

# BJSTD

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# CONTENTS

## EDITORIAL

- MOTHER-TO-CHILD TRANSMISSION OF THE HIV: OLD CONCEPTS, NEW PERSPECTIVES? ..... 115  
*Vicente Sperb. Antonello*

## ARTICLES

- COVERAGE OF PAP SMEAR AND MORTALITY FROM CERVICAL CANCER IN BRAZIL FROM 2006 TO 2014..... 117  
*COBERTURA DOS EXAMES DE COLPOCITOLOGIA ONCÓTICA E MORTALIDADE POR CÂNCER DO COLO DE ÚTERO NO BRASIL NO PERÍODO DE 2006 A 2014*  
*Edison Natal Fedrizzi, Nádia Munhoz Ponce*

- FACTORS ASSOCIATED WITH *CHLAMYDIA TRACHOMATIS* INFECTION IN WOMEN RESIDENT IN THE STATE OF RORAIMA, BRAZIL ..... 125  
*FATORES ASSOCIADOS À INFECÇÃO POR CHLAMYDIA TRACHOMATIS EM MULHERES RESIDENTES NO ESTADO DE RORAIMA, BRASIL*  
*Bianca Jorge Sequeira, Edvaldo Carlos Brito Loureiro, Wagner do Carmo Costa*

- EVALUATION OF THE COMPLIANCE WITH THE GOALS PROPOSED BY THE WORLD HEALTH ORGANIZATION FOR THE ELIMINATION OF CONGENITAL SYPHILIS FROM A UNIVERSITY HOSPITAL OF RIO DE JANEIRO, BRAZIL ..... 131  
*AVALIAÇÃO DO CUMPRIMENTO DAS METAS PROPOSTAS PELA ORGANIZAÇÃO MUNDIAL DA SAÚDE PARA A ELIMINAÇÃO DA SÍFILIS CONGÊNITA EM UM HOSPITAL UNIVERSITÁRIO DO RIO DE JANEIRO*  
*Luciane Rodrigues Pedreira de Cerqueira, Denise Leite Maia Monteiro, Stella Regina Taquette, Nádia Cristina Pinheiro Rodrigues, Caroline Tavares da Mota Monteiro, Bianca de Melo Araújo, Alexandre José Baptista Trajano, Flávio Monteiro de Souza*

- CONTRIBUTION TO THE STUDY OF EPIDEMIOLOGICAL SURVEILLANCE OF CONGENITAL SYPHILIS IN A HOSPITAL OF THE UNIFIED HEALTH SYSTEM LOCATED IN THE BAIXADA FLUMINENSE REGION, RIO DE JANEIRO STATE, BRAZIL ..... 138  
*CONTRIBUIÇÃO AO ESTUDO DA VIGILÂNCIA EPIDEMIOLÓGICA DE SÍFILIS CONGÊNITA EM UM HOSPITAL DA REDE DO SISTEMA ÚNICO DE SAÚDE DA BAIXADA FLUMINENSE, ESTADO DO RIO DE JANEIRO*  
*Carolina Galvão, Wesley Caixeta Borges, Philippe Godefroy, Sergio Araújo Martins Teixeira, Eduardo Martins Gerde, Alfredo de Almeida Cunha*

## CASE REPORT

- MULTIPLE SYPHILITIC CHANCRE ON THE VULVA AND ON BOTH BREASTS: CASE REPORT ..... 143  
*CANCRO SIFILÍTICO MÚLTIPLO EM VULVA E EM AMBAS AS MAMAS: RELATO DE CASO*  
*Adrián Orsini, Mauricio Ledesma*

## LETTER FROM THE EDITORS

- THE INCREASED PREVALENCE OF *TRICHOMONAS VAGINALIS* IN A SCENARIO OF CERVICAL CANCER SCREENING WITHOUT CYTOLOGY ..... 148  
*O AUMENTO DA PREVALÊNCIA DE TRICHOMONAS VAGINALIS EM UM CENÁRIO DE TRIAGEM DE CÂNCER CERVICAL SEM CITOLOGIA*  
*José Eleutério Junior, Mauro Romero Leal Passos*

## EVENTS

- ADS..... 150



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## *Mother-to-child transmission of the HIV: old concepts, new perspectives?*

I read very carefully the interesting article by Barcellos et al. on human immunodeficiency virus (HIV) vertical transmission in the postnatal period through breastfeeding. The authors explained in a very elucidating and detailed way the cases of postnatal infection, as well as the clinical and epidemiological aspects. In this regard, we could look into a number of questions about HIV diagnosis, HIV pre and post-exposure prophylaxis, and antiretroviral adherence in women living with HIV<sup>(1)</sup>.

HIV postnatal transmission through breastfeeding has been described since the 1980s<sup>(2)</sup>, and 30 years later we are still seeking greater beliefs for this scenario. How to deal with this problem? Although we do not have definitive solutions, we can rehearse some answers and at least aim for satisfactory results after 30 years of study.

The high rates of HIV infection in the population, as described by Barcellos et al.<sup>(1)</sup>, and especially in Brazilian women, highlight the need for early diagnosis and management of patients with HIV infection and those at risk of acquisition<sup>(3)</sup>. In this scenario, the pregnant/puerperal partner should actively participate during pre and post natal care, especially with HIV testing in conjunction with the patient. A recent study conducted in Porto Alegre, Rio Grande do Sul, Brazil, investigated partners of pregnant women with HIV negative results in the antenatal period. From 663 partners who accepted HIV testing, four (0.6%) were diagnosed for HIV infection<sup>(4)</sup>, enhance the importance of partner's testing for the prevention of maternal seroconversion, especially in the postnatal period. Thus, early HIV identification makes it possible to reduce the risk of maternal-fetal transmission with the initiation of antiretroviral treatment, use of intrapartum zidovudine, cesarean section, and orientation not to breastfeed the child<sup>(5)</sup>.

The present study reports that more than two-thirds of mothers were sexually exposed as a way of HIV infection<sup>(1)</sup>. Thus, interventions that reduce the risk of maternal primary infection would be decisive for the prevention of infection in the late breastfeeding baby. Combined prevention is a strategy that makes use of different approaches to HIV transmission prevention, with structural, behavioral and biomedical interventions. There were two prominent measures in recent years: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for HIV<sup>(6)</sup>. Both strategies have been shown to be safe and available in the public health system. The use of antiretroviral drugs in the mentioned situations would benefit the mother and the infant, even though the child is under breastfeeding, since the studies, although limited in number, mostly show a positive impact for the infant of mother under active use of antiretroviral therapy. This measure would prevent maternal HIV infection through the use of PrEP or PEP when indicated<sup>(7)</sup>.

Another aspect to be considered is the adherence to antiretrovirals by patients living with HIV. Vertical postnatal transmission of HIV depends on factors related to the mother and the infant, such as the mother's viral load. Hence reducing the HIV burden to undetectable levels is the most effective way to prevent the occurrence of new cases in newborns, indirectly from an HIV-positive partner, and directly when the mother is living with HIV<sup>(8)</sup>. In Brazil, it is estimated that adherence to antiretroviral treatment is around 75%<sup>(9)</sup>. Ensuring that these patients achieve therapeutic success through regular use of antiretrovirals should be a compromise between managers, patients and society<sup>(8)</sup>.

Finally, the present article brings to light a neglected topic today: vertical HIV transmission in the postnatal period through breastfeeding. Recognizing patients at risk of primary infection and intervening with effective HIV education and prevention measures, such as the use of condoms, PrEP and PEP; testing mother and partners periodically for HIV; and stimulating adherence to antiretrovirals by patients living with HIV are determinants for modifying this adverse scenario in our country. We must intensify our efforts to ensure exclusive breastfeeding as a healthy and developmental reference for the mother-baby binomial, bringing security to all involved and favorable perspectives on their horizon.

**VICENTE SPERB. ANTONELLO**

**MD, MSc, PhD, Department of Prevention and  
Infection Control - Hospital Fêmeina, Porto Alegre, Brazil.  
E-mail: vicente@ghc.com.br**

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# COVERAGE OF PAP SMEAR AND MORTALITY FROM CERVICAL CANCER IN BRAZIL FROM 2006 TO 2014

## COBERTURA DOS EXAMES DE COLPOCITOLOGIA ONCÓTICA E MORTALIDADE POR CÂNCER DO COLO DE ÚTERO NO BRASIL NO PERÍODO DE 2006 A 2014

*Edison Natal Fedrizzi<sup>1</sup>, Nádia Munhoz Ponce<sup>1</sup>*

### ABSTRACT

**Introduction:** Despite the widespread programs of prevention and screening of cervix cancer in Brazil, the country still remains in the third position of the most malignant neoplasm and the third cause of female death due to cancer. The Human papillomavirus vaccine is a recent addition to the National Immunization Program. Due to its short time of implementation, it is still insufficient to evaluate the reduction of this disease. Screening and treatment of precancerous lesions through oncotic colposcopy have significantly reduced the incidence and mortality of cervix cancer. However, so that it occurs, a high population coverage is required, which is not the case of Brazil. **Objective:** To analyze the number of Pap smear obtained from January 2006 to December 2014 in the Brazilian female population by the public health system, comparing it to the number of cervix neoplasia deaths during the same period. **Methods:** A cross-sectional study evaluating the number of Pap smear and mortality due to cervix cancer in the female population aged 25 to 64 years. The number of Pap smear carried out was obtained through the Cervix Cancer Information System, and the population statistics was provided by the Brazilian Institute of Geography and Statistics (IBGE). The number of deaths was obtained through the Mortality Information System developed by the Health Ministry. **Results:** The coverage by Pap smear in Brazil was shown to be declining during the analyzed period. The Brazilian region with the lowest average coverage was the Northern (14.58%), and it is also the region with the highest number of deaths from cervix cancer (average of 12.58 deaths per 100,000 women). The region with the highest average coverage was the Southeast (17.14%), which presented the lowest rates of death from this neoplasm (average of 5.28 deaths per 100,000 women). The highest number of deaths from cervix cancer during the period from 2006 to 2014 occurred in the 50 to 54 age group. **Conclusion:** Brazilian Pap smear coverage remains very low and the mortality rates are high and constant over the last years.

**Keywords:** pap smear; neoplasia; cervix; mortality.

### RESUMO

**Introdução:** Apesar de já conhecidos os métodos de prevenção e rastreamento, o câncer de colo de útero ocupou no Brasil, em 2016, a terceira posição nas neoplasias femininas mais incidentes e a terceira causa de óbito por câncer nas mulheres. A vacina contra o Papilomavírus humano foi recentemente introduzida no Programa Nacional de Imunizações, mas o tempo ainda é insuficiente para avaliar a redução dessa doença. O rastreamento e o tratamento das lesões pré-cancerosas por meio da colposcopia têm demonstrado reduzir significativamente a incidência e a mortalidade do câncer do colo de útero. No entanto, para que isso ocorra, é necessária alta cobertura populacional, o que não acontece no Brasil. **Objetivo:** Analisar a quantidade de exames citopatológicos do colo uterino coletados entre janeiro de 2006 a dezembro de 2014 na população feminina brasileira pelo Sistema Único de Saúde (SUS), comparando-o ao número de óbitos por neoplasia cervical nesse mesmo período. **Métodos:** Estudo transversal avaliando o número de colposcopia oncológicas e mortalidade por câncer de colo de útero na população feminina dos 25 aos 64 anos. O número de citopatologias foi obtido por intermédio do Sistema de Informação do Câncer do Colo do Útero e os dados populacionais por estimativas censitárias fornecidas pelo Instituto Brasileiro de Geografia e Estatística (IBGE). O número de óbitos foi obtido pelo Sistema de Informações sobre Mortalidade do Ministério da Saúde. **Resultados:** A cobertura pelo exame citopatológico no Brasil mostrou-se decrescente ao longo dos anos analisados. A região brasileira com menor cobertura média foi a Norte (14,58%), também sendo a com maior número de óbitos por câncer de colo uterino (média de 12,58 óbitos por 100 mil mulheres). A região com maior cobertura média foi a Sudeste (17,14%), que obteve as menores taxas de morte dessa neoplasia (média de 5,28 óbitos por 100 mil mulheres). A faixa etária que mais apresentou óbitos no Brasil, de 2006 a 2014, foi a de 50 a 54 anos. **Conclusão:** A cobertura nacional pela colposcopia oncológica permanece muito baixa e com altas e constantes taxas de mortalidade nos últimos anos. **Palavras-chave:** teste de papanicolaou; neoplasia; colo do útero; coeficiente de mortalidade.

## INTRODUCTION

Cervix cancer is the third cause of cancer in Brazilian women, not considering non-melanoma skin cancer<sup>(1)</sup>. Nowadays, it is known that the Human Papillomavirus (HPV) is responsible for the development of this neoplasm in almost 100% of the cases<sup>(2)</sup>.

The prevention of contact with HPV, through the routine use of condoms<sup>(3)</sup>, is one of the ways to avoid this neoplasia. Vaccination<sup>(4)</sup> and early diagnosis of precancerous changes, i.e., the cervix intraepithelial neoplasia (CIN), should be added.

Pap smear (PS) of the cervix, also known as papanicolaou, is the most widely used method in the trace of the cervix cancer worldwide

and a great way of prevention, as long as there is an excellent coverage between women<sup>(5)</sup>. Several countries in the world have observed an important decrease of this cancer since a national organized program has been adopted and achieved a high coverage of women tracked<sup>(6,7)</sup>.

Although PS is implemented as a screening method for more than half a century in the Brazilian and world female population<sup>(6)</sup>, the incidence and mortality from cervix cancer still remain high<sup>(5,8)</sup>. In 2016, it was the fourth most common female neoplasm and the fourth cause of women death in the world<sup>(9)</sup>.

In Brazil, it still persists as the third most common female neoplasm in incidence, only following the colorectal and breast cancers<sup>(1)</sup>. Its incidence rate also varies according to the Brazilian region. In the North region, it is the most incident female neoplasia (estimated 23.97 per 100,000 women in 2016)<sup>(8)</sup>, statistically compared to what is observed in countries like India (20.2 per 100,000 women

<sup>1</sup>Gynecology and Obstetrics Department, Universidade Federal de Santa Catarina (UFSC) – Florianópolis (SC), Brazil.

in 2012)<sup>(10)</sup>. On the other hand, the South region has the lowest incidence rates (estimated 15.17 per 100,000 women in 2016)<sup>(8)</sup>, holding the fourth position.

Concerning Brazilian mortality, it represents the third cause of death from cancer, following only breast and bronchial/lung cancers<sup>(11)</sup>. In 2014, the highest rates were found in the Northern region of the country (14 deaths per 100,000 women) and the lowest ones in the Southeast (4.95 per 100,000 women)<sup>(12)</sup>.

## OBJECTIVE

To analyze the number of PS observed in the Brazilian female population aged 25 to 64 from January 2006 to December 2014 by the Public Health System (Sistema Único de Saúde — SUS), and compare it with mortality due to this type of cancer in the same period.

## METHODS

This is a cross-sectional design study, whose objective is to review the amount of PS of the female population of Brazil, from January 2006 to December 2014, compared to the female population according to the age group in this same period. Cervix cancer deaths rates were also evaluated in women in the 25 to 64 age group during this period.

The time interval evaluated was 2006 to 2014, whenever the information was completed, through the Information System of Cervix Cancer (Sistema de Informação do Câncer do Colo do Útero — SISCOLO), in the Informatics Department of the SUS (DATASUS), on the Ministry of Health website<sup>(13)</sup>.

The age group chosen for the study variables was 25 to 64, as it represents the age determined by the National Cancer Institute (Instituto Nacional de Câncer José Alencar Gomes da Silva — INCA) in its final recommendation (2016) to screening with Pap smear in Brazil<sup>(7)</sup>.

To estimate the female population, the Projection of the Union Population by Sex and Age Groups 2000–2030, a platform of the Brazilian Institute of Geography and Statistics (IBGE), a component of DATASUS, was used through the 25 to 64 years old age filter<sup>(14)</sup>.

The number of deaths by cervix cancer in women in the 25 to 64 age group was obtained through the database of the Mortality Information System (SIM) of the Ministry of Health<sup>(12)</sup>.

Statistical analysis of the data was performed through Microsoft Excel 2010 software.

To evaluate the national PS coverage, the quotient between the absolute value of exams was carried out each year in the 25 to 64 age group, and the female population estimate in this same age group every year was multiplied by the constant 100.

The specific mortality coefficient for cervix cancer has been obtained by the division of the number of deaths from cervix cancer of women from 25 to 64 years old, and the population estimate of this same age group every year was multiplied by the constant 100,000.

The number of deaths from cervix cancer was also computed in intervals of age groups every four years, starting at age 15 and ending at age 79.

The SISCOLO data are close to real values, since this system was created to control the coverage of population surveys and follow-up of women with altered tests<sup>(15)</sup>. The data concerning the number of PS of the SISCOLO platform and mortality from cervix cancer were obtained from the DATASUS website, and therefore in the public domain.

## RESULTS

From January 2006 to December 2014, 66,132,790 PS among women between the ages 25 to 64 was obtained from the SUS base. The year showing the highest number of collections was 2009 (8,493,656 tests), and 2014 the lowest (3,082,765 tests) (**Table 1**).

There was a progressive increase of the female population in the age group studied, with a maximum population growth rate of 2.41%/year (2006 to 2007) and a minimum of 1.59%/year (from 2013 to 2014), totaling the increase of 17.81% in the female population from 2006 to 2014.

Over the years, the percentage of the Brazilian PS coverage kept a decreasing linear trend, despite the variations occurred in the period (**Figure 1**).

The comparative evaluation between PS coverage in five Brazilian regions over the nine years of the study shows that, except for 2014, the region with the lowest population coverage was the Northern one, with the average of 14.58%, and always below the Brazilian average, of 16.09%. The Southeast region showed the best coverage, with 17.14% (**Figure 2**).

The regions with the highest PS coverage were led from 2006 to 2008 by the Northeast region (18.24 and 17.59% variation). Between

**Table 1** – Pap smear annual coverage<sup>1</sup> of female population aged 25 to 64 from 2006 to 2014.

Year	Pap smear numbers	Female Brazilian population (25 to 64 years of age)	Annual coverage (%)
2006	7,373,121	45,330,817	16.26
2007	7,854,856	46,454,770	16.91
2008	7,989,372	47,584,598	16.79
2009	8,493,656	48,684,881	17.45
2010	8,268,155	49,732,496	16.62
2011	8,041,393	50,728,309	15.85
2012	7,986,381	51,667,784	15.46
2013	7,043,091	52,556,386	13.40
2014	3,082,765	53,407,458	5.77
Total	66,132,790		

<sup>1</sup>Number of PS/ Female population of the mentioned year.

Source: Cervix Cancer Information System<sup>(13)</sup> and Brazilian Institute of Geography and Statistics<sup>(14)</sup>.

2009 and 2010, the leadership of coverage occurred in the South region (ranging from 19.55 and 17.46%). In 2011, the Southeast region obtained maximum coverage among the five regions (17.02%). In 2012 and 2013, the South region led the coverage again (ranging from 16.49 to 14.37%), as shown in **Figure 3**. Data of 2014 show the North region with the highest coverage (7.39%), and the Southern region with the lowest (2.08%).

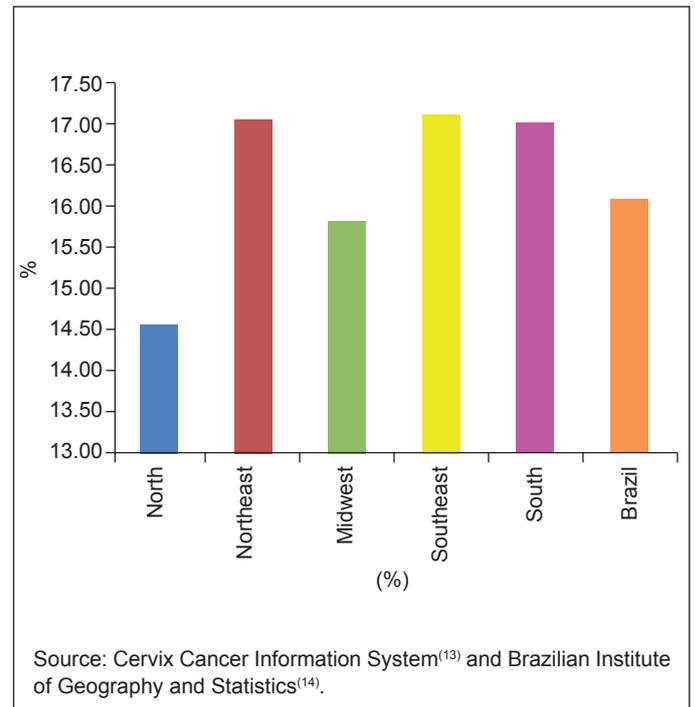
In the period between January 2006 and December 2014, 30,456 cervix cancer deaths were registered in the Brazilian female population aged 25–64 years (**Table 2**).

There was an absolute increase in the total number of deaths from this kind of neoplasia: from 3,059 deaths, in 2006, to 3,651 deaths in 2014 (19.35%) (**Figure 4**).

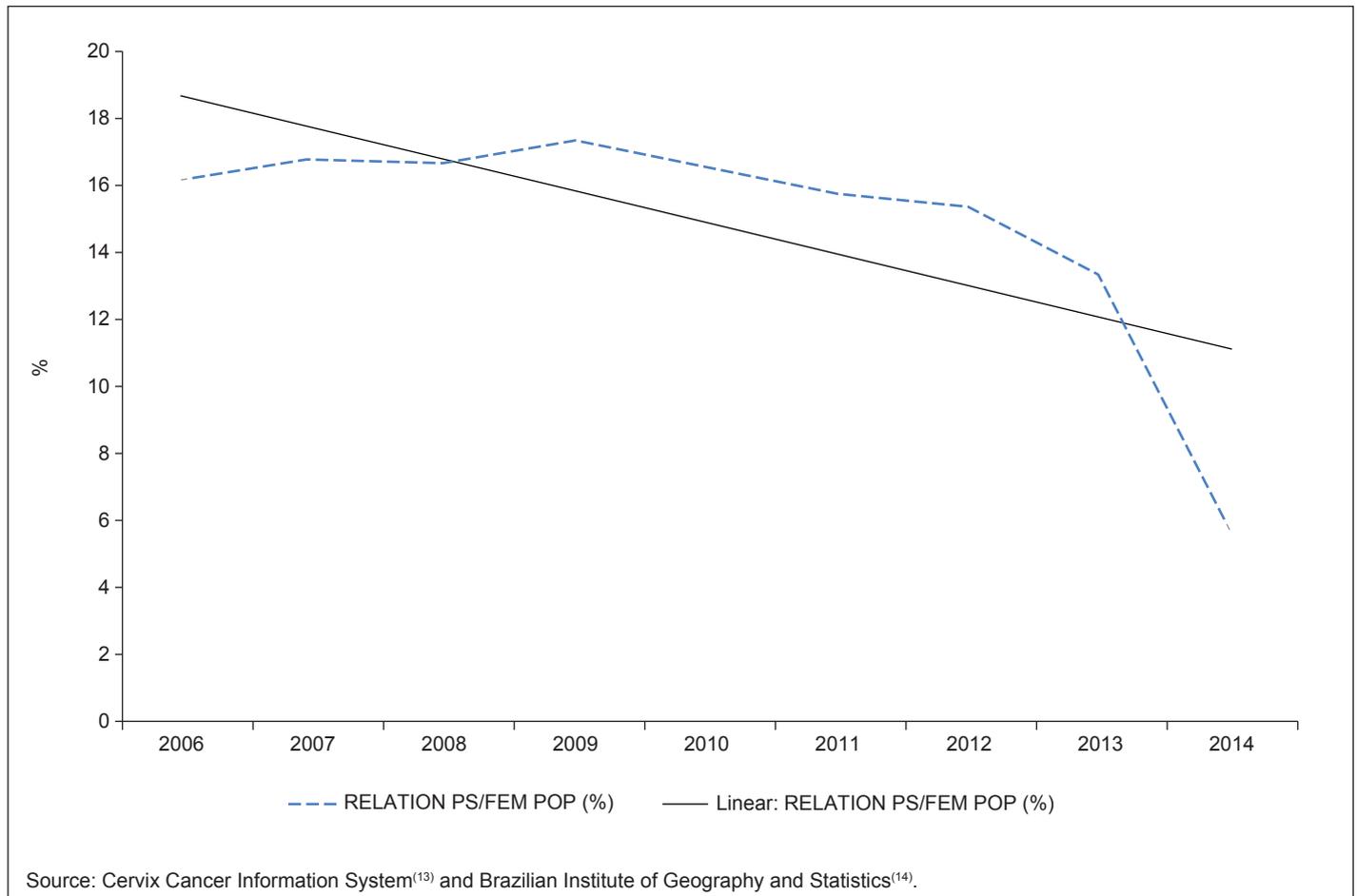
It is observed that the specific mortality coefficient in Brazil showed an increasing tendency between 2006 and 2014 (**Figure 5**).

When all cervix cancer deaths between 2006 and 2014 are added and distributed according to the age group, the highest percentage of deaths from this neoplasia is concentrated in age group 50 to 54, totaling 11.62% of the total deaths (45,509 deaths). The lowest percentage was found in age groups below 25 years, accounting for 0.61% of total deaths (**Figure 6**).

The comparison of the number of cervix cancer deaths in the population among all the five regions of Brazil over the nine years of study shows that the Northern region had the highest number of deaths, with the gradual increase tendency. Although the chart does not make it



**Figure 2** – Comparison between the average coverage by Pap smear (PS) among the five regions of Brazil and the Brazilian average between 2006 and 2014.



**Figure 1** – Relation between the number of Pap smear (PS) and the female population (fem pop) aged 25 to 64 in Brazil from 2006 to 2014.

clear, the Northeastern region also showed a linear trend of increase of specific mortality rates, differently from the Midwest, Southeast and South regions, which kept linear decreasing trends (Figure 7).

By comparing the same mortality coefficient of cervix cancer in Brazil (Figure 5) with the one from other regions (Figure 7), it is graphically observed a lower national variation in relation to other regions with a tendency to stability.

## DISCUSSION

The cervix cancer, as a slowly advancing disease, with the average of 10 to 15 years between infection by high-risk oncogenic HPV and the development of invasive cancer<sup>(16)</sup>, allows the diagnosis of precursor lesions and its treatment, preventing the consequent invasion. Based on that finding, the periodical preventive examination

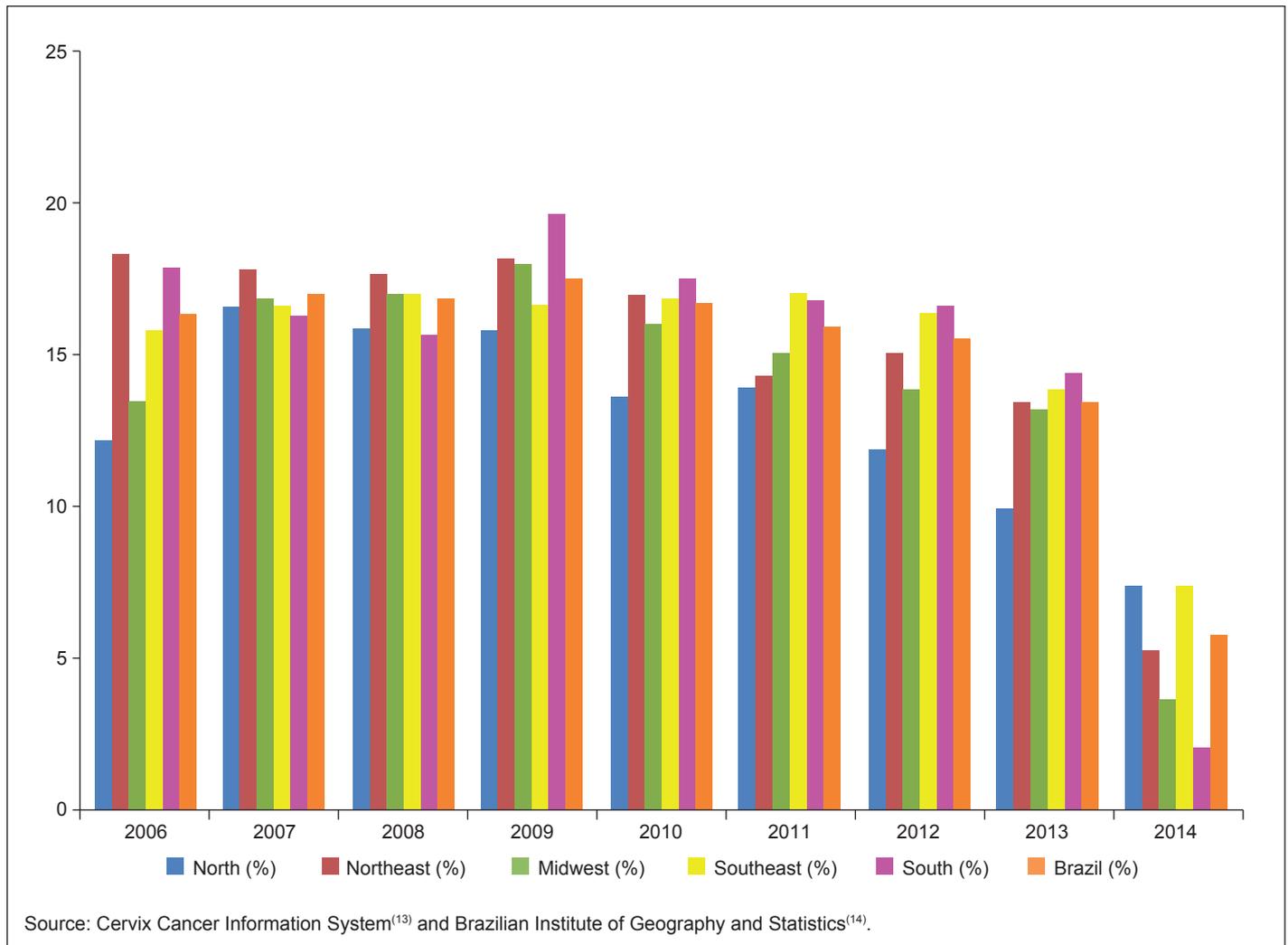
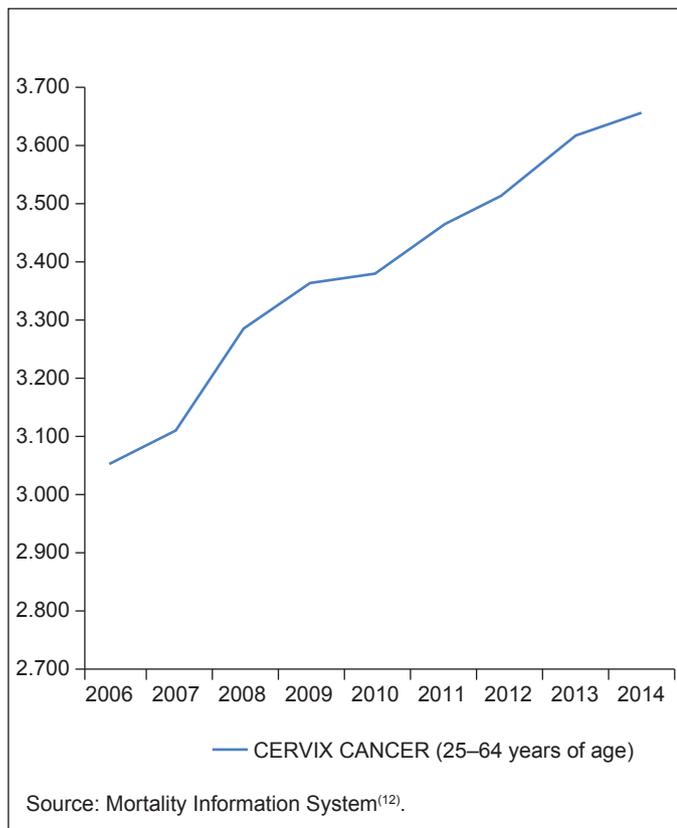


Figure 3 – Coverage by PS of the five Brazilian regions and Brazil between 2006 and 2014.

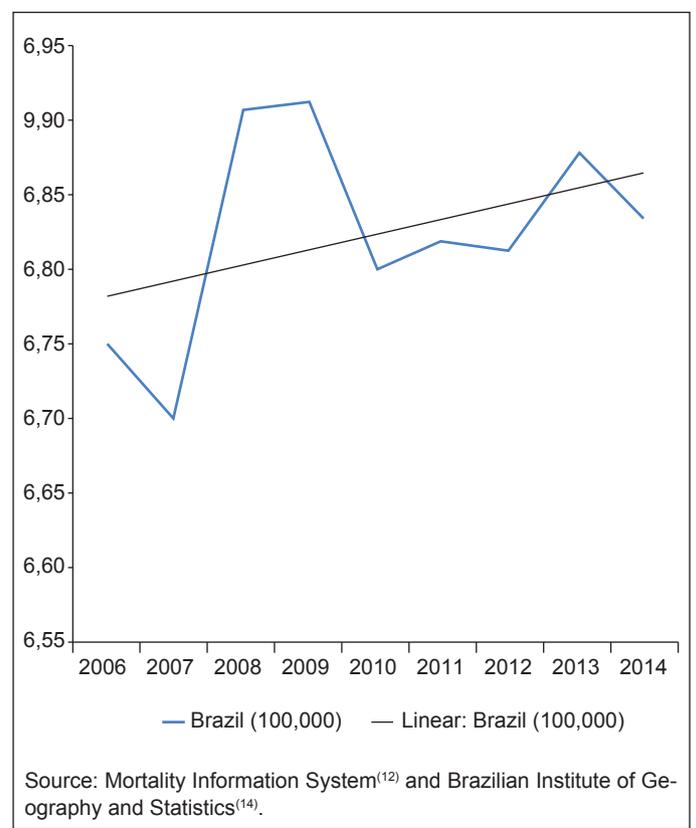
Table 2 – Mortality coefficients of cervix cancer in the Brazilian female population aged 25 to 64 from 2006 to 2014.

Year	Number of deaths from cervix cancer	Brazilian female population	Specific mortality coefficient (100,000)
2006	3,059	45,330,817	6.748168691
2007	3,112	46,454,770	6.698989146
2008	3,287	47,584,598	6.907697318
2009	3,366	48,684,881	6.913850729
2010	3,384	49,732,496	6.804404106
2011	3,461	50,728,309	6.822620482
2012	3,520	51,667,784	6.812755894
2013	3,616	52,556,386	6.88022955
2014	3,651	53,407,458	6.836123899
Total	30,456		

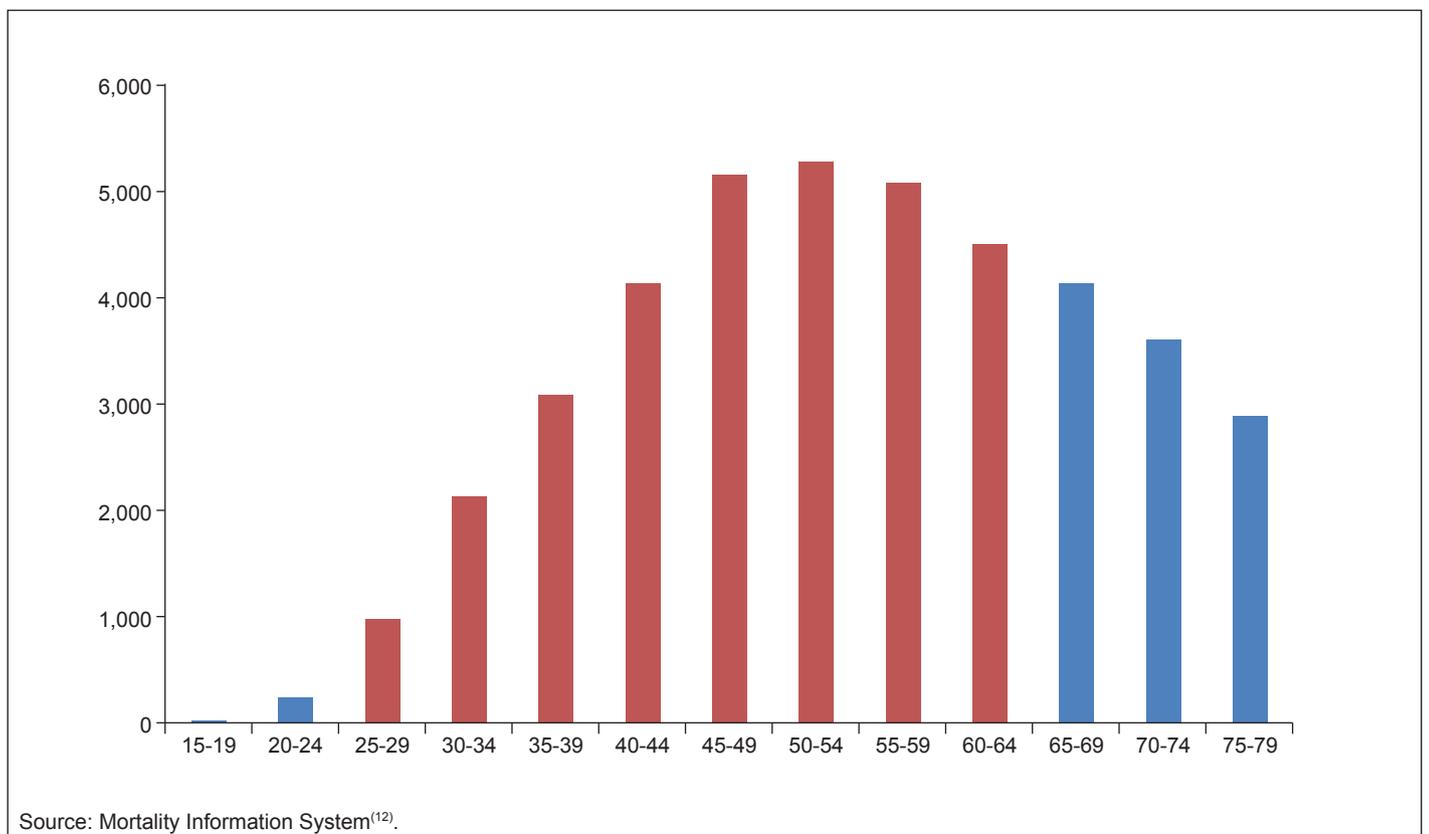
Source: Mortality Information System<sup>(12)</sup> and Brazilian Institute of Geography and Statistics<sup>(14)</sup>.



**Figure 4** – Absolute number of deaths from cervix cancer of Brazilian female population aged 25 to 64 in Brazil from 2006 to 2014.



**Figure 5** – Specific mortality coefficient from cervix cancer in Brazil of women aged 25 to 64 from 2006 to 2014 per 100,000 women.



**Figure 6** – Total number of deaths from cervix cancer in Brazil, from 2006 to 2014, distributed according to the age group.

(or Pap Smear) has been an extremely useful tool in reducing cervix cancer in countries where its use is carried out in a systematic and organized way<sup>(6,7)</sup>.

According to the 2016 Brazilian Guidelines for the Trace of the Cervix manual<sup>(7)</sup>, the beginning of the PS collection should happen at the age of 25 for sexually active women, avoiding the screening before that age. In 1986, a study conducted by the International Agency for Research on Cancer (IARC) estimated that PS examination at the age of 20 would result in the reduction of less than 1% of the cumulative incidence of cervix cancer in the studied population<sup>(17)</sup>. Other investigations carried out later, including in Brazil, corroborated the previous IARC's study and demonstrated that the screening in women under 24 years old not only loses effectiveness in preventing future cancers, but can also result in unnecessary expenses, over-treatment, social stigmatization and anxiety for patients<sup>(7,18)</sup>. Women with no history of invasive neoplasia and who have had two negative results in the last five years can discontinue the screening at the age of 64, because there is little risk of HPV infection and cancer progression<sup>(19)</sup>.

Generally, countries that can achieve coverage by PS screening performed every three to five years and exceeding 50% of the population have the mortality rate of less than three per 100,000 women per year. If the coverage is above 70%, mortality rates are reduced to 2 deaths or less per 100,000 women for every year<sup>(20)</sup>. In terms

of coverage, Brazil is still far from this scenario, since according to SISCOLO analysis<sup>(13)</sup> the number of PS performed in the Brazilian female population in the 25–64 age group shows that the average coverage in Brazil in nine years of study was of 16.09%. Even if different women performed the exam annually, the coverage would be of 48.27% in three years. In addition, a SISCOLO's data analysis noted that more than 80% of women underwent a PS in recent years, revealing that probably the same group of women was being screened, keeping a portion of the female population excluded from the screening process, which would justify the high number of cases of cervix cancer occurring in Brazil today<sup>(13)</sup>.

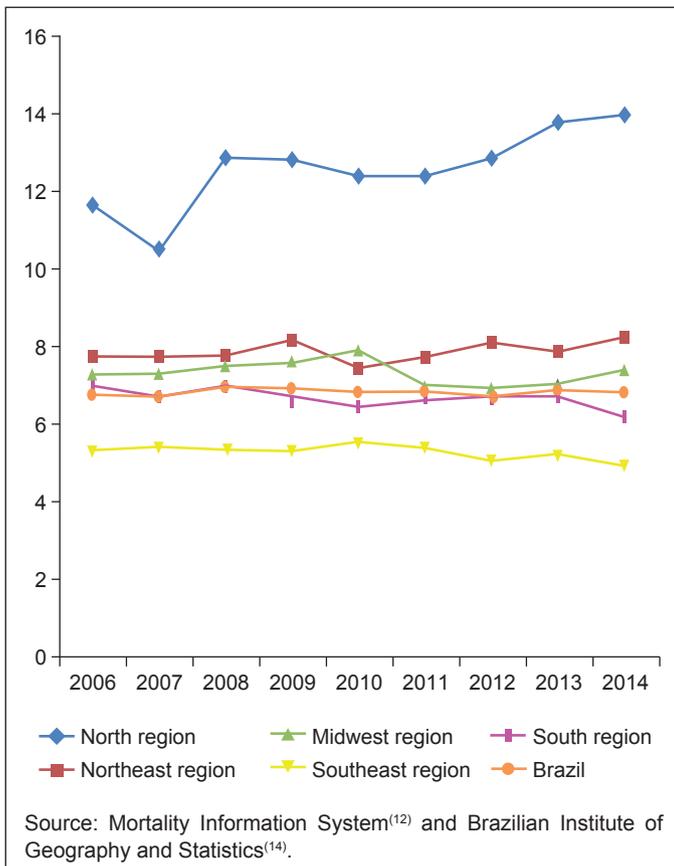
Contrary to the expected world trend, the Brazilian PS coverage decreased over the nine years of study, not following even the population growth. In an interregional comparison, disparities in coverage for exams were also observed: the lowest coverage rates were found in the Northern region of the country (average of 14.58%), where the incidence of cervix cancer is the first among the cases of cancer in women, excluding non-melanoma skin cancer<sup>(8)</sup>.

There are three critical assessments of the data collected for analysis. First of all, data were extracted from the SISCOLO platform<sup>(13)</sup>, a virtual database fed exclusively by public services offered by SUS. Thus, the percentage of tests conducted over the network or private health supplement, which corresponds to 24%<sup>(21)</sup>, is not accounted for. Secondly, as only the collected exams number is registered, and not the number of women who were attended, it is possible that some women have collected more than one exam in the same year or have collected tests annually, not respecting the interval of three years of each collection, which would overestimate the coverage by the PS exam. Thirdly, although the data in the study were used for the year 2014, caution is required when interpreting the data from this year, because coverage by PS showed extremely reduced in all states and may be associated with incomplete filling on the SISCOLO platform.

In addition, it is important to point out that if all women within the age group recommended for screening were to undergo PS by SUS, there would possibly be no physical structure nowadays in Brazil to support the demand<sup>(22)</sup>.

In an attempt to minimize these biases, the study also evaluated death rates from cervix cancer, i.e., a parameter whose data are restricted to public source, taken from the death certificate and fed into the SIM<sup>(12)</sup>. The rates of death from this neoplasia remained virtually constant in the nine years of study, from 6.75 deaths per 100,000 women, in 2006, to 6.84 in 2014, indicating that the current coverage for PS in Brazil is insufficient to change the profile of the mortality from this neoplasia. Extremes of mortality from cervix cancer are observed in the world: in 2012, the East African countries presented a mortality of 27.6 per 100,000 women. On the other hand, countries like Australia and New Zealand reported rates of 1.5 death per 100,000 women in the same period<sup>(23)</sup>.

The specific mortality from cervix cancer varied according to the Brazilian region, showing the highest rates in the Northern region of the country (average of 12.58 deaths per 100,000 women from 2006 to 2014), an expected result, since a region with the lowest coverage for PS generates vulnerability in the population health. These values are close to those ones of underdeveloped countries, such as India (mortality of 12.4 per 100,000 women)<sup>(10)</sup>.



**Figure 7** – Comparison of specific mortality coefficient by cervix cancer among the five Brazilian regions and Brazil over nine years (2006 to 2014) per 100,000 women.

The concentration of the highest mortality rate from cervix cancer between 50 and 54 years of age (11.62% of the total number of deaths) during the nine years of the study reflects data already found in the literature. In Taiwan, in 2011, the two highest concentrations of deaths were women between 45 and 54 years of age (14.4%) and over 55 (18.1%)<sup>(24)</sup>. In Ireland, the average age of diagnosis of this neoplasm was 46 years old, while the average mortality occurred at 56 years of age<sup>(25)</sup>.

In a completely preventable disease such as cervix cancer, it is unacceptable that such high levels of Brazilian mortality remain in the last nine years. It is necessary that the country takes over a screening program through oncotic colposcopy in a very organized way, modifying the current infrastructure or, therefore, adopts new prevention strategies. Among these new modalities, it is suggested the vaccination against HPV<sup>(26)</sup>, already available in the basic health network for girls and boys up to 14 years of age<sup>(27)</sup>. In addition, changes in the ways of screening are also valid, using HPV DNA testing<sup>(28)</sup>, a more sensitive and self-collecting methodology accessible to many Brazilian regions that are difficult to access in the current forms of screening<sup>(29)</sup>. According to Ronco et al.<sup>(28)</sup>, protection afforded by the HPV DNA testing adds about 60 to 70% efficacy in screening for high-grade neoplasms compared to traditional cytopathology.

In countries like Mexico, it is possible to find an innovative prevention and screening program, which consists of vaccinating women from 12 to 16 years, cytology in women aged 24 to 34, and screening women over 35 years for HPV DNA with later follow-up for cytology in women with positive HPV DNA<sup>(30)</sup>. The American Cancer Society, in conjunction with the American Society for Colposcopy and Cervical Pathology and the American Society of Screening for Prevention and Early Detection of Cancer, in the latest 2012 newsletter<sup>(31)</sup>, recommended that no screening by any method should be performed under 21 years of age, keeping only vaccination. From 21 to 29 years of age, isolated cytology should be carried out every three years, and there is no evidence of safety at longer intervals. In the age group 30 to 65, cytology can be maintained every three years, or accompanied by HPV DNA testing every five years. Studies indicate that the frequency could be safely reduced by performing the exam every five years, rather than the three years of cytopathology, making a more rational use of financial resources in each nation<sup>(28)</sup>.

## CONCLUSION

Brazil has remained in the last nine years with extremely low coverage of oncotic colposcopy and a constant mortality rate, demonstrating the urgent need to change the strategy for cervix cancer prevention in our country.

## Conflict of interests

The authors declare no conflict of interests.

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**Address for correspondence:**

**EDISON NATAL FEDRIZZI**

Centro de Pesquisa Clínica Projeto HPV

Universidade Federal de Santa Catarina

Avenida Governador José Boabaid, 272 – Córrego Grande

Florianópolis (SC), Brasil

CEP: 88037-200

E-mail: [enfedrizzi@uol.com.br](mailto:enfedrizzi@uol.com.br)

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# FACTORS ASSOCIATED WITH *CHLAMYDIA TRACHOMATIS* INFECTION IN WOMEN RESIDENT IN THE STATE OF RORAIMA, BRAZIL

## FATORES ASSOCIADOS À INFECÇÃO POR *CHLAMYDIA TRACHOMATIS* EM MULHERES RESIDENTES NO ESTADO DE RORAIMA, BRASIL

Bianca Jorge Sequeira<sup>1</sup>, Edvaldo Carlos Brito Loureiro<sup>2</sup>, Wagner do Carmo Costa<sup>3</sup>

### ABSTRACT

**Introduction:** *Chlamydia trachomatis* is an obligate intracellular bacterium. The genital infection caused by this bacterium is considered the most common sexually transmitted bacterial disease in the world. However, despite the magnitude of the problem, the state of Roraima does not address studies that establish its prevalence in the female population. **Objective:** To determine the prevalence of genital *C. trachomatis* in women living in Roraima and to evaluate the correlation of results with sexual behavior. **Methods:** A descriptive, cross-sectional and quantitative study involved 273 sexually active women, aged 18–60, resident in Roraima. In the beginning, 273 endocervical samples were collected through speculum examination in order to carry out the direct immunofluorescence test for *C. trachomatis*. In addition to laboratory tests for the detection of *C. trachomatis*, a survey was conducted through a clinical-epidemiological questionnaire, which determined the sociocultural and sexual profile of each participant. **Results:** The prevalence of *C. trachomatis* infection was determined in 33.73%. Association between *C. trachomatis* infection and women who have a family income greater than five minimum wages was also observed. Besides, chlamydial infection was connected with pain and bleeding during intercourse. The link between *C. trachomatis* infection and anal sex was demonstrated as well. Having a partner who works or had worked in mining and more than one sexual partner was pointed as a risk factor. **Conclusion:** The results indicate the high prevalence of *C. trachomatis* infection among the studied population, and factors such as practice of anal sex and having as a sexual partner someone who works or had worked in mining were pointed as associated with the infection.

**Keywords:** *Chlamydia trachomatis*; epidemiology; sexually transmitted disease; Brazil.

### RESUMO

**Introdução:** A *Chlamydia trachomatis* consiste em uma bactéria intracelular obrigatória. A infecção genital causada por ela é considerada a doença bacteriana sexualmente transmissível mais comum no mundo. Todavia, apesar da magnitude do problema, Roraima não apresenta estudos que estabeleçam sua prevalência na população feminina. **Objetivo:** Determinar a prevalência da infecção genital por *C. trachomatis* em mulheres residentes em Roraima e avaliar a correlação dos resultados com possíveis fatores associados. **Métodos:** Estudo descritivo, transversal e de caráter quantitativo envolveu 273 mulheres sexualmente ativas com idades variando entre 18 e 60 anos residentes no estado de Roraima. Foram colhidas 273 amostras endocervicais por intermédio de exame especular para a realização do teste de imunofluorescência direta para *C. trachomatis*. Foi aplicado a cada participante um questionário clínico-epidemiológico que traçou o perfil sociocultural e sexual dos integrantes da pesquisa. **Resultados:** A prevalência da infecção por *C. trachomatis* foi de 33,73%. Foi demonstrada associação para a infecção por *C. trachomatis* em mulheres que possuem renda familiar mensal maior que cinco salários-mínimos. Houve ligação da infecção por clamídia com as variáveis dor e sangramento durante o ato sexual. Foi evidenciada relação entre a infecção por *C. trachomatis* e a prática do sexo anal. Ter um parceiro que trabalha ou trabalhou no garimpo foi apontado como fator de risco. Por fim, este estudo demonstrou associação para a infecção por *C. trachomatis* em mulheres que possuem mais de um parceiro sexual. **Conclusão:** Os resultados indicam a alta prevalência de infecção por *C. trachomatis* entre a população estudada. Fatores como a prática do sexo anal e possuir como parceiro sexual alguém que trabalha ou já trabalhou em garimpo foram apontados como associados à infecção.

**Palavras-chave:** *Chlamydia trachomatis*; epidemiologia; doença sexualmente transmissível; Brasil.

## INTRODUCTION

*Chlamydia trachomatis* is an obligate intracellular bacterium not often producing symptoms and whose D and K serotypes are responsible for urogenital sexually transmitted infections<sup>(1,2)</sup>. The genital infection caused by this bacterium is the leading sexually transmitted bacterial infection<sup>(3)</sup>. According to the World Health Organization (WHO), around 50 million new cases are diagnosed every year in all continents<sup>(4)</sup>. Infection with *C. trachomatis* represents the highest proportion among all curable sexually transmitted diseases (STDs). It is frequent the detection of women with tubal damage, sometimes irreversible, provoked by this agent, determining permanent infertility<sup>(5)</sup>. If the infection with this pathogen is neither diagnosed nor

treated in time, it can progress and cause pelvic inflammatory disease, chronic pelvic pain, and infertility<sup>(6)</sup>.

The age would be one of the risk factors, and the most susceptible people are the younger individuals aged between 20 and 25 years, probably due to a greater sexual activity or number of partners<sup>(7)</sup>. The prevalence of the infection between adolescent and young adults in the 14 to 24 age group is four times higher than the prevalence between those ones in the 25 to 39 age group. Data from the National Coordination of STD/AIDS (Coordenação Nacional de DST/AIDS) indicate that almost two million new cases occur annually in Brazil<sup>(8)</sup>.

Estimates indicate more than 10 million new sexually transmitted infections occurrence in Brazil, which can progress to symptomatic and asymptomatic disease<sup>(9)</sup>. Such incidence becomes worrisome if we consider that the population living in the state of Roraima, located in far Northern Brazil, in the Amazon region, deals routinely with poverty and sexual contact with people from bordering countries, such as British Guiana and Venezuela. Many women living in Roraima are tricked into working in mines of neighboring countries, driving

<sup>1</sup>Centro de Ciências da Saúde, Universidade Federal de Roraima (UFRR) – Boa Vista (RR), Brazil.

<sup>2</sup>Instituto Evandro Chagas (IEC) – Ananindeua (PA), Brazil.

<sup>3</sup>Faculdade Cathedral de Ensino Superior – Boa Vista (RR), Brazil.

them to prostitution. However, when such women are infected with STD in those mines, they return to Brazil to be treated by the Public Health System (Sistema Único de Saúde — SUS), or in some cases they do not even look for treatment, becoming thus a potential vehicle for transmission of diseases<sup>(10)</sup>.

Despite the magnitude of the problem, in Brazil the epidemiological behavior of this infection is not accurately known, since cervicitis and urethritis are not notifiable diseases, and most public services have no laboratory tests for the diagnosis<sup>(11)</sup>. In Roraima, the existing data are scarce and often unreliable due to underreporting caused mainly by the often asymptomatic *Chlamydia* infection and the difficulty for women from the interior of the municipalities to access the state health services.

## OBJECTIVE

Determine the prevalence of genital infection with *C. trachomatis* in women resident in the state of Roraima and evaluate the results correlation between eventual associated factors.

## METHODS

This research has been characterized as a descriptive, cross-sectional and quantitative study and involved 273 sexually active women, conducted to the Reference Center of Women's Health (Centro de Referência de Saúde da Mulher), in the city of Boa Vista, Roraima, for preventive examination of cervical cancer, aged between 18 and 60 years and resident in Roraima. In addition to the samples collection for the direct immunofluorescence (DIF) testing for the detection of *C. Trachomatis*, a semi-structured questionnaire was also applied, and it traced the sociocultural and sexual profile of the participants. Samples and data collections were made between April, 2014, and July, 2015. Collections occurred in the Reference Center of Women's Health, a public health institution that is reference in Roraima.

Endocervical samples were collected through specular examination of each participant for the detection of *C. trachomatis* and fixed with methanol on specific blades. Blades were conditioned and maintained at -20°C until they were transported to the Bacteriology Section of the Instituto Evandro Chagas (IEC), in the city of Ananindeua, state of Pará, Brazil.

The tests for DIF were carried out in the IEC. This method is based on the direct detection of the antigen in cells or tissues, intracellular or membranous, using a specific marked antibody. The DIF test used consists of monoclonal antibodies tagged with immunofluorescence (DFA Chlamydia Fluorect®-Omega Diagnostics), a method employed in laboratories for *C. trachomatis* diagnosis, mainly because of its lower cost when compared to other methods. This method applied in endocervical clinical specimens allows a diagnosis in approximately 30 minutes, and it is extremely valuable to the diagnosis and the epidemiological control of urogenital infection with *C. trachomatis*<sup>(12)</sup>.

From the total of 273 collected samples, 18 were excluded, as they presented a number below 100 cells in the blades' smears for DIF, or had excessive mucus or blood, which would endanger the accomplishment of the test.

Descriptive analyses were carried out for the interpretation of the data collected through the clinical-epidemiological questionnaire including average with standard deviation for quantitative variables of parametric nature. The comparison between the samples' averages was performed by Student T test, since the equivalence of sampling variances is ensured. Otherwise, the Mann-Whitney test was used. The Chi-square test was used for comparison between proportions. The estimate of the variable association quantification was performed through *odds ratio* for a confidence interval of 95% (CI 95%) (Newcombe-Wilson method). The significant variables in univariate analysis were reviewed in a multivariate analysis (logistic regression method) to obtain the adjusted and independent *odds ratio*. The statistical program used was the Epi Info 7 (CDC, Atlanta, United States), settling the level of 5% for rejection of the null hypothesis.

With respect to ethical criteria, this research was evaluated and approved by the Ethics Committee of the Universidade Federal de Roraima (UFRR), through the co-corroborated opinion n° 408.996.

## RESULTS

The prevalence of infection with *C. trachomatis* in the group evaluated in the state of Roraima, of 255 research participants, was 33.73%. The social and demographic characteristics of the participants of the study are described in **Table 1**.

Among the 255 research participants, 127 were in the 40–60 age group (49.81%), 76 in the 29–39 age group (29.80%), and 52 in the 18–28 age group (20.39%). The most prevalent age group for infection for *C. trachomatis* was the 29–39 years one (43.05%), followed by 40–60 (31.00%), and the lowest prevalence in the 18–28 age group (25.95%).

The relationship between race/color and infection with *C. trachomatis* showed a small difference between the mestiza and the white women: the first group, 37.50%, and the second group, 37.14%. Among black women, the prevalence was of 33.33%, while the brown women, despite representing the largest group, presented the lowest prevalence (32.99%).

Marital status related positive result for *C. trachomatis* infection pointed out that the prevalence was highest among the group of single women (39.28%), and followed by married women, which were grouped along with the group who reported living a common-law marriage (30.37%). Widows had the lowest prevalence (16.66%).

With regard to education, a single participant has a postgraduate degree (0.39%), and had a positive result for *C. trachomatis*, but as it is a sample of a single element, this result may not be statistically relevant. The highest prevalence of *C. trachomatis* infection was among those women with incomplete elementary school (47.91%), followed by those ones who not completed high school (44.44%), have incomplete college degree (38.46%), complete high school (33.33%), college degree (31.25%) and complete elementary school (20.00%).

Finally, the analysis of the monthly income exhibited that the highest prevalence occurred between the group of women with monthly family income exceeding five minimum wages (41.17%), followed by the group with the income of four or five wages (37.09%) and two or three minimum wages (32.37%). The lowest prevalence, 29.73%, was found in the group that owns the lowest income up to a monthly minimum wage.

As described in **Table 2**, the Chi-square test (significance level  $p < 0.05$ ) only demonstrated a statistically significant association between the positive result for *C. trachomatis* and the family income variable ( $p = 0.001$ ). Through the analysis of Chi-square residues, it was possible to identify that the monthly family income exceeding five minimum wages would be associated with infection with *C. trachomatis* in the sample under study. No association was observed between age group ( $p = 0.129$ ), marital status ( $p = 0.198$ ), education ( $p = 0.150$ ), place of residence ( $p = 0.852$ ) and race/color ( $p = 0.963$ ).

Regarding the number of sexual partners, 36 women (14.11%) did not have any sexual partner at the time of the research, 199 (78.00%) had only one, and 20 women (7.89%) had more than one sexual partner. The highest prevalence of infection with *C. trachomatis* is the group of women who had more than one partner (70.00%), followed

by those ones with only one (32.16%). The lowest prevalence was verified among women who did not have any sexual partner (28.57%).

About the use of condoms during intercourse, of 254 women who answered this question, 238 declared not using a condom during intercourse (93.70%) and 16 reported the use of condom during sex (6.30%). The prevalence of *C. trachomatis* infection among women who do not use condoms during sex is of 33.61%. Those ones who claimed to use it showed prevalence of 37.51%.

Among women who answered this question, 215 (84.31%) reported never having worked in mining, while 40 (15.69%) work or had worked in it. The group of those ones who never worked in mining presented 29.76% prevalence for *C. trachomatis* infection, and the group who reported working or having worked in minings presented a much higher prevalence, of approximately 55%.

Relating to the existence of a relationship between infection with *C. trachomatis* and the fact that women have a sex partner who works or had worked in mining, 166 women (65.09%) reported have never had sex with such a partner, while 89 women (34.91%) reported had lived this experience. The prevalence of infection with *C. trachomatis* among women who have never had intercourse with people who work or have worked in mining was of 21.68%, and the prevalence of those ones whose answer was yes was of 56.18%.

**Table 1** – Sociodemographic profile of women living in Roraima, Brazil, who participated in the research from 2014 to 2015.

Explanatory variables	n	%
City of residence		
Amajari	2	0.78
Boa Vista	215	84.31
Bonfim	4	1.57
Cantá	9	3.58
Caracarái	4	1.56
Mucaja	4	1.56
Normandia	1	0.39
Pacaraima	5	1.96
Rorainópolis	3	1.17
São João da Baliza	3	1.17
São Luiz do Anauá	2	0.78
Uiramutã	3	1.17
Age group (years old)		
18–28	52	20.39
29–39	76	29.80
40–60	127	49.81
Marital status		
Married	138	54.11
Single	109	42.74
Widow	8	3.15
Education		
Illiterate	11	4.31
Incomplete elementary school	44	17.25
Complete elementary school	32	12.54
Incomplete high school	8	3.13
Complete high school	111	43.52
Incomplete college degree	15	5.88
Complete college degree	33	12.94
Postgraduate degree	1	0.43
Monthly family income (minimum wage)		
Up to 1	40	15.68
2–3	133	52.15
4–5	65	25.49
More than 5	17	6.68
Race/Color		
White	30	11.76
Mestiza	8	3.13
Black	17	6.66
Brown	200	78.45

**Table 2** – Association between the sociodemographic characteristics of women living in Roraima, Brazil, with a positive result of direct immunofluorescence for *Chlamydia trachomatis* from 2014 to 2015.

Sociodemographic characteristics	n	Positive n (%)	p-value
Age group			
18–28	54	15 (27.0)	0.129
29–39	72	31 (42.0)	
40–60	129	40 (31.0)	
Marital status			
Married	135	41 (31.0)	0.198
Widow	7	1 (14.5)	
Single	112	44 (40.5)	
Education			
Illiterate	11	0 (0.0)	0.115
Incomplete elementary school	48	23 (48.0)	
Complete elementary school	30	6 (20.0)	
Incomplete high school	9	4 (44.4)	
Complete high school	111	37 (33.3)	
Incomplete college degree	13	5 (38.5)	
Complete college degree	32	10 (31.3)	
Postgraduate degree	1	1 (100.0)	
Residence			
Capital	215	72 (33.5)	0.852
Interior	40	14 (35.0)	
Race/Color			
White	35	13 (37.1)	0.963
Mestiza	8	3 (37.5)	
Black	15	5 (33.3)	
Brown	197	65 (32.9)	
Family Income (wages)			
Up to 1	37	11 (29.8)	0.001
2–3	139	45 (32.3)	
4–5	62	23 (37.0)	
More than 5	17	07 (41.2)	

About the practice of anal sex, 175 (68.89%) reported had never practiced anal sex, while 79 (31.11%) claimed that do practice it. Concerning the prevalence of *C. trachomatis* infection among these 254 women, those ones who never practiced anal sex corresponded to 26.28%, while the other group was of 49.37%.

On the occurrence of miscarriages, however, of the 254 women who answered this question, 208 (81.89%) reported never had an abortion, while 46 (18.11%) claimed had already have it. The prevalence of infection with *C. trachomatis* between women who did not have an abortion was of 30.77%, and the second group of women was of 47.82%.

Finally, in case of pain and bleeding during sex, among 254 participants who responded to the question about pain, 155 (61.02%) claimed not to feel pain during sex, while 99 (38.98%) reported feeling pain. As far as pain during sex is concerned, the infection with *C. trachomatis* has a higher prevalence among women who reported feeling pain (51.51%). Those ones who reported no pain showed the prevalence of 22.58%. As for the bleeding, 199 (78.03%) women reported does not suffer bleeding during sex, while 56 (21.97%) claimed to suffer. When the positive result for *C. trachomatis* infection was related to the occurrence or absence of bleeding, the prevalence of infection among the group who reported no bleeding was of 25.62%, while the group who reported bleeding pointed out the prevalence of 62.50%.

Chi-square analysis constated that the variables pain ( $p=0.0001$ ) and bleeding during sexual intercourse ( $p=0.0001$ ) were associated with chlamydial infection in the sample analyzed. On the other hand, the association between *Chlamydia* and the occurrence of miscarriage ( $p=0.0391$ ) was not evidenced.

The association between the variables and the positive result for *C. trachomatis* are described in **Table 3**. The result of the simple logistic regression identified the following: women with more than one sexual partner are 5.28 times more likely to get the infection;

**Table 3** – Association between risk factors with positive result for *Chlamydia trachomatis* in women residing in Roraima, Brazil, from 2014 to 2015.

Variable	% ( $\chi^2$ )	p-value	OR (95%CI)
Number of sexual partners			
>1	70.00	0.0008	5.28 (1.95–14.20)
0 or 1	39.60		
Anal sex			
Yes	49.30	0.0005	2.73 (1.56–4.76)
No	26.29		
Works or had work in mining			
Yes	55.00	0.0031	2.88 (1.44–5.73)
No	29.77		
Have a sexual partner who work or had worked in mining			
Yes	56.18	>0.0001	4.62 (2.64–8.09)
No	21.69		
Use of condom			
Yes	37.50	0.9640	1.18 (0.41–3.37)
No	33.61		
Partner with STD			
Yes	36.00	0.9756	1.11 (0.45–2.64)
No	33.48		

OR: odds ratio; IC: confidence interval; STD: sexually transmitted diseases.

those ones who practice anal sex are 2.73 times; the fact the woman works or had worked in mining increases the possibility of being infected by *Chlamydia* by 2.88 times; and those ones that have a partner who works or had worked in mining increases the risk of infection by 4.62 times. However, using condoms or having a STD partner did not show an association factor for *Chlamydia* infection in the analyzed sample.

On the other hand, multivariate logistic regression established that having more than one sexual partner ( $p=0.0098$ ), practicing anal sex ( $p=0.0017$ ) and having a sexual partner who works or had worked in mining ( $p=0.0002$ ) indicated a significant association with *C. trachomatis* infection. The variable “having worked or worked in mining” was not statistically significant. Women who had more than one sexual partner are 4.27 times more likely to be infected with *C. trachomatis*, 2.99 times those ones who practice anal sex, and 3.66 times those ones who have sex partners who work or worked in mining (**Table 4**).

## DISCUSSION

Epidemiological studies on infection with *C. trachomatis* have documented a high prevalence (1 to 30%) of the microorganism in active young and sexually women<sup>(13)</sup>. In India, the prevalence in 2009 among women was of 23%<sup>(14)</sup>. In Latin America, where countries do not have an effective program for the screening of this pathogen in their health policies, the data are few, but very expressive: in Argentina, the prevalence is of 26.4%<sup>(15)</sup>, 7.6% in Peru, and 6.9% in Chile<sup>(16)</sup>.

In Brazil, it is estimated the occurrence of approximately 1,967,200 new cases of *Chlamydia* every year<sup>(9)</sup>. The results of this survey differ from the ones obtained in studies about other regions of Brazil, as the investigation carried out in 2007 in the city of Recife involving 171 women. The referred research used the DIF technique in endocervical samples and showed the prevalence of 3.5% infection with *C. trachomatis*<sup>(17)</sup>. Another study carried out at the Instituto Fernandes Filgueiras, Rio de Janeiro, Brazil, also using DIF, pointed out the prevalence of 11% of *C. trachomatis* infection among women who had the normal oncotic cytology of a total group of 279 women<sup>(18)</sup>. The work developed at Hospital das Clínicas of the Medical School

**Table 4** – Results of multivariate logistic regression on the association between risk factors with positive results for *Chlamydia trachomatis* in women residing in Roraima, Brazil, from 2014 to 2015.

Variable	OR	95%CI	p-value
Number of sexual partners			
>1	4.27	1.41–12.90	0.0098
0 or 01	1.00		
Anal sex			
Yes	2.99	1.50–5.93	0.0017
No	1.00		
Work or had worked in mining			
Yes	0.95	0.40–2.26	0.9137
No	1.00		
Have a sexual partner who works or had worked in mining			
Yes	3.66	1.83–7.31	0.0002
No	1.00		

OR: odds ratio; IC: confidence interval; STD: sexually transmitted diseases.

of the Universidade de São Paulo, applying the same technique, found the prevalence of 7.8% among symptomatic women, and 4.3% among asymptomatic women<sup>(19)</sup>.

Other studies developed through another analysis technique, the polymerase chain reaction (PCR), such as the one held in 2011, in São Paulo, Brazil, with 781 women, pointed out an infection prevalence with *C. trachomatis* of 8.4%<sup>(20)</sup>. In a research carried out in a city in Southern Brazil, in 2008, the prevalence of *C. trachomatis* infection was of 10.7%<sup>(21)</sup>.

This study pointed out to the prevalence of 33.73% for *C. trachomatis* infection among women residing in the state of Roraima, a high percentage when compared to the ones of other Brazilian states. However, this result can be understood when this percentage is compared with data from health information systems that show Roraima as one of the Brazilian states with the highest prevalence of Human Immunodeficiency Virus (HIV) and Human Papilloma Virus infections.

In this study, the age was not considered as an associated factor for *C. trachomatis* infection. This result diverges from other studies that claim that one of the risk factors for *C. trachomatis* infections would be the age group, characterized as more susceptible individuals aged between 20 and 25 years old, probably due to this group's higher sexual activity or number of partners<sup>(22,23)</sup>.

Regarding education, several surveys show that the highest rates of infection with *C. trachomatis* are among the women with a level of education from the 5<sup>th</sup> to the 8<sup>th</sup> grade of elementary education<sup>(22)</sup>, i.e., a low level of education. However, these statements differ from the result of this study, which concluded that in the analyzed sample low education cannot be considered a risk factor for infection with *C. trachomatis*. On the other hand, confirming the results of this survey, a study conducted by Oliveira et al. in a rural area of Northeastern Brazil pointed out that the educational level is not associated with the risk of STD infection. According to the same authors, similar results were obtained in studies carried out in the rural areas of Nepal and China<sup>(18)</sup>.

Concerning to family income, the result achieved in this research diverges completely from the results available in the literature<sup>(24,25)</sup>, since it points out that the higher prevalence of this infection occurred among women who reported the highest monthly income (above five minimum wages) and the lowest prevalence occurred among women with lower income (less than one minimum wage). Therefore, a higher purchasing power acts as an associated factor for the infection with *C. trachomatis* in the sample analyzed. So, a higher monthly income does not create the awareness that women of Roraima need to protect themselves against infection with this microorganism.

With respect to the number of partners, having more than one sexual partner is part of the risk score for this infection<sup>(24)</sup>. The results of this study indicate that having more than one sexual partner is a variable associated with infection with *C. trachomatis* between women of Roraima. This finding is consistent with studies claiming that the number of sexual partners and the frequent exchange of partners are risk factors for infection and reinfection with *C. trachomatis*<sup>(21)</sup>.

As for the condom use during sex, despite the very low adhesion, since 93% of women declared not using it, this fact is not configured as a variable associated with infection with *C. trachomatis*, diverging from the literature on the topic<sup>(22)</sup>. Therefore, a doubt arises whether women who have claimed always using a condom during sex did not tell the truth or use it incorrectly.

As Roraima is a state of international borders with two countries (Venezuela and British Guiana), where the practice of gold and diamond mining is legal, we decided to evaluate the relationship between the positive result for *C. trachomatis* infection and the fact that women work or had worked in mines or have sex partners in this activity. In this way, the fact that women related sex with a partner who had worked or works in mining was cited as a factor associated with chlamydial infection in this research, both univariate and multivariate. On the other hand, the fact that the participant of the research had some day worked or still work in mining was shown as a variable linked with the infection only in univariate analysis, failing to be in the multivariate analysis. Among the studied literature, it was not evidenced any correlate study between women or their sexual partner working in mining and the increase of the prevalence of *C. trachomatis* infection.

With respect to the presence of symptoms such as pain and bleeding during intercourse, studies revealed that most of the infected women is asymptomatic<sup>2,24</sup>. Diverging from these authors, in this study the bleeding during sex was present at 62.50% of women with *C. trachomatis* infection, and pain in 51.51%. It is appropriate to point out that none of the samples collected for DIF was bloody, thus not impairing the quality of the results. In this way, the results of this study indicate that, for this sample, bleeding and pain during intercourse is correlated with the infection by this microorganism.

Finally, with regard to sex, no study was found in the literature evaluating the association between the practice of anal sex and the increased risk of *Chlamydia* infection, but the present study showed that women having anal sex are 2.99 times more likely to be infected with this microorganism.

Some limitations became evident during this research, and among them the most relevant one was the insufficiency of data on the epidemiology of *C. trachomatis* infection in the state of Roraima, including official information systems of the Ministry of Health, hindering the establishment of parameters to determine the sampling universe and to institute a more regionalized discussion of the results. Added to that, another limitation to be mentioned is the DIF method, since a trained microscopist is required to accomplish it, and it is difficult to process a large number of samples. Experience in the interpretation of the immunofluorescence is fundamental as the nonspecific antibody binding to other micro-organisms can occur, leading to a false-positive result<sup>(12)</sup>.

## CONCLUSION

The results showed a high prevalence of infection with *C. trachomatis* in women resident in the state of Roraima, as well as the correlation between this infection and associated factors related to intercourse, such as multiple partners, non-adherence to condom use, anal sex practice, and intercourse with partners who work or had worked in mines. In this way, the findings indicate the inefficiency of public health policies to fight the infection with *C. trachomatis* in Roraima, besides the need of a more effective sex education work.

## Conflict of interests

The authors declare no conflict of interests.

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### Address for correspondence:

**BIANCA JORGE SEQUEIRA**

Centro de Ciências da Saúde – Universidade Federal de Roraima – Campus Paricarana

Avenida Capitão Ene Garcez, 2.413 – Aeroporto

Boa Vista (RR), Brasil

CEP: 69304-000

E-mail: bianca.costa@ufr.br

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# EVALUATION OF THE COMPLIANCE WITH THE GOALS PROPOSED BY THE WORLD HEALTH ORGANIZATION FOR THE ELIMINATION OF CONGENITAL SYPHILIS FROM A UNIVERSITY HOSPITAL OF RIO DE JANEIRO, BRAZIL

*AVALIAÇÃO DO CUMPRIMENTO DAS METAS PROPOSTAS PELA ORGANIZAÇÃO MUNDIAL DA SAÚDE PARA A ELIMINAÇÃO DA SÍFILIS CONGÊNITA EM UM HOSPITAL UNIVERSITÁRIO DO RIO DE JANEIRO*

*Luciane Rodrigues Pedreira de Cerqueira<sup>1</sup>, Denise Leite Maia Monteiro<sup>1,2</sup>, Stella Regina Taquette<sup>1</sup>, Nádia Cristina Pinheiro Rodrigues<sup>1,3</sup>, Caroline Tavares da Mota Monteiro<sup>4</sup>, Bianca de Melo Araújo<sup>4</sup>, Alexandre José Baptista Trajano<sup>1,5</sup>, Flávio Monteiro de Souza<sup>1</sup>*

## ABSTRACT

**Introduction:** The World Health Organization (WHO) considers Brazil as one of the 15 priority countries for the control of syphilis among pregnant women due to the high prevalence of the disease and the large population of the country. Despite the easy prevention and treatment of the disease, its progress in the country is epidemic. The disease is responsible for more than 300,000 fetal and neonatal deaths, and 520,000 fetal adverse outcomes annually in the world. **Objective:** To verify if the goals proposed by WHO for the elimination of congenital syphilis are being fulfilled in the pregnant women assistance. **Methods:** Cross-sectional study with data collected from laboratories, medical records and questionnaires of 79 parturients with the disease hospitalized at the Pedro Ernesto University Hospital (HUPE) of the Universidade do Estado do Rio de Janeiro (UERJ), Perinatal Nucleus, in Rio de Janeiro, Brazil, between 2012 and 2014. **Results:** The incidence of congenital syphilis in HUPE was the following: 26.6 cases per 1,000 live births (LB). The average age of pregnant women was 26 years, most non-white (81%), single (82.1%), and less than nine years of education (57.7%). History of previous sexually transmitted infections (STI) was reported by 35.4% (28/79) and 20% showed (16/79) Human Immunodeficiency Virus (HIV) coinfection. The majority (72.2%) did not use condoms regularly. In the evaluation of the goals recommended by WHO, only the enrolment reached 92.4% (90% goal), 87.3% of the participants were tested (90% goal), 72.2% of the pregnant women were treated (100% goal), 51.0% of them were treated before the 24<sup>th</sup> week of gestation (80% goal) and 19.0% of partners treated the disease (80% goal). Regarding the condom use orientation during prenatal care, 52.5% of the parturients confirmed the use of the preservative (100% goal). **Conclusion:** The basic and strategic rules defined by WHO for the control of congenital syphilis in the country have not been accomplished to the daily loss of thousands of opportunities to save lives during prenatal care.

**Keywords:** syphilis; pregnancy; prenatal care; prevalence.

## RESUMO

**Introdução:** O Brasil é considerado pela Organização Mundial da Saúde (OMS) um dos 15 países prioritários para o controle da sífilis entre as gestantes, pela alta prevalência da doença e grande população do país. Apesar de fácil prevenção e tratamento, a doença avança no país, que vivencia uma epidemia. É responsável anualmente no mundo por mais de 300 mil mortes fetais e neonatais e 520.000 desfechos adversos fetais. **Objetivo:** Verificar se as metas propostas pela OMS na eliminação da sífilis congênita estão sendo cumpridas na assistência das gestantes. **Métodos:** Estudo de corte transversal com dados coletados nos laboratórios, prontuários e questionários de 79 parturientes com a doença internadas no Núcleo Perinatal do Hospital Universitário Pedro Ernesto (HUPE), da Universidade do Estado do Rio de Janeiro (UERJ), no Rio de Janeiro, entre 2012 e 2014. **Resultados:** A incidência de sífilis congênita no HUPE foi de 26,6 casos a cada 1.000 nascidos vivos (NV). A média de idade das parturientes infectadas era de 26 anos, e elas em sua maioria eram não brancas (81%), solteiras (82,1%) e tinham menos de nove anos de estudo (57,7%). História de infecções sexualmente transmissíveis (IST) prévia foi relatada por 35,4% (28/79) e 20% tinha (16/79) coinfeção pelo vírus da imunodeficiência humana (HIV). A maioria (72,2%) não fazia uso regular de preservativos. Na avaliação das metas recomendadas pela OMS, somente a captação alcançou 92,4% (meta 90%). Foram testadas 87,3% das participantes (meta 90%), tratadas 72,2% das gestantes (meta 100%), sendo 51,0% antes da 24.<sup>a</sup> semana de gestação (meta 80%), e tratados também 19,0% dos parceiros (meta 80%). Em relação à orientação sobre o uso de preservativos durante o pré-natal, 52,5% o confirmou (meta 100%). **Conclusão:** As regras básicas e estratégicas definidas pela OMS para o controle da sífilis congênita no país não estão sendo cumpridas, o que leva diariamente à perda de milhares de oportunidades de salvar vidas durante o pré-natal.

**Palavras-chave:** sífilis; gestação; assistência pré-natal; prevalência.

## INTRODUCTION

The World Health Organization (WHO) estimates the annual occurrence in the world of 357 million cases of sexually transmitted infections (STI), such as chlamydia, gonorrhoea, syphilis and trichomoniasis<sup>(1)</sup>.

Syphilis has a notable importance, as it can contaminate the fetus in any stage of pregnancy by transplacental route and cause adverse

<sup>1</sup>Universidade do Estado do Rio de Janeiro (UERJ) – Rio de Janeiro (RJ), Brazil.

<sup>2</sup>Centro Universitário Serra dos Órgãos (UNIFESO) – Teresópolis (RJ), Brazil.

<sup>3</sup>Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz (FIOCRUZ) – Rio de Janeiro (RJ), Brazil.

<sup>4</sup>Colégio de Aplicação, UERJ – Rio de Janeiro (RJ), Brazil.

<sup>5</sup>Universidade do Grande Rio (UNIGRANRIO) – Rio de Janeiro (RJ), Brazil.

fetal outcomes, such as natimortality, stillbirth, low-birth weight, prematurity, fetal malformations, deafness, neurological impairment and active infection at birth.

According to the 2013 WHO's bulletin, 1.9 million pregnant women were infected with the disease in the world, with 66% of occurrence of unfavourable outcomes in cases of untreated syphilis<sup>(2)</sup>. Syphilis in pregnancy is annually responsible for more than 300,000 fetal and neonatal deaths, and 520,000 adverse fetal outcomes worldwide<sup>(3)</sup>.

The percentage of pregnant women with syphilis diagnosed and treated in the world is still not accurate, but global estimates suggest less than 10% of coverage for the diagnosis and treatment of the disease during pregnancy<sup>(4,5)</sup>.

Brazil is considered by WHO one of the 15 priority countries for the control of syphilis, due to the high prevalence of the disease and the large population of the country<sup>(6)</sup>.

The National Notifiable Disease System (Sistema de Informação de Agravos de Notificação  $\frac{3}{4}$  SINAN) reported the total of 227,663 cases of acquired syphilis in the period from 2010 to June 2016 in Brazil. Parallel to the increase in the number of syphilis cases in the adult population, an increase in the number of notifications of the disease among pregnant women occurred in the country. From 2005 to June 2016, 169,546 cases of syphilis in pregnant women were notified to SINAN, 42.9% of them in the Southeast, 21.7% in the Northeast, 13.7% in the South, 11.9% in the North, and 9.8% in the Midwest<sup>(1)</sup>.

The upward curve of syphilis in pregnant women in Brazil is worrying. We are living an epidemic of the disease, as revealed by the Ministry of Health in 2016. The detection rate of the disease has increased 95% in Brazil between 2012 and 2015: 0.59% in 2012; 74% in 2013; 0.97% in 2014; and 1.15% in 2015. From 2005 to 2013, the increase of syphilis cases in pregnant women was by 1,047%<sup>(7,8)</sup>, and was the double from 2010 to 2014<sup>(1)</sup>.

High rates of syphilis in pregnant women mean high incidence of congenital syphilis and millions of missed opportunities. In the last 10 years, the syphilis infant mortality rate has increased 150% in Brazil — from 2.2 per 1,000 born-alive (BA) in 2004 to 5.5 per 1,000 BA in 2003<sup>(8)</sup>. From 1998 to June 2016, 142,961 cases of congenital syphilis in children under 1 year of age were reported to SINAN. Of them, 64,398 (45.0%) were in the Southeast, 44,054 (30.8%) in the Northeast, 14,300 (10.0%) in the South, 11,846 (8.3%) in the North, and 8,363 (5.8%) in the Midwest<sup>(1)</sup>.

In Brazil, regional works demonstrate significant differences in the prevalence of the disease in accordance with the studied region. The rates range from 0.4% in Itajaí (Southern)<sup>(8)</sup> and Vitória (Southeast)<sup>(9)</sup> to 7.7% in Fortaleza (Northeastern)<sup>(10)</sup>. In the same states, but in different cities, there are also significant differences, such as in Salvador (0.9%)<sup>(11)</sup> and Vitória da Conquista (2.8%)<sup>(12)</sup>, both located in the state of Bahia, in the Northeast. There are cities with low prevalence in the country where the disease is under control, and others where the disease is epidemic, indicating that there is no uniformity of syphilis distribution in Brazil.

In Brazil and in the world as well, the increased incidence of congenital syphilis (CS) and its serious consequences, such as

natimortality, contrast with the occurred with HIV, that has been reducing its transmission rate despite the complex and expensive clinical treatment protocols<sup>(3)</sup>.

In Brazil, it was observed that 51.6% of pregnant women with syphilis were in the age group of 20 to 29 years, 46.7% declared being brown race/color, and 20.9% reported education from 5<sup>th</sup> to 8<sup>th</sup> incomplete grade<sup>(1)</sup>.

WHO recommends enrolling and testing at least 90% of pregnant women for the effective control of the disease and treating a proportion exceeding 80% of the partners, as well as 100% of pregnant women. Among pregnant women treated, at least 80% of those who have been contaminated at gestational age should receive treatment before the 24<sup>th</sup> week of pregnancy. It is also necessary to provide treatment programs for all partners of pregnant women infected, as well as guidance on the use of condom and advice on ways of preventing the disease<sup>(13)</sup>.

## OBJECTIVE

To verify if the goals proposed by WHO to eradicate congenital syphilis in these patients assistance are met.

## METHODS

### Study design

Cross-sectional study.

### Studied population

A total of 2,041 pregnant women were enrolled after admission to a public hospital in the metropolitan region of the city of Rio de Janeiro, from January 2012 to December 2014. The institution involved in the study was the HUPE of the UERJ.

### Data collection

At HUPE, blood samples are routinely collected for syphilis investigation upon admission, with both non-treponemal testing (Venereal Disease Research Laboratory — VDRL) and confirmatory treponemal test (Treponema Pallidum Hemagglutination — TPHA). The confirmation via treponemal test is important due to a possible false-positive result. All the tests are performed in the clinical analysis laboratory of HUPE. According to the Brazilian Ministry of Health protocol, blood samples are collected for syphilis testing from all parturients. An active search for syphilis serology results (treponemal and non-treponemal tests) with the respective titrations was conducted by accessing the database of the hospital laboratory. A thorough review of the medical records of the pregnant women and their newborns was also conducted. The data from the HUPE epidemiology service was evaluated in order to identify the total number of infected pregnant women and newborns to avoid underestimating the results. A survey was conducted on the state's Department of Health website to collect data on syphilis reports during pregnancy, as well as reports of congenital syphilis on the SINAN and the number of live births

in the Live Births Notification System (Sistema de Informações sobre Nascidos Vivos — SINASC).

### Inclusion criteria

The following parturients were eligible for the study: pregnant women admitted for delivery with a live fetus of any gestational age and weight, stillbirths with gestational age  $\geq 22$  weeks or weight  $\geq 500$  grams. The following cases were defined as syphilis during pregnancy: parturients admitted with laboratory evidence of positive VDRL (any titer) collected at the time of admission and confirmed by the treponemal test; parturients' infant (stillbirth or live birth) reported as a case of CS, identified in any of the information systems consulted.

### Exclusion criteria

The following parturients were excluded: the ones with positive VDRL resulting from previous syphilis adequately treated (complete treatment with benzathine penicillin, according to the clinical stage of the disease, complete treatment of the partner, documentation confirming the couple's treatment, drop in VDRL titers after adequate treatment, treatment completed more than 30 days before delivery).

### Variable definition

The following situations will be included as CS cases: all the gestation occurrences (live-born or stillborn) identified in any of the information systems as premature congenital syphilis; all newborns with VDRL titers higher than the maternal ones; and all newborns with clinical manifestations suggestive of clinical or complementary CS tests<sup>(14)</sup>.

The socio-demographic variables studied were the following: age, ethnicity, marital status, education, drug use, alcoholism, and smoking. Less than nine years of study was considered low educational level. The sex and reproductive variables evaluated were as it follows: age of sexarch, condom use during pregnancy, history of STI, gestational age of the first pregnancy, number of pregnancies, parity, and number of previous abortions. The following Ministry of Health recommendations were considered: appropriate treatment of pregnant women during prenatal care when done with benzathine penicillin according to the clinical stage of the disease and before 30 days of childbirth; partner considered treated after receiving proper treatment to the clinical phase of the disease and performing serological examination<sup>(15)</sup>.

WHO recommendations considered suitable for the control of congenital syphilis are the following: capturing and testing 90% of pregnant women, treating 80% of partners and 100% of pregnant women (80% before the 24<sup>th</sup> week), and providing advice to all pregnant women concerning the use of condom in pregnancy<sup>(6)</sup>.

### Epidemiological definitions

Following the Ministry of Health recommendation for the calculation of the CS incidence, the number of CS cases identified

in the study was used as the numerator and the number of live births at that location and period, multiplied by 1,000, as the denominator<sup>(16)</sup>.

### Ethical aspects

This research complies with the Declaration of Helsinki and the Brazilian National Health Council (Conselho Nacional de Saúde — CONEP) Resolution no. 466/2012. The project was approved by the UERJ Research and Ethics Committee (COEP), under the no. 034.3.2012. Written informed consent was obtained from all the subjects and from the legally authorized representatives of the minors who agreed to take part in the research. Anonymity and data confidentiality were guaranteed.

## RESULTS

The incidence of CS was 22.0 per 1,000 LB in 2012, 17.0 per 1,000 LB in 2013, and 44.8 per 1,000 LB in 2014.

The socio-demographic profile of pregnant women with syphilis showed that women ages ranged from 13 to 45 years, with average of 26 years, with 17.0% under the age of 19 years and 13.9% more than 35 years. Most of them were non-white (81.0%), had less than nine years of education (57.7%), and were single (82.1%). Of them, 10.9% reported drug use, 15.4% alcoholism, and 29.2% smoking (Table 1).

Our research showed that 35.4% of women had previous history of STI. Among them, 16 (20.0%) had HIV co-infection. Other STI reported were gonorrhea and human papilloma virus (HPV). Most of them (72.2%) did not use condoms regularly; only 27.8% reported constant use, and 53.7% occasional (Table 2).

Regarding the assistance coverage, 92.4% of pregnant women were assisted during the prenatal period. Gestational age of prenatal onset varied between 5 and 36 weeks. The average start of prenatal care was  $17.1 \pm 8.0$  weeks. Gestational age of testing for syphilis during pregnancy ranged between 6 and 36 weeks with the average of  $20.0 \pm 8.8$  weeks.

**Table 1** – Socio-demographic parturients profile.

Variable	Category	Frequency/n	% (CL 95%)
Age (years)	<19	14/79	17.7 (10.0–27.9)
	(13–45 years)	54/79	68.0 (56.9–78.4)
	$\mu=(26.4 \pm 7.3)$	11/79	13.9 (7.2–23.5)
Ethnicity	Caucasian	15/79	19.0 (11.0–29.4)
	Non-caucasian	64/79	81.0 (70.6–89.0)
Education (years)	>9	33/78	42.3 (31.2–54.0)
	$\leq 9$	45/78	57.7 (46.0–68.8)
Marital status	Other	14/78	17.9 (10.2–28.3)
	Single	64/78	82.1 (71.7–89.8)
Drug use	No	57/64	89.1 (78.8–95.5)
	Yes	07/64	10.9 (4.5–21.2)
Alcoholism	No	55/65	84.6 (73.5–92.4)
	Yes	10/65	15.4 (7.6–26.5)
Smoking	No	51/72	70.8 (58.9–81.0)
	Yes	21/72	29.2 (19.0–41.1)

CL: confidence limit.

In relation to the treatment of women in labour, 72.2% received proper treatment during the prenatal period. The treatment was carried out between the 6<sup>th</sup> and 38<sup>th</sup> week of pregnancy. The average gestational age of the treatment was 23.9±9.4 weeks.

Concerning the treatment of the partner, it was adequate for just 19%. The only rule recommended by WHO complying with the assistance of pregnant women was the enrolment, which reached 92.4% (90% goal).

With respect to testing, treatment of pregnant women and their partners, the rates were lower than those ones indicated by WHO. Of all, 87.3% were tested (90% goal), 72.2% were treated (100% goal) and 19.0% of partners treated (80% goal). Besides not having achieved the goal in relation to the treatment of women in labour, only 51.0% of women were treated before the 24<sup>th</sup> week of gestation (80% goal). In reference to the guidance on use of condoms during the prenatal period, 52.5% of women reported being orientated on the need of the use of condom during the prenatal period (100% goal) (Table 3).

**Table 2** – Sexual and reproductive history of infected parturients.

Variable	Category	Frequency/n	% (CL 95%)
Previous STI story	Yes	28/79	35.4 (25.0–47.0)
	No	51/79	64.6 (53.0–75.0)
Regular condom use	Never	29/54	18.5 (9.6–27.4)
	Occasionally	10/54	53.7 (9.3–31.4)
	Always	15/54	27.8 (16.5–1.6)
Prior abortion	<1	54/74	73.0 (61.4–82.6)
	≥1	20/74	27.0 (17.4–38.6)
Age at first gestation (years) (11–42 years) μ=(20.0±6.4)	<20	37/64	57.8 (44.8–70.1)
	≥20	27/64	42.4 (29.9–55.2)
Sexarch (years) (7–21 years) μ=(14.5±2.7)	<15	34/64	53.1 (17.3–37.7)
	≥15	30/64	46.9 (34.3–59.8)
Parity (0–6) μ=(3.0±2.0)	>1	58/79	73.4 (62.3–82.7)
	≤1	21/79	26.6 (17.3–37.7)

CL: confidence limit; STI: sexually transmitted infections.

**Table 3** – Evaluation of the goals proposed by World Health Organization (WHO) in the eradication of syphilis at Pedro Ernesto University Hospital (HUPE).

Variable	WHO goal (%)	Result found % (95%CI)
Enrollment	90	92.4 (82.4–97.2)
Prenatal testing	90	87.3 (78.0–93.8)
Pregnant women treatment	100	72.2 (60.9–81.7)
Treatment <24 weeks	80	51.0 (36.6–65.2)
Partner treatment	80	19.0 (11.0–29.4)
Guidance on condom use	100	52.5 (39.1–65.7)

95%CI: interval of confidence of 95%.

## DISCUSSION

The WHO and the Pan-American Health Organization (PAHO) define the elimination of congenital syphilis as the occurrence of 0.5 or less cases of congenital syphilis for every 1,000 live births<sup>(17,18)</sup>.

The high incidence of congenital syphilis (26.6 per 1,000 LB) found in this study demonstrates the fragility of the country's health system in eradicating syphilis. The number is higher than the one described in our state in 2015 (16 per 1,000 LB)<sup>(7)</sup> and at least five times greater than the incidence of the disease in Brazil, according to the Estudo Nascir (3.51 per 1,000 LB)<sup>(19)</sup>.

The incidence of congenital syphilis found in this study was more than 50 times higher than the Ministry of Health's elimination goal recommended by WHO and PAHO to eradicate the disease<sup>(20)</sup>.

In relation to the demographic profile of the infected women, the average age of 26 years was similar to that one found in other studies with national representation, such as those by Cunha and Merchan-Hamann<sup>(21)</sup> and Domingues et al.<sup>(22)</sup> (25.2 and 25.7 years, respectively). About the age group, 17.7% were under 20 years, less than the number described in the 2015 epidemiological bulletin, which showed 24% of pregnant women with syphilis below that age<sup>(14)</sup>.

The majority of women with syphilis were white (81%), which is justified by the fact that black or brown population tends to have lower income, less access to education and less qualified health care in the country<sup>(14,21,23)</sup>.

On the other hand, when the frequency of non-white women compared to white women was considered, it was observed that in 2014, in the state of Rio de Janeiro, only 19.6% (5,626) of the 28,693 live births in establishments administered by the state sphere were of white mothers<sup>(24)</sup>. This proportion, which refers to public hospitals, as presented in this study, approaches the frequency found in our observation. This seems to indicate that in the present study the large proportion of non-white mothers is in fact a characteristic of the population assisted in the hospital units studied rather than a feature associated with the disease itself.

Concerning the level of education similar to our study (<9 years/57.7%), other authors related the positivity of syphilis with lower education level<sup>(10,14,21)</sup>. Mothers of children with congenital syphilis have a lower educational level when compared to pregnant women in general<sup>(14)</sup>. The low educational level is related to less access to information, limited understanding of the importance of health care, and disease prevention measures<sup>(23)</sup>.

In maternity hospitals administered by the state of Rio de Janeiro, however, in 2014, 27,247 of 28,693 women who gave birth to living children (95.5%) had from zero to 11 years of education, showing that the population assisted by these units is characteristically of less education than the set of all parturients of the state (81.6%)<sup>(24)</sup>.

Most women were single (82.1%) and had no regular partner, demonstrating that sexual behavior may be related to a higher risk of acquiring a STI. Nonato et al. found similar results and estimated that 69.5% of patients did not live with their partners<sup>(23)</sup>. However, when the marital state of pregnant women assisted in maternity hospitals managed by the state of Rio de Janeiro in 2014 was evaluated, it was observed that 22,946 out of

28,693 mothers of live births (80%) were single<sup>(24)</sup>. Once again, it suggests that the population assisted in the maternity hospitals under this study showed that this feature is not specifically related to the disease itself.

It was not verified in our study the relationship between the use of drugs (alcohol, tobacco or illegal drugs) and syphilis. Casal et al. describes this association<sup>(25)</sup>. Nevertheless, information bias may have occurred, as we cannot guarantee that the majority of the women reported the reality when questioned about the use of illicit drugs.

The facts that the majority of pregnant women with syphilis do not use condom and 35.4% of women have reported previous history of STI are signals for the need of a careful guidance of pregnant women on ways of preventing not only syphilis, but also other sexually transmitted diseases. The emphatic guidance on the risk of STI and their ways of prevention, although essential, is still an obstacle in the control of the disease, since many professionals do not feel free to approach this subject with their female patients<sup>(25)</sup>. By providing advice to these pregnant women, we increase the chance of partners assistance at the health service, which is an essential issue for the syphilis control<sup>(26)</sup>.

Among the pregnant women studied, 20% had co-infection with HIV. This is similar to other international studies that describe this relationship<sup>(27,28)</sup>. Regarding the relationship between syphilis and sexual behavior of patients, we also noted that more than half of the patients got pregnant before 20 years of age and sexarch before 15 years of age, which confirms the described by Casal et al.<sup>(25)</sup> and Manda et al.<sup>(28)</sup>, who demonstrated a greater chance of syphilis in patients with sexarch before 16 years.

With regard to obstetric antecedents, 27% of women reported prior abortion and 74.4% related at least one previous pregnancy, differing from the studies by Nonato et al.<sup>(23)</sup> and Emmanuel et al.<sup>(29)</sup>, which showed a negative association between previous abortions or pregnancies and syphilis, suggesting that the history of a previous obstetric event protects these pregnant women from the disease.

A possible limitation of this study is some secondary data acquired in medical records and, therefore, dependent on who made the registry, although we tried to acquire information from many different sources to confirm the data and avoid this tendency.

We have not fulfilled the strategic rules set by WHO in the testing, treatment of the couple and guidance on condom during prenatal assistance. In case these basic strategies are not urgently taken, we will not be able to eliminate the congenital syphilis in the country.

Although prenatal coverage had reached 92.4%, it was not enough to ensure CS control, which was also noted by Campos et al.<sup>(30)</sup>.

Regarding testing for syphilis, our study estimated that 12.7% of women were not tested during pregnancy. The coverage found was similar to other studies in Brazil, describing coverage close to 90%<sup>(22,31)</sup>. This testing failure causes a direct impact in the increasing prevalence of the disease. It is known that women who initiate early prenatal care, have tested in the first two quarters and receive early appropriate intervention have a higher chance of generating a healthy child<sup>(32)</sup>. The offer of antenatal qualified services changes the outcomes, and its absence can elevate the perinatal mortality by up to five times. The reduction of the stillbirth and natimortality is

46 and 42%, respectively, when these women are tested and properly treated<sup>(32)</sup>.

Universal prenatal screening of pregnant women can reduce 64,000 fetal deaths in the world each year, 25,000 neonatal deaths, 32,000 cases of CS, prevent loss of 2.6 million days of life and save US\$ 20,8 millions in medical costs<sup>(33)</sup>.

According to WHO, 95% of pregnant women until 2013 had undergone tests for syphilis during the prenatal period in 42 countries. However, in more than 40 countries less than 50% of them were tested<sup>(6)</sup>.

With regard to treatment, although the testing had reached 87.3% of women in labour, only 72.2% of them with average gestational age of 24 weeks received proper treatment during the prenatal period. Maternal syphilis treatment reduces the risk of congenital infection, but does not eliminate it, and the earlier the treatment, the lower the chances of mother-to-child transmission<sup>(30)</sup>.

Although the data from Ministry of Health point out that, despite the majority of mothers of children with congenital syphilis have had access to prenatal care and received a diagnosis of syphilis during pregnancy, the vertical transmission of syphilis was not interrupted due to the difficulty in treating these pregnant women. Among the obstacles to treatment, there is the low administration of penicillin in pregnant women during prenatal care, despite the slight increase in the application of penicillin G benzathine in the basic health units — from 50.4% to 53.6% —, between the first and second half of 2014. In the second half of 2014, there were problems in the supply of raw materials and diluents for the manufacture of the medication. In spite of the laboratories' affirmation that the supplies problem was resolved, the distribution to states and municipalities still follows a slow schedule due to the repressed demand and the increase of requests<sup>(7)</sup>.

The low coverage in the treatment of the partners was similar to that one found by national studies, demonstrating the inadequacy of the treatment<sup>(14,34)</sup>. Congenital syphilis notifications in the state of Rio de Janeiro was still smaller than our coverage, identifying that only 10.3% of pregnant women had their partners treated<sup>(35)</sup>. According to Campos et al.<sup>(36)</sup>, the need of treatment is notified by the woman herself in 78.6% of the cases. The lack of reference to attention, care and counseling of these partners is one of the main reasons responsible for the failure of this treatment<sup>(25)</sup>. Approximately 40% of the health professionals reported some difficulty in the partner approach, although 70% have participated in the training in dealing with the disease in the last five years<sup>(37)</sup>.

In the context of social inequalities related to the prevalence of the disease, the low quality prenatal assistance aggravates the situation of syphilis in the country<sup>(21)</sup>. The evaluation of pregnant women prenatal care and the treatment of the partner are great tools to identify factors related to the maintenance of the high prevalence of the disease and provide the basis for the creation of strategies to correct the problem.

Unlike expected, syphilis, a sexually transmitted disease caused by aetiological agent well set with easy-to-interpret diagnostic tests, effective treatment and effective prevention, advances in the country and in the world. It is up to us, health professionals, who live daily with this sad reality, eradicate congenital syphilis by esteeming the excellence of our pregnant women assistance. By then thousands

of babies will continue dying. In the middle of the 21<sup>st</sup> century, the epidemic of syphilis in pregnant women and CS is still ignored and underestimated by all of us.

## CONCLUSION

Despite being a high complexity and a reference hospital in a major city and its metropolitan region, the CS numbers and pregnant women characteristics of each registered case reveal the abyss of public health care, increased by the fact that the strategic and basic rules set by WHO for the control of CS in the country are not being met, driving daily to the loss of thousands of opportunities to save lives during the prenatal period.

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## Conflict of interests

The authors declare no conflict of interests.

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**Address for correspondence:****LUCIANE RODRIGUES PEDREIRA DE CERQUEIRA**

Rua Constança Barbosa, 188, sala 309 – Meier

Rio de Janeiro (RJ), Brasil

CEP: 20735-090

E-mail: dralucerqueira@gmail.com

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# CONTRIBUTION TO THE STUDY OF EPIDEMIOLOGICAL SURVEILLANCE OF CONGENITAL SYPHILIS IN A HOSPITAL OF THE UNIFIED HEALTH SYSTEM LOCATED IN THE BAIXADA FLUMINENSE REGION, RIO DE JANEIRO STATE, BRAZIL

*CONTRIBUIÇÃO AO ESTUDO DA VIGILÂNCIA EPIDEMIOLÓGICA DE SÍFILIS CONGÊNITA EM UM HOSPITAL DA REDE DO SISTEMA ÚNICO DE SAÚDE DA BAIXADA FLUMINENSE, ESTADO DO RIO DE JANEIRO*

*Carolina Galvão<sup>1</sup>, Wesley Caixeta Borges<sup>2</sup>, Philippe Godefroy<sup>3</sup>, Sergio Araújo Martins Teixeira<sup>4</sup>, Eduardo Martins Gerde<sup>5</sup>, Alfredo de Almeida Cunha<sup>6</sup>*

## ABSTRACT

**Introduction:** Syphilis is a sexually transmitted disease (STD) of bacterial etiology. If it is not early diagnosed and immediately treated in pregnant women, possible repercussions can occur, such as fetal deformities, miscarriages and stillborn, or syphilitic neonate with syphilis (congenital syphilis), causing serious public health problems. **Objective:** To describe the prevalence of congenital syphilis in a hospital of the Unified Health System (Sistema Único de Saúde — SUS) of the Baixada Fluminense region, Rio de Janeiro, Brazil. **Methods:** Identified cases of congenital syphilis in the Hospital Estadual da Mãe (HMAE) from January 2013 to January 2014. Retrospective and descriptive study of data collected from medical records. Descriptive analysis with categorical variables proportions. **Results:** 175 cases of congenital syphilis in 6,274 births (2.7%) were analyzed. Around 80.0% of women with syphilis received prenatal care. As for the distribution of the number of sexual partners of pregnant women with syphilis who received treatment during prenatal care, only 5 of 175 records registered that their partners also received treatment, while 16 patient records contained information that the partner did not carry out the treatment, and 154 showed no information about the pregnant women partners. **Conclusion:** The absolute majority of cases of congenital syphilis occurred in pregnant women who had undergone prenatal care. It demonstrates that it is necessary to improve the quality of basic care in order to eliminate this severe problem of Brazilian public health. **Keywords:** congenital syphilis; epidemiological surveillance; sexually transmitted diseases; prenatal care; health systems.

## RESUMO

**Introdução:** A sífilis consiste numa doença sexualmente transmissível (DST) clássica de etiologia bacteriana que, caso não seja diagnosticada em tempo hábil com tratamento imediato, pode provocar, no caso de gestantes, possíveis repercussões, como deformações fetais, aborto e natimorto sífilítico ou neonato com sífilis (sífilis congênita), caracterizando-se assim como um grave problema de saúde pública. **Objetivo:** Descrever a prevalência de sífilis congênita em um hospital da rede do Sistema Único de Saúde (SUS) da Baixada Fluminense, Rio de Janeiro. **Métodos:** Casos identificados de sífilis congênita no Hospital Estadual da Mãe (HMAE) no período de janeiro de 2013 a janeiro de 2014. Estudo descritivo e retrospectivo de dados coletados dos prontuários médicos. Análise descritiva com proporções das variáveis categóricas. **Resultados:** Foram analisados 175 casos notificados de sífilis congênita em 6.274 partos (2,7%). Cerca de 80,0% das mulheres com sífilis realizaram o pré-natal. Quanto à distribuição do número de parceiros sexuais de gestantes com sífilis que fizeram tratamento durante o pré-natal das gestantes, de 175 prontuários somente de cinco constava a informação de que parceiros das gestantes realizaram o tratamento com a gestante, enquanto 16 prontuários continham a informação de que o parceiro não havia realizado o tratamento, e em 154 prontuários não obtivemos informações sobre os parceiros das gestantes. **Conclusão:** A maioria absoluta dos casos de sífilis congênita ocorreu em gestantes que tinham realizado pré-natal. Isso demonstra que é necessário melhorar a qualidade da atenção básica, a fim de eliminar esse grave problema da saúde pública brasileira.

**Palavras-chave:** sífilis congênita; vigilância epidemiológica; doenças sexualmente transmissíveis; cuidado pré-natal; sistemas de saúde.

## INTRODUCTION

Syphilis is traditionally characterized as a sexually transmitted disease (STD) and has impact on public health, as it consists of a

sentinel disease caused by *Treponema pallidum* bacterial pathogen. If it is not early diagnosed with immediate treatment, reaching the cure becomes a challenge, since there may be gradual repercussions in the patient's body. If this infection is during the pregnancy period, an even greater attention should be paid to the maternal-infant binomial, due to the possibility of fetal deformities, miscarriage and stillbirth<sup>(1)</sup>.

The main route of transmission is the sexual contact, but it is also transmitted for the baby through the placenta, as well as by blood transfusion. The signs and symptoms of this disease can vary, be complex and reach the respiratory, cardiovascular, nervous and digestive systems. Syphilis has a slow evolution, and its periods or phases are divided into symptomatic and asymptomatic, besides classified in primary, secondary and tertiary.

<sup>1</sup>São Francisco Hospital e Maternidade – Niterói (RJ), Brasil. Hospital Estadual da Mãe – Mesquita (RJ), Brazil. Hospital Maternidade Therezinha de Jesus – Juiz de Fora (MG), Brazil.

<sup>2</sup>Associação Brasileira de Ensino Universitário (UNIABEU) – Rio de Janeiro (RJ), Brazil.

<sup>3</sup>Hospital da Mulher Heloneida Studart – São João de Meriti (RJ), Brasil.

<sup>4</sup>Universidade do Estado do Rio de Janeiro (UERJ) – Rio de Janeiro (RJ), Brazil.

<sup>5</sup>Hospital Estadual da Mãe – Mesquita (RJ), Brazil.

<sup>6</sup>Instituto de Educação e Pesquisa, Hospital Maternidade Therezinha de Jesus – Juiz de Fora (MG), Brazil.

Paz et al.<sup>(2)</sup> declared that the definition of congenital syphilis cases has been undergoing different modifications in the last two decades not only in Brazil, but throughout the world.

Referring to Brazil, syphilis became a compulsory notification disease on September 22, 1986, through Ministry of Health Ordinance No. 542 along with acquired immunodeficiency syndrome (AIDS). The notification is made through diagnosis of the disease and filling in the form of notification and investigation of cases of congenital syphilis, being an attribution of the health professionals to join these data or any type of illness classified as compulsory notification<sup>(2)</sup>. Compulsory notification information is forwarded and filed in the Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação — SINAN)<sup>(3)</sup>.

In order to analyze the progression of congenital syphilis (CS) in the country, the Epidemiological Bulletin AIDS/DST of 2011 reported that, from 1998 to June 2011, 62,881 CS cases were set down in children under 1 year of age. The Southeast region registered 28,724 (45.7%); the Northeast region, 19,815 (31.6%); the North region, 5,910 (9.4%); the South region, 4,622 (7.3); and the Midwest region, 3,810 (6.0%)<sup>(4)</sup>.

The Epidemiological Bulletin AIDS/DST in 2010, with regard to the detection of CS in Brazil, observed a rate of 2.3 cases per 1,000 live births, and Northeast and Southeast showed the highest rates: 2.6 and 2.5, respectively<sup>(4)</sup>.

In this context, according to the Epidemiological Bulletin from 2012, between 1998 and July 2012 SINAN received 80,041 cases of CS in children under 1 year of age. Just in the Southeast, 36,770 (45.9%) of CS were registered; in the Northeast, 25,133 (31.4%); the North, 6,971 (8.7%); the South, 6,143 (7.7%); and the Midwest, 5,024 (6.3%)<sup>(5)</sup>.

The Southeastern region had a larger quantity of data, standing out widely among the other Brazilian regions, requiring more attention from the government on health policies and strategies, as well as the attention of health professionals regarding the disease signaling and concern about health orientation and patients education.

Through the analysis of these data, we have realized the significant CS progression around the country. All regions had changes and the number of cases has increased.

Then the following motivation arose: we do not know the type of instruction, health education and care that women participating in the study had in the end of their lives, and we do not know if the prenatal care of these patients was carried out in a complete way, with blood testing for CS, detection of positivity for the disease or not. These aspects also influence the onset of CS, because, if prenatal care is not carried out and the disease is detected in the mother and measures are not taken, the child can be born with the disease. The survey of these data through the analysis of the medical records answered these questions.

According to Rodrigues and Guimarães, 40% of pregnant women with primary or secondary syphilis (SFS) develop fetal loss, and 50% of newborns of mothers with unhealed or inadequately treatment do not show diseases symptoms at birth, which cause serious consequences in the future<sup>(6)</sup>.

It has been observed a worldwide aggravation of syphilis among individuals in general and particularly CS, making it one of the most challenging public health problems of the early millennium<sup>(7)</sup>.

Lorenzi and Madi, in a research on CS in a university hospital in Southern Brazil from June 1<sup>st</sup> 2000 to May 31<sup>st</sup> 2001 reported that the

prevalence of CS noticed was of 1.5%, which corresponds to 27 cases in 1,739 births. The CS level found was 15.5 per 1,000 live births, out of the standard prescribed by the Pan American Health Organization (PAHO)<sup>(7)</sup>.

## OBJECTIVE

To evaluate the prevalence of CS in the hospital subject of the study, between 2013 and 2014 (January to January, respectively), and to verify if the numbers are beyond the recommended by the PAHO of 1 case per 1,000 live births, and if there was epidemiological surveillance of these cases.

## METHODS

A descriptive and observational research of quantitative and retrospective nature was carried out. The purpose of this study was to verify the reality by analyzing data collected through vehicles (instruments) that then provided the description of the phenomenon analyzed through the frequency distribution, its correlation with possible variables that best characterize and explain it. It can occur through field research using theoretical evidence as the basis of its construction, in order to answer to the study objective through data collected from the participants who express the analyzed phenomenon<sup>(8)</sup>.

The research scenario was the Hospital Estadual da Mãe (HMAE), in Mesquita, Rio de Janeiro state, Brazil, selected as a reference in the care of pregnant women in the Unified Health System (Sistema Único de Saúde — SUS) network. It covers low-income individuals, promoting middle-level care in the Baixada Fluminense, in the metropolitan Region I of the state of Rio de Janeiro, and attending about 600 births per month. The institution was inaugurated in June 2012 and offers 70 beds in joint accommodation, eight beds for intermediate neonatal unit and 12 pre-partum, childbirth and postpartum rooms. The hospital also offers post-anesthesia room (PAR), newborns assistance, surgical center, post-natal care and maternity, as well as joint accommodation and neonatal intensive care unit (ICU).

The following data were collected: number of cases of congenital syphilis reported; age of the patients during gestation; number of women who underwent prenatal care; number of Venereal Disease Research Laboratory (VDRL) examinations carried out by women analyzed during this period; number of patients who had their sexual partners treated for syphilis; number of women diagnosed during gestation who underwent syphilis treatment during the study period; number of cases of stillbirths by syphilis, abortion and death in the years selected for collection; and results of the serological tests for syphilis collected in the babies' peripheral blood.

The inclusion criteria was women admitted to the HMAE and who had previously prenatal care in the same location and were submitted to natural childbirth or caesarean section, as well as those cases arising from labor, even without the patient having performed prenatal care in the hospital in the months of January 2013 to January 2014; medical records with a completed gynecological anamnesis form (a maximum of five blank data); and the medical records that met the definition criteria for CS of the National STD/AIDS Program of the Brazilian Ministry of Health.

The exclusion criteria were: women who received the first care at the HMAE gynecological nursing consultation outside the studied

period; gynecological anamnesis records with more than five blank answers; and medical records without gynecological anamnesis.

Concerning statistical analysis, the data were treated by measures of simple frequency (absolute and relative).

This research covered all ethical aspects of human research in accordance with Resolution no. 196 of October 10, 1996. The present work is part of the project entitled "Results of the National Program of Humanization of Delivery and Childbirth in a maternity hospital of Baixada Fluminense" and was approved under no. CAAE 51591815.9.0000.5103, opinion no. 1,370,513 of the Research Ethics Committee of the Faculdade de Ciências Médicas e da Saúde Juiz de Fora (FCMS) Suprema. This project was developed at the HMAE, unit of the Hospital e Maternidade Therezinha de Jesus.

## RESULTS

The total of 175 cases of notified CS were analyzed. Some women who had their data collected during delivery were affected by syphilis during pregnancy and undergone prenatal care. This data is described in **Table 1**, in which it is observed that prenatal consultations have increased in frequency in August and September 2013, with 14 and 17 cases, respectively. About 80.0% of women with syphilis performed prenatal care (**Table 1**), but 16 (three without a prenatal consultation and 13 without a documented report) were not documented in the present study.

The total of 276 women were tested (VDRL) for syphilis at the HAME, 104 (59.42%) of which during prenatal care and 172 (98.28%), concerning 175 patients, at the time of delivery (**Table 2**).

**Table 3** shows the number of women who underwent human immunodeficiency virus (HIV) testing during prenatal or at the time of delivery, in which 87 (49.71%) of them underwent prenatal and 171 (97.71%) concerning the 175 patients at the time of delivery.

Regarding the distribution of the number of sexual partners of syphilitic pregnant women who were treated during prenatal care (**Table 4**), only five records of 175 showed the information that partners also carried out the treatment, while 16 related that partner

**Table 1** – Number of women affected by syphilis during gestational period who underwent prenatal care during the studied period at Hospital Estadual da Mãe, Mesquita (RJ), Brazil.

Month of the prenatal care	Yes n (%)	No n (%)	Total
January 2013	13 (7.42)	0 (0.00)	13
February 2013	10 (5.71)	1 (0.57)	11
March 2013	6 (3.42)	1 (0.57)	7
April 2013	10 (5.71)	1 (0.57)	11
May 2013	9 (5.14)	1 (0.57)	10
June 2013	11 (6.28)	0 (0.00)	11
July 2013	10 (5.71)	3 (1.71)	13
August 2013	14 (8.00)	3 (1.71)	17
September 2013	17 (9.71)	3 (1.71)	20
October 2013	8 (4.57)	1 (0.57)	9
November 2013	9 (5.14)	1 (0.57)	10
December 2013	10 (5.71)	0 (0.00)	10
January 2014	13 (7.42)	4 (2.28)	17
Total	140 (80.00)	19 (10.85)	159

**Table 2** – Number of women who underwent Venereal Disease Research Laboratory (VDRL) in prenatal care or in delivery during the study at Hospital Estadual da Mãe, Mesquita (RJ), Brazil.

Month of the VDRL	Prenatal n (%)	Delivery n (%)	Total
January 2013	9 (5.14)	14 (8.00)	23
February 2013	11 (7.42)	14 (8.00)	25
March 2013	4 (2.28)	9 (5.14)	13
April 2013	7 (4.00)	12 (6.85)	19
May 2013	5 (2.85)	12 (6.85)	17
June 2013	5 (2.85)	11 (7.42)	16
July 2013	9 (5.14)	13 (7.42)	22
August 2013	11 (7.42)	19 (10.85)	30
September 2013	9 (5.14)	20 (11.42)	29
October 2013	8 (4.57)	10 (5.71)	18
November 2013	8 (4.57)	12 (6.85)	20
December 2013	6 (3.42)	10 (5.71)	16
January 2014	12 (6.85)	16 (9.14)	28
Total	104 (61.65)	172 (99.36)	276

**Table 3** – Number of women who underwent anti-human immunodeficiency virus (HIV) testing during the gestation period during the study at Hospital Estadual da Mãe, Mesquita (RJ), Brazil.

Month of the anti-HIV	Prenatal n (%)	Delivery n (%)	Total
January 2013	9 (5.14)	14 (8.00)	23
February 2013	6 (3.42)	14 (8.00)	20
March 2013	5 (2.85)	9 (5.14)	14
April 2013	7 (4.00)	12 (6.85)	19
May 2013	5 (2.85)	12 (6.85)	17
June 2013	5 (2.85)	12 (6.85)	17
July 2013	7 (4.00)	13 (7.42)	20
August 2013	4 (2.28)	18 (10.28)	22
September 2013	8 (4.57)	19 (10.85)	27
October 2013	7 (4.00)	10 (5.71)	17
November 2013	7 (4.00)	11 (7.42)	18
December 2013	6 (3.42)	10 (5.71)	16
January 2014	11 (7.42)	17 (9.71)	28
Total	87 (50.8)	171 (91.94)	258

**Table 4** – Number of sexual partners of pregnant women with syphilis who had received treatment.

Month	Treated n (%)	Not Treated n (%)	Total
January 2013	0 (0.00)	1 (0.57)	1
February 2013	1 (0.57)	1 (0.57)	2
March 2013	0 (0.00)	0 (0.0)	0
April 2013	1 (0.57)	0 (0.0)	1
May 2013	0 (0.00)	1 (0.57)	1
June 2013	0 (0.00)	2 (1.14)	2
July 2013	0 (0.00)	1 (0.57)	1
August 2013	1 (0.57)	2 (1.14)	3
September 2013	0 (0.00)	2 (1.14)	2
October 2013	1 (0.57)	1 (0.57)	2
November 2013	0 (0.00)	3 (1.71)	3
December 2013	0 (0.00)	0 (0.00)	0
January 2014	1 (0.57)	3 (1.71)	4
Total	5 (2.85)	17 (9.69)	22

did not receive the treatment and in 154 medical records we did not obtain information about the pregnant women partners.

The number of cases of CS/month, the number of deliveries/month and percentage are presented in **Table 5**.

## DISCUSSION

In addition to the data collected in the HMAE, the scenery of this survey, CS data of the municipality of Mesquita were also studied through Epidemiological Surveillance of the Health Department of the mentioned municipality, taken from the SINAN<sup>(3)</sup>. The data for diseases and damages reported in each municipality are sent to the municipality's Secretary of Health, and then sent to the State Health Department and finally to the Ministry of Health, which analyzes, reviews, separates cases eventually retried, and feeds the national, regional and state statistics<sup>(3)</sup>.

Cases of syphilis in pregnant women, CS, adult syphilis (excluding the primary form), and unspecified syphilis were recorded by the Ministry of Health to date. In Mesquita, the following descriptions were informed:

- syphilis in pregnant women in 2013: 20 cases; 2014 with 17 cases. In a total we have 37 cases reported;
- CS in 2013: 22 cases; and 2014 with 25 cases, totaling 47 notifications;
- syphilis in adults (excluding primary form) in 2013: one case only. No cases were recorded in 2014 to date;
- not specified syphilis in 2013: 47 cases; 2014 a total of 31 notifications. So, the total of 78 notifications for this type of syphilis.

Adding all the categories of separated and reported syphilis in Mesquita between 2013 and 2014 (up to October), there is the total of 163 cases registered in the Ministry of Health. It is worth mentioning that, according to the guidance of the Epidemiological Surveillance of the municipality, the data for 2014 were not updated by the Ministry of Health due to delays in the analyzes, and may have suffered constant changes in the sum of the cases.

As determined by data from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística — IBGE) and Baixada Fluminense website, there is the total of 13 municipalities in the Baixada Fluminense region and Mesquita is the sixth city with the highest number of inhabitants: 168,376. The city with the most inhabitants is Duque de Caxias, with 855,048 inhabitants, and Paracambi has the lowest number, 47,124 inhabitants. It would be of great value if syphilis and CS rates were obtained from all the municipalities of Baixada Fluminense region, so that a syphilitic profile of the entire area could be described<sup>(9)</sup>.

During the period delimited for research (January 2013 to January 2014), there was a large number of deliveries at the HMAE. According to data provided by the administrative management of the hospital, including normal deliveries, forceps and cesarean sections, 6,275 deliveries occurred during the 13 months mentioned for data collection.

The combination of the data described raises the possible occurrence of facts that deserve attention due to their discrepancy, since the case numbers pointed out in this study are from the only public maternity in Mesquita. There may have been underreporting of cases, or irregular database feeding on reported cases, generating a moving value of the number of cases. However, this study, as observed by Schetini et al. in a study in the city of Niterói, Rio de Janeiro, observed the occurrence of an embarrassing and similar situation regarding the number of cases in the municipality and the hospital unit<sup>(10)</sup>.

Since 2003, Saraceni and Leal<sup>(11)</sup> related that Rio de Janeiro distinguishes as the state with the highest number of CS cases in the Southeast of Brazil. Schetini<sup>(10)</sup> data also confirmed the information, in addition to the study by Souza et al.<sup>(12)</sup>, both developed in maternity hospitals in Rio de Janeiro. Our study meets these findings confirming this high aggravating casuistry as it is a disease sentinel.

The high incidence of CS in the present study therefore may indicate a bias in the quality of prenatal care classified as an efficient and preventive event and, when it does not occur in an appropriate way, generates the need for a careful evaluation of the health system for the approach used<sup>(10,13)</sup>. For this reason, Brazil is one of the countries that expressed its support for the fight against CS, with the goal of reaching the target of 1 per 1,000 live births<sup>(14)</sup>. However, Saraceni and Leal<sup>(11)</sup> pointed out that, within the very expressive number of cases in our country, Rio de Janeiro is the state that has one of the highest rates of CS, followed by São Paulo, both located in the Southeast region.

**Table 5** shows the study's number of births per month and the number of cases found in CS every month. The arithmetic average of 13.4 CS cases was observed per month, or 2.6%, considering the average of 482 births per month<sup>(11)</sup>.

Souza et al.<sup>(12)</sup> described the neonatal repercussions of CS in newborns notified as a CS case in a hospital in the SUS in Niterói, Rio de Janeiro state, from January 2005 to June 2006, observing birth weight and serology of newborns with CS notification and treatment. The sample was formed from 35 records of notification of CS of the Surveillance Center of Hospital Universitário Antônio Pedro (HUAP). Using data from the notification, Souza et al. carried out a home visit for blood collection. The population consisted of 29 live births, four stillbirths and two abortion patients. Only two cases in the study (6.9%) showed CS bone alterations. The VDRL test performed on cerebrospinal fluid (CSF) was shown to be non-reactive for all patients evaluated.

**Table 5** – Cases of congenital syphilis (CS)/month and deliveries/month.

Month	CS cases	Deliveries	% of CS/deliveries*
January 2013	14	460	3.0
February 2013	14	439	3.1
March 2013	9	514	1.7
April 2013	12	521	2.3
May 2013	12	514	2.3
June 2013	12	483	2.4
July 2013	13	488	2.6
August 2013	19	461	4.1
September 2013	21	467	4.4
October 2013	10	471	2.1
November 2013	12	464	2.5
December 2013	10	461	2.1
January 2014	17	532	3.1
Total	175	6,275	35.7
Média aritmética	13.4	482.6	2.7

\*Normal, forceps and cesareans.

Still in the same study, the VDRL result of the newborn serum at birth was positive for 23 (79.31%) patients. Crystalline penicillin G (PGC) was administered in 26 (89.65%) cases, procaine penicillin G (PGP) in two (6.9%), and one patient used crystalline penicillin G and procaine penicillin G, requiring great effort to treat these cases. Fetal death and miscarriage were the worse outcomes reverberated around CS. VDRL was negative in all cases, although the use of antibiotic schemes were not in accordance with the protocol proposed by the Ministry of Health<sup>(12)</sup>.

Based on the references described in the manual on the control of STD, the Epidemiological Bulletin<sup>(14)</sup>, cases of CS should reach a target of one or less cases for 1,000 live births. In all months of this study, the results were especially high, since the average of 482 cases per month did not allow us to obtain the average of 13 CS cases per month in only one hospital. For a better understanding, matching the total number of cases (175) with the ratio of 1/1,000 live births, we would have to have a total of 174,825 births distributed in the 13 months of study. Nevertheless, we have 6,275 births, giving us a total of only six CS cases.

At the end of this study, we verified that, even though the Ministry of Health has established with the World Health Organization (WHO) the goal of reducing the number of cases of CS, this target has not yet been reached. I.e., syphilis is still perpetuating and there are some possible situations that cause it to persist. Among them, we have low prenatal care, absence of effective screening programs and follow-up of pregnant woman, many pregnant women that arrive at the hospital only at the time of delivery without prenatal care, women who are treated during pregnancy and their partners are not, inadequate treatment in pregnancy, due to disregard for the pregnant woman as penicillin G benzathine (PGB) treatment is painful and injections cause discomfort.

## CONCLUSION

The CS findings at the HMAE in Mesquita in the months chosen for investigation were considered very high (more than five times) in relation to the proposal established by the Ministry of Health. The absolute majority of cases of CS occurred in pregnant women who had undergone prenatal care. It demonstrates that it is necessary to improve the quality of basic care in order to eliminate this serious problem in the Brazilian public health CS numbers.

## Conflict of interests

The authors declare no conflict of interests.

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### Address for correspondence:

**ALFREDO DE ALMEIDA CUNHA**

Hospital Estadual da Mãe

Avenida Dr. Carvalhães, 400 – Rocha Sobrinho

Mesquita (RJ), Brasil

CEP: 26572-530

E-mail: aacunha@uol.com.br

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# MULTIPLE SYPHILITIC CHANCRE ON THE VULVA AND ON BOTH BREASTS: CASE REPORT

## CANCRO SIFILÍTICO MÚLTIPLO EM VULVA E EM AMBAS AS MAMAS: RELATO DE CASO

*Adrián Orsini<sup>1</sup>, Mauricio Ledesma<sup>1</sup>*

### ABSTRACT

Multiple syphilitic chancre is not frequent in the immunocompetent patient. On the other hand, extragenital lesions are more common in the mouth and anus, and it is rare to find them in the breast. We report the case of an 18 year-old patient who attended the consultation with three syphilitic chancres: one on the vulva and one on each areola.

**Keywords:** syphilis; chancre; areolas.

### RESUMO

O cancro sífilítico múltiplo não é frequente no paciente imunocompetente. Por outro lado, as lesões extragenitais são mais comuns na boca e no ânus, sendo raras encontrá-las na mama. Apresentamos o caso de uma paciente de 18 anos que compareceu à consulta com três cancros sífilíticos: um na vulva e um em cada aréola.

**Palavras-chave:** sífilis; cancro; aréolas.

## INTRODUCTION

Syphilis is a systemic infectious disease, usually of sexual contagion, whose protean clinical has made it known in the history of medicine as “the great impostor”. It is produced by a spirochete, *Treponema pallidum*, subspecies *pallidum*.

The transmission of the disease occurs by direct contact with wet lesions (chancre, *Condylomata lata*) present in the primary and secondary stages. Spirochetes can enter through intact mucous membranes or skin with abrasions. Blood is infectious during episodes of bacteremia.

Among the contagion routes to consider, the sexual activity is the main one, and equally involves genital, oral or anal sex. A patient is more infectious in the early stages of the disease. About 30% of casual sex partners and 90% of stable partners of an infectious individual acquire the disease. Koumans et al.<sup>(1)</sup> reported that 31% of patients with early syphilis related having two or more sexual partners in the previous month, and 8% exchanged money or drugs for sex in the previous three months.

The association with other sexually transmitted infections (STI) is not a minor problem and forces the search of all of them. Chesson et al.<sup>(2)</sup> estimated that 25% of all reported cases of primary and secondary syphilis in 2002 in the United States were manifested in people infected with human immunodeficiency virus (HIV). When compared to the general population, the incidence in these patients was considerably higher.

The region with the highest syphilis rate worldwide is Latin America and the Caribbean<sup>(3)</sup>. The World Health Organization (WHO) has estimated that, of the 12 million new infections that occur annually worldwide, three million are precisely in Latin America and the Caribbean.

The primary lesion, the chancre, develops at the site of inoculation and begins as a reddish macula, rapidly progressing to a papule, usually unique, round or oval, painless, with smooth and well-defined borders. Its size usually reaches between 10 and 20 mm, although it can be smaller. In patients infected with HIV, the lesions can be multiple and reach larger diameters. A few days later, the chancre ulcerates, and shows an over-elevation and induration of the edges, of cartilaginous consistency. Except that it is overinfected, the lesion looks clean and remains painless. Unilateral or bilateral regional adenopathy is observed. Usually, the lymph nodes are painless, enlarged and not suppurating. The diagnosis is difficult in women, since the chancre is located in the vaginal or cervical mucosa and goes on unnoticed. The extragenital location (most frequently oral or anal) is the most infected, and the lesion can be painful and necrotic. The chancre evolves spontaneously to healing within two to six weeks and usually leaves no trace. The adenopathy may persist after the disappearance of the chancre.

As mentioned, the syphilitic chancre is usually a single lesion, although in certain cases it can be multiple, depending on the amount of the inoculum, the possibility of different entrance doors occurring simultaneously, and even due to autoinoculation before the tenth day of infection. The finding of multiple chancres in immunosuppressed individuals is more frequent, particularly in patients with HIV (70%, compared to 30% of HIV negative patients)<sup>(4)</sup>. Generally, multiple chancres appear close to each other in the genital area, and more rarely coexist in other areas. The extragenital location of the chancre varies between 2 and 31% of cases<sup>(5)</sup>. It can affect any site, the most frequent extragenital location, being the mouth (between 40 and 70%) with approximately one fifth of them on the lips<sup>(6)</sup>. The location in the mammary region (nipple or areola) of the primary syphilitic lesion is rather rare<sup>(7)</sup>. Less common is the possibility of finding both breasts commitment.

We present a case of multiple syphilitic chancre located on the vulva and both breasts.

<sup>1</sup>Consultorio de Control de Infecciones en Ginecología (CIG), Obra Social del Personal de Maestría (OSPM), Hospital Municipal General de Agudos José M Penna – Buenos Aires, Argentina.

## CASE REPORT

We present the case of an 18-year-old white patient, nulliparous, who attended the consulting room due to a week-long lesion on the vulva, located in the middle third of the left major lip. She also reported an injury in right breast areole and another one in left breast areola, both painful that arose at the same time as the vulvar lesion.

Background: menarche: 13 years of age. Menstrual rhythm: 5/30. Start of sexual relations: 15 years of age. Number of sexual partners: two (male). Contraceptive method: condom. Habits: tobacco (four to five cigarettes/day) and occasional consumption of marijuana. Family gynecologic background: unknown. Breast pathology antecedents: denies. History of STI: denies.

On examination, in the middle third of the left major lip it was observed an ulcerated lesion, rounded, approximately 12 to 15 mm in diameter, with raised and indurated edges, not painful, which according to the patient dates from a week of evolution (**Figure 1**). The left major lip was also discreetly increased in thickness in relation to the right.

Concomitantly to the vulvar lesion, two similar ulcers appeared in both areolas, approximately 8–10 mm in diameter, with raised and indurated, but painful edges (**Figures 2 and 3**). There were no palpable axillary adenopathies.

A microbiological study of the vaginal contents was carried out, finding a habitual microbiota. Routine serologies were requested for the diagnosis of STI, and the following results obtained:

- serology for HIV: negative;
- serology for hepatitis B and C: negative;
- Venereal Disease Research Laboratory test (VDRL): positive 1/32 dilutions, with positive *Treponema pallidum* particle agglutination assay (TPPA).

Treatment indicated was two doses of penicillin benzathine 2,400,000 IU. The couple was called for evaluation and serology requested. The first dose of the antimicrobial was applied.

After seven days of treatment, the patient showed up to receive the second dose and underwent a clinical examination. An increase in the size of the vulvar lesion was observed, although it remained painless (**Figure 4**), and there was a slight improvement in the evolution of the lesions located in both breasts (**Figures 5 and 6**).

A week later, the patient returned for clinical evaluation of the lesions, and it was observed that the lesion in the vulva increased even more in size, becoming painful when rubbing on the underwear (**Figure 7**), while the lesions located in both breasts had almost disappeared (**Figure 8**).



**Figure 1** – Left major lip ulcerated lesion.



**Figure 2** – Right breast lesion next to nipple.



**Figure 3** – Left breast lesion next to nipple.



**Figure 4** – Left major lip lesion: first week of treatment.

The patient was examined the following week, and it could be noted that the lesion on the vulva began to evolve towards healing, and the pain also disappeared (**Figure 9**).



**Figure 5** – Right breast lesion: first week of treatment.



**Figure 6** – Left breast lesion: first week of treatment.



**Figure 7** – Lesion of vulva: second week of treatment.

Regarding the couple, there were no clinical lesions, but the VDRL was positive, with 1/128 dilutions and positive TPPA. Three doses of benzathine penicillin were prescribed for diagnosis of syphilis of unknown duration.

It is important to highlight that patient was examined one month later for clinical control, and a total resolution of the primary syphilitic lesion was observed, but a herpetic lesion on the right major lip arose (**Figure 10**), demonstrating once more the usual association with STI.



**Figure 8** – Lesions of both breasts: second week of treatment.



**Figure 9** – Vulvar lesion evolution.



**Figure 10** – Herpetic lesion on the right major lip.

## DISCUSSION

Classically, the syphilitic chancre is described as a unique ulcerated lesion, painless, with indurated borders, usually of genital location. However, the presence of more than one primary lesion is possible, being described in the medical literature up to 19 lesions in a patient<sup>(8)</sup>, and even the diagnosis of multiple chancres without involvement of the genital area is mentioned<sup>(9)</sup>.

Extragenital localization can occur on any mucosa and on areas of skin that present continuity. The involvement of the mouth, and particularly of the lips, constitutes the most frequent extragenital infection, sometimes manifesting itself with extensive oral ulcers<sup>(10)</sup>.

The primary lesion in the fingers of the hand is rare, although it is preferably described in health professionals, who may contract the disease accidentally<sup>(11)</sup>. Extragenital involvement in less frequent regions, such as neck or thorax<sup>(12)</sup>, are mentioned as rare cases in the medical literature.

Concerning the involvement of nipple or areola, there are not many cases published. Lee et al. mention two cases of male patients diagnosed with syphilitic chancre as a single lesion in the nipple<sup>(7)</sup>. Fukuda et al., on the other hand, presented the case of a 29-year-old male with a multiple primary lesion involving the lip, penis and areola-nipple<sup>(13)</sup>. We have not found in the bibliography the commitment of both areolas in the primary disease.

## Conflict of interests

The authors declare no conflict of interests.

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**Address for correspondence:****ADRIÁN ORSINI**

Consultorio de Control de Infecciones en Ginecología de la Obra Social del Personal de Maestranza  
Avenida Caseros, 3379  
Ciudad Autónoma de Buenos Aires, República Argentina  
E-mail: [adrianorsini@hotmail.com](mailto:adrianorsini@hotmail.com)

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# THE INCREASED PREVALENCE OF *TRICHOMONAS VAGINALIS* IN A SCENARIO OF CERVICAL CANCER SCREENING WITHOUT CYTOLOGY

## *O AUMENTO DA PREVALÊNCIA DE TRICHOMONAS VAGINALIS EM UM CENÁRIO DE TRIAGEM DE CÂNCER CERVICAL SEM CITOLOGIA*

José Eleutério Junior<sup>1</sup>, Mauro Romero Leal Passos<sup>2</sup>

There is currently a strong trend in developed countries and in some developing countries to start adopting the screening of preinvasive lesions of cervical cancer through molecular biology techniques, placing the cytology (Pap smear), in some schemes, as a helper method of positive cases screening. In other flowcharts, cytology is no longer used, and the positive cases for human papillomavirus (HPV) are subjected to triage in other ways (such as HPV genotyping), or forwarded straight to colposcopy<sup>(1)</sup>.

Meanwhile, infection with *Trichomonas vaginalis* (TV), that mostly has no symptoms and is considered the most common curable sexually transmitted infection (STI) around the world<sup>(2)</sup>, is not screened, being the conventional or liquid base Pap smear a tool for the diagnosis, even acknowledging a sensitivity around 50%<sup>(3)</sup>.

Due to the concern of an increase in misdiagnosis and not treatment of this infection, with the replacement of Pap smear by molecular biology in cervical cancer screening, Hui *et al.*<sup>(4)</sup> carried out a study taking into account the current screening program in Australia, which uses DNA-HPV screening and cytology tracing. Considering the hypothesis that by the new way of screening for cervical cancer with DNA-HPV, with an increased interval of the screening and that only HPV-positive cases will be submitted to cytology, there will be as a result an increasing *T. vaginalis* prevalence. The authors have developed a mathematical model to describe the transmission of *T. vaginalis* in the general population and created three scenarios for the study:

1. DNA-HPV screening;
2. Pap smear screening;
3. combination of scenarios 1 and 2.

In the mentioned study, the authors assume that, “although there is no robust estimates of TV prevalence in urban Australia, limited published data suggest that it is around 0.4% or less”<sup>(5,6)</sup>. It was thus possible to observe that the screening program change in that country will result in an increase of more than seven times

(from 0.4 to 2.8%) in the prevalence of *T. vaginalis* in 20 years if no additional measures are taken for this diagnosis and if there is no fall in the prevalence of high-risk HPV. If the prevalence of high-risk HPV continues to fall as the result of HPV vaccination, the TV prevalence may reach 3%.

It is clear that there is a worldwide increase in the incidence of trichomoniasis, particularly in developing countries. Precisely in these countries, the only tools for the parasite diagnosis are cervicovaginal content scanning microscopy for fresh analysis (unfortunately less and less used in medical practice) and stained cytology (Papanicolaou), with sensitivity of 60 and 50%, respectively<sup>(3)</sup>. Studies such as that by Hui *et al.*<sup>(4)</sup> demonstrate one of the side effects of the change of public health strategies with major impact and that should be taken into account in the planning of women’s health care.

The low diagnosis and consequent low treatment of genital trichomoniasis, the most prevalent STI in the world, strengthen vaginal microbiome alterations and facilitate the acquisition of other infections, especially human immunodeficiency virus (HIV)<sup>(7)</sup>.

Specifically in Brazil, we have few statistical data regarding trichomoniasis. Isolated studies have shown the prevalence of 2.6%, in the fresh test, up to 16% in the culture of reproductive age women<sup>(8)</sup> — much higher than that of Australia, and therefore more worrying.

The use of molecular biology in the screening of the etiologic agent of cervical cancer (HPV) by public and private health programs in countries that have decided to incorporate this methodology may be a great ally for screening other STIs, added to the joint research of *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *T. vaginalis*.

### Conflict of interests

The authors declare no conflict of interests.

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<sup>1</sup>Maternal and Child Health Department, Universidade Federal do Ceará – Fortaleza (CE), Brazil.

<sup>2</sup>Sector of Sexually Transmitted Diseases Department and Microbiology and Parasitology Department, Universidade Federal Fluminense – Niterói (RJ), Brazil.

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**Address for correspondence:****JOSÉ ELEUTERIO JÚNIOR**

Bloco Didático da Faculdade de Medicina, Universidade Federal do Ceará

Rua Prof. Costa Mendes, 1608 – 2º Andar, Rodolfo Teófilo  
Fortaleza (CE), Brasil

CEP: 60.430-140

E-mail [prof.eleuterio@gmail.com](mailto:prof.eleuterio@gmail.com)**MAURO ROMERO LEAL PASSOS**

Rua Amapá, 22 apto. 503, São Francisco

Niterói (RJ), Brasil

CEP: 24365-100

E-mail: [maurodst@gmail.com](mailto:maurodst@gmail.com)

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Uncaria tomentosa 50mg/g



## TRATAMENTO DE HERPES SIMPLES



1. REDUÇÃO DO TEMPO DA INFECÇÃO;<sup>1</sup>
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- ✓ Resolução das lesões em 75% dos casos<sup>3</sup>
- ✓ Baixa taxa de recorrência local: de 13-16%<sup>3</sup>

até 100%  
de remissão  
de lesões  
quando combinado  
a outras terapias<sup>3,7</sup>



**CONTRAINDICAÇÕES:** FAIXA ETÁRIA INFERIOR A 12 ANOS. **INTERAÇÕES MEDICAMENTOSAS:** DEVE SER UTILIZADO COM PRECAUÇÃO EM PACIENTES QUE ESTÃO FAZENDO USO DE IMUNOSSUPRESSORES.

**Ixium®** (imiquimode). **Apresentações:** creme – embalagens contendo 12 sachês com 250 mg cada. **Indicações:** Ixium® está indicado no tratamento do condiloma acuminado (verrugas externas, genitais e anais), causado por vírus HPV (Human Papillomavirus) em pacientes a partir de doze anos de idade, no tratamento do carcinoma basocelular superficial, confirmado por biópsia, em pacientes adultos e no tratamento da ceratose actínica em adultos. **Contraindicações:** esse medicamento é contra-indicado na faixa etária inferior a 12 anos. Pacientes com hipersensibilidade a qualquer um dos componentes do produto. **Advertências e precauções:** Ixium® não foi avaliado e não é recomendado no tratamento de infecções intravaginal, cervical, uretral, retal ou intra-anal causadas pelo HPV. Não se recomenda a administração de Ixium® em ulceração do pênis, ulceração da vulva, queimaduras solares e situações em que a pele não esteja completamente recuperada e/ou íntegra. Este medicamento somente deve ser aplicado na pele. A aplicação de Ixium® na infecção genital/anal por HPV não destrói o vírus, mas auxilia na eliminação da verruga. Portanto, novas verrugas podem aparecer durante o tratamento. Este medicamento pode fazer a pele ficar mais sensível ao sol, portanto é necessário evitar a exposição da pele ao sol e o bronzeamento artificial. Homens não circuncidados que estiverem tratando verrugas localizadas sob o prepúcio devem retrair-lo e limpar a região diariamente. A área tratada não deve ser coberta por gaze, bandagem ou ser ocluída de qualquer outra forma. Antes de prescrever Ixium®, deve-se verificar o histórico médico do paciente, especialmente em casos de problemas no sistema imune, infecção por HIV, pressão alta, determinadas complicações da medula óssea ou transplante de órgão (doença enxerto contra hospedeiro [DECH]) e doenças autoimunes (artrite reumatóide, escleroderma, disfunção da tireóide e lúpus). Durante o tratamento de verruga genital/anal, deve-se evitar o contato sexual enquanto o creme estiver na pele. Preservativos podem ter sua eficácia reduzida pelo creme e podem deixar de prevenir a gravidez ou a contaminação por HPV ou HIV. **Interações medicamentosas:** as interações com outros medicamentos, incluindo fármacos imunossupressores, não foram estudadas. Contudo, interações com fármacos sistêmicos provavelmente são limitadas pela mínima absorção de Ixium® através da pele. Ixium® deve ser utilizado com precaução em pacientes que estão fazendo uso de medicamentos imunossupressores, devido às suas propriedades imunostimulantes. **Reações adversas:** muito comuns: eritema, inflamação local, úlcera superficial da pele, infecções fúngicas, coceira, formação de crostas, descamação e vesículas. Incomuns: dor nas costas, dor de cabeça, hiperqueratose, rinite, eritema grave e infecção respiratória superior. Raras: alopecia, arrepios, diarreia, tonturas, dispepsia, fadiga, febre, linfadenopatia, sinusite, vômitos e reações inflamatórias intensas, incluindo exsudação ou erosão cutânea. Foram descritos fenômenos de alteração na cor da pele na área tratada com Ixium®. As informações de acompanhamento dos casos sugerem que estes eventos podem tornar-se definitivos em alguns pacientes. **Posologia:** no tratamento de verrugas genitais externas em adultos, Ixium® deve ser aplicado três vezes por semana, antes de deitar, e deverá permanecer na pele durante 6 a 10 horas. O tratamento com Ixium® deverá ser mantido até o desaparecimento das verrugas perianais ou genitais externas ou por um período máximo de dezesseis semanas por cada episódio de verrugas. No tratamento de carcinoma superficial basocelular em adultos, aplicar Ixium® durante seis semanas, cinco vezes por semana, antes de deitar e deixar atuar sobre a pele durante aproximadamente oito horas. No tratamento de ceratose actínica, Ixium® deve ser aplicado duas vezes por semana, por 16 semanas, antes de deitar, deixando atuar sobre a pele por aproximadamente oito horas. MS: 1.0390.0176. Farmoquímica S/A. CNPJ 33.349.473/0001-58. **VENDA SOB PRESCRIÇÃO MÉDICA.** SAC 08000 25 01 10. Para ver o texto de bula na íntegra, acesse o site [www.fqm.com.br](http://www.fqm.com.br). **Referências:** **1)** Kravtchenko N. et al. *British Journal of Dermatology*, 2007, 157 (Suppl. 2), 34-40. **2)** Ixium. Bula do produto. **3)** Eigentler TK. et al. *J Am Acad Dermatol*. 2007, 57(4):616-21. **4)** Szeimies RM. et al. *J Am Acad Dermatol*. 2004, 51(4):547-55. **5)** Hoyme UB et al. Effect of adjuvant imiquimod 5% cream on sustained clearance of anogenital warts following laser treatment. *Infect Dis Obstet Gynecol* 2002;10:79-88. **6)** Carrasco D et al. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. *J Am Acad Dermatol* VOLUME47, NUMBER4 S212-16. **7)** Lacey CJN et al. 2012 European guideline for the management of anogenital warts. *JEADV* 2013,27,e263-e270.

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# Gynopac®

## tioconazol + tinidazol e secnidazol

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### INDICADO PARA INFECÇÕES VAGINAIS:

candidíase, tricomoníase, vaginose bacteriana ISOLADAS OU MISTAS<sup>1</sup>



### 2 OPÇÕES DE POSOLOGIA:

1X AO DIA POR 7 DIAS <sup>OU</sup>  
2X AO DIA POR 3 DIAS<sup>1</sup>

INDIVIDUAL

CREME VAGINAL +  
2 COMPRIMIDOS  
DE 1g DE SECNIDAZOL<sup>1</sup>



CREME VAGINAL + 2 COMPRIMIDOS DE 1g DE SECNIDAZOL<sup>1</sup>

+2 COMPRIMIDOS  
DE 1g DE SECNIDAZOL  
PARA O PARCEIRO<sup>1</sup>



CASAL

**CONTRAINDICAÇÃO:** PRIMEIRO TRIMESTRE DA GRAVIDEZ. **INTERAÇÃO MEDICAMENTOSA:** O SECNIDAZOL PODE INTERAGIR COM OS SEGUINTE FÁRMACOS: VARFARINA, INDADIONA, CIMETIDINA, DISSULFIRAM E LÍLIO.

**Gynopac®** (tioconazol + tinidazol e secnidazol). **Apresentações:** Comprimido revestido - Embalagem contendo cartela com 2 ou 4 comprimidos de secnidazol; Creme - Embalagem contendo bisnaga com 35 g de tioconazol + tinidazol + 7 aplicadores. **Indicações:** Gynopac® é indicado no tratamento das infecções vulvares e vaginais causadas por Candida, Trichomonas e Gardnerella, isoladas ou mistas. **Contra-indicações:** Primeiro trimestre da gravidez, durante a amamentação, especialmente imediatamente após o parto, hipersensibilidade a outros derivados imidazólicos e a qualquer componente da fórmula. **Advertências e precauções:** não é aconselhável o uso de Gynopac® nos dois últimos trimestres de gravidez. O uso de bebidas alcoólicas ou de medicamentos que contenham álcool deve ser evitado durante o tratamento e até quatro dias após seu término. **Interações medicamentosas:** o secnidazol pode interagir com os seguintes fármacos: varfarina, indadiona, cimetidina, dissulfiram e lítio. **Reações adversas:** Reações locais como irritação, dor, prurido, eritema, edema, sensação de queimação, reações alérgicas, rash eritematoso. Pode ocorrer sensação de gosto metálico na boca, náuseas, vômitos, dores abdominais, aftas, urticárias e erupções na pele. **Posologia:** creme vaginal - o conteúdo de um aplicador cheio (5 g) deve ser aplicado uma vez à noite, ao deitar-se, durante sete dias consecutivos, ou como alternativa, duas vezes ao dia, durante três dias. Comprimido - Tomar de uma só vez os dois comprimidos de 1000 mg (2g) de secnidazol. Quando indicado, após avaliação do casal, a mesma dosagem deve ser administrada ao cônjuge. M.S.: 1.0390.0165. VENDA SOB PRESCRIÇÃO MÉDICA. SAC 08000 25 01 10. Para ver o texto de bula na íntegra, acesse o site [www.fqm.com.br](http://www.fqm.com.br).

**Referências Bibliográficas:** 1. Bula do(s) produto(s) Gynopac®.



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