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Copyright AJCEM 2026: <https://dx.doi.org/10.4314/ajcem.v27i4.4>**Review Article****Open Access****A scoping review of vulvovaginal candidiasis: Bridging the critical gaps toward precision diagnosis, treatment and recurrence prevention**^{*1,2}Okeke, P. C. U., ^{1,2}Nwafia, I. N., and ^{1,2}Emeribe, S. C.¹Department of Medical Microbiology, University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu, Nigeria.²Department of Medical Microbiology, College of Medicine, Faculty of Basic Clinical Sciences, University of Nigeria, Ituku-Ozalla, Enugu, Nigeria.*Correspondence to: princess.okeke@unn.edu.ng; Tel: +2348037117982; ORCID: <https://orcid.org/0009-0004-2522-2416>**Abstract:**

Vulvovaginal candidiasis (VVC) is among the most common mucosal fungal infections affecting women, with recurrent disease (RVVC) affecting an estimated 138 million women annually. Despite its frequency, major gaps remain in diagnosis, treatment and prevention. This scoping review identifies critical gaps across the VVC disease pathway and proposes a precision framework to transform management from episodic treatment toward prediction, targeted therapy and durable recurrence prevention. A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and African Journals Online using keywords related to VVC, antifungal resistance, microbiome, and treatment. Studies published between 1990 and 2026 addressing epidemiological, microbiological, immunological, diagnostic, therapeutic or translational aspects of VVC were included. Data were synthesized thematically. Major gaps identified include: the true burden of microbiologically confirmed symptomatic disease remains uncertain; symptoms are nonspecific while *Candida* colonization may occur without disease, creating a fundamental diagnostic problem; the biological mechanisms determining why some women remain asymptomatically colonized whereas others develop symptomatic or recurrent disease are incompletely understood; the vaginal microbiome and mycobiome are emerging as important determinants of disease phenotype, but most studies remain cross-sectional; *Candida* biofilms, strain-level variation and host inflammatory responses may contribute to persistence and recurrence, but their clinical significance requires better longitudinal investigation; and newer agents such as oteseconazole and ibrexafungerp have expanded therapeutic options, yet questions remain concerning comparative effectiveness, resistance, cost, access and long-term ecological effects. A precision framework integrating clinical phenotype, *Candida* biology, host susceptibility, microbial ecology and treatment history could transform VVC management. Priority areas include standardized disease definitions, longitudinal host-microbe studies, species- and strain-level characterization, antifungal susceptibility surveillance, microbiome and mycobiome research, patient-centred outcomes, and implementation studies in underrepresented populations.

Keywords: Recurrent vulvovaginal candidiasis; vaginal microbiome; mycobiome; antifungal resistance; precision medicine; antifungal stewardship.

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Copyright 2026 AJCEM Open Access. This article is licensed and distributed under the terms of the Creative Commons Attribution 4.0 International License <http://creativecommons.org/licenses/by/4.0/>, which permits unrestricted use, distribution and reproduction in any medium, provided credit is given to the original author(s) and the source. Editor-in-Chief: Prof. S. S. Taiwo**Une revue de portée de la candidose vulvovaginale: Comblar les lacunes critiques vers un diagnostic, un traitement et une prévention des récides de précision**^{*1,2}Okeke, P. C. U., ^{1,2}Nwafia, I. N., et ^{1,2}Emeribe, S. C.¹Département de Microbiologie Médicale, Hôpital Universitaire de l'Université du Nigeria (UNTH), Ituku-Ozalla, Enugu, Nigéria

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Résumé:

La candidose vulvovaginale (CVV) est l'une des infections fongiques muqueuses les plus courantes touchant les femmes, la forme récurrente (CVVR) touchant environ 138 millions de femmes chaque année dans le monde. Malgré sa fréquence, d'importantes lacunes subsistent dans le diagnostic, le traitement et la prévention. Cette revue de portée identifie les lacunes critiques tout au long du parcours de la maladie CVV et propose un cadre de médecine de précision pour faire évoluer la prise en charge d'un traitement épisodique vers la prédiction, un traitement ciblé et une prévention durable des récurrences. Une recherche documentaire exhaustive a été menée dans PubMed, Scopus, Web of Science et African Journals Online à l'aide de mots-clés relatifs à la CVV, à la résistance antifongique, au microbiome et au traitement. Les études publiées entre 1990 et 2026 portant sur les aspects épidémiologiques, microbiologiques, immunologiques, diagnostiques, thérapeutiques ou translationnels de la CVV ont été incluses. Les données ont été synthétisées de manière thématique. Les principales lacunes identifiées comprennent : le fardeau réel de la maladie symptomatique confirmée sur le plan microbiologique demeure incertain ; les symptômes sont non spécifiques alors que la colonisation par *Candida* peut survenir sans maladie, ce qui crée un problème diagnostique fondamental ; les mécanismes biologiques déterminant pourquoi certaines femmes demeurent colonisées de manière asymptomatique alors que d'autres développent une maladie symptomatique ou récurrente sont mal compris ; le microbiome et le mycobiome vaginaux apparaissent comme des déterminants importants du phénotype de la maladie, mais la plupart des études demeurent transversales ; les biofilms de *Candida*, la variation au niveau des souches et les réponses inflammatoires de l'hôte pourraient contribuer à la persistance et à la récurrence, mais leur signification clinique nécessite une meilleure investigation longitudinale ; et de nouveaux agents tels que l'otéséconazole et l'ibrexafungerp ont élargi les options thérapeutiques, mais des questions demeurent concernant leur efficacité comparative, la résistance, le coût, l'accès et les effets écologiques à long terme. Un cadre de précision intégrant le phénotype clinique, la biologie de *Candida*, la susceptibilité de l'hôte, l'écologie microbienne et les antécédents thérapeutiques pourrait transformer la prise en charge de la CVV. Les domaines prioritaires comprennent la normalisation des définitions de la maladie, les études longitudinales hôte-microbe, la caractérisation au niveau des espèces et des souches, la surveillance de la sensibilité antifongique, la recherche sur le microbiome et le mycobiome, les résultats centrés sur la patiente, et les études de mise en œuvre dans les populations sous-représentées.

Mots-clés: Candidose vulvovaginale récurrente; Microbiome vaginal; Mycobiome; Résistance antifongique; Médecine de précision; Gestion raisonnée des antifongiques

Introduction:

Vulvovaginal candidiasis (VVC) is a common infection of the female lower genital tract caused predominantly by *Candida* species. Approximately 75% of women are estimated to experience at least one episode during their lifetime, although precise estimates vary considerably according to population, case definition and diagnostic methodology (1-4). The global burden is substantial. A recent global systematic review and meta-analysis included 114 studies and more than 1.2 million women, demonstrating the widespread occurrence of VVC while also highlighting substantial heterogeneity between studies (5). In sub-Saharan Africa, a systematic review of 41 studies involving 15,723 participants estimated a pooled prevalence of 33%, with *Candida albicans* accounting for 71.7% of identified isolates and non-*albicans Candida* (NAC) species accounting for approximately 24% (6).

Recurrent VVC constitutes a particularly challenging phenotype. Denning et al., (7) estimated that approximately 138 million women experience RVVC annually, with the burden pro-

jected to increase as the global female population grows. Other epidemiological studies have demonstrated considerable variation in the estimated probability of recurrent disease following an initial episode (8,9). Yet the field faces an important paradox. VVC is common and familiar to clinicians, but some of its most fundamental questions remain unanswered. Why does *Candida* colonization produce symptoms in some women but not others? Why do some women develop repeated episodes despite apparently appropriate therapy? Why does suppressive treatment control recurrence while failing to provide durable cure in many women? Why do some women experience persistent symptoms despite negative or inconclusive microbiological findings? Why is antifungal resistance becoming an increasing concern in a disease that has historically been highly responsive to azole therapy?

These questions indicate that VVC should no longer be considered simply a localized fungal infection. Contemporary evidence supports a multifactorial model involving *Candida* biology, host response, vaginal microbial ecology, environmental exposures and treatment

history (10-15). This review therefore focuses not merely on what is known about VVC, but on unresolved gaps in the epidemiology, diagnosis, and treatment of VVC, and the research required to bridge these gaps (Table 1).

Methodology:

This scoping review was conducted following the methodological framework outlined by Arksey and O'Malley (16) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (17). The review aimed to map the current evidence on vulvovaginal candidiasis and identify critical gaps in epidemiology, diagnosis, treatment and recurrence prevention.

Research question:

What are the critical gaps in the understanding, diagnosis, treatment and prevention of vulvovaginal candidiasis, and what research is needed to bridge these gaps?

Search strategy:

A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and African Journals Online (AJOL) using combinations of the following keywords: "vulvovaginal candidiasis", "recurrent vulvovaginal candidiasis", "*Candida albicans*", "non-*albicans Candida*", "antifungal resistance", "vaginal microbiome", "mycobiome", "biofilm", "diagnosis", "treatment", "oteseconazole", "ibrexafungerp", "fluconazole", "probiotics", "Africa", and "sub-Saharan Africa". The search was limited to studies published in English language between 1990 and 2026.

Inclusion criteria:

Studies were included if they addressed epidemiological, microbiological, immunological, diagnostic, therapeutic or translational aspects of vulvovaginal candidiasis. Both original research and review articles were considered. Studies were excluded if they focused solely on systemic candidiasis, non-vaginal forms of candidiasis, or did not address VVC.

Table 1: Important research gaps on vulvovaginal candidiasis and future research needs

Critical gap	Current challenge	Research needed
Disease definition	Heterogeneous case definitions	Standardized clinical-microbiological criteria
Colonization vs disease	<i>Candida</i> detection may not indicate causation	Biomarkers of pathogenic infection
RVVC phenotype	Recurrence treated as one condition	Biological phenotyping
Host susceptibility	Predictors poorly understood	Prospective host-factor studies
<i>Candida</i> strain biology	Species-level data dominate	Longitudinal genomic studies
Microbiome	Mostly cross-sectional	Longitudinal bacteriome studies
Mycobiome	Understudied	Integrated fungal community profiling
Biofilms	Clinical relevance uncertain	In vivo/clinical correlation
Resistance	Surveillance incomplete	Standardized susceptibility surveillance
NAC VVC	Limited comparative evidence	Species-specific clinical trials
Treatment	Suppression ≠ cure	Durable recurrence-prevention strategies
New antifungals	Limited comparative data	Head-to-head effectiveness studies
Probiotics	Heterogeneous evidence	Strain-specific trials
Patient outcomes	Underrepresented	Quality-of-life/sexual-health endpoints
Africa/LMICs	Major evidence gaps	Multicentre longitudinal studies
Cost	Limited implementation evidence	Health-economic studies

NAC=Non-*albicans Candida*; VVC=Vulvovaginal candidiasis; RVVC= Recurrent vulvovaginal candidiasis; LMICs=Low-and-middle-income countries

Study selection:

All identified records were imported into EndNote and duplicates were removed. Two reviewers independently screened titles and abstracts against the inclusion criteria. Full texts of potentially relevant articles were then retrieved and assessed for eligibility by the same two reviewers. Disagreements were resolved through consensus or by consultation with a third reviewer. The study selection process is documented in a PRISMA-ScR flow diagram in Fig 1 (18).

Data extraction and synthesis:

A standardized data-charting form was developed to extract key information from included studies, including author, year, country, study design, population, VVC definition, species identified, antifungal susceptibility, treatment outcomes, microbiome findings, and identified gaps. Data were synthesized thematically, organized by key domains including epidemiology, pathogenesis, diagnosis, treatment, resis-

tance, microbiome, host factors and research gaps.

Results

A total of 1,570 records were identified from four databases (PubMed, Scopus, Web of Science, and African Journals Online). An additional 35 records were identified through citation searching, bringing the total to 1,605 records. After removing 425 duplicates, 1,145 records were screened by title and abstract. Of these, 895 records were excluded as not relevant to VVC or outside the scope of the review. The remaining 250 full-text articles were assessed for eligibility, of which 128 were excluded for various reasons (not focused on VVC, no gap identification, duplicate/overlapping data, full text not available, or not in English). Ultimately, 122 studies were included in the final scoping review.

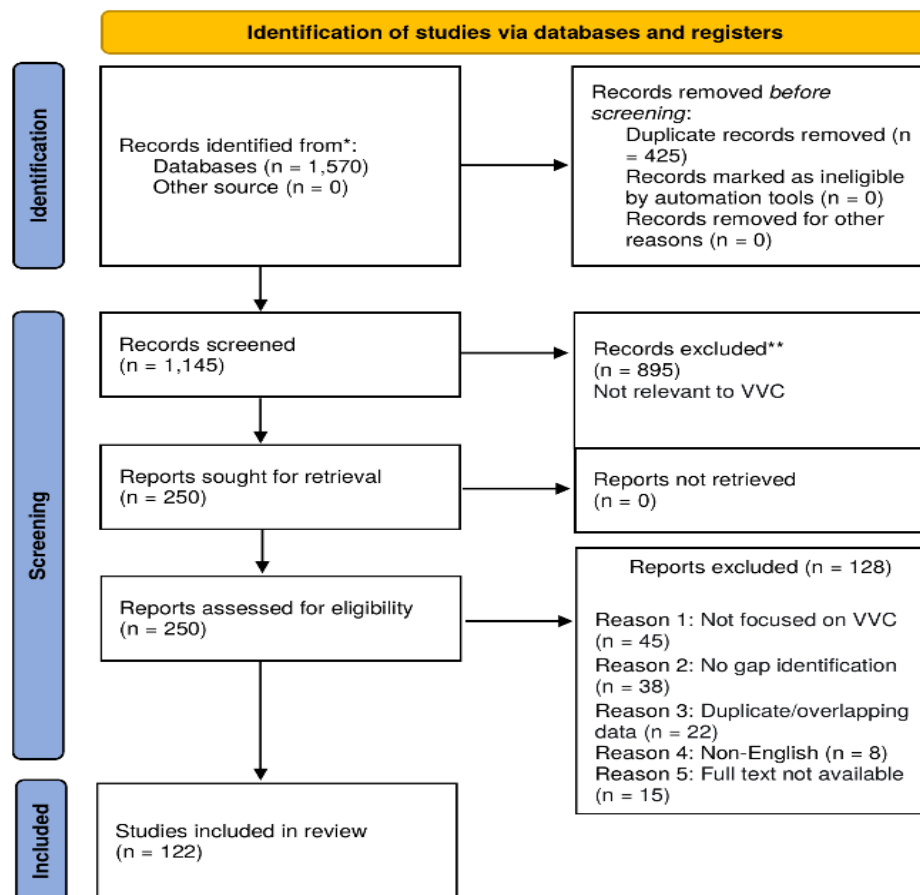


Fig 1: PRISMA-ScR flow diagram illustrating the study selection process for the scoping review

VVC evidence and critical gaps:

Epidemiology: A common disease with an uncertain denominator:

VVC is widely distributed across geographical and socioeconomic settings. *Candida albicans* remains the dominant species, but the relative contribution of NAC species varies considerably between populations (19,20). The apparent prevalence of VVC is strongly influenced by how the disease is defined. Studies may identify women with VVC according to self-reported symptoms, clinician diagnosis, microscopy, culture, molecular detection, positive *Candida* culture with symptoms, or positive *Candida* culture regardless of symptoms. These approaches do not identify the same population. The challenge is illustrated by the distinction between *Candida* colonization and symptomatic infection. *Candida* may be present in the vagina without causing disease, and therefore detection alone cannot establish causation (1,2). The 2026 global meta-analysis provides an important contemporary estimate of disease burden, but the substantial heterogeneity across studies demonstrates that the field still lacks a universally standardized epidemiological framework (5).

The critical gap here is the fact that the true burden of symptomatic, microbiologically confirmed VVC remains uncertain. Future epidemiological studies should clearly distinguish: (i) *Candida* colonization; (ii) symptomatic VVC; (iii) severe VVC; (iv) recurrent VVC; (v) persistent/refractory VVC; and (vi) non-infectious vulvovaginal conditions. Without this distinction, prevalence estimates remain difficult to compare and may substantially overestimate disease.

Recurrent VVC: The major unresolved clinical challenge:

RVVC is generally defined clinically as repeated symptomatic episodes over a defined period. The CDC currently uses three or more symptomatic episodes within one year, whereas older studies and some international literatures have used four or more episodes (1,8). This apparent simple difference illustrates a larger challenge, as definitions have not always been harmonized across studies. The global burden of RVVC is nevertheless substantial. Denning et al., (7) estimated approximately 138 million cases annually worldwide, with the highest prevalence in women aged 25--34 years.

RVVC is not merely repeated uncomplicated VVC (21,22), women with recurrent disease may experience: repeated clinical consultations, repeated laboratory testing, repeated antifungal exposure, treatment failure, anxiety

concerning recurrence, sexual difficulties, disruption of work and daily activities, and substantial financial burden. Quality-of-life studies on RVVC demonstrate impairment across physical, psychological, social and sexual domains (23).

The critical gap here is that RVVC is insufficiently phenotyped. The label RVVC probably encompasses several biologically distinct conditions: persistent infection→relapse→reinfection→recurrent susceptibility→non-infectious mimics. Treating all of these as a single disorder limits therapeutic progress.

Candida colonization versus symptomatic disease:

One of the most important diagnostic challenges in VVC is that *Candida* can be a commensal organism. The CDC notes that approximately 10-20% of women may harbour *Candida* or other yeasts vaginally without requiring treatment (1). Therefore, a positive *Candida* test does not automatically establish *Candida* as the cause of symptoms. This becomes particularly important with highly sensitive molecular tests.

A molecular assay may detect *Candida* DNA in a woman whose symptoms are caused by; bacterial vaginosis, trichomoniasis, vulvar dermatitis, lichen sclerosus, desquamative inflammatory vaginitis, genitourinary syndrome of menopause, irritant or allergic vulvitis or another condition (24). Consequently, increased analytical sensitivity is not synonymous with increased clinical specificity. The diagnosis of VVC should instead integrate symptoms + signs + laboratory evidence + species + clinical context.

The critical gap here is that there is no universally accepted biomarker that reliably distinguishes pathogenic *Candida* from asymptomatic colonization. This is one of the most important opportunities for future research. Potential biomarkers could include fungal burden, transcriptional activity, virulence-associated markers, host inflammatory signatures, metabolomic profiles, and microbial community signatures.

Candida species: Beyond *Candida albicans*:

Candida albicans remains the dominant cause of VVC (19), However, NAC species are clinically important, particularly in recurrent, complicated and treatment-refractory disease (20,25). Common NAC species include *Candida glabrata* (*Nakaseomyces glabratus*), *Candida tropicalis*, *Candida krusei* (*Pichia kudriavzevii*), and *Candida parapsilosis*. A systematic review in sub-Saharan Africa found *C. glabrata* (*N. glabratus*), *C. krusei* (*P. kudriavzevii*) and *C. tropi-*

calis among the leading NAC species (6). *Candida glabrata* (*N. glabratus*) is particularly challenging because it does not form the pseudo-hyphae or hyphae characteristic of *C. albicans* and may therefore be missed by conventional microscopy (1). NAC species may also have reduced susceptibility to commonly used azoles, complicating treatment (20,25). However, the presence of a NAC does not automatically establish causation. Some women with positive cultures are minimally symptomatic or asymptomatic (1,25).

The critical gap is that species identification is increasingly necessary, although species identification alone is insufficient. The future direction in the identification of agents of VVC should be species identification→susceptibility→strain→clinical phenotype.

Risk factors and host susceptibility to VVC:

VVC has been associated with pregnancy, hormonal exposure, diabetes, antibiotic exposure, immunosuppression and other host and behavioural factors (19,26,27). However, these associations do not explain the majority of recurrent disease. The CDC notes that although RVVC can be secondary to frequent antibiotic use, diabetes or other host factors, most women with RVVC have no obvious predisposing condition (1). This is an important observation as it suggests that the conventional risk-factor model for VVC is incomplete. Host susceptibility may involve: epithelial barrier characteristics, innate immune responses, genetic susceptibility, inflammatory signaling, hormonal regulation, metabolic factors, and microbiome composition (10,28, 29,30,31).

The critical gap here is that we do not yet have a clinically useful model for predicting which women will progress from colonization or acute VVC to RVVC. Prospective cohorts could address this by identifying predictors before recurrence occurs.

Host immunity and inflammation:

VVC is unusual among *Candida* infections because it commonly affects immunocompetent women. The pathogenesis therefore cannot be explained by systemic immune deficiency (10,28,32). Studies of recurrent disease have demonstrated complex host immune responses involving local and systemic cellular immunity (29,30,31,33). Rare genetic human deficiencies in dectin-1 and caspase recruitment domain family member 9 (CARD9) signaling, which cause severe mucocutaneous candidiasis, illustrate how central innate pattern recognition is to antifungal host defense more broadly (34,35).

More recent work has emphasized the role of the vaginal epithelium as an active immunological interface. The epithelial response to *Candida* may involve pattern-recognition receptors binding, epithelial signaling pathways, neutrophil recruitment, inflammatory cytokines production, and tissue inflammation (10,28,29, 30,31). The toxin, candidalysin, secreted by hyphal forms of *Candida* is a well-characterized trigger of this epithelial danger response, activating NLRP3 inflammasome signaling and driving neutrophil recruitment at the vaginal mucosa (36,37). Importantly, inflammation may contribute substantially to symptoms. This creates a potential paradox, whereby the host response that attempts to control *Candida* may itself contribute to symptomatic disease.

The critical gap here is that the relationship between fungal burden and inflammatory severity remains poorly defined. Two women with similar *Candida* loads may experience very different clinical disease. Future studies should therefore measure; *Candida* quantity + *Candida* phenotype + host inflammatory response.

The vaginal microbiome:

The vaginal microbiome has become one of the most important areas of VVC research. *Lactobacillus*-dominated communities have traditionally been associated with vaginal health, but the relationship is more complex than a simple "*Lactobacillus* present versus absent" model (12,13,14,15,38,39,40). Studies of RVVC have identified differences in bacterial community composition, including alterations involving *Lactobacillus* species (13,14).

A study of women with RVVC identified reduced representation of some health-associated *Lactobacillus* species, including *Lactobacillus crispatus*, alongside increased *Lactobacillus iners*, and demonstrated interactions between *Lactobacillus* and *Candida* biofilms (14). Vaginal lactobacilli, notably *L. crispatus*, can directly inhibit *Candida* growth and hyphal transformation in vitro, providing a plausible mechanism for this association (41). Other studies have demonstrated considerable interindividual variability rather than a single characteristic "RVVC microbiome" (15).

The critical gap here is that there is no single microbiome signature that defines RVVC. This is important because it challenges the simplistic proposition that restoring *Lactobacillus* alone will necessarily cure recurrent disease.

Mycobiome: The missing fungal ecosystem:

Most microbiome research has focused on bacteria. However, the vaginal fungal community, the mycobiome, may also influence

disease. *Candida* exists within a broader microbial ecosystem and interacts with bacterial organisms, epithelial cells and host immune responses (12-15,42). One mycobiome study found that the identity of the infecting *Candida* species was itself associated with a characteristic bacterial community structure, suggesting the mycobiome and bacteriome shape one another rather than existing independently (43). This raises several questions; Does the composition of the vaginal mycobiome predict disease? Do non-*albicans* *Candida* species interact with *C. albicans*? Does repeated antifungal exposure alter fungal community structure? Does mycobiome disruption predispose to recurrence? These questions remain inadequately answered.

The critical gap here is the fact that VVC research has not yet fully integrated the bacterial microbiome and fungal mycobiome. Future studies should examine the bacteriome and mycobiome simultaneously, rather than treating *Candida* as an isolated pathogen.

Causality: Does dysbiosis cause VVC or result from it?

This is perhaps the most important conceptual problem in microbiome research. Most existing studies are cross-sectional. Therefore, when a woman with RVVC has an altered microbiome, we cannot necessarily determine whether dysbiosis → *Candida* overgrowth → VVC or *Candida* disease → inflammation → treatment → microbiome disruption. Repeated antifungal and antibiotic exposure may itself alter microbial communities.

The critical gap identified here is the absence of longitudinal microbiome studies, which are urgently required. The ideal study design should obtain samples before symptoms → during acute VVC → after treatment → during remission → at recurrence. This would allow researchers to identify microbial changes that precede rather than simply accompany disease.

Biofilms and persistence of *Candida*:

Candida biofilms are increasingly recognized as potential contributors to persistence and reduced antifungal susceptibility (44-47). Clinical isolates from women with recurrent disease show heterogeneous biofilm-forming capacity that correlates with reduced fluconazole sensitivity, and direct microscopic evidence has now demonstrated *Candida* biofilms on human vaginal epithelium itself, with tolerance to fluconazole at clinically relevant concentrations (48,49). A biofilm-competent mouse model further shows that biofilm formation generates antifungal-tolerant persister cells at higher fre-

quency than planktonic growth (50).

Biofilms can alter fungal physiology, gene expression and antifungal response. A dynamic interkingdom model has also been proposed in which *Candida* and *Lactobacillus* interact within the vaginal environment (14). However, this evidence is not unanimous. One histologic study of vaginal biopsies found predominantly invasive, polymicrobial disease without clear biofilm structures, and cautioned against over-interpreting biofilm biology as the dominant mechanism of recurrence (51). This disagreement is itself informative, and much of the biofilm evidence overall remains derived from laboratory or limited clinical studies, a tension an earlier editorial on vaginal biofilms had already anticipated (52).

The critical gap here is the fact that the clinical importance of vaginal *Candida* biofilms remains uncertain. Future studies should determine whether biofilm-associated phenotypes predict treatment failure, recurrence, antifungal resistance, and persistence of particular *Candida* strains.

Persistence, relapse or reinfection?

When VVC recurs, clinicians often assume that *Candida* has returned. But returned *Candida* does not necessarily mean the same *Candida*. Recurrence could represent: (i) persistence of the original strain; (ii) evolution of the original strain; (iii) reinfection with a new strain; (iv) recolonization from another body site; or (v) recurrence of symptoms from a non-*Candida* condition. Traditional culture cannot adequately distinguish these possibilities. Early karyotyping work suggested that recurrence often reflects persistence and microevolution of a single strain rather than reinfection, but this was based on a small number of isolates and predates modern whole-genome approaches (53).

The critical gap is that strain-level longitudinal studies are lacking. Whole-genome sequencing of serial isolates could determine whether recurrent episodes arise from one persistent lineage or multiple independent acquisition events. This could fundamentally alter our approach to RVVC.

Diagnosis of VVC: Where the current model breaks down:

Clinical symptoms of VVC are common but non-specific. Pruritus, soreness, dyspareunia, external dysuria and abnormal discharge may occur with several vulvovaginal disorders (1). Microscopy remains useful, particularly because it can provide rapid evidence of yeast and inflammatory findings. Culture remains important in complicated disease because it permits

species identification and, where appropriate, susceptibility testing (1,54).

Molecular assays offer greater analytical sensitivity but create a new interpretive challenge: detection is not equivalent to causation. Head-to-head comparison of nucleic acid amplification testing against culture, Gram stain, and microscopy confirms substantially higher sensitivity for molecular detection, which sharpens rather than resolves this interpretive problem (55). For complicated VVC, current guidance recommends culture or PCR to confirm the diagnosis and identify NAC species (1).

The critical gap here is the lack of diagnostic algorithms that distinguish analytical detection from clinical disease, which are needed in this field. A future ideal diagnostic test should answer the following questions: Is *Candida* present in suspected VVC? Is the *Candida* active? Is the *Candida* pathogenic? Which species of *Candida* is involved? and is the *Candida* resistant to antifungal agents?

Antifungal resistance:

Azole resistance is becoming an increasingly important concern, particularly in recurrent or refractory disease (1,6,56,57). Resistance arises through convergent mechanisms including target-site mutation, efflux pump overexpression, and intrinsic reduced susceptibility in some non-*albicans* species, as documented for *C. glabrata* (*N. glabratus*) surveillance isolates (58,59). Standardized susceptibility testing itself has methodological gaps relevant to VVC. Specifically, reference broth microdilution protocols are performed at neutral pH, whereas the vaginal environment is acidic, and susceptibility results can differ substantially under vaginally-relevant pH conditions (60,61).

Literature from sub-Saharan African shows limited available susceptibility data on *Candida*. In the African meta-analysis, reported fluconazole resistance among *C. albicans* isolates varied substantially between countries, while susceptibility testing was available from only a subset of studies (6). The challenge is compounded by differences in susceptibility methods, breakpoints, species identification, previous antifungal exposure, and study populations.

The critical gap here is the fact that the global burden of clinically meaningful azole resistance in VVC is poorly quantified. Surveillance should therefore integrate antifungal exposure + species + susceptibility (minimum inhibitory concentration) + resistance mechanism + treatment outcome. Laboratory resistance without clinical correlation is insufficient. Emerging multi drug-resistant species outside the traditional NAC spectrum, such as *Candida auris*, under-

score why resistance surveillance cannot remain static (62,63).

Antifungal stewardship:

Repeated empirical treatment can produce a cycle of symptoms → empirical antifungal → temporary improvement → recurrence → repeat empirical antifungal. The challenge is that persistent symptoms may not represent persistent *Candida*. The CDC recommends clinical reassessment for women whose symptoms persist after treatment or recur shortly after therapy (1). This is particularly important because unnecessary treatment may expose patients to adverse effects, increase cost, delay diagnosis of other vulvovaginal disorders; and contribute to antifungal selection pressure.

Antifungal stewardship should therefore become a component of VVC care, following the general antifungal stewardship principles already established for invasive candidiasis and other fungal disease priorities (64,65).

Treatment of uncomplicated and recurrent VVC:

Short-course topical or oral azole regimens remain highly effective for uncomplicated VVC (1). The major therapeutic challenge is therefore not that current drugs are ineffective against ordinary *C. albicans* VVC. The greater challenge is recurrence, complicated disease, NAC species and resistance. This distinction is important because it directs research toward the patients who remain underserved rather than simply developing new drugs for uncomplicated disease.

Suppressive fluconazole remains a major treatment strategy for RVVC. The landmark randomized trial by Sobel et al., (66) demonstrated that weekly fluconazole substantially reduced symptomatic recurrence during six months of maintenance therapy. At six months, 90.8% of women receiving fluconazole remained disease-free compared with 35.9% receiving placebo. However, after treatment was stopped, recurrence increased, demonstrating that suppression is not equivalent to durable cure (66). This finding remains central to the modern understanding of RVVC. The fundamental therapeutic challenge is therefore how to prevent recurrence after antifungal suppression ends.

Newer antifungal agents:

The therapeutic landscape of fungal infections has changed considerably, with the introduction of newer antifungal agents such as oteseconazole and ibrexafungerp.

Oteseconazole is a novel oral azole designed to selectively inhibit fungal CYP51. Phase 3 studies demonstrated substantial reduction in RVVC recurrence compared with placebo (67,

68). This built on earlier phase 2 dose-ranging and acute-VVC studies of the same compound (then designated VT-1161) that established proof of concept for once-weekly oral CYP51 inhibition (69,70). A subsequent randomized trial comparing oteseconazole directly with fluconazole in severe VVC, and a formal regulatory approval review, further contextualize its place in the therapeutic landscape (71,72).

In the VIOLET trials, oteseconazole demonstrated markedly lower recurrence rates through follow-up than placebo (68). This represents an important advance. However, several questions remain unanswered: Which patients should receive oteseconazole? Is it superior to prolonged fluconazole maintenance in real-world practice? What are the long-term resistance implications? How accessible is it in low-resource settings? What is its cost-effectiveness? and what is its impact on the vaginal microbiome?

Ibrexafungerp is an oral triterpenoid glucan synthase inhibitor that provides a non-azole mechanism of action (73). Two pivotal phase 3 trials in acute VVC (VANISH 303 and VANISH 306) established its efficacy against placebo prior to the recurrence-prevention data from CANDLE (74,75). It demonstrated efficacy in VVC, and subsequent evidence has expanded interest in its role in recurrent disease (76). The CANDLE phase 3 study evaluated monthly oral ibrexafungerp for prevention of recurrent VVC, providing important evidence for a non-azole maintenance strategy (2). This is particularly relevant in an era of increasing concern about azole resistance. The critical gap here is the lack of comparative effectiveness research, which is needed. The key question is no longer simply "Does the new drug work?" It is "Which drug works best for which phenotype, at what cost, with what long-term ecological and resistance consequences?"

Non-*albicans* *Candida*: The persistent therapeutic challenge:

VVC caused by NAC is a particularly difficult therapeutic challenge because some species have reduced susceptibility to azoles and because the clinical significance of a positive culture may be uncertain (20,25). The CDC specifically emphasizes the need to exclude other causes of symptoms when NAC species are detected because some women may have minimal or no symptoms (1). This is a critical point. The treatment challenge is therefore not simply antifungal resistance. It is also diagnostic uncertainty + species biology + limited comparative clinical evidence.

The critical gap here is the fact that evi-

dence-based species-specific treatment algorithms remain inadequate for NAC VVC. There is a need for randomized studies stratified by *Candida* species.

Probiotics and microbiome-directed therapy:

The idea of restoring a protective vaginal microbiome is attractive (77). However, clinical evidence has not consistently demonstrated that commercially available *Lactobacillus* preparations prevent VVC. A Cochrane systematic review of probiotics for VVC in non-pregnant women likewise found the evidence base too heterogeneous to support routine use (78). A randomized controlled trial by Pirodda et al., (79) found that oral or vaginal *Lactobacillus* preparations did not prevent post-antibiotic vulvovaginal candidiasis. This illustrates an important principle that biological plausibility does not equal clinical efficacy.

Different *Lactobacillus* strains have different properties, and probiotic preparations should not be considered interchangeable, a point developed at length in reviews of *Lactobacillus* derivatives for vaginal health (80). *In vitro* studies showed that specific strains such as *L. rhamnosus* GR-1 and *L. reuteri* RC-14 have measurable antifungal activity against *C. glabrata* (*N. glabratus*) isolates, while others show no such effect, underscoring that strain-level, not genus-level, evidence should guide selection (81,82).

The critical gap is the fact that microbiome therapy requires phenotype-specific clinical trials rather than generic probiotic studies. Future research should focus on investigating strain-specific interventions, live biotherapeutic products, vaginal rather than oral delivery, metabolite-based therapies, microbiome restoration, and bacteriophage or ecological approaches where appropriate.

Patient-centred outcomes:

VVC research has historically emphasized microbiological cure. Yet for women, the most important outcomes may be symptom resolution, absence of recurrence, sexual health, psychological wellbeing, ability to work, treatment convenience, and affordability. A study of women with RVVC demonstrated substantial impairment in physical, psychological, social and sexual domains (23).

The critical gap to fill here is the need for clinical trials to measure what outcome matters to patients. A woman who has a negative culture but persistent severe symptoms, is not necessarily experiencing therapeutic success. Likewise, a woman with microbiological clearance but major treatment-related toxicity may not

regard therapy as successful. Therefore, future trials should include validated patient-reported outcome measures.

Africa and other underrepresented populations:

The evidence base for VVC is geographically uneven. The systematic review of sub-Saharan African showed a substantial burden of VVC disease but also emphasized the limited availability of susceptibility data (6). Hospital-based studies from individual countries illustrate this unevenness directly: cohorts from Nigeria, Ethiopia, and Ghana each report differing species distributions and, in the Ghanaian case, direct evidence of antifungal-resistant *C. albicans* in recurrent disease, while a genome-wide association study from Kenya represents one of the only attempts to date to extend host-genetic susceptibility research beyond populations of European ancestry (83-86).

Immunological studies in African cohorts, including work characterizing cervical T_{H17}-like cell activation in asymptomatically colonized South African adolescents, further suggest that host-immune correlates of colonization versus disease may not be uniform across populations. An open question in a recent scoping review of immune responses in African women with vaginal candidiasis makes this explicit (87,88).

The critical gap here is the evidence-equity challenge in VVC research. The women most affected by diagnostic and therapeutic inequities may be the least represented in the evidence used to formulate guidelines. This creates an important research opportunity. African studies should move beyond repeated single-centre prevalence surveys toward multicentre surveillance, standardized diagnostics, species-level characterization, antifungal susceptibility testing, longitudinal RVVC cohort studies, microbiome/mycobiome studies, cost-effectiveness research, and implementation science. This is especially important because treatment strategies developed in high-income countries may not be directly transferable to settings where diagnostic facilities are limited, molecular assays are expensive, antifungal susceptibility testing is unavailable, newer antifungals may be inaccessible, and over-the-counter treatment is common.

Toward a precision model of VVC:

We propose that future VVC research should conceptualize disease as the interaction of five domains:

Domain 1: *Candida* species, strain, fungal burden, virulence, biofilm phenotype, and antifungal susceptibility.

Domain 2: Host genetics, immunity, ep-

ithelial biology, hormonal state, and diabetes/metabolic status.

Domain 3: Microbial ecosystem: bacterial microbiome, mycobiome, microbial metabolites, and interkingdom interactions.

Domain 4: Environment and treatment: antibiotics, antifungal exposure, hormonal exposure, sexual and reproductive factors, and healthcare access.

Domain 5: Clinical phenotype: asymptomatic colonization, acute VVC, severe VVC, RVVC, and refractory disease.

These domains interact dynamically: Colonization → ecological/host perturbation → symptomatic disease → treatment → ecological change → remission or persistence → recurrence. This model will provide a more useful framework for future research than treating *Candida* as an isolated pathogen.

What the ideal future study should look like:

A high-quality prospective RVVC cohort should recruit women before recurrence and follow them longitudinally. At baseline, assessment should include detailed clinical phenotype, metabolic assessment, medication history, antibiotic exposure, reproductive/hormonal history, and quality-of-life assessment. At each VVC episode, assessment should include microscopy, culture, species identification, susceptibility testing, *Candida* burden estimation, symptom severity, and inflammatory markers assessment. For selected cohorts, assessment should include bacterial metagenomics, mycobiome sequencing, metabolomics, host transcriptomics, and whole-genome sequencing of sequential *Candida* isolates.

Samples should be collected before disease → during disease → after treatment → during remission → at recurrence. Such studies could finally answer whether microbial or host changes precede recurrence or merely accompany it.

From association to prediction:

The ultimate goal of VVC research should be prediction. A clinically useful model might eventually estimate probability of symptomatic VVC, followed by probability of recurrence, followed by probability of treatment failure, and ultimately optimal treatment for the patient's biological phenotype. Such a model would represent a genuine transition toward precision medicine.

Antifungal stewardship in the precision era:

New antifungal agents should not simply replace older agents sequentially. The field should adopt an antifungal stewardship framework based on: (i) confirming the diagnosis; (ii)

identifying species when disease is complicated; (iii) assessing susceptibility when indicated; (iv) distinguishing recurrence from persistent non-infectious symptoms; (v) minimizing unnecessary exposure; and (vi) selecting newer agents for appropriate phenotypes. This is particularly important because novel agents may be more expensive and because their widespread use could eventually create new resistance pressures.

An eight-point priority research agenda:

We propose eight immediate priorities for VVC research:

Priority 1: Standardize definitions: Develop internationally accepted definitions for VVC, RVVC, refractory VVC, microbiological cure, clinical cure, and recurrence.

Priority 2: Develop better diagnostics: Move from *Candida* detection toward determination of *Candida*-associated disease.

Priority 3: Establish resistance surveillance: Create standardized international VVC antifungal susceptibility surveillance systems.

Priority 4: Build longitudinal cohorts: Follow women from colonization through disease and recurrence.

Priority 5: Integrate microbiome and mycobiome research: Study bacterial and fungal ecosystems together.

Priority 6: Investigate strain persistence: Use genomic methods to distinguish relapse from reinfection.

Priority 7: Compare therapeutic strategies: Conduct head-to-head trials of fluconazole, oteseconazole, ibrexafungerp and other emerging therapies in clearly defined phenotypes.

Priority 8: Address global inequity: Build research capacity and generate high-quality evidence from Africa, Asia, Latin America and other underrepresented populations.

Discussion

VVC has traditionally been approached as a straightforward infection: identify *Candida* and give an antifungal. This model works well for uncomplicated *C. albicans* VVC. However, it falls short for recurrent, complicated, NAC, or treatment-resistant disease. The real challenge is not just the organism, it is the relationship between the organism, the host, and the vaginal ecosystem. The colonization versus disease distinction is a key example. *Candida* can be present without symptoms, and women with symptoms may have conditions unrelated to *Candida* (1,25). Thus, a positive molecular or culture result should not automatically be taken as proof of causation.

Recurrence presents a similar problem. Weekly fluconazole can effectively suppress RVVC, but recurrence often returns after treatment stops (66). This shows that antifungal therapy can control symptoms without removing the underlying predisposition. The arrival of oteseconazole and ibrexafungerp is a meaningful advance (2,67,68,73,76) because it shows that new drugs can improve recurrence prevention. However, new drugs alone are not enough. If recurrence is driven by host factors, ecological changes, or persistent strains, then long-term control will need more than repeated antifungal courses.

The microbiome may hold part of the answer. However, current evidence does not support simple claims that “low *Lactobacillus* causes VVC” or that probiotics work for everyone (12-15,79). Instead, we need to learn which microbial communities are linked to which clinical patterns, and whether those communities are a cause, a consequence, or both. The African data highlight another issue: research inequality (6). A disease cannot be fully understood when large regions lack data on species distribution, resistance patterns, recurrence rates, or treatment outcomes. The future VVC research agenda must be both scientifically advanced and globally inclusive.

Conclusion:

Vulvovaginal candidiasis is common, clinically important and increasingly complex. The major challenge facing the management of VVC is no longer simply the availability of effective antifungal drugs. The deeper challenge is that we still have limited ability to determine who will develop symptomatic VVC disease, why disease recurs, why treatment fails, and how recurrence can be prevented sustainably. The critical gaps span the entire disease pathway, from epidemiological definition and diagnosis to *Candida* biology, host immunity, microbiome interactions, resistance, treatment and patient-centred outcomes.

Future VVC research should therefore move from *Candida* detection→antifungal treatment toward clinical phenotype + *Candida* species/strain + host susceptibility + microbial ecology + treatment history → precision diagnosis → individualized therapy → recurrence prevention. The field of VVC research should prioritize longitudinal, multicentre studies integrating clinical phenotyping, microbiology, antifungal susceptibility testing, genomics, microbiome/mycobiome analysis and patient-reported outcomes.

The most important conceptual transition is from episodic treatment to precision pre-

vention. Ultimately, the goal should not simply be to develop more antifungal drugs. It should be to understand which woman is at risk, why she develops disease, which *Candida* phenotype is responsible, why treatment succeeds or fails, and which intervention can prevent recurrence without unnecessary antifungal exposure. That is the research agenda capable of moving VVC from a repeatedly treated common infection to a disease managed through precision diagnosis, targeted treatment and durable prevention.

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Contributions of authors:

PCUO conceived the review concept and designed the study framework. SCE conducted the literature search and data extraction. PCUO synthesized the evidence and drafted the initial manuscript. INN critically revised the manuscript for intellectual content. All authors reviewed and approved the final version of the manuscript.

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References:

- Centers for Disease Control and Prevention. Vulvovaginal candidiasis. In: Sexually Transmitted Infections Treatment Guidelines, 2021. Atlanta: CDC; 2021.
- Goje, O., Azie, N. E., Angulo, D. A., Sobel, R., Nyirjesy, P., and Sobel, J. D. A phase 3, multicenter, randomized, placebo-controlled trial of monthly oral ibrexafungerp to reduce the incidence of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol.* 2025; 233: 617.e1-617.e18. doi:10.1016/j.ajog.2025.07.040.
- Sobel, J. D., Faro, S., Force, R. W., et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol.* 1998; 178 (2): 203-211. doi:10.1016/S0002-9378(98)80001-X.
- Rathod, S. D., and Buffler, P. A. Highly-cited estimates of the cumulative incidence and recurrence of vulvovaginal candidiasis are inadequately documented. *BMC Women's Health.* 2014; 14: 43. doi:10.1186/1472-6874-14-43.
- Rafat, Z., Alipour, N., Esmaeili, E., et al. Vulvovaginal candidiasis: a global perspective through systematic review and meta-analysis. *Microb Pathog.* 2026; 212: 108284. doi:10.1016/j.micpath.2026.108284.
- Mushi, M. F., Olum, R., and Bongomin, F. Prevalence, antifungal susceptibility and aetiology of vulvovaginal candidiasis in sub-Saharan Africa: a systematic review with meta-analysis and meta-regression. *Med Mycol.* 2022; 60 (7): myac037. doi:10.1093/mmy/myac037.
- Denning, D. W., Kneale, M., Sobel, J. D., and Rautemaa-Richardson, R. Global burden of recurrent vulvovaginal candidiasis: a systematic review. *Lancet Infect Dis.* 2018; 18 (11): e339-e347. doi:10.1016/S1473-3099(18)30103-8.
- Blostein, F., Levin-Sparenberg, E., Wagner, J., and Foxman, B. Recurrent vulvovaginal candidiasis. *Ann Epidemiol.* 2017; 27 (9): 575-582.e3. doi:10.1016/j.annepidem.2017.08.010.
- Foxman, B., Muraglia, R., Dietz, J. P., Sobel, J. D., and Wagner, J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. *J Low Genit Tract Dis;* 2013; 17 (3): 340-346. doi:10.1097/LGT.0b013e318273e8cf.
- Willems, H. M. E., Ahmed, S. S., Liu, J., Xu, Z., and Peters, B. M. Vulvovaginal candidiasis: a current understanding and burning questions. *J Fungi (Basel).* 2020; 6 (1): 27. doi:10.3390/jof6010027.
- Zhu, W., and Guo, L. Advances in vulvovaginal candidiasis research: a comprehensive review from epidemiology, diagnosis, treatment to resistance mechanisms. *Front Microbiol.* 2026; 17: 1811011. doi:10.3389/fmicb.2026.1811011.
- Kalia, N., Singh, J., and Kaur, M. Microbiota in vaginal health and pathogenesis of recurrent vulvovaginal infections: a critical review. *Ann Clin Microbiol Antimicrob.* 2020; 19: 5.
- Bradfield Strydom M., Khan, S., Walpole, R. L., Ware, R. S., and Tiralongo, E. Interplay of the microbiome and antifungal therapy in recurrent vulvovaginal candidiasis: a narrative review. *J Med Microbiol.* 2023; 72 (5): 001705. doi:10.1099/jmm.0.001705.
- McKloud, E., Delaney, C., Sherry, L., et al. Recurrent vulvovaginal candidiasis: a dynamic interkingdom biofilm disease of *Candida* and *Lactobacillus*. *mSystems.* 2021; 6 (4): e00622-21. doi:10.1128/mSystems.00622-21.
- Liang, Y., Huang, Z., Fan, S., et al. Highlight signatures of vaginal microbiota and metabolome contributed to the occurrence and recurrence of vulvovaginal candidiasis. *Microbiol Spectr.* 2024; 12 (12): e01521-24. doi:10.1128/spectrum.01521-24.
- Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol.* 2005;8(1):19-32. doi: 10.1080/1364557032000119616
- Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* 2018;169(7):467-473. doi: 10.7326/M18-0850

18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: [10.1136/bmj.n71](https://doi.org/10.1136/bmj.n71)
19. Gonçalves, B., Ferreira, C., Alves, C. T., Henriques, M., Azeredo, J., and Silva, S. Vulvovaginal candidiasis: epidemiology, microbiology and risk factors. *Crit Rev Microbiol*. 2016; 42 (6): 905-927. doi: [10.3109/1040841X.2015.1091805](https://doi.org/10.3109/1040841X.2015.1091805).
20. Mäkanjuola, O., Bongomin, F., and Fayemiwo, S. A. An update on the roles of non-*albicans* *Candida* species in vulvovaginitis. *J Fungi (Basel)*. 2018; 4 (4): 121. doi: [10.3390/jof4040121](https://doi.org/10.3390/jof4040121).
21. Sobel, J. D. Recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol*. 2016; 214 (1): 15-21. doi: [10.1016/j.ajog.2015.06.067](https://doi.org/10.1016/j.ajog.2015.06.067).
22. Donders, G., Sziller, I. O., Paavonen, J., et al. Management of recurrent vulvovaginal candidosis: narrative review of the literature and European expert panel opinion. *Front Cell Infect Microbiol*. 2022; 12: 934353. doi: [10.3389/fcimb.2022.934353](https://doi.org/10.3389/fcimb.2022.934353).
23. Fukazawa, E. I., Witkin, S. S., Robial, R., et al. Influence of recurrent vulvovaginal candidiasis on quality-of-life issues. *Arch Gynecol Obstet*. 2019; 300 (3): 647-650. doi: [10.1007/s00404-019-05228-3](https://doi.org/10.1007/s00404-019-05228-3).
24. Simonetta, C., Burns, E. K., and Guo, M. A. Vulvar dermatoses: a review and update. *Mo Med*. 2015; 112 (4): 301-307.
25. Sobel, J. D. Treatment of vaginitis caused by non-*albicans* *Candida* species. *Expert Rev Anti Infect Ther*. 2024; 22 (5): 289-296. doi: [10.1080/14787210.2024.2347953](https://doi.org/10.1080/14787210.2024.2347953).
26. Eckert, L. O., Hawes, S. E., Stevens, C. E., et al. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol*. 1998; 92 (5): 757-765.
27. Talapko, J., Škrlec, I., Alebić, T., Jukić, M., and Včev, A. *Candida albicans*-the virulence factors and clinical manifestations of infection. *J Fungi (Basel)*. 2021; 7 (2): 79. doi: [10.3390/jof7020079](https://doi.org/10.3390/jof7020079).
28. Fidel, P. L Jr., and Sobel, J. D. Immunopathogenesis of recurrent vulvovaginal candidiasis. *Clin Microbiol Rev*. 1996; 9 (3): 335-348.
29. Fidel, P. L Jr., Lynch, M. E., and Sobel, J. D. Systemic cell-mediated immune reactivity in women with recurrent vulvovaginal candidiasis. *J Infect Dis*. 1993; 168 (6): 1458-1465.
30. Fidel, P. L Jr., Ginsburg, K. A., Cutright, J. L., et al. Vaginal-associated immunity in women with recurrent vulvovaginal candidiasis. *J Infect Dis*. 1997; 176 (3): 728-739.
31. Fidel P. L Jr. History and update on host defense against vaginal candidiasis. *Am J Reprod Immunol*. 2007; 57 (1): 2-12.
32. Rosati, D., Bruno, M., Jaeger, M., ten Oever, J., and Netea, M. G. Recurrent vulvovaginal candidiasis: an immunological perspective. *Microorganisms*. 2020; 8 (2): 144. doi: [10.3390/microorganisms8020144](https://doi.org/10.3390/microorganisms8020144).
33. Lobo, M., Cerqueira, C., Rodrigues, A. G., and Lisboa, C. Recurrent vulvovaginal candidosis and its underlying mechanisms: a systematic review. *J Fungi (Basel)*. 2025; 11 (5): 357. doi: [10.3390/jof11050357](https://doi.org/10.3390/jof11050357).
34. Ferwerda, B., Ferwerda, G., Plantinga, T. S., et al. Human dectin-1 deficiency and mucocutaneous fungal infections. *N Engl J Med*. 2009; 361 (18): 1760-1767. doi: [10.1056/NEJMoa0901053](https://doi.org/10.1056/NEJMoa0901053).
35. Glocker, E. O., Hennigs, A., Nabavi, M., et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009; 361 (18): 1727-1735. doi: [10.1056/NEJMoa0810719](https://doi.org/10.1056/NEJMoa0810719).
36. Moyes, D. L., Wilson, D., Richardson, J. P., et al. Candidalysin is a fungal peptide toxin critical for mucosal infection. *Nature*. 2016; 532 (7597): 64-68. doi: [10.1038/nature17625](https://doi.org/10.1038/nature17625).
37. Willems, H. M. E., Lowes, D. J., Barker, K. S., et al. Candidalysin is a potent trigger of the NLRP3 inflammasome in vaginal epithelial cells. *J Infect Dis*. 2022; 225 (8): 1423-1432. doi: [10.1093/infdis/jiab602](https://doi.org/10.1093/infdis/jiab602).
38. Ravel, J., Gajer, P., Abdo, Z., et al. Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci USA*. 2011; 108 (Suppl 1): 4680-4687. doi: [10.1073/pnas.1002611107](https://doi.org/10.1073/pnas.1002611107).
39. Gajer, P., Brotman, R. M., Bai, G., et al. Temporal dynamics of the human vaginal microbiota. *Sci Transl Med*. 2012; 4 (132): 132ra52. doi: [10.1126/scitranslmed.3003605](https://doi.org/10.1126/scitranslmed.3003605).
40. O'Hanlon, D. E., Moench, T. R., and Cone, R. A. Vaginal pH and microbicidal lactic acid when lactobacilli dominate the microbiota. *PLoS One*. 2013; 8 (11): e80074. doi: [10.1371/journal.pone.0080074](https://doi.org/10.1371/journal.pone.0080074).
41. Jang, S. J., Lee, K., Kwon, B., You, H. J., and Ko, G. Vaginal lactobacilli inhibit growth and hyphae formation of *Candida albicans*. *Sci Rep*. 2019; 9: 8121. doi: [10.1038/s41598-019-44579-4](https://doi.org/10.1038/s41598-019-44579-4).
42. Bradford, L. L., and Ravel, J. The vaginal mycobiome: a contemporary perspective on fungi in women's health and diseases. *Virulence*. 2017; 8 (3): 342-351. doi: [10.1080/21505594.2016.1237332](https://doi.org/10.1080/21505594.2016.1237332).
43. Zhao, C., Li, Y., Chen, B., et al. Mycobiome study reveals different pathogens of vulvovaginal candidiasis shape characteristic vaginal bacteriome. *Microbiol Spectr*. 2023; 11 (3): e0315222. doi: [10.1128/spectrum.03152-22](https://doi.org/10.1128/spectrum.03152-22).
44. Harriott, M. M., and Noverr, M. C. Importance of *Candida*-bacterial polymicrobial biofilms in disease. *Trends Microbiol*. 2011; 19 (11): 557-563.
45. Rodríguez-Cerdeira, C., Gregorio, M. C., Molares-Vila, A., et al. Biofilms and vulvovaginal candidiasis. *Colloids Surf B Biointerfaces*. 2019; 174: 110-125. doi: [10.1016/j.colsurfb.2018.11.011](https://doi.org/10.1016/j.colsurfb.2018.11.011).
46. Nobile, C. J., and Johnson, A. D. *Candida albicans* biofilms and human disease. *Annu Rev Microbiol*. 2015; 69: 71-92. doi: [10.1146/annurev-micro-091014-104330](https://doi.org/10.1146/annurev-micro-091014-104330).
47. Rodríguez-Cerdeira, C., Martínez-Herrera, E., Carnero-Gregorio, M., et al. Pathogenesis and clinical relevance of *Candida* biofilms in vulvovaginal candidiasis. *Front Microbiol*. 2020; 11: 544480. doi: [10.3389/fmicb.2020.544480](https://doi.org/10.3389/fmicb.2020.544480).
48. Sherry, L., Kean, R., McKloud, E., O'Donnell, L. E., Metcalfe, R., Jones, B. L., and Ramage, G. Biofilms formed by isolates from recurrent vulvovaginal candidiasis patients are heterogeneous and insensitive to fluconazole. *Antimicrob Agents Chemother*. 2017; 61 (9): e01065-17. doi: [10.1128/AAC.01065-17](https://doi.org/10.1128/AAC.01065-17).
49. Pan, Y., Sun, Y., Chen, L., et al. *Candida* causes recurrent vulvovaginal candidiasis by forming morphologically disparate biofilms on the human vaginal epithelium. *Biofilm*. 2023; 6: 100162. doi: [10.1016/j.biofilm.2023.100162](https://doi.org/10.1016/j.biofilm.2023.100162).
50. Wu, X., Zhang, S., Li, H., et al. Biofilm formation of *Candida albicans* facilitates fungal infiltration and persist cell formation in vaginal candidiasis. *Front Microbiol*. 2020; 11: 1117. doi: [10.3389/fmicb.2020.01117](https://doi.org/10.3389/fmicb.2020.01117).
51. Swidsinski, A., Guschin, A., Tang, Q., et al. Vulvovaginal candidiasis: histologic lesions are primarily polymicrobial and invasive and do not contain biofilms. *Am J Obstet Gynecol*. 2019; 220 (1): 91.e1-91.e8. doi: [10.1016/j.ajog.2018.10.023](https://doi.org/10.1016/j.ajog.2018.10.023).
52. Sobel, J. D. Editorial commentary: vaginal biofilm: much ado about nothing, or a new therapeutic

- challenge? Clin Infect Dis. 2015; 61 (4): 607-608. doi:10.1093/cid/civ358.
53. Vazquez, J. A., Sobel, J. D., Demetriou, R., Vaishampayan, J., Lynch, M., and Zervos, M. J. Karyotyping of *Candida albicans* isolates obtained longitudinally in women with recurrent vulvovaginal candidiasis. J Infect Dis. 1994; 170 (6): 1566-1569.
 54. Akinosoglou, K., Schinas, G., Papageorgiou, D., et al. Rapid molecular diagnostics in vulvovaginal candidosis. Diagnostics (Basel). 2024; 14 (20): 2313. doi:10.3390/diagnostics14202313.
 55. Danby, C. S., Althouse, A. D., Hillier, S. L., and Wiesenfeld, H. C. Nucleic acid amplification testing compared with cultures, Gram stain, and microscopy in the diagnosis of vaginitis. J Low Genit Tract Dis. 2021; 25 (1): 76-80. doi:10.1097/LGT.0000000000000578.
 56. Fisher, M. C., Hawkins, N. J., Sanglard, D., and Gurr, S. J. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. Science. 2018; 360 (6390): 739-742. doi:10.1126/science.aap7999.
 57. Perlin, D. S., Rautemaa-Richardson, R., and Alastruey-Izquierdo, A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017; 17 (12): e383-e392. doi:10.1016/S1473-3099(17)30316-X.
 58. Sanglard, D., Ischer, F., Monod, M., and Bille, J. Cloning of *Candida albicans* genes conferring resistance to azole antifungal agents: characterization of CDR2, a new multidrug ABC transporter gene. Microbiol. 1997; 143 (2): 405-416. doi:10.1099/00221287-143-2-405.
 59. Castanheira, M., Deshpande, L. M., Davis, A. P., Carvalhaes, C. G., and Pfaller, M. A. Azole resistance in *Candida glabrata* clinical isolates from global surveillance is associated with efflux overexpression. J Glob Antimicrob Resist. 2022; 29: 371-377. doi:10.1016/j.jgar.2022.05.004.
 60. Clinical and Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 4th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2017. CLSI standard M27.
 61. Danby, C. S., Boikov, D., Rautemaa-Richardson, R., and Sobel, J. D. Effect of pH on in vitro susceptibility of *Candida glabrata* and *Candida albicans* to 11 antifungal agents and implications for clinical use. Antimicrob Agents Chemother. 2012; 56 (3): 1403-1406. doi:10.1128/AAC.05025-11.
 62. Lockhart, S. R., Etienne, K. A., Vallabhaneni, S., et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis. 2017; 64 (2): 134-140. doi:10.1093/cid/ciw691.
 63. Akinosoglou, K., Livieratos, A., Asimos, K., Donders, F., and Donders, G. G. Fluconazole-resistant vulvovaginal candidosis: an update on current management. Pharmaceutics. 2024; 16 (12): 1555. doi:10.3390/pharmaceutics16121555.
 64. Pappas, P. G., Lionakis, M. S., Arendrup, M. C., Ostrosky-Zeichner, L., and Kullberg, B. J. Invasive candidiasis. Nat Rev Dis Primers. 2018; 4: 18026. doi:10.1038/nrdp.2018.26.
 65. World Health Organization. WHO Fungal Priority Pathogens List to Guide Research, Development and Public Health Action. Geneva: WHO; 2022.
 66. Sobel, J. D., Wiesenfeld, H. C., Martens, M., et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N Engl J Med. 2004; 351 (9): 876-883. doi:10.1056/NEJMoa033114.
 67. Martens, M. G., Maximos, B., Degenhardt, T., et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. Am J Obstet Gynecol. 2022; 227 (6): 880.e1-880.e11. doi:10.1016/j.ajog.2022.07.023.
 68. Sobel, J. D., Donders, G., Degenhardt, T., et al. Efficacy and safety of oteseconazole in recurrent vulvovaginal candidiasis. NEJM Evid. 2022; 1 (8): EVIDo2100055. doi:10.1056/EVIDo2100055.
 69. Brand, S. R., Degenhardt, T. P., Person, K., et al. A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of orally administered VT-1161 in the treatment of recurrent vulvovaginal candidiasis. Am J Obstet Gynecol. 2018; 218 (6): 624.e1 - 624.e9.
 70. Brand, S. R., Sobel, J. D., Nyirjesy, P., Ghannoum, M. A., Schotzinger, R. J., and Degenhardt, T. P. A randomized phase 2 study of VT-1161 for the treatment of acute vulvovaginal candidiasis. Clin Infect Dis. 2021; 73 (7): e1518-e1524. doi:10.1093/cid/ciaa1204.
 71. Wang, X., Chen, L., Ruan, H., et al. Oteseconazole versus fluconazole for the treatment of severe vulvovaginal candidiasis: a multicenter, randomized, double-blinded, phase 3 trial. Antimicrob Agents Chemother. 2024; 68 (1): e0077823. doi:10.1128/aac.00778-23.
 72. Hoy, S. M. Oteseconazole: first approval. Drugs. 2022; 82 (9): 1017-1023. doi:10.1007/s40265-022-01734-y.
 73. Sobel, J. D. Ibrexafungerp for the treatment of vulvovaginal candidiasis. Drugs Today (Barc). 2022; 58 (4): 149-158. doi:10.1358/dot.2022.58.4.3381586.
 74. Schwebke, J. R., Sobel, R., Gersten, J. K., et al. Ibrexafungerp versus placebo for vulvovaginal candidiasis treatment: a phase 3, randomized, controlled superiority trial (VANISH 303). Clin Infect Dis. 2022; 74 (11): 1979-1985. doi:10.1093/cid/ciab750.
 75. Phillips, N. A., Rocktaschel, M., and Merjanian, L. Ibrexafungerp for the treatment of vulvovaginal candidiasis: design, development and place in therapy. Drug Des Devel Ther. 2023; 17: 363-367. doi:10.2147/DDDT.S339349.
 76. Grant, L. M., and Orenstein, R. Treatment of recurrent vulvovaginal candidiasis with ibrexafungerp. J Investig Med High Impact Case Rep. 2022; 10: 23247096221123144. doi:10.1177/23247096221123144.
 77. Amabebe, E., and Anumba, D. O. C. The vaginal microenvironment: the physiologic role of lactobacilli. Front Med (Lausanne). 2018; 5: 181. doi:10.3389/fmed.2018.00181.
 78. Xie, H. Y., Feng, D., Wei, D. M., et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. Cochrane Database Syst Rev. 2017; 11 (11): CD010496. doi:10.1002/14651858.CD010496.pub2.
 79. Pirotta, M., Gunn, J., Chondros, P., et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. BMJ. 2004; 329 (7465): 548. doi:10.1136/bmj.38210.494977.DE.
 80. Chee, W. J. Y., Chew, S. Y., and Than, L. T. L. Vaginal microbiota and the potential of *Lactobacillus* derivatives in maintaining vaginal health. Microb Cell Fact. 2020; 19: 203. doi:10.1186/s12934-020-01464-4.
 81. Chew, S. Y., Cheah, Y. K., Seow, H. F., Sandai, D., and Than, L. T. L. Probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 exhibit strong

- antifungal effects against vulvovaginal candidiasis-causing *Candida glabrata* isolates. J Appl Microbiol. 2015; 118 (5): 1180-1190. doi:10.1111/jam.12772.
82. Rossoni, R. D., de Barros, P. P., de Alvarenga, J. A., et al. Antifungal activity of clinical Lactobacillus strains against *Candida albicans* biofilms: identification of potential probiotic candidates to prevent oral candidiasis. Biofouling. 2018; 34 (2): 212-225. doi:10.1080/08927014.2018.1425402.
 83. Ugwa, E. A. Vulvovaginal candidiasis in Aminu Kano Teaching Hospital, North-West Nigeria: hospital-based epidemiological study. Ann Med Health Sci Res. 2015; 5 (4): 274-278. doi:10.4103/2141-9248.160185.
 84. Bitew, A., and Abebaw, Y. Vulvovaginal candidiasis: species distribution of *Candida* and their antifungal susceptibility pattern. BMC Women's Health. 2018; 18: 94. doi:10.1186/s12905-018-0607-z.
 85. Sarpong, A. K., Odoi, H., Boakye, Y. D., Boamah, V. E., and Agyare, C. Resistant *C. albicans* implicated in recurrent vulvovaginal candidiasis (RVVC) among women in a tertiary healthcare facility in Kumasi, Ghana. BMC Women's Health. 2024; 24: 412. doi:10.1186/s12905-024-03251-6.
 86. Omosa-Manyonyi, G. S., Ricano Ponce, I., Rosati, D., et al. Genetic susceptibility to recurrent vulvovaginal candidiasis in an African population from Nairobi, Kenya. Sci Rep. 2025; 15: 12149. doi:10.1038/s41598-025-95772-7.
 87. Happel, A. U., Gasper, M., Balle, C., et al. Persistent, asymptomatic colonization with *Candida* is associated with elevated frequencies of highly activated cervical Th17-like cells and related cytokines in the reproductive tract of South African adolescents. Microbiol Spectr. 2022; 10 (2): e01626-21. doi:10.1128/spectrum.01626-21.
 88. Jonani, B., Herman, B. R., Arturo, J. F., Kwizera, R., Mboowa, G., and Bongomin, F. Immune responses to vaginal candidiasis in African women: a scoping review of cytokine profiles, T-cell activation, and gene expression. PLoS One. 2025; 20 (4): e0322072. doi:10.1371/journal.pone.0322072.