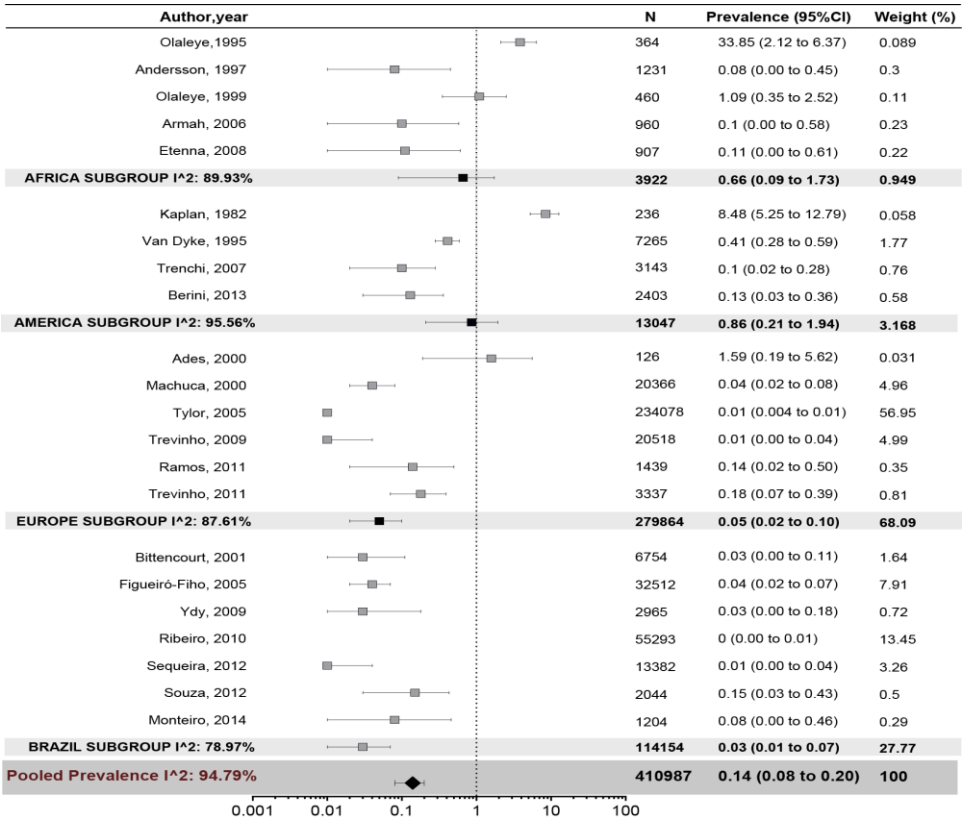

Figure 3. Forest Plot of HTLV-2 Prevalence in Pregnant Women

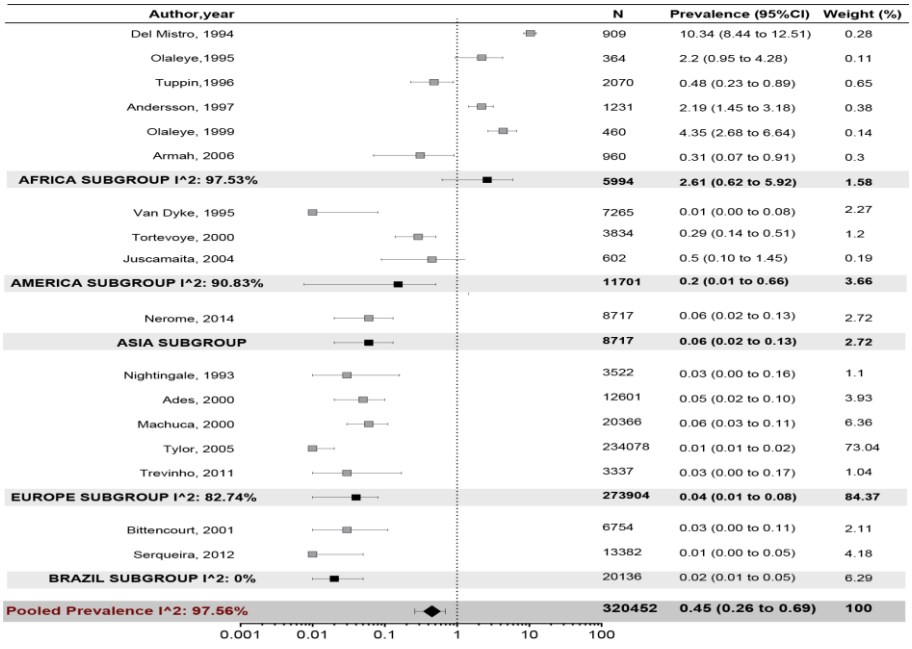

Figure 4. Forest Plot of HTLV-indeterminate WB prevalence in Pregnant Women

The estimated pooled prevalence of VT in 11.039 breastfed children was 14.1% (95%CI: 10.2-18.6) ranges from 12.2% in America to 16.1 % in Asia (Figure 5). This estimation was found in most studies conducted in the period 1990-2006, principally in Japan and Caribbean regions. Recent studies in Brazil[30] and Africa[31] estimated VT rate of 20.4% and 25.5% respectively, above the pooled prevalence.

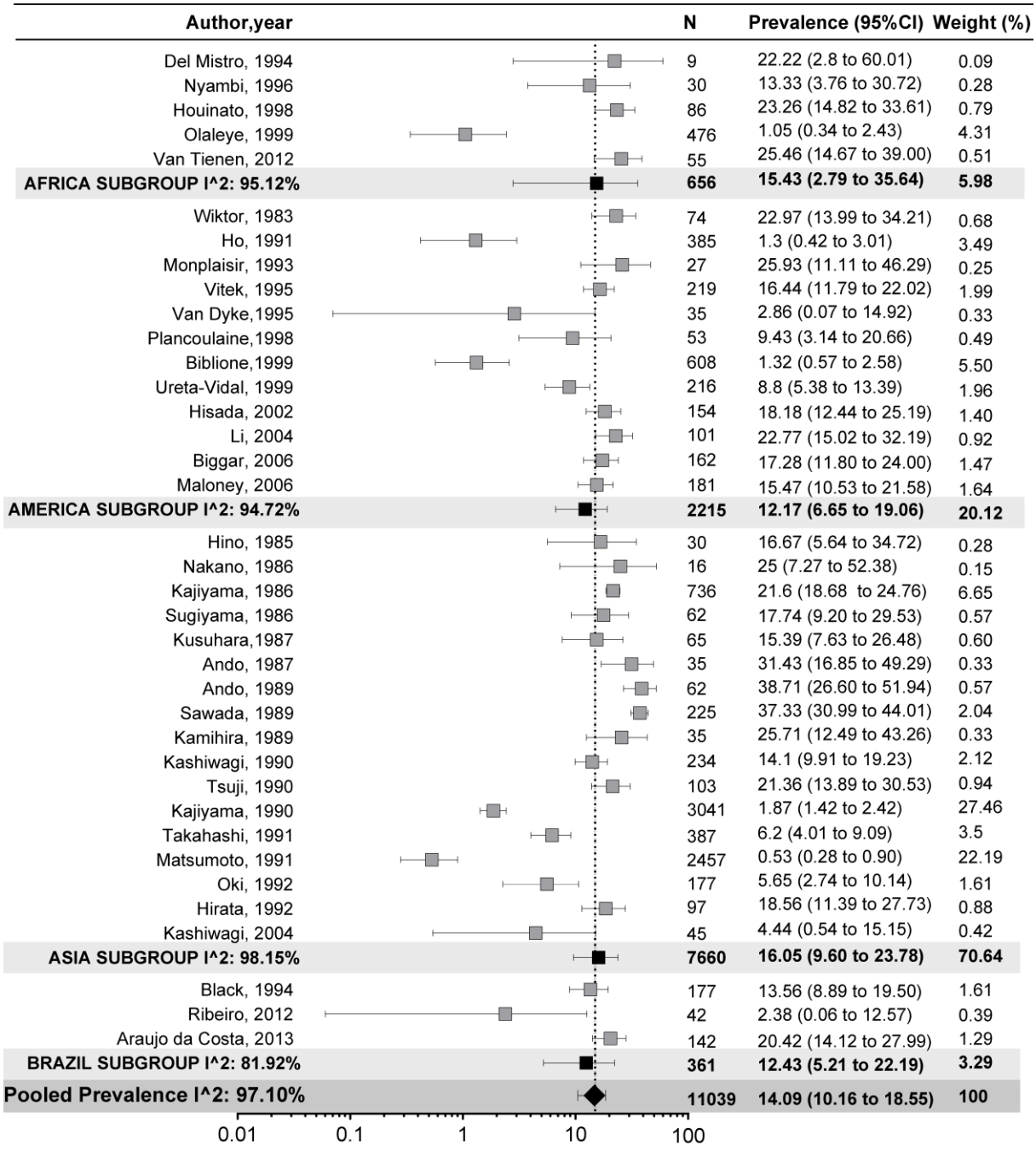

Figure 5. Forest Plot of Prevalence of HTLV among Breastfed Children

Figure 6 is a forest plot of the pooled prevalence of HTLV among non-breastfeed children, the pooled prevalence of VT was 4.4% (95% CI:3.3-6.0). The prevalence for the Asian and American subgroup was 5.9% (95%IC:4.4 -7.8) and 2.8 (95%IC:0.5-6.7), respectively. In Brazil, one study reported a high prevalence, but the sample number is very low, which can lead to overestimates[24] and in two studies, no infected children were found.

The pooled prevalence in non-breastfeed children was 3 times lower than the pooled prevalence in breastfeed children (4.44% vs 14.1%). No recent studies were found.

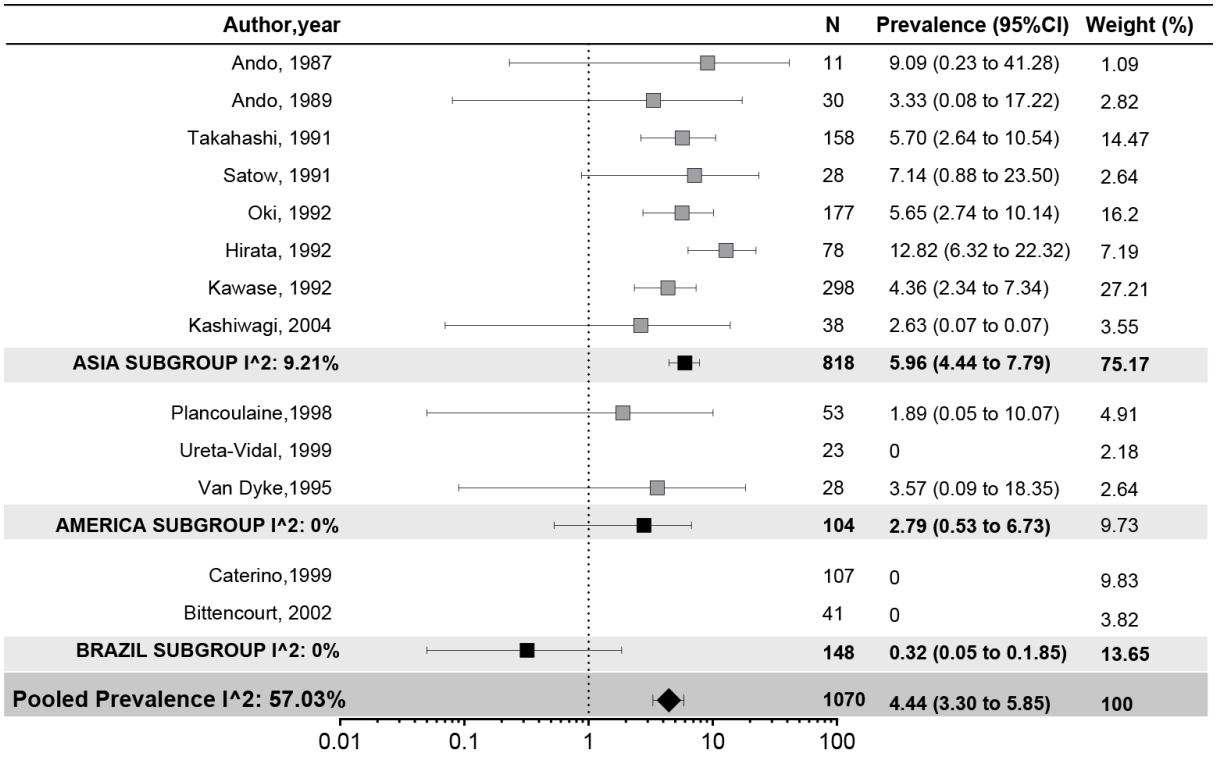

Figure 6. Forest Plot of HTLV Prevalence among Non-Breastfed Children

Associated Factors and Fetal Outcomes of the HTLV Infection

The associated factors with the HTLV seropositivity in pregnant women and their children were analyzed in 20 studies. Of those, the studies in Japan and Jamaica have shown immunological markers associated with the VT, whereas the sociodemographic characteristics have been described in Brazilian studies. Only 3 studies reported fetal outcome (Table 3).

The meta-analysis of specific data for associated factors was not performed because the studies did not have the necessary data for all the mothers and the children involved in the study. It was also noted that different units of measurement, were being applied within the data that was collected.

Twelve studies reported that immunological factors in both asymptomatic and symptomatic pregnant women increased o risk the VT. The reasons for the same are associated with the presence of high antibody titers against specific HTLV proteins (*tax*, *env*, and *gap*) [2-10,28,32], and HTLV proviral load in peripheral blood mononuclear cells[3-5,15,17] and in the breast milk[15-17 33,34]. The regulatory protein Tax ($p40^{tax}$) is encoded by the HTLV RNA genome[1-3] and is important for the complete viral replication and transformation of HTLV[7] infected cells by activating the transcription of the long repeat sequences (LTRs). Levels of antibodies against this protein (anti-$p40^{tax}$) in seropositive pregnant women may contribute to the development of tax-specific antibodies in children[1-3,6,28,32] and to the infection of up to 50% of children[4,6-7, 35]. The anti-$p40^{tax}$ levels in children are elevated from 24% at 6 months after infection to 80% at 2 years of follow-up[3]. In other studies, either the presence of anti-p40tax was not an independent risk factor for vertical transmission (OR 1.8, CI 0.57-5.8)[13], or serum-activity was low due to sequence variations in the immunogenic region of protein[8].

The high level of antibodies to envelope glycoprotein (gp46) is also associated VT with in long-term breastfeeding (> 6 months)[8,10]. However, there are other maternal antibodies on the external envelope of glycoproteins (Env1/5 and RE3) that appear to be cytotoxic and neutralizing; thereby, contributing to the protection against HTLV transmission in bottle-fed children[8] or in babies who are breastfed for less than 3 months[18]. This suggests a protective effect mediated by natural killer (NK) cell-inhibitory receptors and in the suppression of the immune response generated by the passive transfer of maternal antibodies, as with other viruses (Hepatitis B and Rubella).

Two studies related to the production of antigens concluded that the transmission of HTLV among mothers with high antigen levels was 10 times more than the mothers with low level (37.5% vs 3.2%)[36]. However, they do not provide clarity on the immunological effects that

control the production of antigens. Another author indicates that the production of HTLV antigens may not be correlated with the humoral immune response[37].

Maternal antibodies play an important role in the protection of HTLV exposed child during the few first months of the child´s life[2,9,28]. The transfer of these occurs in the prenatal period[9] and decreases in the next 3-6 months[6,11,28] followed by disappears after 6-9 months[9,14,38] or 24 months of age[12]. Studies suggest that, after the maternal antibody titers decline[13], the risk for HTLV infection in children increased at 6-7[9] or 9-18 months after birth[11].

In the studies analyzed, no specific cut-off point for the determination of the levels of anti-HTLV antibody titers was mentioned, which could aid in identifying the mothers and child who were infected. But the authors estimated these levels to be above 4.000 copies[39-41], 1:778632, >1280[42]. The estimated risk for VT from carrier mother to the child was between 2.2 (adjusted OR 2.2 10.-3.3) per quartile[40] and 3.2 (HR: 3.2 , CI 1.7-5.6) per $\log_{10}$ increase[41]. The differences in antibody titers in pregnant women suggest that there is a variable immune response and that the transmission can be produced by genetic condition in which T cells vary in replication[36]. Higher titers of neutralizing antibodies and anti sp peptide antibodies were still associated with a greater than twofold increased risk of transmission.

Similarly, high maternal viral load was associated with VT [15, 13]. Studies estimated an increased risk of VT using different points for levels of viral load: the risk ranged from 1.9 – 5.5% for each quartile increase in mother´s $\log_{10}$ proviral load[31, 33,40,41]. Studies estimated the risk for log titer as > 1:11 (RR 2.2; CI 1.3-8.5)[10], 1/2800 with risk ranging from 1.7 (OR, 1.7 per $\log_2$ titers, 95% CI: 1.2-2.4)[5] to 3.4 (OR, 3.4 per quartile, CI 1.5-7.5)[13] for viral load between 271 copies/10.000 cells[12] and 500 copies/cell[5,13,42]. Additionally, the high anti-HTLV-1 antibody titer in pregnant women was correlated with a high provirus load (P 5=0.0003, r = 0.41)[40,42].

The proviral load in breast milk was found to be 73%[15] and 89%[16] by amplification of the HTLV DNA, and was a strong predictor of VT[42] (RR = 2.38 per log10 95% CI, 1.09-5.22). Li[33] demonstrated the strong correlation among viral load in peripheral cell with the viral load in breast milk (r=0.57 p< 0.001), which indicated that a load lower than 0.18% predicts a prevalence of 4.7 / 1000 people / month and a load of more than 1.5%, of 28.7 / 1000 people / month1[5], regardless of the duration of breastfeeding.

Provirus load increased to 0.25 $\log_{10}$ units in children with high antibody titers and to 0.32 $\log_{10}$ those with anti- Tax antibodies and eczema[32].

Since the 1980s, breastfeeding has been strongly associated with the vertical transmission of HTLV[39] demonstrated a reduction in the prevalence of HTLV in children, from 20% to 2.5%, after the non-breastfeeding measure was taken by HTLV mothers who were seropositive. A

longer duration of breastfeeding was associated as an independent factor with regards to the seropositivity of HTLV in children[8]. Authors found positive cases in children breastfed for> 3 months[2,7],> 6 months[10],> 7 months[9, 38], between 6[1] and 12 months[13,28] and > 12 months with (OR 3.4 CI 95% 1.5-7.5) [13]. It was also observed that there is no difference in the rates between children who are not breastfed and children who had been breastfed <6 months[9-10]. Studies in Jamaica estimated a 2.5-fold increased risk in breastfed babies for a breastfeed duration that is longer than six months[10, 15], the transmission rate was 32% in children breastfed for 12 months compared with 9% for shorter periods of breastfeeding[10].

The existence of HTLV infection in non-breastfed children suggests that there is another mechanism of vertical transmission by routes other than transmission via breast milk[2,24]. Studies report the detection of HTLV antigen in blood found in the umbilical cord (approximately 7%) by the IF[19, 20] or by PCR[21, 24, 25], but others authors had different results either because they did not find antigens in the same[14,15, 22,23, 28,43,44] or because they do not find seroconversion after 24 to 48 months upon birth of the HTLV exposed children[24,25]. A study of non-breastfed children found 100% vertical transmission, with a possible route via of transplacental or intrapartum infection. 75% of the babies were vaginal delivery; thus increasing the probability of greater micro-transfusion of blood from mother to fetus, and transmission during birth through a contaminated birth canal. However, the sample number for the above mentioned study was low[24].

The studies also reported high mother to child transmission between phylogenetic groups and groups with genetic predisposition. The molecular variation of HTLV is minimal. As a reason, studies between family clusters have allowed the identification of migrations of infected populations or phylogenetic groups, among which the spread of virus has been silent and prolonged. In Gabon (Etenna et.al)[45], a study showed that subtype B or Central African ground in the general population is present in pregnant women and their offspring. In Brazil, studies in Kayapo indigenous pregnant women in Vila Kararao indicated the presence of HTLV-2 subtype C and in the indigenous population in Pará the HTLV-2 subtype A[46]. Magalhaes et al[25]. described transcontinental A subgroup cosmopolitan subtype A, similarly found in Caribbean indigenous Moir Marron and indigenous of West of Africa[20]. In Panamá, it has been identified in the Guaymi Indians[47].

In French Guianese children of African origin, it was observed that there is a genetic predisposition for being affected by the 6q27 chromosome in HTLV transmission. The study described the need for a mapping of 6q27 region linkage disequilibrium to identify the

polymorphisms associated with predisposition to HTLV infection in the 1.5% of the population[26].

The risk of transmission through breastfeeding increases by 1.75 times with each increase in the concordance of 3 to 6 types of human leukocyte antigen (HLA) class I haplotypes, as observed for HIV[18]. Studies have observed that the presence of HLA antigens in lymphocytes activates the NK inhibitory receptors and suppresses the immune system response. Van Tienen et al.[31] identified identical LTR sequences between mothers and children.

Others studies informed that there is a possibility that HTLV may be transmitted from mothers to breastfed infants through the oropharynx or intestinal tract, because the digestive tract is enriched with lymphoid cells and M cells, which are targets of HTLV[11]. Otherwise, lymphocytes transmitted through breast milk survive the destruction caused by gastric digestion due to rapid transit through the stomach and the alkaline pH of breast milk, which neutralizes the effects of stomach acids[18].

The sociodemographic characteristics of carrier mother were evaluated principally in Brazilian studies. Pregnant women with age > 30, face a risk factor of 5.2 (adjusted OR 5.2 1.8-19.3)[48] for TV. Another study estimated the same, but no significant difference was found.

The mean age for a child to be affected by the HTLV infection was estimated to be 14 months. A status married of pregnant women is estimated to be associated with a risk factor of 2.2 (OR 2.2, 1.14-4.32)[5] to 7.0 (adjusted OR 7.0, 1.8-66.8) [8]. Some differences were noted in the study conducted by Mello[26], which estimates the risk factor for single individuals to be 7.99 (OR 7.99 1.07-59.3). Lower maternal income had a significant influence on VT[5, 33, 40, 41] with risk of 2.72 (RR=2.72, 1.34-5.50 per quartile)[33] at 3.27 (OR 3.27, 1.04-10.64)[5].

Few studies evaluated the fetal outcome of HTLV maternal infection. There was no significant difference between weight and gestational age in the studied children and no results of placental changes or perinatal mortality were reported. Some studies reported higher serum-prevalence of HTLV in females (OR 2.7, CI 1.3-5.7)[5]. In Peru, the history of abortion was associated with the high prevalence of HTLV in pregnant women[25]. One study reported that 6.7% of the pregnant women who had an abortion (all in the first trimester of gestation) were affected by HTLV, 26.5% reported a history of spontaneous abortions and 31.7% presented more than two abortions.

Studies registered that the interventions and health policies to prevent the spread of HTLV from mother to child were applied in a varied and isolated way. The preventive actions in each country depended on the level of development of the same. Among these measures, the most

noted one was the screening and orientation of pregnant women for the suspension of breastfeeding.

These measures have been implemented in Japan since 1987 in the prevention program for HTLV infection in the general population[8]. In African countries, the above measures are not done across the population, as non-breastfeeding can have an adverse effect due to the high probability of malnutrition and other infections[2]. In Europe, actions are selectively directed at the at-risk population, so the pregnant women who receive screening are those with a history of drug use, sexually transmitted diseases, sex workers or immigrants from endemic areas[21].

Some studies describe the need for obstetrical interventions such as cesarean delivery as a method to reduce transmission[5]. Other studies suggest that at the time of delivery, gynecologists need to take steps to ensure that newborns do not swallow maternal blood[1]. Hisada[13] proposed that reducing maternal viral load or maintaining the level of passive antibodies in the infant could reduce vertical transmission during breastfeeding.

Risk of bias between the studies

The funnel plots and Egger`s test were used to evaluate the risk of bias between the studies (Figures 7,8 and 9). No evidence of publication bias was observed. Articles with less than 20 sample sizes, were excluded because they were affecting the robustness of the results.

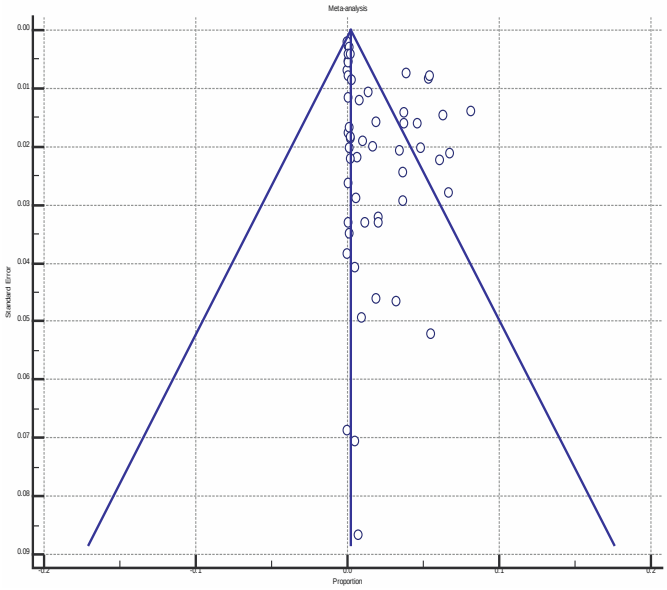

Figure 7. Funnel plot studies with HTLV-1 prevalence in pregnant women

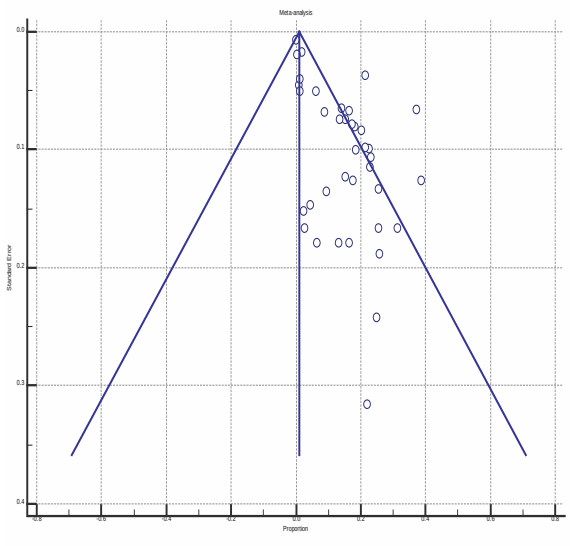

Figure 8. Funnel plot prevalence of HTLV among breastfed children

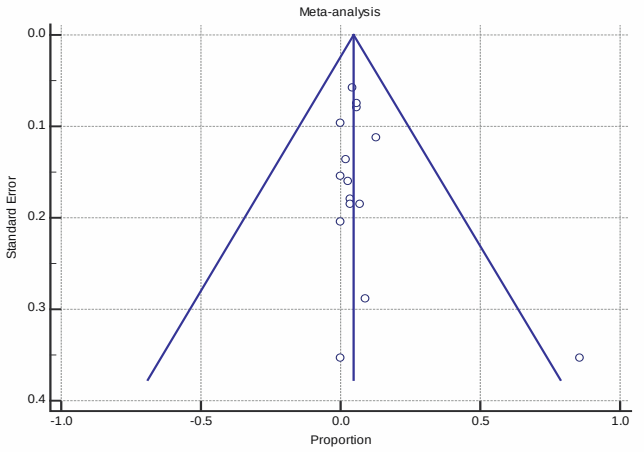

Figure 9. Funnel plot prevalence of HTLV among non- breastfed children

Discussion

We conducted a systematic review and meta-analysis on 82 studies that were chosen for our research. The pooled prevalence of maternal HTLV-1 was 1.3% (95%CI: 2.9-3.2) and vertical transmission rate in breastfed children was 14.1% (95%CI: 10.2-18.6) and in non-breastfed children was 4.4% (95%CI: 3.3-6.0). The associated factors with increases the risk of VT were: high immunological markers in the HTLV carrier (the mother) and her breast milk, breastfeeding > 6 months, genetic predisposition and sociodemographic factors with maternal age > 30 years and lower maternal income. Few studies that evaluated the fetal outcome of HTLV maternal infection showed higher positive rate in newborn females and women with a history of abortion. More studies were necessary to confirm the above mentioned results.

The prevalence of HTLV infection in pregnant women was different for both within the same country and in different countries considered for the study. The prevalence rate varied from 0.1% to 4.9%, with the rates being higher in Japan and lower in Europa. We observed that the maternal HTLV rate decrease from 1980s to 2016, leading us to think that the prevalence of the carrier state of pregnant women has decreased. It was observed that the geographical distribution of HTLV infection in the study group was wide, finding infection in non-endemic areas such as European countries. This may be due to the migration of populations at risk and the absence of measures to prevent the spread of infection. In addition to the previous social factor, sexual behaviors and cultural risk practices, as well as poverty may contribute to the distribution of maternal HTLV[49].

The seroprevalence of indeterminate cases was similar compared to HTLV 2. Studies described that the reason for this prevalence remains unclear. One possibility may be due to the cross-reactivity of the present epitopes or a reaction caused by an immune response to retroviruses, or by patterns that correspond to an HTLV seroconversion. Proipieti shows that there is a phenomenon of false positives, as mentioned in African studies, and has been attributed to possible cross-reaction with malaria antigens.

Additionally, the prevalence of HTLV in pregnant women could help estimate the prevalence in the general population. Different authors of the studies included in the review showed that the prevalence of HTLV infection was higher in pregnant women than in drug users and blood donors (as blood donors are usually tested and thereby considered to be low risk). The high prevalence of HTLV in pregnant women than in donors was noted as being 50 times higher in Spain[21], 40 times higher in Brazil[24] and up to 6 times higher in the United Kingdom[23]. In Argentina, the prevalence was 10 times higher in pregnant women than in donors[27]. Though, the prevalence rate was noted as being different in Japan, where the rate was similar for pregnant women and blood donors.

The studies showed that vertical transmission is the main route of HTLV infection among the population in Japan. In the Caribbean and in Brazil, both vertical and horizontal routes are frequent. In Africa, the main route of infection in the general population is controversial; Liu concluded that vertical transmission is the most frequent, while Bissau found that vertical transmission does not contribute significantly to the prevalence of the virus. According to Fox, the serodiscordance between African mothers and children leads us to think that the horizontal transmission is the predominant way of transmission of HTLV in children. This is because children with other diseases, such as malaria, are exposed to blood transfusions, to the application of medicines by unqualified people, and to the practice of reusing contaminated medical instruments. They are also exposed to some cultural practices which include the use of non-sterilized instruments of corporal scarification and to the practice of children are raised by a wet nurse. Additionally, these children are exposed to infected animals.

The estimation of global vertical HTLV-1 transmission rate in breastfed children was high (14.1%) compared to non-breastfed children (4.4%). This rate in Japan and Caribbean was reduced either by the absence of breastfeeding or by reducing the time of breastfeeding. In Brazil, studies related HTLV spread to vertical transmission. The studies in a family cluster observed a transmission rate of 20.4% from mother to child in Pará State (mostly for HTLV-2)[30]. The HTLV interfamily transmission rate was 32.5%[26] in Bahia state. Ribeiro found a vertical transmission rate of 2.4% in some children breastfeed for a period of 7 days. It was

observed that HTLV-2 was present in a few of the studied regions, since this type of virus occurs more frequently in several American Indian tribes and pygmies in Central Africa[21] and among drug users residing in North America[22] and in Europe[23].

Despite the demographic, socioeconomic and cultural differences in the studied regions, the prevalence of vertical transmission was similar in endemic countries (Jamaica, Japan), suggesting that these factors are less frequently associated with vertical transmission, but influence the prevalence of infection in women during their reproductive years.

Studies estimate that in pregnant women older than 30 years, age is one of the independent factors for HTLV seropositivity, indicating that sexual contact has been the main route for the dissemination of the virus in these women[5,10, 22,25,26]. In the United Kingdom, women over 35 years of age and from the Caribbean have a relative risk of 2.9 (95% CI: 1.2-7.1) of vertical transmission[22].

Results from individual studies showed that immunological markers: high antibody titers against specific HTLV proteins and HTLV proviral load in peripheral blood mononuclear cells and in the breast milk, increased the risk of VT. Nevertheless, with regards to the reasons as to why HTLV-I transmission from mother to child only occurs in a certain proportion of breastfed children, more studies need to focus on the immune response of children. Percher proposes to focus research on the role of the duration of breastfeeding and the response of the immune system of children exposed to HTLV by different routes. Alarcon[48] proposes the analysis of the evolution of clones infected with HTLV, direct measurement of the cytotoxic response of T-lymphocytes against tax and the measurement of replication virus in these children in relation to the viral markers of HTLV. Another authors proposes determine if genetic factors influence the in the levels of viral load or antibody titer, which are effective for the transmission[50].

The combination of in vivo / in vitro studies also allows us to delineate the role of factors such as the components of milk (for example, lactoperoxidase), the proviral loading, and the antibody titer in HTLV-1 transport through the intestinal epithelium.

Fujino's systematic review[51] shows that the study by Kazi et al., 1998, analyzed cord blood samples by short PCR for the gag and pX regions and by nested long PCRs directed for the gag-pX, gag-pol and pol-pX regions and found additional bands smaller than the predicted sizes, concluding that the HTLV-1 provirus in cord blood is usually defective.

Additionally, the difference in HTLV-1 infection rates between placenta and umbilical cord blood samples suggest that there is a placental barrier system against HTLV-1 transmission from the mother to the fetus.

Although the studies in this systematic review did not examine the route of HTLV transmission through the saliva, Fujino[51] and Percher[52] observed that there are few studies that demonstrate direct evidence for this route.

The results presented provide a broad knowledge of the prevalence and risk factors associated with vertical transmission. It is important to detect carriers of the virus in at-risk populations, identify risk factors in women of reproductive age and promote practices and policies that reduce exposure to the virus and the additional risks throughout the population.

Limitations

Our review included an extensive literature search of four databases without restrictions over time and with specific criteria for inclusion and quality. However, the data available in original studies were limited due to the use of different measurements, statistical analysis and different cut-offs for antibody levels and viral load interpretation. This variation made it difficult to interpret and compare the studies pertaining to the risk factors of vertical transmission. However a qualitative analysis of the data was performed.

Our research on the geographical distribution of HTLV maternal infection was influenced by the greater number of studies in endemic areas. We found fewer studies for non-endemic areas because of the absence of quality publications, publication language or the complete absence of studies in some of these areas.

In the studies analyzed, the estimation of the HTLV vertical transmission rate could have generated controversial results; mainly in the studies of family groups due to the use of different diagnostic tests and interpretations in the results. Another reason was the virological characteristics of the virus and the immune response in the newborn.

Conclusions

It is evident from the above mentioned literature that there is a heterogeneity in the prevalence of HTLV-1 and HTLV-2 infection among pregnant women and children in different geographic regions. The studies analyzed allowed us to know the reasons as to why there is still a high rate of vertical transmission in children born to HTLV seropositive mothers, despite taking preventive measures such as not breastfeeding. The high rate of HTLV infection in women of childbearing age, the lack of screening in all pregnant women or the evaluation of immunological markers in infected pregnant women, and the social changes with high migration of the populations at risk are factors for the persistence of the spread of HTLV virus.

There is a lack of follow-up research that allows the analysis of the gestational outcomes, the immunological and genetic markers specific to the pregnant woman that could help perform a timely intervention in order to prevent of vertical transmission.

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Appendix 1: Table 2. Main studies characteristics and quality of included studies (Newcastle-Ottawa Scale, NOS)

	FIRST AUTHOR, PUBLICATION YEAR	LOCATION	YEAR OF STUDY	STUDY DESIGN	CONFIRMATION TEST	SAMPLE SIZE (N)	POPULATION	HTLV-1, % (n)	HTLV-2, % (n)	SELECTION	COMPARABILITY	OUTCOMES ASSESSMENT	TOTAL QUALITY SCORE
1	Ades, 2000[53]	North Thames/UK	1986	Cross-sectional	Immunoblotting	126010	Pregnant Women	0.05 (59)	0.002 (2)	**	*	**	5
2	Alarcon, 2006[48]	Lima/Peru	1996-1997	Cross-sectional	WB	2492	Pregnant Women	1.7 (42)	_	****	**	**	8
3	Ando, 1993[54]	Okinawa/Japan	1985- 1993	Cross-sectional	IF	2003	Pregnant Women	6.09 (122)	_	***		***	6
4	Ando, 1987[55]	Okinawa/Japan	1983-1985	Cross-sectional	IF	2232	Pregnant Women	6.8(151)	_	****			4
				Cohort	cultured cell	24 11	Breast fed children bottle-fed children	46.0 (11) 9.0 (1)	_	***		**	5
5	Ando Y,1989[56]	Okinawa/Japan	1986-1988	Cross-sectional	IF	4641	Pregnant Women	6.3(293)	_	****		**	6
				Cohort	IF	30	bottle-fed children	3.0 (1)	_	**		**	4
6	Araujo da Costa, 2013[30]	Pará/ Brazil	2007-2010	Cross-sectional	PCR / RFLP	142	mother-child pairs	20 (29)	_	***	*	**	6
7	Armah, 2006[57]	Ghana/Africa	2003	Cross-sectional	WB	960	Pregnant Women	2.1 (20)	0.1 (1)	***		**	5
8	Berini, 2013[23]	5 regions/Argentina	2005-2009	Cross-sectional	WB - PCR	2403	Pregnant Women	0.1 (3)	0.1 (3)	****		**	6
9	Biggar, 2006[41]	Jamaica/Caribbean	1989 -1990	Cohort	WB	162	Breast fed children	17.3 (28)	_	***		***	6
10	Biglione, 1999[58]	Formosa /Argentina	1992-1993	Cross-sectional	PA - WB	608	children Matacos and Tobas Amerindians	_	1.3 (8)	****		**	6
11	Bittencourt, 2001[5]	Salvador,Bahia/Brazil	1996-1998	Cross-sectional and Case-control	WB/ PCR	6754	Parturient	0.84 (57)	0.03 (2)	****	**	**	8
12	Bittencourt, 2002[6]	Salvador,Bahia/Brazil	1998	Cross-sectional	PCR	41	bottle-fed children	0	_	**	*	***	6
13	Black, 1994[46]	Pará/ Brazil	1970-1991	Cross-sectional	WB	177	familial aggregation	_	13.5 (24)	****		**	6
14	Broutet, 1996[59]	Fortaleza/Brazil	1993-1994	Cross-sectional	WB	814	Pregnant Women	0.1 (1)	0.1 (1)	***		**	5
15	Caterino, 1999[60]	São Paulo/Brazil	1990 -1993	Case-control	WB	107	Bottle-fed children born to HIV-1 infected mother	0		**	*	*	4
16	Delaporte, 1995[61]	Zaire/Africa	1990	Cross-sectional	WB	1160	Pregnant Women	3.7 (43)		***		**	5
17	Del Mistro, 1994[62]	Gambia/Africa	1992	Cohort	WB		par mae criança			***		**	5

Table 2. (Continued)

	FIRST AUTHOR, PUBLICATION YEAR	LOCATION	YEAR OF STUDY	STUDY DESIGN	CONFIRMATION TEST	SAMPLE SIZE (N)	POPULATION	HTLV-1, % (n)	HTLV-2, % (n)	SELECTION	COMPARABILITY	OUTCOMES ASSESSMENT	TOTAL QUALITY SCORE
18	Etenna 2008[45]	Gabon/Africa	2005	Cross-sectional	WB	907	Pregnant Women	0.5 (19)		***	*	***	7
19	Fabbro, 2008[63]	Campo Grande/Brazil	2005	Cross-sectional	WB-PCR	116,689	Pregnant Women	0.1 (153)	0.02 (19)	****		***	7
20	Figueiro-Filho,2005[24]	Mato Grosso do Sul/ Brazil	2002 -2003	Cross-sectional	WB- PCR	32512	Pregnant Women	0.05 (15)	0.04(14)	***	*	**	6
						7	Bottle-fed children	85.5 (6)	_				
21	Hino, 1985[14]	Nagasaki/Japan	1976 -1981	Cross-sectional	IF	5015	Pregnant Women	3.7 (187)	_	****		**	6
						30	Breast fed children	17.0 (5)	_				
22	Hino, 1995[39]	Nagasaki/Japan	1987 -1992	Case-control	WB	889	Pregnant Women			****		**	6
23	Hirata,1992[64]	Ishigaki/Okinawa/Japan	1986 -1991	Cohort	WB	175	Bottle-fed children	12.5 (10/78)	_	****		**	6
							Breast fed children	18.6 (18/97)	_				
24	Hisada,2002[40]	Jamaica/ Caribbean	1989-1990	Cohort	WB	154	Breast fed children	18 (28)	_	****	*	***	8
25	Ho, 1991[65]	Hawaii/USA	1987 -1988	Cohort	WB	385	Breast fed children	1.3 (5)	_	***	*	*	5
26	Houinato, 1998[66]	Benin/Africa	1989- 1990 and 1991-1995	Cohort	WB	86	cluster familiar	23.3 (20)	_	***		**	5
27	Juscamaita, 2004[67]	Ayacucho/Perú	2002-2003	Cross-sectional	INNOLIA	602	Pregnant Women	0,.5 (3)	_	***		**	5
28	Kajiyama, 1986[10]	Yaeyama/Japan	1986	Cross-sectional	IF	947	cluster familiar			****		**	6
29	Kajiyama, 1990[68]	Yaeyama/OkinawaJapan	1983- 1986	Cross-sectional	IF	3041	Breast fed children	1.9 (57)	_	****	*	**	7
30	Kamihira, 1989[69]	Nagasaki/Japan	1986 -1987	Cross-sectional	WB	35	cluster familiar	25.7 (9)	_	****		**	6
31	Kaplan, 1982[27]	USA	1986-1988	Cross-sectional	WB/RIPA/ PCR		Crianças	0		****		***	7
32	Kashiwagi, 1990[70]	Okinawa/Japan	1980-1988	Cross-sectional	IF/WB	234	Breast fed children	14.4 (33)	_	***	*	***	7
33	Kashiwagi, 2004[71]	Okinawa/Japan	1989-2000	Cross-sectional	WB	3837	Pregnant Women	4.6 (177)	_				
			1995-1999		WB	76	Bottle-fed children	3.2 (1/31)		***	*	***	7
							Breast fed children	4.4 (2/45)					
34	Katamine, 1994[72]	Nagasaki/Japan	1989 -1994	Cohort	PCR	7	Bottle-fed children	0	_	***	*	**	6

Table 2. (Continued)

	FIRST AUTHOR, PUBLICATION YEAR	LOCATION	YEAR OF STUDY	STUDY DESIGN	CONFIRMATION TEST	SAMPLE SIZE (N)	POPULATION	HTLV-1, % (n)	HTLV-2, % (n)	SELECTION	COMPARABILITY	OUTCOMES ASSESSMENT	TOTAL QUALITY SCORE
35	Kawase, 1992[73]	Nagasaki/Japan	1992	Cohort	PCR	298	Bottle-fed children	4.4 (13)	_	**	*	**	5
36	Kusuhara,1987[74]	Okinawa/Japan	1968-1983	Cross-sectional	IFI	65	Breast fed children	15.4 (10)	_	***	*	***	7
37	Li, 2004[33]	Jamaica/Caribbean	1989 -1999	Cohort	WB	101	Breast fed children	22.8 (23)	_	****	*	***	8
38	Machado Filho, 2010[75]	Amazonas/Brazil	2008	Cross-sectional	PCR	674	Pregnant Women	0	_	***	*	***	7
39	Machuca, 2000[29]	Spain	1996 -1999	Cross-sectional	WB - PCR	20366	Pregnant Women	0,01(2)	0,04(8)	****	*	***	8
40	Madden, 1987[76]	USA	1959 -1964	Case-control	IFI-WB	210	Pregnant Women	0	0	***	*	**	6
41	Magalhães,2008[25]	Cruz das Almas, Bahia/Brazil	2004-2005	Cross-sectional	WB	408	Pregnant Women	1.0 (4)	0	***		**	5
42	Maloney, 2006[32]	Jamaica/Caribbean	1989 - 1999	Cohort	PCR	181	Breast fed children	15.5 (28)	_	****	*	***	8
43	Mansuy, 1999[77]	Martinique Island/Caribbean	1995-1996	Cross-sectional	WB	467	Pregnant Women	1.9 (9)		***		***	6
44	Matsumoto,1991	Chiba,Iwate,Ishigaki Island/Japan	1990	Cross-sectional	WB	2457	cluster familiar	0.5 (13)	_	****			4
45	Melo, 2000[78]	Mozambique/Africa	1997	Cross-sectional	WB	132	Pregnant Women	0.7 (1)		***		**	5
46	Mello, 2014[26]	South of Bahia/Brazil	2008 -2010	Cross-sectional	WB - PCR	2766	Pregnant Women	1.1 (29)	_	***	*	***	7
47	Monplaisir,1993	Martinique Island/Caribbean	1987	Cross-sectional	WB	3970	Pregnant Women	1.9 (75)	_	****	*	**	7
48	Monteiro, 2014[79]	Rio de Janeiro/Brazil	2012 -2013	Cross-sectional	WB	1204	Pregnant Women	0.6 (7)	0.1 (1)	****	*	***	8
49	Moura, 2015[80]	Maceio/ Brazil	2007-2012	Cross-sectional	WB - PCR	54813	Pregnant Women	0.2 (118)	_	***	*	***	7
50	Nakano, 1986[81]	Okinawa/Japan	1983-1984	Cross-sectional Case-control	IFI	1269 16	Pregnant Women Breast fed children	6.7 (85) 25.0 (4)	_ _	****	*	**	7
51	Nerome,2014[82]	Kagoshima/Japan	2012	Cross-sectional	IFI-WB	8717	Pregnant Women	1.3 (122)	_	****		***	7
52	Nightingale,1993[83]	Birmingham/England	1990-1991	Cross-sectional	WB-RIPA	3522	Pregnant Women	0.1 (5)	_	***		**	5
53	Nyambi,1996[85]	Gabon/Africa	1987	Cohort	WB - PCR	30	Breast fed children	13.3 (4)	_	***	*	***	7
54	Okoye, 2014[19]	Nigeria/Africa	2010	Cross-sectional	WB	200	Pregnant Women	0.5 (1)	_	**		**	4
55	Olaleye, 1995	Idaban/Africa	1995	Cross-sectional	WB	364	Pregnant Women	5.4 (20)	3.8 (14)	***		**	5

Table 2. (Continued)

	FIRST AUTHOR, PUBLICATION YEAR	LOCATION	YEAR OF STUDY	STUDY DESIGN	CONFIRMATION TEST	SAMPLE SIZE (N)	POPULATION	HTLV-1, % (n)	HTLV-2, % (n)	SELECTION	COMPARABILITY	OUTCOMES ASSESSMENT	TOTAL QUALITY SCORE
56	Olaleye, 1999[18]	Nigeria/Africa	1993	Cross-sectional	WB	460 476	mother-child pairs Breast fed children	3.3 (15) 1.1 (5)	1.1 (5)	***	*	***	7
57	Olbrich-Neto, 2004[84]	Botucatu/Brazil	2003	Cross-sectional	WB	913	Pregnant Women	0,1 (1)		**		***	5
58	Oliveira, 2006[86]	Goiana/Brazil	2005	Cross-sectional	PCR	15484	Pregnant Women	0.1 (16)		***		**	5
59	Oki, 1992[38]	Kagoshima/Japan	1986-1991	Cross-sectional	IF	16283 207	Pregnant Women Breast fed children Bottle-fed children	5.4 (885) 6.7 (2/30) 5.6 (10/177)	– –	**** ****		*** ***	7 7
60	Plancoulaine, 1998[50]	French Guiana/Caribbean	1998	Cohort	IF- WB	53	cluster familiar	9.4 (5)		***	*	***	7
61	Ramos,2011[87]	Alicante/Spain	2006-2009	Cross-sectional	WB - PCR	1429	Pregnant Women	0.07 (1)	0.14 (2)	***	*	**	5
62	Ramos,2011[88]	Ethiopia/Africa	2008	Cross-sectional	WB	165	Pregnant Women	0	_	***		*	4
63	Ribeiro, 2010[89]	Minas Gerais/Brazil	2007	Cohort	PCR	42	Breast fed children	2.4 (1)	_	***	*	**	6
64	Satow, 1991[90]	Kaanto/Japan	1991	Cross-sectional	cultured cell	28	Bottle-fed children	7.1 (2)	_	***	*	***	7
65	Sawada,1989[91]	Nagasaki/Japan	1989	Cross-sectional	WB	225	mother-child pairs	37.2 (84)	_	***		**	5
66	Sequeira, 2012[92]	Pará/Brazil	2008	Cross-sectional	WB	13382	Pregnant Women	0.3 (39)	0.01 (1)	****			4
67	Souza, 2012[28]	São Luís/Brazil	2011	Cross-sectional		2044	Pregnant Women	0.2 (4)	0.2 (3)	****		**	5
68	Takahashi, 1991[93]	Kagoshima/Japan	1985-1990	Cohort	IFI	14537	Pregnant Women	5.4 (780)	_	****	*	**	7
69	Takezaki,1985[16]	Kyusyu/Japan	1985-1990	Cohort	IFI	5090	mother-child pairs	8.2 (415)	_	****	*	***	8
70	Taylor,2005[94]	Europa	2005	Cross-sectional	LIA - WB	234.078	Pregnant Women	0.03 (73)	0.01 (17)	****		**	6
71	Tortevoye, 2000[20]	French Guiana/Caribbean	1991-1997	Cross-sectional	WB	3834	Pregnant Women	3.8 (144)	0	****		***	7
72	Tosswill, 1990	London/England	1980	Cross-sectional	WB	2893	Pregnant Women	0.2 (6)		***		**	5
73	Trenchi, 2007[22]	Cordoba/Argentina	2000	Cohort	IF WB	3143	Pregnant Women	0.1 (3)	0.1 (3)	****		**	6
74	Treviño, 2009[95]	Spain	2006-2007	Cross-sectional	WB -PCR	20518	Pregnant Women	0	0.01 (2)	****			4
75	Trevino, 2011[86]	Spain	2009-2010	Cross-sectional	WB - PCR	3337	Pregnant Women	0	0.6 (6)	****		**	6
76	Tseliou,2006	Greece	1997-2005	Cross-sectional	WB- LINE		Pregnant Women			****			4

Table 2. (Continued)

	FIRST AUTHOR, PUBLICATION YEAR	LOCATION	YEAR OF STUDY	STUDY DESIGN	CONFIRMATION TEST	SAMPLE SIZE (N)	POPULATION	HTLV-1, % (n)	HTLV-2, % (n)	SELECTION	COMPARABILITY	OUTCOMES ASSESSMENT	TOTAL QUALITY SCORE
77	Tsuji,1990[97]	Nagasaki/Japan	1990	Cross-sectional	IF	18320	parturiente crianca	3.9(718)	_	****	*	***	8
78	Tuppin1996[98]	CongoAfrica	1992	Cross-sectional	WB	2070	cluster familiar	0.7 (14)	0	****		*	5
79	Umemoto,1994[35]	Kagoshima/Japan	1986-1992	Cross-sectional	antitax		par mae filho			***		**	5
80	Ureta-Vidal, 1999[42]	French Guyana/Caribbean	1991-1993	Cross-sectional	WB	216	mother-child pairs	8.8 (19)		***	*	***	7
81	Van Dyke, 1995[21].	USA	1990-1992	Cohort	WB-IF	35	mother-child pairs	2.9 (1)		****		**	6
82	Van Tienen, 2012[31]	Guiné Bissau/Africa	2011	Cross-sectional	PCR	55	Pregnant Women	25.5 (14)		***	*	***	7
83	Vitek, 1995	Panama	1995	Cross-sectional	WB	219	cluster familiar	16.4 (36)		***	*	***	7
84	Wiktor, 1993[99]	Jamaica/Caribbean	1983-1985	Cohort	WB	2.329	Parturient	3.5 (81)		****		**	6
85	Yamada, 2014[17]	Hokkaido/Japan	2013	Cross-sectional	WB PCR	33617	Pregnant Women	0.1 (34)		****		**	6
86	Ydy, 2009[100]	Cuiabá/Brazil	2008	Cross-sectional	WB	2965	Pregnant Women	0.2 (6)	0.1 (1)	***		**	5
87	Yoshinaga, 1995[36]	KyushuJapan	1988-1991	Cross-sectional	IF	1658	Parturient	3.7 (61)		****		**	6

WB: Western bloot. IF: Indirect immunofluorescence. PCR: Polymerase Chain Reaction
Score NOS: Low risk of bias: 6 or more. High risk of bias :5 or fewer

Table 3. Risk factor for vertical transmission of HTLV from included studies.

	Variable				Study
	Total	**HTLV + (%)**	**HTLV – (%)**	**Statistical Analysis**	**Author**
Sociodemografic					
Age (years) < 20	659	4		1	Alarcon, 2006[46]
20-30	1303	21		ADJUSTED OR: 2.8(1.0-9.9)	
> 30	530	17		ADJUSTED OR: 5.2(1.8-19.3)	
< 24		2 (25.0)	646(54.6)	p-value: 0.10	Monteiro,2014
>25		6 (75.0)	546(45.8)		
9-19		4(16.7)	718(26.3)	OR 1.0	Mello, 2014[26]
20-29		18(75.0)	1504(55.2)	2.15 (0.72-6.37)	
>30		2 (8.3)	504(18.5)	0.71(1.12-3.90)	
>30	2416	7	2409		Oliveira,2006
31-35	113	5		10 (11.7-87.8)	
>36	69	9		3.5 (4.37-28.3)	Armah, 2006
Education level <10		3(37.5)	425(35.5)	p-value:0.5	Monteiro, 2014
(years) >10		5(62.5)	767(64.1)		
>9 years	9058	6	9052	P < 0,05	Oliveira,2005
< 9 years	6426	10	6416		
Marital Status: single	355	1		1.0	Alarcón, 2006
Married or living to gether	2121	41		ADJUSTED OR: 7.0(1.8-66.8)	
Married		(49.0)	(31.9)	OR: 2.2 (1.14-4.32)	Bittencourt, 2001
Single		(51.0)	(68.0)		
Married		1 (4.2)	706 (25.8)	OR: 1.0	Mello, 2014[26]
Single/divorced/widow		23 (95.8)	2031 (74.2)	7.99 (1.07-59.3)	
Family income		(41.2)	(24.6)	OR: 3.27 (1.04-10.64)	Bittencourt, 2001
< 1mw – 1mw		(47.1)	(52.5)	1.75 (0.59-5.39)	
2mw – 5mw		(11.8)	(23.0)	-	
+ 5 mw					
Income, Jamaican					Biggar, 2006[41]
> 200		69	6	HR: 1.0	
101-200		57	12	2.2(0.8-5.9)	
<100		34	10	3.4(1.2-9.5)	
Income, Jamaican					Hisada,2002
< 100	32(21)	10(36)	22(18)	P value: 0.02	
101-200	55(37)	12(43)	43(36)	Adjusted OR: 3.0(1.4-6.3)	
>200	62(41)	6(21)	56(46)	Per tertile	
Lower maternal income				RR=2.72 (1.34-5.50) per quartile	Li, 2004
Number of sexual partners: > 2					
1-2		(50.0)	(27.8)	OR: 2.58 (1.32-5.07)	Bittencourt, 2001
		(50.0)	(72.1)		
History Blood transfusion	109	6		ADJUSTED OR:2.6(0.9-6.1)	Alarcón,2006
		(11.5)	(3.3)	OR: 3.85 (1.03-14.3)	Bittencourt, 2001
Obstetrics					
Previous pregnancy					Alarcón, 2006
None	972	8		1.0	
One or more	1520	34		ADJUSTED OR: 2.8(1.5-5.5)	
Number of pregnancies <2		3(37.5)	728(69.7)		Monteiro, 2014
>2		5(62.5)	317(30.3)	p-value:0.06	
History abortion	729	23		ADJUSTED OR:2.0(1.0-3.8)	Alarcon, 2006[46]
Miscarriage <2	38.682	(0.2)		p-value: 0.04	
>2	2.557	(0.4)			
Mode delivery: Vaginal					Ribeiro
Age at first intercourse:					Alarcon, 2006[46]
>20	690			1.0	
<20	1797	5		ADJUSTED OR:2.9 (1,4-6,9)	
		37	1797		
Clinical					
Reported eczema like lesion		(15.6)	(0.85)	OR: 21.4 (2.54-179.3)	Bittencourt, 2001
Duration of breastfeeding, months				p-value: 0.001	Hisada, 2002
>12.0	64(43)	20(70)	44(36)	ADJUSTED OR: 1.0	

6.1-12.0	37(25)	6(22)	31(26)	2.4(0.39-14.8)	
< 6.0	48(32)	2(8)	46(38)	10.8(2.0-57.8)	
Duration of breastfeeding					
Short-term		(4.4)		RR=3.68, P value: 0.02	Takahashi, 1991
Long-term		(14.4)			
Longer duration of breastfeeding				RR:2.72(1.16-6.39) per tertile	Li, 2004
Provirus load in milk				RR= 1.98 (1.21-3-23)per quartile	
0.60-1.50	20(19.8)	8 (34.8)	12(15.4)	p-value: 0.01	
>1.50	17(16.8)	9(39.1)	8(10.3)		
Provirus load,					Hisada, 2002
<2.20	39(26)	3(11)	36(29)	p-value: 0.001	
2.20-3.10	39(26)	1	37(30)		
3.11-3.80	39(26)	7)	29(24)	ADJUSTED OR: 1.9(1.1-3.4) per	
>3.8	22(22)	10(36)	20(17)	quartile	
		13(46)			
Provirus load				RR=1.88 (1.05-3-38) per quartile	Li, 2004
2.00-8.00	22(21.8)	7(30.5)	15(19.2)	P value: 0.04	
> 8.00	21(20.8)	10(43.5)	11(14.1)		
< 500 copies	78	2(2.6)		P value: 0.004	Ureta-Vidal, 1999[42]
>500 copies	111	17 (15.3)			
Viral load					Biggar, 2006[41]
< 2.20	58	2			
2.20-3.10	50	10		HR: 2.6 (1.6-4.3) Per log_{10} increase	
>3.11	35	13			
Proviral load					
0.6-1.4	14	1 (7)			
1.5-2.4	11	5(45)		OR: 3.5 (1.6-7.7) per quartile	Van Tienen, 2012[31]
> 2.4	16	8(50)			
Antibody titer					Hino, 1995[39]
Long-feeding group		944 (80-11092)	385 (30-4966)	P value: < 0.001	
Log_2, maternal antibody	212	21 (9.9)		Adjusted OR: 2.2(1.4-3.6)	Ureta-Vidal, 1999[42]
HTLV-1 Antibody titer					Hisada, 2002
< 1000	36(24)	1(3)	35 (29)	P-VALUE: 0.001	
1000-4000	36(24)	3(11)	33(27)	ADJUSTED OR: 2.2(1.0-3.3) per	
4001-10.000	38(25)	10(36)	28 (23)	quartile.	
>10.000	40(27)	14(50)	26 (21)		
Antibodies					
< 1000	37	1			
1000-4000	38	3			Biggar, 2006[41]
4001-10.000	38	10		HR: 3.2 (1.7-5.6) Per log_{10} increase	
>10.000	42	14			
Antibody titer				RR: 1.05 (0.62-1.8) per quartile	Li, 2004
<1/320	81	1 (1.2)		P value: 0.001	Ureta Vidal, 1999[42]
1/640	48	5 (10.4)			
>1280	83	15 (18.1)			
$<log_{10}$, maternal proviral load					
	189	19(10.1)		Adjusted OR: 2.6(1.1-6.1)	
High antibody titer > 1:7786				Adjusted OR: 0.39 (-0.01-0.78)	Maloney, 2006[32]
HTLV-1 antigen producing mothers in peripheral blood mononuclear cell					
High		(9.6)		P value: <0.005	Yoshinaga, 1995[36]
Low		(0.6)			
In Breast milk mononuclear cells					
High	17	(10.2)		P value: <0.005	
Low	44	(0.3)			
$P40^{tax}$ antibody					Sawada, 1989
Positive	132	67(50.8)	65 (49.2)	P value: < 0.001	
Negative	93	17(18.3)	76 (91.7)		
Antitax p40					Hisada, 2002
Positive	79(53)	22(81)	57(47)	P value: 0.001	
Negative	70(47)	5(19)	65(53)	ADJUSTED OR: 1.7(0.46-6.3)	
Children of HTLV-1 seropositive				p-value: < 0.05	Kamihira, 1989
mother with anti-$p40^{tax}$	11	6 (54.5)			
Without anti-$p40^{tax}$	24	3 (12.5)			

Children of HTLV-1 seropositive				Umemoto, 1994[35]
women with anti $p40^{tax}$ positive	27	8 (29.6)	P value: < 0.05	
negative	37	3 (8.1)		
Tax-specific antibody positive			Adjusted OR: 0.56(0.15-0.98)	Maloney, 2006[32]
HLA clas I type concordance			HR: 1.0	Biggar, 2006[41]
3	93	12	1.8(0.8-4.0)	
4	53	12	2.8(0.8-9.9)	
5	12	3	4.1 (0.5-32.6)	
6	4	1		
Fetal outcome				
Pregnancy outcomes: stillbirths, miscarriages, maternal dealth				
Boys	107	6(5.6)	p-value: 0.04	Ureta-Vidal 1999[42]
Girls	109	15(13.8)	adjusted OR: 4.1(1.7-10.0)	
Boy	27	8(30)	OR: 1.0	Van Tienen, 2012[31]
Girl	28	6(21)	0.9(0.3-3.1)	
Abortion/miscarriages	134	5	ADJUSTED OR: 1.4(1.0-3.1)	Alarcon,2006[46]

Appendix 1: Search strategy

The search strategy was defined by the descriptors MeSH (Medical Subject Headings), DECs (Health Sciences Descriptors) or Emtree according to the database consulted.

Medline/Plubmed (MeSH):

((((Infectious disease transmission, vertical[MeSH] OR vertical transmission[tiab] OR mother and child transmission[tiab] OR HTLV vertical transmission[tiab] OR Childbirth infectio*[tiab])) OR (parturition[MeSH] OR pregnancy outcome[MeSH] OR delivery, obstetric[MeSH] OR Pregnant women[MeSH] OR Pregnancy Complications, Infectious[MeSH] OR childbirth[tiab] OR child[MeSH] OR Child, Preschool[MeSH] OR maternal HTLV infection[tiab])) AND (seroepidemiologic studies[MeSH] OR seroepidemiological study[tiab] OR seroprevalence[tiab] OR prevalence[tiab] OR prevalence[MeSH] OR maternal sérum screening tests[MeSH] OR serologic test[MeSH])) AND (HTLV[tiab] OR HTLV-1I Infections[MeSH] OR HTLV-1 Infections[MeSH] OR HTLV-1I Antigens[MeSH] OR HTLV-1 Antigens[MeSH] OR Human T-lymphotropic vírus*[tiab] OR HTLV-1[tiab] OR HTLV seroprevalence[tiab])

Lilacs/BIREME (DECs):

(tw:(transmissão vertical OR transmissão perinatal OR transmissão vertical de doença infecciosa)) OR (tw:(complicações infecciosas na gravidez OR gravidez OR criança OR recém-nascido OR parturient* OR gestantes OR pré-escolar OR parto)) AND (tw:(estudos soroepidemiológicos OR soroepidemiologia OR soroprevalência OR prevalência)) AND (tw:(vírus 1 linfotrópico t humano OR vírus 2 linfotrópico t humano OR infecções por HTLV-1 OR infecções por HTLV-1i))

EMBASE (Emtree):

Vertical transmission AND ('seroepidemiology'/de OR seroepidemiology OR 'hiv'/de OR HIV) AND test AND ('birth'/de OR birth OR 'pregnancy'/de OR pregnancy AND outcome OR 'delivery'/de OR delivery) AND [article]/lim AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND [humans]/lim AND [embase]/lim

4.METODOLOGIA

A metodologia do estudo da soroprevalência em parturientes dos retrovírus (HIV-HTLV) e vírus das Hepatites (B e C) está descrita no artigo Nº2. A metodologia do estudo dos casos de sífilis materna e congênita está descrita no artigo Nº3.

A continuação se apresenta a metodologia usada para avaliar as crianças menores de 10 anos expostas aos vírus estudados.

A população alvo são as crianças menores de 10 anos, filhas de mães soropositivas para HIV, HTLV-1 e 2, HBV e HCV atendidas em duas maternidades públicas de Salvador - Bahia, Brasil, Maternidade de Referência Professor José Maria Magalhães Neto (MRPJMMN) e Maternidade Climério de Oliveira (MCO). Estudo transversal com coleta de dados entre outubro de 2016 e junho de 2018. As parturientes com testes confirmatórios dos vírus estudados, foram convidadas a autorizar à coleta da amostra de sangue de seu filho nascido no período do estudo e dos filhos anteriores, com idades menores que 10 anos, para triagem sorológica para o vírus detectado.

Os testes laboratoriais usados para medir a transmissão vertical nas crianças menores de 10 anos das mães soropositivas foram realizados no LAPI. Para HIV e HCV foram realizadas as cargas virais. Para HBV foram realizadas medições dos antígenos de superfície da hepatite B.

O diagnóstico da infecção pelo HTLV-1/2 baseou-se na detecção inicial específica de anticorpos, por meio de Ensaios Imunoenzimáticos (ELISA) Wiener, disponíveis comercialmente, e subsequente confirmação das amostras reativas pela técnica da Reação em Cadeia da Polimerase (PCR).

Nova amostra de sangue com EDTA K_3 foi coletada de cada indivíduo para extração do DNA genômico, utilizando PURELINK GENOMIC DNA KIT da Invitrogen. O DNA amostral foi obtido através da lise pela proteinase *K,* conforme descrito no protocolo de extração do kit.

Qualitativamente amplificamos duas regiões *Tax* e *Pol*. Para isso, utilizamos um conjunto de *primers* Sk43/Sk44 e Tax1/Tax2 para amplificação do gene *tax*

(Heneine,1992) e para amplificação do gene *pol,* utilizamos os primers Sk110/Sk111 e POL 1.1/POL3.1 em uma PCR primária convencional e um Nested PCR (Heneine,1992; Tuke,1992). A reação de PCR foi realizada num volume total de 50 ul de mix constituído por 2,5 mM de $MgCl_2$, 0,4 mM de cada dNTP (Invitrogen), uma unidade de polimerase de ADN Taq (Invitrogen), 0,2 uM de cada iniciador (Kowok et al., 1988), tampão Taq 1x e 20 µl do produto.

A reação consistiu em uma desnaturação inicial a 94ºC por 10s, 30 ciclos de 94ºC durante 30s, 53ºC por 1 min e 72ºC durante 1 min, seguido de uma extensão final a 72ºC por 10 min em um termociclador Eppendorf. Todos os produtos da PCR foram submetidos à eletroforese em gel de agarose a 2% corado com SYBER Green para foto documentação na luz ultravioleta.

5. RESULTADOS

5.1. Soroprevalência dos retrovírus (HIV/HTLV) e vírus das hepatites (B/C) em parturientes. Artigo 2

ARTIGO ORIGINAL Nº 2

SEROPREVALENCE AND FACTORS ASSOCIATED WITH HIV / HTLV AND HEPATITIS B/C INFECTIONS IN PARTURIENT WOMEN OF SALVADOR, BAHIA

SEROPREVALENCE AND FACTORS ASSOCIATED WITH HIV / HTLV AND HEPATITIS B/C INFECTIONS IN PARTURIENT WOMEN OF SALVADOR, BAHIA

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ABSTRACT

BACKGROUND:The heterogeneity in detection rates of HIV/HTLV and Hepatitis B/C infections among pregnant women and the continuous exposure to risk factors limits the adoption of preventive and control actions. **OBJECTIVE:** To evaluate the HIV, HTLV, Hepatites B and C seroprevalence rates, and associated risk factors in parturient in Salvador, Brazil. **METHODS:** This is a cross-sectional study with 2,099 parturient attended in two public maternity hospitals in Salvador, Brazil. One blood sample for serological screening, and socio-demographic, obstetric and clinical data were collected. **RESULTS**: HIV seroprevalence rate was 1.5% (of which 0.6% were new cases); seroprevalence rates for HTLV, HBV and HCV were 0.4%, 0.4% and 0.1%, respectively. Univariate analysis showed a significant association between socio-demographic and behavioral factors and retroviral infections, while viral hepatitis was mainly associated with parenteral exposure. In a multivariate analysis, multiple sexual partners (OR 3.3 95% CI: 1.1-9.2), history of sexual/domestic violence (OR 2.8 95%

CI:1.1-6.9), syphilis coinfection (OR 2.6 95% CI 1.0-6.9), use of illicit substances (OR 2.5 95% CI 1.2-5.5) and low schooling level (OR 2.3 95% CI 1.1-4.9) were the independent risk factors for HIV infection. The history of stillbirth and low birth weight infants was significantly associated with HTLV positive status, showing a negative impact on gestation. **CONCLUSIONS:** The seroprevalence rates for HIV, HCV, HBV and HTLV-1 were similar to that found in previous studies in other Brazilian regions. Of the high individual and social vulnerability detected in seropositive parturient, indicate the need to improve the coverage and efficiency of preventive, detection and monitoring strategies.

KEYWORDS: Seroprevalence, Risk factors, Parturient, HIV, HTLV, Hepatitis B, and C.

INTRODUCTION

Serological screening for human retrovirus infections HIV-1 / Human T-Cell Lymphotropic Virus (HTLV 1/2) and Hepatitis B (HBV) / C (HCV) virus in pregnant women is essential for monitoring of vertical transmission (VT) of these infections. VT of such viral diseases is a serious public health problem associated with important morbimortality.

In Brazil, from 2007 to June 2017, 108,134 cases of pregnant women with HIV were reported, of which 16.8% dwelled in the Northeastern (NE) region, according to the Notifiable Diseases Information System (SINAN). In the same period, an increased detection rate of HIV-positive pregnant women was observed in NE region, from 1.2 to 2 cases per 1,000 live births (LB), which is lower than the national rate (2.7 cases per 1,000 LB) [1].

In the same region, 9.8% of Hepatitis B cases were reported in pregnant women. The detection rate of Hepatitis B virus infection in the period 2003-2016 showed a slight variation, with a drop in the last year to 0.2 cases per 1,000 LB, and the NE is the region with the lower rates that observed for the entire (0.4 cases per 1,000 LB). In the same period, the rate of detection

of hepatitis C cases showed an increasing trend in all Brazilian regions, 64.1% of cases were detected in the Southeastern, 24.5% in the South and 5.5% in the NE regions[2]. Regarding HTLV-1 infection rate, the city of Salvador, capital of the state of Bahia, shows a seroprevalence of 1.8% in the general population and 0.84% in pregnant women[3,4].

Although there is more comprehensive information on seroprevalence rates and epidemiological data regarding HIV-1, there is scarce data on the transmission of other potentially chronic viral infections (HTLV, HBV, and HCV) in Brazil. This study aims to evaluate the seroprevalence rates for these agents and the risk factors associated with their occurrence in parturient in Salvador, Bahia.

METHODS

Study population

The study population consisted of 2,099 parturients attended at two public maternity hospitals in Salvador-Bahia, Brazil: Maternidade de Referência Professor José Maria Magalhães Neto (MRPJMMN) and Maternidade Climério de Oliveira (MCO). The two institutions are the leading public maternity hospitals in the city of Salvador, the capital of the state of Bahia, located in the Brazilian NE region. According to the Live Births Information System (SINASC), during 2014, 45,992 live births were recorded in Salvador, with an estimated 3,833 births per month.

Study design and sampling

This is a cross-sectional study with data collection from April 2016 to June 2017. The sample size was calculated with an estimated mean prevalence of 0.7% of infections in pregnant women in Salvador, 80% power of detection of differences, 95% confidence interval, and an excess of 10% to cater for any losses.

Parturients who sought maternities MRPJMMN and MCO at birth and who agreed to participate in the research were included in the study, after signing the informed consent form. Mothers who were unable to provide answers were excluded.

One blood sample was collected for additional serology and an interview was conducted through a questionnaire about sociodemographic factors (age, marital status, schooling, occupation, ethnicity and data on risk behaviors and vulnerability conditions), obstetric factors (obstetric history, number of antenatal visit, hepatitis B vaccine), clinical/epidemiological factors (co-infections, time of diagnosis of infection, partner serological status) delivery/childbirth/puerperium factors (premature rupture of membranes, type of delivery, invasive methods, weight, gestational age and breastfeeding).

Serological tests

We used the laboratory tests of parturient's routine admission in the two maternities. Rapid tests were employed in the MRPJMMN (Abon Biopharm, Hangzhou, China) and the MCO (Alere Determine™ HIV1/2, Ireland) to detect HIV antibodies. The VIKIA® test (BioMérieux, Brazil) was adopted in both maternities for the qualitative identification of hepatitis B virus surface antigen. HCV screening was performed at the MCO using the Alere™ HCV test (Standard Diagnostic INC, Republic of Korea).

These two maternities do not perform HTLV screening as admission routine. HTLV and HCV serological were performed in the Infectious Diseases Research Laboratory (Laboratório de Pesquisa em Infectologia, LAPI). HTLV antibodies were detected using ELISA Recombinant v4.0 (Wiener lab., Argentina), and 3rd generation ELISA (Wiener lab., Argentina) was used for HCV. Positive results for infections were confirmed by Western blot (HTLV) or PCR (HCV).

Statistical analysis

The Statistical Package Social Sciences (SPSS) software, version 22, was used for statistical analysis. The significant level was set for values of $p<0.05$. Prevalence rates were calculated for each virus studied. The associations between categorical variables were assessed using univariate analysis, adopting Pearson's Chi-square test and the risk was expressed as Odds Ratio (OR) and 95% confidence interval. The comparisons of the continuous variables were made by the Student´s t-test or Mann Whitney, when applicable. A multiple logistic regression model was constructed by the stepwise method, with inclusion of variables with an estimated level of significance lower than 0.2, to evaluate the strength of association of the different factors with HIV seropositivity. Variables with significance level lower than 0.05 were maintained in the final model. The results were expressed as adjusted odds ratio (OR) and 95% confidence intervals.

Ethics Committee

The Institutional Research Ethics Committee of UFBA approved the study (report Nº 2.385.099 of September 12, 2015), and in the Climério de Oliveira Maternity Ethics Committee.

RESULTS

A total of 2,099 parturients, equivalent to 19.1% of the 10,965 deliveries attended at the MCO and MRPJMMN maternities during the collection period, were included in the study. Most of them (71.2%) lived in Salvador, had a mean age of 27.3 ± 6.9 years (range from 14 to 46 years), with a proportion of 6% of adolescents (<18 years). There was no significant difference between the characteristics of the participants in the two maternities. The sociodemographic profile of the study population is shown in Table 1. The women participants reported having had about

2.2± 1.5 pregnancies. Obstetric and clinical characteristics of the participating parturients are shown in Table 2.

Table 3 shows the results of the seroprevalence of viruses studied in maternity hospitals. Ten samples were reactive for HTLV antibodies (nine were confirmed by WB, 0.4%, 95% CI: 0.2-0.7), one patient had two negative HTLV serological tests results in another laboratory. One HTLV-positive patient was coinfected by HIV, and syphilis. Concerning HBV infection, reactive HBsAg test was detected in eight parturients (0.4%, 95% CI: 0.2-0.7), and nine parturients were positive for HCV serology of these, three tested negative in a second sample, and three parturients did not attend for a confirmatory test. Two participants had a positive HCV PCR and one had a negative PCR result. Hence, HCV seropositivity was 6/2099 (0.3%, 95% CI: 0.1-0.6) taking into account only the reactive ELISA, and of 0.1% (95% CI: 0.03-0.4) with PCR-RNA as confirmatory test.

The highest seroprevalence was observed for HIV infection (33/2099), with a prevalence per period of 1.5% (95% CI 1.1-2.1), consisting of a point prevalence of 0.9% of diagnosed cases before the current pregnancy, and 0.6% corresponding to the new confirmed cases in the collection period. No significant difference was found when comparing the characteristics of women with a previous diagnosis and women classified as newly diagnosed cases.

Univariate analysis showed a significant association between HIV or HTLV infection with deprivation of liberty, low family income, history of violence, four or more pregnancies and lack of antenatal care (Table 4). Among parturients with VIH were observed a high number of active syphilis infection cases (66%). Mean age, history of stillbirth and low birth weight showed significant difference between HTLV-positive/negative parturient.

Univariate analysis for the seroprevalence of Hepatitis B and C viruses indicated that there was a significant difference in the variables related to the parenteral exposure route. The logistic

regression model taking as result seropositivity for HTLV, HBV, and HCV was not performed due to the low number of reactive samples.

In the final multiple logistic regression model (Table 5), significantly odds of HIV positivity was seen among women with multiple sexual partners or a history of domestic violence (OR 3.3 95% CI: 1.1-9.2 and OR 2.8 95% CI: 1.1-6.9). HIV infection was also associated with syphilis coinfection (OR 2.6 95% CI: 1.0-6.9), use of illicit substances (OR 2.5 95% CI: 1.2-5.5) and low schooling (OR 2.3 95% CI: 1.1-4.9).

DISCUSSION

In this study, seroprevalence in parturients in the MCO and MRPJMMN maternity hospitals in Salvador was 1.5% for HIV and 0.4% for HTLV, and 0.4% and 0.1 % for hepatitis B and C viruses, respectively. We observed a high proportion of women with a previous diagnostic of HIV and sociodemographic and behavioral risk factors that increase HIV/AIDS and other STDs in a context of vulnerability. Additionally, we observed that the presence of HTLV infection in the gestational period has a significant relationship with the occurrence of a history of stillbirths and low birth weight infants.

The mean age (27.6 years) of the study population is above the national average of pregnant women (25.7)[5]. There was a statistically significant difference in the ages of HTLV-infected women (34.3 vs. 27.2, p=0.04) suggesting that the HTLV transmission route in this population is due to sexual exposure, as already shown in previous studies. The same increase in mean age was observed in HIV-positive parturients (29.1) and hepatitis B (29.1) and C (30.9) viruses, but without statistical significance.

Seroprevalence for HIV (1.5%) was high in the study, compared to the result (0.8%) obtained by Nóbrega et al.[6] in a study conducted in the city of Salvador in 2009, which recorded a 61.4%

frequency of diagnosis during antenatal period or at delivery. Our study, on the other hand, found a high proportion (64%) of HIV cases diagnosed before the current pregnancy, indicating that more women living with HIV are becoming pregnant. This was also observed in a National study[5] and in a study with pregnant women from São Paulo in 2010[7].

Considering only new cases (0.6%), this study detected a higher HIV rate in pregnant women (6 cases per 1,000 LB), than that found in a similar population in Salvador (2.9 to 2.7 cases per 1,000, with a peak of 3.7 in 2012) from 2003 to 2014[8]. In this context, published reports show HIV prevalence rates of 0.3% for pregnant women[9-19] and 1.2% for parturients[5,20-24] in Brazil since 2000, that varies by population and region, despite national studies[5,25] showing the same prevalence (0.4%) for both groups.

Our results indicate a high HIV prevalence in women with socioeconomic and behavioral vulnerabilities. Similar results were described by Santos[26] in 2005. Other authors also found independent HIV risk factors in women with sexual risk behaviors (low adherence to condom use, multiple sexual partnerships[27] and use of illicit drugs[28]) and in those with situations of social vulnerability (victims of domestic violence[4,27] and low schooling[5-6,21-24]). Our findings demonstrate the persistence of the same vulnerability pattern for HIV infection in women. The significant association between poorer antenatal care for HIV-infected women than that observed for seronegative ones reinforces the role of access to healthcare information and adherence to preventive actions as vulnerability markers.

Domingues et al[5] showed that HIV infection is associated with syphilis infection (adjusted OR: 4.7; 95% CI 2.01-11.21), in our study the estimate was lower (adjusted OR: 2.6; 95% CI 1.0-6.9). However, factors like persistent high-risk behavior and high number of cases of maternal syphilis (4.7%)[29] in the study population, have resulted in increased coinfection syphilis / HIV. Regarding other coinfections, authors like Fabbro et al[30] found a 3.3% proportion of HIV/HTLV coinfection in pregnant women, whereas our study reported only one case of

HIV/HTLV/syphilis. The low proportion of coinfections by the viruses included in our study, despite the share of transmission routes and similar risk factors in infected parturients, indicates that there are other mechanisms for the simultaneous presence of these infections, especially for retroviruses. Studies in the general population indicate that the role of HTLV-1 infection on HIV disease is still controversial [31].

The seroprevalence for HTLV (0.4%) was low compared to studies with parturients in the state of Bahia (0.8-1%) in Salvador (1991) [3-4], Cruz das Almas (2007) [32] and Ilhéus-Itabuna (2014) [33]. At national level, HTLV seroprevalence in pregnant/parturient women is heterogeneous and depends on the region. It ranges from 0.1% in Mato Grosso do Sul[9,34], Matto Grosso[35], Goiânia[36] and Botucatu (SP)[37] to 1.7% in Vitória (ES)[27]. HTLV screening in health institutions is performed only in the prenatal follow-up, but pregnant women show low level of information on previous tests. In addition, the lack of records of previous serological tests make difficult to evaluate the prevalence of this agent in such population. It was evidenced in our study when we found most women were unaware of having performed HTLV screening or did not have the result at the time of delivery.

A significant association between gestational outcomes (stillborn and low birth weight history) and HTLV seropositivity was detected. Although we were unable to find any previous report on such findings[38], a potential mechanism to explain the negative impact of HTLV infection on pregnancy is the alteration in the placenta due to the activation of apoptosis as a protective mechanism for the presence of virus to avoid transplacental transmission. This type of response is more frequently found in placentae of HTLV-1-positive women when compared to non-infected ones[39]. There is no conclusive evidence on HTLV transmission during pregnancy, but some data suggest that there may be transplacental transmission of HTLV to fetus, once up to 12% of non-breastfed children can be infected. In addition, pro-viral DNA HTLV-1 has been

detected in the umbilical cord's mononuclear cells, reinforcing the potential for viral transmission before or during delivery[39].

The seroprevalence rates for HBV and HCV hepatitis virus infections (0.4% and 0.1%, respectively) confirm the low prevalence of viral hepatitis in general population of NE region (prevalence below 2%)[40]. In the present study, the HBsAg antigen was positive in eight parturients (0.4%), similar to a previous study conducted in 1995 in Salvador, which detected a prevalence rate of 0.6% in a similar population[4]. Both prevalence rates are similar to the results found in other cities of Brazil[7,10-11,17-19,24,27], which ranged from 0.3%[9] to 3.2%[41](highest prevalence in Amazon region). Despite the low prevalence, screening of hepatitis infection and immunization of all pregnant women are necessary to reduce the probability of transmission of this disease by the vertical route, which is responsible by about 90% of cases of chronic hepatitis in children.

We observed that 73.7% of the parturients had received at least one dose of vaccine in prenatal care and 26.3% were not vaccinated or were unaware of their vaccination status. The evaluation of vaccination coverage was impaired due to the lack of registration of the vaccines use in the prenatal care card, and to the absence of parturient's vaccine card, at admission to maternities. This finding exposes a flaw in antenatal care to guide pregnant women about the relevance of vaccination and the need of its formal registration, to allow health professionals to identify cases of delay or abandonment of vaccination schedule. In the study´s population, viral hepatitis were related to parenteral exposure, through sharing objects of personal use, such as razor blades and manicure nail pliers, or accidental contact with biological material. These findings reveal the low level of awareness on risks for acquiring viral infections through such route. Blood transfusion or tattooing were not associated with a higher risk of viral hepatitis in this population.

HCV infection during pregnancy is still poorly studied in Brazil, with rare reports on the

prevalence of HCV in parturients or VT rates. The 0.1% active (viremic) HCV and 0.3% non-viremic HCV prevalence rates, are similar to previous studies. One of them[42], performed at the MRPJMMN maternity hospital from 2009 to 2011, found a prevalence rate of 0.2% among pregnant women, and others in different Brazilian cities[10,12,24,43-46] showed rates ranging from 0.1%[9,15,47] to 1.6%[27]. However, much of the studies were done only by calculating seroprevalence based on the ELISA anti-HCV positive, without confirmatory tests, which demonstrates that even considering only serological results for detection of HCV infection, prevalence rates were mostly low. The non-availability of treatment for hepatitis C during pregnancy and taking into account that 50% to 85% of the cases evolve to chronicity, (and eventually to development of cirrhosis and hepatocellular carcinoma)[47], increases the relevance of early detection and implementation of efforts to educate pregnant women to prevent infection.

Since the creation of the National STD and AIDS Program (PN_DST/AIDS), in 1985, guidelines and prophylactic, diagnostic and treatment actions for the prevention of the vertical transmission of sexually transmitted diseases (STDs), currently free of charge in the Single System of Health (SUS) were oriented. Over the past two decades, initiatives like increased prenatal care coverage and rapid testing[48], including the monitoring of pregnant women and exposed children[49], and guidelines preparation for prevention of vertically transmitted[50] have been implemented. Such efforts contributed to improved rates of detected infections such as HIV and hepatitis B and C in pregnant women and to the prevention of vertical transmission of HIV through prophylaxis and HBV by vaccination. However, our findings indicate the need of a permanent monitoring on the adequate implementation of such initiatives, especially for women presenting individual or social vulnerability, or those already living with STI.

The main limitation of our study was the evaluation of pregnant women in reference maternity hospitals, which may contribute to the detected high HIV seroprevalence, but the large sample

size allowed us the identification of the main risk factors for acquisition of blood or sexually borne infections for parturients in Salvador.

The seroprevalence rates of screened viruses in is an essential information for the proper monitoring of VT[27]. Moreover, given the typical characteristics of these viruses, such as the prolonged incubation period, high transmissibility and the possibility of developing chronic diseases, coupled with a scenario of individual and social vulnerability we can conclude that the preventive and therapeutic actions of health programs must be intensified and maintained overtime to reduce new cases of infection in women and their partners.

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Disclosure of interests

None declared.

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Table 1. Socio-demographic characteristics among parturient women at maternity hospitals MCO and MRPJMMN. Salvador- Bahia. Brazil. 2016-2017

VARIABLES		TOTAL N= 2099 (%)
Maternity hospital	MCO	1078 (51.3)
	MRPJMMN	1022 (48.7)
Age in years	14 - 19	337 (16.1)
	20 - 29	1020 (48.6)
	30 - 39	633 1.6)
	> 40	79 (3.8)
Fixed partnership	Yes	1583 (75.4)
	No	513 (24.5)
	Ignored	3 (0.2)
Education in years	< 8	569 (27.1)
	> 8	1528 (72.7)
Occupation	Housewife	855 (40.7)
	Service workers. sellers of commerce. shops and market	610 (29.1)
	Student	245 (11.6)
	Others*	390 (18.6)
Employment	Yes	727 (34.6)
Race (self-reported)	Brown	1041 (50.3)
	Black	847 (40.9)
	White	144 (7.0)
	Other (Asian. Indigenous)	39 (1.8)
Risk behavior and vulnerability conditions:		
Own house		1188 (57)
Overcrowding**		297 (4.1)
Low family income***		977 (46.5)
Alcohol and/or drugs users		350 (16.8)
Deprived of their liberty (prisoner)		90 (4.3)
Exchange sex for money		18 (0.9)
Sexual and/or domestic violence		140 (6.7)
Multiple sexual partner in pregnancy		84 (4.0)
Other vulnerable conditions****		100 (5)

***** Others occupations as workers in service-producing industries. administrative service workers

** overcrowding: more than three people sleeping in the same room

***Household income *per capita* < 0.5 salary

**** Immigrants. frequent moving to domicile

Table 2. Obstetrics and clinics characteristics among parturient women at maternity hospitals MCO and MRPJMMN. Salvador- Bahia. Brazil. 2016-2017

VARIABLES		TOTAL N= 2099 (%)
Number of gestations	1	851 (40.5)
	2 - 3	923 (44.0)
	>4	323 (15.5)
Miscarriage	Yes	485 (23.2)
Stillbirth	Yes	98 (4.7)
Number of antenatal visits	None	56 (2.9)
	1-5	582 (30.0)
	>6	1300 (67.1)
	Ignored	161 (7.7)
First antenatal visit (trimester)	First	1354 (66.7)
	Second	559 (27.5)
	Third	117 (5.8)
Dose of Hepatitis B vaccine	0	336 (16.0)
	1-2	857 (41.1)
	3	629 (30.4)
	Ignored	280 (13.3)
Not performing reasons for antenatal care	She thinks that she did not need because she had experience with the previous pregnancy or "I did not want to do it"	21 (42.8)
	Unaware of the importance of antenatal care or "discovered late"	14 (28.5)
	No time for work or travel	11 (19.6)
	Difficulty in accessing health services	8 (14.2)
Syphilis Co-infected		98 (4.7)
Exposure		
Sexual	Unprotected sexual practices	1572 (74.9)
	Partner with history of STD	16 (0.8)
Parenteral	Sharing object of personal use	585 (28.3)
	Tattoo. piercing. dental treatment	796 (38.0)
	Blood transfusion	74 (3.6)
	Accidental exposure to blood	28 (1.4)
Vertical transmission	SIM	15 (0.7)
Rupture of membranes	< 4 horas	482 (68.5)
	> 4 horas	221 (31.5)
Type of delivery	Vaginal	1183 (56.4)
	Cesarean	906 (43.3)
Weight of the newborn	> 2500 gr	1745 (83.1)
	< 2500 gr	352 (16.8)
Gestational age (weeks)	> 37	1762 (83.9)
	< 37	334 (15.9)

Table 3. Seroprevalence of HIV, HTLV, HEPATITIS B/C infection, moment of diagnosis and residence of parturient women at maternity hospital MCO and MRPJMMN, Salvador, Bahia, Brazil. 2016-2017

	HIV**		**HTLV**		**HBV**		**HCV**	
N=2099	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Test								
Elisa +	33	1.5	10	0.5	8	0.4	6	0.3
Confirmatory*	33	1.5	9	0.4	8	0.4	2	0.1
Total n, %(IC 95%)	33	1.5 (1.1-2.1)	9	0.4 (0.2-0.7)	8	0.4 (0.2-0.7)	2	0.1 (0.03-0.4)
Moment of diagnosis								
Before antenatal care	19	57.6	2	22.2	5	62.5	1	50.0
During antenatal care	11	33.3	5	55.5	2	25.0	1	50.0
During Childbirth	3	9.01	2	22.2	1	12.5	0	0
Home municipality								
Salvador	23	69.9	6	66.6	4	50.0	2	100
Other	10	30.3	3	33.3	4	50.0	0	0

*Confirmatory Test for HIV and HTLV: Western Blot. For HCV: PCR ARN
** 1 patient had a serological diagnosis of HIV, HTLV and syphilis infection
+: positive tests
P: Prevalence

Table 4. Univariate analysis of socio-demographic, obstetric and clinical factors associated with Retroviral (HIV-HTLV) infections among parturient women in maternity hospitals MCO and MRPJMMN. Salvador-Bahia, Brazil 2016-2017

VARIABLES		HIV (+) n (%)	HIV(-) n (%)	p- Value	Odds ratio (CI 95%)	HTLV (+) n (%)	HTLV (-) n (%)	p- Value	Odds ratio (CI 95%)
Age (mean SD. CI95%)		29.1	27.3	0.1	-	34.3	27.2	0.04	-
Fixed partnership	No	12 (36.4)	501(24.3)	0.10	1.8 (0.9-3.7)	2(20.0)	511 (24.5)	0.7	0.7 (0.2-3.6)
	Yes	21 (63.6)	1562(75.7)	0.10	1.0 (0.9-1.1)	8 (80.0)	1575 (75.5)	0.7	1.0 (0.9-1.0)
Education in years	<8	18 (54.5)	551 (26.7)	<0.001	3.3(1.7-6.6)	4 (40.0)	565(27.1)	0.3	1.8 (0.5-6.4)
Race	Non - White	27 (81.8)	1858 (91.3)	0.06	0.4 (0.2-1.0)	10 (100.0)	1860 (91.1)	0.3	1.0 (0.1-0.11)
	White	3 (9.1)	141(6.9)	0.6	1.3 (0.4-4.4)	0	143 (7.0)	0.4	-
Alcohol and/or drugs users		14 (42.4)	336 (16.4)	<0.001	3.7 (1.8-7.6)	3 (30.0)	343(16.7)	0.3	2.1 (0.6-8.3)
Private of liberty		4(12.1)	86 (4.2)	0.03	3.1(1.1-9.1)	2(20.0)	87 (4.2)	0.01	5.6 (1.2-27.0)
Multiple sexual partner		5(15.2)	79 (3.9)	0.001	4.4 (1.7-12.0)	0	84 (4.1)	0.6	-
Low family income		21 (77.8)	956 (52.3)	0.008	3.2 (1.2-7.9)	8 (80.0)	969 (52.5)	0.08	3.6 (0.7-17.0)
Sexual and/or domestic violence		7 (22.6)	133 (6.6)	<0.001	4.1 (1.7-9.7)	4 (40.0)	135 (6.7)	< 0.01	9.3 (2.5-33.3)
Overcrowding		8 (24.2)	236 (11.4)	0.02	2.4 (1.1-5.5)	2 (20.0)	242 (11.6)	0.4	1.9 (0.4-9.0)
Number of gestations	1	6(18.2)	845 (40.9)	0.008	0.3 (0.1-0.8)	1(10.0)	850(40.7)	0.04	0.2 (0.02-1.2)
	>4	11 (33.3)	314 (15.2)	0.004	2.7 (1.3-5.8)	5 (50.0)	320(15.3)	0.002	5.5 (1.5-19.2)
Number of prenatal visits	None	3 (9.7)	53 (2.8)	0.02	3.8(1.1-12.7)	1 (14.3)	53(2.8)	0.02	5.8 (0.6-49.4)
	< 6	16 (51.6)	622 (32.6)	0.03	2.2 (1.1-4.5)	4 (57.1)	627(32.8)	0.2	2.7 (0.5-12.2)
	First antenatal visit during the third trimester	4 (13.3)	113 (5.7)	0.07	2.6 (0.9-7.5)	0	117 (5.8)	0.5	-
Stillbirth		3 (9.1)	95 (4.6)	0.2	2.1 (0.6-6.9)	3(30.0)	95 (4.6)	<0.001	8.8(2.2-34.0)
Miscarriage		10 (30.3)	475 (23.1)	0.3	1.5 (0.7 -3.2)	2 (25.0)	473 (23.0)	0.2	2.2 (0.6-7.9)
Syphilis		6 (18.2)	92 (4.5)	<0.001	4.7 (1.9-12.0)	1 (10.0)	99 (4.8)	0.4	2.2 (0.3-17.6)
Parenteral Exposure	Sharing object of personal use	5 (15.6)	580 (28.4)	0.1	0.5 (0.2-1.2)	4 (40.0)	574 (28.2)	0.4	1.7 (0.5 -6.0)
	Tattoo,piercing,dental treatment	16 (48.5)	780 (37.9)	0.2	1.5 (0.8-3.0)	5 (50.0)	784 (38.4)	0.4	1.6 (0.4 - 5.5)
	Blood transfusion	1 (3.1)	68 (3.5)	0.9	0.9 (0.1 – 6.6)	1 (10.0)	73 (3.4)	0.3	3.0 (0.4-24.0)
Vertical transmission		3 (9.1)	12 (0.6)	<0.001	16.5 (4.4 -61.4)	0	15 (0.8)	0.8	-
Partner with history of STD		1(3.1)	15 (0.7)	0.1	4.2 (0.5 -32.9)	1 (10.0)	15 (0.7)	0.001	15.0 (1.8-126.2)
Pregnancy outcomes	Weight < 2500 g	7 (21.9)	348 (16.8)	0.5	1.3 (0.6-3.1)	4 (40.0)	348(16.7)	0.05	3.3 (0.9-11.8)
	Gestational age < 37 weeks	9 (27.3)	325 (15.8)	0.07	2.0 (1.0-4.4)	3 (30.0)	331 (15.9)	0.2	2.3 (0.5 -9.0)

Table 5. Multiple logistic regression of risk factors for HIV infection in parturient women. Maternity hospital MCO e MRPJMMN, Salvador-Bahia, Brazil 2016-2017.

VARIABLE	Crude OR	CI 95%	Adjusted OR	CI 95%
HIV-1				
Multiple sexual partner	4.4	1.7 – 12.0	3.3	1.1-9.2
Sexual or domestic violence	4.1	1.7-9.7	2.8	1.1 -6.9
Syphilis Co-infection	5.7	2.4 – 13.5	2.6	1.0 -6.9
Alcohol and/or drugs users	3.7	1.8 – 7.6	2.5	1.2 – 5.5
Low schooling < 8 years	3.3	1.7 – 6.6	2.3	1.1 – 4.9

OR: *odds ratio*; 95%CI: 95% confidence interval; the final model parameters: χ^2 model: 288,27; 0,016 (Cox &Sell); 0,109 (Nagelkerke)

5. 2 Soroprevalência e transmissão vertical da sífilis. Artigo Nº 3

ARTIGO ORIGINAL Nº3

HIGH PREVALENCE OF SYPHILIS IN PARTURIENT WOMEN AND CONGENITAL SYPHILIS CASES, IN PUBLIC MATERNITIES IN SALVADOR-BAHIA, BRAZIL

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Commentary

High prevalence of syphilis in parturient women and congenital syphilis cases in public maternities in Salvador-Bahia, Brazil

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Syphilis is an infection that can be transmitted from infected mothers to their babies during pregnancy. According to the Brazilian Notifiable Diseases Information System, 37 436 cases of maternal syphilis and 20 474 of congenital syphilis were reported in Brazil in 2016. Between 2010 and 2016, the detection rate in pregnant women increased from 3.7 to 12.4 cases per 1000 live births. This led to a progressive increase of the congenital syphilis rate during 2010–2016 from 2.4 to 6.8 cases per 1000 live births.[1]

These rates are far from the national target: by the year 2015, the congenital syphilis rate should have been 0.5 cases per 1000 live births.[2] An increase in maternal and congenital syphilis cases has been reported for Salvador and other large cities in Brazil. In 2015, the maternal syphilis prevalence rate was 4.1% at a large maternity hospital.[3] However, in 2016, the detection rate of maternal syphilis in Salvador was 22 cases per 1000 live births, higher than that observed at a national level (12.4). Other capital cities reported even higher rates, which reached 34.2 in Rio de Janeiro and 33.7 in Vitória. Salvador is the capital with the fourth highest rate of congenital syphilis (16 cases per 1000 live births), after Porto Alegre (29.2), Recife (22.9) and Fortaleza (18.0).[1]

In this commentary we highlight the current prevalence rate and factors associated with maternal and congenital syphilis in two major public maternity hospitals in Salvador, Brazil. We evaluated 2099 parturient women and their 2139 babies (40 of them were twins) who attended Maternidade Climério de Oliveira (MCO) and Maternidade Professor José Maria Magalhães Neto (MPJMMN), from April 2016 to June 2017. Parturient women were screened for syphilis by both non-treponemal Venereal Disease Research Laboratory – VDRL (Laborclin, Pinhais, PR, Brazil), and rapid treponemal tests (Alere Syphillis, Standard Diagnostic Inc., Republic of Korea). Parturients with a positive rapid treponemal test were further analyzed for syphilis. Maternal syphilis cases were defined as women with a reactive rapid test and a VDRL titre of 1 : 8, or those with a reactive rapid test, a VDRL titre of <1 : 8, and a history of previous inadequate treatment. We defined cases of probable congenital syphilis as children born to mothers with inadequate treatment for gestational syphilis (treatment <30 days before delivery and/or treatment with drugs other than benzathine penicillin) or children born to mothers with gestational syphilis who presented with the typical clinical manifestations of congenital syphilis. A structured questionnaire was used to access the sociodemographic, clinical and obstetric factors associated with syphilis in parturient women. Clinical information was obtained by reviewing the medical record of mothers and newborns.

We detected a high prevalence (3.7%) of probable cases of congenital syphilis and a higher proportion of maternal syphilis with previous inadequate treatment than observed in previous published works.[1,4] The rapid test was positive in 4.7% of parturients. Among them, 52.0% had VDRL titer <1:8, and 6.1% had a nonreactive VDRL. Eighteen parturients with VDRL <1:8 (31.6%) had a history of previous adequate treatment for syphilis. Among their neonates (N = 100 because of two twin pregnancies), 87.0% were reactive to VDRL, 31.0% had VDRL titers ≥1:8. Eighty (80%) neonates were considered as probable cases of congenital syphilis, because of previous, inadequate treatment of their mothers. Maternal syphilis was significantly associated with lower educational level, being unmarried, history of alcohol and/or illicit drug use, family history of incarceration (either women or their sexual partners), frequent residence change, multiple sexual partners, and past domestic

or sexual violence. No antenatal care, first antenatal visit at third trimester, previous stillbirths or termination of pregnancy and sharing objects of personal use also were significantly associated with syphilis. In a multivariate analysis use of alcohol and/or illicit drugs, first antenatal visit at third trimester, fewer (<8) years of formal education and multiple sexual partners remained as risk factors for maternal syphilis. Among women with a positive rapid test, 63.3% were diagnosed during antenatal care, only 48.9% of these before the third trimester. Two thirds (68.4%) of women with a positive rapid test had received at least one dose of benzathine penicillin. The average length of hospital stay was 10.5 days for the neonates classified as probable cases of congenital syphilis. Some typical clinical features of congenital syphilis were observed at birth or during the hospital stay: jaundice (47.5%), thrombocytopenia (7.5%), anemia (5.0%) and nonspecific long bone x-ray alterations (5.0%). In addition, we detected that 6.1% of parturients were coinfected by syphilis and HIV. This association was expected, since 71.8% reported unprotected sex, and 11.4% had multiple sexual partners in the current pregnancy, boosting (two-fold increase) the risk for infection by syphilis.

The main risks for syphilis detected in this population were: low maternal schooling, alcohol and/or drug use, multiple sex partners and poor access to antenatal care. In addition, lack of follow-up of the pregnant women with syphilis and lack of reporting of syphilis status in medical records or antenatal cards were detected. These results demonstrate that the main barriers to syphilis eradication are still present at both the individual and public health levels, and reinforce the need for better antenatal coverage and integration of health services, to ensure efficacious prevention of congenital syphilis.

Early engagement of at-risk women in antenatal care programs would provide a chance of early recognition of risk behaviors.[5–7] Attending regular antenatal care improves detection, prevention and treatment of STI. We detected a 2.6 higher likelihood of syphilis in parturients with a late presentation to antenatal care. This confirms previous studies in Bahia, that found a close association between late/incomplete antenatal care engagement and syphilis.[4,8,9] The association between syphilis and late presentation to antenatal care indicates existing barriers to access health services, lack of interest, or low awareness of the importance of early pregnancy screening and monitoring.[6,8]

Available data from Brazil show that the frequency of treatment for women's sexual partners among congenital cases of syphilis varied between 11.5%,[1] to 23.6%.[4] In addition, the proportion of cases with missing information on treatment of the parturent's sexual partners was high (46.9%), as well as the lack of information on preventive and therapeutic measures for syphilis in medical records. For these reasons, the adequate interpretation of reactive serological tests for syphilis in newborns is difficult, which could result in a higher rate of congenital syphilis, hospitalization and expenses in the health sector.

The scarcity of benzathine penicillin that affected Brazil and other countries since 2014 due to the shortage of raw material for its production,[1] possibly contributed to the high proportion of mothers with untreated or inadequately treated syphilis during pregnancy, potentially increasing the rate of congenital syphilis cases. Additionally, we detected the use of alternative syphilis treatments for women in labor and their newborns, based on the use of either cephalosporins (18.7%), or the combination of penicillin derivatives plus cephalosporins (6.2%).

The high prevalence of probable cases of congenital syphilis detected in our study is similar to the available data for Brazil.[1] Health authorities tend to attribute the increase in the prevalence rate to a successful effort to improve the detection rate of syphilis. However, the high prevalence of well-established risk factors for maternal syphilis and the absence of visible efforts to improve access to health care for pregnant women are reflections of the failure of the current policy for congenital syphilis prevention. In addition, a substantial percentage of probable cases of congenital syphilis were clearly associated with the lack of antenatal care or inadequate maternal treatment. The shortage of benzathin penicillin should have been anticipated and its effects could have been minimised by alternative careful planning. However, health authorities only moved towards a solution when the absence of a reliable alternative became obvious. This delay to act probably had a high cost in terms of prevention of congenital syphilis in Brazil. These facts highlight the maintenance of several barriers in gaining access to qualified health services, especially for the most vulnerable populations.

The early diagnosis and treatment of syphilis in pregnant women and their sexual partners are relatively simple and effective preventive measures are available.[2] Delayed antenatal care, depletion of supplies of benzathine penicillin in health care units, and an increase in the proportion of women infected by syphilis, are clear failures in detection, treatment and monitoring of syphilis in parturient women in Brazil.[1]

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Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

LV and SA contributed equally for this manuscript, with all steps. MA contributed, mainly, with data collection. MS and CB had overall responsibility for the study and coordinated it. All authors were responsible for the drafting of the manuscript and gave approval for the final version.

Details of ethical approval

This study was reviewed by Climerio de Oliveira Maternity Ethic Committee and was approved on March 2nd, 2017. Reference: 2040710.

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5. 3 Transmissão vertical dos retrovírus (HIV/HTLV) e vírus das hepatites (B/C)

Transmissão vertical do HIV

Foram analisadas 48 crianças expostas à TV do HIV pelas 33 parturientes soropositivas. 35 crianças nasceram durante o período do estudo (2 pares de gêmeos, e uma participante esteve gravida por duas vezes no estudo), e foi excluída uma criança por ser natimorto. 13 crianças menores de 10 anos de gravidez anterior, foram incluídas.

Carga viral não detectável tiveram 34 crianças (70,8%), 3 crianças nascidas em 2009, 2012 e 2014 estão infectados (6,25%) e 11 crianças (23%) ainda não tem carga viral ou é desconhecido seu estado de infecção. Dessas 11 crianças houve perda do acompanhamento devido a que 4 mães não compareceram depois do contato (uma mãe com gêmeos), 4 mães mudaram-se de município e 2 não foi possível o contato direito com a participante por telefone.

O diagnóstico de HIV nas mães ocorreu em 59% (19) casos antes da gravidez do estudo, com média de 8,8 ± 4,6 anos de diagnóstico. 16,8%(10) durante o pré-natal e 17,8% (3) no momento do parto.

Em quanto à condição clinica das participantes, não foi possível classificar pela contagem do CD4, porque a maioria elas não tinham a exame no momento da entrevista ou não foi registrado no prontuário. Uma parturiente morreu por aids e duas foram levadas à unidade de terapia intensiva (UTI) no pós-parto. Uma paciente foi coinfectada com HTLV e sífilis e 6 (18,2%) com sífilis.

Em relação ao uso de TAR pelas parturientes, 72,7% (24/33) usaram na gestação. A maior parte das parturientes, 48,5% (16/33) tinham carga viral detectável com uma variabilidade de 218 a 165.424 cópias/ml, com média de 17.894,4 e desvio padrão 27.792,8. 39,3% (13/33) das parturientes tiveram carga viral indetectável e não se obteve esta informação em 4 parturientes (12,5%).

Verificou-se que 35 (100%) recém-nascidos receberam a terapia antirretroviral de AZT com solução oral, nas primeiras 24 horas no ambiente hospitalar. Inclusive naquelas duas crianças cujas mães tiveram o parto fora da instituição de saúde e naquele que a mãe esteve no período expulsivo do parto. Nenhuma das crianças recebeu aleitamento materno.

Dos 35 recém-nascidos expostos ao HIV no período de estudo, 62,8% eram de sexo feminino e 37,2% do sexo masculino. O peso ao nascer teve uma média de 2.778 ± 482,6 gramas e a idade gestacional variou de 28 a 41 semanas com uma média de 37 ± 2,1semanas. Realizou-se parto vaginal em 18% (6/33), desses 2 foram na via pública.

Transmissão vertical do HTLV

Das 9 parturientes identificadas com HTLV positivo houve 8 recém-nascidos expostos e um natimorto, durante o período do estudo. Não foi possível o contato de 1 mãe. No total foram testadas 10 crianças: 7 nasceram no período de estudo e 3 crianças menores de 10 anos. Daquelas, 5 crianças foram testadas por meio da técnica de reação em cadeia da polimerase (PCR), havendo positividade em 4 casos. 4 crianças maiores de 18 meses foram testadas para sorologia do HTLV com resultado negativo. 1 criança menor de 18 meses apresentou testes sorológicos positivos (ELISA e WB) mas não compareceu para nova amostra com PCR. A taxa de transmissão vertical de HTLV nesse grupo de crianças não amamentadas foi 40% (4/10).

As características das mães com filhos positivos para HTLV foram: a média de idade de 27±0,5 anos com um rango de 24 e 43 anos, com ensino médio completo, 2 com residência em Salvador e 2 fora de Salvador (San Miguel Calmon e Ilha Veracruz). O diagnóstico de HTLV nas mães das 4 crianças ocorreu na gestação. 1 paciente com antecedente de transfusão de sangue e todas desconheciam o estado sorológico para HTLV do parceiro sexual.

3 (66,6%) crianças nasceram por cesárea e foram do sexo masculino. O peso ao nascer foi em média de 3.084,8±510,8 gramas e a idade gestacional variou de 36 a 39 semanas com uma média de 38,3 ± 1,8 semanas.

Transmissão vertical do HBV

Dentre as 8 gestantes avaliadas como HBV positivas, houve 7 recém-nascidos e 1 natimorto. Foram avaliadas 4 de 13 crianças expostas (6 irmãos expostos). Todos os casos com HBsAg não reagente. Os 7 recém-nascidos receberam vacina contra hepatite B e imunoglobulina humana anti-hepatite B (IGHB) antes da alta hospitalar.

Os marcadores sorológicos para hepatite B das mães soropositivas indicaram que 75% (6/8) tiveram hepatite B crónica (HBsAg e AntiABc total, reagentes), 25% não tiveram marcadores sorológicos. Foi medido o HBeAg em 50% das parturientes, sendo não reagente e foi encontrada só uma parturiente com carga viral (HBV-DNA), com resultado não indetectável.

Em relação ao conhecimento do estado de infecção pelo HBV do parceiro, 37,5% das parturientes relataram como positivo.

Transmissão vertical do HCV

Foi avaliada uma criança de 8 meses com duas sorologias anti-HCV não reagentes. A mãe tinha carga viral de $2,42x10^2$ UI/ml.

6. CONSIDERAÇÕES FINAIS

O presente estudo desenvolvido em duas maternidades públicas de Salvador com 2099 parturientes estimou uma prevalência de 1,5% para HIV, 0,4% para HTLV, 0,4% para HBV e 0,1% para HCV. A avaliação das crianças expostas desses vírus estimou uma taxa de transmissão vertical de 6,2% para HIV, 40% para HTLV, 0% para HBV e não foi avaliada a transmissão para HCV. Os fatores sociodemográficos, de comportamento e obstétricos das mães associados às infecções dos vírus estudados evidenciaram um contexto de vulnerabilidade individual e social.

As taxas de prevalência encontradas no estudo são similares aos dados recentes do Ministério de Saúde e de outros estudos realizados nas gestantes/parturientes de Brasil. Os fatores de risco sociodemográficos e comportamentais associados à prevalência ter sido encontrados em estúdios anteriores[8,13], isto demostra que no Brasil a persistência de patrões de vulnerabilidade na mulher para contrair e transmitir ITS.

A ocorrência da transmissão vertical das infecções pelos vírus estudados e de outras ITS é um processo dinâmico, a depender de vários fatores desencadeantes ou causadores da persistência do ciclo de transmissão. Uns dos principais fatores é a detecção precoce das ITS nas mulheres em idade reprodutiva que chegam aos serviços de Ginecologia e Planeamento Familiar e das gestantes no pré-natal, sendo uma oportunidade para a identificação das mulheres em situação de vulnerabilidade e para a implementação das medidas preventivas para a TV, já preconizadas pelo ministério de Saúde.

A informação sobre as tendências das taxas de detecção de gestantes para HIV e HBV exceto para HVC e HTLV, estão disponíveis nos relatórios do Ministério de Saúde. Na região Nordeste (NE), em 2006, foi registrado um aumento de forma significativa nessas taxas, com 2,4 casos de HIV por 1.000 NV e 0,4 casos para HBV com resultados baixos comparados em nível nacional (2,6 x 1.000 NV para HIV e 0,5 x 1.000 NV para HBV)[5]. Esta tendência de aumento se refletiui no número de crianças expostas aos vírus e crianças infectadas, por exemplo, houve aumento de 8,7% na

taxa de detecção de AIDS em menores de cinco anos, que passou de 2,3 para 2,5 casos por 100 mil habitantes[2].

Ao longo do trabalho de campo nas maternidades de estudo, observamos que no pré-natal a testagem está sendo feito para os 4 vírus do estudo, e no momento de parto, com testes rápido para HIV, HBV e HVC (só maternidade MCO). Não obstante, foi difícil verificar as ações de detecção e preventivas, como uso de antirretrovirais e vacinação de HBV, feitas no pré-natal devido à falta de informação no cartão de gestante ou não disponibilização do mesmo na hora do parto, ou era desconhecido pela participante. Isto evidencia rotura no sistema de referência e contra-referência no pré-natal, parto e pós parto, com a possibilidade de demora nas tomadas de decisão e a perda dos casos positivos.

No que se refere ao momento do diagnóstico das infecções, o estudo observou alta proporção de parturientes com diagnostico HIV e HBV antes da gestação atual (59% e 62,5% respectivamente), fato similar com outros estudos. Os resultados são considerados importantes para aprimorar as ações preventivas, de acompanhamento e de aconselhamento nas mulheres vivendo com alguma ITS e que pretendem engravidar, com a possibilidade de estruturar uma intervenção específica para a redução da TV.

Apesar da queda na taxa de transmissão vertical de HIV evidenciada na revisão dos estudos brasileiros e nesta pesquisa (6,2%), ainda se requerem esforços na implementação e adesão das ações priorizadas pelo Ministério de Saúde desde 1985 para eliminar o chance de infecção fetal, atualmente gratuitas no Sistema Único de Saúde (SUS). Nas últimas três décadas, foram implementadas iniciativas como, aumento da cobertura de pré-natal e testes rápidos, incluindo, o monitoramento de gestantes e crianças expostas, e e preparação de diretrizes para prevenção de transmissão vertical, e cumprir com as prioridades do Programa Nacional Brasileiro em resposta à meta 90-90-90. Já é demostrado que a plena implementação das recomendações existentes pode ocasionar uma significativa redução da TV do HIV, na quase totalidade dos casos [4,5,], como em Cuba e Tailândia.

Dentre as parturientes do estudo houve significância estatística para a relação entre acesso e acompanhamento no pré-natal nas mulheres HIV soropositivas em comparação com as mulheres soronegativas, onde a maior parte das mulheres soropositivas não fizeram pré-natal ou iniciaram o acompanhamento no final da gravidez. Essa diferencia estabelece barreiras na cobertura e na qualidade do pré-natal para a eliminação da TV, porque levaram a diagnóstico tardio e retardo nas ações de tratamento, observamos no estudo que 72,7% tinham usado TAR na gestação e 39,3% tiveram carga viral indetectável no período do parto. Além disso, o parto vaginal se apresentou no 18% das mães soropositivas, sendo 2 na via pública.

Podemos adicionar como outro fator na persistência da transmissão vertical, as condições de vulnerabilidade das parturientes que geraram respostas e atitudes desfavoráveis ante a adesão do atendimento, aconselhamento e acompanhamento da equipe de saúde. Os resultados do estudo indicaram alta prevalência das infecções pelos retrovírus em mulheres com baixa escolaridade, violência doméstica e comportamento sexuais de risco (baixa adesão ao uso do preservativo, múltiplas parcerias sexuais e uso de drogas ilícitas). Esses fatores também influenciaram no acompanhamento das crianças expostas.

Ainda foi limitada a avaliação da TV pelo HBV devido à perda de seguimento do 30,1% das crianças. Essa situação, também é relatada no estudo de Kuper e Oliveira[14] onde 90% das crianças nascidas de mães com hepatite B não tiveram acompanhamento após o parto.

A taxa de transmissão vertical do HTLV (40%) nesta pesquisa foi alta similar ao estudo de Figueiró-Filho[15] em Mato Grosso do Sul. Nesse estudo, avaliou-se a ocorrência da TV em 7 crianças das 37 mães soropositivas para HTLV, e se confirmou por médio de PCR a positividade em todos os casos (100% de TV), das quais, 1 criança (9%) amamentou por período superior a 6 meses, por opção materna. O autor registrou uma perda de seguimento de 88,4%. Apesar do pequeno número de crianças analisadas nas duas pesquisas, evidenciou-se que a infecção materna pelo HTLV também afeta as crianças não amamentadas. Além disso, na revisão sistemática da literatura apresentada neste trabalho, encontrou-se a taxa global de

transmissão vertical em 1.455 crianças não amamentadas de 4.21%, e foram associados outros fatores, diferentes à amamentação, como títulos altos de marcadores imunológicos na mãe e na leite materna, predisposição genética e fatores sociodemográficos como idade maior de 30 anos e baixa renda familiar. Os estudos foram conduzidos em Japão e Jamaica e na década 90s. Esses resultados justificam a necessidade de realizar estudos recentes e de seguimento em todas as crianças de mães soropositivas.

A pesquisa apresentou uma alta proporção de crianças com perda de seguimento para conhecer o perfil sorológico: 23% para HIV, 9% para HTLV e 30,1% para HBV. As mães não compareceram ao LAPI, depois do contato telefónico e as crianças não tem registro no sistema de informação do laboratório de HUSPES. A falta de seguimento dessas crianças interferem no desfecho da exposição à TV dos vírus estudados e evidencia o desconhecimento e conscientização das mães sobre a importância da adesão ao seguimento pelo risco de ter crianças infetadas e que requerem tratamento.

Como uma limitação do estudo, destaca-se a pouca informação, por parte das participantes e disponibilizada nos prontuários e cartão da gestante, limitou o conhecimento das medidas realizadas no pré-natal e o estado clinico e imunológico no momento do parto para avaliar os fatores de risco de TV dos vírus estudados.

Outra limitação do estudo foi o acompanhamento das crianças expostas até conhecer seu estado de infecção ou não infectado. Apesar dos telefonemas, de oferecer os testes na cidade de residência e facilitar o transporte até o LAPI, houve baixa resposta no seguimento por parte das mães. Os fatores de vulnerabilidade identificados nessas mães, parecem influenciar, negativamente, a adesão ao seguimento. Evidenciando a necessidade do monitoramento contínuo dos casos específicos, através de estudos longitudinais.

Em conclusão evidenciou-se uma alta prevalência de TV do HTLV e da Sífilis em recém-nascidos em duas maternidades publicas do município de Salvador, e alta proporção de crianças ainda sem estado de não infectado ou infectado pelo HIV e HBV. As ITS estudadas são um importante problema de saúde pública e merecem

atenção não só das maternidades como também dos profissionais envolvidos nos programas de saúde sexual e reprodutiva da mulher. Um monitoramento permanente nas ações preventivas e de adesão terapêutica, se faz necessário para obter menos casos de TV.

7. PERSPECTIVAS FUTURAS

Nossos achados indicam a necessidade de um monitoramento permanente através de dados primários e secundários das tendências das IST principalmente dos patógenos estudados, e sobre a resposta à implementação das iniciativas para melhorar as taxas de infecções detectadas, especialmente para as mulheres que apresentam vulnerabilidade individual ou social, ou aquelas que já vivem com IST.

Outro fator que ainda precisa de mais estudo, é a patogêneses dos vírus na gestação na população brasileira, que permita uma intervenção oportuna na prevenção da TV. Na revisão da literatura observamos que existe escassez de estudos brasileiros com dados conclusivos sobre os fatores de risco da transmissão vertical dos vírus das hepatites (B/C) e do HTLV das crianças, principalmente na resposta imunológica da mãe e da criança, dos câmbios na barreira placentária e dos marcadores genéticos específicos nas gestantes soropositivas. Neste estudo não foi possível avaliar a transmissão vertical do HCV pelo número de casos (2).

Também existe a necessidade de estudos para avaliar outros produtos da gestação das mães soropositivas para HTLV, como os abortos, óbitos fetais e óbitos neonatais. Nosso estudo observou que a infecção pelo HTLV no período gestacional tem impacto negativo a ter associados fatores como o antecedente de natimortos e filhos com baixo peso ao nascer. Igualmente, na revisão sistemática foi associado o antecedente de abortos.

Esse trabalho evidenciou que a eliminação da TV das infecções estudadas ainda representa um importante desafio para o controle das ITS em mulheres e sua transmissão para seus filhos, principalmente quando estão em condição de vulnerabilidade. Os dados e afirmações apresentadas neste trabalho podem contribuir para o desenvolvimento de mais pesquisas nessa área, e de estratégias para reforçar as ações dos programas de saúde materna e infantil, atualmente encaminhados.

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APÊNDICE I – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto de Pesquisa: Avaliação dos Fatores de Risco e da Prevalência da Transmissão Vertical das Infecções por Vírus Hepatites B e C, e Retrovírus (HIV E HTLV-1/2) em Parturientes Atendidas nas Maternidades: Professor José Maria de Magalhães Neto e Climério de Oliveira, em Salvador, Bahia"

Pesquisadora Responsável: **LUDY ALEXANDRA VARGAS TORRES**

Contato: **(71) 92104033**

Introdução

Você está sendo convidada para participar desta pesquisa porque é parturiente atendida nas Maternidades: Maternidade de Referencia Professor José Maria Magalhães Neto (MRPJMMN) ou Maternidade Clemério de Oliveira (MCO). Está é uma pesquisa que coletará uma amostra de sangue para a detecção de alguns vírus, e também as informações epidemiológicas e clínicas das parturientes e crianças menores 10 anos de mãe com resultados positivos. Este documento é chamado Termo de Consentimento Livre e Esclarecido, que contêm informações sobre a pesquisa. Após ler este Termo e discutir suas dúvidas com os pesquisadores responsáveis do estudo, você decidirá se quer ou não participar. Se quiser, você e os pesquisadores assinarão e datarão duas vias deste documento, uma delas ficará com você e outra ficará arquivada com os pesquisadores.

É importante que você saiba que sua participação é totalmente voluntária. Você pode decidir participar ou não, a qualquer momento, sem prejuízo algum para o seu acompanhamento médico ou para o seu tratamento.

Por que esta pesquisa está sendo feita e quais são os objetivos?

O objetivo principal deste estudo é medir a infecção mãe-filho dos vírus HIV, HTLV, Hepatites B e C, e os fatores de risco associados em parturientes e crianças menores 10 anos de mães com resultados positivos, do município de Salvador e atendidas nas maternidades acima.

O que eu deverei fazer caso decida participar da pesquisa?

Se você aceitar participar deste estudo ou autoriza a participação de sua criança, os responsáveis por ele precisarão coletar amostra de sangue para identificar a presença dos vírus HIV, HTLV, Hepatite B e Hepatite C, os quais poderão ser transmitidos de mãe para filho. Além disso, será necessário coletar informações sobre suas condições de saúde e isso será feito através de uma entrevista contendo um questionário. Este questionário contêm perguntas sobre sua idade, raça, nível socioeconômico, escolaridade, estado civil; gestações anteriores, pré-natal; condições de vulnerabilidade, parceiros sexuais.

Quantas pessoas participarão da pesquisa?

Aproximadamente 2.200 parturientes atendidas nas maternidades acima deverão participar desta pesquisa, assim como as crianças menores de 10 anos de mães com resultados positivos. As mulheres serão convidadas a participar da pesquisa no dia seguinte ao seu parto, quando já estiverem descansadas e clinicamente estáveis. Esperamos avaliar em média 2 crianças por mãe soropositiva para um dos vírus. Caso se confirme positividade média de 1.0% deveremos avaliar aproximadamente 220 crianças. Esta amostra incluirá recém-nascidos e crianças nascidas de gestações anteriores, com idade menor ou igual a 10 anos.

Os questionários serão aplicados por estudantes de medicina treinados pelos investigadores, e pela Dra. Ludy Vargas, que também supervisionará o processo de coleta de dados.

Quanto tempo durará a pesquisa?

Essa pesquisa durará aproximadamente 1 (um) ano.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto de Pesquisa: Avaliação dos Fatores de Risco e da Prevalência da Transmissão Vertical das Infecções por Vírus Hepatites B e C, e Retrovírus (HIV E HTLV-1/2) em Parturientes Atendidas nas Maternidades: Professor José Maria de Magalhães Neto e Climério de Oliveira, em Salvador, Bahia"

Eu corro algum risco por participar deste estudo?

Não são esperados riscos físicos nesta pesquisa, mesmo quando efetuada por pessoal treinado, a coleta de sangue pode ocasionar dor, sangramento ou hematoma no local da punção e, raramente, infecção. Além disso, serão coletadas informações sobre seus hábitos, o que pode ocasionar algum constrangimento. Todas as providências serão tomadas para minimizar estes desconfortos. O aconselhamento de mães com testes positivos será realizado pelo profissional que coletará as informações para a pesquisa. Quando indicado, a paciente será encaminhada para seguimento em ambulatório especializado do HUPES. As suas informações serão tratadas de modo sigiloso.

Eu terei algum benefício por participar deste estudo?

É possível que você não obtenha um benefício direto pela sua participação nesta pesquisa, mas os resultados obtidos poderão ser de utilidade para identificar a presença e fatores de risco associados à transmissão de mãe para filho dos vírus HIV, HTLV, Hepatites B e C, entre as parturientes residentes no município de Salvador.
Sua participação neste estudo não interferirá no tratamento que você está recebendo nem no acompanhamento habitual que realiza no hospital.

Terei despesas por participar desta pesquisa?

Você ou seu filho não terão nenhuma despesa por participar deste estudo, todos os custos decorrentes serão cobertos pelos pesquisadores.

E quanto a confidencialidade dos dados?

Os dados do estudo são confidenciais e apenas terão acesso, os pesquisadores do estudo, o pessoal autorizado que analisará os dados, e o Comitê de Ética que aprova a realização da pesquisa **(Comitê de Ética em Pesquisa da Faculdade de Medicina da Bahia - FMB)**. O questionário que você irá responder esta de acordo com as regulamentações do Código de Ética Médica do Conselho Federal de Medicina e com a legislação brasileira que visa proteger o participante da pesquisa (Lei 466/12).

Esta pesquisa não divulgará dados pessoais que possam identificá-la. Os resultados desta pesquisa serão analisados e possivelmente publicados em revistas médicas, mas em momento algum seu nome será exposto ou divulgado. Toda a informação será registrada de forma anônima.

Quais as minhas alternativas?

Se você não quiser participar deste estudo, seu acompanhamento de atenção continuará sendo na Maternidade.
Você não deixará de receber os cuidados necessários, por não participar da pesquisa.

Quais são os meus direitos como voluntária em uma pesquisa?

A participação nesta pesquisa tem caráter voluntário e ainda que você decida participar, conserva a possibilidade de se retirar a qualquer momento e por qualquer motivo, sem prejuízo algum. Esta decisão não afetará a sua relação com seu médico nem o seu acesso a futuros tratamentos.
Se decidir participar, será solicitado que você dê o seu consentimento por escrito assinando este documento.

Quem devo procurar em caso de dúvidas?

Se tiver alguma dúvida sobre a sua participação nessa pesquisa ou sobre as informações contidas neste documento favor entrar em contato com:

Dr. Carlos Roberto Brites Alves
Rua Augusto Viana, s/nº, Canela,
CEP: 40110-060, Salvador, Bahia.
Telefone: (71) 3283-8123/ 3283-8062

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto de Pesquisa: Avaliação dos Fatores de Risco e da Prevalência da Transmissão Vertical das Infecções por Vírus Hepatites B e C, e Retrovírus (HIV E HTLV-1/2) em Parturientes Atendidas nas Maternidades: Professor José Maria de Magalhães Neto e Climério de Oliveira, em Salvador, Bahia"

Se tiver dúvidas como dar seu consentimento ou sobre os seus direitos como participante da pesquisa, favor entrar em contato com:

Comitê de Ética em Pesquisas em Seres Humanos
Faculdade de Medicina da Bahia – FMB/UFBA.
Largo do Terreiro de Jesus, s/n.
Centro Histórico, CEP 40.026-010
Salvador, Bahia, Brasil.
Telefones: (71) 3283-5564 / 8726 4038

PÁGINA DE ASSINATURAS

FUI DEVIDAMENTE ORIENTADA QUANTO A TODOS OS PROCEDIMENTOS DO ESTUDO. LI (OU LERAM PARA MIM) ESTE TERMO DE CONSENTIMENTO, TIVE CHANCES DE ESCLARECER MINHAS DÚVIDAS E ENTENDI TODAS AS INFORMAÇÕES. CONCORDO VOLUNTARIAMENTE EM PARTICIPAR DESTE ESTUDO.

_____
Nome do (a) participante (parturiente ou criança menor 10 anos)

_____ *Data* __ / __ / _____
Assinatura do (a) participante. dia mês ano

_____
Nome do representante legal do participante ou criança menor de 10 anos

_____ *Data* __ / __ / _____
Assinatura do representante legal do participante o criança menor de 10 anos . dia mês ano

_____
Nome da pessoa que obteve o consentimento.

_____ *Data* __ / __ / _____
Assinatura da pessoa que obteve o consentimento. dia mês ano

_____
Nome da testemunha imparcial, se necessário.

_____ *Data* __ / __ / _____
Assinatura da testemunha imparcial se necessário, dia mês ano

APENDICE II – Questionário para entrevista

FICHA PARA AVALIAÇÃO DA PREVALÊNCIA E FATORES DE RISCO DAS INFECÇÕES POR VIRUS HEPATITES E RETROVIRUS EM PARTURIENTES, NAS MATERNIDADES: PROFESSOR JOSÉ MARIA DE MAGALHÃES NETO E CLIMÉRIO DE OLIVEIRA SALVADOR, BAHIA .

Número do(s) Prontuário(s): _____ Maternidade: _____ 1= MRPJMN 2= MCO

FATORES SOCIODEMOGRÁFICOS

1. Data de nascimento da mãe: ___/___/_____

2. Estado Civil:
   1. Solteira ☐ 3. Viúva ☐ 5. Divorciada/separada ☐
   2. Casada ☐ 4. União estável ☐ 9. Ignorado ☐

3. Escolaridade:
   0. Sem escolaridade ☐ 3. Ensino médio completo ☐ 4. Educação superior completa ☐
   1. Fundamental I (1ª a 4ª serie) ☐ 4. Ensino médio incompleto ☐ 5. Educação superior incompleta ☐
   2. Fundamental II (5ª a 8ª serie) ☐ 9. Ignorado ☐

4. Residência:_____ Número de pessoas num mesmo quarto? _____

5. Ocupação habitual _____ Com emprego? 1. Sim _____ 2. Não _____

6. Auto- declaração Raça/cor
   1. Branca ☐ 3. Amarela ☐ 5. Parda ☐
   2. Preta ☐ 4. Indígena ☐ 9. Ignorado ☐

7. Comportamentos de risco e situações de vulnerabilidades vivenciadas durante a gestação: (1. Sim, 2. Não, 9. Ignorado)

1. Condições da moradia:
   1. Própria ☐ 2. Alugada ☐ 3. Familiar ☐ 4. Sem moradia (rua, albergue) ☐

2. Usuária de álcool, drogas, tabagismo ☐
3. Privada de liberdade (presidiária) ou Parceira de presidiário ☐
4. Praticas sexuais desprotegidas ☐
5. Múltiplas parcerias sexuais * ☐
6. Profissional do sexo ☐
7. Família de baixa renda** ☐
8. Violência sexual e doméstica (física ou verbal) ☐
9. Outras situações de vulnerabilidade*** ☐

* Mais de um parceiro na gestação da criança em investigação
** Renda familiar mensal per capita de até meio salário mínimo ou renda familiar mensal de até três salários mínimos.
*** 9.1. Imigrante, 9.2. Mudança frequente de domicílio/ residência, 9.3. Mudança forjada

FATORES OBSTÉTRICOS

8. Antecedentes obstétricos:
   1. Número de gestações ☐ 2. Número de nascidos vivos ☐ 3. Número de abortos ☐ 4. Número de natimortos ☐

9. Número total de consultas no pré-natal: _____

10. Trimestre da gestação do primeiro pré-natal
    1. Primeiro ☐ 2. Segundo ☐ 3. Terceiro ☐ 9. Desconhecido ☐

11. Esquema vacina hepatites B SIM 1ª dose ____ 2ª dose ___ 3ª dose ___ 9. Ignorado ____

12. Motivo(s) da não realização do pré-natal: (1: Sim, 2: Não, 9: Ignorado)

Desconhece a importância do pré-natal ☐
Trabalha e não teve tempo ☐
Local muito distante, não tinha dinheiro para ir ao pré-natal ☐
Privada de liberdade (presidiária) sem acesso ao serviço de pré-natal ☐
Muda com frequência de endereço ☐
Trabalha e o empregador não deixou ☐
Acha que não precisava, porque já tinha experiência em gestação anterior ☐
Unidade de Saúde não realiza teste para gravidez ☐

FATORES CLÍNICOS

13. Presença de infecções associadas nesta gestação (1: Sim, 2: Não, 9: Ignorado)

Sífilis ☐ HIV ☐ HTLV ☐
DST, qual? _____ ☐ Hepatite B ☐ Hepatite C ☐

14. Categoria de exposição da mãe para a infecção pelos vírus: HIV, Hepatite B e C (1: Sim, 2: Não, 9: Ignorado)

Transmissão Vertical ☐ Compartilhamento de objetos de uso pessoal, agulhas, seringas. ☐
Acidente com material biológico ☐ Transfusão de sangue/hemoderivados ☐
Sexual ☐ Transplante ☐
Uso de Droga Injetável ☐ Outra especificar (ver final *)_____ ☐

15. Momento do diagnóstico da infecção (1: Sim, 2: Não, 9: Ignorado)

Antes do pré-natal ☐ Após o parto ☐ Desconhecido ☐
Durante o pré-natal ☐ Durante o parto ☐

16. Valor do primeiro CD4 no pré-natal: _____células/mm3

17. Estado sorológico do parceiro

Negativo ☐ Positivo _____ ☐ Não testado ☐

18. No caso do diagnóstico materno de infecção pelo HIV ter sido realizado após o pré-natal, qual foi o motivo?

Não fez pré-natal ☐ Fez pré-natal, foi solicitado o teste anti-HIV, mas houve falha no fluxo do serviço ☐
Teste rápido anti-HIV não disponível no serviço ☐ Fez pré-natal, foi solicitado teste anti-HIV, mas houve falha no fluxo do laboratório ☐
Fez pré-natal e não foi solicitado o teste anti-HIV ☐ Erro de diagnóstico (falha no entendimento do diagnóstico pelo profissional de saúde) ☐

FATORES PARTO/PÓS-PARTO

19. Ocorreu ruptura de membranas (bolsa rota):

SIM ☐ Quanto tempo (horas) ____ NÃO ☐

20. Via de parto: vaginal ___ cesárea ___

21. Manobras invasivas: (1: Sim, 2: Não, 9: Ignorado) Amniotomia ___ Episiotomia ___ Uso de fórceps ___

22. Recém Nascido: Vivo__ Morto__

23. Sexo: F ____ M ___

24. Peso da criança ao nascer: _____gramas

25. Idade gestacional da criança ao nascer: _____semanas

26. Amamentação (1: Sim, 2: Não, 9: Ignorado): _____

* Outra especificação categoria de exposição da mãe para a infecção: Tatuagem; DST previa; Contato domiciliar (não sexual) com caso/portador de HBV ou HCV; Contato intra-institucional com caso de Hepatite B e/ou C; Tratamento dentário; outro procedimento médico invasivo.

TELEFONO: _____ ou _____

ANEXO I – Parecer do CEP-

FACULDADE DE MEDICINA DA BAHIA DA UFBA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO DOS FATORES DE RISCO E DA PREVALÊNCIA DA TRANSMISSÃO VERTICAL DAS INFECÇÕES POR VÍRUS HEPATITES B E C, E RETROVIRUS (HIV E HTLV-1/2) EM PARTURIENTES ATENDIDAS NAS MATERNIDADES: PROFESSOR JOSÉ MARIA DE MAGALHÃES NETO E CLIMÉRIO DE OLIVEIRA, EM SALVADOR, BAHIA

Pesquisador: CARLOS BRITES

Área Temática:

Versão: 3

CAAE: 46904415.2.0000.5577

Instituição Proponente: FACULDADE DE MEDICINA DA BAHIA

Patrocinador Principal: Fundação Bahiana de Infectologia

DADOS DO PARECER

Número do Parecer: 1.240.278

Apresentação do Projeto:

Trata-se de projeto de pesquisa visando conhecer a taxa de transmissão vertical do HIV, HTLV-1/2, HBV e HVC e os fatores de risco associados, em parturientes e nas crianças de mães soropositivas, atendidas em duas maternidades de Salvador-BA. Os pesquisadores justificam que "A doenças sexualmente transmissíveis (DST) e suas complicações em recém-nascido constituem-se num problema de saúde pública, porque algumas DST não são diagnosticadas e tratadas a tempo, levando a perpetuar o ciclo de transmissão e culminar numa transmissão vertical. Os dados epidemiológicos mostram ainda altas taxas nacionais de transmissão vertical no país, isso sugere a persistência dos fatores como são o diagnóstico tardio das infecções na gestação, a baixa adesão ás recomendações por parte dos serviços de saúde, a qualidade da assistência e seguimento, principalmente nas regiões com menor cobertura de serviços e menor acesso à rede de saúde. " (Formulário simplificado). É um estudo tipo transversal e terá duração de 36 meses.

Terá como população alvo 2.100 parturientes e crianças filhas de mães positivas para HIV, HTLV -1 e 2, HBV e HCV atendidas nas Maternidades Professor JOSÉ MARIA DE MAGALHÃES NETO (MRPJMMN) e MATERNIDADE CLIMÉRIO DE OLIVEIRA (MCO), em Salvador – Bahia. Consta anuência

Endereço: Largo do Terreiro de Jesus, s/n
Bairro: PELOURINHO **CEP:** 40.026-010
UF: BA **Município:** SALVADOR
Telefone: (71)3283-5564 **Fax:** (71)3283-5567 **E-mail:** cepfmb@ufba.br

de ambas as instituições campo da pesquisa. Registram, os pesquisadores, que "O programa Nacional de Brasil STD/AIDS demostrou que a transmissão mãe a criança pelo HIV-I representa 92,1% dos casos em criança menores de 13 anos em 2010. A incidência de casos HIV positivo em crianças menores de 5 anos se reduziu a 35% (de 5,4 a 3,5 casos por 100.000 população) entre 1999 – 2010(2). O protocolo para prevenção de transmissão vertical de HIV e sífilis da Secretaria de Vigilância em Saúde mostrou que o 35% da transmissão vertical do HIV ocorre durante a gestação, o 65% no Peri parto, 7-22% amamentação e 25% quando não são realizadas intervenções ou profilaxias." A pesquisa envolverá consulta a prontuários, entrevistas com as parturientes e coleta de sangue destas e de filhos menores de 10 anos. Consulta à Plataforma Lattes demonstra que o Pesquisador Responsável "Tem experiência em pesquisa, com ênfase em Doenças Infecciosas e Parasitárias, atuando principalmente nos seguintes temas: HIV, aids, HTLV, coinfecção HIV-HTLV, infecções hospitalares, e oncovirologia". Constam, ainda, outros integrantes aqui considerados como Pesquisadores Colaboradores, a saber: Manoel Alfredo Curvelo Sarno, Rone Peterson Cerqueira Oliveira, Ludy Alexandra Vargas Torres (Doutoranda do Programa de Pós-Graduação em Medicina e Saúde UFBA), Gisela Serra Rodrigues Costa (graduanda de medicina - UFBA). Haverá testes laboratoriais: teste de triagem para HIV, HTLV, HBV, HCV. Na análise estatística consta que "Os dados obtidos no questionário, bem como os oriundos dos resultados dos exames laboratoriais, serão registrados em banco de dados no software SPSS, versão 21 e a análise estatística será realizada no mesmo programa. Para a aceitação das hipóteses alternativas foi considerado um intervalo de confiança de 95%, com nível de significância estatística de $p<0,05$.

Serão calculadas frequências e proporções para as principais variáveis. As associações entre variáveis categóricas serão avaliadas através de análise uni variada, utilizando o teste do qui-quadrado, com correção de Yates, ou teste exato de Fisher, quando aplicável, e expressas através de ODDS RATIO (OR) e intervalos de confiança de 95%. Variáveis contínuas serão comparadas através do teste de Kruskal-Wallis ou teste t de Student." A pesquisa terá um custo total de R$ 119.070,00 com informação da contrapartida. No Formulário simplificado consta apoio financeiro da Fundação Bahiana de Infectologia. Chama a atenção carta enviada ao Coordenador do CEPFMB respondendo a pendências.

Objetivo da Pesquisa:

Principal:

"Estimar a taxa de transmissão vertical do HIV, HTLV-1/2, HBV e HCVe os fatores de risco associados em parturientes do município de Salvador, atendidas nas maternidades: Maternidade

de Referência Professor
José Maria de Magalhães Neto (MRPJMMN) e Maternidade Climério de Oliveira (MCO)."

SECUNDÁRIOS
1. "Avaliar a soro-prevalência de infecção pelos HIV, HTLV-1 e 2, HBV e HCV em parturientes do município de Salvador, Bahia.

2. Determinar a frequência de transmissão vertical em crianças menores de 10 anos filhos de mães soropositivas.

3. Avaliar prevalência da imunidade prévia para HBV.

4. Determinar os fatores de risco para a transmissão vertical;

Avaliação dos Riscos e Benefícios:
RISCOS:
"Não são esperados riscos físicos nesta pesquisa, além daqueles decorrentes de punção venosa para coleta de sangue. Mesmo quando efetuada por pessoal treinado, a coleta de sangue pode ocasionar dor, sangramento ou hematoma no local da punção e, raramente, infecção. Além disso, serão coletadas informações sobre seus hábitos, o que pode ocasionar algum constrangimento. TODAS AS PROVIDÊNCIAS serão tomadas para minimizar estes desconfortos".

BENEFÍCIOS:
"A redução da transmissão vertical se viabiliza quando é possível conhecer a condição das parturientes e fazer estratégias eficazes para o rastreamento da infecção e proteção do feto, este estudo permitirá a conhecimento da taxa de transmissão vertical, da prevalência das infecções pelos vírus de hepatites e retrovirais, e dos fatores relacionados ao maior risco de transmissão. Avaliar a prevalência das infecções pelos vírus estudados em gestantes, pode sensibilizar ante a magnitude deste problema e fortalecer as ações de maior efetividade em prevenção, tratamento e seguimento dos casos positivos. Além de isso, conhecer os fatores de risco permitirá superar os impedimentos estruturais para a utilização serviços essenciais e a atenção integral na mulher no período pré concepcional, pré-natal e pós-parto.

Comentários e Considerações sobre a Pesquisa:

A pesquisa tem validade social, científica e econômica. Mas se fazem necessários alguns esclarecimentos de modo particular na metodologia. Sobre a "seleção de participantes: será selecionado aleatoriamente um grupo de parturientes que tenham procurado as maternidades MRPJMMN e MCO por ocasião do parto (destaque nosso). Para evitar perdas excessivas, caso haja recusa de participação, a parturiente com o número seguinte à que recusou será convidada. " A amostra prevista é de 2.100 mulheres. Esclarecer número previsto de crianças. " ...Todas as providências serão tomadas para minimizar estes desconfortos". Ao dar entrada, em trabalho de parto, as gestantes serão convidadas a participar do estudo, e após assinatura de termo de consentimento livre e esclarecido, deverá ser coletada amostra de sangue para sorologia (tal procedimento já faz parte da rotina na admissão à maternidade)." Nesta circunstância a parturiente estará tranquila o suficiente para tomar uma decisão? "No dia seguinte ao parto, após descanso da parturiente e inclusão da mesma como sujeito de pesquisa, será realizada entrevista com a aplicação de um questionário elaborado especificamente para esse fim, por profissionais previamente treinados." ... "se a mãe é soro positiva para os vírus estudados, será convidada para autorizar a coleta amostra de sangue de criança menor de 10anos, para identificar na criança ..." Parece-nos possível que algumas dessas parturientes não saiba da condição de soro positividade.

Considerações sobre os Termos de apresentação obrigatória:

O Protocolo contém a documentação exigida pela Res. 466/12 e Norma Operacional 01/2013 embora alguns mereçam comentários.

- Folha de Rosto - Assinam Diretora FMB-UFBA e Presidente da Fundação Baiana de Infectologia.

- Autorização das instituições - carta anuência maternidade José Maria Magalhães Neto assinada por Rone Peterson – coordenador ensino e pesquisa, mas que também integra a equipe de pesquisa (ver Norma Operacional Anexo II item 3).

-Instrumento de coleta de dados (questionário) – algumas questões podem causar forte desconforto. Eis porque a necessidade de aplicação de forma a garantir a privacidade. ADEQUADO.

- Declaração dos Pesquisadores Colaboradores se comprometendo em atender à Res. 466/12. ADEQUADO.

Assentimento / Justificativa de Ausência	TCLE_Datado_10Agosto2015.doc	14:28:50	CARLOS BRITES	Aceito
Outros	Carta_Resposta_Parecer_N_1224936_13092015.docx	22/09/2015 12:00:54	CARLOS BRITES	Aceito
Declaração de Pesquisadores	Declaracao_Gisela.pdf	22/09/2015 12:02:05	CARLOS BRITES	Aceito
Declaração de Pesquisadores	Declaracao_Resolucao_466_12_Ludy_Vargas.pdf	22/09/2015 12:02:23	CARLOS BRITES	Aceito
Declaração de Pesquisadores	Declaracao_Fernanda_Bastos.pdf	22/09/2015 12:05:48	CARLOS BRITES	Aceito
Outros	Carta_Anuencia_MRPJMMN.pdf	22/09/2015 12:13:37	CARLOS BRITES	Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_536816.pdf	22/09/2015 12:14:26		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SALVADOR, 22 de Setembro de 2015

Assinado por:
Eduardo Martins Netto
(Coordenador)

Endereço: Largo do Terreiro de Jesus, s/n
Bairro: PELOURINHO **CEP:** 40.026-010
UF: BA **Município:** SALVADOR
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Maternidade Climério de Oliveira
Universidade Federal da Bahia

EBSERH

MATERNIDADE CLIMÉRIO DE OLIVEIRA
Rua do Limoeiro, nº 137, Nazaré – 40055-150 – Salvador-BA
Telefone: (71) 3283-9211
https://www.ebserh.gov.br/web/mco-ufba secretaria.mco@ufba.br/superintendência.mco@ufba.br

Memorando nº 07/2017_GEP/MCO-UFBA

Salvador, 26 de junho de 2017

Para: Coordenação de Neonatologia/ Divisão de Enfermagem (Coordenação da Enfermaria Canguru, Alojamento Conjunto)/SAADT (laboratório)/SAME/UTIN/Estatística/Educação Continuada/Portaria

Prezados (as) Senhores (as) Coordenadores (as) e chefes,

Vimos, através desta, autorizar Dra. Ludy Alexandra Vargas Torres, Sávio Vinicius Burity Amorim Nunes Amaral e Tarcisio Taylon de Aguiar Fausto membros da equipe de pesquisa do projeto de pesquisa "Avaliação dos fatores de risco e da prevalência da transmissão vertical das infecções por vírus hepatites B e C, e retrovírus (HIV e HTLV-1/2) em parturientes atendidas nas maternidades: Professor José Maria de Magalhães Neto e Climério de Oliveira, em Salvador, BA", CAAE: 46904415.2.3001.5543, com situação do parecer "APROVADO" pelo Comitê de Ética em Pesquisa da Maternidade Climério de Oliveira e do Comitê de Ética em Pesquisa da Faculdade de Medicina da Bahia.

Atenciosamente,

JAMES JOSÉ DE CARVALHO CADIDÊ
Gerente de Ensino e Pesquisa
Matrícula Siape nº 1890378
CPF 095235375-04
Email: jamescadide@hotmail.com

JAMES JOSÉ DE CARVALHO CADIDÊ
Gerente de Ensino e Pesquisa
Maternidade Climério de Oliveira/UFBa
Siape nº 1890378