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Epidemiology, Clinical Features and Antifungal Resistance Profile of *Candida auris* in Africa: Systematic Review

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Abstract

Candida auris since it discovery in 2009 is becoming a severe threat to human health due to its very quickly spread, its worldwide high resistance to systemic antifungal drugs. In resource-constrained settings where several conditions are met for its emergence and spread, this worrisome fungus could cause large hospital and/or community-based outbreaks. This review aimed to summarize the available data on *C. auris* in Africa focusing on its epidemiology and antifungal resistance profile. Major databases were searched for articles on the epidemiology and antifungal resistance profile of *C. auris* in Africa. Out of 2,521 articles identified 22 met the inclusion criteria. In Africa, nearly 89% of African countries have no published data on *C. auris.* The prevalence of *C. auris* in Africa was 8.74%. The case fatality rate of *C. auris* infection in Africa was 39.46%. The main *C. auris* risk factors reported in Africa were cardiovascular disease, renal failure, diabetes, HIV, recent intake of an-

timicrobial drugs, ICU admissions, surgery, hemodialysis, parenteral nutrition and indwelling devices. Four phylogenetic clades were reported in Africa, namely clades I, II, III and IV. *Candida auris* showed a pan-African very high resistance rate to fluconazole, moderate resistance to amphotericin B, and high susceptibility to echinocandins. Finally, *C. auris* clade-specific mutations were observed within the *ERG2*, *ERG3*, *ERG9*, *ERG11*, *FKS1*, *TAC1b* and *MRR1* genes in Africa. This systematic review showed the presence of *C. auris* in the African continent and a worrying unavailability of data on this resilient fungus in most African countries.

Keywords

Africa, Antifungal Resistance, *Candida auris*, Clinical Features, Phylogenetic Clades

1. Introduction

Candida auris is an emerging fungal pathogen recognized as a human colonizer in 2009 [1] and a causative agent of invasive fungal infections in 2011 [2]. Since then, this worrisome yeast has rapidly emerged worldwide as a significant healthcare threat causing outbreaks, especially in intensive care settings [3] [4] [5]. *Candida auris* infection covers a wide spectrum of clinical diseases, from superficial infections to life-threatening invasive fungal infections [6]. The crude mortality rate of this new fungal pathogen ranges from 30% to 70%, depending on the patient's underlying conditions and the therapeutic management [7] [8] [9]. The emergence and spread of *C. auris* raises public global health threat due to its unique characteristics. Indeed, this fungus is characterized by its ability to colonize the human body, and its aptitude to survive in an abiotic environment for weeks [10]. This situation is associated with horizontal transmission, causing outbreaks in health care settings [11]. Furthermore, *C. auris* is frequently misidentified by standard microbiological techniques [12]. Finally, this fungus displayed a markedly decreased susceptibility to the three major classes of antifungal drugs currently approved for systemic use (azoles, echinocandins, and polyenes) [13]. Some *C. auris* isolates were reported as multidrug resistant, and others as pan-resistant [13] [14] [15]. The unique characteristics of this fungus prompted the Centers for Disease Control and Prevention (CDC) in the U.S to classify it as an urgent threat to public health, making *C. auris* one of the only five pathogens, and the single fungal pathogen to be classified as such [16]. In Europe, after the first outbreaks in 2014 and 2015, the European Centre for Disease Prevention and Control (ECDC) alerted healthcare facilities to strengthen control measures in order to prevent further hospital outbreaks [17]. Faced with the urgent need to control this fungus, organizations such as the Public Health England (PHE) or the Infection Prevention and Control (IPC) group of the International Society for Antimicrobial Chemotherapy (ISAC) have also published

recommendations for the management and control of this new yeast fungal pathogen [18] [19]. Finally, *C. auris* has been classified in the critical group of the WHO priority fungal pathogens list due to its ability to cause invasive acute and subacute systemic fungal infections for which there is antifungal drug resistance or other processing and management issues [20]. However, effective and sustainable control of this resilient fungus requires in-depth knowledge of its epidemiology and biology in all parts of the world, global awareness of its threat to public health and the adoption of recommendations on a global scale [21]. Some conditions encountered in many health facilities in resource-constrained countries like those in Africa, namely overwhelmed and overcrowded hospitals; compromised hygiene and infection control measures; overuse of antibiotics; and low awareness of fungal infections could promote the rapid spread of this fungus and undermine its global control efforts [22]. In addition, international travel to and from African countries might also promote the emergence of *C. auris* in this continent. This review highlights the available literature on *C. auris* in Africa, with particular insight into its epidemiology, clinical features and antifungal resistance profile.

2. Methods

Search Strategy, Selection Criteria, Data Extraction and Synthesis

The proposal for the present systematic review was registered on PROSPERO (registration number: CRD42023412158). PubMed, ScienceDirect, Google Scholar, and African Journal OnLine (AJOL) were searched for articles published in English. A search strategy was developed based on the epidemiology, clinical features, and antifungal resistance of *C. auris* in Africa. Studies reporting original data on *C. auris* in Africa, such as case reports, case series (≥2 cases), and observational studies were eligible for this review. No restriction was imposed on the publication date and the study design. Studies were excluded if they were commentary article and if the study population was outside African countries. Studies were also excluded if the available data did not make it possible to extract the relevant data for this review. After the literature search, the title and abstract of all citations were screened to assess their potential eligibility by two independent reviewers. Following the duplicates removed, the remaining full-text articles were also screened for inclusion by the two independent reviewers. The discrepancies between the two reviewers were resolved by discussion and consensus, if necessary, by involving a third reviewer. The systematic review was conducted as per PRISMA (Preferred Reporting Items for Systematic and Meta-analyses) guidelines [23]. Data extraction was only performed for studies that met all inclusion and exclusion criteria. The following data were extracted: country, authors, study design, prevalence, risk factors, case fatality rate, phylogenetic clades, clinical features, distribution of *Candida* species, site of *C. auris* isolation, antifungal resistance profile, and antifungal resistance mechanism of *C. auris.* For epidemiological purposes, the CDC tentative MIC breakpoints

(μg/mL) for determining *C. auris* resistant isolates were used as follows: fluconazole, ≥32; amphotericin B, ≥2; caspofungin, ≥2; anidulafungin ≥4; micafungin, ≥4 [24]. The MIC breakpoints (μg/mL) for resistance proposed by Lockhart *et al.* were used for voriconazole (≥2) and flucytosine (≥128) [25].

3. Results

3.1. Search results

A total of 2521 citations were found across four electronic databases (PubMed = 50, ScienceDirect = 203, AJOL = 58, and Google Scholar = 2210) of which 2430 were excluded after reading the titles, abstracts and type of study. Of the 91 screened, 28 duplicate articles were removed. From this screening, 63 papers were eligible for full-text screening. From this last screening process, 40 were excluded based on eligibility criteria and 23 eligible articles were retained (**Figure 1**). A study whose available data did not allow extracting the number of *C. auris* cases and the total number of cases was excluded from this study [26]. Thus, finally, 22 articles were considered for data analysis in this review.

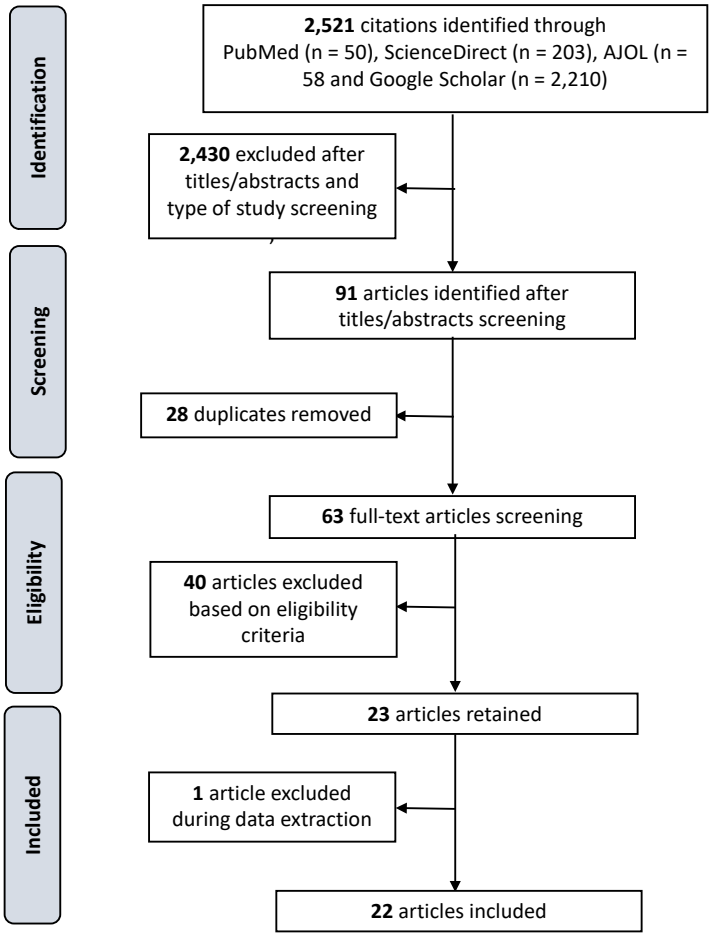

Figure 1. Flow chart of articles selected for the systematic review on the epidemiology, clinical features and antifungal resistance profile of *C. auris* in Africa, adapted from the PRISMA guidelines [23].

3.2. Epidemiology of *C. auris* in Africa

3.2.1. Distribution of *C. auris* in Africa

Data reported in Africa showed that only 6 African countries, namely Algeria, Egypt, Kenya, Nigeria, South Africa and Sudan, have published data on *C. auris i.e.* 11.11% (6/54) of African countries [27]-[48]. Three countries (Algeria, Egypt and Nigeria) reported fewer than 10 *C. auris* cases [44] [45] [46] [47] [48]. In Sudan and Kenya, 26 and 86 *C. auris* cases were reported respectively [41] [42] [43]. The country with the most reported cases of *C. auris* in Africa was South Africa with over 1000 cases (**Figure 2**) [27]-[40].

3.2.2. Prevalence of *C. auris* in Africa

The prevalence of *C. auris* in Africa was 8.74%. This prevalence in the specific group of intensive care patients and those with *C. auris* bloodstream infection (BSI) were 13.56% and 9.38%, respectively (**Table 1**). It is also important to know that a case report and 4 case series reported 1, 4, 4, 85, and 1692 *C. auris* isolates in Africa [28] [31] [37] [44] [48].

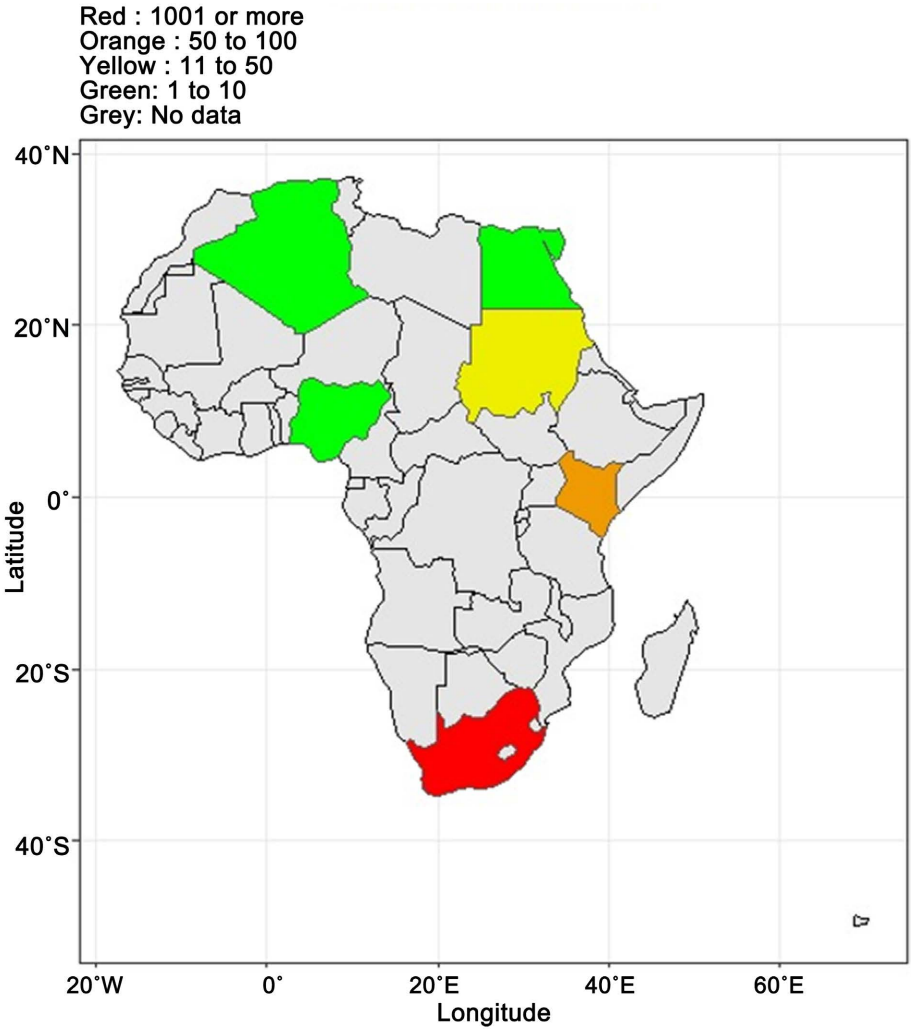

Figure 2. Distribution of *C. auris* across African countries.

Table 1. Prevalence of *C. auris* in Africa.

Country	Authors	Study population	n	N	References
Algeria	Zerrouki	Any specimen from ICU patients	7	87	[45]
Egypt	Khairat	Any routine specimens	0	400	[46]
	Maxwell	Any routine specimens	0	414	[47]
Kenya	Adam	Blood culture	77	201	[41]
	Solomon	Blood culture from ICU and HDU patients	9	31	[42]
South Africa	Chibabhai	Positive blood culture with yeast	82	618	[27]
	Hussain	Patients older than 18 years with a positive blood culture with *Candida* species	0	108	[29]
	Law	Any routine specimens	8	74	[30]
	Knorring	Any routine specimens from pediatric oncology patients	1	39	[39]
	Mashau	Blood specimens form neonates patients (0 - 27 days)	59	2956	[33]
		CSF specimens form neonates patients (0 - 27 days)	1	51	
	Schalkwyk	Blood culture	794	5876	[38]
	Shuping	Blood culture	47	1720	[36]
	Withers	Blood culture from neonates with pediatric surgical pathology	14	198	[40]
Sudan	Badri	Blood culture	26	100	[43]
TOTAL % (n/N)			8.74 (1125/12,873)		

n: number of *C. auris* cases; N: total number of cases; ICU: intensive care unit; HDU: high dependency unit; CSF: cerebrospinal fluid.

3.2.3. Distribution of *Candida* Species in Africa

Table 2 summarizes the distribution of *Candida* species in Africa. These data showed that *Candida parapsilosis* (39.91%) was the most prevalent *Candida* species in Africa. The second, third and fourth most prevalent *Candida* species were *Candida albicans*, *C. auris* and *Nakaseomyces glabrata* with 27.58%, 9.40%, and 6.68%, respectively. The other *Candida* species were *Candida tropicalis* (1.66%), *Pichia kudriavzevii* (1.44%), *Candida famata* (0.03%), *Candida lusitaniae* (0.01%), and *Candida duobushaemolumonii* (0.01%).

3.2.4. Factors Associated with *C. auris* in Africa

The associated factors reported in Africa with *C. auris* infection can be categorized into comorbidity, "history of antimicrobial use", and "hospitalization related factors". The main comorbidity factors associated with *C. auris* infection in Africa were cardiovascular disease (CVD), renal failure, diabetes (insipidus and mellitus), and tumor diseases (pituitary adenoma, prostate cancer, or malignancy). Other comorbidities such as living with human immunodeficiency virus (HIV), coronavirus disease 2019 (COVID-19), systemic lupus erythematosus (SLE), Wegeners granulomatosis, and dyslipidaemia were also reported. The recent intake of broad-spectrum antibiotics was the most frequent "history of antimicrobial use" factor associated with *C. auris* infection in Africa. The recent

Table 2. Distribution of *Candida* species in Africa.

Country	Author	*Candida* species										References
		Specimens	CP	CA	CAU	CT	NG	PK	CF	CD	CL	Other *Candida* spp.	
South Africa	Chibabhai	Blood	193	196	82	-	72	21	-	-	-	54	[27]
	Knorring	Any specimens	17	11	1	-	-	-	-	-	-	10	[39]
	Law	Any specimens	0	48	8	2	11	4	-	-	-	1	[30]
	Mashau	Blood or CSF	1014	965	60	-	-	-	-	-	-	968*	[33]
	Schalkwyk	Blood	2600	1353	794	140	598	98	-	-	-	293	[38]
	Shuping	Blood	785	572	47	48	95	44	-	-	-	129	[36]
	Withers	Blood	22	2	14	-	-	-	-	-		15	[40]
Kenya	Adam	Blood	-	50	77	-	-	-	-	-	-	74	[41]
	Solomon	Blood	6	8	9	3	-	-	3	1	1	-	[42]
Total (N = 11619)		n	4637	3205	1092	193	776	167	3	1	1	1544	
		%	39.91	27.58	9.40	1.66	6.68	1.44	0.03	0.01	0.01	14.49	

CP: *C. parapsilosis*; CA: *C. albicans*; CAU: *C. auris*; CT: *C. tropicalis*; NG: *Nakaseomyces glabrata*; PK: *Pichia kudriavzevii*; CF: *C. famata*; CD: *C. duobushaemolumonii*; CL: *C. lusitaniae*, CSF: cerebrospinal fluid; *: other yeasts species; n: number of *C. auris* isolates by *Candida* species; N: total number of *Candida* isolates.

intake of antifungal drugs has also been associated with this infection in Africa. Most factors associated with *C. auris* infection in Africa were related to "hospitalization related factors". The main "hospitalization related factors" reported were ICU patients, indwelling devices, recent surgery, hemodialysis, and parenteral nutrition. Other "hospitalization related factors" were also reported such as extension of hospital stay, mechanical ventilation, and history of recent hospitalization (Table 3).

3.2.5. Phylogenetic Clade Distributions of *C. auris* in Africa

Globally 4 phylogenetic clades were reported in Africa: clades I, II, III and IV. The most prevalent clades were clades I and III, with 47.39% each. Clades IV and II accounted for 3.79% and 1.42%, respectively. No cases of clade V have yet been reported in Africa (Table 4).

3.2.6. Case Fatality Rate of *C. auris* Infection in Africa

The case fatality rate (CFR) of *C. auris* infection in Africa was 39.46%. This CFR in the specific group of patients with *C. auris* bloodstream infection (BSI) was 38.97%. Out of 5 case reports of *C. auris* infection with outcome data reported in Africa, 4 died (Table 5) [44] [48].

3.3. Clinical Features of *C. auris* in Africa

3.3.1. Clinical Features

One study evaluated the clinical features of *C. auris* in Africa (Table 6) [35]. The data reported in this study showed that fever was more frequently observed in *C.*

Table 3. Factors associated with *C. auris* infection in Africa.

Authors	Comorbidity	History of antimicrobial using	Hospitalization related factors	References
Chibabhai	-	-	-ICU patients -Recent surgery	[27]
Zerrouki	-Renal failure -Diabetes insipidus -Heart disease -Arterial hypertension -Dyslipidaemia -Pituitary adenoma	-Recent intake of broad-spectrum antibiotics -Recent intake of antifungal drugs	-Extension of hospital stay -Recent surgery -Indwelling devices (central venous catheters, arterial catheters, nasopharyngeal tubes and urinary catheters) -Mechanical ventilation -History of recent hospitalization -Hemodialysis	[45]
El-Kholy	-Wegeners granulomatosis	-	-ICU -Parental nutrition -Hemodialysis	[48]
Oladele	-Diabetes mellitus -Hypertension -COVID-19 -Prostate cancer -SLE	-Recent intake of broad-spectrum antibiotics	-Parenteral nutrition -Hemodialysis -Indwelling devices (urinary catheterization, postoperative drain)	[44]
Adam	-HIV -Renal Failure -Diabetes -Hypertension -Malignancy*	-Recent intake of broad-spectrum antibiotics	-ICU -Indwelling devices (central venous catheters)	[41]

COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; ICU: intensive care unit; SLE: systemic lupus erythematosus; *: the type of malignancy was not specified.

Table 4. Phylogenetic clade distributions of *C. auris* in Africa.

Country	Author	Number of isolates in				Total	References
		clade I	clade II	clade III	clade IV		
Algeria	Zerrouki	1	1	2	3	7	[45]
Nigeria	Oladele	2	0	0	2	4	[44]
South Africa	Magobo, 2020	83	2	0	0	85	[31]
	Naicker	14	0	98	3	115	[34]
Total (N = 211)	n	100	3	100	8	211	
	%	47.39	1.42	47.39	3.79	100	

n: number of isolates by clade; N: total number of isolates.

auris group than *C. albicans* and *N. glabrata* groups ($p < 0.001$). These data also showed that compared to *C. albicans* group, sepsis was more common in *C. auris* group ($p = 0.04$).

Table 5. Case fatality rate of *C. auris* infection in Africa.

Country	Authors	Site of isolation	Case fatality rate		References
			n	N	
Kenya	Adam	Blood	22	77	[41]
South Africa	Maphanga	Blood	35	75	[32]
	Schalkwyk	Blood	42	102	[38]
	Parak	Any specimen	19	45	[35]
Total % (n/N)			39.46 (118/299)		

n: number of fatal cases; N: number of *C. auris* infection cases.

Table 6. Clinical features of *C. auris* in Africa.

	C. auris % (n/N)	*C. albicans* % (n/N)	*N. glabrata* % (n/N)	p-values	
				C. auris vs. *C. albicans*	*C. auris* vs. *N. glabrata*
Hypotension	29.27 (12/41)	22.22 (10/45)	33.33 (15/45)	0.45	0.68
Altered mental state	39.02 (16/41)	31.11 (14/45)	39.53 (17/43)	0.44	0.91
Fever	68.29 (28/41)	31.11 (14/45)	33.33 (15/45)	<0.001*	0.001*
Temperature spikes	75 (21/28)	50 (7/14)	6.67 (1/15)	-	-
Sepsis	70.73 (29/41)	48.89 (22/45)	53.33 (24/45)	0.04*	0.1
Septic shock	26.83 (11/41)	20 (9/45)	26.67 (12/45)	0.45	0.99

* Statistical significance ($p < 0.05$); n: number of patients with the clinical sign; N: total number of patients.

3.3.2. Site of *C. auris* Isolation

A total of 70.71% (2416/3417) of *C. auris* strains were isolated from sterile sites versus 29.29% (1001/3417) from non-sterile sites (Table 7 and Table 8). Of the strains isolated from sterile sites 81.71% were from blood isolation (Table 7). Urine and respiratory tract fluid were the main non-sterile sites of *C. auris* isolation with 68.83% and 19.68%, respectively (Table 8).

3.4. Antifungal Resistance of *C. auris* in Africa

3.4.1. Distribution of Resistant *C. auris* in Africa

Table A1 (in **Annex**) summarizes the distribution of *C. auris* resistant isolates in Africa. Available data in Africa showed that at least 80% of *C. auris* isolates were resistant to fluconazole regardless of the antifungal susceptibility testing (AFST) method (BMD, E-test or Vitek methods). The proportions of these fluconazole-resistant isolates ranged from 81.44% to 91.3%, depending on the AFST method. MICs values for fluconazole-resistant isolates ranged from 32 to ≥256 mg/L regardless of the method used. According to the BMD method, 29.14% (153/525) of fluconazole-resistant isolates had MICs values ≥ 256 mg/L. Proportions of fluconazole-resistant isolates with MICs values ≥ 256 mg/L were 35.71% (5/14) and 31.64 (25/79) with E-test and Vitek methods, respectively. *Candida auris* resistance to amphotericin B was 18.60% and 4.82% for BMD and E-test,

Table 7. Repartition of *C. auris* isolates across sterile sites.

Country	Authors		Number of isolates in sterile sites						Total	References
			Blood	CSF	Tissue	Fluid	Bone	CVC tips		
Algeria	Zerrouki		-	-	-	4	-	-	4	[45]
Egypt	M. El Kholy		1	-	-	-	-	-	1	[48]
Kenya	Adam		77	-	-	-	-	-	77	[41]
	Solomon		9	-	-	-	-	-	9	[42]
Nigeria	Oladele		3	-	-	-	-	-	3	[44]
South Africa	Chibabhai		82	-	-	-	-	-	82	[27]
	Govender		344	2	49	56		288	739	[28]
	Magobo, 2014		4	-	-	-	-	-	4	[37]
	Magobo, 2020		2	-	4	-	-	19	25	[31]
	Maphanga		400	-	-	-	-	-	400	[32]
	Mashau		59	1	-	-	-	-	60	[33]
	Naicker		86	-	-	-	-	-	86	[34]
	Parak		26	-	2	1	1	15	45	[35]
	Schalkwyk		794	-	-	-	-	-	794	[38]
	Shuping		47	-	-	-	-	-	47	[36]
	Withers		14	-	-	-	-	-	14	[40]
Sudan	Badri		26	-	-	-	-	-	26	[43]
Total (N = 2416)		n	1974	3	55	61	1	322	2.416	
		%	81.71	0.12	2.28	2.52	0.04	13.33	100	

CSF: Cerebrospinal fluid; n: number of isolates per sterile site; N: total number of isolates in sterile site; CSF: cerebrospinal fluid; CVC: central venous catheter.

Table 8. Repartition of *C. auris* isolates across non-sterile sites.

Country	Authors		Number of isolates in non-sterile sites							Total	References
			Urine	Respiratory tract fluid	Skin	Mucosal	Wound	Irrigation fluid	Environment1		
South Africa	Govender		622	173		45		-	-	840	[28]
	Magobo, 2020		22	3	-	-	-	5	-	30	[31]
	Naicker		1	-	11	-	-	-	10	22	[34]
	Parak		20	-	2	1	-	-	-	23	[35]
Algeria	Zerrouki		23	20	-	-	40	-	-	83	[45]
Nigeria	Oladele		1	1	1	-	-	-	-	3	[44]
Total (N = 1001)		n	689	197	14	46	40	5	10	1001	
		%	68.83	19.68	1.40	4.60	4.00	0.50	0.99	100	

1: hands of healthcare workers, handwashing basin, bed linen and bed rails, windowsill, curtain, drying rack and on the floor around a bed; CVC: central venous catheter; n: number of isolates per non-sterile site; N: total number of isolates in non-sterile site.

respectively. MICs values for amphotericin B-resistant isolates ranged from 2 to 12 mg/L regardless of the AFST method used, with 2.80% (3/107) and 8.70% (2/23) of these isolates exhibiting MICs values of 8 mg/L with BMD and E-test methods respectively. Resistance to echinocandins (micafungin and anidulafungin), regardless of the AFST method used, was less than 2%. MICs values for micafungin-resistant isolates ranged from 4 to 16 mg/L, with 33.33% (3/9) of these isolates exhibiting MICs values of 8 mg/L with BMD method. According to the E-test method 100% (2/2) of two micafungin-resistant isolates exhibited MICs values of 16 mg/L. Only one *C. auris* anidulafungin-resistant isolate was reported in Africa with MIC value of 4 mg/L. Available data on *C. auris* in Africa also showed voriconazole resistance to be 2.26%, 31.25%, and 6.94% with BMD, E-test, and Vitek methods, respectively. MICs values for voriconazole-resistant isolates ranged from 2 to ≥32 mg/L with 7.69% (1/13) of these isolates exhibiting MICs values ≥ 8 mg/L with BMD method. According to E-test method, 40% (2/5) of voriconazole-resistant isolates exhibited MICs values ≥ 12 mg/L. No cases of flucytosine-resistant isolates have yet been reported in Africa.

Table 9 depicts the antifungal susceptibility profile of *C. auris* isolates across the phylogenetic clades. Of the 105 *C. auris* isolates with whole genome sequencing (WGS) analysis data, 93 (88.57%) were resistant to at least one antifungal agent, and only 12 isolates (11.42%) were susceptible to all antifungal agents (Table 9). All 17 clade I isolates (100%) were resistant to at least one antifungal agents. Of this clade I, 70.59% (12/17) were resistant to both fluconazole and amphotericin B, and one (5.882%) was pan-resistant (fluconazole, amphotericin B, and micafungin). Among clade III isolates, 91.14% were resistant to at least one antifungal agents, 8.86% to both fluconazole and amphotericin B, and two (2.53%) were pan-resistant (fluconazole, amphotericin B, and micafungin). Of the eight clade IV isolates, 50% (4/8) were resistant to at least one antifungal agent. All four resistant clade IV isolates were fluconazole-resistant, and one isolate was also resistant to caspofungin. The only one clade II *C. auris* strain reported in Africa was susceptible to all antifungal agents.

3.4.2. Mechanism of *C. auris* Antifungal Resistance

Table A2 (in **Annex**) summarizes the mechanism of *C. auris* antifungal resistance in Africa. *Candida auris* clade-specific mutations were observed within the *ERG2*, *ERG3*, *ERG9*, *ERG11*, *FKS1*, *TAC1b* and *MRR1* genes in Africa. Out of the 30 clade I isolates reported, 14 fluconazole-resistant isolates had Y132F *ERG11* substitutions, while 2 fluconazole-resistant isolates had Y132F/L125F *ERG11* substitutions. The remaining clade I fluconazole-resistant isolates had uncommon substitutions namely one E39D *ERG2*, one L148I, R937S, I701V, and I694V *FKS1HP1* (*FKS1* hot spot1), one A651P *TAC1b*, and 8 A657V *TAC1b* substitutions. Three clade I echinocandin (anidulafungin and micafungin)-susceptible isolates had D642Y substitution due to a mutation within the *FKS1HP1* region. Among clade III 68 fluconazole-resistant isolates and 8 fluconazole-susceptible isolates had VF125AL *ERG11* substitutions. One and 15 clade III fluconazole-

Table 9. Antifungal susceptibility profiles of *C. auris* isolates across phylogenetic clades.

Antifungal	Authors, N	Number (%) in				References
		Clade I	Clade II	Clade III	Clade IV	
Resistant isolates (n = 93)						
Fluconazole	Maphanga and Naicker	1	-	60	2	[32] [34]
	Zerrouki	-	-	2	2*	[45]
	Oladele	2	-	-	-	[44]
Amphotericin B	Maphanga and Naicker	-	-	1	-	[32] [34]
	Zerrouki	-	-	-	-	[45]
	Oladele	-	-	-	-	[44]
Fluconazole and amphotericin B	Maphanga and Naicker	12	-	7	-	[32] [34]
	Zerrouki	1	-		-	[45]
	Oladele	-	-		-	[44]
Fluconazole, amphotericin B, and micafungin	Maphanga and Naicker	1	-	2	-	[32] [34]
	Zerrouki	-	-	-	-	[45]
	Oladele		-		-	[44]
Susceptible isolates (n = 12)						
Fluconazole	Maphanga and Naicker	-	-	-	-	[32] [34]
	Zerrouki	-	-	-	-	[45]
	Oladele	-	-	-	-	[44]
Amphotericin B	Maphanga and Naicker	-	-	-	-	[32] [34]
	Zerrouki	-	-	-	-	[45]
	Oladele	-	-	-	-	[44]
Fluconazole and amphotericin B	Maphanga and Naicker	-	-	-	-	[32] [34]
	Zerrouki	-	-	-	-	[45]
	Oladele	-	-	-	-	[44]
Fluconazole, amphotericin B, and micafungin	Maphanga and Naicker	-	-	7	1	[32] [34]
	Zerrouki		1		1	[45]
	Oladele				2	[44]
Total		17	1	79	8	

*: one isolate was also resistant to caspofungin.

resistant isolates had S195G *TAC1b* and A651P *TAC1b* substitutions, respectively. Among clade III 68 fluconazole-resistant isolates and 8 fluconazole-susceptible isolates also exhibited uncommon N647T *MRR1* substitutions. Two clade III echinocandin-resistant isolates and one clade III echinocandin-susceptible isolate had S639P *FKS1HP1* substitutions. One clade III echinocandin-susceptible isolate had uncommon T125I, C1253fs [fs = frameshift], and G1250S substitutions due to a mutation within the *FKS1HP1* region. Two clade IV flucona-

zole-resistant isolates and three clade IV fluconazole-susceptible isolates had uncommon E343D, N335S, and K177A *ERG11* substitutions. One clade IV amphotericin B-resistant isolate and one clade IV amphotericin B-susceptible isolate had uncommon M351V and A27T *ERG9* substitutions. Two clade IV amphotericin B-susceptible isolates and one clade IV amphotericin B-susceptible isolate also had uncommon S58T *ERG3* substitution and within the *MRR1* gene (S30T, N70S, E76_P77delnsDS, D80E, N133S, K138E, K167N, L211V, R249K, R280G, R413K, and K534N), respectively.

4. Discussion

This systematic review shows that nearly 89% of African countries have no published data on *C. auris* even though several favourable conditions for its emergence and spread on this continent are met. This lack of data on *C. auris* in the large majority of African countries could further hide the existence of undiagnosed cases of *C. auris* infection. These potential undiagnosed cases of *C. auris* could promote the occurrence of large hospital outbreaks. The management of such outbreaks in many of these African hospitals would be very difficult due to scarcity of infrastructure, overcrowded hospitals, compromised hygiene and infection control measures, [22] unavailability of effective antifungals and because most of patients in these countries are economically deprived. Moreover, the control of accessibility in most of these hospitals not being strict, it cannot be ruled out that this situation could also promote community-based outbreaks of *C. auris* infection. It is important and very urgent that studies be carried out to map *C. auris* in all African countries. Medical personnel and national health authorities in African countries must be quickly made aware of the threat posed by this new resilient fungus. Finally, each African country should establish a management protocol for *C. auris* including preventive measures and diagnosing and treating of this fungal pathogen. The prevalence of *C. auris* in Africa was 8.74%. This prevalence could be only the tip of the iceberg given the lack of data in most African countries and the difficulty of diagnosing this fungus with routine laboratory methods. This prevalence is consistent with data from a previous study [49]. The prevalence of *C. auris* BSI in this study (9.38%) was lower than in previous similar studies, with more than 17% [50] [51]. The low prevalence of *C. auris* in this review could be due to undiagnosed *C. auris* cases in Africa but may also be due to the currently low spread of this fungus in Africa. A recent study conducted in the United States showed that *C. auris* BSI was more frequently reported in non-Hispanic Black patients [52]. Studies should be conducted in Africa to understand better the influence of the black race on the occurrence of *C. auris* BSI. The overall and specific case fatality rate of *C. auris* in Africa was nearly 39%. This case fatality rate was more or less higher than those reported in previous studies [52]-[57]. Early diagnosis and rapid administration of effective antifungal treatment combined with effective and rapid management of other comorbidities are key factors for patient survival. *Candida auris* was the third cause of invasive candidiasis in Africa. This crucial data must considered in

managing of patients with invasive candidiasis in Africa, given *C. auris* low sensitivity to systemic antifungal drugs, particularly fluconazole [13] [14] [15]. If the management of *C. auris* cases isolated from a sterile site seems obvious, particular attention should also be paid in case of colonization (isolation in non-sterile site such as skin or mucosa). Indeed, nearly 10% of patients colonized with *C. auris* develop invasive candidiasis, especially those subjected to mechanical ventilation and the placement of invasive devices in intensive care settings [58]. Risk factors associated with *C. auris* infection reported in Africa were consistent with data from previous worldwide studies [59] [60] [61] [62] [63]. One study assessing the clinical features of *C. auris* in Africa showed that fever and sepsis were more frequently observed in *C. auris* group than *C. albicans* and *N. glabrata* groups [35]. However, this study failed to attribute these differences to the sole fact of *C. auris* infection. Furthermore, this study did not compare the clinical features of patients with *C. auris* infection with those of patients with non-fungal infections, particularly bacterial ones. In short, this study failed to provide clinical-based evidence of pathognomonic clinical signs of *C. auris* infection. The absence of such specific clinical signs with *C. auris* infection makes its diagnosis very delicate, especially in resource-constrained settings where the lack of qualified human resources and diagnostic methods is glaring. However, some biological parameters accessible in these resource-limited settings, such as C-reactive protein (CRP) and procalcitonin (PCT), could contribute to the discrimination between fungal and bacterial infections. Some studies reported that a substantial elevation of CRP value associated with a low PCT value in immunocompromised patients could indicate an invasive fungal infection rather than a bacterial infection [64] [65] [66]. These combined CRP and PCT data associated with the presence of *C. auris* risk factors and the ineffectiveness of broad-spectrum antibiotic treatment could play a crucial role in the suspicion of *C. auris* infection in resource-limited settings. An experimental murine model showed that the highest fungal load of *C. auris* isolates was detected in the kidney followed by spleen, liver and lung [60]. Clinical studies must be conducted to assess the existence of such a phenomenon in humans and its possible impact on the occurrence or worsening of certain diseases, such as renal failure. In accordance with previous studies, [25] [67] [68] [69] the data in this review showed a pan-African very high resistance rate to fluconazole, moderate resistance to amphotericin B, and high susceptibility to echinocandins. So, identifying all *Candida* at the species level particularly those isolated from sterile specimens, is important to ensure the better candidiasis management [70]. It is also important in Africa to avoid fluconazole as the first-line empirical treatment in cases of invasive candidiasis, especially those due to *Candida* non-*albicans*. No cases of flucytosine-resistant isolates have yet been reported in Africa. In resource-constrained settings a combination of amphotericin B and flucytosine would be potentially useful for treating invasive *C. auris* infections if studies confirm its efficacy as it has been for the treatment of cryptococcosis [32]. In accordance with previous study the present review confirmed that the resistance to each antifungal is closely linked

to the type of clade the isolate belongs to [71]. In Africa, four phylogenetic clades were reported, namely clades I, II, III and IV, with clades I and III being the most widespread clades. The existence of several clades in the same area could lead to an increase in the genetic diversity of *C. auris* and an increase in its virulence and the exchange of drug resistance alleles [13]. Thus, global efforts to fully understand the biology of *C. auris* should be continued to provide the most sensitive protocol for detecting potential *C. auris* hybrids [13]. *Candida auris* clade-specific mutations were observed within the *ERG2*, *ERG3*, *ERG9*, *ERG11*, *FKS1*, *TAC1b* and *MRR1* genes in Africa. In according with previous study, [72] clade I *C. auris* fluconazole-resistant isolates reported in this review commonly exhibited Y132F *ERG11* substitutions. However, no case of other predominant mutations in *ERG11*, namely F126L and K134R, were observed with clade I fluconazole-resistant isolates in Africa [72]. Other common mutations observed with clade I fluconazole-resistant were A657V *TAC1b* substitutions. These last mutations are frequently associated in the same isolate with the *ERG11* Y132F variant, resulting in a marked increase in MIC values, suggesting an additive effect of resistance to fluconazole [73]. African *C. auris* clade III appeared to have specific VF125AL *ERG11* substitutions [73]. Following previous studies the main mutations reported with echinocandin-resistant isolates in Africa were S639P *FKS1HP1* region [74] [75]. The differences in mutations observed between the different clades are probably due to the specificity of the resistance mechanism depending on the clade and the antifungal agents tested. Finally, uncommon mutations observed with African *C. auris* isolates, particularly those found with susceptible isolates, may be linked to natural evolutionary divergence, rather than antifungal resistance mechanisms [32].

5. Conclusion

This systematic review showed the presence of *C. auris* in Africa and worrying unavailability of data on this resilient fungus in most African countries. The absence of such data could mean undiagnosed cases of *C. auris*. This situation in the African settings of a scarcity of financial and qualified human resources combined with the weakness of health systems could favour large hospital and/or community-based outbreaks. National, regional and continental health-care authorities must be quickly made aware of the extreme threat posed by this resilient fungus and strategies for its control and management quickly adopted in the African continent.

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Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

IWY, SND, and SB designed the study. IWY and SND selected, extracted, and synthesized data. IWY and SND wrote the manuscript. All authors revised the final version of the manuscript. All authors read and approved the final manuscript.

Disclaimer

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Annex

Table A1. Distribution of resistant *C. auris* isolates in Africa.

Antifungal	Author, n	Number of resistant isolates with MIC (mg/L) of											Total number of resistant isolates		References
		BMD													
		≥2	3	4	6	8	12	16	≥32	≥64	128	≥256	n1	% (n1/N)	
Voriconazole (N = 575)	Magobo (2020), 85	2	-	3	-	1	-	-	-	-	-	-	13	2.26	[31]
	Adam, 21	7	-	-	-	-	-	-	-	-	-	-			[41]
	Maphanga, 400	-	-	-	-	-	-	-	-	-	-	-			[32]
	Shuping, 61	-	-	-	-	-	-	-	-	-	-	-			[36]
	Oladele, 4	-	-	-	-	-	-	-	-	-	-	-			[44]
	Magobo (2014), 4	-	-	-	-	-	-	-	-	-	-	-			[37]
Fluconazole (N = 575)	Magobo (2020), 85	-	-	-	-	-	-	-	5	23	27	27	525	91.30	[31]
	Maphanga, 400	-	-	-	-	-	-	-	58	83	110	110			[32]
	Shuping, 61	-	-	-	-	-	-	-	13	25	4	13			[36]
	Oladele, 4	-	-	-	-	-	-	-	1	1	-	-			[44]
	Magobo (2014), 4	-	-	-	-	-	-	-	-	1	-	3			[37]
	Adam, 21	-	-	-	-	-	-	-	-	-	21	-			[41]
Micafungin (N = 554)	Magobo (2020), 85	-	-	5	-	2	-	-	-	-	-	-	9	1.62	[31]
	Maphanga, 400	-	-	1	-	1	-	-	-	-	-	-			[32]
	Shuping, 61	-	-	-	-	-	-	-	-	-	-	-			[36]
	Oladele, 4	-	-	-	-	-	-	-	-	-	-	-			[44]
	Magobo (2014), 4	-	-	-	-	-	-	-	-	-	-	-			[37]
Anidulafungin (N = 554)	Magobo (2020), 85	-	-	1	-	-	-	-	-	-	-	-	1	0.18	[31]
	Maphanga, 400	-	-	-	-	-	-	-	-	-	-	-			[32]
	Shuping, 61	-	-	-	-	-	-	-	-	-	-	-			[36]
	Oladele, 4	-	-	-	-	-	-	-	-	-	-	-			[44]
	Magobo (2014), 4	-	-	-	-	-	-	-	-	-	-	-			[37]
Amphotericin B (N = 575)	Maphanga, 400	104	-	-	-	3	-	-	-	-	-	-	107	18.60	[32]
	Magobo (2020), 85	-	-	-	-	-	-	-	-	-	-	-			[31]
	Adam, 21	-	-	-	-	-	-	-	-	-	-	-			[41]
	Shuping, 61	-	-	-	-	-	-	-	-	-	-	-			[36]
	Oladele, 4	-	-	-	-	-	-	-	-	-	-	-			[44]
	Magobo (2014), 4	-	-	-	-	-	-	-	-	-	-	-			[37]
		E-test													
Voriconazole (N = 16)	Zerrouki, 7	-	-	2	1	-	1	-	1	-	-	-	5	31.25	[45]
	Solomon, 9	-	-	-	-	-	-	-	-	-	-	-			[42]
Fluconazole (N = 16)	Zerrouki, 7	-	-	-	-	-	-	-	-	-	-	5	14	87.5	[45]
	Solomon, 9	-	-	-	-	-	-	-	-	9*	-	-			[42]

Continued

Micafungin (N = 416)	Maphanga, 400	-	-	-	-	-	-	2	-	-	-	-				[32]
	Zerrouki, 7	-	-	-	-	-	-	-	-	-	-	-	2	0.481		[45]
	Solomon, 9	-	-	-	-	-	-	-	-	-	-	-				[42]
Amphotericin B (N = 477)	Maphanga, 400	15	2	4		1		-	-	-	-	-				[32]
	Shuping, 61	-	-	-	-	-	-	-	-	-	-	-	23	4.82		[36]
	Zerrouki, 7	-	-	-	-	-	1	-	-	-	-	-				[45]
	Solomon, 9	-	-	-	-	-	-	-	-	-	-	-				[42]
								Vitek								
Fluconazole (N = 97)	Adam, 72	-	-	-	-	-	-	-	-	54	-		79	81.44		[41]
	Parak, 25	-	-	-	-	-	-	-	-	-	-	25				[35]
Voriconazole (N = 72)	Adam, 72	-	-	-	-	-	-	-	-	-	-	-	5	6.94		[41]

Tentative breakpoints: amphotericin B ≥ 2 mg/L; anidulafungin/micafungin ≥ 4 mg/L; caspofungin ≥ 2 mg/L; fluconazole ≥ 32 mg/L; flucytosine ≥ 128 mg/L; voriconazole ≥ 2 mg/L; n: sample size for each study; n1: total number of resistant isolates by antifungal agent; N: sample size for each antifungal agent; MIC: minimum inhibitory concentration; BMD: broth microdilution; *: MICs values ranged from 64 to 256.

Table A2. Mechanism of *C. auris* antifungal resistance in Africa.

			Gene mutations																	
			ERG11				*ERG9*	*ERG3*	*ERG2*	*FKS1HP1*				*TAC1b*			*MRR1*			
Authors	Antifungal profile		VF125AL	Y132F	Y132F/L125F	E343D/N335S/K177A	M351V/A27T	S58T	E39D	S639P	D642Y	T125I/C1253fs/G1250S	L148I/R937S/I701V/I694V	S195G	A651P	A657V	N647T	Multiple	References
			Number of isolates with a mutation in clade I																
Maphanga and Naicker	Fluconazole	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[32] [34]
		R	-	14	-	-	-	-	-	-		-	1	-	1	8	-	-	
	Echinocandin	S	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	
		R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Oladele	Fluconazole	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[44]
		R	-	-	2	-	-	-	1	-	-	-	-	-	-	-	-	-	
			Number of isolates with a mutation in clade III																
Maphanga and Naicker	Fluconazole	S	8	-	-	-	-	-	-	-	-	-	-	-	1	-	8	-	[32] [34]
		R	68	-	-	-	-	-	-	-	-	-	-	1	15	-	68	-	
	Echinocandin	S	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	
		R	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	

Continued

			Number of isolates with a mutation in clade IV																	
Maphanga and Naicker	Fluconazole	S	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	[32] [34]
		R	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Amphotericin B	S	-	-	-	-	1	2	-	-	-	-	-	-	-	-	-	-	1	
		R	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	
Oladele	Fluconazole	S	-	-	-	2*	-	-	-	-	-	-	-	-	-	-	-	-	-	[44]
		R	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	

Tentative breakpoints: amphotericin B ≥ 2 mg/L; anidulafungin/micafungin ≥ 4 mg/L; caspofungin ≥ 2 mg/L; fluconazole ≥ 32 mg/L; *: one isolate with N335S/E343D and the other with E343D/N335S/K177A; Multiple: S30T/N70S/E76_P77delnsDS/D80E/N133S/K138E/K167N/L211V/R249K/R280G/R413K/K534N; fs = frameshift.