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1 **Overview about *Candida auris*: what's up 12 years after its first description?**

2 Guillaume Desoubieux<sup>1</sup>, Alix T. Coste<sup>2</sup>, Christine Imbert<sup>3</sup>, Christophe Hennequin<sup>4, #</sup>

3 1. Parasitologie – Mycologie – Médecine tropicale, Hôpital Bretonneau, F-37044 CHRU Tours,  
4 France

5 2. Institute of Microbiology, University hospital Lausanne, 1011 Lausanne, Switzerland

6 3. Laboratoire Ecologie et Biologie des Interactions, Université de Poitiers, UMR CNRS 7267, F-  
7 86073 Poitiers, France

8 4. Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine, CRSA, AP-HP, Hôpital Saint-  
9 Antoine, Service de Parasitologie-Mycologie, F-75012 Paris, France

10

11 \*Corresponding author: [christophe.hennequin@sorbonne-universite.fr](mailto:christophe.hennequin@sorbonne-universite.fr)

12 Hôpital St-Antoine, laboratoire de Parasitologie - Mycologie

13 184 Rue du Faubourg Saint-Antoine, 75012 Paris - FRANCE

14 Tel.: +33(0)1 49 28 30 30 Fax: +33(0)2 47 47 8082

15 **Abstract**

16 *Candida auris* has been described as an emerging yeast species during the last decade. As many as  
17 25% of its strains may naturally exhibit multi-drug resistance to the currently available antifungal  
18 drugs. Probably due to its ability to survive more than two weeks on inert surfaces, several large  
19 outbreaks have been reported, primarily due to nosocomial transmissions. In addition, due to a  
20 rapid worldwide spreading, *C. auris* is now considered as a major public health threat. This review  
21 aims at describing the current knowledge about *C. auris*, with specific focuses on its global  
22 epidemiology, virulence features, most reliable diagnostic approaches, and the current and future  
23 therapeutic options.

24

25 Keywords: *Candida auris*; epidemiology; genetic; diagnosis; resistance

26

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28

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30

31 Number of table: 1

32 **Introduction**

33 First described in 2009, *Candida auris* has rapidly been placed in the spotlight, not only of medical  
34 journals, but also making the headlines of mass media (1,2) (Figure 1). Indeed, this yeast species  
35 causing large hospital outbreaks and characterized by a high level of antifungal resistance has  
36 emerged as a major threat for the public health over the last ten years (3,4). *Candida auris* cases  
37 have now been reported over all the continents (Figure 2) (5–8). However, the true prevalence of  
38 *C. auris* over the world remains partly unknown as the species identification can be challenging,  
39 notably in low-income countries. Yet, it is critical that all microbiology laboratories are able to  
40 rapidly recognize the species and test the *in vitro* susceptibility for every *C. auris* isolates (9).  
41 Indeed, a rapid and reliable detection is of utmost importance to limit the nosocomial transmission.  
42 Controlling and preventing the spread of *C. auris* requires the isolation of any colonized/infected  
43 individual and the screening of any contact cases. Sampling the medical environment for detecting  
44 a source of contamination can complete the investigation. The reinforcement of standard hygiene  
45 measures remains also a key-feature to limit outbreaks expansion.

46 This brief review focuses on the latest scientific data published on *C. auris*, regarding its  
47 epidemiology and virulence, the diagnostic approaches, and the preventive and curative strategies.

48

49 **Epidemiology: history and current trends**

50 The origins of *Candida auris* and its initial ecological niche(s) are still largely unknown to date.  
51 The emergence of very different clades in different places of the world in a very short period of  
52 time is particularly intriguing. Some have suggested the global warming may have played a role in  
53 the selection of this organism (10,11). It is then assumed that spreading may have been ensured

54 thanks to animals with high body temperature, *e.g.* birds, that would have been responsible for  
55 distributing the fungus into urban areas where it could subsequently infect humans (10).

56 Soon after the species was first described from an isolate collected from the external ear canal of a  
57 Japanese patient in 2009 (1), several clusters of cases were reported from India in 2009-11 ( $n=12$   
58 patients) and 2010-14 ( $n=90$ ) (12,13). However, it was *a posteriori* shown that *C. auris* had been  
59 introduced in some countries, notably France, before the original description of the species (14).

60 Similar conclusions arose from Asia, where retrospective analysis of stored strains have detected  
61 the presence of *C. auris* before 2009 in South Korea (15,16). So far, Portugal, Ireland Republic,  
62 and Scandinavian countries (except Norway) are the only western European nations having not  
63 declared any case (17,18).

64 It clearly appears that *C. auris* has a noticeable propensity to generate outbreaks. Some of the  
65 largest ones are summarized in Table 1. However outbreak spreading is not systematic as shown  
66 with a single case of colonization reported in France (Tours) in 2020, in a Lebanese patient who  
67 visited Iran and India before arriving in Europe (9). To date, the United States of America has been  
68 the country with the highest number of cases declared: 1,157 cases of proven or probable infection  
69 notified to the Center for Diseases Control (CDC) and more than 3,043 cases of colonization were  
70 reported (<https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html>). However, it is  
71 noteworthy that the incidence of *C. auris* infection in the US is actually greatly heterogeneous  
72 depending on the geographic areas: more than 285, 242 and 245 deep-seated infections have been  
73 reported in the state of New York, Illinois and California, respectively (19,20), while some  
74 neighbor states, such as Vermont, Wisconsin or Oregon, are free of *C. auris* detection to date. A 4-  
75 cases cluster has also been reported from Canada (Greater Vancouver area) in 2018 (21). More  
76 recently, several South American countries have reported *C. auris* outbreaks for the first time in  
77 the context of COVID-19 pandemic (22). Similarly, in India, *C. auris* was responsible for 60%

78 cases of candidemia in a single COVID-19 ward (23). Considering the length of stay of such  
79 infected patients in ICU, the viral infection may represent an indirect predisposing factor for the  
80 (re)emergence of *C. auris* (9,22,23).

81 In the more advanced countries, after the occurrence of large outbreaks, cases became more  
82 sporadic and *C. auris* only represent a minority of candidiasis cases, sometimes grouped in small  
83 clusters (4,24). In contrast, in some low-income countries such as South Africa, *C. auris* may  
84 represent as much as 14% of the causative species for candidemia (25) and has become the fifth  
85 most common cause of fungal bloodstream infection in children (26).

86 Thanks to whole genome sequencing (WGS) population genetic studies revealed that *C. auris*  
87 species is split into four major clades (27). Genetic distribution follows the geographic origin of  
88 the strains with clade I, so-called the South Asian clade, made of strains of Indo-Pakistani origin,  
89 clade II, referred to as the East clade, made of Korean and Japanese strains, clade III is the South  
90 African clade, and clade IV referenced as the South American clade composed of Colombian and  
91 Venezuelan strains. In the USA, the clade I is largely predominant, except in Illinois and Indiana  
92 where clades III and IV are the most prevalent (19), suggesting different timing for the introduction  
93 of those strains. In Europe, most *C. auris* isolates belong to the clade I (7), although the strains of  
94 the Valencia hospital (Spain) were slightly genotypically-distinct from all those previously  
95 reported (24). Noteworthy, a strain of the clade II was also found in Austria (28). In 2019, some  
96 Iranian authors suggested the existence of a potential fifth clade, separated from the other clades  
97 by >200,000 single-nucleotide polymorphisms (SNP), in a patient who had never traveled outside  
98 the country (29).

99

100 **Virulence: is something different from other *Candida* species?**

101 Virulence of *C. auris* is more and more investigated using a wide variety of models, either *in vitro*  
102 (30), *in vivo* - mouse (31,32), or invertebrate nematodes like *Caenorhabditis elegans* (33,34), or  
103 the wax moth *Galleria mellonella* (34–36) -, or *ex vivo* – oral (31) and skin models (37). As  
104 commonly seen with opportunistic fungal pathogens, results greatly vary according to the model,  
105 but some results also support difference in virulence according to the tested strains.

106 By studying more than 100 *C. auris* isolates-, Carvajal *et al.* looking at the mortality at day-5 post  
107 infection, in a *G. mellonella* model, were able distinguish between a highly pathogenic population  
108 (35.5% of the isolates) and a moderately pathogenic one- (36). In a mouse model undergoing  
109 cortisone acetate-induced immunosuppression, Abe *et al.* reported that the capability of  
110 colonization and dissemination from gastro-intestinal tracts was higher for four strains isolated  
111 from pathogenic condition (bloodstream infections) than for two non-invasive strains (isolated  
112 from chronic otitis media) (32). The virulence of *C. auris* was also compared to other *Candida*  
113 species. Using the *G. mellonella* model, Romera *et al.* concluded on a higher pathogenicity of *C.*  
114 *albicans* clinical strains, when considering the larva death rate as primary outcome (35). However,  
115 other authors observed that the pathogenicity pattern of a *C. albicans* reference strain (SC5314)  
116 was somewhat comparable to that of 38% of their 107 *C. auris* isolates (36).

117 Understanding how *C. auris* invade the epithelial layer, while it does not form hyphae, remains a  
118 challenge. Indeed, Ben-Ami *et al.* reported considerable virulence of *C. auris* in mice, more than  
119 what could be expected for a *Candida* species that produces no – or only rudimentary, after  
120 experimental passages through mammalian hosts (38) – hyphae. Depending on isolates from  
121 certain clades, the formation of large yeast cell aggregating in infected tissue, a phenomenon also  
122 found in *Galleria* larvae infected (39,40) and in a model of neutropenic mice, may play a role in  
123 the virulence (41). Actually, the capacity to form aggregates, referred to as the aggregative

124 phenotype, is a unique pathogenic feature displayed by some isolates of *C. auris* (30). Recent  
125 results suggested that the non-aggregative phenotype of *C. auris* isolates may exhibit some level  
126 of immune evasion (30). For instance, Hernando-Ortiz *et al.* recently concluded that the  
127 pathogenicity of 11 non-aggregative clinical isolates was higher than that of an aggregative strain  
128 in a nematode and the wax moth host models. (34). In contrast, Carvajal *et al.* observed no  
129 significant difference in *G. mellonella* mortality induced by either aggregative ( $n=35$ ) or non-  
130 aggregative *C. auris* strains ( $n=72$ ) (36), which was consistent with some previous findings (35).

131 Recent data also showed the ability of *C. auris* to adhere and to form biofilm. Highlighting the  
132 importance of the model, Vila *et al.* showed that *C. auris* avidly adhere to an *ex-vivo* oral tissue  
133 (tongue epithelium), but failed *in vivo* to colonize the oral cavity (31). Through *in vitro* tests, Vila  
134 *et al.* observed that *C. auris* formed less biofilm than *C. albicans*, despite some substantial  
135 variability for the former (31). Using scanning electron microscopy, they also demonstrated the  
136 formation in 72 hours of biofilm within catheter lumens implanted subcutaneously in mouse, *C.*  
137 *auris* and *C. albicans* producing comparable levels of biofilm. The influence of the environmental  
138 conditions was also highlighted by Horton *et al.* who compared biofilm produced by *C. auris* and  
139 *C. albicans* strains in a synthetic sweat medium mimicking axillary skin conditions and in RPMI  
140 culture medium (37). Interestingly, *C. auris* produced a significantly denser biofilm than  
141 *C. albicans* in the mimicked skin medium, whereas the almost contrary was observed in RPMI  
142 medium (32,33). Using an immunosuppressed mouse model, Abe *et al.* found that invasive strains  
143 of *C. auris* form more biofilm than non-invasive ones (32). They correlated this difference to the  
144 higher capability of the formers to colonize the gastrointestinal tract (32). Hernando-Ortiz *et al.*  
145 also suggested that the biofilm formation could be related to the aggregative phenotype, as the  
146 strains exhibiting this trait produced more biofilm than the non-aggregative ones (34), a result



147 inconsistent with others previously published (42). Recent analyses suggested that, irrespective of  
148 the ability to produce biofilm, the transcriptome of aggregative cells was significantly different  
149 from that of non-aggregative ones during the biofilm formation (30). Of note, these data have to be  
150 interpreted with caution, because of the low number of strains that were studied and the great  
151 variability of their capacity to form biofilm independently of their aggregative/non aggregative  
152 phenotype.

153 Despite a dramatic increase in our knowledge in the biology of *C. auris*, altogether, these results  
154 highlight how parceled is our understanding of the pathogenicity that is obviously a multifactorial  
155 phenomenon. Further studies comparing large groups of strains belonging to the different clades in  
156 different models are thus warranted.

157

158 **Diagnosis: steps to reach a reliable identification**

159 Identification of *C. auris* is crucial to initiate adequate treatment and contain hospital outbreaks.  
160 As a member of the *Candida/Clavispora* clade, *C. auris* does not have different requirements for  
161 growth from other *Candida* species (43). Colonies can be easily obtained after 24 hours incubation  
162 at 30-35°C on conventional media, such as Sabouraud dextrose agar or malt extract agar. Of note,  
163 *C. auris* is tolerant to temperature up to 42°C (9), which is not the case of many other *Candida*  
164 species. On the conventional CHROMagar Candida® chromogenic media (Becton-Dickinson,  
165 Rungis, France), *C. auris* colonies appear white, pink, or purple (9). On the CAN2® plates  
166 (bioMérieux, Capronne, France), colonies are initially whitish, and then display a light reddish-  
167 pink color, very close to that of *Candida kefyr* or *Candida tropicalis* (9). Two specific chromogenic  
168 media, so called CHROMagar Candida Plus® (Becton-Dickinson, Rungis, France) and HiCrome  
169 *C. auris* MDR® selective agar (HiMedia, Mumbai, India), have been recently set-up to isolate and

170 presumptively identify *C. auris* with an almost 100% sensitivity and specificity rates after 36-48 h  
171 of incubation (44–46). *C. auris* can also grow in blood culture vial, in aerobic flasks or using Fungal  
172 IC/F® bottles (Becton-Dickinson, Rungis, France) (personal data). At direct examination, the  
173 yeasts appear ovoid and budding without pseudo-hyphae.

174 When using auxanogram, *C. auris* can be recognized through its capability of assimilation of N-  
175 acetylglucosamine, succinic acid and gluconic acid. However, the species is not referenced in most  
176 of the databases of former handbooks, thus leading to false negative results or misidentifications  
177 (47), notably with strains of the *Candida haemulonii* clade (13).

178 Nowadays, definitive identification of *C. auris* species can be achieved by the mean of mass  
179 spectrometry MALDI-TOF combined with an up-to-date spectra database. This is the case for the  
180 Bruker Biotyper® (Palaiseau, France) and the bioMérieux Vitek® systems (Capronne, France), as  
181 well as the independent user-made MSI® library (Paris, France).

182 Several molecular tools have also been developed for the identification and/or detection of *C. auris*.  
183 Once colonies are isolated onto agar plates, they can be confidently identified by sequencing either  
184 the D1/D2 region of the large subunit (LSU) or the internal transcribed spacer (ITS) of the  
185 ribosomal DNA. Interestingly, combining the analysis of these two loci allows the assignation of  
186 strains to one of the four major clades without recourse to WGS approaches (48). Otherwise, a few  
187 molecular protocols have been proposed to detect *C. auris* directly from swabs (49,50), allowing  
188 thus rapid screening of asymptomatic patients. Recently, two commercial kits have been evaluated  
189 with noticeable differences in terms of sensitivity and specificity (51).

190

191 **Therapeutic options: multi-resistance and current limits**

192 Almost all *C. auris* strains exhibit *in vitro* resistance to fluconazole, with strains from certain clades  
193 also showing elevated minimum inhibitory concentrations (MICs) to the other azole antifungal  
194 agents higher than those of other *Candida* species, especially *C. albicans* and even *C. glabrata* (52)  
195 (53). Some resistance profiles were found to be clade-dependant (54): for example, fluconazole  
196 and voriconazole exhibited significantly higher MICs against isolates of the South African lineage  
197 than against isolates of the Southern Asian lineage. In addition, lesser susceptibility to amphotericin  
198 B and to echinocandins has been reported in some isolates, and rapid emergence of multidrug  
199 resistance (defined by resistance against at least two antifungal classes) has been documented to  
200 occur during antifungal treatment. Clinical breakpoints were recently proposed for echinocandins  
201 with values set at 2, 4, and 4 µg/mL, for caspofungin, anidulafungin, and micafungin, respectively,  
202 at 2 for amphotericin B and at 32 for fluconazole (no data are available for other azole drugs) (55).  
203 Using these values, Chowdary *et al.* showed that 90% of 350 Indian strains were resistant to  
204 fluconazole, 8% to amphotericin B, and 2% to echinocandins, with 25% of the strains exhibiting a  
205 multidrug profile (56). These data were used to propose therapeutic recommendations, suggesting  
206 an echinocandin as first line therapy in the case of proven or probable diagnosis of *C. auris* invasive  
207 infection (57).

208 The investigation of molecular mechanisms underlying the phenotype of azole resistance in *C.*  
209 *auris* first allowed the demonstration of homologues of genes involved directly or not in the  
210 ergosterol biosynthesis pathway in *C. albicans*. A limited number of non-synonymous point  
211 mutations (F126, Y132, K143 and F444 (3)) were found the *ERG11* homologue that correlates with  
212 an increase in azoles MICs (56,58). Moreover, two homologues of the *C. albicans TAC1* gene, so  
213 called *TAC1a* and *TAC1b*, have also been described. In *C. albicans*, Tac1 is a transcription factor  
214 regulating the ABC transporters Cdr1 and Cdr2, two efflux pumps, which overexpression due to

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Commenté [CH2]: Manque la ref 54 non ?

Commenté [CH3]: je ne comprends pas ce que fait cette ref ici ?

Mis en forme : Couleur de police : Texte 1

Mis en forme : Couleur de police : Texte 1

215 Tac1 gain of function mutation is responsible for azoles resistance. However, only *TAC1b*  
216 displayed a (moderate) role in azole susceptibility of *C. auris* (59–61): Li *et al.* and Ryback *et al.*  
217 specified the role of two gain-of-function mutations in *TAC1b*, at position S611P and A640V,  
218 respectively (59,61). Thus, some authors clearly pointed out the importance of the Cdr1 protein in  
219 the azole resistance of *C. auris* (61,62), whereas others evidenced a Cdr1-independent pathway of  
220 action for Tac1b, which remains to be elucidated (59–61). Mrr1 is another transcription factor that  
221 regulates the expression of the Major facilitator transporter Mdr1 which overexpression due to  
222 Mrr1 gain of function mutation is responsible for fluconazole resistance. ~~However, up to now, no~~  
223 ~~clear role of the~~Recent data suggest a role of *C. auris* homologue of *MRR1*, ~~has been~~  
224 ~~demonstrated~~in azole susceptibility. Indeed, deletion of *MRR1a* in clade III strains (60), and N647T mutation  
225 (Dr F. Lamoth, personal communication) were shown to be responsible for azoles decrease  
226 susceptibility. Regarding the resistance to echinocandins, the role of the S639F mutation in *FKSI*  
227 hot-spot 1 has been highlighted (56). Some strains were shown to exhibit an eagle effect in presence  
228 of high concentration of caspofungin *in vitro*, but with no apparent impact on the *in vivo* efficacy  
229 at human dosage in a murine model of infection (63).

230 A very recent *in vitro* study demonstrated by WGS the high potential of *C. auris* to rapidly adapt  
231 to drug pressure whatever the antifungal drug (64). The elevation of MIC resulted from acquisition  
232 of different point mutations in genes already known to be associated with antifungal resistance  
233 (64,65), but also by duplicating part of the genome carrying those genes to further increase MIC,  
234 as previously shown in *C. albicans* (66,67). This was further supported by karyotyping experiments  
235 described by Bravo Ruiz *et al.* (68) who showed how extreme the genomic plasticity of *C. auris* is  
236 when the yeast is confronted to a large range of stresses. It is thus crucial to explore in the near  
237 future innovative therapeutic options. New triazoles or tetrazoles (VT-1598) appeared to be

**Commenté [DIH4]:** Je pense que tu peux écrire une phrase à ce sujet, Alix. Le temps que l'article soit revu et publié, peut-être que le tien sera accepté avant (sinon, on mettra unpublished data)

238 efficient on azole-resistant *C. auris* strains (69). The new echinocandin, referred as rezafungin, was  
239 also found to be as or more active than other echinocandin drugs both *in vitro* (70–72) and in mouse  
240 models (73,74). More interestingly, new antifungals currently under development, such as  
241 ibrexafungrep, the first drug of the triterpenoid class, and the fosmanogepix could be available  
242 soon. The latter, first member of a new therapeutic class targetting the Gwt1 protein (involved in  
243 GPI anchor biosynthesis pathway), exhibits interesting results, including on strains that are multi-  
244 resistant to current treatments (69,75).

#### 245 **Prevention: which prophylactic means in healthcare facilities?**

246 While modes of acquisition remain uncertain, the ability to form biofilms and to acquire antifungal  
247 resistance points out the need to rapidly implement appropriate prevention measures to limit the  
248 spread of *C. auris* in healthcare facilities. In a recent study carried out in a Chicago hospital, 31  
249 colonized residents were found to have high *C. auris* burden on their skin, estimated at  $1.22 \times 10^5$   
250 cells/swabbing by culture. This was positively correlated with contamination of their surrounding  
251 environment with the demonstration of *C. auris* on all handrails of beds, on doorknobs and  
252 windowsills (76). Therefore, every patient suspected to host *C. auris* either because of a history of  
253 contact-case or a recent stay in an endemic country should be systematically screened. Serial  
254 sampling sessions have to be repeated weekly until hospital discharge (77). All cases of *C. auris*  
255 colonization or infection should be clearly identified and notified to a multi-disciplinary staff  
256 specialized in hygiene issues and nosocomial infection (4,78). Deployment of subsequent  
257 containment measures should expectedly lead to a gradual decline in the incidence of positive cases  
258 and prevent further emergence of cluster. Thus, strict isolation of concerned subjects, similar to  
259 that set up for patients harboring multi-drug resistant bacteria, is highly recommended.

260 It is considered that *C. auris* can be transmitted either by direct or indirect contact (79). For instance  
261 contaminated reusable skin/surface temperature probes have been clearly demonstrated the source  
262 of infection in an English hospital outbreak (80). It is thus crucial to recall healthcare gives the  
263 importance to thoroughly wash their hands when moving from one patient to another. Gloves, lab-  
264 coat must also be changed, and all and medical instruments, like stethoscopes, ultrasound devices,  
265 or thermometers, carefully cleaned. For cleaning inert material, quaternary ammonium  
266 disinfectants should be avoided because they have been shown to be ineffective against *C. auris*  
267 (81). In contrast, sodium hypochlorite, peracetic acid, and hydrogen peroxide have been  
268 experimentally proven to reduce the fungal load as measured by CFU counting by 5.0 to 6.0 Log<sub>10</sub>  
269 (81,82). Disposable wipes soaked with sodium hypochlorite must be preferred for cleaning  
270 surfaces. Recent reports suggested chlorhexidine- or iodine-povidone-based products to be greatly  
271 efficient to reducing the fungal burden on the skin (83–85). Those skin antiseptics should be used  
272 for cleaning localized wound or to reduce the cutaneous burden before surgery for example.  
273 National guidelines regarding prevention ~~measures~~measures and the optimal care of patients  
274 infected or colonized with *C. auris* have been recently published (78,86).

275 Beside the human impact, controlling *C. auris* in healthcare facilities leads to a huge overcosts. In  
276 a tertiary care center in London, the cost for implementing specific measures were assessed at £1  
277 million (1.332 M€, 1.176 M\$), followed by £58,000/month during the subsequent year (87).

278

## 279 **Conclusion**

280 In less than 15 years, *C. auris* became of major fungal pathogen, both because of its capability to  
281 generate large outbreaks and the possible therapeutic dead-end it represents. Critical advances in

282 the knowledge of this species have been obtained, but mycologists have to keep staying vigilant  
283 for reliably diagnosing the cases during possible advent of outbreaks in their healthcare facilities.

284

#### 285 **Ethics**

286 Not applicable

287

#### 288 **Disclosure of conflicts of interest**

289 AC, CI and CH are editors-in-chief of the *Journal of Medical Mycology*; GD serves as a recurrent  
290 associate editor.

291

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294

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723

## 724 Figure legends

725 **Figure 1: Number of publications per year retrieved about “*Candida auris*” in the PubMed**  
726 **database as of August 10<sup>th</sup> 2021** (including original articles and reviews).

727  
728 **Figure 2: Countries from which *Candida auris* cases have been reported, as of February 15,**  
729 **2021**  
730 <https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html#historical>.

731

732 **Table 1 : Listing of the major outbreaks of *Candida auris* cases reported so far.** Were only considered the available articles written  
 733 in English and those that mentioned original description of  $\geq 2$  clustered cases.

Reference	Country (city)	Period	Number of cases of colonization or infection (Nb of centers)	Genotypic analysis (clade)
Arensman <i>et al.</i> 2020 (88)	USA (Chicago, IL)	Jan. 2008 – April 2019	28 (8 centers)	NA
Chowdhari <i>et al.</i> 2013 (12)	India (Dehli)	2009-2011	12 (2 centers)	AFLP: 1 clone (I)
Kathuria <i>et al.</i> 2015 (13)	India (Dehli)	2010-2014	90 (5 centers)	NA
Adam <i>et al.</i> 2019 (89)	Kenya (Nairobi)	Sept. 2010 – Dec. 2016	77* (1 center)	PFGE: 1 clone
Chakrabarti <i>et al.</i> 2020 (90)	India (multiple sites)	April 2011 – Sept. 2012	22 (27 centers)	NA
Chakrabarti <i>et al.</i> 2015 (90)	India (multiple places)	April 2011 – Sept. 2012	48* (27 centers)	NA
Rudramurthy <i>et al.</i> 2017 (91)	India (multiple places)	April 2011 – Sept. 2012	74 (19 centers)	AFLP: 88% with similar profiles (I)
Chowdhary <i>et al.</i> 2014 (92)	India (Kochi)	Nov. 2011 - June 2013	7 (1 center)	AFLP: 1 clone (I)
Sarma <i>et al.</i> 2013	India (Gurgaon)	2011	2 (1 center)	NA
Calvo <i>et al.</i> 2016 (93)	Venezuela (Maracaibo)	March 2012 - July 2013	18 (1 center)	AFLP: 1 clone (IV)

Magobo <i>et al.</i> 2014 (94)	Republic of South Africa (Johannesburg)	Oct. 2012 – Oct. 2013	4 (1 center)	NA
Govender <i>et al.</i> (95)	Republic of South Africa (multiple places)	Oct. 2012 – Nov. 2016	1692 ( $\geq 94$ centers) including 1087 cases in 20 centers	NA
Chatterjee <i>et al.</i> 2015 (96)	India (Bengaluru)	2012-14	34* (1 center)	PFGE: 1 clone
Adams <i>et al.</i> 2018 (20), Ostrowsky <i>et al.</i> 2020 (97) and Zhu <i>et al.</i> 2020 (98)	USA (New York, NY)	May 2013 - April 2017	112 (19 centers)	WGS: 2 clones (I)
Chow <i>et al.</i> 2018 (19)	USA (multiple places)	May 2013 – Aug. 2017	133 (not specified)	WGS (mostly I)
Parra-Giraldo <i>et al.</i> 2015 (47)	Colombia (Bogotá)	Nov. 2013 – Feb. 2015	3 (1 center)	MALDI-TOF: 2 clones
Borman <i>et al.</i> 2016 (39)	United Kingdom (multiple places)	2013	12* (6 centers)	NA
Lockhart <i>et al.</i> 2017 (3)	Pakistan (not specified)	2014-2015	18 (2 centers)	WGS: 1 clone (I)
Ben-Ami <i>et al.</i> 2017 (99)	Israel (Tel Aviv)	May 2014 - April 2015	6 (2 centers)	NA
Khan <i>et al.</i> 2018 (100)	Kuweit (not specified)	May 2014 – Sept. 2017	56 (not specified)	PCR fingerprinting 1 clone (6 strains only)
Berrio <i>et al.</i> 2020 (101)	Colombia (Barranquilla and Cartagena)	July 2014 – Oct.	34 (2 centers)	Not specified: 2 clones
Sayeed <i>et al.</i> 2019 and 2020 (102,103)	Pakistan (Karachi)	Sept. 2014 – March 2017	92 (1 center)	WGS: 1 clone (I)

Ahmad <i>et al.</i> 2020 (104)	Kuwait (multiple places)	2014-2018	126 (8 centers)	ITS sequencing (I)
Caceres <i>et al.</i> 2020 (105)	Colombia (multiple places)	Jan. 2015 – Sept. 2016	40 (4 centers)	NA
Eyre <i>et al.</i> 2019 (80)	United Kingdom (Oxford)	Feb. 2015 - August 2017	60 (1 center)	WGS (mostly III)
Farooqi <i>et al.</i> 2020 (106)	Pakistan (Karachi)	April 2015 – Jan. 2016	30 (1 center)	NA
Escandón <i>et al.</i> 2018 (107,108)	Colombia (multiple places)	Feb. 2015 - July 2016	45* (6 centers)	NA
		Sept. 2016 - May 2017	78* (24 centers)	NA
Schelenz <i>et al.</i> 2016 (4)	United Kingdom (London)	April 2015 - July 2016	50 (1 center)	AFLP: 1 clone
Ruiz-Gaitán <i>et al.</i> 2017-19 (24,109–111)	Spain (Valencia)	April 2016 - January 2017	140 (1 center)	AFLP: 1 clone (I)
Shastri <i>et al.</i> 2020 (112)	India (Dehli)	April 2016 – Sept. 2017	42 (1 center)	AFLP and ITS/28S rDNA sequencing: 1 clone (I)
Vallabhaneni <i>et al.</i> 2017 (113)	USA (multiple places)	May 2016 – Aug. 2016	7 (6 centers)	NA
Belkin <i>et al.</i> 2018 (114)	Israel (Tel Hashomer)	July 2016 – Jan. 2017	2 (1 center)	WGS (III)
Taori <i>et al.</i> 2019 (87)	United Kingdom (London)	July 2016 – Feb. 2017	34 (1 center)	WGS (I)
Tian <i>et al.</i> 2021 (115)	China (Shenyang)	April 2016 – March 2018	93* (1 center)	WGS (III)

Pacilli <i>et al.</i> 2020 (116)	USA (Chicago, IL)	Aug. 2016 – Dec. 2018	490 (4 centers)	NA
Mohsin <i>et al.</i> 2017 (117)	Oman (Muscat)	Aug. 2016 – Jan. 2017	2 (1 center)	AFLP: 2 clones
Al-Siyabi <i>et al.</i> 2017 (118)	Oman (Muscat)	Dec. 2016 – Feb. 2017	5 (1 center)	NA
Park <i>et al.</i> 2019 (119)	USA (New York, NY)	2016-2018	9 (1 center)	NA
Morales-López <i>et al.</i> 2017 (120)	Colombia (multiple places)	Feb. 2017 – July 2017	17 (6 centers)	NA
Theodoropoulos <i>et al.</i> 2020 (121)	USA (Worcester, MA)	May 2017 – Oct. 2017	5 (1 center)	WGS: 1 clone (I)
Abdalhamid <i>et al.</i> 2018 (122) and Almaghrabi <i>et al.</i> 2020 (123)	Kingdom of Saudi Arabia (Dammam and Riyadh)	June 2017 – Oct. 2018	10 (2 center)	WGS: 2 clones (I)
Sathyapalan <i>et al.</i> 2021 (124)	India (Kochi)	Sept. 2017 - 2019	15 (1 center)	NA
Barantsevith <i>et al.</i> 2019 (125,126)	Russian federation (Moskow and Siberian region)	Oct. 2017 – Dec. 2017	49 (1 center) and 38 (2 centers)	ITS and D1/D2 sequencing (I)
Bajpai <i>et al.</i> 2020 (127)	India (Dehli)	NA	5 (1 center)	NA
Mulet Bayona <i>et al.</i> 2020 (128,129)	Spain (Valencia)	Nov. 2017 – May 2020	334 (1 center)	Not specified (III)
Alobaid <i>et al.</i> 2021 (130)	Kuweit (multiple places)	Jan. 2018 – Dec. 2018	33 (12 centers)	NA

Alfouzan <i>et al.</i> 2020 (131)	Kuweit (Farwaniya)	Jan. 2018 - June 2019	71 (1 center)	ITS sequencing and microsatellite typing (I)
Alshamrani <i>et al.</i> 2020 (132)	Kingdom of Saudi Arabia (Riyadh)	March 2018 – June 2019	23 (1 center)	NA
Salah <i>et al.</i> 2021 (133)	Qatar (Doha)	April 2018 – Nov. 2020	40 (2 centers)	WGS: 2 clones (I)
Eckbo <i>et al.</i> (21)	Canada (Vancouver, BC)	Spring 2018	4 (1 center)	WGS: 1 clone (I)
Lane <i>et al.</i> 2020 (134)	Australia (Melbourne)	July 2018 – Dec. 2018	4 (1 center)	Not specified (I)
Sexton <i>et al.</i> 2021 (76)	USA (Chicago)	December 2018	31 (1 center)	NA
O'Connor <i>et al.</i> 2019 (135)	United Kingdom (London)	Dec. 2018 – Jan. 2019	4 (1 center)	NA
Umamaheshwari <i>et al.</i> 2021 (5)	India (Karnataka)	Dec. 2018– March 2019	8 (1 center)	ITS and 26S sequencing (I)
Di Pilato <i>et al.</i> (136)	Italy (Genoa)	July 2019 – May 2020	10 (1 center)	WGS: 1 clone for 9 isolates (I)
Price <i>et al.</i> 2021 (137)	USA (Los Angeles, CA)	Sept. 2019– Sept. 2020	6 (2 centers)	WGS: 3 clones (mostly III)
Alvarado-Socarras <i>et al.</i> 2021 (138)	Colombia (Bucaramanga)	NA	8 (1 center)	NA



Tse <i>et al.</i> 2021 (139)	Hong Kong	2019	15 (1 center)	WGS: 1 clone (I)
Patterson <i>et al.</i> 2020 (140)	United Kingdom (London)	April 2020 – Sept. 2020	7 (2 centers)	MALDI-TOF (I)
Moin <i>et al.</i> 2021 (141)	Pakistan (Karachi)	April 2020 – Dec. 2020	6 (1 center)	NA
Chowdhary <i>et al.</i> 2020 (23)	India (Dehli)	April–July 2020	10 (1 center)	NA
Piatti G <i>et al.</i> 2021	Italy (Genoa)	June 2020 – Jan. 2021	77 (1 center)	NA
Prestel <i>et al.</i> 2021 (142)	USA (FL)	July 2020 – Aug. 2020	6 (1 center)	NA
Hanson <i>et al.</i> 2021 (143)	USA (Miami, FL)	Summer 2020	15 (1 center)	WGS: 1 clone (III)
Allaw <i>et al.</i> 2021 (144)	Lebanon (Beirut)	Oct. 2020 – Dec. 2020	14 (1 center)	NA
Nobrega de Almedia <i>et al.</i> 2021 (145)	Brazil (Savaldor de Bahia)	December 2020	7 (1 center)	Microsatellite typing (I)
Bacchani <i>et al.</i> 2021 (146)	India (Jaipur)	NA	24 (1 center)	NA
Lyman <i>et al.</i> 2021 (147)	USA (TX and Washington, DC)	Jan. 2021 – April 2021	22 (not specified)	NA

734 Abbreviations: \*number of isolates (not specified whether each one corresponded to a distinct patient); AFLP amplified fragment length  
735 polymorphism; BC British Columbia; CA California; DC district of Columbia; Dec. December; Feb. February; FL Florida; IL Illinois;  
736 Jan. January; MA Massachusetts; MALDI-TOF matrix-associated LASER desorption ionization – time of flight; NA not available; Oct.  
737 October; PFGE pulsed-field gel electrophoresis; Sept. September; Nov. November; NY New York; TX Texas; USA United States of  
738 America; WGS whole genome sequencing