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On the emergence, spread and resistance of *Candida auris*: host, pathogen and environmental tipping points

Arunaloke Chakrabarti* and Prashant Sood

Abstract

Over a decade ago, a multidrug-resistant nosocomial fungus *Candida auris* emerged worldwide and has since become a significant challenge for clinicians and microbiologists across the globe. A resilient pathogen, *C. auris* survives harsh disinfectants, desiccation and high-saline environments. It readily colonizes the inanimate environment, susceptible patients and causes invasive infections that exact a high toll. Prone to misidentification by conventional microbiology techniques, *C. auris* rapidly acquires multiple genetic determinants that confer multidrug resistance. Whole-genome sequencing has identified four distinct clades of *C. auris*, and possibly a fifth one, in circulation. Even as our understanding of this formidable pathogen grows, the nearly simultaneous emergence of its distinct clades in different parts of the world, followed by their rapid global spread, remains largely unexplained. We contend that certain host–pathogen–environmental factors have been evolving along adverse trajectories for the last few decades, especially in regions where *C. auris* originally appeared, until these factors possibly reached a tipping point to compel the evolution, emergence and spread of *C. auris*. Comparative genomics has helped identify several resistance mechanisms in *C. auris* that are analogous to those seen in other *Candida* species, but they fail to fully explain how high-level resistance rapidly develops in this yeast. A better understanding of these unresolved aspects is essential not only for the effective management of *C. auris* patients, hospital outbreaks and its global spread but also for forecasting and tackling novel resistant pathogens that might emerge in the future. In this review, we discuss the emergence, spread and resistance of *C. auris*, and propose future investigations to tackle this resilient pathogen.

INTRODUCTION

The last decade has seen the emergence and worldwide spread of *Candida auris*, a nosocomial fungus that has become a 'serious threat' for healthcare facilities around the globe [1]. At the time of this writing, *C. auris* has been reported from 42 countries [2], although given the difficulties with its identification, it is likely to have spread even further. Unlike other yeasts, *C. auris* displays characteristics that are reminiscent of bacteria and these unusual properties make it a formidable public health threat. It is often multidrug-resistant with high levels of intrinsic and acquired resistance to azoles and amphotericin B, and occasionally to echinocandins [3, 4]. It is exceptionally well adapted to the nosocomial environment, resists common disinfectants, persists on medical equipment and dry hospital surfaces for up to 4 weeks, and readily colonizes the axillae, groin and nares of patients [5–10]. Furthermore, conventional diagnostic methods often misidentify *C. auris* and only matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry and ribosomal DNA sequencing can reliably distinguish it from other yeasts [10, 11]. All these factors allow *C. auris* to easily spread horizontally in a hospital and cause recalcitrant outbreaks [7, 9]. They also contribute to the high mortality rates (30–60%) seen with *C. auris* invasive infections and have made this fungus the leading cause of candidemia in some hospitals of India, Kenya and South Africa [3, 12–14]. Furthermore, *C. auris* strains display substantial genetic heterogeneity from one region of the world to another. Whole-genome-sequencing-based

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Author affiliations: [1]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
***Correspondence:** Arunaloke Chakrabarti, arunaloke@hotmail.com
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Abbreviations: ABC, ATP-binding cassette; AIDS, acquired immunodeficiency syndrome; CDC, Centres for Disease Control and Prevention; DDD, daily defined doses; DNA, deoxyribonucleic acid; ECDC, European Centre for Disease Prevention and Control; GPI, glycosylphosphatidylinositol; MALDI-TOF, matrix-assisted laser desorption ionization-time of flight; MFS, major facilitator superfamily; MIC, minimum inhibitory concentration; NET, neutrophil extracellular trap; PCR, polymerase chain reaction; PHE, Public Health England; SNP, single nucleotide polymorphism; UK, United Kingdom; USA, United States of America.
Three supplementary tables are available with the online version of this article.
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phylogenetics has identified four distinct clades of *C. auris*, which have likely originated in South Asia (clade I), East Asia (clade II), South Africa (clade III) and South America (clade IV) [15, 16]. A strain from a possible fifth clade has also been identified in Iran [17, 18].

The medical mycology community has risen to the challenge of *C. auris*. Comprehensive basic science, epidemiological, clinical and infection control studies are rapidly generating valuable insights to combat and contain this public health threat. However, even as our knowledge about *C. auris* grows, considerable gaps remain in our understanding of its emergence, spread and resistance. Firm evidence so far remains unavailable to explain why, where and how *C. auris* originated and what host–pathogen–environmental pressures are driving its spread and resistance.

Several theories have been put forth to explain the emergence and spread of *C. auris*. One hypothesis proposes that the recent advances in fungal molecular diagnostics have facilitated the identification of *C. auris*. *C. auris* was most likely being missed until recently, due to the reliance on conventional phenotypic methods being used across the world. However, a reanalysis of 20788 global *Candida* spp. isolates collected by the SENTRY Antifungal Surveillance Programme between 1997–2016, found only six misidentified *C. auris* isolates in their collection, isolated between 2009–2016 [19]. Another hypothesis contends that the emergence of *C. auris* is possibly linked to the selection pressure created by the widespread use of agricultural fungicides, as has been seen with the emergence of azole-resistant *Aspergillus fumigatus* [20]. The impact of selection pressure proposed by this hypothesis may explain the emergence of *C. auris* to some extent, however, data indicates that the global hotspots of high fungicide use and *C. auris* emergence do not coincide, suggesting that there may be other factors at play [20]. A third hypothesis suggests that *C. auris* evolved thermal tolerance due to increasing global warming of the planet, thereby enabling it to cross-over the human thermal restriction zone. The theory suggests that *C. auris* first adapted to an intermediate avian host and spread to rural human habitations. Thereafter it spread further into the urban healthcare environment, facilitated by human migration [21]. While the thermotolerance of *C. auris* may explain some aspects of its evolution, the yeast has so far not been isolated from any avian host [22]. Furthermore, there has been no evidence of rural-to-urban *C. auris* transmission and environmental amplification in rural areas. So far there has been little evidence of *C. auris* community transmission, except a report of its isolation from swimming pools in the Netherlands [23] and a case of *C. auris* pyelonephritis in a patient with no recent hospitalization [24]. Even after a decade of its emergence, specific clades of *C. auris* continue to dominate the parts of the world where they originated. In contrast, other regions like the USA and the UK have detected multiple clades circulating in these countries [25, 26]. Global human migration is believed to have led to the entry of multiple clades in these latter regions. However, human migration alone fails to explain why a similar admixture of multiple clades has not been witnessed in the regions where *C. auris* originally emerged. Several studies have also attempted to explain the antifungal resistance mechanisms of *C. auris*. Even though these studies have delineated several resistance mechanisms that are analogous to those seen in other *Candida* species, they do not completely explain the extremely high levels of resistance that are often seen in *C. auris* isolates [3]. In view of the above unanswered questions, we present here a synthesis of available information on the emergence, spread and resistance of *C. auris* to identify potential areas of future investigations.

EMERGENCE AND GLOBAL SPREAD

Analysing the geospatial emergence of *C. auris* lends useful insight into the potential factors that could have driven its origin and spread. After *C. auris* was first identified in 2009, in the ear discharge of a 70-year-old Japanese patient [27], ongoing prospective surveillance and retrospective analyses of national and international yeast culture collections have helped piece together the timeline of its emergence and spread (Fig. 1). The earliest *C. auris* isolate was uncovered in South Korea, dating back to 1996, as a misidentified isolate [28]. Further misidentified isolates were discovered in Japan (1997) [29] and Pakistan (2008) [15]. By 2009 *C. auris* had not only been identified as a novel species, but reports of invasive infections and hospital outbreaks had also started appearing. It simultaneously emerged in South Africa [30] and India in 2009 [31], and soon after in Kenya (2010) [13] and China (2011) [32]. By 2012 *C. auris* had emerged in Venezuela [33] and soon after in Colombia (2013) [34].

The period around 2012–13 appears to be a watershed before which four genetically distinct clades of *C. auris* were emerging in different parts of Asia, South Africa and South America, and after which these independently emerged clades started rapidly spreading to other countries facilitated by human migration. By 2013 *C. auris* had entered Europe, with early sporadic cases appearing in the UK [35]. This was soon followed by protracted outbreaks in the UK over 2015–17 [9, 36]. *C. auris* now steadily started spreading across Europe through Germany (2015) [37], Belgium (2016) [38], Norway (2016) [39, 40], Spain (2016) [41], France (2017) [42], Switzerland (2017) [43], Austria (2018) [44], Greece (2018) [45], the Netherlands (2018) [46, 47], Poland (2018) [47], and most recently to Italy (2019) [48]. During this period cases reached Australia (2015) as well [49]. Around the same time when cases emerged in the UK, *C. auris* had entered the USA (2013) as well [50], and it triggered prolonged large outbreaks in New York, New Jersey and Chicago over 2013–17 [8, 51]. Soon after, in 2017, *C. auris* cases emerged in Canada [52]. Meanwhile intensive care outbreaks were occurring in Venezuela and Colombia (2015–17) [53, 54], and spread was also noted in Panama [55], Costa Rica [56] and Chile [57] between 2016 and 2019, and most recently in Mexico in 2020 [58]. Meanwhile, *C. auris* continued to spread across the Middle East, North Africa and South Asia. By 2014, it had appeared in Kuwait [59] and Israel [60], and was followed by cases in Oman (2016) [61], UAE (2017) [62], Egypt (2017) [63],

Fig. 1. The emergence and spread of *C. auris*. World map showing the countries where *C. auris* has been isolated to date. Most countries have detected multiple cases in more than one healthcare institution, with some countries experiencing prolonged outbreaks. In contrast, some countries have so far reported only single cases with no further transmission [2]. The timeline below depicts the years in which *C. auris* was first isolated in different countries, showing near-simultaneous emergence and spread of *C. auris* across Asia, Africa and South America between 2008 and 2013.

Saudi Arabia (2017) [64] and Sudan (2019) [65]. Recently, in 2018, a genetically distinct isolate, potentially a new clade of *C. auris*, emerged in Iran [17, 18]. On the other side of Asia, *C. auris* expanded to Singapore (2012) [66], Russia (2016) [67], Taiwan (2017) [68], Bangladesh (2018) [69], Malaysia (2018) [70] and Thailand (2018) [71].

A few things stand out in the above timeline. A rapid, concurrent global emergence of genetically distinct *C. auris* clades was seen between 2008 and 2013, with only rare isolates detectable prior to 2008. This suggests a relatively recent emergence of this yeast. However, the timeline also raises the question whether there were certain factors in Asia, South Africa and South America that were evolving on a different trajectory as compared to North America, Europe and Australia? Did these factors predispose the independent emergence of *C. auris* in the former regions? We further examine these questions in the following sections.

HOST–PATHOGEN–ENVIRONMENTAL FACTORS AND TIPPING POINTS

The concurrent emergence of distinct clades of *C. auris* in different parts of the world begs an explanation that can shed light on its origin and evolution. We suspect that a complex interplay of host, pathogen and environmental factors probably reached a tipping point in certain parts of the globe to trigger the emergence of *C. auris*. To substantiate this we examine the available evidence on each of these aspects.

Beginning with the pathogen, the *C. auris* genome has been under considerable scrutiny to trace its origin and evolution. The four genetically distinct clades of *C. auris* have been found to differ from each other by 40000–200000 single nucleotide polymorphisms (SNPs) showing high inter-clade genetic diversity. In contrast, their intra-clade diversity is 17-fold lower and strains circulating within a given clade differ from each other by a mere 2–600 SNPs [15, 16]. These vast inter-clade differences suggest that *C. auris* most likely emerged independently in different parts of the world. Building on these findings, Chow *et al.* employed Bayesian 'molecular clock' phylogenetics to date the origin of clades I-IV [26]. They confirmed the recent origin of *C. auris* and showed distinct phylogeographic separation of the clades. Of the four clades, clade II is the oldest and genetically most diverse, having separated from the nearest common ancestor some 341 years back. Thereafter, clades III and I emerged approximately 176 and 142 years ago, respectively. Most recently, clade IV strains originated some 36 years ago. Further analysis revealed that antifungal resistant, outbreak-causing strains from clades I, III and IV, appear to have originated around 36 years back (1984–85) and have predominantly contributed to the recent

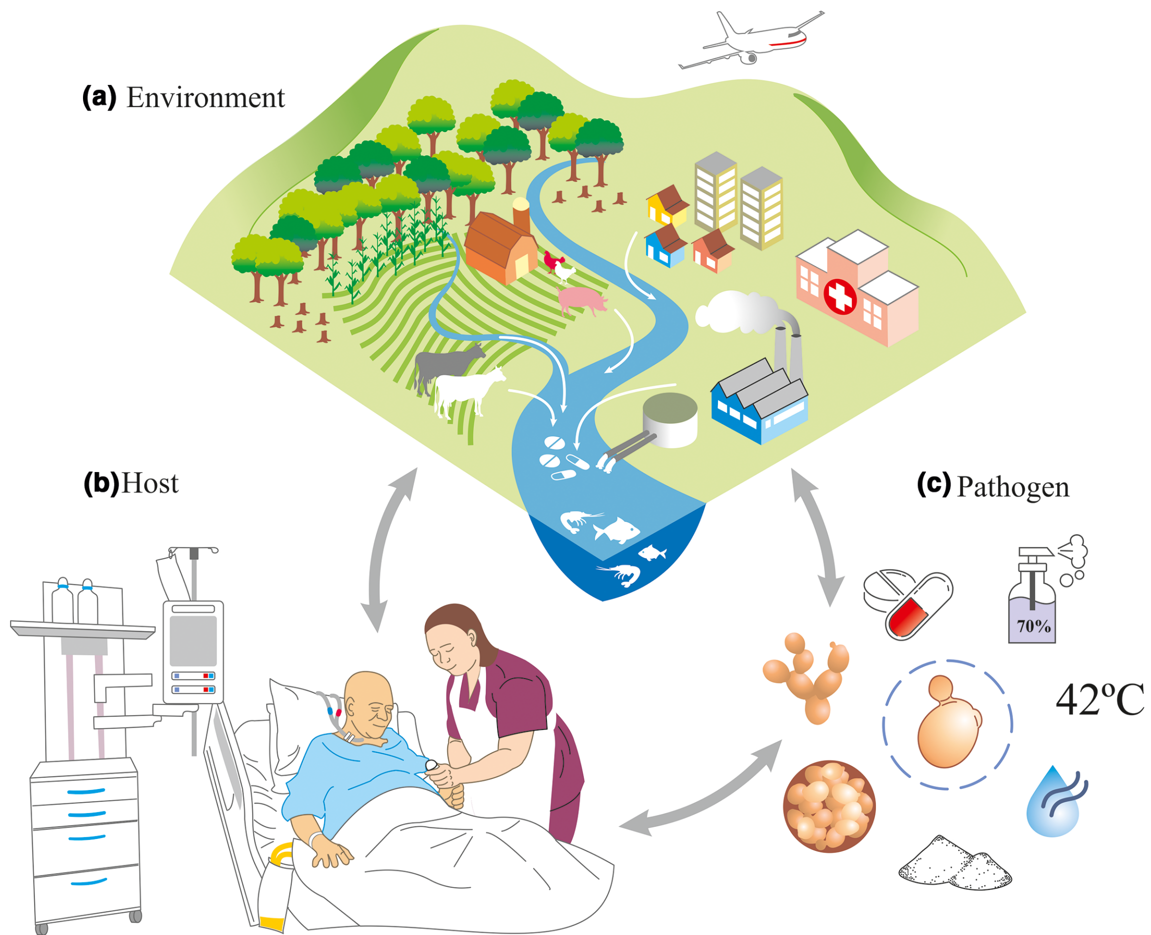

Fig. 2. Potential host–pathogen–environmental factors driving the emergence and spread of *C. auris*. (a) Environmental degradation caused by deforestation, expanded land use, industrial farming, aquaculture, human travel and climate change have probably disrupted and amplified the environmental niche of *C. auris*, bringing it closer to humans. An exponential increase in antimicrobial use in medicine, agriculture, animal husbandry and industry (white arrows) have also likely induced *C. auris* to acquire multiple resistance mechanisms. (b) Critically ill patients exposed to multiple invasive procedures and broad spectrum antimicrobials are increasing in our hospitals and are susceptible to *C. auris*. Within hospitals *C. auris* contaminates and persists on inanimate surfaces and medical equipment, causing horizontal spread and outbreaks. (c) As a pathogen, *C. auris* exhibits high-level resistance to antifungals and hospital disinfectants, tolerates temperatures up to 42 °C, resists desiccation, thrives in high-salt environments like human skin and sweat, forms robust biofilms, and switches into azole-resistant aggregative forms. These properties make *C. auris* a hardy nosocomial pathogen.

global population expansion of these clades. Although clades I and III are the most closely related but do not show any recent genetic admixing [26].

Sekizuka *et al*. further dissected the phylogenetics of clade II isolates recovered from Japan [29]. Remarkably, all of these strains were isolated from non-invasive ear infections, showed higher antifungal susceptibility, failed to form biofilms and were metabolically distinct from other clades. These clade II isolates had 61 cell-wall and stress-response genes completely missing in them and showed stable copy-number variations distinct from other clades. These findings reiterate that clade II strains are closest to the common ancestor, and have possibly separated from it after gene duplication events. These strains subsequently adapted to the human host causing non-invasive infections. However, possibly under the selection pressure of antifungals, antibiotics and the human immune system, *C. auris* accumulated new copy-number variations and accessory genes via horizontal gene transfer, and evolved into a more invasive and resistant organism [29].

The above findings compel us to weigh in the impact of environmental and human population changes that have occurred over the twentieth century, especially building up to the early 1980s when the resistant, outbreak-causing *C. auris* likely emerged, and then from 1980s onwards when these strains globally expanded, as Bayesian 'molecular clock' phylogenetics studies suggest [26]. A crucial ecotoxicological disruption that this period has witnessed is the overwhelming saturation of our biosphere with antibiotics and antifungals. This period has seen an exponential increase in the use of antimicrobials for human therapeutics, agriculture, animal

husbandry, aquaculture, plastic and timber preservation, and as antifouling agents [72] (Fig. 2a). More specifically, azole antifungals entered clinical use in the 1970s and became widely available by the 1980s, fuelled by the AIDS epidemic. The use of triazole fungicides simultaneously increased in agriculture [72]. In addition, the mismanagement of agricultural runoffs and pharmaceutical effluents have worsened ecological contamination [73]. The intense selection pressure imposed by such high levels of antimicrobials on natural microbiomes, has led to the emergence of drug-resistant bacteria and fungi, as has been recently seen with azole-resistant *Aspergillus fumigatus* [74]. It is plausible that environmental contamination with antifungals and antibiotics approached a tipping point in different parts of the world and contributed to the emergence of *C. auris* as well.

The abuse of antimicrobials is not the only disruption recent decades have witnessed. Several disruptive practices in agriculture, aquaculture, deforestation and land use could also have contributed to the amplification and emergence of *C. auris* [75] (Fig. 2a). All *C. auris* hospital outbreak investigations have concluded that *C. auris* was acquired from extraneous sources rather than from the patients' endogenous flora. Although, an environmental reservoir of *C. auris* has not yet been reported, it is possible that *C. auris* might have its own environmental niche. *Candida* species have been found associated with insects, rubber and cassava plantations, mangrove trees and various flowering plants [75]. Hence, assuming that *C. auris* exists in the environment, disruptive industrial farming, aquaculture and land use expansion that have occurred globally over the past decades, could have amplified the natural reservoir of *C. auris* and brought it closer to human populations (Fig. 2a). The worldwide expansion of shrimp aquaculture since the 1970s is a case in point. In order to increase shrimp yield, the farmers have been known to use large amounts of antibiotics and fungal probiotics like *C. haemulonii* to ward off bacterial and viral infections, and boost shrimp immunity. However, it remains unknown if the strains of *C. haemulonii* being used are actually *C. auris* [76–78]. Furthermore, *C. auris* is closely related to the members of *C. haemulonii* complex and shares several genetic and phenotypic properties with them [16]. It is thus possible that *C. auris* could have originated from these species under disruptive environmental pressures.

Besides the pressure of antimicrobials and industrial farming, anthropogenic activities have also contributed to the greater problem of climate change. Casadevall *et al.* have hypothesized that a warmer climate could be responsible for the emergence of *C. auris* [21]. Higher ambient temperatures narrow the thermal restriction zone, which is the difference between the average environmental temperature and the basal human body temperature. This thermal restriction zone is believed to safeguard humans from most environmental fungi due to their inability to grow at human body temperature. However, the increase in environmental temperature could have amplified *C. auris* in the environment given its higher thermal tolerance unlike other *Candida* species [21]. However, this hypothesis fails to explain the simultaneous emergence of genetically distinct clades in specific regions of the globe.

While tipping points in the pathogen's genome and the environment could have contributed to the emergence of *C. auris*, the changing human-population structure over the last few decades has also created dense clusters of susceptible hosts in hospitals for this yeast to flourish. Studies have demonstrated that host-population structures influence the invasion and adaptation of new pathogens. Homogenous clusters of susceptible host populations increase the fixation probability of a new pathogen, and pathogens have been seen to evolve differently in hospital patients, as compared to community networks [79]. As humans live longer, more and more individuals have been experiencing major surgeries, organ transplants, chemotherapy, cardiorespiratory ailments, renal failure, diabetes and immunosuppression [80, 81]. These patients undergo acute and long-term medical care and experience multiple invasive procedures like central venous catheterization, invasive mechanical ventilation, surgical drainage and urinary catheterization [51, 81, 82] (Fig. 2a). They get exposed to multiple broad spectrum antibiotics, antifungals and antiseptics [80, 83]. All of these factors dramatically alter the normal host microbiota, creating favourable conditions for *C. auris* to colonize and invade [84]. Could the expansion of such dense clusters of susceptible hosts have possibly reached a tipping point in tandem with the changes in the environment, to allow *C. auris* to emerge as an efficient nosocomial pathogen?

CONTRASTING GEOSPATIAL TRENDS IN ANTIMICROBIAL USAGE AND HOST POPULATIONS

To further explore the above factors, we decided to examine the global trends of three key variables: country-level data on healthcare antibiotic consumption (2000–2015) [85, 86], antifungal consumption (2002–2018) [87–90], and the number of acute and long-term care beds (1980–2015) [91, 92] in healthcare facilities. *C. auris* is known to afflict patients in acute and long-term care [51, 81, 82], however such patient populations are difficult to measure and their data are largely unavailable [93, 94]. Hence we used country-level data on acute and chronic care beds as a surrogate, as has been done previously [93]. We used these data to look for significant trends and change-points [95–97] in antimicrobial consumption and patient populations, and compared these trends and fluctuations with the time periods when *C. auris* emerged in each country. Further, we compared the results from Asia, South Africa and South America with those from Australia, Europe and North America, to see if these factors were evolving differently between these regions (for detailed methods and results see Supplementary Material, available in the online version of this article).

Our analysis revealed distinct trends and change-points in countries where *C. auris* appears to have emerged independently as compared to countries where it has likely been

introduced by human migration (Fig. 3). A sharp, sustained and significant rise in healthcare antibiotic consumption was seen in Colombia, India, Pakistan, South Africa, South Korea and Venezuela starting 2004–2006, with these countries witnessing the emergence of outbreak causing *C. auris* clades soon after, between 2008 and 2013. However, Japan, where no *C. auris* outbreaks have been recorded to date [29], showed an opposite trend of declining antibiotic consumption. In contrast, Australia, Europe and North America witnessed a more gradual increase in antibiotic consumption over 2004 to 2015, with these regions seeing the arrival of *C. auris* between 2013 and 2019 (Fig. 3) (Table S1). Healthcare antifungal consumption data was sparsely available in the literature. However, it revealed that South Korea has been seeing a sharp rise in antifungal consumption with a significant change-point around 2005, 4 years prior to the rise in incidence of invasive *C. auris* infections in the country. Antifungal data for South Korea were unavailable prior to 2002, preventing us from examining the trends before and after 1996 when *C. auris* first appeared in the country. In contrast, antifungal consumption in European nations showed a gradual increase starting 2010–2012, with some countries like France even witnessing a net decline in antifungal consumption (Fig. 3) (Table S2). The available data on healthcare beds was richer and spread-out between 1980 and 2015. Columbia, India, Japan, Pakistan and South Korea showed an uneven but net increase in acute and chronic care beds from 1983 to 2009. However, Venezuela revealed a net decline. In contrast, Australia, Europe and North America have been witnessing a sharp, sustained and significant decline in number of beds since the mid-1980s (Fig. 3) (Table S3).

Overall, our analysis highlights that potential factors like antimicrobial consumption and susceptible patient populations appear to have been evolving on different trajectories in countries where *C. auris* emerged independently, as compared to other nations. This analysis does not try to prove causation. It merely puts forth preliminary evidence that healthcare antimicrobial usage and susceptible patient populations have been building up in Colombia, India, Pakistan, South Africa, South Korea and Venezuela for the last 3–4 decades. Along the way, these regions witnessed significant change-points around 4–6 years (for antimicrobial consumption) and 7–14 years (for healthcare beds) prior to the emergence of *C. auris* (Fig. 3) (Tables S1–S3). These change-points were followed by further acceleration in these adverse trends and possibly denote tipping points, which lent impetus to the emergence of *C. auris* in these countries. In contrast, similar trends and change-points were missing in Australia, Europe and North America during the same period and prior to the entry of *C. auris* in these regions. This evidence suggests that these factors along with other host–pathogen–environmental factors could have collectively experienced similar tipping points and adverse trends prior to the emergence of *C. auris* in specific regions of the world. Furthermore, as has been seen with other pathogens, geospatial topologies of host–pathogen–environmental interactions vary from region to region, exerting varied evolutionary pressures and triggering varied responses in a pathogen [98–100]. This could be a reason for the emergence of genetically diverse *C. auris* clades in different parts of the globe. While the above analysis has examined only three factors, a more comprehensive multivariate geospatial analysis can potentially help unravel the key players influencing the emergence and spread of *C. auris*, and predict high-risk regions where it might emerge in the future. This analysis also points out that single environmental or organism characteristics like antimicrobial consumption or thermotolerance cannot uniformly explain the emergence of *C. auris*. This is evident from the contrary trends we saw for Japan and Venezuela in our analysis. This analysis also falls short on examining trends in regions and over time-periods where no data were available.

DRIVERS OF NOSOCOMIAL ADAPTATION AND LOCAL SPREAD

While *C. auris* emerged independently in different parts of the world, its local and international transmission has been driven by a unique set of interconnected host–pathogen–environmental factors. Human movement and international travel has been a major driver. Individuals exposed to healthcare systems in countries reporting multiple cases and outbreaks have carried strains to other countries. Phylogeographic analysis has revealed multiple introductions of different clades in the USA (clades I–IV), Canada (clades I–III), UK (clades I–III), Kenya (clades I and III), Israel (clades III and IV), Germany (clades I and III), Spain (clade III), France (clade I), Australia (clade III), Saudi Arabia (clade I) and UAE (clade I) [25, 26]. These multiple introductions have been followed by clonal expansion and local spread in many of these countries [25, 26].

The healthcare facility environment plays a crucial role in the local spread of *C. auris*. An infected patient admitted to a facility becomes an efficient source of contact transmission. Patients shed *C. auris* in their immediate environment to varying distances. *C. auris* contamination has not only been seen on bed rails, bed pans, mattresses, linen, pillows, furniture, door handles, flooring, walls, radiators and windowsills, it can even spread as far as bathing areas, sinks, mop buckets and cleaning equipment [7, 9, 82, 101] (Fig. 2b). Medical equipment that comes in contact with the patient also gets readily contaminated, for example, temperature probes, blood pressure cuffs, glucometers, housekeeping carts, alcohol gel dispensers, dialysis equipment, ultrasound machines, computer monitors, keypads and cell phones [9, 36, 82, 101]. Healthcare workers and doctors attending to the patient have also been noted to get transiently colonized in their hands, nares and groin in up to 1% of cases [9, 101]. In the local environment, *C. auris* is able to efficiently survive on inanimate objects. It can survive for 7 days on steel and porous surfaces and for 14 days on plastics. It can further exist in a viable-but-nonculturable state on plastic surfaces for up to 4 weeks [5, 102]. On hospital surfaces *C. auris* not only survives desiccation but also resists quaternary ammonium compound disinfectants, peracetic acid, standard ultraviolet-C cycle

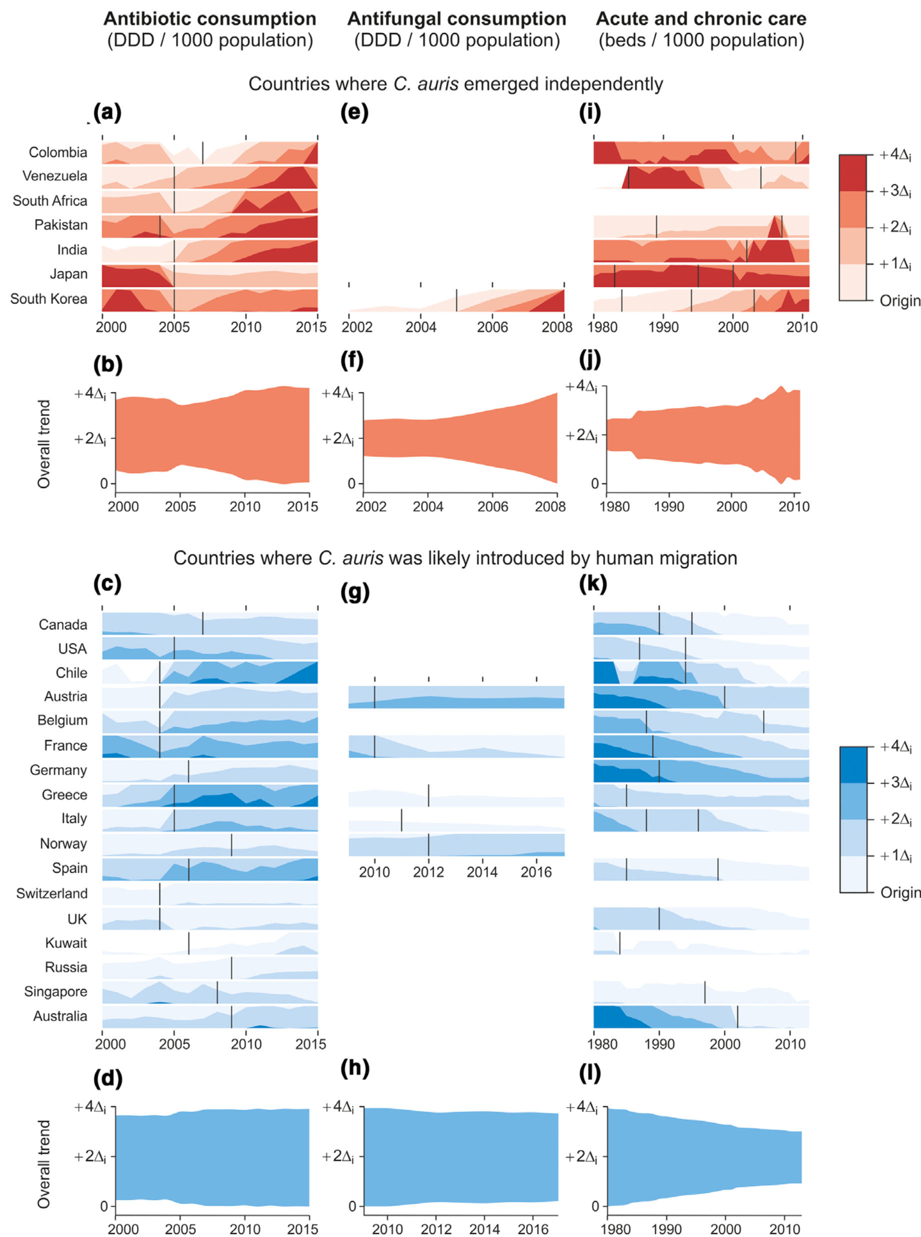

Fig. 3. Trends in healthcare antimicrobial consumption and patient beds in countries where *C. auris* has been reported. This figure contrasts the trends between countries where *C. auris* clades I–IV have emerged independently (panels in red), versus countries where they have likely been introduced by human migration (panels in blue). Vertical black bars in country-level plots denote change-points where significant changes in trend were detected. Colour gradations indicate zero- to fourfold increase in antimicrobial consumption and patient beds. (a) Dark red gradients depict a sharp rise in antibiotic consumption beginning 2004–06 in countries where *C. auris* outbreak clades emerged independently during 2008–13. However, Japan, where no *C. auris* outbreaks have been reported to date, depicts an opposite trend. The combined trend of these countries is depicted in (b) and highlights the sharp increase in antibiotic consumption seen. (c) In contrast, the dark blue gradients in countries where *C. auris* was introduced by human migration over 2012–19, depict a more gradual increase in antibiotic consumption over 2004–15, which is further evident in the overall trend for these countries (d). Only sparse antifungal consumption data were available. (e, f) South Korea, where invasive *C. auris* infections emerged in 2011, depicts a sharp rise in antifungal consumption after 2005. (g) In contrast, countries witnessing *C. auris* introductions by human travel, depict a gradual increase to even significant decline (France) in antifungal consumption, which is further evident in the overall trend seen for these countries (h). (i) The number of acute and chronic care beds depict an uneven but sustained increase during 1983–2009 in countries where *C. auris* outbreak clades emerged independently. Venezuela however, witnessed an opposite trend. (j) The overall trend for these nations also depicts a sharp rise in the number of beds starting mid-1980s. (k) In contrast, nations where *C. auris* entered through human migration show a steady decline in the number of beds from mid-1980s to 2010, and the sharp decline is clearly evident in the overall trend for these countries (l). Countries with unavailable data or unconfirmed *C. auris* clades are not depicted. (DDD, daily defined doses.)

times and standard concentrations of sodium hypochlorite [1, 103, 104] (Fig. 2c). In institutions unaware of these threats and in overcrowded developing world hospitals with compromised infection control, sequential bed occupancy and reuse of medical equipment become the source of prolonged hospital outbreaks, which have even compelled intensive care units to shut down. For subsequent patients arriving in a contaminated environment, contact times of just 4 h is sufficient to infect them, resulting in invasive infections within 48 h of admission [9, 105].

Pre-admission screening of patients for *C. auris* is not yet a norm in healthcare institutions because only a few studies have tried examining its cost–benefit. The lack of a rapid, point-of-care test also makes such screening difficult. In a large-scale preadmission screening in the UK, only one patient was found colonized out of 2200 [9]. In another small study from India, none were found colonized at admission [106]. However, in the USA, most patients with *C. auris* infections have had recent healthcare exposure [40]. The USA and the UK have issued guidelines for screening patients with travel history to *C. auris* endemic countries [40], but such guidelines will need to be expanded to all high-risk patients as the incidence of *C. auris* infections increases in different countries. It remains unclear how long individuals exposed to a nosocomial environment can harbour *C. auris* and if they continue to shed *C. auris* in the community. Studies have shown that the colonization of nares, groin, axilla, skin, urinary tract, vagina and rectum with *C. auris* can last from 1 month to 3 years, and perhaps indefinitely, in patients who have received treatment at healthcare facilities [5, 10, 40, 82]. Reinfection in such patients has been noted to occur up to 3 years after the initial invasive infection [49]. It is possible that predisposed individuals carry *C. auris* for long durations even after being successfully discharged from the hospital.

Counteracting the above factors for controlling *C. auris* infections in a healthcare facility requires a multidisciplinary effort between the clinical departments, diagnostic laboratory, the infection control team and the antimicrobial stewardship team. The detection of even a single case requires a full outbreak-level investigation [1, 107]. Further admissions to the infected area are stopped, and infected individuals are identified by contact tracing. Axillary, nasal, groin, rectal and urinary specimens of patients, contacts, and healthcare workers should be screened [1, 107]. Patients are isolated in either single-person isolation rooms, with ante-room and airlock control, or cohorted to a dedicated section of the hospital [107, 108]. Dedicated healthcare staff are assigned for these patients. Strict contact precautions should be followed, including rigorous hand hygiene with alcohol or chlorhexidine rubs, and personal protective equipment for healthcare staff. Dedicated medical equipment or single-use items like blood pressure cuffs and linen should be used for patients. Visitors should also follow rigorous hand hygiene and wear protective aprons. Regular decontamination of high-touch areas, and terminal cleaning and disinfection of patient environment are absolutely critical. The Centres for Disease Control and Prevention (CDC), Atlanta, USA, the European Centre for Disease Prevention and Control (ECDC), and Public Health England (PHE) recommend the use of hospital-grade disinfectants effective against *Clostridium difficile* spores, like high-strength (>1000 ppm) chlorine disinfectants, hydrogen peroxide with silver nitrate, phenol or ultraviolet-C radiation for environmental decontamination [1, 9, 50, 104, 106, 107, 109]. Inter-departmental and inter-institutional patient transfers should be carefully planned and notified in advance. Where possible infected patients should be scheduled last for the day, for surgery, procedures or imaging, and the room should be thoroughly disinfected after use [1, 50, 106, 107]. Patients who have previously been infected or colonized should be flagged for subsequent hospital visits and admissions [1, 107, 108].

The antimicrobial stewardship team also plays a crucial role in checking unnecessary antibiotic and antifungal use, rapid case identification, appropriate management of cases, and coordinating with the infection control team to limit transmission [110, 111]. Institutions experiencing *C. auris* transmission should review and revise their hospital antimicrobial policies. The risk–benefits of antifungal prophylaxis should be weighed for every case and treatment decisions should be based on local drug susceptibility patterns [107, 111].

The effectiveness of the infection control and antimicrobial stewardship teams hinges on the ability of the microbiology laboratory to provide rapid and reliable species-level identification and susceptibility patterns. Despite their accuracy, MALDI-TOF and DNA sequencing remain largely inaccessible to resource-limited laboratories due to the cost and expertise involved. To overcome this, simpler, inexpensive techniques have been developed. PCR and real-time PCR assays have been developed that can identify *C. auris* reliably [112, 113]. Allele-specific asymmetric PCR, duplex *ERG11* PCR and simplex *FKS1* HS1 PCR have also been developed to detect common azole and echinocandin resistance causing mutations [114]. A simple, inexpensive selective medium has also been developed recently that can reliably identify *C. auris* isolates. The medium employs 12.5% NaCl and 9 mM ferrous sulphate in yeast peptone dextrose agar. When incubated at 42 °C for up to 72 h, it identifies *C. auris* isolates with 100% sensitivity and specificity [115]. These simpler, novel techniques need further validation in laboratories across the world, and can significantly improve the timely identification and control of *C. auris* infections in resource-limited settings.

PATHOGEN CHARACTERISTICS THAT DRIVE NOSOCOMIAL INFECTIONS

Focusing further on the pathogen, what characteristics does *C. auris* possess that enable it to thrive in the hospital environment? *C. auris* frequently colonizes the skin and nares of infected patients. It is shed into the hospital environment and onto medical equipment along with desquamated skin cells, sweat and surface fatty acids [116]. Once in the environment, *C. auris* rapidly adapts to the dry abiotic milieu by activating the stress-activated protein kinase, Hog1, which provides

it resilience against desiccation and helps maintain its cell morphology [116, 117]. This transition also induces biofilm formation. Unlike *C. albicans*, *C. auris* forms low-burden biofilms on inanimate objects [118]. But if the inanimate surface is contaminated with dried-up sweat and fatty acids, as might often be the case during contact transmission from a colonized patient, then *C. auris* can form dense biofilms with up to 30-fold higher cellular burden than *C. albicans* [116]. These biofilms are highly resistant to desiccation, osmotic stress and disinfectants like chlorhexidine and hydrogen peroxide [116, 119]. These biofilms in turn contaminate the skin of subsequent patients and healthcare workers that come in contact with them. On human skin, *C. auris* thrives even better due to its thermal, salt and fatty acid tolerance [27, 116] (Fig. 2c). It rapidly forms multilayer biofilms in regions like axilla and groin, with tenfold higher cellular burden than *C. albicans* [116]. It invades breached skin and mucosa to colonize central catheters, endotracheal tubes, urinary catheters and other indwelling devices, and seeds the bloodstream therefrom [84, 116].

During biofilm formation *C. auris* activates a battery of genes encoding GPI-anchored cell-wall proteins and adhesins like, *IFF4*, *CSA1*, *PGA7*, *PGA26*, *PGA52*, *HYR3*, *ALS5* and *SAP5* [120]. These proteins help in adherence and persistence of biofilms on biotic and abiotic surfaces. The biofilms also express *KRE6* and *EXG* genes for extracellular matrix production. The extracellular matrix provides structural integrity to the biofilm and protects the yeast from environmental stressors, chemicals and disinfectants by sequestering them and preventing their action [3, 120]. *C. auris* biofilms also express a plethora of transporters and efflux-pumps including the ATP-binding cassette (ABC) transporters like *SNQ2* and *CDR1*, and the major facilitator superfamily (MFS) transporters like *YHD3*, *RDC3* and *MDR1*. These transporters confer further resistance to antifungals and toxic chemicals [120].

The inclement host skin surface and inanimate hospital environment also induce metabolic rewiring in *C. auris*. They upregulate the tricarboxylic acid cycle favouring aerobic respiration, which increases ATP production, decreases oxidative stress and improves cellular fitness [121]. Simultaneously, lipid and amino acid metabolism are upregulated with increased production of ergosterol, glycerophospholipids and lysophospholipids. These structural lipids enhance cellular integrity, help assemble efflux pumps and transporters on membranes, and help the yeast to persist in harsh environments. Cell-wall integrity pathway genes including *ROM2*, *TPK2* and *MCK1* are also activated, as are iron transporters and iron metabolism genes. A large number of secreted proteinases, lipases, phospholipases, hydrolases and aspartyl proteases are also expressed, which help in biofilm formation, combatting cell damage and host invasion [121].

Besides the above mechanisms, *C. auris* also demonstrates a strain-dependent phenotypic switch, which converts it into aggregative forms. These aggregative forms are induced by exposure to sub-inhibitory concentrations of triazoles and echinocandins in the environment, and are formed when budding daughter cells fail to separate possibly due to altered ergosterol biosynthesis. Aggregative strains have been frequently seen among isolates from clades I and III. They are much more resilient than non-aggregative strains, resist detergents and disinfectants, colonize abiotic surfaces more efficiently and readily persist in the hospital environment [35, 122–124]. *HOG1* is believed to be activated in aggregative strains providing them with resistance to osmotic and oxidative stress [117]. However, they appear to be less virulent in animal models and form less robust biofilms as compared to non-aggregative strains [35, 118]. *In vitro*, both aggregative and non-aggregative *C. auris* strains are more cytotoxic to host cells in and around a skin wound (e.g. catheterization site) rather than on intact skin. However, invading aggregative strains induce a significantly stronger pro-inflammatory immune response in the host than non-aggregative strains, suggesting that the latter might be more efficient at immune evasion [84].

C. auris also possesses mating loci with each clade fixed for either the *MTL*a or *MTL*α mating type. While the *MTL*a locus has been seen in the South Asian and South American clades, the *MTL*α is prevalent in the South African and East Asian clades [16]. With the world witnessing multiple introductions of different *C. auris* clades in different countries, a growing concern is the risk of genetic admixture among strains of opposite mating type circulating within a single healthcare institution. Such mating events could lead to increased genetic diversity, exchange of drug resistance alleles, and emergence of novel resistance and virulence mechanisms. For a pathogen which is already proving difficult to contain, such events could accelerate its spread across the globe. Interestingly, clades of opposite mating type have been seen circulating in healthcare facilities in Kenya, but so far no hybridization and genetic admixture has been observed [16, 26]. This threat also underscores the need for species and clade-level surveillance in hospitals globally.

When interacting with the host, *C. auris* deftly evades the immune system. Unlike other *Candida* species, patients infected with *C. auris* do not necessarily have neutropenia. Instead, their neutrophils fail to engage, phagocytose and produce neutrophil extracellular traps (NETs) when exposed to *C. auris* [15, 81, 110, 125]. Such immune evasion and impaired neutrophil activity possibly contributes to the adverse outcomes of patients. Similar patterns of immune evasion have also been seen with *C. lusitaniae*, suggesting that these two species share altered fungal components that have diverged from other *Candida* species [110]. Unlike neutrophils, peripheral blood mononuclear cells recognize *C. auris* more readily and produce a robust cytokine response that is different from that seen against *C. albicans* [126]. Early response to both species is elicited by β-glucans, however, the late response to *C. auris* shows much broader immune upregulation and is mediated by small, structurally unique mannoproteins. These mannoproteins carry a unique M-α–1-phosphate side chain in their acid-labile component. Cytokine production has also been found to vary within the

C. auris clades. Clades I and IV trigger the strongest cytokine response, followed by clades II and III, and potential clade V strains produce the poorest response. Clade II isolates show simpler mannan structures and are phagocytosed more efficiently. These clade-specific differences possibly affect the levels of colonization and persistence of *C. auris* in the host [126].

THE ANTIFUNGAL RESISTANCE MACHINERY OF *C. AURIS*

Among the numerous traits that make *C. auris* a formidable pathogen, its high-level resistance to antifungals is a major impediment to successfully managing its infections. Based on the tentative minimum inhibitory concentration breakpoints provided by the CDC, 90% of *C. auris* strains are resistant to fluconazole, 30% to amphotericin B and 5% to echinocandins. Multidrug resistance is seen in 41% of the strains and pan-resistance in 3–4% [3, 120]. However, these global estimates show regional and clade-specific variations. For instance, strains from Colombia and South Korea show fluconazole resistance as low as 11% [3, 101]. In fact, clade II isolates show the highest fluconazole sensitivity rates of up to 86% [26]. In contrast, clade I isolates show highest overall resistance, with 97% being resistant to fluconazole, 54% to amphotericin B and 49% showing multidrug resistance [26]. Amphotericin B resistance has so far been seen in clades I and IV, with resistance rates as high as 50% in Venezuela [3, 26]. Echinocandins are frequently recommended as the antifungals of choice for managing *C. auris* infections. However, resistance to echinocandins is also being seen in some countries. Micafungin resistance has been seen sporadically in clades I and III, but is highest in clade IV with up to 9% strains from Venezuela being resistant. High levels of echinocandin resistance have also been seen in strains from India [26].

C. auris employs multiple antifungal resistance mechanisms, which can be broadly classified under drug target mutation, target overexpression, drug extrusion and biofilm formation. Resistance also induces global changes in a strain's carbon metabolism, sterol, glycerolipid and sphingolipid synthesis, membrane architecture, efflux pump expression and biofilm formation [3, 121]. Both resistant and sensitive strains can coexist in the same population, and genetically related isolates can carry different resistance alleles. Clade-specific variations in resistance mechanisms are also widely seen [26]. All these features suggest that the high-level antifungal resistance seen in *C. auris* is more likely to be a recently acquired trait rather than an intrinsic property.

Studies on azole resistance in *C. auris* have captured the above traits in fine detail. Azole antifungals inhibit lanosterol 14-α-demethylase, an enzyme required for the synthesis of ergosterol, which is an essential building block of the fungal cell membrane. Lanosterol 14-α-demethylase is encoded by the *ERG11* gene and mutations that alter the enzyme's catalytic sites prevent azoles from exerting their action [127] (Fig. 4). Azole-resistant *C. auris* strains frequently carry three *ERG11* substitution mutations – Y132F, K143R and F126L [15, 26]. Of these, Y132F is the commonest, with 53% clade I and 40% clade IV resistant strains harbouring it. The K143R and F126L mutations are predominantly seen in clades I (43%) and III (96%), respectively [26]. Fluconazole exposure also induces a sevenfold increase in *ERG11* expression, mediated by an increase in *ERG11* copy numbers. The consequent overexpression of lanosterol 14-α-demethylase confers resistance by overwhelming the antifungal capacity of azoles [128] (Fig. 4). Up to 6% of resistant isolates harbour 2–3 copies of *ERG11* and 94% of these strains belong to clade III. Six additional regions of the *C. auris* genome of azole-resistant isolates from clades I, II and IV also show increased copy numbers. These copy-number variations seem to affect their microevolution and adaptation rather than antifungal resistance [26]. Transient gene duplication of *ERG11* and *CDR1* has also been noted in older *C. auris* cells exposed to azoles, which seem to confer fluconazole tolerance in them [129]. The molecular chaperone Hsp90 has also been found to increase tolerance to azoles in *C. auris* [130] (Fig. 4). Beside these mechanisms, the overexpression of drug efflux pumps also confers high-level resistance to azoles in *C. auris*. Both ABC and MFS class of transporters are expressed at high levels in resistant *C. auris* strains compared to their counterparts in *C. glabrata* and *C. haemulonii*. Among the 20 ABC transporters expressed in *C. auris*, *CDR1* serves as the dominant azole efflux pump and when acting in concert with *MDR1*, it can increase azole resistance by 64- to 128-fold [131, 132] (Fig. 4). Oligopeptide and glutathione transporters are also found in high numbers in the *C. auris* genome. These transporters could be ferrying out not only azole molecules but also oxidized glutathione derivatives from inside the cell, to counteract oxidative stress and cellular damage [16].

In vitro evolutionary experiments have revealed that fluconazole exposure can rapidly induce high-level fluconazole resistance in *C. auris* strains. Stable mutations appear in the zinc-cluster transcription factor, *TAC1B*, within 96 h and a few generations of fluconazole exposure [4] (Fig. 4). These mutations increase fluconazole resistance by eightfold and have been seen in all four clades from across the globe. Fourteen non-synonymous mutations and one deletion have been found to occur in *TAC1B*, of which the A640V substitution was the commonest, always occurring with the *ERG11* K143R mutation. Other *TAC1B* mutations include the following: an A657V substitution in clade I isolates; a F862_N866del frame-shift mutation in clade IV strains, co-occurring with the *ERG11* Y132F mutation; and the R495G and F214S substitutions in *in vitro* fluconazole evolved *C. auris* strains [4]. Evolution by fluconazole exposure also induces three–fivefold increase in *CDR1* and twofold increase in *MDR1* expression. This increase in efflux pump co-expression lowers fluconazole uptake in evolved cells by 50%. Other mechanisms which co-occurred in these evolved strains included *ERG11* overexpression and a twofold increase in *TAC1B* copy numbers (Fig. 4). This rapid and simultaneous evolution of multiple resistance mechanisms in fluconazole exposed *C. auris* cells is possibly facilitated by its haploid genome, and

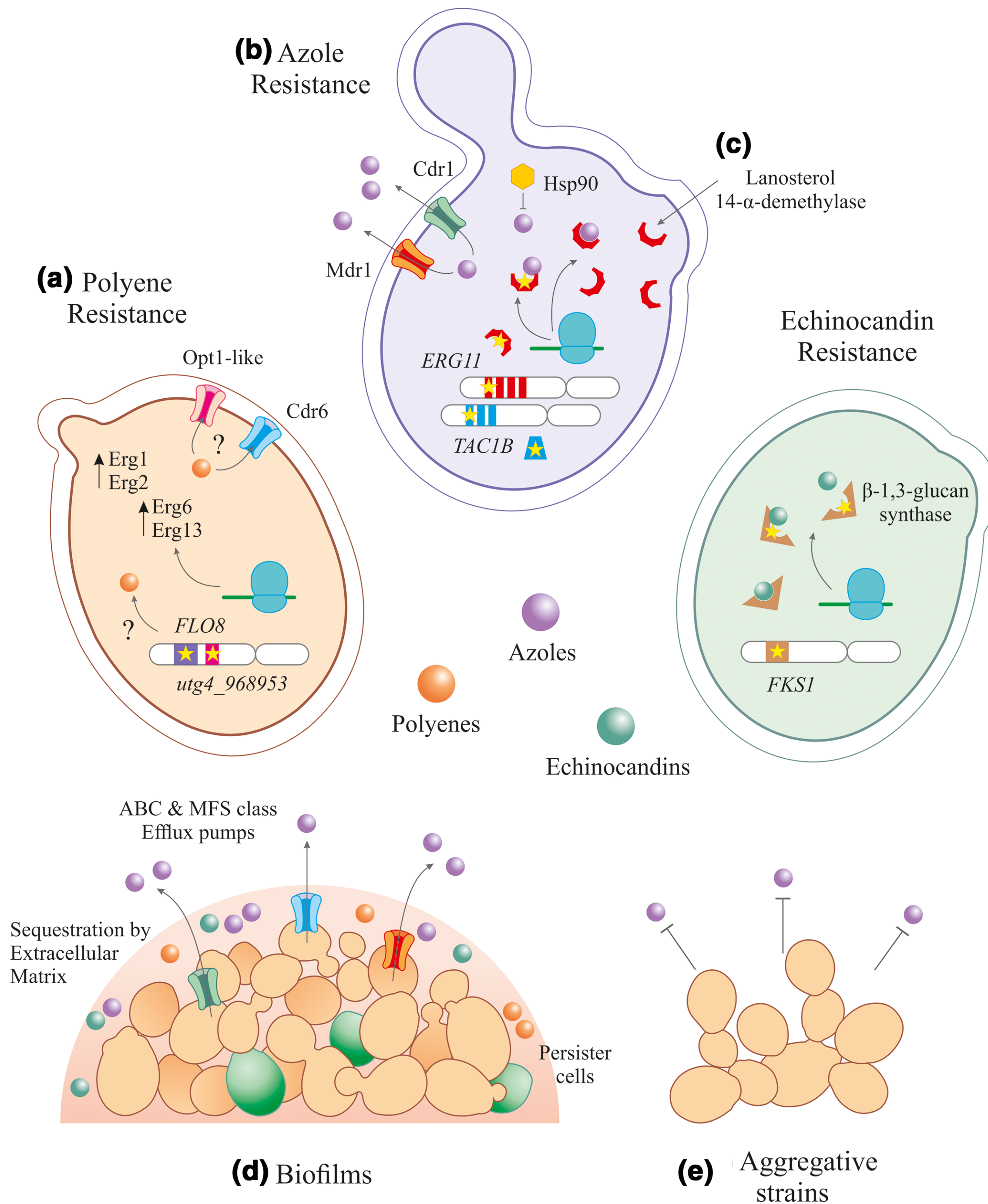

Fig. 4. Antifungal resistance mechanisms in *C. auris*. (a) Polyene resistance is incompletely understood. Mechanisms include, non-synonymous mutations in *FLO8* and *utg4_968953* membrane transporter, Cdr6 and Opt1-like efflux pumps, and *ERG1*, *ERG2*, *ERG6* and *ERG13* upregulation. (b) *C. auris* resists azoles using multiple mechanisms including, mutations and copy-number variations in *ERG11* and *TAC1B*, overexpression of Cdr1 and Mdr1 efflux pumps, and Hsp90-induced azole tolerance. (c) Echinocandin resistance involves *FKS1* mutations, which reduce the affinity of *β*–1,3-glucan synthase for echinocandins. (d) *C. auris* biofilms resist all classes of antifungals by sequestering 50–90% of the drug in the extracellular matrix, expressing large number of ATP-binding cassette (ABC) and the major facilitator superfamily (MFS) class of efflux pumps, and harbouring persister cells, which can survive high levels of environmental and chemical stress. (e) *C. auris* also forms aggregative forms, which exhibit high levels of azole resistance.

these mechanisms act in concert to exert high-level additive resistance to azoles [4].

In contrast to azoles, little is known about how *C. auris* resists polyenes. Polyenes, including the commonly used amphotericin B, act by binding to ergosterol in the fungal cell membrane, creating pores in the membrane, and killing the fungus by leaking its contents to the exterior. Initial studies have found five SNPs in different genomic locations including, non-synonymous substitutions in *FLO8* and an uncharacterized trans-membrane protein, in amphotericin-B-resistant *C. auris* strains [101]. Upregulation of *ERG1*, *ERG2*, *ERG6* and *ERG13* genes has also been noted [16]. Efflux pumps like a *CDR6* homologue and *OPT1*-like trans-membrane tetra- and penta-peptide glutathione transporters are also upregulated in amphotericin-B-resistant strains [16, 131] (Fig. 4). These genetic changes possibly alter the synthesis and composition of the *C. auris* cell membrane sterols, and prevent the accumulation of amphotericin B by pumping it out of the cell. However, further studies are needed to confirm and fully elucidate the resistance mechanisms employed by *C. auris* against polyenes.

Echinocandins are a class of antifungals, which act by inhibiting β−1,3-glucan synthase, which is required for the synthesis of β-glucan. By impairing the production of β-glucan, echinocandins compromise the integrity of the fungal cell wall, thereby killing the fungus. β−1,3-glucan synthase is encoded by the *FKS1* and *FKS2* genes. Two conserved regions in these genes known as HS1 and HS2, are prime hotspots for resistance causing mutations. These mutations decrease the enzyme's affinity for echinocandins and render the drug ineffective [127]. Echinocandin-resistant *C. auris* strains frequently carry S639P, S639F and S639Y substitution mutations in their *FKS1* hotspot (Fig. 4). Of these, the S639F and S639Y mutations are frequently seen in clades I and III, and S639P in clade IV [26, 128, 133, 134]. The S639F mutation appears to confer pan-echinocandin resistance and S639 substitutions has been found associated with micafungin resistance in 90% of echinocandin-resistant *C. auris* strains [26, 133, 135].

Besides the major antifungal classes discussed above, *C. auris* resistance has also been seen towards flucytosine and allylamines. Flucytosine is a nucleoside analogue, which inhibits fungal nucleic acid synthesis. Upon entry into a fungal cell, it requires further activation by the fungal uracil phosphoribosyltransferase encoded by the *FUR1* gene, to exert its antifungal activity [127]. Rhodes *et al.* found a F211I substitution in the *FUR1* gene of a flucytosine-resistant *C. auris* strain. However, no similar mutations have been observed in other *Candida* species [134]. Thus, further studies are needed to confirm if the substitution confers flucytosine resistance in *C. auris*. Similarly, Wasi *et al.* found significant upregulation of a *CDR6* ABC transporter homologue in a terbinafine-resistant *C. auris* strain [131]. But it remains to be confirmed if the transporter plays a role in conferring allylamine resistance in *C. auris*.

C. auris complements the above drug-specific resistance mechanisms with adaptive resistance through phenotype modification. Biofilm formation is a major defence mechanism, which protects *C. auris* from all classes of antifungals. *C. auris* can form both low and high biomass biofilms depending on the microenvironment [116, 118]. These biofilms are highly resistant to azoles, amphotericin B and micafungin, and employ multiple mechanisms to resist these compounds (Fig. 4). *C. auris* biofilms express a large number of ABC and MFS class efflux pumps at concentrations two–fourfold higher than normal, increasing biofilm resistance to azoles by 4–16-fold [120]. The biofilm extracellular matrix is rich in glucan and mannan polysaccharides, which sequester antifungals and prevent them from acting on the cells. For instance, matrix polysaccharides can sequester up to 50–90% of fluconazole present in the microenvironment [3, 136]. Mature biofilms also harbour persister cells and produce high levels of superoxide dismutase, which help in biofilm persistence and maintaining cellular fitness against oxidative stress and antifungals [121] (Fig. 4). Overall, *C. auris* biofilms can raise their resistance to voriconazole by fourfold, amphotericin B by 20-fold, and to micafungin by 60-fold, raising the minimum biofilm eradication concentration of azoles and echinocandins 512-fold higher than that for planktonic cells [118, 137]. Another resistant phenotype distinct from biofilms are the aggregative forms formed upon exposure to sub-inhibitory concentrations of azoles and echinocandins. Besides being resistant to disinfectants and the harsh hospital environment, they also show significant levels of azole resistance [122–124] (Fig. 4).

FUTURE DIRECTIONS

Despite its emergence more than a decade ago *C. auris* continues to spread across the globe unabated. Even as we gain greater understanding on how to tackle this pathogen, significant challenges remain. Rapid and reliable identification of *C. auris* for routine diagnosis, outbreak detection and infection control remains a primary challenge because MALDI-TOF and sequencing facilities are not available in a large majority of healthcare institutions [10, 11]. This also hampers the correct assessment of its global and regional spread, and its overall burden. New diagnostic modalities are emerging like PCR, and real-time PCR assays for species-level identification and resistance detection [112, 113]. A selective culture medium has also been developed with well-defined growth conditions [115]. These simpler, less expensive technologies can be validated in laboratories across the world and utilized in resource-limited settings. Eventually, we anticipate that rapid point-of-care molecular diagnostics will emerge that will give us the means to screen patients at admission. The need to quickly and effectively identify *C. auris* in patients and hospitals, also draws attention to the need for identifying its potential environmental reservoirs and how it spreads in the nosocomial environment. With growing understanding of these nosocomial niches, robust infection control will remain our best defence against *C. auris*. Multidisciplinary strategies will be required to control and prevent the spread of *C. auris*

in healthcare institutions including, outbreak-level preparedness, contact tracing, isolation and cohorting, dedicated staff and hospital equipment, rigorous hand hygiene and barrier precautions, day-to-day and terminal environmental disinfection, novel disinfection protocols, and planned patient transfers, procedures and discharge [1, 107]. Studies are also needed to assess the population prevalence and community transmission of *C. auris*, and to evaluate if pre-admission surveillance of high-risk patients by point-of-care tests can help identify and contain *C. auris* infections before they contaminate a healthcare facility and set off outbreaks.

The emergence of *C. auris* remains unexplained. Understanding why, how and where *C. auris* emerged is vital because it can help us forecast the emergence of new, resistant pathogens in the future and improve our preparedness to tackle them. The varied behaviour of *C. auris* across different clades and geographical regions, with respect to its virulence, pathogenicity, resistance levels, resistance mutations and mating loci, pose a significant challenge to unravel the factors that drove its emergence. We suspect that interactions between multiple host–pathogen–environmental factors reached tipping points in different parts of the globe, to drive its emergence, spread and acquisition of resistance. Local and global variations between these interacting factors possibly drove the pathogen to evolve differently across different clades. While this remains a conjecture, the preliminary analysis presented in this review on the evolving trends in antimicrobial consumption and changing patient populations, suggests that a more granular, large-scale, multivariate geospatial analysis of putative host–pathogen–environmental factors might help identify the factors that are driving its emergence and spread, and help anticipate where it will emerge in the future.

Another significant challenge with *C. auris* is understanding the mechanisms behind its high-level resistance to antifungals and disinfectants. While comparative genomic approaches have helped identify several resistance mechanisms that are also found in other *Candida* species, they fail to fully explain the high-level resistance seen in *C. auris*. Comparative approaches are limited in their capacity to identify novel resistance mechanisms that *C. auris* might be employing [3]. Elegant *in vitro* evolutionary studies have demonstrated how *C. auris* rapidly acquires resistance within a few generations of fluconazole exposure, and have unravelled new genetic determinants driving azole resistance [4]. More such studies are needed to fully unravel the resistance mechanisms operating in *C. auris*. The regional and clade-level variations in resistance, and the potential for inter-clade genetic admixture also calls for routine species and clade-level surveillance in hospitals. Until we have a full understanding of how *C. auris* resists antifungals and create novel antifungals to counteract those mechanisms, antimicrobial stewardship will remain crucial for preventing and controlling *C. auris* nosocomial infections. Hospitals tackling *C. auris* infections should best avoid unnecessary antifungal prophylaxis, especially in patients carrying a low risk of fungal infections, and should use broad spectrum antibiotics cautiously in general [107, 111]. Judicious use of available antifungals based on local antifungal susceptibility data and MIC breakpoints will be needed to conserve the antifungal armamentarium available to us.

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Conflicts of interest
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