

Review

Prevalence of vulvovaginal candidiasis among pregnant women in Africa: A systematic review and meta-analysis

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Abstract

Introduction: Vulvovaginal candidiasis (VVC) is a yeast infection of the vulva, which is caused by *Candida* species and affects women worldwide. Pregnant women are more vulnerable to VVC due to certain risks. Moreover, their offspring are also exposed to the risk of preterm birth. In this context, ascertaining the burden of VVC is of paramount importance and this meta-analysis was conducted to estimate the occurrence of VVC among pregnant women in Africa.

Methodology: Database search was carried out through PubMed, Scopus, Science-Direct, and Google Scholar from the date of inception until December 2020. All the studies on the prevalence of VVC among African pregnant women were included in the analysis. The pooled prevalence was estimated based on the Random-effect model DerSimonian-Laird approach with Freeman-Tukey double arcsine transformed proportion. Heterogeneity was assessed using I^2 test and subsequently explored using subgroup and meta-regression analysis.

Results: A total of sixteen records having a sample size 4,185 were included in this study. The overall prevalence of VVC was pooled at 29.2% (CI 95%: 23.4 – 33.0). Subgroup analysis revealed a higher prevalence in Eastern Africa, followed by Western Africa and North Africa (35%, 28%, and 15% respectively). Moderator analysis indicated that the studies that used advanced methods of detection had a higher prevalence ($p = 0.048$). In addition, the large sample size was associated with higher prevalence ($p \leq 0.001$). No other moderators were found to be statistically significant.

Conclusions: The overall prevalence of VVC among African pregnant women is comparable to other studies worldwide. However, appropriate identification techniques and larger sample size could likely be associated with an increased prevalence. Our findings necessitate the need for further investigations to determine the geographical distribution of VVC across African regions.

Key words: Prevalence; vulvo-vaginal; candidiasis; pregnancy; meta-analysis; Africa; women health.

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Introduction

Vulvovaginal candidiasis (VVC) is a superficial yeast infection of the vulva and/or vagina. It is mostly caused by an overgrowth of the commensal pathogen *Candida* species [1]. *C. albicans* was known to be the primary pathogen responsible for the infection, however, an epidemiological shift toward Non-*Candida albicans* (NCA) is now observed across the globe [2]. Other species such as *C. glabrata*, *C. krusei*, and *C. parapsilosis* are emerging causative agents and in some

clinical settings in a higher proportion than *C. albicans*. Alarmingly, co-infection of *C. albicans* and NCA has been also reported [3,4].

There are several risk factors implicated in the development of VVC. Physiological changes associated with pregnancy -most importantly increased estrogen level- increase the risk to develop VVC from 20% among non-pregnant women to 30% during pregnancy [5]. A previous study also showed that approximately 70% to 75% of women above the age of 18 suffer at

least one attack of *Candida* vaginosis in their lifetime. Some women were affected only once in their lifetime, while others were affected occasionally with a varying degree of severity, with the development of chronic or recurrent VVC [6]. Furthermore, another estimate showed that 8% to 10% of adult women are susceptible to recurrent VVC [5].

To the best of our knowledge, previous regional and international meta-analyses provide insight into bacterial vaginosis (BV) and sexually transmitted infections (STIs) among women [7]. However, these studies present limited data on the occurrence of VVC among pregnant women. These studies have discussed the high risks of various vaginal infections. Of these, one quantitative synthesis of 18 HIV prevention studies indicated the prevalence of BV is 40% [7]. Another systematic review on 86 studies showed a relatively higher prevalence of BV in African women as compared to women from Asia and America [8]. Several epidemiological studies have shown the impact of intrauterine infection in preterm birth. Goldenberg *et al.* reported that nearly 40% of preterm birth were caused by either bacterial or fungal vaginal infections [9]. Roberts *et al.* declared that congenital cutaneous candidiasis has been associated with VVC, while the preventable and controlled measures of VVC have been successfully associated with a low incidence of preterm birth [10].

Since *Candida* species are the most common attributor of vaginal infection during pregnancy such as VVC, understanding the epidemiology of VVC is

expected to build a foundation for improving the diagnostic tools as well as providing better therapeutic guidelines. In this context, this meta-analysis was conducted to ascertain the pooled prevalence of VVC among pregnant women in African countries and to stratify the prevalence by regions, years, and causative agents. Furthermore, the study aims at suggesting possible reasons that might contribute to the epidemiological diversity across the countries whenever possible.

Methods

Information sources

A literature search was conducted by two independent reviewers using electronic databases (PubMed, Scopus, Science-Direct, and Google Scholar) from the date of inception to December 2020. The PubMed search strategy served as a reference for the development of search strategies for the other databases. The search terms used were (“prevalence” OR “epidemiology” OR “rate”) AND (“Vaginal infection” OR “Vulvovaginal Candidiasis”) AND (“pregnant woman”) AND (“Africa”). A manual search for each African country was also included. The reference list of each study along with grey literature was also searched to identify the potential studies. The search included only published articles and was limited to human studies regardless of the age group.

Inclusion criteria

The observational studies evaluating the prevalence of VVC were included in this review. The studies conducted in one of the African countries and answered the review question were included in the qualitative and quantitative synthesis of results.

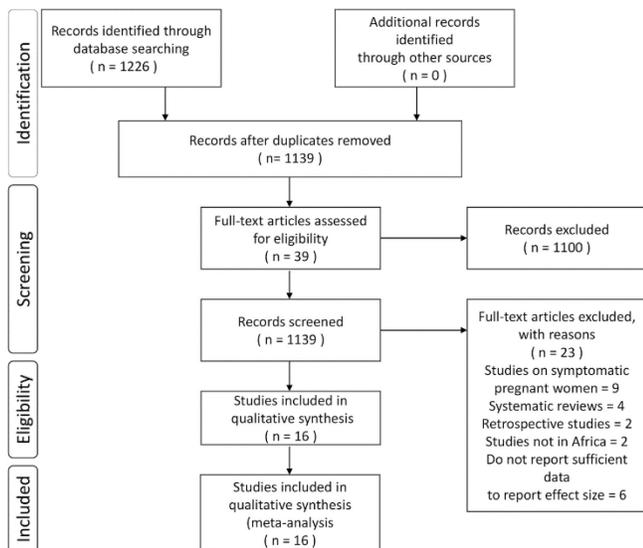
Exclusion criteria

All the studies on symptomatic pregnant women and those conducted outside of African regions were excluded from this review. Moreover, all the studies other than cross-sectional studies and those with non-extractable data were also excluded from the analysis.

Data extraction

Two researchers independently screened all titles and abstracts retrieved from the electronic databases. The full text of each potentially eligible article was obtained and screened independently to ascertain whether it meets the inclusion criteria or not. The required results from each study were collected using a data collection form. Any conflict or deviation was solved through mutual consultation and concurrence.

Figure 1. Flow chart showing the process of selecting studies for meta-analysis, as recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram).



Study selection

A total of 1,226 studies were initially identified and considered potentially relevant. Of these, 85 studies were duplicates, and 1,102 did not meet the inclusion criteria. Thirty-nine studies were evaluated in detail to determine whether they described the prevalence of VVC among pregnant women. Of these, 16 studies were included in qualitative and quantitative synthesis of results. Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection.

Quality assessment

The quality appraisal of the included studies was carried out by Joanna Briggs Institute (JBI) Critical Appraisal Checklist for epidemiological studies. This checklist assesses the methodological quality and the possibility of bias through eight items, where each item has four possible answers: yes, no, unclear, and not applicable. The quality assessment of each study is described in Supplementary Table 1. Publication bias was assessed qualitatively through the funnel plot.

Quantitative synthesis and Analysis

The sample size and cases from each study were used to pool the prevalence. A random-effects model was assumed using the DerSimonian-Laird approach with Freeman- Tukey double arcsine transformed proportion at 95% CI. All statistical analyses were done using the Open-Meta software. The I^2 statistic was used to assess heterogeneity across the included studies.

Figure 2. Eight African countries included in the study stratified by region.

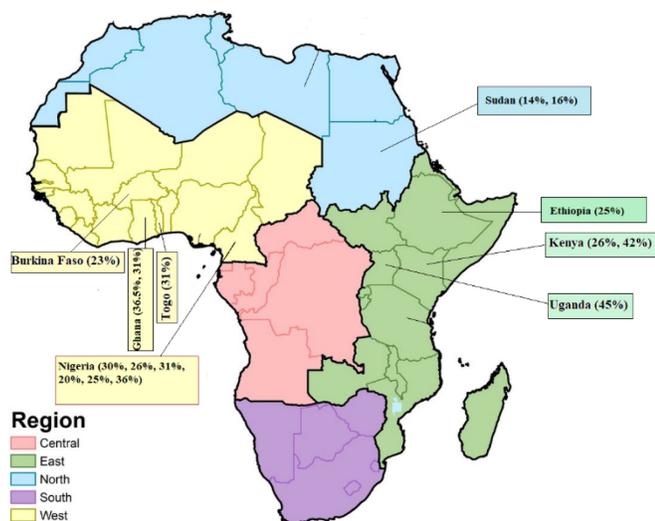
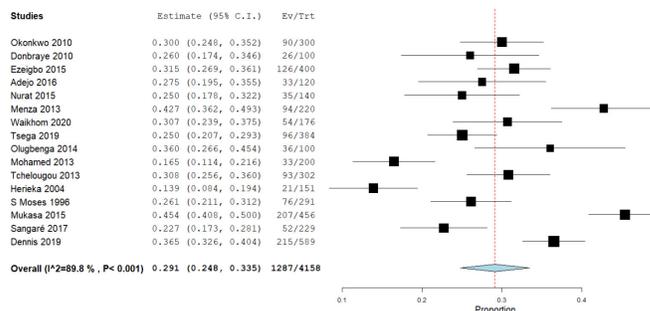


Figure 3. Forest plot showing the prevalence of each study and the pooled prevalence of VVC among pregnant women in Africa.



Results

Selection and descriptive characteristics of the studies

Our search reported 16 studies across eight African countries (Figure 2). These studies followed a cross-sectional design and were published between 1996 and 2020. Six studies were from Nigeria, 2 each from Sudan, Kenya, and Ghana, and one report each from Ethiopia, Burkina-Faso, Togo, and Uganda. The cumulative sample size was 4,158 which varied from 100 to 589 across these studies. A detailed description of the study characteristics is given in Table 1.

Prevalence of VVC

The pooled prevalence of VVC using the random-effect model was 29.1% (CI 95%: 24.8 – 33.5), lowest (14%) in Sudan, and highest (45.4%) in Uganda. Significant heterogeneity was observed across these studies ($I^2 = 89.8%$ and $p < 0.001$). The pooled prevalence and prevalence of each individual study is shown in Figure 3.

Risk of Bias Assessment

The risk of bias of individual studies using JBI critical appraisal for studies reporting prevalence data is shown in Supplementary Table 1. The funnel plot was inspected visually for symmetry (equal dots on both sides), indicating the absence of publication bias, regression test for funnel asymmetry was indicated ($p = 0.272$). The funnel plot of Double arcsine transformed proportion and standard error is shown in Figure 4.

Assessment of heterogeneity

The heterogeneity was found to be significant across the 16 included studies ($I^2 = 89.8%$). Subgroup and meta-regression analyses were conducted ascertain the source of heterogeneity.

Subgroup analyses

A subgroup analysis based on African sub-regions was conducted to stratify the studies into three regions; North, East, and West, while there were no studies from Southern and Central Africa. A relatively higher prevalence (29.5%) was reported in Eastern Africa (4 studies) and heterogeneity remains to be high ($I^2 = 59.95\%$). On the other hand, studies from North Africa (2 studies) were homogenous ($I^2 = 0.00\%$) with a low prevalence (15.3%). The majority of the studies (10 studies) were conducted in Western Africa where prevalence was found to be 29.9% ($I^2 = 94.7\%$). The subgroup analysis based on different African regions is shown in Figure 5.

Moderator analysis

Further heterogeneity investigation was carried out using mixed-effect meta-regression based on year of publication, sample size, and method of detection.

Figure 4. Funnel plot of publication bias of double arcsine transformed proportion and standard error.

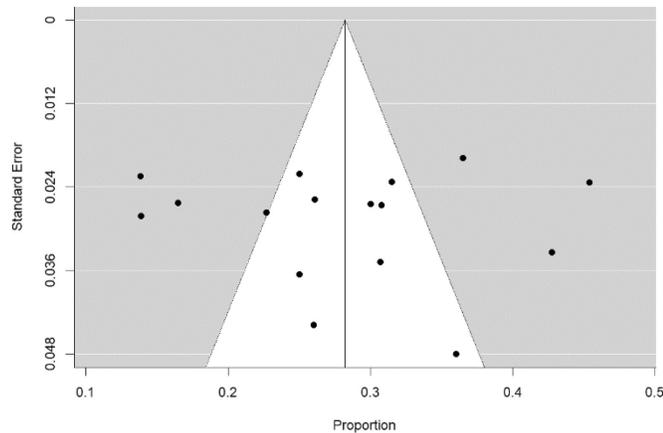
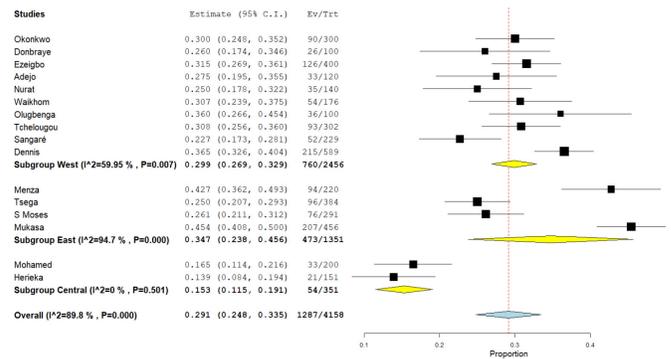


Table 1. Characteristics of the included studies.

S. No.	Study ID	Year	Country	Sample selection	Sample size	Prevalence of VVC (%)	Ref
1	Okonkwo	2010	Nigeria	All	300	30%	[11]
2	Donbraye	2010	Nigeria	All	100	26%	[12]
3	Ezeigbo	2015	Nigeria	All	400	31.5%	[13]
4	Adejo	2017	Nigeria	All	121	27.2%	[14]
5	Nurat	2015	Nigeria	All	140	25%	[15]
6	Menza	2013	Kenya	All	220	42.7%	[16]
7	Waikhom	2020	Ghana	All	176	31%	[17]
8	Tsega	2019	Ethiopia	All	384	25%	[18]
9	Olugbenga	2014	Nigeria	All	100	36%	[19]
10	Mohamed	2014	Sudan	All	200	16.6%	[20]
11	Tchelougou	2013	Togo	All	302	30.77%	[21]
12	Herieka	2004	Sudan	All	151	13.9%	[22]
13	Moses	1996	Kenya	All	291	26.2%	[23]
14	Mukasa	2015	Uganda	All	456	45.4%	[24]
15	I. Sangaré	2017	Burkina Faso	All	229	22.71%	[25]
16	Dennis	2019	Ghana	All	589	36.5%	[26]

Figure 5. Forest plot of subgroup analysis based on geographical subregions in Africa.



Continuous variables were considered for both types of analysis. The moderator analysis indicated that studies that adopted methods or techniques that were able to detect all or most of the possible species reported a higher prevalence in comparison to studies that screened only one specie, the association was found to be statistically significant ($p \leq 0.001$). The sample size aids in explaining the heterogeneity as a significant relationship was found between the effect size and the sample size ($p = 0.049$), indicating that the studies with a higher sample size reported a higher prevalence of VVC. The year of publication was not significantly correlated with the effect size ($p = 0.316$). Meta-regression analysis is provided in Table 2 (Meta-regression figures are provided in Supplementary Figures 1 and 2).

Discussion

This study is the first of its kind to underscore the available literature on the epidemiology of VVC among pregnant African women. Moreover, the current study

also provides an insight into the possible reasons behind the variations in VVC prevalence between these studies. Out of 4,185 pregnant women from 8 different countries, the overall prevalence of VVC was 29.2% (CI 95%: 24.8 – 33.5). Pregnant women from eastern regions were more susceptible to VVC (34.4%, CI 95%: 23.8 – 45.6) than women from western (29.9%, CI 95%: 26.9 – 32.9) and central regions (15.3%, CI 95%: 11.5 – 19.1).

The pooled prevalence in this analysis is more, less, or in line with previous investigations conducted worldwide. Our results were comparable with the studies conducted in Argentina (25%), the Kingdom of Saudi Arabia (34%), and Jamaica (31%) [11-13]. However, a relatively high prevalence was reported in Lebanon (42%) and Brazil (44%) [14-16], and a low prevalence was observed in China (13%) and Kuwait (20%) [17]. These disparities across the studies are primarily attributed to various factors including sampling, clinical settings, study design and methodology, and variations in risk factors. Unfortunately, we were unable to get data from many countries due to the fact that the majority of reported prevalence was from low to middle-income countries. This indicates that either these infections were associated with a poor population or these populations were more inclined towards childbearing, inclining the researchers to investigate the complications during pregnancy. However, more scientific evidence is the need of the hour to draw a firm conclusion.

A higher prevalence was also reported by studies in some African countries (not included in this study since they did not meet the inclusion criteria) such as Tanzania (65%), Cameroon (55%), and Libya (43%) [18-20]. The probable reason for such discrepancies is the selection bias since all these studies were conducted in symptomatic pregnant women. It is pertinent to mention that authors in the included studies managed to analyze the results by separating the symptomatic and non-symptomatic patients. Sangaré *et al.* reported the overall prevalence to be 22%, however, the prevalence among symptomatic pregnant women was 58% ($p < 0.001$) [21]. Such reported prevalence implies the

necessity and utility to define an appropriate study population while conducting epidemiological studies on VVC.

Though the estimated pooled prevalence in this study is in concordance with the available literature, significant heterogeneity was observed ($I^2 = 89.8\%$). Several attempts have been made to explore the sources of heterogeneity using subgroup and meta-regression analysis. The variation between the studies was not surprising as is an attempt to pool results of observational studies. This paradox is in line with the previous meta-analysis which investigates the prevalence of BV and STIs in the Africa regions, and the prevalence of BV worldwide. Interestingly, both studies concluded that the high prevalence of BV in the eastern region and low in the central and western regions [7,8].

Since *C. albicans* is the most common causative pathogen for VVC, the isolation of non-*C. albicans* species from vaginal swab is rare [2]. Detection of *C. albicans* is somewhat easier and could be done using wet preparation and germ tube, however, confirming non-*C. albicans* isolates require extra-diagnostic techniques such as culture on chromogenic media, API kits, sugar assimilation tests, and PCR [22,23]. In this context, diagnostic cost and lack of expertise might be another reason that most of the investigators have primary focus on *C. albicans*. The association between the method of detection and prevalence of VVC ($p = 0.001$) is an interesting aspect of this study. The higher prevalence was reported in Kenya (42%) and Uganda (45%) [24,25] and interestingly these studies adopted either API kits or chromogenic media and sugar assimilation tests as identification techniques. This can be compared to a lower prevalence reported in Kenya (25%) in which wet preparation was used to identify VVC [26]. Moreover, an Ethiopian study which had used chromogenic media for detecting *Candida* species reported the 25% prevalence of VVC among pregnant women [27]. Since pregnancy is a well-established risk factor for VVC, a higher prevalence (41%) was also reported by another study on non-pregnant women, in which the authors adopted an automated VITEK 2

Table 2. Result of Meta-regression using Year of publication, Sample size, and Method of detection as a continuous variable, Mixed-effect model.

	Coefficient	CI Lower Bound	CI Upper Bound	Std. error	p value
Intercept	-6.651	-21.388	8.086	7.519	0.367
Year of publication	0.003	-0.004	0.011	0.004	0.316
Intercept	0.199	0.108	0.290	0.046	< 0.001
Sample size	0.000	0.000	0.001	< 0.001	0.048
Intercept	0.17	0.094	0.246	0.039	< 0.001
Method of detection	0.074	0.03	0.119	0.023	< 0.001

compact system to diagnose VVC [28]. The two studies from Sudan reported the lowest prevalence of VVC (13% and 16%) [29,30]. Interestingly, these studies used wet preparation for detection. However, a slightly higher proportion was also estimated in another study from Sudan (33%) [31]. The possible reason for this variation is that the later used chromogenic media which recovered 90 out of 104 isolates (86.2%). In the same study when germ tube and wet preparation were used only 72 isolates (69.2%) were identified [31]. Considering the recently observed mycological shift of *Candida species* from *C. albicans* to a non-*C. albicans*, this finding is alarming and points toward the necessity of using identification techniques other than wet preparation and germ tube test that are able to identify at least the medically important *Candida* species during the diagnostics workup of VVC.

The development of VVC depends on several host risk factors such as stages of pregnancy and age of the pregnant women. Intra-population differences in these risk factors were not similar across the studies which in turn might precipitate the overall heterogeneity. During the analysis, we noticed that pregnant women in the third trimester were at higher risk than those in the first and second trimester (nine studies reported detailed prevalence at each trimester) [21,24,26,27,32-37]. Out of 800 pregnant women with VVC, 416 (52%) were in the third trimester, 273 (34.23%) in the second, and 111 (13.87%) in the first trimester. The results are in concordance with the findings, of previous studies [5,38]. It is important to note that the studies with high prevalence included a higher sample of pregnant women in the third trimester, however, results remain insignificant during the analysis ($p = 0.916$). It is pertinent to mention that there was a relationship between the age of pregnant women and the prevalence of VVC. Eight studies gave sufficient data to ascertain such association (mean age from 23 to 29) [21,26,27,29,32,36,37,39]. These studies reveal that the prevalence of VVC increases with the increasing age of the women ($p = 0.019$). These findings necessitate the vigilant monitoring of pregnant women with advanced age and in the third trimester, as they are most likely to develop the infection due to increasing age. Moreover, clinicians should consider the preventable approaches for this particular age group.

Our results show that the sources of variation are not only limited to the study design, sampling, and methods of detection. Other risk factors such as the use of antimicrobials could also affect the finding. Most of the studies did not provide complete data to analyse this factor. However, data from some studies gave a clue

about of possible contribution of antimicrobial use among patients. A report from Nigeria found that the prevalence increased from 30% to 80% with the use of antibiotic ($p = 0.035$) [36]. Likewise, administration of antibiotics was reported to increase the prevalence from 21% to 46% ($p = 0.003$) [27]. Additionally, type, duration, and route of administration of antibiotics also affect the incidence of VVC differently. This finding indicates that slight differences in a clinical setting of the study populations will have a great impact on the prevalence of VVC. These confounding factors should be considered while designing and/or comparing cross-sectional studies. Future research should consider the use of antimicrobials as a risk factor of VVC.

It is important to note that VVC occurs in an area where huge microbial diversity exists, i.e., vaginal microflora, the occurrence of this phenomenon is an essential cause of variation that must be considered. Indeed, VVC has been reported by some studies to be associated with a loss of *Lactobacilli* population [40,41] that are important beneficial microorganisms. Factors that impact vaginal microflora such as geographical diversity might also affect the susceptibility to VVC. These factors may cause variability in the prevalence of VVC. These findings are in line with data from Burkina Faso where a low prevalence was reported (22%) in comparison to Kenya and Uganda (42% and 45% respectively) [21]. Vaginal infections such as bacterial vaginosis are reportedly low in Burkina Faso and higher in Eastern regions of Africa [8]. Moreover, microbiome data analysis from related studies revealed that, pregnant women from Burkina Faso harbor a higher population of *Lactobacilli* in comparison to women from the eastern region, in which *Parvimonas* species Types 1 and 2, *Gemellaa saccharolytica*, *Mycoplasma hominis*, *Leptotrichia Sneathia*, *Eggerthella* species Type1, and vaginal *Megasphaera* species were the dominant vaginal microflora [42].

Beside the dramatic increase in the rate of deep and superficial fungal infection in the last two decades, several factors such as high cost, toxicity, and availability of limited antifungal agents have complicated the clinical management of VVC [43]. However, the emergence of resistant strains and the development of secondary resistance by species that were known to be sensitive is the main challenge for the researcher. Another notable observation was that high resistance was mainly attributed to the NCA [32]. It was observed that *C. albicans* was 0.61% resistant to clotrimazole, whereas *C. glabrata* and *C. famata* were found to be 50% and 36% resistant, respectively. *C. krusie* showed a resistance of 71.43% to fluconazole

[25]. This indicates a high resistance rate of NCA compare to *C. albicans*. In addition, the prevalence of NCA was found to be increasing compared to that of *C. albicans*. According to a report from Burkina-Faso where the prevalence of VVC was 22.71%, NCA accounted for 59.61% [21].

There have been many attempts to overcome the resistance by developing new compounds and/or potentiating the existing antifungal agents to increase the activity against MDR *Candida* species. An example is the oil macerates of North Sardinia plants that showed interesting activity against *C. krusei*, *C. glabrata*, and *C. parasilosis* [43]. In addition, *Ruta graveolens* essential oil has potent fungicidal activity against *C. tropicalis* and *C. albicans* that was suggested to be attributed to increased intracellular leakage of macromolecules. *Ruta graveolens* was also noted to have a synergistic effect with amphotericin B [44]. Another strategy focuses on increasing the efficacy of antifungal agents by inhibiting the ABC transport pump that is responsible for the efflux of the drug outside the cell. The P-glycoproteins which have been screened against different *Candida* species gave a satisfying result when combined with fluconazole [45]. Recently, the activity of four different Styryloquinoline compounds as ABC transport pump inhibitors and the role of the hydroxyl group attached to the quinolone moiety was investigated, the study reveals that the addition of unprotected hydroxyl group at carbon 4 and 8 in the quinolone moiety dramatically increased the antifungal activity against a wild and mutant strain of *Candida* species. Additionally, the same compound demonstrates a strong synergistic action when combined with fluconazole [46].

This study is accompanied by a few limitations which must be considered while interpreting the results. The studies included in this review do not entirely represent the whole of Africa. There is a dire need to conduct epidemiological estimation in the African regions where data is currently lacking. Furthermore, the impact of certain moderators was practically impossible due to the unavailability of some data (stages of pregnancy) and inconsistency of the data (age level of the participating pregnant women).

Conclusions

This study indicated a high prevalence of VVC in Eastern regions of Africa, followed by western and Northern regions. Moreover, a higher prevalence was reported in studies where identification techniques were able to screen most of *Candida species*. Variations across the studies were detected and the sources of

heterogeneity and potential reasons of such variations were explored. Further large-scale studies are needed in other regions of Africa for which epidemiological data on VVC is currently lacking.

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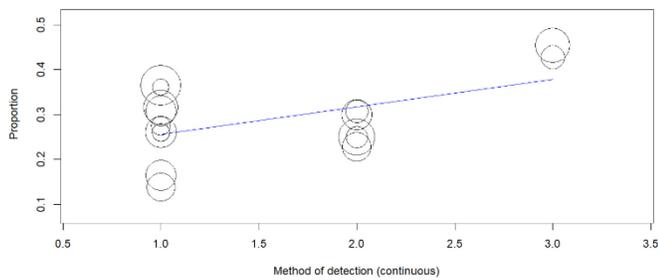
Annex – Supplementary Items

Supplementary Table 1. Methodological Quality Assessment as per Joanna Briggs Institute (JBI) Critical Appraisal Checklist for studies.

Study ID	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?
Okonkwo	Y	Y	Y	Y	NA	N	N	Y	NA
Donbraye	Y	N	N	Y	NA	N	Y	Y	NA
Ezeigbo	Y	Y	Y	Y	NA	N	N	N	NA
Adejo	Y	N	N	N	NA	N	Y	N	NA
Nurat	Y	N	N	Y	NA	Y	N	N	NA
Menza	Y	Y	Y	Y	NA	Y	N	Y	NA
Waikhom	Y	Y	Y	Y	NA	Y	Y	Y	NA
Tsega	Y	Y	Y	Y	NA	Y	Y	N	NA
Olugbenga	Y	N	N	Y	NA	N	Y	Y	NA
Mohamed	Y	Y	N	Y	NA	N	Y	Y	NA
Tchelougo	Y	Y	N	Y	NA	N	Y	Y	NA
Hericka	Y	Y	N	Y	NA	N	N	N	NA
Moses	Y	Y	N	Y	NA	N	N	N	NA
Mukasa	Y	Y	Y	Y	NA	Y	Y	N	NA
I. Sangaré	Y	Y	Y	Y	NA	Y	Y	Y	NA
Dennis	Y	Y	Y	Y	NA	Y	Y	Y	NA

Y: Yes; N: No; U: Unclear; NA: Not/Applicable

Supplementary Figure 1. Meta-regression of VVC based on Method of detection.



1: wet preparation and germ tube; 2: Chromogenic media; 3: ABI kits or chromogenic media + sugar assimilation.

Supplementary Figure 2. Meta-regression of VVC based on Sample size.

