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Targeting Biofilm-Mediated Resistance: A Novel Insight into Fluconazole–Gentamicin Synergy in Vulvovaginal Candidiasis

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A B S T R A C T

Vulvovaginal candidiasis (VVC) affects up to 75% of women worldwide, with recurrent episodes posing significant clinical and psychosocial challenges. While *Candida albicans* remains the predominant pathogen, Candida non-albicans species are increasingly reported and frequently exhibit antifungal resistance. Biofilm formation further complicates treatment, conferring enhanced tolerance to antifungal agents. This study investigated the species distribution, antifungal susceptibility, biofilm production, and the potential synergistic effect of fluconazole–gentamicin combination therapy against *Candida* isolates from VVC. A total of 120 vaginal *Candida* isolates from women aged 18–40 years were collected over eight months (June 2022–January 2023). Identification was performed using conventional mycological methods and CHROMagar. Antifungal susceptibility testing followed CLSI guidelines. Biofilm formation was assessed by microtiter plate assay, and minimum inhibitory concentrations (MICs) of fluconazole, gentamicin, and their combination were determined using broth microdilution. *Candida albicans* accounted for 35% of isolates, followed by *C. parapsilosis* (30%), *C. glabrata* (15%), *C. krusei* (11%), and *C. tropicalis* (9%). Fluconazole resistance was observed in 14.1% (17/120) of isolates, the majority of which 13 (76.4%) were strong biofilm producers. Combination therapy with fluconazole–gentamicin demonstrated a marked reduction in MIC values, with 84.6% (11/13) of resistant isolates showing restored susceptibility (MIC ≤ 2 µg/mL), compared to fluconazole or gentamicin monotherapy. Our findings suggest that fluconazole–gentamicin combination therapy exhibits promising synergistic activity against fluconazole-resistant *Candida* isolates, highlighting a potential alternative strategy for difficult-to-treat VVC cases.

Introduction

VVC is a very common fungal infection prominently in pregnant women than adolescent age and is estimated that 30% of pregnant women in the third trimester have *Candida* colonisation in their vagina (1). At least once in their lives, about 70% of females have reported having vaginal candidiasis (2). Recurrent vulvovaginal candidiasis (RVVC) is being reported by almost 8% of the females and is characterised by three or more episodes annually (3). The major cause of RVVC are *Candida albicans* along with Candida non albicans which increases the case to up to a rate of 10% (4). Physical and mental health of the patient, financial situation and marital relationships, risk of Diabetes mellitus, HIV infections, pregnancy induced rise in hormonal level, irregular menstruation, poor hygiene and broad -spectrum usage of antibiotics are all impacted by VVC infection, which may also contribute to infertility (5,6). When a woman's system undergoes a change due to pregnancy, diabetes, or the use of drugs like antibiotics or corticosteroids, she is more likely to get vaginal yeast infection (7). Globally VVC, which affects an additional 40% to 50% and an extra 5% of RVVC episodes, affects around 75% of adult women (8). The prevalence of VVC in India accounts for about 30% (9).

The invasive infections are mainly caused by *C. albicans* illustrating about 45-65 % of cases followed by Candida non albicans includes *C. glabrata, C. tropicalis, C. krusei, C. parapsilosis* which accounts for emerging infections caused by fungus for about 30-35% (10). *C. albicans* are the primary cause of candidemia, Candida non-albicans species have been shown to produce an increasing number of infections and frequently display antifungal treatment resistance (11). Biofilms are collections of sessile microorganisms that are tightly packed and covered in a self-made material (12).

Most medical devices, including stents, implants, endotracheal tubes, pacemakers, and other kinds of catheters, have *Candida* biofilms on them as a virulence factor (13). It is the key virulence factor in Candida pathogenesis, conferring protection against host defences and antifungal agents. Standard antifungal therapy challenges like drug toxicity, resistance, and high recurrence rates. *Candida* has been found to have both innate and acquired antifungal medication resistance. Combination therapy has emerged as a promising approach. Fluconazole combined with other agents shows potential synergy. Gentamicin, an aminoglycoside, has been explored for synergistic activity with fluconazole against resistant *Candida* isolates. This study was conducted to investigate species distribution, antifungal susceptibility, biofilm production and evaluate the synergistic effect of fluconazole and gentamicin against *Candida* isolates from vulvovaginal candidiasis.

Materials and Methods

Sample Collection and Identification of *Candida* Isolates

A total of 120 *Candida* isolates were taken from the suspected vaginal samples. The sample collection was conducted over an eight-month period, from June 2022 to January 2023. The collected vaginal swabs were cultured onto conventional plates including blood agar plate and MacConkey agar plate for the isolation of bacteria and the Sabouraud Dextrose agar (SDA) plate for the isolation of fungus. The plates were incubated for 24-48 hours at 37˚C and 25˚C. The macroscopic and microscopic examination of the plates were performed. Standard mycological examinations done for the identification and speciation of the yeasts that includes Gram staining, Germ tube test, *Candida* CHROMagar (Hi-Media Laboratories) medium for colony characterisation and chlamydospore formation on Corn meal agar (CMA) with Tween80 (Hi-Media Laboratories).

Participant selection criteria

The study included clinically suspected cases of vulvovaginal candidiasis within the age group of 18–40 years, from which *Candida* species were isolated using vaginal swab specimens. Only samples yielding pure growth of *Candida* spp. were considered for analysis. Exclusion criteria involved vaginal swabs that showed mixed growth of bacteria or fungi other than *Candida* spp., samples with inadequate specimen quality, repeat isolates from the same patient (to avoid duplication) and patients who were currently receiving antifungal or aminoglycoside therapy at the time of sample collection.

Ethical clearance

The study is approved by the Institutional Ethical Committee (ethical clearance no. 8413/IEC/2022) of SRM Medical College Hospital and research Centre.

Antifungal Susceptibility Testing (AFST)

The AFST was performed on each isolate using the Kirby Bauer disc diffusion technique on Muller-Hinton agar (cation-adjusted) supplemented with 0.5 g/ml methylene blue and 2% glucose (Hi-Media Laboratories). The antifungal discs used were Fluconazole (25µg), Itraconazole (30µg), Voriconazole (1µg) and Amphotericin B (100U) (Hi-Media Laboratories). Following the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI), the zone sizes were measured and evaluated.

Biofilm formation assay

The biofilm formation was performed by the broth microdilution method using ELISA technique. The determination of biofilm production was performed with few modifications of Munmun B. Marak *et al.,* (16). Each *Candida* isolate colony was inoculated into tubes containing 2ml of Brain Heart Infusion Broth (BHIB), and the tubes were then incubated for 24 hours at 37 °C. Broth culture was diluted at the ratio of 1: 20 using freshly prepared BHIB and 200µl was poured into microtiter plate and were incubated at 37°C to 24 hours. After the incubation was over, the microtiter plate was emptied, washed three times with distilled water, and then inverted to blot. 200µl of 1% crystal violet was added to each well, and the mixture was incubated for 15 minutes. After incubation for 15 mins microtiter plate was rinsed with distilled water thrice. To each well, 200 µl of an 80: 20 w/v ethanol-acetone mixture was added. The positive control used were *Candida albicans* ATCC 14053 strains and negative control was sterile BHIB broth. Using an ELISA reader, the microtiter plate was read at 492 nm, and spectrophotometric analysis was used to record the OD values. Biofilm formation was scored as low (0+), intermediate (1+ to 2+) and strong (3+) (14).

Broth Microdilution Assay for antifungal susceptibility

The Minimal Inhibitory Concentration (MIC) of fluconazole, gentamicin, and their combination was determined using the Clinical and Laboratory Standards Institute (CLSI) M27-A3 broth microdilution method, with results interpreted according to CLSI M27-S4 (2012) guidelines for yeasts. Rosewell Park Memorial Institute 1640 (RPMI-1640) medium with glutamine and without bicarbonate was used as the synthetic broth medium. Fluconazole (potency: 750 µg/mg) and gentamicin (potency: 900 µg/mL) stock solutions were prepared in sterile distilled water (50 mL each). For combination testing, equal volumes (50 mL each) of fluconazole and gentamicin stock solutions were mixed prior to use. MIC assays were performed in sterile 96-well microtiter plates. Each well contained serial dilutions of the respective drugs along with the standardized yeast inoculum. Wells containing 100 µL of drug-free medium plus 100 µL of inoculum served as positive controls, while wells with 200 µL of RPMI-1640 medium alone served as negative controls. Fluconazole-resistant *Candida* isolates were specifically tested against fluconazole, gentamicin, and their combination.

Results and Discussion

During the study period, 120 clinically confirmed *Candida* isolates were recovered from patients aged 18–40 years. Initial microscopic examination using Gram staining revealed the presence of Gram-positive budding yeast cells, which is characteristic of *Candida* species (Figure 1A). For further identification, the isolates were subjected to multiple methods like germ-tube test for rapid presumptive identification of *Candida albicans* (Figure 1B) and the Dalmau plate culture technique on cornmeal agar for assessing chlamydospore production and pseudohyphae formation (Figure 2). The isolates were further identified and differentiated at the species level using *Candida* CHROMagar, a selective and differential medium that enables the presumptive identification of *Candida* species based on colony shape and pigmentation (Figure 1C).

The age-wise distribution of the 120 *Candida* isolates collected in this study was as follows: 13 isolates (10.8%) were from individuals aged 18–20 years, 36 (30%) from those aged 21–25 years, 42 (35%) from the 26–30-year age group, 17 (14.1%) from the 31–35-year group, and 12 (10%) from individuals aged 36–40 years. Species identification revealed that *Candida albicans* accounted for the highest proportion with 42 isolates (35%), followed by *C. parapsilosis* with 36 isolates (30%), *C. glabrata* with 18 isolates (15%), *C. krusei* with 13 isolates (11%), and *C. tropicalis* with 11 isolates (9%).

The clinical presentation of patients from whom *Candida* isolates were obtained is summarized in Table 1. The

most frequent complaint was milky white vaginal discharge with itching and burning sensation, reported in 52 (43.33%) patients, followed by combined discharge and burning sensation in 15 (12.50%) patients, and burning with itching in 13 (10.83%) patients. Complaints of discharge alone (10.83%), burning alone (9.17%), itching alone (7.50%), and discharge with itching (5.83%) were less common.

Antibiogram showed that the most of the strains were sensitive to voriconazole and only 2 isolates (1.66%) were resistant. Most of the *C. parapsilosis* 29 (80.5%) were resistant to itraconazole, 17 (40.4%) of *C. albicans*, 4 (30.7%) of *C. krusei*, 3 (27.2%) of *C. tropicalis* and the least by 2 (11.11%) of *C. glabrata*. Out of 120 isolates, 17 (14.16%) isolates were resistant to fluconazole. One *Candida* isolate was resistant to the four antifungal drugs used.

Out of 17 fluconazole resistant *Candida* isolates, 13(76.4%) isolates showed strong biofilm production out of which 6 were *C. albicans*, 2 were *C. glabrata*, 1 *C. tropicalis*, 4 *C. parapsilosis* and 0 *C. krusei*. 3 isolates were intermediate with 2 *C. parapsilosis* and 1 *C. tropicalis* followed by 1 *C. parapsilosis* showed weak biofilm production. All 13 Fluconazole resistant strong biofilm producing isolates were subjected for determination of MIC of fluconazole, gentamicin and their combination.

The MIC of fluconazole drug for 13 isolates, where 2 (15.3%) isolates showed MIC of ≤ 2 µg/mL, 3 (23.07%) were intermediate with the MIC value between 4-32 µg/mL and 8 (61.5%) isolates showed MIC value of ≥ 64 µg/mL. MIC of gentamicin drug for 13 isolates, 3 (23.07%) isolates showed MIC of ≤ 2 µg/mL, 4 (30.7%) were intermediate with MIC between 4-32 µg/mL and 6 (46.1%) isolates showed MIC of ≥ 64 µg/mL. The MIC values of both fluconazole and gentamicin for different *Candida* species are shown in Table 2. MIC identification of combination therapy using fluconazole and gentamicin, 11 isolates showed MIC of ≤ 2 µg/mL, 1 isolate intermediate with MIC between 4-32 µg/mL and 1 isolate showed MIC of ≥ 64 µg/mL (Table 3).

VVC is an invasive fungal infection with high incidence and recurrence rate. The pathogenesis and recurrence of VVC, which are thought to be induced by a variety of factors like increasing resistance, the host local immunological response against *Candida*, and changes in the virulence factor of *Candida. Candida* spp. colonises the vagina at a higher rate and it may be isolated from the vagina in 30% of pregnant women and 20% of healthy, asymptomatic women (14, 15). Studies on the incidence of *Candida* species have varied results. In the present study, *C. albicans* was the most frequently isolated species (35%), followed by *C. parapsilosis* (30%).

This finding aligns with the work of Sashi Kandel *et al.,* (16) who also reported *C. albicans* as the predominant isolate, though at a higher proportion (65.3%). In contrast study conducted by Pavithra *et al.,* (17) showed higher incidence of Candida non albicans (83.01%) suggesting a possible regional or population-specific variation in species distribution. Such differences may be attributed to host factors, local prescribing practices, or environmental influences.

Candida forms organized biofilms on the vaginal epithelium that shield cells from host defenses and drugs. These biofilms exhibit less drug penetration, enhanced efflux pumps, stress-adaptation and a matrix that chemically sequesters azoles. The ability of *Candida* to form biofilms plays a central role in both colonization and pathogenicity. In this study, majority of strong biofilm producers, 13(76.4%) were *C. albicans* and 4 (23.5%) were Candida non albicans which was supported by Shirshak Lamsal *et al.,* (18).

Candida albicans generally produces denser, hyphal biofilms with a potent matrix, whereas numerous non-albicans species (like *C. parapsilosis*) generate structurally distinct biofilms exhibiting varied drug responses; clinical studies from RVVC cohorts associate enhanced biofilm formation with diminished azole susceptibility and increased recurrence rates (19). Most standards characterize RVVC as three to four symptomatic episodes per year, indicating that typical azole treatments suppress symptoms but often do not eradicate biofilm communities, leading to symptom recurrence post-therapy. Maintenance treatments, such as weekly fluconazole, diminish but do not eradicate recurrences, highlighting the need for therapies that address biofilm resistance (20).

Antifungal resistance is a significant clinical challenge in the treatment of VVC, exacerbated by the excessive use of azoles and the adaptive strategies of Candida, such as the overexpression of efflux pumps, mutations in ERG11, and tolerance associated with biofilms (21).

Figure.1 A: Gram staining demonstrating Gram Positive Budding yeast cells, B: Germ tubes are seen as long tube-like projections extending from yeast cells, C: Differentiation of Candida species on Candida CHROMagar

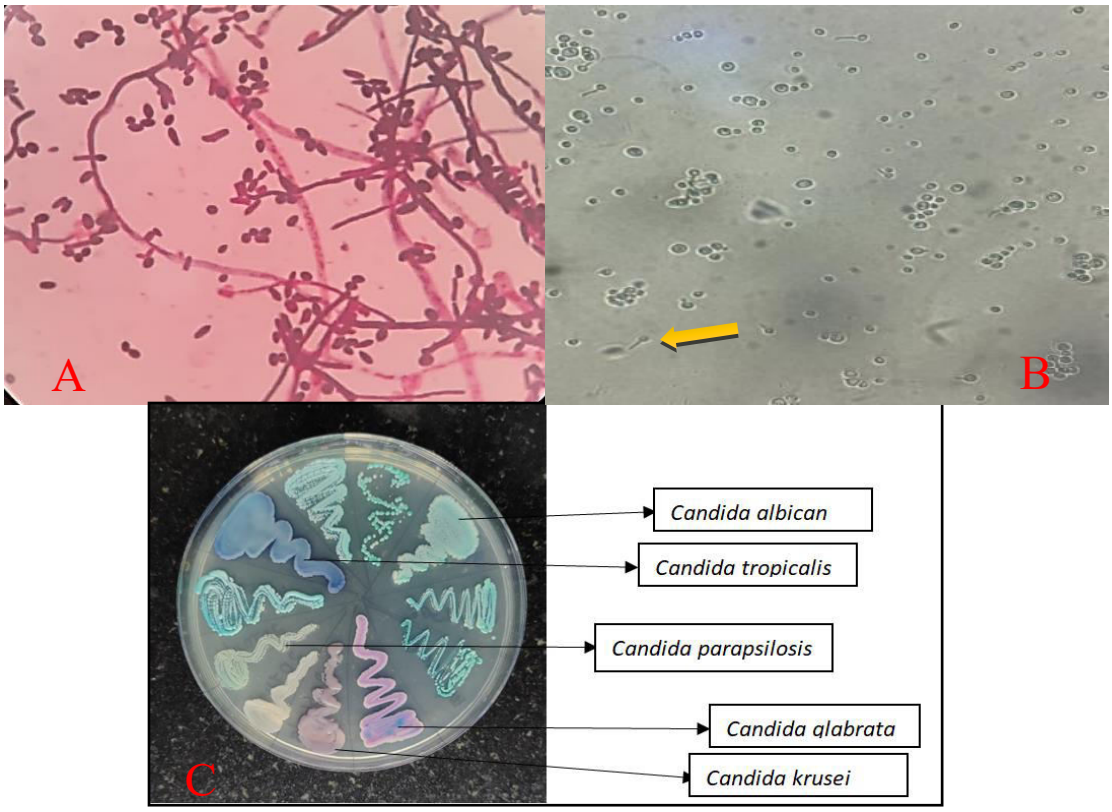

Figure2 Dalmau plate technique of A: Candida albicans, B: Candida tropicalis; C: Candida glabrata; D: Candida parapsilosis

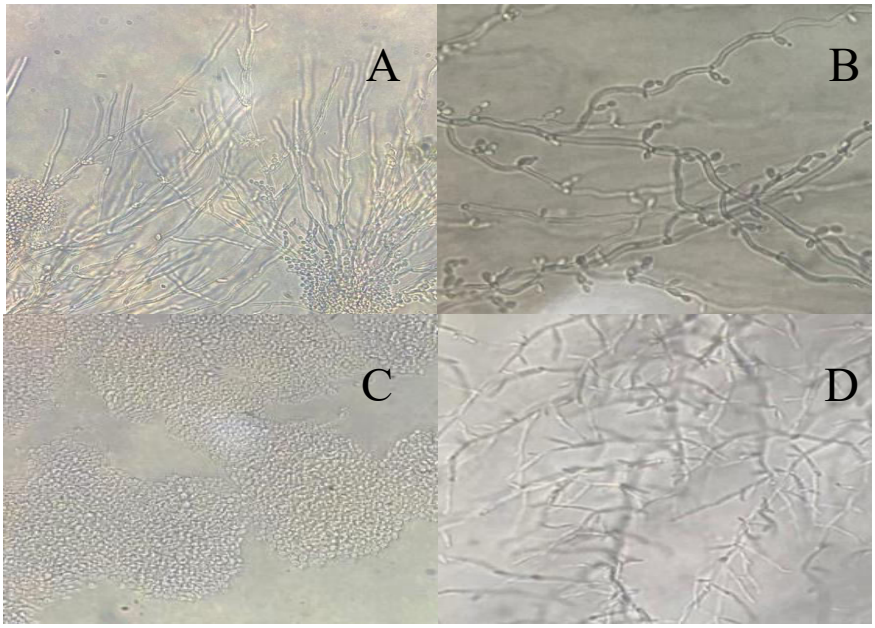

Table.1 Distribution of complaints among patient isolates

Complaints	N (%)
Milky white vaginal discharge	13 (10.83)
Itching sensation in genital area	9 (7.50)
Burning sensation	11 (9.17)
Milky white discharge and burning sensation	15 (12.50)
Burning and itching sensation	13 (10.83)
Itching and milky white discharge	7 (5.83)
Milky white discharge, itching and burning	52 (43.33)
Total	120

Table.2 Minimum Inhibitory Concentration (MIC) Distribution of Fluconazole and Gentamicin against Candida Species (n=13)

***Candida* Species**	**n**	**MIC range (µg/mL)**	**≤0.25**	**0.5**	**1**		**2**	**4**	**8**	**16**	**32**	**≥64**
Fluconazole												
CA	6	0.5 – ≥64	-	-	1		-	-	-	-	-	5
CP	4	0.5 – ≥64	-	-	1		-	1	-	-	-	2
CT	1	16	-	-	-		-	-	-	1	-	-
CG	2	8 – ≥64	-	-	-		-	-	1	-	-	1
CK	0	-	-	-	-		-	-	-	-	-	-
Gentamicin												
CA	6	0.5 – ≥64	-	1	-		-	-	-	1	-	4
CP	4	0.5 – ≥64	-	1	-		1	-	1	-	-	1
CT	1	4	-	-	-		-	1	-	-	-	-
CG	2	4 – ≥64	-	-	-		-	1	-	-	-	1
CK	0	-	-	-	-		-	-	-	-	-	-

Table.3 MIC distribution of fluconazole-resistant *Candida* species (n = 13) when treated with a combination of fluconazole and gentamicin. The table shows MIC ranges and the number of isolates at each concentration for individual *Candida* species.

***Candida* Species**	**n**	**MIC range (µg/mL)**	**≤0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**≥64**
Fluconazole – gentamicin combination											
CA	6	1 – ≥64	-	-	2	3	-	-	-	-	1
CP	4	1 – 4	-	-	3	-	1	-	-	-	-
CT	1	2	-	-	-	1	-	-	-	-	-
CG	2	1 – 2	-	-	1	1	-	-	-	-	-
CK	0	-	-	-	-	-	-	-	-	-	-

Biofilm communities, abundant in β-glucan matrix, create a protective environment that reduces fluconazole penetration and contributes to recurrence despite apparently adequate therapy. While aminoglycoside–azole synergy has been reported largely in vitro or in non-vaginal isolates, our dataset shows that, in VVC clinical isolates—many of which are strong/intermediate biofilm producers—84.6% responded with MIC ≤2 µg/mL to the combination.

These findings were comparable to those of Lu *et al.,* (1), who also demonstrated effective synergism at low MIC levels (<0.5 µg/mL).

This indicates that even biofilm-tolerant vaginal isolates may be made sensitive wit1h combination treatment. Mechanistically, gentamicin may disrupt membrane integrity, inhibit efflux, and destabilize biofilm matrix, thereby restoring fluconazole susceptibility.

Significantly, the majority of combination-susceptible isolates in our population exhibited strong to moderate biofilm production, supporting the concept that gentamicin mitigates biofilm-mediated tolerance.

The rising incidence of antifungal resistance, particularly with extensive use of azoles has contributed to the emergence of treatment failures in VVC. Therefore, species-level identification and antifungal susceptibility testing should be emphasized in clinical practice to guide appropriate empirical therapy.

In conclusion, VVC remains a significant clinical concern, with *Candida* species—particularly *Candida albicans* being the predominant causative agent, accounting for a prevalence of 14.16% in our study population with strong biofilm-forming capacity contributing to persistence and treatment difficulty.

Importantly, the combination of fluconazole and gentamicin demonstrated promising synergistic activity, particularly against biofilm-producing isolates, suggesting its potential as an alternative therapeutic approach in resistant cases.

These findings emphasize the need for routine species-level identification, biofilm assessment, and AFST to guide targeted therapy. Continuous surveillance and evaluation of novel drug combinations are crucial to improve management outcomes and reduce recurrence of VVC.

Declaration

Informed consent

This study was approved by the Institutional Ethics Committee of SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India. Informed consent was obtained from all participants prior to inclusion in the study, in accordance with institutional ethical guidelines and policies.

Conflict of interest

The authors declare there is no conflict of interest.

Authors' contribution

Dakshina M Nair - Writing—review and editing, Writing—original draft, Visualization, Validation, Resources, Methodology, Data curation, Conceptualization; K. V. Leela - Formal analysis, Conceptualization, Supervision; Sujith Sri Surya R - Visualization, Validation, Supervision; Deeksha P - Visualization and Validation; Alankritha Yadhunandhan - Formal analysis

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None.

Data availability

All datasets during this study are included in the manuscript.

List of abbreviations

VVC – Vulvovaginal candidiasis
RVVC – Recurrent Vulvovaginal candidiasis
CA- *Candida albicans*;
CP- *Candida parapsilosis*
CT- *Candida tropicalis*
CG- *Candida glabrata*
CK- *Candida krusei*
SDA - Sabouraud Dextrose agar
CMA – Corn Meal agar
AFST – Antifungal Susceptibility testing
CLSI - Clinical and Laboratory Standards Institute
ELISA – Enzyme-linked immunosorbent assay
BHIB- Brain heart infusion broth

MIC- Minimum inhibitory concentration
RPMI- Rosewell Park memorial institute

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