# A Review of Studies on *Candida* Species in Peninsular Malaysia

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## Abstract

Data on the epidemiology and the antifungal susceptibility of *Candida* species infections in Malaysia is still limited. The study aimed to review and compare studies reporting the prevalence of *Candida* species and antifungal susceptibility of *Candida* infections in Peninsular Malaysia. Data from 22 studies published between 2009 and 2018. Data was collected using National Center for Biotechnology Information and Google Scholar using the keywords "*Candida* and Malaysia." Around 19 *Candida* species were identified in a total of 35,608 *Candida* isolates analyzed in these studies. In most studies examined, *C. albicans* (66.3%) was the predominant species, followed by *C. glabrata* (11.7%), *C. parapsilosis* (10.7%), *C. tropicalis* (9.5%), and *C. krusei* (1.19%). Vaginal swabs yielded the most isolates, followed by the respiratory system, urine, blood, oral, pus, and other locations. The demographic, racial, and gender data were recorded only in two studies. Totally, eight studies examined 396 isolates for antifungal susceptibility to common antifungal medications. The average antifungal susceptibility of isolates and efficacy of drugs in these studies ranged between 45 and 99% for most common antifungal drugs. Caspofungin had the highest susceptibility at 99%, whereas itraconazole had the lowest at only 45%. Overall, this review provided a comprehensive summary of all the current research on predominant *Candida* species in Peninsular Malaysia.

**Keywords:** Antifungal drugs, *Candida* infections, Malaysia, prevalence

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## Introduction

*Candida* infections are undoubtedly the most prevalent among opportunistic and invasive mycoses worldwide. There are around 154 species in this genus,[1,2] out of which more than 30 species of *Candida* have been reported to cause infections.[3,4] Among them, the six most frequently isolated species in human infections include *C. albicans*, C. *glabrata*, *C. parapsilosis*, *C. krusei* (*Pichia kudriavzevii*), and *C. lusitaniae*.[2] C. *albicans* is the most common species found worldwide.[2]

Recent developments in diagnostic methods, especially molecular identification methods, have resulted in the discovery of new infection-causing species of *Candida* worldwide (e.g., C. *dubliniensis*, *C. fermentati, C. nivariensis, C. bracarensis*, and recently *C. auris*).[5-7] The Centers for Disease Control and Prevention (CDC) did a population-based study on candidemia in the United States from 1992 to 93 and again from 2008 to 11. They found that the incidence of candidemia caused by C. *parapsilosis* and C. *glabrata* rose two-and-four-fold, respectively, between those years, indicating a rise in the prevalence of those two species in that region.[8] Similarly, various other prevalence studies from different institutions, cities, countries, and broad geographic regions have reported the emergence of various non-*albicans Candida* (NAC) species and their potential to develop antifungal resistance as well.[9-12]

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With the rising prevalence of various species, *Candida* infections have also increased, with over 700,000 cases of invasive candidiasis annually worldwide, according to a global review on *Candida* published in 2017 by Bongomin *et al.*[13] According to that report, the highest rate of candidemia was observed in Asia, followed by the Americas, Europe, and Africa. Among these, the highest candidemia was reported in Pakistan (38,795 cases, 21 cases per 100,000), and the lowest incidence figures were reported in Jamaica (136 cases, 5 per 100,000).[13] However, this review did not address the prevalence of *Candida* in Malaysia.

The resistance of *Candida* infections to antifungal drugs is also on the rise, along with the enhanced prevalence of candidemia and candidiasis, especially among immunocompromised patients. This situation can be linked to compromised healthcare systems, inadequate resources, poor infection control implementation, unavailability of diagnostic tests, excess empirical therapy, less knowledge about fungal infections, or misuse of antifungals.[13] Local epidemiological data concerning the prevalence and antifungal susceptibility of pathogens is essential in guiding empirical antifungal therapy in patients and managing the disease in every country.[14-16] Some species are inherently resistant to antifungals, such as *C. krusei* isolates to fluconazole[8] and *C. glabrata* isolates to flucytosine, azoles, and caspofungin.[17] Moreover, resistance to common antifungals like fluconazole and echinocandins has increased in NAC species compared with C. *albicans* isolates. The lack of local epidemiological data in many countries and differences in the quality of the data indicate that the global burden of candidemia is still underestimated.

Data on the epidemiology and the antifungal susceptibility of *Candida* species infections in Malaysia is still limited. For the proper management of *Candida* infections, it is crucial to determine the prevalence and antifungal susceptibility pattern of *Candida* infections in all geographical regions of Malaysia. This review attempts to report the overview of studies reported on the prevalence, species distribution based on the identification, and antifungal susceptibility pattern of *Candida* species infections in Malaysia. This effort may highlight the need to work on the epidemiology of *Candida* infections in Malaysia and conduct studies that can fill the gap in identifying and treating such fungal infections.

# Materials and Methods

## Study design

A review of a total of 22 published articles was conducted in Malaysia. The study was approved by the Medical Research Ethics Committee of AIMST University and the National Medical Research Register (Advancing medical research in Malaysia) NMRR-20-1588-53243 (IIR).

## Inclusion criteria and exclusion criteria

All hospital-based studies on *Candida* species published in Malaysia written in English between 2009 and 18 were included. Studies published before 2009 in which *Candida* speciation was not conducted were excluded from consideration.

## Study selection and data management

Studies were gathered from the National Center for Biotechnology Information (NCBI) and Google Scholar by conducting keyword searches for articles containing the keywords "*Candida* and Malaysia." Preliminary titles and abstracts were screened out initially, identifying the potentially valuable studies. The full papers of these studies were screened for content to ensure that information was useful in our analysis. Eligible articles based on inclusion criteria were selected for data extraction. Full texts of these eligible articles were again assessed against the predefined inclusion criteria and a quality assessment process; studies satisfying these criteria were finally included in the review [Figure 1]. A total of 27 articles were identified in the initial search, with 22 articles analyzed for this detailed analysis and review based on inclusion criteria [Figure 1].

## Data extraction and analysis

The data obtained from the full text of these 22 articles were organized, analyzed, and summarized in excel worksheets. These studies were conducted in different universities, hospitals, and reference laboratories in Malaysia. Results were analyzed and compiled using basic mathematical and statistical techniques. The results are briefed in the form of tables and figures.

# Results

Almost all the studies were conducted in the southern region of Malaysia. A total of 35608 *Candida* isolates were collected in these studies for different purposes. In total, 19 *Candida* species were identified along with 60 unidentified *Candida* isolates in these studies. The most common methods used for identification were CHROMagar, microscopy, biochemical tests, and API 20C Aux.

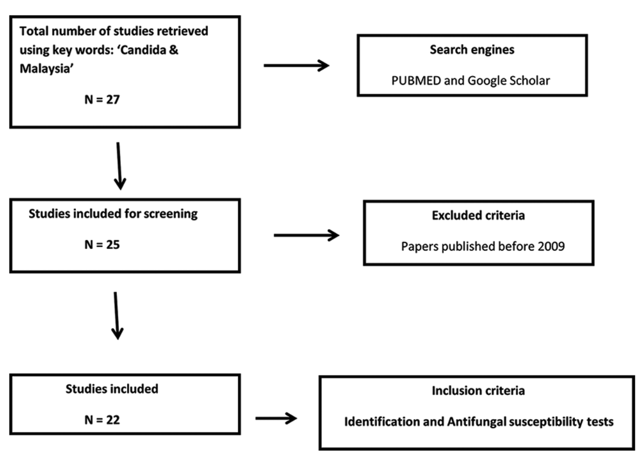


**Figure 1:** Flow chart showing the process of studies selection

The most dominant species was *C. albicans*, with a prevalence of 66.3% (n = 23640). However, in a few studies, NAC marginally outnumbered *Candida albicans*. Among NAC species, the prevalence of *C. glabrata* was the most frequently detected, with n = 4169 (11.7%), followed by *C. parapsilosis* 3842 (10.7%), C. *tropicalis* 3392 (9.5%), and *C. krusei* 424 (1.19%), which are among the most common NAC species [Figure 2].

Other NAC included C. *rugosa* (26), C. *lusitaniae* (12), C. *famata* (12), C. *dubliniensis* (10), C. *pelliculosa* (6), C. *sake* (5), C. *kefyr* (1), C. *guiliermondii* (3), C. *melibiosica* (2), and one isolate each of C. *valida,* C. *inconspicua*, C. *orthopsilosis*, and C. *globosa* (one each). Almost 60 isolates were unidentified. Only one study reported a fatal case of C. *auris* and C. *tropicalis* in a neutropenia patient in Malaysia in 2018.[18]

Most of these infections were identified as vaginal yeast infections with the highest number of isolates collected from high vaginal swabs 23318 (65.4%). These were followed by 4963 (13.9%) from the respiratory tract, 3911 (10.9%) from urine, 2118 (5.9%) from the blood, 328 (0.92%) from the oral, 293 (0.82%) from pus, and 677 (1.9%) from other sites [Figure 3].

Only two studies kept track of demographic, racial, and gender data. According to them, there were 117 *Candida* species found in Malay people, 58 in Chinese people, 29 in Indians, and 32 in other people. The *Candida* isolates collected from the males were 106, and from the females were 92[19,20] [Figure 4].

**Table 1: Antifungal susceptibility pattern found in *Candida* isolates from the studies in Peninsular Malaysia**

| Antifungal Drugs | Susceptibility (%) | Resistance (%) |
|---|---|---|
| Caspofungin | 99 | 1 |
| Amphotericin B | 98 | 2 |
| 5-Flucytocine | 97.5 | 2.5 |
| Voriconazole | 94.5 | 5.5 |
| Ketoconazole | 83.6 | 16.4 |
| Fluconazole | 82.7 | 17.3 |
| Itraconazole | 45 | 55 |

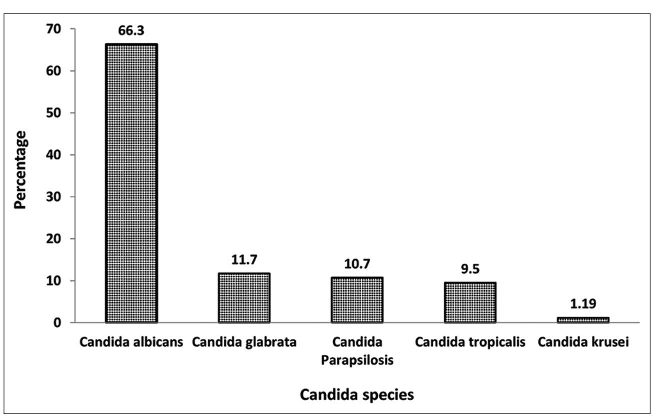


**Figure 2:** Distribution of five common *Candida* species

Only eight studies were performed antifungal susceptibility tests against the most common antifungal drugs. All studies used Clinical and Laboratory Standards Institute criteria to interpret results. Two studies used an epsilometer test strip, and others used a Sensititre YeastOne kit to check the antifungal susceptibility.[21–28]

The highest susceptibility was shown for caspofungin, while the lowest susceptibility was shown for itraconazole (99 vs. 45%, respectively) with the remaining showing a range between 82 and 98% [Table 1]. These results indicated that most infections were easily contained with prompt treatment.

There were some exceptions to these findings in a few instances. In a study, all strains of *C. krusei* were resistant to fluconazole, and 50% were susceptible in a dose-dependent manner to voriconazole.[28] While in another study, all *Tropicalis* were resistant to fluconazole.[23] There were 66 and 33% of C. *glabrata* that were resistant to fluconazole and voriconazole. These instances suggested the need for further studies to further delineate the mechanism of resistance in these species.

## Discussion

This literature search found only 22 studies from 2009 to 19 using the keywords "*Candida* and Malaysia" on NCBI and Google Scholar. *Candida* species were studied for various objectives in these studies, including review articles. Although we may likely miss some studies (due to the intrinsic limitations in our Medline search strategy and limiting the language to English). However, our primary purpose was to cover 10 years of research on the topic and find out the overall current status of work done on *Candida* species, including its prevalence concerning the type of species and antifungal susceptibility. The prevalence studies on *Candida* concerning age, gender, and ethnicity were not previously done in Malaysia on a large scale. The review articles on the topic are also not available in large numbers.

In this review, 19 *Candida* species were identified, along with 60 unidentified *Candida* isolates, among 35664 samples. This problem may be due to the lack of more sensitive and specific

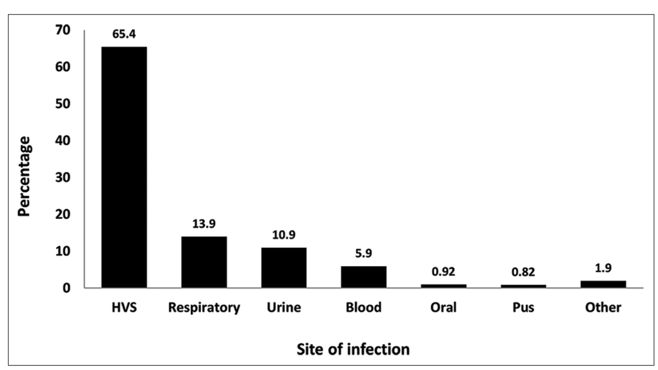


**Figure 3:** Distribution of different *Candida* species in different clinical samples

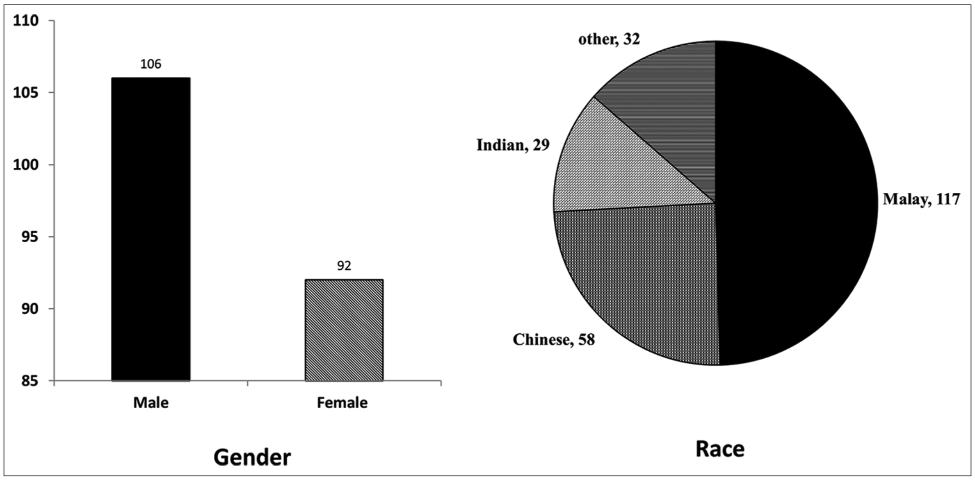


**Figure 4:** Demographic racial and gender data of *Candida* infections

identification methods, including molecular identification for *Candida* infections. Genetic-based identification methods are more in demand to solve these issues and to give specific identification of such infections. But molecular methods are not standardized and are not in use routinely for fungal infections. The results of this study are comparative to another laboratory-based large-scale surveillance study published in 2015 in Malaysia in which 16 *Candida* species were identified among 34392 samples, but that was only a laboratory-based report from 2000 to 13.[7]

Overall, we found that *C. albicans* was the most dominant species among others, with a number of 23640 (66.3%). However, in some studies, NAC marginally outnumbered *C. albicans*. These results agree with the global trend of *Candida* infections.[7,10,29,30]

Among the "common" NAC species in this study, C. *glabrata* (4169 (11.6%)) was the most predominant species, followed by *C. parapsilosis* 3842 (10.7%), *C. tropicalis* 3392 (9.5%), and *C. krusei* 424 (1.19%), respectively. The results of the global SENTRY Antifungal Surveillance Program (2008–09) and the ARTEMIS DISK Global Antifungal Surveillance Program from 1997 to 2007 are the same. According to these studies, C. *albicans* was the most common *Candida* species, followed by C. *glabrata*, C. *parapsilosis*, C. *tropicalis*, and C. *krusei*. The only difference is that C. *tropicalis* was the third most common *Candida* species in the ARTEMIS surveillance program, which is not the case with the SENTRY program.[10,29]

In this study, 19 types of *Candida* were found. In another study before this one, 16 *Candida* species were found in the Malaysian population.[7]

It shows that the number of *Candida* species that cause infections in Malaysia is growing, and the appearance of new species that did not cause infections in the past. C. *auris*, first found in 2009, is an example. As a multidrug-resistant pathogen, C. *auris* has been linked to human disease in many places. It has also caused outbreaks in different parts of the world.[31]

A fatal case of *C. auris* and *C.* t*ropicalis* in a neutropenia patient was reported in 2018 in Malaysia.[18]

Other information regarding "race" and "gender" was examined only in two studies.[19,32] In both studies, the number of male patients was marginally higher than that of female patients. It contrasts with the common trend of *Candida* infections because, usually, *Candida* is considered a dominant female infection based on published data. It is estimated that around 75% of all women experience at least one episode of vaginal *Candida* infection during their childbearing years, of which about half have at least one recurrence.[30] We found another study similar to our data in which male patients had more *Candida* infections than females. It was a population-based surveillance study conducted to assess invasive *Candida* species infections in the Calgary Health Region for 5 years.[33]

Though it is very rare, males can get a yeast infection from unprotected intercourse with a woman who has *Candida* vaginitis or who is immunocompromised because of other long-term illnesses.

According to this study, most *Candida* species were isolated from high vaginal swabs (23318, or 65.3%) and the respiratory tract (4963, or 13.9%). These findings also agree with other prevalence studies in Malaysia.[34,35] The reason for the increased growth of yeast infections in these sites is the wet and acidic environment of these sites, which increases the occurrence and growth of yeast infections.[35]

Candidemia is the most common form of bloodstream *Candida* infection associated with high mortality rates, even with the introduction of newer antifungal agents. In a global and multi-national prevalence study,[13] the estimated burden of candidemia was found for 29 countries, including Asian countries, but Malaysia was not included in that study. Our study found that 5.9% of people in Malaysia have candidemia, which is similar to the 5.9% figure from Uzbekistan in the study above.[13]

*In vitro* susceptibility testing is often used to select agents with likely activity for a given infection. However, perhaps its most important use is for identifying agents that will not work, i.e., detecting resistance. Regardless of their importance, susceptibility tests are not routinely done in most microbiology laboratories in Malaysia.

This review found only 8 out of 22 studies performed antifungal susceptibility tests.[21-28] The analysis of these studies shows the increasing resistance of NAC, especially against fluconazole and itraconazole. These results followed previous studies conducted in different parts of the world.[29,36]

According to the CDC, almost 7% of all *Candida* bloodstream isolates were resistant to fluconazole, especially NAC, such as *C. glabrata* and *C. parapsilosis*.[37] Although a low level of resistance to fluconazole is intrinsic in some *Candida* infections, increasing the level of antifungal resistance is an alarming issue for the world.

This review found that itraconazole had the lowest antifungal susceptibility, whereas caspofungin had the highest. Caspofungin has a 3 g/ml (−1) MIC against *C. parapsilosis*.[19] Caspofungin has been used successfully for several *Candida* infections.[38,39] Echinocandins and posaconazole would be the primary medications of choice for *Candida* infections associated with immunological suppression. Numerous studies conducted by many writers have corroborated this position.[39,40]

This review recommends more research on the prevalence, identification, and antifungal resistance pattern of *Candida* species from other regions of Malaysia.

The studies included are referenced in the list of references.[19-28,32,41-51]

## Conclusions

This study stresses the necessity for further large-scale prevalence investigations in all parts of the country. In the future, antifungal usage in Malaysia should be based on the susceptibility or resistance pattern of the isolates. The following points might be stressed based on Malaysian and worldwide studies: *Candida albicans* was the most prevalent, followed by *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei*. The most common locations were vaginal swabs, followed by respiratory, urine, blood, oral, pus, and miscellaneous sites. Caspofungin had the highest antifungal susceptibility, whereas itraconazole had the lowest. With the added threat of SARS-CoV-2 infection and COVID-linked mycoses, the Malaysian burden of fungal diseases may also rise, so new management techniques must be found for newly emerging pathogens like C. *auris*.

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### Conflicts of interest

There are no conflicts of interest.

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