Global Prevalence of Antifungal-Resistant Candida parapsilosis: A Systematic Review and Meta-Analysis

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Abstract: A reliable estimate of Candida parapsilosis antifungal susceptibility in candidemia patients is increasingly important to track the spread of C. parapsilosis bloodstream infections and define the true burden of the ongoing antifungal resistance. A systematic review and meta-analysis (SRMA) were conducted aiming to estimate the global prevalence and identify patterns of antifungal resistance. A systematic literature search of the PubMed, Scopus, ScienceDirect and Google Scholar electronic databases was conducted on published studies that employed antifungal susceptibility testing (AFST) on clinical C. parapsilosis isolates globally. Seventy-nine eligible studies were included. Using meta-analysis of proportions, the overall pooled prevalence of three most important antifungal drugs; Fluconazole, Amphotericin B and Voriconazole resistant C. parapsilosis were calculated as 15.2% (95% CI: 9.2–21.2), 1.3% (95% CI: 0.0–2.9) and 4.7% (95% CI: 2.2–7.3), respectively. Based on study enrolment time, country/continent and AFST method, subgroup analyses were conducted for the three studied antifungals to determine sources of heterogeneity. Timeline and regional differences in C. parapsilosis prevalence of antifungal resistance were identified with the same patterns among the three antifungal drugs. These findings highlight the need to conduct further studies to assess and monitor the growing burden of antifungal resistance, to revise treatment guidelines and to implement regional surveillance to prevent further increase in C. parapsilosis drug resistance emerging recently.

Keywords: Candida parapsilosis; prevalence; antifungal drug resistance; global; systematic review; meta-analysis

1. Introduction

Candida species, the causative agents of the majority of human fungal infections, are becoming a major public health concern [1,2]. In intensive care units (ICUs) around the world, the majority of fungus-related systemic bloodstream infections are caused by species of Candida, leading to high death rates and significant healthcare expenses for both governments and hospitalized patients [3,4]. Although Candida albicans is the most common and invasive species, its dominance has declined over the last two decades as the number of invasive infections caused by non-albicans Candida species has increased [5]. Of these, the Candida parapsilosis (C. parapsilosis) complex, which consists of the three cryptic species:
C. parapsilosis sensu stricto, C. metapsilosis and C. orthopsilosis, is of particular importance, whereas C. parapsilosis has the highest prevalence among the cryptic species [6].

Despite the availability of antifungal drugs for treating Candida infections, the mortality rate continues to increase [7]. Using a new class of antifungal drugs for infected patients has not improved their prognosis [8]. Drugs such as azoles are used for treating Candida infection and have seen an increase in Candida resistance due to general and long-term use [9,10]. Indeed, an increase in the rate of azole-resistant C. parapsilosis isolates is concerning and requires better understanding of how antifungal drug resistance emerges.

Despite the clinical and economic implications of yeast infection drug resistance, it is still poorly studied in comparison to antibiotic resistance in bacteria pathogens [11]. Although fungal pathogens account for a substantial proportion of bloodstream infection etiologies, they have received relatively less epidemiological attention. Therefore, it is of great significance to conduct a systematic review to understand the global burden of C. parapsilosis drug resistant isolates. Accordingly, the aim of this systematic review and meta-analysis (SRMA) is to survey the available data on the antifungal resistance in human’s bloodstream infections caused by C. parapsilosis. This will be carried out by systematically retrieving and reviewing this data and generating an updated and comprehensive assessment of the burden of C. parapsilosis drug resistance.

2. Materials and Methods

2.1. Protocol and Reporting Guideline

A precise protocol was agreed upon before the search began, outlining the databases to be searched, eligibility criteria, and all other methodological details. The study was carried out in accordance with the updated guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [12] (Table S1).

2.2. Search Strategy

To identify studies on the prevalence and pattern of antifungal resistance of C. parapsilosis bloodstream infections worldwide, a systematic literature search was conducted in PubMed, Scopus, ScienceDirect and Google Scholar databases. Only articles written in English were included. There were no constraints on study period, study design, or place of publication (Table S2).

2.3. Data Management and Study Selection

Initially, all the records identified based on a systematic literature search were exported to Endnote X8 (Clarivate Analytics, London, UK) to be managed. After that, duplicate potential articles were removed by automatic strategy as well as manual search before the screening and assessment of the remaining articles based on title and abstract was independently carried out by two reviewers (D.Y., M.H.A.). Thereafter, the full texts of potential records were downloaded and assessed for eligibility according to the inclusion and exclusion search criteria, by two authors (D.Y., K.H.). Any disagreement or uncertainty were revealed by discussion and consensus.

2.4. Data Extraction

The relevant data were extracted from eligible studies by two authors (D.Y. and M.H.A.). Precautions were taken to minimize errors and ensure consistency in data extraction. The following data were extracted to a predesigned Excel spreadsheet: author name, year of publication, study period, study design, country, target group, gender, method of species detection, method of antifungal susceptibility testing (AFST), sample size, total number of cases tested and number of C. parapsilosis species resistant cases for several antifungals. Overall, the data from the studies recruited from various geographical locations across the world were analysed.
2.5. Quality Assessment

Risk of bias of all selected studies was independently assessed by two authors (D.Y., A.A.M.) using the Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies [13]. For each article, the final score has been determined as the proportion of ‘yes’ answers for eight items, and subsequently the studies were categorized into “high risk of bias” (low quality) when overall score ≤ 49, “moderate risk of bias” (moderate quality) for score of 50–69% and “low risk of bias” (high quality) if the score ≥ 70%. Disagreements between the reviewers were cleared up by discussion and verification [14,15].

2.6. Data Analysis

The data entered in the Excel sheet were analysed using the R package and software. The proportion of resistance to several antifungals was calculated as the number of resistant cases relative to the total number of isolates tested for the relevant antifungal through the use of the Metaprop command. Accordingly, the prevalence of resistance to the studied antifungals (at 95% confidence intervals (CI)) was estimated for each eligible study and subsequently for the world by pooling the antifungal resistance prevalence rates of all included studies using the random-effect model. Heterogeneity between the studies was evaluated by the $I^2$ statistics in accordance with Cochran’s Q-test. A cut-off value > 75% of $I^2$ statistic was indication of substantial heterogeneity [16], whilst a $p$ value of <0.05 was considered to be a significant degree of heterogeneity. Publication bias was tested graphically using a funnel plot and statistically by Egger’s regression test.

2.7. Subgroup and Sensitivity Analysis

For the purpose of exploring the potential sources of heterogeneity, a subgroup analysis was carried out based on different subgroups which are the enrolment time of study, country where the study was conducted, and the AFST method used by using metaprop codes in meta and metafor packages of R (version 3.6.3), in RStudio (version 1.2.5033). Data analysis and the creation of the Forest and Funnel plots were performed.

3. Results

3.1. Study Selection

In a flow diagram, Figure 1 shows the results of the literature search and article selection processes. A total of 925 records were initially identified through electronic database searches. After excluding 493 duplicate records, the title and/or abstract of the remaining 432 studies were assessed for inclusion, from which 93 were eligible for full-text screening. Finally, a total of 79 studies met the eligibility criteria and included in this SRMA from which 71 studies were for fluconazole resistance prevalence, 63 for amphotericin B and 58 for voriconazole resistance.

3.2. Characteristics of Included Studies

The detailed characteristics of the 79 included studies are summarized in Table 1. Seventy-nine studies published between 1995 and 2022 met the inclusion criteria for antifungal resistance. A total of 14,371 C. parapsilosis isolates were identified and subjected to AFST. Fifty (63.3%) of the studies were conducted in America and Asia (24, 26 respectively), 19 (24.1%) in Europe, and 6 (7.6%) in Africa. With respect to the study design, the majority (68.4%, n = 54) were cross-sectional studies, (2.5%, n = 2) prospective or retrospective cohort, (1.3%, n = 1) case control, and the remaining 5 (6.3%) were population-based surveillance studies. Of the 79 articles, 71 provided data on fluconazole resistance, 63 for amphotericin B, 58 for voriconazole, 46 for caspofungin, 40 for itraconazole, 34 for micafungin and anidulafungin each and 23 for Posaconazole. Meta-analysis was performed for the three most important antifungal drugs.
| No | Study ID [References] | Study Design | Country | No. of Patients | Clinical Isolates Identification Method | AFST Method | Total Isolates Tested | Tested Antifungals |
|----|-----------------------|--------------|---------|----------------|----------------------------------------|-------------|---------------------|-------------------|
| 1  | Ahmadi 2020 [17]      | NR           | NR      | NR NR NR       | Molecular methods                      | BMD         | 15                  | FLC               |
| 2  | Alcoceba 2022 [18]    | NR           | Spain   | 53 17          | Molecular methods                      | BMD         | 104                 | FLC, AMB, POS, VOR, ANF and MCF. |
| 3  | Alencar 2017 [19]     | Cross sectional | Brazil | NR NR NR       | Molecular methods                      | Vitek-2, BMD | 7                  | FLC, AMB, ITC and VOR. |
| 4  | Almirante 2006 [20]   | Prospective Case Control | Spain | 43 35          | Conventional methods                   | BMD         | 78                  | FLC, AMB, ITC, VOR and CAS. |
| 5  | Arastehfar 2020a [21] | Cross sectional | Turkey | 123 91         | Both conventional and molecular methods | BMD         | 225                 | FLC and VOR.       |
| 6  | Arastehfar 2021 [22]  | Cross sectional | Turkey | NR NR NR       | Molecular methods                      | BMD         | 213                 | AMB, ANF and MCF.  |
| 7  | Arastehfar 2020b [23] | Cross sectional | Iran   | 45 45          | Molecular methods                      | BMD         | 98                  | FLC, AMB, ITC, ANF and MCF. |
| 8  | Asadzadeh 2017 [24]   | Cross sectional | Kuwait | NR NR NR       | Both conventional and molecular methods | E-test, Vitek-2, BMD | 442                 | FLC, AMB, VOR, CAS and MCF. |
| 9  | Asadzadeh 2008 [25]   | Cross sectional | Kuwait | NR NR NR       | Both conventional and molecular methods | E-test      | 114                 | FLC, AMB, POS and CAS. |
| 10 | Ataides 2015 [26]     | Cross sectional | Brazil | NR NR NR       | Both conventional and molecular methods | E-test      | 87                  | FLC, AMB, ITC, POS, VOR and CAS. |
| 11 | Barchiesi 2001 [27]   | Cross sectional | Italy  | NR NR NR       | Conventional methods                   | BMD         | 46                  | FLC, AMB and ITC.  |
| 12 | Bonfietti 2012 [28]   | Cross sectional | Brazil | NR NR NR       | Both conventional and molecular methods | BMD         | 152                 | FLC, AMB and ITC.  |
| 13 | Cantón 2011 [29]      | Prospective Cohort | Spain  | 231 169        | Both conventional and molecular methods | Sensititre YeastOne, BMD | 364                 | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 14 | Castanheira 2020 [30] | Cross sectional | 25 countries | NR NR NR       | Both conventional and molecular methods | BMD         | 431                 | FLC, AMB, POS, VOR, CAS, ANF and MCF. |
| 15 | Cattana 2017 [31]     | Cross sectional | Argentina | NR NR NR       | Both conventional and molecular methods | BMD         | 59                  | FLC, AMB, ITC, VOR, CAS and ANF. |
Table 1. Cont.

| No. | Study ID [References] | Study Design | Country | No. of Patients | Clinical Isolates Identification Method | AFST Method | Total Isolates Tested | Tested Antifungal |
|-----|------------------------|--------------|---------|----------------|----------------------------------------|-------------|----------------------|------------------|
|     |                        |              |         |                | Both conventional and molecular methods | Vitek-2, BMD | 29                   | FLC and VOR.     |
| 16  | Corzo-Leon 2021 [32]   | Cross sectional | Mexico  | 45  29         | Both conventional and molecular methods | BMD         | 81                   | FLC, AMB, ITC and VOR. |
| 17  | Da Silva 2015 [33]     | Cross sectional | Brazil  | 27  54         | Both conventional and molecular methods | BMD         | 105                  | CAS, ANF and MCF. |
| 18  | Davari 2020 [34]       | Cross sectional | Iran    | NR  NR         | Both conventional and molecular methods | BMD         | 36                   | FLC, AMB, VOR and CAS. |
| 19  | de Aguiar Cordeiro 2014 [35] | NR          | Italy   | NR  NR         | Both conventional and molecular methods | BMD         | 6                    | FLC, AMB and MCF. |
| 20  | de Paula Menezes 2020 [36] | Cross sectional | Brazil  | NR  NR         | Both conventional and molecular methods | BMD         | 181                  | FLC, POS and VOR. |
| 21  | Demirci-Duarte 2021 [37] | Cross sectional | Turkey  | NR  NR         | Both conventional and molecular methods | BMD         | 120                  | FLC, AMB and ITC. |
| 22  | Dizbay 2010 [38]       | Cross sectional | Turkey  | 13  14         | Conventional methods                  | E-test, BMD | 283                  | FLC, AMB, ITC, POS, VOR, CAS and MCF. |
| 23  | Ensieh 2017 [39]       | Cross sectional | Iran    | NR  NR         | Molecular methods                     | E-test, BMD | 189                  | FLC, VOR, ANF and MCF. |
| 24  | Fekkar 2021 [40]       | Cross sectional | France  | NR  NR         | Both conventional and molecular methods | BMD         | 187                  | FLC, AMB, ITC, VOR and CAS. |
| 25  | Fernández-Ruiz 2014 [41] | Cross sectional | Spain   | 127 63         | Both conventional and molecular methods | E-test, Vitek-2, BMD | 100                  | FLC, AMB, ITC and MCF. |
| 26  | Figueiredo-Carvalho 2014 [42] | Cross sectional | Brazil  | NR  NR         | Both conventional and molecular methods | BMD         | 287                  | CAS, ANF and MCF. |
| 27  | Garcia-Effron 2012 [43] | Cross sectional | Spain   | 179 108        | Both conventional and molecular methods | BMD         | 58                   | FLC, AMB, ITC, VOR and MCF. |
| 28  | Ge 2012 [44]           | Cross sectional | China   | NR  NR         | Both conventional and molecular methods | BMD         | 188                  | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 29  | Ghezzi 2017 [45]       | Retrospective cohort | Italy   | 264 188        | Both conventional and molecular methods | BMD         | 141                  | FLC, AMB, ITC and VOR. |
| 30  | Gonçalves 2010 [46]    | Cross sectional | Brazil  | 86  60         | Both conventional and molecular methods | BMD         | 141                  | FLC, AMB, ITC and VOR. |
| No | Study ID [References] | Study Design | Country | No. of Patients | Clinical Isolates Identification Method | AFST Method | Total Isolates Tested | Tested Antifungals |
|----|----------------------|--------------|---------|----------------|------------------------------------------|-------------|----------------------|------------------|
| 31 | Govender 2016 [47]   | Cross sectional | South Africa | 279/513 | 234/513 | Both conventional and molecular methods | BMD | 531 | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 32 | Grossman 2015 [48]   | Cross sectional | USA | NR | NR | Both conventional and molecular methods | E-test, BMD | 706 | FLC. |
| 33 | Hilmioglu-Polat 2018 [49] | Cross sectional | Turkey | NR | NR | Molecular methods | BMD | 170 | FLC, AMB, VOR, CAS and ANF. |
| 34 | Hirai 2014 [50]      | Cross sectional | Japan | 37/51 | 14/51 | Conventional methods | DP-Eiken | 51 | FLC, AMB, ITC and VOR. |
| 35 | Jalel 2015 [51]      | Cross sectional | Tunisia | NR | NR | Both conventional and molecular methods | E-test | 17 | FLC, AMB, ITC and VOR. |
| 36 | Khan 2011 [52]       | Cross sectional | Kuwait | NR | NR | Both conventional and molecular methods | E-test | 86 | CAS and ANF. |
| 37 | Khodavaisy 2020 [53] | Cross sectional | Iran | 34 | 67 | Molecular methods | BMD | 101 | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 38 | Liu 2018 [54]        | Cross sectional | China | 22 | 10 | NR | E-test | 32 | FLC, AMB, VOR and CAS. |
| 39 | Lockhart 2008 [55]   | Cross sectional | 25 countries | NR | NR | Both conventional and molecular methods | E-test, BMD | 1929 | FLC, AMB, CAS, ANF and MCF. |
| 40 | Magobo 2020 [56]     | Cross sectional | South Africa | NR | NR | Both conventional and molecular methods | NR | 73 | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 41 | Magobo 2017 [57]     | Cross sectional | South Africa | NR | NR | Both conventional and molecular methods | E-test, BMD | 143 | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 42 | Maria 2018 [58]      | Cross sectional | India | 42 | 35 | Both conventional and molecular methods | E-test, Vitek-2, BMD | 77 | FLC, AMB, VOR, CAS and MCF. |
| 43 | Mariangela 2015 [59] | Cross sectional | Brazil | NR | NR | Both conventional and molecular methods | Vitek-2, BMD | 43 | FLC, AMB, ITC, VOR and CAS. |
| 44 | Martini 2020 [60]    | Cross sectional | Italy | NR | NR | Molecular methods | Sensititre YeastOne, BMD | 241 | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| No. | Study ID [References] | Study Design | Country   | No. of Patients | Clinical Isolates Identification Method | AFST Method | Total Isolates Tested | Tested Antifungal |
|-----|-----------------------|--------------|-----------|-----------------|----------------------------------------|-------------|----------------------|------------------|
| 45  | Mashaly 2014 [61]     | Cross sectional | Egypt     | 29 (M) 39 (F)   | Both conventional and molecular methods | E-test      | 68                   | FLC, AMB and ITC. |
| 46  | Melo 2011 [62]        | NR           | Brazil    | NR (M) NR (F)   | Both conventional and molecular methods | NR          | 20                   | FLC and AMB.     |
| 47  | Mesini 2020 [63]      | Cross sectional | Italy     | 386 (M) 274 (F) | Both conventional and molecular methods | Sensititre YeastOne, BMD | 194           | FLC, VOR, CAS, ANF and MCF. |
| 48  | Miranda-Zapico 2011 [64] | Cross sectional | Spain     | NR (M) NR (F)   | Both conventional and molecular methods | Sensititre YeastOne, BMD | 94            | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 49  | Modiri 2019 [65]      | NR           | Iran      | NR (M) NR (F)   | Molecular methods                      | BMD         | 17                   | FLC, AMB, ITC, POS, VOR and CAS. |
| 50  | Neji 2017 [66]        | Cross sectional | Tunisia   | NR (M) NR (F)   | Both conventional and molecular methods | Sensititre YeastOne, BMD | 65            | FLC, AMB, ITC, VOR and CAS. |
| 51  | Pfaller 2008 [67]     | Surveillance | Many countries | NR (M) NR (F) | Both conventional and molecular methods | E-test, BMD | 2834                | FLC VOR, CAS, ANF and MCF. |
| 52  | Pfaller 1995 [68]     | NR           | USA       | NR (M) NR (F)   | Molecular methods                      | BMD         | 60                   | FLC, AMB and ITC. |
| 53  | Pharkjaksu 2018 [69]  | Cross sectional | Thailand  | NR (M) NR (F)   | Molecular methods                      | Sensititre YeastOne, BMD | 96            | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 54  | Pinhati 2016 [70]     | Cross sectional | Brazil    | 25 (M) 15 (F)   | Both conventional and molecular methods | Vitek-2, BMD | 28                   | FLC, AMB and ANF. |
| 55  | Prażyńska 2014 [71]   | Cross sectional | Poland    | NR (M) NR (F)   | Conventional methods                   | BMD         | 28                   | AMB. |
| 56  | Puig 2021 [72]        | Cross sectional | Spain     | NR (M) NR (F)   | Both conventional and molecular methods | MALDI-TOF   | 30                   | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF. |
| 57  | Pulcrano 2012 [73]    | NR           | Italy     | NR (M) NR (F)   | Both conventional and molecular methods | BMD         | 31                   | AMB and VOR.     |
| 58  | Raghuram 2012 [74]    | Cross sectional | USA       | NR (M) NR (F)   | Both conventional and molecular methods | NR          | 16                   | FLC and CAS.     |
| 59  | Ramos-Martinez 2022 [75] | Cross sectional | Spain     | 61 (M) 27 (F)   | Both conventional and molecular methods | BMD         | 31                   | FLC, AMB, POS, VOR and CAS. |
| 60  | Reissa 2008 [76]      | NR           | USA       | NR (M) NR (F)   | Both conventional and molecular methods | E-test, BMD | 34                   | FLC, AMB, ITC, POS, VOR and CAS. |
| No. | Study ID [References] | Study Design | Country  | No. of Patients | Clinical Isolates Identification Method | AFST Method | Total Isolates Tested | Tested Antifungal |
|-----|----------------------|--------------|----------|----------------|----------------------------------------|-------------|----------------------|------------------|
| 61  | Roberto 2020 [77]    | NR          | Brazil   | NR NR          | Molecular methods                      | MALDI-TOF-MS, BMD | 20                   | CAS, ANF and MCF. |
| 62  | Ruiz 2013 [78]       | Cross sectional | Brazil   | NR NR          | Molecular methods                      | E-test      | 49                   | FLC, AMB, ITC, VOR and CAS. |
| 63  | Růžička 2007 [79]    | NR          | Czechia  | NR NR          | Conventional methods                   | BMD         | 19                   | AMB, ITC and VOR. |
| 64  | Sakamoto 2021 [80]   | Cross sectional | Japan    | 96 51          | Conventional methods                   | DP-Eiken    | 39                   | FLC, AMB, ITC, VOR, CAS and MCF. |
| 65  | Sarvikivi 2005 [81]  | Cross sectional | Finland  | NR NR          | Both conventional and molecular methods | BMD         | 26                   | FLC. |
| 66  | Silva 2009 [82]      | Cross sectional | Portugal | NA NA          | Both conventional and molecular methods | BMD         | 160                  | FLC, AMB, POS, VOR, CAS and ANF. |
| 67  | Singh 2019 [83]      | Surveillance | India    | NR NR          | Both conventional and molecular methods | BMD         | 199                  | FLC, AMB, ITC, POS and VOR. |
| 68  | Souza 2015 [84]      | Surveillance | Brazil   | NR NR          | Both conventional and molecular methods | Vitek-2, BMD | 9                    | FLC, AMB, VOR and ANF. |
| 69  | Tay 2009 [85]        | NR          | Malaysia | NR NR          | Both conventional and molecular methods | E-test      | 42                   | FLC, AMB, ITC, KET and VOR. |
| 70  | Thomaz 2018 [86]     | NR          | Brazil   | NR NR          | Both conventional and molecular methods | BMD         | 17                   | FLC, AMB, VOR, ANF and MCF. |
| 71  | Thomaz 2021 [87]     | NR          | Brazil   | NR NR          | Molecular methods                      | E-test, BMD | 112                  | FLC, AMB, VOR, ANF and MCF. |
| 72  | Thomaz 2022 [88]     | NR          | Brazil   | NR NR          | Molecular methods                      | Disk Diffusion | 65                  | FLC. |
| 73  | Tosun 2013 [89]      | NR          | Turkey   | NR NR          | Both conventional and molecular methods | BMD         | 36                   | FLC, AMB, VOR, CAS and ANF. |
| 74  | Treviño-Rangel 2012 [90]| NR          | Mexico   | NR NR          | Both conventional and molecular methods | BMD         | 344                  | FLC CAS, ANF and MCF. |
| 75  | Vigezzi 2019 [91]    | NR          | Argentina| NR NR          | Both conventional and molecular methods | BMD         | 10                   | FLC, AMB, ITC, POS, VOR, CAS and ANF. |
| 76  | Wu 2020 [92]         | Cross sectional | China    | 33 25          | NR                                      | NR          | 58                   | FLC, AMB, ITC, VOR, and MCF. |
| No | Study ID [References] | Study Design | Country | No. of Patients | Clinical Isolates Identification Method | AFST Method | Total Isolates Tested | Tested Antifungal |
|----|------------------------|--------------|---------|----------------|----------------------------------------|-------------|----------------------|------------------|
| 77 | Xiao 2015 [93]         | Surveillance | China   | NR NR         | Conventional methods                  | E-test, Sensititre YeastOne BMD | 392      | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF |
| 78 | Yamin 2020 [94]        | Cross sectional | Malaysia | NR NR         | Conventional methods                  | NA         | 343      | FLC, AMB, VOR, and CAS |
| 79 | Zhang 2020 [95]        | Surveillance | China   | 232 87        | Molecular methods                      | Sensititre YeastOne BMD       | 319      | FLC, AMB, ITC, POS, VOR, CAS, ANF and MCF |

AFST: Antifungal Susceptibility testing, BMD: Broth Microdilution, FLC: Fluconazole, AMB: Amphotericin B, ITC: Itraconazole, KET: Ketoconazole, POS: Posaconazole, VOR: Voriconazole, CAS: Caspofungin, ANF: Anidulafungin, MCF: Micafungin, NR: Not reported.
3.2. Characteristics of Included Studies

The detailed characteristics of the 79 included studies are summarized in Table 1. Seventy-nine studies published between 1995 and 2022 met the inclusion criteria for antifungal resistance. A total of 14,371 C. parapsilosis isolates were identified and subjected to AFST. Fifty (63.3%) of the studies were conducted in America and Asia (24, 26 respectively), 19 (24.1%) in Europe, and 6 (7.6%) in Africa. With respect to the study design, the majority (68.4%, n = 54) were cross-sectional studies, (2.5%, n = 2) prospective or retrospective cohort, (1.3%, n = 1) case control, and the remaining 5 (6.3%) were population-based surveillance studies. Of the 79 articles, 71 provided data on fluconazole resistance, 63 for amphotericin B, 58 for voriconazole, 46 for caspofungin, 40 for itraconazole, 34 for micafungin and anidulafungin each and 23 for Posaconazole. Meta-analysis was performed for the three most important antifungal drugs.

3.3. Prevalence of Fluconazole-Resistant C. parapsilosis Isolates

The pooled prevalence of fluconazole-resistant C. parapsilosis, as well as the results of subgroup analysis, are shown in Table 2. The results of the seventy-one studies included in this part of the SRMA show a varied picture of fluconazole resistance rates, ranging from 0% to 100%. In 22 (31.0%) studies, all the identified isolates were susceptible to fluconazole with resistance rates of 0%, while in two other studies, fluconazole resistance was found in 100% of the tested C. parapsilosis isolates. The pooled resistance rate of C. parapsilosis to fluconazole across the 71 observational studies was estimated to be 15.2% (95% CI: 9.2–21.2) (Figure 2). Significant heterogeneity was observed across all the included studies ($I^2 = 98\%$, $p < 0.0001$). In addition, subgroup analysis was carried out based on enrolment time, country, continent and AFST method to further investigate the potential sources of heterogeneity.
Figure 2. Forest plot representing the pooled prevalence of Fluconazole-Resistant *Candida parapsilosis* isolates.

The fluconazole resistance rate has risen dramatically in the last six years, from 11.6% before 2016 to 36.7% in the period from 2016 to 2022. According to the meta-analysis, Africa had the highest prevalence of fluconazole resistance at 27.7% (95% CI: 2.7–52.8), followed by America at 21.2% (95% CI: 7.6–34.7) and Europe at 13.3% (95% CI: 1.3–25.3), while Asia had the lowest frequency of fluconazole resistance at 6.0% (95% CI: 2.9–9.1). Based on the country level (Table S3), the highest prevalence rate of fluconazole-resistant *C. parapsilosis* isolates was reported in South Africa at 51.5%, followed by Mexico at 27.0%, then Brazil at 25.3%. The lowest RA prevalence was reported in Finland and Argentina at 0.0%, followed by Japan and Portugal (0.6%), then China (1.7%). Notably, remarkable differences in fluconazole resistance rate obtained with AFST methods were observed. A slightly high overall estimate was observed when broth microdilution (16.5%; CI: 8.5–24.5) or E-test and broth microdilution (13.0%; 95% CI: 0.5–25.6) were used, while a very low number of *C. parapsilosis* isolates were found to be fluconazole-resistant through DP-Eiken
test (0.6%; 95% CI: 0.0–2.9) and all isolates were fluconazole susceptible when MALDI-TOF was used (0.0%; 95% CI: 0.0–11.6).

Table 2. Pooled C. parapsilosis antifungal resistance in different subgroups.

| Subgroups          | Prevalence of Antifungal Resistance [95% CIs] (%) | No. of Studies Analysed | Total No. of Subjects | Heterogeneity | Publication Bias, Egger's Test (p-value) |
|--------------------|-------------------------------------------------|------------------------|-----------------------|---------------|-----------------------------------------|
|                    | Fluconazole                                     |                        |                       |               |                                         |
|                    | Total                                           | 15.2 [9.2; 21.2]       | 71                    | 13,582        | 98% <0.0001                             |
| Enrolment time      | Before 2016                                     | 11.6 [4.9; 18.3]       | 43                    | 10,244        | 97% <0.01                              |
|                    | 2016–2022                                       | 36.7 [10.9; 62.6]      | 8                     | 1126          | 99% <0.01                              |
| Continent           | Europe                                           | 13.3 [1.3–25.3]       | 15                    | 2064          | 98% <0.01                              |
|                    | America                                          | 21.2 [7.6–34.7]       | 23                    | 1831          | 97% <0.01                              |
|                    | Asia                                             | 6.0 [2.9–9.1]         | 23                    | 3237          | 90% <0.01                              |
|                    | Africa                                           | 27.7 [2.7–52.8]       | 6                     | 897           | 98% <0.01                              |
|                    | Broth Microdilution                              | 16.5 [8.5–24.5]       | 43                    | 5107          | 98% <0.0001                             |
|                    | E-test and Broth Microdilution                   | 13.0 [5.5–25.6]       | 12                    | 7371          | 98% <0.01                              |
| AFST method         | E-test                                          | 11.3 [0.0–30.2]       | 8                     | 474           | 97% <0.01                              |
|                    | DP-Eiken                                        | 0.6 [0.0–2.9]         | 2                     | 90            | 0% NA                                  |
|                    | MALDI-TOF                                       | 0.0 [0.0–11.6]        | 1                     | 30            | NA NA NA                               |
|                    | Amphotericin B                                  | 1.3 [0.0–2.9]         | 63                    | 9049          | 96% <0.01                              |
| Enrolment time      | Before 2016                                     | 1.6 [0.0–4.1]         | 40                    | 6023          | 98% <0.0001                             |
|                    | 2016–2022                                       | 0.0 [0.0–0.2]         | 8                     | 1138          | 0% 1 NA                                |
| Continent           | Europe                                          | 0.1 [0.0–0.4]         | 15                    | 1733          | 0% 1 NA                                |
|                    | America                                          | 0.2 [0.0–0.7]         | 18                    | 1015          | 0% 0.95                               |
|                    | Asia                                             | 0.0 [0.0–0.2]         | 22                    | 3044          | 9% 0.34                               |
|                    | Africa                                           | 0.2 [0.0–0.05]        | 6                     | 897           | 0% 1 NA                                |
|                    | Broth Microdilution                              | 0.1 [0.0–0.2]         | 40                    | 4514          | 0% 1 NA                                |
| AFST method         | E-test and Broth Microdilution                   | 5.3 [0.0–15.5]        | 9                     | 3512          | 100 <0.0001                            |
|                    | E-test                                          | 5.3 [0.0–1.1]         | 7                     | 409           | 0% 0.95                               |
|                    | DP-Eiken                                        | 0.0 [0.0–2.1]         | 2                     | 90            | 0% 1 NA                                |
|                    | MALDI-TOF                                       | 0.0 [0.0–11.6]        | 1                     | 30            | NA NA NA                               |
|                    | Voriconazole                                    | 4.7 [2.2–7.3]         | 58                    | 10,031        | 91% <0.01                              |
| Enrolment time      | Before 2016                                     | 3.2 [1.2–5.2]         | 37                    | 8030          | 93% <0.01                              |
|                    | 2016–2022                                       | 17.9 [2.0–35.6]       | 7                     | 1132          | 98% <0.01                              |
| Continent           | Europe                                          | 5.3 [0.8–9.7]         | 15                    | 2042          | 90% <0.01                              |
|                    | America                                          | 9.2 [0.0–19.2]        | 14                    | 778           | 94% <0.01                              |
|                    | Asia                                             | 1.2 [0.3–2.0]         | 22                    | 3117          | 67% <0.01                              |
|                    | Africa                                           | 12.0 [2.4–21.6]       | 5                     | 829           | 96% <0.01                              |
|                    | Broth Microdilution                              | 4.4 [2.1–6.8]         | 37                    | 4679          | 90% <0.01                              |
| AFST method         | E-test and Broth Microdilution                   | 9.2 [0.0–22.1]        | 9                     | 4417          | 97% <0.01                              |
|                    | E-test                                          | 0.0 [0.0–0.8]         | 6                     | 341           | 0% 1 NA                                |
|                    | DP-Eiken                                        | 0.0 [0.0–2.1]         | 2                     | 90            | 0% 1 NA                                |
|                    | MALDI-TOF                                       | 0.0 [0.0–11.6]        | 1                     | 30            | NA NA Na                               |

AFST: antifungal susceptibility testing; CIs: Confidence intervals; NA: Not applicable.
3.4. Prevalence of Amphotericin B-Resistant C. parapsilosis Isolates

The pooled prevalence of amphotericin B-resistant *C. parapsilosis*, as well as the results of subgroup analysis, are shown in Table 2. The results of the 63 studies included in this part of the SRMA show a slightly varied picture of amphotericin B resistance rates, ranging from 0% to 46.9%. In 51 (81.0%) studies, all the identified isolates were susceptible to amphotericin B with resistance rates of 0%, while one study showed the highest amphotericin B resistance rate of 46.9% of the tested *C. parapsilosis* isolates. The pooled resistance rate of *C. parapsilosis* to amphotericin B across the 63 observational studies was estimated to be 1.3% (95% CI: 0.0–2.9) (Figure 3). Significant heterogeneity was observed across all the included studies ($I^2 = 96\%$, $p < 0.01$). Accordingly, subgroup analysis was carried out based on enrolment time, country, continent and AFST method to further investigate the potential sources of heterogeneity.

An amphotericin B resistance rate of 1.6% has been reported before 2016, while it decreased to 0.0% during 2016–2022. According to the meta-analysis, the four continents showed almost the same resistance rate from 0.0–0.2% (95% CI: 0.0–0.7). Based on the country level (Table S3), the highest prevalence rate of amphotericin B-resistant *C. parapsilosis* isolates was reported in Malaysia at 2.9% (95% CI: 0.0–8.3), followed by Portugal at 1.2% (95% CI: 0.2–4.4). Notably, remarkable differences in amphotericin B resistance rate obtained with AFST methods were observed. A slightly high overall estimate was

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**Figure 3.** Forest plot representing the pooled prevalence of Amphotericin B-Resistant *Candida parapsilosis* isolates.
observed when broth microdilution and E-test (5.3%; 95% CI: 0.0–15.5) or E-test (5.3%; 95% CI: 0.0–1.1) were used.

3.5. Prevalence of Voriconazole-Resistant C. parapsilosis Isolates

The pooled prevalence of voriconazole-resistant C. parapsilosis, as well as the results of subgroup analysis, are shown in Table 2. The results of the 58 studies included in this section of the SRMA reveal a varied picture of voriconazole resistance rates, ranging from 0.0 to 62.5%. In thirty-one (53.4%) studies, all the identified isolates were susceptible to voriconazole with resistance rates of 0%, while the highest resistance rate was 62.5% of the tested C. parapsilosis isolates. The pooled resistance rate of C. parapsilosis to voriconazole across the 58 observational studies was estimated to be 4.7% (95% CI: 2.2–7.3) (Figure 4). Significant heterogeneity was observed across all the included studies (I² = 91%, p < 0.01). Accordingly, subgroup analysis was carried out based on enrolment time, country, continent and AFST method for further investigation of the potential sources of heterogeneity.

![Forest plot representing the pooled prevalence of Voriconazole-Resistant Candida parapsilosis isolates.](image-url)
The voriconazole resistance rate has increased obviously in the last six years, from 3.2% before 2016 to 17.9% (2016–2022). According to the meta-analysis, Africa had the highest prevalence of voriconazole resistance at 12.0% (95% CI: 2.4–21.6), while Asia had the lowest frequency of voriconazole resistance at 1.2% (95% CI: 0.3–2.0). Based on the country level (Table S3), the highest prevalence rate of voriconazole-resistant C. parapsilosis isolates was reported in South Africa at 19.7% (95% CI: 13.5–25.8), followed by Mexico at 17.2% (95% CI: 5.8–35.8), then Brazil at 11.7% (95% CI: 0.0–25.5). The lowest RA prevalence was reported in Argentina, Czechia, India, Iran and Japan at 0.0%. Clearly, remarkable variations in voriconazole resistance rate obtained with AFST methods were noticed. A slightly high overall estimate was observed with E-test and broth microdilution (9.2%; 95% CI: 0.0–22.1), followed by broth microdilution (4.4%; 95% CI: 2.1–6.8).

3.6. Quality Assessment and Publication Bias

Supplementary Table S4 presents the results of the JBI critical appraisal checklist’s assessment of the 79 included studies’ quality. In summary, 72 (91.1%) of the studies were found to have a low risk of bias, whilst seven (8.9%) were found to have moderate risk of bias. Visual assessment of the symmetrical and asymmetrical funnel plots (Figure 5) revealed the absence and presence of publication bias, respectively. This was statistically confirmed by the Egger’s test for fluconazole, amphotericin B and voriconazole (p < 0.0001, 0.1828 and <0.0001 respectively).

4. Discussion

Invasive fungal infections caused by nosocomial pathogens such as non-albicans Candida including C. parapsilosis have emerged, besides a gradual increase in bloodstream infec-
tions in healthcare settings, as a result of the widespread administration of broad-spectrum antibiotics, immunosuppressive drugs, and chemotherapy, increased organ transplantation, application of medical support technology, the extension of human life, along with the increase in the prevalence of acquired immune deficiency syndrome (AIDS) [96–98]. Antifungal drugs are currently the most effective treatment for Candida infections [99,100]. Amphotericin B is considered as a representative of polyene antifungal drugs and has been widely used in the treatment of severe fungal infections [101]. It has been reported that amphotericin B is effective in treating more than 70% of fungal infections. However, it has several clear side effects, mainly nephrotoxicity. The first-generation azoles such as fluconazole and itraconazole show relatively good efficacy [102]. However, the bioavailability of itraconazole differs greatly, and fluconazole resistance develops readily [103]. In contrast, the new triazoles such as voriconazole and Posaconazole show a broader antifungal spectrum, higher bioavailability, and significantly fewer adverse effects than the first-generation triazole drugs. Echinocandins such as caspofungin, micafungin and anidulafungin, inhibit the synthesis of glucan synthase, and inhibit formation of the cell wall, ultimately resulting in cell death [104]. Caspofungin was the first echinocandin to be approved by the US Food and Drug Administration (FDA) and proven to be safe and efficacious against Candida species comparatively [105].

Although many authors have broadly addressed the burden of C. parapsilosis candidemia and other invasive candidiasis prevalence and antifungal susceptibility profiles, no SRMA summarizes this issue up to date. Here, we conducted a SRMA to address the prevalence of drug-resistant C. parapsilosis globally by synthesizing data published to date on C. parapsilosis antifungal susceptibility worldwide and provide a point of reference for subsequent studies. The findings of this SRMA were generated by pooling eligible data on the prevalence of antifungal resistant C. parapsilosis reported in 79 published studies.

The increasing number of nosocomial C. parapsilosis complex infections has raised concerns about conducting antifungal susceptibility tests to optimize clinical treatments. According to CLSI and IDSA, as the first-line drugs, the standardized regimen for C. parapsilosis infections treatment are azoles (fluconazole and voriconazole), amphotericin B, then caspofungin. In the present SRMA, data concerning prevalence of fluconazole, amphotericin B and voriconazole resistance are available and sub-grouped based on the enrolment time, country/continent and AFST method.

A total of 71 studies were included, from which the pooled estimate revealed that 15.2% (95% CI 9.2–21.2) of all C. parapsilosis cases, 11.6% of cases before 2016 and 36.7% of the cases from 2016 to 2022 had resistance to fluconazole. In the 71 included studies, C. parapsilosis clinical isolates were identified using conventional and/or molecular methods. Conventional methods, such as morphological characterization on CHROMagar and Cornmeal agar, and biochemical assimilation on API 20C, ID 32C, Vitek 2 and AUXACOLOR, were the most frequently employed methods, while ITS, D1/D2, PCR-RFLP-SADH, AFLP and MALDI-TOF-MS are among the molecular identification techniques. These studies were conducted in 20 different countries from four continents (Europe, America, Asia and Africa). Based on the available literature, Argentina (0.0%; 95% CI 0.0–2.3) and Finland (0.0%; 95% CI 0.0–13.2) have the lowest prevalence. On the other hand, South Africa (51.5%; 95% CI 20.2–82.7) has the highest prevalence. Variation could be seen between and cross continents. For instance, although South Africa has the highest prevalence, the prevalence of fluconazole resistant C. parapsilosis in different counties in the same continent, e.g., Tunisia (3.2%; 95% CI 0.0–7.4) and Egypt (7.4%; 95% CI 2.4–16.3), are dramatically low. It is unclear whether this difference in relative prevalence is the result of different sample size and different geographical regions or both. Data on AFST method of fluconazole resistant C. parapsilosis were available. Broth microdilution (16.5%; 95% CI 8.5–24.5) was the highest resistance to fluconazole.

In this study, we also investigated the prevalence of amphotericin B resistant C. parapsilosis from a total of 63 studies, from which the pooled estimate showed that 1.3% (95% CI 0.0–2.9), 1.6% of cases before 2016 had been resistance to amphotericin B. The range
of prevalence of amphotericin B resistance among the 20 different countries was 0.0–2.9%. Malaysia has the highest prevalence of amphotericin B resistance (2.9%; 95% CI 0.0–8.3). Data on AFST method of amphotericin B resistance showed that the studies using both broth microdilution and E-test have the highest prevalence of amphotericin B resistant \( \text{C. parapsilosis} \) (5.3%; 95% CI 0.0–15.5).

In addition, voriconazole resistance prevalence was determined among 58 studies, in which 4.7% (95% CI 2.2–7.3) of all \( \text{C. parapsilosis} \) cases, 3.2% of cases before 2016 and 17.9% of cases from 2016 to 2022 have resistance to voriconazole. The highest voriconazole resistant \( \text{C. parapsilosis} \) prevalence was reported in Africa (12.0%; 95% CI 2.4–21.6), while the lowest was in Asia (1.2%; 95% CI 0.0–19.2). In Brazil, the prevalence of voriconazole resistance was 11.7% (95% CI 0.0–25.5; \( I^2 > 75\% \); \( p \) value < 0.05), while in South Africa the prevalence was the highest (19.7%; 95% CI 13.5–25.8; \( I^2 < 75\% \); \( p \) value < 0.05). In contrast, the lowest voriconazole resistance prevalence was in China (0.9%; 95% CI 0.0–2.8). The highest prevalence of voriconazole resistance was found when testing using both, broth microdilution and E-test (9.2%; 95% CI 0.0–22.1), similar to amphotericin B resistance prevalence.

Before 2016, the prevalence of fluconazole resistance was the highest, followed by voriconazole resistance, while the prevalence of amphotericin B was the lowest. A similar pattern of antifungal resistance prevalence was found in the period from 2016 to 2022. This finding shows a steady increase in the prevalence of fluconazole resistant \( \text{C. parapsilosis} \) in the last seven years compared to studies conducted before 2016. Regardless of the high rate of fluconazole resistance in many parts of the world, fluconazole remains one of the most effective antifungal drugs. However, the high resistance rate in this study should not be neglected because fluconazole-resistant precursors might accumulate in developing country settings.

Overall, the prevalence of fluconazole resistant \( \text{C. parapsilosis} \) was higher than the prevalence of voriconazole resistant \( \text{C. parapsilosis} \) all over the four continents (ranging from 6.0–27.7, 1.2–12.0 respectively). Consequently, it is recommended to change the first-line treatment of \( \text{C. parapsilosis} \) infections from fluconazole towards voriconazole, especially in Africa, which showed sharply increased fluconazole resistance prevalence. Even though the prevalence of amphotericin B resistance is not significantly high all over the world, it is not recommended as first-line treatment for \( \text{C. parapsilosis} \) infections because it has many side-effects, cannot be administered orally, and due to its toxicity. In contrast, the same scenario of antifungal resistance could not be concluded if countries were compared. Hence, it is worthy to monitor the prevalence of antifungal resistance nationally in different countries to determine the most suitable first-line treatment for each country, because the present viewpoint might be changed if more studies were conducted locally.

Although many novel molecular AFST methods have emerged recently, broth microdilution and disc diffusion (E-test) remain the gold standard AFST assays according to CLSI and EUCAST reports, able to determine antifungal resistance with high sensitivity and specificity. The overall prevalence of fluconazole resistance \( \text{C. parapsilosis} \) identified in the current study was consistent with the finding of SRMA from India (resistance to fluconazole = 17.63%), amphotericin B = 2.15%, voriconazole = 6.61% [106].

In general, high rates of resistance to fluconazole are unfortunate realities in the majority of \( \text{C. parapsilosis} \) infections. Such high rates could reflect the frequent, unjustified and inadequate extensive usage in general care while having an unknown impact on antifungal susceptibility.

Finally, a key strength of this SRMA is a comprehensive estimation of global \( \text{C. parapsilosis} \) antifungal-resistance, despite the alarming indicative results at the level of continent, in most of the included studies rates was obtained from a smaller sample size. Therefore, expanded surveillance as well as additional studies with a large and systematic sample collection covering various geographical regions across the world are highly recommended. However, there are several limitations. First, the included studies did not encompass all the countries of the world, and only a limited number of representative studies in the same country were analysed, so the estimated prevalence might not fully reveal the magni-
tude of drug-resistant \textit{C. parapsilosis} for each county. Second, substantial heterogeneity was observed in the included studies, although this observation is common in meta-analyses estimating prevalence. Finally, the potential effect of gender, age, socioeconomic status, and lifestyle of the included patients on the prevalence of antifungal resistant \textit{C. parapsilosis} could not be analyzed because of the unavailability of data in many of the included studies.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/tropicalmed7080188/s1, Table S1: PRISMA checklist. Table S2: Detailed Search Strategy. Table S3: Pooled \textit{C. parapsilosis} antifungal resistance in different countries. Table S4: Quality assessment of the included studies.

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