Epidemiology of Culture-confirmed Candidemia Among Hospitalized Children in South Africa, 2012–2017

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Background: We aimed to describe the epidemiology of candidemia among children in South Africa.

Methods: We conducted laboratory-based surveillance among neonates (≤28 days), infants (29 days to <1 year), children (1–11 years) and adolescents (12–17 years) with *Candida* species cultured from blood during 2012–2017. Identification and antifungal susceptibility of viable isolates were performed at a reference laboratory. We used multivariable logistic regression to determine the association between *Candida parapsilosis* candidemia and 30-day mortality among neonates.

Results: Of 2996 cases, neonates accounted for 49% (n = 1478), infants for 27% (n = 806), children for 20% (n = 589) and adolescents for 4% (n = 123). The incidence risk at tertiary public sector hospitals was 5.3 cases per 1000 pediatric admissions (range 0.39–119.1). Among 2943 cases with single-species infections, *C. parapsilosis* (42%) and *Candida albicans* (36%) were most common. *Candida auris* was among the 5 common species with an overall prevalence of 3% (n = 47). Fluconazole resistance was more common among *C. parapsilosis* (55% [724/1324]) versus other species (19% [334/1737]) ($P < 0.001$). Of those with known treatment (n = 1666), 35% received amphotericin B deoxycholate alone, 32% fluconazole alone and 30% amphotericin B deoxycholate with fluconazole. The overall 30-day in-hospital mortality was 38% (n = 586) and was highest among neonates (43% [323/752]) and adolescents (43% [28/65]). Compared with infection with other species, *C. parapsilosis* infection was associated with a reduced mortality among neonates (adjusted odds ratio 0.41, 95% confidence interval: 0.22–0.75, $P = 0.004$).

Conclusions: Candidemia in this setting mainly affected neonates and infants and was characterized by fluconazole-resistant *C. parapsilosis* with no increased risk of death.

Key Words: candidemia, children, azole, South Africa

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Candida is among the leading causes of bloodstream infections in neonatal and pediatric patients globally. Pediatric *Candida* infections are particularly concerning because they are associated with a high crude mortality rate which ranges from 12% to 37% in high-income countries and 8.9%–75% in low- and middle-income countries (LMICs).[1] In a study in the United States, the attributable mortality of candidemia in children was estimated at 10%, with an additional 21.1 in-hospital days and 92,266 US dollars in excess costs.[2] *Candida* species also account for at least 5% of reported healthcare-associated outbreaks in neonatal units.[3]

The epidemiology of candidemia has been changing globally with an overall increasing incidence due to advances in medical interventions and prolonged survival of patients with immunocompromising illnesses.[1,4] Despite regional variations, a declining trend in the incidence of pediatric candidemia has been reported in US and European studies.[5–8] In LMICs, the incidence of candidemia in children is not well studied.[1] Although candidemia accounts for 0.6%–6% of all pediatric bloodstream infections in South Africa, the incidence in children is rarely reported.[9,10]

There has also been a shift in the *Candida* species causing candidemia globally, although the dominant species varies by region.[1,11] Single- and multicenter studies in South Africa have shown a shift from *Candida albicans* to *Candida parapsilosis* as the major cause of candidemia.[4,12,13] Of concern is that the shift to

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non-*C. albicans* candidemia is associated with species that have reduced susceptibility to first-line antifungals such as fluconazole.[13] A study among children with candidemia showed that while fluconazole resistance was absent among *C. albicans* isolates, 50% of non-*C. albicans* species were resistant.[14] One study in a neonatal unit reported fluconazole resistance in 85% of *C. parapsilosis* isolates.[12] Moreover, the multi-drug resistant *Candida auris* is now the third most common species among South African patients with candidemia and approximately 15% of *C. auris* bloodstream infections are reported among children.[13]

Although the incidence of candidemia is higher among children, particularly neonates, there are few studies in LMICs focused on candidemia in children compared with adults.[2,13] We conducted candidemia surveillance at multiple centers across South Africa to determine the incidence risk and species distribution of *Candida*. We compared the clinical characteristics of cases among broad childhood age groups and assessed the association between *C. parapsilosis* and mortality among neonates with an a priori hypothesis that a high prevalence of fluconazole resistance in *C. parapsilosis* would result in a higher risk of mortality compared with infections with other *Candida* species.

MATERIALS AND METHODS

Study Design

We conducted multicenter, laboratory-based surveillance for candidemia from January 1, 2012 to December 31, 2017. The surveillance was conducted in 3 distinct 2-year surveillance periods including; 2012–2013 where tertiary-level public sector hospitals in Gauteng and Western Cape provinces participated; 2014–2015 where 1 tertiary-level hospital in Gauteng Province and selected public sector hospitals in all provinces, except the Western Cape Province participated; and finally 2016–2017 where we expanded the surveillance program nationally and included both public and private sector hospitals. During all 3 surveillance periods, we used the same case definition and methods which have been described in detail elsewhere.[13,15] Briefly, all patients with a positive *Candida* blood culture were enrolled and participating diagnostic laboratories submitted all their isolates to the Mycology Reference Laboratory at the National Institute for Communicable Diseases (NICD) for confirmatory testing. Surveillance officers collected demographic and clinical information from patients at designated enhanced surveillance sites. We obtained the number of admissions at facilities where these data were available. In this study, we defined a case of pediatric candidemia as any patient <18 years old with a positive blood culture for one or more *Candida* species. When multiple positive cultures were collected within a 30-day period in the same patient, we considered that these contributed to a single episode of candidemia. We classified infections as healthcare-associated when the first positive blood culture specimen was collected ≥3 days after admission and community-associated when the specimen was collected <3 days after admission.[16] Among neonates, we used the same cutoff to distinguish early- and late-onset fungemia. We categorized children into broad age groups: neonates (≤28 days of age), infants (29 days to <12 months of age), children (1–11 years of age) and adolescents (12–17 years of age).

Laboratory Testing

A detailed description of the reference laboratory methods has been published previously.[13,15] Species confirmation of viable isolates were performed using the Vitek-2 system (bioMérieux, Marcy l'Etoile, France) or the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry flex analysis system (Bruker Daltonics, Bremen, Germany). For isolates that were not processed at the reference laboratory owing to nonviability, breakages or contamination, the diagnostic laboratory species identity was used. Antimicrobial susceptibility testing of viable isolates was performed using commercially available dried broth microdilution panels containing Alamar blue (Thermo Fisher Scientific, Cleveland, OH). Minimum inhibitory concentrations (MICs) of amphotericin B were determined by Etest (bioMérieux). MICs of antifungals were interpreted using the Clinical and Laboratory Standards Institute breakpoints.[17] We interpreted *C. auris* MICs using the Centers for Disease Control and Prevention tentative breakpoints.[18]

Data Analysis

We calculated the overall incidence risk as the sum of all cases divided by the sum of admissions at sentinel sites with available admission data. Chi-square and Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively. We used multivariable logistic regression to determine if *C. parapsilosis* candidemia compared with infection with other species was associated with an increased 30-day mortality among neonates. Only neonates with single-species infections were included in this part of the analysis. All statistical analyses were performed using Stata statistical software (Version 14; StataCorp LP, TX).

Ethical Considerations

The GERMS-SA surveillance study was approved by the Human Research Ethics Committee (Medical) of the University of Witwatersrand (No: M10464).

RESULTS

Incidence and Cases

During the study period, we identified 2996 pediatric cases of candidemia, 1745 (58%) of which were identified from 132 centers participating during 2016–2017 (Fig. 1). During 2012–2013, 2014–2015 and 2016–2017, pediatric admissions data were available for 9, 21, and 16 public sector hospitals, respectively. The overall incidence risk of pediatric candidemia was 5.3 cases per 1000 admissions (range: 0.39–119.1). Of the 2996 cases, neonates accounted for 49% (n = 1478), infants for 27% (n = 806), children for 20% (n = 589) and adolescents for 4% (n = 123) (Table 1). The median age of all cases at the time of diagnosis was 30 days (interquartile range [IQR]: 14–317 days) and 52% (1562/2956) were male. Overall, a majority of the cases were admitted to pubic sector hospitals (91%, n = 2724) and diagnosed in Gauteng Province (64%, n = 1922).

Candida Species Distribution

Of the 2996 pediatric cases, 2321 (78%) had a confirmed *Candida* species identification at the reference laboratory. The distribution of *Candida* species among viable isolates tested at the reference laboratory (n = 3317) was similar to the species distribution of isolates identified at diagnostic laboratories and not submitted for confirmation (n = 695) (Fig. 1). Of the 2996 cases, 53 (2%) had infections with more than 1 *Candida* species (mixed). Among 2943 cases with single-species infections, *C. parapsilosis* accounted for 42% (n = 1234) and *C. albicans* for 36% (n = 1058). Of the 1720 single-species infections reported during 2016–2017, *C. parapsilosis* (46%, n = 785), *C. albicans* (33%, n = 572), *Candida glabrata* (6%, n = 95), *C. auris* (3%, n = 47) and *Candida tropicalis* (3%, n = 48) were the 5 most common species (Table 1). *C. parapsilosis* was more common than *C. albicans* among neonates (45% vs. 36%) and infants (44% vs. 36%), similar among children (35% vs. 34%); and lower than *C. albicans* among adolescents (30% vs. 37%) ($P < 0.001$ for all comparisons). All cases of *C. auris*

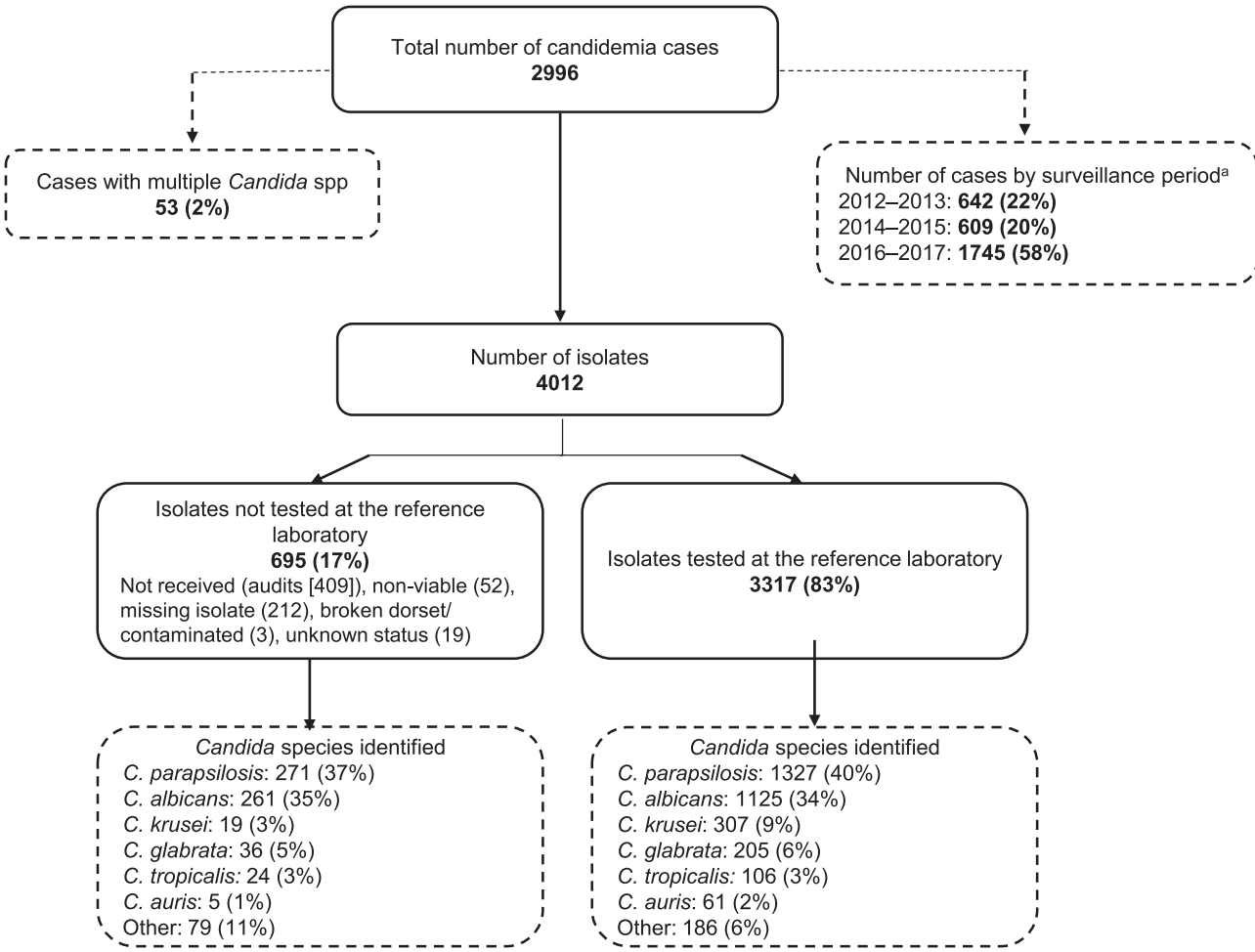

FIGURE 1. Pediatric cases of candidemia in South Africa between January 2012 and December 2017. [a]Eleven centers participated during the 2012–2013 surveillance period, 22 during the 2014–2015 period and 132 during the 2016–2017 period.

candidemia occurred during 2016–2017 and most were children (4% [24/574]) and adolescents (5% [6/122]). During 2016–2017, 84% (1474/1745) of the cases occurred in public sector facilities, and compared with the private sector, a lower proportion were due to *C. parapsilosis* (44% vs. 55%) and *C. auris* (2% vs. 6%) ($P < 0.001$ for all comparisons).

Antifungal Resistance

Of the 3317 isolates (from 2321 cases) tested at the reference laboratory, 3304 (99.6%) had susceptibility testing results for azoles (fluconazole and/or voriconazole), echinocandins (anidulafungin and/or micafungin) and/or amphotericin B (Table 2). For isolates with Clinical and Laboratory Standards Institute-defined species-specific breakpoints or intrinsic resistance, the overall resistance to fluconazole was 35% (1058/3061) and was higher in *C. parapsilosis* (55% [724/1324]) than other *Candida* species (19% [334/1737]) ($P < 0.001$). Of the 334 other *Candida* species that were resistant to fluconazole, most were *Candida krusei* (92%, n = 307), then *C. albicans* (4%, n = 13), *C. glabrata* (3%, n = 10) and *C. tropicalis* (1%, n = 4). Most of the fluconazole-resistant *C. parapsilosis* were isolated from neonates (60%, n = 434), followed by infants (31%, n = 226), children (7%, n = 53) then adolescents (2%, n = 11) ($P < 0.001$). The proportion of fluconazole-resistant *C. parapsilosis* isolates was similar in private sector hospital (58% [76/131]) and public sector hospital (54% [648/1193]) ($P = 0.713$). Three of the 3061 (0.1%) isolates tested, including 1 *C. albicans*, 1 *C. krusei* and 1 *C. tropicalis* were resistant to echinocandins. Of the 61 *C. auris* isolates tested, 90% (n = 55) were resistant to fluconazole and all were susceptible to amphotericin B (Table 2).

Clinical Characteristics

Of the 2996 cases, 2313 (77%) were admitted to a sentinel site and had a case investigation form completed. The median time from admission to candidemia diagnosis was 13 days (IQR: 6–22 days) and most of the infections were healthcare-associated (86% [1864/2179]) (Table 3). Only 9% (100/1117) of neonates had early-onset fungemia. Among children <5 years of age with available maternal HIV status data, 34% (381/1136) were HIV-exposed. The overall prevalence of HIV infection was 17% (94/569) and was highest among adolescents (37% [16/43]) ($P < 0.001$). Among those with completed information, 73% (1676/2291) had been admitted to an intensive care unit at some point during their admission, but the proportion was higher among neonates (89% [1056/1182]) and infants (72% [448/619]) compared with children (33% [133/405]) and adolescents (46% [39/85]) ($P < 0.001$). Central venous catheters (CVCs) were in situ among 51% (1049/2049) of the cases. The

TABLE 1. Distribution of *Candida* Species by Age Group, Province, Health-Sector and Surveillance Period Among Children With Single-Species Candidemia in South Africa, 2012–2017

Characteristics	All Cases (N = 2996) n (%)*	Single-species Cases (N = 2943) n (%)*	*C. parapsilosis*	*C. albicans*	*C. krusei*	*C. glabrata*	*C. tropicalis*	*C. auris*	Other	*P*
			n (%)*							
Age group										
Neonates	1478 (49)	1457 (50)	651 (45)	531 (36)	95 (7)	87 (6)	21 (1)	7 (0.5)	65 (5)	<0.001
Infant	806 (27)	790 (27)	348 (44)	288 (36)	23 (3)	38 (5)	32 (4)	10 (2)	51 (7)	
Children	589 (20)	574 (20)	199 (35)	194 (34)	31 (5)	17 (3)	38 (7)	24 (4)	71 (12)	
Adolescents	123 (4)	122 (4)	36 (30)	45 (37)	7 (6)	15 (12)	2 (2)	6 (5)	11 (9)	
Province										
Gauteng	1922 (64)	1891 (64)	835(44)	630 (33)	124 (7)	104 (6)	46 (2)	47 (3)	105 (6)	<0.001
KwaZulu-Natal	329 (11)	324 (11)	133 (41)	118 (36)	10 (3)	17 (5)	18 (6)	0 (0)	28 (9)	
Free State	272 (9)	267 (9)	137 (51)	97 (36)	7 (3)	10 (4)	3 (1)	0 (0)	13 (5)	
Western Cape	193 (6)	186 (6)	55 (30)	80 (43)	8 (4)	8 (4)	18 (10)	0 (0)	17 (9)	
Eastern Cape	103 (3)	102 (3)	25 (25)	50 (49)	3 (3)	5 (5)	2 (2)	0 (0)	17 (17)	
Others	177 (6)	173 (6)	49 (28)	83 (48)	4 (2)	13 (8)	6 (4)	0 (0)	18 (10)	
Health-sector†										
Private	271 (16)	267 (16)	149 (55)	65 (24)	3 (1)	15 (6)	6 (2)	15 (6)	14 (5)	<0.001
Public	1474 (84)	1453 (84)	644 (44)	507 (37)	41 (3)	80 (6)	32 (2)	32 (2)	70 (7)	
Surveillance period										
2012–2013	642 (21)	630 (21)	274 (44)	260 (41)	13 (2)	28 (4)	28 (4)	0 (0)	27 (4)	<0.001
2014–2015	609 (20)	593 (20)	175 (30)	226 (38)	99 (17)	34 (6)	17 (3)	0 (0)	42 (7)	
2016–2017	1745 (58)	1720 (58)	785 (46)	572 (33)	44 (3)	95 (6)	48 (3)	47 (3)	129 (8)	

*Percentages may not sum to 100 due to rounding.
†Comparisons for the health sector were done for the 2016–2017 national surveillance period.

proportion of cases for whom CVCs were removed after the diagnosis of candidemia (87% [834/960]) was lower among adolescents (76% [34/45]) compared with neonates (90% [427/476]), infants (88% [224/254]) and children (81% [149/185]) ($P = 0.002$). The median time to antifungal therapy relative to the positive specimen collection date was 2 days (IQR: 0–4 days); however, the duration was shorter for infants (2 days, IQR: −0.25–3) ($P = 0.016$). Most received amphotericin B deoxycholate alone (35%, n = 590), followed by fluconazole alone (32%, n = 527), then amphotericin B deoxycholate and fluconazole (30%, n = 502) and other antifungal agents/combinations (3%, n = 47). The overall median stay in hospital was 34 days (IQR: 18–54) with infants staying the longest (44 days [IQR: 21–67.5]) compared with all other children ($P < 0.001$). The crude 30-day in-hospital mortality was 38% (586/1530) and was highest among neonates (43% [323/752]) and adolescents (43% [28/65]), followed by infants (37% [159/427]) and children (27% [76/286]) ($P < 0.001$).

Neonatal Single-species Infections

Of 1478 neonatal cases, 1457 (99%) had single-species infections and among these, the median age was 14 days (IQR: 9–20) and 53% (758/1429) were male. Of the 1025 neonates with available data, 266 (26%) were born with a low birth weight (<2500 g) and 612 (60%) were born with a very low/extremely low birth weight (<1500 g). Of the 523 *C. parapsilosis* isolates, 68% (n = 354) were resistant to fluconazole while 16% of other *Candida* species (including 1 *C. tropicalis*, 4 *C. albicans* and 89 *C. krusei* isolates) were resistant. More neonates with *C. parapsilosis* infections were treated with amphotericin B deoxycholate-containing regimens than neonates infected with other species (82% [278/341] vs. 71% [264/371]) ($P = 0.001$). Overall, most neonates had their CVCs removed after candidemia diagnoses (90% [419/468]). The crude 30-day in-hospital mortality was 43% (317/743). Neonates with *C. parapsilosis* candidemia (37% [98/262]) were less likely to die than those infected with other species (45% [162/358]) (unadjusted odds ratio 0.72, 95% confidence interval: 0.52–1.00, $P = 0.051$) (Table 4). After adjusting for sex, birth weight, abdominal pathology, type of feeding, any surgery, prior total parenteral nutrition and antibiotic treatment, *C. parapsilosis* candidemia was still associated with a lower mortality (adjusted odds ratio 0.41, 95% confidence interval: 0.22–0.75, $P = 0.004$).

DISCUSSION

In our study, we found a high incidence of pediatric candidemia at public sector hospitals. Neonates and infants accounted for almost 80% of the children with candidemia. *C. parapsilosis* accounted for the majority of infections and there was a high overall resistance to fluconazole in this species. In our subanalysis of *C. parapsilosis* and its association with mortality among neonates, we found that despite a high prevalence of fluconazole resistance, *C. parapsilosis* was associated with a lower mortality compared with infection with other *Candida* species.

The incidence of candidemia among children in sub-Saharan Africa is unclear due to the lack of population-level studies. Nonetheless, the incidence of candidemia reported in single- and multicenter surveillance and observational studies among adults and children in LMICs ranges between 0.28 and 5.1 cases per 1000 admissions.[1] The incidence in our public sector hospitals is consistent with this reported range, but is higher than that reported in a population-based pediatric study conducted in 25 hospitals in 8 Latin American countries (0.8 cases per 1000 admissions)[19] and a national US study (0.43 cases per 1000 admission).[2] Large outbreaks, overcrowded wards, scarce infrastructure and staffing resources, and lack of antifungal stewardship programs in hospitals in our setting are possible contributing factors to the high incidence.[1,20] Similarly, these factors may also explain the large variation in incidence in our facilities.

The commonest *Candida* species in our study was *C. parapsilosis*, accounting for nearly half of all cases of candidemia. However, *C. albicans* remained the dominant species in less-populous provinces and among adolescents in our setting. *Candida albicans* is the dominant species in children in China, Latin America, Europe, the United States and England, ranging between

TABLE 2. Antifungal Susceptibility of *Candida* Isolates From Hospitalized Children With Candidemia, South Africa, 2012–2017

Antifungal Agent*	Number Tested	Number of Isolates With Minimum Inhibitory Concentration (mg/L) of: 0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	MIC_{50}	MIC_{90}	MIC Range	% Resistant
Fluconazole																				
C. parapsilosis	1324			2	11	72	206	142	52	115	**169**	**170**	**171**	**119**	**69**	**26**	8	64	0.06–256	55
C. albicans	1120	4	2	1	170	570	285	61	11	3	**1**	**5**	**3**	**2**	**1**	**1**	0.25	0.5	0.008–256	1
C. krusei†	307					1				**1**	**2**	**10**	**95**	**189**	**9**		64	64	0.25–128	100
C. glabrata	205					2	1	2	6	11	44	87	42	**6**	**4**		16	32	0.25–128	5
C. tropicalis	105				1	1	7	57	30	5	**1**	**1**	**1**	**1**			1	2	0.12–64	4
C. auris‡	61											6	**13**	**25**	**4**	**13**	64	256	16–256	90
Other§	182	1	1		15	25	36	27	28	34	9	4	2				1	4	0.015–32	
Voriconazole																				
C. parapsilosis	1324	396	89	104	138	170	175	**148**	**83**	**13**	**8**						0.12	1	0.006–8	19
C. albicans	1120	1055	33	14	9	2	4		**2**		**1**						0.008	0.015	0.008–8	0.3
C. krusei	307	1	1	8	44	177	69	6	1								0.25	0.5	0.015–2	0
C. tropicalis	105	3	11	45	34	11	1										0.06	0.25	0.008–0.5	0
Other§	448	89	27	49	48	76	105	45	6	2	1						0.25	1	0.008–8	
Anidulafungin																				
C. parapsilosis	1324	8	1	4	2	24	352	749	183	1							1	2	0.015–4	0
C. albicans	1120	699	210	150	58	2		**1**									0.015	0.06	0.008–0.6	0.1
C. krusei	307	36	183	65	21	1			**1**								0.03	0.06	0.015–2	0.3
C. glabrata	205	101	92	9	2	**1**											0.03	0.03	0.015–0.25	0
C. tropicalis	105	16	24	30	31	4											0.06	0.12	0.012–0.25	0
Candida guilliermondii	13						3	9	1								1	1.6	0.5–2	0
C. auris‡	61			12	40	8	1										0.12	0.25	0.06–0.5	0
Other§	169	70	26	17	37	11	6	2									0.06	0.25	0.012–1	
Micafungin																				
C. parapsilosis	1324	10	1	1	5	21	261	787	236	2							1	2	0.008–4	0
C. albicans	1120	1062	45	6	2	5											0.008	0.015	0.008–0.3	0
C. krusei	307	2	5	149	146	4			**1**								0.06	0.12	0.008–2	0.3
C. glabrata	205	201	2		2												0.015	0.015	0.008–0.12	0
C. tropicalis	105	42	54	7	1	1											0.03	0.03	0.008–0.15	0
C. guilliermondii	13					2	7	4									0.5	1	0.25–1	0
C. auris‡	61		1	23	32	4		1									0.12	0.12	0.03–1	0
Other§	169	32	50	61	12	6	3	5									0.06	0.12	0.008–1	
Amphotericin B																				
C. auris‡	61	2			3	33	13	10									0.38	0.75	0.003–1	0
Other§	3216	460	353	451	561	917	233	189	42	3	2	2	3				0.125	0.5	0.002–32	

The number of isolates that were resistant to antifungals are indicated in bold-face. Although breakpoints for caspofungin are defined, susceptibility testing results were not reported due to lot-to-lot variation of the potency of caspofungin powder.

*With the exception of amphotericin B for which the Etest method was used, antifungal susceptibility testing was performed using broth microdilution.

†All *Candida krusei* isolates are intrinsically resistant to fluconazole.

‡Tentative breakpoints of *C. auris* for fluconazole, anidulafungin, micafungin and amphotericin B were ≥32, ≥4, ≥4 and ≥2 mg/L, respectively.

§Other *Candida* species for which species-specific Clinical and Laboratory Standards Institute breakpoints were not defined.

35% and 68%.[5,6,19,21–24] Nonetheless, *C. parapsilosis* remains the most common non-*albicans Candida* species in these regions. *C. auris* and *C. krusei* were notably increased during 2014–2015 and 2016–2017, respectively. This was due to outbreaks of *C. krusei* in 1 public sector facility and the emergence and establishment of *C. auris* as an endemic pathogen in some facilities.[20,25] Similar to fluconazole-resistant *C. parapsilosis*, *C. auris* is likely to gain a foothold in public sector hospitals and become a common pathogen in neonatal and pediatric wards.[15] As of December 2020, *C. auris* outbreaks had been reported to the NICD in 3 neonatal units in Gauteng Province (NICD, unpublished data).

Consistent with previous South African reports, we found that just over half of *C. parapsilosis* isolates were resistant to fluconazole.[4,12,15] Although this high prevalence is unusual, reports describing the emergence of resistance to azoles in *C. parapsilosis* are increasing.[26] Most of the fluconazole-resistant *C. parapsilosis* in our study were isolated from neonates and infants which could be explained by the emergence, establishment and subsequent inter- and intra-facility spread of resistant clones in neonatal units, where fluconazole is widely used as prophylaxis and treatment.[15,27] Nearly half (48%) of the infants in our study were ≤2 months of age (data not shown) suggesting many were likely admitted to neonatal units at the time of their diagnosis. Increased attention to infection control and antifungal stewardship are warranted in neonatal units to reduce *Candida* infections and antifungal resistance.

Most children and adolescents in our setting had predisposing conditions and related medical treatment factors that likely exposed them to invasive infections with *Candida* species in community and healthcare settings. These included low birth weight, malignancy, CVCs, mechanical ventilation, and prior exposure to antifungals and antibiotics.[2,23,28–30] Healthcare-related factors, including invasive therapies, were more frequent among neonates and infants in our study. This, together with frequent low birth weight and other underlying conditions and healthcare system inadequacies, may explain the disproportionate representation of neonates in the pediatric population with candidemia.[23,29,30] The larger proportion of neonates affected by candidemia is an important issue that needs consideration. In other multicenter studies in the United States and Latin America, neonates accounted for only 29% of all pediatric cases and in a recent multi-national European study, neonates accounted for 36% of all pediatric cases, much lower proportions than in our setting.[5,19,24]

TABLE 3. Demographic and Clinical Characteristics of Children With Candidemia in South Africa, 2012–2017

Characteristics	All	Neonates	Infants	Children	Adolescents	*P*
	n (%)					
Number of cases	2996	1478 (49)	806 (27)	589 (20)	123 (4)	
Median age (IQR)	30 d (14–331)	14 d (10–20)	2 mo (1.3–4.9)	2 y (1–6)	14 y (13–16)	
Sex						0.550
Male (vs. female)	1562 (52)	770 (53)	409 (51)	321 (55)	62 (50	
Birth weight in grams						
Normal (≥2500 g)		150 (14)	—	—	—	
Low (<2500 g)		270 (26)	—	—	—	
Very low/extremely low (<1500 g)		624 (60)	—	—	—	
Intensive care unit admission*	1676 (73)	1056 (89)	448 (72)	133 (33)	39 (46)	<0.001
Mechanical ventilation†	629 (31)	372 (36)	186 (33)	51 (13)	20 (25)	<0.001
CVC *in situ*‡	1049 (51)	519 (50)	280 (51)	201 (53)	49 (61)	0.304
CVC removal after candidemia	834 (87)	427 (89)	224 (88)	149 (81)	34 (76)	0.002
Previous exposures						
Total parenteral nutrition[d]	930 (45)	610 (59)	243 (43)	65 (17)	12 (15)	<0.001
Prior systemic antifungals[d]	380 (19)	169 (16)	141 (25)	47 (13)	23 (28)	<0.001
Prior systemic antimicrobials[d]	1468 (71)	753 (73)	411 (72)	242 (62)	62 (76)	<0.001
Underlying conditions¶						
Malignancy	138 (8)	1 (0.1)	11 (3)	100 (35)	26 (39)	<0.001
Immunosuppressive treatment	96 (6)	5 (0.5)	7 (2)	61 (21)	23 (34)	<0.001
Burns	55 (2)	1 (0.1)	11 (2)	41 (7)	2 (2)	<0.001
HIV positive‖	94 (17)	11 (5)	20 (17)	47 (25)	16 (37)	<0.001
Median CD4 cell percentage (IQR)	19.6 (12.2–31.7)	44.6 (42.2–49.8)	20.1 (13.2–29.7)	14.8 (6.9–26.5)	—	0.329
Median CD4 count cells/mm^3 (IQR)		—	—	—	140 (19–305)	
Antifungal treatment						<0.001
Amphotericin B deoxycholate	590 (35)	366 (42)	149 (32)	60 (21)	15 (26)	
Fluconazole	527 (32)	194 (22)	168 (37)	138 (49)	27 (47)	
Fluconazole and amphotericin B	502 (30)	300 (35)	127 (28)	66 (23)	9 (16)	
Other drug/combinations	47 (3)	9 (1)	13 (3)	18 (6)	7 (12)	
Median time to treatment (d)**	2 (0–4)	2 (0 to 4)	2 (−0.25 to 3)	2 (0 to 4)	2 (0 to 5)	0.016
Median days of hospitalization before candidemia (IQR)	13 (6–22)	12 (7–17)	23 (6–39)	11 (2–22)	14 (5–31.7)	0.001
Healthcare-associated/late-onset fungemia	1864 (86)	1017 (91)	493 (84)	287 (74)	67 (80)	0.001††
Median days in hospital (IQR)	34 (18–54)	33 (20–47)	44 (21–67.5)	29 (14–53)	32 (17.7–56)	<0.001
30-d in-hospital mortality	586 (38)	323 (43)	159 (37)	76 (27)	28 (43)	<0.001

For patients or caregivers who provided informed consent, the HIV status was confirmed by rapid antibody tests or a PCR test done during this admission. For children <18 months, only documented HIV infection confirmed with a PCR test was included

*At any point during this admission.

†On the day of positive specimen collection.

‡On or before the day of positive specimen collection.

§≤14 days within positive specimen collection.

¶Preexisting conditions which may have led to the patient developing candidemia.

‖Includes self- or caregiver reported HIV status.

**When a patient was prescribed more than 1 antifungal at different time points, the date of earliest prescribed antifungal was considered the day of treatment initiation.

††*P*-value applies to the comparison between infants, children and adolescents only.

Similar to other studies, the crude mortality for patients with candidemia in our study was high and even higher among neonates and adolescents.[1,21] Studies on children suggest that mortality associated with *C. parapsilosis* does not differ from infections with other *Candida* species.[28,30] A meta-analysis showed that *C. parapsilosis* is associated with a 10% mortality rate among neonates.[31] The mortality rate among neonates with *C. parapsilosis* in our study was substantially higher than this, and we hypothesized that high resistance to azoles likely played an important role as antifungal resistance has been associated with poor patient outcomes due to inappropriate or delayed therapy.[32–34] However, *C. parapsilosis* candidemia was associated with a 59% lower mortality compared with infections with other species, suggesting resistance had minimal impact on mortality. Reasons for this may be that most neonates were treated with amphotericin B deoxycholate and nearly all had their CVCs removed after candidemia diagnosis.

Our study had limitations which should be considered when interpreting the results. Because we conducted surveillance at selected hospitals during various time points, our results are likely skewed to facilities which participated multiple times during these surveillance phases. We did not have admissions data for most hospitals and none for private sector hospitals. Thus, the incidence calculated in our study represented the burden of candidemia in tertiary-level public sector hospitals. We did not collect any additional information on hospital-level factors such as surveillance for infections, antifungal prophylaxis, antibiotic and antifungal prescribing practices, and infection control practices. We were therefore unable to ascertain reasons for differences in *Candida* distribution, antifungal resistance and clinical outcomes, including mortality attributable to candidemia. Lastly, there was a substantial amount of missing data across variables we analyzed, which may have impacted our comparisons between children as well as estimates in our model. We believe our results still provide valuable insight on the epidemiology of pediatric candidemia in LMICs.

CONCLUSIONS

Our study provides a snapshot of candidemia in children in an upper-middle-income country in sub-Saharan Africa, indicating

TABLE 4. Multivariable Logistic Regression Model of the Association of *C. Parapsilosis* and the 30-Day Mortality Among Neonates With Candidemia in South Africa, 2012–2017

	Alive (N = 360)	Died (N = 260)	30-day Mortality		30-day Mortality	
Characteristic	n (%)		Unadjusted OR[a] (95% CI[b])	*P*	Adjusted OR (95% CI)	*P*
Candida species						
Other *Candida*	196 (55)	162 (45)	ref			
C. parapsilosis	164 (63)	98 (37)	0.72 (0.52–1.00)	0.051	0.41 (0.22–0.75)	0.004
Sex						
Female	189 (57)	445 (43)	ref			
Male	235 (58)	173 (42)	0.96 (0.72–1.29)	0.824		
Birth weight						
Normal (≥2500 g)	95 (78)	27 (22)	ref			
Low (<2500 g)	131 (67)	65 (33)	1.76 (1.04–2.96)	0.032		
Very low/extremely low (<1500 g)	176 (49)	186 (51)	3.77 (2.35–6.06)	<0.001		
Type of feeding						
Formula/mixed	80 (54)	67 (46)	ref			
Exclusive breast-feeding	240 (70)	102 (30)	0.49 (0.33–0.73)	<0.001		
Healthcare-related exposures						
Total parenteral nutrition*	226 (55)	183 (45)	1.94 (1.40–2.69)	<0.001		
Any surgery†	69 (58)	51 (42)	1.04 (0.70–1.55)	0.830		
Prior antibiotics*	272 (56)	210 (44)	1.97 (1.38–2.83)	<0.001		
Abdominal pathology	37 (46)	44 (54)	2.13 (1.31–3.46)	0.002		

*≤14 days within positive specimen collection.
†At any point during this admission.
OR indicates odds ratio.

a high incidence of candidemia and emphasizing the high burden of infections among neonates in LMICs. We show a high prevalence of fluconazole resistance and evidence of the emergence of *C. auris* among children, which is likely to establish itself in pediatric wards if antifungal stewardship and infection prevention and control programs are not strengthened.

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