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Global epidemiology of emerging *Candida auris*

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The discovery in 2009 of a new species of yeast, *Candida auris*, heralded the arrival of a novel emerging human infectious disease. This review highlights the unique characteristics of *C. auris* that have lled to it being of public health concern worldwide, namely public health concern, namely its global emergence, its ability to cause nosocomial outbreaks in healthcare settings, its innate and emerging resistance to multiple antifungal drugs and its resilience in the face of hygiene and infection control measures. Genomic epidemiology has identified four emergences of *C. auris* marked by four clades of the pathogen. These clades of *C. auris* are genetically dissimilar and are associated with differential resistance to antifungal drugs, suggesting that they will continue to phenotypically diverge into the future. The global emergence of *C. auris* testifies to the unmapped nature of Kingdom Fungi, and represents a new nosocomial threat that will require enhanced infection control across diverse healthcare and community settings.

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Introduction

Since its discovery in 2009 [1•], *Candida auris* has been identified in more than 30 countries on six continents [2•]. A retrospective SENTRY review identified a 2008 isolation from Pakistan; however, *C. auris* is generally considered rare before 2009 suggesting that it represents a newly emerging human infection. In contrast to other *Candida* species, *C. auris* spreads easily in health-care setting causing nosocomial outbreaks [3,4]. This fungus' ability to persist, both on the human host and also on inanimate surfaces, has been well documented [5,6] and is likely a key trait explaining its emergence. Exhibiting intrinsic resistance to fluconazole [7•] and variable susceptibility to other azole antifungal drugs, 5-flucytosine [8•], amphotericin B [9], and echinocandins [8•,10,11], *C. auris* has been widely acknowledged as multi-drug resistant (MDR) [12,13]. This, along with its ability to persist and easily transmit, alongside its highly proliferative clonal life-history, has led to *C. auris*' pandemic potential by causing an expanding range of nosocomial infections worldwide [1•,3,7•,14–18].

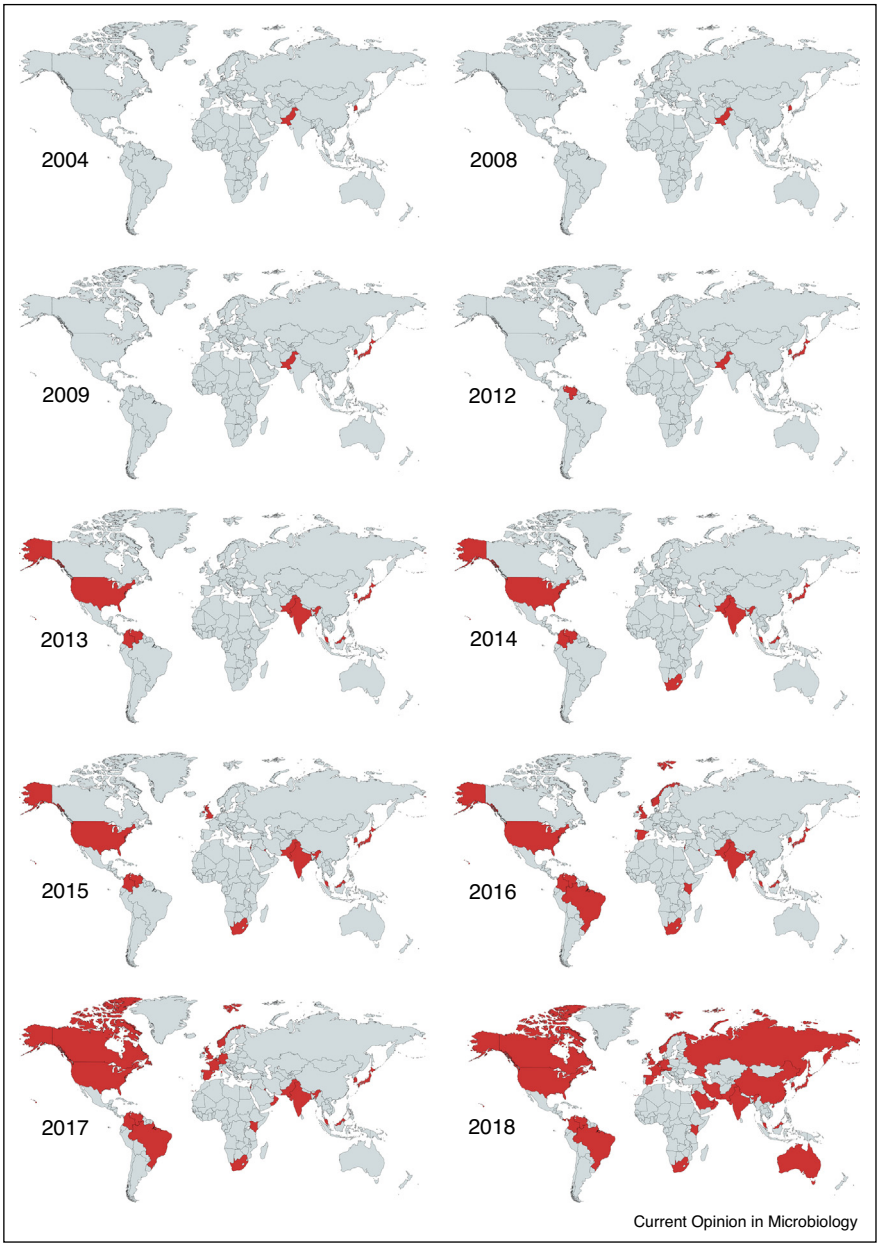
Emergence of *C. auris*

C. auris was first discovered and described in 2009 following isolation from discharge from the ear canal of a patient in Japan [1•] and was taxonomically placed as a close relative to the *Candida haemulonii* complex. Since its discovery, *C. auris* has caused a 'stealthy pandemic', emerging across the globe (Figure 1) and is now recorded in all continents except Antarctica (Figure 2). However, *C. auris* is thought to have been misidentified as *C. haemulonii* on a number of occasions [4,13,19], suggesting that *C. auris* has likely been circulating as a human pathogen before 2009. The USA Centers for Disease Control and Prevention (CDC) queried the international surveillance system SENTRY, and discovered four isolates from between 2009 and 2015 that were identified as *C. haemulonii* however were indeed *C. auris* [7]. A study from South Korea, which identified 15 isolates of *C. haemulonii* in 2009 from the ear canals of patients with chronic otitis were later identified to be *C. auris* [20]. In the same year, the first cases of nosocomial infection caused by *C. auris* were also reported in South Korea; this study also queried the South Korean isolate collection, and discovered the earliest isolate of *C. auris* was discovered in 1996 [15]. However, retrospective analysis of over 15 000 isolates from the SENTRY collection show no misidentifications before 2009 [7•] and over 5000 archived isolates from Taiwan before 2016 were negative, showing that the currently observed global distribution of *C. auris* is most likely explained by a process of rapid spatial emergence from a small number of foci. This observation is confirmed by ongoing genomic epidemiology showing multiple contemporary introductions and ongoing transmission in the USA as well as other global settings [2].

Genomic epidemiology

Investigation into the *C. auris* genome has shown it to possess over 5000 protein coding genes [7•,8•,21], and expresses several virulence factors such as biofilm formation and adherence [22,23], although to a lesser extent than *C. albicans* [22,24]. Muñoz *et al.* performed RNA-seq and discovered expansions of entire gene families were linked to drug resistance and virulence [21], which have

Figure 1



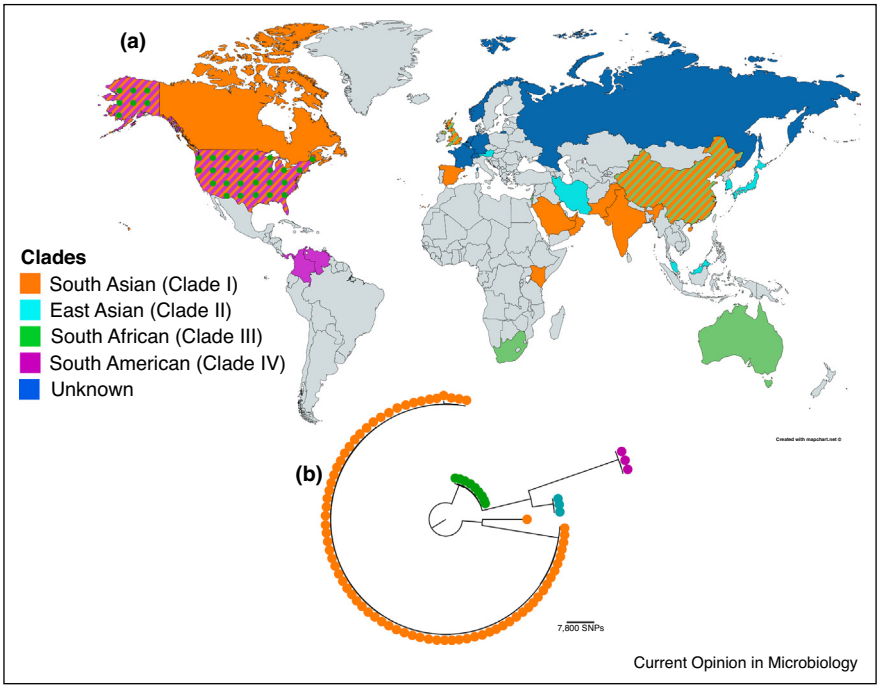
Timeline showing the expanding worldwide detection of *C. auris*.

also been described in *C. albicans* [25]. Whilst the roles of specific genes were not characterised as part of the study, Muñoz *et al.* demonstrated that expansions of transporters and lipases within *C. auris* are a likely mechanism of virulence that is shared with other species of *Candida* yeasts [21].

Whilst initially thought to have high virulence, and exhibiting crude mortality rates from *C. auris*-associated candidaemia from between 33–72% [17,26,27], assessment from the UK Brompton outbreak showed no direct association with mortality [3]. Currently, there is an urgent need to contextualise the virulence of *C. auris* against that observed from other candidaemia-causing yeasts such as *C. albicans* and *Candida glabrata* as there is much uncertainty surrounding the clinical consequences of detecting *C. auris* candidaemia.

Genetic analysis using whole genome sequencing has revealed deep divergence within the *C. auris* species, with large variation between geographic clades separated by thousands of single nucleotide polymorphisms (SNPs)

Figure 2



(a) Global distribution of *Candida auris* clades (as of 28th February 2019) and **(b)** RAxML phylogeny showing the relationship amongst *C. auris* clades.

[2,7•,8•]. This divergence has led to the identification of four distinct geographic clades (I–IV), each with minimal genetic diversity within each clade: South Asian (clade I), South African (clade III), South American (clade IV) and East Asian (clade II; Figure 2). The East Asian clade (containing the type isolate of *C. auris*) appears to infect the ear only, whereas the other clades are known to cause invasive infections, nosocomial transmission and healthcare outbreaks [28]. There appear to be specific drug resistance mutations in the *ERG11* gene (encoding the target of azole antifungal drugs) that a strongly associated with resistance to azoles across the following geographic clades: F126T in South Africa, Y132F in South America, and Y132F or K143R in South Asia [2•,7•,8•]. The appearance of the Y132F and K143R mutations has recently been shown to increase resistance to fluconazole in *C. auris* [29]. There appears to be no [antifungal-resistance mutation in *ERG11* associated with the East Asian clade, which coincides with the higher rate of susceptibility observed in isolates from this clade. Clonal isolates from the South Asian clade have been identified at three hospitals located thousands of miles apart in India, confirming the nation-wide nature of transmission and potential for antifungal-resistance mutations to spread should they evolve [12]. Similarly, isolates from hospitals located approximately 700 km apart in Colombia were found to be genetically identical [30]. Isolates of similar genotypes have also been seen to cluster regionally within countries, usually around a hospital [2•,31], marking local networks of transmission.

One such a cluster was observed in the UK in 2015. An initial case of *C. auris* was reported in the Royal Brompton Hospital, a specialist cardio-thoracic centre in London, in April 2015 in a 20 bed mixed adult intensive care unit (ICU) [3]. The following week, a patient in the adjacent bed to the index case was identified as *C. auris* culture positive from a sputum sample, and they subsequently developed an intravascular line infection. Formal outbreak measures were introduced in November 2015 when nine cases were identified, some with candidaemia. The number of cases within the Royal Brompton Hospital rose rapidly at the start of 2016. As healthcare associated transmission was a possibility within the ICU, environmental sampling of areas surrounding colonised patients was carried out, which showed contamination with *C. auris*. It was also observed during the outbreak that once patients were skin colonised, daily washes with the recommended 2% chlorhexidine wash cloth did not eradiate *C. auris* [5]. Therefore, due to the uncertainty over the time and source of the introduction of *C. auris* into the hospital, rapid development of molecular epidemiological tools was required. The handheld MinION nanopore sequencing device from Oxford Nanopore Technologies, UK (ONT) and Illumina was used to whole genome sequence (WGS) multiple isolates with a diverse

temporal range over the outbreak to describe the genetic epidemiology of the outbreak, both within the hospital and in the global context. Temporal analysis of the sequences placed the introduction of *C. auris* into the hospital as March 2015, one month before the index case, and placed the outbreak globally within the South Asian clade [8•]. Similar patterns of introduction and local spread have recently been described in other settings, notably the USA, where isolates from all known lineages of *C. auris* have been reported (Figure 2), and including a number of cases where patients are thought to have acquired infections from exposures in other countries [2•].

Antifungal resistance and transmission in *C. auris*

Currently, candidaemia infections caused by *C. albicans* are widely managed via the use of echinocandin therapy, and in some cases in combination with amphotericin B [17,32]. Intravenous amphotericin B not in combination with another drug has resulted in treatment failure [15]; however, the mechanistic nature of this resistance is not yet understood. Whilst there are currently no established breakpoints for antifungal susceptibility in *C. auris*, it is generally accepted that most isolates are multi-drug resistant, based on applying *C. albicans* breakpoints (both CLSI and EUCAST) [33].

Reduced susceptibility to fluconazole, which displays high MICs in many cases (>64 mg/l) have been seen in over 90% of cases [3,7•,34], and reduced susceptibility to voriconazole, itraconazole, posaconazole, and isavuconazole have also been demonstrated [3,8•,12]. Varying susceptibility to amphotericin B has also been shown [7,11,16,17,34,35], with Escandon *et al.* presenting four novel non-synonymous mutations that may be associated with resistance [30]. However, Muñoz *et al.* demonstrated that there was a transcriptional response to voriconazole and amphotericin B, with a small number of differentially expressed genes post-exposure to both drugs, suggesting that the mechanism of resistance to these drugs may be epigenetic rather than mutation-based [21]. Data on susceptibility to 5-flucytosine (5FC) are limited, but reports from India and the UK have shown raised MICs [3,7•,8•,36]. Because of the varying susceptibility of *C. auris* to azoles and amphotericin B, public health recommendations have led to the use of echinocandins as front-line therapy for infections [27,37]. Despite this, however, reduced susceptibility to echinocandins associated with polymorphisms in the *FKS1* gene has been identified [8•,10,11] suggesting that, here too, antifungal resistance has evolved and may be of clinical significance. In a small percentage of cases, elevated MIC's were found against all of the three major classes of antifungals. Increasing the copy numbers of ERG11 has recently been suggested as a mechanism of drug resistance in *C. auris* [21], similar to that seen in *C. albicans* [38] and *Cryptococcus neoformans* [39]. Clearly, the ongoing evolution of *C. auris* in the face of antifungal therapies needs to be closely monitored.

Following the 'Brompton experience', guidelines from Public Health England report that colonisation by *C. auris* is highly persistent and is difficult to eradicate [40]. Specifically, reusable items of medical equipment, specifically axillary skin-surface temperature probes, are known to be predictors of colonisation by *C. auris* [41•]. Withdrawal of temperature probes following an outbreak in an Oxford (UK) hospital was shown to reduce the incidence of infection [41•]. Further, daily skin decolonisation of patients with 2% aqueous chlorhexidine wipes was shown to be effective during an outbreak in a tertiary care hospital in Spain [32]. Overall, experience in attempting to contain the emergence of *C. auris* is showing that a one-size-fits-all approach to *Candida* infection control cannot be assumed.

Future directions

Currently, nothing is known about the origins and initial emergence of *C. auris*; its propensity to survive on inanimate objects within the hospital alongside resistance to disinfection protocols suggests the existence of an unknown non-human environmental reservoir. However, similar to other *Candida* species, the true nature of *C. auris*' ancestral reservoirs currently remains elusive [42–44]. The detection of clonal *C. auris* isolates on multiple continents simultaneously with distinct geographical antifungal resistance mechanisms suggests at least four independent emergence events followed by clonal expansion and the ongoing evolution of resistance in response to antifungal therapy [8•]. Recent comparative genomic analysis has shown that most of the *Candida* mating and meiosis genes are present, and that each of the *C. auris* clades are fixed for either the *MTLa* or *MTL* α mating loci as follows: South Asian clade I, *MTLa*; South African clade III, *MTLα*; South American clade IV, *MTLa*; and East Asian clade II, *MTLα* [21]. These findings suggest that recombination is possible if clades of opposite mating types encounter one another. A recent study confirmed that *C. auris* is capable of efficient recombination [45]; such mating, if it occurs, could lead to the spectre of more complex genotypic and phenotypic diversity evolving in the future with potentially novel antifungal and virulence characteristics.

Given the difficulties in identifying *C. auris*, there is a need for not only species level identification, but also clade-specific identification if the antifungal resistance characteristics of the clades continue to diverge [46]. There is a need to develop global surveillance tools, similar to those seen in the Ebola and Zika outbreak response [47], not only for *C. auris*, but for other human emerging fungal pathogens, such as *Rasamsonia* and *Exophiala* species. These surveillance tools need to be open access, web-based, and be available to all parts of the globe, especially in places where there is limited funding

for healthcare. These tools should be able to differentiate between the geographic clades; standard molecular typing techniques have proven unsuccessful or incomparable between laboratories. It is essential that these tools also rapidly identify *C. auris*; the use of the WGS and the MinION sequencer sequencer from ONT has demonstrated that outbreak-specific references can be generated rapidly for the use of single nucleotide polymorphism (SNP) changes and phylogenetic analyses [8•,41]. As sequencing technology develops, it is likely rapid sequencing of *C. auris* isolates can be achieved in 48 hours or less leading to the potential for bedside diagnostics twinned with molecular epidemiology of nosocomial patterns of transmission. Currently, it is not often known when patients become colonised – whether from the hospital environment or endogenous carriers [27] – and the extent of carriage in the community remains largely unexamined. Therefore, epidemiological studies that incorporate WGS to investigate the genetic diversity of environmental and clinical isolates are needed more widely. There is also a need for studies that examine the genetic diversity of clinical isolates from multiple body sites in patients. This is because the differential exposure to antifungal drugs for isolates from mucosal sites versus systemic infections is likely to lead to the differential evolution of resistance, which may lead to downstream clinical complications.

As echinocandins are the front-line therapy for *C. auris* infection treatment, new drugs may be needed to combat high-grade echinocandin resistance if it evolves. New drug options, such as rezafungin (previously called CD101), and the ß-glucan synthesis inhibitor SCY-078, have already shown promise [22,48]. More broadly, there is a need for novel antifungal chemistries as the worldwide emergence of resistance to antifungal drugs continues to challenge human health and food security [49•].

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