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1988-2019 31 anos na vanguarda das DST
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1988-2019 31 anos na vanguarda das DST
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WHY IS THE NONAVALENT HPV VACCINE SO IMPORTANT FOR BRAZIL?

POR QUE A VACINA NONAVALENTE CONTRA O HPV É TÃO IMPORTANTE PARA O BRASIL?

Edison Natal Fedrizzi[1]

ABSTRACT
Genital Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. It presents from latent infection to anogenital and oropharyngeal carcinoma in both men and women. Cervical cancer is still the most prevalent cancer associated with HPV and in many countries, such as Brazil, is considered an epidemic, although Pap smears are available in public and considered a way of prevention of the disease. However, in Brazil, the coverage of this test is very low, reflecting the maintenance of high mortality for this disease for decades. The most effective way to prevent this disease, of course, is to prevent HPV infection with vaccination. High vaccine coverage using the 4HPV vaccine, which is available in Brazil, would provide a significant reduction in cancer in our country, whereas the use of 9HPV would prevent almost all high-grade lesions, true precursors of cervical cancer.
Keywords: Papillomaviridae; papillomavirus infections; Papanicolaou test; papillomavirus vaccines.

RESUMO
A infecção genital pelo papilomavírus humano (HPV) é a infecção de transmissão sexual mais frequente no mundo inteiro. Ela se apresenta desde a infecção latente até o carcinoma da área anogenital e orofaringe em homens e mulheres. O câncer de colo de útero ainda é o mais prevalente associado ao HPV e em muitos países, como no Brasil, é considerado uma epidemia, apesar de o exame de Papanicolaou estar disponível nas redes públicas e ser considerado uma forma de prevenção da doença. No entanto, no Brasil, a cobertura deste exame é muito baixa, refletindo na manutenção da alta mortalidade por esta doença há décadas. A forma mais eficaz de prevenção desta doença, sem dúvida, é a prevenção da infecção pelo HPV através das vacinas. Uma alta cobertura vacinal, utilizando a vacina 4HPV, que é a disponível no Brasil, proporcionaria uma redução importante do câncer em nosso meio, ao passo que a utilização da 9HPV, preveniria a quase a totalidade das lesões de alto grau, verdadeiras precursoras do câncer de colo de útero.
Palavras-chave: Papillomaviridae; infecções por papillomavirus; teste de Papanicolau; vacinas contra papillomavirus.

INTRODUCTION

Genital HPV infection is the most frequent Sexually Transmitted Infection (STI) in both women and men[1]. It is estimated that at least 50% of sexually active individuals will enter in contact with HPV at some point in their lives, and that 80% of women will have this contact up to 50 years of age[2]. We can consider this an epidemic infection in Brazil, because there are from 9 to 10 million infected people with this virus, and 700,000 more new cases are found every year[3].

Recently, preliminary results of the prevalence of HPV infection in Brazil were published in the POP Study (Papillomavirus Prevalence Study in Brazil), a cross-sectional study with 7,586 individuals sexually active (5,812 women and 1,774 men) from 16 to 25 years old, in the 26 capitals of Brazil and the Federal District. HPV prevalence was 54.6% with positive high-risk HPV in 38.4% of the participants. The highest prevalence was in Salvador City, with a positivity rate of 71.9%, and the lowest rate in Recife, with 41.2%[4].

Worldwide, 32 million new cases of genital warts are estimated each year (Brazil, around 1.9 million/year), and the vast majority is associated to HPV 6 (70% of cases) and 11 (20% of cases)[5].

HPV INFECTION AND CANCER

For the biennium 2018-2019, 16,370 new cases of cervical cancer per year in Brazil are estimated, with a risk of 15.43 cases/100,000 women occupying the third position, only after breast and colon/rectum cancer. However, without considering non-melanoma skin cancer, cervical cancer is the first most incident in the Northern region (25.62/100,000 women)[6]. The estimate of deaths is 8,079 cases/year (7.5/100,000 women)[7]. If we consider other types of HPV-related cancers, we can also consider HPV-induced cancer an epidemic in Brazil (**Table 1**)[7].

HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82, 26, 53, 66 and 73 are the most often considered high oncogenic risk, and HPV types 6, 11, 40, 42, 43, 44, 53, 54, 54, 61, 70, 72, 73, 81, CP6108, low risk[8]. In general, HPV 16 and 18 account for 70% of cases of cervical cancer, and 80-90% of cases of HPV cancers induced in other areas, whereas HPV 6 and 11 are the causes of at least 90% of anogenital warts and almost all larynx papillomatoses[9]. High-risk HPV is still responsible for cancer of other organs, such as anus, in 90%; 70% of the vagina, 50% of the penis; 40% of the vulva; and 13-72% of the oropharynx[10].

HPV VACCINE EFFICACY

Currently, the most effective way to prevent infection and HPV-associated diseases is the use of vaccines. Up to date, three vaccines are available on the international market: the bivalent or Cervarix® (2HPV — protection against HPV 16 and 18), the quadrivalent or

Table 1 – Crude incidence rates of HPV-related cancers/100,000.

	Male	Female
Cervical cancer	-	15.2
Anal cancer	0.3-1.2	0.8-1.7
Vulvar cancer	-	0.8-2.7
Vaginal cancer	-	0.0-0.9
Penile cancer	0.3-2.0	-
Oropharyngeal cancer	3.7	0.8

HPV: Human papillomavirus.
Source: ICO/IARC Information Centre. Human Papillomavirus and Related Diseases Report – Brazil, 2019[7].

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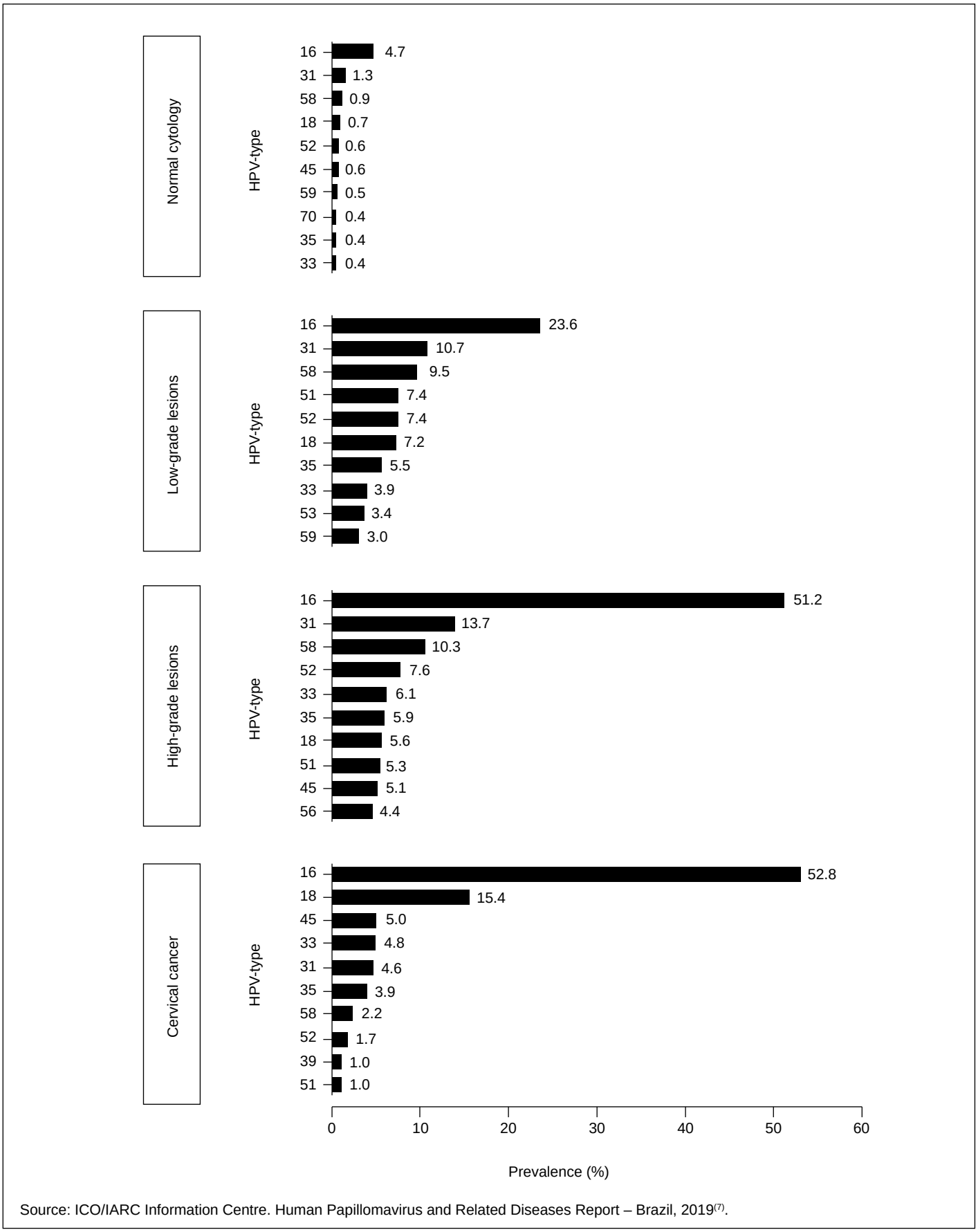


Source: ICO/IARC Information Centre. Human Papillomavirus and Related Diseases Report – Brazil, 2019[7].

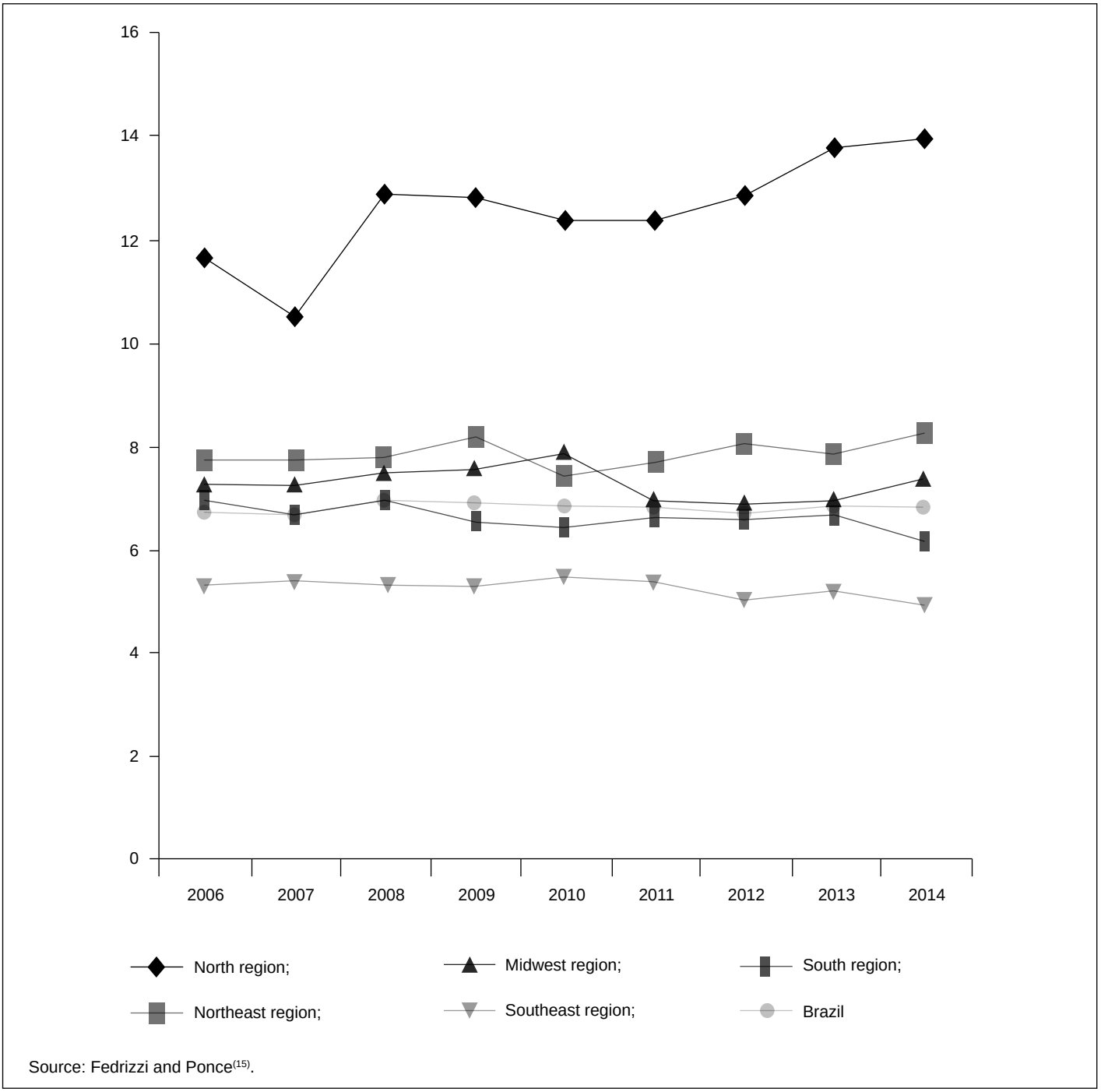
Figure 1 – Comparison of the ten most frequent human papillovirus (HPV) oncogenic types in Brazil among women with and without cervical lesions.

Table 2 – Human papillovirus (HPV) types in the cervix with and without lesion in Brazil.

HPV INFECTION	HPV 16, 18 (%)	HPV 16, 18, 31, 33, 45, 52, 58 (%)
Normal Cytology	5.4	9.2
LSIL	30.8	62.3
HSIL	56.8	99.6
Cervical cancer	68.2	86.5

LSIL: low-grade lesion; HSIL: high-grade lesion.
Source: ICO/IARC Information Centre. Human Papillomavirus and Related Diseases Report – Brazil, 2019[7].

Gardasil® (4HPV — against HPV 6, 11, 16, and 18), and the nonavalent or Gardasil 9® (9HPV — against HPV 6, 11, 16, 18 , 31, 33, 45, 52 and 58), which were highly effective and safe in clinical trials with rates of 95-100% efficacy in the prevention of genital warts and precancerous lesions of the lower genital tract associated to HPV 16 and 18 (2HPV and 4HPV) and for the other five types of high-risk HPV for nonavalent vaccine[11]. Although the 9HPV vaccine has been approved by the Brazilian National Health Surveillance Agency (ANVISA) in December 2017, it is not available in the national market yet.



Source: Fedrizzi and Ponce[15].

Figure 2 – 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 most appropriate moment for the use of HPV vaccine is before exposure to the virus. However, the most recent studies also show benefits for already infected women, including those with cervical intraepithelial neoplasia (CIN) 2/3 lesions, showing a decrease in recurrences of roughly 75–88% for vaccinated women[12]. Although there is an age recommendation for the use of the vaccines in the label, they were highly safe, immunogenic, and effective also in elderly men and women[12].

HPV DISEASES AND HPV VACCINATION IN BRAZIL

Since March 2014, the 4HPV vaccine is available on the public vaccination calendar in Brazil. Currently, the National Immunization Program (PNI) provides the vaccine to girls aged from 9 to 14, and boys aged from 11 to 14, as well as men and women aged from 9 to 26 years with an immune problem (HIV infection, radio/chemotherapy for cancer, bone marrow and solid organs transplantation[13,14].

When we evaluate the Brazilian scenario as to HPV types among women with and without cervical lesion (**Figure 1**), we observe a great variability between the different types of HPV and the severity of lesions[7].

THE IMPORTANCE OF 9HPV VACCINE

When we classify HPV lesions associated to viruses 16 and 18 (direct protection with the 2HPV and 4HPV vaccine), and viruses 16, 18, 31, 33, 45, 52, and 58 (direct protection with the 9HPV vaccine), we observed a significant increase in the protection of lesions with the 9HPV vaccine. If we do not consider the possible cross-protection and consider a protection of 100% of the vaccine, we will be protecting a low-grade lesion (LSIL) by 30.8% using 2HPV and 4HPV vaccines, whereas we double this protection to 62.3% when we use the 9HPV vaccine. This difference becomes more evident for real precursor lesions of cancer, high-grade lesions (HSIL), where we obtain a protection of 56.8% with 2HPV and 4HPV vaccines, and to virtually, the totality of the cases (99.6%) with the vaccine 9HPV[7] (**Table 2**).

Unfortunately, the mortality by cervical cancer remained unchanged in several decades in Brazil, regardless of the various programs and campaigns carried out over these years for the Pap smear use, as demonstrated in a recent analysis of nearly 10 years in our country (**Figure 2**)[15]. It is quite clear that the most effective way to prevent this disease is with the HPV vaccination. Brazilian health authorities must take urgent actions to get high HPV vaccination coverage again (as occurred with the first dose in the year of implementation of the public vaccination program) by restarting vaccination in schools, spreading information for the public and health professionals, facilitating the access to Basic Health Units (expanding working hours), and adopting the 9HPV vaccine as soon as possible, so that we can definitively change this reality in Brazil, of about 16,000 new cases/year and 8,000 deaths/year by cervical cancer, a disease absolutely preventable.

CONCLUSION

Cervical cancer mortality in Brazil has remained the same for several decades, regardless of public campaigns and programs to encourage it, especially due to its low coverage. One of the best strategies to change this scenario is HPV vaccination, which should achieve high vaccination coverage and replacement of 4HPV vaccine for 9HPV as soon as possible.

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Conflict of interests

Researcher of the quadrivalent and nonavalent vaccine trials in men and women by the company MSD.

Ethics Committee

There is no need for this action.

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Editors' note on nonavalent HPV vaccine (9HPV)

Nota dos editores sobre a vacina nonavalente contra o HPV (9HPV)

Mauro Romero Leal Passos[1], *José Eleutério Junior*[2]

In the first place, I would like to emphasize and thank the great initiative and exceptional Editorial by Professor Edson Fedrizzi.

Despite all that has been said, we should not fail to mention that the frequent use of male or female condoms (long forgotten in educational campaigns, of free distribution in public events and put for sale at commercial establishments) is an essential method to prevent all sexually transmitted diseases (STDs), including the Human papillomavirus HPV, hepatitis B, and HIV. Frequently, people infected with STD are those who already acquired another STD. Vaccination against HPV does not protect these people against other STDs. Therefore, since there are no vaccines against classic STDs (except for hepatitis B), any information on HPV should (and, in fact, have) support vast actions against all other STDs.

On the other hand, appeals for the prevention of HPV infections and associated diseases should not insist on exclusive statements that this is a vaccine against cervical cancer. In our point of view, keeping on spreading messages that cause fear/terror with "heavy" words, such as cancer, means missing a valuable opportunity to create a "kind" channel to broadly talk about sex and STDs, without prejudice, to the entire population, especially adolescents. We point out that this is also the vaccine against premalignant and malignant lesions of the penis, anus, vulva and oropharynx.

Sure of the importance of the HPV vaccine, we support the expansion of the administration by the Brazilian public health system for people of both genders, aged from 9 to 17, *people of both genders up to 45 years of age* living with HIV, solid organs transplanted people, bone marrow, oncologic, people victims of rape and sexual abuse, and for users of pre- and post-HIV prophylaxis (PrEP and PEP). These groups of people have the most severe outcomes when affected by HPV. At this moment, 9HPV vaccine is the best way to prevent HPV infections/diseases.

We must also get out of the monotony that is up to the public sector only to fight STDs. All sections and actors, including health and education professionals (public, private, and non-governmental organizations), public and private health managers/supplementary medicine (diseases prevention and treatments impact corporate finances), professionals from health scientific societies and education, communication and social sciences, media professionals in general, social influencers, and people in general are also responsible, considering we lack books, plays, movies, social media posts, lectures, seminars, articles, and interviews in newspapers and magazines on the matter, that is, general pieces of raising awareness. Every action leads to more information, dialogues about sexuality, and emotional and social repercussions involving STDs. It will provide the basis for correct information, minimizing the impact of fake news and actions of anti-vaccine groups[1].

For a long time, since the pre-launch, launch and post-launch dissemination of bi and quadrivalent vaccines against HPV in Brazil, we have been "flooded" by vaccine producing companies with the speech that we have to make and offer what is most effective against infections/diseases caused by different types of HPV. Thus, we work on a day-to-day basis on various problems.

Today, the world made available a vaccine with a higher action spectrum against HPV. However, as already said, the 9HPV vaccine has been approved in Brazil since 2017. However, it is not available neither to the Brazilian population (in the public and private sphere) nor to several other countries in Latin America and Africa. Areas in which infections/diseases (including cancer) caused by HPV are the largest in the world. Please refer to the Brazilian data already available.

We have information that the 9HPV vaccine is already available in China, where the public service, as far as we know, has not sponsored the purchase of 4HPV vaccine for public vaccination in same the scale that Brazil has implemented and implements since 2014.

As informed by immunization market professionals, the producer of 4HPV and 9HPVvaccines is having trouble to meet the demands, especially with the entry in the Chinese market.

The commercialization of the 9HPV vaccine to new countries, however, given that the manufacturer cannot produce for all the market, made impossible to the Brazilian population (public and private) to have the best product in the prevention/fight against infections/diseases caused by HPV, because this is an evolution of 4HPV, implemented in Brazil in the public network since 2014, and commercialized, concurrently, in the private system since 2007.

Situations like these strengthen the speech that above respecting and solidifying advances in public health, by the concept of private pharmaceutical companies, is the opening of new fields of business, trades and profit. Issues such as improving people's health are secondary[2].

As far as we know, the 9HPV vaccine is available in public and private spheres in the United States, Canada, Chile, Ecuador, Peru, Croatia, Denmark, Scotland, Gibraltar, Italy, Lietchtentein, Wales, Portugal, United Kingdom, Czech Republic, Serbia, Switzerland, Turkmenistan, Israel, Qatar, South Korea, Singapore, Australia, New Zealand, China, Hong Kong[3].

When will Brazil have the 9HPV vaccine available, at least for the private system, like what happened with 2HPV and 4HPV?

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Analysis of monitored cases of acquired syphilis in Porto Alegre, Rio Grande do Sul

Análise de casos monitorados de sífilis adquirida em Porto Alegre, Rio Grande do Sul

Gustavo Haas Lermen[1], Lisiane Morelia Weide Acosta[2], Fabiana Ferreira dos Santos[3], Juanita Natasha Garcia de Oliveira[1]

ABSTRACT

Introduction: Syphilis is a systemic and curable sexually transmitted infection, exclusive to humans. Brazil is experiencing an increasing incidence of syphilis in recent years. Porto Alegre has an incidence rate of acquired syphilis (AS) four times higher than the national one. **Objective:** To describe the epidemiological profile of monitored cases of AS, through rapid tests, in the city of Porto Alegre/Rio Grande do Sul in the first semester of 2018. **Methods:** The study has a cross-sectional, observational, epidemiological, and analytical design, and the study population was included in the Porto Alegre AS monitoring spreadsheet in the first semester of 2018, totaling 1,453 participants. We performed descriptive analyses with absolute and relative frequencies to develop the profile. The χ^2 test for bivariate analysis verified the association between sociodemographic variables and the adequate treatment outcome, with a 95% significance level. **Results:** The profile found had a predominance of males, white people, individuals aged 20 to 29, with incomplete elementary school, and not homeless. We identified an association in the bivariate analysis between the adequate treatment outcome and the variables schooling, gender, age, and homelessness. **Conclusion:** Actions that seek to structure and organize the processes related to AS monitoring are important, especially due to the association of sociodemographic variables that indicate social vulnerability with the adequate treatment outcome.

Keywords: syphilis; epidemiological monitoring; epidemiology; monitoring.

RESUMO

Introdução: A sífilis é uma Infecção Sexualmente Transmissível de caráter sistêmico, curável, e exclusiva do ser humano. O Brasil vive um período de crescimento dos casos de sífilis nos últimos anos. Porto Alegre possui um coeficiente de incidência de sífilis adquirida quatro vezes maior que o nacional. **Objetivo:** O objetivo deste estudo foi descrever o perfil epidemiológico dos casos monitorados para sífilis adquirida, por meio de testes rápidos, no município de Porto Alegre/RS, no primeiro semestre de 2018. **Métodos:** O delineamento é epidemiológico observacional analítico transversal, sendo todos os casos inseridos na planilha de monitoramento da SA de Porto Alegre no primeiro semestre de 2018, que totalizou 1.453 usuários. Análises descritivas foram realizadas com frequência absoluta e relativa para caracterizar o perfil. Foi utilizado o teste de χ^2 em análise bivariada para verificar a associação das variáveis sociodemográficas com o desfecho do tratamento adequado, com nível de significância de 95%. **Resultados:** O perfil encontrado foi predominância do sexo masculino, brancos, na faixa etária de 20 a 29, ensino fundamental incompleto e não estar em situação de rua. Houve associação na análise bivariada entre os desfechos do tratamento adequado e as variáveis escolaridade, sexo, faixa etária e situação de rua. **Conclusão:** Ações que buscam estruturar e organizar os processos relativos ao monitoramento da SA são importantes, especialmente por haver associação de variáveis sociodemográficas que indicam vulnerabilidade social com o desfecho de tratamento adequado da sífilis.

Palavras-chave: Sífilis; Vigilância Epidemiológica; Epidemiologia; Monitoramento.

INTRODUCTION

Brazil has been experiencing a growing incidence of syphilis in recent years. In 2016, 87,593 cases of acquired syphilis (AS) were reported. Stratified by regions, the Southern Region holds the second place, corresponding to 24.2% of the reported cases. In addition, the detection rate in Brazil in the aforementioned year was 42.5 cases of AS per 100,000 inhabitants. The South Region exceeded this rate with 72 cases per 100,000 inhabitants, while Rio Grande do Sul (RS) had the highest rate in the country (93.7 cases per 100,000 inhabitants)[1]. The capital of the state, Porto Alegre (POA), had a coefficient of AS incidence four times greater than the national one[2] and was the fifth capital with the highest detection rate according to data from the General Coordination of Health Surveillance (*Coordenadoria Geral de Vigilância em Saúde* – CGVS)[3].

Syphilis is a systemic and curable sexually transmitted infection (STI), exclusive to human beings, caused by the bacterium *Treponema pallidum*. Estimates indicate that 12 million new cases of syphilis occur annually in the world adult population[4]. The infection is transmitted by sexual contact, direct contact with open lesions, transfusion of contaminated blood, and transplacentally[5].

Most people with syphilis tend not to be aware of the pathology, due to the absence of symptoms, depending on the stage of infection, which can enable transmission to their sexual partners. Thus, it is a silent disease getting worse over the years, reaching other stages, and, despite having effective diagnosis and treatment, which is free for the population, it remains a public health problem until today.

For case detection, the general population of Porto Alegre has access to free rapid tests (RT), without following the regionalization logic, that is, the user has the right to undergo the procedure in any Basic Health Unit (BHU) without the need for scheduling[6]. All pregnant women should have an RT in the first and third trimester of pregnancy, according to the low-risk prenatal care protocol[7].

The increasing identification and diagnosis with the advent of the RT stand out, since this tool is fundamental for investigation and

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necessary referrals, aiming at comprehensive, effective, and successful care[5]. However, there are gaps regarding the systematization of the follow-up required for the confirmation of diagnosis, treatment, outcome, and, consequently, the reduction in the *Treponema* transmission chain.

The Research Ethics Committee of the Municipal Health Department of Porto Alegre approved this study under protocol no. 2931412.

In order to transpose the test to address the high incidence problem, the Municipal Health Department (*Secretaria Municipal de Saúde* — SMS) began a monitoring process of rapid tests reactive for AS in BHUs of the Primary Care Network (*Rede de Atenção Primária* — RAP) and Specialized Care Services (*Serviços de Atenção Especializada* — SAE) of the city of Porto Alegre in the state of Rio Grande do Sul.

This article aims at analyzing this work and its initial results. Therefore, to evaluate the situation of the city and its regions, the analysis was also carried out by District Administrations (DAs), administrative structures, and regional managers, which are the agencies responsible for discussion and practice, where all health care strategies of the public health system are elaborated. DAs are distributed in eight health regions, with defined geographical boundaries and population to determine the services offered[8].

OBJECTIVE

To describe the epidemiological profile of monitored AS cases based on RTs in the city of Porto Alegre/Rio Grande do Sul in the first semester of 2018.

METHODS

This is an analytical cross-sectional epidemiological study. The study population comprised all cases entered in the Porto Alegre AS monitoring spreadsheet in the first semester of 2018, excluding pregnant women or those who became pregnant before the completion of the treatment, and users who refused any form of treatment.

The AS monitoring spreadsheet only has the cases of RT reactive for syphilis, deriving from the electronic form completed by health services with information regarding the tests in general, shared between care and management, generating tables for different DA services for each corresponding month.

Data from the AS monitoring spreadsheet corresponding to the first semester of 2018 were compiled and stored using Google Drive Sheets, and included the independent sociodemographic variables of the survey: the BHU that performed the test and its respective DA, gender, ethnicity, age, schooling, housing situation, and date of completion of the RT. We emphasize that sociodemographic factors were self-reported.

In the monitoring process, the evaluation of the pathology treatment consisted of consulting digital medical records from the electronic system of the public health system (*Sistema Único de Saúde eletrônico* — e-SUS), which is the registration tool used by the RAP. Thus, the follow-up of the cases was assessed and classified by treatment according to the clinical stage of the disease and current care protocol, the Clinical Protocol and Therapeutic Guidelines (*Protocolo Clínico e Diretrizes Terapêuticas* — PCDT) for Comprehensive Care for People with Sexually Transmitted Infections[5]. In addition, information concerning the presence of clinical manifestations and follow-up with non-treponemal infection test was added to support the categorization.

The outcome of the AS treatment was categorized as follows:

- Adequate: treatment registered with the appropriate dose of benzathine penicillin within the acceptable time frame (14-day interval tolerance between applications), which matches the clinical stage of AS; alternative treatments (doxycycline and ceftriaxone) associated with a non-treponemal test to observe bacterial load reduction and absence of treatment in case of prior notification of the disease, and non-reactive non-treponemal test or low titrations (≤1:4), according to the recorded clinical history;
- Inadequate: incorrect dose of benzathine penicillin, outside the tolerance range of administration, and with medicines not included in the current care protocols;
- Pending: when there is no record in the information systems about the complete treatment with benzathine penicillin according to the clinical stage of the pathology, or lack of current non-treponemal test results when necessary to confirm the disease, and in the absence of registration of follow-up non-treponemal test, when alternative treatments were performed.

The detection rate in the DA regions was calculated through the number of cases of RT reactive for AS in each DA, divided by the total number of tests performed in the respective administration, multiplied by one hundred. We performed descriptive analyses of all sociodemographic variables investigated with their absolute and relative frequency distributions to build the epidemiological profile.

The process of notification verification was carried out in partnership with the General Coordination of Health Surveillance (*Coordenadoria Geral de Vigilância Sanitária* — CGVS), through the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* — SINAN), which was consulted to check whether the cases of AS meeting these criteria were included, that is, if the notification was made by the services according to the information notice no. 02-SEI/ 2017[9].

We adopted the chi-square test and linear trend p-value in ordinal categorical variables in a bivariate analysis to verify the association of sociodemographic variables with the treatment outcome, with a 95% significance level, using the statistical software SPSS (IBM SPSS Statistics 22). This analysis combined the treatments considered "Inadequate" and "Pending" to enable the investigation with two outcomes. We conducted a descriptive analysis with the Epi Info software (Epi Info™, CDC). Age groups were classified according to SINAN.

RESULTS

A total of 16,588 RTs for syphilis were performed in RAP and SAE in the city of Porto Alegre in the first semester of 2018, and 1,817 (11%) of them were reactive for syphilis. The analysis of the study population excluded 353 pregnant women, 7 who became pregnant during the treatment period, and 4 who refused any treatment, resulting in a total of 1,453 patients monitored for AS in the studied period.

According to **Table 1**, the distribution of the 1,453 cases of AS monitored during the study period was not homogeneous in the DA

territories, and the detection rate of syphilis by RT was higher in the Center region.

Table 2 presents the profile of the patients, showing a slight predominance of males (50.7%), and that 53.6% of the sample declared being white. Most participants belonged to the age group 20 to 29 years (34.1%), with a minimum age of 14 years and maximum of 86 years, and had incomplete elementary school (34.3%). The vast majority of the sample was not homeless (94.9%).

As demonstrated in **Table 3**, the East/Northeast DAs had the highest percentage of adequate treatment. Inadequate treatment was predominant in the Glória/Cruzeiro/Cristal DAs, and pending cases were more frequent in the Center DA, reaching 81.4%. The overall analysis of the city revealed that Porto Alegre has an adequate treatment percentage of 37.6%.

Table 4 shows an association in the bivariate analysis between treatment outcomes and the sociodemographic variables schooling, gender, age group, and homelessness, and a linear trend in the schooling and age group variables, that is, the higher the schooling and age, the higher the prevalence of adequate treatment. We found no association with the variable ethnicity.

Table 5 indicates that, although most AS cases are notified to SINAN (52.1%), the number and percentage of cases with no notification is high, even in the National List of Compulsory Notification, despite this communication being mandatory to health professionals.

The detection rate of RT for syphilis was 11% in Porto Alegre during the study period, higher than expected according to the incidence data presented by the Epidemiological Bulletins for the city, and higher than reported by the surveillance regarding syphilis in pregnant women, estimated in 4%[1,2].

The analysis per health region showed that the Center DA had a detection rate higher than the one in the city, reaching 14.5%. The administration and policies for prevention, care, and monitoring of syphilis in the city and its territory should take this fact into account. Concomitantly, this DA presented a large percentage (81.4%) of cases with pending treatment, which might be due to the testing of people from other cities who have access to the central region of Porto Alegre, or because this location has the highest concentration of homeless people[10].

The sociodemographic profile found in this study was similar to the analysis based on the compulsory notifications of AS from the Epidemiological Bulletin of Syphilis[1]. Most of them have incomplete elementary school, are white, male, and aged between 20 and 29 years. However, with respect to gender, this bulletin reveals a difference of 1.5 cases in males for each case in females, while in the present study, the proportion was practically equal between genders; nonetheless, the analysis showed statistical significance, with prevalence of females in cases with adequate treatment.

The minimum age of 14 years in reactive tests for syphilis is worrying and reinforces the need for preventive actions against STIs among adolescents. The group in question belongs to a priority segment targeted by the Syphilis No project. This project is a partnership between the Ministry of Health and the Universidade Federal do Rio Grande do Norte that aims to expand the population's access to diagnosis and treatment in the basic health network. The initiative presents a wide range of strategies to disseminate information, achieve its purposes, and reach the priority populations (young people, pregnant women, sexually active population, and health professionals)[11].

Homeless people represented 5.1% of the cases of RT reactive for syphilis, showing the importance of care focused on social vulnerability. The study corroborates this issue due to the association of adequate treatment and not being homeless. Porto Alegre has 2,115 homeless adults, according to research conducted by the Universidade Federal do Rio Grande do Sul (UFRGS), representing 0.1% of the population of the city[10].

Table 1 – Number of reactive cases for acquired syphilis (n=1,453), tests performed (n=16,588), and detection rate according to District Health Administrations in Porto Alegre in the first semester of 2018.

District Administration	Reactive n	Tests n	Detection Rate
Center	285	1,908	14.9
Glória/Cruzeiro/Cristal	251	2,874	8.7
East/Northeast	155	1,919	8.1
North/Eixo Baltazar	126	1,998	6.3
Northwest/Humaitá/ Navegantes/Islands	112	1,694	6.6
Partenon/Lomba do Pinheiro	292	3,200	9.1
Restinga/Far South	113	1,365	8.3
South/South Center	119	1,630	7.3

Table 2 – Sociodemographic variables of individuals monitored for acquired syphilis (n=1,453) in the primary care network and specialized care services of Porto Alegre in the first semester of 2018.

Variable	N (%)
Schooling	
Illiterate	23 (1.6)
Incomplete elementary school	499 (34.3)
Complete elementary school	224 (15.4)
Incomplete high school	250 (17.2)
Complete high school	309 (21.3)
Incomplete higher education	70 (4.8)
Complete higher education	78 (5.4)
Ethnicity	
White	779 (53.6)
Black	404 (27.8)
Multiracial	239 (16.4)
Indigenous	12 (0.8)
Asian	8 (0.6)
Unknown	11 (0.8)
Gender	
Female	716 (49.3)
Male	737 (50.7)
Age group (years)	
10 to 14	7 (0.5)
15 to 19	173 (11.9)
20 to 29	496 (34.1)
30 to 39	316 (21.8)
40 to 49	197 (13.6)
50 to 59	150 (10.3)
60 to 69	89 (6.1)
70 or older	25 (1.7)
Mean (±standard deviation) (minimum; maximum)	34.6(±14.4) (14.86)
Homeless	
No	1,379 (94.9)
Yes	74 (5.1)

The bivariate analysis also evidences the association of vulnerability with the treatment outcome through the schooling variable, showing a linear relationship between better education and the greater frequency of adequate treatment. In Brazil, schooling is often used as a proximal income. This fact may indicate another aspect of vulnerability associated with treatment in this study. According to the information collected by the Institute of Applied Economic Research (*Instituto de Pesquisa Econômica Aplicada* — IPEA), the main factor of expansion in working income was the increase in schooling[12].

Table 5 – Distribution of cases meeting the criteria for mandatory notifications (n=432) among individuals monitored for acquired syphilis in the primary care network and specialized care services of Porto Alegre in the first semester of 2018.

Notified to SINAN	n (%)
Yes	225 (52.1)
No	207 (47.9)

SINAN: Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação*).

Table 3 – Treatment outcome of monitored cases of acquired syphilis according to District Administrations in Porto Alegre in the first semester of 2018.

	Adequate n (%)	Inadequate n (%)	Pending (%)	Total n (100%)
District Administration				
Center	52 (18.2)	1 (0.4)	232 (81.4)	285
Glória/Cruzeiro/Cristal	112 (44.6)	7 (2.8)	132 (52.6)	251
East/Northeast	72 (46.5)	3 (1.9)	80 (51.6)	155
North/Eixo Baltazar	56 (44.4)	0 (0)	70 (55.6)	126
Northwest/Humaitá/Navegantes/Islands	41 (36.6)	1 (0.9)	70 (62.5)	112
Partenon/Lomba do Pinheiro	115 (39.4)	1 (0.3)	176 (60.3)	292
Restinga/Far South	47 (41.6)	4 (3.5)	62 (54.9)	113
South/South Center	51 (42.9)	5 (4.2)	63 (52.9)	119
Total of Porto Alegre	546 (37.6)	22 (1.5)	885 (60.9)	1,453

Table 4 – Prevalence of adequate (n=546) and inadequate/pending (n=907) treatments for acquired syphilis according to sociodemographic variables of monitored cases in Porto Alegre in the first semester of 2018.

Variable	Adequate n (%)	Inadequate/Pending n (%)	P*
Schooling			
Illiterate	9 (1.6)	14 (1.5)	
Incomplete elementary school	201 (36.8)	298 (32.9)	
Complete elementary school	84 (15.4)	140 (15.5)	
Incomplete high school	99 (18.1)	151 (16.6)	0.001
Complete high school	123 (22.5)	186 (20.5)	
Incomplete higher education	15 (2.8)	55 (6.1)	
Complete higher education	15 (2.8)	63 (6.9)	
Ethnicity			
White	265 (48.5)	514 (56.6)	
Black	170 (31.2)	234 (25.8)	
Multiracial	99 (18.1)	140 (15.4)	0.098
Indigenous	5 (0.9)	7 (0.8)	
Asian	3 (0.6)	5 (0.6)	
Unknown	4 (0.7)	7 (0.8)	
Gender			
Female	295 (54)	421 (46.4)	0.005
Male	251 (46)	486 (53.6)	
Age group (years)			
10 to 14	3 (0.5)	4 (0.4)	
15 to 19	79 (14.5)	94 (10.4)	
20 to 29	185 (33.9)	311 (34.3)	
30 to 39	85 (15.6)	231 (25.5)	<0.001
40 to 49	70 (12.8)	127 (14)	
50 to 59	59 (10.8)	91 (10)	
60 to 69	51 (9.3)	38 (4.2)	
70 or older	14 (2.6)	11 (1.2)	
Homeless			
No	533 (97.6)	846 (93.3)	<0.001
Yes	13 (2.4)	61 (6.7)	

*P for heterogeneity of proportions (dichotomous variable) and linear trend (ordinal variable).

The 2010 IBGE census[13] revealed that Porto Alegre has a black population of 10.2%, multiracial of 10%, and indigenous of 0.23%. These same population segments presented respectively 27.8, 16.4, and 0.8% of RT reactive for AS. This information shows an increased risk of a reactive result for this pathology, again reinforcing the need for attention to social vulnerability in the follow-up of syphilis cases. However, this study found no association between the variable ethnicity and the adequate treatment outcome.

We emphasize that, although the incidence of syphilis is high in Porto Alegre, as published in epidemiological bulletins, cases are still underreported, and in the studied period — one semester — , 47.9% of cases had not been notified despite meeting the notification criteria for AS.

CONCLUSION

This study identified a higher than expected RT detection for syphilis, which corroborates data from epidemiological bulletins showing an elevated incidence of AS in Porto Alegre. In addition, some DAs of the city had higher detection rates, despite the presence or absence of adequate treatment in the regions. This information enables a situation diagnosis of the city and can support management actions and public policies, while Brazil focuses on the Syphilis No program.

The development of actions to structure and organize the processes for AS monitoring becomes indispensable, especially due to the evidence of an association between sociodemographic variables that indicate social vulnerability and the adequate treatment outcome. We underline that the diagnosis and treatment of people with STIs and their sexual partners break the transmission chain, preventing possible complications. This is the only way we can fight a disease that has no vaccine but can be treated and cured.

Based on this study, we propose to continue monitoring the cases to expand and improve information about syphilis aggravation and management. We also suggest adding other variables related to income, sexual orientation, and gender identity to this analysis information, which would enable other preventive strategies.

Participation of each author

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Conflict of interests

The authors declare no conflict of interests.

Approval by the Human Research Ethics Committee

The Research Ethics Committee of the Municipal Health Department of Porto Alegre approved this study under protocol no. 2931412.

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Program for Prevention of Mother-to-Child Transmission of Syphilis and HIV in Brazil: missed opportunities

Programa de prevenção da transmissão materno-infantil de sífilis e HIV no Brasil: oportunidades perdidas

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ABSTRACT
While antenatal screening for HIV and syphilis is part of the national policy in Brazil, screening and treatment coverage remain inadequate in many parts of the country. This study aimed to describe missed opportunities concerning mother-to-child transmission (MTCT) from the point-of-view of pregnant women, health professionals, and health care managers. A semi-structured interview was conducted in six Brazilian states. Pregnant women, health professionals, and health care managers were interviewed to identify failures in the process of care for pregnant women and MTCT of syphilis or HIV. The project had a quantitative approach but included open-ended questions to capture the views of participants regarding the feasibility of strategies adopted for controlling MTCT. The sample consisted of 109 women, 62 health professionals, and 34 health care managers. The median age of women was 24 (range: 15–46) years, and the median schooling was 8 years. Eighty percent of those interviewed received prenatal care. Among those who attended antenatal visits, the median was 6.43 (range: 1–20) visits. Managers and health professionals had a median of 10 (range: 4–25) working years. In the interviews, the managers declared that they had provided tests and treatment for these infections, but health professionals stated that they did not have tests or treatment available to offer, and most women complained about the difficulties of receiving treatment. Organizing the logistics and breaking down barriers related to care in Brazil is challenging. An adequate health care system and policy factors that address this situation can help to eliminate MTCT by implementing strategies adopted to control these infections in the country.
Keywords: Mother-to-child transmission; HIV; syphilis; health system; health policy.

RESUMO
Embora o rastreamento para HIV e sífilis no pré-natal faça parte da política nacional no Brasil, a cobertura do rastreamento e tratamento permanece inadequada em muitas partes do país. O objetivo deste estudo foi descrever as oportunidades perdidas de transmissão materno-infantil (TMI) do ponto de vista de gestantes, profissionais de saúde e gestores de saúde. Uma entrevista semiestruturada foi realizada em seis estados brasileiros. Foram entrevistadas gestantes, profissionais de saúde e gestores dos serviços de saúde, com o objetivo de identificar falhas no processo de atendimento às gestantes e à TMI de sífilis ou HIV. A abordagem do projeto foi quantitativa, mas perguntas abertas foram incluídas para capturar as opiniões dos participantes sobre a viabilidade das estratégias adotadas para o controle da TMI. Participaram do estudo 109 mulheres, 62 profissionais de saúde e 34 gestores. A mediana de idade das mulheres foi de 24 (intervalo:15-46) anos e a mediana de escolaridade foi de 8 anos. Oitenta por cento dos entrevistados fizeram consultas de pré-natal. Entre as que participam de consultas pré-natais, a mediana foi de 6,43 (intervalo: 1 a 20). Gestores e profissionais de saúde tiveram uma mediana de 10 anos de trabalho (intervalo: 4-25). Nas entrevistas, os gestores disseram que haviam fornecido testes e tratamento para essas infecções, mas os profissionais de saúde disseram que nem sempre tinham testes ou tratamentos disponíveis para oferecer às pacientes e a maioria das parturientes reclamou das dificuldades em receber tratamento. Organizar a logística e derrubar barreiras de cuidado ainda representam um desafio no Brasil. O sistema de saúde com funcionamento adequado e uma ação política de enfrentamento da situação podem ajudar a eliminar a TMI, quando atuam na aplicação das estratégias adotadas pelo país no controle dessas infecções.
Palavras-chave: Transmissão da mãe para o filho; HIV; Sífilis; Sistema de saúde; Política de saúde

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INTRODUCTION

Brazil is a multifaceted country experiencing complex economic, social, and environmental changes. Social, economic, and regional inequalities are still extreme and rampant; basic living conditions must be dramatically improved for a large part of the population. Health problems are often a result of social and environmental changes and remain unabated[1].

Sexually transmitted infections (STIs), including HIV infection and syphilis, are important public health issues that lead to perinatal morbidity and mortality[2,3]. Neonates who survive with HIV or congenital syphilis are at a greater risk of low birth weight, premature delivery, congenital anomalies, and long-term sequelae — such as deafness

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and neurological impairment, for example[3,4]. These consequences are preventable if health clinics are prepared to provide adequate care, and if infected mothers are identified earlier during pregnancy and receive proper treatment[5,6]. In this process, antenatal HIV and syphilis testings are essential to prevent the mother-to-child-transmission (MTCT) of these infections and offer an opportunity for women and other family members to find out their status and access treatment[7,8].

Prevention of MTCT of HIV and syphilis are significant and recognized steps towards achieving the United Nations Sustainable Development Goals, particularly the health-related goals of decreasing pregnancy complications and child and maternal mortality[9]. In 2010, the Pan American Health Organization (PAHO) countries agreed to implement strategies for eliminating MTCT of syphilis and HIV by 2015. HIV elimination goals consisted of a reduction in the incidence of HIV cases in children to 0.3 cases/1,000 live births and an MTCT rate ≤2%; syphilis elimination goals included prevalence of 0.5 cases/1,000 live births. In 2016, these goals were changed and extended upon by the Plan of Action for the Prevention and Control of HIV and Sexually Transmitted Infections 2016–2021[10].

While antenatal screening for HIV and syphilis are part of Brazil's national policy, both screening and treatment coverage remain inadequate in many parts of the country, mainly due to technical and logistical problems. Together, the health care system and new policies are capable of eliminating MTCT while overcoming barriers and integrating surveillance, as well as strengthening service delivery and community leadership[11].

In Brazil, an estimated 0.38% of all pregnant women are infected with HIV, corresponding to almost 11,000 pregnant women infected with HIV per year. A total of 108,134 cases of pregnant women with HIV were notified from 2000 to June 2017. Over ten years, the detection of HIV in pregnant women increased 23.8%[12]. In 2016, Brazil had 87,593 cases of acquired syphilis, 37,436 cases of syphilis in pregnant women, and 20,474 cases of congenital syphilis, with 185 deaths among them. The detection rate of syphilis in pregnant women and the incidence rate of congenital syphilis were 12.4/1,000 live births and 6.8/1,000 live births, respectively[13].

A previous study in Brazil evaluated the cascade of HIV care in pregnant women and identified flaws in all stages of care. It showed a lack of connection between primary care and referral centers for HIV/AIDS, which could organize the care delivery for families and promote better outcomes for children[14]. Another study described increased detection rates of syphilis in pregnancy and revealed that better organization of health services and professional awareness could improve the care offered to these patients[15].

In Brazil, both prenatal care and childbirth coverage are close to 100%; syphilis and HIV tests and drugs are available for free to prevent MTCT. Formula for HIV-exposed children is also available. It is crucial to identify the gaps that could help eliminate these infections in Brazil.

OBJECTIVE

This study aimed to describe the missed opportunities in preventing MTCT in Brazil based on the perspective of women in the maternal ward who delivered babies with HIV and/or syphilis, health professionals, and health care managers working in the same institutions.

METHODS

In 2015, a sample consisting of cases of pregnant women notified for syphilis and/or HIV with a positive newborn was chosen in the state capital and one city in six Brazilian states: Amazonas, Ceará, Espírito Santo, Rio de Janeiro, Rio Grande do Sul, and the Federal District. Participants were equally chosen among states. The selection was based on the availability of complete data in the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* — SINAN) form from the mother and her child. The maternity hospitals involved presented different characteristics, according to the states where they belonged, but all of them were part of Brazil's public health care system (*Sistema Único de Saúde* — SUS). MTCT cases were chosen from the SINAN database, and women were invited to participate in the interview. Physicians, nurses, and managers working in the same institution where these cases happened were also invited to participate in the interview and share their views on MTCT of HIV and syphilis in their health care center and city.

A semi-structured interview, including demographical (age, gender, education, occupation, time working in the field, etc.) and health care access data (prenatal care, access to HIV/syphilis diagnosis and treatment, follow-up, professional years of experience, training opportunities for professionals, etc.), was conducted with 20 women aged 15 years or over, who delivered their babies at the chosen health center, 10 health professionals, and five health care center managers in each Brazilian state. The data collected were entered in an Excel worksheet (Microsoft®) and analyzed in SPSS 19.0. We used measures of central tendency and dispersion for continuous variables and measures of frequency for categorical variables to build the participants' profile.

A smaller number of women in the maternal ward who delivered babies with HIV and/or syphilis, health professionals, and health care managers working in the same institutions were invited for an in-depth interview focusing on why they thought the transmission had occurred and what were the failures. We opted for the individual interview because it is a faster method for obtaining qualitative data, and also more suitable for this project, since participants had little free time to answer the questions. Moreover, interviews allow people to talk on their own terms. Interviews took place at private venues chosen by participants and lasted 30–40 minutes; they were recorded and later transcribed and de-identified for analysis. We included open-ended questions to understand better how HIV and syphilis counseling and diagnosis were carried out at health care centers and grasp the opinions of women, health professionals, and managers about health care access and approach, including laboratory and medical supplies and professional training. These answers would offer better knowledge and the possibility of reassessing the relevance of current strategies or the control of MTCT of HIV and syphilis.

From the in-depth interviews, we extracted and included quotes to complement the descriptive approach and provide a better understanding of the missed opportunities to prevent MTCT of HIV and syphilis. Interviews focused on the participants' perceptions of existing workflows between diagnosis and care delivered to each case, and how they reacted to them. With this technique, we were able to find more about the words they use, their priorities and concerns[16]

regarding MTCT, and its implications for health care units. It could offer answers on how to improve services and professional approach.

Interviews were conducted after the participants invited signed an informed consent form. We assigned names to the participants to preserve their anonymity and confidentiality. The Research Ethics Committee from the Universidade Federal do Espírito Santo approved the project (#640,580/2014). Privacy and confidentiality were protected in all phases of the project using data codification.

RESULTS

A total of 109 parturient women, 62 health professionals, and 34 health care managers were interviewed. The median age of parturient women was 24 years, ranging from 15 to 46, and the median schooling was 8 years. Among those who attended antenatal visits, the median was 6.4 (range: 1–20) visits. Managers and health professionals had a median of 10 (range: 4–25) working years in the field.

Table 1 describes the perception of care by parturient women infected with HIV and syphilis. We highlight that 62.4% of them considered health professionals prepared to counsel them about HIV and syphilis during antenatal care. A total of 21.1% decided against talking about their diagnosed infections with their partners.

Table 2 presents the characteristics and perspectives of health professionals involved in HIV and syphilis cases. Interestingly,

Table 1 – Perception of the health care system reported by women who delivered babies with HIV and/or syphilis in Brazil, 2014.

Variables	N (%)
Considered health professionals prepared to counsel them about HIV and syphilis during antenatal care	
No	26 (23.8)
Yes	68 (62.4)
Did not attend antenatal care	15 (13.8)
Quality care in the maternity hospital	
Excellent/very good	31 (28.4)
Good	63 (57.9)
Bad	15 (13.7)
Received counseling about diagnosis in the hospital	
No	23 (21.1)
Yes	86 (78.9)
Who counseled you about the infections in the hospital?	
Health team (physician and nurse)	28 (25.7)
Physician alone	42 (38.5)
Nurse alone	31 (28.4)
No one	8 (7.3)
Did you receive treatment for the infection?	
No	9 (8.2)
Yes	100 (91.8)
Did the baby receive care for PMTCT?	
No	7 (6.4)
Yes	102 (93.6)
Did health professionals advise you to talk to your partner?	
No	14 (12.8)
Yes	95 (87.2)
How did you talk to your partner about the diagnosis?	
He already knew it	25 (22.9)
We were together in the center when the health professional disclosed the diagnosis	51 (50.8)
I decided not to talk about it with my partner	23 (21.1)
I do not have any contact with my partner anymore	10 (9.2)

HIV: human immunodeficiency virus; PMTCT: prevention of mother-to-child transmission.

Table 2 – Profile and perspectives of health professionals involved in the care of cases of mother-to-child transmission of HIV and syphilis in Brazil, 2014.

Variables	N (%)
Professional age	
<30	11 (17.7)
30–35	8 (12.9)
>35	43 (69.4)
Profession	
Physician	28 (45.2)
Nurse	31 (50.0)
Social worker	2 (3.2)
Psychologist	1 (1.6)
Years in professional practice	
<5	12 (19.4)
5–9	12 (19.3)
10–15	11 (17.7)
>15	27 (43.5)
Received training for PMTCT of HIV and syphilis	
No	32 (51.6)
Yes	30 (48.4)
Would like to be trained for PMTCT of HIV and syphilis	
No	13 (21.0)
Yes	49 (79.0)
Syphilis diagnosis available in your health center	
Point-of-care test	25 (40.3)
VDRL	34 (54.8)
Both tests	3 (4.8)
HIV diagnosis available in your health center	
Point-of-care test	57 (91.9)
Elisa	5 (8.1)
How long it takes to receive the HIV test results?	
Less than 1 hour	40 (64.5)
1–24 hours	17 (27.4)
2–7 days	1 (1.6)
8 or more days	4 (6.4)
How long it takes to receive the syphilis test results?	
Less than 1 hour	19 (30.6)
1–24 hours	27 (43.5)
2–7 days	7 (11.3)
8 or more days	9 (14.6)
Have access to confirmatory tests for HIV and syphilis	
No	11 (17.7)
Yes	51 (82.3)
Have regular access to diagnostic tests for HIV and syphilis	
No	5 (8.1)
Yes for both infections	52 (83.9)
Yes for HIV but not for syphilis	5 (8.0)
Medicines available to prevent MTCT of HIV and syphilis	
Yes for both infections	57 (91.9)
Yes for HIV but not always for syphilis	5 (8.1)

HIV: human immunodeficiency virus; MTCT: mother-to-child transmission; PMTCT: prevention of MTCT; VDRL: venereal disease research laboratory; Elisa: enzyme-linked immunosorbent assay.

despite almost 50% of them having declared being trained in MTCT of HIV and syphilis, 79% reported that they would like to receive training in the prevention of MTCT. **Table 3** shows the characteristics and perspectives of health care managers involved in the HIV and syphilis cases included in this study; 61.8% reported that they had been in their current management position for less than five years, and less than 50% had received any kind of management training.

In the in-depth interviews, we tried to understand the offer of diagnosis and treatment in the units as a way to measure how the managers and health professionals perceive the availability of supplies, training, clinical support, and supervision. The managers declared that they had provided tests and treatment for these infections in their health centers. Some answers are quoted below:

> I cannot explain this! We buy tests and antibiotics. We also provide training for health professionals. What more we can do? (Ana, 36)

> I know there are problems! It is a complicated situation. We try to do our best, but sometimes things do not work out the way they should! (Jorge, 42)

However, health professionals stated that they did not always have tests or treatment available to offer to their patients. They also complained that they did not feel confident enough to perform rapid tests and that they would like to receive more training. Training and supplies sometimes were missing.

> Sometimes there are no rapid tests at the center, and I need to recommend regular tests, but Elisa (HIV) or VDRL (Syphilis) results can take at least a week. (Miguel, 28)

> I would like to receive more training to feel more confident in carrying out rapid tests. I am still doubtful about how to use it. They are treponemal tests, how can I know if it is not just a scar? (Elisa, 33)

> When the pregnant woman tests positive, I offer counseling and send her on to treatment. I cannot administer penicillin in my center because conditions are not safe, and pregnant women must seek out another health center. (Paulo, 45)

In the interviews with the women, the main goal was to discuss access and barriers to receive appropriate and comprehensive care. Most parturient women complained about how hard it was to understand the disease and receive treatment. It is hard to have effective care if you do not understand the problem you have to handle.

> The doctor was nice to me. He told me I needed to receive treatment for syphilis to try to protect my baby, but he did not explain anything about the disease to me. What is syphilis? I was wondering what it means. (Maria, 22)

> The health center did not have penicillin, and they sent me to the hospital, but I did not go because I did not have

Table 3 – Profile and perspectives of health care managers in centers that treated cases of mother-to-child transmission of HIV and syphilis in Brazil, 2014.

Variables	N (%)
Professional age	
<30	3 (8.8)
30–35	8 (23.5)
>35	23 (67.6)
Professional background	
Physician	13 (38.2)
Nurse	16 (47.1)
Other professions	5 (14.6)
Years working as a manager	
<5	21 (61.8)
5–9	6 (17.6)
10–15	4 (11.8)
>15	3 (8.8)
Received management training for health care services	
No	19 (55.8)
Yes	15 (44.2)
Received management training for PMTCT of HIV and syphilis	
No	17 (50.0)
Yes	17 (50.0)
Thinks that management training for PMTCT of HIV and syphilis is necessary	
No	15 (44.1)
Yes	19 (55.9)
HIV and syphilis tests available in the health centers	
Point-of-care for both infections	12 (35.3)
VDRL for syphilis and Elisa for HIV	5 (14.7)
Point-of-care for HIV and VDRL for syphilis	17 (50.0)
How long it takes to receive the HIV test results?	
Less than 1 hour	23 (67.6)
1–24 hours	4 (11.8)
2–7 days	3 (8.8)
8 or more days	4 (11.8)
How long it takes to receive the syphilis test results?	
Less than 1 hour	14 (41.2)
1–24 hours	10 (29.4)
2–7 days	4 (11.8)
8 or more days	6 (17.6)
Have access to confirmatory tests for HIV and syphilis	
No	8 (23.5)
Yes	26 (76.5)
Have regular access to diagnostic tests for HIV and syphilis	
Yes for both infections	30 (88.2)
Yes for HIV but not for syphilis	4 (11.8)
Medicines available to prevent MTCT of HIV and syphilis	
Yes for both infections	31 (91.2)
Yes for HIV but not always for syphilis	3 (8.8)
Penicillin available in antenatal clinic and hospital	
No	4 (11.8)
Yes	30 (88.2)
Antiretroviral drugs available in antenatal clinic and hospital	
No	2 (5.9)
Yes	32 (94.1)
The unit has a program to follow patients with positive tests	
No	21 (61.8)
Yes	13 (38.2)

HIV: human immunodeficiency virus; MTCT: mother-to-child transmission; PMTCT: prevention of MTCT; VDRL: venereal disease research laboratory; Elisa: enzyme-linked immunosorbent assay.

> money to pay for the bus fare, and I could not lose another day of work. (Helena, 26)

> I did not tell my partner about the diagnosis because I was afraid he would beat me. I thought it was enough to do the treatment alone. (Marta, 31)

It was important to listen to the different health care actors and observe the importance of a better linkage among managers, health professionals, and the client's needs to offer an effective health care access for pregnant women. As important as access to a health unit is to receive the right diagnosis, treatment, and counseling.

DISCUSSION

The findings suggest problems in the communication of all parties involved in antenatal care and maternal wards, with different information obtained depending on who is answering the questions. They may also indicate inadequate approaches to training and supervision, as per the answers from both managers and health professionals. Although prenatal care is available for almost all pregnant women in Brazil and the public health system offers universal screening for HIV and syphilis, our data showed that broken communication between health care providers and the women admitted for care leads to technical and logistical challenges, as expressed during the in-depth interviews. Women's needs may be better fulfilled with more comprehensive care. The Brazilian Ministry of Health distributes more than 12 million HIV rapid tests and more than 9 million syphilis rapid tests per year to the 27 states[12,13]. The states are responsible for the logistics to reach all their cities. Cities, in turn, have health centers to deliver care to the population, including prenatal care. Knowledge and communication in the health system are important tools for organizing services and adequate care[17].

In 2014, the World Health Organization (WHO) presented a guide that included joined processes and criteria for validation of EMTCT (elimination of MTCT) of HIV and syphilis[18]; one year later, Cuba became the first country to achieve EMTCT of both HIV and syphilis[19]. Other countries have followed Cuba and, in 2016, Thailand and Belarus were validated for EMTCT of HIV and syphilis, Moldova for EMTCT of syphilis, and Armenia for EMTCT of HIV[20]. Several countries have EMTCT plans in place, including Brazil, and others are set for EMTCT validation by a target date[6,18]. The countries that have achieved EMTCT have similar strategies established to ensure universal and equitable antenatal care services, which include HIV and syphilis testing and treatment at no cost to pregnant women[21]. Brazil has the same strategies of these countries, but being a vast country with a large population and huge regional inequalities has hampered the efforts to reach EMTCT. Policy makers and stakeholders must develop strategies according to the characteristics of each region. All regions have shown a combination of strategies referring to social, economic, and regional policies to promote development in a more widespread way over the last few years; however, limitations to policies implemented for the universalization of the health system remain[22].

The study was carried out during a period when the penicillin was not available in most Brazilian health centers, due to the global shortage of the drug. Nevertheless, even when the drug is available, resistance to the intramuscular administration of penicillin at primary care level is still present in health centers across Brazil and should be addressed as a priority to eliminate MTCT of syphilis. The literature has good evidence that penicillin is safe to use in health facilities[23]. Regarding HIV infection, no one complained about drug availability or problems with antiretroviral adherence. Prevention of MTCT has been an important step in inhibiting HIV infection in children. However, improving the uptake of and adherence to care continues to be a significant challenge in resource-poor settings[24].

We also found that, at times, pregnant women did not receive appropriate counseling. A significant factor that prevents Brazil from achieving EMTCT of HIV and syphilis is the quality of prenatal care. Despite efforts to improve obstetric and neonatal quality of care, this topic remains a challenge in the Brazilian public health system, both in terms of enhancing its quality as such, and of introducing changes to the principles of care[25]. Studies that have evaluated prenatal work processes demonstrated that not all recommended practices are followed, and some are far below the desired, including the time of prenatal care initiation[26-28]. Moreover, there are social and economic problems influencing the provision of care. Although health care is considered universal in Brazil through SUS, some women lack funds to reach the health centers, do not have help to leave their older children while away, or cannot miss work[1,26]. We highlight that providing free and easy access to health units for prenatal care is not enough if the clinics do not offer adequate diagnosis and treatment. Public health in Brazil needs to improve the dialog among the different care actors. Managers, health professionals, and pregnant women need to be included in the decisions and solutions because it is the only way to have effective control of MTCT cases in Brazil.

In addition, the inadequacy of national registries has also been pointed out as one of the obstacles to improving the quality of prenatal care, as missing and partial information will mislead policy makers and managers in health planning. The government needs to know the number of cases to be able to buy the necessary test and drug supplies. There is also a long way to go to incorporate evaluation as a systematic activity, allowing managers to intervene and redirect actions[20]. Therefore, improving training in both care and surveillance, as well as monitoring health professionals in charge of prenatal care through medical record review is paramount to reach EMTCT goals. Domingues et al.[29] assessed knowledge, practices, and attitudes of health professionals delivering prenatal care in the city of Rio de Janeiro, and found that lack of knowledge about protocols and limitations regarding management of patients with STI were among the main barriers to dealing with the burden of syphilis. The present study showed that less than 50% of health professionals considered themselves well trained in MTCT of HIV and syphilis, and almost 80% would like to be trained again.

One of the limitations of our study was the small sample size for the descriptive analyses. However, our intention was not to reach statistical power but rather to understand who the professionals in the states are, and what their perceptions regarding the MTCT program are. Face-to-face and audio-recorded interviews are always complicated, and we cannot rule out the possibility of response bias due to the general tendency to give socially acceptable answers. Nevertheless, these limitations do not diminish the importance of the

study in increasing visibility to a relevant problem and the urgency in scaling up actions toward EMTCT in Brazil.

Primary care units and maternity hospitals need to provide easy and effective access to health services to offer quality prenatal and labor care for their clients. It is also important to prepare managers and health professionals to answer clients' needs because only a flexible and personal agenda can improve the services. The way the health care system and certain policy factors are set up can serve as barriers to successful engagement in HIV and syphilis care activities in our fragmented health service. Nonetheless, with robust governmental will and leadership in local communities, opportunities can arise to increase emphasis and improve efforts in this field[19]. The success of such efforts depends on overcoming obstacles between actors and integrating surveillance and care, which influence the spectrum of engagement.

CONCLUSION

The key message from our study is the need to improve communication — among policy makers, managers, health professionals, and the general population. New guidelines have to reach their public — physicians and nurses — in order to be read, accepted, and implemented. Managers have to follow the availability of tests and drugs closely, avoiding shortages that could hamper efforts already in place to tackle syphilis and HIV. Moreover, the general population should be better informed about STIs and their impacts on their lives and the lives of others — and also to be heard by their caregivers, who must be able to answer their questions and help them to find their own answers.

Participation of each author

All authors were active and had equal participation in the study.

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Conflict of interests

The authors declare no conflict of interests.

Ethics Committee Approval for Human Research

The Research Ethics Committee from the Universidade Federal do Espírito Santo approved the project (#640,580/2014).

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ANTIRETROVIRAL AGENTS AGAINST HUMAN IMMUNODEFICIENCY VIRUS: AN OVERVIEW OF CURRENT DRUGS AND NEW PERSPECTIVES

AGENTES ANTIRETROVIRAIS CONTRA O VÍRUS DA IMUNODEFICIÊNCIA HUMANA: UMA VISÃO GERAL DAS DROGAS ATUAIS E NOVAS PERSPECTIVAS

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ABSTRACT

Introduction: Since its discovery in the 1980s, the human immunodeficiency virus (HIV) has been the target of many studies. Nowadays, estimates show that 36.7 million people are infected with HIV worldwide. In Brazil, HIV infection overcomes 840 thousand people. Globally, only 53% of the HIV infected people are under antiretroviral therapy. Significant advances in antiretroviral therapy have been made since the introduction of zidovudine in 1987. **Objective:** To advance the discoveries of the available antivirals demonstrating their functional specificities. **Methods:** We performed a systematic review with a bibliographic survey in the Index Medicus/MEDLINE and PubMed databases for periodical and indexed articles, from 2013 to 2018 that reported on antiretrovirals used or not in the clinical practice. **Results:** Currently, there are six classes of antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors (CCRIs), and HIV integrase strand transfer inhibitors (INIs or INSTIs). In summary, several antiretroviral agents under development make HIV entry, reverse transcription, integration, and maturation emerging drug become targets. **Conclusion:** A multifaceted approach to antiretroviral therapy, using combinations of inhibitors that target different steps of the viral life cycle, has the best potential for long-term control of HIV infection.

Keywords: AIDS; HIV; antiretroviral therapy, highly active.

RESUMO

Introdução: Desde sua descoberta na década de 1980, o vírus da imunodeficiência humana (HIV) tem sido alvo de muitos estudos. Atualmente, as estimativas mostram que 36,7 milhões de pessoas estão infectadas pelo HIV em todo o mundo. No Brasil, a infecção pelo HIV supera 840 mil pessoas. Globalmente, apenas 53% das pessoas infectadas pelo HIV estão sob terapia antirretroviral. Avanços significativos na terapia antirretroviral (TARV) foram feitos desde a introdução da zidovudina (AZT) em 1987. **Objetivo:** O objetivo deste estudo foi descrever a descoberta dos antivirais disponíveis atualmente, demonstrando suas especificidades funcionais. **Métodos:** Foi realizada uma revisão sistemática com levantamento bibliográfico nas bases de dados Index Medicus/MEDLINE e PubMed para artigos periódicos e indexados, no período de 2013 a 2018, que relataram antirretrovirais utilizados ou não na prática clínica. **Resultados:** Atualmente, existem seis classes de medicamentos antirretrovirais: inibidores nucleosídeos da transcriptase reversa (NRTIs), inibidores não-nucleosídeos da transcriptase reversa (NNRTIs), inibidores da protease (IPs), inibidores de fusão (FIs), inibidores de entrada (CCRIs) e transferência da cadeia da integrase do HIV inibidores (INIs ou INSTIs). Em resumo, vários agentes antirretrovirais em desenvolvimento fazem da entrada do HIV, da transcrição reversa, da integração e da maturação, alvos dos medicamentos emergentes. **Conclusão:** Uma abordagem multifacetada para a TAR, usando combinações de inibidores que visam diferentes etapas do ciclo de vida viral, tem o melhor potencial para o controle da infecção pelo HIV a longo prazo.

Palavras-chave: AIDS, HIV, terapia antirretroviral

INTRODUCTION

HIV is the etiologic agent of acquired immunodeficiency syndrome (AIDS). This syndrome is characterized by a decrease in the total number of T CD4$^+$ cells, as well as an increase in the incidence of opportunistic infections and progressive failure of the immune system. The first report of AIDS occurred in the early 1980s, with cases of homosexuals with depletion of circulating T lymphocytes in Los Angeles, United States[1].

HIV-1 is a single-stranded RNA virus inserted on the *Retroviridae* family. Its particle possesses 100 to 150 nanometers of diameter with a lipid envelope that contains spike-form glycoproteins[2,3]. HIV can infect some immune system cells that express CD4 receptors, such as CD4$^+$ T helper cells, macrophages, and dendritic cells. Typically, HIV-1 infection is characterized by an initial phase of high-level viremia, followed by a long period of persistent virus replication at a lower level. Viral persistence occurs despite specific antiviral immune responses, which include the generation of neutralizing antibodies[4]. The progression of HIV infection can be divided into three phases: acute or primary, persistent chronic phase, and AIDS. The markers of AIDS progression, which clinically define these steps, are the CD4$^+$ T cell count, the plasma viral load, and the presence or absence of clinical manifestations[5].

Three decades and a half after its discovery and recognition, HIV has emerged as a global epidemic present in all continents, despite the massive campaigns of prevention and growing treatment strategies. The 2017 statistics showed that there were about 36.7 million people living with HIV in 2016[6]. Since 1980 until 2016, 842,710 people have been HIV infected in Brazil, and in terms of access to antiretroviral therapy, a total of 495.275 individuals are under treatment[7]. Studies have indicated that morbidity and mortality from HIV

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infection have decreased since the introduction of ART. Although the decrease in statistics is evident, the lack of effective treatment and/or protective vaccine and strategies capable of inhibiting the virus replication are still the significant challenges of scientists[8,9].

OBJECTIVE

The aim of this study is to address the importance of less toxic compounds with higher antiviral activity that can reduce the morbidity and mortality of HIV infection. In addition, it aimed to produce a correlation between azidothymidine (AZT) and other drugs that even though are available for clinical use, have high levels of toxicity.

METHODS

We conducted a research in Index Medicus/MEDLINE and PubMed databases on articles that reported the currently available antiretrovirals. For this analysis, we used the keywords "AIDS", "HIV" and "antiretroviral therapy" in the database to find articles from the last five years (from 2013 and 648 articles), evaluated and followed our exclusion criteria that are articles that fully descriptively address compounds in clinical use or compounds that are in the preclinical (experimental) phase. In addition, the compounds have established toxicity and mechanism of action data. Therefore, only 38 articles were selected to compose this paper.

RESULTS

Forty-five articles from indexed journals and 38 selected for this review work were evaluated. We observed that since the discovery of AZT as the first drug available for use in the HIV infection treatment that shows great results, several substances have been studied and made available to make up the current treatment, which has been very effective.

DISCUSSION

Antiretroviral therapy

After 35 years from HIV discovery, many studies have been done and achieved for creating anti-HIV drugs. There is still no cure for such disease; therefore, once the highly active antiretroviral therapy (HAART) — the treatment currently used for HIV seropositive individuals — has been initiated, it must be continued throughout the patient's life[10]. The HIV-1 reverse transcriptase (RT), protease (PR) and integrase (IN) enzymes, as well as the main steps of the replicative cycle, are the main targets of antiretroviral therapy.

HAART consists of a combination of drugs that aim to inhibit enzymes and/or fusion/entry mechanisms of the virus into the cell during the steps of the HIV replicative cycle. A remarkable effect of HAART is the regeneration of $CD4^+$ and $CD8^+$ T cells and re-establishment of the immune function stably at long term. Therapy acts to reduce viral load in blood plasma, promoting higher survival to individuals[11-13]. Initially, the use of two nucleoside RT inhibitors (NRTI) and one non-nucleoside RT inhibitor (NNRTI) or two NRTIs and a third drug, either an integrase inhibitor or the protease inhibitor as HAART standard approach, is recommended for the treatment of AIDS[14,15].

There are 28 available drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV infection, including: eight nucleoside reverse transcriptase inhibitors (NRTIs); five non-nucleoside reverse transcriptase inhibitors (NNRTIs); ten protease inhibitors (PIs); one fusion inhibitor (FI); one entry inhibitor (CCRI); three integrase inhibitors (INIs or INSTIs), as see in **Table 1**[16-18].

Despite the continued developments in AIDS treatment and virus combat, infected individuals remain susceptible to viral and bacterial infections, such as influenza and pneumococcus, which can raise the level of morbidity and mortality. Therefore, alternative strategies and new targets need to be considered to combat the increasing AIDS pandemic[19].

Table 1 – Antiretroviral drugs currently used in the HIV infection treatment.

Drug Class Mode of action	Generic name	Year of approval
Nucleoside reverse transcriptase inhibitors (NRTIs) They are phosphorylated by cellular enzymes; competitively inhibit viral DNA synthesis or cause DNA chain termination	zidovudine (ZDV, azidothymidine, AZT)	1987
	didanosine (ddI, dideoxyinosine)	1991
	zalcitabine (ddC, dideoxycytidine)	1992
	stavudine (d4T)	1994
	lamivudine (3TC)	1995
	abacavir (ABC)	1998
	tenofovir (TDF)	2001
	emtricitabine (FTC)	2003
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) They are non-competitive inhibitors of viral DNA synthesis; directly connect the enzyme	nevirapine (NVP)	1996
	delavirdine (DLV)	1997
	efavirenz (EFV)	1998
	etravirine (ETR)	2008
	rilpivirine (RPV)	2011
Protease inhibitors (PIs) They bind to the active site of protease, thereby inhibiting enzyme function	saquinavir (SQV)	1995
	indinavir (IDV)	1996
	ritonavir (RTV)	1996
	nelfinavir (NFV)	1997
	amprenavir (APV)	1999
	lopinavir (LPV)	2000
	fosamprenavir (FOS-APV)	2003
	atazanavir (ATV)	2003
	tipranavir (TPV)	2005
	darunavir (DRV)	2006
Fusion inhibitors (FI) They bind to HR1 region of envelope glycoprotein gp41	enfuvirtide (T-20)	2003
Entry inhibitors – CCR5 co-receptor antagonist (CCRI) They inhibit the interaction of glycoprotein gp120 with CCR5 chemokine receptor	maraviroc (MVC)	2007
HIV integrase strand transfer inhibitors (INI or INSTI) They block integrase, preventing the insertion of viral DNA into the host DNA	raltegravir (RAL)	2007
	elvitegarvir (EVG)	2012
	dulotegravir (DTG)	2013

Source: adapted from Pau and George[16], da Cunha, Maselli[17], FDA[18].

Pharmacokinetic enhancer

Most of HIV protease inhibitors need a pharmacokinetic enhancer to assure their efficiency. Although ritonavir is a protease inhibitor, it is commonly used as a pharmacokinetic enhancer. Due to high daily doses and some side effects related to ritonavir use, the administration of cobicistat has become more frequent. In addition, cobicistat (COBI) inhibits cytochrome CYP3A more selectively than ritonavir[20].

COBI is a pharmacokinetic enhancer (pharmacoenhancer) that inhibits the metabolism of the atazanavir and darunavir antiretrovirals HIV-1 protease inhibitors (PIs) and is known for prolonging their effects. It was first approved by the US Food and Drug Administration (FDA) in 2012 combined with other drugs (elvitegravir/emtricitabine/tenofovir). Then, its single use was approved in 2014. More recently, in 2015, its use combined with atazanavir (ATV/COBI) and darunavir (DRV/COBI) was approved for use in treatment-naive and treatment-experienced adults in combination with other ARV agents[21].

COBI possesses a structure analog to ritonavir. Synthesized from ritonavir, it is an inhibitor of human cytochrome P-450 (CYP) 3A and is used to increase the systemic exposure of antiretrovirals metabolized by CYP3A enzymes, in other words, it helps to optimize the activity of these antiretrovirals[20,21].

COBI inactivates CYP3A like ritonavir, in a concentration- and time-dependent manner. However, unlike ritonavir, COBI has no anti-HIV activity, which is essential to develop no resistance to antiretrovirals. Moreover, it does not disrupt the antiviral activity of PIs and several other ARVs against HIV. As a nonselective CYP3A inhibitor, the use of ritonavir becomes difficult in patients receiving multiple medications. COBI has demonstrated high efficacy. It can be compared and is considered non-inferior to standard RTV as a pharmacoenhancer. Hence, COBI offers an alternative to ritonavir boosting, with efficacy and safety in treatment-naive and -experienced adults[22,23].

Microbicides

Microbicides are experimental products containing drugs that could be inserted into the vagina or rectum to safely block sexual transmission of HIV. A microbicide would deliver an anti-HIV agent to the mucous membranes, lining the surface of the vagina or rectum through a substance, such as a gel, intravaginal ring, or film. A safe, effective, desirable, and affordable microbicide against HIV could help to prevent many new infections. Microbicide development is a challenge due to many factors, such as: no precedent that guarantees the strategy success, difficulty of achieving secure therapeutic levels, lack of markers, among others[24].

There are some essential characteristics for prioritizing microbicide development. They are safety, efficacy, cost, acceptability, appropriate drug delivery, long-term effectiveness, potential for resistance and impact on therapy, prioritization of best-in-class products[25].

Women are two to four times more susceptible than men to acquire sexually transmitted HIV infection, and recent research from the Joint United Nations Programme on HIV/AIDS (UNAIDS) show that 51% of people living with HIV worldwide are women. Moreover, AIDS-related illnesses remain the leading cause of death among women at reproductive age (15–49 years) in the world[26,27].

Microbicides currently used for pre-exposure prophylaxis strategy to prevent the sexual transmission of HIV are astodimer, dapivirine, and tenofovir[28].

Astodimer

Astodimer or VivalGel is a topical microbicide that is applied to the vagina, rectum, or used in condoms during a sexual intercourse. Studies have demonstrated the antiviral and antibacterial activities of the active principle. Astodimer belongs to a class of drugs that inhibits virus entry into the cell through polyanion, electrostatically creating an environment that prevents adsorption[25,29].

Dapivirine

Dapivirine is a non-nucleoside reverse transcriptase inhibitor that prevents the conversion of viral RNA to pro-viral DNA. It is also used as a topic pre-exposure prevention. One study evaluated the distribution of drug concentration of vaginal canal of women who used a silicone ring containing 25 mg of Dapivirine. The concentration was higher in the entire length of ectocervix than in endocervix[28].

Tenofovir

Tenofovir is a nucleoside reverse transcriptase inhibitor that was developed as a pre-exposure prophylaxis. Tenofovir clinical trials have shown promising results, with low anal and vaginal mucosal irritability. A study evaluated the use of 1% tenofovir vaginal gel for 30 months. There was an increase in cases of mild and self-limiting diarrhea, except for the group receiving the gel compared to the placebo group[30].

MARINE NATURAL PRODUCTS IN THE REPLICATION OR INFECTIVITY OF HIV AS A CANDIDATE FOR NEW ANTIRETROVIRALS

Marine organisms, as well as their derivatives, are sources of biologically active compounds. The Brazilian coast has a great marine biodiversity, with a broad range of resource of compounds with potential anti-HIV-1 activity[31]. Researchers' interest in investigating marine natural products is because the current antiretroviral therapy provides an emergence increase of drug resistance. Thus, it is important for the identification of new drugs with inhibitory action of both reverse transcriptase and other viral enzymes. Literature has demonstrated that the compounds have promising antiviral activity.

Studies have shown many compounds with rich chemical diversity and high biological activity against different microorganisms, especially HIV. A study of 257 pure compounds showed that at least four had an interesting potential to induce the production of latent proviruses, which may be an interesting combination strategy and may generate a more efficient low-dose combined effect[32]. Other studies with marine compounds had high repercussion and showed significant results, as flavonoids isolated from Caribbean seagrass acting as integrase inhibitors[33]. Nanotechnology active compounds with superior pharmacokinetics for site-specific delivery appear to be an interesting strategy for the use in more deadly diseases, such as cancer, HIV/AIDS, and neurological disorders. However, a large number of active compounds against HIV can be removed from the marine environment, such as polysaccharides, lectins, Aspernigrins with

anti-HIV-1 activities and Manzamine, although the best strategy is possibly for compounds that act directly on the virus[34].

In 2004, Pereira and Leão-Ferreira[35] demonstrated antiviral activity of two diterpenes isolated denominated hydroxidictiodial and dictiodial from brown alga *Dictyota menstrualis* against HIV-1. Values between 40 and 70 μM of EC_{50} in PM-1 cells were obtained. The diterpenes also inhibited the synthesis of pro-viral DNA, and reverse transcriptase was inhibited in a dose-dependent manner with the maximal inhibitory effect varying from 70 to 95% by both compounds. Cirne-Santos et al.[36] showed that diterpene 8,10,18-trihydroxy-2, 6-dolabelladiene (dolabelladienetriol) isolated from marine brown alga *Dictyota pfaffii* inhibits the HIV-1 infection. Dolabelladienetriol was able to inhibit the activity of RT enzyme in a dose-dependent manner, reaching the value of 16.5 μM of IC_{50}. Infected peripheral blood mononuclear cells (PBMCs) and macrophages presented EC_{50} of 8.4 and 1.85 μM, respectively. These results show that the diterpene can be a candidate to a new antiretroviral, including for viral reservoirs.

After those and other results, Paixão[37] proposed the formulation of a microbicide gel for women with active principles obtained from isolated products of *Dictyota menstrualis* and *Dictyota pfaffii* algae, which act inside the cell preventing HIV replication and inhibiting enzymes of virus life cycle[37].

In 2014, Pardo-Vargas et al.[38] reported three new dolabellane diterpenes isolated from Brazilian brown alga *Dictyota pfaffii* with antiviral activity against HIV-1 in MT-2 cells. They presented high values of CC_{50}, varying between 1345 and 1,456 μM. Compounds also inhibited 52, 69 and 83% of the HIV-1 replication, suggesting that these diterpenes could be considered potential new agents for HIV-1 therapy.

Isolated compounds of another brown alga, *Canistrocarpus cervicornis*, demonstrated inhibitory activity against HIV-1 replication and low cytotoxic effect in cell culture. Marine dolasthanes and secodolastane diterpenes inhibit virus replication in a dose-dependent manner. Diterpenes also showed excellent performance to reduce the infective capacity of HIV, which suggests the existence of a mechanism that prevents virus adsorption in the host cell. The promising results of algae extracts in combating HIV-1 replication and its potential virucidal effect require further studies, such as pharmacodynamic tests and *in vitro* and *in vivo* models[39].

Nogueira et al.[40] demonstrated the antiviral effect of extracts from red alga *Acanthophora spicifera* on HIV-1 replication. PBMCs were used to evaluate the cytotoxicity (CC_{50}) of dichloromethane, ethyl acetate, acetone, and methanol extracts. The respective values were: 31, 45, 38, and 179 μg/mL. The antiviral activity showed that ethyl acetate extract inhibited 60% of viral replication in infected cells, whereas the maximum inhibition was 79% for RT. The results evidence the promising use of *A. spicifera*, especially as a RT inhibitor.

Pioneer studies on the potential antiviral to develop microbicides as a preventive and topical use in genital mucosa are being developed, mainly the use of explant technology due to its easy study of the human mucosal tissue. Stephens et al.[41] determined the pretreatment effect with the compound extracted from brown alga *Dictyota pfaffii* dolabelladienetriol in inhibition of HIV-1 replication, and the protective effect of this compound in *ex vivo* explant model. The compound showed high inhibitory activity in PBMCs, achieving from 60 to 80%, and prevented HIV-1 replication macrophages. Tests with explant model (stratified squamous tissue) confirmed the low cytotoxicity of dolabelladienetriol and inhibited viral replication from 21 to 95%, maintaining the viability of the tissue, producing a protective effect on it. These findings indicate the need for further studies to the development of new antiretrovirals.

CONCLUSIONS

The current available antiretroviral therapy is composed of highly effective drugs that have improved morbidity and mortality of infected individuals, although many have significant toxic effects. The search for new antiretrovirals that have high activity and low toxicity is undoubtedly an important strategy to increase the arsenal of drugs for effective treatment and control of HIV infection. This fact can still be fundamental, especially considering that there are no vaccines available for HIV infection.

Participation of each author

Ingrid Barcelos de Oliveira, Doctoral student, worked on writing the review article. Claudio Cesar Cirne-Santos is the co-advisor and worked on article review. Caroline de Souza Barros worked on the article review. Rosa Teixeira Pinho worked on the article review. Izabel Christina Nunes de Palmer Paixão is project coordinator.

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Conflict of interests

The authors declare no conflict of interests.

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Recurrent vulvar condiloma treatment in infant: a case report

Tratamento de condiloma vulvar recorrente em lactente: um relato de caso

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ABSTRACT

Introduction: Anogenital warts are one of the major clinical manifestations of the Human Papillomavirus (HPV). Case reports in children have grown in the last decades; however, there are still difficulties in determining the virus epidemiology and the best therapy for this age group. **Objective:** To report a case of recurrent vulvar condyloma in a sexually abused infant who presented complete resolution of the lesions after the use of topical imiquimod. **Methods:** Data research and medical record review were performed in addition to a qualitative study consisted of a wide literature appreciation on the subject. **Results:** After undergoing extensive therapy, the patient was successfully treated using topical imiquimod. **Conclusion:** Observation of this particular case suggests that imiquimod may be a safe and effective therapeutic alternative for the treatment of condyloma in the pediatric population. However, theoretical foundations for such conduct are scarce. Thus, the need for further studies on the subject is reinforced.

Keywords: Condylomata acuminata; Papillomaviridae; vulvar diseases; imiquimod.

RESUMO

Introdução: As verrugas anogenitais constituem uma das principais manifestações clínicas da infecção pelo vírus do Papiloma Humano (HPV). Relatos de casos em crianças têm crescido nas últimas décadas; contudo, ainda há dificuldades em determinar a epidemiologia do vírus e definir a melhor terapêutica para essa faixa etária. **Objetivo:** Relatar um caso de condiloma vulvar recorrente em uma lactente abusada sexualmente que apresentou resolução completa das lesões após o uso de imiquimode tópico. **Métodos:** Foi realizado levantamento de dados e revisão de prontuário, além de estudo qualitativo composto por apreciação ampla da literatura acerca do tema em questão. **Resultados:** Depois de ser submetido à extensa terapêutica, a paciente foi tratada com sucesso utilizando imiquimode tópico. **Conclusão:** A observação desse caso específico sugere que o imiquimode pode ser uma alternativa terapêutica segura e eficaz para o tratamento de condiloma na população pediátrica. Entretanto, embasamentos teóricos para tal conduta são escassos. Assim, reforça-se a necessidade do desenvolvimento de mais estudos sobre a temática.

Palavras-chave: Condiloma acuminado; HPV; doenças da vulva; imiquimode.

INTRODUCTION

Anogenital warts are one of the main clinical manifestations of Human Papillomavirus (HPV) infection[1,2]. According to the medical literature, cases reported in pediatric age have grown in recent decades[2,3]. However, determining the epidemiology of the virus and defining the best therapy for the lesions in this age group is still a major dilemma in Pediatrics[4,5].

Studies indicate that the period between the initial infection and the emergence of clinical manifestations of the virus vary from three weeks to eight months, except in children, as the period is still unknown[2]. In adulthood, the virus is transmitted primarily via sexual intercourse, while the main forms of HPV transmission in children, in addition to sexual transmission (either oral-genital, genital-genital, genital-anal contact or digital manipulation of the children's intimate parts), include vertical transmission, self-inoculation and direct or indirect personal contact with contaminated objects or surfaces[4,6-9].

The prevalence of HPV in sexually abused children varies from 5 to 33%, and around 16% in children without suspicion of abuse[5]. The incidence of sexual abuse is difficult to estimate, mainly because a large percentage of these cases goes unnoticed[8]. In addition, this condition is associated with high rates of adverse outcomes, with physical and psychological consequences for the child[8]. In regard to the implications of a sexual abuse investigation, other forms of contagion should always be considered before transmission is defined as occurred by sexual abuse[7].

Several treatment options are available for genital warts, but few of them are adequate for children[10]. The selected therapy should then be individualized, considering mainly the child's tolerability[7].

According to the above mentioned, registering a case of recurrent vulvar condyloma in infant is proposed, in order to illustrate the difficulties found for its therapeutic approach.

CASE REPORT

The case report was approved by the local Ethics and Research Committee with Opinion No. 3.370.374.

A nine-month-old child admitted to the University Hospital of Universidade Federal de Juiz de Fora (UFJF) with vulvar condylomatosis (**Figure 1**), already under the care of the Tutelary Council, was referred to the surgery center for lesion excision. Cauterization of the lesions with an electric scalpel was the primary option. The child was discharged three days after the procedure with recommendation of local care. After approximately 45 days of cauterization,

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the patient returned to the outpatient clinic with recurrence of the lesions (**Figure 2**).

After resurgence of the condylomatous lesions, weekly cauterizations with 70% trichloroacetic acid were elected as treatment. The procedure was performed for two months, but there was still recurrence of the symptoms (**Figure 3**).

Due to the systematic recurrence of the lesions, the treatment with *Thuya occidentallis* was chosen. After 30 days of application of a creamy formulation of *Thuya Occidentalis* (three times a week), the condylomatous lesions disappeared. However, the lesions reappeared after two months. Then, using Imiquimod for three weeks (three times a week) in a residual condyloma, a definite improvement of the lesions was finally observed (**Figure 4**).

DISCUSSION

The way infants acquire condyloma should be a priority in medical care. It is important to determine whether there is any evidence of sexual abuse and try to establish the origin of the virus. Faced with situations such as the suspicion of sexual abuse reported in this work, it is also essential that care is provided by a multidisciplinary team, ensuring a complete medical and social assessment[7,11].

Suspicion of abuse should be raised regarding the following facts: the explanations about the lesion are vague or absent, there are different versions of the fact, and when the story is inconsistent with the physical findings[12,13]. In this context, the case reported here

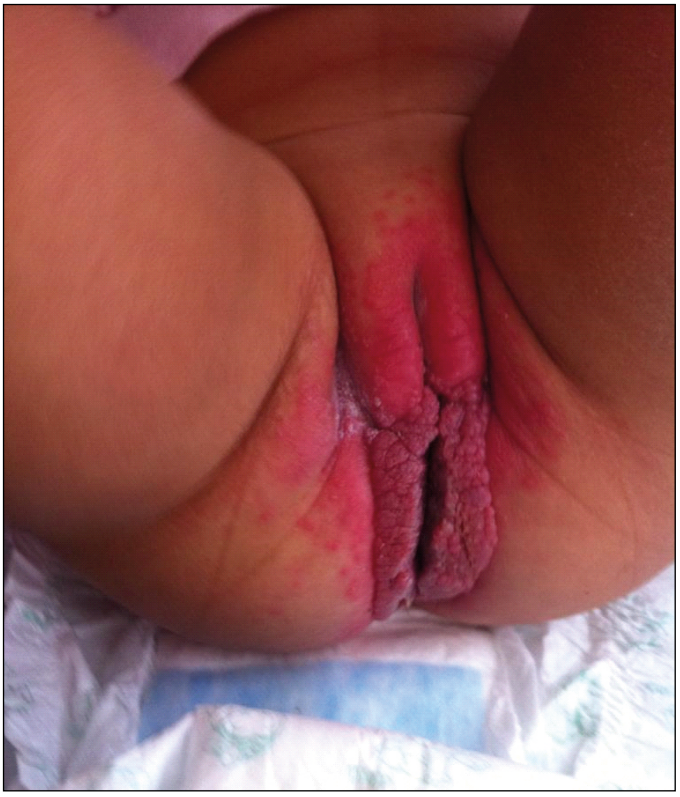

Figure 1 – Multiple vegetative lesions conflowing in the perineal and perianal region, and perilesional erythema present in the first care, prior to any treatment.

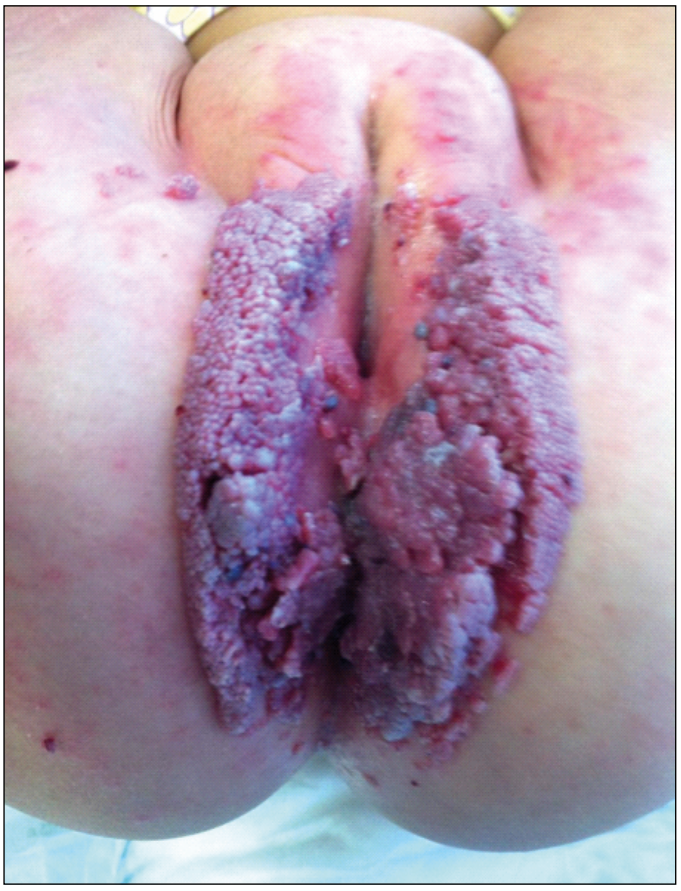

Figure 2 – Recurrence of vegetative lesions 45 days after resection with electric scalpel.

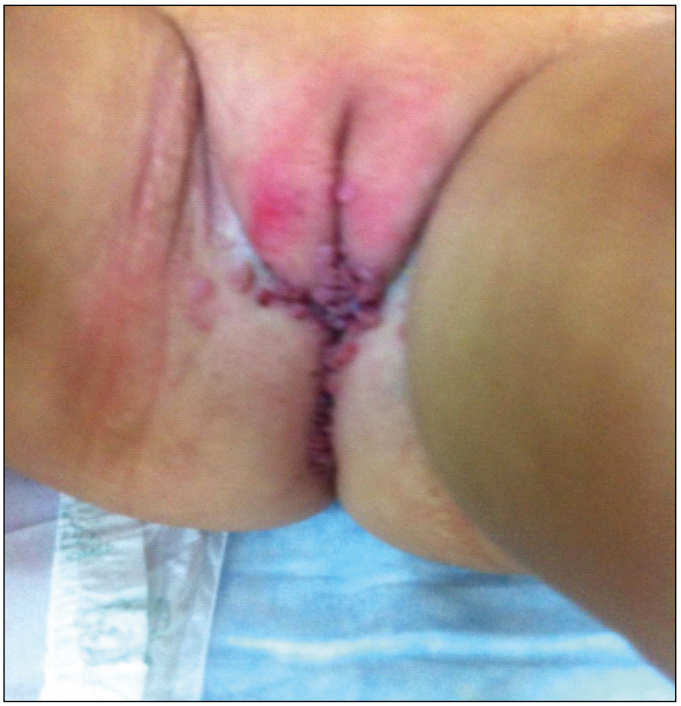

Figure 3 – Papular lesions, in lower volume, relapsed in the perineal and perianal region after treatment with 70% trichloroacetic acid.

was submitted to a multidisciplinary team, communicated to the Child Protection Council, and after the sexual abuse by the father was confirmed, the Tutelary Council carried on with the legal-assistance measures.

Regarding the treatment of anogenital lesions in pediatric age, it is known that studies with this approach are still limited, with no consensus regarding the best method to be used. Thus, the therapeutic choice should be individualized and defined according to the experience of the service, since each therapeutic option presents its advantages and disadvantages, and there is no medication considered superior and capable of eliminating HPV so far[7].

Treatments may be topical (destructive by chemical, physical, immunomodulator or excisional agents) or systemic[14]. Conventional treatment consists of the lesion chemical destruction through topical application of podophylin, 5-fluorouracil, trichloroacetic acid and podophyllotoxin. Physical destruction methods include cryotherapy, laser, electrocauterization, and surgical excision[15].

Topical treatments, such as imiquimod 5% cream and podophylin 20%, are options that should be considered, whenever possible, as they are less traumatic and have fewer sequelae. However, studies are conflicting and there is no consensus asserting that such methods are effective and free from adverse effects in patients under 12 years of age. At the time the patient was attended at our service, there were scarce studies that verified the safety of Imiquimod 5% in infants, and its use was disregarded at first[7,16,17].

Another therapeutic method used is the high-frequency surgery, used mainly in those cases with numerous lesions, a situation whose topical treatment with chemical agents could be toxic due to the quantity required. This procedure was elected first in this study since this was the case of the patient reported. It consists of applying a high frequency current to excise the affected site. The technique is relatively simple and quite cost-effective, since it is performed with local anesthesia and without the need for a surgery center[18].

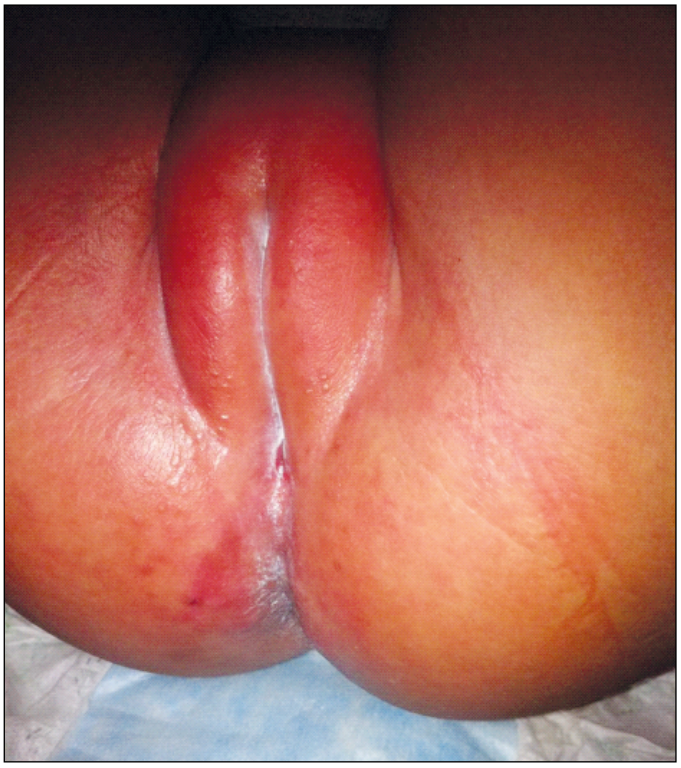

Figure 4 – After the treatment with Imiquimode.

As the treatment for high-frequency surgery did not show the expected effect, it was thought to use trichloroacetic acid, given the importance of its destructive therapeutic effect that causes the hydrolysis of cellular proteins, leading to apoptosis, without systemic toxicity (unlike other topical methods). Other effects consist mainly of local symptoms, such as pain at the site of application, burning, and hyperpigmentation[19,20]. It is important to stand out, however, that the patient, despite demonstrating discomfort during the application of the acid, did not evolve with alteration of perilesional skin staining.

In refractory cases to standard treatments, as the one of this study, the use of phytotherapy may be an alternative. *Thuja occidentalis* is a phytotherapeutic option described in the literature. In folk medicine, the extract has been used to treat repetition bronchitis, enuresis, cystitis, psoriasis, uterine carcinomas, amenorrhea, and rheumatologic symptoms. *T. occidentalis* can be used orally or by topical application. It is known to cause significant increase of some inflammatory mediators in order to activate a local inflammatory response, showing a possible antiviral activity. However, further studies are needed to clarify their exact action mechanism[21-24].

Finally, due to the difficulty of complete resolution of the lesions based on this bibliography, the infant was submitted to imiquimode therapy. Imiquimod is a local application synthetic immunomodulating agent that acts on the innate and cellular immune system mediated by interferon alfa and tumor necrosis factor-alpha (IFN-α) [17]. Recent studies have shown that the imiquimod treatment in the child population shows good results, especially in lesions located in mucous membranes, where absorption is enhanced. The resolution of the lesions is usually obtained in 72 to 84% of the cases, and local recurrence rates range from 5 to 19%.

One of the main treatment advantages is the fact that it can be carried out at home and painless, as pain is a frequent symptom in destructive methods. Topical treatment is well tolerated, having as its main side effect contact dermatitis, occurring mainly in places of skin occlusion[17]. Although erythema is often reported in the literature, no important adverse effect occurred during the approach of the case presented in this report, and this was the definitive therapy for the resolution of recurrent lesions.

CONCLUSION

The observation of this specific case suggests that imiquimod may be a safe and effective therapeutic alternative for the treatment of condyloma in the pediatric population. However, data regarding treatment in this age group are scarce, which hinders the conduct of refractory cases to those known to be safe and described by the literature. Thus, the importance of developing more studies on the theme is reinforced. Moreover, although vertical transmission is the main form of transmission, sexual abuse should always be considered, since only the diagnostic suspicion from the health professional, as happened in this reported experience, is able to facilitate the investigation and conduct of the case.

Participation of each author

All authors contributed equally.

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Conflict of interests

The authors declare no conflict of interests.

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Giant condylomata acuminata of Buschke-Lowenstein: Surgical method as effective treatment and Imiquimod as adjuvant therapy in an immunocompetent patient

Condiloma acuminado gigante de Buschke–Lowenstein: método cirúrgico como tratamento eficaz e imiquimode como terapia adjuvante em uma paciente imunocompetente

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ABSTRACT

Introduction: Giant condylomata acuminata, also known as Buschke-Lowenstein tumor is a rare form of tumor of the anogenital condylomata acuminata, which is a sexually transmitted infection (STI) caused by the human papillomavirus (HPV). **Objective:** To report a case of giant condylomata acuminata in an immunocompetent patient. **Case report:** The patient was referred to the Outpatient Clinic for Sexually Transmitted Infections and AIDS at a public hospital in the city of Vitória, Espírito Santo State, Brazil, reporting the onset of progressive growth verrucous lesions on the external genitalia for four months. The patient underwent surgical ablation, and giant condylomata diagnostic confirmation was obtained through histopathology. She was treated with 5% imiquimod cream in routine applications for eight consecutive weeks to avoid recurrence and was also vaccinated for HPV after the procedure. **Conclusion:** Surgery excision is the treatment of choice in extensive genital condylomata lesions to exclude malignancy. Imiquimod use as adjuvant therapy for reducing recurrence seems to be adequate.

Keywords: Papillomavirus infections; imiquimod; condylomata acuminata.

RESUMO

Introdução: O condiloma acuminado gigante, também conhecido tumor de Buschke-Lowenstein, é uma apresentação rara do condiloma acuminado anogenital, que é uma infecção sexualmente transmissível (IST) causada pelo papilomavírus humano (HPV). **Objetivo:** Relatar um caso de condiloma acuminado gigante em uma paciente imunocompetente. **Relato de caso:** A paciente foi encaminhada para o ambulatório de infecções sexualmente transmissíveis e AIDS de um hospital público na cidade de Vitória, Espírito Santo, Brasil, relatando o aparecimento de lesões verrucosas de crescimento progressivo na genitália externa por quatro meses. A paciente foi submetida à exérese cirúrgica e a confirmação diagnóstica de condiloma gigante foi obtida através da histopatologia. Ela foi medicada com imiquimode creme a 5% em aplicações rotineiras por oito semanas consecutivas para evitar recorrências e foi também vacinada contra o HPV após o procedimento. **Conclusão:** Exérese cirúrgica é o tratamento de escolha em lesões condilomatosas extensas para excluir malignidade. O uso de Imiquimode como terapia adjuvante para redução de recidivas mostrou-se adequado.

Palavras-chave: infecções por Papillomavirus; imiquimode; condiloma acuminado.

INTRODUCTION

Giant condylomata acuminata, also known as Buschke-Lowenstein tumor, is a rare form of tumor of the anogenital condylomata acuminate[(1)], which is a sexually transmitted infection (STI) caused by the human papillomavirus (HPV). Approximately 40 of known HPV have tropism for the anogenital site, and giant condylomata is associated with infection by HPV 6 and 11[(2)]. It is characterized by an extensive exophytic benign warty lesion with the potential for malignancy and local aggressive behavior[(1)]. Several therapeutic possibilities have been reported for the management of the giant condylomata acuminata, with variable outcomes. Surgical local excision is the treatment of choice in most hospital services, alone or in association with other treatment options like radiation therapy, topical and intralesional chemotherapy, systemic interferon α-2b, carbon dioxide laser, and topical therapies including 5% imiquimod that can reduce recurrence, podophyllin and therapeutic vaccine, which is currently under research[(2)]. Although several warts are considered benign, a long-lasting genital lesion can turn malignant due to contact between the virus and the immunologic system. Thus, the time to remove the giant condylomata acuminata to prevent a carcinomatous transition needs to be prompt.

OBJECTIVE

This study aimed to report a giant condylomata acuminata in an immunocompetent patient and to describe the therapeutic management.

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CASE REPORT

A 21-year-old female patient, married for about six months, farmer, with incomplete high school, and no condom use in oral and vaginal sexual intercourse was referred to the Outpatient Clinic for Sexually Transmitted Infections and AIDS at a public hospital in the city of Vitória, Espírito Santo State, Brazil, reporting onset of progressive growth verrucous lesions on the external genitalia for four months. She was treated with benzathine penicillin and oral metronidazole previously and denied smoking, drinking, or drug use. The tumor was painful and bleeding due to secondary bacterial infection. Physical examination revealed bilateral coalescent verrucous lesion occupying the whole extension of labia majora and minora as well as perianal lesions clinically compatible with Buschke-Lowenstein giant genital condylomata (**Figure 1**).

Cervical examination was unchanged, and cervical and vaginal cytology, colposcopy, and otolaryngologic examination were unchanged; moreover, serological tests for HIV, viral hepatitis, and syphilis presented no abnormalities. The sexual partner underwent serological tests that were unchanged, and genital inspection did not present condylomata lesions. Hospitalization was indicated, and gentamicin was administered for two weeks. The patient underwent a surgical ablation, and giant condylomata diagnostic confirmation was obtained through histopathology, which showed hyperkeratosis and papillomatosis with multiple koilocytes, with fast mitotic activity and no cellular atypia, suggestive of HPV infection (**Figure 2**).

HPV 11 was identified by the PCR test. After surgery, in a 30-day follow-up consultation, she presented persistent perianal lesions (**Figure 3**). The patient was submitted to 70% trichloroacetic acid application in the perianal lesions for seven weeks, with resolution of the condition. She underwent the use of 5% imiquimod cream in routine applications for eight consecutive weeks to avoid recurrence (**Figure 4**) and was vaccinated for HPV after the procedure. On her three-year follow-up, she remained disease-free, having periodic consultations, using a barrier method to prevent new STI and without any recurrence.

The study project was submitted to the Ethical Committee for Research of the Federal University of Espírito Santo.

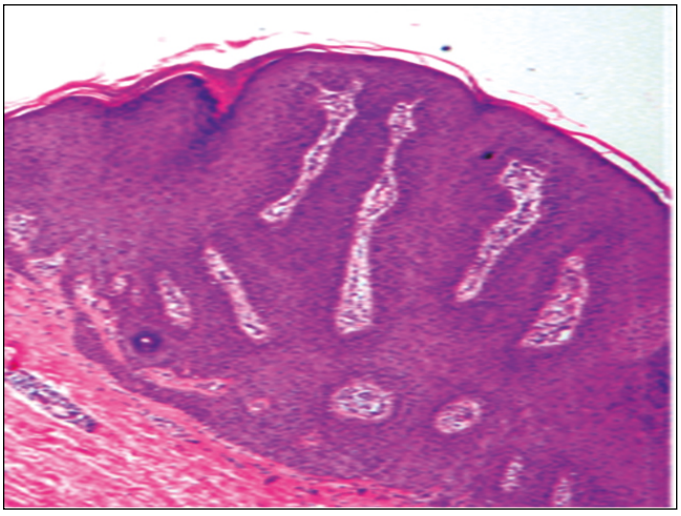

Figure 2 – Histopathological findings showing hyperkeratosis and papillomatosis with multiple koilocytes, consistent with HPV infection (hematoxylin and eosin staining, ×10).

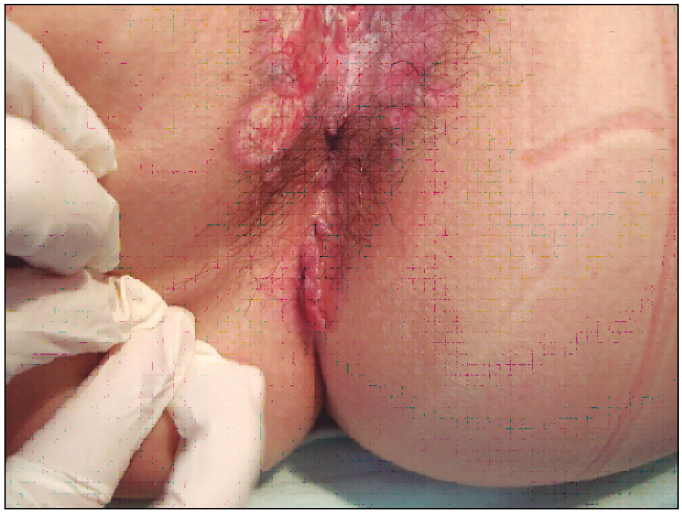

Figure 3 – Persistent perianal lesion after vulvar electrosurgical resection.

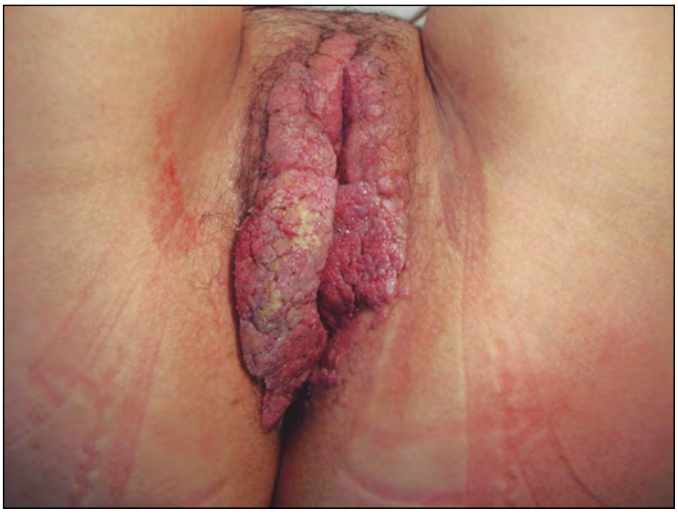

Figure 1 – Giant condylomata acuminata of the vulva. Large, irregular, ulcerative cauliflower-like tumor, covering the vulvar and perianal area.

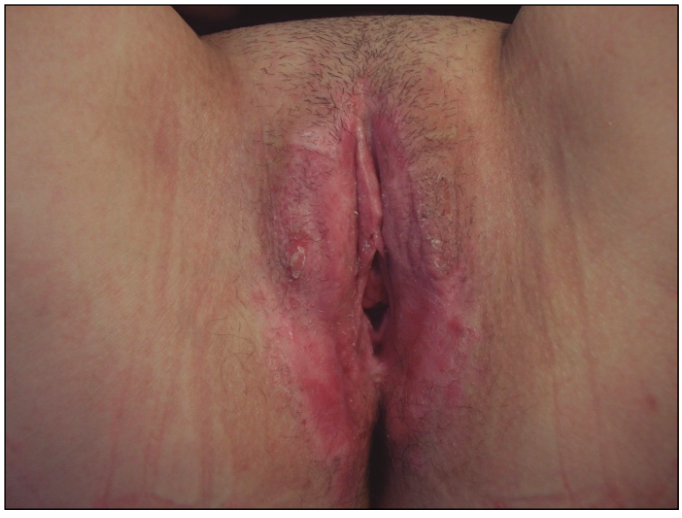

Figure 4 – Patient's vulva, six months after surgery. Complete resolution of the genital condylomata.

DISCUSSION

Giant condylomata acuminata is a very rare clinical condition[1]. Currently, surgery can be avoided in some patients due to developed topical therapeutic methods[3]. Conversely, surgical excision remains the standard therapy in cases of high-risk condylomata acuminata or if topical therapy appears unworkable due to the size of the affected lesion[3,4]. Here, a case of a rapid-growth HPV lesion in a female patient was reported, who was very embarrassed about her condition and lived in a difficult access region. The condition, HPV 11, was identified by PCR test, in concordance with literature reviews[2,3]. The patient was evaluated for STI and cervical cancer prevention due to its HPV association, as cytological screening to detect precursor lesions is still paramount in some Brazilian regions[5]. She underwent high-frequency surgical excision, which is indicated for extensive condylomata lesions due to its advantages in controlling hemostasis, resolution rates in 90% of cases, and recurrence of about 25%[2-4]. Moreover, surgical ablation is the first option to exclude malignancy and to avoid the development of giant condilomata[4,6]. Recurrences may occur in 25 to 66% of cases after surgical treatment, according to some authors[3,7], which are avoided by use of imiquimod after surgery in regular applications for eight consecutive weeks as well as by HPV vaccination. HPV vaccines have been known for their protecting results on cervical cancer and genital warts, though the treatment outcome is still indefinite. Therapeutic vaccine for HPV aims to generate cell-mediated immunity and studies on the subject are in progress[8,9]. Currently, a prospective study suggested that HPV vaccines could be effective in the management of genital warts[9].

Imiquimod, an immune response modulator, has also been used, in regular applications, as an alternative therapy in HPV lesions by inducing the production of interferon alfa and cytokines, enhancing the immune response against HPV infected cells[3,10].

Therefore, the association of surgical techniques and topical 5% imiquimod therapy was successful in this case report, highlighting that the controlling needs to be individualized.

CONCLUSION

Surgery excision is the treatment of choice in extensive genital condylomata lesions and should be readily instituted to exclude malignancy. Imiquimod use as adjuvant therapy for reduced recurrence seems to be appropriate, as in the present case.

Participation of each author

Helena Lucia Barroso dos Reis, Antônio Chambo Filho, and Neide Aparecida Tosato Boldrini conceived the study, collected data, and analyzed and interpreted clinical data. Antônio Chambo Filho, Helena Lucia Barroso dos Reis, and Neide Aparecida Tosato Boldrini attended to the patient. João Victor Jacomele Caldas, Carolina Azevedo Feltz, Danielle de Oliveira Machado, and Lucas Donateli Rosa performed the systematic review. Dennis de Carvalho Ferreira and Marize de Freitas Santos Neves performed laboratorial studies. Helena Lucia Barroso dos Reis and Antônio Chambo Filho developed the first draft. All authors approved the subsequent draft versions. All authors approved the final submitted version.

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Conflict of interests

The authors declare no conflict of interests.

Ethical approval

The study was approved by the Ethics Committee of the Universidade Federal do Espírito Santo and informed consent was waived for this study.

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Nonavalent HPV vaccine: what are the advantages?

Vacina nonavalente contra o HPV: quais são as vantagens?

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INTRODUCTION

Sexually transmitted infections caused by the human papillomavirus (HPV) are the most prevalent in the world and can cause from genital warts to premalignant lesions, which can lead to cervical cancer, vaginal and vulvar neoplasms, anal and penile cancer, if left untreated. Non-genital pathologies may also be related to HPV, such as oropharyngeal cancer and recurrent respiratory papillomatosis[1-3].

HPV can be transmitted whenever there is direct contact of infected hair and mucosa during sexual intercourse. It can also occur via the maternal fetal route (pregnancy, intra and peripartum)[4]. The lesions are imperceptible in many cases, without manifestations of infection, which may facilitate transmission.

This virus affects men and women and is found not only in anogenital regions, but also in extragenital ones. Infection can be manifested in clinical, subclinical and latent forms[5], with subclinical and asymptomatic forms predominating in men[6].

Around 90% of the HPV infections are eliminated in almost two years and, therefore, there is no need of any pharmacological treatment[7]. However, when there is a persistent infection, different pathologies may be present depending on the virus sub-genotype. Infections caused by low-risk oncogenic sub-genotypes may be related to genital warts and respiratory papillomatosis, and high-risk oncogenic subtypes may be associated with the pathogenesis of cervical, anal, penile, vulva, and vaginal and oropharyngeal cancer. Studies have also associated HPV with other cancers, such as oral cavity squamous cell carcinoma[8].

In an attempt to reduce the number of HPV-associated pathologies, there are three vaccines present in the world market currently: Cervarix® (bivalent vaccine) produced by GlaxoSmithKline; Gardasil® (quadrivalent vaccine) by Merck, and most recently, the Gardasil 9® (nonavalent vaccine) was released. All three vaccines are highly immunogenic, effective and safe. The only difference between them is the HPV sub-genotypes that are present[9]. HPV vaccination has been known as a mean to significantly reduce the incidence of related anogenital cancers and the appearance of genital warts[10].

In Brazil, the quadrivalent vaccine (Gardasil®) is available free of charge in the Unified Health System (SUS) units for girls aged 9 to 14 and boys aged 11 to 14. In 2018, the second-generation Gardasil, Gardasil9®, was approved by ANVISA (Brazilian Health Surveillance Agency). Considering the world scenario, in which HPV has been associated with pathologies of a large number of morbidities and mortality, does the nonavalent vaccine have advantages over the other vaccines in the market?

This paper aims to evaluate the advantages and/or disadvantages of the nonavalent vaccine in relation to the other two vaccines by performing a literature review, using Scielo and PubMed databases and the keywords: "HPV", "Vaccine and HPV", "Nonavalent Vaccine and HPV", "Quadrivalent Vaccine and HPV", in Portuguese and English.

HUMAN PAPILLOMAVIRUS

HPV are viruses belonging to the *Papillomaviridae* family, which has over 39 genera. The classification by type is based on the comparison of L1 gene nucleotide sequences of the various HPVs, each type differs from the other types by at least 10% in the sequence of L1 nucleotides.[11,12]. Papillomaviruses that share an identity of 60 to 70% in this gene are designated as species, while types in a given species have show an identity between 71 and 89%[1,13]. The genera *Alpha*, *Beta*, *Um* and *Nupapillomavirus* are capable of infecting humans and have more than 200 types[12-14]. They are viruses of about 55 nm long, with a double-stranded DNA genome of approximately 5 to 8 Kb that is not coated with a lipoprotein envelope. The viral genome may be present in the episomal (circular) form associated with nuclear histones in benign lesions, or it may be integrated into the host cell genome as in malignant lesions. In the latter case, there is a greater risk of cell transformation as a result of early viral protein expression[15].

The genome has about ten open reading frames (ORF) that consist of an early region (E) formed by proteins expressed in the early phase of the replicative cycle, responsible for viral transcription and replication. The late region (L), responsible for the proteins expressed in the later phase of the HPV cycle, are the structural proteins. There is also a long control region (CSF), which is important for the regulation of viral genome transcription and replication events and where the origin of replication is located. The early proteins are E1, E2, E4, E5, E6, and E7. These proteins can interfere in the host cell to the point of immortalizing it. The E6 and E7 oncoproteins direct the degradation of tumor suppressor proteins p53 and pRB, respectively. Therefore, they can contribute to the progression of the carcinogenesis process and genomic instability[16,17]. Late proteins are L1 and L2. They are structural proteins that form the capsid and are responsible for the virus immunogenicity and for carrying gender-specific antigenic determinants[11,12,14].

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HPV has tropism for cutaneous, mucosal, and cervical epithelial cells, preferentially infecting the most basal layers, in which there is greater cell proliferation[15]. Based on the ability to produce malignant lesions, HPV can be divided into low, moderate and high risk types. Persistent HPV-16 infection is the most potent type among the neoplasm-associated viral types. It is known to lead to the development of cancer in various body regions, resulting in infected cells to immortalize genomic instability, inhibit response to DNA damage and escape from apoptosis[18]. Types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are also associated with cancer, especially cervical cancer.

Type 68 has limited evidence in human studies, but strong mechanistic evidence of cervical cancer. Types 26, 53, 66, 67, 70, 73 and 82 present limited evidence in humans in the development of cervical cancer. Finally, types 6 and 11, which belong to the alpha papillomavirus ten species, are classified as non-carcinogenic to humans based on epidemiological evidence and absence of carcinogenic potential in the studied mechanisms[18].

Epidemiology

Around 15% of all human cancers are believed to be caused by viral infections, and 5% may be attributed to HPV infection. Regarding cervical cancer, about 99% of cases are related to HPV[1-3,7-9]. This persistent infection, in turn, can lead to the development of several neoplastic forms, in addition to cervical cancer, such as vagina, vulva, penile, anus, and oropharynx[1-3,7-9]. Cervical cancer is among the most prevalent cancers in the world, with 530,000 new cases per year[19].

In Brazil, cervical cancer is the third most common tumor in the female population and the fourth leading cause of death in women, with 16,340 (7.9%) new cancer cases of cervical cancer and 5,430 deaths of women per year, according to the National Cancer Institute[20].

Around half of women diagnosed with cervical cancer are under 50 years old, and more than two thirds are diagnosed in less developed countries. Southeast Asia (especially India), Latin America, and sub-Saharan Africa are areas with the highest percentages of cases. HPV 16 and 18 together account for 71% of cervical cancer globally. This percentage increases to 90% when we include HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58[19].

Recent studies have been conducted to evaluate the prevalence of the young Brazilian population. The study population conducted by the Brazilian Department of Health consisted of 5,812 women and 1,774 men, with a mean age of 20.6. The city of Salvador had 71.9% of HPV-positive participants, and the lowest rate was in the city of Recife, with 41.2% of survey participants[21].

The distribution and prevalence of HPV types vary based on the degree of cervical disease, age, and geographic location of patients[22-25]. The prevalence of HPV 16 and 18 has been observed in more severe lesions, but they are also the most frequent types observed in women with normal cytology[26]. A recent study carried out in Ghana showed that infection with high-risk types alone was seen in 32.3% of participants, while infection with multiple high-risk types was 9.7%.

The five most common HPV types detected were: 16 (7.4%), 52 (7.2%), 35 (4.8%), 59 (4.7%), 56 (3.9%)[27]. HPV-18 has been found in many regions as the second most common and in some Brazilian studies as well[28-31]. HPV-31 ranks second in frequency in Europe, HPV-52 is especially frequent in Africa and North America, and HPV-45 is in third place in Africa, Central/West Asia, North America, and Oceania[28,32]. In Brazil, HPV 31 and 33 are the second most prevalent types in the Northeast and Central regions[33,34].

In Mato Grosso do Sul, HPV-66 was detected in 22% of HPV-positive samples[35], and HPV-58 was the most frequent type (19.8%) in HIV-infected women followed by HPV-53 (15.5%) in Rio de Janeiro[36]. HPV DNA was detected in 67.5% of women. In a study in the state of São Paulo, HPV-16 (40%) was the most prevalent type in most patients with lesions, followed by HPV 31 (13.3%), 45 (13.3%) and 18 (4.1%). Multiple infections occurred in 15% of the cases, and infections with other types of HPV were detected in 14% of the samples. Thus, HPV 16 and 18 infections do not always occur in a solitary manner (single infection) and are associated with other types of HPV on several occasions[37].

HPV VACCINES

Three types of the HPV vaccine are available for the prevention of HPV-related diseases nowadays. The bivalent vaccine (Cervarix®) acts against HPV types 16 and 18. The quadrivalent vaccine targets types 6, 11, 16 and 18 (Gardasil®). More recently, the nonavalent vaccine (Gardasil 9®), which includes the most oncogenic genotypes prevalent and relevant low risk types 6, 11, 16, 18, 31, 33, 45, 52 and 58[38], was released.

Bivalent vaccine

This vaccine contains the viral capsid protein L1 and is produced by recombinant DNA technology using the *Trichoplusnia ni* insect cell baculovirus expression system to obtain VLPs, which are analogous viral particles of the two most common types present in neoplasms, cervical lesions, HPV-16 and HPV-18, accounting for 70% of the cases of this type of cancer[38].

Stimulation to the organism by the viral subtypes present in the VLP triggers the production of neutralizing antibodies against them, which provides the protection by the vaccine[39]. The adjuvant used in this vaccine is ASO4 with 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid-A[38]. Cervarix® is not a replicative vaccine and may be given together with other inactivated or replicative vaccines. However, its use is not recommended in pregnant women[38].

Side effects include injection site reactions, such as pain (91.8%), redness (48%), and edema (44.1%). Some people who received the vaccine described fatigue (55%), myalgia (49%), arthralgia (21%), and hives (7%) after immunization. In approximately 6,400 patients who received the vaccine, 28% reported gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain, and 13% developed fever within seven days after vaccination[40].

Quadrivalent vaccine

The quadrivalent HPV vaccine (Gardasil-4®) is also produced by a recombinant DNA technique in *Saccharomyces cerevisiae* yeast using the virus capsid protein L1, resulting in the production of

virus-like particles (VLP). These VLP resemble the virus, with the same shape and size, but are not infectious because they do not have genetic material. The quadrivalent vaccine is composed of HPV 6, 11, 16, and 18 capsid L1 proteins[39,41]. Protection is conferred by stimulating the body's production of neutralizing antibodies against viral subtypes present in the VLP[39].

It is known that the vaccine protects the HPV genotypes present in its cross-protection between other viral types due to gene similarity. The quadrivalent vaccine appears to provide partial cross-protection (around 59%) against types 31 and 45. Although these data have not been confirmed yet, there is also evidence of cross-protection against types 33, 52, and 58[41]. Studies have also shown a 38% efficacy of this vaccine against subtypes 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 in preventing cervical intraepithelial neoplasms 2 and 3 and adenocarcinoma *in situ*[42].

The quadrivalent vaccine, or Gardasil®, was approved by Anvisa in 2006. Brazil was one of the first countries to approve the HPV vaccine. It was implemented in the national immunization program by the Brazilian Department of Health in SUS in 2014. When it was released, the vaccine was recommended only for girls aged 11 to 13, but it has been currently applied to girls aged between 9 and 14 and boys from 11 to 14 years old[41].

Nonavalent vaccine

Following the first licensed Gardasil-4® (first generation vaccine), the second generation vaccine was Gardasil-9®, which covers types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and these types together account for 90% of cervical cancer cases and other intraepithelial neoplasms. This increases the protection of the population against persistent infections that could lead to some mucous or skin cancers[43].

It is also produced by a recombinant DNA technique through expression in *Saccharomyces cerevisiae* yeasts, and VLP formed by capsid proteins of nine distinct viral subtypes will protect against the HPV types associated with approximately 90% of cervix cancer cases in women and 80 to 95% of other HPV-associated anogenital cancers in men and women[43-45].

The nonavalent vaccine, or Gardasil-9®, was approved by the US Food and Drug Administration (FDA) in 2014. In 2017, the second-generation vaccine was approved and registered by Anvisa and was indicated for girls and women, as well as for boys and men aged 9 to 26[46].

In a study by the Merck Sharp & Dohme Pharmaceuticals, comparing the two vaccines and highlighting the advantages of the second-generation vaccine, the Gardasil-9® not only presents the same benefits as Gardasil-4®, it also promotes immunization of the population of five types. This is more than the first-generation vaccine, showing better results against HPV 31, 33, 45, 52 and 58 related to undetermined atypical squamous cells and positive high-risk HPV or worse abnormality in the Pap smear[47]. A major advantage is also the extended age range indicated for vaccination, as the age range for Gardasil-4® vaccination is 9 to 26 years and is indicated for women and men older than 45[48].

In Brazil, surveys were conducted to estimate the prevalence of new cases per 100,000 inhabitants, with the highest prevalence recorded in states with the lowest level of regional development. This is a national profile that follows the world profile, where the highest prevalence rates are found in the in the Midwest, North, Northeast, Southeast and South regions, respectively. The most common oncogenic viral types in Brazil are HPV 6, 11, 16, 18, and 31[49].

COST-EFFECTIVENESS

There are 13 types of HPV known to cause cervical cancer and contribute to cancer in the anogenital region, vagina, vulva, anus, and penis, as well as in the oropharynx, mainly tonsillar region and tongue base[19,50]. Estimates of the possible health and economic effects of HPV vaccination provide vital evidence to support the introduction of the vaccine into national programs[51]. To assess the cost and benefit ratio of HPV vaccination, a quality-adjusted incremental cost per year of life (QALY) calculation is made from the expanded scenario, assessing the vaccination costs and those related to associated pathologies[52]. Recent work has shown a gain in QALY, and when vaccination occurs in both men and women, this gain is even greater[51-53].

Thus, vaccination, even with all related expenses, leads to a gain in public health. The nonavalent vaccine is an important advance, as the nine types present in the vaccine account for about 90% of cervical cancer cases. Non-vaccination vaccination can bring substantial additional public health benefits and is a very positive cost-effective intervention.

CONCLUSION

The great advantage of the nonavalent vaccine is protection of types that are represented among the most prevalent in some Brazilian regions, which were not present in the quadrivalent vaccine. Thus, it is believed that the nonavalent vaccine may present a new tool to control cases of persistent infections by high-risk types not covered by the quadrivalent vaccine and, in the long term, lead to a decrease in the number of cases of cervical cancer and other HPV-related cancers. We hope this paper will be important to disseminate knowledge of the new HPV vaccine efficacy. Further studies are expected to be conducted so this vaccine may be soon implemented in the National Immunization Program, replacing the quadrivalent vaccine, protecting the population against the most common infections and preventing injuries caused by HPV.

Participation of each author

Aislan Cristina Rheder Fagundes Pascoal was responsible for project design, literature review, manuscript writing. Marília Barcelos Marqui, Luana Tiuma Borba and Luiza de Souza Duarte were responsible for literature review and manuscript writing. Vinicius D'Ávila Bitencourt Pascoal and Fabiana Nunes Germano were responsible for manuscript revision.

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Conflict of interests

The authors declare no conflict of interests.

Ethics Committee Approval for Human Research

It is not applicable because it is a bibliographic review.

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