Nano-in-nano containing curcumin and benzydamine hydrochloride for the treatment of vulvovaginal candidiasis: from development to biological application in vitro and in vivo
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Prevalence of vulvovaginal candidiasis in Brazil:
A systematic review

Gabriela Corrêa Carvalho, Rafaela Aparecida Prata de Oliveira, Victor Hugo Sousa Araújo, Rafael Miguel Sábio, Lídia Raquel de Carvalho, Taís Maria Bauab, Ione Corrêa, Marlus Chorilli*


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Abstract

Vulvovaginal candidiasis (CVV) is a condition whose signs and symptoms are related to inflammation caused by Candida spp infection. It is the second leading cause of vaginitis in the world, representing a public health problem. The present systematic review comes with the proposal of analyze and identify the available evidence on CVV prevalence in Brazil, pointing out its variability by regions. For this, a systematic literature review was carried out with meta-analysis of cross-sectional and cohort studies, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guide recommendations, and was registered in the International Prospective Register of Systematic Reviews (PROSPERO 2020 CRD42020181695). The databases used for survey were LILACS, Scielo, Scopus, PUBMED, Web of Science and CINAHL. Fifteen studies were selected to estimate CVV prevalence in the Brazilian territory. South and Southeast regions have higher prevalences than the North and Northeast regions, no data were found for the Midwest region. The estimated prevalence for Brazil is 18%, however, it is suggested that this number is higher due to underreporting and the presence of asymptomatic cases. Therefore, new epidemiological studies are recommended throughout Brazil, to elucidate the profile of this disease in the country, in addition to assisting in the elaboration of an appropriate prevention plan by state.
1. Introduction

Vulvovaginal Candidiasis (VVC) is a disease which signs and symptoms are related to inflammation resulting from infection by Candida spp. (Bonifácio et al., 2015; dos Santos Ramos et al., 2016; Sangamithra et al., 2013). After bacterial vaginoses, VVC is the most common cause of vaginitis and it is estimated that about 70-75% of women will present this pathology at some point in their lives (Anderson et al., 1989; Donders & Sobel, 2017; Sobel, 2007). According to Gonçalves and collaborators (2016), the incidence of VVC in different countries varies from 12.1% to 57.3%, where Brazil has the third highest index, behind only Nigeria and Tunisia (Amouri et al., 2011; Okungbowa et al., 2003). These data are reinforced by several other studies carried out in other countries such as Burkina Faso (Sangaré et al., 2018), Argentina (Mucci et al., 2017), Lebanon (Ghaddar et al., 2020), India (Krishnasamy et al., 2020), Saudi Arabia (Venugopal et al., 2020), Ghana (Konadu et al., 2019; Waikhom et al., 2020) and India (RANI et al., 2020), where the prevalence values obtained were within this range.

Despite VVC prevalence, in Brazil there is a lack and an out datedness of epidemiological data on this disease, what leads to VVC underestimation (Brandão et al., 2018). Which can be attributed not only to the fact that it is not a notifiable disease, but also due its asymptomatic cases (Brandão et al., 2018). This lack of information can be detected in other countries like India (Rani et al., 2020), Ethiopia (Tufa & Denning, 2019), Namibia (Dunaiski & Denning, 2019) Saudi Arabia (Venugopal et al., 2020) and Greece (Gamaletsou et al., 2016), where this lack of data motivated epidemiological studies to be carried out. In a study conducted in Mumbai, India, it was observed that 30.7% of women without VVC symptoms had Candida sp. in their vaginal microbiota (Pramanick et al., 2019). Although the prevalence of this disease varies according to the different regions (Farr et al., 2021) a similar value, 33.83%, was also observed by work carried out by researchers from Turkey on asymptomatic women (Cengiz et al., 2020).

It also stands out that as it is a local infection, not associated with mortality, patients sometimes do not look for a health service, leading to a self-medication, this fact also corroborates with underestimation data (Czechowicz et al., 2021; Venugopal et al., 2020; Yano et al., 2019). In a study conducted in the United States of America, 24.1% of women were self-diagnosed with VVC, which is worrying when thinking about self-medication and resistance to antifungals (Araujo et al., 2020; Yano et al., 2019).

Due to the fact that the data found in the literature regarding the epidemiological profile of VVC in Brazil are obsolete and incomplete, a new assessment about the behavior of this pathology is necessary. Considering the previous aspects, the present systematic review comes with the proposal to analyze and identify the available evidence on the prevalence of VVC in Brazil, pointing out its
variability in different regions and updating the data related to the epidemiological profile to assist in a better understanding about this pathology in the Brazilian territory.

2. Methodology

2.1. Protocol design and registration

A systematic literature review was carried out with a meta-analysis of cross-sectional and cohort studies. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the identification: PROSPERO 2020 CRD42020181695. This review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide (PRISMA) (Altman et al., 2015).

2.2. Defining the problem and establishing the guiding question

To perform the guiding question, it was used the PICO anagram (population; intervention; comparation and outcome), according to Table 1. It is worth mentioning that depending on the review method, not all elements of the PICO strategy are employed. In this review, the third element, the comparison, was not used (Santos et al., 2007).

Table 1: Description of the PICO strategy.

<table>
<thead>
<tr>
<th>PICO strategy</th>
<th>Elaboration of the Study Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Women in any age group in Brazil diagnosed with vulvovaginal candidiasis</td>
</tr>
<tr>
<td>Intervention</td>
<td>Prevalence of vulvovaginal candidiasis</td>
</tr>
<tr>
<td>Comparation</td>
<td>Not applicable in this study</td>
</tr>
<tr>
<td>Outcome</td>
<td>Vulvovaginal candidiasis</td>
</tr>
</tbody>
</table>

Thus, the guiding question of this research was: "What is the estimated prevalence of vulvovaginal candidiasis in Brazil?"

2.3. Eligibility criteria

Cross-sectional studies conducted in Brazil that evaluated the prevalence of vulvovaginal candidiasis in women were considered eligible. To be included, the studies needed to present the prevalence or data that would make possible to calculate it. Inclusion criteria were established as primary studies whose sampling was carried out in Brazil that investigated the prevalence of VVC throughout life as a primary or secondary outcome in women of any age group, together with the population number at the time of the study. There was no time limitation or language restriction. Studies with a cohort design (incident cases) were not excluded because they present data from the
Studies with a cohort design (incident cases) were not excluded because they present data from the population number at the time of throughout life as a primary or secondary outcome in women of any age group, together with the primary studies whose sampling was carried out in Brazil that investigated the prevalence of VVC prevalence or data that would make possible to calculate it. Inclusion candidiasis in women were considered eligible. To be included, the studies needed to present the

2.3. Prevalence of vulvovaginal candidiasis in Brazil?

Table 1: Description of the PICO strategy

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women in any age group in Brazil diagnosed with vulvovaginal candidiasis</td>
<td>Vulvovaginal Yeast Infection</td>
<td>Yeast Infections</td>
<td>Brazil</td>
</tr>
</tbody>
</table>

To perform the guiding question, it was used the PICO anagram (population; intervention; comparison and outcome), according to

2.2. Analyzes guide (PRISMA)

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the identification: PROSPERO 2420 CRD42020181695. This review responded to the objective proposed by this study, and finally the third stage was reading the full article, obeying the pre-defined inclusion and exclusion criteria (Moralejo et al., 2018). Aiming to minimize bias in the selection of articles, an open review process was carried out, where the article was evaluated by two researchers (Conterno et al., 2020; Higgins et al., 2019; Moralejo et al., 2018; Tacconelli, 2010). Articles selection was carried out independently, based on the eligibility criteria of the review, based on the guiding question. This is a scientific process that facilitates the improvement of the quality, accuracy, reading, and credibility of the content to be published (Nayak et al., 2005).

In the screening phase of the articles, each researcher registered the agreement or disagreement of the article in a screening program, Rayyan (Ouzzani et al., 2016). A form prepared by the authors was used to extract data from the selected studies with information about study period, city/state, study population, study population characteristic, study type, number of cases and prevalence 95%
confidence interval (CI). In this form was added information about latitude and longitude, population in the last census (2010) and estimated population (2020) and manuscript. For those articles where there was disagreement between the researchers, a third researcher made the decision to include or not (Corrêa et al., 2013; Munn et al., 2014, 2015).

2.6. Data analysis

Proportions and 95% confidence intervals (CIs) for each study in each region were calculated and the pooled proportion and 95% CI either. This pooled proportion was calculated based on the DerSimonian weights for the random effects model. The Cochran Q statistic and I² test was used to test heterogeneity (Andrade et al., 2019; Carvalho et al., 2017; Corrêa et al., 2013).

3. Results and discussion

In the searched databases 56 articles were found, of these, 5 were excluded for being duplicate. Of the remaining 51 articles, it was performed a pre-selection based on the reading of the title and abstract, where 28 articles were selected for reading in full. Only 15 articles met all inclusion criteria and were selected for analysis and data tabulation (Figure 1), being that three studies were carried out in pregnant women, one in patients with VVC symptoms and one conducted in women using intrauterine devices (IUDs). The other studies were carried out with women from a specific region or from a specific health unit. For the localization, a study was conducted in a northern city, four in northeastern cities, two in southern cities and six in southeastern cities and two studies neither identify the city nor state, not being used only for qualitative synthesis. No study was found in the Midwest region. Table 2 highlights the main points of the studies in publication chronological order.
56 articles were found through database searching

5 were excluded for being duplicate

51 articles selected for reading the title and abstract

23 were excluded, reasons:
- Performed outside of Brazil;
- The type of study;

28 articles selected for reading in full

13 were excluded, reasons:
- Not having enough data to calculate CVV prevalence;
- The type of study;
- Study based on patient report

15 studies included in quantitative synthesis and 13 in qualitative synthesis

**Figure 1:** Search diagram.
Table 2: Articles about prevalence of vulvovaginal candidiasis in Brazil.

<table>
<thead>
<tr>
<th>Study period</th>
<th>City/State</th>
<th>Study population</th>
<th>Study population characteristic</th>
<th>Study type</th>
<th>Number of cases</th>
<th>Prevalence 95% CI</th>
<th>Latitude/Longitude*</th>
<th>Population in the last census (2010)**</th>
<th>Estimated population (2020)**</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>January to April 2016</td>
<td>Natal/ Rio Grande do Norte</td>
<td>41 samples</td>
<td>Pregnant patients</td>
<td>Cross-sectional</td>
<td>-</td>
<td>48.78%</td>
<td>5° 46' 45.3252° S 35° 12' 3.2976° W</td>
<td>803,739</td>
<td>890,480</td>
<td>(Brandão et al., 2018)</td>
</tr>
<tr>
<td>April 2013 to October 2014</td>
<td>Rio Grande/ Rio Grande do Sul</td>
<td>263 patients</td>
<td>Women assisted in Gynecology clinic of the University Hospital of the FURG</td>
<td>Cross-sectional</td>
<td>71</td>
<td>15%</td>
<td>32° 2' 43.368° S 52° 6' 57.096° W</td>
<td>197,228</td>
<td>211,965</td>
<td>(Brandolt et al., 2017)</td>
</tr>
<tr>
<td>September 2012, to January 2013</td>
<td>Botucatu/ São Paulo</td>
<td>1519 patients</td>
<td>Women aged 14–54 years attending 18 primary healthcare units</td>
<td>Cross-sectional</td>
<td>75</td>
<td>4.9%</td>
<td>22° 53' 9.3876° S 48° 26' 38.8248° W</td>
<td>127,328</td>
<td>148,130</td>
<td>(Marconi et al., 2015)</td>
</tr>
<tr>
<td>September 2008 to August 2010</td>
<td>Salvador/ Bahia</td>
<td>100 patients</td>
<td>Sexually active adolescents followed at an adolescent gynecology clinic</td>
<td>Cross-sectional</td>
<td>-</td>
<td>22%</td>
<td>12° 58' 39.8964° S 38° 30' 5.8644° W</td>
<td>2,675,656</td>
<td>2,886,698</td>
<td>(Mascarenhas et al., 2012)</td>
</tr>
<tr>
<td>Strategy of the Primary Care Services</td>
<td>2006 to 2008</td>
<td>Botucatu/ São Paulo</td>
<td>289 patients</td>
<td>Low-risk pregnant women attending in the public Primary Care Service</td>
<td>Cross-sectional</td>
<td>34</td>
<td>11.8%</td>
<td>-</td>
<td>22° 53' 9.3876&quot; S 48° 26' 38.8248&quot; W</td>
<td>127,328</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------------</td>
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<td>-------------</td>
</tr>
<tr>
<td>March 2004</td>
<td>Serra Pelada/ Pará</td>
<td>209 patients</td>
<td>Women attended in the clinic</td>
<td>Cross-sectional</td>
<td>-</td>
<td>5.70%</td>
<td>2.6-8.8</td>
<td>20° 0' 16.596&quot; S 41° 1' 47.352&quot; W</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>August 2003 to March 2004</td>
<td>Vitória/ Espírito Santo</td>
<td>299 patients</td>
<td>Women aged 15 to 49, assisted in an area served by the Family Health Program (PSF)</td>
<td>Cross-sectional</td>
<td>28</td>
<td>9.3%</td>
<td>1.3-5.3</td>
<td>20° 19' 0.6204&quot; S 40° 18' 35.7156&quot; W</td>
<td>327,801</td>
<td>365,855</td>
</tr>
<tr>
<td>-</td>
<td>Pacoti/ Ceará</td>
<td>592 patients</td>
<td>Women from seven hamlets and the center of the municipality, aged 12 to 49 years</td>
<td>Cross-sectional</td>
<td>74</td>
<td>12.50%</td>
<td>10.0-15.5</td>
<td>4° 13' 31.98&quot; S 38° 55' 13.764&quot; W</td>
<td>11,607</td>
<td>12,288</td>
</tr>
<tr>
<td>September 2002 to March 2004</td>
<td>-</td>
<td>130 patients</td>
<td>Patients with vulvovaginal candidiasis symptoms</td>
<td>Cross-sectional</td>
<td>-</td>
<td>63%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>October 2000 to</td>
<td>-</td>
<td>250 patients</td>
<td>Patients (regardless of symptoms)</td>
<td>Cross-sectional</td>
<td>69</td>
<td>27.60%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Chapter 2

<table>
<thead>
<tr>
<th><strong>September 2001</strong></th>
<th><strong>April to August 2002</strong></th>
<th><strong>Females who visited the laboratory for examinations of vaginal secretion</strong></th>
<th><strong>Cross-sectional</strong></th>
<th><strong>32</strong></th>
<th><strong>-</strong></th>
<th><strong>-</strong></th>
<th><strong>23° 25' 15.6&quot; S</strong>&lt;br&gt;<strong>51° 55' 59.0016&quot; W</strong></th>
<th><strong>35.077</strong></th>
<th><strong>430,157</strong></th>
<th><strong>(Consolaro et al., 2004)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-</strong></td>
<td><strong>União dos Palmares/Alagoas</strong></td>
<td><strong>341 patients</strong></td>
<td><strong>Women of reproductive age in rural Alagoas</strong></td>
<td><strong>Cross-sectional</strong></td>
<td><strong>20</strong></td>
<td><strong>5.8%</strong></td>
<td><strong>3.7–9.1</strong></td>
<td><strong>23° 9' 23.904&quot; S</strong>&lt;br&gt;<strong>36° 1' 35.868&quot; W</strong></td>
<td><strong>62,358</strong></td>
<td><strong>65,790</strong></td>
</tr>
<tr>
<td><strong>May to November 2001</strong></td>
<td><strong>Campinas/São Paulo</strong></td>
<td><strong>223 patients</strong></td>
<td><strong>New users of IUD (TCu-380A IUD) in a family planning clinic</strong></td>
<td><strong>cohort study</strong></td>
<td><strong>12</strong></td>
<td><strong>5.40%</strong></td>
<td><strong>-</strong></td>
<td><strong>22° 55' 58.5264&quot; S</strong>&lt;br&gt;<strong>47° 4' 25.842&quot; W</strong></td>
<td><strong>1,080,113</strong></td>
<td><strong>1,213,792</strong></td>
</tr>
<tr>
<td><strong>January 1998 to December 1999</strong></td>
<td><strong>-</strong></td>
<td><strong>205 patients</strong></td>
<td><strong>Women attending the Gynecology and Obstetric Ambulatory Clinic of the University of Espírito Santo</strong></td>
<td><strong>cohort study</strong></td>
<td><strong>78</strong></td>
<td><strong>-</strong></td>
<td><strong>-</strong></td>
<td><strong>-</strong></td>
<td><strong>-</strong>&lt;br&gt;<strong>(Ribeiro et al., 2001)</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Source: (Latitude and Longitude Finder, 2020); **Source: (IBGE, 2020)*
3.1. Southern and Southeast region

The Southern region of Brazil is composed of three states, having a territorial area of 576,783,781 km² (Garlet et al., 2019). Large part of this territory is in the South Temperate Climate Zone and the population is mostly composed of Caucasians (Pereira et al., 2015). Only two studies were found in this region, both performed on women attending a particular health service, with only one bringing the prevalence value of VVC in the study population, which was 15% (Brandolt et al., 2017; Consolaro et al., 2004). Consolaro at al. (2004) conducted a study in the city of Maringá, state of Paraná, and among their objectives sought to establish the correlation of colonies number and isolated species with VVC symptoms. It was observed that \textit{C. albicans} was the most isolated in symptomatic women, while non-\textit{C albicans} species were more isolated in asymptomatic women. It is also noted that the disease severity increases as a function of the increasing of isolated \textit{C. albicans}. Additionally, in women with recurrent CVV (RVVC), \textit{C. albicans} was the most isolated species. The correlation between the isolated species and the type of symptom was not statistically relevant.

In addition to RVVC being a cause of morbidity, its main problem is related to the resistance to conventional treatment (Sobel, 2016). Despite the study carried out in Maringá does not specify the age of the studied group in another study carried out in Brazil, it was observed that the most common age group is women with 24 years with RVVC patients. The authors justify by the occurrence of emotional stresses and the use of contraceptives, common at this age, both RVVC predisposing factors (Consolaro et al., 2004; Muniz, 2018). The increase in hormones, such as β-estradiol and progesterone, a common situation in the use of oral contraceptives and during pregnancy, favor the development of VVC because they positively influence both the fungus adhesion to epithelial cells and their resistance to drugs commonly used in therapy (Gonçalves et al., 2020; Luan et al., 2020).

Unlike the article carried out in Maringá, the other study conducted in the southern region, Rio Grande do Sul state, it was observed that \textit{C. albicans} was the most isolated species in both groups, symptomatic and asymptomatic, 74.3 and 62.9%, respectively (Brandolt et al., 2017; Consolaro et al., 2004).

The Southeastern region, which has the highest number of studies, is the most populous in the country and an important economic hub for Brazil and South America. On the other hand, it is the second smallest Brazilian region having an area of approximately 1,000,000 km², consisting of four states, with a predominantly tropical climate. With a predominantly Caucasian population, its territory extends between 15 ° and 25 ° south latitude (Neto, 2005; Penna et al., 2020). Of the six studies carried out in this region, four were carried out in the state of São Paulo, of these one in the city of Campinas and three in the city of Botucatu. The rest were conducted in the state of Espírito Santo, one in the city of Vitória and the other not had the city identified.
Two of the three studies carried out in Botucatu were in low-risk pregnant women and the prevalence of VVC found was 10.2 and 11.8% (Gondo et al., 2010; Gondo et al., 2011). While Gondo et al. (2011) observed in his research that 92% of patients with VVC had symptoms, Gondo et al. (2010) realized that the prevalence had little association with symptoms, highlighting the importance of routine diagnosis. Asymptomatic VVC is known to be a risk factor for the patient as it may indicate previous therapeutic failure, resistance of the organism to complete eradication of the fungus and recolonization (Giraldo, 2000; Watson et al., 2013). VVC is a very common disease in women of reproductive age. It is worth mentioning that in the case of pregnant women, the risk becomes greater as this disease can be associated with complications such as premature rupture of membranes, chorioamnionitis, premature birth, and congenital cutaneous candidiasis (Aguin & Sobel, 2015).

The other study, also carried out in this city, has as a study group women of reproductive age (14–54 years) and the prevalence of VVC found was 4.9%. In this study it was observed that the detection of *Candida sp.* in the samples was inversely associated with the presence of bacterial vaginosis, 5.6 and 3.5% in patients with and without bacterial vaginosis, respectively (Marconi et al., 2015). This correlation pattern is in line with the literature where candidiasis showed a protective behavior against bacterial vaginosis (Guédou et al., 2013).

Finally, the other study carried out in the state of São Paulo was performed in the city of Campinas in women using TCu-380A IUDs. The prevalence observed in the study was 5.4%. Although this study also assessed the prevalence of bacterial vaginosis, the correlation between both illness was not determined. The authors pointed out that candidiasis was more significantly acquired after 6 months of using the device, but was significantly ceased without treatment (Lago et al., 2003). Due to the fact that Candida species have the ability to adhere to inert surfaces, tissue or at the air-liquid interface, IUD presence increases the chance of biofilm formation, favoring the occurrence of VVC. This virulence factor increases the pathogenicity of this fungus because biofilm consists of microorganisms’ community, previously planktonic, highly organized attached to a surface. As a safe haven, it provides less susceptibility to drugs, increasing microbial resistance making it difficult to treat the patient (Borges et al., 2018; de Barros et al., 2020; Rodríguez-Cerdeira et al., 2019; Silva et al., 2012).

Due to the number of studies found in the literature for this State, it was possible to calculate the estimated prevalence of VVC. The data in Figure 2 shows the general state prevalence and the 95% CIs for each selected study, based on a random effects model. Thus, it is possible to observe that the estimated prevalence of VVC for the state of São Paulo is 8%.
Prevalence of vulvovaginal candidiasis in Brazil

For the state of Espírito Santo, the two selected studies targeted women served at a specific health service. The first study was carried out in the city of Vitória and had a VVC prevalence of 9.3%, while the other one had neither its city identified nor the calculated prevalence (Barcelos et al., 2008; Ribeiro et al., 2001). The study carried out in Vitória aimed to describe the prevalence and behavioral profile for genital infections in women seen at a local health service. Although it is not considered a sexually transmitted disease, the authors included it in the study because it is a frequent cause of demand for the health system by patients. It was noticed that the factors associated with genital infection were abnormal cervical mucus, previous human immunodeficiency virus (HIV) testing, having had more than one partner in the past year and having had more than a partner in life (Barcelos et al., 2008). Although it can be sexually transmitted, VVC is not considered a sexually transmitted disease because in addition to being part of the vaginal microbiota, it also affects celibate women (Davis, 2020).
The other study carried out in the state of Espírito Santo also focused on women attended by a health service. It is worth noting that the prevalence of this disease was higher in symptomatic patients than in asymptomatic patients, being 60 and 25%, respectively. It should also be noted that \textit{C. albicans} was the most isolated species in both groups, 90 and 46%, respectively. The second most frequently isolated species was \textit{C. glabrata}, 6 and 13%, respectively (Ribeiro et al., 2001). Several articles in the literature report \textit{C. albicans} as the most prevalent species (El-Houssaini et al., 2019; Farahyar et al., 2020; Gerwien et al., 2020; Ghaddar et al., 2020; Krishnasamy et al., 2020; Maraki et al., 2019).

Based on the studies found for the Southern (except studies related to the state of São Paulo) and Southeast region, the estimated prevalence of VVC was calculated. The data in Figure 3 shows the prevalence of these regions and the 95% CIs for each selected study, based on a random effects model. Therefore, the estimated prevalence of VVC for these regions is 23%.

\textbf{Figure 3:} VVC prevalence in Southern and Southeast region with 95% confidence interval. Legend: RS: Rio Grande do Sul; ES: Espírito Santo; PR: Paraná.
3.2. Northern and Northeast Region

These two regions are the poorest in the country as they have the highest proportion of people living on ¼ of the minimum wage per capita (IBGE, 2015). The Northern region, made up of seven states, the Equator line passes in this region so the climate is predominantly tropical (Júnior et al., 2015). Despite being the largest region in the country, comprising 45% of the entire national territory, it has the lowest demographic density, attributable to the Amazon Forest that makes human habitation difficult. This region has a predominantly black and brown population (Cunha et al., 2017; IBGE, 2015).

In this region only one study was found which aims to describe the frequency of genital infections and the reproductive profile in women living in Serra Pelada, a mining region in the state of Pará. In the studied population, the prevalence rate for VVC was 5.7%. Although samples were collected to carry out this study, the authors highlighted that due to the low socioeconomic condition of the region, women do not have access to the clinical laboratory under normal primary care conditions and therefore the diagnosis of VVC is based on signs symptoms. Additionally, the rate of patients' adherence to the study, 14% of local adult female population, considered high by the authors, reflects the lack of health services in the community, highlighting the need and the success that would be achieved with the implementation of the same (Miranda et al., 2009).

A diagnosis based only on signs and symptoms is not recommended because, besides being variable among patients, they are still nonspecific and can be confused with other pathologies leading to a misdiagnosis and wrong treatment. The use of laboratory tests to confirm the diagnosis is desirable because it avoids delays in the diagnosis, investigation of simultaneous infections and long-term complications. As later initialize the treatment, more severe the symptoms for the patients (Anderson et al., 2004; Mitchell, 2004; Sanches et al., 2020; Venugopal et al., 2020).

The Northeastern region, composed of nine states, has a territorial area of 1,588,196 km², approximately 18% of the entire Brazilian territory. Despite being located in a tropical region, it does not show the rainfall pattern, characteristic of this area, showing in some years to be an extremely dry area and others extremely rainy. It also presents three sub-climates, humid coastal climate, tropical climate, and semi-arid tropical climate (Costa et al., 2020; Lacerda et al., 2015). This region has a predominantly black and brown population (IBGE, 2015).

Four studies were found in this region. In the first study carried out in Rio Grande do Norte, the prevalence of VVC in symptomatic pregnant patients was 48.78%. The authors warned of the possibility of misdiagnosis and ineffective treatments, which elevate this disease as an economic public health problem. They also emphasized that because VCC is not a notifiable disease, it causes a shortage of epidemiological data (Brandão et al., 2018).
Another study also carried out in the northeast region, in Salvador, Bahia, was also motivated by the lack of epidemiological information, in this case in adolescent patients. The authors observed that the prevalence of VVC for the studied group was 22%. Although the association of this disease with risk factors (such as family income, education, ethnic groups, conjugal status, tobacco, alcohol and illegal drug use, age at first sexual intercourse, age at menarche, sexual abuse, condom and contraceptives use and number of sexual partners) was studied, no significant correlation was observed with any of them (Mascarenhas et al., 2012). On the other hand, in the study carried out in Maringá, the authors concluded that emotional stresses and the use of contraceptives are risk factors (Consolaro et al., 2004). In the study carried out in Campinas, IUD use was also considered a risk factor (Lago et al., 2003).

In a study carried out in Pacoti in Ceará, also in the Northeastern region of Brazil, the authors point out that population studies more accurately reflect a particular characteristic of a population than studies with a specific population, but these data are lacking in Brazil. In their study, the authors evaluated women of reproductive age who started the sexual life of seven hamlets in the municipality of Pacoti, and observed that the prevalence of VVC was 12.5%. In parallel, the authors assessed the prevalence of symptoms, and the most prevalent for this disease was abnormal vaginal discharge (56.8%) followed by Lower abdominal pain (50%) (Oliveira et al., 2007). However, in a study carried out in Botucatu, Southeast region, another pattern of prevalence of symptoms was observed, discharge (80.5%) followed by itching (56.1%) (Gondo et al., 2010). Evidencing the non-specificity of symptoms and the difficulty of obtaining precision in a diagnosis based only on signs and symptoms. In the last study carried out in the Northeast region, the authors determined the prevalence of sexually transmitted diseases in rural communities in the municipality of União dos Palmares, Alagoas. VVC had a prevalence of 5.8%, in addition vaginal pruritus had a significant association with VVC (Soares et al., 2003).

It was possible to calculate the prevalence of CVV for Northern and Northeast region based on the studies found. The data in Figure 4 shows the prevalence and 95% CIs for each selected study in these regions, based on a random effects model. Thereby, remark was made that 16% is the estimated prevalence of CVV for these regions.
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Figure 4: VVC prevalence in Northern and Northeast region with 95% confidence interval. Legend: RN: Rio Grande do Norte; BA: Bahia; AL: Alagoas; CE: Ceará; PA: Pará.

3.3. Midwest Region

This region has five states and covers an area of 1,606,371.5 km², with a predominance of brown population with a predominantly tropical climate (Castro et al., 2020; Pereira et al., 2015; IBGE, 2015). It should also be noted that the country's federal capital is located in this region (IBGE, 2020). No study was found in this region.

3.4. Brazilian territory

Brazil is the fifth largest country on the planet, with a territorial area of 8,510,295.914 km², and a population of 211,755,692 people (Castro et al., 2020; IBGE, 2020). From the 15 studies found, it was possible to calculate the estimated prevalence of CVV for Brazil. The prevalence of and the 95% CIs for each study, following a random effects model, is shown in Figure 5. Accordingly, it has been identified that the estimated prevalence of CVV for Brazil is 18%. The fact of the low prevalence for
a disease considered a public health issue worldwide, may be due to the fact that few studies have been found, showing the underreporting of this disease. This observation can be attributed to the lack of health services in the country, or to the cases of asymptomatic VVC (Brandão et al., 2018; Miranda et al., 2009; Venugopal et al., 2020).

<table>
<thead>
<tr>
<th>City – State, year</th>
<th>Prevalence rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natal - RN, 2018</td>
<td>0.49 (0.33, 0.65)</td>
</tr>
<tr>
<td>Rio Grande - RS, 2017</td>
<td>0.27 (0.22, 0.33)</td>
</tr>
<tr>
<td>Salvador - BA, 2012</td>
<td>0.22 (0.14, 0.31)</td>
</tr>
<tr>
<td>Botucatu - SP, 2015</td>
<td>0.05 (0.04, 0.06)</td>
</tr>
<tr>
<td>União dos Palmares - AL, 2003</td>
<td>0.06 (0.04, 0.09)</td>
</tr>
<tr>
<td>Botucatu - SP, 2011</td>
<td>0.10 (0.07, 0.15)</td>
</tr>
<tr>
<td>Pacoti - CE, 2007</td>
<td>0.13 (0.10, 0.15)</td>
</tr>
<tr>
<td>Vitória - ES, 2008</td>
<td>0.09 (0.06, 0.13)</td>
</tr>
<tr>
<td>Maringá - PR, 2004</td>
<td>0.20 (0.14, 0.27)</td>
</tr>
<tr>
<td>Botucatu - SP, 2010</td>
<td>0.12 (0.08, 0.16)</td>
</tr>
<tr>
<td>Serra Pelada - PA, 2009</td>
<td>0.06 (0.03, 0.10)</td>
</tr>
<tr>
<td>Campinas - SP, 2003</td>
<td>0.05 (0.03, 0.09)</td>
</tr>
<tr>
<td>ES, 2001</td>
<td>0.38 (0.31, 0.45)</td>
</tr>
<tr>
<td>Unidentified localization, 2006</td>
<td>0.63 (0.54, 0.71)</td>
</tr>
<tr>
<td>Unidentified localization, 2004</td>
<td>0.28 (0.22, 0.34)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.18 (0.12, 0.26)</td>
</tr>
</tbody>
</table>

**Figure 5:** VVC prevalence in the Brazilian territory with 95% confidence interval. Legend: RN: Rio Grande do Norte; RS: Rio Grande do Sul; BA: Bahia; SP: São Paulo; AL: Alagoas; CE: Ceará; ES: Espírito Santo; PR: Paraná; PA: Pará

Due to the number of studies per state, it was possible to calculate the prevalence of VVC only for the state of São Paulo, whereas for the others it was necessary to group the regions. In the case of Brazilian regions, the South and Southeast regions have a higher prevalence than the north and northeast regions, as illustrated in **Figure 6**. On the other hand, it is worth noting that in spite of the
North and Northeast regions having a more favorable climate (the tropical one) for the growth of this fungi, due the relative humid environment, the low prevalence can be attributed the smaller number of articles recovered in these areas (Dou et al., 2015; Jackson et al., 2019).

\[\text{Figure 6: Brazil Regional Division and their estimated VVC prevalence}\]

\[\text{4. Conclusions}\]

VVC is a worldwide public health problem. Although VVC is not considered a sexually transmitted disease, it can be transmitted sexually and, is therefore, prevalent in women of childbearing age. After the evaluation of a systematic literature review with a meta-analysis of cross-sectional and cohort studies the estimated prevalence of VVC in Brazil is 18%. Our studies suggest that this value may be higher in the Brazilian territory, due to the underreporting of this disease and asymptomatic cases. It is also noteworthy that if a greater number of studies were found by state, it would be possible to estimate the prevalence by state, a limiting factor of this review. Thus, the conduction of further epidemiological studies throughout Brazil is recommended to improve the knowledge of its real
prevalence, as well as that of each state. It would assist in elucidation of a better profile of this disease in Brazil, beyond the development of an adequate plan for its prevention by state.

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6. References


Prevalence of vulvovaginal candidiasis in Brazil


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CHAPTER 3

Infection caused by Candida auris: state of the art

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